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Increased incidence of syphilis in men who have sex with men and risk management strategies, Germany, 2015

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In Germany, the number of reported syphilis cases increased between 11% and 22% per year between 2010 and 2014. We analysed syphilis surveillance data and data of four behavioural surveys on men who have sex with men (MSM) in Germany (2003, 2007, 2010, 2013) to assess if this rise is ongoing and to find possible explanations for it. Syphilis notifications increased in 2015 by 19% to a total of 6,834. This was mainly due to increasing notifications in MSM of all age groups in larger German cities. Data from the behavioural surveys on MSM in Germany showed a simultaneous increase of selective condom use as HIV-status-bases risk management strategy and the number of syphilis cases. MSM diagnosed with HIV reported condomless anal intercourse with non-steady partners more frequent than MSM not diagnosed with HIV or untested for HIV, but the latter also reported higher frequencies of this behaviour in the more recent surveys. Transmission in HIV-positive MSM probably plays an important, but not exclusive role, for the syphilis dynamics in Germany. A risk adapted routine screening for sexually active MSM and potentially innovative approaches to increase early screening and treatment of syphilis such as internet counselling, home sampling, home testing and broadening venue-based (rapid) testing, should be critically evaluated to effectively reduce syphilis infections.

Introduction

Syphilis incidence among men who have sex with men (MSM) has been on the rise globally during the last years. Especially in western countries, sharp increases in numbers of syphilis infections were observed [1-4]. In Europe, the syphilis incidence was 5.1 cases/100,000 inhabitants overall, with distinct differences between countries, probably due to the differences in the notification systems, completeness of data and healthcare structures [3]. Since 2009, the syphilis incidence increased in Europe in men, especially in western European countries, while the incidence decreased in women concurrently. In Germany, the number of reported syphilis cases doubled between 2001 and 2004 to over 3,000 per year and remained mainly stable until 2009. Between 2010 and 2014, the number increased between 11% and 22% per year [5].

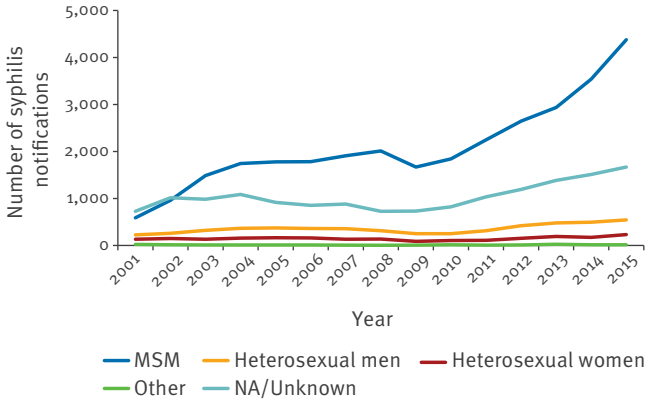
High rates of bacterial sexually-transmitted infections (STIs) including syphilis are reported for MSM coinfected with HIV from many countries, e.g. Australia, Canada, England, Germany, and Spain [6-10]. We discuss reasons for the increasing syphilis incidence in MSM, in particular the increase in risky sexual behaviour, such as a higher frequency of condomless sexual intercourse, while applying HIV serostatus knowledge-based risk management strategies, particularly HIV-serosorting [11-16].

Syphilis is a STI caused by *Treponema pallidum*. It has different stages of disease (primary, secondary, latent, and tertiary syphilis), of which especially the first and second stages are highly infectious. Syphilis can lead to severe sequelae such as serious cardiovascular or neurological impairments and also death, and increases the risk of HIV acquisition and transmission [17,18]. As congenital syphilis, *T. pallidum* can also be transmitted to a fetus during pregnancy and can cause severe health impairments of the newborn, including premature delivery and stillbirth. Syphilis can still be treated effectively with penicillin [17].

To assess the epidemiological dynamics of syphilis in Germany and to shape appropriate public health interventions, we analysed data of the mandatory syphilis notification system reported between 2001 and 2015.

Figure 1

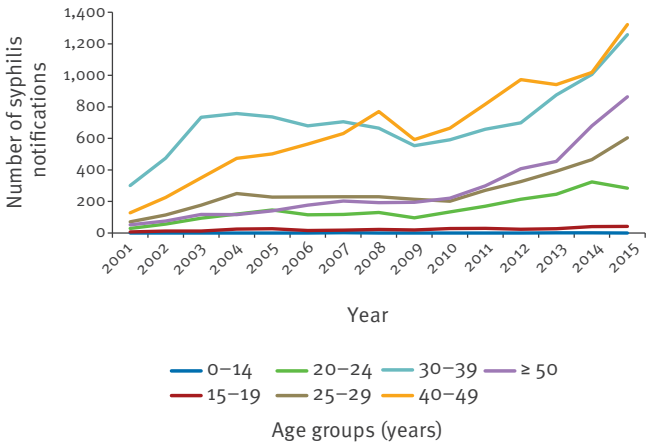
Number of syphilis notifications, by transmission group, Germany, 2001–2015



MSM: men who have sex with men; NA: not available.

Figure 2

Number of syphilis notifications in MSM, by age group, Germany, 2001–2015



MSM: men who have sex with men.

Additionally, we analysed data of four waves of a behavioural survey among MSM in Germany to assess potential changes in relevant sexual behaviours.

Methods

Mandatory syphilis notification

In Germany, syphilis diagnoses have been notified anonymously on the basis of the Protection against Infection Act in Germany [19] since 2001 by laboratories, with physicians inserting relevant clinical information. Syphilis cases are defined as cases diagnosed by direct detection of *T. pallidum* by microscopic or histological examination OR a positive screening test and a confirmation test (a combination of *T. pallidum* particle agglutination test (TPPA), *T. pallidum* haemoagglutination test (TPHA), Immuno-Assay, fluorescence *Treponema* antibody absorption test (FTA-ABS), Immunoblot) AND venereal disease research laboratory (VDRL)/rapid plasma reagin (RPR) activity or IgM antibodies OR clinical information consistent with syphilis [17].

Potential double notifications were identified by comparing cases by demographic data, diagnosis date, antibody titres, and clinical information. We analysed syphilis cases by year of diagnosis, age, sex, area of residence, and transmission group.

Behavioural surveys

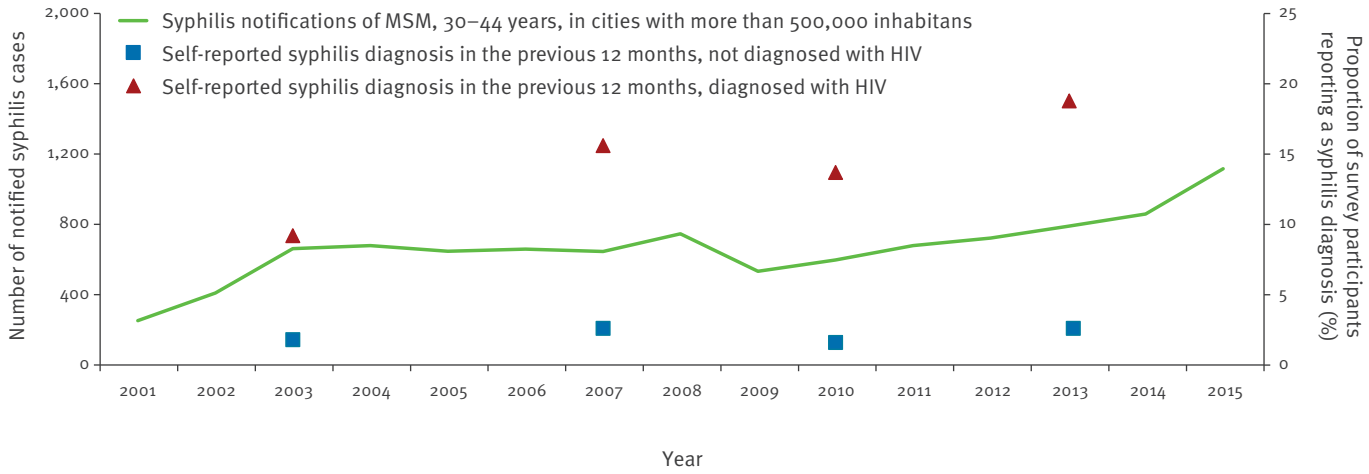
Self-reported data on sexual risk behaviours and diagnoses of HIV and syphilis among MSM were collected during four waves of a behavioural MSM survey in 2003, 2007, 2010, and 2013. Survey participants were recruited exclusively online in the 2010 and 2013 surveys, and by a combination of print questionnaires distributed by gay magazines and online questionnaires in the 2003 and 2007 surveys. The methods and the results of this survey have been published elsewhere in German [20-23]. These surveys are part of the HIV behavioural surveillance in Germany implemented in the late 1980s [22]. Although they use the same or very similar questions, their comparability is restricted, mainly due to the different recruitment methods. Recruitment bias affected information on age, city size, and sexual identity. This is why we restricted the analysis to a subgroup of men self-identified as gay, aged 30–44 years, and living in cities with more than 500,000 inhabitants (in descending order according to the number of inhabitants: Berlin, Hamburg, Munich, Cologne, Frankfurt am Main, Stuttgart, Dusseldorf, Dortmund, Essen, Bremen, Leipzig, Dresden, Hanover, Nuremberg). This subgroup is less affected by the change in recruitment methods. The sample sizes of the surveys were: 4,750 in 2003, 8,170 in 2007, 54,387 in 2010, and 16,734 in 2013. The subgroup of gay-identified men aged 30–44 years and living in cities with more than 500,000 inhabitants consisted of 1,039 (22%) men in 2003, 1,315 (16%) in 2007, 8,242 (15%) in 2010, and 1,547 (9.2%) in 2013.

We analysed trends in condomless anal intercourse (cAI) with *steady* and *non-steady* partners in the previous 12 months (scAI respectively nscAI), and with partners of *unknown* HIV status (ucAI), also stratified by HIV status, as well as the proportion of MSM getting tested for HIV in the previous 12 months, to explore the increasing syphilis transmission among MSM. Data on syphilis testing were only collected in 2010 and 2013 in the behavioural surveys.

Data were analysed using descriptive statistics.

Figure 3

Number of syphilis notifications and self-reported syphilis diagnoses in MSM aged 30–44 years and living in cities with more than 500,000 inhabitants, Germany, 2001–2015



MSM: men who have sex with men.

During the survey years, the following numbers of MSM participated in the behavioural surveys: 2003 (n = 1,039), 2007 (n = 1,315), 2010 (n = 8,242), 2013 (n = 1,547).

The total number of syphilis notifications fulfilling the inclusion criteria was 10,120.

Results

Data from mandatory syphilis notification

As at 1 March 2016, 54,747 newly diagnosed cases of syphilis had been notified in Germany between 1 January 2001 and 31 December 2015, with cases increasing since 2010 (Figure 1). In 2015, 6,834 cases were reported, corresponding to a 19.4% increase compared with 2014. Incidence was 8.5 per 100,000 inhabitants overall, with highest incidences above 20.0 mainly in larger German cities such as Berlin (39.0), Cologne (35.6), Munich (30.0), Frankfurt am Main (29.5), Dusseldorf (26.6), Leipzig (23.7), Hamburg (21.4) and Stuttgart (20.4). They were especially high in Berlin inner city areas with 62.8–117.8/100,000 inhabitants. Notified cases increased in 14 of 16 German federal states in 2015.

Men accounted for 93.8% of cases in 2015 (n = 6,834). The transmission route was reported for 75.6% of cases (n = 5,166); of these, 84.7% occurred in MSM, 15.0% among heterosexual persons, and 0.3% were acquired through other routes of transmission.

In 2015, 84.9% of MSM diagnosed with syphilis originated from Germany (n = 3,758), and 95.6% of syphilis cases in MSM were reportedly acquired in Germany (n = 3,981). Since 2008, at least half of the syphilis cases among MSM have been diagnosed in men aged 40 years and older (n = 54,744, Figure 2). Since 2007, the proportion of MSM diagnosed in primary or secondary stages of disease has remained between 60.4% and 67.7% (n = 40,005). Since 2006, physicians provided information on re-infection for 64.8% of all reported syphilis cases: between 40.4% and 50.9% of all syphilis cases reported in MSM were categorised as re-infection (n = 21,761).

