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Progressing towards tuberculosis elimination in the European Union and European Economic Area

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The year 2015 marks the year by which the Stop TB partnership Global Plan, in line with the United Nations Millennium Development Goal (MDG) 6 on HIV/AIDS, malaria and tuberculosis (TB), committed to meet the target to halt and begin to reverse the incidence of tuberculosis (TB) [1,2].

On the occasion of World Tuberculosis Day on 24 March, the World Health Organization Regional Office for Europe (WHO/Europe) and the European Centre for Disease Prevention and Control (ECDC) annually publish a joint report on TB surveillance and monitoring, based on data collected at national level in the European Union (EU)/European Economic Area (EEA) countries and countries in the WHO European Region overall. This report allows to assess the progress made towards prevention and control of TB in the EU/EEA and in the WHO European Region.

The latest report shows that in 2013, a total of 64,844 TB cases were reported in 30 EU/EEA countries, 6% (4,175 cases) less than in 2012 [3]. Notification rates already started to decline before 2004 [4] and this decline continued in the past 10 years, i.e. from 19.1 in 2004 to 12.7 TB cases per 100,000 population in 2013 [3,5]. Thus the target set for TB in the MDG 6 has been reached, and suggests that effective TB programmes are in place in the EU/EEA. Overall, the 2013 TB surveillance data show no significant changes from trends observed in previous years. Remarkably, the proportion and number of cases with multidrug-resistant (MDR) TB remained virtually unchanged between 2008 and 2013: EU/EEA countries reported 1,484 MDR TB cases (4.1% of cases with drug susceptibility testing (DST) results) and 139 extensively drug-resistant (XDR) TB cases.

A tool frequently used for TB prevention, especially to prevent severe forms of TB in children, is the *Bacillus Calmette-Guérin* (BCG) vaccine. According to the International Union Against Tuberculosis and Lung Disease, countries that reach a low TB incidence may consider discontinuation of universal BCG vaccination [6]. In 2007, France changed its BCG vaccination policy

from universal BCG vaccination to vaccination of children considered to be at high-risk for TB [7]. In this issue of *Eurosurveillance*, Bui et al [8] present results of an evaluation of the impact of the changed policy and show that TB meningitis incidence did not increase and remained rare in France. However, the authors also point out the need to continue to carefully monitor the impact of the selective vaccination policy. Their study provides a good example of how new policies for TB vaccines can be evaluated using both notification and laboratory data.

To target prevention and control activities, experts need to know the specifics of 'their' epidemic. In many EU/EEA countries, HIV status of TB cases remains unknown at the national level [3]. McDonald et al. in this issue, used probabilistic data linkage of anonymised TB and HIV patient data to investigate the extent of TB and HIV co-infection and to identify risk factors for such co-infections in Scotland [9]. They concluded that TB and HIV co-infection was relatively uncommon in Scotland and that co-infected patients belonged to certain risk populations. Clinicians should be aware of the possibility of co-infection and take appropriate diagnostic measures in these groups. In countries where HIV cases are reported anonymously or where patient confidentiality legislation prevents collection of information on HIV status for individual TB patients, record linkage is a good method for gathering information on TB-HIV co-infections to better target prevention and control measures.

The epidemiological situation of TB in Europe is overall improving. However, this may mask some disparities between countries. In 2013, TB incidence ranged from less than 10 per 100,000 population in 18 countries to over 40 per 100,000 in three countries in the EU/EEA [3]. MDR and XDR TB persist and high rates of MDR TB are reported in neighbouring countries of the EU/EEA. Furthermore, the proportion of patients who successfully completed their treatment is still below the WHO target of 85% in a large number of the EU/EEA countries. In countries with low notification rates

TB is concentrating in vulnerable populations such as in people originating from countries with a high TB burden, the urban poor, and prisoners. This results in TB notification rates of >40 per 100,000 population in some cities in low incidence countries [10]. For all these reasons, TB is still a public health concern across Europe.

The long-term goal for the EU is to control and ultimately eliminate TB [11]. In order to progress further towards this goal it is essential to target prevention and control activities so that they fit the epidemiological situation in the respective countries or areas. This includes, for example, maintaining expertise and awareness on TB in low incidence settings and tailoring TB control measures to the most at risk populations. Also, efforts should be maintained to ensure good quality TB programmes that enable prompt identification and adequate management of TB patients as well as necessary infection control measures. Furthermore, existing tools need to be better implemented, i.e. diagnostic tests, medicines, and vaccines, and new tools need to be developed and introduced. Therefore, investments in research and development of new tools on TB need to continue and even expand.

Elimination of TB and MDR TB in the EU/EEA and its Eastern Partnership countries is the topic of the 'Eastern Partnership Ministerial Conference on Tuberculosis (TB) and its multidrug resistance' organised by the Latvian Presidency of the Council of the EU, in Riga, Latvia, on 30 and 31 March 2015 [12]. At this conference, ministers and high level representatives from Ministries of Health, Social Affairs and Finance of the EU/EEA and Eastern Partnership countries as well as high level representatives of the European Commission, members of the European Parliament, representatives of international institutions and non-governmental organisations, and communities and people affected by TB, will discuss intergovernmental and multi-sectorial collaboration to boost commitment and favourably impact on the TB burden. It is expected that this conference should accelerate progress towards TB elimination in the EU/EEA and beyond.

Conflicts of interest

None declared.

Authors' contributions

MvdW and DA jointly drafted the manuscript and both approved the final version.

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Excess mortality among the elderly in European countries, December 2014 to February 2015

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Since December 2014 and up to February 2015, the weekly number of excess deaths from all-causes among individuals ≥ 65 years of age in 14 European countries have been significantly higher than in the four previous winter seasons. The rise in unspecified excess mortality coincides with increased proportion of influenza detection in the European influenza surveillance schemes with a main predominance of influenza A(H3N2) viruses seen throughout Europe in the current season, though cold snaps and other respiratory infections may also have had an effect.

In temperate countries in the northern hemisphere, the weekly number of deaths among the elderly (individuals aged ≥ 65 years) frequently exhibits sharp increases above normal expected levels of mortality during the winter season. The extent of this excess mortality varies considerably between years and between countries. This excess mortality in the elderly is often attributed to seasonal influenza, especially in seasons dominated by influenza A (H3N2), but factors other than influenza including other respiratory tract infections or environmental conditions (e.g. cold spells) can also play an important contributory role [1,2].

The European monitoring of excess mortality for public health action (EuroMOMO) network (www.euromomo.eu) monitors weekly 'real-time' all-cause age-specific excess mortality in countries in Europe through a standardised approach, allowing pooling of results. In the current winter of 2014/15, there has been an increased number of excess deaths observed among the elderly. We describe this observed excess mortality in Europe

using all-cause mortality data up to and including week 9, 2015. The contributions of influenza and other factors to the excess mortality are also considered.

Analyses of all-cause mortality in Europe

Country level analyses

On a weekly basis, partners in EuroMOMO collect data on the number of deaths from all causes, and undertake timely data analyses by the use of a common algorithm. A time-series Poisson regression is used to predict the number of weekly deaths, adjusted for a linear trend and seasonal variation. The algorithm also corrects for any reporting delay, i.e. delays in the time between date of death and the date the death is registered, which can be lengthy [3].

The main indicators generated are: (i) the total weekly number of all deaths corrected for reporting delay in registration; (ii) the expected weekly number of deaths (baseline); (iii) the weekly number of excess deaths (defined as observed number minus the expected number of deaths); (iv) the standard deviation around the baseline (z-score); and (v) the cumulated total mortality (all age groups) and stratified by age groups (<5 , 5–14, 15–64 and ≥ 65 years).

For this study, sixteen European countries, namely, Belgium, Denmark, Estonia, Finland, France, Greece (municipalities of Athens, Keratsini-Drapetsona and Pireas and prefectures of Magnisia, Sporades, Kerkira, Achaia, Kavala and Thasos), Hungary, the Netherlands, Portugal, Spain, Sweden, Switzerland and the United

Kingdom (UK: England, Northern Ireland, Wales, and Scotland) provided data for all-cause mortality analyses at country level.

Pooled country data analyses

Although sixteen countries submitted data to EuroMOMO, partners with marked delays in receiving data were not included in the pooled analyses. This resulted in data from 14 countries (Belgium, Denmark, Estonia, Finland, France, Hungary, the Netherlands, Portugal, Spain, Sweden, Switzerland and the UK (England, Wales, and Scotland)) being included for such analyses. We used the stratified method as previously described [4]. The time-series in the pooled analysis included data from week 23, 2010 to week 9, 2015.

Comparison of mortality patterns

We used z-scores to standardise outputs enabling comparison of mortality patterns between different countries and between different time-periods. Excess mortality above two z-scores from the baseline in two consecutive weeks, was defined as above the normal level of the standard variation of data. The EuroMOMO hub, situated at Statens Serum Institut in Denmark, compiled the data outputs from individual partners.

Analyses in an epidemiological context

We collected information on influenza activity from influenza activity maps at the European Centre for Disease Prevention and Control (ECDC)'s website [5,6] and the joint ECDC/World Health Organization (WHO) Regional Office for Europe bulletin, FluNews Europe [7]. This included weekly indicators of intensity of transmission on influenza-like illness and proportion of positive influenza virus detections in the sentinel surveillance schemes in European countries. Finally, EuroMOMO network participants provided information on the epidemiological situation in the respective contributing countries, including temperature data.

Results

The country-specific analyses showed that in the present winter of 2014/15, all-cause excess mortality among the elderly has been above two z-scores from the baseline, for two consecutive weeks or more, in Belgium, France, Greece, Hungary, the Netherlands, Portugal, Spain, Switzerland, Sweden, England, Northern Ireland, Scotland and Wales. Mortality started to increase between week 50 and 52 of 2014, and an excess above baseline was first observed in England, the Netherlands and Portugal (week 50). As of week 9 2015, the mortality was still elevated in five of the 13 countries that were affected in consistent patterns of excess mortality in the elderly. Significant

TABLE

Excess mortality ≥ 2 z-scores over baseline among individuals aged ≥ 65 years and assessment of transmission intensity of influenza-like-illness in EuroMOMO countries, by week, week 49, 2014–week 9, 2015^a (n=16 countries)

Country	Year - Week												
	2014				2015								
	49	50	51	52	1	2	3	4	5	6	7	8	9
Belgium	Low	Low	Low	Low	Low	Low	Medium	High	High	High	High	High	Medium
Denmark	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Estonia	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium	Medium	Medium	Medium
Finland	Low	Low	Low	Low	Low	Medium	Medium	Medium	Medium	Medium	Medium	High	High
France	Low	Low	Low	Low	Low	Medium	Medium	Medium	Medium	Medium	High	High	Medium
Greece ^b	Low	Low	Low	Low	Low	Medium	Medium	High	Medium	Medium	Medium		
Hungary	Low	Low	Low	Low	Low	Low	Low	Medium	High	High	High	High	High
The Netherlands	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium
Portugal	Low	Low	Low	Low	Medium	Medium	Medium	High	Medium	Medium	Medium	Medium	Low
Spain	Low	Low	Low	Low	Low	Medium	Medium	Medium	High	Medium	Medium	Medium	Medium
Sweden	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	High	High	High	High
Switzerland	Low	Low	Low	Low	Low	Medium	Medium	Medium	High	High	High	High	High
UK-England	Low	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Low	Low	Low	Low
UK-Northern Ireland	Low	Low	Low	Low	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium
UK-Scotland	Low	Low	Low	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium
UK-Wales	Low	Low	Low	Low	Low	No info	Low	Low	Low	No info	Low	No info	No info

■ Excess mortality (≥ 2 z-scores over baseline) among individuals aged ≥ 65 years

EuroMOMO: European monitoring of excess mortality for public health action; UK: United Kingdom; z-score: standardised deviation from the baseline.

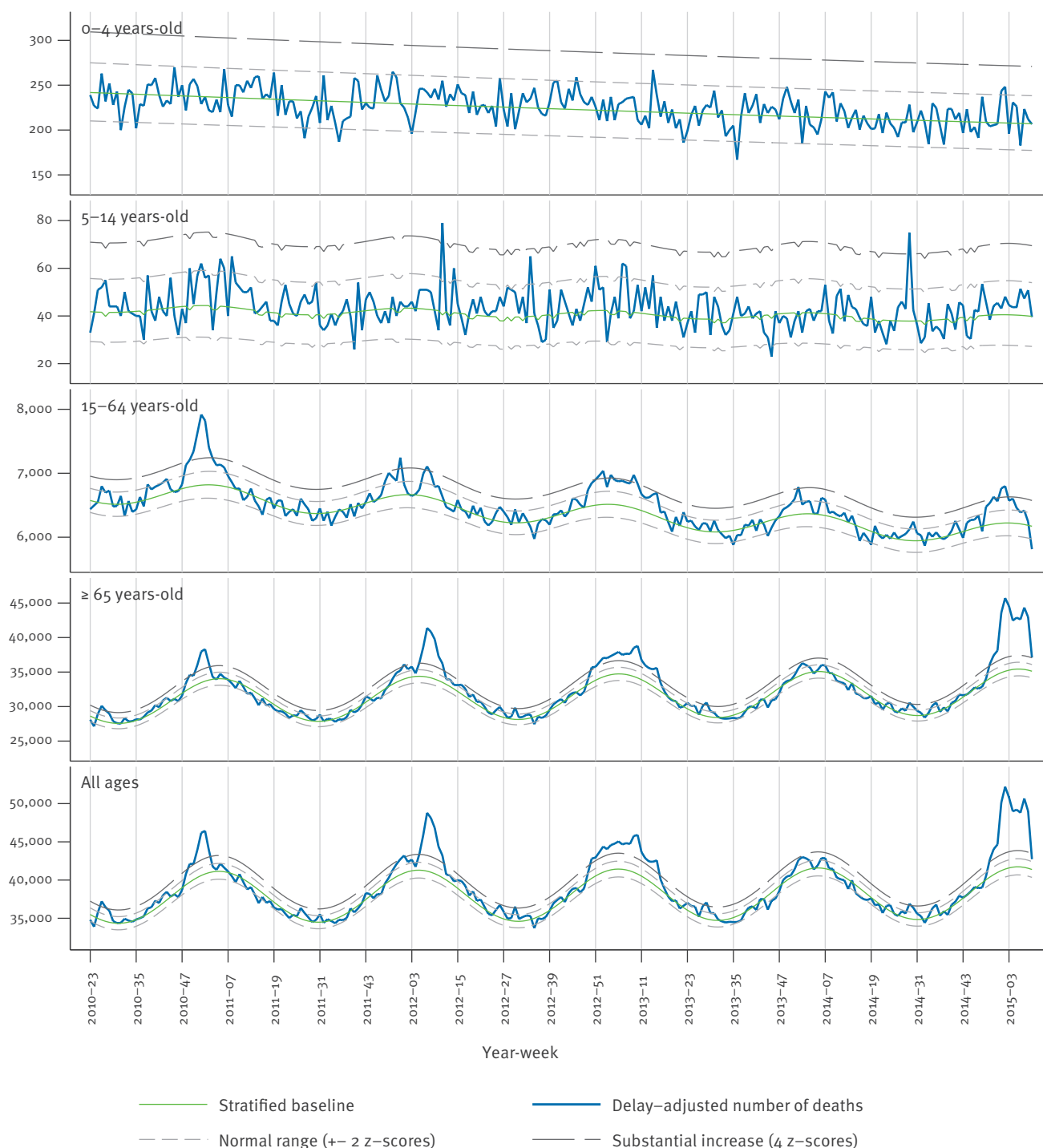
The terms high, medium and low in the cells of the table refer to the intensity of influenza-like illness transmission.

