Advancing bio-behavioural surveys for understanding HIV risk factors amongst Men who have Sex with Men

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Abstract

A considerable number of studies targeting the HIV epidemic amongst Men who have Sex with Men (MSM) have been published over the last decade. Despite concerted efforts promoted by the World Health Organization (WHO), the European Commission, and the Joint United Nations Programme on HIV/AIDS (UNAIDS), there remains a need for the harmonised collection of reliable and comparable bio-behavioural data across European countries within the framework of a Second-Generation Surveillance System (SGSS) approach. Linked to this, there is also increasing recognition that innovative and reliable approaches are needed to engage effectively with so-called 'hard-to-reach' strata within diverse MSM communities in order to generate robust and generalisable prevalence estimates on the HIV epidemic. Complementing such estimates, better understandings of the epidemiological patterns including associated risk factors for HIV and other sexually transmitted infections (STI) amongst MSM are required. Finally, an important issue in the literature relates to the need for effective initiatives targeting MSM populations that are based on research evidence and tailored for vulnerable populations, and designed specifically to increase access to testing and HIV/STI treatment.

This appraisal utilises eleven published papers to describe the contribution that has been made to the development of HIV bio-behavioural survey methodology, to improve further the current knowledge base regarding behavioural risk factors influencing the HIV epidemic amongst MSM, and to new approaches to increase testing and treatment.

A first strand within this thesis sets the foundations of the methodological issues that have been further advanced through the implementation of two multi-site European projects, namely, Sialon and Sialon II. The thesis concentrates on the successful adaptation and implementation of advanced methods targeting hard-to-reach MSM, improving existing venue-based and network-based sampling

methodologies, as well as championing the use of international indicators embedded in a SGSS multi-site survey. This demonstrates the significant contribution of this research in producing HIV/STI estimates with increased precision, generalisability, and comparability across European countries.

A second strand within this thesis based on several different (albeit related) projects supported by relevant publications, examines and expands upon the knowledge of risk and health-seeking behaviours amongst MSM. Despite the growing body of knowledge in the field, the analysis performed particularly on Sialon and Sialon II datasets is unique, as no previous data are available based on sampling methods designed specifically for hard-to-reach MSM, in the context of a pan-European bio-behavioural study.

Building on the Sialon research and its related publications, a final strand of the thesis focuses on the recent field evaluation of the innovative WHO Point-Of-Care Testing strategy, assessing its feasibility and usefulness when targeting MSM. The results of such evaluation research provide key insights on weaknesses and opportunities of this novel approach.

The thesis concludes with an overview of the strengths and limitations of advancing bio-behavioural surveys for understanding HIV risk factors amongst MSM as well as considerations of future potential developments particularly in terms of advanced sampling methodologies.

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List of annexes

List of acronyms

AIDS	Acquired Immune Deficiency Syndrome
ECDC	European Centre for Disease Control and Prevention
EMIS	European MSM Internet Survey
ESTICOM	European Surveys and Training to Improve MSM Community Health
ERC	(WHO) Research Ethics Review Committee
EU	European Union
EU/EEA	European Union/European Economic Area
GAM	Global AIDS Monitoring
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
LGBTI	Lesbian, Gay, Bisexual, Trans and Intersex
MARP	Most-At-Risk Population(s)
MSM	Men who have Sex with Men
MSMO	Men who have Sex with Men Only
MSMW	Men Who have Sex with Both Men and Women
NPV	Negative Predictive Values
POCT	Point-Of-Care Testing
PPV	Positive Predictive Values
RDS	Respondent-Driven Sampling
RP2	(WHO) Research Project Review Panel
SDG	Sustainable Development Goals
SGSS	Second-Generation Surveillance System
STI	Sexually Transmitted Infections

TLS	Time-Location Sampling
UNAIDS	Joint United Nations Programme on HIV and AIDS
WHO	World Health Organization

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I am grateful also to all the anonymous participants of the projects and surveys mentioned in this appraisal. Their contribution has been the main and silent pillar of all the scientific publications on which this thesis is based.

Any tree has roots, and the roots of this work lie in the course I attended years ago as part of my graduate programme, led by Dr Massimo Mirandola. I am invaluably indebted to him, for the constant support and learning opportunities I received, over the years and in many ways. Together with him, I would like to thank also all the colleagues from the CRRPS, the CReMPE, the Verona University Hospital and the University of Verona. I would also like to acknowledge all the colleagues who contributed to the different projects mentioned in this appraisal, and also the people I met over the years through the several meetings and initiatives I had the privilege be involved in. From them I have received probably more than what I was able to give.

Finally, my greatest gratitude goes to my family, to whom this work is dedicated.

Author's declaration

I declare that the research and studies contained in this critical appraisal, unless otherwise indicated in the manuscript, are the original work developed by myself, the author.

The appraisal has not been submitted to any other university.

All the mentioned publications in which I am the author / co-author have been developed, written and published with my substantial contribution.

Signed:

Dated:

Preface

This thesis summarises my academic journey over the last ten years in the field of public health and specifically in the field of HIV and Sexually Transmitted Infections (STI) epidemiology amongst hard-to-reach populations. The work spans a number of different (albeit related) multi-site projects implemented within large European and International Consortiums. Operating in a range of professional roles from project manager to independent and lead researcher, I have made substantial contributions to these projects and produced a diverse yet synergistic body of peer-reviewed papers.

The papers presented in this thesis explore not only a variety of different topics (e.g. HIV prevention, HIV/STI epidemiology, stigma and discrimination), but also a range of different methods and methodological approaches which have pushed the boundaries of knowledge in their respective fields (see for example, Sections 3, 4, and 5 of this thesis). However, the common theme throughout this body of works is perhaps an epistemological trajectory that can be traced over the 10 years I have been academically active.

For the benefit of the reader, this trajectory can perhaps be considered as a roadmap or journey that provides a sense of direction whilst navigating through the thesis. At the start of this journey in the early stages of my career, my approach to research was very much a positivistic one embracing quite traditional epidemiological methods and perspectives. During this time, the overarching thrust of my work was to generate methodologically robust data, particularly HIV-STI prevalence estimates, amongst hard-to-reach populations to strategically inform prevention activities. Two studies (Sialon and Sialon II) discussed in this thesis fall into this particular approach where the core objective of the research was to develop and implement bio-behavioural surveys across multiple countries targeting Men who have Sex with Men (MSM) in order to generate reliable and comparable epidemiological data.

As the studies developed, I began to realise that I was actually pushing the scientific boundaries of what was known at that time in terms of sampling methodologies in the context of bio-behavioural surveys, providing in many cases, fundamental HIV-STI prevalence estimates at European level. However, I also started to realise that maybe these advances did not go far enough. In other words, although quantitative methodologies are key to understanding global epidemics such as HIV and other STIs, wider approaches can also be valuable in order to better grasp the complexity of not only the epidemics themselves, but also provide insights to support new strategies in the field of HIV-STI prevention.

Such understandings over time have led me towards an arguably more diverse research approach along my professional journey. Indeed, following this early period where the large majority of my publications were epidemiologically oriented, I have gradually moved towards more psychologically oriented papers including research with qualitative designs allowing me to explore concepts such as outness and stigma among MSM as well as understanding inequalities that impact on epidemiological patterns. For example, a key publication in Section 4.8 (see page 52) based on the European Health4LGBTI project adopted a qualitative approach (focus groups) to map the experiences of Lesbian, Gay, Bisexual, Trans and Intersex (LGBTI) people in accessing healthcare, as well as map the experiences of healthcare workers when providing care for LGBTI people. Such an approach enabled me to generate rich and in-depth insights into the health and social inequalities experienced by LGBTI people as well as identify (and offer resolutions to) barriers to accessing culturally competent healthcare.

Thus, the structure behind this present thesis could be described as a progressive professional shift or journey from a positivist epidemiological approach towards embracing more diverse and wide-ranging methods and methodologies that adopt a more constructivist approach, where co-construction

processes and the systematic investigation of different perspectives are the core scientific activities. With this in mind, hopefully the reader can now navigate at ease through the sections and papers presented in this thesis, and in doing so, understand my ten-year journey of research and professional growth.

Aim of the thesis

The aim of the thesis is to systematise my body of published papers produced between 2009-2019, to present the different levels and types of contributions and to link them with the core issues of concern in the literature.

During this ten-year period, there have been significant changes and developments in the field of public health more broadly, but also in HIV/STI research specifically in terms of epidemiological patterns and methodological approaches for conducting bio-behavioural surveys and promoting prevention/testing. The first part of the thesis therefore provides the reader with an overview of the core, multifaceted and diverse challenges in the field, highlighting the characteristics of the epidemiological situation(s), as well as the relevant developments in terms of diagnostic and therapeutic innovations and global synergies to promote infections prevention and control. Key issues of concern in the literature about HIV epidemics, particularly in terms of reliability and generalisability of the HIV prevalence estimates, as well as the effectiveness in developing strategies to enhance testing and early treatment, are described, to clarify how the author have addressed some significant unresolved challenges in the HIV and MSM literature.

A second aim of the thesis is to present systematically a detailed description of the contribution made by the author to three different domains of knowledge, based on several different (albeit related) projects: methodology for conducting bio-behavioural surveys, HIV/STI risk behaviours amongst MSM and effective testing and treatment approaches.

The final aim of this thesis is to propose areas for future development, with particular reference to potential methodological advancements in the field of bio-behavioural surveys targeting hard-to-reach populations.

Introduction

The work in this thesis is based on four projects. The first project is Sialon, funded by the EU through the 2003-2008 Public Health Programme (Work Plan 2007), with partners from seven EU countries (Czech Republic, Greece, Italy, Romania, Slovakia, Slovenia, Spain). The core objective of this two-year initiative (2008-2010) was to carry out a bio-behavioural survey targeting MSM, adopting non-invasive testing methods based on oral fluid and utilising innovative sampling methodology, to obtain reliable information on HIV prevalence and risk behaviours in seven sites.

The second project, Sialon II, was co-funded under the 2008-2013 Public Health Programme (Work Plan 2010) and implemented between 2011 and 2015 in 13 EU countries (Belgium, Bulgaria, Germany, Italy, Lithuania, Poland, Romania, Slovak Republic, Slovenia, Spain, Sweden, and United Kingdom). The aim of the project was to promote targeted and meaningful prevention complemented by a bio-behavioural survey targeting MSM, adopting two innovative sampling methods for hard-to-reach populations and using common research protocols across sites.

The third project was a tender funded by the European Parliament, named Health4LGBTI. The project was implemented between 2016 and 2018 with the aim to improve understanding of the health inequalities experienced by lesbian, gay, bisexual, trans and intersex (LGBTI) people across Europe and to develop and pilot a training package targeting healthcare professionals who are providing healthcare to LGBTI people.

The fourth and final project on which this thesis is based is the ongoing global WHO ProSPeRo initiative focused on Sexually Transmitted Infections Point-Of-Care Testing (POCT) (https://www.who.int/reproductivehealth/topics/rtis/pocts/en/). Established by the Reproductive Health and Research Department of the World Health Organization, the aim of this project is to

evaluate and implement low-cost POCTs, in a wide range of countries including Australia, Brazil, China, Ethiopia, France, Guatemala, Italy, Latvia, Malta, Morocco, Peru, Slovenia, South Africa, Spain, Uganda, United Kingdom, and Ukraine).

Based on the above four projects, the thesis documents the contributions my research has made over a ten-year period. During this time, I have contributed to scientific papers, book chapters and project reports (see Annex 2 for a table summarising projects and related core publications). From these publications, 11 peer-reviewed papers have been selected specifically as the body of published works for this PhD by publication (see Annex 1). It should be underlined that such selected publications have been prepared and delivered in the context of the above-mentioned EU-funded projects and/or in the context of large international consortia. In most cases, as is common practice for these types of collaborative research projects, scientific publications have been prepared and delivered by selected writing groups, involving representatives from the different consortium partners who were interested in contributing to specific papers. No solo publications are thus generally possible and/or available as an output of such projects. Amongst the selected publications, I co-authored two papers as first author, four papers as second author, one paper as third author, and four papers placed after the third author. This thesis is built upon my unique contributions to knowledge and impact through high quality research, which is demonstrated throughout the present document.

The main thrust of this thesis revolves around the author's contribution to knowledge in three core areas as follows:

i. Improved knowledge on methodology: a description of the theoretical development and practical implementation of specific methodological approaches for bio-behavioural survey is provided. This includes a description of the specific enrolment approach for hard-to-reach populations (MSM) developed over the years in different contexts and

specifically adapted for the Sialon II project. The section also includes a description of how the core principles of the Second-Generation Surveillance System (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2002) have been adapted and embedded in the project implementation.

ii. Improved knowledge of HIV/STI risk behaviours amongst MSM: the core results from two multi-site bio-behavioural surveys are presented. This section includes a description of the key issues of concern in the literature at the time, the core research question and the improved knowledge on specific MSM's risk behaviours, health needs and related prevention actions that came about as a result of the projects' outcomes and publications.

iii. Improved knowledge on testing and treatment approaches: the theoretical background and the practical implementation of an ancillary component of the Sialon II project is presented, namely Point-Of-Care Testing (POCT). POCT technology has been promoted at international level by WHO to increase access to testing and prompt referral for high-risk target populations such as MSM. This section of the thesis also includes an overview of the key issues of concern in the literature which represent the basis for POCT use and a POCT pilot project implemented in Verona, as well as the description of prevention initiatives promoted in different countries.

In short, this thesis maps the different contributions in each of these three areas, using as a basis (and as titles of the sub-sections) the peer-reviewed journal articles selected for this appraisal.

2. Background

Overview

The available data on HIV/STI at European level confirm that these diverse and multifaceted epidemics continue to represent a pressing public health issue. Notwithstanding the rapid development of testing technologies and therapeutic tools in recent years and despite the concerted efforts in promoting prevention and testing campaigns, HIV and other STIs remain a reality particularly amongst vulnerable groups such as MSM (Mirandola, Gios, Davis, Furegato, Breveglieri, Folch, …, Stehlíková, 2016) (Mirandola, Gios, Sherriff, Marcus, Toskin, Rosinska, … on behalf of the Sialon II Network, 2018). Recent reports from the European Centre for Disease Control and Prevention (ECDC) highlight that in more than half of the European Union/European Economic Area (EU/EEA) countries, HIV prevalence amongst MSM is estimated to be approximately 5%, or possibly even higher (European Centre for Disease Prevention and Control [ECDC], 2015) (ECDC, 2017). In the same geographical area, in terms of new HIV positive diagnosis, MSM accounted for roughly 50% of cases (ECDC, 2017). Considering the data prospectively, whilst the number of new cases has been relatively stable over the last decade, the number of new diagnoses amongst MSM aged 20–24 years doubled in the period 2004-2013 (ECDC, 2017). These available reports and recent scientific publications underline how strongly MSM are disproportionally affected by HIV in the current European epidemic scenario, compared to non-MSM populations such as heterosexuals (Chapin-Bardales, Schmidt, Guy, Kaldor, McGregor, Sasse, …, Sullivan, 2018) (Mirandola et al., 2016) (Mirandola et al., 2018).

There have been great strides in terms of diagnostic and therapeutic innovations and global synergies to further promote infections prevention and control. Epidemiological data however, are continuously confirming the increasing number of infections, particularly amongst specific target populations (including young MSM). This scenario represents a challenge for researchers and policy makers alike.

The reliability of available epidemiological data and of new approaches to improve survey methodologies, allowing an increased knowledge on the epidemic patterns and trajectories, are still relevant research questions in the scientific literature.

Key issues of concern in the literature about HIV epidemics

Despite concerted efforts by national and international agencies in monitoring the HIV epidemics and in promoting broad prevention campaigns, there remains a need for harmonised collection of reliable and comparable bio-behavioural data across European countries within the framework of a Second-Generation Surveillance System (SGSS) approach (UNAIDS, 2010). Complementing such estimates, better understandings of the epidemiological patterns including associated risk factors for HIV and other STI amongst MSM communities are required. A further important issue in the literature relates to the need for effective initiatives targeting MSM populations that are based on research evidence and tailored for vulnerable populations, and designed specifically to increase access to testing and HIV/STI treatment (Dubois-Arber, Jeannin, Spencer, Gervasoni, Graz, Elford, … van de Laar, 2010). Such key concerns can be summarised and grouped according to four main areas:

i. Heterogeneity of methodologies in implementing HIV epidemiological surveillance targeting MSM: the approaches adopted for epidemiological purposes significantly vary across countries, with a subsequent lack of data comparability (UNAIDS, 2002);
ii. Reliability/generalisability of survey estimates (e.g., HIV prevalence estimates), particularly for data regarding hidden strata within the MSM communities: results reliability and generalisability are commonly poor, due to the specific methodologies adopted (Alfvén, Erkkola, Ghys, Padayachy, Warner-Smith, Rugg & de Lay, 2017);
iii. Improved knowledge of risk and health-seeking behavioural patterns: an increased understanding of these patterns (particularly among most at risk populations) might lead to an

enhanced knowledge of factors and processes, which are hampering and/or accelerating the HIV epidemic (Chapin-Bardales et al., 2018);

iv. Effectiveness in developing strategies to enhance testing and early treatment: little is known about how to maximise the potential for strategies to effectively promote testing and treatment, particularly amongst vulnerable strata within the MSM population (Campbell, Lippman, Moss & Lightfoot, 2018).

The first main concern is related to the different methodologies adopted in implementing HIV epidemiological surveillance targeting MSM, with a subsequent lack of data comparability. Over the years, considerable efforts have been invested in developing epidemiological surveys targeting MSM. However, some critical issues have emerged across the different studies implemented in this field. First, the use of varying enrolment methodologies adopted for monitoring purposes. This was considered of crucial concern when interpreting and comparing data from different surveys within the same country (and/or region), and between different countries (National Research Council US Panel on the Evaluation of AIDS Interventions, 1991) (ECDC, 2009). This divergence was related mainly to the adoption of different sampling methods (ranging from the widespread use of convenience sampling to the use of quasi-probabilistic approaches, and from online surveys to survey collecting only biological information) and diverse tools for collecting data. In the case of behavioural information, for instance, questionnaires commonly utilised different time-span periods when focusing on health and/or risk behaviour (e.g., exploring HIV testing frequency using different time periods, such as 3-6 and/or 12 months) (ECDC, 2009). Alternatively, across many studies, different wording and different items were used to collect data on testing habits and attitudes. In case of biological data (biomarkers), different testing algorithms were adopted, making a reliable comparison amongst the results and estimates from different surveys almost impossible (ECDC, 2016). Against this backdrop, international agencies have repeatedly stressed the importance of harmonised surveillance and monitoring systems adopting common and standardised indicators (UNAIDS, 2002),

together with the implementation of Second Generation HIV Surveillance Systems (SGSS), that is, the collection of linked biological and behavioural data (UNAIDS, 2002). These aspects have both been addressed explicitly in the design of the Sialon I and II studies.

A second source of concern in the literature relates to the reliability and the generalisability of the HIV prevalence estimates produced in the context of HIV surveillance and bio-behavioural surveys, particularly regarding hard-to-reach MSM whom may be 'hidden' and thus either not respond or are not reached by such surveys. Two main approaches are usually used in order to calculate HIV prevalence estimates: clinical-based surveys versus population-based surveys (ECDC, 2015). According to the former, data are collected from patients who access a clinical/testing service via the formal healthcare system such as a clinic or hospital setting. This process is generally known as a surveillance of HIV infection using 'HIV case notification' (ECDC, 2015). This process may however potential exclude or underrepresent hidden groups within Most-At-Risk Populations (MARP) such as MSM, who may be less likely to access such clinical/testing services (Beyrer, Baral, Kerrigan, El-Bassel, Bekker & Celentano, 2011). This means therefore that generalisability of the HIV estimates produced using this method can be quite problematic. Alternatively, population-based surveys are usually structured to reach members of a target population 'outside' of formal healthcare facilities or systems (Gama, Martins & Dias, 2017). This therefore requires specific methodological adaptations including the adoption of specific and/or strategic enrolment approaches to reach the target population, which thus incur related biases. Once again, this means that the generalisability of the HIV prevalence estimates produced can be questionable.

Reliable and generalisable data on HIV/STI prevalence is important because of the difficult task of determining the size of the denominator, that is, the total number of MSM (Gama et al., 2017). This represents a relevant problem, as unknown size and regional distribution of this population makes extremely difficult to generalise the data to the target population, and – when possible – this

generalisation might be fraught with several biases (particularly with selection bias) (Marcus, Schmidt, Kollan & Hamouda, 2009). Moreover, the lack of locally and/or nationally representative (probability-based) surveys is problematic. Together, the lack of integrated and multi-site surveys targeting high-risk subpopulations such as MSM has been challenging and hampering the collection of data that could potentially deepen the understanding of mechanisms of HIV epidemic amongst MSM (Beyrer et al., 2011). The use of appropriate sampling methods was explored particularly in the 2000-2010 decade (Magnani, Sabin, Saidel & Heckathorn, 2005) (Gama et al., 2017). Over this period, there was an attempt to understand how different approaches could be successfully adopted in different contexts, with the purpose of effectively reaching hidden strata of at-risk populations and of consequently generating estimates allowing to characterise the different strata within a specific MARP. The effectiveness and feasibility of advanced epidemiological approaches still represents one of the core topics of the scientific debate (Magnani et al., 2005) (Brookmeyer, 2010) (Gama et al., 2017). The concern about how to collect reliable data and/or how to effectively triangulate the different sources of information required to map the HIV epidemic (e.g., biological and/or behavioural data), is a recurrent topic of the debate. The need for large-scale, comprehensive and complementary surveys combining biological and behavioural data was constantly underlined also by international and European institutions (UNAIDS, 2002) (ECDC, 2009).

Linked to the above issue, the third area of concern in the literature is the need for improved knowledge of risk and health-seeking behavioural patterns (Chapin-Bardales at al., 2018). An improved understanding of these patterns could lead to an enhanced knowledge of factors and processes, which impact and/or accelerate the HIV epidemic. Yet despite concerted efforts in tailored prevention initiatives, epidemiological data confirm an increasing number of infections particularly amongst specific segments of MSM communities. This clearly indicates the need for more accurate data that could potentially deepen the understanding of mechanisms of HIV transmission, particularly amongst hidden strata of the MSM population (Mirandola et al., 2018).

A fourth strand of concern in the literature was related to the need for HIV prevention programmes linked with (and based on) reliable data to monitor the HIV epidemic (Sullivan, Carballo-Diéguez, Coates, Goodreau, McGowan, Sanders, … Sanchez, 2012). In particular, the need for efficient strategies to efficiently improve access to testing and early treatment, mostly amongst hidden segments within the MSM population, was highlighted jointly by researchers and international institutions (Sullivan et al., 2012) (Toskin, Blondeel, Peeling, Deal & Kiarie, 2017). This includes the need for developing and validating new technologies and approaches to make testing procedures more accessible, easy-to-use and acceptable for patients and healthcare staff.

Towards new methodologies in HIV epidemiology and testing and treatment promotion approaches

Over the last two decades, attempts to set up a comprehensive set of methodologies to improve HIV surveillance have been proposed (Gall, Sabin, Frescura, Sabin, Erkkola & Toskin, 2017). Indeed since 2002, the ECDC, UNAIDS and WHO have highlighted the need for homogeneous monitoring systems, proposing a set of standardised indicators to the be adopted in surveillance planning (UNAIDS & WHO, 2002). The reason behind this structured set of indicators was to promote a multi-faced approach: (i) to harmonise the use of tools, algorithms and indicators across the different HIV surveillance systems; (ii) to promote the triangulation of different types of information (behavioural and biological data); and (iii) to improve adoption of tailored indicators for specific segments of the MARP (e.g., young people, pregnant women, sex workers, etc.), including specific items for MSM (e.g., condom use during anal sex, testing and knowledge about serostatus, etc.).

Since their first appearance, this set of indicators and related methodologies have been successfully improved over the years. The Global AIDS Monitoring (GAM) indicators[1], jointly promoted by WHO and UNAIDS combine the collection and use of biological and behavioural data to inform prevention strategies and for epidemic monitoring purposes (UNAIDS, 2017) (WHO & UNAIDS, 2009) (UNAIDS, 2014) (Alfvén, Erkkola, Ghys, Padayachy, Warner-Smith, Rugg & de Lay, 2017) (UNAIDS, 2016). This approach, that is the triangulation of information from different sources (biological samples and behavioural data), could represent the ideal extension of the Second-Generation Surveillance Systems (SGSS), a paradigm launched since 2002 by UNAIDS (UNAIDS, 2002).

A standardised set of GAM indicators is crucial given their role in providing specific data and information to monitor the implementation of the Sustainable Development Goals (SDG) and the UNAIDS 90–90–90 strategy, recently endorsed by the European Commission (EC) Communication on 'Next steps for a sustainable European future' (Gall et al., 2017).

Parallel to this process, significant efforts have been made in advancing and implementing novel approaches to facilitate the effective enrolment of hard-to-reach populations such as MSM. Considering the exponential use of internet platforms and internet accessible smart devises (e.g., phones, tablets) over the last decade, internet based surveys have been extensively adopted to implement behavioural surveys targeting MSM, and they have proven to be effective in recruiting large strata of the MSM communities and in being valuable and sustainable complements to national surveillance systems (Marcus, Hickson, Weatherburn, Schmidt, & EMIS Network, 2013) (Weatherburn, Schmidt, Hickson, Reid, Berg, …, Marcus, 2013). Furthermore, as they rely purely on

[1] It should be noted here that indicators' name has been changed many times over the last decade, from *UNGASS* to *GARPR*, until the current official acronym, which is *GAM*. For the sake of uniformity, the acronym *GAM* is used throughout this document.

self-reported information, such methods seem to be useful to estimate the approximate number of new HIV infections amongst MSM given the lack of reliable data from national surveillance systems (Marcus et al., 2013). In addition to internet-based enrolment strategies designed to reach MARPs such as MSM, two main methods have been developed in the last decade: Time-Location Sampling (TLS) and Respondent-Driven Sampling (RDS). TLS has been used in many contexts and targeting different MARP (including MSM), demonstrating to be an effective strategy (Stueve, O'Donnell, Duran, San Doval, & Blome, 2001) (Williamson & Hart, 2007). The same applies to RDS, which has also been shown to be a reliable method for gathering bio-behavioural information (Abdul-Quader, Heckathorn, Sabin & Saidel, 2006) (Kendall, Kerr, Gondim, Werneck, Macena, Pontes, …, McFarland, 2008). This said, specific assumptions and related biases are present for both these methodologies, and the effective implementation in different contexts is still a sensitive and unresolved issue.

In recent years, an innovative approach to increase testing and prompt referral to treatment has been proposed (Toskin et al., 2017). This new methodology attempts to respond to the challenge of an effective testing and early treatment approach suitable for different target populations, particularly for MSM (Sullivan et al., 2012). This novel method is partially enabled by the innovative technologies and devices currently available on the market, namely the rapid diagnostic tests for HIV/STIs. The rapid diagnostic technologies are enabling an international effort to promote low-threshold or community testing facilities (Schmidt, 2017) as well as efficient testing and treatment pathways through the implementation of Point-Of-Care Testing (POCT). WHO supports the use of POCT at international level as a way to move from laboratory-based testing to a clinic-based approach on the basis that this strategy can facilitate (in terms of timing, availability and acceptability) access to testing and prompt referral to treatment (Toskin et al., 2017). Considering some preliminary and encouraging results, both these strategies may play a key role in expanding testing and treatment

access, particularly for hard-to-reach populations such as MSM and vulnerable sub-groups (Toskin et al., 2017).

Main unresolved challenges in the HIV and MSM literature

Despite the availability of the GAM indicators and SGSS guidelines and the fact that an increasing number of initiatives are implemented in line with this approach, much remains to be done. This is also underlined in relevant reports promoted by the European Commission (European Commission [EU], 2016). The core four challenges mentioned at the beginning of this background section (heterogeneity of methodologies; reliability / generalisability of the estimates; need for an improved knowledge of risk and health-seeking behavioural and effectiveness in developing strategies to enhance testing and early treatment) are still unanswered (Levi, Raymond, Pozniak, Vernazza, Kohler & Hill, 2016). The extensive implementation of such methodological approaches is patchy and requires strengthening across countries, as to date there remains considerable variability in response rates and the use of GAM indicators and SGSS guidelines are far from being implemented as a standard approach (Dubois-Arber et al., 2010) (Alfvén et al., 2017). As example, in 2012, GAM data on key populations (including MSMS) were reported in approximately only 30% of cases (Gall et al., 2017).

In addition to this, the question of how to efficiently embed the GAM indicators within the context of SGSS survey remains a challenge. The issue is further complicated when trying to extend the use of GAM indicators and SGSS principles beyond a clinical-based survey approach, towards a population-based survey approach (Gama et al., 2017). In other words, this means linking GAM indicators, SGSS and novel enrolment approaches such as TLS and RDS, specifically designed for hard-to-reach populations, to allow a reliable triangulation of data coming from hidden strata of the target populations. To-date, few studies have been able to address simultaneously all these aspects (Alfvén et al., 2017).

Considering the testing and treatment strategy promoted through the POCT initiative, little is known about the actual *impact* of POCT adoption (Toskin et al., 2017). A first issue relates to the clinical performances of the rapid tests when adopted in specific settings (i.e. the possibility of false positives and false negatives). As an example, positive predictive values (PPV) and negative predictive values (NPV) are related to the specific characteristics of the population (prevalence of the disease): therefore, the same POC test –when used to test different populations – might result in different performances. This might be related to the epidemiological characteristics of the population in itself, rather than to the performance of the test. This implies that specific validations are required to better understand the performance of the tests, in light of the specific epidemiological patterns within a specific target population. An additional challenge is represented by the assessment of the acceptability of POCT approach when included in the current clinical practice. This implies the clarification of the acceptability from the viewpoint of the users (e.g., health care staff) and from the perspective of the clients (e.g., MSM attending clinics and/or community testing facilities where POCT is adopted).

In the case of the latter, different target populations (e.g., MSM, sex workers, pregnant women, etc.) might experience different levels of acceptability, considering also environmental and broad social factors (Stahlman, Hargreaves, Sprague, Stangl & Baral, 2017). Finally, and most importantly, a comprehensive assessment of the potential impact of the human component (e.g., role of the health care staff performing and/or reading POCT results) when adopting POCTs should be carefully taken into consideration (Toskin et al., 2017).

Discrimination and stigma as overarching driving factors

In addition to the above-mentioned issues, discrimination and stigma have also been identified as a factor in the shaping of the HIV epidemic affecting MSM in Europe and worldwide (Stahlman et al.,

2017) (Campbell et al., 2018). An increasing body of literature has highlighted how stigmatising environments are deeply shaping MSM's experience in terms of diminished access to HIV/STI prevention services (Campbell et al., 2018). MSM exposed to such a stigmatising environment are also experiencing critical patterns in terms of risk-behaviours and mental health issues (Pachankis, Hatzenbuehler, Hickson, Weatherburn, Berg, Marcus & Schmidt, 2015) (Berg, Weatherburn, Ross & Schmidt, 2015) (Pachankis, Hatzenbuehler, Berg, Fernández-Dávila, Mirandola, Marcus, …, Schmidt, 2017). In other words, stigma (internalised, interpersonal and structural) is fuelling the HIV epidemic and fostering health inequalities (Berg, Ross, Weatherburn & Schmidt, 2013). Despite the considerable number of studies in this field, further research is needed to understand the correlation between stigma and risk behaviour and health seeking behaviour.

Contributions

The work summarised in this thesis address the main issues of concern in the literature regarding:

i. The need for (more) robust and harmonised methodological approaches in implementing HIV epidemiological surveillance, particularly amongst hard-to-reach populations (e.g., MSM);
ii. The need for reliable and generalisable survey estimates (e.g., HIV prevalence estimates), particularly regarding hidden strata within the MSM communities;
iii. The need for additional data on and insights into risk and health-seeking behaviours amongst MSM, especially amongst hard-to-reach MSM, with a specific focus on the role of stigma/discrimination as overarching factors enabling (or hindering) health-seeking behaviours;
iv. The need for (more) reliable tools and strategies for promoting and increasing testing and treatment amongst MSM.

Contribution to an improved knowledge on surveillance methodologies

With regards to the need for robust methodological approaches for collection of reliable and comparable data, I further advanced the literature on this matter by designing and implementing a multi-site bio-behavioural survey targeting MSM and implemented in thirteen European Countries (http://sialon.eu/en/). Sialon II was a three-year project which simultaneously embraced the core approaches internationally advocated by ECDC, UNAIDS and WHO.

The challenge was to include in a unique model (meaning, in a unique project) aspects which were well-developed and adopted as separated components and that (to my knowledge) had not previously been embedded in a comprehensive and multi-site survey in a systematic way (Dubois-Arber et al., 2010) (Alfvén et al., 2017).

A relatively comprehensive model had already been developed and implemented during the former Sialon project. A bio-behavioural survey targeting MSM was implemented, adopting a non-invasive outreach testing method based on oral fluid sample collection and the international (GAM) core indicators for the survey questionnaire. TLS was adopted as an enrolling method. A previous experience of such a survey using TLS and targeting MSM in an EU country was piloted in Scotland (Williamson & Hart, 2007), through a two-site cross-sectional survey in Glasgow and Edinburgh. The Sialon two-year project advanced the knowledge in terms of bio-behavioural survey adopting TLS, expanding the bio-behavioural approach in a multi-country survey, implemented in seven EU Countries: Czech Republic, Greece, Italy, Romania, Slovakia, Slovenia, and Spain. The model was then further improved and integrated into the Sialon II project. See Figure 1 for an overview of the model of the Sialon II multi-site survey.

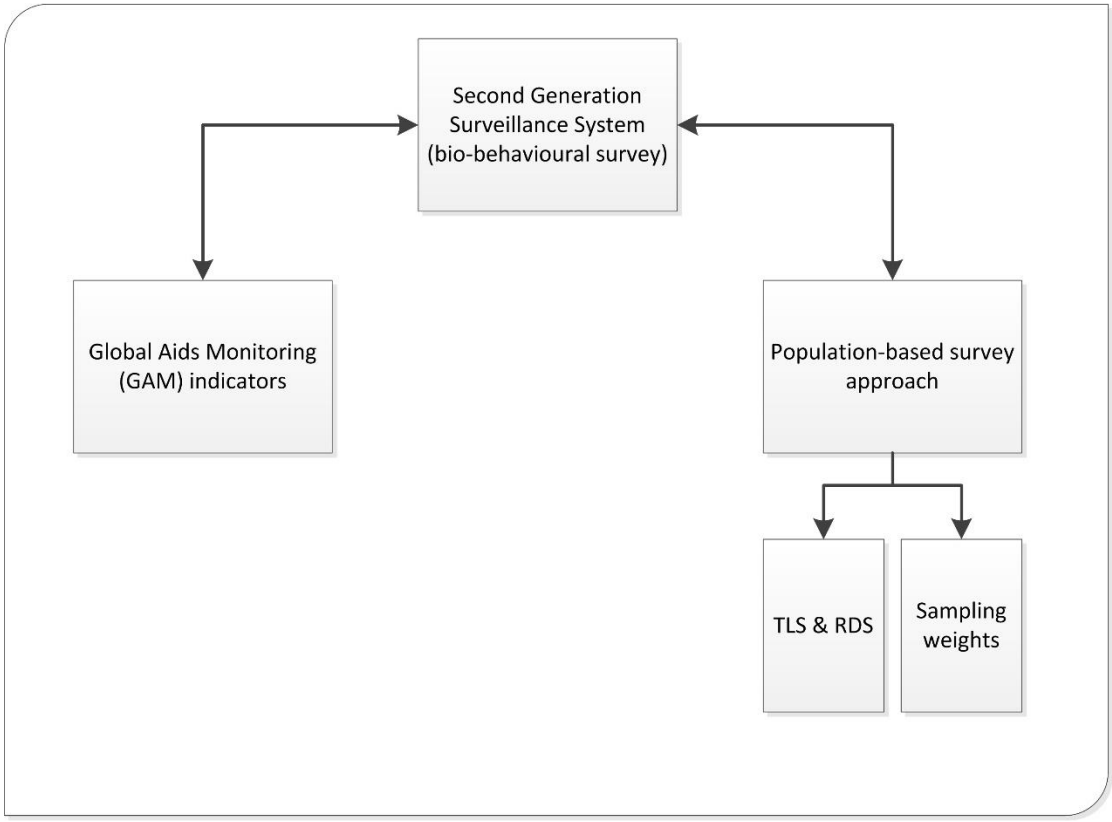

Figure 1. The different components embedded in the Sialon II bio-behavioural multi-site survey

In terms of GAM indicators, these were included in the Sialon II study questionnaire. To further improve comprehension and usability of the questionnaire and the appropriate inclusion of the GAM items in the data collection tool, a participatory approach was adopted, involving experts from:

i. International institutions (European Commission, ECDC, WHO, UNAIDS);
ii. European Public Health bodies and Universities/Research Institutions;
iii. Local LGBTI associations (thirteen, one per country).

In terms of SGSS principles, that is, the parallel collection of biological and behavioural samples from the same individual, standard algorithms for the analysis of biological samples were adopted to allow uniformity and comparability of the data (UNAIDS, 2002) (Gall et al., 2017). This required a careful balancing between uniformity prerequisites and local standard procedures across the thirteen

study sites. It should be noted that the decision to include SGSS principles implied the concomitant collection of biological samples and behavioural information for the same participant. This decision had an impact also in terms of enrolling methodologies that were identified and adopted in the context of the project.

In terms of enrolling participants, the core challenge was to target effectively hidden strata of the MSM population when collecting biological samples along with behavioural information. It was clear that the lack of involvement of these groups in surveillance systems / surveys could lead to a substantial misunderstanding of the dynamics of the HIV epidemic (Magnani et al., 2005) (Gama et al., 2017). With this in mind, the bio-behavioural survey was structured adopting the main methods widely used in the last decade to enrol hard-to-reach MSM: Time-Location Sampling (TLS) and Respondent-Driven Sampling (RDS). The use of Internet-based sampling methodologies was excluded for this kind of survey, because of the need for collecting biological data for each participant. It is worth noting that a few years after the Sialon project, there were some initiatives that adopted mixed strategies linking Internet-based approaches and Respondent-Driven Sampling (Strömdahl, Lu, Bengtsson, Liljeros & Thorson, 2015) or Internet-based approaches with the collection of biological samples for testing (Merchant, Clark, Liu, Romanoff, Rosenberger, Bauermeister & Mayer, 2018) (Elliot, Rossi, McCormack & McOwan, 2016).

An additional advance in the methodology of Sialon II was the inclusion of sampling weights in the survey structure. The inclusion of weight was an important improvement in this field (Clark, Konda, Silva-Santisteban, Peinado, Lama, Kusunoki & Sanchez, 2014), allowing an enhanced precision of the estimates and therefore enabling an appropriate description of the interpretative limitations of the results. To allow for sampling weight calculations, additional items were included in the questionnaires on the venues attendance (TLS) or on network size (RDS). For TLS, a specific procedure was structured on the basis of previous theoretical and methodological publications (Karon

& Wejnert, 2012), whilst for RDS the weighting approach was adopted in line with the most advanced methodological and statistical tools (Heckathorn, 1997) (Gile, 2011) (www.hpmrg.org).

To further improve the feasibility and local adaptations of both TLS and RDS surveys, I coordinated a formative research study with a view to understanding the factors allowing for successful implementation of the two methods, balancing between organisational prerequisites and scientific requirements (Dudareva-Vizule & Marcus, 2013). The formative research included information purposively collected through a specific questionnaire and EMIS 2010 data for the specific study sites. The mapping exercise included data on previous local experiences with different study methodologies and target groups, availability of gay-friendly commercial and non-commercial sites, prevention activities in place, availability of HIV/STIs/Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV) testing and therapy, legislation and stigmatisation. Additional information and data from EMIS 2010 were used to further characterise the MSM population in each respective study area (e.g., demographic characteristics, outness, gay-venue attendance by study area) (Dudareva-Vizule & Marcus, 2013).

An overarching participatory approach was adopted to ensure the ideal convergence of scientific procedures and perspectives and expectations from health professionals and the LGBTI communities. The continued involvement of the LGBTI (MSM) communities was a driving factor to ensure a smooth and non-stigmatising implementation of the project. This was also reinforced in the GAM guidelines, where it is specifically stated that the civil society, including NGOs and people living with HIV, should be involved in the research process (UNAIDS, 2017).

I contributed to implementing the core foundation of the project, namely the comprehensive integration of GAM indicators within a multi-site second generation HIV surveillance systems approach and in participatory collaboration with MSM communities, adopting the most advanced

(and improved) methodologies to enrol hard-to-reach segments of the MSM population. The outputs of this effort will be described in the following sections, linking together different publications I authored/co-authored (see Appendix 2). The integration of these components in the Sialon II survey allowed:

i. The implementation of a bio-behavioural survey adopting standard procedures in 13 EU countries, executing the WHO/UNAIDS purpose to make survey estimates comparable across countries;
ii. Through the use of TLS/RDS approaches integrating weights, to obtain reliable (and comparable) data from hard-to-reach population in 13 EU cities (following a population-based survey approach rather than a clinic-based approach);
iii. To generate a unique dataset, comprising comparable data coming from hard–to-reach segments of the MSM population, gathered through the biggest bio-behavioural survey targeting MSM ever carried out in Europe;
iv. To allow statistical analysis for weighted estimates and ad-hoc statistical modelling to explore prevention needs, risk behaviours patterns for a considerable number of MSM/cities in the EU.

In the following sections, the different publications are chronologically linked per area (improved knowledge on surveillance methodology, improved knowledge on risk behaviours amongst MSM, improved knowledge on testing and treatment approaches), providing a description of the interlinked foundations across the papers.

Specific attention is paid to two aspects mentioned in the previous sections, that is, the urgency of piloting and validating POCT, as well as the urgency of increasing the skills of health care professionals in the process of creating LGBTI-friendly healthcare services.

With regards to the first issue, a specific study is presented. Through this study, an assessment of the actual impact of POCT in the clinical routine has been made. Even if the theoretical background of the use of POCT is well developed and promising practices are in place, the publication is concretely assessing the clinical performances of POCT (dual test for Syphilis) targeting MSM when adopted in specific settings. The uniqueness of this piloting study was related to the use of weighted estimates for Syphilis (gathered through the Sialon II project), allowing a precise assessment of the performance (PPV and PPN) of the POCT. In addition, and this was the first time for a POCT study targeting MSM, a comprehensive assessment of the potential impact of the human component (role of the health care staff in performing and/or reading the POCT results) when using POCT was made.

With regards to the second issue, that is, the urgency of increasing the skills of health care professionals in the process of creating LGBTI-friendly healthcare services, a paper based on the project 'Health4LGBTI: Reducing health inequalities experienced by LGBTI people' is presented[2]. As a result of this two-year project (2016-2018), an advanced understanding of specific health inequalities experienced by lesbian, gay, bisexual, trans and intersex (LGBTI) people when accessing healthcare services was obtained.

[2] https://ec.europa.eu/health/social_determinants/projects/ep_funded_projects_en#fragment2

3. Improved knowledge on surveillance methodology

Amongst the selected publications, two papers are presented in this section focusing on methodological advancement. Their contribution to the international literature and practice is analysed, with specific focus on advancement in designing and implementing multi-countries studies embracing the core approaches internationally advocated by ECDC, UNAIDS and WHO for bio-behavioural survey targeting MSM.

3.1 HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona (2008-2009) [Annex 3, 3.1, page 79]

In the decade 2000-2010, few examples were available – at least in the EU – of the comprehensive adoption of TLS in the context of bio-behavioural survey targeting MSM and focusing on HIV/STI. One of the few experiences was a survey implemented in Scotland, adopting TLS as a method to enrol MSM and to collect both biological and behavioural information from the same participant (Williamson & Hart, 2007). The manuscript describing this pioneering study, whilst showing that TLS was a viable method to conduct bio-behavioural survey and therefore to gather prevalence data based on MSM recruited in gay venues, revealed several weaknesses. First, the survey was implemented in two sites in the same country (in Glasgow and Edinburgh), with presumably a relatively homogeneous social and cultural context. Second, only a limited description of the methodological adaptation of TLS was included in the paper (e.g., explanation on how the venue-day-time units were constructed and considered for the data analysis). Third, there was a lack of matching between the indicators adopted for collecting behavioural information and the international (WHO/UNAIDS/ECDC) recommendations. Fourth, a oral fluid collection kit was used to collected saliva samples to test for HIV participants, leading to ethical issues (need for pre/post-test counselling

in case participants were asking for the result) and methodological issues (reliability of the tests results).

However, the publication from Williamson and Hart (2007) provided invaluable evidence that with appropriate adaptations a bio-behavioural survey targeting MSM in gay venues was possible and potentially helpful in estimating HIV prevalence. Through the Sialon project, described in the first publication selected for this thesis (Mirandola, Folch, Krampac, Nita, Stanekova, Stehlikova, …, the SIALON network, 2009) [Annex 3, 3.1, page 79], a considerable improvement has been made in terms of bio-behavioural survey targeting MSM and adopting enrolling methodologies specifically designed for hard-to-reach populations. The project was conceived to include: (i) the international (GAM) core indicators as reference for the survey questionnaire; (ii) the triangulation of behavioural information and laboratory-based data (HIV testing) in line with the SGSS approach; (iii) an improved design of the TLS methodology to reach MSM attending gay venues (MacKellar, Gallagher, Finlayson, Sanchez, Lansky & Sullivan, 2007) (Williamson & Hart, 2007); and (iv) the extension of a bio-behavioural TLS survey to seven sites, across different countries and contexts (Central, Southern, Eastern European Countries).

An additional progression described in the paper was the collection of saliva/oral fluid for laboratory testing. The few studies available at that time generally adopted rapid tests to generate HIV prevalence data, leading to the abovementioned ethical and performance issues (Williamson & Hart, 2007). The use of laboratory testing, that is, the collection of saliva using oral fluid collection kits to be refrigerated and sent to a reference laboratory for testing, allowed to accommodate the methodology in line with feasibility and standard testing requirements, and arguably therefore increasing the reliability of the test results. This distinctive aspect, that is, the collection of oral fluid for separate laboratory test, was used to label the project, adopting the word *sialon*, which means ‘saliva/oral fluid’ in Ancient Greek.

The methodology and results of the Sialon project were published in *EuroSurveillance* (Mirandola et al., 2009) [Annex 3, 3.1, page 79]. The paper described the survey implemented in the six selected European cities: Barcelona (Spain), Bratislava (Slovakia), Bucharest (Romania), Ljubljana (Slovenia), Prague (Czech Republic), and Verona (Italy). Methodological issues, like the use of TLS to enrol participants, were discussed, together with the prevalence estimates (based on oral fluid testing) and behavioural data.

The publication showed that for surveillance and epidemiological purposes, the use of TLS as a sampling method is feasible and efficient, particularly in cities with highly developed gay scenes. Moreover, the findings showed that the use of saliva samples are acceptable for the MSM populations in outreach settings, simplifying diagnostic processes and ensuring satisfactory reliability of the test results. The Sialon project was at that time the largest bio-behavioural survey targeting MSM ever carried out in Europe, contributing to provide robust estimates on the HIV epidemic amongst MSM at European level. Moreover, this selected publication has played an important role in advancing the core methodologies of cross-sectional, multi-site bio-behavioural survey. The paper described how, for the first time, the different principles highlighted in the scientific literature and endorsed by the main international organisation (SGSS, GAM indicators and use of enrolment approaches designed for hard-to-reach populations) were embedded in a unique European survey.

3.2 Bio-behavioural HIV and STI surveillance among Men who have Sex with Men in Europe: the Sialon II protocols [Annex 3, 3.2, page 89]

This protocol publication is likely to represent the single most important and potentially influential paper contained within this critical appraisal as it refers to the core methodologies adopted in the Sialon II project, developed and implemented after the former Sialon. As mentioned, the Sialon

project was certainly an important step forward in terms of survey methodological advancements, compared to the scientific literature available at that time. Nevertheless, some critical issues and research questions remained unanswered.

First, the core assumption of TLS (when adopted also to collect biological samples) is that the target of the study (MSM communities members in this case) should be reached through physical venues in a given study site. By scaling up this method at EU level, it was clear that TLS was not fully applicable in contexts with a limited number of gay venues, or in contexts where the gay communities were not well developed. For instance, considering the specific methodological requirements, cities with a well-developed gay scene in terms of number of venues such as bars, saunas, discos (e.g., Barcelona, Spain) were presumably more suitable for TLS survey than cities with a limited number of gay commercial venues (e.g. Vilnius, Lithuania). In addition, other factors such as the availability of gay venues owners to allow data collection at site level, the availability of data collectors to be trained, the capacities of local researchers/NGOs' teams represented potential critical issues, considering the importance of these aspects for a proper implementation of a TLS survey. Therefore, the need for flexible enrolment approaches adaptable to different organisational contexts and suitable for different social scenarios was clear (Gama et al., 2017).

An additional challenge related to the HIV prevalence estimates produced in the context of the Sialon survey. HIV estimates, as well as data describing socio-demographic and behavioural information, were not weighted, with consequent limited generalisability of the data. Some pioneering publications were suggesting the possibility of embedding weights in the context of TLS surveys (Karon & Wejnert, 2012), but in the majority of the studies available at that time this methodological development was simply missing or considered only from a theoretical viewpoint (Williamson & Hart, 2007) (Gama et al., 2017).

A third level of improvement was related to the possibility to link together research and prevention, in line with documents delivered by the EC, suggesting to strictly combine targeted prevention with meaningful surveillance (EU, 2016).

The second publication selected for this thesis (Gios, Mirandola, Toskin, Marcus, Dudareva-Vizule, Sherriff, …, Rafila, 2016) [Annex 3, 3.2, page 89] describes the methodological advancements embedded in the Sialon II bio-behavioural survey, funded under the Second Programme of Community Action in the field of Health (2008-2013) (Work Plan 2010). The Sialon II project was conceived as a multi-centre biological and behavioural cross-sectional survey, combining two methods for enrolling hard-to-reach population: the TLS approach based on venues (already adopted in the former project) and an additional method based on social networks, that is, Respondent-Driven Sampling (RDS). For both TLS and RDS methods, the methodologies have been purposively designed to allow the use of sampling weights in estimates calculations. Finally, a specific prevention component, tailored according to the enrolment methods adopted in the 13 European study sites, was put in place as part of the survey.

Three components were included in the survey and described in the publication:

i. The implementation of a preliminary formative research in each participating country to assess feasibility and suitability of enrolling methods adopted (either TLS or RDS) and to collect contextual information;
ii. The implementation of a bio-behavioural survey using TLS (in nine cities) and RDS (in four cities);
iii. The concomitant implementation of a targeted HIV/STI prevention campaign during the data collection period, in each site.

The paper (Gios et al., 2016) [Annex 3, 3.2, page 89] embraces a description of the operational components integrating to the most advanced enrolling approaches for hard-to-reach populations, such as the RDS (Heckathorn, 1997) and TLS (MacKellar et al., 2007) methodologies, as well as of the research algorithms adopted in the largest bio-behavioural survey targeting MSM ever carried out in Europe.

For the first time, different sampling methods were embedded in a unique multi-site European survey targeting MSM. TLS was used as an enrolling method in nine cities, where this method was considered ideal after the formative research phase (Dudareva-Vizule & Marcus, 2013): Brussels (Belgium), Sofia (Bulgaria), Hamburg (Germany), Warsaw (Poland), Lisbon (Portugal), Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden), and Brighton (UK). RDS was used in four sites, namely Verona (Italy), Vilnius (Lithuania), Bucharest (Romania), and Bratislava (Slovakia).

An additional core aspect of the survey (and this is also reflected in this paper) was the extensive work in terms of research procedures harmonisation, from the enrolling methods to the laboratory algorithms, from the data analysis plan to the ethical considerations. In fact, the implementation of a multi-site survey targeting a vulnerable population such as MSM implied a complex and challenging process of development and adaptation of the research methodologies to the different countries and contexts.

The paper covers also the description of the ethical reviewing process which was conducted prior to the survey. Considering the adoption of the UNAIDS-WHO indicators, and in line with the collaboration established also with these institutions in the framework of the project development, the Sialon II survey protocol was submitted to both WHO Research Project Review Panel (RP2) and

the WHO Research Ethics Review Committee (ERC)3. The Sialon II protocols were approved by both RP2 and ERC. The study became the first European bio-behavioural survey targeting MSM officially approved by WHO.

In terms of knowledge on methodology, this publication led to an increased understanding of reliable and sustainable methodologies to implement bio-behavioural surveys in EU Member States in line with the SGSS approach.

[3] Prior to data collection, research protocols were submitted to the Ethics Committee in each study site. Parallel to this process, the research protocols were also submitted to WHO RP2 and ERC, and this component was managed primarily from my side, together with WHO colleagues and the research team in Verona.

4. Improved knowledge on risk behaviours amongst MSM

Amongst the selected works, the publications presented in this section focus on knowledge and profiling of MSM attitudes and behaviours, based on data collected in the context of the projects Sialon, Sialon II, and Health4LGBTI. The section is structured considering six areas of knowledge:

i. HIV test seeking behaviour amongst MSM (Mirandola et al., 2016) [Annex 3, 3.3, page 102];
ii. Demographic and behavioural characteristics of Men Who have Sex with Both Men and Women – MSMW (Mirandola, Gios, Sherriff, Pachankis, Toskin, Ferrer, …, Niedźwiedzka-Stadnik, 2017) [Annex 3, 3.4, page 110];
iii. GAM reporting (Mirandola et al., 2018) [Annex 3, 3.5, page 125];
iv. Illicit drug use amongst MSM (Rosińska, Gios, Nöstlinger, Vanden Berghe, Marcus, Schink, ..., the Sialon II Network, 2018) [Annex 3, 3.6, page 139];
v. Factors related with condom use (Sherriff, Jones, Mirandola, Gios, Marcus, Llewellyn, …, the Sialon II Network, 2019) [Annex 3, 3.7, page 152];
vi. Role of the stigma on HIV-related behaviours amongst MSM and access to services (Leluţiu-Weinberger, Rendina, Mirandola, Gios, Folch, Rafila & Pachankis, 2019) [Annex 3, 3.8, pag. 167] (Gios, Mirandola, Sherriff, Toskin, Blondeel, Dias, …, Alexiev, in press) [Annex 3, 3.9, page 180] (Zeeman, Sherriff, Browne, McGlynn, Mirandola, Gios, …, Amaddeo, 2018) [Annex 3, 3.10, page 201] (Zorzi, Cordioli, Gios, Del Bravo, Toskin, Peeling, …, Mirandola, 2017) [Annex 3, 3.11, page 210].

As a general note, it is important to point out that the data presented in these publications are unique; particularly those based on Sialon and Sialon II. First, the implementation of a bio-behavioural survey adopting standard procedures in different EU cities (6 cities for Sialon, 13 cities for Sialon II)

generated *per se* a unique set of data (including data on laboratory-based test to determine HIV/STI status), allowing for estimates to be compared across sites in different countries. This homogeneous (at least in terms of tools and procedures adopted to collect the data) dataset is particularly useful when exploring behavioural patterns and HIV/STI prevalence data across different sites (Dubois-Arber et al., 2010) (Gall et al., 2017). Secondly, through the use of enrolment methodologies specifically designed for capturing hidden strata of the MSM population (integrating also weighted estimates, in the case of Sialon II), it was possible to generate not only comparable but also reliable data from hard-to-reach populations. That is, the estimates produced can be generalised (with specific limitations) to specific groups within the MSM population, that was not always possible to capture by means of a clinic-based survey. Finally, the specific methodological framework adopted particularly for Sialon II (weights) allowed statistical analysis with weighted estimates and ad-hoc modelling to explore prevention needs, risk behaviours patterns for a considerable number of hard-to-reach MSM/cities in EU, including also weighted estimates for lab-based HIV/STI prevalence data.

4.1 Socio-demographic factors predicting HIV test seeking behaviour among MSM [Annex 3, 3.3, page 102]

As mentioned previously there are only a few examples of multi-sites studies targeting MSM that adopted outreach methods to reach hidden strata of the MSM population, collecting both behavioural and biological data. Based on the unique dataset collected through the Sialon project in six European cities, the main aim of this publication was to assess the relationship between HIV test seeking behaviour and a number of factors ranging from individual to social (Mirandola et al., 2016) [Annex 3, 3.3, page 102]. By adopting a multi-level analysis on data collected from 2,400 MSM, factors such as age, sexual orientation, residence, household composition, educational status and perceived homonegativity were shown to play a major role on testing behaviours. These results have confirmed

an increasing body of knowledge in the field of test seeking behaviour amongst MSM (Mirandola et al., 2017). This confirmation coming from this research is fundamental, considering that only few studies were based on wide multi-site population-based surveys. This is a key issue, as exploring test-seeking behaviour considering data gathered on a clinic-based approach might lead to a substantial bias: MSM attending clinics might be *per se* more likely to know and to attend testing services. The fact that test-seeking behaviour was explored using data collected through a multi-site TLS survey represented a clear advancement in providing useful insights on factors associated with increased testing.

In addition, the results were in line with the need for specific initiatives to increase testing, by implementing comprehensive actions addressing stigma and discrimination toward specific sub-population within the MSM communities.