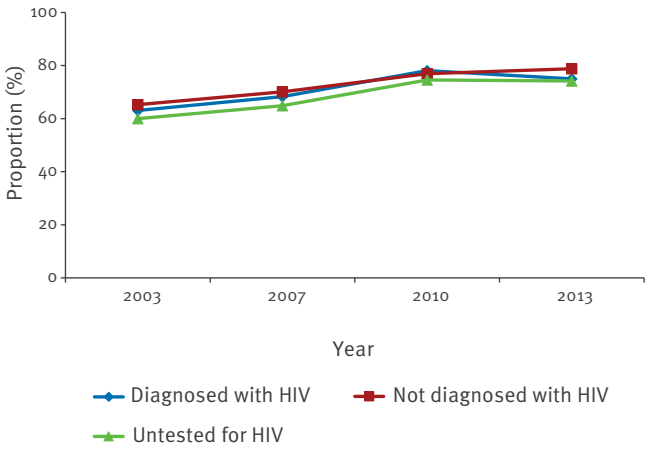
Data from behavioural surveys

In the analysed subsample of men self-identified as gay, aged 30–44 years and living in cities with more than 500,000 inhabitants, the HIV prevalence was 15.9% in 2003 (n = 1,039), 14.9% in 2007 (n = 1,315), 16.9% in 2010 (n = 8,242), and 22.3% in 2013 (n = 1,547). The trend of self-reported syphilis cases was similar to the trend in syphilis notifications (Figure 3); the increasing trend was almost entirely based on respondents with HIV. Between 2003 and 2013, the proportion of MSM diagnosed with HIV (n = 1,934) reporting newly diagnosed syphilis, increased from 9.3% to 19.0%, while the proportion of MSM not diagnosed with HIV (n = 9,397) and self-reporting a recent syphilis diagnosis, fluctuated between 1.7% and 2.7%.

HIV-testing in the previous 12 months increased from 32.8% (2003) to 34.8% (2007), 41.5% (2010) and 48.4% (2013). Among all MSM reporting a syphilis diagnosis in the previous 12 months (2003: 29; 2007: 60; 2010: 306; 2013: 58), the proportion of MSM diagnosed with HIV increased from 48.3% (2003) to 50.0% (2007), 62.4% (2010), and 69.0% (2013). Partly, sexual behaviour differed considerably by self-reported HIV status. The proportions of scAI were high and increasing for MSM independently of their HIV status (Figure 4).

Figure 4

Proportions of survey respondents self-reporting condomless anal intercourse with steady partners (scAI) in the previous 12 months, by HIV status of respondents, MSM aged 30–44 years and living in cities with more than 500,000 inhabitants, Germany, 2003–2013

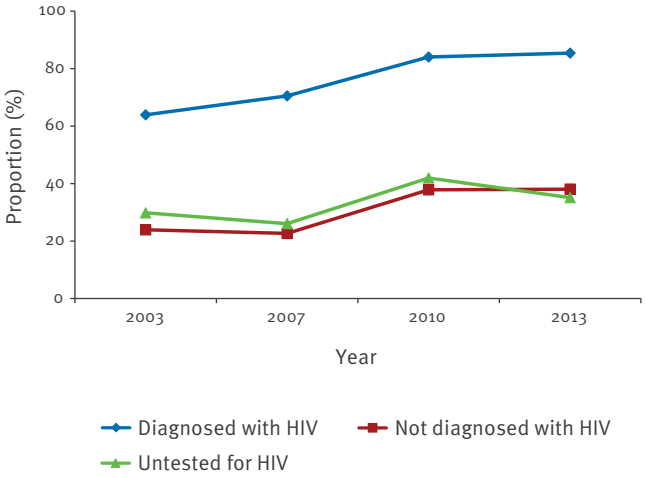


MSM: men who have sex with men.

During the survey years, the following numbers of MSM participated in the behavioural surveys: 2003 (n = 472), 2007 (n = 624), 2010 (n = 3,272), 2013 (n = 586).

Figure 5

Proportions of survey respondents self-reporting condomless anal intercourse with non-steady partners (nscAI) in the previous 12 months, by HIV status of respondents, MSM aged 30–44 years and living in cities with more than 500,000 inhabitants, Germany, 2003–2013



MSM: men who have sex with men.

During the survey years, the following numbers of MSM participated in the behavioural surveys: 2003 (n = 740), 2007 (n = 870), 2010 (n = 5,132), 2013 (n = 966).

The proportion of MSM diagnosed with HIV and reporting nscAI (n = 1,334) was more than double compared with the respective proportion of MSM not diagnosed with (n = 1,857) or not tested for HIV (n = 272) (Figure 5). Reporting of nscAI increased over the years for all those groups, with the exception of 2013, for MSM untested for HIV. We found the strongest increase with 59% between 2003 and 2013 for MSM not diagnosed with HIV.

With slight decreases, the proportions of MSM reporting ucAI stayed stable between 2003 and 2013 (Figure 6). MSM diagnosed with HIV reported ucAI more frequently than MSM not diagnosed with or not tested for HIV.

Testing for syphilis was reported much more frequently by survey respondents diagnosed with HIV compared with survey respondents not diagnosed with HIV. The proportion of respondents diagnosed with HIV reporting at least one syphilis test in the previous 12 months increased in our subsample from 80% in 2010 to 88.5% in 2013. Among respondents tested for, but not diagnosed with HIV this proportion increased from 33.5% in 2010 to 35.8% in 2013. The proportion of MSM reporting a syphilis test in the previous 12 months and never tested for HIV decreased from 5.7% in 2010 to 3.2% in 2013.

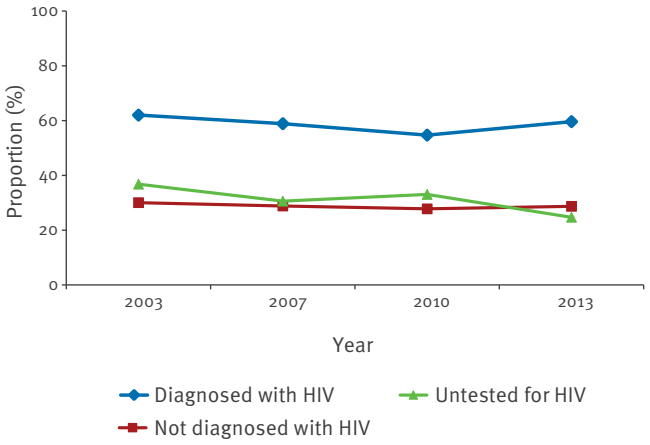
Discussion

We found an accelerating increase of syphilis notifications in Germany since 2010. This increase was mainly due to a rise in the number of newly diagnosed cases in MSM, acquired domestically. The epidemic is mostly concentrated in larger cities and more densely inhabited regions of Germany, where the proportion of MSM is higher [24,25]. Berlin as a centre of sex tourism for MSM [26] was heavily affected. The increase applied to MSM in all age groups, and was strongest in older age groups in terms of absolute numbers.

The analysis of survey data on sexual behaviours of MSM in Germany provided an indication that changes in sexual behaviours of MSM taking place during the last years may have played an important role in the increase in the number of syphilis cases. We observed a coincident increase of HIV-status-based risk management (selective condom use, 'serosorting') and increasing syphilis cases. cAI with steady partners (scAI) has become increasingly common, regardless of HIV status. Apart from scAI, we found distinct differences between MSM diagnosed and not diagnosed with HIV. If the partner was a non-steady partner, cAI was more commonly reported by MSM diagnosed with HIV than if the partner was a steady partner. MSM not diagnosed with or untested for HIV less commonly reported cAI with non-steady partners, but the proportion reporting cAI increased in the more recent surveys. We found almost no changes over time in ucAI, both for MSM diagnosed with HIV and for those not diagnosed with HIV; only among MSM untested for HIV, the proportion reporting this behaviour decreased over time. Even though the proportion of MSM diagnosed with HIV and

Figure 6

Proportions of survey respondents self-reporting condomless anal intercourse with partners of unknown HIV status (ucAI) in the previous 12 months, by HIV status of respondents, MSM aged 30–44 years and living in cities with more than 500,000 inhabitants, Germany, 2003–2013



MSM: men who have sex with men.

During the survey years, the following numbers of MSM participated in the behavioural surveys: 2003 (n = 708), 2007 (n = 876), 2010 (n = 4,272), 2013 (n = 961).

reporting ucAI was much higher than that of MSM not diagnosed with HIV or untested for HIV, it is most likely that MSM diagnosed with HIV were effectively treated with antiretrovirals, and thus not infectious for HIV, and therefore not compelled to discuss their own HIV status or that of their sex partner.

There was an increase in cAI in MSM with both steady and non-steady partners. However, we believe that for the increasing syphilis incidence, the increase in cAI with non-steady partners is much more relevant because having different sex partners is one of the major risk factors for acquiring syphilis among MSM [26].

An increase in cAI was also reported from the United States (US) behavioural surveillance system in MSM [27]. However, the authors' interpretation did not link this to serosorting, because the increase appeared to be independent from the HIV test status and was also observed among MSM never tested. We can confirm from our data that increased reporting of cAI can be observed independently of the HIV testing history. However, we argue that MSM never tested for HIV are participating in serostatus communication, most of them assuming that they are not infected. This assumption was supported by our data since the proportion of men reporting cAI with partners of unknown HIV status was stable or even declined, based on a question which was not used in the US surveillance. This question ('Did you have anal intercourse without a condom with a partner with unknown HIV test result?') may also be negated by MSM who have never been tested, but assume or are told by their partners that these partners are HIV-negative. It is probable that MSM in this group practice serosorting similarly to MSM being HIV-negative. In any case, there is evidence from MSM behavioural surveys that a fraction of men never tested for HIV report telling their partners being HIV-negative [26].

An increase in syphilis cases was seen in both first and second generation surveillance. Survey data showed that syphilis among MSM seemed to be largely and increasingly concentrated among MSM with diagnosed HIV. However, variation in recruitment methods, sample sizes and sample composition of the MSM surveys limit the generalisability of behavioural trends to the overall MSM population in Germany. Although no increase in the proportion of self-reported syphilis diagnoses could be observed among survey respondents without diagnosed HIV, we would like to point out that the absolute numbers of syphilis cases in this population could still be higher than the number of syphilis infections among MSM living with HIV.

Survey participants could not be proven representative either for all MSM diagnosed with HIV or for the total MSM population, and differing self-selection biases may distort the composition of the survey respondents. If we ignore such unknown biases and extrapolate the observed syphilis incidence among survey respondents diagnosed with HIV and not diagnosed with HIV, to the estimated population of all MSM diagnosed with HIV (n = 42,000 at the end of 2013 [28]) and all MSM not diagnosed with HIV in Germany (n = 700,000 [29]), we would have to expect more cases among HIV-negative than among HIV-positive MSM. We hypothesise that the susceptible population connected to sexual networks created by online- and smartphone-dating might have expanded over the recent years [30]. This could explain increasing numbers of syphilis cases among HIV-negative MSM without an increase in the proportions observed in the surveys. The increasing total number of survey participants over time is compatible with this hypothesis. Molecular epidemiological data would allow for an in-depth analysis of the transmission dynamics of syphilis in Germany and could generate evidence if syphilis infections occurred mainly in core sexual networks of HIV-positive MSM, but these data are not yet available.

Until 2015, the German syphilis notification system provided no data on the HIV status of the reported person. Since 2016, the notification system has been amended and reporting of coinfection with HIV and other STIs has been implemented. This change will enable us to better evaluate the impact of HIV coinfection on the dynamics of syphilis.

About a third of notified cases among MSM were diagnosed with syphilis in late stages of disease, and reinfections were common. This underlines the importance

of effective behavioural prevention and broad screening offers for MSM regarding syphilis and other STIs [31]. Consistent condom use independent of HIV status should be promoted for anal intercourse to reduce syphilis transmission. In our subsample from the behaviour surveys, a large majority of MSM diagnosed with HIV have been screened for syphilis in the last 12 months [32]. This does not seem to have a large impact on syphilis incidence in this group. While guidelines have changed and consecutively also screening practices may have changed over time in Germany (so far no direct audits of practices and adherence to guidelines have been conducted), practices are more likely to be influenced by reimbursement rules and concerns rather than by guidelines. In Germany, syphilis testing is easily reimbursable for people diagnosed with HIV through a special reimbursement framework for HIV care while syphilis screening (testing without symptoms) of MSM not diagnosed with HIV may be restricted by reimbursement concerns, in the absence of an official screening programme irrespective of guideline recommendations.

Modelling exercises in Australia and Canada concluded that the frequency of syphilis screening probably needs to be increased to at least biannual screening, in order to achieve an epidemiological impact [33-35]. German guidelines advise for a risk-adapted frequency of screening for MSM [36]. For sexually active MSM especially with changing sex partners, routine screening for syphilis seems to be paramount [37]. To foster this, potentially innovative approaches to increase early screening and treatment such as Internet counselling, home sampling, home testing and broadening venue-based (rapid) testing, should be critically evaluated.

Conflict of interest

None declared.

Authors' contributions

Klaus Jansen drafted the article, conducted data analysis and led the writing of the paper. Ulrich Marcus conducted data analysis and drafted the article. Axel Schmidt, Jochen Drewes and Viviane Bremer conducted data analysis and discussed the data and perspectives. All authors provided contributions to the paper and approved the final version.