^a Corresponding to 1 December 2014–1 March 2015.

^b Mortality data is missing in week 8 and 9, 2015. Mortality data is derived from municipalities of Athens, Keratsini-Drapetsona and Pireas as well as prefectures of Magnisia, Sporades, Kerkira, Achaia, Kavala and Thasos.

FIGURE 1

Number of deaths by week and modelled baseline obtained from pooled analysis of data from EuroMOMO countries, week 23, 2010–week 9, 2015^a (n=14 countries)



EuroMOMO: European monitoring of excess mortality for public health action; UK: United Kingdom; z-score: standardised deviation from the baseline.

Participating countries: Belgium, Denmark, Estonia, Finland, France, Hungary, Netherlands, Portugal, Spain, Sweden, Switzerland, UK (England), UK (Scotland), UK (Wales).

^a Corresponding to 7 June 2010–1 March 2015.

excess mortality was not yet observed in Estonia and Finland, and although excess mortality was recorded in Denmark this has, at present, only occurred over a single week. The Table describes the weekly patterns of excess mortality in relation to the assessment of intensity of influenza transmission as reported by ECDC.

The pooled analysis, which shows excess mortality across 14 participating countries combined, revealed a sharp rise in mortality among individuals aged ≥ 65 years across Europe starting from week 49, 2014, crossing four z-scores above baseline in week 50, and reaching 21 z-scores in week 2 of 2015 (Figure 1). Some excess mortality was also observed in the age group 15–64 years, reaching four z-scores in week 51, 2014. In younger individuals, mortality has been within the expected range, although among children < 5 years, z-scores slightly over 2 were reached in week 1 and 2, 2015.

Figure 2 shows the excess mortality among the elderly (estimated from the pooled model expressed as the number of z-scores above the baseline) in the 14 countries included and the proportion positive for influenza

detections in the European sentinel surveillance schemes. By visual inspection, the increase in excess mortality follows the same pattern as the increase in per cent positive influenza virus detections. Both start to increase around week 49 of 2014 but influenza per cent-positive reaches a plateau around week 4 to 8 while excess mortality seems to peak in week 2, 2015, but remains elevated at least until week 8. Of note, the reduction of mortality after week 8 still does not represent a decrease below the 2 z-scores.

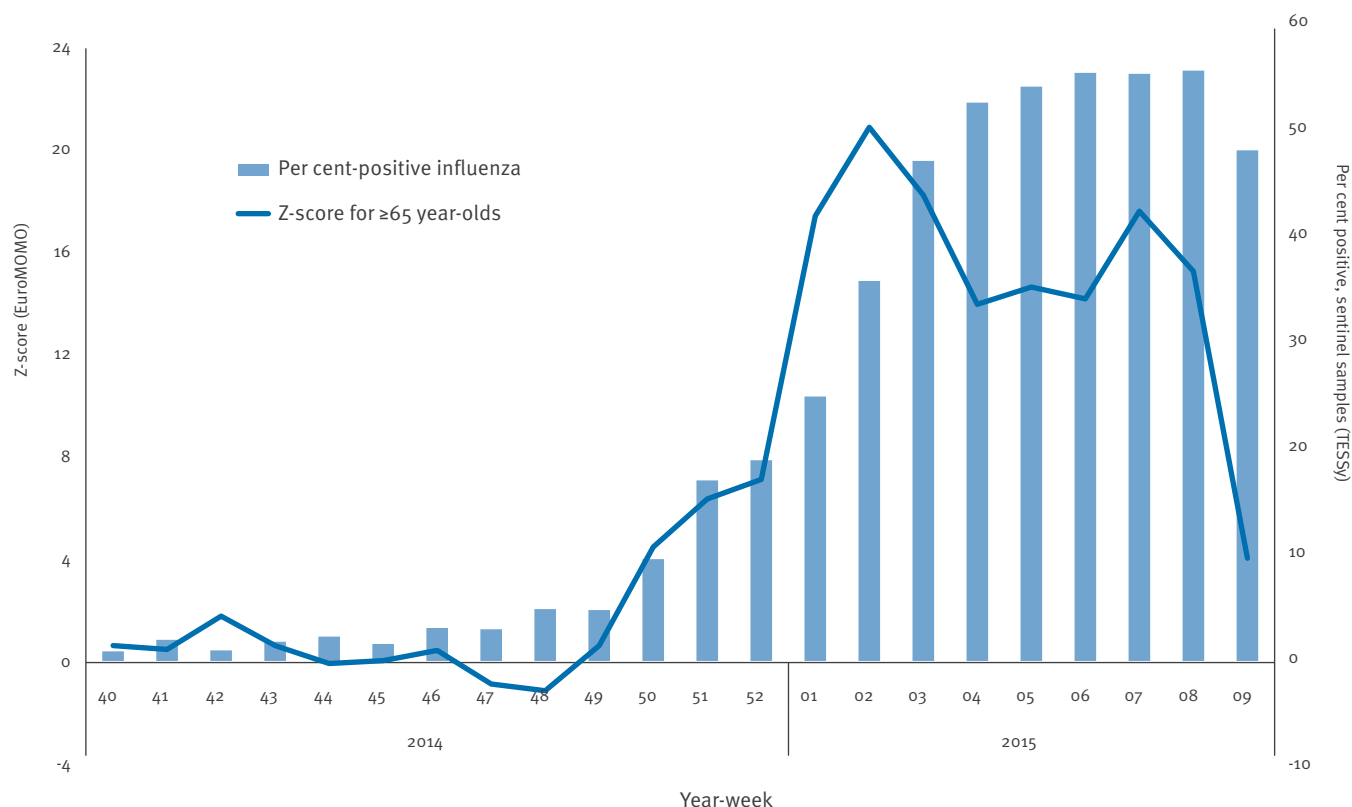
Discussion

We found evidence of a significant increase in excess all-cause mortality predominantly in the elderly in 13 of the 16 countries examined. The weekly patterns of excess mortality in relation to the intensity of influenza transmission show that in most weeks excess mortality coincides with medium or high influenza activity (78 of 97 weeks with excess mortality).

The current influenza season in the northern hemisphere has been predominated by influenza A(H3N2) virus [8], which according to FluNews Europe accounted for 56% of the detections across European Community

FIGURE 2

Excess mortality among those aged ≥ 65 years, expressed as the number of z-scores above the baseline (left axis) and the proportion positive for influenza detections in the European sentinel surveillance schemes (right axis), week 40, 2014–week 9, 2015^a



EuroMOMO: European monitoring of excess mortality for public health action; TESSy: The European Surveillance System; UK: United Kingdom; z-score: standardised deviation from the baseline.

Participating countries for mortality data include Belgium, Denmark, Estonia, Finland, France, Hungary, the Netherlands, Portugal, Spain, Sweden, Switzerland and the UK (England, Wales, and Scotland)

^a Corresponding to 29 September 2014–1 March 2015.

(EC)/ European Economic Area (EEA)/WHO European region countries [7]. It is expected that a winter season with predominance of influenza A(H3N2) has higher mortality impact on the elderly than a season with predominant influenza A(H1N1) or a season with low influenza A transmission [1,2]. Since its appearance in 2009, influenza A(H1N1)pdm09 has been a prevailing virus type, and this type is known to have less impact on the elderly [1,2,9-11]. Furthermore, in the present winter season 2014/15, most of the influenza A(H3N2) viruses characterised in Europe until week 9, 2015 exhibit antigenic differences from the virus included in the 2014/15 northern hemisphere influenza vaccine [5-8]. A reduction in the effectiveness of the A(H3N2) component of the influenza vaccine has been reported from several countries [12-15], which in consequence may lead to higher morbidity and mortality in vaccinated populations.

There are inconsistencies in the mortality findings, e.g. Finland and Sweden had several weeks of medium intensity of influenza transmission but until 1 March 2015 only two consecutive weeks with significant excess mortality were noted in Sweden and none in Finland. Furthermore, some countries see a pattern of an early rise in mortality whereas increases in influenza transmission (as assessed in the primary care sector) seems to appear later; this pattern, however is not unusual as will be discussed below.

There are several possible explanations for these observations. Firstly, an early rise in mortality may suggest that other factors, besides influenza, contribute to the occurrence of excess mortality. Temperature data from this winter indicate cold snaps in France, Greece, Spain and Switzerland (data not shown, available from the authors). Other infections, including respiratory syncytial virus (RSV)-associated disease might further add to excess mortality in some countries, but not in others. For example, the French syndromic surveillance systems noted intense activities for pneumonia and bronchitis starting from the end of 2014 (A. Fouillet, personal communication February 2015). Secondly, the assessment of influenza transmission intensity using primary care surveillance data is qualitative and is based on the available information and thus reflects the specific attributes of national surveillance systems, such as the population under surveillance. Influenza-like illness (ILI) consultations in primary care should be compared cautiously between countries, and although work has attempted to standardise this measure, ILI remains a concept to be treated with care, as it may not fully capture intensity of transmission [16,17]. Finally there may be a range of influenza-related factors such as differences in vaccination uptake; the effectiveness of the available vaccines against seasonal influenza or differences in circulating viruses and the extent of drift.

The pooled analyses of excess mortality result in a pattern that appears consistent with the European

virological influenza data. The two time series follow a parallel increase, with an apparent stabilisation of the virological data from week 4, 2015. The interval from week 50, 2014, to week 3, 2015 when per cent-positive increases is likely to represent the time-period with most intense circulation of influenza virus, and it is at the end of this ascent that the impact on mortality is expected to be highest. The apparent decrease in excess mortality at the end of the observation period needs to be treated with caution as it may be affected by an uncertainty in the adjusted delays in reporting of deaths.

The similar temporal pattern between the increase in per cent positive influenza virus detections and excess mortality is not a proof of causality. Nonetheless, it indicates that it is likely that influenza is an important contributor to the observed excess mortality among the elderly given previous evidence of attribution [2,9,10,18,19]. Pooling of data, in this case both data on number of deaths and virological influenza data across Europe, provides more statistical power than country-specific analyses and may enhance patterns that are not apparent in individual countries or populations [4]. On the other hand, details may be lost when pooling data (e.g. excess in an individual country can be diluted when others experience no excess) and therefore the two approaches of data analysis and visualisation are complementary.

Studies have shown that multivariable regression models can be successfully used to estimate the impact of mortality risks from influenza viruses while adjusting for the impact of other determinants including extreme temperature [1,2,9,18,19]. In order to assess the public health impact of influenza at the population level, we are working to develop a common European approach to estimate the number of excess deaths associated with influenza adjusting for other such factors, as discussed previously [3].

The influenza season in 2014/15 differs from the two past seasons across Europe. The past seasons showed a mixed and heterogeneous pattern of influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B with inter-country differences in the dominant circulating sub-type. Although the current season is not dominated entirely by influenza A(H3N2) across Europe, this influenza type is certainly more commonly detected compared with the previous two seasons. It is well recognised that A(H3N2) tends to particularly impact the elderly (as was seen in seasons before the 2009 pandemic). In the current winter, the effect of this virus may possibly be exacerbated by the emergence of a drift variant. Furthermore, the available vaccine may not effectively cover this subtype. We hypothesise that the observed excess mortality among the elderly is a result of this epidemiological situation, potentially aggravated by the added effects of cold snaps and other respiratory infections. Further work is planned at the end of the season to investigate this hypothesis.

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Conflict of interest

None declared.

Authors' contributions

KM designed and wrote the first version of the manuscript. LE did the analyses, graphs and figures. AM coordinated all correspondences between authors and implemented most comments. KM, JN and LE implemented additional comments from authors. All authors provided data and contributed in the writing of, and approved the final version of the manuscript.

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Risk factors for TB and HIV coinfection in Scotland, 2001 to 2010

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The number of patients with tuberculosis (TB) increased steadily in Scotland between 2005 and 2010. Human immunodeficiency virus (HIV) infection has been a contributory factor to increases in TB in a number of comparable industrialised countries. This study investigated the extent of, and risk factors for, TB and HIV coinfection in Scotland from 2001 to 2010. Patients with TB in the national TB database were linked to those in the national HIV database using probabilistic data linkage. Patient records were anonymised to maintain confidentiality. From 2001 to 2010, 106/4,097 (2.6%, 95% CI: 2.1 to 3.1) TB patients matched with HIV patients, equating to a 10-year incidence of 2.1 cases per million population. Patients with both TB and HIV were more often born outside the United Kingdom, were of black African ethnicity, had refugee status and had extra-thoracic lymph node involvement or cryptic/disseminated TB disease. Individuals with TB and HIV coinfection were younger and symptomatic for a shorter time before their diagnosis of TB, compared with TB patients without HIV. TB and HIV coinfection was relatively uncommon in Scotland in the study period. Clinicians should recognise the potential for HIV infection among TB patients and the importance of offering an HIV test to all TB patients.