4.2 Socio-demographic Characteristics, Sexual and Test-Seeking Behaviours Amongst Men Who have Sex with Both Men and Women [Annex 3, 3.4, page 110]

Based on the analysis of the data collected during Sialon II project (13 European cities), this paper, published in *Aids and Behavior*, contains a detailed and comprehensive examination of a multi-level approach, to explore the relationship between socio-demographic, social and serum factors amongst MSMW versus Men who have Sex with Men Only (MSMO) (Mirandola et al., 2017) [Annex 3, 3.4, page 110]. The concept for the paper was underpinned by the idea that within the MSM population, men who have sex with *both* men and women (MSMW) are particularly exposed to HIV/STI risk and thus vulnerable as they are seemingly less likely to seek HIV testing compared to MSM only (Phillips, Cambiano, Miners, Lampe, Rodger, Nakagawa, … Delpech, 2015). Moreover, MSMW are particularly relevant from an epidemiological perspective considering their potential role as 'bridging population' to other sub-groups. The terms bridging population has been used to describe processes

where HIV/STIs can be transmitted from a high-risk group (e.g., MSM) to groups where the prevalence of such diseases is usually very low (e.g., heterosexual populations) (Aral, 2000). The uniqueness of the Sialon II data represents a useful tool to advance knowledge on the specific sub-population of MSMW within the MSM communities across the 13 European cities participating in the Sialon II study. Particularly behaviourally bisexual men represent a difficult target population to reach and to explore, and they might be less likely to participate in research studies or surveys targeting MSM. As demonstrated in previous studies, TLS and RDS are considered as effective tools in recruiting diverse sub-population within the MSM communities, including MSMW. In fact, across all the Sialon II participants, almost one out of ten of the enrolled participants identified as MSMW (12.64%).

The analysis confirmed the specific vulnerability of MSMW, considering the low level of HIV testing and outness, and the high levels of perceived stigma, which characterise this specific sub-population.

4.3 Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey [Annex 3, 3.5, page 125]

The paper 'Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey' specifically focuses on the GAM estimates (Mirandola et al., 2018) [Annex 3, 3.5, page 125]. This publication is likely to represent one of the most influential papers presented in this thesis, as it summarises the main advancement in the field of bio-behavioural surveys targeting MSM. Published in *EuroSurveillance*, the paper is based on the methodological publication on the Sialon II protocols, and describes in detail the weighted estimates for the different GAM indicators adopted in Sialon II (1.11 – prevention programme; 1.12 – Condom use; 1.13 – HIV testing; 1.14 – HIV prevalence). This publication represents a significant improvement in delivering reliable GAM indicators data considering the previous publications in the field. First, it was the first scientific

publication in Europe presenting weighted estimates of the GAM indicators. This has been an unresolved issue in the current literature, as the majority of the publications and GAM reporting (when available) were based on data with no weights (Alfvén et al., 2017). It is clear that this article represents a relevant reference when considering HIV/STI estimates amongst MSM in Europe, invaluably advancing the available literature on the HIV epidemic monitoring/surveillance, by providing – for the first time – GAM weighted estimates for MSM from thirteen European cities.
In addition, a further advancement is linked with the city-level correlations between GAM indicators, which were explored in the paper. This exercise showed a significant correlation between preventive campaigns and levels of condom use and HIV testing levels amongst MSM. Again, this represents a unique case in which weighted GAM estimates are correlated at city level, showing the potential of the GAM indicators in monitoring the effectiveness of prevention activities and in identifying prevention needs even at site level.

The GAM weighted estimates and results presented in the paper were of such significance that in addition to the paper, a supplementary report on the GAM indicators was produced specifically for the ECDC. The report, entitled 'Sialon II Project: GAM[4] indicators in Barcelona, Bratislava, Brighton, Brussels, Bucharest, Hamburg, Lisbon, Ljubljana, Sofia, Stockholm, Verona, Vilnius and Warsaw among MSM (Sialon II Network, 2015)', contained the preliminary results of the Sialon II survey. Data and estimates presented in the report were then utilised adopted by ECDC in their 2014 progress report on the monitoring of the implementation of the 'Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia' (ECDC, 2015). This important contribution of Sialon via both the paper (Mirandola et al., 2018) [Annex 3, 3.5, page 125] and this report, demonstrate the scientific quality of the data collected through the project and the relevance of the estimates calculated

[4] As already mentioned, the indicators' name has been changed many times over the last decade. For sake of uniformity, the acronym *GAM* is used.

in line with the GAM indicators. These data – through the ECDC reporting dissemination – contributed to further improve the knowledge of the actual HIV/STI epidemic at European level.

4.4 Prevalence of drug use during sex amongst MSM in Europe: Results from a multi-site bio-behavioural survey [Annex 3, 3.6, page 139]

An additional area of improvement of knowledge on the HIV spread amongst MSM is represented by a deeper understanding of the factors driving the epidemic including drug use prior and during sex. The article presented here and published in the *International Journal of Drug Policy*, adopted a multivariable multi-level logistic random-intercept model to explore the use of drugs during sex amongst MSM (Rosińska et al., 2018) [Annex 3, 3.6, page 139]. The model showed a great variability amongst study sites, concerning substance and polydrug use during sexual encounters. What was found was that whilst one third of the MSM reported the use of one drug during their last sexual intercourse, one out of ten reported the use of two or more drugs. The use of all the substances considered in the analysis was also significantly associated with multiple sex partners.

Also in this case the fact that substance use amongst MSM is associated with broader societal factors, namely, with stigmatisation, was confirmed.

4.5 Factors related to condomless anal intercourse between men who have sex with men with steady versus casual partners: results from a European bio-behavioural survey [Annex 3, 3.7, page 152]

In this paper, published in the *Journal of Public Health (Oxford)*, factors associated with condomless anal intercourse (CAI) amongst MSM were explored through bivariate and multivariate multilevel logistic regression analyses (Sherriff et al., 2019) [Annex 3, 3.7, page 152].

The concept for this paper was conceived based on the existence of ostensibly different patterns in CAI between MSM in steady vs those in casual relationships, which can be important when planning public health and health promotion initiatives. The findings, based on the unique Sialon II dataset, indicate the need for additional research to better understand how partner type and partnership dynamics may influence CAI and therefore facilitating HIV and/or STI transmission chain within the MSM communities, and the need for planning cultural/contextual sensitive campaigns to properly target the different MSM population strata.

4.6 The role of gay-related stigma in HIV-risk behaviour among sexual minority men in Europe [Annex 3, 3.8, page 167]

As mentioned in the previous papers, stigma can deeply shape the risk and health behaviours particularly of vulnerable populations such as MSM (Pachankis et al., 2015). This concept of stigma as an overarching factor hampering health behaviours, including testing, was certainly not new in the literature. However, this paper, based on the valuable sample enrolled through the Sialon project and representing an interesting basis to further explore this construct, is a relevant contribution in the field. The fact that both biological and behavioural data have been collected from hidden strata of the MSM population was a unique opportunity to assess the impact of stigma in terms of health-seeking behaviours and risk-taking behaviours. Based on the former Sialon study (Leluţiu-Weinberger et al., 2019) [Annex 3, 3.8, page 167] this paper, published in *Aids and Behavior*, models gay-related stigma in six European cities: Barcelona (Spain), Bratislava (Slovakia), Bucharest (Romania), Ljubljana (Slovenia), Prague (Czech Republic), and Verona (Italy). The results demonstrated that stigmatised MSM are more likely to report sexual risk and alcohol/drug use during sex, increasing the potential exposure to HIV and STI. These results were in line with the previous paper on drug use published on Sialon II data, and contributed to further support the idea that stigma serves as precursor to risk behaviour, reinforcing health inequalities.

4.7 Being in the closet. Correlates of outness amongst MSM in 13 European cities [Annex 3, 3.9, page 180]

The present paper was published by the *Journal of Homosexuality* (Gios et al., in press) [Annex 3, 3.9, page 180]. This paper differs from the previous publications in the thesis, in that it is focusing primarily on psychosocial aspects of stigma. In fact, the aim of the paper was conceived considering outness as a cornerstone of the analysis, using the dedicated items included in the Sialon II questionnaire. Particularly, the fact that strata of MSM population have been enrolled using specific sampling approaches, led to explore the specific role of outness in terms of promoting or hampering risk behaviours. The novelty of this paper was – again – the fact that the sample was of particular interest for exploring the impact of outness. TLS and RDS are considered as effective tools to catch very hidden strata within the MSM communities, presumably strata composed by men who are less likely to be out compared to other enrolling methodologies (except Internet-based methods) (Brookmeyer, 2010) (Gama et al., 2017). Basing the analysis on the data collected in the thirteen European cities, the paper presents a multi-level model to explore the relationship between socio-demographic, social and behavioural factors amongst MSM who are out about their own sexual orientation (‘out’) and who are not open about their own sexual orientation (‘in the closet’) (Gios et al., in press) [Annex 3, 3.9, page 180].

A total of 4,901 MSM were enrolled in the study and were classified as ‘out’ in 71% of the cases. MSM ‘out’ were more likely to report HIV testing and being reached by HIV prevention programmes compared to MSM who were ‘in’. The results provided important confirmation of the key role of outness in shaping MSM’s behaviours.

4.8 A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities [Annex 3, 3.10, page 201]

This paper (Zeeman et al., 2018) [Annex 3, 3.10, page 201], published in the *European Journal of Public Health*, is based on the 'Health4LGBTI: Reducing health inequalities experienced by LGBTI people' project, funded by the EU Parliament (2016-2018). Part of the project was focused on the improved understanding of specific health inequalities and barriers experienced by lesbian, gay, bisexual, trans and intersex (LGBTI) people when accessing healthcare services. A narrative synthesis of 57 papers, ranging from systematic reviews to meta-analyses and original primary research, was used as basis for this publication (Zeeman et al., 2018) [Annex 3, 3.10, page 201].

Whilst a growing body of evidence is available on this matter, a comprehensive and wide-ranging review of the literature to establish 'what is known' about the health inequalities of LGBTI in Europe was missing. Through this comprehensive review, the key role of heteronormativity (or *heterosexism*) was identified as one of the main factors hampering access to health services (including testing in the case of the MSM), and the need for and increased knowledge by health professionals to further improve LGBTI-friendly services was highlighted.

This publication was an invaluable contribution towards an improved knowledge of the inequalities still experienced by LGBTI, and MSM in particular, at EU level. It is worth mentioning that the work carried out for this paper greatly contributed as a scientific basis for the second component of the Health4LGBTI project, that is, the preparation of a training programme for health care professionals (McGlynn, Browne, Pollard, Sherriff, Zeeman, Aujean, …, Niedźwiedzka-Stadnik, 2017) (Rosinska, Zakrzewska, Rodzinka, Amaddeo, Donisi, Farinella, …, Browne, 2018) (Amaddeo, Donisi, Farinella, Buniotto, Sanchez-Lambert, Pinto, …, Browne, 2018). This training has been piloted in six European countries (Belgium, Bulgaria, Italy, Lithuania, Poland and UK) and it is currently publicly available on the European Commission website (English Version).

5. Improved knowledge on testing and treatment approaches

Amongst the selected publications, some papers are linked with an improved knowledge of novel testing and treatment approaches, as well as prevention actions which have been implemented in different European countries. In this respect, the present section covers three main areas:

i. A field evaluation of two rapid tests for Syphilis in clinical settings (in Verona, Italy);
ii. HIV/STI prevention actions implemented in the different study sites;
iii. A training programme for health care professionals to reduce health inequalities experienced by LGBTI people.

5.1 Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy [Annex 3, 3.11, page 210]

This paper (Zorzi et al., 2017) [Annex 3, 3.11, page 210], published in *Sexually Transmitted Infections*, is based on an ancillary protocol implemented in the context of the Sialon II study, focusing on the evaluation of two rapid tests that were under evaluation by WHO. Study participants included MSM recruited from the Sialon II Respondent-Driven Sampling survey in Verona (2013 – 2014) and MSM attending the Infectious Diseases Unit of the Verona University Hospital screening facility (2015 – 2016). The tests evaluated in the ancillary study were (i) the SD Bioline Syphilis 3.0 (Standard Diagnostics, South Korea) and (ii) the DPP Syphilis Screen & Confirm Assay (Chembio Diagnostic Systems, USA).

This ancillary field evaluation was conceived in line with the WHO POCT initiative (Toskin et al., 2017). As mentioned, even if the theoretical background of the POCT was well developed at that time and promising practices were in place, some core research questions were still open. First, a question related to the exact clinical performances of a POCT tests, in this case, a dual test for Syphilis

(treponemal and non-treponemal component). Second, a question related to the potential impact of the human component when using POCT, as one of the core assumptions of these rapid tests is that they should be performed (from test preparation to results reading) by health care staff. This paper represents an important advancement in the literature. It describes how weighted estimates for Syphilis (gathered through the Sialon II project and related to Verona, the site where both Sialon II and the POCT evaluation took place) were adopted in the context of the POCT validation, allowing a precise assessment of the performance (PPV and PPN) of the POCT itself. In addition, the description of a specific identification system for the health care staff in charge of the POCT performance and reading was included. This component was key to properly assess the impact of such a component within the entire POCT process.

Considering the partnership with WHO for this specific component, the Verona POCT project protocol was submitted to the local Ethics Committee in Verona, and to both the WHO Research Project Review Panel (RP2) and to the WHO Research Ethics Review Committee (ERC).

The publication describing this piloting project was released in a special issue of the *Sexually Transmitted Infection* journal (Zorzi et al., 2017) [Annex 3, 3.11, page 210]. The special issue was specifically focusing on Point-Of-Care Testing (POCT) approach, providing assumptions and strategic objectives of the use of POCT, as well as some evaluation and/or piloting exercises of POCT in real life settings. The field evaluation implemented in Verona was one of the selected papers for this issue, considering the solid innovation that was brought by this evaluation in terms of assessment of the clinical performance of a POCT in a real setting and targeting a specific population MSM, and the comprehensive assessment of the impact of human component.

The results of the field evaluation were promising, despite some clear limitations. POCT proved to be feasible and acceptable in terms of performance, considering the specific characteristics of the

MSM population (prevalence of Syphilis). However, the general diagnostic performance of the syphilis POCTs was lower compared to the one declared by the company. This result was essential as it contributed to an improved understanding of the actual performance of rapid tests when used in real-word settings (e.g., STI clinics), compared to the laboratory-based performance.

The contribution toward an advanced knowledge in this field is significant. Due to this evaluation, it was possible to confirm the potential of the POCT technology in specific contexts and targeting a specific population. The results also underlined the importance of specific training for users and the adoption of supporting documentation to reduce misinterpretation of the results due to human subjectivities.

This publication, and the project upon which it was based, was adopted as case study by WHO, and it has provided a strong methodological background for the development of research protocols for a global independent laboratory-based and field evaluation of POCT in different continents (ProSPeRo Study). The WHO POCT global study (https://www.who.int/reproductivehealth/topics/rtis/pocts/en/) is currently ongoing to provide further evidence of the usefulness of POCT worldwide (Toskin et al., 2017).

5.2 Prevention actions

Amongst the results of the different projects presented in this thesis, besides the abovementioned scientific publications, several prevention initiatives can be outlined. Some of these were mentioned and included in the final report of the projects, when possible. In other cases, prevention activities were implemented after the end of the projects and after the final reporting period, and therefore they are not included in any official document. However, in the last section of this thesis some of these actions are mentioned, as they are strictly related both to the project's implementation and to the

different scientific contributions. They also represent concrete outputs of the research activities described in this appraisal.

5.2.1 Testing across 13 European cities

One of the core results produced in the context of the Sialon II project was the number of MSM tested in the different sites: in the framework of the survey, 4,966 MSM were enrolled and 4,116 tested for HIV in the context of the overall project. For the RDS component, where additional testing was foreseen, 1,305 tests for Syphilis, HBV and HCV were also performed in the four cites, that is, Verona (Italy), Vilnius (Lithuania), Bucharest (Romania), and Bratislava (Slovakia).

5.2.2 Prevention actions in 13 European cities

Parallel to the data collection phase, prevention initiatives have been implemented by local NGOs in the 13 study cities. Over 9,000 prevention info-packs (containing condom, lubricant and information on local testing facilities) were distributed during the survey implementation across the participating sites. More than 2,000 scratch-cards, containing a quiz on health and risk behaviours, were distributed and used by the data collectors to provide peer-to-peer prevention messages. In many cases, local NGO took over the prevention activities, supporting the continued condom-distribution, the on-going dissemination of prevention materials produced in the context Sialon II even after the project ended. Finally, yet importantly, setting up of local NGO prevention networks – which were involved since the beginning in the Sialon II project design and implementation – has led to 14 local new prevention activities reported by the partners of the Sialon II network, so far.

5.2.3 Opening of new services as result of the Sialon II project

In addition to the several prevention actions promoted by the local NGOs, as a result of the Sialon II project implementation and on the basis of the preliminary results produced (particularly, data related

to the HIV prevalence and level of testing at local level), some sites decided to initiate specific services targeting MSM. In Bratislava (Slovakia), after the closure of the Sialon II project (2016), the local research team launched a new rapid HIV testing service. In Warsaw (Poland) the opening hours of the local HIV-testing sites have been increased to further promote testing opportunities particularly among the MSM communities, on the basis of the information and feedback collected through the Sialon II survey.

5.3 Health4LGBTI project

An additional field of the research described in the present appraisal is the Health4LGBTI project. As mentioned, this project was implemented between 2016 and 2018 with the aim to improve understanding of health inequalities experienced by lesbian, gay, bisexual, trans and intersex (LGBTI) people across Europe and to develop and pilot a training package targeting healthcare professionals who are providing healthcare to LGBTI people.

A published paper based on the narrative synthesis, which was carried out on 57 papers, was already mentioned as relevant scientific output of this project (Zeeman et al., 2018) [Annex 3, 3.10, page 201]. Most importantly, through the project a set of tools have been made publicly available (https://ec.europa.eu/health/social_determinants/projects/ep_funded_projects_en#fragment2), including:

i. A document summarising a state-of-the-art review of the health inequalities experienced by LGBTI people, and the barriers faced by health professionals (Zeeman, Sherriff, Browne, McGlynn, Aujean, Pinto, …, Pierson, 2017);

ii. A report on two focus groups studies (targeting LGBTI patients and health care professionals) mapping the obstacles faced both by LGBTI people and health professionals (McGlynn et al., 2017);

iii. A training course for healthcare professionals (including manual for trainers, slide-sets and training materials) (Amaddeo et al., 2018).

So far, data related to the use of such materials are not available. However, the fact that these materials have been prepared by a strong network of public health institutions, NGOs and universities, and that they are made officially available by the EC represent a solid advancement to further provide healthcare system in Europe with concrete tools to promote non-discriminatory services and to further reduce health inequalities amongst LGBTI.

In this respect, some public health entities from the network are currently exploring the possibility to launch specific training courses based on these materials (this is the case for the UK and for Italy).

6. Conclusion and next steps

This appraisal demonstrates the significant contributions that have been made over the last years, both in terms of research actions and in terms of publication of papers in peer reviewed scientific journals. The selected publications have supported the advancement of methodological knowledge in bio-behavioural surveys and of understanding risk factors amongst MSM, reinforcing the idea that specific enrolling methodologies targeting hard-to-reach MSM, hand-in-hand with tailored survey strategies, could lead to important insights into behavioural, social and demographical patterns, which are ultimately influencing the HIV/STI epidemic.

The publications based on Sialon II and on the Health4LGBTI project have provided clear evidence of the overarching role of discrimination/stigma in the shaping of the HIV epidemic, further advancing insights into and knowledge on preventive actions that could be promoted at different levels.

From this perspective, one of the core contributions of this appraisal is the paper describing the Point-Of-Care Testing (POCT) study implemented in Verona and targeting MSM. This can be considered a unique and solid intervention in terms of assessment of clinical performance and feasibility of POCT in a real clinical setting (Zorzi et al., 2017) [Annex 3, 3.11, page 210]. Although POCT is widely promoted and more and more health systems worldwide are adopting this method as part of a comprehensive prevention strategy, there is a considerable amount of contextual and procedural information that needs to be explored. To our knowledge, the paper presented in this thesis is the first one clearly demonstrating that ideal conditions do not always apply and that the full potential of POCT can only be realised if used appropriately and accurately embedded in the clinical setting. The confirmation of the relevance of this study lies in the fact that the piloting project implemented in Verona was adopted as case study by WHO and the local protocol was used to develop research

protocols for global independent laboratory-based and field evaluation of POCT in different continents. The WHO global study is currently ongoing to provide further evidence of the usefulness of POCT worldwide (https://www.who.int/reproductivehealth/topics/rtis/pocts/en/) (Toskin et al., 2017).

Considering the advancements summarised in the present appraisal, this last section puts forward some proposals for future areas of development.

The first area where further progress could be made concerns the Sialon II data. The Sialon II data represent a unique source of information at European level which could be further analysed, particularly in the light of new and more recent projects targeting MSM. For example, it is worth mentioning EMIS (European MSM Internet Survey), an internet-based pan-European survey targeting MSM, recently implemented in the context of the ESTICOM (European Surveys and Training to Improve MSM Community Health) project and funded by the EU, which is greatly contributing to the knowledge of MSM health, risk patterns and needs at European level (https://www.esticom.eu/Webs/ESTICOM/EN/homepage/home-node.html). Even if Sialon II and the EMIS survey have been implemented in different time-periods, the specific data collected though the Sialon II project (including biological samples – not collected through the Internet-based survey – and behavioural information) can be further modelled to improve our understanding of the behavioural and health/risk patterns amongst MSM, hand-in-hand with the results coming from other European surveys, EMIS included.

Following on from this logic, an additional area of development might be represented by mixed methods in enrolling hidden strata of risk populations in the context of bio-behavioural surveys, that is, combining different methodologies (such as TLS and RDS) and connecting them with the potential of Internet-based surveys. Theoretically, TLS can be applied to Internet-based surveys, if considering

websites and apps as virtual venues, which allow the identification of specific venue-time sampling units. RDS can also be potentially used to recruit hard-to-reach population members through a virtual social network in the context of a bio-behavioural survey. Actually, while many researchers have theoretically explored pros and limitations of RDS in comparison with other recruitment methodologies (including Internet-based methodologies) (Card, Armstrong, Lachowsky, Cui, Zhu, Roth & Hogg, 2018), only few studies have explored the potential use of RDS when applied to virtual networks. Some pioneering studies have recently been implemented, complementing the RDS approach by including a virtual space of enrolment, that is, recruiting seeds online through social networking mobile phone app and including an HIV testing component (Lachowsky, Lal, Forrest, Card, Cui, Sereda, …, Hogg, 2016). The results of these studies are proving encouraging. At the same time, additional research is needed to further explore and use the full potential of virtual networks when enrolling hard-to-reach populations in the context of bio-behavioural surveys.

A second line of future development is the opportunity to implement a Sialon III project. This would represent an obvious continuation of the collaboration established over the years across all sites, as well as a reasonable re-use of methodologies and expertise already in the hands of the institutions participating in the Sialon II network. From an epidemiological perspective, this would also allow to adopt sophisticated analysis (e.g., trend analysis), consequently gaining more robust data on the HIV epidemic patterns, particularly in terms of monitoring the development of the epidemic in itself. For this to occur appropriate resources (economical and organisational resources) would be required and this might represent a significant challenge. In fact, from direct experience and considering the tendency in terms of international calls and funding priorities, it is likely that over time the probability to fund such a complex (and expensive) bio-behavioural survey will decrease.

Finally, an additional area of research lies in further advancing the knowledge of how POCT can be used to reduce barriers to testing in different cultural and organisational contexts. This strand of

research is currently in progress: thanks also to the contribution presented in this thesis, WHO has set up a multi-continent, multi-protocol validation study to assess (i) the performance of POCT compared to laboratory tests (Clinic-based Evaluation) and (ii) the acceptability and feasibility of POCT in non-clinical settings (Utility Evaluation) (https://www.who.int/reproductivehealth/topics/rtis/pocts/en/). For the clinic-based evaluation, in addition to HIV and Syphilis, other tests and infections have been considered (Genital and Extragenital Chlamydial Infections, Gonococcal Infections, Trichomoniasis Infections) and different sub-populations have been targeted (MSM, women with vaginal discharge, pregnant women, sex workers). The WHO study on POCT will provide preliminary results in the first half of 2020.

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Zorzi, A., Cordioli, M., Gios, L., Del Bravo, P., Toskin, I., Peeling, R.W., …, Mirandola, M. (2017). Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy. *Sex Transm Infect*, 2017 Dec;93(S4):S51-S58. doi: 10.1136/sextrans-2016-053065

Annex 1 – Selected publications included in the appraisal and their impact [5]

n°	Publication [6]	Year of the publication	Journal	IF	Citations (Google Scholar) [7]
1	Mirandola, M., Folch, C., Krampac, I., Nita, I., Stanekova, D., Stehlikova, D.,…, [**Gios, L.**], …, the SIALON network. (2009). HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009. *Euro Surveill*, 14(48):pii=19427	2009	EuroSurveillance	No IF in 2009	56
2	**Gios, L.**, Mirandola, M., Toskin, I., Marcus, U., Dudareva-Vizule, S., Sherriff, N., …, Rafila, A. (2016). Bio-behavioural HIV and STI surveillance among men who have sex with men in Europe: the Sialon II protocols. *BMC Public Health*, 2016 Mar 2;16(1):212	2016	BMC Public Health	2.420	20
3	Mirandola, M., **Gios, L.**, Davis, R.J., Furegato, M., Breveglieri, M, Folch, C., …, Stehlíková, D. (2016). Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities. *European Journal of Public Health*, doi:10.1093/eurpub/ckw144	2016	The European Journal of Public Health	2.782	9
4	Mirandola, M., **Gios, L.**, Sherriff, N., Pachankis J, Toskin I, Ferrer L, …, Niedźwiedzka-Stadnik M. (2017). Socio-demographic Characteristics, Sexual and Test-Seeking Behaviours Amongst Men Who have Sex with Both Men and Women: Results from a Bio-behavioural Survey in 13 European Cities. *AIDS Behav*, 2017 Jun 22. doi: 10.1007/s10461-017-1831-5	2017	AIDS and Behavior	3.017	9
5	Mirandola, M., **Gios, L.**, Sherriff, N., Marcus, U., Toskin, I., Rosinska, M., … on behalf of the Sialon II Network. (2018). Quantifying unmet prevention	2019	EuroSurveillance	5.983	1

[5] Publications are listed not in chronological order, but reflecting the structure of the thesis and the order in which the papers are presented and included in the appraisal and in the Annex 3

[6] For both Sialon and Sialon II projects, the publication rules imply that all the members of the projects' network can participate, with different levels of involvement, in the publications' preparation and finalisation. For this reason, no solo publications are available.

[7] Updated until August 2019

	needs among MSM in Europe through a multi-site bio-behavioural survey. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin (Euro surveillance - bulletin Europeen sur les maladies transmissibles - European communicable disease bulletin)*, 23(49), 1800097. doi:10.2807/1560-7917.ES.2018.23.49.1800097				
6	Rosińska, M., **Gios, L.**, Nöstlinger, C., Vanden Berghe, W., Marcus, U., Schink, S., ..., & the Sialon II Network. (2018). Prevalence of drug use during sex amongst MSM in Europe: Results from a multi-site bio-behavioural survey. *Int J Drug Policy*, 2018 Feb 2. pii: S0955-3959(18)30002-1	2018	International Journal of Drug Policy	4.244	8
7	Sherriff, N., Jones, A.M., Mirandola, M., **Gios, L.**, Marcus, U., Llewellyn, C., …, The Sialon II Network. (2019). Factors related to condomless anal intercourse between men who have sex with men with steady versus casual partners: results from a European bio-behavioural survey. *J Public Health (Oxf)*, 2019 May 15. pii: fdz052. doi: 10.1093/pubmed/fdz052. [Epub ahead of print] PubMed PMID:31090894	2019	Oxford Journal of Public Health	1.670	-
8	Leluţiu-Weinberger, C., Rendina, H.J., Mirandola, M., **Gios, L.**, Folch, C., Rafila, A., & Pachankis, J.E. (2019). The Role of Gay-Related Stigma in HIV-Risk Behavior Among Sexual Minority Men in Europe. *AIDS Behav*, 2019 Mar;23(3):684-694. doi: 10.1007/s10461-018-2306-z	2018	AIDS and Behavior	3.017	2
9	**Gios, L.**, Mirandola, M., Sherriff, N., Toskin, I., Blondeel, K., Dias, S., …, Alexiev, I. (in press). Being in the closet. Correlates of outness amongst MSM in 13 European cities. *Journal of Homosexuality*, In press	2019 (In press)	Journal of Homosexuality	1.369	-
10	Zeeman, L., Sherriff, N., Browne, K., McGlynn, N., Mirandola, M., **Gios, L.**, …, Amaddeo, F. (2018). A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities. *Eur J Public Health*, 2018 Oct 31. doi: 10.1093/eurpub/cky226	2018	The European Journal of Public Health	2.782	3

11	Zorzi, A., Cordioli, M., **Gios, L.**, Del Bravo, P., Toskin, I., Peeling, R.W., …, Mirandola, M. (2017). Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy. *Sex Transm Infect*, 2017 Dec;93(S4):S51-S58. doi: 10.1136/sextrans-2016-053065	2017	Sex Transm Infect	3. 346	5

Annex 2 – Synoptic table of projects and extended list of publications

Projects	Publications (scientific papers / book chapters)	Year
Sialon	Mirandola, M., Folch, C., Krampac, I., Nita, I., Stanekova, D., Stehlikova, D.,…, [**Gios, L.**], …, the SIALON network. (2009). HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009. *Euro Surveill*, 14(48):pii=19427	2009
	Mirandola, M., Foschia, J.P, Breveglieri, M., Furegato, F., Castellani, C., Davis, R., …, [**Gios, L.]**, Coato, P. (2012). The Sialon Project: Report on HIV Prevalence and Risk Behaviour among MSM in six European Cities. Book Chapter, in *Epidemiology Insights*, InTech – Open Access Publisher, Edited by Maria de Lourdes Ribeiro de Souza da Cunha, ISBN 978-953-51-0565-7, Retrieved from: http://www.intechopen.com/books/epidemiology-insights	2012
	Mirandola, M., **Gios, L.**, Davis, R.J., Furegato, M., Breveglieri, M, Folch, C., …, Stehlíková, D. (2016). Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities. *European Journal of Public Health*, doi:10.1093/eurpub/ckw144	2016
	Staneková D, Mirandola M, **Gios L**, Botsi C, Habekova M, Gonzales-Soler, V., & Nikolopoulos, G.K. (2016). Validation study of a conventional enzyme immunoassay to detect HIV antibodies in oral fluid. *Bratislava Medical Journal*, 2016; 117 (1), 19-21, DOI: 10.4149/BLL_2016_004	2016
	Leluţiu-Weinberger, C., Rendina, H.J., Mirandola, M., **Gios, L.**, Folch, C., Rafila, A., & Pachankis, J.E. (2019). The Role of Gay-Related Stigma in HIV-Risk Behavior Among Sexual Minority Men in Europe. *AIDS Behav*, 2019 Mar;23(3):684-694. doi: 10.1007/s10461-018-2306-z	2018
Sialon II	**Gios, L.**, Mirandola, M., Toskin, I., Marcus, U., Dudareva-Vizule, S., Sherriff, N., …, Rafila, A. (2016). Bio-behavioural HIV and STI surveillance among men who have sex with men in Europe: the Sialon II protocols. *BMC Public Health*, 2016 Mar 2;16(1):212	2016
	Blondeel, K., Toskin, I., Mirandola, M., **Gios**, L., & Temmerman, M. (2016). Sexual competence as an indicator of sexual health, results from Sialon II, a European multi-country bio-behavioral survey among men who have sex with men. *European Journal of Public Health*, 26 (suppl. 1): ckw173.004 DOI: http://dx.doi.org/10.1093/eurpub/ckw173.004	2016
	Mirandola, M., **Gios, L.**, Sherriff, N., Pachankis J, Toskin I, Ferrer L, …, Niedźwiedzka-Stadnik M. (2017). Socio-demographic Characteristics, Sexual and Test-Seeking Behaviours Amongst Men Who have Sex with Both Men and Women: Results from a Bio-behavioural Survey in 13 European Cities. *AIDS Behav*, 2017 Jun 22. doi: 10.1007/s10461-017-1831-5	2017
	Marcus, U., Schink, S., Sherriff, N., Jones, A.M., **Gios L**, Folch, C., …, The Sialon II Network. (2017). HIV serostatus knowledge and serostatus disclosure with the most recent anal intercourse partner in a European MSM sample recruited in 13 cities: Results from the Sialon-II study. *BMC Infectious Diseases*, (2017) 17:730, DOI 10.1186/s12879-017-2814-x	2017
	Marcus, U., Nöstlinger, C., Rosińska, M., Sherriff, N., **Gios, L**., Dias, S. (2018). Behavioural and demographic correlates of undiagnosed HIV infection in a MSM sample recruited in 13 European cities. *BMC Infectious Diseases*, 2018 Aug 6;18(1):368. doi: 10.1186/s12879-018-3249-8	2018
	Rosińska, M., **Gios, L.**, Nöstlinger, C., Vanden Berghe, W., Marcus, U., Schink, S., ..., & the Sialon II Network. (2018). Prevalence of drug use during sex amongst MSM in Europe: Results from a multi-site bio-behavioural survey. *Int J Drug Policy*, 2018 Feb 2. pii: S0955-3959(18)30002-1	2018

	Mirandola, M., **Gios, L.**, Sherriff, N., Marcus, U., Toskin, I., Rosinska, M., … on behalf of the Sialon II Network. (2018). Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin (Euro surveillance - bulletin Europeen sur les maladies transmissibles - European communicable disease bulletin)*, 23(49), 1800097. doi:10.2807/1560-7917.ES.2018.23.49.1800097	2018
	Gios, L., Mirandola, M., Sherriff, N., Toskin, I., Blondeel, K., Dias, S., …, Alexiev, I. (in press). Being in the closet. Correlates of outness amongst MSM in 13 European cities. *Journal of Homosexuality*, In press	2019
	Sherriff N, Jones AM, Mirandola M, **Gios L**, Marcus U, et al. (2019). Factors related to condomless anal intercourse between men who have sex with men with steady versus casual partners: results from a European bio-behavioural survey. *J Public Health (Oxf)*, 2019 May 15. pii: fdz052. doi: 10.1093/pubmed/fdz052. [Epub ahead of print] PubMed PMID:31090894	2019
WHO Point-Of-Care project (Prospero)	Zorzi, A., Cordioli, M., **Gios, L.**, Del Bravo, P., Toskin, I., Peeling, R.W., …, Mirandola, M. (2017). Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy. *Sex Transm Infect*, 2017 Dec;93(S4):S51-S58. doi: 10.1136/sextrans-2016-053065	2017
Health4LGBTI	Festersen, C., Costongs, C., Sherriff, N., Zeeman, L., Amaddeo F., Aujean S., …, [**Gios, L.**], …, Zakrzewska, K. (2018). LGBTI people and health inequalities. *Eurohealth*, Vol.24, No.3, 2018. Retrieved from http://www.euro.who.int/__data/assets/pdf_file/0011/382682/eurohealth-vol24-no3-2018-eng.pdf	2018
	Zeeman, L., Sherriff, N., Browne, K., McGlynn, N., Mirandola, M., **Gios, L.**, …, Amaddeo, F. (2018). A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities. *Eur J Public Health*, 2018 Oct 31. doi: 10.1093/eurpub/cky226	2018

Projects	Publications (reports)	Year
Sialon II	Suligoi, B., Regine, V., **Gios, L**, Mirandola, M., Rodella, A., Zorzi, A. (2016). The Sialon II Project. Recent infections among MSM in Sialon II. Results from the Avidity Index Component of the Sialon II RDS survey. Project Report. Retrieved from www.sialon.eu/	2016
	Mirandola, M., **Gios, L.**, Sherriff, N., Toskin, I., Marcus, U., Schink, S., …, Rosińska, M.. (Editors). (2016). The Sialon II Project. Report on a Bio-behavioural Survey among MSM in 13 European cities. ISBN 978-88-98768-55-4. Verona, Cierre Grafica, 2016. Retrieved from www.sialon.eu/	2016
	The Sialon II Network (2016). City Profiles: Recommendations on HIV Prevention Strategies among Men who have Sex with Men in 13 EU Cities. Retrieved from www.sialon.eu/	2016
Health4LGBTI	Zeeman, L., Sherriff, N., Browne, K., McGlynn, N., Aujean, S., Pinto, N., …, [**Gios, L.**], ..., Pierson, A. (2017). State-of-the-Art Synthesis Report." Retrieved from https://ec.europa.eu/health/sites/health/, Brussels, 2017	2017
	McGlynn, N., Browne, K., Pollard, A., Sherriff, N., Zeeman, L., Aujean, S., …, [**Gios, L.**], …, Niedźwiedzka-Stadnik, M. (2017). Focus groups studies with LGBTI people and health professionals. Retrieved from https://ec.europa.eu/health/sites/health/, Brussels, 2017	2017
	Amaddeo, F., Donisi, V., Farinella, F., Buniotto, C., Sanchez-Lambert, J., Pinto, N., …, [**Gios, L.**], …, Browne, K. (2018). Trainers manual. Retrieved from https://ec.europa.eu/health/sites/health/, Brussels, 2018	2018

Annex 3 – Published Works included as primary sources within the critical appraisal and supporting correspondence

[3.1] Mirandola, M., Folch, C., Krampac, I., Nita, I., Stanekova, D., Stehlikova, D., …, [**Gios, L.**], …, the SIALON network. (2009). HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009. *Euro Surveill*, 14(48):pii=19427

Subject: Lorenzo Gios / PhD by publication / HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

Dear Nigel,

The above mentioned paper described the survey implemented in the context of the Sialon project, funded by the EU through the 2003-2008 Public Health Programme (Work Plan 2007), in the six selected European cities: Barcelona (Spain), Bratislava (Slovakia), Bucharest (Romania), Ljubljana (Slovenia), Prague (Czech Republic), and Verona (Italy). The paper included the description of methodological issues, like the use of Time Location Sampling (TLS) to enrol participants, together with the prevalence estimates (based on oral fluid testing) and behavioural data.

I am writing to confirm that Lorenzo Gios made a significant contribution to the design and implementation of the project, as well as to the paper development. He significantly contributed to the paper revision, particularly on the methodological components, providing important intellectual inputs in the process.

Please, let me know if you need any further information.

Kind regards

Cinta

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HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

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Data from 23 European countries show that the annual number of HIV diagnoses in men who have sex with men (MSM) increased by 86% between 2000 and 2006. This paper reports the main preliminary results of a bio-behavioural survey in MSM with a specific focus on HIV prevalence and use of United Nations General Assembly Special Session (UNGASS) indicators in six cities in Southern and Eastern Europe. Time-location sampling (TLS) was used. A total number of 2,356 questionnaires and 2,241 oral fluid samples were collected (invalid samples 4.1%). The data show different socio-demographic patterns across countries regarding age, level of education, living conditions, living area and self-identity. Southern European cities had the highest percentage of people who had tested for HIV and collected the result. More than 50% of respondents in the sample from Barcelona reported having used a condom last time they had anal sex (57.2%), whilst in all other cities this proportion was below 50%. The cities with the highest HIV prevalence in MSM were Barcelona (17.0%) and Verona (11.8%) whilst lower percentages were reported in Bratislava (6.1%), Bucharest (4.6%), Ljubljana (5.1%) and Prague (2.6%). The low prevalence in Eastern European cities is encouraging. However, with the level of high-risk sexual behaviour documented and the lower frequency of HIV test seeking behaviour, there is a clear risk of an increase in HIV transmission.

Introduction

HIV infection remains an important public health issue in Europe, with evidence of continuing transmission in many countries. Accounting for almost one third (7,693) of all reported newly diagnosed HIV infections reported in 2006 in European Union (EU) and European Free Trade Association (EFTA) countries, Men who have sex with men (MSM) continue to represent a population at high risk of HIV infection [1,2]. Data from 23 European countries show that the annual number of HIV diagnoses in MSM increased by 86% between 2000 and 2006 [2]. The results of some seroprevalence studies in gay community settings or healthcare services suggest levels of HIV prevalence between 10 and 20% among MSM, and available data suggest a possible hidden HIV epidemic in this population group [2,3].

In addition to the spread of HIV, an increase of high risk sexual behaviour among MSM is reported throughout Europe [1,2]. In this context, HIV testing has become a key surveillance activity for monitoring the HIV epidemic especially in hard-to-reach MSM. Since the introduction of highly active antiretroviral therapy (HAART), AIDS has become less indicative of the underlying trends in HIV infection. Another important factor linked to risk behaviour and risk of HIV transmission is the use of alcohol and other psychoactive drugs. According to the literature, alcohol and illicit drug consumption significantly increase the odds of having sex and have a significant positive association with the sexual risk.

Several studies, both in Europe and the United States (US), show a high percentage of MSM who use alcohol and drugs before and during sex and an association between these substances and sexual risk behaviour [4-6]. Additionally other studies suggest that even intermittent, recreational use of these drugs before or during sexual intercourse may lead to high-risk sexual behaviour (e.g. unprotected anal intercourse, UAI), especially with casual partners [7,8]. Recent studies of the sexual risk behaviour of MSM have also described a range of changes in sexual risk-taking behaviour in MSM in recent years, with an increased number of partners in some countries. The number of partners proved to be one of the strongest predictors of unsafe sex; according to the literature, the probability of having had unsafe sex ranged from 17% in men with one partner to 58% in men with more than 20 partners [9-11].

Despite these findings, few studies targeted MSM using outreach methods collecting behavioural and biological data in line with

Second Generation Surveillance System (SGSS) criteria [12,13] and United Nations General Assembly Special Session (UNGASS) indicators [3,14]. The Second Generation Surveillance System combines monitoring of newly diagnosed HIV cases and indicators of sexual behaviour among persons in groups at highest risk for infection.

Previous community-based surveys targeting MSM in Scotland, which included both questionnaires and anonymous oral fluid testing for HIV, found high levels of HIV prevalence and risk behaviour and low uptake of HIV testing [15]. The advantage of oral fluid collection for testing of infection is evident as it is a minimally invasive method for serological monitoring which is easy and safe. It has proven to be acceptable for various target audiences and it does not require trained staff [16,17]. Therefore, the use of oral fluid as a means for biological testing is of crucial importance in order to gather valid and reliable information about the spread of HIV among hard to reach populations such as MSM.

Taking these factors into account, the 2008-2009 study was designed to gather reliable information on HIV prevalence among MSM in Southern and Eastern Europe.

This paper reports preliminary results of the SIALON project Capacity building in HIV/Syphilis prevalence estimation using non-invasive methods among MSM in Southern and Eastern Europe, with a specific focus on HIV prevalence and use of UNGASS indicators.

Methods

Study design

The study was a descriptive multi-centre biological and behavioural cross-sectional survey and was carried out in seven cities of Southern and Eastern European countries: Athens, Greece; Barcelona, Spain; Bratislava, Slovakia; Bucharest, Romania; Ljubljana, Slovenia; Prague, Czech Republic; Verona, Italy. In this report Bratislava, Bucharest, Ljubljana and Prague were defined as Eastern European cities. The survey was designed to obtain an estimate of the prevalence of HIV in the study population, MSM attending gay venues.

Ethics Committee approval was obtained in each participating country and an informed consent form was collected for each respondent. The questionnaires and the oral fluid samples were collected anonymously. In order to make the test result available to interested individuals, a barcode was used to link the respondents to the test result via a card with the same barcode given to the respondents when oral fluid was collected. To comply with all ethical and legal aspects and minimise the risks of diagnostic mistakes, respondents interested in getting their test results were informed that the test result was not meant to be diagnostic and for this reason they should be tested again in line with international/

Figure 1

Age distribution of participants of an HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

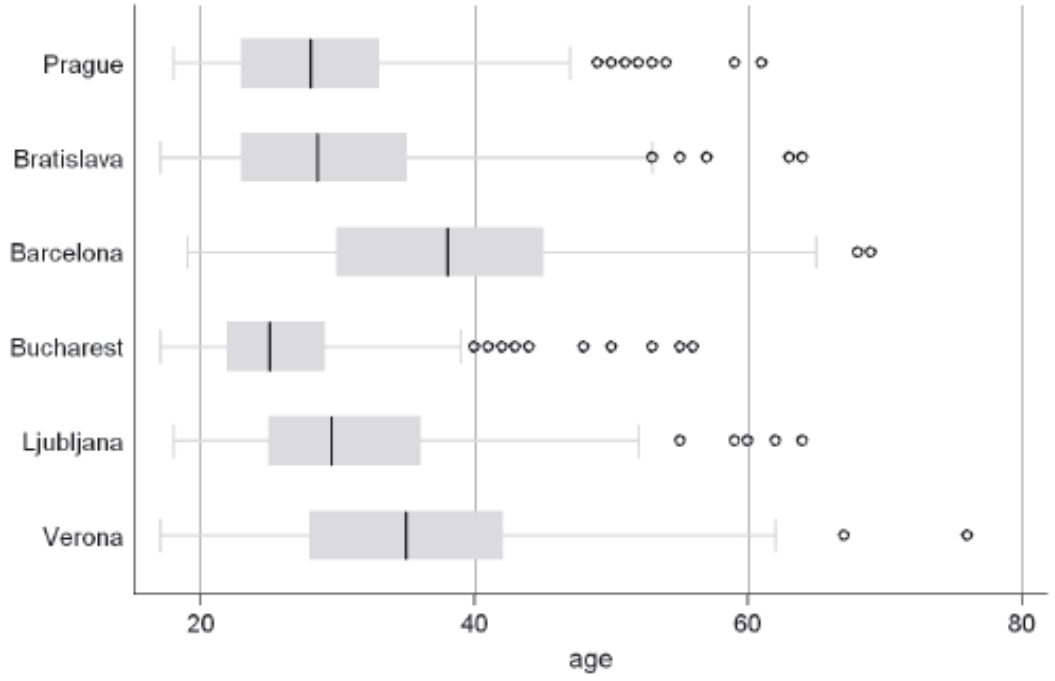


Figure 2

Percentage of men who have sex with men (MSM) who self-identified themselves as gay/homosexual, bisexual and heterosexual; HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

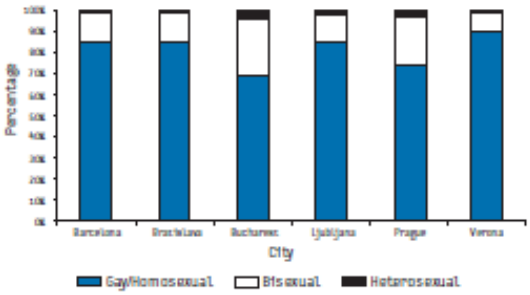


Table 1

United Nations General Assembly Special Session (UNGASS) indicators by city; HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

	UNGASS 8 HIV testing n=2,356	95%CI[a]	UNGASS 19 Condom use n=1,925	95%CI	UNGASS 23 HIV prevalence n=2,243	95%CI
Barcelona	56.2	±4.9	57.2	±5.1	17.0	±3.7
Bratislava	32.1	±4.9	30.8	±5.3	6.1	±2.5
Bucharest	43.2	±4.9	42.7	±5.3	4.6	±2.2
Ljubljana	38.2	±4.8	43.0	±5.6	5.1	±2.2
Prague	41.5	±4.8	29.8	±5.2	2.6	±1.6
Verona	53.0	±4.9	45.6	±5.2	11.8	±3.2

[a] Confidence interval

national guidelines. In case of a confirmed positive HIV test, the person was directed to the infectious disease department for further checks of their clinical situation and start antiretroviral treatment if needed.

Study population

Participants were recruited according to the following four inclusion criteria: having had sex (any kind of sex: oral and anal, penetrative or not) at least once with another man during the last 12 months before the study; having signed a written informed consent form; having agreed to answer the study questionnaire; having accepted to donate an oral fluid sample. Three exclusion criteria were adopted: age below 18 years; currently active injecting drug use (IDU) and having already participated in the study.

Sampling

Time-location (or time-space) sampling (TLS) was used to recruit representative samples of men visiting the gay scene in each city. The method used was consistent with the approach adopted in previous studies [15-21]. In the TLS, spaces (or locations) are venues attended by the target population; times refer to specific days and time periods when the target population congregates in each space. This method allows a sample with known properties to be identified and enables statistical inferences to be made to the larger population of venue visitors. Formative research was conducted in each collection location in order to identify the list of potential TLS units, the attendance time frame, opening days and hours of each venue. Bars, discos, saunas, cruising venues, sex-shops, sex-clubs were identified in all cities. All venues were mapped and visited when information on attendance patterns was not sufficient to prepare a TLS units list. The spaces and their associated days were divided into standardised time segments (four-hour periods). Subjects were enrolled over the entire TLS unit time period. Information on the number of refusals per TLS unit was collected. Furthermore, settings or special gay events that did not occur frequently were identified. A "special events" category was created and included in the sampling list because such occasions may attract members of the target population. The list of TLS units obtained with this process for each collection site included the primary sampling units (PSU). PSU were randomly selected from complete list of eligible TLS list in each city. The sample size estimation for a prevalence study was calculated on

Table 2

Percentage of respondents who consistently used a condom in the last six months with steady and casual partners, separately for anal and oral sex; HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

	Condom use during anal sex with steady partner		Condom use during anal sex with casual partner		Condom use during oral sex with steady partner		Condom use during oral sex with casual partner	
Total	N=1,402		N=1,383		N=1,517		N=1,567	
	%	95%CI[a]	%	95%CI	%	95%CI	%	95%CI
Barcelona	43,0	±7,0	65,4	±5,5	9,3	±4,0	13,1	±3,8
Bratislava	19,9	±5,2	41,7	±6,9	1,2	±1,4	6,2	±3,1
Bucharest	43,1	±6,0	51,8	±6,2	8,6	±3,3	15,1	±4,3
Ljubljana	36,6	±6,1	58,8	±7,2	5,5	±2,7	10,4	±4,0
Prague	25,6	±5,4	36,3	±6,8	5,8	±2,8	9,6	±3,7
Verona	40,2	±6,4	56,1	±5,9	5,8	±3,0	8,1	±3,0

[a] Confidence interval

the basis of previous prevalence estimation studies when available [22]. A total of 2,800 persons (400 per city) were included in the planned survey.

Data collection

Questionnaire

A self-administered pen-and-paper questionnaire was used to obtain information on the social/cultural/environmental context of respondents, access and barriers to voluntary counseling and testing (VCT), behavioural data on sex practices, risk-reducing strategies, condom use), STI history, self-reported/perceived serostatus and type of partner. A steady partner was defined in the questionnaire as "a person who you are committed to and have sex with, not meaning that, you are exclusively monogamous"; casual partner as "person you have sex with, occasionally without a steady partnership". In addition, UNGASS indicators were taken into account when designing the questionnaire [3,14]. The preliminary version of the questionnaire was piloted among MSM attending gay venues to check on the time needed to complete it and to ensure the questions were not ambiguous or confusing. The English version of the questionnaire was translated into the languages of the participating countries and then translated back into English.

A questionnaire manual and a training module were developed in order to guarantee uniform data collection. Specific training of data collectors was held in each country in a one day session by a data collection coordinator. The same coordinator was in charge of monitoring the local data collection and coaching the data collectors during the task. An ongoing evaluation process was organised through regular meetings with data collectors.

Oral Fluid sampling and testing

To collect oral fluids, Oracol oral fluid collection kits (Malvern Medical Developments, Worcester, UK) were used. The main advantages for replacing serum with oral fluid were easy access and non-invasive collection. After collection, oral fluid samples were kept refrigerated and sent to the national reference laboratory for HIV/AIDS in the respective countries no more than 72 hours after collection.

Laboratory testing

The oral fluid samples were sent for the analysis by each national reference laboratory to the Teaching Hospital-University of Verona, Immunology Unit, Verona, Italy. EIA testing GENSCREEN HIV 1/2 version 2, BIO-RAD on oral fluid sample was performed according to the manufacture's instructions [23]. All positive samples were confirmed with a Western Blot test. As quality control, for each oral fluid sample, a total IgG antibodies ELISA test was performed in order to assess the sample suitability for testing. Samples below 3.5 titre (cut-off) were excluded from the study as invalid. A validation study of Bio-Rad OF testing comparing serological testing involving 37 HIV positive patients and 35 controls per country was carried out according to commission decision of 7 May 2002 on common technical specifications for in vitro medical devices. Validation, with 504 paired oral fluid and serum samples, yielded a 99% sensibility and 99% specificity, which gives PPV of 94.6% and NPV of 99.8% for a prevalence of 15%. For a prevalence of 5% these figures are 83.9% and 99.9% respectively.

Enrolment

According to the data collection calendar, trained field workers from gay associations distributed anonymous self-complete questionnaires and Oracol oral fluid collection kits. Both self-complete questionnaire (behavioural data) and oral fluid samples (biological data) were collected for each subject. A barcode was used to link behavioural and biological information. The enrolment period varied between cities. The data collection calendar varied from two months in Barcelona and Verona to nine months Bratislava and Bucharest.

TABLE 3

Number of steady and casual partners in the last six months; HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009

		Barcelona	Bratislava	Bucharest	Ljubljana	Prague	Verona
Steady partner		n=161	n=238	n=256	n=258	n=242	n=221
	Mean	1,6	2,0	3,3	2,1	2,7	2,6
	SD[a]	1,7	2,2	4,5	2,5	3,6	3,6
	P25	1	1	1	1	1	1
	Median	1	1	2	1	1	1
	P75[b]	1	2	3	2	3	3
	IQR[c]	0	1	2	1	2	2
Casual partner		n=269	n=232	n=249	n=219	n=205	n=293
	Mean	16,3	6,1	7,1	5,7	7,5	12,0
	SD	20,5	8,6	9,4	8,9	10,5	16,1
	P25	4	2	2	2	2	3
	Median	10	3	3	3	4	6
	P75	20	6	7	6	10	12
	IQR	16	4	5	4	8	9

[a]SD: standard deviation
[b]P: percentile
[c]IQR: inter-quartile range

Statistical Analysis

As the focus of the study was descriptive, mean, median, standard deviation, quartiles and inter-quartiles were used and proportions with 95% confidence intervals (CI) were calculated for all variables and indicators. STATA 11 survey commands suite was used.

Results

A total of 2,362 questionnaires and 2,365 oral fluid samples were collected in six of the seven cities. The total number of valid questionnaires was 2,356 (99.7%) whilst for the valid oral fluid samples it was 2,241 (94.8%) The proportion of valid oral fluid samples over valid questionnaires by city was respectively: Barcelona 97% (388/400), Bratislava 98% (342/349), Bucharest 86.7% (345/398), Ljubljana 97.7% (389/398), Prague 95.1% (387/407), Verona 96.5% (390/404). Athens, Greece was not included in the analysis as data was not available at the time of this paper.

The time of questionnaire completion ranged from 10 to 20 minutes. The time length was related to age and the type of venues.

Study population

The median age and 1st and 3rd quartile by city are presented in Figure 1. Respondents in Barcelona and Verona had a similar age distribution and were older, (38 and 35 years respectively) than those in the Eastern European cities; in Bucharest the median age of respondents was 25 years, followed by Prague and Bratislava (28 years). In Ljubljana the median age was 29.5 years.

As regards education level, MSM in Barcelona had the highest proportion of university degrees (53.6%) and MSM in Prague the lowest (27.4%).

In most of the cities the largest group of respondents lived alone (living conditions): 41.8% in Prague, 40.8% in Verona, 37.4% in Barcelona and 36.9% in Ljubljana. Exceptions were Bucharest and Bratislava, where respondents lived mostly with their parents (34.1% and 30.2% respectively). In Verona, a high proportion of MSM lived with their parents (30.1%), although a larger number lived alone. Barcelona had the highest proportion of respondents living with friends (22.9%), while the highest proportion living with male partners were in Prague (27.5%) and Bratislava (27.6%) followed by Ljubljana (23.4%). The percentage of respondents living with a heterosexual family (female partner and/or offspring) was generally lower than 8%, ranging from 4.9% in Bratislava to 7.7% in Verona.

In almost all cities the majority of respondents lived in areas with more than 100,000 inhabitants, ranging from 61.4% in Bratislava to 82.9% in Bucharest, with the only exception of Verona, where the majority of respondents lived in a village with less than 10,000 inhabitants (32.7%) or in a small town with 10,000 to 100,000 inhabitants (25.3%).

The data for self-identified sexual orientation are presented in Figure 2. More than 80% of the respondents self-identified themselves as homosexual in Barcelona, Bratislava, Ljubljana and Verona. The highest proportion of bisexuals and heterosexuals was found in Bucharest (27.6% and 3.9% respectively) and in Prague (22.6% and 3% respectively), while the lowest was in Verona (8.7% and 1% respectively). In the remaining cities the percentage of bisexuals was similar, ranging from 12.7% in Ljubljana to 14.4% in Bratislava.

HIV prevalence and testing

Table 1 presents the prevalence of HIV infection among MSM based on the oral fluid tests. The cities with the highest HIV prevalence were Barcelona (17.0%) and Verona (11.8%); lower percentages were reported in Bratislava (6.1%), Bucharest (4.6%) and Ljubljana (5.1%). Prague had the lowest HIV prevalence (2.6%).

In order to monitor HIV testing uptake, UNGASS indicator number eight was used. This indicator comprises the percentage of MSM tested for HIV over the last 12 months who also collected the result. Table 1 presents the UNGASS 8 estimate by city.

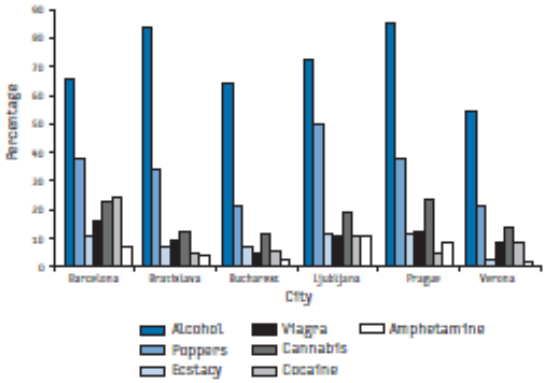
Southern European cities had the highest percentage of tested people who received their HIV test result (56.2% in Barcelona and 53% in Verona), while the Eastern European cities had the lowest percentages, ranging from 32.1% in Bratislava to 43.2% in Bucharest. Among the respondents who had taken an HIV test over the last 12 months, the percentage of subjects who decided to collect the test result was over 90% in Verona and Barcelona (93.9% and 92.6% respectively) while in Prague it was 85.9%, in Bratislava 83.6% and 78.3% in Ljubljana. The lowest percentage was in Bucharest (74.9%).

