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Research article

Travel-associated gonorrhoea in four Nordic countries, 2008 to 2013

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Travel may be associated with a higher risk of gonorrhoea and infection by antibiotic-resistant strains. The objective of this study was to estimate the risk for gonorrhoea among travellers from four Nordic European countries using surveillance data and to identify at-risk travellers to help target interventions. We retrieved gonorrhoea surveillance data from Denmark, Finland, Norway and Sweden and tourism denominator data from the Statistical Office of the European Union. A travel-associated case of gonorrhoea was defined as one for which the reported country of infection differed from the reporting country. During 2008–2013, the four countries reported 3,224 travel-associated gonorrhoea cases, of which 53% were among individuals below 35 years of age. The overall risk associated with travel abroad was 2.4 cases per million nights abroad. The highest risk was observed with travel to Asia (9.4). Cases more likely to be reported as travel-associated were: males, heterosexuals of both sexes, people older than 65 years, and foreign-born individuals. More effective interventions targeting young adults and other at-risk groups are needed. The use of travel-planning websites and social media should be explored further.

Background

Gonorrhoea is a common sexually transmitted infection (STI). Although gonorrhoea can be asymptomatic, particularly in women and in pharyngeal and rectal infections, it is a major cause of urethritis in both men and women. In women, infection can lead to pelvic inflammatory disease, which may cause infertility [1].

The World Health Organization estimates that in 2012 there were over 78 million cases of gonorrhoea globally [2]. In 2013, 52,995 cases of gonorrhoea were reported in European Union (EU)/European Economic Area (EEA) countries (16.9 cases per 100,000 population) [3]. Of these, 2,701 (5.1%) were reported by Denmark, Finland, Norway and Sweden. Notification rate was close to the EU/EEA average in Denmark, Norway and Sweden (10–15 cases per 100,000 population) but lower in Finland (4.9). In these countries, most cases were reported among 25–34 year olds (960 cases; 36%) and among young adults aged 15–24 (908 cases; 34%). Men accounted for 75% of cases (2,012 cases) and 39% (1,050 cases) were reported among men who have sex with men (MSM). The number of reported cases has increased by 61% since 2009.

MSM are a key at-risk group for infection and accounted for 43% of gonorrhoea cases in the EU/EEA in 2013 [3]. The risk of transmission of gonorrhoea can be reduced by consistent and correct condom use during sex [4]. Apart from primary prevention and partner notification, effective treatment is the only option for control of gonorrhoea in the absence of an effective vaccine. European and national treatment guidelines are available [5]. An increasing number of *Neisseria gonorrhoeae* strains have been reported with reduced susceptibility to antimicrobials used for treatment [6].

The relation between travel and infectious diseases is of public health concern for two main reasons. First, travel can facilitate the international spread of diseases. Second, travel may be associated with an additional disease burden due to both different risk and exposure in the destination country compared with the country of origin. Such specific risk may justify targeted preventive measures such as vaccination, prophylaxis [7], or in the case of STIs, the provision of advice before departure and testing upon return.

The historical role of travellers in spreading STIs is well documented [8]. Travel is also a known risk factor for STIs for a number of reasons, including changes in sexual behaviour when travelling [8]. Thus, travel has been shown to remove social taboos and to increase

Table 1

Main characteristics of reported cases with gonorrhoea infection by probable travel status, Denmark, Finland, Norway and Sweden, 2008–2013 (n = 12,645)

	Total	Travelassociated cases		Nontravelassociated cases	
Characteristic	**Number**	**Number**	**%**	**Number**	**%**
Total	**12,645**	**3,224**	**100**	**9,421**	**100**
Sex					
Male	9,635	2,755	85.5	6,880	73.0
Female	3,009	469	14.5	2,540	27.0
Unknown	1	0	NA	1	NA
Age group (years)					
<15	21	2	0.1	19	0.2
15–24	4,438	780	24.2	3,658	38.8
25–34	4,142	940	29.2	3,202	34.0
35–44	2,293	730	22.6	1,563	16.6
45–54	1,181	488	15.1	693	7.4
55–64	430	202	6.3	228	2.4
≥65	139	82	2.5	57	0.6
Unknown	1	NA	NA	1	NA
Transmission					
Heterosexual	7,149	2196	76.8	4,953	58.4
MSM	4,143	652	22.8	3,491	41.2
Other	46	10	0.3	36	0.4
Unknown	1,307	366	NA	941	NA
Country of residence					
Denmark	3,445	365	11.3	3,080	32.7
Finland	1,558	531	16.5	1,027	10.9
Norway	2,299	790	24.5	1,509	16.0
Sweden	5,343	1,538	47.7	3,805	40.4
Origin					
Native	4,824	939	84.8	3,885	94.9
Foreign-born	376	168	15.2	208	5.1
Unknown	7,445	2,117	NA	5,328	NA
Year					
2008	1,632	460	14.3	1,172	12.4
2009	1,683	461	14.3	1,222	13.0
2010	1,991	568	17.6	1,423	15.1
2011	2,109	575	17.8	1,534	16.3
2012	2,526	571	17.7	1,955	20.8
2013	2,704	589	18.3	2,115	22.4

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

the likelihood of casual sexual relationships [9]. Travel is also associated with low condom use and sex may be the main objective of the journey (sex tourism) [9]. Travellers might also have sex with populations with higher prevalence of STIs, such as sex workers, or they might be visiting countries with a high prevalence of STI and therefore increase their risk of infection [9]. In addition, the emergence of antibiotic-resistant strains of gonorrhoea has been linked to countries in south-east Asia and Japan, and therefore travellers might import such strains to Europe [10]. Similarly, the prevalence of strains resistant to antimicrobials might be higher in further countries/regions outside Europe and lead to importation of resistant strains [9].