Introduction

Human immunodeficiency virus (HIV) infection and associated immunosuppression is a major risk factor for the development of active tuberculosis (TB), either through acquisition of new infection or re-activation of latent TB [1]. The incidence of tuberculosis is known to be increased in immunocompromised individuals. Globally, considerable progress has been made to address the TB/HIV co-epidemic; however, global-level targets for HIV testing among TB patients and provision of antiretroviral therapy to those who are HIV positive have not been reached [2]. In Scotland, TB is a statutory notifiable disease [3]. In addition, enhanced surveillance of TB has been undertaken in Scotland since 2000 through the Enhanced Surveillance of Mycobacterial Infections scheme [4]. Enhanced surveillance data on TB provide information on the numbers, distribution and characteristics of TB cases, drug-resistance patterns and treatment outcomes. This surveillance

supports the early identification and treatment of cases and enables the identification of high-risk populations. Annual case numbers increased steadily in Scotland, from 365 cases in 2005 (7.2 per 100,000 population) to 508 cases in 2010 (9.6 per 100,000), mainly among persons born outside the United Kingdom (UK) [5]. More recent data from 2012 show that 408 TB cases were reported in Scotland, equating to an annual incidence of 7.7 cases per 100,000 population [5].

HIV infection is not a statutorily notifiable in Scotland but HIV surveillance has been undertaken in the country since 1981 through voluntary reporting of new HIV diagnoses by laboratories, acquired immunodeficiency syndrome (AIDS) diagnoses from clinicians, and deaths due to HIV infection or AIDS reported to the General Register Office for Scotland. Records of HIV or AIDS diagnoses, and HIV/AIDS-related deaths that are regarded as relating to the same individual are merged to create one record [6]. Since 1985, there has been a mean of 241 cases (standard deviation (SD): 84.3) of HIV reported in Scotland each year increasing initially from 1984 to 1987, with a mean of 281 cases per year (SD: 29.4), then again from 2002 to 2007, with a mean of 338 cases per year (SD: 58.3) [7].

Current national guidance recommends that all TB cases be offered an HIV test [8-10]. In addition, the TB action plan for Scotland [11] recommends that the HIV status of all TB cases be known as this is a requirement for annual reporting to the European Tuberculosis Surveillance Network at the European Centre for Disease Prevention and Control (ECDC) [12]. Despite these recommendations, the HIV status of TB cases remains unknown at a national level in Scotland as these data are not routinely collected or linked.

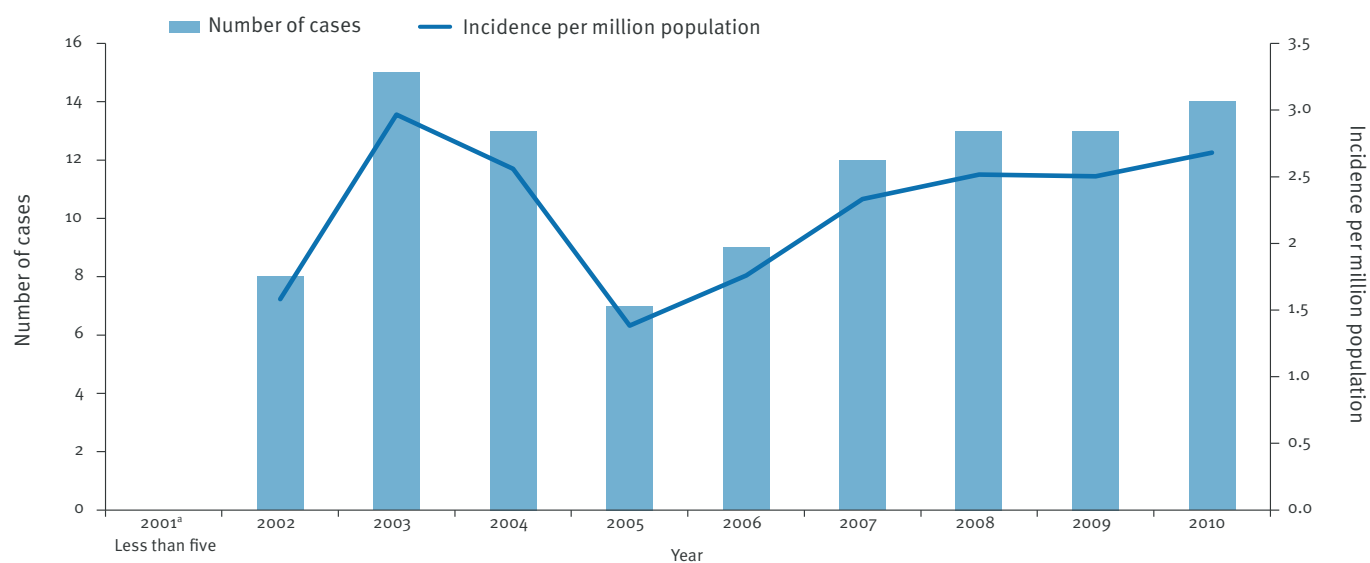
We used record linkage from 1984 to 2010 to investigate the extent of TB and HIV coinfection and identify risk factors for TB and HIV coinfection in Scotland.

Methods

Reports on 4,097 patients diagnosed with TB in Scotland from 2001 to 2010 were extracted from the Enhanced Surveillance of Mycobacterial Infections

FIGURE 1

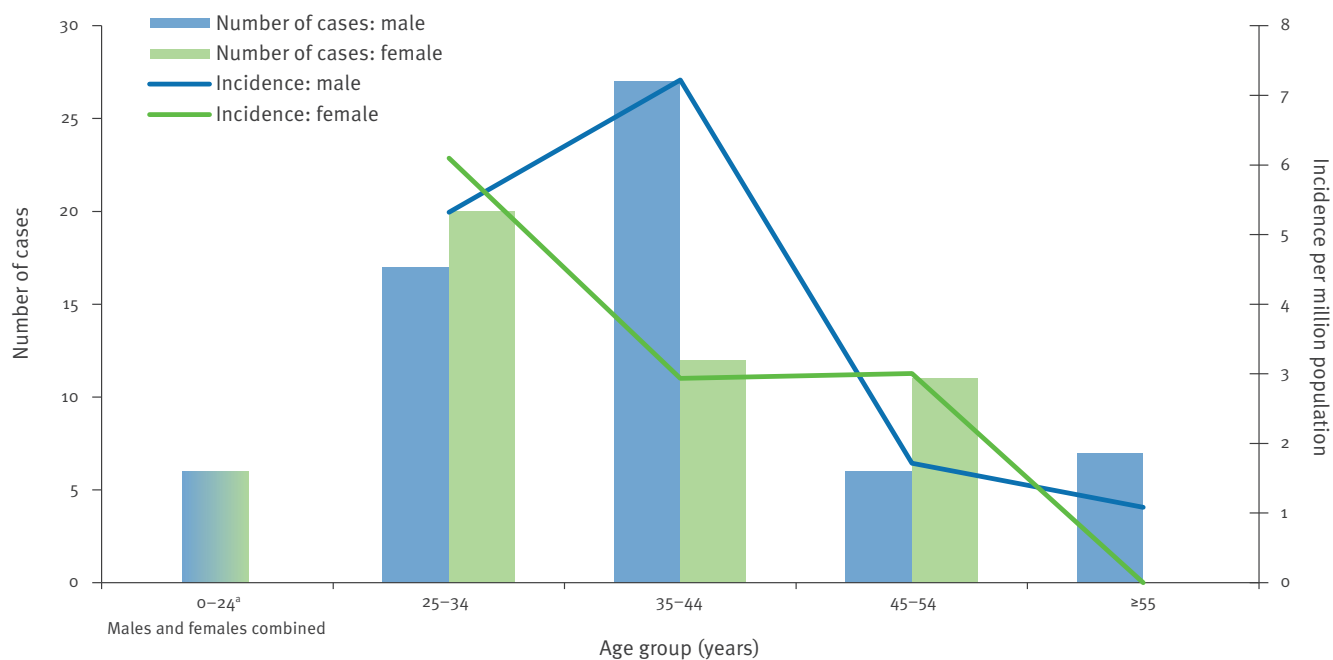
Number of cases and incidence of tuberculosis and human immunodeficiency virus coinfection in Scotland, by year of tuberculosis diagnosis, 2001–10 (n = 106)



^a Data withheld due to numbers of less than five, to reduce potential for deductive disclosure.

FIGURE 2

Age group (age at tuberculosis diagnosis) and sex of tuberculosis and human immunodeficiency virus coinfecting cases in Scotland, 2001–10 (n = 106)



^a Data combined due to numbers of less than five, to reduce potential for deductive disclosure.

database. These named patient data were then replaced by a Soundex code [13], i.e. replacing surnames by their initial letter followed by a three-digit coding of subsequent letters.

The HIV database contains Soundex-coded data for 6,790 patients with HIV antibody positive results in Scotland from 1981 to 2010. The anonymised TB patients were linked to the anonymised HIV patients using probabilistic data linkage [14,15], thus maintaining patient confidentiality. TB and HIV coinfections were assigned a notification year by the year of their TB diagnosis.

Coinfected cases after 2010 could not be included in our analysis due to the time needed to obtain follow-up and outcome data (data collected 12 months after diagnosis) as well as the time needed to validate, carry out the linkage and analysis of the data.

Statistical analysis was performed in SPSS version 21. Characteristics of TB cases and TB and HIV coinfecting cases were compared using chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size). Logistic regression was performed to investigate the association between the number of coinfecting cases and the predictor variables, e.g. ethnicity, refugee status.

Results

Case numbers and trends

From 2001 to 2010, 4,097 tuberculosis cases were reported to Health Protection Scotland, of which 106 (2.6%; 95% confidence interval (CI): 2.1–3.1) were matched to an individual on the HIV database, equating to a 10-year incidence of 2.1 cases per million population (95% CI: 1.7–2.5 per million population). There was a peak in the number of TB and HIV coinfections in

2003, when 15 patients (15/367; 4.1%; 3.0 per million population) were reported (Figure 1). However, there were no statistically significant differences in the proportion of TB cases with HIV infection or the incidence of TB and HIV coinfections from 2001 to 2010.

Age and sex distribution

The most common age group of TB and HIV coinfection was 25–44 years (77/106; 73%) and 58% of cases (62/106) were male (Figure 2). The mean age of cases was 37 years. Coinfected individuals were aged a mean of 8.8 years less than that of TB patients without HIV infection ($p < 0.00001$).

Site of TB

The majority presented with pulmonary TB (69/106; 65%). Our analysis showed that having TB and HIV coinfection was associated with an increased likelihood of pulmonary TB (odds ratio (OR): 2.2 (95% CI: 1.3–3.8), $p = 0.004$), extra-thoracic lymph node involvement (OR: 3.8 (95% CI: 2.1–6.7), $p < 0.0001$) or cryptic/disseminated TB (OR: 5.7 (95% CI: 2.5–13.2), $p < 0.0001$) when compared with TB cases without HIV. There were no other statistically significant differences in site of disease between TB cases and TB and HIV coinfecting cases (Table).

Of the 76 TB and HIV coinfecting patients with known TB drug sensitivities, less than five had drug-resistant TB. However, there was no significant difference in drug resistance rates between those with TB and those with TB and HIV coinfection.

Ethnicity and country of birth

The majority of coinfecting patients were born outside the UK (75/106; 71%). The mean time from entry into the UK until a TB diagnosis was 3.6 years, compared with 7.3 years in cases with TB alone (difference in mean of 3.7 years (95% CI: 2.7–4.8), $p < 0.01$). The likelihood of

TABLE

Logistic regression analysis of risk factors associated with tuberculosis and human immunodeficiency virus coinfection in Scotland, 2001–10 (n = 106)

Risk factor	Number of cases	Odds ratio (95% CI)	P value
Pulmonary TB	69	2.2 (1.3–3.8)	0.004
TB infection of extra-thoracic lymph node	30	3.8 (2.1–6.7)	< 0.0001
Cryptic/disseminated TB disease	8	5.7 (2.5–13.2)	< 0.0001
Black African ethnicity ^a	67	7.6 (3.4–16.9)	< 0.0001
White ethnicity ^a	23	0.3 (0.1–0.7)	0.006
Refugee status ^b	22	5.2 (3.2–8.6)	< 0.0001
History of BCG vaccination ^c	61	1.6 (1.1–2.4)	0.016
History of travel outside the UK for ≥ 2 months ^{b,d,e}	33	2.2 (1.4–3.3)	< 0.0001

BCG: Bacillus Calmette–Guérin; CI: confidence interval; TB: tuberculosis; UK: United Kingdom.

^a Ethnicity data were missing for five cases.

^b Risk factor data were missing for six cases.

^c BCG vaccination status was missing for 31 cases.

^d In the two years preceding their TB diagnosis.

^e Information on travel outside the UK missing for 20 cases.

TB and HIV coinfection was almost eight-times higher among non-UK born TB cases (OR: 7.9 (95% CI: 4.5–14.4), $p < 0.00001$).

The majority of coinfecting cases were of black African (67/106; 63%) or white (23/106; 22%) ethnicity, with very few from other ethnic groups. The likelihood of TB and HIV coinfection was higher among TB cases of black African ethnicity (OR: 7.6 (95% CI: 3.4–16.9), $p < 0.00001$) and lower among those of white ethnicity (OR: 0.3 (95% CI: 0.1–0.7), $p = 0.006$) when compared with those with TB alone (Table). Just over half of black African cases were female (37/67), but male cases were statistically significantly more common among those of non-black African ethnicity (28/34, $p = 0.002$).

Risk factors

A total of 32% (34/106) had a reported risk factor for TB, the most common of which was refugee status (22). Our analysis showed that being a refugee was independently associated with an increased likelihood of TB and HIV coinfection (OR: 5.2 (95% CI: 3.2–8.6), $p < 0.0001$) when compared with those with TB alone (Table).