Condom use

In order to estimate the risk reduction strategies of MSM during the most at-risk sexual behaviour, namely anal sex, UNGASS indicator number 19 was used. This indicator describes the percentage of men reporting the use of a condom during their last anal sex episode with a male partner in the previous six months. Table 1 presents the UNGASS 19 estimate by city. More than 50% of respondents in the sample from Barcelona reported using a condom the last time they had anal sex (57.2%), while in all other cities this percentage was below 50%. In three cities percentages were above 40% (Verona: 45.6%, Ljubljana: 43%, Bucharest:

Figure 3

Percentage of respondents reporting use of alcohol, poppers, ecstacy, Viagra, cannabis, cocaine and amphetamine before or during sex over the last six months; HIV bio-behavioural survey among men who have sex with men in Barcelona, Bratislava, Bucharest, Ljubljana, Prague and Verona, 2008-2009



42.7%), while percentages were lowest in Prague (29.8 %) and Bratislava (30,8%).

Consistent condom use

Respondents were asked to indicate the frequency of protected anal and oral sex both with a steady and a casual partner over the last six months. Consistent condom use is defined as the use of a condom (often or always) in the last six months during sexual intercourse, both receptive and insertive. Sexual behaviour was analysed separately for anal sex and oral sex. Table 2 shows the percentage of consistent condom use by type of partner and city. As far as anal sex is concerned, condom use with a steady partner was declared by 43.1% of respondents in Bucharest and 43% in Barcelona, followed by Verona (40.2%) and Ljubljana (36.6%), while the lowest condom use was reported in Prague (25.6%) and Bratislava (19.9%). Condom use with a casual partner for anal sex is in general more likely to be reported than with a steady partner. The highest level of consistent condom use with a casual partner was reported by MSM in Barcelona (65.4%), whilst the lowest was in Prague (36.3%). In Ljubljana consistent condom use was reported by 58.8% of respondents who had anal sex with a casual partner, followed by MSM in Verona (56.1%), in Bucharest (51.8%) and in Bratislava (41.7%).

As far as consistent condom use in oral sex over the last six months is concerned, the level was dramatically lower compared with anal sex. In Barcelona, 9.3% of respondents reported condom use with a steady partner followed by Bucharest (8.6%); a virtually identical level was reported in Prague (5.8%), Verona (5.8%) and Ljubljana (5.5%). The lowest level of condom use in oral sex with a steady partner was reported in Bratislava (1.2%). For casual partners, consistent condom use in oral sex was reported by 15.1% of respondents in Bucharest, 13.1% in Barcelona and 10.4% in Ljubljana, whilst the lowest proportion was found in Verona (9.1%) and Bratislava (6.2%).

Number of partners

The highest average number of steady partners over the last six months reported by respondents was in Bucharest (3.3) and the lowest in Barcelona (1.6), although the medians show a more similar distribution between the cities, with two partners in Bucharest and one partner elsewhere (Table 2). For casual partners, the highest mean and median were reported in Barcelona (mean 16.3, median 10), followed by Verona (mean 12, median 6) and Eastern European cities (mean ranging from 5.7 to 7.5 and median from 3 to 4).

Psychoactive and recreational drug use over the last six months

Substance use before or during sex over the last six months is demonstrated in Figure 4. As expected, alcohol proved the substance with the highest rate of consumption in each city. The highest percentages were reported in Prague and Bratislava (85% and 83.7% respectively), whilst the lowest level was in Verona (54.2%).Poppers are one of the most popular substances in the gay scene and some authors refer to it as a gay drug [4]. The highest rate of poppers use was found in Ljubljana (49.8%) whilst lower use was reported in Prague, Bucharest and Barcelona (38.1%, 34.2% and 37.6% respectively). The lowest percentages were reported in Verona (21.6%) and Bucharest (21%). For ecstacy, the percentages of consumption were 11.4% in Prague, 11.3% in Ljubljana and 10.9% in Barcelona. Sixteen per cent MSM in Barcelona reported use of viagra, 12.7% in Prague. Lower levels of consumption were reported in Bucharest (4.7%), Verona (8.6%) and Bratislava (9.1%).High levels of Cannabis use were reported in Prague, Barcelona and Ljubljana (23.8%, 23.2% and 19.1% respectively), while lower rates were reported in Verona (13.4%), Bratislava (12.5%) and Bucharest (11.5%). A high consumption of Cocaine was found in Barcelona (24.5%). Similar levels of consumption were found in the MSM samples in Prague (5.1%), Bratislava (5.2%), Bucharest (5.8%) and Verona (8.3%). The rate of amphetamine use ranged between 1.9% in Verona and 10.4% in Ljubljana.

Discussion and conclusion

Valid and comparable data on HIV prevalence related to HIV risk behaviour in a hard to reach population are lacking. However, such information is important for development of effective prevention strategies. In order to respond to this limitation, the SIALON project, used three key elements of behavioural and prevalence studies among MSM for improving data comparability: time and location sampling (TLS) method, oral fluid testing in outreach settings and UNGASS indicators.

The use of TLS as a sampling method proved to be feasible and efficient in cities with highly developed gay scenes as well as in cities with less developed scenes. As previous studies among MSM have shown, TLS increases the possibility of involving a variety of participants, producing more valid results [15]. A generalisation of the estimates obtained with this method to the wider population of MSM attending sampled venues is also possible. TLS can be adopted on a larger scale and the method is easily applicable in cities with a considerable number of eligible gay venues. It is more difficult to implement in cities where the gay community is poorly organised and where there are few specific and easily accessible venues. Few venues means that the venues available are over-visited by data collectors, thus reducing the acceptance of the data collection process both to owners of venues and attendees. This aspect may impact the representativeness of the MSM sample of the whole MSM population and therefore reduce the efficiency of TLS. In addition, the TLS method does not take into account other ways of recruiting, such as the internet, gay magazines, chat room etc. However, as one of the main focuses of our study was to estimate HIV prevalence through the collection of biological samples, these alternative sources of recruitment were excluded.

For surveillance and epidemiological purposes, oral fluid testing has clear advantages over venopuncture in community settings and is an alternative screening tool in outreach settings among high-risk populations. Oral fluid testing simplifies the diagnostic process in specific populations in which drawing blood is difficult and dangerous. As previously demonstrated in other studies, the number of oral fluid collections in all sites confirmed the general acceptability of the study by MSM in outreach settings [16,24]. In our study, an info-pack containing a condom, a lubricant and information about STD prevention and screening centres available in the area was given to respondents in order to facilitate the enrolment and to promote safer sex and testing practice, during the data collection.

The introduction of UNGASS indicators is a key measure for the basic monitoring of HIV across countries with comparable indicators. According to UNAIDS, data from multiple countries collected following UNGASS procedures can supply critical information and comparative insights at the regional and the global level. Data can provide a snapshot as well as trend analysis of the epidemiology of HIV over time [3,14]. As far as our study results are concerned, the data shows a variety of socio-demographic patterns among the cities in relation to age, education, living conditions,

living area and self-identity. At this stage, the results presented in this paper are mainly descriptive and this is of course a limitation of the study. A multilevel, multivariate analysis will be carried out in the future to better understand the relationship between HIV prevalence and other factors.

HIV testing (UNGASS 8) is an important indicator of the healthcare system's ability to reach MSM and to efficiently provide access to screening. Verona and Barcelona had the highest percentages of tested people who collected the HIV test result. This finding reflects not only the lower access to HIV testing in Eastern European cities, but also how VCT is organised and might be an indicator of health practitioners' attitudes on health seeking behaviour. The high percentage of MSM seeking the test result in Verona and Barcelona seems to indicate better VCT practice. Differences in stigma, health service organisation and country specific barriers to accessing VCT could explain the gap between Southern and Eastern European cities. Data on condom use (UNGASS 19) seem to suggest that protected sex is more frequently performed in Southern European cities, particularly in Barcelona. Interestingly, HIV prevalence was highest in Barcelona and Verona, where condom use was also highest. This may reflect a different distribution of HIV prevention programmes. In more detail, data about the type of sexual partner, sexual intercourse and condom use confirm the findings of other studies. It is evident that the differentiation between steady and casual partners leads to different distribution of sexual practice. According to the literature, in some countries the number of sexual partners seems to have increased in recent years [25,26]. This may be a good proxy variable for unsafe sex [9]. As expected, throughout our sample, the number of casual partners was higher than the number of steady partners, although in some countries this difference was far more marked than in others. When considering different sexual behaviour (anal and oral sex) related to different types of sexual partners in the last six months, similar patterns occur. As already well-established by other studies, the rates of condom use differ in relation to the kind of partners and sexual practices: protected sex with casual partners is more frequent than with a steady partner, and protected anal sex is more frequent than protected oral sex [27].

As far as substance use is concerned, alcohol consumption is broadly reported in all cities, with the highest levels in Prague and Bratislava. These findings may be related to the younger age of respondents but also to some contextual variables in Eastern European cities. According to the international literature, poppers seems to be the main substance used in the MSM population [4]. Our findings confirm the high levels of poppers consumption, especially in Ljubljana, Prague and Barcelona. As far as the use of other illicit drugs is concerned, cannabis is widely used, but there are large differences between cities. With regard to cocaine consumption, in Barcelona, 24.5% of respondents reported they had used it sometimes or often during the last six months, before or during sex. Even though an overestimation of substance use could not be excluded, it seems that drug use was frequent in our sample. Taking into account the fact that even an intermittent recreational use of drugs before or during sexual intercourse may lead to high-risk sexual behaviour, the data seem to be relevant and suggest a need for prevention programmes targeting MSM, with particular attention to alcohol, poppers and drug use.

Despite possible biases in this prevalence study in some countries, the data emerging from the survey show varying levels of HIV infection among the recruited MSM. The highest prevalence was in Barcelona and Verona, while the prevalence in Eastern European countries was lower. Previous studies carried out in some of the cities participating in this study, came to different prevalence estimates. In Barcelona HIV prevalence found in a last previous study carried out in MSM venues (using a convenience sample) was slightly higher than the prevalence found in this study [28]. The lower figures found in Ljubjana and Bratislava in previous studies, may be partly related to a different sampling method and lower number of samples collected [29,30].

The low prevalence found in the four Eastern European cities is encouraging. However, with the level of unprotected anal sex in some of these cities, even with casual partners, and a generally low frequency of HIV test- seeking behaviour, the potential for further HIV transmission in Eastern European cities is evident.

Members of the SIALON network:

Ivo Procházka, Czech AIDS Help Society (ČSAP), Czech Republic; Alex Horký, Czech Youth Queer Organization,Czech Republic; Zeno Menegazzi, Arcigay Italia; Alin Robert Zoltan, ACCEPT Romania, Romania; Jaro Gyurik, Združenie Prevencia AIDS (ZPA), Slovakia; Miran Sotinc, ŠKUC Magnus, Slovenia; Rafa Muñoz, Stop Sida,Spain.

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RE: Lorenzo Gios / PhD by publication / Bio-behavioural HIV and STI surveillance among Men who have Sex with Men in Europe: the Sialon-II protocols.

02.08.2019

Unser Zeichen:

Dear Nigel,

I am writing to you in relation to the abovementioned paper, which is based on the SIALON-II project protocols. Lorenzo Gios was responsible for the study conception and design, as well as for the implementation component of the research protocols. He also took a lead role in conceptualising the abovementioned paper and for completing the first draft. He also led process of paper finalisation, coordinating the inputs and revisions from the different co-authors contributing to the manuscript.

Kind regards,

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Dear Nigel,

I'm writing to you in relation to the abovementioned paper, which is based on the Sialon II project protocols. Mr. Lorenzo Gios was responsible for the study conception and design, as well as for the implementation component of the research protocols.

Lorenzo also took a lead role in conceptualising the abovementioned paper and for completing the first draft. He also led the process of paper finalisation, coordinating the inputs and revisions from the different co-authors contributing to the manuscript.

Kindest regards,
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Bio-behavioural HIV and STI surveillance among men who have sex with men in Europe: the Sialon II protocols

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Abstract

Background: Globally, the HIV epidemic continues to represent a pressing public health issue in Europe and elsewhere. There is an emerging and progressively urgent need to harmonise HIV and STI behavioural surveillance among MSM across European countries through the adoption of common indicators, as well as the development of trend analysis in order to monitor the HIV-STI epidemic over time. The Sialon II project protocols have been elaborated for the purpose of implementing a large-scale bio-behavioural survey among MSM in Europe in line with a Second Generation Surveillance System (SGSS) approach.

Methods/Design: Sialon II is a multi-centre biological and behavioural cross-sectional survey carried out across 13 European countries (Belgium, Bulgaria, Germany, Italy, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK) in community settings. A total of 4,966 MSM were enrolled in the study (3,661 participants in the TLS survey, 1,305 participants in the RDS survey). Three distinct components are foreseen in the study protocols: first, a preliminary formative research in each participating country. Second, collection of primary data using two sampling methods designed specifically for 'hard-to-reach' populations, namely Time Location Sampling (TLS) and Respondent Driven Sampling (RDS). Third, implementation of a targeted HIV/STI prevention campaign in the broader context of the data collection.

Discussion: Through the implementation of combined and targeted prevention complemented by meaningful surveillance among MSM, Sialon II represents a unique opportunity to pilot a bio-behavioural survey in community settings in line with the SGSS approach in a large number of EU countries. Data generated through this survey will not only provide a valuable snapshot of the HIV epidemic in MSM but will also offer an important trend analysis of the epidemiology of HIV and other STIs over time across Europe. Therefore, the Sialon II protocol and findings are likely to contribute significantly to increasing the comparability of data in EU countries through the use of common indicators and in contributing to the development of effective public health strategies and policies in areas of high need.

Keywords: HIV, Surveillance, MSM, Time-location sampling, Respondent-driven sampling

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Background

The HIV epidemic is still representing a pressing public health issue worldwide and in Europe as well [1]. Current documents published by the European Centre for Disease Control (ECDC) and focusing on the WHO European Region clarify that 136,235 new HIV diagnoses were reported in 2013, with a rate of 15.7 per 100,000. A total of 1,715,434 infections diagnosed in the WHO European Region represent the current number of persons leaving with HIV.

In terms of transmission, according to the 2013 data, the highest proportion of new HIV diagnoses was reported in men who have sex with men (MSM): this specific sub-population accounts for 42 % of all new infections in EU/EEA countries (compared to 40.4 % in 2012) [2].

For this specific population, in EU/EEA countries where data are available, since 2004 HIV diagnoses have increased by 33 %, confirming that MSM could be considered as a very high risk population for acquiring HIV, as a considerable part of the new HIV infected people across Europe is reported among this sub-population.

In addition, in younger MSM an increase of new diagnoses is dramatically reported for the EU/EEA area: between 2004 and 2013, the number of new HIV positive MSM aged 20-24 years almost doubled, whilst in adult MSM (30–39 years old) the estimates remain relatively stable. These high estimates (for the new diagnoses in particular) could be partially due to increasing HIV testing behaviours, but they could also indicate onward transmission in this specific population. Indeed, with regards the latter, according to the current scientific literature an increase of high risk sexual practices (such as unprotected anal intercourse) has been reported among MSM across Europe [1, 3]

In terms of serum-status awareness, almost one third of those infected in Europe are estimated to be unaware of their seropositive status [1].

Data seems to suggest that the current situation is becoming increasingly critical from a public health perspective.

Set within this context, HIV diagnosis has become a key surveillance activity for monitoring the HIV epidemic especially in 'hard-to-reach' populations such as MSM. Reliable data, including trends in risk behaviours over time, are of crucial importance in order to understand whether and by how much rates are increasing or decreasing and which (sub-) populations are affected the most. Consequently, the international literature, such as UNAIDS and WHO reports and publications [4], have stressed the need for public health to embrace three main approaches in monitoring and controlling the epidemic: (i) a structured surveillance system method; (ii) the use of common set of indicators adopted across Europe, and; (iii) specific prevention campaigns targeting MSM and testing promotion as the cornerstone of the HIV response.

In terms of structured surveillance initiatives and in response to the growing awareness of the urgency for a comprehensive and effective response, a number of European countries have implemented surveys specifically targeting MSM [5] focusing primarily on the monitoring of risk behaviours. However, a Second Generation Surveillance System (SGSS) approach [4], whereby both biological (e.g. oral fluid) and behavioural data (e.g. from questionnaires) are collected and analysed jointly, has only been adopted in a limited number of countries [6]. This is problematic and limits the value of such targeted initiatives due to, amongst other things, a lack of reliability and comparability of data at the European level [7]. A SGSS approach is defined by the WHO as the "regular, systematic collection, analysis and interpretation of information for use in tracking and describing changes in the HIV/AIDS epidemic over time" [8]. SGSS is important because it not only allows the public health sector to monitor the spread of infections in a given population and to analyse trends over time, but it can also facilitate countries to improve their planning and evaluation of prevention and treatment activities.

With regards to the second approach (i.e. the use of a common set of indicators adopted across Europe to monitoring and controlling the epidemic), despite some European countries adopting a SGSS approach, implementation is regrettably patchy and not systematic. Furthermore, even where examples of a SGSS approach are evident, there is often considerable variation between countries in terms of specific indicators utilised and reported. Such challenges highlight the need for HIV and STI behavioural surveillance among MSM across EU countries to be harmonised for high-risk population such as MSM [5]. This call to action has been taken up by the United Nations General Assembly in 2001, which in a Special Session on HIV/AIDS proposed the construction of a set of core indicators, namely the UNGASS indicators [9, 10] to kick-start such harmonisation in the collection of data at the international level. These UNGASS indicators have been revised and updated periodically until post-2012 when they became known as the Global AIDS Response Progress Reporting (GARPR) indicators (see [11] for the most recent guidelines, released at the beginning of 2014).

In terms of the third approach (i.e. targeted prevention campaigns), such specific HIV/STI prevention campaigns targeting MSM and promoting testing represent the cornerstone of the HIV response. Yet although many EU Member States (public health sectors and voluntary/third sectors) have routinely and for some time,

implemented prevention programmes targeting MSM specifically, current prevention and treatment strategies appear to be not sufficient [12] . It has to be acknowledged that the evidence-base for primary HIV prevention does not reach the same degree of graded evidence as bio-medical prevention approaches due to the complexity of intertwined behavioural and structural factors. This is not surprising given that health promotion and public health interventions are complex, non-linear, and multi-layered processes often with no simple measurable outcomes. They are therefore difficult to evaluate, resulting in a general lack of evidence for which HIV programmes might be the most effective [13].

To-date, few studies have been able to address simultaneously all three of the approaches to tackling the HIV epidemic as advocated by UNAIDS and the WHO. However, of those studies that have embraced such an approach, community-based surveys targeting MSM that adopt bio-behavioural measures (e.g. oral fluid testing for HIV and behavioural questionnaires) have found high levels of HIV prevalence and risk behaviours (such as unprotected anal intercourse) as well as critical levels of HIV testing uptake considering the high frequency of unprotected anal intercourse with different partners [14, 15]. Such studies continue to highlight the urgent need for large-scale reliable and comparable second generation surveillance data on MSM that are paired with meaningful STI/HIV prevention, treatment and care.

Consequently, and in line with the most recent EC communication on combating HIV/AIDS in the European Union and neighbouring countries (2009–2013), the overall objective of the Sialon II project is to carry out and promote combined and targeted HIV/STI prevention for MSM complemented by second generation HIV/STI surveillance in collaboration with UNAIDS and WHO. The project is funded by the European Commission under the Second Programme of Community Action in the Field of Health (2008–2013). The Sialon II project is based on the experiences and lessons learned from the former Sialon project, funded under the 2003–2008 Public Health Programme (Work Plan 2007) [15].

In this paper, the Sialon II project protocols are presented which included three parts: (i) the formative research phase (including prevention needs assessment) with the objective to identify the specific community-based settings to carry out data collection and to assess local prevention needs; (ii) the use of innovative surveillance methodologies with the objective to access 'hard-to-reach' MSM in community-based settings; (iii) HIV (HIV1/2) and STI (Syphilis and Hepatitis [HBV/HBC]) testing algorithms, the implementation of targeted prevention activities with the objective to respond to immediate prevention needs when conducting the data collection.

Methods

The Sialon II project is a multi-centre biological and behavioural cross-sectional survey carried out across 13 European countries including: Belgium, Bulgaria, Germany, Italy, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK. The survey has been implemented using the same methodologies (protocols, UNGASS/GARPR indicators, epidemiological algorithms) and prevention strategies in each of the participating countries. The project builds on an experienced, skilled, and cohesive partnership founded through previous collaborations across Europe. All partner institutions are public bodies, representing either public health institutes or universities in their respective countries with skilled and well-equipped laboratories ensuring capable scientific and technical reporting. The Sialon II partnership is rooted more broadly in a further network of local collaborating partners ranging from universities, teaching hospitals, epidemiological centres, gay and/or HIV non-governmental organisations (NGOs) across all participating countries. This extended network has been a key resource for the project ensuring on the one hand, relevant specialisation in HIV/STI research, and on the other, suitability to social, cultural, policy and political contexts in each country as well as actively enabling the participation and views of the target group (MSM) to be taken into account.

In what is to follow, the three related yet distinct components (i.e. formative research; primary data collection; targeted prevention activities) are described in more detail.

Formative research

During 2011–12, formative research (FR) was carried out in all 13 participating countries. Information was collected via a combination of a dedicated FR questionnaire and focused analysis of secondary data from the European MSM Internet Survey (EMIS) [16, 17]. The FR questionnaires were completed by each project partner from the respective study country in partnership with their local collaborating partner (e.g. NGO). Each questionnaire explored a number of areas such as: the proposed study site; previous experiences with different study methodologies and target groups; data on gay-friendly commercial and non-commercial sites; testing opportunities, regulations, and treatment guidelines for HIV, STIs, HBV, and HCV; contextual factors such as legislation relating to gay issues (e.g. date of homosexuality becoming legal, possibility of gay marriage or officially recognised civil partnerships, protection from discrimination regarding sexual orientation etc.) and stigmatisation. In addition to the contextual information provided by the country partner, EMIS data were also used to further characterise the MSM population in each respective study area. This allowed for compiling a comprehensive 'picture'

of each study area which described the relevant context, in which the data collection took place, included information such as demographic characteristics, proportions of MSM among the adult population, as well as data such as the degree of 'out-ness' reported by MSM in the study area, self-reported internalised homo-negativity, gay-venue attendance, and self-reported HIV and STI history.

During the FR process, gay-friendly commercial (e.g. cafés, bars, discos, sex-clubs, saunas, porn-shops) and gay friendly non-commercial sites (e.g. community centres and cruising areas) were described in detail using a number of indicators such as the estimated number of MSM attending the venue per day during a week, opening hours, special events, logistical aspects for performing sampling, opportunities for sexual contact in the venue, availability of condoms, lubricants and other prevention activities, and so on.

Findings from the FR were presented and discussed during a dedicated study meeting with all network partners present (including collaborating partners such as NGOs). A FR report was compiled and provided to all national study sites in order to better tailor both the planned TLS and RDS surveys, as well as the targeted prevention actions [17].

Primary data collection

Following, and informed by, the FR phase, a TLS survey (3,661 participants) was planned and implemented during 2013–2014 in nine cities and countries: Belgium (Brussels), Bulgaria (Sofia), Germany (Hamburg), Poland (Warsaw), Portugal (Lisbon), Slovenia (Ljubljana), Spain (Barcelona), Sweden (Stockholm), and the UK (Brighton). In the remaining four partner countries, an RDS survey (1,305 participants) was planned and implemented in Italy (Verona), Lithuania (Vilnius), Romania (Bucharest), and Slovakia (Bratislava) (see Table 1 - Timeline in the Sialon II study by sampling method and city; Table 2 - MSM enrolled in the Sialon II study by sampling method and city). In all cases the following inclusion criteria for MSM participation were used: must have had any kind of sex (oral or anal, penetrative or not) at least once with another man during the previous 12 months; able to provide anonymous informed consent; agree to complete the study questionnaire; agree to provide either an oral fluid sample (for TLS) or blood sample (for RDS). Exclusion criteria were: being younger than 18 years old, and having already participated in the study.

Prior to biological sample collection in both TLS and RDS study arms, informed consent was collected for each participant. A self-administered pen-and-paper questionnaire was then administered to all participants to obtain data on: the social and cultural context of respondents; behavioural data on sex practices; risk-reduction strategies such as not having anal intercourse with non-steady partners, condom use, and HIV serostatus disclosure; STI history; self-reported serostatus, and number and type of sexual partners. The questionnaire was designed by the Sialon II network in line with the GARPR indicators. A preliminary version of the questionnaire was piloted in each country with the collaboration of local gay and/or HIV NGOs. Subsequently, a 'final' English version of the questionnaire was translated into each of the languages of the participating countries and then back-translated into English for quality control. The same questionnaire was used in both surveys (TLS and RDS): in the TLS version additional items were included focusing on the venues in the given city (for weight calculations), whilst in the RDS survey extra items were used in order to assess the network size of the participants.

Table 1 Timeline in the Sialon II study by sampling method and city

Sampling method	City and Country	Starting month	Ending month
Time-Location Sampling (TLS)	Brussels, Belgium	April 2013	July 2013
	Sofia, Bulgaria	July 2013	September 2013
	Hamburg, Germany	April 2013	August 2013
	Warsaw, Poland	May 2013	September 2013
	Lisbon, Portugal	April 2013	August 2013
	Ljubljana, Slovenia	May 2013	October 2013
	Barcelona, Spain	May 2013	June 2013
	Stockholm, Sweden	May 2013	August 2013
	Brighton, UK	April 2013	June 2013
Respondent-Driven Sampling (RDS)	Verona, Italy	June 2013	June 2014
	Vilnius, Lithuania	June 2013	August 2014
	Bratislava, Slovakia	June 2013	August 2014
	Bucharest, Romania	February 2014	November 2014

Table 2 MSM enrolled in the Sialon II study by sampling method and city

Sampling method	City and country	Overall sample
Time-Location Sampling (TLS)	Brussels, Belgium	406
	Sofia, Bulgaria	411
	Hamburg, Germany	408
	Warsaw, Poland	408
	Lisbon, Portugal	409
	Ljubljana, Slovenia	416
	Barcelona, Spain	408
	Stockholm, Sweden	377
	Brighton, UK	418
Respondent-Driven Sampling (RDS)	Verona, Italy	400
	Vilnius, Lithuania	322
	Bratislava, Slovakia	400
	Bucharest, Romania	183
	TOTAL	4.966

In both surveys, in line with the project protocol, a unique identification number (barcode) was used in order to identify each questionnaire and to link the behavioural information with the biological data (e.g. oral fluid). This approach was used in order (i) to guarantee the privacy/anonymity of the participants and (ii) to minimise the potential for any mistakes in linking the different types of information (bio-behavioural in both TLS and RDS survey.

Time-location sampling

TLS has been used successfully in previous studies and has demonstrated to be an effective and reliable method for gathering both behavioural and biological data in 'hard-to-reach' populations [14, 15, 18–20]. Based on assumption of an HIV prevalence in the study population of at most 15 % based on results from the previous Sialon project, a precision of 5 %, a significance level of 95 % and a design effect of 2, a random clustered sample size of 392 MSM per city was calculated. Taking into account the possibility of invalid samples, a final target of n = 408 per city was planned.

With regards to venues and participants eligibility, any physical public or private locations attended by MSM could be included as venues in the universe (e.g. commercial venues such as cafés, discos/dubs, bars, sex shop, sex cinema, saunas, spas etc. as well as non-commercial venues such as cruising settings and special events). One exception were venues that specifically serve HIV positive members of the priority population, since including these types of venues would artificially increase representation of HIV positive individuals in the final sample. Virtual meeting places such as websites and smartphone apps were not included.

In order to finalise the sampling frame, once the initial list of venues or initial universe of venues was elaborated based on the findings of the formative research, MSM venues and venue-day-time (VDT) units were identified and two sampling frames constructed [19]. The first sampling frame (or venues sampling frame) comprised a list of venues that met the attendance requirements and were willing to participate (eligible venues). The second sampling frame (VDT sampling frame) comprised a list of venue-specific sampling periods of four hours each (VDT). In constructing this second frame, for each venue and for each day of the week, the VDT units were determined according to two key criteria: i) logistical feasibility and safety for data collectors; and ii) VDTs were expected to yield at least 10 eligible MSM. Consequently, at this stage some venues identified previously as being potential data collection sites were excluded due to various reasons such as low levels of attendance of eligible MSM participants, specific attendance patterns, and/or operational barriers or lack of permission by the venue owners/manager.

Where possible, in order to verify characteristics of potentially eligible VDTs, project partners and/or their collaborating partners (e.g. NGOs) interviewed the respective venue owners. This process also allowed (where necessary) the counting of MSM attending the VDT by use of a 'clicker' (Type 1 Enumeration) [21] assuming that most attendees would be eligible. In order to discern venue specific sampling periods, standardised enumerations were conducted of the MSM attending venues during possible high attendance day-time periods. The result of this process was the creation of the final VDT sampling frame. As data collection proceeded, these sampling frames were then updated on a monthly basis (e.g. where new venues may have opened, others closed, or the VDT proved to be unproductive).

Following completion of the final sampling frame, a three-stage sampling plan to select venues, VDTs, and participants was used. Based on the monthly sampling frames, a set of venues equal to the number of sampling events planned for the upcoming month were randomly selected (stage 1 of randomisation). Selected venues were then sorted in ascending order of VDTs beginning with the venue with the least number of VDTs (which is less flexible for scheduling on the calendar); one VDT was selected from this venue (stage 2 of randomisation). The VDT selected was scheduled on the calendar by choosing any available day on which the VDT falls. After this sampling event was scheduled, a VDT was selected randomly for the next venue. The process was repeated for each venue selected in first stage of randomisation. Stage 1 and 2 of randomisation were carried out in two

independent steps because if they had combined in only one step, the venues with many VDTs would have been more likely to be selected than those with fewer VDTs.

In addition to venues, each country could also select purposefully up to a maximum of three events to schedule into the sampling calendar (infrequent events to attract members of the target population e.g. gay pride), and thus were excluded from the sampling frame. As the sampling calendar was filled, if the selected VDT could not be scheduled because there were no days available in any week of the month in question, a new VDT was selected randomly from the remaining VDTs of that venue. If no VDT from that venue could be scheduled in any week of the month, then another venue was selected randomly from the set of venues not chosen in stage 1, until the sampling-event was filled. If there was no choice, overlapping VDTs were scheduled.

More VDTs than needed were scheduled as alternatives VDTs. When data collectors did not achieve the sample size in the primary venue they could go to an alternative VDT until they had reached the sample size. Alternatives VDTs were scheduled in different days and/or timetable. They also were chosen randomly to minimise selection bias. If an event was cancelled before their occurrence for some unforeseen reasons it was rescheduled, that means to change VDT in another week of the month, the same local, day and period but in another week (alternates venues were not used to replace cancelled sampling events).

Data collection was planned from between two to six months during 2013–2014 depending on the country in question. The decision of exactly when to commence was based on negotiations between the project partner and collaborating partner and informed by the findings from the FR. In the final stage three of the randomisation, eligible men were sampled at selected venues in accordance with the monthly calendar with the aim to collect data from eight men.

Respondent-driven sampling

RDS [22] was used to recruit representative samples of MSM linked to the gay community in each selected city (Verona, Vilnius, Bucharest, and Bratislava). This specific approach has been used in previous studies [23–25] targeting different sub-groups or populations (e.g.: MSM, sexual workers, IDUs) and has been shown to be a reliable method for gathering both behavioural and biological data in hidden or 'hard-to-reach' populations.

As with TLS, formative research was conducted prior to data collection in collaboration with local gay NGOs in each participating city in order to properly identify potential interview sites, incentives (amount and type of incentive), expected network size in the selected city, as well as characteristics of the network structures. According to the RDS literature, for a sample size of 400 between six to eight seeds should be selected. For the present study, five MSM seeds were selected in collaboration with the local gay NGO (NGO representatives and/or MSM recruited in gay venues were designated as seeds by the project team). A specific training session for seeds was organised in each city, where the project aims and methodology were explained, including confidentiality and other ethical issues arising.

Selected seeds were requested to identify and recruit peers from their social network. For this purpose, each seed was given three 'recruitment coupons', containing a unique identification number (barcode), address of the interview location, as well as the names and contacts of the research team. A dedicated software package was developed by the research team in order to generate and print the recruitment coupons (including the identification barcode). This software was designed specifically for generating and managing barcodes to be read using a barcode reader, in order to avoid any potential mistake in the process of code management.

A primary and a secondary incentive were delivered according to the RDS approach [26]. In order to receive the secondary incentive (an incentive for each recruited peer), each participant was required to recruit a maximum of three eligible peers, and each of the recruited peers was required to take part in the survey.

Trained health professionals were involved in the collection of the biological sample (serum) in each sites, whilst trained project staff was involved in the collection of the behavioural information (questionnaire, additional items on the network size information), as well as in the coupon distribution process.

The screener (project staff) clarified the project goals and methodology, ensuring that each participant met the eligibility requirements. Participants were also provided with a short document containing all the information related to the survey. After signing the consent form, the self-administered behavioural questionnaire was presented to the participant and on completion, pre-test counselling was provided according to local standard procedures. A biological sample was then collected by the project team following the local procedures. All biological samples were labelled with the participant's identification number and sent to the laboratory for analysis. Participants were provided with the appropriate incentive as well as with three numbered coupons (with a specific code number). Instructions on how to select members of the social network were delivered. Finally, the participant was invited to come back to pick-up the results of the tests using a card reporting his unique code. When results were given, a post-test counselling was offered according to local and WHO standards.

Laboratory testing

In line with the scientific literature [27–29], the algorithms for laboratory testing were developed taking into account both the international gold-standards for STI testing and the local laboratory procedures in each country, as well as the WHO-STI surveillance guidelines.

TLS study

HIV antibodies were tested in oral fluid samples using a non-invasive collection method. To collect oral fluid sample, saliva collection devices (ORACOL; Malvern Medical Developments, Worcester, UK) were used. After collection, oral fluid samples were kept between 4 °C and 8 °C and sent to the laboratory for HIV/AIDS in the respective countries no more than 72 hours after collection. Before testing the samples were processed according to the manufacturer's procedure.

HIV-antibody testing on the oral fluid samples was performed according to the manufacturer's instructions of GENSCREEN HIV 1/2 version 2, BIO-RAD. All HIV-reactive samples were re-tested with Vironostika HIV Ag/Ab, Biomerieux and double sample volume of oral fluid compared to serum was used for oral fluid testing (the antigen component of the test was not supposed to react if oral fluid samples are used). In the case of an HIV-reactive result in one or both tests, participants who came back for their test results were encouraged during post-test counselling to be re-tested from blood according to the algorithm for RDS study. As a quality control, for each oral fluid sample, a total IgG antibodies ELISA test Human IgG ELISA Kit 1x96, Quantitative/Immunology Consultants Laboratory was used in order to assess the sample suitability for testing. Before testing, each sample was diluted 1/250 by a recovery buffer. Samples below 3.5 titre (cut-off) were excluded from the study as being invalid.

RDS study

Serum samples collected through the RDS method were tested for HIV, HVB, HCV and Syphilis in each country by EC marked commercial diagnostic kits following usual testing guidelines. Serum samples were tested first with an HIV 4th generation ELISA test. For newly diagnosed individuals, positive results were confirmed from the second sample by a Western Blot. Participants with HIV-positive results were counselled and subsequently referred into local care systems for further management of their HIV status. HIV-positive samples were shipped to a central laboratory under refrigerated conditions for Avidity Index calculation.

In terms of STI testing, for HBV infections all samples were tested in each participating country following usual testing guidelines for HBsAg, anti-HBcAb total and anti-HBsAb testing. According to the tests results and to a detailed interpretation of the Hepatitis parameters, a prompt referral of participants to a reference centre for further management of their status was ensured. For HCV infection all samples were tested in each participating country following usual testing guidelines. Screening testing was performed with ELISA anti-HCV diagnostic kits and HCV reactive samples were confirmed using line/strip immunoassays. Participants with positive results were referred into the local care systems for further evaluation of their status. Finally, for Syphilis, collected serum samples were tested in each participating country using treponemal and non-treponemal tests. Each sample was tested by both RPR and TPHA qualitative test to assist in the interpretation of results. In the case of reactive results RPR and/or TPHA quantitative tests were performed. Participants with reactive results were referred into the local care systems for further evaluating the need for treatment.

Prevention activities

HIV and STI surveillance for both TLS and RDS have been implemented within the broader context of the Sialon II prevention activities. HIV/STI prevention and testing promotion activities are theoretically grounded in two theoretical concepts, i.e. the Minority Stress Model [30] and the Information-Motivation-Behavioural skills model (IMB) [31]. While the former multilevel model, which predicts health outcomes among minority groups such as MSM has contextual relevance, the latter targets individual, cognitive and motivational factors. The development of the prevention activities has also been informed by the formative research activities (see above). In order to ensure comparability across data collection sites, the Sialon II prevention protocols describe the different prevention and training activities for field implementation including: (i) prevention packages (comprising condoms, lubricants, and leaflets with specifically tailored information) which have been developed, designed, and distributed to the target group throughout the data collection period, and (ii) interactive peer-to-peer health education activities that took place at the end of the enrolment process (or in case the participant declined to be enrolled). These activities focused on improving knowledge and building motivation for safer-sex among the participants along the theoretical dimensions of the IMB model. On the basis of a series of multiple-choice question cards, participants exchanged information on sexual health, HIV/STI prevention and testing with data collectors/educators or seeds. In addition (or alternatively depending on the situation), HIV/STI prevention information has been offered to participants.

As a further support mechanism, a dedicated section of the Sialon II project website was developed to include HIV/STI prevention information as well as details of local voluntary counselling testing (VCT) services. In

each country, project teams consulted local NGOs with regards to appropriate 'MSM friendly' VCT sites both in the respective cities and at regional levels. This inventory informed the final selection of VCT services made available to respondents through the prevention package. Moreover, TLS data collectors/educators and RDS-seeds received a specific training session based on the Sialon II prevention manual which included information on HIV/STI prevention and testing, adaptable strategies for different situations and settings to empower participants to adopt healthy behaviours, and the role of meaningful HIV/STI surveillance and prevalence data in prevention activities [17]. For RDS, participants additionally benefited from discussing prevention issues during the pre/post-test counselling sessions at the participating study sites.

Ethical issues

In order to comply with all ethical and legal obligations, in both TLS and RDS surveys the name of the participant has not been collected. As noted earlier, a unique barcode was attached to the questionnaire and to the biological sample for each individual allowing anonymous linkage between the two kinds of information for later analysis. Finally, the result of the tests was made available to the study participants through the same barcode attached to a card given to individuals during the sample collection.

Participants enrolled in the study were asked to provide informed consent. Individuals were given the possibility to withdraw from the study at any time without explanation. In case of a confirmed positive test, participants were offered a confirmation test on a different biological sample and encouraged to get a referral to local care for further checks and treatment in line both with the international guidelines and local standard pathways of care.

In order to ensure no harm for the respondents enrolled in the Sialon II surveys and to harmonise all the data collection procedures, a specific training manual for data collectors has been developed. The coordinators were also in charge of monitoring the local data collection and coaching the data collectors during activities. On-going monitoring activities were carried out so that any potential difficulty or issue in preserving privacy and confidentiality was supervised.

The Sialon II protocols have been submitted to the relevant ethics committee in each participating city, where official approval was obtained prior to any data collection.

The ethics committee which granted approval were: Instituut voor Tropische Geneeskunde, Antwerp (Belgium); National Centre of Infectious and Parasitic Diseases, Sofia (Bulgaria); Robert Koch Institute Charite, Berlin (Germany); Azienda Ospedaliera Universitaria Integrata – Verona University Hospital (Italy); Vilniaus Regioninis Biomediciniu Tyrimu Etikos Komitetas Vilnius Medical University (Lithuania); Komisja Bioetyczna Narodowym Instytucie Zdrowia Publicznego, Warsaw (Poland); Conselho de Ética do Instituto de Higiene e Medicina Tropical, Lisbon (Portugal); Institute Matei Bals, Bucharest (Romania); Slovak Medical University, Bratislava (Slovakia); Komisija Republike Slovenije za Medicinsko Etiko, Ljubljana (Slovenia); German Trias i Puyol Hospital, Barcelona (Spain); Regionala etikprovningsnamden i Stockholm (Sweden); Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton (UK).

Parallel to this process, the protocols were first submitted to the WHO Research Project Review Panel (RP2) for the technical approval in 2012, whilst in 2013 the Research Ethics Review Committee (WHO ERC) was consulted for a special evaluation of the ethical components. The Sialon II protocols were approved both by RP2 and by WHO-ERC, thus becoming part of a WHO collaborating study in February 2013. As a consequence of this, periodical monitoring reports on the status of the survey implementation have been prepared and submitted to the WHO-ERC committee for review and approval.

Data analysis and main results

Data analysis will be carried out in line with the sampling method adopted in each study site. Data management will be carried out using DataEntry, R (v3.1.0), STATA (STATA Statistical Software Release 13, College Station, TX: StataCorp LP) and SPSS. In line with the sampling approach adopted, estimates will be weighted. For RDS, the software used for the analysis will be RDS Analyst (www.hpmrg.org), a suite of R commands developed by Mark S. Handcock, Ian E. Fellows, Krista J. Gile (2015 RDS Analyst: Software for the Analysis of Respondent-Driven, Sampling Data, Version 0.52). Data will be analysed as part of the protocol in 2015 and results will be available in 2016.

Discussion

A second generation surveillance approach to monitoring and controlling the HIV epidemic is a critical tool for state-of-the art public health. However to-date, adoption of the SGSS approach is far from systematic in terms of implementation across EU countries. Consequently, reliable, valid and comparable data on undiagnosed HIV prevalence related to sexual risk behaviour in 'hard-to-reach' populations such as MSM are lacking. This deficiency is problematic because it leaves a considerable gap in terms of the ability of European Member States to develop and implement targeted and evidence-based HIV/STI prevention strategies. In order to maximise the

benefits of SGSS approaches, European Member States need to harmonise their HIV and STI behavioural surveillance systems through the adoption of a common set of indicators in comparable SGSS studies targeting high-risk populations [5].

This paper describes the protocols of the Sialon II project, the aim of which has been the implementation of a large-scale bio-behavioural survey among MSM in Europe using a SGSS approach, as well as the carrying out of meaningful and targeted HIV/STI prevention. These project protocols offer an important contribution to the epidemiology of HIV/STIs as well as European public health more broadly. Specifically, implementation of the Sialon II protocols, which take into account the most recent GARPR indicators [11], offer a unique opportunity to pilot a large-scale bio-behavioural survey in line with the SGSS approach in a substantial number of EU countries. The Sialon II protocol and findings (that will be available on the project website as well as in additional scientific publications from 2016) are likely to contribute significantly to increasing the comparability of data in EU countries through the use of common indicators and in implementing effective public health strategies and policies in areas of high need. In addition to this, data collected through the former Sialon project and through the Sialon II survey could represent the basis for implementing additional surveys – in line with the SGSS – in order to develop trend analysis to monitor the HIV-STI epidemic over time.

Two key discrete yet linked elements of the protocols appear to be particularly valuable for the implementation of the Sialon II surveillance and prevention programme including: (i) the use of TLS and RDS methodologies to access 'hard-to-reach' MSM (sub)populations, and (ii) a project philosophy underpinned by principles of community based participation. In terms of the former, as sex between men is often highly stigmatised in many European countries, MSM can be 'hard-to-reach' which in turn, can make HIV/STI surveillance as well as prevention programmes and/or interventions particularly challenging to implement and evaluate.

In terms of limitations, the use of two different sampling strategies could represent a limitation for the study, as it has been shown in other studies that through TLS and RDS methods different segments of the total MSM population can be enrolled and this can result in different sample characteristics, and the differences may persist also after applying weighting corrections to the result estimates: this might limit the results from the Sialon II survey. However, in Sialon II protocols, the deployment of TLS and RDS methods have been particularly beneficial, as they represent the most advanced and available approaches for generating statistically representative samples from 'hidden' and most-at-risk populations (in this case MSM).

Finally, the Sialon protocols may provide a useful and feasible model for community-based organisations to conduct decentralised and de-medicalised HIV testing in the future, as such protocols were tested across highly heterogeneous settings. This approach is increasingly seen as an important strategy to increase coverage of HIV testing and to de-stigmatise and normalise HIV testing in the communities, with the aim to contain the HIV epidemic among MSM.

Conclusions

It is likely that the implementation of the Sialon II protocols will contribute to a better understanding of MSM HIV/STI prevention needs as well as the existence of gaps with respect to existing HIV/STI prevention provision. Moreover, by involving the MSM community in all aspects of the study through both the partnership itself and collaborations with local gay NGOs in the participating countries, as well as working intersectorally with public health institutions and universities, it is possible to increase the capacity of all stakeholders in using innovative sampling methods for collecting bio- behavioural data among MSM in future second generation surveys. The data collected through implementing the protocols may contribute to estimating HIV/STI prevalence and undiagnosed infections in the MSM population, as well as modelling of STI epidemic patterns, increasing comparability of data in EU countries and implementing effective public health strategies and policies in areas of high need.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LGI MMI participated in the development of the RDS component, in the conception and design of the protocol and in drafting the manuscript. LGI, MMI and ITO participated in the WHO review and thereby in the refinement and adaptation of the protocols. UMA and SDV participated in the formative research component, in the conception and design of the protocol and in drafting the manuscript. NSH participated in the conception and design of the protocol and in drafting the manuscript. MFU participated in the early stages of development of the protocols and in drafting the manuscript. MBR participated in the data collectors training component and data collection, in the early stages of development of the protocols, in the conception and design of the protocol and in drafting the manuscript. CFO and LFE participated in the TLS component, in the conception and design of the protocol and in drafting the manuscript. SKB and AMO participated in TLS statistical analysis component, the conception and design of the protocol and in drafting the manuscript. CNO and WVB participated in the prevention component, in the conception and design of the protocol and in drafting the manuscript. SDI participated in the conception and design of the protocol, in the protocols adaptation to the country specific context, in data collectors training and in drafting the manuscript. BSU and MRO participated in Syphilis and other STIs component, in the conception and design of the protocol and in drafting the manuscript. IVE, VRE, SCA and IKL participated in the conception and design of the protocol, in the protocols adaptation to the country specific context and in drafting the manuscript. DST and IAL participated in the laboratory component, in the conception and design of the protocol and in drafting the manuscript. LGI and MMI amended the final manuscript which was reviewed by all other authors. All authors read, amended and approved the final manuscript.

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From: **Massimo Mirandola** massimo.mirandola@univr.it
Subject: Lorenzo Gios / PhD by publication / Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities
Date: 18 July 2019 at 11:47
To: Nigel Sherriff N.S.Sherriff@brighton.ac.uk
Cc: Lorenzo Gios gios.lorenzo@gmail.com

Dear Prof. Sherriff,

I am writing to confirm that Lorenzo Gios greatly contributed to the paper "Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities". He significantly contributed to the conception, design, data analysis and development of the manuscript. He also reviewed and approved the final draft with substantial intellectual inputs.

Kind regards
Massimo

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Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities

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Background: HIV testing is generally accepted as being the lynchpin of a prevention strategy to tackle the HIV epidemic among MSM. However, few studies have analysed in detail the factors that influence HIV test seeking behaviour. **Methods**: The objective of this article is to analyse the relationship between HIV test seeking behaviour and individual, social and demographic factors in a sample of MSM recruited though a multi-centre bio-behavioural cross-sectional study. A multi-level analysis was conducted to identify factors associated with HIV test seeking behaviour. **Results**: A total of 2400 men were included in the sample. Age, self-reported sexual orientation, residence, household composition, educational status and perceived homonegativity all seem to impact on test seeking behaviour. **Conclusions**: The results suggest the need for more targeted testing promotion strategies among MSM that take structural and environmental factors into consideration, as part of a comprehensive public health strategy to address the HIV epidemic.

Introduction

HIV infection is one of the major public health challenges in European Countries and Men who have Sex with Men (MSM) represent the population with the highest risk of acquiring STI (sexually transmitted infections) and HIV in particular.[1].

About 30% of people living with HIV in the EU are not aware of their serum status.[2] Undiagnosed HIV infection is a probable source of a substantial number of new HIV infections. It is estimated that MSM with undiagnosed HIV infection were responsible for 3.5 times as many transmissions as MSM with diagnosed HIV infection.[3,4]

In this framework it is clear that HIV testing, early diagnosis and access to treatment are key to tackling the HIV/AIDS epidemic.[5]

Despite some practical and ethical issues related to its use at population-wide level,[6] the Treatment as Prevention approach is now considered not only an important public health tool to reduce the risk of HIV transmission but also to improve the quality of life of HIV-positive individuals.[7] In addition, a proper antiretroviral therapeutic regime reduces the viral loads and consequently can play a crucial role in the epidemic reducing the likelihood of HIV transmission. In fact, awareness of the HIV-positive status is crucial for reducing risk behaviours and, consequently, for reducing the probability of transmitting the HIV infection.[8,9] Expanding HIV testing is not only meant to increase the proportion of HIV-positive people who know they are infected but also to give them a better life expectancy .[10,11]

The HIV test seeking behaviour, as a component of health seeking behaviour,[12] is conceived as the active search of an individual to be tested in order to know his/her serological status. This attitude is influenced by both individual and structural factors.[13] Despite the fact that MSM tend to test more frequently compared with the general population, the levels of testing among MSM (and bisexual in particular) remain persistently low in many countries when considering the high HIV prevalence within this group. Some studies have shown gay men with undiagnosed infection are not tested regularly or delay HIV testing, are afraid of receiving a positive result, and have low-risk perceptions despite reporting HIV-related sexual risk behaviours and STI infection.[14] Despite some relevant available data, a deeper understanding of undiagnosed infections and test seeking behaviours determinants is needed, especially among sub-populations of MSM.

This article explores the relationship between HIV test seeking behaviour and individual, social and demographic factors in a sample of MSM, aiming to provide researchers, policy makers and public health stakeholders with key insights into testing patterns in such a high-risk population.

Methods

Study design

This paper is based on data collected through the EU-funded SIALON project.[15] The project consisted of a multi-centre biological and behavioural cross-sectional survey targeting MSM, implemented in six cities: Barcelona, Spain; Bratislava, Slovakia; Bucharest, Romania; Ljubljana, Slovenia; Prague, Czech Republic; Verona, Italy. The cities were selected on the basis of geographical regional representativity (Southern and Central-Eastern Europe), the lack of reliable existing data and budget considerations.

The recruitment of the male participants was carried out according to the following inclusion criteria: having had sex (any kind of sex) at least once with another man during the year previous

to the study; having signed a written informed consent form; having agreed to answer the study questionnaire; having accepted to donate an oral fluid sample.

The following exclusion criteria were adopted: being younger than 18-years old; being an active injecting drug user and having already participated in the survey.

In each participating country, research protocols were approved by local Ethics Committees.

Sampling

Time-location sampling (TLS) was used to recruit quasi-representative samples of men visiting the gay scene in each city.[16]

The sample size estimation for a HIV prevalence study has been calculated on the basis of previous studies,[17] when available. In particular, an HIV prevalence of 5% was assumed for Central and Eastern EU countries, whilst 15% was assumed as a common prevalence for Southern European countries.

Data collection

Prior to data collection, a specific formative research of the venues was conducted for each city in order to identify the list of potential venues and related Venue-Day-Time (VDT) units. VDT units were divided into two categories, according to the median attendance: 'high' and 'low' attendance (15 and 5 enrolled MSM, respectively).

According to the category of venues (disco, bar, sauna, cruising setting and naked party/sexy shop), the VDT units were randomly selected from the sampling frame and homogeneity between the venues was guaranteed.

A period of two months was scheduled for data collection during which time trained field workers from local gay associations distributed anonymous self-administered questionnaires, oral fluid collection kits and prevention materials.

Questionnaire

Informed consent was obtained and a self-administered pen-and-paper questionnaire was used to gather information on the social-cultural context, access and barriers to voluntary counselling and testing centres (VCT), behavioural practices, STI history and self-reported serum-status (as per GARPR guidelines).[18] The perceived social attitude towards homosexual/bisexual men was measured by an 'homonegativity' scale.

Dependent variable and predictors

The dependent variable has two modalities: the first represents the respondents tested at least once in their life; the second represents the respondents who never tested. Respondents were asked about their testing practice and history. When previous testing was reported, data on the year of the last HIV test together with the test result was also collected.

The participants' age was evaluated and included as a predictor in the multivariable models. Variables explored in terms of factors associated with the dependent variable include education level (none; primary; secondary; university; other), location of residence (countryside: <1000 inhab.; village: 1000–10 000; small town: 10 000–100 000; City: >100 000), composition of household (alone; with a partner: man or woman; with family/wife and children; with friends; with parents/relatives), self-reported sexual identity (homosex; bisex; hetero; other), being reached by prevention programmes (as per the UNGASS-GARPR definition). The perceived social attitude towards homosexual/bisexual men, as measured by a 3 item- 'homonegativity scale for micro-level where higher scores indicate a respondents' positive perception of people's attitude towards MSM in family, school and friends was also considered.

Data analysis

A total of 2400 persons (about 400 per city) were included in the study.

In line with the objective of the article, that is to analyse the relationship between HIV test seeking behaviour and individual, social and demographical factors, a 95% CI was calculated for each variable. A bivariate variable analysis was performed using Pearson Chi^2 tests for categorical variables and Kolmogorov-Smirnov test for equality of distribution functions or Kruskal-Wallis equality-of-populations rank test chi-squared for ordinal and continuous variables.

A multivariable multi-level logistic random-intercept model was estimated.[19] The multi-level analysis was conducted to identify factors associated with HIV test seeking behaviour studying the contribution of variability associated with each level to the total variability in the sample. This procedure takes into account the hierarchical structure of the data collected by cities.

Due to the non-independent nature of the data, univariate multilevel logistic random-intercept regression models were used to identify which predictors were significantly associated ($P < 0.05$) with the outcome variable.

Significant predictors identified from the univariate models were analysed for multicollinearity by using a pairwise deletion correlation matrix with Bonferroni correction.

Model assumptions were examined by using the likelihood-ratio test. Last, odds ratios and their associated 95% CI were then calculated and reported.

To take the sampling procedure into consideration, a random intercept model and two random coefficient models were performed.

The reason for adding the coefficient models is based on the hypothesis that the marginal efect of the covariates varies across the clusters.

STATA Statistical Software Release 13 was used (College Station, TX: StataCorp LP).

Results

A total of 2400 men were included in the sample: 407 in Prague, 393 in Bratislava, 400 in Barcelona, 398 in Bucharest, 398 in Ljubljana and 404 in Verona. Table 1 presents the variables distributions by city. The age distribution was not similar across the cities (K-W = 400.584, df 5, $P < 0.05$).

With regards to education, the percentages of men with a university degree ranged from 27.39% in Prague to 53.59% in Barcelona. In terms of composition of household, 69.39% of the respondents in Prague declared they were living alone or with a male partner; the lowest proportion of MSM living alone or with a male partner was calculated for Bucharest (47.33%). More than 60% of participants from all cities reported they are living in metropolitan areas (city with more than 100 000 inhabitants), with the sole exception of Verona (41.94%).

The highest percentages of respondents self-identified as homosexual are reported in Verona, Bratislava and Barcelona (90.25, 85.38 and 84.89%, respectively). The highest proportions of respondents who self-identified as bisexuals were reported in Eastern European cities such as Bucharest (31.44%).

In terms of testing, the number of MSM who declared to have never been tested in their life is quite high in Bratislava (40.60%), whilst low percentages are reported in Verona (16.18%) and Barcelona (14.55%).

As regards to being reached by HIV prevention programmes (e.g. free condom distribution), there were considerable differences across the study cities. More than three out of four MSM enrolled in the study had received condoms for free (89.17% in Barcelona). Low percentages of free condom distribution are reported in Prague (65.62%) and in Bratislava (42.71%).

Table 1 Socio-demographic characteristics of the samples

Predictor	Barcelona	Bratislava	Bucharest	Ljubljana	Prague	Verona
Age						
Mean (SD)	38.17 (10.22)	30.24 (8.97)	26.29 (6.59)	31.12 (8.27)	29.25 (8.30)	35.81 (10.29)
Median	38	28.5	25	29.5	28	35
Education						
Primary	11.28	3.61	11.36	3.78	9.04	9.66
Secondary	35.13	56.19	57.39	55.16	63.57	52.74
University	53.59	40.21	31.25	41.06	27.39	37.60
Living alone or with a male partner	56.28	57.91	47.33	60.30	69.39	52.74
Living in a metropolitan area	80.15	64.19	82.86	64.36	73.54	41.94
Sexual orientation: gay/homosexual	84.89	85.38	68.56	85.24	74.29	90.25
Reached with HIV prevention programme (condom)	89.17	42.71	81.47	87.63	65.62	75.19
HIV testing						
Never tested	14.55	40.60	36.07	27.39	32.32	16.18
Perceived positive social attitude towards Homo-bisexual men						
Mean (SD)	10.53 (2.43)	10.40 (2.24)	8.94 (2.48)	10.42 (2.45)	10.55 (2.28)	9.88 (2.35)
Median	11	10	9	10	11	10

Table 2 Multi-level multivariate models

	Model 0		Random intercept model		Random coeffident model		Random coefficient model	
					Sex orientation		Sex orientation and age	
Predictor	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value
Fixed part								
Age	1.06 (1.04–1.07)	<0.05	1.04 (1.03–1.06)	<0.05	1.04 1.03–(1.07)	<0.05	1.05 (1.03–1.07)	<0.05
Education: university degree	1.30 (1.01–1.64)	<0.05	1.31 (1.03–1.68)	<0.05	1.32 (1.03–1.70)	<0.05	1.32 (1.03–1.69)	<0.05
Living alone or with a male partner	1.52 (1.21–1.91)	<0.05	1.64 (1.30–2.08)	<0.05	1.63 (1.29–2.06)	<0.05	1.62 (1.28–2.06)	<0.05
Living in a metropolitan area	1.75 (1.40–2.21)	<0.05	1.90 (1.49–2.43)	<0.05	1.94 (1.52–2.48)	<0.05	1.96 (1.53–2.52)	<0.05
Sexual orientation: gay/homosexual	1.85 (1.40–2.44)	<0.05	1.73 (1.31–2.31)	<0.05	1.73 (1.30–2.30)	<0.05	1.78 (1.08–2.92)	<0.05
Reached with HIV prevention programme (condom)	1.82 (1.44–2.30)	<0.05	1.59 (1.24–2.06)	<0.05	1.59 (1.23–2.05)	<0.05	1.54 (1.19–1.99)	<0.05
Perceived positive social attitude towards Homo-bisexual men	1.06 (1.02–1.12)	<0.05	1.07 (1.02–1.12)	<0.05	1.07 (1.02–1.13)	<0.05	1.07 (1.02–1.13)	<0.05
Random part								
$\sigma 1^2$ city level			0.10	0.07	0.25	0.28	0. 22	0.31
$\sigma 2^2$ sex orient. at city level					0.13	0.16	0.24	0.22
$\sigma 3^2$ age at city level							0.003	<0.05
Loglikelihood	−981.3754		−972.460		−970.869		−968.971	

CIs in brackets.