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Research article

People living with HIV in Estonia: engagement in HIV care in 2013

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Estonia had the highest rate of newly diagnosed human immunodeficiency virus (HIV) cases in the European Union (24.6/100,000) and an estimated adult HIV prevalence of 1.3% in 2013. HIV medical care, including antiretroviral therapy (ART), is free of charge for people living with HIV (PLHIV). To maximise the health benefits of HIV treatment, universal access should be achieved. Using data from surveillance and administrative databases and the treatment cascade model, we assessed the number of people infected with HIV, diagnosed with HIV, linked to HIV care, retained in HIV care, on ART, and with suppressed viral load (HIV-RNA: ‹200 copies/mL). We identified that about one quarter of the 8,628 HIV-positive people estimated to live in Estonia in 2013 had not been diagnosed with HIV, and another quarter, although aware of their HIV-positive serostatus, had not accessed HIV medical care. Although altogether only 12–15% of all PLHIV in Estonia had achieved viral suppression, the main gap in HIV care in Estonia were the 58% of PLHIV who had accessed HIV medical care at least once after diagnosis but were not retained in care in 2013.

Introduction

In 2013, Estonia had the highest rate of new human immunodeficiency virus (HIV) infections (24.6/100,000) and the third highest rate for acquired immunodeficiency syndrome (AIDS) diagnoses (1.8/100,000) in the European Union and European Economic Area (EU/EEA) [1]. The estimated HIV prevalence in the population aged 15–49 years was 1.3% [2]. People who inject drugs (PWID) have been disproportionately represented in the HIV-positive population since the beginning of the HIV epidemic in 2001 [1].

Estonia's capacity to manage its response to HIV and AIDS has greatly increased over the past decade, particularly through initial funding from the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria in the mid 2000s [3]. In 2013, to confront the epidemic, the National HIV/AIDS Prevention Strategy for the period 2006 to 2015 was being implemented and medical care including antiretroviral therapy (ART) was free of charge for people living with HIV (PLHIV) throughout the study period, regardless of their medical insurance status [4]. In that period, HIV care was mainly provided by the government healthcare system through infectious disease clinics/departments in five major hospitals. Following the European HIV treatment guidelines, ART was recommended in 2013 for any HIV-positive person (without prior ART exposure) with a CD4+ T-cell count‹350 cells/mm3 [5]. For people with CD4+ T-cell counts above this level, when special conditions applied, ART was also carefully considered [5].

Potent combined ART has transformed HIV infection from an acute to a chronic disease and can reduce HIV transmission to HIV-uninfected partners [6]. Thus, availability of, and access to, ART are essential not only for individual, but can potentially also provide public health benefits [7]. Yet to maximise the health benefits of ART, health systems must ensure an effective cascade of high quality services provided to PLHIV [8].

The HIV/AIDS treatment cascade as a model to map PLHIV who actually receive the full benefit of the medical care they need for HIV, was first described by Gardner and colleagues [9]. Examining steps of the cascade allows to identify gaps in care for PLHIV and implement improvements. The cascade model has been applied in several countries to assess the performance of national healthcare programmes [10-12].

Our aim was to describe and quantify PLHIVs' engagement with HIV/AIDS care in Estonia in 2013, applying the concept of the HIV care cascade.

Methods

This was a cross-sectional review synthesising national-level HIV data, applying public health metrics

for monitoring HIV care services, with focus on selected highest priority indicators.

Data sources

We used the UNAIDS Spectrum estimate of the number of PLHIV in Estonia in 2013 [13]. Further, national databases were used to estimate the number of PLHIV at the next steps of the HIV treatment cascade in Estonia in 2013:

(i) The Estonian Health Board (EHB): An agency of the Estonian Ministry of Social Affairs (EMSA), responsible for passive surveillance of communicable diseases (including HIV), recording all newly diagnosed (confirmed by reference laboratory) HIV cases in Estonia; with nationwide coverage; data available online [14].

(ii) The Estonian Health Insurance Fund (EHIF): An institution operating within the administration area of EMSA as an independent legal body; the core purchaser of healthcare services for the compulsory health insurance system in Estonia, possessing healthcare utilisation data, covering all medical services and service costs (except ART medication costs) provided to PLHIV; with nationwide coverage. EHIF assigns each individual an identification code, enabling longitudinal tracking of care provided to individuals without personal identification (pseudo-identification). For study purposes special requests for data were submitted to EHIF.

(iii) the Estonian HIV Cohort Study (E-HIV): A database operated by the Estonian Society for Infectious Diseases which contains detailed and longitudinal demographic and clinical data of PLHIV in Estonia [15]. These include date of HIV confirmation, mode of HIV acquisition and course of HIV care (including dates of clinical appointments, ART provision, dates and results of CD4+ T-cell counts and viral load values) and concomitant diseases [15]. E-HIV was established in April 2009 and includes data from consenting PLHIV in HIV medical care; it also includes some retrospective data. For this study, data on 2,398 individuals with records from 1 September 2012 to 31 August 2013 were retrieved, whereas EHIF had records of 3,252 PLHIV for the same period.

(iv) In addition, data on vital events (AIDS related deaths) were obtained from the Estonian Causes of Death Registry (ECDR).

The specifications for computing the HIV cascade indicators retrieved from each of the databases are detailed in Table 1.

Measures and definitions

For HIV treatment cascade indicators, we used the metrics developed by the United States Centers for Disease Control and Prevention (CDC) [16] and the Institute of Medicine (IOM) [17], adapted to Estonian data sources. Specifically we assessed: the number of persons (i) infected with HIV, (ii) diagnosed with HIV, (iii) linked to HIV care, (iv) retained in HIV care, (v) on ART, and (vi) with suppressed viral load (HIV RNA < 200 copies/mL). We also recorded whether PLHIV had started HIV medical care within three months of diagnosis [17]. We also looked at PLHIV CD4+ T-cell counts at different stages of HIV care to characterise their health state and the stage of the disease (HIV/AIDS).

We used only non-identifiable (anonymised or aggregated) data for this study, and the procedures met local data protection regulations.

PLHIV diagnosed with HIV

We obtained the number of PLHIV registered with the EHB from 1 January 1988 to 31 August 2013 [14]. In Estonia, patients have had to reveal their identity to get the HIV-positive preliminary/screening test result confirmed only since January 2009 [3]. From 2004 to 2008, 34% of new HIV cases were diagnosed anonymously at AIDS counselling centres, with 19% of individuals who tested positive admitting that they had had a positive test earlier [3]. Recording all these anonymous cases at the EHB probably caused some multiple registration of new HIV-positive cases [3]. In the current analysis, based on the five-year data from the AIDS counselling centres, we estimated that until 2009, altogether 6% (those anonymously testing positive and reporting having tested positive before) to 34% (those anonymously testing positive) of all the new HIV cases in Estonia may have been registered more than once.

To account for the deaths of PLHIV over time, we used national vital events statistics on the number of AIDS-related deaths. Due to role of PWID in the Estonian epidemic, we also considered the number of overdose-related deaths among HIV-positive PWID. To obtain an estimate for overdose-related deaths, we used the number of deaths with the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) code X42: 'accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified' [18]; this accounted for the proportion of injected opiate deaths among the ICD-10 X42 deaths and the proportion of PWID ever having tested HIV-positive reported in local studies (data not shown).

Our 2013 estimate of the number of people diagnosed with HIV was therefore based on the number of people ever (between the first case in Estonia in 1988 and the end of our study on 31.08.2013) tested positive for HIV, and subtracting the number of AIDS-related deaths and a specified number of deaths from illicit drug overdose (in the same time period).

PLHIV linked to HIV care

To estimate linkage to and retention in HIV medical care, we used the following case-finding definition to obtain data from the EHIF database: all medical claims with HIV-related ICD-10 codes (B.20–B.24, F02.4, R75,

Table 1

Operational definitions for the six stages of the cascade of HIV care in Estonia, 2013

Stage	Operational definition, data with respective time period	Data source(s)
Living with HIV	The Spectrum estimate for 2013	UNAIDS
Diagnosed with HIV (alive in 2013)	Aggregated number of confirmed HIV-positive tests (individuals) minus the aggregated number of deaths (AIDS deaths, specified proportion of deaths related to illicit drug overdose) Time period: 1 January 1988[a]– 31 August 2013[b]	EHB; ECDR
Linked to HIV care (alive in 2013)	The number of individuals with at least one HIV-related healthcare visit, based on individual anonymised reimbursement claims of HIV-related healthcare services: visit dates, medical services provided to PLHIV (with dates), healthcare providers issuing the claims Time period: 3 February 2000[c]–31 August 2013[b]	EHIF
Retained in HIV care	The number of individuals with two or more HIV-related healthcare visits (at least three months apart) within the past 12 months Time period: 1 September 2012–31 August 2013[d]	EHIF
On ART	Step 1: The proportion of individuals on ART among those retained in care, based on individual anonymised data from E-HIV: HIV confirmation date, ART initiation date, dates and results of $CD4^+$ T-cell and HIV RNA tests, dates of other provided medical services Step 2: The number of individuals on ART among those retained in care according to EHIF, when applying the proportion obtained in Step 1 to individuals retained in care according to EHIF Time period: 1 September 2012–31 August 2013[d]	E-HIV; EHIF
Virally suppressed	Step 1: The proportion of individuals on ART with the most recent (within the past 12 months) HIV RNA level < 200 copies/mL, based on individual anonymised data from E-HIV Step 2: The number of individuals virally suppressed according to EHIF, when applying the proportion obtained in Step 1 to individuals on ART according to EHIF Time period: 1 September 2012–31 August 2013[d]	E-HIV; EHIF

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; ECDR: Estonian Causes of Death Registry; EHB: Estonian Health Board; EHIF: Estonian Health Insurance Fund; E-HIV: Estonian HIV Cohort Study; HIV: human immunodeficiency virus; PLHIV: people living with HIV; UNAIDS: Joint United Nations Programme on HIV/AIDS.

[a] The first HIV case in Estonia was diagnosed in 1988.

[b] End of our study period.

[c] Earliest date appearing on an HIV-related medical service reimbursement claim (the date of opening the medical service account) in the EHIF electronic database since its inception.

[d] To evaluate the situation in 2013, data from this 12-month period were used.

Z21), including all healthcare service(s) provided to the patient(s) [18,19].

We estimated the number of HIV-positive people linked to HIV care by 2013, i.e. having ever accessed HIV/AIDS medical care in Estonia, from cumulative data from the healthcare services utilisation database of the EHIF from database inception till the end of our study (31 August 2013), only including data on PLHIV who were alive on 31 August 2013.

EHIF does not record data on HIV-related medical services provided to PLHIV in prison, as these services are financed through the Ministry of Justice. However, as only a few cases of HIV have been newly diagnosed in the detention system (personal communication: K. Kivimets, Estonian Ministry of Justice, 30 January 2014), we assumed that the majority of HIV-infected persons incarcerated on 31 August 2013, would have had at least one HIV-related contact with the medical care system before incarceration and would thus already be included in the EHIF database.

PLHIV retained in HIV care

Our estimate of retention in HIV care was based on data from the EHIF. Following the IOM definition for 'retained in HIV care' [17], we considered PLHIV having had two or more consultations for HIV medical care (at least three months apart) within the past 12 month-period (1 September 2012–31 August 2013). Patients diagnosed less than three months before the end of the study period were excluded from this analysis.

PLHIV on antiretroviral therapy

Data on PLHIV receiving ART were available from the E-HIV database. The proportion of PLHIV on ART was assessed among individuals considered 'retained in care' on 31 August 2013 and registered with E-HIV. This proportion was applied to the population 'retained in care' according to EHIF to calculate the population-based ART coverage estimate.

PLHIV on ART with suppressed viral load

The proportion of individuals on ART in whom the virus was suppressed, was assessed from data from E-HIV. Individuals with their most recent HIV RNA level < 200 copies/mL during the study period (1 September 2012–31 August 2013) were considered to have achieved viral suppression. This proportion was applied to the population 'retained in care' and on ART according to EHIF to calculate the population-based estimate.

In addition to estimating the six cascade steps, we also assessed the timing of initiation of HIV care, and

Table 2

The HIV care cascade estimates in Estonia, 2013

People	Number of people	Proportion among PLHIV
Living with HIV	8,628 (6,941–10,783)	100%
Diagnosed with HIV (alive in 2013)	6,251 (5,077–7,424)	72% (47–100)
Linked to HIV care (alive in 2013)	4,375	51% (41–63)
Retained in HIV care	1,855	21% (17–27)
On ART	1,521	18% (14–22)
Virally suppressed	1,065	12% (10–15)

ART: antiretroviral therapy; HIV: human immunodeficiency virus; PLHIV: people living with HIV.