The majority (61/75) were known to have had a BCG vaccination and approximately one third (33/86) had a history of travel outside of the UK for two months or more in the two years preceding their TB diagnosis. Very few cases (6/98) were known to have a previous diagnosis of TB. Logistic regression analysis showed that having a history of BCG vaccination (OR: 1.6 (95% CI: 1.1–2.4), $p = 0.016$) and travel outside the UK for two months or more in the two years before their TB diagnosis (OR: 2.2 (95% CI: 1.4–3.3), $p < 0.001$) were independently associated with an increased likelihood of TB and HIV coinfection when compared with those with TB alone (Table).

Suspected source of HIV transmission

Of the 106 coinfecting cases, the main reported routes of HIV acquisition were via heterosexual intercourse (84/106; 79%) and sex between men (12/106; 11%). Those born outside the UK were more likely to have acquired HIV through heterosexual intercourse (OR 8.3 (95% CI: 2.2–30.2), $p = 0.002$), while those born in the UK were more likely to acquire HIV through sex with other men (OR: 13.1 (95% CI: 2.5–73.1), $p = 0.002$).

Individuals of black African ethnicity were more likely to have acquired HIV via heterosexual intercourse (OR: 24.0 (95% CI: 6.5–108.5), $p < 0.0001$) while those of white ethnicity were more likely to have acquired their HIV infection through sex with other men (OR: 59.2 (95% CI: 8.4–1308.7), $p < 0.00001$).

Eight of the 99 with transmission data were reported to have acquired HIV within Scotland, whereas the majority acquired the virus from outside the country – 71/99 from Sub-Saharan Africa and 10/99 from south and

south-east Asia. A total of 10/99 cases were reported to have acquired their HIV infection from other regions.

TB treatment outcome at one year

The TB treatment outcome was recorded for 75% of coinfecting cases (79/106). Of these, 72% (57/79) were known to have successfully completed their TB therapy within 12 months of their diagnosis, 16% (13/79) did not complete treatment, 11% (9/79) were lost to follow-up or the outcome of TB therapy was recorded as unknown. The main reasons patients did not complete treatment within 12 months were either they were still on treatment (7/79) or had died (5/79). There were no statistically significant differences in successful treatment completion at one year between those with TB alone versus those with TB and HIV coinfection (2,516/3,245; 77.5% treatment success for those with TB only).

The outcome of HIV treatment was not included in this study.

Discussion

This is the first national retrospective record linkage study to describe the characteristics and risk factors for TB and HIV coinfection in Scotland. Our results show there was a low incidence of TB and HIV coinfection in Scotland in the study period, with less than 3% of TB cases also having an HIV diagnosis. This is lower than the percentage of those tested with TB who were living with HIV reported in North America (8.3%) but similar to the 3.5% reported in western and central Europe in 2012 [16] and to a seroprevalence study undertaken in Scotland in 1993, in which less than 2% of notified TB cases tested positive for HIV [17].

Not all persons diagnosed with TB will accept an HIV test and there are undiagnosed HIV-positive individuals who would not be identified in this study. The results of our study indicate that the majority of coinfections are imported into the country by young migrant populations who have recently arrived in the UK from countries with high incidences of TB and HIV. The mean time from entry to the UK until TB diagnosis was statistically significantly lower for those with TB and HIV coinfections than those with TB alone (3.6 years vs 7.3 years). This is in contrast to that reported in the United States where the time to diagnosis was much longer and there were no statistically significant differences between TB and TB/HIV patients (14 years vs 13.1 years) [18] but similar to England and Wales where TB and HIV coinfection was more common in those who entered the UK in the five years or less before their TB diagnosis [19].

The majority of patients with TB and HIV coinfection presented with pulmonary disease, which is associated with a higher risk of transmission. Therefore there may be an increased risk of TB transmission to other high-risk contacts.

The most common age group of those coinfectd was 25–44 years, and the mean age was 37 years which is similar to that reported in England and Wales (34.7 years) [19]. TB and HIV coinfectd individuals were almost nine years younger than those with TB infection alone, suggesting that HIV infection shortens the length of time to reactivate latent TB disease or that new infection is a more common cause of TB in HIV-positive patients than reactivation of latent TB [20].

Analysis of our study population showed that having TB and HIV coinfection was associated with having an increased likelihood of extra-thoracic lymph node involvement or cryptic/disseminated TB infection, which may be due to the effects of immunosuppression.

The majority of coinfectd cases were of black African ethnicity, which is similar to that reported in England and Wales between 2002 and 2010, when 84% of heterosexual TB/HIV coinfections were in black Africans [21,22]. In our study, more than half of Black African patients were women but in all other ethnic groups, the majority were men. In Scotland, most coinfectd individuals are reported to have acquired their HIV infection in Sub-Saharan Africa or south and south-east Asia, where they are more likely to have acquired their HIV infection via heterosexual intercourse. However, those born in the UK were more likely to be men who acquired their HIV infection through sex with other men.

Approximately one third of coinfectd cases had an identified risk factor for TB, the most common of which was having refugee status, which was associated with an increased likelihood of TB and HIV coinfection. Most cases had received BCG vaccination and having a history of BCG vaccination was associated with an increased likelihood of having TB and HIV coinfection. This does not suggest that BCG vaccine is ineffective at preventing TB disease among HIV-infected individuals as BCG coverage may be higher in countries with a high incidence of TB. For some of the risk factors investigated, the number of coinfectd cases was small and the findings need to be confirmed in larger studies.

ECDC recommends that information on TB outcome be known for 100% of cases and that 85% should successfully complete their TB treatment within 12 months [12]; the data from our study indicate that we have failed to meet these target levels, as the outcome of TB treatment was unknown for almost a third of cases. Therefore we cannot assess if optimum management of these cases resulted in successful treatment of TB therapy and this linkage study does not provide information on longer-term mortality among these patients.

Conclusions

Probabilistic data linkage was the most appropriate method for analysing TB and HIV coinfection in Scotland. TB and HIV coinfection was relatively uncommon in Scotland in the study period. Clinicians should

recognise the potential for TB and HIV coinfection and the importance of prompting a HIV test for all TB cases, to ensure optimum management of coinfectd patients and promote targeted prevention and control activities.

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Conflict of interest

None declared.

Authors' contributions

Eisin McDonald: study design, data analysis, manuscript; Lesley Wallace: study design, manuscript; Alison Smith-Palmer: study design, manuscript; Oliver Blatchford: study design, manuscript.

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Impact of the BCG vaccination policy on tuberculous meningitis in children under 6 years in metropolitan France between 2000 and 2011

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In France, *Bacillus Calmette–Guérin* (BCG) vaccination by multipuncture device was withdrawn in 2006. In 2007, universal mandatory BCG vaccination was replaced by vaccination of high-risk children. To evaluate the impact of these changes on tuberculous meningitis (TBM) epidemiology, data on culture-positive and culture-negative (or unknown microbiological result) TBM in ≤5 years olds were collected from 2000–2011. Ten culture-positive and 17 culture-negative TBM cases were identified, with an annual incidence rate ranging from 0.16 to 0.66 cases per 10 million inhabitants. The average annual numbers of TBM cases were 2.7 and 1.8 from 2000–2005 and 2006–2011, respectively. In Ile-de-France where all children are considered at risk, the overall incidence rates were 1.14 and 0.29 per million for the two periods. In other regions where only at-risk children are vaccinated since 2007, rates were 0.30 and 0.47, respectively. None of these differences were significant. Annual incidence rates for each one-year age group cohort were comparable before and after changes. Childhood TBM remains rare in France. No increase in incidence was observed after changes in BCG vaccination strategy. Ongoing surveillance should be maintained, as a slight increase in TBM in the coming years remains possible, in the context of suboptimal vaccination coverage of high-risk children.

Introduction

Tuberculous meningitis (TBM) is estimated to account for ca 1% of all tuberculosis (TB) cases in developed countries [1,2]. TBM is the most severe form of TB, and it is associated with a high mortality: 7–65% in developed countries, and up to 69% elsewhere [2–4]. The suspicion of TBM is based on a combination of epidemiological, clinical, and preliminary cerebrospinal fluid (CSF) findings. The confirmation of the TB aetiology for meningitis is done by direct isolation of *Mycobacterium tuberculosis complex* in the CSF.

Children aged 6 months to 5 years are among the age groups most frequently suffering from TBM [1,5]. TBM symptoms in these children are not specific and a definite diagnosis, i.e. through smear-positive CSF and/or culture-positive CSF, is a rare event highly dependent on the volume of the CSF sample [6]. New diagnostic techniques based on gene amplification have been developed but their sensitivity and specificity suggest they may not be as helpful as expected [7]. Thus, TBM diagnosis is often based on a bundle of criteria that may vary according to centres, despite a recent effort in diagnosis standardisation.

Bacillus Calmette–Guérin (BCG) vaccination in early childhood is one of several TB control interventions to prevent TBM. Two meta-analyses published in the early 90s have confirmed the effectiveness of BCG against extra-pulmonary TB (mainly meningitis) with an effectiveness varying depending on the study design from 64% to 86% [8,9]. This led the World Health Organization (WHO) to renew its recommendation in favour of BCG vaccination for infants in all countries [10]. Such a strategy has been applied in most countries, including France, where BCG vaccination has been mandatory since 1950 for children entering collective life, i.e. at the latest when 6 years old (age of mandatory schooling). Vaccine coverage at that age has been consistently close to 100%, due to law enforcement by the Ministry of Education [11]. In January 2006, the multipuncture device (Monovax, Sanofi Pasteur MSD, France), which was used for more than 90% of BCG vaccinations, was withdrawn from the French market and replaced by the intradermal BCG device (SSI, Statens Serum Institut, Denmark), the technique recommended by WHO. The difficulty of using the latter technique in young infants by untrained medical staff as well as its less favourable safety profile compared with the multipuncture device, led to a decrease in BCG coverage of

more than 50% in a few months, despite the vaccination still being mandatory [12].

In July 2007 in France, universal mandatory BCG vaccination was replaced by a strong recommendation to vaccinate children at higher risk of TB, as soon as possible after birth. The main rationale for this change was the decreasing incidence of TB in France, with 2002 to 2004 incidences of both sputum smear-positive TB cases and meningitis in children below the thresholds recommended by the International Union against Tuberculosis and Lung Diseases (IUATLD) for considering a possible discontinuation of BCG vaccination [13]. The heterogeneity of the risk of infection, questioning the benefit/risk balance of BCG in low risk children, was also an important factor in the decision [14]. High risk groups targeted by the new vaccination strategy include mainly children born or whose parents were born in highly TB-endemic countries and children living in the two French regions with high incidence rates of TB: French Guiana, located overseas (26.2/100,000 in 2006), and Paris and its surrounding departments known as Ile-de-France region (17.1/100,000 in 2006) [15].

In Ile-de-France, where all children are targeted by the new policy, administrative data, complemented with data from surveys in the public sector, were used to monitor the BCG vaccination coverage. It has progressively increased from ca 50% in children born in 2007 to ca 80% in children born in 2010 [16]. In the rest of France, the vaccination coverage for high risk children was much lower, estimated, in 2008, between 32% and 40% for children followed-up in the private sector [17,18], representing around 90% of the children, and, in 2009, at 62% for those followed-up in Maternal and Child Health Clinics [19].

A simple modelling exercise, carried out before the decision of discontinuation of systematic BCG vaccination, has concluded that the switch to a vaccination strategy targeting high-risk children only could lead to an annual increase, after 15 years, of up to four and nine cases of TBM in children, for vaccination coverages of 95% and 50%, respectively, in those children, and considering an effectiveness of the vaccine of 85% against meningitis in children [14].

In order to assess the impact of the change in the BCG strategy and of the suboptimal vaccination coverage in high-risk children, we conducted a retrospective survey of the TBM incidence in children aged ≤ 5 years for the period 2000 to 2011. Our primary objective was to compare the pre and post 2006 annual incidence rates of TBM in children.

Methods

Tuberculous meningitis data collection

In France, TB has been a mandatorily notifiable disease since 1964 through the Mandatory Notification System

(MNS). For each TB case, each physician or microbiologist has to send a standardised paper notification form to the corresponding Regional Health Authority. After data anonymisation and validation, data are annually transmitted to the National Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS) in St Maurice. Any patient with clinical and/or radiological signs compatible with TB and treated by an anti-TB treatment should be reported, whether or not there is a culture-positive sample at the time of notification.

In addition to the MNS, a nationwide laboratory network set-up in 1992 for the surveillance of multidrug-resistant TB (MDR-TB), has collected annual data on culture-positive TBM among patients aged ≤ 5 years since the year 2000, from all laboratories performing mycobacteria culture. This network is coordinated by the National Reference Centre (NRC) for mycobacteria and resistance of mycobacteria to anti-tuberculosis drugs, in Paris [20].

All cases of TBM diagnosed in metropolitan France in patients aged ≤ 5 years, and recorded between 1 January 2000 and 31 December 2011 in MNS and NRC databases were included. Because all data were anonymised before recording in both databases, we had to go back to regional health authority data files and to local laboratories to identify cases based on notifying healthcare institution, physician or microbiologist identifiers, and patient birth date. Thereafter, a questionnaire was sent to physicians and/or microbiologists in order to collect additional information, especially on bacteriological results and outcome.

A confirmed case was defined as a patient aged ≤ 5 years with a positive culture of *M. tuberculosis* complex in a CSF sample or a brain biopsy during the study period. Cases notified as TBM but with missing data or negative culture were considered as possible cases. No additional information was recorded for possible cases.

Incidence rates computation

Because the risk of TBM varies with age, even within the 0 to 5 years age group, and of the progressive replacement of the fully vaccinated cohorts by partially vaccinated birth cohorts, we stratified the analysis by age. For each year of age (0–5) defined by the age at diagnosis, we calculated and compared the TBM incidence rates in two groups of children, those born before 1 January 2006, referred to as fully vaccinated cohorts and those born after, referred to as partially vaccinated cohorts. Despite the change in vaccine strategy in 2007, we chose 1 January 2006 as the trade-off between the two cohorts because the vaccine coverage dropped immediately after the withdrawal of the multipuncture device from the French market.