The perceived social attitude towards homosexual/bisexual men, as measured by a three item-'homonegativity' scale (Cronbach's alpha = 0.66) shows a significant variation across the cities, with a higher positive perception in Barcelona and Prague (Mdn 11) as compared with Verona, Bratislava and Ljubljana[10] and Bucharest.[9]

Results from the multivariate models are presented in table 2. The baseline model (model 0) includes the socio-demographic factor (age) and the individual-level factors found to be associated with test seeking behaviour variable used in bivariate analyses. The likelihood-ratio test which compares models fitted by maximum likelihood, confirms that the random intercept model provides a better fit compared with the ordinary logistic model ($\chi^2 = 17.83$; $P \leq 0.05$).

The first multilevel model is a random intercept model, which includes the socio-demographic factor (age) and the individual-level factors found to be associated with test seeking behaviour variable used in bivariate analyses and controlled for the contextual city level.

In addition two random coefficient models are added to the previous model, including the sexual orientation effect at city level and the age random coefficient at city level (final model).

The final model reveals that variations exist in the mean effect of the predictors over the response variable. The variation is significant at all hierarchical levels. Moreover, the intercept has significant random effects at cluster level and this suggests that a multilevel analysis better describes the association between the dependent variables and the predictors.

The likelihood ratio test performed among the three multilevel models suggests that the final model (Random Coefficient Model with variance for sexual orientation at city level and variance for age at city level) provides a better fitting compared with the previous ones in representing the model assumptions.

All predictors identified in the model are positive. When describing all factors separately, for MSM living in a metropolitan area the odds ratio for test seeking is 1.96 ($P < 0.05$) compared with those living in small cities, showing a significant association. Living alone or with a male partner shows a significant positive effect associated with the dependent variable (OR = 1.64; $P < 0.05$). MSM self-identifying as homosexual are more likely to seek an HIV test, when compared with the participants who defined their sexual orientation as heterosexual or bisexual (OR = 1.77; $P < 0.05$). Being reached by HIV prevention programmes was also significantly associated with an increased odds of seeking an HIV test in the sample (OR = 1.53; $P < 0.05$). MSM reporting a university degree are more likely to seek an HIV test (OR = 1.31; $P < 0.05$), compared with participants who reported a basic educational status (primary or secondary).

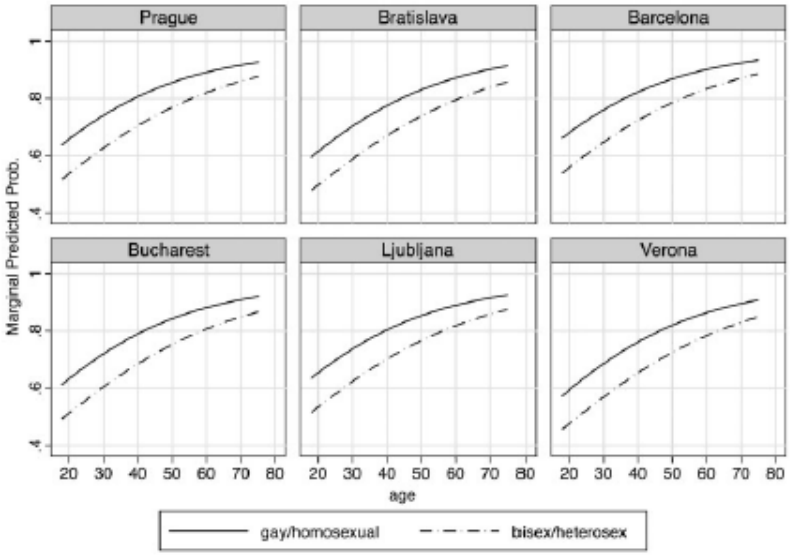

Figure 1 Plots of marginal predicted probabilities of test seeking behaviour by city and sexual orientation

The perceived social attitude towards homosexual/bisexual men, as measured by a three item-'homonegativity' scale for micro-level where higher scores indicate a respondents' positive perception of people's attitude towards MSM in family, school and friends, was found to be significantly associated with test seeking behaviour (OR = 1.07; $P < 0.05$).

Finally, age is an obvious predictor (OR = 1.01) and for this reason it is included in the model. The model predicts an increase of test seeking behaviour with the increase of age (1% OR for each year).

Figure 1 represents the marginal predicted probabilities of test seeking behaviour plotted against the age of respondents and sexual orientation among the six cities. The graph shows that overall men self-identifying as gay/homosexual are more likely to seek an HIV test when compared with those self-identifying as bisexual or heterosexual. The same pattern can be identified when considering the intra-city differences: a span of ~15 years of age separates self-identified homosexual/gay MSM from those self-identifying as bisexual/heterosexual.

Discussion

Some specific limitations should be clarified. With the exception of the laboratory testing results, the data consist of self-reported information, which can be subject to inaccuracy. Items specifically focusing on the perception of low risk for HIV-infection are not included in the study. Previous surveys have shown that risk perception can play an important role in facilitating test seeking behaviour.[20]

Furthermore, the sampling methods adopted could have had an impact on the representativeness of the MSM sample in some study sites. When few venues were present in a specific study site, some places could have been overvisited by data collectors in order to collect the target sample and hence potentially disturbing the attendees and reducing the acceptance of the data collection. In addition, in line with the TLS method, different ways of recruiting (e.g. Internet) have not been taken into account. Finally, considering the specific contexts and the characteristics of the gay communities in the selected cities, the results might be generalised with caution.

Despite these constraints, the data provide relevant inputs for better understanding factors associated with test seeking.

Test seeking behaviour seems to vary across cities and the association between place of residence and test seeking is one of the most relevant findings of the study. Especially in some cities, residence of the metropolitan areas could potentially have access to a greater number of HIV testing services, along with relatively greater anonymity when compared with residents of smaller areas. Metropolitan areas could represent an environment where less stigma is attached to sexual orientation and where there is an increased possibility of being part of supportive gay community.

Being reached by specific HIV prevention programmes also represents an important factor in facilitating health seeking behaviours. This result seems to confirm the positive effect of prevention campaigns targeting this at-risk population.

Sexual identity seems to have an impact across all cities in terms of test seeking behaviour: men identifying as gay/homosexual are more likely to seek an HIV test compared with those identifying as bisexual or heterosexual. Such associations are in line with other studies.[21] In addition, data show that factors such as a perceived positive social attitude towards homo-bisexual men and self-identification of homosexuality may facilitate test seeking behaviours.

MSM with a low educational status seem also to be less likely to seek an HIV test, in line with other scientific findings.[22]

When considering the intra-city differences, a span of ~15 years of age separates self-identified homosexual/gay MSM from those self-identifying as bisexual/heterosexual. For example, in Verona a 20-year old MSM who identifies himself as gay/homosexual has the same probability of being tested as a 35 year old bisexual/heterosexual MSM. This calls for targeted testing promotion campaigns for this specific population, in order to reduce the 15 years' time-span and related risk exposure.

When describing potential clustering of different factors, results suggest that the environmental conditions, including place of residence and exposure to prevention programmes, could play a crucial role in facilitating test seeking.

Moreover, other factors that could be considered as a bridge between individual and environmental aspects are positively

associated with test seeking, namely, having a perceived positive social attitude towards homo-bisexual men and living alone or with a male partner. In the latter case, this could be due to the fact that MSM living alone or with a male partner could be more independent, perceive less stigma or live within a steady primary relationship. Such aspects can support interpersonal skills and promote a sense of self-efficacy, strongly linked with health seeking behaviours.[23]

There is no association between the number of partners and the dependent variable, whilst this association was found in previous studies.[24]

In general, these findings seem to confirm the importance of structural factors such as prevention programmes and levels of social stigma, which may represent an enabling factor for HIV/STI testing among MSM.[25]

Data suggest that special attention should be paid to specific sub-populations, such as younger men and bisexual men, as they seem to show lower levels of test seeking behaviours. This may be related also to sexual identity. Indeed, other studies have confirmed that bisexual men and younger men may have additional fears related to disclosure of their sexual orientation, and this is associated with lower levels of health seeking behaviours.[26] In addition, the model shows that in any case one MSM in ten will be never tested for HIV, reinforcing the need for further enlarging the proportion of MSM who will receive an HIV test.

The results provide important information on the barriers and facilitators to test seeking which could help in designing more efficient testing promotion campaigns. The findings related to educational status could indicate the need for information campaigns targeting disadvantaged communities. Furthermore, findings related to sexual identity and perceived homonegativity suggest that any specific measures to address low testing uptake should be complemented by broader actions addressing stigma and discrimination toward MSM.

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Conflicts of interest: None declared.

Key points

- Most marginalized sub-populations, such as lower educated, young and bisexual MSM are less likely to seek a HIV test when compared with their counterparts.
- Findings related to the role of residency on test seeking behaviour point to the need to identify solutions for promoting testing uptake in non-metropolitan areas.
- The confirmation of the positive effects of prevention programmes would seem to suggest the importance of continued implementation and intensification of such interventions.
- Results suggest that any specific measures to address low testing uptake should be complemented by broader actions addressing stigma and discrimination toward MSM.

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courier
60 College Street
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Dear Nigel,

I am writing to you in relation to the paper "Socio-demographic Characteristics, Sexual and Test-Seeking Behaviours Amongst Men Who have Sex with Both Men and Women: Results from a Bio-behavioural Survey in 13 European Cities", based on the EU-funded Sialon II project.

I confirm that Lorenzo Gios made an important contribution to this paper. He was particularly involved in its conception and design, as well as in the data analysis component. He also made a significant contribution to the paper finalization, providing relevant intellectual inputs.

Sincerely,

John E. Pachankis

John Pachankis, Ph.D.
Associate Professor
Social and Behavioral Sciences
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AIDS Behav
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ORIGINAL PAPER

Socio-demographic Characteristics, Sexual and Test-Seeking Behaviours Amongst Men Who have Sex with Both Men and Women: Results from a Bio-behavioural Survey in 13 European Cities

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Abstract Within the MSM population, men who have sex with both men and women (MSMW) are identified as a high-risk group both worldwide and in Europe. In a multi-centred bio-behavioural cross-sectional study, we aimed to assess the relationship(s) between socio-demographic factors, stigma, sexual behavioural patterns, test seeking behaviour and sero-status amongst MSMW. A multi-level analysis was conducted to identify factors associated with being MSMW versus Men who have Sex with Men Only (MSMO). A total of 4901 MSM were enrolled across the 13 study sites. Participants were categorised as MSMW in the 12.64% of the cases. Factors such as educational status, perceived homonegativity, testing facilities knowledge and HIV testing lifetime seem to be relevant factors when characterising the MSMW group. The results highlight the vulnerability of MSMW and the wide spectrum of risky behavioural and psycho-social patterns, particularly in terms of HIV testing, 'outness', and perceived stigma.

Resumen Los Hombres que tienen Sexo con Hombres y Mujeres (HSHM) son un grupo de población de alto riesgo dentro de los HSH. Evaluar la relación entre factores socio-demográficos, estigma, patrones de conducta sexual y de búsqueda de la prueba y el estado serológico de los HSHM. Estudio bio-conductual multicéntrico transversal. Análisis multinivel para identificar factores asociados con ser HSHM respecto a los Hombres que Sólo tienen Sexo con Hombres. Se reclutaron 4.901 HSH en 13 ciudades, siendo un 12,64% HSHM. El nivel educativo, la homonegatividad

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percibida, el conocimiento de los lugares de realización de la prueba y la prueba del VIH alguna vez son factores relevantes para caracterizar los HSHM. Los resultados subrayan la vulnerabilidad de los HSHM y la diversidad de conductas y patrones psicosociales de riesgo, particularmente en términos de la prueba del VIH, visibilidad de la identidad sexual y estigma percibido.

Keywords MSMW · Risk behaviours · HIV · Time–location sampling · Respondent-driven sampling

Background

Despite concerted public health efforts, the HIV epidemic is still expanding in many countries especially amongst MSM communities [1]. Although there are many factors both individual and structural that are likely to impact on this dynamic, one of the most relevant facilitating factors is the high number of UAI partners amongst the MSM population [2, 3].

Within the MSM population, bisexual males or men who have sex with both men and women (MSMW, also referred to as behaviourally bisexual men) are identified as a high-risk group both worldwide and in Europe [4–6]. This is because MSMW represent a sub-group with both behavioural and psycho-social vulnerabilities [7, 8] compared to men who have sex with men only (MSMO).

Psychosocial factors can play a crucial role in determining MSMW vulnerability, particularly in terms of risk behaviour, and for these reasons this sub-population can be identified as a priority population for targeted HIV and STI prevention interventions [9, 10].

In addition, and from a purely epidemiological perspective, arguably MSMW may also represent a critical priority group because of their potential "bridging role" for STIs and HIV; a view that has been expressed previously in a number of studies [11–13]. A better understanding of the behavioural patterns of this population may therefore represent a key factor for reducing the potential transmission of HIV and other STIs within the target population and also to women, who are less likely to acquire STIs compared to MSMO [5].

In terms of behavioural risk patterns, some studies suggest that there is a lower prevalence of HIV infection amongst MSMW compared to those reporting only sex with men, on the basis that MSMW seem to be more likely to use a condom with male partners and less likely to engage in receptive anal sex compared to MSMO [14–17]. On the contrary however, other more recent studies have found that MSMW are more likely to be infected with HIV compared with both heterosexual men and MSMO [7]. Furthermore, it has been reported that MSMW who are in a relationship with a female partner are more likely to have unprotected sex with male and female partners and consequently, are also more likely to acquire STIs [7, 18].

Due to such behavioural risk patterns, HIV testing practices represent a crucial factor for MSMW. Indeed, current evidence shows that MSMW are less likely to seek HIV testing compared to MSMO [19, 20]. Further research is therefore needed to understand better and assess not only the patterns of attitudes concerning health seeking behaviours such as HIV testing, but also the entire risk-behaviour spectrum amongst this specific population [21].

Disclosure of sexual orientation may represent another potential risk factor for HIV-related behaviours with particular relevance to bisexual men, even compared to gay men [22]. Non-disclosure of sexual orientation amongst MSMW has been attributed to high levels of perceived stigma, as well as certain legal, cultural, and social norms [22]. Such barriers to disclosure have been argued to drive MSMW underground and place them out of reach of HIV-preventative services, knowledges, and behaviours, thereby increasing their risk for HIV infection [23, 24].

Despite a number of studies in the literature focusing on MSMW, this group nevertheless continues to represent a hard-to-reach and relatively unknown sub-population within the MSM community for two main reasons. First, the different categorisations of MSMW that have been proposed and used in previous studies, mean that it is difficult to gain reliable and valid surveillance data for this population. Second, the different sampling approaches that have been adopted to then enrol these MSMW (categorised in diverse ways) to epidemiological surveys means that data are not necessarily always comparable.

In terms of MSMW categorisation, public health research on HIV/STI and sexual health amongst bisexual men has relied traditionally on behavioural and identity-related definitions to assess this population. Yet, defining bisexuality purely on the basis of self-identity can lead to a misclassification if the actual behaviour is not considered [9]. Furthermore, a definition of bisexuality based purely on actual behaviour can lead to an underestimation of those who self-identify as bisexual but who have not had sex with a male/female partner over the period of time investigated by a survey methodology. Therefore in some studies, a combination of the two definitions or categorisations (behavioural-based or identity-based) has been used [25].

Linked to MSMW categorisation, in terms of sampling approaches and subsequent recruitment, behaviourally bisexual men represent a difficult target population to reach because they might not necessarily identify as being members of the gay or bisexual community and therefore may arguably be less likely to participate in research studies or surveys targeting MSM. Consequently, two

sampling methodologies currently defined as the 'gold-standard' for conducting bio-behavioural surveys targeting hard-to-reach population such as MSM have been advocated including venue based methods such as time and location sampling, (TLS), and network-based approaches such as respondent-driven sampling (RDS). Indeed, previous studies have demonstrated that TLS and RDS are effective in recruiting diverse samples of MSM (sub)populations [4, 26]. The strengths of these sampling methodologies lie in: (i) the possibility of recruiting participants who are present in the study area (whether they identify themselves as members of the gay or bisexual community or not) and; (ii) the possibility to enrol participants whom might not be in contact with health and/or other social care services, therefore providing researchers with a unique snapshot of the current community(ies) of MSM in the given study area relative to other sampling approaches.

Sialon II

The Sialon II project co-funded by the European Commission under the Second Programme of Community Action in the Field of Health (2008–2013), was a multi-centre biological and behavioural cross-sectional survey carried out across 13 European cities including: Brussels (Belgium), Sofia (Bulgaria), Hamburg (Germany), Verona (Italy), Vilnius (Lithuania), Warsaw (Poland), Lisbon (Portugal), Bucharest (Romania), Bratislava (Slovakia), Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden), and Brighton (UK).

The project brought together governmental and non-governmental experiences and perspectives from groups ranging from the European Union, ECDC, the WHO, and UNAIDS to local public health institutions, universities, and gay associations. The project also built on the experiences gained through the previously conducted EU-funded Sialon I study [3]. In Sialon II, the adoption of TLS and RDS meant that the project was able to recruit diverse sub-populations of MSM in the study cities including MSMW, but also MSM who inject drugs, MSM sex workers, MSM immigrants, and MSM tourists.

The purpose of this paper is to assess the relation between socio-demographic factors (such as area of residence, educational status), stigma (perceived stigma, level of 'outness'), sexual behavioural patterns (number and type of partners and sexual practice), health care service utilisation and test seeking behaviour, as well as sero-status amongst behaviourally identified MSMW, in order to be able to identify factors associated with being MSMW versus MSMO. The aim is to provide a better understanding of the factors associated with health-relevant behavioural patterns, with particular reference to HIV test-seeking behaviour amongst this specific sub-group. Based on previous research, we hypothesise that MSMW will be less open about their sexual orientation and will perceive higher levels of stigma compared to MSMO [22, 24]. We assume that MSMW's sexual behavioural patterns will differ significantly from those of MSMO, including higher levels of non-steady male partners [27], lower levels of testing [19], and poorer knowledge of testing facilities compared to MSMO [19]. We also assume that age may play a significant role in characterising MSMW compared to MSMO: the probability of having sex with men and women might decrease with increasing age, probably due to a potential 'stabilisation' of sexual identity or sexual preferences (even if this phenomenon represents a controversial issue within the scientific community) [28].

Due to the unique sample from which the present analysis are based upon, and because of the distinctive characteristics of the Sialon II survey (i.e., TLS and RDS methodologies, common protocols, and testing algorithms), results presented in this paper may offer unique insights for more effective prevention campaigns tailored to MSMW, with the aim of both tackling the HIV epidemic amongst male partners and reducing the potential for transmission to female partners [29–31].

Methods

Study Design

Sialon II was a multi-centre biological and behavioural cross-sectional survey carried out across 13 European cities. Detailed study procedures as well as bio-behavioural data collection and testing methodologies have been presented elsewhere [26].

Study Population

Participants were individuals present in the study cities at the moment of data collection who met the following inclusion criteria: having had any kind of sex with another man during the previous 12 months before the enrolment; agreeing to participate in the study, and; agreeing to donate either an oral fluid or blood specimen.

Enrolment

Time–location sampling (TLS) and respondent driven sampling (RDS) were used to recruit study participants. According to the methodology for carrying out surveys using these sampling approaches [32, 33], preliminary formative research was conducted in each survey site prior to data collection taking place. Formative research comprised activities to assess: (i) prevention needs of local

MSM populations including an overview of local (e.g., NGO) experiences in prevention activities and behavioural and/or biological data collection in the study sites; (ii) age-groups to be considered in the survey implementation (using data and information from previous studies where possible); (iii) availability of commercial venues and/or cruising settings in light of TLS survey implementation; (iv) social networks/seeds and appropriateness of incentive strategies in light of RDS survey implementation; (v) existence and levels of HIV testing services; (vi) levels of stigma and general data regarding the MSM population for the given study area (i.e., desk-based research using data and information from previous studies where possible).

The Sialon II survey was implemented using the same methodology (i.e., protocols, laboratory algorithms etc.) in each of the 13 study sites [26]. A total of 5200 participants (target number 400 per city) were planned to be enrolled in the survey.

Instruments

Questionnaire

A self-administered pen-and-paper questionnaire was used to collect behavioural data from respondents. The preliminary version of the questionnaire (designed by the Sialon II network in line with the GARPR indicators [1] and previous EC-funded European projects), was piloted amongst MSM in each study site. The English version of the questionnaire was then translated into the languages of the participating cities and back translated into English.

Laboratory Testing of Biological Samples

In cities where the TLS method was used, HIV antibodies were tested in oral fluid (OF) samples using GEN-SCREEN HIV 1/2 version 2, BIO-RAD. As a quality control for testing suitability of the samples, a total IgG antibodies ELISA test Human IgG ELISA Kit 1 × 96, Quantitative/Immunology Consultants Laboratory was used. All HIV-reactive samples were re-tested with Vironostika HIV Ag/Ab, Biomerieux. In cities where the RDS method was used, blood samples were collected and processed in a clinical setting (e.g., hospital, infectious disease department etc.) according to the local contextual procedures, and serum was extracted according to the local laboratory standard procedure(s). Serum samples were tested with a HIV 4th generation ELISA/CLIA test. Reactive results were confirmed with a Western Blot test. In line with the protocols, participants with HIV-positive results were provided with post-test counselling and referred subsequently to the local care systems for further management of their HIV status.

Ethics

Prior to data collection, research protocols were submitted to, and approved by, an appropriate institutional ethical review board in each participating city, as well as by the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC) during 2012–2013. A dedicated bar-code system was adopted in order to link anonymously the different types of data collected from participants (i.e., behavioural data and biological samples) as well as guarantee the anonymity and confidentiality of the respondents' data. For the TLS survey, respondents who wanted to collect their tests results could do so using their unique bar code ID. For the RDS survey where respondents were tested directly in a hospital/clinical setting, test results were available according to the local standards (including pre and post-test counselling).

Variables Definition

Dependent Variable

In this study, participants were identified as either behaviourally MSMW or MSMO based on their self-reported sexual behaviours during the last 6 months with male and/or female partners (steady and/or non-steady). Despite the limitations mentioned previously of a purely behaviourally based definition, this was the only possible way to define it with regards to the core survey questions common to both study arms (TLS-RDS).

Independent Variables

Independent variables in this study included: age (based on self-reported year of birth), educational status (secondary school or lower, high school or post-secondary, or university/higher), 'outness' (the extent to which participants reported being open about their sexual attraction towards men with others based on a five point item ranging from 1 "out to no-one" to 5 "out to all or almost all"; further categorised as "some, most or all" vs. "none or few"), origin (migrant/immigrant or visitor vs. native-born in the study country), type of partners (steady/non-steady), sexual practice (based on the self-reported sexual behaviours in the last 6 months, no anal intercourse, anal intercourse, unprotected anal intercourse), testing facility knowledge (knowing where to go for HIV testing), HIV testing (lifetime and in the last 12 months), STI testing in the last

12 months, being reached by prevention programmes in the last 12 months (condom distribution), and HIV status based on laboratory testing. Finally, perceived stigma towards gay/bisexual people was assessed using a 5-point likert scale ranging from 1 (very negative) to 5 (very positive) regarding respondents' perceptions of homophobia, through the question "In your experience, what is most people's attitude towards gays or bisexuals in the following contexts?" across three domains: (1) work/school; (2) parents, and; (3) friends/acquaintances (Cronbach's alpha 0.73). The scale's range varied from a minimum of 3 to a maximum of 15 points (from negative to positive experiences). A reversed scoring system was used for a more intuitive interpretation.

Data Analysis

Descriptive and Bivariate Analysis

For quantitative variables, mean, median, standard deviation, Wilcoxon–Mann–Whitney test and Kruskal–Wallis test by ranks were used. For nominal variables, percentages and Fisher's exact test were used. Bivariate analyses were carried out using a multivariate logistic model with $p < 0.05$ as the threshold for variable inclusion.

Multi-level Modelling

In order to account for the hierarchical structure of the data collected by city and the consequent clustering of observations within a city, a multivariable multi-level logistic random-intercept model was estimated [34]. The multi-level analysis was conducted to identify factors associated with being MSMW versus MSMO as defined by self-reported behaviours. Predictors associated with the outcome variable with a probability <0.05 were considered significant. STATA Version 14.2 was used for all analyses (College Station, TX: StataCorp LP).

Results

Sialon II Study Sample

A total of 4901 MSM were enrolled across the 13 study sites. TLS was used in Brussels, Sofia, Hamburg, Warsaw, Lisbon, Ljubljana, Barcelona, Stockholm, and Brighton, whilst RDS was used in Bratislava, Bucharest, Verona, and Vilnius. Table 1 presents the number of participants enrolled in the study by city, the number of valid questionnaires, and the number of oral fluid samples collected and tested. In countries where TLS was used, 3596 participants were enrolled, whilst in countries where RDS was used 1305 were enrolled. A comprehensive description of the study sample is available in the Sialon II bio-behavioural survey technical report [4].

Characteristics of the MSMW Sample

Participants were categorised as behaviourally bisexual men (MSMW) in 589 cases (12.64% of the total sample). The mean age for this sub-population was not statistically different from the MSMO sub-sample (Table 2).

In terms of residence area, similar patterns were recorded both for MSMW and MSMO, whilst when considering education MSMW were significantly less likely to hold a university degree or higher (47.44%), compared to MSMO (56.79%) ($p < 0.05$).

In terms of 'outness', that is the extent to which participants are open about their sexual attraction to men with others, there was a substantial difference between the two groups ($p < 0.05$). MSMW reported being significantly less 'out' (39.46% for the category "some, most or all") compared to MSMO (75.08%).

In terms of origin, the number of survey participants who reported having been born in the city in which they were recruited was significantly lower amongst MSMW compared to MSMO ($p < 0.05$).

When considering the type of sexual partners, MSMW reported a relatively higher number of non-steady sexual partners ($p = 0.05$) and occasions in which they had had unprotected anal intercourse in the last 6 months compared to MSMO ($p < 0.05$).

Knowledge of testing facilities showed a significant variation between those classified as MSMW (87.89%) compared to MSMO (94.74%) ($p < 0.05$). A similar pattern was also apparent for lifetime HIV testing ($p < 0.05$).

In terms of prevention programmes (i.e., being reached by prevention programmes such as free condom distribution in the last 12 months), parallel patterns were recorded for the two groups. MSMW indicated that they were reached by prevention programmes in 58.80% of cases, whilst 63.55% of MSMO reported this ($p = 0.4$). However, MSMW were less likely than MSMO to report testing for STIs (other than HIV) in the last 12 months ($p < 0.05$). A similar pattern was also observed when considering HIV testing over the last 12 months. 50.97% of MSMW were tested for HIV in the previous 12 months compared to 57.96% of MSMO ($p < 0.05$).

Regarding biologically-measured HIV sero-status, there was no significant difference regarding odds of infection between the two groups ($p = 0.14$): MSMW 8.92% versus MSMO (10.86%). Finally, in terms of respondents' perceived stigma towards gay/bisexual people, MSMW reported a significantly higher perception of stigma than MSMO.

Table 1 Number of valid and invalid questionnaires and valid samples collected in the Sialon II survey

	Questionnaires collected	Valid questionnaires	% Invalid questionnaires	Valid samples collected
Barcelona	408	402	1.5	400
Bratislava	400	400	0	400
Brighton	418	411	1.7	402
Brussels	406	391	3.7	379
Bucharest	183	183	0	183
Hamburg	408	407	0.2	390
Lisbon	409	408	0.2	371
Ljubljana	416	394	5.3	347
Sofia	411	411	0	361
Stockholm	377	366	2.9	356
Verona	400	400	0	400
Vilnius	322	322	0	322
		406		
Warsaw	408		0.5	405

Characterising MSMW (Multilevel Multivariate Model)

Results from the multivariate model are shown in Table 3. Not all predictors initially identified through the bivariate analyses and included in the model were significantly associated with the dependent variable, namely being MSMW. The final estimated model based on a random intercept at city level, resulted as the best possible one. In fact, the inclusion of random slopes for other predictors did not provide any additional improvement of the model.

Area of residence did not play a significant role in differentiating MSMW from MSMO nor did participants' education or origin (being a migrant, immigrant or visitor vs. being native-born in the study country) ($p > 0.05$). In addition, being reached by prevention programmes and testing behaviours in the last 12 months (HIV and STI testing), as well as HIV status based on laboratory testing—which were statistically significant ($p < 0.05$) when considered separately—were not significantly associated with the dependent variable once included in the model.

In contrast, being 'out' regarding sexual attraction to other men represented a significant factor in differentiating between the two groups. Participants who only reported being 'out' with "none or few" people, were nearly four times as likely to report having practised sex with both women and men (OR 3.60; $p < 0.05$) compared to those who reported being 'out' to "most or all". This indicates that MSMW were less open about their own sexual orientation compared to MSMO.

In terms of sexual partners, MSMW were also more likely to report sexual relations with non-steady partners in the last 6 months (OR 1.65; $p < 0.05$). Considering the type of sexual practice adopted in the 6 months before the enrolment period, MSMW were more likely to report UAI with men (OR 0.44; $p < 0.05$) compared to MSMO.

Being knowledgeable about testing facilities was significantly associated with a reduced odds of being MSMW (OR 0.63; $p < 0.05$), suggesting that MSMO were better informed regarding services providing voluntary counselling and testing (VCT) compared to MSMW.

The multilevel multivariate model showed lower odds of being MSMW when predicting from "at least once lifetime HIV testing" versus never having been tested (OR 0.69; $p < 0.05$). This suggests that MSMW were less likely than MSMO to have tested for HIV when considering lifetime HIV testing history.

Participants perceiving a friendlier environment (less stigma) for gay and bisexual people were more likely to be MSMO than MSMW. The score of people's attitude on the gay/bisexual scale was positively associated with being MSMW with an OR of 1.11 ($p < 0.05$) showing that the higher the negative perception the higher the odds of having sex with both men and women. The predicted probability of reporting sex with both men and women increased as perceived stigma increased; however, when we combined the effect of the perceived stigma and 'outness', the model predicted different marginal probabilities as shown in Fig. 1. The predicted probability of having sex with both men and women, increases independently with an increase in negative attitude perception; however when the variable of being 'out' or not is included, the increase in the number of men declaring MSMW increases steeply.

Finally, with regards to age, the model showed a decrease in the odds of being MSMW (OR 0.99; $p < 0.05$) as age increased, meaning that MSMW were more likely to be younger than MSMO.

Table 2 Percent of MSM with various characteristics, by sexual identification (bivariate analysis)

Characteristic	MSMW ($n = 589$)		MSMO ($n = 4069$)		p value
Age					0.11
Mean	32.55		34.44		
Median	31		32		
SD	10.72		11.11		
Area of residence					0.10
Outside the study city	164	28.23%	1104	27.37%	
In the study city	417	71.77%	2929	72.63%	
Educational status					0.00
High school or lower	298	52.56%	1724	43.21%	
Degree or higher	269	47.44%	2266	56.79%	
Out-ness					0.00
Some, most or all	219	39.46%	2968	75.08%	
None or few	336	60.54%	985	24.92%	
Origin					0.01
Foreigner	107	18.23%	686	16.91%	
Native-born	480	81.77%	3371	83.09%	
Non-steady partners	452	88.45%	3.126	84.46%	0.05
Sexual practice					
No anal intercourse	157	26.66%	594	14.60%	
Anal intercourse	134	22.75%	988	24.28%	0.00
Unprotected anal intercourse	298	50.59%	2487	61.12%	0.00
Testing facilities knowledge	501	87.89%	3745	94.74%	0.00
HIV testing (lifetime)	351	65.36%	2941	79.06%	0.00
Being reached by prevention programmes (condom distribution) in the last 12 months	334	58.80%	2516	63.55%	0.40
STI testing in the last 12 months	254	43.87%	2010	50.81%	0.03
HIV test in the last 12 months	288	50.97%	2258	57.96%	0.01
HIV status (lab based)	51	8.92%	425	10.86%	0.14
LGB stigma perception					0.00
Mean	8.99		7.63		
Median	9		8		
SD	2.62		2.49		

Discussion

This study offers a valuable characterisation of MSMW which can usefully inform preventative actions targeting this relatively sizeable sub-group of the sexual minority population [22, 23]. Furthermore, the use of up-to-date sampling methodologies for bio-behavioural surveys (TLS-RDS) provides further strength to the study results in reaching the MSM population subgroups (particularly with RDS), therefore overcoming some of the most relevant limitations in previous studies targeting this specific group.

According to our findings, MSMW appear to be characterised by a low level of 'outness', that is, they tend to be less open with family, friends, and co-workers about their own sexual attraction compared to MSMO. Although this finding has been reported in other studies, it should be noted that such studies were in some cases targeting MSMW from specific ethnic minority groups, such as bisexual black men in the US [7, 35, 36], whereas data on MSMW from a large multi-site bio-behavioural survey implemented in European sites are lacking.

Considering information on testing facilities, MSMW report less knowledge of HIV testing services compared to MSMO [37]. This result is in line with recent research which documents that MSMW have an increased vulnerability that can potentially lead to a higher risk of infection [29]. This could partially be related to the 'stigma' perceived by MSMW who do not consider themselves part of gay or bisexual communities, and which may therefore not only reduce the likelihood of such MSMW from being

Table 3 Multilevel multivariate model

Dependent variable: being MSMW versus MSMO	OR	95% CI		*P*
Fixed part				
Area of residence				
Out-side the study city	1			
Study city	0.90	0.70	1.16	0.43
Educational status				
Secondary school (high school) or lower	1			
University or higher	0.80	0.63	1.03	0.08
Out-ness				
Some, most or all	1			
None or few	3.60	2.79	4.65	0.00
Origin				
Emigrant/immigrant or visitor	1			
Native-born	0.80	0.58	1.10	0.17
Non-steady partner				
No	1			
Yes	1.65	1.14	2.38	0.01
Sexual practice				
No anal intercourse	1			
Anal intercourse	0.51	0.36	0.73	0.00
Unprotected anal intercourse	0.44	0.32	0.60	0.00
Testing facility knowledge				
No	1			
Yes	0.63	0.43	0.93	0.02
HIV testing (lifetime)				
Never tested	1			
Tested at least once	0.69	0.49	0.97	0.04
Being reached by prevention programmes (condom distribution) in the last 12 months				
No	1			
Yes	1.07	0.83	1.37	0.60
STI testing in the last 12 months				
No	1			
Yes	0.94	0.67	1.32	0.71
HIV testing in the last 12 months				
No	1			
Yes	1.29	0.88	1.89	0.19
HIV status (lab based)				
Non-reactive	1			
Reactive	1.00	0.66	1.50	0.99
LGB stigma perception	1.11	1.05	1.16	0.00
Age	0.99	0.98	1.00	0.04
Const.	0.15	0.07	0.35	0.00
Random part				
City				
σ^2	0.08	0.02	0.31	

LR test = 6.80, $p \geq 0.05$

exposed to information on testing facilities (thus reducing HIV/STI testing uptake) but may also lead to MSMW to perceive themselves as being at a lower risk of acquiring HIV/STIs compared to MSMO [38].

In terms of testing, the model shows that participants who tested at least once for HIV in their lifetime were less likely to be MSMW than MSMO. Linking to the previous point of MSMW possibly not perceiving themselves as being 'at-risk, this result is in line with the findings from previous studies [9, 29] and may have potential critical impacts in terms of HIV positivity knowledge and a resulting bridging effect. Results on types of sexual partners seem to confirm this risk, also taking into account the fact that MSMW are more prone to report sexual encounters with non-steady partners compared to MSMO: this association has been confirmed in the present analysis as well as in other publications [25].

When considering sexual practices, our findings indicate that MSMW are less likely to engage in UAI compared to MSMO. This finding represents the core output of this analysis, considering the current debate on this matter. In fact, some studies confirm the relatively low level of UAI amongst the MSMW compared to MSMO [14–17, 39], where they are reported as engaging in less risky behaviour [7, 18]. In addition, the model clearly indicates a decrease in the odds of practicing sex with both men and women with an increase in age that can perhaps partially be related to the 'stabilisation' of sexual preferences.

Taking into account the associations with perceived stigma towards gay/bisexual individuals, MSMW in the present sample seem to perceive a more stigmatising environment, which might increase reluctance to disclose sexual orientation and thus impact on access to testing facilities [19].

The results of the present study have important implications for MSMWs' health and prevention actions as they show the importance of stigma as negative factor for disclosing sexual orientation and/or sexual identity; a key factor for communicating with both types of partners (male/female) such as assessing risk and, discussing possible risk-reduction strategies. Indeed these findings are in line with the broader research evidence which suggests disclosure of sexual orientation by MSMW to their male and female partners may facilitate negotiations concerning risk-reduction [27]. Specific programmes tailored to MSMW promoting HIV prevention and encouraging regular HIV testing amongst this target group, may therefore be necessary in contributing to the reduction of HIV acquisition and onward transmission. Particularly when delivering sexuality-related counselling, as one of the critical interventions to promote well-being through increasing self-esteem, self-regulation and self-efficacy [40–42], these factors should be considered carefully. In

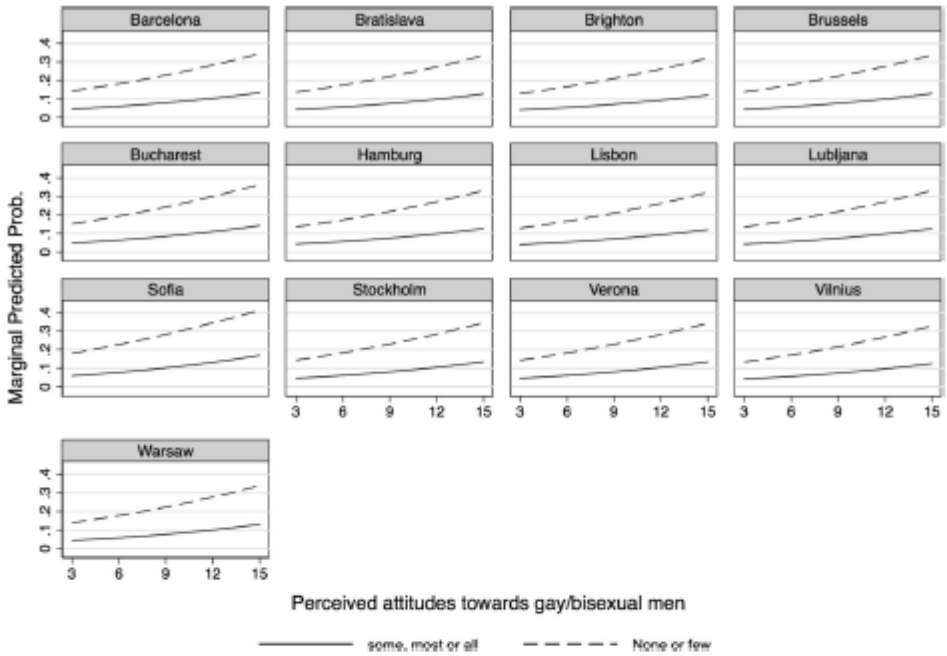

Fig. 1 Plots of marginal predicted probabilities of MSMW and perceived people's attitude on gay/bisexual scale by out-ness and city

the case of counselling offered to MSMW, particular attention should be paid to multiple partnerships and related communication/disclosures.

Bearing in mind that the social environment contributes greatly to shaping individual behaviours, an additional implication relates to the so-called macro level, that is, a 'double-stigma' from both gay and heterosexual communities [43]. The fact that MSMW seem to be less open regarding their sexual orientation compared to MSMO could potentially be due to and/or lead to such possible 'double-stigma' [9]. Consequently, a high level of experienced psychosocial vulnerability (e.g., lower levels of perceived social support from both members of the gay and heterosexual communities in general) could also be expected in this specific population [9]. Therefore it seems extremely important to identify specific contextual actions that ultimately can lead to the promotion of better social contexts for MSM in general and MSMW in particular. This might represent a crucial factor when considering the global health of MSMW, as low levels of perceived social support from family and friends generally lead to negative effects on physical and mental health [44]. This lack of perceived support from a community or a social group might be particularly relevant for MSMW, as they may not identify themselves as members of either heterosexual or gay communities [45]. Therefore, promoting settings and socio-cultural environments that are not only gay-friendly, but also open to a multifaceted range of sexual identities and orientations might be a key factor in promoting well-being and sexual health also amongst MSMW.

Notwithstanding the strengths of the Sialon II survey, namely the use of the gold- standard methodologies for bio-behavioural data collection amongst hard to reach populations and the characteristics of the overall survey sample, results must be interpreted in light of certain limitations.

Excluding the data related to laboratory testing and that obtained through automated procedures, information collected via self-administered pen-and-paper questionnaires is subject to recall bias, especially for recall of specific sexual practices.

In terms of sampling methodology, despite the fact that both TLS and RDS represent the current state-of-the-art approaches to implementing bio-behavioural studies targeting hard-to-reach populations such as MSM, the sampling methods adopted could have had an impact on the representativeness of the sample in the study sites. Moreover, web-based recruitment methods have not been taken into account, with the potential underrepresentation of a sub-population of MSM relying only on web and mobile phone 'Apps' for sexual encounters.

The generalisability of the findings may be limited by contextual factors (such as legislation/local policy, social norms) not included or measured in this survey, which characterise the gay communities in the selected study cites.

In addition, participants were identified as behaviourally MSMW or MSMO using their self-reported sexual behaviour during the last 6 months with male or female partners (steady and/or non-steady), rather than referring to the self-reported sexual identity or sexual orientation.

An additional limitation could be the lack of sexual identity/sexual orientation items investigated in the survey. Sexual self-identity can be extremely informative [23], as it might be influenced by contextual factors (e.g., stigma, self-disclosure) [13] and therefore provide indirect information of unobserved factors influencing individual behaviour.

The results presented in this article can not only inform actions and prevention campaigns in the surveyed cities, but considering the different geographical areas of Europe, they may also be useful for the broader European context. To our knowledge, Sialon II is the only multi-site integrated bio-behavioural survey of its kind to have been implemented in the EU, and the results presented here therefore can add to an increasing body of research focusing on MSMW, especially for the European area.

Conclusions

Over the years, a sometimes limited focus on MSMW characterisation has been reported in epidemiological research. This lacuna could be due partially to the fact that the bisexuality definition and psycho-social and behavioural implications seem to represent a critical issue from a theoretical viewpoint [46], and also because of a greater emphasis on analysing the potential bridging effect rather than on profiling the MSMW population in itself with its specific health needs [25].

These survey results corroborate insights from other studies [7, 9], highlighting the elevated vulnerability of MSMW and the wide spectrum of potentially risky behavioural and psycho-social patterns, particularly in terms of HIV testing, 'outness', and perceived stigma.

Addressing the distinctive spectrum of MSMW's sexual health needs and characteristics appears to be both quite challenging and urgent from a public health perspective. Promoting sexual health and preventing risky behaviours, such as low levels of HIV testing, with purposefully designed campaigns might prevent severe consequences both for the MSMW group in itself and for other subpopulations, such as female partners of MSMW [7].

Further research is needed to understand better the behavioural patterns and prevention needs of this specific population, as well as disclosure dynamics, clarifying in particular (i) the behavioural and psychological patterns which characterise MSMW, (ii) the unique mental concerns reported by MSMW compared to MSMO, and (ii) the relation between mental health and stigmatising contexts at the macro level as well as personal determinants of risk including sexual behaviour and test seeking [47].

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Author's Contribution MMI, LGI, NSH, ITO, LFE, SDI, IVE, DST, SCA, ENA participated in the design of the survey questionnaire and the organisation and implementation of the survey in the survey cities. This analysis was conceived by MMI and LGI. Data were analysed by MMI and LGI. The first manuscript draft was jointly written by MMI and LGI. All authors (MMI, LGI, NSH, JPA, ITO, LFE, SDI, IVE, DST, SCA, MNI, ENA) contributed writing to the following drafts. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Prior to data collection, research protocols were submitted to, and approved by, an appropriate institutional ethical review board in each participating city, as well as by the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC) during 2012–2013.

Informed Consent According to the study protocol procedures, informed consent was obtained from all individual participants included in the study.

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Teymur Noori

From: Teymur Noori
Sent: 18 July 2019 11:32
To: N.S.Sherriff@brighton.ac.uk
Cc: Lorenzo Gios
Subject: Lorenzo Gios / PhD by publication / Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey

Dear Nigel,

I am writing you to confirm that Lorenzo Gios provided a key contribution to the paper mentioned in the subject of this email. He significantly contributed to the concept of the manuscript, to the data analysis and development of the first draft. He also significantly contributed to the paper improvement and finalisation, adding relevant theoretical elements and implications of the results described in the paper.

The paper, based on the Sialon II project and published in Eurosurveillance in 2018, represents an invaluable contribution to the knowledge on the HIV epidemic among MSM in Europe.

Please do not hesitate to contact me should you have any further questions.

Warmest regards,
Teymur

22/9/19

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RESEARCH ARTICLE

Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey

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Introduction: The HIV epidemic represents an important public health issue in Europe particularly among men who have sex with men (MSM). Global AIDS Monitoring indicators (GAM) have been widely and jointly promoted as a set of crucial standardised items to be adopted for monitoring and responding to the epidemic. **Methods:** The Sialon II study, implemented in 13 European cities (2013-14), was a complex multicentre integrated bio-behavioural cross-sectional survey targeted at MSM, with a concomitant collection of behavioural and biological (oral fluid or blood specimens) data. Rigorous sampling approaches for hard-to-reach populations were used (time-location sampling and respondent-driven sampling) and GAM indicators were calculated; sampling frames were adapted to allow weighted estimates of GAM indicators. **Results:** 4,901 MSM were enrolled. HIV prevalence estimates ranged from 2.4% in Stockholm to 18.0% in Bucharest. When exploring city-level correlations between GAM indicators, prevention campaigns significantly correlated with levels of condom use and level of HIV testing among MSM. **Conclusion:** The Sialon II project has made an important contribution to the monitoring and evaluation of the HIV epidemic across Europe, integrating the use of GAM indicators within a second generation HIV surveillance systems approach and in participatory collaboration with MSM communities. It influenced the harmonisation of European data collection procedures and indicators via GAM country reporting and contributed essential knowledge informing the development and implementation of strategic, evidence-based HIV prevention campaigns for MSM.

Introduction

The HIV epidemic represents an important public health issue in Europe, particularly among men who have sex with men (MSM). For example, across the entire European Region, one new HIV diagnosis case in every four is attributable to MSM. Moreover, in 15

Table 1

Definitions for numerators and denominators

GAM	Nominator	Denominator
1.11 (Prevention programme)	Number of MSM who replied 'yes' to both questions related to the prevention programmes as per GAM guidelines (knowledge of HIV testing services and condoms received in the last 12 months in the context of broad prevention campaigns – outreach service)	Total number of MSM who participated in the survey
1.12 (Condom use)	Number of MSM who reported that a condom was used the last time they had anal sex	Number of MSM who reported having had anal sex with a male partner in the last 6 months
13 (HIV testing)	Number of MSM who reported having been tested for HIV during the last 12 months and who knew their results	Number of MSM included in the sample
1.14 (HIV prevalence)	Number of MSM with a reactive HIV test (based on laboratory results)	Number of MSM tested for HIV in the context of the survey

GAM: Global AIDS Monitoring indicators; MSM: men who have sex with men.

EU/EEA countries (Austria, Croatia, Cyprus, Czech Republic, Germany, Greece, Hungary, Ireland, Malta, Netherlands, Poland, Slovakia, Slovenia, Spain and the United Kingdom), MSM accounted for roughly 50% of all new HIV cases [1,2]. According to the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO), the 2014 HIV prevalence among MSM aged 25 years or younger is 2.9%, while for MSM older than 25 years, it is estimated to be 7.7%. Thirty-four percent of HIV cases attributed to sex between men are usually diagnosed before the age of 30 [1,3].

While over the last few years there has been a general increase in new HIV infections among MSM in the EU/EEA, among young MSM the increase has been particularly noticeable [4]. Indeed, the number of MSM aged 20–24 years newly diagnosed with HIV almost doubled between 2004 and 2013, while in MSM aged 30–39 years old there seems to be a relative stabilisation of new cases [1]. To reverse these trends, there is a need for strategic, large-scale comprehensive and complementary prevention measures such as increased HIV and Sexually Transmitted Infections (STIs) testing, condom promotion, access to pre-exposure prophylaxis (PrEP) and early treatment initiations [2].

The picture is arguably even more problematic in some Eastern European and Central Asian countries where, although the HIV epidemic among this population is often similar, the existence of relatively more stigmatising environment(s) are probably less conducive to the reporting of data that could potentially deepen the understanding of mechanisms of HIV transmission among MSM [5].

In order to target prevention strategies effectively and to monitor their impact at a local/regional and country level, a better understanding of the epidemiological patterns and identification of the most affected subpopulations, are key enabling factors in tackling the multifaceted HIV epidemic. In Europe this particularly relates to MSM and there is a clear need for a harmonised collection of reliable and comparable data on epidemiology and coverage of prevention measures in this population.

Consequently, international agencies (namely, the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO and ECDC) have called for countries to use robust surveillance and monitoring systems that adopt common and standardised indicators [6]. A key part of this international effort for harmonisation is the promotion and implementation of second generation HIV surveillance systems (SGSS), which collect and link biological and behavioural data [6]. The Global AIDS Monitoring indicators (GAM) are part of the SGSS and comprise a set of standardised items widely and jointly promoted by the WHO and UNAIDS [7,8].

However, despite concerted efforts by these international agencies, the implementation of such a methodological approach is patchy and requires both adoption and strengthening across countries [8]. Although country reporting to the UNAIDS GAM has improved consistently over the years, to date there remains considerable variability in response rates [8].

A recent review of the GAM reporting process has highlighted a lack of data relating to key populations. For example, in 2012, GAM data on key populations were reported in approximately only 30% of cases [9].

A standardised set of GAM indicators is crucial given their role in providing specific data and information to monitor the implementation of the Sustainable Development Goals (SDG) and the UNAIDS 90–90–90 strategy, recently endorsed by the European Commission (EC) Communication on 'Next steps for a sustainable European future' [10]. The EC has co-funded several projects in the area of HIV/AIDS, two of which have aimed specifically to implement a joint survey across different EU/EEA countries adopting the main principles of SGSS and the GAM approach as

Table 2

Enrolment method, mean age, age group, by city, European Union cities (n = 13)

City	Recruitment type	Mean age (range)	Age group in years (GAM disaggregation)		Total
			< 25	25 +	
Barcelona	TLS	37.2 (19–79)	42	360	402
Brighton	TLS	35.1 (18–74)	67	344	411
Brussels	TLS	34.9 (18–68)	50	341	391
Hamburg	TLS	38.0 (18–79)	39	368	407
Lisbon	TLS	37.9 (19–76)	35	373	408
Ljubljana	TLS	30.5 (18–73)	121	273	394
Sofia	TLS	29.6 (18–58)	115	296	411
Stockholm	TLS	31.7 (18–81)	77	289	366
Warsaw	TLS	28.8 (18–71)	92	314	406
Bratislava	RDS	30.3 (18–62)	118	282	400
Bucharest	RDS	30.8 (19–58)	47	134	181
Verona	RDS	31.9 (18–70)	104	293	397
Vilnius	RDS	30.7 (19–59)	83	239	322

GAM: Global AIDS Monitoring Indicators; RDS: Respondent-Driven Sampling; TLS: Time-Location.
Cities presented with white background: TLS survey. Cities presented with light blue background: RDS survey.

cornerstones. The two projects are the Sialon project [11] and the more recent Sialon II project [12,13]. In particular, in the Sialon II project a total of 13 countries with very different cultural and social environments with 30 institutions including public health institutions and non-governmental organisations (NGOs) were involved. The meaningful participation of Lesbian-Gay-Bisexual-Trans-plus (LGBT +) communities in all participating countries has been key in designing and implementing the study.

The value of the Sialon II project lays in the sampling approach (Time-Location Sampling (TLS) and Respondent-Driven Sampling (RDS)) and the use of GAM indicators. The methodology adopted allowed the weighted estimation of GAM indicators, presented in this manuscript. To our knowledge, this is the first paper delivering weighted estimates for GAM indicators in a large number of European cities set within the framework of a SGSS specifically targeting MSM.

The objectives of this paper are to present weighted estimates of the GAM indicators among MSM based on the Sialon II bio-behavioural survey implemented in 13 European cities (2013-14) and to discuss the usefulness of these GAM indicators in monitoring the HIV epidemic and responses across EU countries.

Methods

Detailed descriptions of the study procedures and methods have been published elsewhere [12]. Here we present a short overview of the main methodological aspects.

Study design

The Sialon II study was a complex multi-centre integrated bio-behavioural cross-sectional survey with a concomitant collection of behavioural data and biological data (oral fluid or blood specimens).

Setting

The survey was implemented in 13 European cities. The decision to use TLS or RDS in each study site was based on preliminary formative research and organisational issues. TLS was adopted in nine cities: Brussels (Belgium), Sofia (Bulgaria), Hamburg (Germany), Warsaw (Poland), Lisbon (Portugal), Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden) and Brighton (United Kingdom (UK)). The setting for data collection included social and/or commercial venues and cruising settings preliminarily identified through formative research [14] and then selected randomly for data collection sampling calendars. RDS was used in four cities: Verona (Italy), Vilnius (Lithuania), Bucharest (Romania) and Bratislava (Slovakia). Regarding the latter, enrolment was based on the individuals' social network and for the data collection locally accredited healthcare facilities (e.g. a hospital) were used. Data collection for all sites took place from April 2013 to November 2014.

Sample size

The sample size estimation was carried out based on the results from the former Sialon I project and other available studies [11]. Based on assumptions of HIV prevalence in the target population of at most 15%, a precision of 5%, a significance level of 95% and a design effect of 2.0 provided a random clustered sample size calculation of 392 MSM per study site. Taking into account the possibility of invalid samples, a final

target of 408 MSM per city for TLS and 400 for RDS was planned.

Participants

Inclusion criteria were having had any kind of sex with another man during the previous year before enrolment, providing informed consent and agreeing to donate either an oral fluid (TLS) or blood specimen (RDS).

The exclusion criteria were being younger than the legal age of consent (18 years old) or having already participated in the study.

Data sources/measurement

Behavioural data

Behavioural data were collected through a pen-and-paper self-administered questionnaire. Core items were developed in line with the GAM indicators [7]. To allow for sampling weight calculations, additional items were included in the questionnaires on the venues attendance (TLS) or on network size (RDS).

Biological data

Biological specimens were obtained from participants of both study arms (TLS/RDS). In cities where TLS was used, specimens were tested for HIV antibodies using Genscreen HIV 1/2 version 2, Bio-Rad (Marne la Roquette, France). A total IgG antibodies ELISA test Human IgG ELISA Kit 1x96, Quantitative/Immunology Consultants Laboratory was also used for oral fluid (OF) sample testing suitability and quality control. All HIV-reactive samples were re-tested with Vironostika HIV Ag/Ab, Biomerieux (Marcy-l'Étoile, France). Samples reactive to the first ELISA HIV test, but negative to the second, were classified as negative.

In cities where RDS was used, blood specimens were collected and processed for serum extraction according to the respective national guidelines for safety and quality assurance. Serum samples were tested with a HIV fourth generation ELISA/CLIA screening test. A Western Blot test was used to confirm the positive cases.

Variables

The variables used for the present analysis included the GAM indicators suggested for MSM target population [15]. All proposed items included in the GAM guidelines for MSM were used in the survey questionnaire. Numerators and denominators were defined as seen in Table 1.

Statistical methods

The analysis was carried out according to the GAM indicator guidelines [15]. For all indicators, estimates were carried out with the following age disaggregation: < 25 years old and ≥ 25 years old. Age was calculated on the basis of the self-reported year of birth. Analyses were conducted using STATA Version 14.1 (StataCorp, College Station, Texas, United States). To allow calculation of the sampling weights, a specific procedure was devised on the basis of previous publications and methodological guidelines [12,16,17].

For the TLS survey, individual weights were assigned as the inverse of the product of the following: (i) the probability of the participant being at the sampled venue given he was at the sampled venue type (number of visits to sampled venue/number of visits to all types of venues); (ii) the length of the sampling time (out of all Venue-Day-Time units on the particular day) and (iii) the proportion of sampled individuals during the event in relation to the estimated number of visitors during the sampling event, a modification of the method proposed by Karon and Wejnert [17].