PLHIV CD4+ T-cell counts at the start of HIV care and at ART initiation using data from the E-HIV database. For timeliness of PLHIV accessing HIV care, we looked at individuals newly diagnosed with HIV in the study year and calculated the time from HIV confirmation to linkage to HIV medical care for each patient. For this analysis, linkage to care was defined as the first visit to an infectious disease doctor (qualified to follow and treat people infected with HIV in Estonia) when a CD4+ T-cell count and/or HIV RNA level was measured. We considered linkage to HIV medical care to be timely when this first visit took place within 90 days of HIV confirmation [17]. For this calculation, to allow all patients newly diagnosed with HIV at least 90 days to access HIV medical care, only those newly diagnosed by 1 June 2013 were included. We also looked at E-HIV data on patients' CD4+ T-cell counts obtained during the first HIV medical visit (as defined above) and at ART intiation.

Information bias in data sources was mitigated by detailed data review at face-to-face meetings of the research team and consultations with HIV medical care providers and community partners. We compiled cross-comparisons of the data, discussed any discrepancies and, if necessary, obtained additional data and consultations until consensus was reached.

Results

People living with HIV

According to the most recent UNAIDS estimation there were 8,628 (range: 6,941–10,783) PLHIV in Estonia in 2013 [13].

People diagnosed with HIV

A total of 8,605 new HIV cases were registered in Estonia from 1988 to 31 August 2013 according to the EHB: 6,909 in the period 1988 to 2008, and 1,696 in the period 2009 to 2013 [14]. Accounting for the potential 6–34% multiple registrations of new cases until 2009 [3], we estimated that the actual number of people diagnosed with HIV in Estonia over this time may have ranged from 6,242 to 8,164 (mean: 7,203).

According to the Estonian Causes of Death Registry (ECDR), 455 AIDS-related deaths were recorded up to 31 August 2013 (personal communication: G. Denissov, ECDR, 4 December 2103). According to the national drug information centre, there were 1,118 deaths by drug overdose in Estonia between 1999 and 2012 [20], and in 2013 (until 31 August 2013), an additional 81 such deaths (personal communication: G. Denissov, ECDR, 12 February 2015). Of these deaths, 88–94% could be attributed to injection drugs [20]. Thus, we estimated that between 1999 and 31 August 2013, between 1,055 ((1,118 + 81) × 0.88) and 1,127 ((1,118 + 81) × 0.94) deaths related to injection drug overdose may have occurred. However, we also had to take into account that not all those who died from the overdose would have been HIV-positive. According to data from local studies among PWID from 2005 to 2013, the proportion of PWID having ever tested HIV-positive ranged from 27 to 63% (data not shown). Considering that, we estimated that between 285 (1,055 × 0.27) and 710 (1,127 × 0.63) PLHIV may have died from injection drug overdose in Estonia in this period.

Taking into account multiple registration of newly diagnosed HIV cases, the AIDS-related deaths and the deaths due to injection drug overdose among PLHIV, we calculated that between 5,077 (6,242 – 455 – 710) and 7,424 (8,164 – 455 – 285) individuals diagnosed with HIV (mean: 6,251) were living in Estonia on 31 August 2013. Hence, altogether 72% of the 8,628 PLHIV estimated to live in Estonia in 2013 can be expected to have been diagnosed with HIV.

PLHIV linked to HIV care

Since the inception of the EHIF electronic database of medical claims in 2000, altogether 4,375 HIV-positive patients (alive by the end of our study) had received at least one HIV-related medical service (with the HIV-specific ICD-10 code on the medical claim) by (or referred from) an infectious disease doctor, department or clinic. Thus, according to EHIF data, 51% of the 8,628 HIV-positive people estimated to be in Estonia in 2013 could be considered to have ever accessed HIV medical care by the end of our study.

PLHIV retained in HIV care

In 2013, altogether 1,855 PLHIV (21% of the total 8,628 HIV-positive people estimated to live in Estonia) were considered 'retained in care' according to EHIF data.

PLHIV on antiretroviral therapy

In 2013, 1,250 PLHIV could have been considered 'retained in care' according to E-HIV. Of those, 1,022 (82%) also received ART. Applying this proportion, we estimated that 1,521 (1,855 × 0.82) of the PLHIV 'retained in care' according to EHIF were also 'on ART'. This translates into 18% of the total 8,628 HIV-positive people estimated to live in Estonia in 2013.

PLHIV on ART with suppressed viral load

E-HIV included at least one viral load test result during the study period for 1,021 of the 1,022 PLHIV continuously in care and on ART. Of these, 712 (70%) had achieved viral suppression (HIV RNA < 200 copies/mL) at their most recent test. We thus estimated that 1,065 (1,521 × 0.70) of PLHIV continuously in care and on ART had achieved viral suppression. This translates into 12% of the total 8,628 HIV-positive people estimated to live in Estonia in 2013.

All estimates for the steps of the HIV care cascade in Estonia in 2013 are summarised in Table 2.

When looking at the timing of PLHIV linkage to HIV care, we found that according to E-HIV, 111 individuals were newly diagnosed with HIV during the study period (1 September 2012–31 August 2013). Excluding patients with missing data and allowing all patients 90 days to reach HIV care, we found that 86% of those newly diagnosed (74 patients of 86) had accessed HIV care within 90 days of testing HIV-positive.

Regardless of how long (up to 90 days or more) it had taken people diagnosed with HIV to access HIV medical care, more than half (62%) of the 90 individuals registered during the study period had a CD4+ T-cell count ≤ 350 cells/mm3 at registration as newly diagnosed with HIV. Considering data from E-HIV, we also found that majority of PLHIV starting ART (31 of 37 individuals) had had a CD4+ T-cell count ≤ 350 cells/mm3 at treatment initiation.

Discussion

We found that in Estonia, as in other countries where engagement in HIV care has been evaluated [8-12,21], PLHIV are lost at each stage of the HIV care cascade; in 2013, only 12% of the total 8,628 HIV-positive people estimated to live in Estonia had achieved viral suppression. Engagement in different steps of HIV care in Estonia in 2013 resembles that recently described in Georgia [10], a country with similar political and economic history and HIV epidemic (driven by injection drug use until 2011) [22]. However, without unified standards for defining the stages of the cascade [12,23], PLHIV's engagement in different stages of HIV care can only be compared between countries after carefully evaluating that similar definitions and methods of analysis and data sources have been used.

Our results are less positive than a recent analysis based on expert opinion which suggested that 60% of PLHIV in Estonia in 2013 had seen an infectious disease specialist by 31 December 2013 (personal communication: M. Maimets, Tartu University Hospital/ Estonian Society for Infectious Diseases, 26 July 2015) [13]. The difference from the 51% we calculated could derive from the expert analysis going back to the earliest (pre-epidemic) years of HIV in Estonia (1988–99) and including people who, although diagnosed and linked to care during that period, were not retained in care after 2000. In Estonia, antiretroviral drugs are distributed through a centralised system governed by the EMSA. According to the ministry, at the end of our study period (31 August 2013) 2,647 PLHIV were receiving ART (personal communication: E. Bauer, EMSA, 2 December 2013), representing 31% of all PLHIV estimated to live in Estonia in 2013 [13]. The difference from our estimate of 18% PLHIV on ART can be explained by different definitions used, as the EMSA figure represents cross-sectional prevalence, without retention in HIV care (as defined in our study) as a prerequisite. One might debate whether each step in the cascade should derive from the previous one(s), e.g. whether setting retention in care as a prerequisite for the following 'on ART' and 'virally suppressed' steps actually helps define PLHIV receiving proper care for HIV. In case ART data are easily available, as is the case in Estonia, one might be tempted to skip the 'retained in care' step, especially considering the recent developments in HIV medical care in the world. In 2014, UNAIDS set new targets to confront the HIV epidemic, focusing on four of the six steps in the classic cascade [24]. By the end of 2015, all major international HIV treatment guidelines, following the 'test and treat' approach, had introduced a recommendation to prescribe ART to all PLHIV upon diagnosis [25-28]. This should rapidly scale up ART distribution, and thus retention as an independent step in the HIV care cascade is likely to lose value. This also applies to Estonia, where the current guidelines from the European AIDS Clinical Society are followed [26] and persons living with HIV are treated irrespective of their CD4+ T-cell count. However, considering that retention would help evaluate the quality of HIV healthcare (other than ART) provided to PLHIV, monitoring retention would inform the national response to HIV. Although the Estonian National HIV/AIDS Prevention Strategy, which provided a framework for activities against HIV at the time of the study in 2013, ended in 2015 [4], the activities have been incorporated into the National Health Plan 2009–2020 and have continued [29,30].

According to our findings, the main gaps in PLHIV engagement in HIV care in Estonia in 2013 were that (i) about one quarter of the 8,628 persons estimated to live with HIV had not been diagnosed with HIV, (ii) another quarter, although aware of their HIV-positive serostatus, had not accessed HIV medical care and (iii) more than half of PLHIV, having accessed HIV medical care from an infectious disease specialist after diagnosis, were not retained in care. These findings highlight the need for continuous and enhanced effort to identify people with HIV for linkage and retention in care. Based on the absolute number of PLHIV concerned, the biggest issue were people not retained in care they had once been linked to. However, had we applied a more permissive definition for retention (e.g. utilisation of HIV healthcare services once a year in consecutive years), the second most important issue of PLHIV not tested for or not diagnosed with HIV would have become the biggest.

We found that the majority of PLHIV, diagnosed during the study period (1 September 2012–31 August 2013) had accessed specialised HIV care within three months of learning their HIV-positive status. However, this timely linkage occurred too late in the course of the disease, given the low CD4+ T-cell counts of PLHIV at initiation of specialist care (62% with ≤ 350 cells/mm3). Late linkage to HIV care seems to be related to delayed testing. In 2013, 52% of PLHIV in Estonia had a CD4+ T-cell count below 350 cells/mm3 when newly diagnosed, compared with the EU/EEA average of 47% [1], indicating the need to prioritise and intensify HIV testing policies and procedures in Estonia [31]. According to national recommendations, HIV testing is mandatory for blood and organ donors (and in some cases for people in the armed forces) and recommended for pregnant women, prisoners, people with hepatitis, tuberculosis, sexually transmitted dieases and a history of injection drug use or engagement in risky sexual behaviours [3], but screening only these target groups could be insufficient. Therefore local and national guidelines recommend routine HIV screening for all patients aged 16–49 years in healthcare facilities (except in emergency care, where clinical indications apply) in two counties most affected by HIV in Estonia [32]. However, healthcare providers experience challenges in implementing this policy due to lack of training, support and financial resources [31]. All testing programmes and centres should introduce guidelines and have pathways to ensure that people testing positive for HIV get linked to appropriate care [31]. In addition to implementing routine testing, emphasis on groups most at risk of acquiring HIV would facilitate earlier diagnosis [31]. A recent study among PWID, the key risk population in Estonia, revealed that about half of them had not been tested for HIV in the past year [33]. Introducing HIV testing in settings frequently attended by PWID (i.e. needle and syringe exhange sites) could scale up HIV testing among PWID in Estonia.

Our study also showed that more than half of PLHIV who accessed HIV medical care at least once after being diagnosed with HIV were not retained in care in 2013. This gap indicates the need to monitor the quality of HIV healthcare in Estonia, and to retain all steps (e.g. retention in care) in the cascade. Acknowledging the high proportion of PLHIV with current or past drug addiction in Estonia, the recent World Health Organization (WHO) evaluation report on HIV/AIDS treatment and care in the country highlighted the need to expand provision of integrated HIV and related services (e.g. antiretroviral and opioid substitution therapy) as an opportunity to improve HIV care [31].

Our study has several limitations related to measurements at each stage of the cascade of care. The true number of those infected with HIV in Estonia is not known, and we therefore used an estimate derived from UNAIDS. Estimates of the HIV care cascade are very sensitive to the HIV prevalence estimate. After our study was conducted, the WHO evaluation in 2014, based on a crude estimate for the number of people living with undiagnosed HIV in Estonia, suggested that the number of PLHIV might have been around 13,500 [31] instead of the UNAIDS estimate of 8,628 used in our study [13]. In 2017, the Estonian National Institute for Health Development (NIHD) will initiate a project to estimate the number of PLHIV in Estonia (personal communication: K. Rüütel, NIHD, 16 October 2016), using the HIV modelling tool from the European Centre for Disease Prevention and Control (ECDC) [34]. Future research into the HIV care cascade should weigh all the available estimates.