Each case was assigned to one of the two groups depending on their birth cohort: all cases that occurred up to 2005, were assigned to the fully vaccinated

cohorts as well as cases aged 1 year and more in 2006, 2 years or more in 2007, 3 years or more in 2008, 4 years or more in 2009, 5 years in 2010. In 2011, all cases occurred in children belonging to the partially vaccinated cohorts (Figure). Two analyses were performed, one with only confirmed cases and the other with confirmed and possible cases.

The analysis was done separately for Ile-de-France (around 22% of the birth cohorts) where BCG remains recommended for all children, and the rest of the country. Population data for incidence rate computations were annual population estimates obtained from the French National Institute of Statistics and Economic Studies (INSEE, www.insee.fr). Data on the size of each one-year age group, for each year and for each of the two groups of regions were used. We considered TB incidence in the general population to be stable during the study period.

Statistical analysis was performed by using STATA (STATA Corp, College Station, TX, US). Fisher's exact test was used for comparison of incidence rates.

Ethics approval

Approval was obtained from the National Commission for Information Technology and Civil Liberties (CNIL, Number 1375404) in 2010, according to the French law.

Results

From 2000 to 2011, 29 cases of TBM were notified to the MNS. Among them, four were excluded because of duplicate notification ($n=2$), of diagnosis made before 2000 ($n=1$), and of misdiagnosis (viral meningitis) found subsequently to the notification ($n=1$). Two others were not included because they were from French Guiana and Guadeloupe Island, i.e. outside metropolitan France. Consequently, eight confirmed cases (culture-positive TBM) and 15 possible cases (10 culture-negative CSF and 5 with lost records preventing evaluation) were included in the study.

During the same period, the NRC network recorded 12 cases of TBM among children ≤ 5 years old. One was the

patient from French Guiana also identified by the MNS, who did not fulfil inclusion criteria. Nine confirmed and two possible cases (1 culture-negative CSF and 1 with lost records) were thus retained.

A total of seven confirmed cases were identified in both systems; one case was reported only to the MNS, and two were registered only in the NRC network. Consequently, a total of 10 culture-positive cases of TBM were identified by both sources combined between 2000 and 2011. Finally, a total of 27 cases, including 10 confirmed cases and 17 possible cases, were basis for the analysis.

TABLE 1

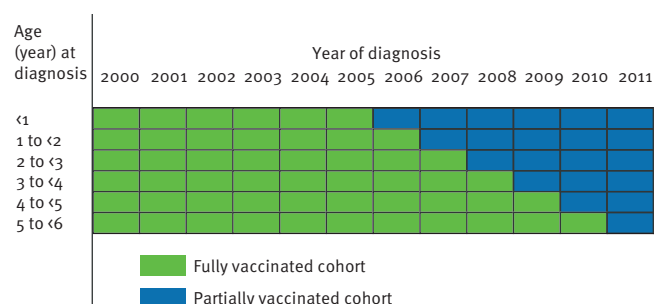
Characteristics of culture-positive tuberculous meningitis cases in children ≤ 5 years old, metropolitan France, 2000–2011 ($n=10$)

Characteristic	N
Male	6
Age (years)	
0 – < 1	5
1 – < 2	1
2 – < 3	3
5 – < 6	1
Median (months)	8.5
Place of birth	
France	6
North Africa	1
Sub-Saharan Africa	3
HIV status	
Negative	7
Unknown	3
BCG vaccination	
Yes	3
No	6
Unknown	1
Cerebral localisation of TB	
CSF	10
Tuberculoma/nodule	0
Contact with TB patient	9
Extra-cerebral TB manifestations	
None	3
Pulmonary	2
Disseminated	4
Unknown	1
Outcome	
Full recovery	2
Sequelae	6
Death	2

BCG: Bacillus Calmette–Guérin; CSF: cerebrospinal fluid; TB: tuberculosis.

FIGURE

Fully and partially Bacillus Calmette–Guérin-vaccinated cohorts by year of and age at tuberculous meningitis diagnosis, metropolitan France 2000–2011 ($n=25$)



Characteristics of culture-positive tuberculous meningitis cases

Among the 10 identified culture-positive cases, six were French-born, and four were born in Africa (Table 1). Six cases were male. The HIV status was known for seven cases and was negative for all of them. BCG vaccination status was known for nine cases, of which six had not been vaccinated. All six were from outside the Ile-de-France region, five were French-born and one was foreign-born. Two of the six, including the foreign-born case, were born before 2006, i.e. at a time when BCG vaccination was mandatory for all children. Among all 10 cases, nine had an identified putative TB source case, three foreign-born and six French-born cases including the four unvaccinated cases born since 2006. Among the latter four, one had relatives born in Africa, and three had French-born parents without identified risk factors for TB.

A total of seven cases had extra-cerebral manifestations of TB disease, including two with pulmonary TB, four with disseminated TB, and one with an unrecorded site of disease. Most of the cases (n=8) recovered, but 6 had neurological sequelae, and 2 died (Table 1).

TBM incidence rates

From 2000 to 2011, the annual number of confirmed TBM cases varied from 0 to 1, and the annual incidence rate from 0 to 0.17 cases per 10 million inhabitants. The total (confirmed and possible cases) number of TBM cases reported each year to both systems varied from 1 to 4, and the annual incidence rate from 0.16 to 0.66 cases per 10 million. These correspond to annual TBM

incidences in children aged ≤ 5 years below 10 cases per 10 million children (Table 2).

There was no significant time trend related to the initial dramatic drop of coverage in 2006 followed by the change in the vaccination policy, neither for confirmed cases nor for the total (confirmed and possible) number of cases. The average annual numbers of TBM cases (confirmed and possible) were 2.7 and 1.8 in the periods from 2000 to 2005 and 2006 to 2011, respectively.

Incidence rates of childhood TBM by one-year cohorts before and after the change in vaccination policy are provided in Table 3 for all cases. In the Ile-de-France populations, the cohort-specific incidence rates seem lower in partially vaccinated cohorts when compared with fully vaccinated ones, although none of the differences are statistically significant. In the rest of France, cohort-specific incidence rates appear comparable in both groups. A similar conclusion can be drawn when only considering confirmed cases (data not shown).

Discussion

Any change in BCG vaccination strategy is expected to impact paediatric TBM epidemiology because BCG vaccination has been proven to be effective in preventing invasive TB in young children [8,9]. We evaluated the impact on TBM epidemiology of the changes in BCG vaccination strategies implemented in France in 2006 and 2007.

From 2000 to 2011, the annual number of TBM in children aged ≤ 5 years in metropolitan France has remained

TABLE 2

Numbers and annual incidence rates of confirmed, possible and total tuberculous meningitis cases in children ≤ 5 years old, metropolitan France, 2000–2011 (n=27)

Year	Incidence rate of confirmed cases ^a		Per 10 million inhabitants (general population)	Number of possible cases ^b	Total number of cases	Total incidence rate of TBM	
	Number of confirmed cases	Per 10 million children				Per 10 million children	Per 10 million inhabitants (general population)
2000	1	2.32	0.17	1	2	4.64	0.34
2001	1	2.28	0.17	2	3	6.85	0.51
2002	1	2.26	0.17	1	2	4.51	0.34
2003	1	2.24	0.17	1	2	4.48	0.33
2004	0	0	0	3	3	6.67	0.50
2005	1	2.21	0.16	3	4	8.84	0.66
2006	1	4.20	0.16	2	3	6.60	0.49
2007	1	2.19	0.16	0	1	2.19	0.16
2008	1	2.19	0.16	2	3	6.57	0.48
2009	1	2.18	0.16	0	1	2.18	0.16
2010	1	2.16	0.16	0	1	2.16	0.16
2011	0	0	0	2	2	4.29	0.32
Total	10	-	-	17	27	-	-

TBM: tuberculous meningitis.

^a Culture-positive.

^b Culture-negative and undefined.

very low, i.e. from 0 to 1 culture-positive cases and from 0 to 3 additional possible cases. However, definitive diagnosis of TBM in children is difficult and it is estimated that *M. tuberculosis* is not identified in up to 60% of TBM cases [6]. Hence, it is likely that a few cases of TBM were overlooked. However, to address this and minimise underdiagnosis, we combined data from two surveillance systems (MNS, NRC) to improve case ascertainment. We also included cases born abroad for whom the French vaccination strategy may not be applicable. In addition, the inclusion of possible cases in the analysis took into account, at least partially, the difficulties in TBM definite diagnosis [6]. After inclusion of possible cases, the yearly incidence rate of TBM in the period from 2000 to 2011 varied between 0.16 and 0.66 per 10 million inhabitants. Thus it is unlikely that the true incidence rate exceeded the threshold proposed by the IUATLD of 1 case of TBM among <5 years old children per 10 million inhabitants, below which the TBM incidence should remain for at least five years before considering to discontinue BCG vaccination [13].

No increase in TBM incidence has been observed after the shift from universal to selective BCG vaccination in children. In addition, no statistically significant differences could be observed when comparing the age-specific incidences rates among the fully- and the partially vaccinated cohorts. Of note, a recent cross-analysis of the French National Hospital Discharge Database has shown a stable sensitivity of the MNS for all TB cases including TBM, throughout the period from 2000 to 2010 (data not shown). However, the steady incidence rates of TBM across all ages in the recent years, in a context of constant decrease in overall trend in TB [21], call for attention, although the number of confirmed TBM in children is lower than in the 1990s [22].

From 1995 to 2005, vaccination coverage estimates in children aged 24 months in France were around 85% and virtually 100% at 6 years of age [11,23]. After the withdrawal of the multipuncture device in January 2006, coverage decreased immediately for all children

[11]. In Ile-de-France region, where the incidence of TB was 18.2 per 100.000 in 2007 and where all children remain targeted by BCG vaccination, coverage at 9 months of age increased progressively from 73.1% to 80.6% for the 2008 and 2011 birth cohorts, respectively (data not shown). Furthermore, a study conducted in 2010 in Ile-de-France region in children aged ≤5 years has shown that children born to at least one parent originating from a high-TB incidence country were significantly better vaccinated than other children (97.3% vs 78.6%) [24]. This has likely contributed to the absence of increase of TBM in the Ile-de-France region. In the rest of the country, the BCG coverage of high-risk children under the age of 6 years remains insufficient. It was estimated at 40% in 2008 for children followed in the private sector and 62% in 2009 for children followed in Maternal and Child Health clinics, where health professionals may feel more comfortable to perform BCG vaccination, due to the higher number of children they care for [17,19]. Follow-up of BCG sales data are not in favour of a recent increase in coverage (data not shown). Therefore, the absence of increase of TBM outside the Ile-de-France region may be temporary and such an increase may still occur in the future.

The best-documented experience in Europe of shifting from universal to selective vaccination of groups at risk comes from Sweden. Routine vaccination of newborns was discontinued in 1975. After an initial drop in overall vaccine coverage to less than 2%, the coverage increased up to 13.2% of the birth cohort in 1983 and it was estimated that 79% of foreign-born children were vaccinated in 1985. Only one case of TBM was diagnosed from January 1969 to March 1975 and two cases from April 1975 to December 1985 [25]. Other countries such as the UK, Finland or Norway have recently switched from universal BCG vaccination to targeted vaccination [26]. However, data available to date do not allow assessing the impact of this change on the risk of TBM in children.

Our analysis is based on the assumption of a constant risk of infection for children. This simplification has

TABLE 3

Number, and incidence rates per million children for tuberculous meningitis cases^{a,b} in children ≤5 years old, by one-year age cohort and region according to vaccination strategy, metropolitan France, 2000–2011, (n=25)

Age group (year)	Number of one-year age cohorts (birth-cohorts)		Ile de France region					Other regions				
			Number of cases		Incidence rate (per million)		p value	Number of cases		Incidence rate (per million)		p value
	FV	PV	FV	PV	FV	PV		FV	PV	FV	PV	
0–1	13	11	4	1	1.91	0.53	0.2	6	6	0.79	0.91	0.5
2–3	17	7	2	0	0.76	0	0.5	1	0	0.10	0	0.7
4–5	21	3	3	0	0.95	0	0.7	2	0	0.16	0	0.8
All ages	51	21	9	1	1.14	0.29	0.1	9	6	0.30	0.47	0.3

FV: fully vaccinated; PV: partially vaccinated.

^a The exact date of birth was missing for two cases.

^b Possible (culture-negative and undefined) and confirmed (culture-positive).

probably not affected our conclusions because the number of notified pulmonary cases of TB has only decreased by 5% between 2005 and 2011.

In conclusion, childhood TBM remains very rare in France and no increase in incidence rates was observed after two consecutive major changes in BCG vaccination strategies. This favourable result supports the 2007 decision to stop universal BCG vaccination. However, as suggested by modelling of the impact of a selective strategy with sub-optimal coverage, a slight increase in TBM in the 15 years following the change remains possible [14]. Therefore, there is a need for a comprehensive surveillance combining the different sources of data and case definitions, as done in the current analysis, in order to carefully monitor the median and long-term impact of this selective vaccination policy.

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Conflict of interest

None declared.

Authors' contributions

VTB and JR designed the study, collected and analysed data, and wrote the manuscript. DLB, DA, DC participated in the design of the study, in data analysis and in the writing of the manuscript. VJ participated in the design of the study and in data interpretation and final reading of the manuscript.