For the RDS survey, and in line with a RDS approach [18], weighted estimates were calculated using RDS Analyst (www.hpmrg.org), a suite of R commands developed by Handcock and colleagues (2015 RDS Analyst: Software for the Analysis of Respondent-Driven, Sampling Data, Version 0.52). Gile's Sequential Sampler approach was used for calculating the sampling weights. This approach is based on the inclusion probabilities of members of the sample which are based on reported network sizes [16]. This method is recommended when the sample is a significant fraction of the target population. Therefore, in order to use this method, population size estimates were carried out for each city. The calculation was based on the total number of inhabitants for the city area and the expected percentage of MSM (according to the consensus among the project's scientists and according to the scientific literature, given there is currently no comprehensive and precise agreement among experts on MSM population size estimations within the general population) [19,20]. All point estimates were reported with their respective sample size, 95% Confidence Intervals (CI), and estimated design effect.

Ethics

All procedures adopted in the present study were in line with the 1964 Helsinki declaration and its amendments. Survey protocols were approved by the appropriate ethics committee in each participating city as well as by both the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC). The name or any other identifier of the MSM enrolled in the study was not collected. All respondents were entitled to collect their test result at a nominated centre indicated to the participant during study enrolment. In case of a positive result, further testing, counselling, clinical follow up and ARV treatment were provided in line with the respective national guidelines.

Results

A total of 4,901 MSM were enrolled across the 13 participating cities. In TLS study sites, 3,596 participants were enrolled, while in RDS sites a total of 1,305 participants were enrolled. Participants enrolled per

enrolment method/city, age mean, Min-Max, age group, are shown in Table 2. A detailed description of the sample is available in the Sialon II project report [13].

GAM 1.11 (Prevention programmes)

In eight of the nine cities where TLS was implemented, more than half of respondents answered positively to both questions (Table 3, GAM 1.11). The sole exception was Warsaw where 28.8% (95% CI: 23.3–34.3) of the participants had been reached by a prevention programme. Where RDS was implemented, less than half of the MSM answered yes to both the GAM questions, except for the older participants (≥ 25 years) in Bucharest (50.7%; 95% CI: 38.4–62.9) and young MSM (< 25 years) in Vilnius (58.3%; 95% CI: 43.4–72.3).

The highest percentages of MSM reporting to be reached with an HIV prevention programme in the last 12 months were reported in Sofia and Hamburg (88.4%; 95% CI: 82.9–94.1 and 81.4%; 95% CI: 77.6–85.1 respectively). In Bratislava and Warsaw, the lowest proportions of MSM participating in the survey had been reached by an HIV prevention programme (22.6%; 95% CI: 17.0–26.8 and 28.8%; 95% CI: 23.3–34.3, respectively).

In all cities (except Brighton, Hamburg and Lisbon), older participants (≥ 25 years) had been reached more over the last 12 months than the younger participants (< 25 years), although differences between these age categories were small in most cities.

GAM 1.12 (Condom use)

Condom use according to the GAM definition, ranged from 45.2% (95% CI: 38.1–51.4) in Bratislava to 69.6% in Lisbon (95% CI: 64.5–74.3) (Table 3). With the exception of a few sites (Bratislava, Bucharest, Lisbon, Verona and Warsaw) condom use was higher for the young MSM category (< 25 years). Among older MSM (≥ 25 years), estimates of condom use varied between 46.7% in Bratislava (95% CI: 38.5–54.8) to 72.0% in Lisbon (95% CI: 65.2–77.9). It should be noted that for some cities, the number of participants in the younger age group was low and therefore the precision of the estimates is reduced.

GAM 1.13 (HIV testing)

The level of HIV testing as per GAM guidelines is reported in Table 3. The highest proportions of participants (total) reporting having received an HIV test within the last 12 months and who also knew the result of that test, were reported in Brussels (68.1%; 95% CI: 56.4–79.8) and Barcelona (63.0%; 95% CI: 52.6–73.4). In Lisbon only 21.1% (95% CI: 12.5–29.8) of younger men reported a HIV test with the collection of the test result in the last year, which represented the lowest levels in the study. The second lowest estimate after Lisbon was found in Bratislava with 29.0% (95% CI: 19.1–39.0) followed by Brighton 36.1% (95% CI: 22.7–49.6) and Bucharest 39.0 (95% CI: 21.8–56.2). In several cities there were significant differences between age groups with regard to receiving an HIV test within the last 12 months and knowing the results. Participants from Brussels, Lisbon, and Warsaw reported differences greater than 20% for the two age groups.

GAM 1.14 (HIV prevalence)

HIV prevalence was calculated based on the oral fluid-based laboratory testing for TLS and from serum-based laboratory tests for RDS. HIV prevalence estimates varied by city with the lowest level reported in Stockholm (2.4%; 95% CI: 1.1–5.2) and the highest level in Bucharest (18.0%; 95% CI: 9.1–27.0) (Table 3). Five cities had an HIV prevalence between 10–20% (Brussels, Barcelona, Lisbon, Brighton, Bucharest), three cities between 5–10% (Hamburg, Warsaw, Verona), and five cities below 5% (Stockholm, Vilnius, Ljubljana, Bratislava and Sofia).

City-level correlations between GAM indicators

When exploring city-level correlations between GAM indicators (Figure) a significant correlation was found between prevention programmes indicator (defined as condom availability and testing site knowledge) and HIV testing (correlation coefficient 0.52, p-value = 0.006). In addition, a correlation was found between preventive programmes indicator and condom use (correlation coefficient 0.45, p-value = 0.022). Data suggest that the higher the prevention programmes indicator the higher the level of condom use and testing among MSM, in both age groups.

Discussion

HIV remains a public health priority in the EU and the data from the Sialon II study has made an important contribution to the monitoring and evaluation of the HIV epidemic across Europe, by integrating the use of GAM indicators within a second generation HIV surveillance systems approach and in participatory collaboration with MSM communities. It has influenced the harmonisation of European data collection procedures and indicators via GAM country reporting and contributed essential knowledge informing the development and implementation of strategic, evidence-based HIV prevention campaigns for MSM.

The percentage of MSM reached with prevention programmes (as measured by GAM 1.11) showed significant differences both between and within cities. Although the use of different sampling methods can partially explain some of the differences between RDS vs TLS cities, the comparison among cities surveyed with the same sampling methodology provides valid indications on MSM prevention needs. In Warsaw, the number of individuals reached with prevention programmes is generally low, particularly for younger MSM. With the exception of Brighton, Hamburg, Lisbon and Vilnius, older MSM seem to be reached more frequently compared with younger MSM. Cities surveyed using RDS present, in general, a lower number of MSM reached with prevention programmes, and with the exception of Vilnius (where a specific programme was

Table 3a

GAM indicators (weighted estimates) among MSM, design effect and number of participants, by city and age group, European Union cities (n = 13)

City	Age group< 25				Age group 25 +				Total			
	Sample size	Point estimate	95% CI	Estimated design effect	Sample Size	Point estimate	95% CI	Estimated design effect	Sample size	Point estimate	95% CI	Estimated design effect
GAM 1.11 (Prevention programmes)												
Barcelona	40	59.0	39.2–78.8	1.7	352	74.9	70.7–79.2	0.9	392	72.7	68.4–77.0	0.9
Brighton	63	64.0	43.8–84.1	2.8	328	54.5	39.8–69.2	7.5	391	56.3	45.3–67.2	4.9
Brussels	47	49.1	18.0–80.2	4.6	324	64.4	55.1–73.7	3.2	371	62.1	51.9–72.3	4.2
Hamburg	37	84.3	69.8–98.7	1.5	357	81.0	76.6–85.4	1.2	394	81.4	77.6–85.1	1.0
Lisbon	35	79.9	63.9–95.9	1.4	364	64.4	51.2–77.6	7.2	399	66.0	52.7–79.3	8.2
Ljubljana	119	48.6	38.8–58.3	1.2	265	50.9	44.4–57.4	1.1	384	50.4	44.4–56.4	1.4
Sofia	112	84.7	79.7–89.7	0.6	291	89.7	81.9–97.6	5.1	403	88.4	82.9–94.1	3.2
Stockholm	61	72.7	51.6–93.7	3.5	245	78.0	70.1–85.9	2.3	306	76.6	66.8–86.3	4.2
Warsaw	91	25.5	13.0–38.0	1.9	311	30.2	22.5–37.9	2.3	402	28.8	23.3–34.3	1.5
Bratislava	115	19.2	10.0–27.5	2.0	276	24.0	17.0–29.5	2.1	391	22.6	17.0–26.8	1.9
Bucharest	46	27.4	12.6–42.4	1.4	122	50.7	38.4–62.9	2.0	170	45.9	36.1–55.7	1.7
Verona	99	27.7	15.5–39.5	2.2	275	39.1	30.6–47.7	2.7	375	35.9	28.9–43.0	2.5
Vilnius	82	58.3	43.4–72.3	2.2	236	30.1	22.0–35.6	1.6	318	37.5	30.1–42.8	1.7
GAM 1.12 (Condom use)												
Barcelona	36	84.6	70.5–92.7	1.05	267	65.7	56.5–73.9	2.26	303	68.7	59.1–77.0	2.95
Brighton	46	56.8	34.9–76.3	1.88	222	51.7	40.9–62.4	2.81	268	52.4	41.3–63.4	3.48
Brussels	39	83.7	67.3–92.8	0.95	253	57.6	44.5–69.8	4.51	292	60.7	47.7–72.3	4.97
Hamburg	29	74.9	44.0–91.9	2.90	252	49.1	38.8–59.6	2.80	281	52.5	42.6–62.1	2.84
Lisbon	30	53.1	28.5–76.3	2.65	294	72.0	65.2–77.9	1.45	324	69.6	64.5–74.3	0.95
Ljubljana	91	57.6	35.8–76.8	3.35	204	47.1	37.7–56.6	2.13	295	49.5	42.6–56.5	1.50
Sofia	114	80.0	71.7–86.2	0.85	278	59.3	54.5–64.0	0.72	392	64.7	60.6–68.5	0.70
Stockholm	38	62.6	44.2–78.0	1.71	160	56.9	43.9–69.0	2.47	198	58.4	47.0–69.0	2.61
Warsaw	67	51.4	37.3–65.3	1.70	215	57.0	47.9–65.7	1.70	282	55.4	48.2–62.4	1.50
Bratislava	88	41.7	27.2–53.1	1.96	202	46.7	38.5–54.8	1.74	290	45.2	38.1–51.4	1.67
Bucharest	31	34.6	11.8–56.9	1.84	85	62.3	47.8–76.8	2.00	116	56.6	43.7–69.5	2.06
Verona	87	55.7	39.5–71.1	2.62	235	63.9	55.2–73.9	2.70	324	61.6	53.9–70.1	2.70
Vilnius	67	59.6	45.2–74.3	1.77	177	55.3	46.0–65.5	2.02	244	56.6	48.9–65.0	1.91

GAM: Global AIDS Monitoring indicators; MSM: men who have sex with men.

Cities presented with white background: TLS survey. Cities presented a light blue background: RDS survey.

Estimated design effect: The design effect is a correction factor used to adjust required sample size for cluster sampling.

Reference items: GAM 1.11 (i) Do you know where you can go if you wish to receive an HIV test?, (ii) In the last twelve months, have you been given condoms?; GAM 1.13 (i) Have you been tested for HIV in the last 12 months?, (ii) If yes: I don't want to know the results, but did you receive the results of that test?; GAM 1.12 and 1.14 did not have reference items.

TABLE 3B

GAM indicators (weighted estimates) among MSM, design effect and number of participants, by city and age group, European Union cities (n = 13)

City	Age group< 25				Age group 25 +				Total			
	Sample size	Point estimate	95% CI	Estimated design effect	Sample Size	Point estimate	95% CI	Estimated design effect	Sample size	Point estimate	95% CI	Estimated design effect
GAM 1.13 (HIV testing)												
Barcelona	41	62.5	53.2–71.8	0.4	345	63.6	53.1–74.0	3.9	386	63.0	52.6–73.4	4.7
Brighton	63	36.1	22.7–49.6	1.2	313	54.6	43.9–65.3	3.3	376	47.3	43.3–51.3	0.6
Brussels	50	42.5	18.6–66.4	2.9	317	72.1	59.8–84.4	5.7	367	68.1	56.4–79.8	6.0
Hamburg	37	69.5	53.0–86.0	1.1	350	53.3	41.1–65.6	5.1	387	53.6	43.4–63.7	4.2
Lisbon	34	21.1	12.5–29.8	0.4	360	63.3	56.0–70.6	2.0	394	60.9	53.4–68.4	2.4
Ljubljana	117	40.1	23.5–56.6	3.4	256	47.4	41.9–53.0	0.8	373	46.4	40.5–52.3	1.4
Sofia[a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stockholm	62	52.1	39.0–65.2	1.1	229	57.9	47.1–68.6	2.6	291	56.3	45.6–66.9	3.5
Warsaw	91	37.6	27.2–48.1	1.0	301	60.6	48.6–72.6	4.5	392	54.0	45.7–62.2	2.8
Bratislava	112	29.0	19.1–39.0	1.9	228	41.0	31.8–48.8	2.2	340	37.2	30.4–43.0	1.9
Bucharest	47	39.0	21.8–56.2	1.6	122	44.8	32.5–57.1	2.0	171	43.3	33.1–53.5	1.9
Verona	99	50.2	36.3–64.0	2.3	233	47.3	36.1–57.1	3.1	335	47.7	38.6–56.1	3.2
Vilnius	81	38.3	24.8–50.5	1.8	192	39.1	29.0–47.6	2.1	273	38.8	31.2–45.0	1.7
GAM 1.14 (HIV prevalence)												
Barcelona	42	0.8	0.1–6.6	0.5	358	16.4	12.4–21.5	1.2	400	14.2	10.1–19.5	1.2
Brighton	65	2.9	0.5–15.5	1.5	337	20.7	15.7–26.8	1.4	402	17.6	13.8–22.3	0.9
Brussels	49	0.5	0.1–4.3	0.3	330	14.4	8.6–23.0	3.1	379	12.3	7.6–19.4	4.9
Hamburg	37	1.9	0.3–9.9	0.6	353	8.1	4.1–15.4	3.3	390	7.5	3.9–13.8	3.6
Lisbon	33	1.2	0.1–9.2	0.5	338	18.9	14.2–24.8	1.4	371	17.1	12.4–23.0	2.6
Ljubljana	107	1.4	0.2–11.1	1.1	240	5.3	2.2–12.2	2.6	347	4.4	2.1–8.9	1.8
Sofia	99	0.1	0.0–16.1	0.1	262	3.9	1.0–14.0	4.1	361	3.0	0.9–9.1	0.8
Stockholm	73	0.0	0.0–0.0	0.0	283	3.4	1.5–7.4	1.3	356	2.4	1.1–5.2	2.2
Warsaw	92	1.6	0.7–3.7	0.3	313	9.7	5.7–15.9	1.9	405	7.2	4.3–11.9	2.0
Bratislava	118	2.1	0.0–4.7	1.5	282	5.3	1.8–8.4	2.2	400	4.3	2.2–6.2	1.4
Bucharest	47	11.6	2.1–21.0	1.1	134	18.5	8.4–28.7	2.4	183	18.0	9.1–27.0	2.6
Verona	104	3.8	0.0–9.6	3.0	293	12.2	3.8–20.8	5.6	400	9.6	4.5–14.9	3.5
Vilnius	83	0.0	0.0–0.0	NA	239	4.6	0.4–9.2	3.3	322	3.4	0.0–6.9	3.6

GAM: Global AIDS Monitoring indicators; MSM: men who have sex with men; NA: not available.

[a]Results from Sofia for GAM 1.13 are missing due to incorrect translation.

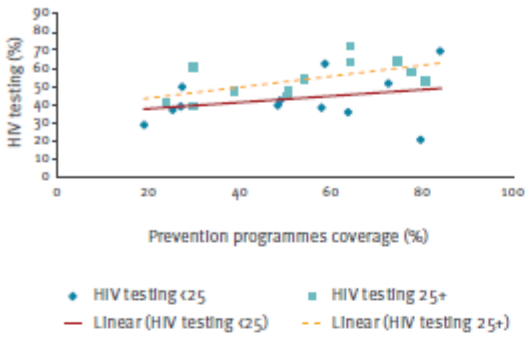
Cities presented with white background: TLS survey. Cities presented a light blue background: RDS survey.

Estimated design effect: The design effect is a correction factor used to adjust required sample size for cluster sampling.

Reference items: GAM 1.11 (i) Do you know where you can go if you wish to receive an HIV test?, (ii) In the last twelve months, have you been given condoms?; GAM 1.13 (i) Have you been tested for HIV in the last 12 months?, (ii) If yes: I don't want to know the results, but did you receive the results of that test?; GAM 1.12 and 1.14 did not have reference items.

Figure

HIV testing (GAM 1.13) vs prevention programmes (GAM 1.11), European Union cities (n=13)



run by an NGO before and during the data collection period), younger MSM showed the lowest level. These estimates are consistent with the literature and suggest the need for targeted prevention programmes tailored to locations and communities that can also accommodate for the needs of sub-populations, such as young MSM, MSM who are tourists and bisexuals [21,22].

Data focusing on the GAM 1.12 (Condom use) indicate that in the majority of the surveyed cities, condom use with any kind of partner was lower for younger men. However, the sample sizes for younger men were small for several cities and the association between age and condom use was not consistent across all study cities. In another publication based on the same Sialon-II-dataset, authors looked at condom use from another perspective e.g. any anal intercourse without a condom during the previous 6 months and not just from the last sexual encounter. The authors reported that almost half of the HIV-uninfected individuals reported condomless anal intercourse (CLAI). This was reported slightly more often by men living in Central European study cities and more frequently with steady partners compared with non-steady partners [23].

Based on the estimates of this GAM indicator there is a clear need to either increase condom use among younger men or to complement prevention strategies by providing meaningful access to other similarly effective HIV prevention tools such as HIV pre-exposure prophylaxis. Despite the fact that condom and lubricant distribution is often considered a simple and somewhat naïve approach to facilitate condom use, it is commonly acknowledged in the literature that fear of disapproval and discrimination by healthcare providers can deter gay, bisexual and other MSM from accessing mainstream health services [18]. Indeed, this limitation, could reduce access to free condom distribution, as well as low threshold HIV and STIs testing in healthcare settings [24].

A study by Marcus et al. [25] modelling the relationship between unprotected anal intercourse (UAI) and HIV disclosure with the same study dataset, found that among those respondents being aware of being HIV positive, condom use with steady partners was higher than among HIV negative men. However, condom use with non-steady partners was also lower. Men unaware of being infected with HIV reported the lowest condom use with non-steady partners [23,25].

It is possible that a large number of MSM are unaware of their HIV status. It is estimated that in western and central Europe a noteworthy number of people at risk are not getting tested or can experience difficulties in being tested for HIV and STIs [2]. Based on surveillance data, ECDC estimates that a number of European countries may have a considerable proportion of late HIV diagnoses [2]. The testing behaviour as measured by the GAM 1.13 depicts a very different situation among the surveyed cities. In Barcelona, Hamburg, Sofia, Stockholm and Verona, approximately half of the participants (all ages) reported having received an HIV test within the last 12 months and knew the result of that test. In Brighton, Brussels and Warsaw more than half of older participants reported a known HIV test result within the last 12 months while among younger participants, it was below that level. In Lisbon only one in five younger men reported a known HIV test result in the last year which represented the lowest levels in the study.

In several cities there were differences between the two age groups with regards to receiving an HIV test within the last 12 months and knowing the results. For instance, participants from Brighton, Brussels, Lisbon, and Warsaw all reported differences of greater than 20% for the two age groups; however, considering the time span is limited to the last 12 months, the differences cannot be directly attributed to the age effect where, for example, older individuals may have had an increased opportunity to be tested over time. Furthermore, older participants were tested more frequently and within a shorter timeframe than the younger men, suggesting that increasing access to culturally sensitive HIV counselling, testing and antiretroviral therapy for MSM, found to have HIV, is an urgent health priority particularly for the younger generations. The current levels of HIV testing are insufficient to link gay, bisexual and other MSM with appropriate healthcare support shortly after acquiring HIV infection. Therefore, currently, testing frequencies can remain insufficient to effectively reduce the period of infectiousness of people who newly acquire HIV.

Alternative approaches such as the use of point of care tests (PoCTs) for HIV and STIs in low threshold community testing and LGBT venue-based testing, home collection testing, and HIV self-testing may represent effective approaches to increase diagnosis and linkage to care.

The problem of late diagnosis reflects a lack of access to and uptake of HIV testing and counselling services in many countries [26]. A late diagnosis also means that a person has remained unaware of their HIV status for an indeterminate length of time, thus increasing the risk of transmitting the virus. The most recent surveillance data showed that despite significant efforts dedicated to the prevention and control of HIV, the rate of new HIV diagnoses has not substantially declined in the EU/EEA, but it has increased substantially over the last decade in the European Region.

Although HIV prevalence as an epidemic indicator is not a good parameter of the HIV infection spread dynamic, it can be helpful to provide an indirect picture of the epidemic history and patterns for some cities. HIV prevalence estimates (GAM 1.14), as measured by testing biological specimens (and not self-reported serological status), highlight critical levels of HIV infections across Europe among MSM communities despite valuable and concerted public health efforts [15].

Brussels, Barcelona, Lisbon, Brighton and Bucharest when considered globally, present relatively high HIV prevalences within the range of 10–20%. That said, the HIV prevalence estimate for Bucharest is probably less reliable and interpretable compared with the other cities for two main reasons: the existence of an ostensible MSM sub-sample of injecting drug-users within the city sample, and the fact that the target number of MSM to be recruited was not reached (less than 50% of the estimated target sample was recruited). Compared to these relatively high HIV prevalences, more 'intermediate' levels of HIV prevalence were evident in four other participating cities (Hamburg, Warsaw, Verona, and Sofia) where it ranged from 5 to 10%. Finally, in the cities of Stockholm, Vilnius, Ljubljana, and Bratislava, relatively lower HIV prevalences were observed with results below 5%. Other smaller studies carried out in some of these cities (with different or similar sampling methods) have produced similar results [11,27].

When exploring city-level correlations between GAM indicators, the data confirmed that prevention programmes correlate with both the level of condom use and of HIV testing among MSM, which might warrant additional efforts in implementing preventative actions. Despite numerous interventions targeting the behaviour, knowledge and attitudes of MSM, an increase of STIs and HIV diagnoses have been recently observed. Outbreaks of syphilis, lymphogranuloma venereum (LGV), hepatitis C viral infection (HCV) and other STIs have been reported in multiple European cities, possibility as a result of risky sexual behaviour and extensive sexual networking [26], but also may be due to an increase in active offering of HIV and STI's testing over the years.

A higher treatment coverage and higher percentage of HIV-positive MSM with undetectable viral load was attained in some Western European cities (Brussels, Hamburg, Brighton and Verona), indicating that when the service provision is proactive and the treatment widely available, the link between testing and treating can effectively influence the HIV epidemic.

Generalisability and limitations

To our knowledge, this is the first paper presenting weighted estimates produced as a result of a standardised collection of GAM indicators for MSM in a large number of European cities adopting a common SGSS approach. The use of this approach (SGSS and GAM Indicators) and the active participation of key LGBT community stakeholders in the project's design and implementation, represent an asset that provides potentially usable data for both public health authorities and NGOs in each partner country.

The use of TLS and RDS methodologies within the context of a bio-behavioural survey using a participatory approach have allowed hidden and different subgroups of MSM to be reached; groups that are usually more difficult to access through surveillance studies [28]. Nevertheless, there are some limitations that should be taken into account when interpreting the results.

First, data can only be generalised to the particular MSM attending the gay venues in each study site (in the case of TLS survey) and only to those MSM socially linked to the gay community for each specific site (in case of the RDS survey). It has also been shown in other studies that these two sampling methods can result in different sample characteristics and the differences may persist even after applying weighting corrections [28].

Second, the generalisability of the findings may also be limited by contextual factors not measured in this survey (e.g. legislation and social norms) and an ecological fallacy cannot be excluded.

Third, an additional source of bias limiting generalisability relates to the self-reported behavioural data. This is of course an issue common to all surveys covering the self-reporting of sensitive information. However, the anonymity of the data collected and the self-administration of the questionnaire, with the careful design of the questionnaire items developed and validated in all cities with the involvement of the LGBT community, may well have reduced any social desirability effect [29]. It is also worth noting that no difficulties or limitations were reported by either respondents or data collectors with regards to the use of the GAM indicators (both TLS and RDS) in terms of interpretation and utility of the items and related indicators.

Fourth, the percentage of participants who reported ever having injected drugs ranged from 1.2% in Bratislava to 19.3% in Bucharest. In the latter, estimates might be difficult to be generalised due to this

sub-population of injecting drug users (IDU)-MSM and to the fact that the target sample was not reached.

Fifth, the precision of the estimates were in some cases not optimal, particularly for the group of younger MSM, due to relatively small sample sizes (<50) and the potential for sampling bias in some cities.

Finally, an isolated limitation to the validity of the survey relates to Sofia (Bulgaria) where, due to an incorrect translation in the items questionnaire related to GAM 1.13, the indicator could not be estimated.

Conclusions

The Sialon II project and the data generated through its implementation represent a collaborative and scientifically robust contribution to the monitoring and evaluation of the HIV epidemic across Europe, integrating the use of GAM indicators within a SGSS approach with active community involvement. The data collected provide new evidence for appropriate planning of HIV prevention campaigns among MSM, clearly responding to the urgent need of concerted use of common indicators, with a particular focus on most at risk populations such as MSM [9]. The project has actively contributed to: (i) common procedures piloting (including most-advanced sampling methods, standards research algorithms, advanced laboratory diagnostics); (ii) harmonised data collection, involving experts from different institutions and with different backgrounds; and (iii) GAM country reporting, with specific reference to MSM.

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Conflict of interest

None declared.

Authors' contributions

MMI, LGI, NSH, UMA, ITO, MRO, SSC, SKB, BSU, CFO, CNO, SDI, DST, IKL, SCA, ARA, CMA, IAL, LZO, TNO, CML participated in the survey design and/or implementation. The first manuscript draft was jointly written by LGI and MMI. All authors (MMI, LGI, NSH, UMA, ITO, MRO, SSC, SKB, BSU, CFO, CNO, SDI, DST, IKL, SCA, ARA, CMA, IAL, LZO, TNO, CML) contributed writing to the following drafts. All authors read and approved the final manuscript. All authors fulfil the ICMJE authorship criteria.

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Od:	Rosińska Magdalena
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DW:	gios.lorenzo@gmail.com
Temat:	Lorenzo Gios / PhD by publication / Prevalence of drug use during sex amongst MSM in Europe: Results from a multi-site bio-behavioural survey

Dear Nigel,

I am writing to confirm that Lorenzo Gios provided a significant contribution to this paper, which was based on the results from the Sialon II project, implemented in 13 European sites.

He took a relevant role in conceptualising the paper, particularly to the development of the first drafts. He also revised the manuscript for important intellectual content, with relevant contributions particularly to the discussion of the results.

Kind regards
Magda

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Research Paper

Prevalence of drug use during sex amongst MSM in Europe: Results from a multi-site bio-behavioural survey

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ABSTRACT

Background: Substance use has been consistently reported to be more prevalent amongst Men who have Sex with Men (MSM) compared to the general population. Substance use, in particular polydrug use, has been found to be influenced by social and contextual factors and to increase the risk of unprotected intercourse among MSM. The objective of this analysis was to investigate the prevalence and predictors of drug use during a sexual encounter and to identify specific prevention needs.

Methods/design: A multi-site bio-behavioural cross-sectional survey was implemented in 13 European cities, targeting MSM and using Time-Location Sampling and Respondent-Driven Sampling methods Multivariable multi-level logistic random-intercept model (random effect of study site) was estimated to identify factors associated with the use of alcohol, cannabis, party drugs, sexual performance enhancement drugs and chemsex drugs.

Results: Overall, 1261 (30.0%) participants reported drug use, and 436 of 3706 (11.8%) reported the use of two or more drugs during their last sexual encounter. By drug class, 966 (23.0%) reported using sexual performance enhancement drugs, 353 (8.4%) – party drugs, and 142 (3.4%) the use of chemsex drugs. Respondents who reported drug use were more frequently diagnosed with HIV (10.5% *vs.* 3.9%) before and with other STIs during the 12 months prior to the study (16.7% *vs.* 9.2%). The use of all the analysed substances was significantly associated with sexual encounter with more than one partner.

Discussion: Substance and polydrug use during sexual encounters occurred amongst sampled MSM across Europe although varying greatly between study sites. Different local social norms within MSM communities may be important contextual drivers of drug use, highlighting the need for innovative and multi-faceted prevention measures to reduce HIV/STI risk in the context of drug use.

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[1] The list of Sialon II Network members is included as Annex 1 in Supplementary file.

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Background

Substance use has been consistently reported to be more prevalent amongst men who have sex with men (MSM) populations compared to the general population (Hunter, Dargan, Benzie, White, & Wood, 2014; Mercer et al., 2016; Mor & Davidovich, 2016; Wohl, Frye, & Johnson, 2008). Studies have addressed legal substances such as alcohol or tobacco as well as diverse illegal substances and medications used without prescription, the use of the last two refered to as drug use.

The available literature suggests that patterns of drug use among MSM differ from men who report sex with women only (Feaster et al., 2016; Hunter et al., 2014; Lhomond et al., 2014; Wohl et al., 2008). Moreover, the evidence also suggests that particular MSM populations may also be more likely to use drugs associated with visiting clubs or venues (e.g. cocaine, ecstasy, γ-hydroxybutyrate – GHB/γ-butyrolactone – GBL, hallucinogens, methamphetamines)(Feaster et al., 2016; Wohl et al., 2008) and less likely to inject opiates (Feaster et al., 2016).

Substance use amongst MSM has also been shown to be associated with societal contextual factors like stigma, poverty, trauma, and, at individual level, internalised homophobia, resulting from negative attitudes towards homosexuality in the environment (Edelman et al., 2016; Wilson et al., 2016). Perceived stigma towards gay/bisexual individuals has also been found to be an important predictor of reduced service use, for example reduced HIV testing uptake, of increased risk behaviours and poorer mental health (Martinez et al., 2016; Pachankis, Hatzenbuehler, Mirandola, et al., 2017; Vanden Berghe, Nöstlinger, & Laga, 2014). The co-occurrence of these negative health outcomes can be framed within the emergent approach of syndemics, consisting of interacting diseases and the social and environmental factors that promote their negative effects on individuals and populations (Singer, Bulled, Ostrach, & Mendenhall, 2017). Syndemics of substance use, depression, and violence have been identified amongst MSM (Jie, Ciyong, Xueqing, Hui, & Lingyao, 2012; Stall et al., 2003; Vanden Berghe et al., 2014) and could be explained within the framework of the minority stress model (Meyer, 2003).

Recent trends in drug use amongst MSM show evolving use patterns specifically associated with sex. In this context, several stimulants termed 'chemsex' drugs (typically mephedrone, GHB/GBL, and crystallised methamphetamine) appear to be increasingly used (Kirby & Thornber-Dunwell, 2013). Chemsex drugs are usually taken to prolong sexual pleasure and activity, increase sexual self-confidence as well as enhance the perceived quality of sex (Weatherburn, Hickson, Reid, Torres-Rueda, & Bourne, 2017). Social and cultural norms in gay subcultures and the party context festive scenes may play an important role in explaining the increasing popularity of chemsex. For example, they may be related to the supposed ubiquity of chemsex or to what it is permitted by or expected from engaging in chemsex (Ahmed et al., 2016).

Substance use amongst MSM, and specifically drug use is a key public health concern because it is often associated with sex in specific contexts and may thus be linked to the transmission of HIV and other sexually transmitted infections (STIs) (Carey et al., 2009; Daskalopoulou et al., 2014). Substance use, in particular polydrug use, has been found to increase the risk of unprotected anal intercourse or sero-discordant unprotected anal intercourse (Daskalopoulou et al., 2014; Santos et al., 2013; Tieu et al., 2014). However, there may be differences between the impact of particular substances on risk taking and HIV/STI risk (Carey et al., 2009; Vosburgh, Mansergh, Sullivan, & Purcell, 2012).

In Europe, the use of psychoactive substances among MSM in association with sex appears to be present consistently, although with different prevalence and patterns across the region (Schmidt et al., 2016). Whilst substance use has been described amongst MSM for some countries, the patterns of use are poorly understood in other countries, in particular in Central- Eastern and Southern Europe. Understanding this phenomenon is important in order to improve individual sexual health (e.g. through counselling) and to strengthen prevention services for STIs including HIV. This is even more so, in view of increasing mobility of MSM in Europe and worldwide and risk behaviours, including drug use, undertaken when travelling (Lee, Sullivan, & Baral, 2017; Vanden Berghe, Nöstlinger, Hospers, & Laga, 2013).

The objective of this analysis was to investigate the prevalence and predictors of drug use during a sexual encounter amongst MSM. Our focus is on the event-based analysis, including sexual partner characteristics and drug use during the same sexual encounter. We aim at characterising sexualised drug use in a large community sample of MSM who participated in the Sialon II study in 13 cities across Europe, both Western and Eastern, in view of specific prevention needs.

Methods

Study design and enrolment

This multi-site bio-behavioural cross-sectional survey was implemented in 13 European cities: Brussels (Belgium), Sofia (Bulgaria), Hamburg (Germany), Verona (Italy), Vilnius (Lithuania), Warsaw (Poland), Lisbon (Portugal), Bucharest (Romania), Bratislava (Slovakia), Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden), and Brighton (UK). A detailed description of the study methodology has been published elsewhere (Gios et al., 2016).

Male individuals were enrolled in the study cities during the data collection period in line with the following inclusion criteria: having had sex (any kind of sex) with another man during the previous 12 months, having provided informed consent, and agreed to donate a biological sample (oral fluid or blood depending on the enrolment approach adopted in the given city). Anonymous data collection took place from April 2013 to November 2014.

Two different data collection methods were used to identify and recruit MSM based on formative research conducted in each study site. Time-Location (or time-space) sampling (TLS) was used in nine cities (i.e. Brussels, Sofia, Hamburg, Warsaw, Lisbon, Ljubljana, Barcelona, Stockholm, and Brighton), whilst Respondent Driven Sampling (RDS) was adopted in four cities (Bratislava, Bucharest, Verona, and Vilnius).

In each city, the survey was implemented through trained community field workers using the same methodology (adopting study protocols, laboratory algorithms, and questionnaires). A target number of 400 MSM per city was planned with an expected total of n = 5,200 participants for the entire survey. Due to difficulties with RDS recruitment in Bucharest, the intended sample size was not reached in Bucharest.

Study population

Overall, a total of 4901 MSM were surveyed: 3596 MSM through TLS and 1305 through RDS. An extensive description of the study sample characteristics is available in the Sialon II bio-behavioural survey report (The Sialon II Project, 2016).

For the purpose of this analysis, we included only those MSM who reported having had anal intercourse with another man during the last six months (N = 4266). Another words we analysed only the anal sex events reported for a well-defined time period (October 2012–November 2014).

Instruments

Questionnaire

A structured pen-and-paper questionnaire was used to collect self-reported behavioural information. The draft questionnaire was translated into the languages of the participating countries and piloted before survey implementation. Translations were back-translated into English to check consistency.

Laboratory testing of biological samples

The TLS protocols stipulated that oral fluid (OF) samples were collected and tested for HIV antibodies using Genscreen™ HIV 1/2 version 2, BIO-RAD. A total IgG antibodies ELISA test Human IgG ELISA Kit 1 × 96, Quantitative/Immunology Consultants Laboratory was used for OF sample testing suitability and quality control. All HIV-reactive samples were re-tested with Vironostika HIV Ag/Ab, BioMérieux. Samples tested positive to the first ELISA HIV test, but negative to the second were classified as negative. Study participants could use their unique personal identifier to receive their test results if they wished. Referral for diagnostic testing and further case management was established in line with local procedures.

The RDS survey included pre/post-test counselling in the enrolment and follow-up process. Blood samples were collected and serum extracted in line with the local standard procedures. Serum samples were tested with a HIV 4th generation ELISA/CLIA screening test. A Western Blot test was used to confirm positive cases. In case of confirmed HIV positive result, a referral procedure was put in place in line with the local standard procedures to ensure proper case management.

Ethics

Local Ethics Committees approved the study protocols at each study site. The WHO Research Project Review Panel (RP2) and successively the WHO Research Ethics Review Committee (ERC) approved the protocol prior to data collection.

Variables definition

Dependent variables

Self-reported substance use during last anal intercourse with a male partner was assessed using the following question: "Before or during your last anal sexual intercourse, did you use the following . . . ?" The substances listed included: alcohol, poppers, ecstasy, erectile dysfunction medications – Sildenafil/Tadalafil (asked by brand names Viagra®/Kamagra/Cialis®), hashish/marijuana, cocaine, amphetamine, and GHB//GBL/ketamine. Participants were also asked to provide names of other substances which they had used. Possible answers were "yes", "no", "prefer not to answer". Missing answers were imputed with "no" and "prefer not to answer" was set to missing, as some participants tended to use this question as a check-box question marking only the "yes" answers. The percent of missing answers by substance varied between 17.1% and 18.5% with an exception of the two most commonly reported substances: alcohol (8.2%) and poppers (14.3%).

Additionally, summary variables were also created: 1) use of party drugs during the last anal sex with a male partner defined as the use of any of MDMA, cocaine or amphetamine; 2) use of sexual performance enhancement drugs defined as the use of either poppers or erectile dysfunction medication (EDM); 3) use of chemsex drugs defined as the use of any of GHB/GBL, ketamine, mephedrone or crystal methamphetamine (the last two recoded from the open text question).

Independent variables

The following independent variables were considered for the analysis: age (calculated using the self-reported year of birth), migration status (native: born & live in the study country; emigrant: born in the study country & live abroad; immigrant: born abroad & live in the study country; visitor: born & live abroad) – recoded in multivariable analysis to mobile (emigrant, visitor or immigrant) or native, educational status (up to and including secondary school, high school or post-secondary education or university/higher), outness (being out about one's own sexual orientation to majority of one's social network or to less than half of the network members), perceived attitudes of parents, at work/school and of friends/acquaintances towards MSM, bisexuality (based on self-reported sexual behaviour in the last six months), self-reported HIV status, diagnosis of a sexually transmitted infection other than HIV (STI) in the past 12 months, having ever injected a drug (lifetime), type of partner/partners during the sexual event for which the drug use was recorded (i.e. with a steady partner, with a non-steady partner, with more than one partner), frequenting gay venues (the number of times the participant attended any gay venues such as social venues, bars, discos, clubs, porn cinemas, cruising areas during past three months; recoded for analysis into two categories with the cutting point at median value), sexual satisfaction (Likert scale from very satisfied to very unsatisfied recorded to very satisfied versus not very satisfied – including all other categories – for the analysis).

Data analysis

The prevalence of use of a substance was defined as the proportion of MSM who reported using the substance during the last sexual encounter associated with anal sex with another men, among MSM who reported having had an anal intercourse with another man within 6 months preceding participation in the study.

Descriptive statistics, Wilcoxon–Mann–Whitney test, and Kruskal–Wallis test by ranks were used for quantitative variables, whilst percentages and Fisher's exact test were used for nominal variables.

Multivariable multi-level logistic random-intercept model (random effect of study site) was estimated to account for the hierarchical structure of the data (Rabe-Hesketh, Skrondal, & Skrondal, 2008). The multi-level analysis was conducted to identify factors associated with the use of alcohol, cannabis, party drugs, sexual performance enhancement drugs and chemsex drugs. Predictors associated with the outcome variable with a probability <0.05 were considered significant and backwards selection was used to identify the most relevant co-variates. Cases with missing values in the studied predictors were excluded from the analysis.

Stata® Version 14.2 was used for all analyses (College Station, TX: StataCorp LP).

Results

Study group characteristics

In total 4266 individuals were included in the study. Participants' median age was 32 years (interquartile interval 25–40 years), 81.4% lived in the country they were born in and, where they were recruited and 55% completed university education (Table 1). A large majority (87.3%) reported only male sexual partners in the past six months and 12.7% reported male and female partners.

Among the participants, 4202 (99.4%) provided sufficient information on whether they had used any substance at the last anal intercourse with a male partner and 3706 (86.8%) – also sufficient to establish the number of substances used. Overall,

Table 1
Characteristics of the study population, including total population and by drug used during last sexual encounter associated with anal sex, Sialon II.

		Total	No drug reported	Any drug reported	Sexual performance drug reported	Party drug reported	Chemsex drug reported	Alcohol reported	Cannabis reported
Total		4266	2941	1261	966	353	142	1904	331
Age (years)	mean/SD; median (IQR)	33.7/10.7; 32 (25–40)	33.4/10.6;31 (25–39)	34.6 (10.8); 33 (26–42)	35.7/10.9;34 (27–43)	32.2/9.1 ; 32 (22–40)	32.2/8.7 ; 32 (25–37)	32.4/9.8; 30 (25–38)	30.9/9.8;29 (23–36)
Age group	18–24	887 (20.8)	643 (21.9)	232 (18.4)	142 (14.7)	75 (21.3)	30 (21.1)	433 (22.8)	102 (30.8)
	25–34	1698 (39.8)	1171 (39.9)	497 (39.4)	381 (39.4)	156 (44.3)	64 (45.1)	833 (43.8)	134 (40.5)
	35–44	989 (23.2)	688 (23.4)	286 (22.7)	236 (24.4)	80 (22.7)	34 (23.9)	390 (20.5)	56 (16.9)
	45–54	483 (11.3)	302 (10.3)	177 (14.0)	146 (15.1)	36 (10.2)	13 (9.2)	183 (9.6)	32 (9.7)
	55+	205 (4.8)	134 (4.6)	68 (5.4)	61 (6.3)	5 (1.4)	1 (0.7)	64 (3.4)	7 (2.1)
	Missing	4	3	1	0	1	0	1	0
Migration Status	native: born & live in the study country	3463 (81.4)	2408 (82.0)	996 (79.4)	765 (79.7)	255 (73.1)	96 (68.6)	1531 (80.7)	259 (78.2)
	emigrant: born in the study country & live abroad	55 (1.3)	37 (1.3)	18 (1.4)	11 (1.1)	4 (1.1)	2 (1.4)	29 (1.5)	5 (1.5)
	immigrant: born abroad & live in the study country	520 (12.2)	348 (11.9)	169 (13.5)	127 (13.2)	67 (19.2)	25 (17.9)	233 (12.3)	48 (14.5)
	visitor: born & live abroad	214 (5.0)	142 (4.8)	71 (5.7)	57 (5.9)	23 (6.6)	17 (12.1)	105 (5.5)	19 (5.7)
	Missing	14	6	7	6	4	4	6	0
Education	secondary or lower	268 (6.4)	159 (5.5)	101 (8.2)	68 (7.2)	43 (12.7)	6 (4.4)	131 (7.0)	47 (14.8)
	high school or post secondary education (vocational school or college)	1610 (38.6)	1075 (37.3)	502 (40.9)	372 (39.2)	131 (38.6)	39 (28.5)	744 (40.0)	139 (43.7)
	university studies or degree	2295 (55.0)	1650 (57.2)	625 (50.9)	509 (53.6)	165 (48.7)	92 (67.2)	987 (53.0)	132 (41.5)
	Missing	93	57	33	17	14	5	42	13
Outness	out to less than half	1737 (42.1)	1261 (44.5)	448 (36.2)	337 (35.5)	114 (33.2)	21 (15.3)	784 (42.1)	94 (28.9)
	out to majority	2385 (57.9)	1571 (55.5)	789 (63.8)	612 (64.5)	229 (66.8)	116 (84.7)	1077 (57.9)	231 (71.1)
	Missing	144	109	24	17	10	5	43	6
Attitude towards MSM at work/school	Negative	1195 (29.1)	842 (29.8)	333 (27.1)	240 (25.6)	94 (27.6)	29 (21.0)	557 (30.0)	83 (25.4)
	neutral or positive	2916 (70.9)	1987 (70.2)	895 (72.9)	698 (74.4)	247 (72.4)	109 (79.0)	1300 (70.0)	244 (74.6)
	Missing	155	112	33	28	12	4	1857	327
Attitude towards MSM by parents	Negative	1161 (28.9)	824 (29.9)	320 (26.5)	228 (24.6)	101 (30.6)	27 (20.1)	523 (28.7)	77 (23.9)
	neutral or positive	2850 (71.1)	1933 (70.1)	886 (73.5)	698 (75.4)	229 (69.4)	107 (79.9)	1298 (71.3)	245 (76.1)
	Missing	255	184	55	40	23	8	83	9
Attitude towards MSM by friends/ acquaintances	Negative	315 (7.8)	218 (7.8)	88 (7.3)	63 (6.8)	27 (8.2)	4 (3.0)	146 (7.9)	24 (7.5)
	neutral or positive	3741 (92.2)	2582 (92.2)	1120 (92.7)	870 (93.2)	301 (91.8)	131 (97.0)	1691 (92.1)	296 (92.5)
	Missing	210	141	53	33	25	7	67	11
Declared HIV status independent of test result	HIV positive	253 (5.9)	116 (3.9)	132 (10.5)	116 (12.0)	43 (12.2)	25 (17.6)	121 (6.4)	28 (8.5)
	HIV negative	3154 (73.9)	2200 (74.8)	931 (73.8)	720 (74.5)	255 (72.2)	109 (76.8)	1440 (75.6)	235 (71.0)
	Other	859 (20.1)	625 (21.3)	198 (15.7)	130 (13.5)	55 (15.6)	8 (5.6)	343 (18.0)	68 (20.5)
	Missing	0	0	0	0	0	0	0	0

Relationships with women and men, last 6 months	male only	3499 (87.3)	2461 (89.2)	1016 (84.0)	799 (86.5)	263 (78.5)	119 (87.5)	1571 (85.4)	240 (75.9)
	female and male partners	508 (12.7)	299 (10.8)	193 (16.0)	125 (13.5)	72 (21.5)	17 (12.5)	269 (14.6)	76 (24.1)
	Missing	259	181	52	42	18	6	64	15
Ever injected drugs	No	3681 (95.6)	2639 (97.4)	1016 (92.3)	793 (93.5)	242 (83.7)	89 (80.2)	1628 (94.1)	262 (90.3)
	Yes	168 (4.4)	71 (2.6)	85 (7.7)	55 (6.5)	47 (16.3)	22 (19.8)	102 (5.9)	28 (9.7)
	Missing	417	231	160	118	64	31	1730	290
Diagnosis of STIs in the last 12 months	No	3774 (88.5)	2671 (90.8)	1051 (83.3)	791 (81.9)	281 (79.6)	104 (73.2)	1644 (86.3)	281 (84.9)
	Yes	492 (11.5)	270 (9.2)	210 (16.7)	175 (18.1)	72 (20.4)	38 (26.8)	260 (13.7)	50 (15.1)
	Missing	0	0	0	0	0	0	0	0
Satisfaction with own sexual life	Not very satisfied	2708 (67.8)	1870 (68.1)	822 (67.8)	617 (66.0)	212 (63.3)	77 (55.8)	1291 (70.4)	207 (66.1)
	Very satisfied	1286 (32.2)	877 (31.9)	390 (32.2)	318 (34.0)	123 (36.7)	61 (44.2)	543 (29.6)	106 (33.9)
	Missing	272	194	49	31	18	4	70	18
Last anal intercourse with	steady partner	1873 (47.6)	1398 (51.8)	457 (38.1)	337 (36.6)	127 (38.6)	52 (40.0)	760 (41.8)	133 (42.4)
	non-steady partner	1813 (46.1)	1212 (44.9)	587 (49.0)	443 (48.1)	149 (45.3)	49 (37.7)	899 (49.5)	145 (46.2)
	more than one partner	246 (6.3)	89 (3.3)	154 (12.9)	141 (15.3)	53 (16.1)	29 (22.3)	138 (8.7)	36 (11.5)
	Missing	334	242	63	45	24	12	87	17
Number of gay venues attended during the past 3 months	mean(SD; median (IQR)	18.8/(42.2; 7 (2–20)	16.7/(39.9; 6 (2–17)	23.7/(46.9;11 (3–26.5)	22.9/(48.1; 11 (1–25)	29.9/(49.0; 15 (5–34)	25.3/(33.7;13.5 (4.5–28.5)	22.9/(48.9; 10 (3–25)	25.3/(50.5; 10 (3–29)

1261 (30.0%) participants reported drug use, and 436 of 3706 (11.8%) reported the use of two or more drugs during their last sexual encounter. By drug class, 966 (23.0%) reported using sexual performance enhancement drugs, 353 (8.4%) – party drugs, and 142 (3.4%) the use of chemsex drugs. Although drug use was prevalent in all age groups, there were differences in age distribution by the class of drug (Fig. 1). Whilst the use of sexual performance enhancement drugs increased with age, the use of party drugs and chemsex drugs was less prevalent in the older age groups.

The proportion of men who attained a university degree was generally lower amongst those who used drugs (50.9% *vs* 57.2%) with an exception of those who used chemsex drugs of whom 67.2% completed university education (Table 1). The proportion of participants who were 'out' (i.e. being open about their sexual orientation) to the majority of their extended social network was higher in the group who had used drugs during the last anal sex (63.8%), especially amongst those who used chemsex drugs (84.7%), than amongst those who did not use drugs (55.5%).

Respondents who used drugs more frequently reported to be diagnosed with HIV (10.5% *vs.* 3.9%) (self-reported status) and to have been diagnosed with another STI during the 12 months prior to the study (16.7% *vs.* 9.2%). Similarly, they were more likely to report a history of injecting drugs (7.7% *vs.* 2.6%). On average, participants reported having attended gay venues 18.8 times (median 7) during the past three months, but the average was higher (23.7 times, median 11) in the group who used a drug during the last sexual encounter.

Finally, the distribution of partner type differed according to drug use. In the group who reported the use of any drug and the group who reported the use of chemsex drugs, 12.9% and 22.3% respectively also reported more than one partner during the event as opposed to 3.3% in the group who did not use any drug. Those who used chemsex drugs more often declared to be very satisfied with their sexual lives (44.2%) than those who had not used drugs (31.9%) or had used drugs of other classes.

Substance use by study site

Substance use during the last sex differed significantly across the study sites (Table 2). The most frequently used substances were alcohol reported by 45.2% of participants, ranging from 23.8% in Verona to 59.6% in Sofia, and sexual performance enhancement drugs reported by 23.1%, ranging from 6.1% in Verona to 42.9% in Brussels. Other substances were used by less than 10% of the overall sample, but with significant variation across cities. Reported party drug use was the highest in Brussels (21.2%), Barcelona (15.3%) and Brighton (13.0%), and chemsex drug use was the highest in Brussels (13.9%), Brighton (9.3%) and Ljubljana (6.0%).

Two most commonly observed patterns of drug use were: 1) predominance of poppers use (>40% of those who used any drugs used only poppers) in Bratislava, Hamburg, Sofia, Stockholm, Vilnius and Warsaw; 2) a large proportion of polydrug use (>20% of those who used any drug used three or more substances) in addition to 20–30% using only poppers in Barcelona, Brighton, Brussels, Lisbon and Ljubljana. For Lisbon and Verona higher proportion of cannabis were reported. Bucharest had a high proportion of missing information on substance use (Supplementary Fig. 1).

Predictors of substance use

The univariable analysis of predictors of substance use is presented in the Supplementary Table 1.

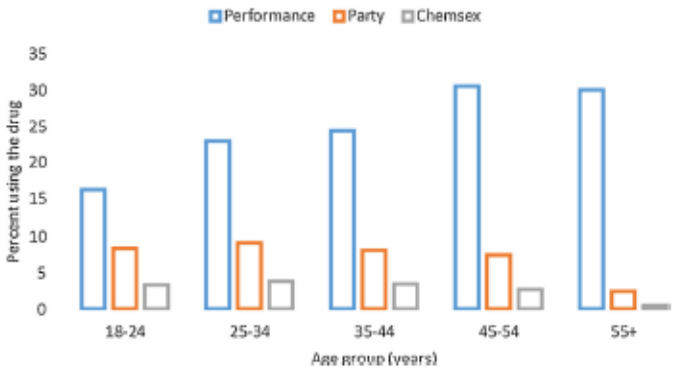

Fig. 1. Party drug, sexual performance enhancement and chemsex drug use before or during last anal sex, by drug class, Sialon II.

Table 2
Substance use during last sexual encounter associated with anal intercourse, by study site, Sialon II.

Study site	Any substance (n,%)*	Any drug (n,%)	Alcohol (n,%)	Cannabis (n,%)	Pperformance drugs (n,%)	Party drugs (N,%)	Chemsex drugs (n,%)	Number of substances among those who used any (mean/SD, median (IQR)
Barcelona	198(55.9)	135(38.1)	146(41.2)	56 (15.8)	101 (28.5)	54 (15.3)	16 (4.5)	2.1/1.6, 1(1–2)
Bratislava	172(50.4)	78(22.9)	133(39.0)	23 (6.7)	67 (19.6)	9 (2.6)	1 (0.3)	1.4/.7, 1(1–2)
Brighton	218(67.7)	138(42.9)	179(55.6)	23 (7.2)	120 (37.3)	42 (13.0)	30 (9.3)	2.0/1.4, 2(1–3)
Brussels	243(71.5)	180(52.9)	179(52.6)	39 (11.5)	146 (42.9)	72 (21.2)	47 (13.9)	2.3/1.6, 2(1–3)
Bucharest	74(48.1)	25(17.7)	68(45.3)	8 (5.9)	11 (8.3)	13 (8.4)	0 (0.0)	1.4/.8, 1(1–2)
Hamburg	192(58.7)	115(35.2)	157(48.0)	26 (8.0)	99 (30.3)	17 (5.2)	4 (1.2)	1.7/1.0, 1(1–2)
Lisbon	159(44.2)	81(22.5)	120(33.3)	28 (7.8)	48 (13.4)	19 (5.3)	7 (1.9)	1.5/1.0, 1(1–2)
Ljubljana	184(54.9)	92(27.5)	154(46.0)	40 (12.0)	59 (17.6)	29 (8.7)	20 (6.0)	1.8/1.4, 1(1–2)
Sofia	270(65.7)	146(35.7)	245(59.6)	23 (5.6)	103 (25.3)	42 (10.2)	2 (0.5)	1.6/.7, 1(1–2)
Stockholm	122(41.9)	59(20.3)	95(32.6)	4 (1.4)	54 (18.6)	9 (3.1)	1 (0.3)	1.5/.9, 1(1–2)
Verona	112(31.2)	56(15.6)	85(23.8)	33 (9.2)	22 (6.1)	16 (4.5)	3 (0.8)	1.5/1.0, 1(1–2)
Vilnius	158(55.2)	37(12.9)	151(52.8)	9 (3.1)	30 (10.5)	7 (2.4)	1 (0.3)	1.3/.9, 1(1–1)
Warsaw	223(66.4)	119(35.4)	192(57.5)	19 (5.7)	106 (31.5)	24 (7.1)	10 (3.0)	1.7/1.1, 1(1–2)
Total	2325(55.1)	1261(30.0)	1904 (45.2)	331 (7.9)	966 (23.1)	353 (8.4)	142 (3.4)	1.7/1.2, 1(1–2)
p-value for difference between sites	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* Percent calculated with respect to non-missing observations.

a. Alcohol use

In the multivariable analysis of alcohol use the significant predictors with the largest effect sizes were the sexual encounter with more than one partner *vs* single steady partner (adjusted odds ratio, AOR 2.4, 95%CI 1.7–3.3) and a history of injecting drugs (2.0, 1.3–2.9). Younger age, lower education, having had both female and male partners *vs* only male, and frequent visiting of gay venues also predicted alcohol use (Table 3).

b. Cannabis use

In turn, cannabis use was associated the most with having both male and female partners (AOR 3.2, 95%CI 2.2–4.5), being out about sexual orientation to majority of the social network (2.5, 1.8–3.4), sexual encounter with more than one partner (2.4, 1.5–3.8) and having injected drugs in the past (2.5, 1.5–4.1). Other important factors, although with smaller effect sizes, included younger age and lower education.

c. Sexual performance enhancement drugs use

The odds of use of sexual performance enhancement drugs significantly increased in sexual encounters with more than one partner *vs* one steady partner (AOR 5.6, 95% CI 4.0–7.9) and in MSM reporting positive HIV status (2.0, 1.4–2.8). Increased odds of using these drugs were also noted for older ages, lower education, having both male and female partners, history of injecting drugs, frequent visiting of gay venues, being satisfied with sexual life and an STI diagnosis in the past 12 months.

d. Party drugs use

The party drug use strongly correlated with history of injecting drugs (AOR 4.8, 95% CI 3.0–7.6) and sexual encounter with more than one partner (3.5, 2.2–5.7), as well as being out to the majority of social network (2.0, 1.4–2.8) and having both male and female partners (2.2, 1.5–3.2). It was also associated with younger age, being mobile (migrant or travelling), negative family attitude towards MSM, frequent attendance at gay venues and an STI diagnosis within the past 12 months.

e. Chemsex drugs use

The use of chemsex drugs was strongly associated with sexual encounter with more than one partner *vs* one steady partner (AOR 7.4, 95% CI 3.9–14.0), history of injecting drugs (5.8, 3.0–11.2) and

Table 3
Factors related to substance use during last sexual encounter associated with anal sex, by substance type. Results of multivariable analysis, Sialon II.