Our analysis is based on unlinked (between databases) and aggregated data and therefore might lack precision. The different sources of data about PLHIV and services used were established at different times, for different purposes, by different institutions. Data availability was the main obstacle to mapping HIV care, as also recognised by other researchers [35]. Missing data on HIV-positive people having died for causes other than AIDS or drug overdose are likely to lead to an overestimate for PLHIV in Estonia in 2013. On the other hand, although we applied carefully constructed case-finding algorithms to identify HIV-positive individuals from the health administrative databases, some cases may have been misclassified, causing an underestimation of HIV care coverage. However, we believe that nationwide coverage of the EHIF, and the EHB strengthen our analysis. In particular, EHIF data (used to derive population-based estimates on medical care linkage, retention and ART coverage) is considered to be representative of medical services provided in Estonia, as EHIF reimburses healthcare providers on a fee-for-service basis. However, none of the databases includes all the information needed to characterise PLHIV at all the stages of HIV care in Estonia, and therefore several assumptions had to be made. Further, for some of the HIV care coverage estimates (the proportion of PLHIV on ART, virally suppressed), we extrapolated data from E-HIV to EHIF data to obtain population-based estimates. Although we are not aware of studies assessing the coverage of E-HIV and factors associated with inclusion in E-HIV (e.g. clinical factors, healthcare utilisation), we might speculate that E-HIV-based proportions are overestimates of those on ART who are virologically suppressed.

Summarising the indicators for the different stages in HIV medical care in Estonia in the format of the well-known HIV treatment cascade [8,9,33] allows easier comparisons between countries of PLHIV engagement in HIV care. However, keeping in mind all the assumptions we had to make during the analysis, such a summary probably gives a simplified picture of the situation in Estonia. It should also be remembered that the point estimates for the number of PLHIV at each step, starting from the UNAIDS estimate for the number of PLHIV in Estonia, include a range, and the ranges of several consecutive estimates overlap.

Our study, identifying the main gaps in connecting PLHIV to sustained and quality care should support policymakers and service providers in Estonia in enhancing services and systems that best support PLHIV as they move through the continuum of HIV medical care.

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None declared.

Authors' contributions

AU, MR and KTL designed the study. MR and KTL performed the data analysis. AU, MR, IL and KTL contributed to interpreting the results. KTL drafted the manuscript and AU, MR and IL contributed to writing it. All authors approved the final version of the manuscript.

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Research article

Real-time real-world analysis of seasonal influenza vaccine effectiveness: method development and assessment of a population-based cohort in Stockholm County, Sweden, seasons 2011/12 to 2014/15

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Real-world estimates of seasonal influenza vaccine effectiveness (VE) are important for early detection of vaccine failure. We developed a method for evaluating real-time in-season vaccine effectiveness (IVE) and overall seasonal VE. In a retrospective, register-based, cohort study including all two million individuals in Stockholm County, Sweden, during the influenza seasons from 2011/12 to 2014/15, vaccination status was obtained from Stockholm's vaccine register. Main outcomes were hospitalisation or primary care visits for influenza (International Classification of Disease (ICD)-10 codes J09-J11). VE was assessed using Cox multivariate stratified and non-stratified analyses adjusting for age, sex, socioeconomic status, comorbidities and previous influenza vaccinations. Stratified analyses showed moderate VE in prevention of influenza hospitalisations among chronically ill adults ≥ 65 years in two of four seasons, and lower but still significant VE in one season; 53% (95% confidence interval (CI): 33–67) in 2012/13, 55% (95% CI: 25–73) in 2013/14 and 18% (95% CI: 3–31) in 2014/15. In conclusion, seasonal influenza vaccination was associated with substantial reductions in influenza-specific hospitalisation, particularly in adults ≥ 65 years with underlying chronic conditions. With the use of population-based patient register data on influenza-specific outcomes it will be possible to obtain real-time estimates of seasonal influenza VE.

Introduction

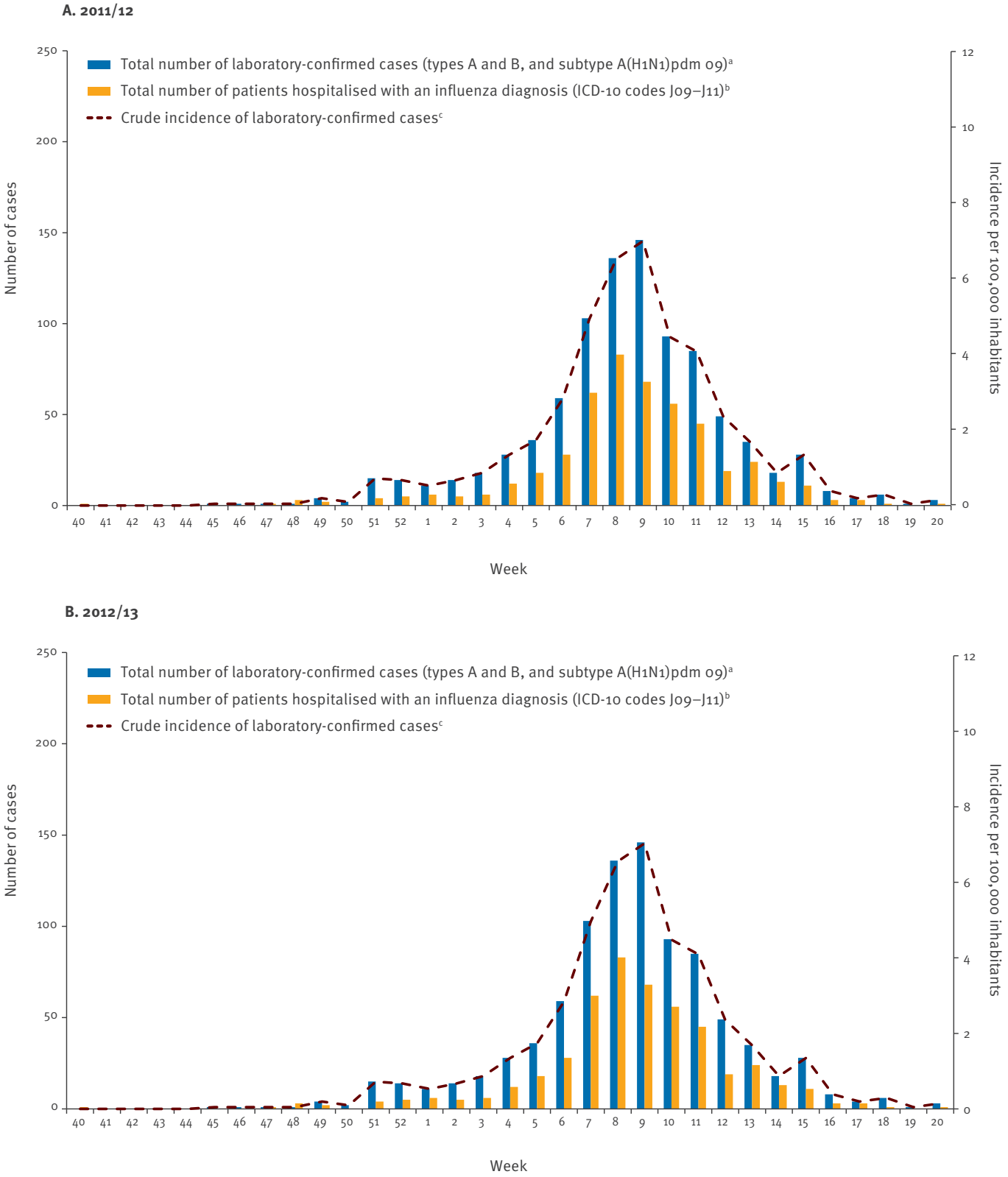
Annual vaccination against circulating influenza viruses remains the best strategy for preventing illness from influenza. A clear challenge, however, is that vaccine effectiveness (VE) varies from year to year [1]. These variations may be due to differences in antigenic match between the vaccine and the circulating strain, the immune status of those who are being vaccinated, or the time interval between vaccination and influenza outbreak.

Influenza outcome specificity is an important factor affecting VE estimates, since outcomes with low specificity will either underestimate or overestimate influenza VE [2,3]. Seasonal influenza VE uncertainty is an important reason for obtaining estimates for in-season vaccine effectiveness (IVE) as early as possible [2,4,5]. Such estimates may help guide the outbreak response, especially if there are signs of an antigenic mismatch that might require complementary public health measures.

There are controversies concerning the overall influenza VE, especially in elderly people, in most studies defined as adults ≥ 65 years of age [6,7]. Real-world evidence of vaccine effectiveness is therefore imperative for future influenza vaccine development and programme evaluation. The seasonal influenza vaccination programme in Stockholm offers vaccination at no out-of-pocket cost to individuals aged 65 years and older, pregnant women, and people of any age with certain underlying risk factors (chronic diseases of the heart, lungs, kidneys or liver, diabetes mellitus, neurological disease affecting the patient's lung function, obesity with a body mass index of › 40, and immunosuppression caused by a disease or treatment). The actual benefit to these targeted groups is largely unknown and the aim of this study was therefore to develop methods for evaluating IVE and the overall seasonal vaccine effectiveness (VE) in all persons, irrespective of underlying risk factors, with medically attended influenza

Figure

Number and incidence of laboratory-confirmed influenza cases, and number of patients hospitalised with influenza diagnosis in Stockholm County, influenza seasons 2011/12–2014/15



ICD: International Classification of Diseases.

Unadjusted incidence calculated by number of laboratory-confirmed cases per 100,000 inhabitants. Numbers reported by calendar week each season.

No data were available on number of laboratory-confirmed hospitalised influenza cases due to anonymous data in the central database for healthcare utilisation, making linkage impossible.

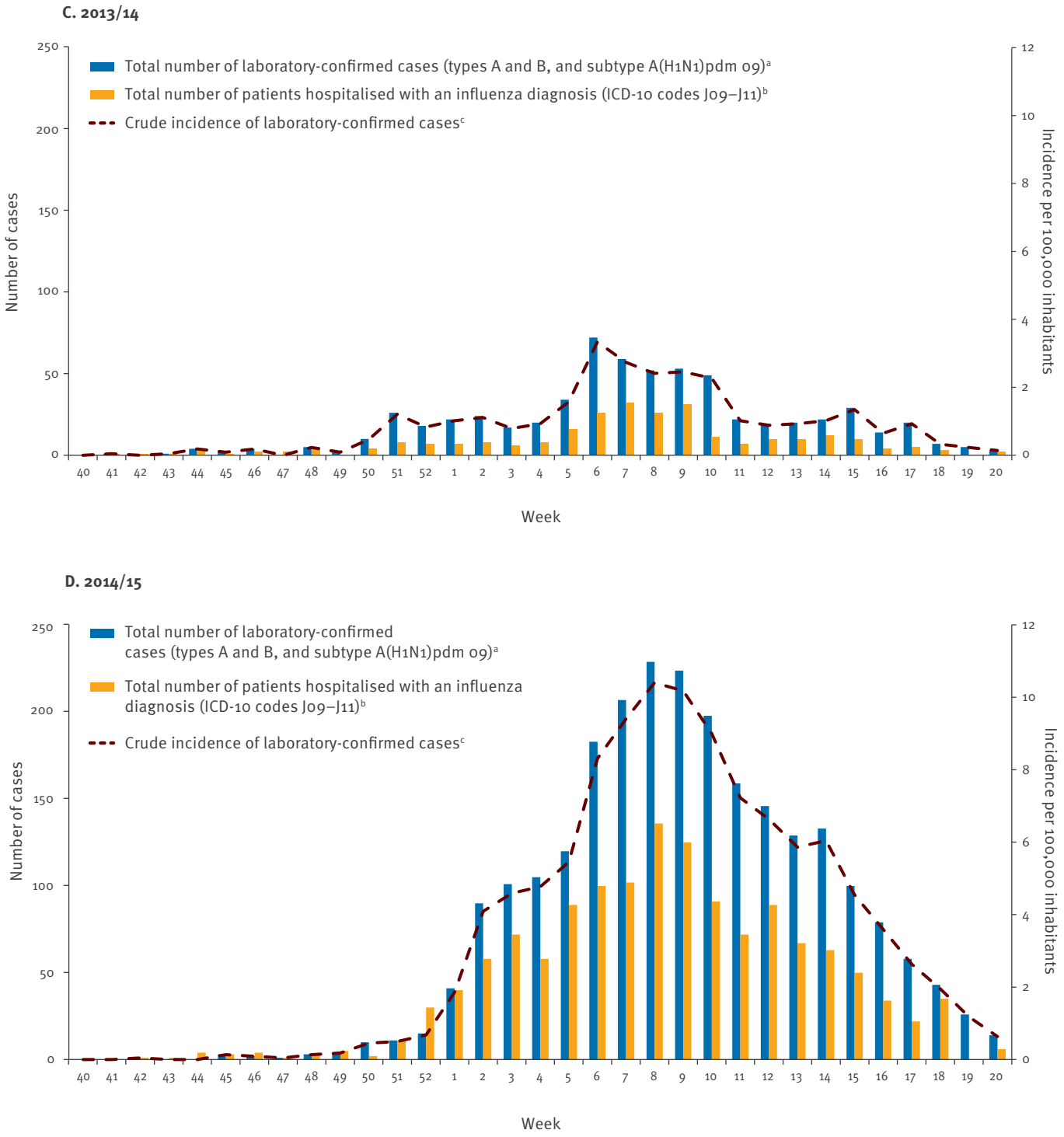
[a] Data obtained from the Public Health Agency of Sweden

[b] Data collected in Stockholm County's central database for healthcare utilisation using ICD-10 codes J09-J11

[c] (Number of laboratory-confirmed cases/number of inhabitants in Stockholm during season) × 100,000.