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Self-sampling for analysis of respiratory viruses in a large-scale epidemiological study in Sweden

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Viral diagnosis of respiratory tract infections has so far required sampling by health professionals, hampering large-scale epidemiological studies of virus-specific disease outcomes. As part of a population-based, prospective study of work-related risk factors for transmission of viral infections (SWEDE-I), we developed a scheme for self-sampling with nasal swabs. Random selection from the gainfully employed population of a medium-sized town in central Sweden resulted in a study cohort of 2,237 men and women aged 25 to 63 years. From September 2011 through May 2012, the cohort reported all instances of respiratory tract infection or gastroenteritis and participants concomitantly sent self-sampled nasal swabs for analysis using regular mail. Diagnosis of 14 viruses was performed. A total of 1,843 samples were received. The week-wise average delay between disease onset and arrival of the specimens at the laboratory varied between four and six days, and the corresponding median delay was between 3.5 and six days. In line with previous community-based studies, picorna- and coronaviruses dominated in specimens obtained from the self-sampling scheme. The results of self-sampling were contrasted to those from contemporaneous routine clinical sampling, on the same age group, in the adjacent Stockholm county. Although higher proportions of positive samples for respiratory syncytial virus and influenza were observed in the clinical sampling scheme, estimations of seasonality for influenza A and picornaviruses derived from both schemes were similar. Our findings show that nasal self-sampling is feasible in large-scale surveillance of respiratory infections and opens new prospects for population-based, virologically verified research on virus spread, burden of disease, and effects of environmental factors or interventions.

Introduction

Epidemiological studies of respiratory infections require laboratory confirmation of causative agents. Even a syndrome such as influenza-like illness (ILI), which is regarded as marker for influenza in

routine surveillance, needs viral diagnosis in a subset of patients [1-3].

Until recently, viral sampling from the respiratory tract demanded professional involvement. This made large-scale sampling in epidemiological studies exceedingly expensive. Now, self-sampling by lay study participants and shipment of nasal swabs via regular mail should be feasible [4-6], since the sensitivity of polymerase chain reaction (PCR) enables detection of infectious agents at low concentrations. Further, viral genetic material remains stable under many conditions despite loss of infectivity and multiplex PCR assays capable of simultaneously examining many viruses can enable a comprehensive overview of circulating respiratory viruses [7].

Knowledge about the spread of specific viruses in the community is fundamental for successful prevention of epidemics. In many countries, the burden and spread of infections in society may differ substantially from what is seen among patients seeking healthcare. Even for influenza, only a minority of cases may show up in healthcare. The majority stay at home, and these cases probably account for the most substantial burden of disease, the largest cost due to loss of productivity, and likely form the main basis for spread of disease.

As part of the study of work environment and disease epidemiology-infections (SWEDE-I), we developed a scheme for self-initiated respiratory self-sampling with nasal swabs in a cohort that constituted a representative sample of the workforce in Eskilstuna – a medium-sized industrial town in central Sweden. The objective was to demonstrate the feasibility of nasal self-sampling as part of the population-based surveillance of respiratory virus infections in the adult, working population. Here, we describe the logistics and results of PCR-based analyses of 14 viruses. The virology results from this self-sampling were contrasted to those obtained in contemporaneous routine clinical

specimens, received during the same time period, from the same age group in the adjacent Stockholm area.

Methods

Study of work environment and disease epidemiology-infections

The study of work environment and disease epidemiology-infections (SWEDE-I) was designed to: (i) identify work-related factors associated with the risk of common acute respiratory infections and viral gastroenteritis, both overall and by causative viral agent, in order to pave the way for preventive measures; (ii) provide empirical data on factors that affect the probability of transmission of common viral infections in various work-related settings, in order to improve the epidemic models needed for predictions and planning when major outbreaks are anticipated. SWEDE-I used, for the first time, a newly developed and extensively tested population-based system for infectious disease surveillance with an analytical epidemiological approach. As part of this study, a scheme for self-initiated respiratory self-sampling with nasal swabs was developed.

Setting

We strived to conduct the self-sampling study within a fairly small, circumscribed and stable population. By restricting to such a population, the proportion of the source population that was constituted by participants would be sufficiently high to allow estimations of the period-specific activity of each virus of interest, as an indirect indicator of the probability of becoming exposed, based on the observations in the studied sample. In a small community with high participation density it is also easier to keep participants alerted to their reporting commitment since information about the study tends to propagate by word-of-mouth. Eskilstuna, a town with 97,373 inhabitants 110 km west of Stockholm, Sweden, corresponded well with our specifications and was chosen as the study site. Trade and industry is varied and includes several traditional manufacturing industries. Most gainfully employed people both live and work in the commune.

Study population

Gainfully employed people, aged 25–63 years, residing in Eskilstuna, constituted the source population. The sampling frame was provided by Statistics Sweden through cross-linkage of the continuously updated population register with the Employment Register. To achieve a premeditated sample size of 2,200, postal invitations were sent to an age- and sex-stratified random sample of 14,008 individuals. The expected under-representation of men and of the age stratum 25–44 years was compensated for in the recruitment by an over-sampling based on observed participation rates in earlier, similar population-based infectious disease surveillance studies [8].

The cohort filled in a series of web- or paper-based questionnaires which comprehensively probed into the

physical and psychological work environment, work tasks, contact patterns, and commuting behaviour, as well as into potential confounding factors such as diet, family structure, living conditions, medical history, personal characteristics, and physical activity.

Participant-initiated disease reporting and self-sampling of nasal secretion

Participants were instructed to self-report all onsets of fever ($>38^{\circ}\text{C}$), upper respiratory tract infection, and gastroenteritis, alone or in combination, immediately as they occurred during the entire study period from 1 September 2011 up to 31 May 2012. Reporting could be done via Internet or via telephone, using interactive voice response. When reporting an infection, the participants answered questions about symptoms in an automated, tree-structured interview. Based on pre-defined algorithms, the diseases could be classified as common cold [9], gastroenteritis, ILI [10], or other/unclassifiable. Frequent reminders by email and mail, and monthly newsletters reminded the participants of their commitment. Additionally, participants were requested to sample nose secretions concurrently with every symptom report. Two kits with nylon flocked dry swabs in plastic tubes (Copan Diagnostics, Inc., Murrieta, CA, US) and an instruction leaflet had been distributed to each participant shortly after entry into the cohort. Each kit was uniquely linked to the participant by a barcode label on the tube. The participant sent the sampled material to the Virology department, Clinical Microbiology Laboratory at Karolinska University Hospital, Solna, via regular, pre-paid mail. When a participant's last kit had been returned, a new one was supplied. The samples were stored at -70°C until tested for enterovirus, human coronavirus (hCoV) 229E, HKU1, NL63 and OC43, influenza A, A(H1N1) pdm09 and B, metapneumovirus (MPV), parainfluenza 1, 2 and 3, respiratory syncytial virus (RSV), rhinovirus, using in-house real-time PCR in 96-well plates [7]. Remaining material was stored in a biobank for five years.

To get confidential feedback on test results, each participant received an individually unique six-character code, which, combined with the unique national registration number, gave access to a secure webpage listing the participant's results by arrival date of the specimen. Each test result was accompanied by a text describing the virus and its associated disease.

Comparison with viral diagnoses in routine healthcare

The virological laboratory used for SWEDE-I also provides diagnostic services to the entire Stockholm county (population 2.1 million). For reference, aggregated weekly test results from all samples collected during the same time period (September 2011 to May 2012) and from persons in the same age group (25–63 years) as the SWEDE-I cohort, who had been diagnosed for some or all of the same viruses were extracted. These samples ($n=1,516$) represent a mixture of in- and

out-patients that were analysed for clinical reasons. Testing was administered in form of two standardised test packages: 73% of subjects (n=1,113) were only tested for influenza A (including A(H1N1)pdm09), influenza B and RSV. 27% (n=403), and typically in-patients, were tested for the full range of viruses analysed for in SWEDE-I, though without distinguishing between different picornaviruses.

Statistical methods

For each virus category, the total number and the percentage of positive swabs for each respiratory virus over all samples tested made are reported separately for the SWEDE-I material and the clinical samples. Percentages are given with exact 95% confidence intervals (CI) [11]. Hypothesis testing of equal percentages of positive tests for specific viruses in both materials was performed with Fisher's exact test (F-test).

To explore temporal trends in incidence, the proportion of new cases each week (as percentage of all cases during the nine-month study period) was computed for the four most frequent virus diagnoses (corona-, influenza A-, metapneumo- and picorna- viruses). Week-wise hypothesis testing of equal proportions in the SWEDE-I and clinical materials was done with F-test.

The distribution of sex, age, country of birth, and immigrant status was examined for SWEDE-I participants found to have a positive test for coronavirus, influenza A and picornavirus. Testing of the hypothesis that these distributions were the same for the virus-affected groups as for all participants who returned at least one nasal swab was done using chi-squared tests.

The weekly averages of number of days between reported onset of a disease episode and receipt of the corresponding nasal swab at the laboratory were plotted against study week, together with a loess smoothing curve for the mean, inversely weighted by weekly standard errors [12]. The smoothing curve was then tested against a null model of constant average delay using an approximate F-test [13]. Differences in this delay between individual positive and negative tests over the entire study period were tested using a Wilcoxon test. For all tests, a p-value of less than 0.05 was considered statistically significant.

Ethics

The study protocol was approved by the Stockholm Regional Ethics Review Board (dnr 2011/360–31/2). All participants gave their informed consent.

Role of the funding source

This research was funded in full by AFA Insurance, Stockholm, Sweden. The sponsor had no role in the conception, design, planning, execution, analysis, interpretation or publication of the study. The corresponding author had full access to all the data in the study.

Results

After two reminders, 2,237 of 14,008 invitees agreed to participate in the SWEDE-I cohort (participation rate 16%). Some key characteristics of the cohort are exhibited in Table 1. The participants sent in 1,843 nasal swabs and made 2,119 disease reports, giving a sampling rate of 87%. Of the nasal swabs, 876 (47.5%; 95% CI: 45.3–49.8%) were shown to contain at least one

TABLE 1

Demographic and clinical characteristics of the cohort for the study of work-related risk factors for transmission of viral infections (SWEDE-I), Sweden, September 2011–May 2012 (n=2,237 participants)

Characteristic	n/N ^{a,b} (%)
Sex	
Men	918/2,237 (41)
Women	1,319/2,237 (59)
Age in years	
Mean (standard deviation)	47 (10)
Median (interquartile range)	46 (39–56)
Age group in years	
25–34	284/2,237 (13)
35–44	718/2,237 (32)
45–54	592/2,237 (26)
55–63	643/2,237 (29)
Household size^c	
1 person	251/1,815 (14)
2 persons	705/1,815 (39)
3 persons	326/1,815 (18)
4 persons	396/1,815 (22)
≥5 persons	137/1,815 (8)
Children below 13 years-old in household	
0 children	1,248/1,815 (69)
1 child	245/1,815 (13)
2 children	235/1,815 (13)
≥3 children	87/1,815 (5)
Highest attained education	
Secondary school (≤9 years)	160/1,798 (9)
Sixth Form (11–13 years)	596/1,798 (33)
University/college < 3 years	260/1,798 (15)
University/college ≥ 3 years	596/1,798 (33)
Other post-sixth form education	186/1,798 (10)
Healthcare work	
Yes	349/1,906 (18)
No	1,557/1,906 (82)
Number of reported disease events	
0	1,158/2,237 (52)
1	654/2,237 (29)
2	267/2,237 (12)
≥3	158/2,237 (7)

^a A total 2,237 participants were in the cohort but not all responded to all questions asked in the questionnaire.

^b Unless otherwise specified.

^c Including the index participant.

virus (henceforth referred to as ‘positive tests’). Since 21 of the samples each contained two or more different viruses (two viral diagnoses in 20 samples, three in one), the total number of virus diagnoses was 898.

The number of returned swabs peaked in the last week of September 2011 (week 39) and fell until the last week of November (week 48), when a phase with variable inflow ensued (Figure 1A). After the last week of February 2012 (week 9), the numbers decreased until the end of the study. The crude number of positive tests showed a similar pattern, but there was a more distinct upward tendency from late November, a climax in mid-February, and a gradual decrease until late April. In the beginning of the self-sampling study, the proportion of positive tests remained at ca 40%, but from mid-November the proportion increased, until it exceeded 60% in early April (week 14) (Figure 1B). Then it abruptly fell back to around 45%.

With the exception of the first and last two weeks of the study, the week-wise average delay between onset of disease episodes and arrival of the specimens at the laboratory varied between four and six days, and the corresponding median delay was between 3.5 and six days. Figure 2 suggests that this average increased slightly towards the end of the study period, although the trend indicated by the smoothing curve failed to reach formal significance ($p=0.06$). Overall, the delay between disease onset and sample arrival appeared fairly stable. Negative tests were slightly but significantly skewed towards longer delays ($p=0.004$).

Of 1,212 episodes with reported nasal discharge, 679 (56.0%) showed positive tests, in stark contrast to 29 (12.1%) of 239 episodes without nasal discharge. Test-negative episodes without nasal discharge were evenly distributed across the entire study period (data not shown).