		Party drugs		Performance drugs		Chemsex drugs		Alcohol		Cannabis	
		Adjusted Odds Ratio* (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value
Age	(per 10 years increase)	0.98 (0.97–1)	0.046	1.02 (1.01–1.03)	0.000	0.95 (0.93–0.97)	0.000	0.98 (0.97–0.99)	0.000	0.97 (0.95–0.98)	0.000
Migration status	Mobile	1.6 (1.1–2.3)	0.010	-*		–		1.5 (1.2–1.8)	0.000	–	
	Native	Ref.						Ref.			
Education	University	0.7 (0.5–0.95)	0.022	0.8 (0.7–0.9)	0.008	1.8 (1.1–2.9)	0.016	0.82 (0.7–0.95)	0.009	0.6 (0.5–0.8)	0.000
	Lower	Ref.		Ref.		Ref.		Ref.		Ref.	
Outness	Out to majority	2.0 (1.4–2.8)	0.000	–		2.3 (1.3–4.2)	0.005	–		2.5 (1.8–3.4)	0.000
	Out to less than half	Ref.				Ref.				Ref.	
Attitude towards MSM by parents/ family	Negative	1.4 (1.1–2.0)	0.025	–		–		–		–	
	Neutral or positive	Ref.									
Self-reported HIV status	Diagnosed with HIV	–		2.0 (1.4–2.8)	0.000	–		–		–	
	Not diagnosed with HIV			Ref.							
Relationships with women and men, last 6 months	female and male	2.2 (1.5–3.2)	0.000	1.4 (1.0–1.8)	0.023	–		1.5 (1.2–1.8)	0.001	3.2 (2.2–4.5)	0.000
	male only	Ref.		Ref.				Ref.		Ref.	
Partner during last anal sex	One non-steady	1.2 (0.9–1.6)	0.257	1.5 (1.2–1.8)	0.000	1.2 (0.7–1.9)	0.591	1.5 (1.3–1.7)	0.000	1.1 (0.8–1.4)	0.756
	More than one partner	3.5 (2.2–5.7)	0.000	5.6 (4.0–7.9)	0.000	7.4 (3.9–14)	0.000	2.4 (1.7–3.3)	0.000	2.4 (1.5–3.8)	0.000
	One steady partner	Ref.		Ref.		Ref.		Ref.		Ref.	
Having ever injected drug	Yes	4.8 (3.0–7.6)	0.000	1.8 (1.2–2.7)	0.009	5.8 (3.1–15)	0.000	2.0 (1.3–2.9)	0.001	2.5 (1.5–4.1)	0.000
	No	Ref.		Ref.		Ref.		Ref.		Ref.	
Visiting gay venues within the last 3 months	≥7 times	1.6 (1.1–2.2)	0.009	1.3 (1.1–1.6)	0.005	–		1.7 (1.4–2.0)	0.000	–	
	<7 times	Ref.		Ref.				Ref.			
Satisfaction with sexual life	Very satisfied	–		1.2 (1.0–1.5)	0.044	–		–		–	
	Not very satisfied			Ref.							
STI diagnosis, past 12 months	Yes	1.6 (1.1–2.4)	0.009	1.7 (1.3–2.2)	0.000	3.0 (1.8–5.1)	0.000	–		–	
	No	Ref.		Ref.		Ref.					
city	(random effect variance)	0.4 (0.1–1.04)		0.4 (0.2–0.9)		2.1 (0.8–5.9)		0.2 (0.1–0.5)		0.2 (0.1–0.7)	

* "-" Indicates that the variable was not included in the final model for a given dependent variable.

an STI diagnosis in the past 12 months (3.0, 1.8–5.1). Younger age and university education predicted chemsex use as well.

Discussion

Our results quantify the frequency of substance use during sexual encounters amongst MSM sampled in study sites across Europe. Alcohol was the most commonly reported substance used by nearly half of the participants. Drug use, most commonly sexual performance enhancement drugs use, was reported in less than a third of anal sex events.

It is important to underline that the data collected for this behaviour referred to the last sexual encounter. Clearly, this estimate is not directly comparable with the proportion of MSM who use drugs in general, be it during sex or in other contexts. Moreover, the proportion of sexual encounters, during which MSM use substances can be interpreted in the context of the frequency of sexual encounters in this group. A study in U.S. established that MSM engaged in an estimated average of 81 sex acts per year (Wall, Stephenson, & Sullivan, 2013). Thus, although possibly using drugs on two different encounters is correlated, it is still very likely that asking about drug use at sex during a three/six-month period would yield a higher estimate of the proportion of MSM, who report this behaviour.

Nevertheless, the relative frequency of using particular substances established in our study is consistent with the results of prior studies in Europe and in the US, which collected information on use during the past six months (Feaster et al., 2016; Schmidt et al., 2016). One notable exception is cannabis, which was relatively more common in these studies than in ours. Because our study asked specifically about the use before or during sex, this may indicate that in this study population cannabis is less used in sexual contexts in contrast to other social situations.

Prevalence of drug use, including the different types of drugs used, varied greatly across the study cities. The use of any drug ranged from 12.9% in Vilnius to 52.9% in Brussels. Although there is a substantial variation between the different study sites as to the particular substances used, we note that poppers as a single substance or in combination with alcohol were the most commonly used substances. Polysubstance use is quite frequent, given that in 4 out of 13 study sites using three or more substances (excluding alcohol) accounted for over 20% of all sexual encounters associated with substance use. To some extent these differences may be related to the characteristics of the participants recruited in different study locations. However, we note that even in the multivariable models the (random) effect of the city remained significant. This draws attention to different social or sub-cultural norms related to drug use within the studied populations, as observed in a prior study (Chard, Metheny, Sullivan, & Stephenson, 2017). Moreover, the observed differences may be related to differences in supply, prices and availability of particular substances on the local markets. Data collated by the European Monitoring Centre for Drugs and Drug Addictions (http://www.emcdda.europa.eu/data/stats2017) indicate substantial diversity in terms of drug prices and prevalence of use between various European countries.

The demographic predictors of drug use identified in our models include age and education. In line with our results younger age was previously described as a predictor of drug use, especially chemsex and polysubstance use (Daskalopoulou et al., 2014; Schmidt et al., 2016; Sewell et al., 2017). In addition, we identified older age as predictor of increased use of sexual performance enhancement drugs, which points to differential patterns of drug use by age. University education predicted less alcohol and drug use in our study, with exception of chemsex drugs, which were in fact more prevalent among the university graduates. The prior findings on the role of university education are mixed. Some studies report higher drug use amongst less educated MSM (e.g. (Sewell et al., 2017)). In others, university education predicted in e.g. higher prevalence of polysubstance use (Daskalopoulou et al., 2014) or education was not associated to chemsex (Glynn et al., 2018). As indicated also by our results, the effect could differ depending on the particular drugs studied.

In our study MSM who also have sex with women (MSMW) showed increased odds of substance use with the largest effect sizes for cannabis and party drug use. There is prior evidence that this sub-population of MSM can have specific patterns of drug use in general (Lhomond et al., 2014). MSMW not only represent a sub-population of MSM with specific needs, but also with different access to services such as HIV screening, with increased odds of both less recent test seeking behaviour and lifetime HIV testing (Mirandola, Gios, Davis, et al., 2017; Mirandola, Gios, Sherriff, et al., 2017).

Generally, amongst specific MSM subpopulations like MSMW, but also migrant MSM, overlapping or dual stigma plays a key role in providing further insight of risky behavioural patterns (Mirandola, Gios, Davis, et al., 2017; Mirandola, Gios, Sherriff, et al., 2017; Pachankis, Hatzenbuehler, Berg, et al., 2017). In our study, being a migrant predicted party drug use and alcohol use, but the difference with respect to the native population was small.

"Outness" appeared to have an enhancing effect on the use of party drugs, chemsex drugs and cannabis in our study. This is unexpected given that concealment has been shown to increase the odds of sexual risk behaviours and suboptimal service use in a recent study (Pachankis et al., 2015). However, drug use was not specifically investigated in that study and the association of "outness" with increased drug use is in fact supported in other studies (Petersson, Tikkanen, & Schmidt, 2016). This relationship could be mediated through attendance at sex parties. Previous research demonstrated the high prevalence of chemsex use during sex parties in public venues (especially gay venues) and was found to be even higher amongst those attending private sex parties (Schmidt et al., 2016). While we corrected in our model for higher attendance in gay venues, we did not have sufficient information about private party attendance.

Drug use was also associated with the type of sexual partner(s). In fact, sexual encounters were more closely related to drug use when more than one sexual partner was involved. Group sex indicated an almost six-times higher chance of using sexual performance enhancement drugs and increased over seven times the chances of using chemsex drugs. This is in line with previous studies associating drug use with sex parties and with multiple partners during sexual encounter (Ahmed et al., 2016; Ober, Shoptaw, Wang, Gorbach, & Weiss, 2009). MSM reporting group sex have been found to exhibit higher sexual risk and polysubstance use. They were also more likely to suffer from psychosocial problems, supporting evidence of syndemic effect (Hirshfield et al., 2015).

Perceived negative attitudes towards gay and bisexuals, as measured in different contexts (at work/school, amongst friends, family and parents), did not correlate with the reported drug use, with the only exception of parental/family negative attitudes increasing the risk of party drug use. These findings do not fully support the general syndemic theory, in line with which the negative social attitudes may result in minority stress, internalized homonegativity and, in consequence, the co-occurrence of mental health problems, including substance use and increased risk taking (Martinez et al., 2016; Pachankis, Hatzenbuehler, Mirandola, et al., 2017; Vanden Berghe et al., 2014). However, also the results of the prior research on syndemics related specifically to substance use are mixed. Some studies suggest that drug use among MSM is a strategy to cope with HIV diagnosis, internalised homonegativity,

and depression (Edelman et al., 2016). On the other hand it has been also indicated that minority stress may be rather associated with substance dependence and less so with recreational substance use (Lea, de Wit, & Reynolds, 2014). This last finding corresponds to our results, as we studied the recreational use, not referring to dependence and/or problem drug use. In addition, other research indicates that recreational drug use may be driven by local social norms (Chard et al., 2017), especially those associated with specific social spaces, clubs or sex-parties (Ahmed et al., 2016; Mereish, Goldbach, Burgess, & DiBello, 2017). We found that being 'out' and frequently attending gay venues increased chances of alcohol and drug use during the last sexual encounter, which indirectly supports the importance of these norms.

Enhancing sexual experience was identified as one of the motivations for sex-related drug use (Bourne, Reid, Hickson, Torres Rueda, & Weatherburn, 2014; Weatherburn et al., 2017). In our multivariable models being very satisfied with one's sexual life was significantly associated with sexual performance enhancement drug use. However, the univariable effect was the strongest for chemsex drugs. It was not significant in the multivariable model, possibly due to smaller number of respondents reporting chemsex drug use.

Finally, even if injecting drugs in the past was only reported by small minority of our respondents (4.4%), our study confirmed strong correlations between having ever injected a drug and drug use during sex. Injection history was associated with approximately five times higher odds of party drug use and almost six times higher odds of chemsex drugs use. As noted by Glass et al. (Glass, Hope, Tanner, & Desai, 2017) injecting drugs associated with sexualised drug use ("slamming") may be on the increase. Although we did not collect information on whether or not injecting took place in the context of sexual encounters, we note that at least the subgroups of MSM who inject drugs and MSM who practice chemsex overlap.

Limitations

There are possible pitfalls in interpreting the results of our study. Firstly, drug use and other covariates were measured through a self-administered questionnaire, which carries the risk of incorrect or incomplete reporting. While anonymity may have mitigated this effect to a certain extent, we cannot exclude the possibility of recall bias and that participants may have under-reported substance use due to social desirability or misinterpretation of the questions. This could be especially true for 'chemsex' drugs as the use of mephedrone and crystal methamphetamine was not asked directly, but established based on an open text field. Adopting a community-based approach in collaboration with trustful community organisations to reach different groups of MSM, potentially contributed to reducing social desirability biases.

A second limitation is related to the sampling methodology. TLS and RDS methods are considered quasi-probabilistic approaches, targeting only those MSM associated with specific MSM communities either through their attendance in gay venues (TLS) or through personal social network (RDS). These approaches are subject to specific drawbacks, including possible over- or under-representation of potential MSM sub-samples (Kendall et al., 2008). Additionally, the difficulties with RDS recruitment in Bucharest could have affected the sample representativeness and the estimates' precision in this city. Nonetheless, the adopted methods represent a benchmark in bio-behavioural surveys and allow reaching wide representation of the target population.

Finally, findings of this analysis should not be directly generalised to all European MSM, as it is not possible to exclude the influence of unmeasured common patterns or contextual factors (such as cultural variations, social norms) not taken into account in this study design. Nevertheless, as the study succeeded in recruitment of a large number of participants across diverse settings in Europe, it offers a pan-European perspective.

Conclusions

We found that drug use before or during sexual encounters occurs among MSM in all studied sites in Europe, although it appears relevant only for a fraction of MSM. While some common predictors were established for all classes of drugs, some important differences found in this study underline the complexity of drug use amongst MSM. The differentiated patterns of drug use between the study sites draw attention to these populations' specific needs and call for innovative and multi-faceted prevention measures to reduce of HIV/STI risk in the context of drug use adapted to local contexts. Although some studies have highlighted the potential role of drug use, particularly 'chemsex', in facilitating the adoption of sexual risk behaviours (e.g. UAI) amongst MSM, by reducing behavioural control when under the influence of drugs (Bourne et al., 2014), the causal relationship is debatable (Digiusto & Rawstorne, 2013; Edelman et al., 2016; Melendez-Torres & Bourne, 2016). Referring to syndemics' theory, both risky behaviour and drug use may be related to social environments stigmatising towards gay and bisexual men (Martinez et al., 2016; Santos et al., 2014; Vanden Berghe et al., 2014).

Consequently, new intervention models underline tailoring the measures to individual profiles, considering possible co-existing conditions, such as depression, potentially mediating drug use and risky behaviours (Achterbergh, van der Helm, van den Brink, & de Vries, 2017; Fletcher & Reback, 2015). Taking on a harm-reduction approach and the implementation of outpatient drug use counselling within LGBTI-focused services was shown to be successful in terms of both reduced drug-use and improved psychosocial outcomes (Lea et al., 2017). These could include the STI/HIV community based services, which may attract MSM who do not perceive drug use as their particular problem. Community-based approaches including outreach may also be of value, changing individual behaviour through targeting social and community norms (Lauby et al., 2017). Our main findings confirm that local social norms within MSM communities may be important contextual drivers of drug use among MSM.

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Authors' contributions

The Sialon II network participated in the design of the survey questionnaire and the organisation and implementation of the survey in the survey cities. All co-authors developed the concept of this manuscript. MR analysed the data. The first draft was jointly written by MR, LG and MM and all authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflict of interests

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugpo.2018.01.002.

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[3.7] Sherriff, N., Jones, A.M., Mirandola, M., **Gios, L.**, Marcus, U., Llewellyn, C., …, The Sialon II Network. (2019). Factors related to condomless anal intercourse between men who have sex with men with steady versus casual partners: results from a European bio-behavioural survey. *J Public Health (Oxf)*, 2019 May 15. pii: fdz052. doi: 10.1093/pubmed/fdz052. [Epub ahead of print] PubMed PMID:31090894

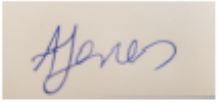
From: Jones Anna-Marie (Sussex Partnership Trust)
Sent: Thursday, August 1, 2019 1:59 PM
To: Nigel Sherriff
Cc: gios.lorenzo@gmail.com
Subject: Lorenzo Gios / PhD by publication / Factors related to condomless anal intercourse between men who have sex with men with steady versus casual partners: results from a European bio-behavioural survey

Dear Nigel,

This email is with regard to the paper focusing on factors related to condomless anal intercourse between MSM with steady versus casual partners which was developed for, submitted to and accepted for publication by the Journal of Public Health (Oxford).

I'm writing to confirm that Lorenzo made a significant contribution to the above mentioned paper. He particularly assisted in the data analysis development, implementation and quality assuring the outputs. He critically revised the paper for important intellectual content and he was involved in the final approval for publication.

Kind regards
Anna-Marie



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Factors related to condomless anal intercourse between men who have sex with men: results from a European bio-behavioural survey

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ABSTRACT

Background Relationship status is an important factor associated with condomless anal intercourse (CAI) amongst men who have sex with men (MSM).

Methods A multi-centre bio-behavioural survey with MSM was conducted in 13 European cities (n = 4901) exploring factors associated with CAI via bivariate and multivariate multilevel logistic regression analyses.

Results Likelihood of CAI with casual partners was associated with being 'out' to a majority (AOR = 1.19;95% CI 1,1.42); knowing their HIV status (AOR = 1.86; 95% CI 1.25,2.76); using substances (1–2 AOR = 1.39; 95% CI 1.16,1.63, 2+ AOR = 1.81; 95% CI 1.35,2.42); being older (AOR = 0.98; 95% CI 0.97,0.99); successful sero-communication (AOR = 0.79; 95 % CI 0.67,0.94); and, not having a recent HIV test (AOR = 0.78; 95% CI 0.66,0.92). CAI with steady partners was associated with successful sero-communication (AOR = 2.72; 95% CI 2.72,3.66); not having a recent HIV test (AOR = 1.26; 95% CI 1.09,1.46), and; being older (AOR = 0.99; 95% CI 0.98,0.99).

Conclusions Understandings of partner type and/or relationship status in relation to CAI amongst MSM can potentially play an important role in the development of culturally appropriate HIV/STI prevention and risk-reduction efforts targeting at-risk MSM. Our results speak to the need to consider segmented and tailored public health and health promotion initiatives for MSM with differing CAI behaviours and relationship profiles.

Keywords HIV, MSM, relationships, respondent-driven sampling, time-location sampling

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Introduction

Epidemiological evidence suggests that sex between men continues to be the main mode of HIV transmission accounting for 40% of all new diagnoses in 2016 across the European Union (EU) and the European Economic Area (EEA).[1] However, although there is now evidence of decreasing diagnoses amongst men who have sex with men (MSM) in some countries including Austria, Belgium, Italy, the Netherlands, Spain, and the United Kingdom,[2] in other EU/EEA countries diagnoses have increased substantially.[1] Such distinct trends mean that it is essential to sustain and, in some cases, strengthen HIV prevention interventions tailored to the local epidemiological context and targeting population groups most at risk; for many countries this means MSM.

In order to develop and implement community-level risk-reduction initiatives targeting MSM, it is necessary to examine not only key sexual behaviours amongst different MSM (sub) populations, but to also understand and consider the context in which they occur; relationships are one such context. Indeed, research demonstrates that relationship status and/or partnership type is an important factor associated with condomless anal intercourse (CAI) and subsequent risk for HIV and sexually transmitted infections (STIs).[3–7]

However, the risk for HIV and other STI acquisition is dependent on other factors than just CAI. Kramer and colleagues have drawn attention to this issue and note that although prevention initiatives commonly target individualistic-behaviours thus regarding CAI as an inherently 'risky' sexual behaviour, such approaches can be unhelpful as they may mask more complex and dynamic issues occurring within MSM in both steady and casual or non-steady relationships including the use of risk-reduction strategies.[8–10] For instance the number of partners as well as knowledge of own and partner's HIV serostatus, the use of 'negotiated safety' agreements,[11] serosorting, and the effective use of anti-retroviral drugs to lower viral load as well as the use of pre-exposure prophylaxis (PrePP)[12,13] may be contingent on the perception of the type of relations.

Nevertheless, examining explanatory factors related to differences in CAI between MSM in steady and casual relationships can be important in order to interrogate segmented public health and health promotion initiatives for MSM with differing sexual behaviour and relationship profiles. Consequently, in this present analysis we utilize data from the EU-funded Sialon II study which was a large multi-centre biological and behavioural cross-sectional survey of MSM in community settings carried out across 13 European cities. The objectives of our analysis were to: (i) investigate CAI and explanatory variables amongst MSM in a large community sample; (ii) explore the differences in CAI between those participants who had steady partners with those who had casual or non-steady partners, and finally; (iii) potentially inform the development (and assist implementation) of risk-reduction initiatives targeting MSM.

Methods

Study design

Detailed study methods are reported elsewhere.[14–16] In summary, the Sialon II study was a complex multi-centre integrated bio-behavioural cross-sectional survey with a concomitant collection of behavioural data and biological data (oral fluid or blood specimens).

Setting

The survey was implemented in 13 European cities. The decision to use Time-Location Sampling (TLS) or Respondent Driven Sampling (RDS) to recruit participants was based on preliminary formative research. TLS (also known as Venue Day Time Sampling, Temporal Spatial Sampling, and Time Venue Sampling) was used to recruit participants in Brussels, Sofia, Hamburg, Warsaw, Lisbon, Ljubljana, Barcelona, Stockholm, and Brighton ($n = 3596$). TLS is a quasi-probabilistic method used to recruit members of a target population at specific times in set venues.[17] In this study, the venues or settings for data collection included social and/or commercial venues and cruising settings preliminarily identified through formative research and which were then selected randomly for data collection sampling calendars.[18] RDS was used in Bratislava, Bucharest, Verona, and Vilnius ($n = 1305$). RDS is similar to snowball sampling in that it requires the target population to be socially networked so participants can invite their peers to participate. However, RDS is different in that it incorporates numerous theoretical assumptions to reduce the numerous biases found in standard snowball sampling methods (see[19]). Enrolment for RDS in Sialon II was based on the individuals' social network and for the data collection, locally accredited healthcare facilities (e.g. a hospital) were used. In TLS cities, participants were recruited during 2013, whilst in RDS cities recruitment started in 2013 and finished in 2014. Prior to the survey we estimated a 50% response rate as part of the sample size calculations. A data collection procedure to record refusals was therefore developed for TLS only. However, not all sites collected this data (with exception of the Brighton site with a 59% response rate). Thus an

overall response and/or refusal rate for the TLS survey is not reported.

Participants

Participants were men present in the cities at the moment of data collection (2013–14) who met the inclusion criteria (18 years or older; had sex with another man during the previous 12 months, and; agreed to donate an oral fluid or blood specimen depending on the sampling approach adopted). Exclusion criteria were being younger than the legal age of consent (18 years old) or having already participated in the study.

Instruments

A self-administered pen-and-paper questionnaire was used to collect behavioural data. The preliminary version of the questionnaire was designed by the Sialon II network in line with the Global AIDS Monitoring indicators (GAM)[16,20] and previous EC-funded European projects (e.g.[21,22]) and then piloted amongst MSM in each study site. The English version of the questionnaire was translated into local languages and back-translated into English.

Ethics

Research protocols were submitted to, and approved by, an institutional ethical review board in each participating city, as well as by the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC). All participants were given a study information sheet and the details were read out to ensure they understood what the study involved, that participation was voluntary, and that they had the right to withdraw at any time without giving a reason. Those willing to take part then signed a consent form. For TLS and RDS, a dedicated barcode system was used in order to link anonymously the different types of data collected (i.e. biological samples and behavioural data). For the TLS survey, respondents who wanted to collect their tests results could do so using their unique bar code ID. For the RDS survey where respondents were tested directly in a hospital/clinical setting, test results were available according to the local standards (including pre and post-test counselling).

Measures

Outcome variables

The primary focus of this analysis was to explore engagement in CAI measured as insertive/receptive unprotected anal intercourse in the last 6 months. Since we initially expected the 'risk' behaviour for those engaging in CAI in the last 6 months to differ depending on the relationship status (steady or casual partner), two separate 'primary' outcomes were created for two separate analyses. The first outcome indicated whether an individual had engaged in CAI with one or more (yes = 1) or zero (no = 0) steady partners. This included 'boyfriends' and 'husbands' (i.e. not being 'single') and excluded partners who were 'sex buddies'. The second outcome indicated whether individuals had engaged in CAI with one or more (yes = 1) or zero (no = 0) casual partners. Casual partners were defined as: those with whom one had had sex with only once (e.g. a 'one-night stand'); and those with whom one had sex with more than once but were not considered a steady partner (such as sex buddies). Some participants categorized current relationships as a mix of casual and steady partners since the two categorizations are not mutually exclusive.

Independent variables

Independent variables included: age (based on self-reported year of birth), education level (secondary school or lower, high school/post-secondary education/vocational school or college, or university degree/higher), migrant status (based on country of birth and country of residence: native, emigrant, immigrant or visitor), 'outness' (the extent to which participants reported being open about their sexual attraction towards men with others: being out to 'less than half' or 'out to the majority'), overall perceived attitude towards gay or bisexual people at work/school and amongst parents/friends/acquaintances (positive, neutral or negative attitude), HIV testing in the last 12 months and results known (no or yes), knowledge of own HIV status (using both self-reported status and status based on laboratory results: newly diagnosed, negative test result, already known), sex role at last anal sex (insertive, receptive, versatile), number of substances (type specified in the questionnaire) used at last anal sex (0, 1–2, 2+), frequency of visits to gay venues during last 3 months where sex-on-premises is possible (0 'no', 1–3 'low' 3+ 'high'), currently having sex with women (no or yes), serostatus communication at last anal intercourse (successful, unsuccessful; this constructed variable distinguishes between successful serostatus disclosure [i.e. a communication that establishes HIV serostatus concordance or discordance, including unilateral HIV infection disclosure], and unsuccessful serostatus disclosure [i.e. a communication where either none or only one of the involved partners disclosed his serostatus, with the exception of unilateral HIV infection disclosure]), see.[23]

Data analysis

Descriptive analysis

For continuous variables median and interquartile range (IQR) were used. For nominal variables count and percentages were used. The Chi-square test was used to examine

the relation between CAI in casual partners and CAI in steady partners as well as to compare CAI rates between pairs of cities.

Bivariate and multivariate multilevel modelling

For all bivariate and multivariate analyses, factors associated with CAI were identified using a two-level multilevel logistic regression model with a random intercept at the city level. The random component accounts for the hierarchical nature of the data. Analyses were carried out on all available cases.

The first step to building a model was to identify those individual independent variables (from the full list above) that were statistically significantly associated with CAI using bivariate analysis. Variables from this pool of potential risk factors were then used for inclusion in the multivariate analysis. The variables were added to the null model one by one using a forward selection process choosing the most significant ($P < 0.05$) variable first. The likelihood ratio test was used to compare the new model with the nested model. For all statistical tests, significance was indicated by $P < 0.05$. The final model estimated the adjusted odds ratios (AORs) and the corresponding 95% confidence interval (95% CI) for factors associated with CAI. We then used the resulting model to explore the relationship between age and risk of engagement in CAI for each city. Analyses were first carried out for modelling CAI with casual partners and then repeated for steady partners. Stata® Version 13 was used for all analyses (College Station, TX: StataCorp LP).

Results

Of 4901 participants who completed the survey, 4340 (88.55%) had sex in the last 6 months and were included in the analysis. The median age was 32 years with an IQR of 15 years. 3624 (83.50%) had at least one casual partner, 2911 (67.07%) had at least one steady partner and 2195 (50.58%) had both. 1374 (31.66%) participants reported CAI with casual partners (median age 31 years; IQR 12 years) and 1482 (34.15%) with steady partners (median age 31 years; IQR 14 years) and 687 (15.83%) reported CAI with both types of partner (median age 30 years; IQR 13 years). Median age for the 2171 (50.02%) who did not have CAI with casual or steady partners was 33 years (IQR 16 years). There was also a significant association ($P < 0.001$) between participant reports of CAI with casual partners and CAI with steady partners. Those who had CAI with steady partners had 2.73 times higher odds of CAI with casual partners (odds = 0.862) compared to those who did not have CAI with steady partners (odds = 0.316).

CAI varied between cities and by relationship status (Table 1). Brussels had the lowest percentage rate of CAI with casual partners and Sofia had the highest (22.7% vs. 53.3%, respectively; $P = 0.001$). Barcelona saw the lowest percentage rate of CAI with steady partners (23.81%) whilst Vilnius (40.34%) had the highest ($P < 0.001$). Table 1 presents the main characteristics of the study population stratified by relationship status. Odds ratios from the bivariate analyses are displayed in Table 2; all statistically significant variables made up the pool of potential factors for the final model.

Casual partners

The results from the multivariate analyses are shown in Table 3 (casual partner). The analysis showed that CAI with casual partners was more likely amongst those who were 'out' to a majority (AOR = 1.19; 95% CI 1,1.42, $P = 0.047$); who knew their HIV status (AOR = 1.86; 95% CI 1.25,2.76, $P = 0.002$); who used 1–2 substances (drugs/alcohol; AOR = 1.39; 95% CI 1.16,1.63, $P < 0.001$); and, who used two or more substances (AOR = 1.81; 95% CI 1.35,2.42, $P < 0.001$). Being older (AOR = 0.98; 95% CI 0.97,0.99, $P < 0.001$); having successful sero-communication (AOR = 0.79; 95% CI 0.67,0.94, $P = 0.006$); and, not having had a recent HIV test (AOR = 0.78; 95% CI 0.66,0.92, $P = 0.002$), were all associated with reductions in the likelihood of CAI.

Steady partners

With reference to the multivariate analyses in Table 4 (steady partner), CAI with a steady partner was more likely for those with successful sero-communication (AOR = 2.72; 95% CI 2.72,3.66, $P < 0.001$) and for those who had not been tested for HIV in the last 12 months (AOR = 1.26; 95% CI 1.09,1.46, $P = 0.002$). It was also approaching significance for those who reported being out to a majority (AOR = 1.16; 95% CI 1.00,1.36, $P = 0.054$). Reduced likelihood of CAI with a steady partner was associated with increasing age for all cities (AOR = 0.99; 95% CI 0.98,0.99, p,0.001).

Age

Figure 1 represents the estimated risk of CAI in respondents who have casual (a) and steady (b) partners by (continuous) age for each of the study cities. The two sets of graphs within Fig. 1 are not directly comparable because they are based on two different models incorporating different underlying theories on behaviours and risk. However, both sets show that overall young MSM are more likely to report higher levels of CAI compared to older MSM and the levels of CAI varies across cities. For instance Brighton has the

Table 1 Characteristics of study participants

Factor	*Total sample*		*Has at least one casual partner*	*Percentage of total population*	*Has at least one steady partner*	*Percentage of total population*
	Count	*%*	*Count*	*%*	*Count*	*%*
Age						
18–24	865	19.9	321	37.1	319	36.9
25–34	1708	39.4	596	34.9	627	36.7
35–44	989	22.8	297	30.0	320	32.4
45–54	530	12.2	111	20.9	163	30.8
55+	244	5.6	48	19.7	53	21.7
Total	4336	100	1373	31.7	1482	34.2
Highest education level						
Secondary or lower	251	5.9	69	27.5	60	23.9
High school or post-secondary	1599	37.5	569	35.6	550	34.4
University or higher	2413	56.6	712	29.5	847	35.1
Total	4263	100	1350	31.7	1457	34.2
Perceived attitude towards homosexuality & bisexuality						
Positive	1921	44.7	596	31.0	698	36.3
Neutral	1655	38.5	556	33.6	577	34.9
Negative	725	16.9	214	29.5	196	27.0
Total	4301	100	1366	31.8	1471	34.2
Outness						
Out to less than half	1776	41.6	558	31.4	558	31.4
Out to majority	2498	58.4	804	32.2	908	36.3
Total	4274	100	1362	31.9	1466	34.3
HIV testing in last 12 months and test result known						
Yes	2335	57.4	805	34.5	803	34.4
No	1733	42.6	478	27.6	581	33.5
Total	4068	100	1283	31.5	1384	34.0
Sex role						
Insertive	1379	36.1	439	31.8	479	34.7
Receptive	1320	34.6	487	36.9	461	34.9
Versatile	1119	29.3	343	30.7	426	38.1
Total	3818	100	1269	33.2	1366	35.8
No. of substances used						
No drugs	1895	44.8	515	27.2	682	36.0
1–2 drugs	1982	46.9	704	35.5	659	33.2
> 2 drugs	350	8.3	146	41.7	133	38.0
Total	4227	100	1365	32.3	1474	34.9
HIV status/knowledge						
Tested negative	3716	91.1	1134	30.5	1263	34.0
Newly diagnosed	146	3.6	52	35.6	46	31.5
Already known	215	5.3	95	44.2	77	35.8
Total	4077	100	1281	31.4	1386	34.0
Had sex with female partners						
No	3266	85.7	1050	32.1	1178	36.1
Yes	543	14.3	170	31.3	154	28.4
Total	3809	100	1220	32.0	1332	35.0

Continued

Table 1 Continued

Factor	Total sample		Has at least one casual partner	Percentage of total population	Has at least one steady partner	Percentage of total population
	Count	%	Count	%	Count	%
Frequentation of sex venues						
No (0)	1091	25.9	344	31.5	405	37.1
Low (1–3)	1772	42.1	511	28.8	589	33.2
High (3+)	1350	32.0	495	36.7	463	34.3
Total	4213	100	1350	32.0	1457	34.6
Serostatus communication						
Unsuccessful	2498	64.6	891	35.7	688	27.5
Successful	1369	35.4	413	30.2	720	52.6
Total	3867	100	1304	33.7	1408	36.4
Migration Status						
Native	3557	82.2	1159	32.6	1201	33.8
Emigrant	60	1.4	26	43.3	31	51.7
Immigrant	492	11.4	130	26.4	156	31.7
Visitor	219	5.1	56	25.6	89	40.6
Total	4328	100	1371	31.7	1477	34.1
City						
Barcelona	357	8.2	85	23.8	85	23.8
Bratislava	374	8.6	163	43.6	140	37.4
Brighton	354	8.2	97	27.4	132	37.3
Brussels	352	8.1	80	22.7	120	34.1
Bucharest	160	3.7	70	43.8	55	34.4
Hamburg	350	8.1	102	29.1	99	28.3
Lisbon	376	8.7	99	26.3	141	37.5
Ljubljana	346	8.0	84	24.3	134	38.7
Sofia	409	9.4	218	53.3	154	37.7
Stockholm	249	5.7	74	29.7	85	34.1
Verona	364	8.4	104	28.6	115	31.6
Vilnius	295	6.8	98	33.2	119	40.3
Warsaw	354	8.2	100	28.2	103	29.1
Total	4340	100	1374	31.7	1482	34.1

largest estimated probabilities of CAI in casual partners: at age 18 years (years) $P = 0.43$ and this drops to $P = 0.19$ for older (78 yrs) MSM; Vilnius had the lowest probabilities and estimates ranged from $P = 0.38$ (18 years) to $P = 0.16$ (78 years). For steady partners, again Brighton has the largest estimated probabilities of $P = 0.43$ (18 years) and $P = 0.26$ (78 years); Bucharest had the lowest probabilities ranging from $P = 0.35$ (18 years) to $P = 0.20$ (78 years). Amongst MSM with steady partners, Barcelona, Brighton, Brussels, Hamburg, Lisbon, Ljubljana and Stockholm can all be grouped together as cities with consistently higher probabilities of CAI at each age; similarly Barcelona, Brighton, Brussels, Hamburg, Sofia and Stockholm all had higher probabilities at each age for CAI in casual partners compared to the other study sites.

Discussion

Main finding of this study

A number of factors were associated with increased likelihood of CAI between MSM with casual partners including being 'out' to a majority, knowing one's own HIV status, and using substances. Reductions in the likelihood of CAI were associated with being older, as well as successful sero-communication, and not having had a recent HIV test. Being older may be related to having experienced more intensive condom promotion and having witnessed the severe consequences of historically untreatable HIV infection. In terms of successful sero-communication: with casual partners sero-communication may be a surrogate for HIV-related concerns and higher intentions of self-protection,

Table 2 Results from bivariate multilevel models identifying potential risk factors for CAI with partners by relationship status

		CAI with casual partners vs no CAI with casual partners								*CAI with steady partners vs no CAI with steady partners*							
Independent Variables		*OR*	*SE*	*z*	*P > z*	*95% Confidence interval for Odds ratio*		*Chi-square*	*P-value*	*OR*	*SE*	*z*	*P > z*	*95% Confidence interval for Odds ratio*		*Chi-square*	*P-value*
						Lower	*Upper*							*Lower*	*Upper*		
Age								36.29	<0.001							25.33	<0.0001
		0.98	<0.01	−6.02	<0.001	0.97	0.99			0.98	<0.01	−5.03	<0.001	0.98	0.99		
	Const.	0.92	0.14	−0.57	0.57	0.68	1.23			0.89	0.11	−0.98	0.33	0.70	1.12		
City	Var(const)	0.11	0.05			0.05	0.26			0.02	0.01			0.01	0.08		
Highest Education level								12.86	<0.001							9.84	0.0073
	Primary	Ref								Ref							
	High school	1.40	0.22	2.16	0.031	1.03	1.90			1.60	0.25	2.94	0.003	1.17	2.18		
	University	1.10	0.17	0.64	0.522	0.82	1.49			1.63	0.26	3.13	0.002	1.20	2.22		
	const	0.38	0.07	−5.36	<0.001	0.27	0.54			0.33	0.05	−7.10	<0.001	0.24	0.45		
City	Var(const)	0.15	0.06			0.06	0.35			0.03	0.02			0.01	0.09		
Perceived attitude towards homosexuality & bisexuality								11.20	0.0037							25.09	<0.001
	Positive	Ref								Ref							
	Neutral	0.95	0.07	−0.65	0.513	0.82	1.10			0.89	0.06	−1.65	0.099	0.77	1.02		
	Negative	0.71	0.07	−3.27	0.001	0.58	0.87			0.60	0.06	−5.00	<0.001	0.50	0.74		
	const	0.49	0.06	−5.64	<0.001	0.39	0.63			0.59	0.04	−7.02	<0.001	0.51	0.68		
City	Var(const)	0.17	0.07			0.07	0.39			0.04	0.02			0.02	0.12		
Outness								15.85	0.0001							16.70	<0.001
	Out to less than half	Ref								Ref							
	Out to majority	1.34	0.10	3.98	<0.001	1.16	1.55			1.33	0.09	4.09	<0.001	1.16	1.53		
	const	0.39	0.05	−7.25	<0.001	0.30	0.50			0.44	0.03	−10.51	<0.001	0.38	0.51		
City	Var(const)	0.18	0.08			0.08	0.42			0.04	0.02			0.02	0.12		
HIV testing in last 12 months and result known								19.80	<0.001							0.45	0. 5044
	Yes	Ref								Ref							
	No	0.73	0.05	−4.45	<0.001	0.63	0.84			0.96	0.07	−0.67	0.504	0.84	1.09		
	const	0.52	0.06	−5.40	<0.001	0.41	0.66			0.52	0.03	−9.76	<0.001	0.46	0.60		
City	Var(const)	0.16	0.07			0.07	0.38			0.03	0.02			0.01	0.10		

Continued

Table 2 Continued

		CAI with casual partners vs no CAI with casual partners								CAI with steady partners vs no CAI with steady partners							
Independent Variables		*OR*	*SE*	*z*	*P > z*	*95% Confidence interval for Odds ratio*		*Chi-square*	*P-value*	*OR*	*SE*	*z*	*P > z*	*95% Confidence interval for Odds ratio*		*Chi-square*	*P-value*
						Lower	*Upper*							*Lower*	*Upper*		
Sex role								6.98	0.0305							4.20	0.1222
	Insertive	Ref								Ref							
	Receptive	1.19	0.10	2.08	0.037	1.01	1.40			1.00	0.08	−0.04	0.968	0.85	1.17		
	Versatile	0.96	0.09	−0.46	0.647	0.81	1.14			1.16	0.10	1.79	0.073	0.99	1.37		
	const	0.47	0.05	−6.53	<0.001	0.37	0.59			0.53	0.04	−7.96	<0.001	0.46	0.62		
City	Var(const)	0.13	0.06			0.05	80.31			0.04	0.02			0.01	0.11		
Substances used								56.72	<0.001							5.79	0.0552
	None	Ref								Ref							
	1–2	1.48	0.11	5.40	<0.001	1.28	1.70			0.87	0.06	−1.97	0.049	0.76	1.00		
	>2	2.35	0.30	6.76	<0.001	1.84	3.02			1.10	0.14	0.75	0.456	0.86	1.40		
	const	0.36	0.04	−8.34	<0.001	0.28	0.46			0.56	0.04	−8.23	<0.001	0.49	0.65		
City	Var(const)	0.16	0.07			0.07	0.36			0.03	0.02			0.01	0.10		
HIV status knowledge								31.32	<0.001							0.5931	0.5931
	Tested negative	Ref								Ref							
	Newly diagnosed	1.33	0.24	1.56	0.119	0.93	1.89			0.91	0.17	−0.51	0.609	0.64	1.30		
	Already known	2.21	0.32	5.46	<0.001	1.67	2.95			1.14	0.17	0.86	0.391	0.85	1.52		
	const	0.43	0.05	−7.56	<0.001	0.34	0.53			0.51	0.03	−11.2	<0.001	0.46	0.58		
City	Var(const)	0.15	0.06			0.06	0.34			0.03	0.02			0.01	0.09		
Had sex with female								2.63	0.1047							13.22	0.0003
	No	Ref								Ref							
	Yes	0.84	0.09	−1.62	0.105	0.69	1.04			0.68	0.07	−3.64	<0.001	0.56	0.84		
	const	0.47	0.06	−6.13	<0.001	0.37	0.60			0.56	0.04	−8.60	<0.001	0.49	0.64		
City	Var(const)	0.18	0.08			0.08	0.41			0.04	0.02			0.01	0.12		
Venues frequency								7.71	0.0211							2.53	0.2826
	No(0)	Ref								Ref							
	Low (1–3)	1.00	0.09	0.04	0.97	0.84	1.19			0.89	0.07	−1.42	0.155	0.75	1.05		
	High (3+)	1.27	0.13	2.27	0.023	1.03	1.57			0.87	0.09	−1.40	0.163	0.72	1.06		
	const	0.43	0.05	−6.78	<0.001	0.34	0.55			0.58	0.05	−6.70	<0.001	0.49	0.68		
City	Var(const)	0.14	0.06			0.06	0.32			0.03	0.02			0.01	0.09		

Serostatus communication							6.56	0.0104									235.77	<0.001
	Unsuccessful	Ref							Ref									
	Successful	0.83	0.06	−2.56	0.01	0.72	0.96		2.99	0.21	15.35	<0.001	2.60	3.44				
	const	0.53	0.06	−5.88	<0.001	0.43	0.66		0.38	0.03	−12.88	<0.001	0.33	0.44				
City	Var(const)	0.12	0.05			0.05	0.30		0.05	0.03			0.02	0.13				
Migration Status							3.27	0.3514									11.98	0.0075
	Native	Ref							Ref									
	Emigrant	1.57	0.43	1.67	0.095	0.92	2.68		2.05	0.54	2.73	0.006	1.22	3.42				
	Immigrant	0.94	0.11	−0.58	0.564	0.75	1.17		0.96	0.10	−0.34	0.732	0.78	1.19				
	Visitor	0.96	0.16	−0.26	0.794	0.68	1.34		1.37	0.21	2.11	0.035	1.02	1.85				
	const	0.46	0.05	−7.1	<0.001	0.37	0.57		0.50	0.03	−11.29	<0.001	0.45	0.57				
City	Var(const)	0.14	0.06			0.06	0.33		0.03	0.02			0.01	0.09				

Notes: z = test statistic for an individual category in the bivariate model; P > z = significance of an individual category in the bivariate model; Wald Chi-square statistic and P-value are used to test the significance of a whole variable in the bivariate model; SE = Standard Error; OR: Odds Ratio

while sero-communication with steady partners may serve to confirm HIV sero-concordance and successful serosorting and to allow more 'intimacy' by practising CAI.

For those with at least one casual partner, having sex with a female and being a migrant were not associated with the likelihood of CAI. Similarly for MSM with at least one steady partner, the likelihood of CAI was positively associated with successful sero-communication and not having had a recent HIV test within the last 12 months; it was also negatively associated with increasing age. Interestingly, regardless of partner type, our analysis indicated a downward trend in the probability of CAI with increasing age. The gradual declining trend, and smaller 95% confidence intervals at the margins, indicated that relationships amongst steady partners are more stable whilst casual partners are more variable. These data suggest that regardless of partner type, prevention strategies may benefit from disproportionately targeting younger MSM.

What is already known on this topic

Previous studies have identified associations between CAI between MSM and relationship status.[4,9,24–26] Concurring with our own findings, prior studies have also found significant associations between CAI and age with younger MSM seemingly more likely to engage in CAI with steady partners.[24] In our study this was also the case although irrespective of partner type.

Of potential relevance to our analysis, a recent study from Australia has shown that a rapid increase in pre-exposure prophylaxis (PrEP) use by gay and bisexual men in Melbourne and Sydney was accompanied by an equally rapid decrease in consistent condom use with casual partners.[13] Future studies may therefore wish to consider the importance of understanding the complex dynamics of partner type/relationship status for the prevention of other STIs as well as considering how CAI behavioural stratification could be used to determine who might benefit from tailored health promotion interventions including HIV PrEP.

What this study adds

Understandings of how partner type or relationship status may shape sexual behaviour such as CAI amongst MSM in European cities may help to play an important role in the development of culturally appropriate HIV/STI prevention and risk-reduction efforts targeting at-risk MSM. Our findings indicate the need for further investigation on how partner type and other partnership characteristics and dynamics

Table 3 Multilevel model results identifying risk factors for CAI with casual partners compared to no CAI with casual partners

Risk factor	*Category*	*AOR*	*SE*	*95% Confidence Interval*		*P-value*
				Lower	*Upper*	
Outness	Out to less than half	Ref				
	Out to majority	1.19	0.11	1.00	1.42	0.047
Had HIV test in last 12 months and results known	Yes	Ref				
	No	0.78	0.07	0.66	0.92	0.002
Sex role	Insertive	Ref				
	Receptive	1.18	0.11	0.98	1.41	0.082
	Versatile	0.88	0.09	0.72	1.07	0.174
Serostatus communication	Unsuccessful					
	Successful	0.79	0.07	0.67	0.94	0.006
Highest Educational level	Secondary or lower	Ref				
	High school	1.05	0.20	0.73	1.54	0.811
	University	0.85	0.16	0.59	1.22	0.375
Age						
	Continuous	0.98	<0.01	0.97	0.99	<0.001
HIV status knowledge	Tested negative	Ref				
	Newly diagnosed	1.04	0.22	0.68	1.56	0.851
	Already known	1.86	0.37	1.25	2.76	0.002
Substances used	None	Ref				
	1–2 drugs	1.39	0.12	1.16	1.63	<0.001
	>2 drugs	1.81	0.27	1.35	2.42	<0.001
Constant		0.89	0.25	0.52	1.53	0.067
City	Variance (Constant)	0.13	0.06		0.05	0.32

LR test vs. logistic regression: chibar2(01) = 47.57 Prob. ≥ chibar2 = 0.0000

Notes: Adjusted Odds Ratio (AOR); Standard Error (SE)

Table 4 Multilevel model results identifying risk factors for CAI with steady partners vs no CAI with steady partners

Risk factor	*Category*	*AOR*	*SE*	*95% confidence interval*		*P-value*
				Lower	*Upper*	
Serostatus communication	Unsuccessful	Ref				
	Successful	2.72	3.66	2.72	3.66	<0.001
Age						
	Continuous	0.99	<0.01	0.98	0.99	<0.001
Outness	Out to less than half	Ref				
	Out to majority	1.16	0.09	1.00	1.36	0.054
Had HIV test in last 12 months and results known	Yes	Ref				
	No	1.26	0.10	1.09	1.46	0.002
Constant		0.50	0.08	0.37	0.67	<0.001
City	Variance (Constant)	0.03	0.02	0.01	0.11	

LR test vs. logistic regression: chibar2(01) = 9.17 Prob. ≥ chibar2 < 0.0012.

Notes: Adjusted Odds Ratio (AOR); Standard Error (SE)

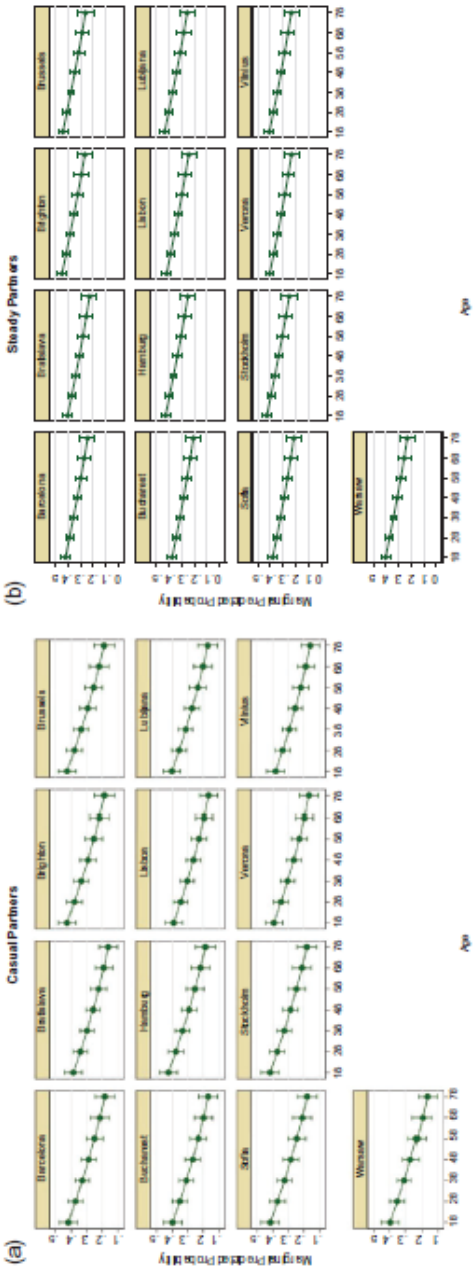

Fig. 1 Marginal predicted probabilities of CAI in casual and steady partners, by age group and city.

may influence CAI and HIV and/or STI transmission amongst MSM.

Limitations of this study

Due to the cross-sectional nature of the study design, no causality or temporality between the associations examined can be inferred. An important limitation relates to the sampling methodology. TLS and RDS methods are considered quasi-probabilistic approaches, targeting MSM through their attendance in gay venues (TLS) or via social networks (RDS). This means that such approaches are subject to specific shortcomings such as the possible over- or under-representation of potential MSM sub-samples.[27] However, TLS and RDS do nevertheless still represent one of the main and current approaches for recruiting most at-risk populations to bio-behavioural surveys.[28] Survey data can of course be subject to specific biases related to the fact that some data were self-reported (excluding the data on HIV status when based on laboratory testing) limiting generalisability. This implies recall and social desirability bias given behaviours such as CAI were explored. The questionnaire has however been designed to overcome these potential biases, for instance through the active involvement of local gay NGOs in each site.[29] It is also possible that although we provided descriptions of different partner types in the survey, variations regarding the interpretation of what constitutes a 'steady' versus a 'non-steady/casual' partner might not be uniform across study participants (e.g. see[7]).

Finally, as an EC co-funded project, the Sialon II project was designed to include cities from countries with different social and cultural contexts. As in many such EC-funded projects, cities were selected on the basis of previous research and collaboration networks and on the basis of pragmatic financial/organisational issues; therefore, some key cities with sizable gay populations have not been covered by the survey.

Despite the above limitations however, our analysis provides important information regarding the association between CAI and partnership characteristics amongst MSM in 13 European cities.

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Conflicts of interest

None.

Contributions

The SIALON II network participated in the design and implementation of the study. This analysis was conceived by NS, AMJ, and CL. Data were analysed by AMJ, NS, MM, and LG. The first draft was jointly written by NS and AMJ. All authors revised the manuscript for content. All authors read and approved the final manuscript.

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July 18, 2019

Nigel Sherriff, PhD
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Dear Dr. Sherriff,

I am writing to confirm that Lorenzo Gios significantly contributed to our co-authored article published in *AIDS and Behavior* in 2019 titled "The Role of Gay-Related Stigma in HIV-Risk Behavior Among Sexual Minority Men in Europe." Lorenzo contributed to the writing and editing of this manuscript by adding relevant elements particularly for its methodological aspects. He was also responsible for the EU-funded project, on which this paper is based.

Please do not hesitate to ask further questions about our collaboration.

Sincerely,

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ORIGINAL PAPER

The Role of Gay-Related Stigma in HIV-Risk Behavior Among Sexual Minority Men in Europe

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Abstract

Sexual orientation stigma stems from discriminatory social contexts and may ultimately impact the behavioral health of stigmatized individuals through stress-related pathways. Sexual minority stigma is of particular concern in Europe given the diversity of social contexts on the continent and sexual minority men's rapidly increasing risk of HIV infection, especially in Central and Eastern Europe, potentially rooted in stigma. This study assesses whether stigma in the ubiquitous social contexts surrounding sexual minority men (e.g., family, workplace, government) may place them at higher risk for HIV contraction across six countries. We utilized a large cross-sectional survey sample of HIV-negative sexual minority men ($N = 2087$; mean age = 31.6, $SD = 9.7$) from six European countries to test whether those who reported sexual orientation stigma also engaged in more HIV risk-related behaviors, including condomless sex with casual partners (in the absence of PrEP) and substance use before and during sex. Regression analyses were performed in *Mplus*. We found that a one standard deviation increase in reported sexual orientation stigma was significantly associated with the following during the last sexual encounter: a 19% increase in odds of sex under the influence of alcohol, 27% increase in odds of sex under the influence of cannabis, 49% increase in odds of sex under the influence of illicit drugs, an 11% increase in odds of condomless sex with casual partners in the past 6 months, and a 26% increase in odds of knowing where to receive an HIV test. Sexual minority men who reported perceiving greater sexual orientation-related stigma within their ubiquitous social contexts were significantly more likely to report sexual risk and alcohol and drug use during their last sexual encounter, yet reported more knowledge of preventive services. Contextual stigma might serve as a precursor to behavioral risks of HIV infection, generating maladaptive stress responses capable of being modified through individually-focused interventions. Structural interventions are also needed to ultimately reduce stigma at its source.

Keywords Sexual minority men · HIV risk · Sexual orientation-related stigma · Drug use · Alcohol use

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Introduction

Stigma toward sexual minorities varies widely across geographic regions, even on the same continent [1]. For instance, while Western European countries promote the equal treatment of sexual minority citizens through affirmative and non-discriminatory laws, policies, and national attitudes, many countries in Central and Eastern Europe lack equal legislative protections for sexual minorities and actively discriminate against them through legislation that promotes inequality and homophobic attitudes [1]. Globally, sexual orientation stigma has been shown to be associated with increased vulnerability to health risks [2, 3] including HIV transmission-risk behavior and substance use [4–8].

After political shifts in Central and Eastern Europe over the past two decades, gay, bisexual, and other men who have sex with men (referred hereafter as sexual minority men) in this region gained unprecedented freedoms of association (with preferred social, sexual and romantic partners) and travel. Consequently, Central and Eastern European sexual minority men who were previously insulated due to strict international travel prohibitions and censure against sexual minorities became newly exposed to the high HIV and substance use prevalence among sexual minority men living in Western Europe and other nearby regions. At the same time of this new exposure, sexual minority men living in Central and Eastern Europe have also been under-equipped with HIV prevention and transmission knowledge. In fact, Eastern Europe represents one of the highest-priority regions in the world for HIV prevention given that the HIV rate there has increased significantly in the past decade, with a particularly alarming increase in transmissions among sexual minority men [9]. For example, in one of the countries included in the current study, Romania, HIV prevalence among sexual minority was less than 10% in 2009, but close to 20% in 2014, based on best available evidence [10, 11].

While lesbian, gay, bisexual and transgender (LGBT) civil rights movements followed democratic reform eastward upon communism's fall [12], with Central and Eastern European sexual minority men's greater visibility came greater vulnerability in terms of increased legal and attitudinal stigma and discrimination [12–19] as a conservative response, primarily driven by religious dogma, to the increasingly overt diversity in sexual identities [20]. Stigma is often defined as an attribute or characteristic that is devalued in certain social contexts [21, 22]. But rather than residing within the stigmatized individuals themselves, stigma is ultimately propagated by social institutions [23]. For instance, social institutions such as workplaces, churches, families, communities, and government can perpetuate stigma toward sexual minorities, thereby thwarting their belongingness to these institutions and driving unhealthy coping reactions [24–27], including HIV-transmission risk behavior and substance use, which can co-occur with sexual behavior to generate HIV risk. Thus, identifying and intervening upon the source of stigma in these social contexts and institutions represents an important public health priority, especially in high-stigma locales [28, 29].

In this study, we examined the relationship between sexual minority stigma present in ubiquitous social contexts and HIV-transmission risk behaviors in a geographically diverse sample of European sexual minority men. Across Europe, sexual minority men represent the highest-risk group for HIV infection [9, 30, 31]. While various forms of stigma, including national laws and policies toward sexual minorities, and self-stigma (i.e., internalized homophobia), have been shown to be associated with European sexual minority men's HIV risk [32–34], no research has examined HIV risk as a function of perceptions of social contextual stigma among geographically diverse European sexual minority men, especially those living in Central and Eastern Europe. We define social contextual stigma to consist of attitudes (or the degree of prejudice) towards sexual minorities (homosexuals or bisexuals) perceived across several life domains: work/school; parents; friends/acquaintances; political; social; and religious. Therefore, we sought to establish the association between social contextual stigma and HIV-transmission risk behavior among HIV-negative sexual minority men living in six European contexts [35, 36]. Europe offers an important geographic context in which to test these hypotheses given the wide variation in national contexts surrounding sexual minority men and the relatively high-quality data available across these contexts.

Method

Study Design

This manuscript is based on data collected through a multicenter biological and behavioral cross-sectional survey of sexual minority men implemented in the context of the SIALON (*saliva* in Ancient Greek) project, co-funded by the European Commission under the Public Health Programme 2003–2008 (GA 2007309) [37]. The survey was co-funded by the EU and implemented in six European cities: Barcelona (Spain), Bratislava (Slovakia), Bucharest (Romania), Ljubljana (Slovenia), Prague (Czech Republic), and Verona (Italy). Study sites were selected to provide comparative geographic contexts, including high- and low-stigma contexts.

The following eligibility criteria were applied: having had any kind of sex at least once with another man during

the previous year; having signed the survey's informed consent, agreeing to answer the study questionnaire and donate an oral fluid sample. Oral fluid data are not included in the current analyses. Exclusion criteria were adopted as follows: being younger than 18 years old; active injecting drugs; and having already participated in the study. Study bio-behavioral data collection procedures are described in detail elsewhere [38, 39].