Figure

Number and incidence of laboratory-confirmed influenza cases, and number of patients hospitalised with influenza diagnosis in Stockholm County, influenza seasons 2011/12–2014/15



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[a] Data obtained from the Public Health Agency of Sweden

[b] Data collected in Stockholm County's central database for healthcare utilisation using ICD-10 codes J09-J11

[c] (Number of laboratory-confirmed cases/number of inhabitants in Stockholm during season) × 100,000.

Table 1A

Baseline characteristics of the cohorts in influenza analysis, Stockholm County, influenza seasons 2011/12 and 2012/13

Characteristic	Influenza season 2011/12			Influenza season 2012/13		
	Total	Vaccinated[a]	Unvaccinated	Total	Vaccinated[a]	Unvaccinated
	n	n (%)	n (%)	n (%)	n (%)	n (%)
Cohort total	2,089,047	205,415 (9.8)	1,883,612 (90.2)	2,121,469	185,646 (8.8)	1 935,823 (91.2)
Sex						
Male	1,034,494	87,659 (8.5)	946,835 (91.5)	1,051,818 (49.6)	79,920 (7.6)	971,898 (92.4)
Female	1,054,553	117,756 (11.2)	936,797 (88.8)	1,069,651 (50.4)	105,726 (9.9)	963,925 (90.1)
Age group in years						
‹ 10	270	388 (0.1)	270,435 (99.9)	276,358 (13.0)	273 (0.1)	276,085 (99.9)
10–19	232	540 (0.2)	231,971 (99.8)	231,869 (10.9)	388 (0.2)	231,481 (99.8)
20–29	283,977	1,373 (0.5)	282,604 (99.5)	291,993 (13.8)	1,014 (0.4)	290,979 (99.6)
30–39	320,932	3,219 (1.0)	317,713 (99.0)	322,867 (15.2)	2,437(0.8)	320,430 (99.2)
40–49	307,966	4,457 (1.4)	303,509 (98.6)	313,605 (14.8)	3,499 (1.1)	310,106 (98.9)
50–59	241,944	8,340 (3.4)	233,604 (96.6)	246,848 (11.6)	6,916 (2.8)	239,932 (97.2)
60–69	223,956	60,580 (27.0)	163,376 (73.0)	224,713 (10.6)	52,719 (23.5)	171,994 (76.5)
70–79	121,415	73,510 (60.5)	47,905 (39.5)	127,570 (6.0)	70,014 (54.9)	57,556 (45.1)
≥ 80	85,523	53,008 (62.0)	32,515 (38.0)	85,646 (4.0)	48,386 (56.5)	37,260 (43.5)
Mosaic income/education categories						
Highest income and education	945,893	94,506 (10.0)	851,387 (90.0)	971,845	85,992 (8.8)	885,853 (91.2)
Middle income and education	360,980	36,871 (10.2)	324,109 (89.8)	372,925	33,095 (8.9)	339,830 (91.1)
Lowest income and education	744,905	73,067 (9.8)	671,838 (90.2)	761,746	66,032 (8.7)	695,714 (91.3)
Missing	37,269	1,450 (3.9)	35,819 (96.1)	14,653	536 (3.7)	14,117 (96.3)
Comorbidity						
Yes	586,470	148,196 (25.3)	438,274 (74.7)	613,183 (28.9)	138,020 (22.5)	475,163 (77.5)
No	1,502,577	57,219 (3.8)	1,445,358 (96.2)	1,508,286 (71.1)	47,626 (3.2)	1,460,660 (96.8)
Previous seasonal vaccination[b]						
Yes	203,736	162,379 (79.7)	41,357 (20.3)	198,361 (9.4)	151,359 (76.3)	47,002 (23.7)
No	1,885,311	43,036 (2.3)	1,842,275 (97.7)	1,923,108 (90.7)	34,287 (1.8)	1,888,821 (98.2)
Pneumococcal vaccination[c]						
Yes	33,374	28,232 (84.6)	5,142 (15.4)	39,502 (1.9)	30,891 (78.2)	8,611 (21.8)
No	2,055,673	177,183 (8.6)	1,878,490 (91.4)	2,081,967 (98.1)	154,755 (7.4)	1,927,212 (92.6)
Pandemrix vaccination[d]						
Yes	1,064,132	163,246 (15.3)	861,669 (84.7)	1,007,546 (47.5)	148,338 (14.7)	859,208 (85.3)
No	1,024,915	42,169 (4.1)	1,021,963 (95.9)	1 113 923 (52.5)	37,308 (3.4)	1,076,615 (96.6)

Influenza season defined as 1 October to 31 May in the following year.

[a] During the 2011/12 influenza season, 99.5% of seasonal influenza vaccinations were carried out using Vaxigrip. During 2012/13, 99.4% of seasonal influenza vaccinations were carried out using Fluarix.

[b] Vaccinated against seasonal influenza during the previous season.

[c] Vaccinated against Streptococcus pneumoniae during time period from 2009 to the season under investigation.

[d] Vaccinated against influenza A(H1N1)pdm09 during the 2009 pandemic.

and pneumonia hospitalisations and primary care cases in Stockholm County, Sweden.

Methods

Study population and period

This study was based on four annual closed cohorts each comprising all individuals registered in Stockholm at the start of each season. The influenza season was defined as starting on 1 October and ending on 31 May the following year.

Data sources

Data were collected using Stockholm County's central database for healthcare utilisation, consultations and diagnoses, VAL. VAL has comprehensive inpatient, hospital outpatient, and primary care data and is used by the County Council to update the national patient register (PR) [8]. Multiple register linkages are possible due to unique personal identification numbers (PIN). Age and sex were retrieved from the primary care listing register in VAL. Immigration and death dates were not available in VAL, necessitating the design of a

Table 1B

Baseline characteristics of cohorts, Stockholm County, influenza seasons 2013/14 and 2014/15

Characteristic	Influenza season 2013/14			Influenza season 2014/15		
	Total	Vaccinated[a]	Unvaccinated	Total	Vaccinated[a]	Unvaccinated
	n	n (%)	n (%)	n (%)	n (%)	n (%)
Cohort total	2,171,207	199,707 (9.2)	1,971,500 (90.8)	2,207,172	205,709 (9.3)	2,001,463 (90.7)
Sex						
Male	1,077,657	84,692 (7.9)	992,965 (92.1)	1,096,957 (49.7)	88,091 (8.0)	1,008,866 (92.0)
Female	1,093,550	115,015 (10.5)	978,535 (89.5)	1,110,215 (50.3)	117,618 (10.6)	992,597 (89.4)
Age group in years						
<10	283,541	488 (0.2)	283,053 (99.8)	287,422 (13.0)	495 (0.2)	286,927 (99.8)
10–19	234,837	521 (0.2)	234,316 (99.8)	236,884 (10.7)	606 (0.3)	236,278 (99.7)
20–29	305,611	1,892 (0.6)	303,719 (99.4)	311,773 (14.1)	2,257 (0.7)	309,516 (99.3)
30–39	327,012	4,715 (1.4)	322,297 (98.6)	330,199 (15.0)	5,343 (1.6)	324,856 (98.4)
40–49	319,407	4,371 (1.4)	315,036 (98.6)	323,168 (14.6)	5,116 (1.6)	318,052 (98.4)
50–59	254,154	7,906 (3.1)	246,248 (96.9)	263,216 (11.9)	9,094 (3.5)	254,122 (96.5)
60–69	224,687	54,003 (24.0)	170,684 (76.0)	222,631 (10.1)	52,957 (23.8)	169,674 (76.2)
70–79	136,323	76,112 (55.8)	60,211 (44.2)	146,285 (6.6)	79,824 (54.6)	66,461 (45.4)
≥ 80	85,635	49,699 (58.0)	35,936 (42.0)	85,594 (3.9)	50,017 (58.4)	35,577 (41.6)
Mosaic income/education						
Highest income and education	990,078	93,330 (9.4)	869,748 (90.6)	1,001,695	97,153 (9.7)	904,542 (90.3)
Middle income and education	381,870	36,128(9.5)	345,742 (90.5)	389,999	37,076 (9.5)	352,923 (90.5)
Lowest income and education	776,802	69,729 (9.0)	707,073 (91.0)	786,842	70,113 (8.8)	716,729 (91.2)
Missing	22,457	890 (4.0)	21,567 (96.0)	28,636	1,367 (4.8)	27,269 (95.2)
Comorbidity						
Yes	635,947	147,899 (23.3)	488,048 (76.7)	653,248 (29.6)	15,187 (23.2)	501,421 (76.8)
No	1,535,260	51,808 (3.4)	1,483,452 (96.6)	1,553,924 (70.4)	53,882 (3.5)	1,500,042 (96.5)
Previous seasonal vaccination[b]						
Yes	179,658	149,881 (83.4)	29,777 (16.6)	193,432 (8.8)	153,515 (79.4)	39,917 (20.6)
No	1,991,549	49,826 (2.5)	1,941,723 (97.5)	2,013,740 (91.2)	52,194 (2.6)	1,961,546 (97.4)
Pneumococcal vaccination[c]						
Yes	48,009	38,801 (80.8)	9,208 (19.2)	55,929 (2.5)	43,833 (78.4)	12,096 (21.6)
No	2,123,198	160,906 (7.6)	1,962,292 (92.4)	2,151,243 (97.5)	161,876 (7.5)	1,989,367 (92.5)
Pandemrix vaccination[d]						
Yes	995,193	156,389 (15.7)	838,804 (84.3)	981,065 (44.5)	157,771 (16.1)	823,294 (83.9)
No	1,176,014	43,382 (3.7)	1,132,632 (96.3)	1 226 107 (55.5)	47,938 (3.9)	1,178,169 (96.1)

Influenza season defined as 1 October to 31 May in the following year.

[a] During 2013/14 and 2014/15, 99.4% of seasonal influenza vaccination were carried out using Fluarix.

[b] Vaccinated against seasonal influenza during the previous season.

[c] Vaccinated against *Streptococcus pneumoniae* during time period from 2009 to the current season under investigation.

[d] Vaccinated against influenza A(H1N1) during the 2009 pandemic.

closed cohort for each season. We used the Stockholm Mosaic system as a proxy for living conditions and socioeconomic status [9]. The Mosaic system is based on eleven mutually exclusive categories (e.g. living in a low-income urban apartment block, multicultural suburb, affluent inner city, countryside, etc.) and involves 120 smaller urban agglomerations. Data on vaccine exposures were retrieved from the vaccination register, Vaccinera, which contains all data on seasonal influenza, pandemic influenza and pneumococcal vaccination of persons belonging to medical risk groups from the region, since 2009. Regional coverage in this database is assumed to be 100% as high-risk persons are vaccinated free of charge within the programme and registration is mandatory and required for reimbursements to the healthcare provider. Data on influenza status and comorbidities were obtained from the inpatient, hospital outpatient, and primary care databases.

Case definition

Cases were defined as a clinical diagnosis of influenza during the season. International Classification of Diseases, 10th revision (ICD-10) codes J09 (influenza due to certain identified influenza viruses), J10 (influenza due to other identified influenza virus) and J11 (influenza due to unidentified influenza virus with pneumonia) were used to identify influenza diagnoses from inpatient, hospital outpatient, and primary care

registers in VAL [10]. In a recent study VAL had over 99% coverage for inpatient care, 90% coverage for hospital outpatient care, and estimated 85% coverage for primary care [8]. National-level reporting estimates a validity of 85–95% for inpatient care, depending on the ICD-10 diagnosis [11]. Influenza cases were classified as inpatient cases if they came from the inpatient register and as outpatient cases if they came from the hospital outpatient or primary care registers. The inpatient register defined the case if an individual existed in multiple registers.

For the purpose of subanalysis, inpatient or outpatient non-influenza pneumonia, using ICD-10 codes J12-J18, was allowed.

Comorbidities were extracted from VAL using ICD-10 codes registered for a period of up to three years before the start of the respective season. ICD-10 codes for tumours (C00-D48), diabetes (E10–14) and circulatory (I00-I99) and non-acute respiratory illness (J40-J99) were extracted.