FIGURE 1

Weekly number of swabs received by the cohort of the study of work-related risk factors for transmission of viral infections (SWEDE-I) and proportion of positive tests among all swabs received, Sweden, September 2011–May 2012 (n=1,843 swabs)

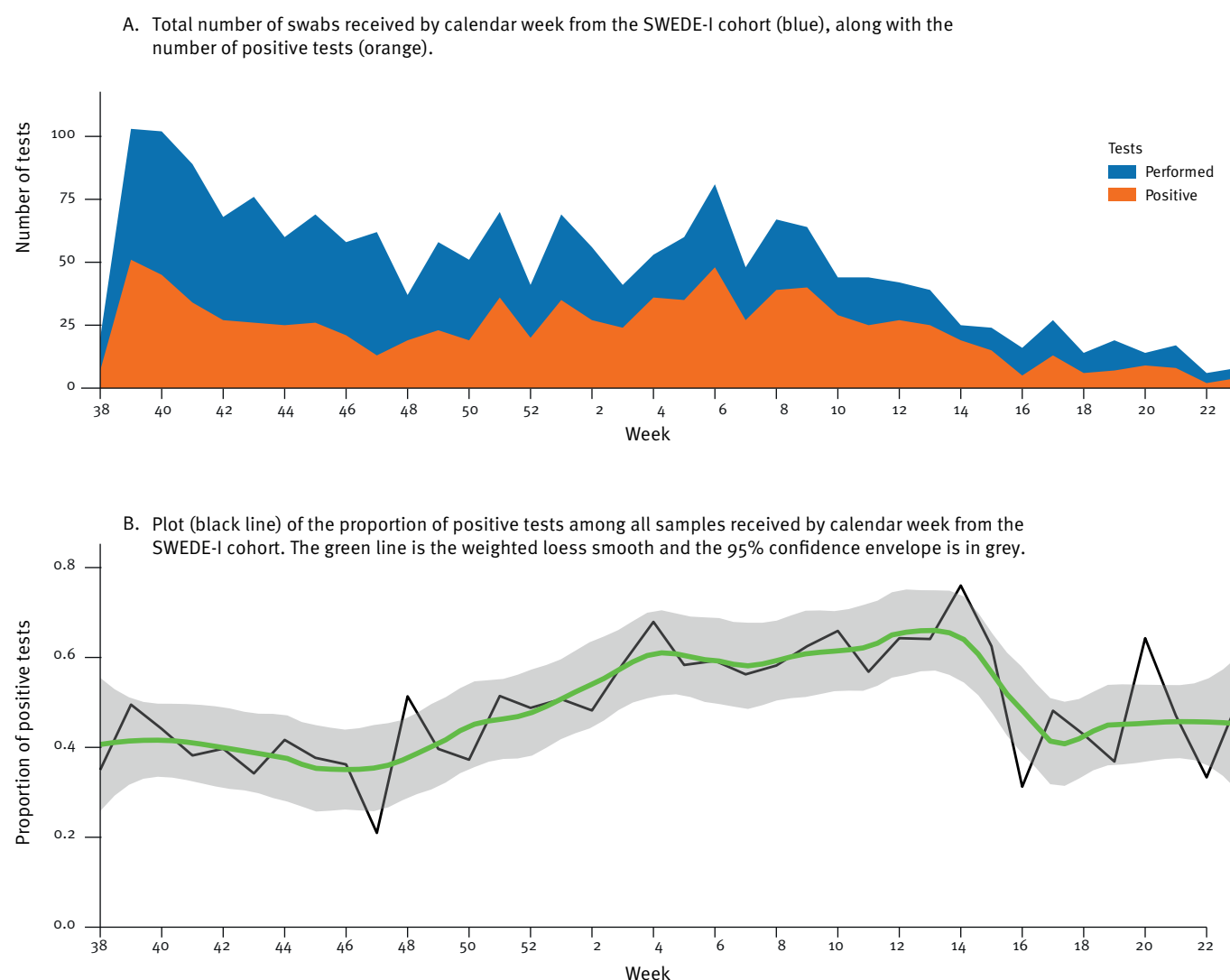
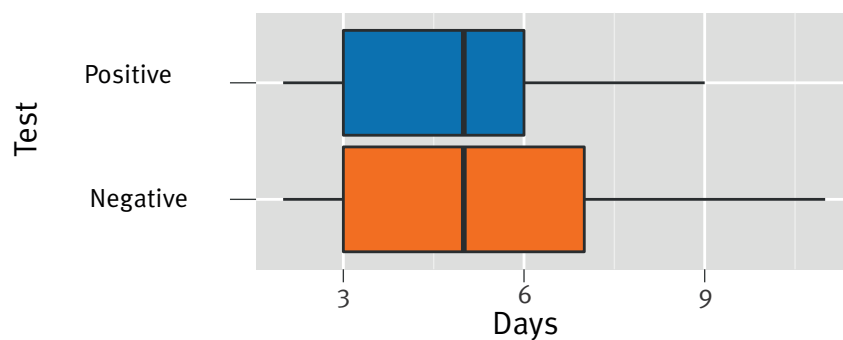


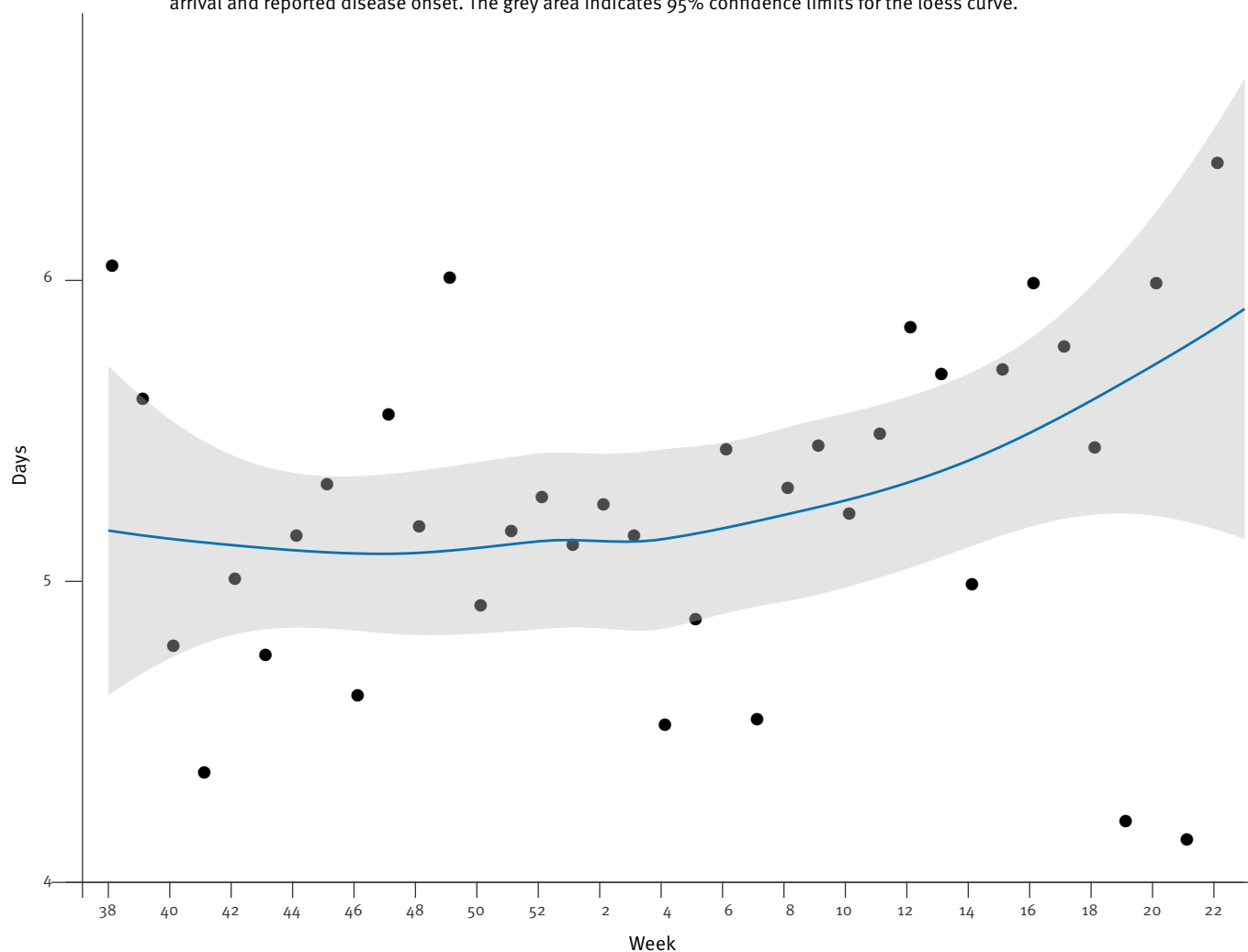
FIGURE 2

Delay between specimen arrival at the laboratory and reported disease episode onset in the cohort performing self-sampling, study of work-related risk factors for transmission of viral infections (SWEDE-I), Sweden, September 2011–May 2012 (n=876 swabs)

- A. Distribution of number of days between reported disease onset and arrival of the specimen at the laboratory for positive and negative tests; the modified boxplots show quartiles and median (box) as well as 5% and 95% quantiles (whiskers).



- B. Loess smoothing curve (blue) weighted by standard errors of weekly averages of number of days elapsed between specimen arrival and reported disease onset. The grey area indicates 95% confidence limits for the loess curve.



Pattern of virus-specific diagnoses

Percentages of virus-specific diagnoses among all samples tested in the SWEDE-I cohort are listed in Table 2 (column 2). In the SWEDE-I material, rhinoviruses were the most common of all tested viruses (20.8% of all samples) and dominated the picornavirus group. Coronaviruses, dominated by HKU1, were found in 16.2% of the samples, followed by seasonal influenza A in 4.6% of the samples and MPV in 2.9%. Among test-positive samples from patients without nasal discharge, the distribution of virus types was essentially the same as that in the entire SWEDE-I cohort (data not shown).

Columns 4 of Table 2 display the diagnostic yield from the clinical material. As for the SWEDE-I samples, corona-, influenza A and picorna-, viruses dominated, in the clinically-isolated samples, however, the rank order differed substantially and the proportion of influenza and RSV positive samples was significantly higher among such samples ($p \leq 6e-05$).

Seasonality of virus-specific diagnoses

The seasonal distributions of virus-specific diagnoses across the study period are shown in Figure 3 as weekly proportions of all specific diagnoses in the study period. From the SWEDE-I samples we found that picornaviruses, which were dominated by rhinoviruses occurred during the entire study period, but with a distinct peak in the last week of September (week 39). The season for coronaviruses lasted from early November until early May (week 18), with a climax in the second week of February (week 6). Seasonal influenza A peaked during the first three weeks of March (weeks 9–11). MPV occurred with three distinct peaks four to seven weeks apart between late December (week 52) and late March (week 13). Again the seasonal pattern among test-positive samples from patients without nasal discharge was very similar to the whole SWEDE-I cohort as just described (data not shown).

Figure 3 also shows the corresponding proportions of virus-specific diagnoses in the clinically-isolated

TABLE 2

Numbers, and percentages among all samples tested, of positive diagnoses for respiratory viruses found respectively for self-sampled and clinically-sampled swabs, Sweden, September 2011–May 2012

Test result	SWEDE-I self-sampled swabs		Clinically sampled swabs		P-value
	Number of positive samples among all samples tested n/N (%) ^a	95% CI	Number of positive samples among all samples tested n/N (%) ^{b,c}	95% CI	
Picornavirus	416/1,843 (22.6)	20.7–24.6	44/403 (10.9)	8.0–14.4	4e-08
Rhinovirus	383/1,843 (20.8)	18.9–22.7	NA	NA	NA
Enterovirus	18/1,843 (1.0)	0.6–1.5	NA	NA	NA
Undecided	15/1,843 (0.8)	0.5–1.3	NA	NA	NA
Coronavirus	298/1,843 (16.2)	14.5–17.9	22/403 (5.5)	3.5–8.1	1e-09
HKU1	167/1,843 (9.1)	7.8–10.5	9/403 (2.2)	1.0–4.2	3e-07
229E	85/1,843 (4.6)	3.7–5.7	7/403 (1.7)	0.7–3.5	0.008
OC43	41/1,843 (2.2)	1.6–3.0	4/403 (1.0)	0.3–2.5	0.120
NL63	5/1,843 (0.3)	0.1–0.6	2/403 (0.5)	0.1–1.8	0.616
Influenza virus	88/1,843 (4.8)	3.9–5.8	380/1,516 (25.1)	22.9–27.3	<2e-16
A seasonal	84/1,843 (4.6)	3.7–5.6	349/1,516 (23.0)	20.9–25.2	<2e-16
A(H1N1)pdm09	0/1,843 (0.0)	0.0–0.2	13/1,516 (0.9)	0.5–1.5	3e-05
B	4/1,843 (0.2)	0.1–0.6	18/1,516 (1.2)	0.7–1.9	8e-04
Metapneumovirus	54/1,843 (2.9)	2.2–3.8	22/403 (5.5)	3.5–8.1	0.015
Parainfluenza virus (PIV)	25/1,843 (1.4)	0.9–2.0	9/403 (2.2)	1.0–4.2	0.182
PIV1	14/1,843 (0.8)	0.4–1.3	2/403 (0.5)	0.1–1.8	0.752
PIV3	10/1,843 (0.5)	0.3–1.0	7/403 (1.7)	0.7–3.5	0.021
PIV2	1/1,843 (0.1)	0.0–0.3	0/403 (0.0)	0.0–0.9	1.000
Respiratory syncytial virus (RSV)	17/1,843 (0.9)	0.5–1.5	42/1,516 (2.8)	2.0–3.7	6e-05

CI: confidence interval; NA: not applicable; SWEDE-I: study of work-related risk factors for transmission of viral infections.

In the SWEDE-I study, 855 samples generated one viral diagnosis, 20 two diagnoses, and one three diagnoses.

^a The rate of positives for the influenza viruses and RSV in the SWEDE-I samples was 105/1,843 = 5.7% and for the other viruses it was 793/1,843 = 43.0%. The overall positivity rate was 876/1,843 = 47.5%.

^b The rate of positives for influenza viruses and RSV in the clinical samples was 422/1,516 = 27.8% and for the other viruses, which were only tested for in a subset of patients, it was 97/403 = 24.1%. The overall positivity rate cannot be calculated for the clinical material.