Ethics

Prior to data collection, informed consent was obtained for each participant. To guarantee anonymity and confidentiality, a barcode was assigned to each enrolled participant to maintain their anonymity. The unique barcode was assigned to each participant when he agreed to take part in the study. The same barcode was used to link all the materials and documents pertaining to the subject (informed consent, questionnaire, biological sample, card to pick up the result). Requiring a card for participants to retrieve results (using the unique barcode) was explicitly requested by the ethics committee. This approach and the related procedure were approved by the ethics committee in each participating site. Study protocols were approved by each study site's ethics committee.

Sampling

Sexual minority men were recruited using time-location sampling (TLS), a venue-based sampling method widely adopted for bio-behavioral surveys among sexual minority men [40]. In line with the main TLS principles, formative research including a gay-venue mapping exercise was conducted in each participating city. A list of venue-daytime (VDT) units was prepared according to the formative research results. A data collection calendar was calculated according to TLS principles, creating VDT units. VDT units were then categorized according to the median attendance on the basis of two categories: "high attendance" (15 sexual minority men) and "low attendance" (5 sexual minority men). A training was delivered to field workers at local LGBT associations, who were in charge of approaching potential participants in the specific VDT unit and distributing questionnaires.

On the basis of the type of venues (e.g., disco, bar, sauna, cruising setting, sex shop/party), VDT units were randomly selected within homogeneous clusters of venues in order to ensure their comprehensive inclusion in the first sampling stage and therefore improve the heterogeneity of the final sample of sexual minority men. Finally, data collectors were selected and trained to distribute anonymous pen-and-paper questionnaires, and an info-pack containing prevention materials and information. Participants competed the questionnaires in the venues where they were recruited, and oral fluid samples were also collected in these locations (via Oracle device), in a pre-identified private area within the venue. Oral fluid, rather than blood, was collected to ensure participants' safety and increase acceptability among participants by preventing the need for venipuncture.

Questionnaire

A preliminary version of the self-administered pen-and-paper questionnaire was prepared with specific reference to the Global AIDS Response Progress Reporting (GARPR) guidelines [39]. A preliminary version of the questionnaire was then piloted among sexual minority men attending gay venues. Feedback regarding layout, wording, and comprehension was collected and included in the final version of the questionnaire. Translation procedures have been previously described elsewhere [37].

The self-administered questionnaire assessed a range of variables, of which we included the following in the current analyses: age, education, relationship status, behavioral practices (including sexual and substance use behaviors), types of sex partners (gender; steady and/or casual), and perceived stigma towards sexual minority men. Sexual orientation was assessed by asking "At present, how would you best define your sexual orientation?" with response options being "gay/homosexual," "bisexual," "heterosexual," or "other." We describe in detail the subset of variables we included in our analyses below.

Dependent Variables

We selected the following dependent variables because they have been shown in previous literature to have significant associations with HIV risk [41–46].

Sexual Behavior, Including HIV-Transmission Risk Behavior

We included two count variables indicating the number of (1) casual partners over the past 6 months and (2) instances of receptive and insertive sex (anal or vaginal) without a condom with casual partners reported over the past 6 months. Further, we included several dichotomous (yes/no) variables: (3) any HIV status-unknown casual partner at the last sexual encounter and (4) whether or not participants were under the influence of alcohol and/or recreational drugs (marijuana or illicit drugs such as cocaine, amphetamine, and/or ecstasy) prior to or during the last sexual encounter.

HIV Testing

We examined two factors related to HIV testing as dependent variables: (1) whether or not participants had an HIV test

in the past 12 months (yes/no), and (2) whether they knew where to receive an HIV test (yes/no).

Predictor Variable

Sexual Orientation Stigma

Participants reported stigma toward sexual minorities in their daily contexts as a response to the following question [35, 36]: "In your experience, what is people's attitude towards homosexuals or bisexuals in the following contexts: work/school; parents; friends/acquaintances; political; social; and religious." Response options ranged from 1 = very negative to 5 = very positive, and scale reliability was 0.76. This variable was z-scored for analyses.

Analytic Strategy

Analyses were conducted using *Mplus* version 8.0. Given the nesting within countries, we initially intended to analyze the data using multilevel modeling. However, the number of level 2 units (i.e., countries) was only six, power to detect any level 2 effects as well as to examine random between-country variability was substantially reduced. In unconditional multilevel models, we found that there was not significant between-country (i.e., random) variability on the majority of the outcomes—subsequent models that attempted to include predictors failed to converge due to difficulties estimation of random variances with a limited number of level 2 units. The lack of between-country variability also suggested that a single-level model that did not account for nesting within country was statistically appropriate. As such, we took the most parsimonious (and more simplistic) approach that was capable of handling the level of complexity observed in these data.

Specifically, we analyzed the eight outcome variables within a series of simultaneous regressions based on the types of analyses we conducted for each of them. The following six outcomes were analyzed using logistic regression given their dichotomous nature: sex under the influence of alcohol, sex under the influence of cannabis, sex under the influence of illicit drugs, knowing where to receive an HIV test, receiving an HIV test in the past 12 months, and having had any HIV-status-unknown casual partners at the last sexual encounter. The following two outcomes were analyzed using Poisson regression given their count nature: number of casual partners and frequency of condomless sex with casual partners in the past 6 months. We utilized robust maximum likelihood (i.e., MLR) estimation, which is known to be the optimal method for analyses with missing data, with the requisite Montecarlo integration. By default, *Mplus* will include participants who have not reported an outcome variable of interest, but will not include participants who have not reported on predictor variables of interest. In order to include participants who were missing predictor variables within the models, we utilized the option to estimate the mean and variance of each predictor variable within the model. The model also included dummy-coded dichotomous indicators for whether participants were missing any of the demographic covariates (1 = yes, 0 = no) and whether they were missing a score on the stigma variable (1 = yes, 0 = no). Upon preliminary examination of associations, the following demographic variables showed significant associations with stigma scores, and were therefore included in all models to adjust for their potential confounding influence: age (in continuous form), education (basic/up to 12 grades vs. above), sexual orientation (gay/homosexual vs. bisexual/heterosexual/other), size of residence (small vs. large, with the latter including settlements with over 100,000 inhabitants), employment (employed vs. unemployed), and relationship status (having had a steady partner in the past 6 months vs. not). We included in analyses only participants whose HIV-negative serostatus was confirmed by this project, using Oracol oral fluid collection kits.

Results

Of the 2424 surveys in the dataset, we excluded 181 HIV-positive participants and 139 without HIV test results given our focus on predicting HIV-transmission risk behavior among HIV-negative participants. Finally, 17 cases missing all of the outcome variables were excluded from analyses, resulting in a final analytic sample of 2087 HIV-negative sexual minority men. Table 1 shows the prevalence of missing data on each of the covariates, which ranged from 3.4 to 6.6%. In total, 4.5% of the sample was missing data for the stigma variable (not shown) and prevalence of missing data on the eight outcomes ranged from 0 to 11%. Across all variables within the model, covariance coverage ranged from 86 to 100%.

Participant Characteristics

Table 1 reports the socio-demographic characteristics of the sample. By design, the sample was nearly evenly divided among the five cities included within the present analyses. The majority of participants reported basic education or less (57.9%), being employed (73.9%), living within a city with population size exceeding 100,000 (66.5%), a gay sexual identity (80.2%), and having had a steady partner within the past 6 months (67.5%). The average age was 31.6 (SD = 9.7).

Table 1 Sample characteristics and associations with sexual minority stigma (N = 2087)

	n	%	*M* (SD)	Test statistic[a]
City, Country				
Prague, Poland	336	16.9	0.42 (0.81)	$F(5, 1988) = 31.1, p < 0.001$
Bratislava, Slovakia	349	17.5	0.00 (0.77)	
Barcelona, Spain	312	15.6	0.47 (0.83)	
Bucharest, Romania	305	15.3	−0.19 (0.93)	
Ljubljana, Slovenia	354	17.8	0.14 (0.91)	
Verona, Italy	338	16.9	−0.04 (0.86)	
Education				
Basic	1151	57.7	0.14 (0.91)	$F(2, 1991) = 0.42, p = 0.66$
University	774	38.8	0.13 (0.84)	
Missing	69	3.4	0.04 (0.96)	
Employment status				
Employed	1481	74.3	0.14 (0.89)	$F(2, 1991) = 0.62, p = 0.54$
Unemployed	433	21.7	0.13 (0.86)	
Missing	80	4.0	0.02 (0.94)	
Residential area				
Small city (population < 100,000)	639	32.0	0.40 (0.90)	$F(2, 1991) = 4.96, p < 0.01$
City (population > 100,000)	1339	67.1	0.17 (0.87)	
Missing	16	0.80	0.03 (1.11)	
Sexual identity				
Gay/homosexual	1628	81.6	0.18 (0.85)	$F(2, 1991) = 11.5, p < 0.001$
Bisexual or heterosexual	343	17.2	−0.07 (0.98)	
Missing	23	1.15	−0.003 (0.96)	
Steady partner in past 6 months				
No	596	29.9	0.12 (0.86)	$F(2, 1991) = 1.57, p = 0.21$
Yes	1353	67.9	0.14 (0.89)	
Missing	45	2.25	−0.90 (1.0)	
	M	*SD*	Range	
Age (*Mdn* = 30.0; valid *n* = 2000)	31.6	9.7	18–76	$r = -0.021, p = 0.37$

[a]ANOVA tests were used to test for differences across groups

Associations of Demographic Characteristics and HIV Risk Behavior

Tables 2 and 3 report the results of the eight simultaneous regression analyses performed. With regard to demographic covariates, age was significantly associated with six of the outcome variables, education was significantly associated with three, employment was significantly associated with two, sexual orientation was significantly associated with five, location of primary dwelling was associated with four, and having a steady/main partner was associated with five.

Associations of Sexual Minority Stigma and Alcohol/Drug Use at Last Sexual Encounter

Stigma was significantly associated with five of the outcomes (Table 2). For the three substance-related outcomes, a one standard deviation increase in stigma was associated with a 19% increase in the odds of sex under the influence of alcohol at the last sexual encounter, a 27% increase in the odds of sex under the influence of cannabis at the last sexual encounter, and a 49% increase in the odds of sex under the influence of illicit drugs at the last sexual encounter.

Associations of Sexual Minority Stigma and Condomless Sex and HIV Testing

Table 3 presents results indicating that stigma was positively associated with one HIV risk outcome in the expected direction. Namely, a one standard deviation increase in stigma was associated with an 11% increase in the odds of condomless sex with casual partners in the past 6 months. Conversely, a one standard deviation increase in stigma was associated with a 26% increase in the odds of knowing

Table 2 Regression models for sexual behavior under the influence and HIV testing awareness predicted by sexual orientation stigma ($n = 2087$)

	Last sex: under the influence of alcohol			Last sex: under the influence of cannabis			Last sex: under the influence of club drugs			Knowing where to get an HIV test		
	B	AOR	95% CI	B	AOR	95% CI	B	AOR	95% CI	B	AOR	95% CI
Age	−0.02	0.98**	[0.97, 0.99]	−0.01	0.99	[0.97, 1.01]	−0.01	0.99	[0.97, 1.01]	0.04	1.04**	[1.01, 1.06]
Missing covariates (ref. = no)	0.21	1.24	[−0.07, 0.49]	0.52	1.68*	[1.05, 2.69]	0.16	1.18	[0.71, 1.95]	−0.52	0.59*	[0.39, 0.90]
Missing stigma (ref. = no)	1.06	2.88***	[0.47, 1.65]	0.46	1.58	[0.60, 4.17]	0.66	1.93	[0.75, 4.94]	−1.02	0.36**	[0.19, 0.68]
University education (ref. = basic)	−0.13	0.88	[0.72, 1.07]	−0.43	0.65*	[0.45, 0.96]	0.04	1.04	[0.71, 1.53]	0.29	1.33	[0.93, 1.92]
Employed (ref. = unemployed)	−0.29	0.75*	[0.59, 0.96]	−0.07	0.93	[0.59, 1.47]	−0.32	0.73	[0.45, 1.19]	0.03	1.03	[0.67, 1.58]
Bisexual orientation (ref. = gay)	0.44	1.55***	[1.22, 1.98]	0.55	1.74**	[1.14, 2.64]	0.83	2.30***	[1.52, 3.47]	−0.25	0.78	[0.52, 1.17]
City dweller (ref. = small city/town)	0.24	1.27*	[1.03, 1.55]	0.31	1.37	[0.91, 2.05]	0.23	1.25	[0.82, 1.92]	0.40	1.50*	[1.06, 2.12]
Had a steady partner (ref. = no)	−0.26	0.77*	[0.63, 0.95]	−0.34	0.71	[0.49, 1.04]	−0.28	0.76	[0.52, 1.11]	0.23	1.26	[0.88, 1.79]
Sexual orientation stigma (z-score)	0.18	1.19***	[1.07, 1.33]	0.24	1.27*	[1.03, 1.56]	0.40	1.49***	[1.22, 1.82]	0.23	1.26*	[1.01, 1.59]

All models were adjusted for demographic characteristics significantly associated with sexual orientation stigma

B unadjusted coefficient, *AOR* adjusted coefficient

$N = 2087$. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Table 3 Regression models for HIV testing behavior and sexual behaviors predicted by sexual orientation stigma ($n = 2087$)

	HIV tested past 12 months			Any HIV status-unknown casual partners			Number of casual partners[a]			Frequency of condomless sex with casual partners[a]		
	B	AOR	95% CI	B	AOR	95% CI	B	AOR	95% CI	B	AOR	95% CI
Age	0.02	1.02***	[1.01, 1.03]	0.03	1.03***	[1.02, 1.04]	0.02	1.02***	[1.01, 1.03]	−0.02	0.98***	[0.97, 0.99]
Missing covariates (ref. = no)	−0.19	0.83	[0.64, 1.08]	−0.26	0.77	[0.59, 1.01]	0.45	1.56	[0.65, 2.47]	0.04	1.04	[0.79, 1.29]
Missing stigma (ref. = no)	−0.30	0.74	[0.45, 1.21]	−0.24	0.79	[0.49, 1.25]	0.03	1.03	[0.63, 1.43]	0.33	1.39	[0.91, 1.86]
University education (ref. = basic)	0.18	1.20	[0.99, 1.44]	0.15	1.16	[0.96, 1.41]	0.42	1.53*	[1.10, 2.11]	−0.39	0.68***	[0.56, 0.82]
Employed (ref. = unemployed)	0.00	1.00	[0.80, 1.26]	−0.04	0.96	[0.76, 1.21]	0.38	1.46*	[1.00, 2.13]	0.05	1.05	[0.84, 1.32]
Bisexual orientation (ref. = gay)	−0.07	0.93	[0.74, 1.18]	−0.31	0.73*	[0.58, 0.93]	0.31	1.37	[0.92, 2.02]	0.10	1.11	[0.92, 1.33]
City dweller (ref. = small city/town)	0.24	1.27*	[1.05, 1.54]	0.03	1.03	[0.85, 1.25]	0.39	1.48***	[1.22, 1.79]	−0.04	0.96	[0.81, 1.14]
Had a steady partner (ref. = no)	0.29	1.34**	[1.10, 1.62]	−0.67	0.51***	[0.42, 0.63]	−0.47	0.63***	[0.53, 0.74]	0.20	1.22*	[1.02, 1.45]
Sexual orientation stigma (z-score)	0.08	1.08	[0.97, 1.20]	−0.09	0.92	[0.83, 1.02]	0.07	1.08	[0.91, 1.27]	0.11	1.11*	[1.01, 1.23]

All models were adjusted for demographic characteristics significantly associated with sexual orientation stigma

B unadjusted coefficient, *AOR* adjusted coefficient

$N = 2087$. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[a]Modeled using Poisson distribution

where to receive an HIV test, though not associated with actual testing in the prior 12 months. Stigma was also not associated with having HIV status-unknown casual partners or with the total number of casual partners in the past 6 months.

Discussion

In this large sample of sexual minority men across six diverse European contexts, those who perceived greater sexual orientation stigma in their daily social institutions were significantly more likely to report sexual risk behavior with casual partners, as well as alcohol, marijuana, and illicit drug use (including cocaine, amphetamine, and MDMA) immediately prior to or during their most recent sexual encounter. While alcohol and drug use are established predictors of HIV-risk behavior [47, 48], the results of this study suggest that perceived high sexual orientation stigma from one's social environment (from family to government), as reported by sexual minority men, might serve as a precursor to these risks, confirming previous findings [49]. At the same time, the impact of stigma on sexual minority men's HIV-related risk is capable of being modified through interventions that support stigmatized individuals' acquisition of skills to ameliorate the effects of stigma on health, and to view stigma as a problematic societal phenomenon, external to the individual, in need of change [50–52]. Below, we highlight how individually-focused interventions can improve stigma coping to reduce sexual minority men's HIV risk alongside structural interventions to reduce stigma at its source in discriminatory social institutions.

According to minority stress theory, sexual minority men living in social contexts marked by prevalent sexual minority stigma likely experience increased stress and associated coping strategies, including maladaptive strategies, for managing that stress [53, 54]. Our results suggest that alcohol and drug use might serve as a prominent mechanism for coping with stigma-related stress among European sexual minority men who frequently encounter social contextual stigma. Our findings show that stigma is particularly associated with alcohol and drug use in the context of sexual activity with other men. Perhaps sex with men invokes shame and guilt through making the stigma of one's sexual orientation particularly salient, with substance use during sex being one way to cope with this salience. Indeed, sexual minority men living in stigmatizing national contexts report high degrees of internalized homonegativity [55–57], which, though unmeasured here, potentially drives distress or cognitive dissonance during same-sex sexual behaviors [58]. Internalized homophobia, in turn, has shown consistent associations with substance use across several studies [49, 59]. These findings suggest that HIV-prevention strategies should build not only knowledge, motivation, and skills for engaging in HIV-prevention behavior, but also build adaptive forms of stigma coping as an important goal to reduce HIV-risk behavior [50, 60].

Our analyses paradoxically showed that those reporting higher levels of social contextual stigma were more likely to know where they could test for HIV, which may be explained by successful efforts by local advocates and NGOs to disseminate health-related information to those who most need it. Although stigma appeared to play a protective role in the sense that higher levels predicted better knowledge regarding HIV testing locations, it was not associated with individuals actually testing more frequently. This finding echoes literature indicating that knowledge is not sufficient to lead to action, and that building behavioral skills for self-efficacy is a necessary step alongside acquiring information [61]. Future research will need to determine the mechanisms through which greater stigma predicts greater knowledge of local testing resources. Results further suggest the need for prevention resources to motivate sexual minority men who perceive high levels of stigma in their daily lives to translate their knowledge of preventive resources into action by increasing their HIV testing frequency.

Finally, one's number of casual partners reported over the past 6 months and not knowing the HIV status of these casual partners had no associations with perceptions of social contextual stigma. However, perceptions of social contextual stigma were associated with a small increase in odds of engaging in condomless sex with casual partners over the past 6 months. This finding supports previous research suggesting that stigma serves as a determinant of sexual minority men's HIV risk [8, 29, 62, 63], but suggests that this risk might only extend to condom use, rather than selection of casual partners, lack of communication with partners about status, or number of partners. Future research might determine the mechanisms, both environmental (e.g., condom availability) and psychological (e.g., condom use self-assertion), as mechanisms linking perceived stigma to lack of condom use with casual partners.

As suggested above, interventions that promote stigma coping by promoting self-assertion and reducing social or emotional avoidance, might be employed fruitfully to increase sexual minority men's condom use, HIV testing, and reduce alcohol and drug use. Evidence suggests that such interventions show preliminary promise [50, 64]. Furthermore, mobile health (mHealth) interventions, which possess acceptability, feasibility, as well as efficacy in reducing HIV risk across various cultural contexts [64–66] may be a particularly useful modality of reaching large numbers of vulnerable sexual minority men who are likely to conceal their identities in highly stigmatizing contexts and prefer to access preventive resources in virtual settings where they feel safest [65, 67–69]. These types of interventions address

several barriers to prevention by directly delivering LGBT-affirmative HIV risk-reduction interventions to vulnerable populations [70], especially those who are otherwise out-of-reach of public health campaigns because of geographical constraints, lack of brick-and-mortar establishments, and/or stigma itself.

Limitations

These findings should be interpreted in the light of several limitations. First, our study is limited by several aspects of our measurement approach. Measuring stigma is complex given the multiple levels of the ecosystem on which it manifests itself (e.g., from structural to individuals). In fact, in choosing to focus on social contextual stigma, we did not capture other forms of this multifaceted construct, including self-stigma (e.g., internalized stigma) and structural stigma (e.g., national laws and policies toward sexual minorities) [24]. Furthermore, we examined prejudice from different sources as an aggregate of contextual stigma, however, stigma experienced from family vs. coworkers or religious institutions may have differential impact on various outcomes. Therefore, future research would benefit from examining these relationships individually, rather than as a cumulative independent variable on outcomes of sexual risk. Still, evidence suggests that these diverse forms of stigma are related to the construct assessed here [27, 62, 71]. Another measurement limitation involves reliance on self-reported stigma, introducing potential confounds between our stress-related outcomes and stigma [72]. The inclusion of an interviewer-based calendar review of sexual behavior and alcohol/drug use history would have allowed for more fine-grained analyses that would include, for example, alcohol and drug use modelling independent of sexual encounters, or for day-level sexual risk behavior. Relatedly, the data were obtained through self-report, which could be considered to be a limitation in an epidemiological study. Lastly, more recent data would provide a clearer picture of the immediate context; yet associations among the variables examined here are likely to persist across time, even if their overall prevalence changes.

Although a small proportion of respondents was missing data, we utilized one of the most widely accepted techniques for handling such data that also allowed us to include them within models. Patterns of missing data were significantly associated with some but not all outcomes, though these effects were accounted for within the models; nonetheless, findings for those models should be interpreted with caution. Sensitivity analyses suggested that our approach of using missing data indicators along with robust maximum likelihood estimation reduced effect sizes for stigma and widened confidence intervals, making it more difficult to detect significant effects, compared to models without such indicators. As such, despite missing data, this conservative approach likely underestimated rather than overestimating the effect sizes and, to the extent it may have been biased, was biased toward non-significance. Because the dataset contained individuals from a diverse group of European countries, we initially hoped to take the nesting of the data into account and consider the role of country-level structural factors. However, with only six countries, the number of Level 2 units within the multilevel model was small, undermining any power to analyze Level 2 predictors and compromising the ability to estimate the Level 2 variance of the eight categorical and count outcomes (i.e., models would not converge due to the combination of model complexity and insufficient Level 2 units of analysis). Future studies with more variability across locations that can also incorporate higher-level predictors are warranted.

Conclusion

Our findings suggest that perceptions of social contextual stigma toward one's sexual orientation serve as an important risk factor for HIV infection. These findings help identify a clear pathway that might jeopardize the health of sexual minority men who live in ubiquitously stigmatizing environments. While our findings suggest that interventions designed to support sexual minority men's stigma coping abilities can protect against risk [50, 51, 64–66, 73–77], concomitant structural changes capable of reducing stigma at its source in stigmatizing political, legal, and institutional structures are also needed. Such changes are especially needed in countries where these structures perpetuate conditions in which sexual minorities are likely to perceive high levels of social contextual stigma and therefore be at greater risk of adverse behavioral health.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Research Involving Human Subjects Informed consent was obtained from all individual participants included in the study. Study protocols were approved by each study site's ethics committee, and are in compliance with the 1964 Declaration of Helsinki for ethical principles for conducting research with human subjects.

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Nigel S. Sherriff
University of Brighton
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02.08.2019

Unser Zeichen:

Dear Nigel,

This is to confirm that Lorenzo Gios was largely responsible for the conception and design of the paper "Being in the closet. Correlates of outness amongst MSM in 13 European cities", based on the data collected though the EU-funded Sialon II survey. He led the manuscript development in terms of analysis of the data, interpretation and revision of the final version approved by all the co-authors.

Best regards,

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Being in the Closet. Correlates of Outness Among MSM in 13 European Cities

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ABSTRACT

Data for MSM continue to show a high risk of acquiring HIV-STIs. Within this population, outness seems to have an impact on both risk-taking and on health seeking behaviors. The objective of this study was to assess the relationship between socio-demographic, behavioral characteristics, testing behaviors, and outness level among MSM using data from a multi-center bio-behavioral cross-sectional study carried out in 13 EU cities. A multilevel analysis was conducted to identify factors associated with being open ("out") versus not being open ("in"). A total of 4,901 MSM were enrolled in the study and were classified as "out" in 71% of the cases. MSM "out" were more likely to report HIV testing and being reached by HIV prevention programs compared to MSM who were "in." The results confirm the key role of outness in relation to different healthy and risky behavior, ranging from testing to party-drug use.

KEYWORDS

MSM; outness; bio-behavioral survey; Time-Location Sampling; respondent-driven sampling; risk behaviors; HIV testing

Introduction

Evidence suggests that lesbian, gay, bisexuals, trans, and intersex (LGBTI) people, and among these communities Men who have Sex with Men (MSM) in particular, are reporting worse general health and mental health compared to the general population (Blondeel et al., 2016; Bybee, Sullivan, Zielonka, &

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Moes, 2009; Zeeman et al., 2018). From a public health perspective, surveillance data for MSM continue to show that the risk of acquiring HIV and Sexually Transmitted Infections (STIs) is particularly high among gay, bisexual and other MSM (Beyrer, Baral, & van Griensven et al., 2012; European Centre for Disease and Control Special Report [ECDC], 2015). A range of different factors may play decisive roles in influencing the epidemics among MSM. These factors range from behavioral aspects such as levels of condom use, and the use of drugs before or during sexual encounters, to other broader and more contextual factors (e.g. the level and quality of prevention campaigns targeting this specific group, potential discriminatory environments or community attitudes toward gay people). In addition, recent data confirms the existence of concentrated epidemics among MSM, presumably due also to sexual networking which might considerably increase the risk of acquiring HIV (Baral, Logie, Grosso, Wirtz, & Beyrer, 2013; Young, Szekeres, & Coates, 2013). These aspects clearly highlight the urgency and need for further prevention efforts in this field, including a better understanding of the factors, which might shape the epidemics and healthy lives among MSM populations (ECDC, 2017).

The findings of previous behavioral studies have led researchers to consider the key role of contextual and psychosocial factors in affecting general health and mental health (Bybee et al., 2009), in hindering HIV test seeking behaviors and treatment (Wao, Aluoch, Odondi, Tenge, & Iznaga, 2016). Among these factors, perceived homophobia and level of outness, generally defined as the degree to which people are open about their sexual orientation and/or behavior), are playing an important role (Bybee et al., 2009; Wao et al., 2016). Perceived homophobia and outness also play a role in enhancing the probability of adopting risk behaviors and thus in acquiring HIV and other STIs (Berg, Weatherburn, Ross, & Schmidt, 2015; Mansergh et al., 2015; Pachankis et al., 2015, 2017; Rosser, Horvath, & Hatfield et al., 2008; Ross, Berg, & Schmidt, 2013). Despite some divergent results, there is broad agreement that hetero-normative environments (if not intolerant environments toward same-sex relations) may negatively affect general wellbeing and healthy behaviors among MSM, including access to health-care services (Whitehead, Shaver, & Stephenson, 2016). This mechanism can also potentially expose this population to a considerable level of stress (Herek, 2004; Singer, Bulled, Ostrach, & Mendenhall, 2017).

In particular, "outness" has a moderating effect both on risk-taking and on health seeking behaviors (Mansergh et al., 2015; Mirandola et al., 2017; Pitpitan et al., 2016; Whitehead et al., 2016), although the direct effect on sexual behaviors is somewhat debatable (Bybee et al., 2009). Both outness and perceived stigma might contribute to a reduction in access to a cluster of health prevention initiatives and services, including condom promotion

and testing and treatment (Ayala et al., 2013; Mirandola et al., 2017). Both disclosure and coming out play also a key role in the general process of identity and sexual identity formation (Feldman & Wright, 2013). Sexual identity is defined from the WHO as an integral part of one's sexual health, providing an approximation of a level of sexual well-being (Toskin, Hawkes, Moreno, Caceres, & Zohrabyan, 2013; WHO, 2010).

Focusing on coming out, broader social norms may impact on this multi-faceted process: migrant MSM or MSM sharing specific cultural backgrounds are likely to experience even more difficulties in disclosing their sexual orientation or identity (Rosario, Schrimshaw, & Hunter, 2004; Xu, Zheng, Xu, & Zheng, 2017).

In addition, segments of MSM population particularly exposed to specific hetero-normative environment can be more likely to adopt bi-sexual behaviors, potentially contributing to the spread of HIV and sexu-ally transmitted infections to the general population (Mirandola et al., 2017; Mirandola et al., 2017).

Considering this scenario, research is needed to investigate more clo-sely the role outness plays within MSM populations and to better char-acterize those MSM who are "out" versus those MSM who are "in the closet" (a generally accepted colloquialism for MSM "not out"). This may help to inform better targeted prevention campaigns focusing on this latter sub-population, whom may be particularly exposed to psychosocial stressors and related risk behaviors (Pitpitan et al., 2016).

The aim of the present analysis is to explore the relationship between outness and demographics, drug use, testing behaviors, sexual satisfaction and perceived stigma among MSM enrolled in the Sialon II bio-behavioral multi-site survey which was co-funded by the European Commission under the Second Programme of Community Action in the Field of Health 2008–2013 (Mirandola et al., 2009; Mirandola et al., 2016; Mirandola et al., 2018; Gios, Mirandola, Toskin, & Marcus et al., 2016). The core assumptions of the analysis are based on key findings which underline that MSM in the closet (compared to MSM who are out) are more likely to: (i) report risk behaviors defined as party-drug use (Chard, Metheny, Sullivan, & Stephenson, 2017); (ii) perceive a high level of stigma toward LGB people (Pachankis et al., 2017); (iii) report low levels of health seeking behaviors (e.g., get tested and/or being reached by prevention programs); and (iv) engage in bisexual behaviors (Mirandola et al., 2017). In the present analysis, these main areas are considered in a unique model based also on previous work suggesting a potential link between perceived stigma, outness levels, and bisexuality (Mirandola et al., 2017; Pachankis et al., 2017).

Materials and methods

Study design

The Sialon II project was a multi-center biological and behavioral cross-sectional survey carried out across 13 European cities including: Brussels (Belgium), Sofia (Bulgaria), Hamburg (Germany), Verona (Italy), Vilnius (Lithuania), Warsaw (Poland), Lisbon (Portugal), Bucharest (Romania), Bratislava (Slovakia), Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden), and Brighton (UK). The survey was implemented adopting the same methodologies (protocols, UN Global AIDS Response Progress Reporting GARPR indicators, epidemiological algorithms) in each study site, whilst two different enrolling methods have been adopted in line with the local context and needs; namely Time-Location Sampling (TLS) and Respondent-Driven Sampling (RDS). Study procedures as well as bio-behavioral data collection and testing methodologies are described elsewhere (Gios et al., 2016).

Participants

The study population comprised male participants present in the study cities during the data collection period. The following inclusion criteria were used to define eligibility: being older than 18 years old, having had sex (any kind of sex) with a man during the last 12 months, providing a consent form, agreeing to donate either oral fluid specimen (in case of the TLS survey) or whole blood specimen (in case of the RDS survey). Exclusion criteria were: being younger than 18 years old, and having already participated in the study.

Survey questionnaire

A pen-and-paper questionnaire was designed based on the GAM indicators guidelines (UNAIDS, 2014) and former relevant projects targeting MSM. Piloting of the questionnaires were conducted as well as translation/back translation to ensure consistency and quality of the items. The self-administered tool was used to gather information on demographic profile, sexual and testing behavior, perceived stigma, and outness.

Variables

Dependent variable

Outness was measured using an item analyzed in previous publications (Mirandola et al., 2016, 2017, 2017). The following question was adopted: "Thinking about all the people who know you (including family, friends, and

work or study colleagues), what proportion knows that you are attracted to men?" Possible options were: "none"; "few"; "less than half"; "more than half"; "all or almost all."

In order to facilitate the analysis, the variable was dichotomized as follows: i) those out to "no one," to "few" the people they know (defined as "in the closet"), ii) those out to "less than half," "more than half" or to "all or almost all" of the people they know (defined as "out"). This categorization is also based on previous studies on outness (Pitpitan et al., 2016).

Independent variables

The following variables were included as explanatory variables based on self-reported data: age, level of education (categorized as secondary school/high school or lower *vs.* university degree or higher), origin (emigrant/immigrant or visitor *vs.* native-born considering the study country), lifetime HIV testing, being reached by prevention programs in the last year (as measured according to the GAM guidelines), use of party drugs, sexual satisfaction and perceived stigma. Information on party drug use was collected using specific items focusing on drugs (ecstasy, cocaine, amphetamine, GHB, ketamine, mephedrone, crystal meth) used during the last anal sex with a male partner. With regards to the perceived stigma data, this was based on the item "In your experience, what is most people's attitude toward gays or bisexuals in the following contexts?" The item addressed three main areas, such work/school, parents and friends/acquaintances. Survey participants were asked to respond using a 5-point Likert scale ranging from 1 (very negative) to 5 (very positive) regarding perceptions of homophobia (Cronbach's alpha .73). To simplify data interpretation, the scale's range—originally ranging from a minimum of 3 to a maximum of 15 points—was reversed. The sexual satisfaction variable was based on the WHO item "How satisfied are you with your sex life?" (WHO, 2010). Four options were possible, ranging from "very satisfied" to "very unsatisfied." The sexual satisfaction variable was dichotomized, considering (i) those reporting either "very satisfied" or "satisfied" answers and (ii) those reporting either "unsatisfied" or "very unsatisfied" responses.

Statistical methods

Descriptive and bivariate analysis

For nominal variables, percentages and Fisher's exact test were used, whilst for quantitative variables, mean, median, standard deviation, Wilcoxon–Mann–Whitney test and Kruskal–Wallis test by ranks were used. Bivariate

analyses were carried out using a multivariate logistic model and $p < .05$ was adopted as a threshold to include variables.

Multi-level modeling

A multivariable multi-level logistic random-intercept model (also known as hierarchical modeling) was estimated. This approach was used specifically for (i) dealing with the structure of the sample (cities), and (ii) the possibility of including random intercepts and slopes when needed (Rabe-Hesketh & Skrondal, 2008). Through this modeling approach, factors associated with being out *vs.* being not out were identified, according to the categorization described above. STATA Version 14.2 was used for all analyses (College Station, TX: StataCorp LP).

Ethics

Prior to data collection, research protocols were submitted to and approved by the ethics committee in each participating city, as well as both by WHO Research Project Review Panel (RP2) and WHO Research Ethics Review Committee (ERC) in 2012–13.

Results

Participants

Across the 13 sites, 4,901 MSM were enrolled in the study (TLS survey: 3,596 participants; RDS survey: 1,305 participants; a total of 4,742 MSM were then considered for outness analysis). An extensive description of the sample, characterizing the main demographic data has been published elsewhere (Mirandola et al., 2016).

Proportions of MSM "out" and "in the closet" across study sites

Considering the entire sample, more than two-thirds of the study participants can be considered "out" (3,358; 71% of the sample). However, the number of MSM reporting to be out versus in the closet greatly varies among the different study sites (Table 1) (Figure 1). Among the Sialon II study sites, cities with the highest proportion of MSM "in the closet" were mainly Eastern European cities such as Bucharest (57%), Vilnius (47%) and Warsaw (45%) (in the first two cities, RDS survey was adopted). Within the study sites, the highest level of MSM defined as "out" were reported in Brighton (86%), Hamburg (85%) and Brussels (83%).

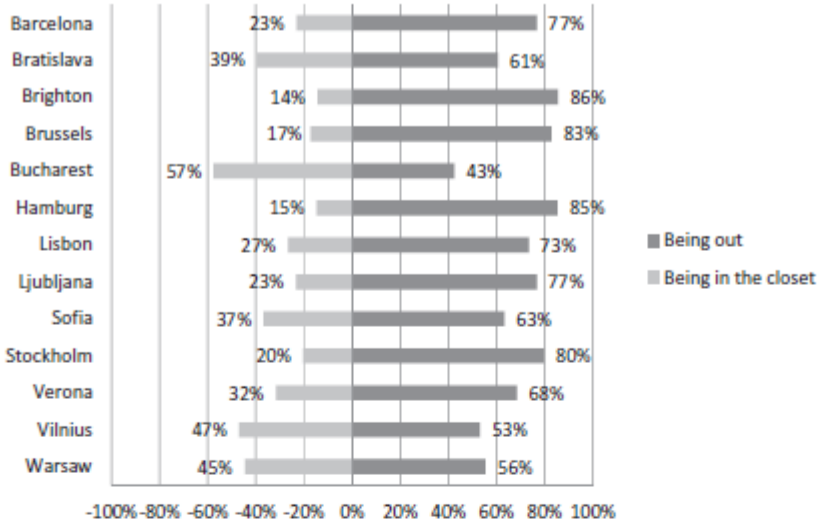

Figure 1. Number of MSM being out and being in the closet, per city.

Table 1. Number of MSM being out and being in the closet, per city.

City	Being in the closet	Being out	Total
Barcelona	90	300	390
	23%	*77%*	*100%*
Bratislava	155	238	393
	39%	*61%*	*100%*
Brighton	57	340	397
	14%	*86%*	*100%*
Brussels	65	315	380
	17%	*83%*	*100%*
Bucharest	100	74	174
	57%	*43%*	*100%*
Hamburg	58	338	396
	15%	*85%*	*100%*
Lisbon	106	293	399
	27%	*73%*	*100%*
Ljubljana	88	292	380
	23%	*77%*	*100%*
Sofia	150	259	409
	37%	*63%*	*100%*
Stockholm	63	248	311
	20%	*80%*	*100%*
Verona	124	269	393
	32%	*68%*	*100%*
Vilnius	150	170	320
	47%	*53%*	*100%*
Warsaw	178	222	400
	45%	*56%*	*100%*
TOTAL	1,384	3,358	4,742
	29%	*71%*	*100%*

Association between outness and demographic data (bivariate analysis)

Data on bivariate analysis are presented in Table 2. Considering demographic data, compared to the participants defined as "in the closet," MSM who are "out" were older (mean age 34.44 *vs.* 32.55 among those "in the closet") and better educated (57% university degree *vs.* 52%, $p < .01$). Compared to MSM in the closet, MSM who are open about their sexual practice are more likely to live in the study city (even if the difference is very small, around 72% in both cases with approximation, $p < .01$) and to be migrant or visitor (17% *vs.*16%, $p < .01$). In terms of participants considered as bisexual (that is, MSM declaring to have had sex with both men and women in the previous 6 months), being Men who have Sex with both Men and Women (MSMW) is more frequent among those "in the closet" compared to those are open about their sexual practice (25% *vs.* 7% among those who are "out," $p < .05$).

Table 2. Percent of MSM with various characteristics, by outness (bivariate analysis).

Characteristic	MSM in the closet (n = 1,380)		MSM out (n = 3,357)		*P value*
Age					0.00
Mean	33.74		34.57		
Median	32.00		32.00		
St. Dev.	11.36		11.12		
Being MSMW					0.00
No	985	75%	2,968	93%	
Yes	336	25%	219	7%	
Area of residence					0.01
Outside the study city	391	28%	927	28%	
In the study city	982	72%	2,410	72%	
Educational status					0.00
Secondary school (high school) or lower	653	48%	1,415	43%	
University or higher	700	52%	1,887	57%	
Origin					0.00
Emigrant/immigrant or visitor	223	16%	560	17%	
Native-born	1,154	84%	2,791	83%	
HIV Testing (lifetime)					0.00
Never tested	431	35%	516	17%	
Tested at least once	810	65%	2,585	83%	
Being reached by prevention programs (condom distribution) in the last 12 months					0.00
No	632	47%	1,126	34%	
Yes	723	53%	2,195	66%	
Use of party drugs					0.09
No	1,184	93%	2,915	90%	
Yes	90	7%	323	10%	
Sexual satisfaction					0.09
Not satisfied	332	26%	711	22%	
Satisfied	936	74%	2,482	78%	
LGB stigma perception					0.00
Mean	7.1		9.5		
Median	7.0		9.0		
St. Dev.	2.3		2.4		

Association between outness and testing, risk behavior (party drugs use), prevention programs, stigma and sexual satisfaction (bivariate analysis)

MSM who are "out" are more likely to report being reached by HIV prevention programs in the last 12 months (66%), compared to those who were classified as being in the closet (53%; $p < .01$). MSM open about their sexual behavior more frequently report being tested for HIV at least once (83% *vs.* 65% among those "in the closet," $p < .01$). Usage of party drugs seems to be more common behavior for those who are "out," compared to the MSM who are not open (10% vs. 7%), even if this difference is not statistically significant ($p > .05$). When considering perceptions of LGB stigma, MSM who are "out" report significantly higher levels of perceived stigma than MSM in the closet (Mean 9.5 *vs.* 7.1, $p < .01$, according to the LBG score used in the present study).

Finally, in terms of sexual satisfaction, minor differences are reported between the two groups ($p > .05$). In general, MSM in the closet are less sexually satisfied than those out. Nine hundred and thirty-six MSM who are in the closet (74%) described themselves as sexually satisfied, whilst 2,482 MSM open about their orientation (sexual behavior) are reporting positive sexual satisfaction (78%).

Being in the closet *vs.* being out (multilevel multivariate model)

Considering the outputs of the bivariate analysis, some predictors identified in that phase of the analysis were not significantly associated with the dependent variable once included in the multilevel multivariate model (see Table 3).

Being MSMW represents a significant factor in characterizing MSM who are open about their own sexual behavior versus MSM in the closet. MSM who are "out" show a decrease in the odds of being MSMW compared to the MSM who are not out (OR = 0.27; $p < .01$). In terms of demographical characteristics, MSM with a high educational status (university degree or higher) report an odds ratio of 1.24 to be "out of the closet" (OR = 1.24; $p < .05$) compared to those who are reporting a secondary school or lower level.

The area of residence was not a significant factor in differentiating MSM "out" or "in the closet" in the model, despite participants who are living in the study city report an odds ratio of 1.14 to be "out of the closet" compared to those who are living outside the study city ($p > .05$). This seems to suggest that MSM "in" were more likely than MSM "out" to live in rural areas, or in small cities/towns. Considering the status of native-born in the country study versus the status of migrant or visitor, MSM who are native-born report a higher OR of being open (OR = 1.43; $p < .05$).

When considering protective factors, such as HIV testing and being reached by prevention programs, the model shows different levels of odds ratio between the two groups. MSM who tested at least once in their life and

Table 3. Multilevel multivariate model.

		OR	95% CI		P
Fixed part					
Being MSMW	No	1			
	Yes	0.27	0.21	0.35	0.00
Area of residence	Out-side the study city	1			
	Study city	1.14	0.94	1.39	0.19
Educational status	Secondary school (high school) or lower	1			
	University or higher	1.24	1.03	1.50	0.03
Origin	Emigrant/immigrant or visitor	1			
	Native-born	1.43	1.11	1.84	0.01
HIV Testing (lifetime)	Never tested	1			
	Tested at least once	1.91	1.53	2.38	0.00
Being reached by prevention programs	No	1			
	Yes	1.34	1.11	1.62	0.00
Use of party drugs	No	1			
	Yes	1.99	1.36	2.90	0.00
Sexual satisfaction	Unsatisfied	1			
	Satisfied	0.93	0.75	1.15	0.49
LGB stigma perception		0.65	0.62	0.68	0.00
Age		0.99	0.98	1.00	0.02
Const.		51.31	27.38	99.96	0.00
Random part					
City					
	Var	0.22	0.09	0.53	
LR test vs. logistic regression: chibar2(01) = 88.56 Prob≥chibar2 = 0.0000					

confirmed that they were reached by prevention programs report a high odds ratio to be out of the closet (OR = 1.91; $p > .01$ and OR = 1.34; $p > .01$, respectively), compared to those who didn't report such behaviors. The model shows that MSM who are out are more likely to report party drugs to use compared to those who are "in the closet" (OR = 1.99; $p < .01$).

The model also shows significant differences among MSM "out" and "in" in terms of stigma perception. MSM who are open about their sexual behavior are less likely to perceive a hostile environment toward LGBT people, compared to the participants who were classified as "in the closet" (OR = 0.65; $p < .01$). In terms of sexual satisfaction, the model does not highlight substantial differences between MSM "out" and MSM "in the closet" (OR = 0.93; $p > .05$). Finally, the lower the odds of being out of the closet are, the higher the age is, even if this difference in terms of OR is relatively narrow (OR 0.99; $p < .05$). This seems to suggest that old MSM are more likely to be open about their sexual behavior, compared to the young MSM.

Discussion

To our knowledge, the data presented in this study are unique. No previous survey has examined outness using sampling methods designed specifically

for "hard to reach" and/or most at-risk populations such as MSM, that is, TLS and RDS, in the context of a wide multi-site European survey (13 European cities).

Levels of outness greatly varied across a study the 13 cities, with higher levels of MSM classified as "in the closet" in Eastern European sites, such as Bucharest (57%), Vilnius (47%) and Warsaw (45%). Among the different sites, the highest levels of participants defined as "out" were found in Brighton (86%), Hamburg (85%) and Brussels (83%).

Compared to the MSM "in the closet," MSM who are "out" were older, better educated, more likely to live in the study city and less likely to be behaviorally bisexual (MSMW) ($p < .05$).

In our analysis considering factors like testing and prevention, MSM who were "out" were more likely to report being reached by HIV prevention programs and HIV testing (lifetime), compared to those who were classified as being in the closet ($p < .01$). MSM open about their same-sex sexual practices were less likely to report high levels of stigma perception compared than MSM in the closet. Results on outness and perceptions of stigmatizing environments seem to confirm that these two factors might be reinforcing each other: a non-LGBT friendly social arena might heavily hamper the disclosure of one's sexual orientation and in doing so lead to a decreased access to testing services (Mirandola et al., 2017).

When considering variables which might be defined as protective factors versus risk factors, the present results seem to highlight a multifaceted characterization of both MSM in the closet and out of the closet.

Compared to MSM who are defined as "in the closet," MSM who are "out" seems to benefit from a set of protective factors, such as a higher level of HIV testing and prevention programs coverage, and have a perception of a lower LGB stigmatizing environment. This is also confirmed in other studies (Berg et al., 2015; Mansergh et al., 2015; Pitpitan et al., 2016). Moreover, MSM who are in the closet are less likely to be party-drugs users compared to MSM who are open about their sexual behavior. This might lead to lower opportunities for MSM in the closet to adopt drug-related risky behaviors. At the same time, this result should be considered cautiously, taking into account (i) the presumably different social network and (ii) the probably diverse level of attendance of sex parties/venues (where drug consumption might be frequent) between MSM out and MSM in. In fact, such a relation between outness and party-drug use could be mediated particularly through attendance at sex parties and other contextual factors (Rosińska et al., 2018).

Notwithstanding the strength of the survey and the uniqueness of the data collected, data presented in this manuscript should be interpreted with caution in light of some limitations. First, in the Sialon II survey recruitment strategies based on websites or gay apps were not foreseen, leading to a possible underrepresentation of specific segments of the MSM populations.

This might imply a low representation of MSM who are experiencing low levels of outness and who are users of MSM-based mobile dating apps to access the gay community.

Moreover, all the data used in the present analysis were based on self-reported information generated through the survey questionnaire(s). Despite the fact that the questionnaire was structured carefully and piloted to ensure easy-to-read/understand items and to participant-friendly questions sequence, recall biases might be present with regards to items focusing on testing.

An additional limitation might lie in the definition of outness in itself, which was and is a sometimes controversial topic within the scientific arenas (Coleman, 1982; Griffith & Hebl, 2002; McDonald, 1982; Meidlinger & Hope, 2014; Whitehead et al., 2016). Still, there is a general agreement in considering a reliable indicator of outness as the proportion of people whom one is out to as homosexual (and/or bisexual) and this approach is currently adopted in several studies (Mansergh et al., 2015; Pitpitan et al., 2016).

In addition, a potential limitation lies in the fact that a possible overlap between party drugs use and sex drugs use was not explicitly covered in this analysis.

Finally, items on sexual identity were not included for all study sites in the questionnaire, and therefore this piece of information is not present in data analysis. This might limit results interpretation, as identity represents an important topic to be considered when investigating MSMs disclosure (Pachankis et al., 2017; Rosario et al., 2004).

In addition, the use of RDS and TLS might have possibly led to capture different sub-populations also in terms of outness (Kendall et al., 2008), and contextual data related to policy, structural and societal perceptions or norms in the different study sites were not included.

Conclusions

Previous research confirms how the social and cultural environment impacts on MSM's openness about their sexual orientation (Pachankis et al., 2017). This is ostensibly also evident in light of the present analysis as MSM who reported a low level of outness also perceive a negative attitude toward gay/bisexual men within their social context, even if with not so different proportions.

It is generally recognized that a high degree of "outness" is linked with positive social supports (American Psychological Association [APA], 2003). Despite this could not be directly confirmed in the present analysis, the fact that MSM in the closet are reporting (i) less prevention/testing levels, (ii) lower perception of a supporting environment and (iii) different use of sex drugs (compared to MSM who are defined as "out") supports the idea that

a cluster of risky patterns is present for this sub-group. Moreover, this pattern can be explained also considering the socio-demographic characteristics of the sample, older and prevalently residing in the big cities and therefore having high probability to be exposed to HIV prevention programs, including testing.

Considering the differences in terms of party drug use, in our analysis, this seems to characterize MSM who are "out" and MSM who are "in." This issue seems to be important, whilst the relationship between outness and party drug use can be mediated through attendance at sex parties, which has not been considered in this analysis.

In addition, even if not significant in the model, the role of sexual satisfaction might be a crucial factor to consider also when planning HIV prevention strategies targeting MSM and/or MSMW (Bourne et al., 2013). For extension, these findings might be considered if not as a confirmation, at least in light of the so-called *syndemic* phenomenon, largely considered as the co-occurrence of psychosocial and health difficulties which are interacting synergistically and which are circularly reinforcing each other fueling the epidemic (Singer, 2009). In fact, the present results confirmed that compared to MSM who are out, MSM in the closet seems to experience a more broad disadvantaged condition, not only in terms of social stress but also in terms of testing and access to prevention initiatives. The connection of such a disadvantaging factors—even if this has not been directly proved in this analysis—is more likely to be present in the case of MSM exposed to multiple stigma and potential risk of acquiring HIV.

The results call for the need for several initiatives including the promotion of gay-friendly services, as well as the promotion of wide prevention strategies targeting particularly those who are "in the closet." From this perspective, initiatives such as at-home HIV testing and HIV testing services supported by the use of new technologies (e.g., apps) are representing promising practices (Maksut, Eaton, Siembida, Driffin, & Baldwin, 2016).

In efforts to tackle HIV epidemics among MSM and to reach the highest level possible of access to HIV prevention and treatment, further studies are required to understand better the different social and behavioral patterns (including sexual wellbeing, health-seeking behaviors and prevention needs) which characterize MSM who are in the closet compared to those are out. This paper sought to identify and describe some of those types of data, coming from the biggest bio-behavioral survey ever implemented in Europe. However, additional information is needed (i) to more closely understand factors which shape the experiences and behaviors of MSM in the closet compared to those out and (ii) to further inform meaningful and targeted prevention strategies, considering the specific prevention needs of this sub-population particularly exposed to a multifaceted range of social stressors.

Authors' contributions

LGI, MMI, NSH, ITO, SDI, DST, CFO, SSC, CNO, WVB, ENA, IAL participated in the design of the survey questionnaire and the organization and implementation of the survey in the survey cities.

This analysis was conceived by LGI and MMI. Data were analyzed by MMI and LGI.

The first manuscript draft was jointly written by LGI and MMI.

All authors contributed writing to the following drafts.

All authors read and approved the final manuscript.

Disclosure statement

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Prior to data collection, research protocols were submitted to, and approved by, an appropriate institutional ethical review board in each participating city, as well as by the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC) during 2012-13.

Informed consent

According to the study protocol procedures, informed consent was obtained from all individual participants included in the study.

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Lorenzo Gios / PhD by publication / Health4LGBTI Network. A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities

Laetitia Zeeman <L.Zeeman@brighton.ac.uk> 1 August 2019 at 14:11
To: Nigel Sherriff <N.S.Sherriff@brighton.ac.uk>
Cc: Lorenzo Gios <gios.lorenzo@gmail.com>

Dear Nigel,

This is to confirm that Lorenzo participated in the conception, design, implementation and supervision of the Health4LGBTI project, on which the paper "Health4LGBTI Network. A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities" is based. He took an important role in the manuscript development, together with critical revision of the final version he also approved.

Kind regards

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Systematic Review and Meta Analyses

A review of lesbian, gay, bisexual, trans and intersex (LGBTI) health and healthcare inequalities

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Background: Lesbian, gay, bisexual, trans and intersex (LGBTI) people experience significant health inequalities. Located within a European Commission funded pilot project, this paper presents a review of the health inequalities faced by LGBTI people and the barriers health professionals encounter when providing care. **Methods:** A narrative synthesis of 57 papers including systematic reviews, narrative reviews, meta-analyses and primary research. Literature was searched in Cochrane, Campbell Collaboration, Web of Science, CINAHL, PsychINFO and Medline. The review was undertaken to promote understanding of the causes and range of inequalities, as well as how to reduce inequalities. **Results:** LGBTI people are more likely to experience health inequalities due to heteronormativity or heterosexism, minority stress, experiences of victimization and discrimination, compounded by stigma. Inequalities pertaining to LGBTI health(care) vary depending on gender, age, income and disability as well as between LGBTI groupings. Gaps in the literature remain around how these factors intersect to influence health, with further large-scale research needed particularly regarding trans and intersex people. **Conclusion:** Health inequalities can be addressed via changes in policy, research and in practice through health services that accommodate the needs of LGBTI people. With improved training to address gaps in their knowledge of LGBTI health and healthcare, health professionals should work in collaboration with LGBTI people to address a range of barriers that prevent access to care. Through structural change combined with increased knowledge and understanding, services can potentially become more inclusive and equally accessible to all.

Introduction

International research increasingly demonstrates that lesbian, gay, bisexual, trans and intersex (LGBTI) people are frequently marginalized and experience significant health inequalities.[1–6] Reducing health inequalities is a fundamental goal of public health and is regarded by the European Union (EU) as being one of the most important public health challenges facing its Member States.[7–9] This emphasis is vital as inequalities impact on both the health outcomes of LGBTI people as well as their experiences of accessing healthcare.[10] Evidence suggests that LGBTI people are more likely than the general population to report unfavourable experiences of healthcare including poor communication from health professionals and dissatisfaction with treatment and care received.[11–13] LGBTI patients can face bias and discrimination in healthcare settings,[13,14] with trans patients reporting most dissatisfaction resulting in some avoiding medical treatment, including emergency care.[15]

Major legislative reform in recent years have resulted in significant progress towards achieving equality for LGBT people.[6] Acknowledgement of the need to endorse and exercise the rights of LGBTI people are increasing within the EU where people are broadly protected against discrimination on grounds of sexual orientation (lesbian, gay, bisexual people), gender identity (trans people) and sex characteristics (intersex people). However significant obstacles remain to full recognition of LGBTI people's fundamental rights. These rights include legal recognition of gender, non-discrimination in the workplace, freedom of expression and freedom of movement.[16] Despite such advances however, social exclusion, stigmatization and discrimination experienced by LGBTI people persist in many healthcare settings.[17,18] This is not only a social justice issue, but growing evidence links these experiences and related minority stress to health inequalities by showing that discriminatory behaviour can impact negatively on both mental health and physical health outcomes.[6,19]

As health inequalities have multiple root causes, reducing these inequalities is complex and there is no simple solution. Moreover, there is a significant lack of research regarding how to address these inequalities. Indeed, in 2016 this journal noted the need for greater

international research to inform LGBT public health initiatives.[20] Tackling inequalities requires a blended approach by addressing the fundamental causes of inequalities, preventing harmful wider social influences and mitigating against negative effects on individuals.[21]

Therefore, this global review was undertaken as part of an EU-funded pilot project that aimed to explore the sources of and modalities for reduction of LGBTI health and healthcare inequalities by determining: (i) what are the causes of LGBTI health inequalities? (ii) What is known about the health inequalities faced by LGBTI people as it relates to healthcare settings? (iii) What is known about the health inequalities of LGBTI people on vulnerable intersections (e.g. rural, younger, older, refugee, those in poverty or disabled)? (iv) What are the potential barriers faced by health professionals when providing care for LGBTI people and how can these barriers be addressed?

Methods

A narrative synthesis design was used to search global literature systematically. This design was chosen due to the complex exploratory nature of the review which aimed to establish 'what is known' about LGBTI health and healthcare inequalities as well as produce a synthesis of current thinking that cuts across the field offering new perspectives and new areas for further research, training and policy development. Whilst such a review may not necessarily provide answers to addressing explicit health problems in given settings, it can nevertheless help policy makers, researchers and practitioners address concerns that occur across the data.[8] In total, 57 relevant papers were extracted and reviewed including: systematic reviews (10), narrative reviews (3), reviews of systematic reviews (2), a meta-synthesis (1) and primary research (41).

Search strategy

Systematic searches were carried out using six electronic databases [CINAHL, PsychINFO, MEDLINE (including PubMed), Web of Science, Cochrane Database of Systematic Reviews, Campbell Collaboration Library of Systematic Reviews]. Additional databases were excluded to prevent duplication. Google Scholar was searched in English and the references of included papers were then checked to identify further relevant articles.

Key terms

Database searches were conducted using various combinations of key words and MeSH terms for the three main areas of interest: health inequalities, the study population (LGBTI people) and health professionals (healthcare inequalities or barriers to providing care for LGBTI people).