Vaccination status

Vaccination dates and seasonal vaccine type were derived from Vaccinera. Three different trivalent inactivated vaccines, Vaxigrip (Sanofi Pasteur MSD, Lyon, France), Fluarix (GSK, Brentford, United Kingdom), and Inflexal V (Crucell, Janssen Vaccines, Leiden, The Netherlands), were used during the seasons covered. No high-dose or adjuvanted vaccines were available in Sweden during the four seasons. Individuals with influenza infection before vaccination, or up to 13 days post-vaccination, were considered to be unvaccinated as were those who did not receive the seasonal vaccine. Those with influenza infection ≥ 14 days post vaccination were considered to be vaccinated. Pandemic influenza (Pandemrix, GSK) vaccination status from 2009/10 was included as a covariate as was pneumococcal vaccination (in the current season or previous seasons since 2009). Vaccination against seasonal influenza in the previous season was also included as a covariate.

Influenza epidemiology

According to the Public Health Agency of Sweden, when compared with previous seasons, influenza activity was high during the most recent of the four seasons (2014/15), moderate during the 2011/12 and 2012/13 seasons, and low during the 2013/14 season [12] (Figure). Influenza A(H3N2) dominated in the 2011/12 and 2014/15 seasons, influenza A(H1N1)pdm09 dominated in 2013/14, whereas both these and influenza B viruses circulated in the 2012/13 season. There was also a significant amount of influenza B cases (approximately one-third of the cases) in 2014/15. In all four seasons influenza peaked during the second half of February.

Statistical analyses

Hazard rate ratios (HRR) comparing influenza inpatient and outpatient incidence among vaccinated and unvaccinated individuals were calculated using Cox regression analyses. Models were adjusted for age (grouped into 10-year intervals), sex, comorbidity status, socioeconomic status, pandemic vaccination, previous season influenza vaccination and pneumococcal vaccination. Stratified analysis of elderly people, aged 65 years or older, and individuals with underlying chronic illnesses was also performed, including age as a linear variable. Vaccination status was included as a time-varying exposure in the model, so individuals could contribute both vaccinated and unvaccinated risk time. In the final model comorbidity was adjusted for as a dichotomous variable as yes or no. The overall seasonal influenza vaccine effectiveness (VE) was calculated as (1 – HRR) x 100%. Both HRR and VE were reported with 95% confidence intervals (CI).

Additional regression analyses modelled VE on inpatient and outpatient pneumonia (ICD-10 J12-J18), adjusting for age (grouped into 10-year intervals), sex, comorbidity status, pandemic vaccination, previous season influenza vaccination and pneumococcal vaccination.

Regression analyses for the pre-influenza periods, 1 June to 30 September of the four seasons under investigation were performed to assess whether there was a healthy-vaccinee bias present in the cohort. Previous studies have reported on such a bias, which would augment VE estimates [13,14]. Pre-season analyses modelling influenza among those vaccinated later during the season were adjusted for age, sex and comorbidity status.

Data management and analyses were carried out using SAS Enterprise software (SAS Institute Inc., Cary, NC).

Ethical consideration

This analysis was part of ongoing programme evaluations required at the Department of Communicable Disease Control and Prevention, Stockholm County Council, Stockholm, Sweden. As this evaluation was a requisite part of Stockholm County Council work processes, it falls outside the mandate for the Regional Ethics committee. PINs have been anonymised in VAL and no data making individual identification possible is retained.

Results

In total, 2–2.2 million individuals were included per season in the study (Tables 1A and 1B). A slightly higher proportion of women were vaccinated compared to men. (Tables 1A and 1B). The number of patients with a clinical diagnosis of influenza was highest in 2011/12 and in 2014/15, seasons dominated by influenza A(H3N2), but the need for hospital treatment was about three times higher in 2014/15 than in 2011/12 (Table 2). The number of people hospitalised with a

Table 2

Hazard ratios with 95% confidence intervals and vaccine effectiveness estimates for seasonal influenza vaccination on influenza outcome including inpatient and outpatient cases, Stockholm County, influenza seasons 2011/12–2014/15

Category	Total number	All cases			Outpatient			Inpatient		
		Cases	HR (95% CI)	VE	Cases	HR (95% CI)	VE	Cases	HR (95% CI)	VE
2011/12										
All										
Unvaccinated	1,883,612	5,109	Ref	NA	4,793	Ref	NA	316	Ref	NA
Vaccinated	205,415	374	0.81 (0.69–0.94)	19% (6–31)	210	0.69 (0.57–0.84)	31% (14–43)	164	1.07 (0.79–1.46)	0
Age ≥ 65 years										
Unvaccinated	140,143	263	Ref	NA	161	Ref	NA	102	Ref	NA
Vaccinated	176,622	299	0.90 (0.72–1.12)	10% (0–28)	149	0.86 (0.64–1.17)	14% (0–36)	150	0.94 (0.68–1.31)	6% (0–32)
2012/13										
All										
Unvaccinated	1,935,823	2,471	Ref	NA	1,885	Ref	NA	586	Ref	NA
Vaccinated	185,646	139	0.60 (0.48–0.77)	40% (23–52)	48	0.55 (0.37–0.81)	45% (19–63)	91	0.53 (0.39–0.73)	47% (27–61)
Age ≥ 65 years										
Unvaccinated	163,988	202	Ref	NA	55	Ref	NA	147	Ref	NA
Vaccinated	162,678	106	0.51 (0.38–0.69)	49% (31–62)	31	0.62 (0.35–1.10)	38% (0–65)	75	0.48 (0.34–0.69)	52% (31–66)
2013/14										
All										
Unvaccinated	1,971,500	2,076	Ref	NA	1,850	Ref	NA	226	Ref	NA
Vaccinated	199,707	105	0.63 (0.48–0.83)	37% (17–52)	57	0.58 (0.41–0.83)	42% (17–59)	48	0.70 (0.44–1.11)	30% (0–56)
Age ≥ 65 years										
Unvaccinated	166,024	129	Ref	NA	58	Ref	NA	71	Ref	NA
Vaccinated	170,752	74	0.54 (0.37–0.79)	46% (21–56)	33	0.59 (0.33–1.05)	41% (0–67)	41	0.51 (0.31–0.83)	49% (17–69)
2014/15										
All										
Unvaccinated	2,001,463	4829	Ref	NA	3,980	Ref	NA	849	Ref	NA
Vaccinated	205,709	829	0.85 (0.76–0.95)	15% (5–24)	298	0.83 (0.70–0.98)	17% (2–30)	531	0.84 (0.72–0.99)	16% (1–28)
Age ≥ 65 years										
Unvaccinated	172,245	697	Ref	NA	212	Ref	NA	485	Ref	NA
Vaccinated	173,075	705	0.82 (0.71–0.93)	18% (7-29)	204	0.89 (0.69–1.15)	11% (0–31)	501	0.79 (0.68–0.93)	21% (7-32)

CI: confidence interval; HR: hazard ratio; NA: not applicable; Ref: reference value; VE: vaccine effectiveness.

International Classification of Diseases, 10th revision codes J09-J11 were used to identify influenza diagnoses [10].

Vaccine effectiveness calculated (1 – HR × 100).

Hazard ratios derived from Cox proportional hazards regression model; adjusted for sex, age (age groups 10-year intervals), comorbidity status, socioeconomic status, previous seasonal vaccination, pneumococcal vaccination and Pandemrix vaccination. As complete case analysis was used, the number of cases decreased due to missing in socioeconomic status.

diagnosis of influenza during the influenza seasons followed the curve of laboratory-confirmed cases in the county (Figure).

In 2011/12, more than 99% of all those vaccinated received Vaxigrip, while in the remaining seasons more than 99% were vaccinated with Flurarix. Almost 30% of the individuals included in the analysis had a documented comorbidity and of these ca 25% were vaccinated. There were no differences in vaccination rates among those with high or low socioeconomic status (Tables 1A and 1B).

For the 2011/12 season, overall VE for inpatient and outpatient care was 19% (95% CI: 6–31), driven primarily by outpatient effects in those younger than 65 years of age (Table 2). For the 2012/13 season, overall VE was higher, 40% (95% CI: 23–52), with stronger VE seen among inpatients, particularly those 65 years of age or older (VE: 52%; 95% CI: 31–66). For the 2013/14

Table 3

Stratified analyses presenting hazard ratios with 95% confidence intervals and vaccine effectiveness estimates for seasonal influenza vaccination on influenza outcome among individuals with comorbidity, Stockholm County, influenza seasons 2011/12–2014/15

Category	Total number	All cases among those with comorbidity			Outpatient among those with comorbidity			Inpatient among those with comorbidity		
		Cases	HR (95% CI)	VE	Cases	HR (95% CI)	VE	Cases	HR (95% CI)	VE
2011/12										
All										
Unvaccinated	438,274	1,624	Ref	NA	1,424	Ref	NA	200	Ref	NA
Vaccinated	148,196	307	0.79 (0.66–0.95)	21% (5–34)	164	0.71 (0.57–0.90)	14% (0.36)	143	0.90 (0.65–1.24)	10% (0–35)
Age ≥ 65 years										
Unvaccinated	8,205	193	Ref	NA	103	Ref	NA	90	Ref	NA
Vaccinated	131,456	249	0.85 (0.66–1.09)	15% (0–34)	117	0.87 (0.61–1.23)	13% (0–39)	132	0.83 (0.60–1.18)	17% (0–40)
2012/13										
All										
Unvaccinated	475,163	949	Ref	NA	607	Ref	NA	342	Ref	NA
Vaccinated	138,020	117	0.54 (0.41–0.70)	46% (30–59)	36	0.56 (0.35–0.89)	44% (11–65)	81	0.50 (0.36–0.69)	50% (31-64)
Age ≥ 65 years										
Unvaccinated	106,110	180	Ref	NA	47	Ref	NA	133	Ref	NA
Vaccinated	123,472	94	0.47 (0.34–0.64)	53% (37–66)	24	0.51 (0.27–0.95)	49% (5–73)	70	0.47 (0.33–0.67)	53% (33–67)
2013/14										
All										
Unvaccinated	488,048	745	Ref	NA	604	Ref	NA	141	Ref	NA
Vaccinated	147,899	93	0.70 (0.51–0.95)	30% (5-49)	51	0.81 (0.54–1.21)	19% (0–46)	42	0.52 (0.32–0.84)	48% (16–68)
Age ≥ 65 years										
Unvaccinated	108,496	104	Ref	Ref	37	Ref	Ref	67	Ref	Ref
Vaccinated	130,592	67	0.55 (0.37–0.82)	45% (18-63)	30	0.78 (0.41–1.48)	22% (0–59)	37	0.45 (0.27–0.75)	55% (25–73)
2014/15										
All										
Unvaccinated	501,421	2,002	Ref	Ref	1,391	Ref	Ref	611	Ref	Ref
Vaccinated	151,827	731	0.85 (0.75–0.97)	15% (3-25)	237	0.84 (0.68–1.03)	16% (0–32)	494	0.85 (0.72–1.00)	15% (0–28)
Age ≥ 65 years										
Unvaccinated	113,444	591	Ref	NA	164	Ref	NA	427	Ref	NA
Vaccinated	133,226	639	0.82 (0.71–0.94)	18% (6-29)	169	0.84 (0.63–1.11)	16% (0–37)	470	0.82 (0.69–0.97)	18% (3-31)

CI: confidence interval; HR: hazard ratios; NA: not applicable; Ref: reference value; VE: vaccine effectiveness

International Classification of Diseases, 10th revision codes J09–J11 were used to identify influenza diagnoses. [10]

[a] Vaccine effectiveness, calculated (1 – HR × 100).

[b] Hazard ratios derived from Cox proportional hazards regression model; adjusted for sex, age (age groups 10 years intervals), socioeconomic status, previous seasonal vaccination, pneumococcal vaccination and Pandemrix vaccination. As complete case analysis was used, the number of cases decreased due to missing in socioeconomic status.

season, overall VE was 37% (95% CI: 17–52), with elderly inpatient care driving the effects (VE: 49%; 95% CI: 17–69 for those 65 years or older). In 2014/15, the study season with the highest burden of hospital treatment of influenza, the VE was again lower and the vaccine effect was strongest for those 65 years, or older, 18% (95 CI: 7–29) overall and 21% (95% CI: 7–32) for inpatient care.

For the two seasons with moderately high VEs, inpatient VE for patients with comorbidities was similar to that of the whole population (Table 3). Stratified analyses on comorbidity showed 48–55% effectiveness against inpatient care in the seasons 2012/13 and 2013/14 for those with underlying chronic illness, both overall and among those 65 years of age or older. VE in outpatient care was not as strongly affected by comorbidity status.

Stratified analyses on previous season influenza vaccination among those 65 years of age or older, showed no clear effects, either protective or negative, against the risk of being hospitalised with a diagnosis of influenza in the current season (data not shown).