^c Of 1,515 total clinical samples, only 403 (27%), typically from in-patients, were tested for the full range of viruses analysed for in SWEDE-I, though without distinguishing between different picornaviruses. All samples were however tested for influenza A (including A(H1N1)pdm09), influenza B and RSV.

samples. Despite the difference in absolute frequencies seen in Table 2, the resulting proportions obtained respectively within the self-sampling and clinical-sampling schemes indicated seasonal occurrences that were overall similar. Influenza A tracked extremely well between the two schemes, the only difference ($p=0.01$) being a second dominant peak in the SWEDE-I cohort, two weeks after the common peak. For the corona-, metapneumo- and picornaviruses, significant differences in weekly proportions of positive swabs among the two sampling schemes were mostly observed towards the end of the study period, with the exception of one obvious peak in week 11 for coronavirus in

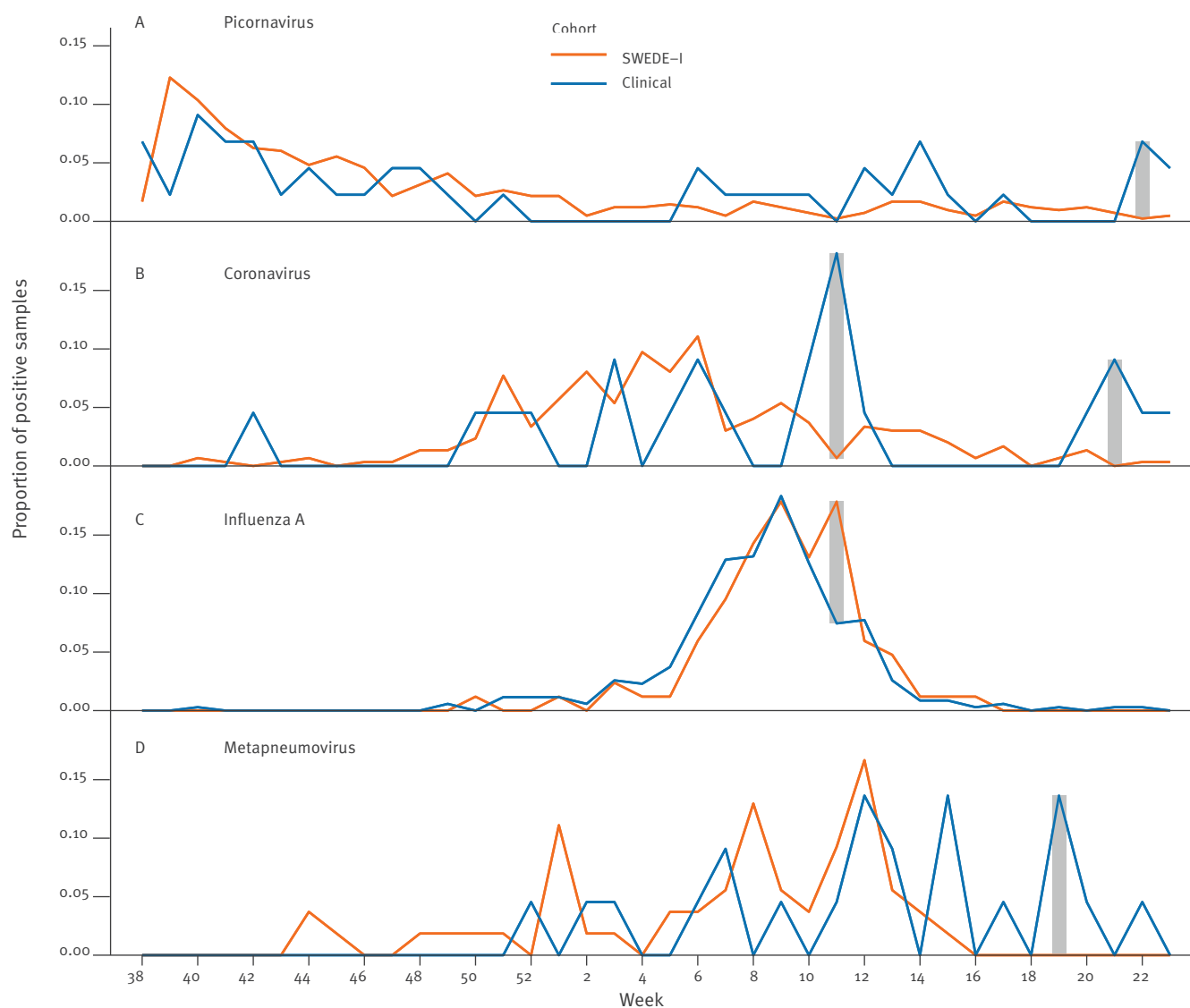
the clinical material, which was completely absent in the SWEDE-I material ($p=0.0004$). The counts for the other viruses considered in this study were too few to allow for seasonal analyses.

Common infections and demographics

The distributions of age, sex and foreign background were remarkably similar among SWEDE-I participants with positive tests for, respectively, coronavirus, influenza A and picornavirus (Table 3). None of these virus-positive groups differed significantly from the total group with tested nasal swabs. People born abroad or with an immigrant background were similarly

FIGURE 3

Weekly proportions of samples positive for (A) picornavirus, (B) coronavirus, (C) influenza A and (D) metapneumovirus relative to the total positive respective samples during the whole study obtained in the self-sampled and clinically-sampled materials, Sweden, September 2011–May 2012



SWEDE-I: study of work-related risk factors for transmission of viral infections.

Each data point represents the proportion of positive samples for a given virus that was received during the specified week relative to the season's total number of positive samples for this virus. Red lines represent self-sampled material from the SWEDE-I cohort in Eskilstuna, blue lines represent samples retrieved from contemporaneous routine clinical material from patients of the same age group seen at Karolinska University Hospital in Stockholm. Weeks in which the proportions differed significantly ($p < 0.05$) between the two materials are marked with a grey bar.

represented in the virus-positive groups. However, the age distributions among participants with coronavirus- and influenza A-positive infections differed significantly; while the majority of the former were 35–54 years of age, influenza A affected mainly participants in the youngest (25–34 years) and oldest (55–63 years) age groups ($p=0.03$).

Discussion

This study demonstrates the feasibility of nasal self-sampling as part of population-based surveillance of respiratory virus infections. During one season 1,843 samples, corresponding to 1.1 per person-year, could be evaluated. Previous reports have indicated that self-sampling earlier in the disease likely compensates for possible losses in sample quality [14,15]. The week-wise average delay between onset of disease episodes and arrival of the specimens at the laboratory varied between four and six days, and the corresponding median delay was between 3.5 and six days. This delay is considered acceptable in terms of sample quality.

While we lack a formal validation against a gold-standard method, we argue for the validity of our results based on a number of separate lines of evidence. With regard to self-reporting of ILI/ acute respiratory infection (ARI), the framework for self-initiated, event-driven infectious disease reporting that we employed had already been developed for a Swedish population-based cohort [8] and used for population-based surveillance in Stockholm County since 2007 [16]. A separate validation study concluded that while there

was significant under-reporting of disease (estimated at 60%), this level of under-reporting was remarkably constant over time and across seasons [16], so that a simple constant correction factor can potentially restore validity of incidence rates, at least in terms of reported disease incidence.

It is possible that the additional requirement of collecting and mailing a nasal sample may have led to increased study fatigue and correspondingly increased under-reporting in the SWEDE-I study, compared with the previous studies: in Figure 1A, we see indeed that the number of tests performed decreases from more than 100 samples/week at the very beginning to ca 20 samples/week at the end. However, Figure 1B indicates that the proportion of positive samples was at about the same level of ca 40% at both times, with in between a peak of ca 60% positive samples coinciding with the peak of the influenza A season seen in Figure 3. Also, within the study period, the numbers of self-sampled specimens submitted to the laboratory decreased more after week 9. This is in agreement with syndromic surveillance in adults for the same period in the whole of Sweden, based on calls for fever and cough to a medical advice line as an indicator for respiratory infections, which shows a sharp decline of contacts from week 9, the last week in February [17]. Taken together, it appears that the fluctuation in positive samples at least is driven more by seasonal and disease-related factors than by varying levels of participation in the study.

TABLE 3

Comparison according to selected demographic variables of SWEDE-I participants testing positive for coronavirus, influenza A, or picornavirus with all participants who returned a nasal swab, Sweden, September 2011–May 2012 ($n=1,843$)

Demographic characteristics	All incoming nasal swabs ($n=1,843$)	Picorna-virus positive ($n=416$)	Corona-virus positive ($n=292$)	Influenza A virus positive ($n=84$)
	n (%)	n (%)	n (%)	n (%)
Sex				
Men	608 (33)	142 (34)	104 (36)	24 (29)
Women	1,235 (67)	274 (66)	188 (65)	60 (71)
Age group in years				
25–34	256 (14)	55 (13)	30 (10)	15 (18)
35–44	618 (33)	140 (34)	90 (31)	24 (29)
45–54	436 (24)	108 (26)	83 (28)	13 (15)
55–63	533 (29)	113 (27)	89 (31)	32 (38)
Foreign born				
Yes	103 (5)	21 (5)	15 (5)	5 (6)
No	1,305 (71)	297 (71)	203 (70)	63 (75)
Missing	435 (24)	98 (24)	74 (25)	16 (19)
Immigrant status^a				
Yes	304 (16)	60 (14)	48 (16)	14 (17)
No	1,102 (60)	257 (62)	170 (58)	54 (64)
Missing	437 (24)	99 (24)	74 (25)	16 (19)

SWEDE-I: study of work-related risk factors for transmission of viral infections.

^a At least one parent born outside Sweden.

With regard to the distribution and burden of viruses in SWEDE-I, we found a similar pattern of rhinovirus-coronavirus-influenza as the three most common diagnoses (at 23%/ 16%/ 5%, respectively) seen in community-based studies in England in the 1990s (34%/ 14%/ 9% for a population aged 0–60+ years [18] and 52%/ 26%/ 10% for a population aged 60–90 years [19]). These community-based studies used active follow-up, with sampling by health professionals, and diagnosis through a combination of virus isolation and serology.

This is strikingly different from the concurrent clinically-isolated sampling scheme results, where the proportion of influenza-positive samples (25%) dominated all other infections, with seasonal influenza A, A(H1N1) pdm09, B being significantly more frequent than in SWEDE-I. At the same time, RSV and MPV were also significantly more common in the clinical materials. Although the lower frequency of viruses causing severe infections in SWEDE-I could be partly due to the self-sampling method, it seems most likely that patients infected with these viruses are overrepresented in healthcare.

Even though we have not been able to demonstrate conclusively in this study that self-sampling has the same sensitivity as healthcare based sampling, our results strongly support the use of the SWEDE-I methodology for influenza surveillance.

With regard to the timing of the circulation of different viruses, we found that the seasonality patterns obtained were rather similar between the SWEDE-I and clinical schemes. This confirms that clinical identification parallels societal spread, as seen in similar self-sampling studies previously [15], but is by no means a measure of societal spread intensity. The higher proportion of positive tests in the SWEDE-I cohort was explained by the abundance of picorna- and coronavirus infections. Self-sampling earlier in the disease may have contributed to their frequent detection, but the most apparent explanation for their scarcity in the clinical material is that they are rarely direct causes of severe disease among adults [20,21]. Interestingly, when influenza A peaked in the SWEDE-I cohort, only ca 30% of the samples were positive for influenza, and another 30% were positive for other tested viruses. This underlines the importance of virological testing to verify that acute respiratory disease is caused by influenza also during the epidemic period.

In the SWEDE-I cohort, the proportion of positives for picorna virus, corona virus and influenza viruses in adult persons from various demographic groups was very similar to the proportion among all samples obtained (Table 3). The similarity in this non-healthcare selected, adult population is obvious both when age, sex and ethnicity are considered. It is difficult to make any other interpretation than that spread of these viruses, with accompanying respiratory symptoms, is rather homogenous among adults of similar age in the

society. The low rate of positives for the other viruses prevented a similar analysis.

Noticeable limitations of the study include the absence of formal validation against gold standard testing, uncertain external validity due to low participation in the invited representative sample, and probable under-reporting among participants. Men, young age groups, and low-educated people were somewhat under-represented in a similar cohort [8]. The number of disease reports per person-year in this study is very similar to a previous validation study in similar cohorts [16]. In the previous study, a relatively constant under-reporting of 60% was identified, based on random control questionnaires on health status the previous week. Assuming a constant overall incidence of virus infections from year to year, the under-reporting was likely similar in the present study. Clearly, more research is needed to improve the completeness of disease reporting. Additional reminders and other incentives may be required.

The rate of positivity was further considerably higher among individuals whose disease was associated with nasal discharge than among those without. We found no indications that this disfavoured any specific virus, but further research is needed to verify whether patients without rhinitis are virally infected, and if so, to improve sampling.

This is a large-scale epidemiological study where self-reporting, self-sampling and modern PCR-based diagnosis were combined for investigation of virus-specific respiratory infection incidence on the population level. The logistics around reporting and self-sampling functioned exceptionally well. Of major importance was the sensitivity of the virological assays used. The methodology has been evaluated [7] and the sensitivity appears to be optimal. The participants received written instructions on how to perform the self-sampling and the instructions were also available on the study web page. In addition the participants could also call the staff at the study centre to ask questions. Shortly after having sent in a sample the participant could log in with their unique code at the study web page, for access to a secure website with their viral test results. The major cost of a virological study is the laboratory analyses, and to contain costs, samples can be stored at -70 °C until analysis in batches during periods of low workload since analysis is not necessary for clinical purpose. While the present cost of virological analyses makes routine sampling for analyses of respiratory viruses in the population unjustifiable, the feasibility of large-scale self-sampling in epidemiological studies may importantly advance the understanding of burden of disease and factors affecting spread.

The discrepancies and similarities with findings in clinical specimens seem logical, and calculations for influenza result in a very relevant incidence for the included population. For some of the viruses, a laboratory

comparison of sensitivity for nasal vs nasopharyngeal aspirates is desirable, but the fact that self-sampling is performed very early during the disease may compensate for a higher sensitivity of clinical nasopharyngeal sampling.

This successful deployment of self-sampling is applicable everywhere and it can be extended to other groups than working adults, and to various geographical areas, so long as the mail transport is reasonably efficient. We believe it may be an important tool in further research on spread of viruses in the population and the effect of interventions such as vaccination. Self-sampling for vaginal and rectal material has already been introduced for diagnosis of venereal diseases [22]. This sampling method can certainly support clinical and syndromic surveillance, as previously suggested [15].

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Conflict of interest

None declared.

Authors' contributions

ON, APly, and AL designed the study; APly and ON were responsible for the enrolment of participants, organization of fieldwork, and data collection; AL and C-GS supported the fieldwork; MRÖ and BZW performed viral analyses and supplied data on viral diagnoses in routine clinical samples; APlo, MRÖ and APly did the statistical analysis; AL, MRÖ, ON, APly, APlo, BZW, and C-GS interpreted the data; APly, ON, APlo, MRÖ, BZW and AL wrote and revised the draft report; APly, ON, APlo, MRÖ, BZW, AL and C-GS reviewed and revised the report. All authors approved the final version of the report for submission.

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