Although some of the search terms used medicalize and or pathologize sexualities, gender identities and sex characteristics, these terms were included to ensure the broadest coverage and to expand retrieval. To maximize the number of relevant studies, literature searches were conducted in two parts (see figure 1) focussing on: search question one (S1) 'health inequalities and the study population LGBTI people including vulnerable intersections such as rural, older, refugee, immigrant, disability, poverty' and; search question two (S2) 'the barriers health professionals encounter to providing care for LGBTI people' (table 1).

Selection criteria

Papers were considered for inclusion if they: (i) were primary research studies; (ii) reviews, systematic reviews or meta-analyses; (iii) were published from 2010 onwards to ensure the most recent studies were captured (except for the inclusion of two pivotal systematic reviews in the field published from 2008); and (iv) were published in English. All editorials, commentaries, non-research and theoretical papers were excluded.

Data extraction

Eligibility for inclusion was assessed initially (by the first author) by screening all identified papers and reports based on titles and abstracts. The full text was then obtained for all selected articles and a second screening performed to determine final eligibility was agreed between the first and second author. Any discrepancies/disagreements were resolved in consultation with the third author. The data extraction process is summarized in figure 1. Geographical restrictions with Europe as a primary focus were applied with a wider international focus where relevant. Of the 57 papers included, 20 were European (any papers that included one or more EU countries), 37 were international (all other countries outside Europe which included America, Australia and Canada).

Results

Studies identified

The first database search on health inequalities and LGBTI people (identified as S1 in figure 1) extracted 2058 papers and 357 were selected for full-text review with 45 meeting the final inclusion criteria. The second database search on health professionals including barriers to providing culturally competent care for LGBTI people (identified as S2 in figure 1) identified 903 papers with 82 selected for full-text review and 12 meeting the final inclusion criteria. Combined, 57 papers were included in this review although only the 40 most relevant studies are cited here due to journal editorial restriction (for a full list of papers see the Supplementary data). Of the 57 papers, 16 were systematic reviews and/or meta-analyses and narrative reviews that each covered in the region of 25 research studies or more (16 systematic reviews × 25 papers each) meant more than 400 research studies were covered by this review. Moreover, papers that were published in addition to these systematic reviews or following these reviews, that met the inclusion/exclusion criteria, were also included. Due to the broad scope of the review, database searches were revisited several times to address gaps in the identified papers for specific (sub)populations e.g. the health outcomes of intersex people and their experiences of accessing healthcare. These iterative search measures were utilized to ensure each of the three questions were addressed in sufficient depth. Furthermore, the terms used to answer the review questions reflect the specific groups reported in research. Some papers reported on LGBT people, whereas others referred to LGB people or more specifically on trans or intersex people alone. These terms were honoured as they were presented in the original papers (table 2).

What are the causes of LGBTI health inequalities?

In general, health inequalities occur due to the consequences of a complex interaction of social, cultural and political factors. For LGBTI people, the root causes likely to contribute to the experience of health inequalities are (i) cultural and social norms that preference and prioritize heterosexuality;[11,22] (ii) minority stress associated with sexual orientation, gender identity and sex characteristics;[19,23] (iii) victimization;[24] (iv) discrimination (individual and institutional)[6,18] and (v) stigma.[17]

Health inequalities occur in a context where heterosexuality prevails as the norm.[14,22] LGBTI people access treatment and care in healthcare settings where it is often assumed that people are heterosexual, cisgender (not trans) and not intersex by default.[22] These forms of heteronormativity and gender normativity can be understood as beliefs and practices where sex (male and female) and gender (masculinity and femininity) are absolute and unquestionable binaries. In heteronormativity opposite sex attraction or heterosexuality is the only conceivable way of being 'normal'.[11,24] As LGBTI people deviate from these norms insofar as their sexual orientation (LGB people), or gender identity (trans people), or sex

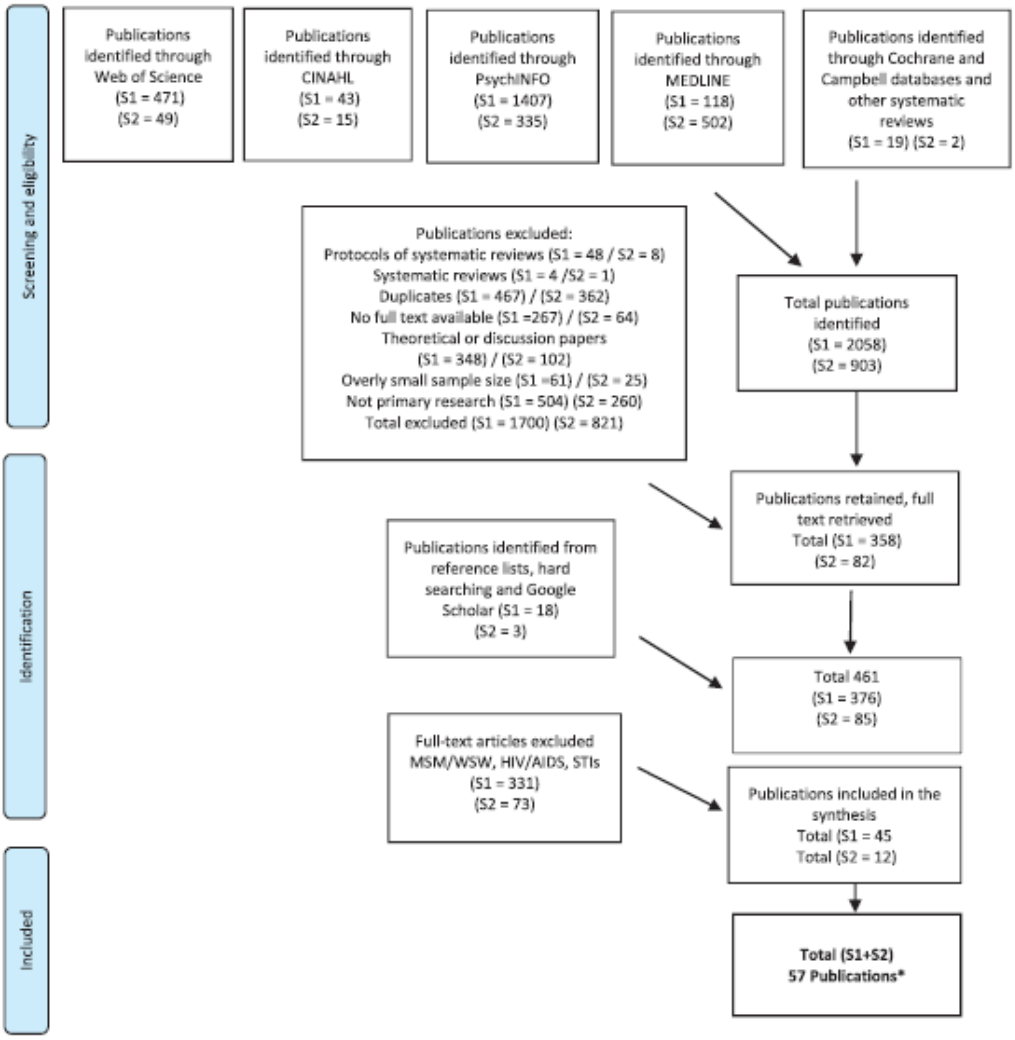

Figure 1 Selection procedure

characteristics (intersex people) they may experience discriminatory attitudes, prejudice or demeaning behaviour.[14,22,24]

Discrimination and prejudice sanction the behaviour of those who deviate from commonly accepted norms. The impact of discrimination is described in minority stress theory, the leading narrative explaining the health inequalities of LGBTI people.[12,19,23] In brief, the minority stress model suggests that because of stigma, prejudice and discrimination, LGBTI people may experience more stress than non-LGBTI people, and that it is this disproportionate experience of stress that can lead to increased incidence of physical and mental health problems.[33] Minority stress occurs where marginalized groups display specific risk factors. Whilst the entire population may display a particular risk factor, the incidence and effects of these risk factors may be more pronounced in smaller subsections of the larger population.[1,19] Due to their minority status (e.g. LGB people only account for up to 6% of the UK population),[6] LGB people were among the social groups most likely to experience higher levels of unpredictable, episodic and day-to-day social or minority stress because of discrimination and stigmatization,[17,19] which creates a hostile environment where LGBTI people face stressful social exchange.[12,19] A meta-analysis of 386 research studies with LGB people undertaken across 19 countries, reported up to 55% of people experienced verbal harassment, 45% experienced sexual harassment and 41% experienced discrimination at higher levels than the general population.[24] For some LGBT people experiences of individual discrimination included hostility, personal rejection, harassment, bullying and violence,[18] whilst for others institutional discrimination occurred where laws and policies in the public domain sustained inequalities such as the prohibition of same-sex marriage, or where laws did not protect against discrimination based on gender identity, sexual orientation or sex characteristics.[6,18] Globally the degree to which LGBTI people are legally protected by anti-discrimination law and the level of legal and social recognition varied significantly. Where LGBTI people did not have legal protection, they were more apprehensive when accessing healthcare due to

Table 1 Key terms

Key search terms
1) What is known about the health inequalities faced by LGBTI people as it relates to healthcare settings? (S1)
Lesbian / gay / homosexual[a] / bisexual / trans[a] / transgender / transsexual[a] / intersex / hermaphroditism / disorders of sex development / queer / transvest[a] / gender identity / questioning / unsure / LGBTI / GLBT / LGB / LGBT / LGBTQ / LGBTU / LGBT & I / same sex / same-sex / sexual minority / sexual orientation and /
or Health inequality[a] / disparity[a] / gradient / disadvantage[a] / determinant[a] and / or
What is known about the health inequalities of LGBTI people focussing on vulnerable intersections (e.g. rural, older, refugee, immigrant, disability, poverty) as it relates to healthcare? (S1)
Intersection[a] / rural areas / rural population / rural health / aged / old[a] / young / disab[a] / poverty / migrants[a] / immigrants/ asylum[a] / refugee / displaced and / or
What are the potential barriers faced by health professionals when providing care for LGBTI people? (S2)
Barrier[a] / gap / beliefs / attitudes / values / norms / perspective / opinion / heteronormative[a] / perception Health service accessibility / healthcare accessibility / health profession[a] / staff / nurs[a] / doctor / clinician[a]

a: Journal requirements allow a maximum of 40 references. The full list and summary of 57 papers are thus provided in an accompanying Supplementary data.

Table 2 Inclusion and exclusion criteria

Inclusion criteria (S1)	Exclusion criteria
Peer reviewed primary research articles published in academic journals, systematic reviews or narrative reviews	Grey literature
Large scope primary research	Overly small sample size
Published in English	Non-English
Published between 2010 and 2016	Prior to 2010
Social determinants	Biological and genetic factors
Physical and mental health	Sexual health
Homosexual, bi, trans and intersex	Sexual practices [e.g. WSW (women who have sex with women) and MSM (men who have sex with men) and sex work][a]
Physical conditions including general health profile, cancer, weight discrepancies	HIV/AIDS and other STIs[b]
Mental conditions including suicide, depression, anxiety, mental distress, self-harm, substance misuse	
Rural, geographically remote areas	Urban areas
Over the age of 18 as per age of consent in EU MS[c]	Under the age of 18[c]
Older LGBTI people	LGBTI war veterans (USA)
Socioeconomic disadvantage or poverty	High income settings
Disabilities	
Migrants, immigrants, asylum seekers, refugees	
Inclusion criteria (S2)	**Exclusion criteria**
Acute care, community, hospitals, health promotion, surgeries, mental health services	Occupational health
Health professionals including gynaecologist, obstetrician, GP, psychologist, psychiatrist, mental health practitioners, nurse, midwife, surgeons, paediatrician, endocrinologist	Lay workers
Human care, treatment, practice	Animal care

a: Research focussing on MSM and WSW were excluded as this review focussed on sexual orientation/identities instead of sexual practices.
b: HIV/AIDS and other STIs were excluded due to being an already well-researched area and the resulting large and diverse literature available.
c: Intersex research with participants under the age of 18 were included due to a peak in health service access during puberty and prior to the age of 18.

anticipated stigma;[12,17] or LGBT people internalized stigma where they devalued themselves because of their gender identity or sexual orientation leading to significant barriers in accessing healthcare.[17]

What is known about the health inequalities faced by LGBTI people?

Health inequalities were experienced differently between LGBTI groups and spanned both physical and mental health. LGB people reported significantly worse physical health compared to the general population with gay men showing an increased incidence of long-term conditions that restricted their activities of daily living. Conditions included musculoskeletal problems, arthritis, spinal problems and chronic fatigue syndrome,[6] whereas gay and bisexual men showed a high incidence of long-term gastrointestinal problems, liver and kidney problems.[6] Lesbian women had a higher rate of polycystic ovaries compared to women in general (80 vs. 32%)[6] and both lesbian, gay and bisexual people showed weight discrepancies compared to the general population.[23,25] Of LGB groups, the general health of bisexual people was poorer compared to lesbian and gay counterparts due to their minority status in both communities.[12]

LGB people are at a higher risk of developing certain types of cancer at a younger age.[26] Gay and bisexual men are twice as likely to report a diagnosis of anal cancer with those who are HIV-positive being at the highest risk.[3] Rates of anal cancer in gay and bisexual men are similar to the prevalence of cervical cancer in general female populations prior to the introduction of cervical screening programmes.[3] This evidence supports the need for anal screening programmes geared towards gay and bisexual men. In contrast there was no conclusive evidence of higher rates of breast cancer in lesbian and bisexual women.[27] However, LGB people who

survived cancer reported the need for psychological and emotional support to address their specific needs.[28] There is a gap in high quality international research on both the cancer burden, general health profile and care needs of trans and intersex people.[3,29]

In relation to mental health, significant inequalities exist with LGBT people being twice to three times more likely to report enduring psychological or emotional problems compared to the general population.[30] Suicide attempts, suicidal ideation, depression and anxiety disorders were 1.5 times higher for LGB people compared to heterosexual peers with alcohol related substance dependence over the previous 12 months being 1.5 times more common in LGB people.[30] Disparities related to mental distress were most pronounced for LGB people under the age of 35, and people over the age of 55.[1] Intersex people also showed a raised incidence of suicide attempts at 19%, with 60% having considered suicide compared to 3% in mainstream populations.[29] Bisexual and trans people showed even greater disparities in mental health compared to lesbian and gay counterparts, increasing the need for specialist mental health services and counselling support.[1,2,18]

Whilst accessing treatment and care, LGBTI people were more likely to report unfavourable experiences. General concerns were around communication with health professionals and overall dissatisfaction with treatment and care provided.[11,12,15,28] Trans people frequently experienced negative interactions with health professionals at gender identity clinics, mental health services and general health services. Where trans people attended gender identity clinics, long waiting times for treatment was shown to negatively impact on their emotional wellbeing.[15]

Like LGBT people, some intersex people experience isolation due to stigma, discrimination or rejection from others.[29] For some intersex people, experiences of adversity were linked to the medicalization of their bodies and being subjected to 'normalising' surgery at a young age or where their bodies were surgically aligned to male or female sex characteristics.[13,29] Dissatisfaction about historic treatment was linked to health professionals not openly discussing information or failing to gain informed consent prior to surgical intervention on intersex minors.[5]

What is known about the health inequalities of LGBTI people on vulnerable intersections?

In contemporary health and social care literature, it is well understood that there is a strong relationship between the social determinants of health inequalities and health outcomes.[10] Various dimensions of social and cultural difference exist including gender, sexual orientation, gender identity, gender expression, sex characteristics, age, ethnicity, race, social class and disability among others.[12] Intersectionality can be understood as the intersections between these dimensions associated with social and cultural difference, that people experience.[6,31] People carry certain markers of difference and for LGBTI people these dimensions can intersect to create multiple marginalizations such as, young trans people experiencing high rates of mental distress where their gender, sexuality, and age intersect compounding the discrimination they face at school.[31] Indeed, the literature shows that living in rural areas creates further health inequalities for LGBT people with reduced access to services, particularly for trans people.[17] Older LGBTI people experienced both physical and mental health difficulties as they aged and became more dependent, however social support seemed to act as a protective factor.[32–34–40] Conversely younger people appeared to be at risk of mental distress and substance misuse in ways that affected their educational attainment.[33] However, targeted resources such as peer support were shown to have positive outcomes.[33] LGBTI people on lower incomes were at risk of mental distress and were more likely to smoke, associated with other factors such as lack of social support and discrimination.[33] LGBTI people were more likely to experience disabilities, and to be younger when doing so.[34] LGBTI refugees and asylum seekers were likely to be at risk of physical and mental distress due to marginalization or abuse experienced in their country of origin linked to their sexual orientation, gender identity or sex characteristics,[35] though further research is needed to understand fully and document the impact of intersectionality.

What are the potential barriers faced by health professionals when providing care for LGBTI people and how can they be addressed?

Health professionals faced a range of challenges when caring for LGBTI people including heteronormativity where heterosexuality is upheld as the status quo or gender normativity where the male-female binary is retained as the norm.[22,24] These norms were evident in practitioners own discomfort and unease whilst addressing the gender identity, sexual orientation or sex characteristics in conversations with LGBTI patients, combined with uncertainty about the use of language or terminology,[28] and not knowing whether people were LGBTI or not.[36] Health professionals were not always aware of key health needs of LGBTI people nor specific health conditions, and may unintentionally have been insensitive towards LGBTI people.[37] Case notes and multidisciplinary forms often failed to recognize the lives and partnerships of LGBTI people.[14] Relevant documentation like leaflets, marketing materials and processes for recording LGBTI patient information can help overcome barriers in communication where health professionals are encouraged to take account of gender and sexual diversity in clinical practice.[11]

When LGBTI people were recognized, or their lives and partnerships were acknowledged, they were more likely to be open and disclose their identity ('come out') or to share relevant health-related information.[11] However some LGBT people had safety concerns or did not 'come out' due to their own need for privacy and confidentiality.[28] Consequently health professionals may not have all the relevant information needed to make a full assessment or to suggest appropriate treatment options.[36] Where LGBT people disclosed their gender identity or sexual orientation in health environments without negative consequences, their visibility correlated to a better rapport with health professionals.[17]

Further barriers occurred where health professionals lacked appropriate knowledge regarding the lives and related health needs of LGBTI people or where health professionals lacked the appropriate culturally specific skills necessary to meet their needs.[11,12,14,29,31,35,36] As one of many examples, mixed methods research found only 41% of older LGBT people in healthcare thought health professionals had sufficient knowledge of LGBT issues whereas 59% thought health professionals did not have adequate knowledge.[36] Global research reviewed was both clear and consistent in arguing for appropriate training of both specialist and generic health professionals to address key gaps in their knowledge and understanding when providing care,[31,35,36,38] as well as informing LGBTI people of how to help reduce the barriers they face when accessing health services.[39] With increased knowledge, health professionals working in partnership with LGBTI people, can contribute to reducing health inequalities.

Discussion

This review has established 'what is known' about the health inequalities of LGBTI people and where change in practice or further research is needed. By identifying these gaps, the findings and recommendations can be of value for health policy makers, practitioners and researchers to help reduce these inequalities.

Recommendations stemming from this review include the need to address high rates of anal cancer in gay and bisexual men, by introducing anal screening programmes to ensure early detection.[3] As for mental health, there were disparities in the mental distress of bisexual and trans people compared to gay and lesbian counterparts,

resulting in the need for greater availability of specialist mental health services and counselling support for these groups.[1,2,18,39] Specialist services are also required for intersex people with long-term follow-up and improved access to counselling support.[29] The review showed lack of substantive research on the general health profile and cancer burden of trans and intersex people,[3,29] with existing research often small in scale and limited in scope.[13,20,29] Further large-scale research is needed to consider the general health and cancer burden of trans and intersex people and to explore their experiences of accessing healthcare. LGBTI people should be included in future research, policy initiatives and decisions about healthcare delivery to represent their own health concerns and to ensure their views of how to improve services are reflected.[6,11,31]

Very little research specifically considers how more than one factor intersect to influence the health outcomes of LGBTI people. Further research is needed to understand fully and document the potential impact of intersectionality. Where this kind of research did exist, studies showed that living in rural areas, being on a low income,[33] being an LGBTI refugee or asylum seeker,[35] being younger,[31,33,34] or older[32,36] and living with disabilities[34] compounded the health inequalities of LGBTI people. Minority stress theory proposes that inequalities occur due to social, cultural and political factors where LGBTI people may experience discrimination associated with their minority status.[19,25,28] In health settings where LGBTI people faced prejudice they were less likely to 'come out'.[11,28,36]

Key but achievable changes are needed in healthcare to address the barriers that prevent access to care.[11,17,38,39] This is essential action in line with European efforts to abolish discrimination on any grounds and to uphold and promote human rights.[7–9,16] Recognition of LGBTI rights continue to vary significantly across European Member States.[16] However structural change can be facilitated via policy, research and in practice combined with training of health professionals to improve their understanding of the lives, partnerships and health concerns of LGBTI people.[31,35,36,38] Inclusion of LGBTI health and healthcare is imperative for curricula at universities and education centres where health professionals are trained. Health professionals will benefit from increased knowledge of historic events where 'homosexuality' was criminalized or medicalized as a 'sexual disorder', or where current framings of intersex variance as 'disorders of sex development' persist in systems of classification such as the WHO International Classification of Diseases (ICD-11) or the APA Diagnostic and Statistical Manual of Mental Disorders (DSM-V). An understanding of the marginalization of LGBTI people via these legal and medical frameworks may result in some avoiding disclosure in health settings acting as a barrier that prevents health professionals from providing effective care.[11,17] Training should show how sustaining traditional heterosexual norms (heteronormativity) and binary gender (gender normativity) may be in tension with the equal rights afforded to LGBTI people in European Member States.[16] With increased understanding of evolving diversity, practitioners can approach LGBTI people without judgement. Where health workers uphold professional values of inclusivity and respect in open communication,[31,35,36,38] LGBTI people may be more empowered to disclose their specific health concerns during consultations.[11,17] Health professionals could work in collaboration with LGBTI people towards a collective goal of truly inclusive and equally accessible services for all.

Limitations

This review has made an important contribution to the field of health inequalities experienced by LGBTI people. Nevertheless, two key limitations should be noted. First, as a narrative synthesis, studies included were not assessed for quality and thus caution must be applied regarding interpretation and generalizability. Second, some of the studies reported in this review combined health profiles for lesbian and bisexual women, or gay and bisexual men or LGB people without considering the health inequalities of each individual group. In other words, our analysis revealed that studies commonly collapsed sexual minorities into a single group. Although combining data can be useful for analytical purposes, it may blur important issues specific to distinct groups and in some cases it was not possible to tease out such distinct issues. Future research designs should differentiate between LGBTI people to ensure analysis can be conducted separately without presuming their issues are the same in ways that neglect intersectional differences.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Key points

- LGBTI people experience significant inequalities in terms of their mental health, physical health, cancer burden and reducing these is a priority of the EU.
- Very little large-scale research has been conducted on the general heath profile of trans and intersex people highlighting the need for further research.
- Norms that favour heterosexuality and gender binaries may lead to marginalization of LGBTI people creating barriers to effective healthcare.
- Health inequalities can be reduced by increasing the knowledge and understanding of health professionals to address these barriers in collaboration with LGBTI people themselves.

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From: Antonella Zorzi <antonella.zorzi@aovr.veneto.it>
Date: Thu, 18 Jul 2019 at 09:12
Subject: Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy
To: Nigel Sherriff <n.s.sherriff@brighton.ac.uk>
Cc: Lorenzo Gios <gios.lorenzo@gmail.com>

Dear Nigel,
I'm writing to confirm that Lorenzo participated in the design of the survey, as well as, in the organisation and implementation of the survey which is the basis for the aforementioned publication.
He took a fundamental role in the data analysis phase, critically revising the paper for development and finalisation.
Kind regards
Antonella

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OPEN ACCESS

Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy

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ABSTRACT

Objectives The incidence of HIV and syphilis among men who have sex with men (MSM) in Europe has recently increased. Rapid point-of-care tests (POCTs) for syphilis can improve access to screening. The purpose of this study was to evaluate the performance of two syphilis POCTs compared with laboratory tests among MSM.

Methods The study was undertaken in Verona, Italy. Asymptomatic MSM, potentially exposed to syphilis, were enrolled prospectively. The POCTs evaluated were SD Bioline Syphilis 3.0 and Chembio DPP Syphilis Screen & Confirm Assay on both serum and fingerprick blood. The results of the POCTs were read by the naked eye by two independent readers and their concordance assessed.

Results A total of 289 MSM were enrolled in the study. Based on laboratory tests, 35 MSM (12.1%) were TPPA-positive alone and 16 (5.5%) were both *Treponema pallidum* particle agglutination test (TPPA) and rapid plasma reagin (RPR)-positive. The specificities of both POCTs were above 99% on both serum and fingerstick blood specimens, while sensitivities varied considerably. The sensitivity of the SD Bioline test was lower on fingerprick blood (51.4% and 54.3%, readers 1 and 2, respectively) compared with that on serum (80.0% and 82.9%). In contrast, the Chembio test exhibited similar sensitivity values for serum and fingerprick samples (57.7% and 64.0% on serum vs 65.4% and 69.2% on fingerprick for the treponemal component; 63.6% on both samples by both readers for the non-treponemal component). The positive predictive value ranged between 100% and 93.9% for the treponemal component of both syphilis POCTs, but was lower (76.3%–100%)%) for the non-treponemal component of the Chembio POCT. The negative predictive value surpassed 90% for both tests on both samples. The agreement between readers was very high (>99%).

Conclusion The diagnostic performance of the syphilis POCTs was lower than expected; however, considering the prevalence of syphilis among MSM, POCTs should be recommended to improve syphilis detection among MSM.

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BACKGROUND

WHO strongly recommends screening for HIV and syphilis, as well as for other STIs among most at-risk populations to reduce the burden of morbidity and mortality associated with undiagnosed and thus untreated infection.[1 2]

In Europe and in the European Economic Area, the main mode of HIV transmission is unprotected sexual intercourse between men. From 2004 to 2013, the number of new HIV cases among men who have sex with men (MSM) increased by 33%, and in 2013, 42% of all new cases were in this population.[3] Furthermore, in this high-risk group, the incidence of syphilis has increased every year since 2008, and in 2014, 63% of new cases were reported among MSM.[4]

In Italy, available data suggest that in urban areas the HIV prevalence rate among MSM is approximately 10%.[5] According to the findings of the EU-funded Sialon II project, an HIV prevalence of 9.6% was estimated among MSM in Verona.[5] In addition, in the same study an overall treponemal seropositivity rate of 12.7% was detected and non-treponemal test positivity confirmed with a positive treponemal test (a better indicator of active disease) was 5.1%.[5] These findings are consistent with the prevalence rates of HIV and syphilis among MSM reported elsewhere in Europe.[3]

Although HIV transmission can be influenced by many factors, the presence of a coexisting syphilis infection might lead to increased viral shedding through ulcers and an increased viral load as a result of the concomitant effect of syphilis on the immune system.[6 7] Both HIV and syphilis may be asymptomatic for long periods but, if untreated, could lead to continued transmission and severe complications. This chain of events could be tackled through early testing and subsequent treatment. Moreover, the introduction of syphilis screening into existing HIV testing programmes would be cost-effective, time-saving and would have a considerable impact on the prevention of transmission, case finding and personal health.[2]

Since 2006, WHO has been actively working to promote a more efficient use of existing diagnostic tools for STIs, as well as to support a more efficient adaptation of such tools to different populations and settings. From this perspective, both development of and evaluation initiatives for new STI diagnostic technologies have been promoted to ensure appropriate performance and availability of these technologies to improve diagnostic services for those populations most at risk.[2]

Point-of-care tests (POCTs) for syphilis are promising tools to improve large-scale screening, especially among hard-to-reach populations, such as MSM, in different settings. The availability of test

results within 20 min allows for prompt clinical decisions and reduces the loss to follow-up.[8]

Therefore, in recent years, a remarkable number of rapid diagnostic tests (RDTs) for syphilis and/or HIV have been developed and several national health systems have scaled up their use as part of their STI testing policies.[9]

Recently, the WHO STI POCT initiative published a target product profile for syphilis POCTs. According to this profile, a syphilis POCT should have a sensitivity of at least 80% and a specificity >90%. These standards ensure acceptable positive predictive value (PPV) and negative predictive value (NPV) and a major effect in terms of clinical utility in low-income, middle-income countries and, by extension, among hard-to-reach populations, where similar high rates of syphilis prevalence (3%–5%) have been reported.[10]

The diagnostic performance of some POCTs and their easy and rapid utility make them, under specific conditions, a practical alternative to standard laboratory testing methods.[11] Nevertheless, the results obtained with POCTs can be influenced by epidemiological/environmental factors. With regards to the human component, the impact of the user's characteristics, such as the ability to properly follow the rapid testing procedures (capillary blood taking, correct timing of adding the buffer and reading), could substantially interfere with the performance of the POCT. Performance, therefore, is dependent not only on the technical characteristics of the POCT itself, but also of human factors that can impact on the correct use and interpretation of the POCT.

To our knowledge, the human factor has not yet been comprehensively analysed as a key component of the testing procedure. While many performance evaluation studies of syphilis POCTs have been published, none of them has specifically targeted MSM as a target study population. In our study, the predictive positive and negative values of the POCTs could be estimated not only as a result of testing the sample of men included in the study, but also using the seroprevalence data derived from an integrated bio-behavioural survey recently carried out among the MSM population living in Verona.[5]

The purpose of this study was to evaluate the analytical and diagnostic performance (including human factors) of two syphilis rapid tests compared with laboratory-based gold standard tests when applied to an MSM population. In particular, laboratory-based treponemal tests were used in comparison with both the SD Bioline treponemal test and the treponemal component of the Chembio test. The Chembio non-treponemal component was compared with a laboratory-based non-treponemal test.

METHODS

Study sites and population

Study participants were asymptomatic MSM, potentially exposed to syphilis as a result of risky behaviours, prospectively recruited from the Sialon II Respondent-Driven Sampling survey implemented in Verona, Italy,[12] from 2013 to 2014 and MSM attending the Infectious Diseases Unit of the Verona University Hospital screening facility from 2015 to 2016. The prevalence of HIV, TPPA and dually TPPA/RPR seropositivity used for the evaluation of the performance of the POCTs was based on the results of an integrated bio-behavioural survey carried out among the Verona MSM population.[5]

Men or male-to-female transgenders, ≥18 years, who had sex with at least another man over the last 12 months and who provided witnessed written informed consent were included in the study. Participants could be enrolled in the study only once.

Study participants were given an automatically generated unique bar code to participate anonymously and to link participants to their own test results. A structured questionnaire was used to collect information about demographic and behavioural characteristics, whereas a specific form was used to collect data about the participant's syphilis history.

The sample size was calculated at an expected prevalence of 10%. This sample size yielded 30 subjects with treponemal positivity, which achieves 85% power to detect a change in sensitivity from 0.58 to 0.85 using a two-sided binomial test and a >99% power to detect a change in specificity from 0.58 to 0.85 using a two-sided binomial test. The target significance level was 0.025 (Bonferroni correction). The actual significance level achieved by the sensitivity was 0.015 and achieved by the specificity was 0.019.

POCTs under evaluation

The tests evaluated in this study were the SD Bioline Syphilis 3.0 (Standard Diagnostics, South Korea) and the DPP Syphilis Screen & Confirm Assay (Chembio Diagnostic Systems, USA).

Both are immunochromatographic assays. SD Bioline Syphilis 3.0 test is a treponemal assay, which detects antibodies of all isotypes (IgG, IgM, IgA) against *Treponema pallidum*. Chembio's DPP Syphilis Screen & Confirm Assay can simultaneously detect antibodies against treponemal and non-treponemal antigens.

Chembio RDT employs a unique combination of protein A and anti-human IgM antibody, which are conjugated to colloidal gold particles for the treponemal test. It uses a recombinant antigen of *T pallidum* and synthetic antigens for the non-treponemal test, separately bound to the membrane's solid phase.[13]

In both tests, the presence of the treponemal and, when available, non-treponemal magenta-coloured lines was evaluated independently by the naked eye by two readers who were blind to each other's results and to the clinical history of the study participants.

The POCTs under evaluation were partially donated by the manufacturers or purchased with external funding, namely from the 2008–2013 EU Public Health Programme, through which the Sialon II Respondent-Driven Sampling survey component has been funded. The manufacturers were not involved in any part of the study (study design, data collection, data analysis, data interpretation and writing of the paper).

Reference laboratory tests

These results were compared with those of the syphilis serological laboratory standard assays. For the treponemal component, two treponemal tests were used: the chemioluminescent assay (CLIA) (ADVIA Centaur Syphilis assay, Siemens Healthcare, Germany) and TPPA (SERODIA-TP-PA, Fujirebio Diagnostics, Sweden). For the non-treponemal component, RPR (Syphilis RPR test, HUMAN Diagnostics Worldwide, Germany) was used as reference test. According to the standard laboratory procedure, the titration for TPPA and RPR was also recorded.

Specimen collection, testing procedures and POCTs results reading

According to the international and local standard guidelines, pre-test and post-test counselling was provided to all participants.

The testing procedures, based on the manufacturers' instructions for fingerprick whole blood, venepuncture whole blood and serum specimens, were strictly followed.

The required amount of capillary (manufacturers' pipettes) and venous blood (5 mL) was collected by trained healthcare staff

of the Verona University Hospital. With reference to obtaining fingerprick blood samples, the manufacturers' instructions were followed step-by-step, such as wiping away the first drop of blood following pricking, collecting the required amount of capillary blood using the capillary pipette provided in both test kits and waiting 20 min (measured with a timer for each test) before reading the results.

In addition, a double reader method [Reader 1-Reader 2, (R1–R2)] was adopted. The readers were medical doctors and nurses in the clinical setting and lab technicians in the laboratory setting. All readers were specifically trained as described in the 'Training and materials' section.

According to the procedure, (i) R1–R2 assessed the RDT results blindly from one to another using two separate forms for recording the assigned result, (ii) neither R1 nor R2 was informed about the clinical history of the patient and (iii) R1 and R2 changed according to the setting (lab/clinical setting). Because of the potential reading bias due to his/her knowledge of the patients' syphilis history, the counsellor involved in the pre-test/post-test counselling was always excluded from the result assessment of the counselled participant.

In the clinical setting, syphilis POCTs performed on fingerstick blood were read immediately. Blood tubes were sent, according to routine procedures, to the Microbiology Unit of the Verona University Hospital where they were centrifuged to obtain serum and to perform the laboratory-based syphilis serological tests. The specimens that could not be processed immediately were stored at 4°C and processed within 3–4 days to allow respondents to receive their syphilis serological results, using the bar code provided at enrolment. The evaluation of POCTs' performance on serum at the Microbiology laboratory was carried out on batches of previously stored (−80°C) serum samples.

During the post-test counselling, in the case of a positive result of serological test for *T pallidum* infection (syphilis), treatment was made available to participants according to the local protocol.

Training and materials

In order to ensure a proper implementation of the research protocol and to standardise the human component in performing the POCTs, the following actions were carried out: (i) specific on-site prevalidation training of health professionals was undertaken for the reading procedures; (ii) the use of specific training materials (including picture examples of different bars of the RDTs to train readers to ensure correct reading); (iii) a coaching programme to ensure proper monitoring of the validation exercise and (iv) the use of a specific set of standardised materials for the readers (eg, posters summarising the POCT procedures displayed in the blood taking settings, a table mat summarising the procedures nurses had to follow when performing the POCTs, posters outlining the reading procedures of the testing always visible in the reading rooms for R1–R2, clarifying the different interpretations of the tests' results).

Ethics

Research protocols were submitted to and approved by the local Ethics Committee (*Comitato Etico per la Sperimentazione Clinica delle province di Verona e Rovigo*). Protocols were also approved by both the WHO Research Project Review Panel (RP2) and the WHO Research Ethics Review Committee (ERC) before initiating data collection.

Anonymity and confidentiality of respondents' data were guaranteed in line with the local standards, while a bar code system has been instituted to allow an appropriate link between the different types of data collected for each individual (demographic and behavioural information, biological samples).

In particular, to comply with all ethical and legal aspects and to minimise the risk of mistakes, participants were informed both during the pre-counselling session and through the informed consent form that only the results of laboratory-based tests would be used to direct patient management. These laboratory results were made available to each participant within a few days of enrolment. Participants were also provided with a phone number to be used (i) to know whether the lab results were available and (ii) to book an appointment for collection of results.

In addition, in cases of positive results, MSM received further information about the infection and the treatment during post-test counselling. According to local procedures, participants could decide to attend the Infectious Diseases Unit of the Verona University Hospital for clinical follow-up or another centre of care. In each case, prompt referral was guaranteed. The treatment provided was in line with national guidelines and standards.

Finally, in line with the protocol, samples were stored at −80°C at the Microbiology Unit of the Verona University Hospital for 1 year after the end of the study. Samples taken without written informed consent were not used for testing and destroyed immediately.

Statistical analysis

Sensitivity, specificity, PPV and NPV for each rapid test were estimated comparing the POCT results with the gold standard lab tests results.[14] The result of each rapid test was compared with the respective gold standard, namely POCT treponemal versus laboratory-based treponemal and POCT non-treponemal versus laboratory-based non-treponemal tests. 95% CIs were also estimated (logit transform).

The concordance between R1–R2 readings was estimated by calculating percentage agreement (concordance) and Cohen's κ (κ for binary variables).[15]

Cohen's κ represents a measure of inter-rater agreement, ranging from −1 to +1, where 0 is the level of agreement that can be expected in case of random chance. According to the literature, thresholds for κ are usually categorised as follows: <0.0 (poor agreement), 0.0–0.2 (slight), >0.2–0.4 (fair), >0.4–0.6 (moderate), >0.6–0.8 (substantial) and >0.8–1.0 (almost perfect agreement).[16]

STATA V.14.2 was used for all analyses.

RESULTS

Study population

A sample of 289 MSM was enrolled in the evaluation study. The mean age of the participants was 31.4 (median: 29; SD 9.2; min 18, max 65). Among the overall sample, 20 individuals reported a previous syphilis diagnosis before study enrolment (6.8%, IC95% 4.4–10.5). All participants provided bio-behavioural information, fingerstick whole blood for syphilis rapid testing, venous whole blood for HIV and syphilis serological testing.

Results of laboratory-based testing

Based on CLIA (ADVIA Centaur Syphilis assay) and TPPA (SERODIA-TP-PA) testing, 35 samples were found to be positive on treponemal testing (12.1%, 95% CI 8.8 to 16.4), while 16 samples were found to be reactive on RPR testing (5.5%, 95% CI 3.4 to 8.8). All RPR (Syphilis RPR test, HUMAN Diagnostics Worldwide)-positive samples were also TPPA positive. No

Table 1 Point-of-care test sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV), per specimen (estimated syphilis prevalence: 12.7%; estimated active syphilis prevalence: 5.1%), according to the assessment of the readers (R1, R2), compared with the lab-based golden standard (TPPA for the treponemal component, RPR for the non-treponemal component)

				Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV (%)	95% CI	NPV (%)	95% CI
Serum	Bioline	TREP	R1	80.0	63.1 to 91.6	100.0	98.6 to 100.0	100.0	78.5 to 99.9	97.2	94.6 to 98.4
			R2	82.9	66.4 to 93.4	99.6	97.8 to 100.0	96.8	81.0 to 99.5	97.6	95.1 to 98.8
	Chembio	TREP	R1	57.7	36.9 to 76.6	99.5	97.0 to 100.0	93.9	68.0 to 99.1	94.2	91.2 to 96.2
			R2	64.0	42.5 to 82.0	99.4	96.9 to 100.0	94.4	69.9 to 99.2	95.0	91.8 to 97.0
		Non-TREP	R1	63.6	30.8 to 89.1	99.5	97.2 to 100.0	86.8	46.9 to 98.0	98.1	96.0 to 99.1
			R2	63.6	30.8 to 89.1	99.0	96.3 to 99.9	76.3	43.0 to 93.2	98.1	95.9 to 99.1
Blood	Bioline	TREP	R1	51.4	34.0 to 68.6	100.0	98.6 to 100.0	100.0	70.1 to 99.8	93.4	91.0 to 95.2
			R2	54.3	36.6 to 71.2	100.0	98.6 to 100.0	100.0	71.3 to 99.8	93.8	91.3 to 95.5
	Chembio	TREP	R1	65.4	44.3 to 82.8	99.5	97.3 to 100.0	95.1	72.8 to 99.3	95.2	92.1 to 97.1
			R2	69.2	48.2 to 85.7	99.5	97.2 to 100.0	95.2	73.6 to 99.3	95.7	92.6 to 97.5
		Non-TREP	R1	63.6	30.8 to 89.1	100.0	98.3 to 100.0	100.0	46.6 to 99.6	98.1	96.1 to 99.1
			R2	63.6	30.8 to 89.1%	99.5	97.4 to 100.0	87.9	49.3 to 98.2	98.1	96.0 to 99.1

R1, reader 1; R2, reader 2.

discordance between the results of the two laboratory treponemal tests was found.

Performance of the POCTs

In line with the availability of the two POCTs, the following testing was performed: 289 (100%) SD Bioline Syphilis 3.0 and 227 (78,5%) Chembio DPP Syphilis Screen & Confirm Assay on fingerprick whole blood, 287 (99.3%) SD Bioline and 205 (70.9%) Chembio DPP on serum.

POCTs sensitivity and specificity, as well as PPV and NPV, compared with the golden standard laboratory tests, varied considerably according to the tests and biological samples (see table 1).

The SD Bioline treponemal test carried out on serum yielded a sensitivity of 80.0% for reader 1 (R1) and 82.9% for reader 2 (R2). With regards to specificity, the performance was 100% for R1 and 99.6% for R2. The PPV of the Bioline test was 100% for R1 and 96.8% for R2, while the NPVs were 97.2% and 97.6%, respectively.

When considering the performance of the Bioline test on fingerstick blood, the sensitivities were 51.4% and 54.3% for R1 and R2, respectively, while specificity was 100.0% for both readers. The test showed high values for PPV (100% for both readers) and NPV (93.4% and 93.8%).

With regards to the Chembio DPP treponemal POCT on serum, the sensitivity values were 57.7% and 64.0% for R1 and R2, respectively, while the specificity values were 99.5% and 99.4. The PPVs (93.9% and 94.4% for R1 and R2) and NPVs (94.2% and 95%) were also acceptable.

On whole blood (fingerprick), the sensitivities of the Chembio DPP treponemal POCT were 65.4% and 69.2%, for R1 and R2, respectively, and a specificity of 99.5% was calculated for both readers. PPVs of 95.1% and 95.2% and NPVs of 95.2% were calculated for R1 and 95.7% for R2.

For the non-treponemal component of the Chembio test on serum samples, a sensitivity of 63.6% was recorded for both R1 and R2 and specificities of 99.5% for R1 and 99.0% for R2. PPV estimates were 86.8% for R1 and 76.3% for R2, while the NPV was 98.1% for both readers.

The results on fingerstick samples (whole blood) showed a sensitivity of 63.6% for both R1 and R2 and specificities of 100.0% and 99.5%, respectively. The PPVs were 100% and 87.9%, while an NPV of 98.1% was calculated for both readers.

RPR and TPPA titration values

In table 2, only positive treponemal reference test has been presented and compared with their respective POCT results. In part A of the same table, TPPA and RPR-positive cases are shown, while in part B, TPPA- positive and RPR-negative cases are listed. Considering only part A, among the 289 MSM recruited in this study, 16 cases were identified as TPPA+/RPR+ (prevalence: 5.5%; 95% CI 3.4 to 8.8). Of these 16 individuals, 4 were also HIV-seropositive. The clinical evaluation provided additional information on the status of the study participants' *T pallidum* infections. Six individuals had a syphilis history and treatment, whereas the remaining 10 subjects had not previously been diagnosed with a *T pallidum* infection. The four HIV-positive individuals were among those who did not have a syphilis history and treatment. In all 16 cases, both the POC treponemal tests (SD Bioline and Chembio treponemal component) yielded a positive result on serum (100%). As far as the Chembio non-treponemal component is concerned, among the TPPA+/RPR+ cases, the test was carried out only on 10 individuals out of 16. In this subsample, three cases would have been missed if only the POCT had been used, considering a RPR titre ≤1:4. One of the cases missed by the test was among the individuals with a syphilis history (possible serofast state), while the other two cases had not been diagnosed previously.

When whole blood specimens were analysed, SD Bioline missed one of the TPPA+/RPR+ cases (TPPA 1:5120, RPR 1:2 and no syphilis history and treatment), while the treponemal component of the Chembio test did not miss any cases (although carried out on only 10 out of 16 participants), while its non-treponemal component missed three cases. The very same cases missed on fingerprick blood specimens were also those missed when serum specimens were tested.

Part B of table 2 shows that the higher the TPPA titre, the better the performance of the POCTs' treponemal component. This is particularly evident when performance was assessed on fingerprick blood specimens.

R1–R2 concordance (Cohen's κ) and agreement on RDTs result assessment

Table 3 shows a very high agreement between R1 and R2 for both POCTs through both concordance percentages and Cohen's κ, the latter ranging from 0.91 to 0.97.[16] With regards to the SD Bioline POCT, κ showed an almost perfect agreement between

Table 2 Syphilis rapid tests results on serum and fingerprick blood among CLIA and TPPA-positive individuals: RPR-positive (part A, 16 samples), RPR-negative (part B, 19 samples)

		Laboratory reference method result			Titres		Syphilis history	*T pallidum* RDTs result on serum*						*T pallidum* RDTs result on blood*					
ID		CLIA	TPPA	RPR	TPPA	RPR		SD Bioline		ChembioT		Chembio NT		SD Bioline		Chembio T		Chembio NT	
								Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
Part A (RPR-positive)	1	+	+	+	20 480	128	Pos	R	R	R	R	R	R	R	R	R	R	R	R
	2	+	+	+	20 480	128	Neg	R	R	R	R	R	R	R	R	R	R	R	R
	3	+	+	+	20 480	32	Neg	R	R	R	R	R	R	R	R	R	R	R	R
	4	+	+	+	20 480	16	Neg	R	R	.	.	.	.	NR	R	.	.	.	.
	5	+	+	+	10 240	16	Pos	R	R	.	.	.	.	R	R	.	.	.	.
	6	+	+	+	5120	16	Neg	R	R	.	.	.	.	R	R	.	.	.	.
	7	+	+	+	20 480	16	Neg	R	R	R	R	R	R	R	R	R	R	R	R
	8	+	+	+	20 480	8	Pos	R	R	R	R	R	R	R	R	R	R	R	R
	9	+	+	+	10 240	8	Neg	R	R	R	R	R	R	R	R	R	R	R	R
	10	+	+	+	20 480	4	Pos	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	11	+	+	+	20 480	4	Neg	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	12	+	+	+	5120	4	Neg	R	R	R	R	R	R	R	R	R	R	R	R
	13	+	+	+	5120	2	Neg	R	R	.	.	.	.	NR	NR	.	.	.	.
	14	+	+	+	20 480	2	Neg	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	15	+	+	+	10 240	1	Pos	R	R	.	.	.	.	R	R	.	.	.	.
	16	+	+	+	10 240	1	Pos	R	R	.	.	.	.	R	R	.	.	.	.
Part B (RPR-negative)	1	+	+	–	10 240	0	Pos	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	2	+	+	–	10 240	0	Pos	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	3	+	+	–	5120	0	Neg	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	4	+	+	–	5120	0	Pos	R	R	.	.	.	.	NR	NR	.	.	.	.
	5	+	+	–	2560	0	Pos	R	R	R	R	NR	NR	R	R	R	R	NR	NR
	6	+	+	–	1280	0	Pos	NR	R	NR	R	NR	R	NR	NR	R	R	NR	NR
	7	+	+	–	1280	0	Pos	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	8	+	+	–	640	0	Pos	R	R	R	R	NR	NR	NR	NR	R	R	NR	NR
	9	+	+	–	640	0	Neg	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	10	+	+	–	640	0	Pos	R	R	NR	.	NR	.	R	NR	R	R	NR	NR
	11	+	+	–	640	0	Neg	R	R	.	.	.	.	NR	NR	.	.	.	.
	12	+	+	–	640	0	Pos	R	R	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	13	+	+	–	320	0	Pos	R	R	.	.	.	.	NR	NR	.	.	.	.
	14	+	+	–	320	0	Neg	R	R	R	R	NR	NR	NR	NR	NR	NR	NR	NR
	15	+	+	–	160	0	Pos	R	R	NR	NR	NR	NR	NR	R	NR	R	NR	NR
	16	+	+	–	160	0	Pos	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	17	+	+	–	160	0	Pos	R	R	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	18	+	+	–	80	0	Neg	NR	NR	NR	NR	NR	NR	NR	NR	R	R	NR	NR
	19	+	+	–	80	0	Pos	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

* Grey boxes indicate discordant results between RDT and reference test.
'.' indicates missing test (Chembio DPP Syphilis Screen & Confirm Assay expired during the study, therefore they were used only in a subsample of men who have sex with men).
Neg, negative; NT, non-treponemal test; NR, no reactive; Pos, positive; R, reactive, RDTs, rapid diagnostic tests; T, treponemal test.

Table 3 Agreement between reader 1 and reader 2: agreement and Cohen's κ values (per type of specimen)

			Agreement (%)	Expected (%)	κ	95% CI	Z	Prob>Z
Serum	BioIne	TREP	99.30	81.77	0.96	0.91 to 1.00	16.27	0.00
	Chembio	TREP	99.51	85.06	0.97	0.90 to 1.00	13.79	0.00
		Non-TREP	99.50	91.94	0.94	0.82 to 1.00	13.37	0.00
Blood	BioIne	TREP	98.96	88.02	0.91	0.82 to 1.00	15.53	0.00
	Chembio	TREP	99.56	84.91	0.97	0.91 to 1.00	14.56	0.00
		Non-TREP	99.56	93.58	0.93	0.80 to 1.00	14.03	0.00

R1 and R2 on both serum samples (κ=0.96) and blood samples (κ=0.91), as well as a high percentage of agreement value (99.30% and 98.96%).

For the treponemal component of Chembio DPP, κ value was 0.97 for both serum and blood, and an agreement of 99.51% (serum) and 99.56% (blood) was reported. With regards to the non-treponemal tests, κ values were 0.94 and 0.93 and an agreement of 99.50% and 99.56% was estimated.

DISCUSSION

The use of POC tests is becoming increasingly frequent worldwide in clinical and low threshold testing settings.

The use of syphilis rapid tests has been extensively reported in the literature among different types of populations, particularly among vulnerable populations (eg, pregnant women, sex workers, injecting drug users (IDUs)); however, to our knowledge, MSM have been less studied. Considering surveillance data on syphilis among MSM, the use of syphilis POC rapid tests can potentially represent an important clinical and public health measure to diagnose syphilis cases among hard-to-reach segments of this target population. In this study, a homogeneous sample was enrolled. All participants were MSM living in the same city and very likely belonging to the same community. In addition, the prevalence of TPPA+ and TPPA+/RPR+ for calculating PPV and NPV was based on a large bio-behavioural survey carried out among MSM in Verona in 2013–2014,[5 12] and therefore, with this more robust prevalence estimate, providing a more valid indication of the real-life POCTs utility among this population. However, the small sample used for this validation study probably represents the most important limitation in terms of result generalisability and performance assessment; therefore, the results of this study should be cautiously interpreted.

Aware of this limitation, the study team used several methodological and operational features to assure appropriate data collection and proper interpretation of the results. The real-life clinical implementation of this study, with the use of fingerprick blood in the clinical setting and serum in the laboratory, provided a good opportunity to assess the diagnostic performance of the two syphilis rapid tests. The performance on both biospecimens resulted in lower-than-expected performance characteristics compared with previous reports in the literature and in the technical specifications provided by the manufacturers. This is particularly evident when fingerprick blood samples were tested. In addition, considering the titration provided by the laboratory tests, it seems that for TPPA titres >1:1280 the misclassification rate for the two POCTs, both on serum and blood, was extremely low. The same pattern can be seen for the non-treponemal test, where with RPR titres ≥1:8 there was virtually no misclassification compared with the non-treponemal component of the Chembio test. As suggested by some studies in prenatal populations, the detection of RPR titres≥1:8 could be very important for pregnant women as this has been significantly associated with adverse pregnancy outcomes.[17] Unfortunately, for other at-risk populations, the use of a decision threshold titre is more problematic owing to possible recent exposure to infection and therefore incubation of early disease. The interpretation of low RPR titres can be even more difficult when patients have previously received treatment with a course of potentially treponemocidal antibiotics for other indications. In fact, 16%–20% of men with a history of adequately treated syphilis can present lifelong low positive RPR titres (ie, they are serofast).[18]

Based on their STI history, participants with a treponemal-positive result were classified as either a newly diagnosed or a serofast case. The non-treponemal Chembio test missed three TPPA+/RPR+ cases; however in terms of clinical utility, at least one case was serofast and therefore negligible in terms of transmission risk and individual health outcome, while the remaining two were possibly cases of late-latent disease. In these latter cases, the clinical implication for the missed treatment could have been relevant for the patient, but not for the community since the transmission risk of a late-latent syphilis is extremely low.[19] It is interesting to note that there was no discordance in these cases when serum and blood test results were compared and that none of the MSM who could be considered serofast was HIV- infected.

Unfortunately, due to unexpected logistical reasons (expiration time and delay in new test procurement), the Chembio POCT results were available only for a subsample of MSM and this represented a further limitation in the interpretation of our findings. However, the TPPA titre and RPR comparisons seem to be in line with the results of previous studies.[20–22] Additional evaluation studies should be implemented, including a more detailed assessment on the potential impact of different cut-off (TPPA and RPR titre) on the Chembio DPP Syphilis Screen & Confirm Assay performance, within a POCT approach.

Sensitivity and specificity varied considerably across tests and biospecimens, as well as PPV and NPV. While the analytical performance of RDTs (sensitivity and specificity) is not affected by the characteristics of the population among which the tests are used, PPV and NPV are strongly influenced by the prevalence of the infection in the target population. In our study, the predictive values seem to be acceptable considering the specific evaluation setting and the reference population (members of the MSM community in Verona). This leads us to consider the use of syphilis POCT as potential alternative to standard methods to improve screening practice, particularly outside hospital settings. Additional evaluations are certainly needed to further assess the potential replacement of standard tests with the POCT approach in different scenarios and the potential impact of such a shift.

As expected the performance of the two POCTs evaluated here proved to be inferior to those of the standard laboratory tests; however, when used strategically, in settings where venepuncture is not safe or impossible to perform, or when the population is very mobile or for legal reasons not entitled to receive the standard medical assistance (ie, migrants, illegal migrants, sex

workers, drug users), these POCTs can be extremely useful in identifying syphilis cases requiring medical assistance and treatment. Furthermore, even though both syphilis POCTs under evaluation seem to be promising, the Chembio POCT seems to be more informative, particularly on fingerprick blood. In a population with such a high prevalence of TPPA positivity, the availability of a rapid syphilis test with a non-treponemal component could be very useful as it allows clinicians to better distinguish between previously treated syphilis and active disease.

This does not imply that a POCT with only a treponemal component is not useful. The treponemal-only test, together with the patient's clinical examination and history, would allow the clinician to identify cases never treated, to plan additional testing in subjects potentially non-adequately treated or, in case of a previous syphilis infection, to treat them despite the marginally hazardous overtreatment risk. The overtreatment risk can be balanced with the benefits of the transmission risk reduction to partners and the breaking of the transmission chain within the community. At a personal level, even though the subject has to be treated with penicillin, adverse events associated with treatment are fortunately limited.

The procedures adopted for this syphilis test validation addressed also the aspect of quality assurance of the test reading in order to guarantee an adequate assessment of the POCTs performance. In accordance with the literature,[23] for reducing the degree of human interpretation and subjectivity, an ad hoc training and supporting documentations for staff, as well as a coaching activity were developed. This can be considered a relevant feature of this POCT study compared with other studies, where the human component was not specifically accounted for or simply considered a negligible factor. According to our results, once the POCT procedures (as described in the 'Methods' section) are strictly followed, the human component does not represent a relevant source of inaccuracy. This is confirmed by the high level of concordance between the readers (Cohen's κ for R1–R2).

To conclude, we believe that this study could be relevant for setting the agenda of future validation studies. Steps and procedures for the future use of POCTs in clinical and community-based testing services have been piloted, assessed and improved for clinical purposes.

From a methodological perspective, despite the fact that POCTs are easy to use, this technology should be linked to specific training for users together with the use of supporting documentation (eg, posters, procedural dashboard) to reduce misinterpretation of the results due to human subjectivity. From a clinical viewpoint, we can consider the human component as having no significant impact on the performance of the POCTs if the healthcare staff is properly trained on POCT use. The complex experimental procedures used for this validation study have not fully allowed the staff to appreciate the flexibility of POCTs in meeting the diversity of medical needs that can make these tools invaluable for this population. The possibility of performing the tests in a variety of locations, including saunas, bathhouses and other non-conventional facilities, makes the POCTs very attractive and useful for certain healthcare systems. Despite the relatively low sensitivity showed by the POCTs in this study, in our opinion they can provide important diagnostic and treatment opportunities among the MSM population studied. In fact, considering the high specificity (close to 100%) the provision of immediate on-site treatment, guided by a clinical and epidemiological evaluation (syphilis history, previous treatment, exposure assessment), could represent a real benefit both for the individuals and for the community as a whole, with a consequent reduction of infection transmission and overall burden of disease.

Key messages

- The point-of-care test (POCT) technology should be linked to specific training for users and the adoption of supporting documentation to reduce misinterpretation of the results due to human subjectivity.
- The potential of POCTs can only be realised if properly used.
- Although syphilis POCTs may lack some sensitivity compared with laboratory-based tests, their use in non-conventional settings, together with on-site treatment, could contribute to a significant reduction in disease transmission among high-risk men who have sex with men populations.

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