The pre-influenza season analyses, 1 June to 30 September, were all statistically insignificant, with HRs of 1.71 (95% CI: 0.80–3.66), 0.87 (95% CI: 0.29–2.56), 1.09 (95% CI: 0.45–2.65), and 0.83 (95% CI: 0.34–2.01), respectively, indicating that vaccination was not associated with either a decreased or increased risk of receiving a diagnosis of influenza in any of these four pre-influenza season periods.

VE for inpatient non-influenza pneumonia in persons aged 65 years or older ranged from 11% to 18% during the four seasons. No effectiveness could be demonstrated against non-hospitalised pneumonia (Table 4).

Discussion

In this study we used influenza and pneumonia diagnosis codes linked with vaccination status from the entire population of a large metropolitan area to evaluate seasonal influenza vaccine effectiveness on inpatient hospitalisations and primary care visits. Our results thus provide important real-world vaccination programme effects in individuals of varying ages and health statuses. Vaccine effects were moderately good both in adults <65 years of age and in elderly people (≥ 65 years of age), including those with comorbidities, during two of the four seasons. Small but significant VE against non-influenza pneumonias was found in persons 65 years or older in all four seasons. However, since the proportion of pneumonia caused by influenza in most studies is less than 20%, a VE of 11–18% for pneumonia hospitalisation in persons aged 65 years or older, of whom about half were vaccinated, could indicate a VE for influenza-related pneumonia as high as 50–75% [3].

Seasonal influenza programme vaccination is typically recommended to prevent severe outcomes in highly vulnerable groups. What constitutes optimal outcome measures for seasonal influenza VE is debatable, however. Commonly used outcome measures are influenza-like-illness (ILI), acute respiratory infection (ARI), or hospitalisation for influenza or pneumonia [6,15,16]. Effectiveness against laboratory-confirmed influenza vaccine type is the most specific outcome measure, although often available for relatively limited populations, such as healthy adults, and as such not fully generalisable to populations targeted for influenza programmes [2,4].

The four pre-influenza season period analyses did not show any difference in the risk of receiving a clinical diagnosis of influenza in vaccinated vs non-vaccinated persons, indicating that there was no healthy-vaccinee bias in the current study. This is in contrast to most studies, including an earlier study from Stockholm [13,14,17,18]. The former Stockholm study was performed in 1998–2001 when the yearly seasonal influenza vaccination campaigns were new and included only adults aged 65 years or older. Vaccines were not offered free of charge as they are today, which may also explain the healthy-vaccinee bias found in that study [14]. In addition, during the last few years, Stockholm's influenza vaccine campaign has been developed specifically to target the chronically ill, irrespective of age.

Randomised control trials (RCTs) measuring influenza VE among elderly people are rare and the only one of high quality showed a 50% effect against serologically confirmed influenza [19]. Pooled observational studies have shown nominal effects among the elderly in nursing homes (ILI VE 23%; hospitalisation for pneumonia VE 45%), but non-significant effects on elderly people living in the community in terms of ILI or influenza [6]. Overall, observational VE estimates range from 25% to 60% in protecting against hospitalisation for influenza or pneumonia among the elderly [6,16,20]. Observational studies are often not able to account for specific effects among the chronically ill, which is a major limitation [16]. When treatment choice, or in this case vaccination status, is driven by an individual's disease status, it is referred to as confounding by indication and is another type of selection bias. The influenza vaccination programme promotes this population selection bias by targeting those with underlying comorbidities. A major strength in our study is that these effect results have accounted for this major bias by linking with patient records and adjusting for comorbidity status. Other strengths were that we adjusted for potential differences stemming from socioeconomic status and controlled for residual effects in seasonal VE estimates due to previous seasonal vaccinations [21,22], pandemic influenza and pneumococcal vaccinations.

The European network Influenza - Monitoring Vaccine Effectiveness (I-MOVE) has monitored VE in a number of countries since 2008 by observational studies using the 'test-negative' or 'screening' designs [1]. Our results among persons with comorbidity showing a very low VE in 2011/12, but a moderately good VE around 50% for prevention of hospitalisation for influenza among persons aged 65 years or older in 2012/13 and 2013/14, are in accordance with those presented by I-MOVE. They found a very low VE during the 2011/12 season, from 43% during the early part of the season down to less than 10% in risk groups when the whole season was analysed [23,24]. The reason for this low VE late in the 2011/12 season may have been a waning vaccine effect in older persons, since the peak came late in the season, or an antigenic drift [24]. During the 2012/13 season, when all three influenza types circulated, I-MOVE reported a moderately high VE in Europe (43–63% depending on influenza type), and also in 2013/14 with a VE for the dominating influenza A(H1N1) pdm09 of 48% [23,25]. Reports from the 2014/15 season from North America and Europe are in accordance

Table 4

Hazard ratios with 95% confidence intervals and vaccine effectiveness estimates for seasonal influenza vaccination on pneumonia outcome including inpatient and outpatient cases, Stockholm County, influenza seasons 2011/12–2014/15

Category	Total number	All cases			Outpatient			Inpatient		
		Cases	HR[a] (95% CI)	VE[b]	Cases	HR[a] (95% CI)	VE[b]	Cases	HR[a] (95% CI)	VE[b]
2011/12										
All										
Unvaccinated	1,884,818	20,088	Ref	NA	15,123	Ref	NA	4,965	Ref	NA
Vaccinated	204,229	4,849	1.15(1.09–1.20)	0	2,267	1.28(1.20–1.37)	0	2,582	0.97 (0.90–1.07)	3% (0–10)
Age ≥ 65 years										
Unvaccinated	141,097	4,735	Ref	NA	1,878	Ref	NA	2,857	Ref	NA
Vaccinated	175,668	4,333	0.93 (0.88–0.99)	7% (1–12)	1,946	1.14 (1.04–1.24)	0	2,387	0.82 (0.76–0.88)	18% (12–24)
2012/13										
All										
Unvaccinated	1,936,790	10,224	Ref	NA	8,013	Ref	NA	2,211	Ref	NA
Vaccinated	184,679	3,606	1.02 (0.96–1.07)	0	1,518	1.05 (0.97–1.13)	0	2,088	0.97 (0.90–1.04)	3% (0–10)
Age ≥ 65 years										
Unvaccinated	164,807	4,697	Ref	NA	1,787	Ref	NA	2,910	Ref	NA
Vaccinated	161,859	3,250	0.95 (0.89–1.00)	5% (0–11)	1,319	1.05 (0.96–1.16)	0	1,931	0.89 (0.83–0.96)	11% (4–17)
2013/14										
All										
Unvaccinated	1,972,363	12,718	Ref	NA	8,527	Ref	NA	4,191	Ref	NA
Vaccinated	198,844	3,737	1.05 (1.00–1.11)	0	1,700	1.20 (1.11–1.29)	0	2,037	0.95 (0.88–1.03)	5% (0–12)
Age ≥ 65 years										
Unvaccinated	166,773	4,247	Ref	NA	1,633	Ref	NA	2,614	Ref	NA
Vaccinated	170,003	3,349	1.00 (0.94–1.06)	0	1,455	1.20 (1.09–1.32)	0	1,894	0.89 (0.82–0.96)	11% (4-18)
2014/15										
All										
Unvaccinated	2,002,587	16,155	Ref	NA	11,336	Ref	NA	4,819	Ref	NA
Vaccinated	204 585	4 636	1.08 (1.03–1.13)	0	2,207	1.17 (1.09–1.25)	0	2,429	0.97 (0.91–1.04)	3% (0–9)
Age ≥ 65 years										
Unvaccinated	166 773	5 264	Ref	NA	2,221	Ref	NA	3,043	Ref	NA
Vaccinated	173 170	4 146	0.98 (0.93–1.03)	2% (0–7)	1,905	1.12(1.03–1.22)	0	2,241	0.89 (0.82–0.95)	11% (5–18)

CI: confidence interval; HR: hazard ratio; NA: not applicable; Ref: reference value; VE: vaccine effectiveness.

International Classification of Diseases, 10th revision codes J12-J18 were used to identify non-influenza pneumonia diagnoses [10].

[a] Hazard ratios derived from Cox proportional hazards regression model; confidence interval; adjusted for sex, age (age groups 10 years intervals), comorbidity status, socioeconomic status, previous seasonal vaccination, pneumococcal vaccination and Pandemrix vaccination. As complete case analysis was used, the number of cases decreased due to missing in socioeconomic status.

[b] Vaccine effectiveness calculated (1 – HR × 100).

with our findings that VE was lower than during the two preceding seasons [26-28]. A possible reason for this lower VE is that circulation of newly emerged A(H3N2) clades 3C.3a and 3C.2a viruses, to which antibodies in humans to the A/Texas/50/2012 antigens contained in the seasonal vaccine, reacted less well [28,29].

Effects among adults under 65 years of age, particularly healthy individuals, should theoretically be higher than in elderly people, as they have a better immune response to vaccination. In contrast, VE among healthy adults below 65 years in our study was similar to, or lower than among the elderly. A possible reason for this finding is a potential misclassification of exposure, since entering influenza vaccination of healthy adults below 65 years in the vaccination register is not requisite, as Stockholm neither recommends nor subsidises influenza vaccinations for these individuals. If healthy individuals aged under 65 years obtain vaccinations via mobile clinics at their workplace or via a healthcare provider, they may not be entered in the vaccination register. As such, some may be inappropriately

classified as unvaccinated in our study, and hence weaken the effect measures of VE. In contrast, persons belonging to risk groups according to the programme will most likely have been registered in the vaccination register, since they are offered the vaccine free of charge and have easy access to caregivers included in the programme. In addition, caregivers are reimbursed only when they adhere to the reporting requirements.

Although we did not see any evidence of a healthy-vaccinee bias in pre-season analyses, the power of this analysis was low since the few cases with influenza diagnoses off-season resulted in wide confidence intervals. Another limitation is that VAL experienced a technical problem while merging primary care data for 2013, and thus it appears as if there are a reduced number of primary care cases for this year. This technical problem is non-differential and, if anything, would generate diluted VEs. Inpatient care is complete and not affected by these technicalities. We could not control for the severity of comorbidity or the severity of the acute disease in order to identify patients in need of intensive care treatment, nor could we analyse mortality outcomes, since these data are not included in the County's surveillance. Negative controls were not included in these analyses, although pneumonia was included as a subanalysis, and while significant VE was found, it was very low because of the diluting effect of such a non-specific diagnosis.

Our study found robust VE against influenza hospitalisation, a proxy for severe disease. This VE was most substantial among adults and the elderly having underlying chronic conditions. Therefore, we believe that public health officials should focus resources also on attaining high coverage in people with underlying diseases, irrespective of age, in addition to the WHO/EU goal of a 75% for coverage among all people 65 years of age or older [30].

The need for additional effectiveness studies for the influenza vaccine with non-specific outcomes such as pneumonia or influenza-like illness has been questioned since the potential for overestimation or underestimation of vaccine effectiveness is too great [3]. Although the influenza diagnoses were not laboratory-confirmed, our study demonstrates that comprehensive population-based patient register data on influenza-specific outcomes, which allow for adjustments of multiple confounders and assessments of potential biases, can and should be used for routine estimates of seasonal influenza IVE and VE. The VEs in our study were in accordance with those from European multicentre studies using the much more laborious test-negative design [25,31,32]. International sentinel surveillance efforts remain vital to gauge circulating types, but are not needed to accurately assess VE across broad populations. In addition, large and expensive RCTs to estimate effects of seasonal influenza vaccines are neither fiscally nor ethically justifiable in the era of reliable electronic medical record data.

Since the beginning of 2016 we have had a regular weekly linkage between Stockholm's central database for healthcare diagnoses, VAL, and the vaccine register [33]. These real-time data showed that the 55–68% IVE seen in persons aged 65 years or older during January and February, when A(H1N1)pdm09 dominated, declined when influenza B (Victoria) took over and was only 43–44% from the end of March, an observation which lead us to take action and recommend that doctors prescribe early antiviral therapy for ILI in this patient group.

In conclusion, results from this population-based evaluation of multiple vaccine seasons show substantial protective VE against being hospitalised with a diagnosis of influenza among elderly and chronically ill persons in all age groups during two of four seasons and lower, but still significant, VE in another. Programmes that target these vulnerable populations can anticipate ca 50% reductions in influenza-specific inpatient care, in seasons with a good antigenic match. We also demonstrate that the use of population-based patient register data on influenza-specific outcomes enables valuable real-time estimates of seasonal influenza vaccine effectiveness.

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Conflict of interest

None declared. Dr Amy Leval became an employee at Janssen-Cilag after the study was designed, initial analyses performed and manuscript drafted. This study was not sponsored by Janssen-Cilag nor does it represent the opinions thereof.

Authors' contributions

All authors participated in the planning, analysis and writing of the manuscript of this study. M-PH had full access to all the data in the study and takes responsibility for the integrity of the data. M-PH and AL take responsibility for the accuracy of the data analyses.

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