Estimating the real risk of travel-associated STIs is challenging. Data, particularly from Europe, are limited, notably because of reporting biases, incompleteness of STI surveillance data [8] and difficulties in obtaining sound data on travel patterns [11]. Yet, with an increasing number of travellers, it is important to better document, prevent and control travel-associated STI. Indeed, over the past 20 years, global tourist departures have doubled to reach half a billion in 2013, and Europe accounts for half of them [12].

Table 2

Number of travel-associated cases of gonorrhoea, number of nights spent and risk by travel region, Denmark, Finland, Norway and Sweden, 2008–2013 (n = 3,224)

	Travelassociated cases		Tourism nights (estimate 2008–2013)	Risk (cases/million nights)
Region	**Number**	**%**		
Total (all regions)	**3,224**	**100**	**1,319,713,232**	**2.4**
Africa	169	5.2	52,777,817	3.2
The Americas				
North America	120	3.7	94,163,334	1.3
Central and South America	116	3.6	38,425,724	3.0
Asia	1,553	48.2	165,075,367	9.4
Europe				
EU 27	1,044	32.4	788,962,938	1.3
Other European countries	196	6.1	155,107,899	1.3
Oceania	26	0.8	25,200,155	1.0

EU: European Union.

While the number of travel associated cases are aggregated for the period 2008–2013, tourism nights were not available for all country-region combinations for all years. The denominator for the risk calculation is therefore the mean of tourism nights for the available years multiplied by six.

The objective of this study is to estimate the risk for gonorrhoea among travellers from four Nordic countries using surveillance and tourism denominator data and to identify at-risk travellers to help target interventions.

Methods

Gonorrhoea data

The epidemiological surveillance of gonorrhoea in Europe is carried out at the national level by EU/EEA countries' public health institutes or similar bodies. At the European level, representatives from the countries form the European Network for STI Surveillance, which is coordinated by the European Centre for Disease Prevention and Control (ECDC). The network comprises all 28 EU countries, plus Iceland and Norway. Each year, all diagnosed cases meeting the EU case definition for gonorrhoea in the previous year are reported to The European Surveillance System (TESSy) database hosted by ECDC [13]. Cases are reported with a set of variables including age, sex, probable mode of transmission, country of birth, and probable country of infection. In addition, a separate and unlinked surveillance system, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP), collects epidemiological and antimicrobial resistance data on a subset of isolates from sentinel laboratories in participating Member States. Euro-GASP surveillance data were not analysed due to the very low completeness of reported epidemiological data on the probable country of infection.

For the purpose of this analysis, we included epidemiological surveillance data from four Nordic countries (Denmark, Finland, Norway and Sweden) for the years 2008–2013. These countries (total population 26 million) have surveillance systems with comprehensive coverage of the population and have reported continuously during the study period (i.e. at least one travel-associated case each year). In addition, Nordic countries share a number of similarities in their outbound tourism patterns, with trips more evenly distributed across the year [14], which support a pooled analysis. A travel-associated case of gonorrhoea was defined as one for which the reported probable country of infection differed from the reporting country. A foreign-born case was defined as a case with a country of birth different from the reporting country.

Tourism data

Tourism denominator data for 2008–2013 were obtained from the Statistical Office of the EU (Eurostat) [15]. We used the total number of nights spent by destination country. This included all tourism nights spent by EU/EEA residents aged 15 years or over, in a collective accommodation establishment or in private tourism accommodation for personal or professional purposes. In most countries, this information is collected through household surveys. Number of nights by sex and age was only available for Denmark. Since tourism nights were not available for all country-region combinations for all years, we calculated the mean of tourism nights for the available years over the study period. To obtain a denominator for the entire study period (6 years), the mean number of tourism nights was then multiplied by six.

Analysis

Travel-associated cases of gonorrhoea were compared with non-travel-associated cases for main characteristics. Risk for travel-associated gonorrhoea was

Table 3

Number of travel-associated cases of gonorrhoea, number of nights spent and risk by sex and age, Denmark, 2008–2013 (n = 365)

Characteristic	Travel-associated cases		Tourism nights	Risk (cases/million nights)
	Number	%	Number (mean 2012–2013)	
Total	**365**	**100**	**53,427,522**	**1.1**
Sex				
Male	315	86.3	27,881,556	1.9
Female	50	13.7	25,545,965	0.3
Age group (years)				
<15	0	NA	NA	NA
15–24	86	23.6	8,659,638	1.7
25–34	116	31.8	8,929,735	2.2
35–44	84	23.0	8,653,369	1.6
45–54	50	13.7	11,391,493	0.7
55–64	20	5.5	8,526,496	0.4
≥65	9	2.5	7,266,792	0.2

NA: not applicable.

While the number of travel associated cases are aggregated for the period 2008–2013, tourism nights were only available for 2012–2013 by age and sex. The denominator for the risk calculation is therefore the mean of tourism nights for the available years multiplied by six.

calculated by dividing the number of travel-associated cases by the number of nights spent in the destination country. For Denmark, risk was also calculated by sex and age group. For all countries, risk was additionally calculated by region of travel. We considered five main regions (Africa, the Americas, Asia, Europe and Oceania). We divided the Americas further into North America (including Greenland) and Central and South America (including Mexico). In Europe, we distinguished EU countries from other European countries (including Turkey).

Continuous variables were compared across strata by the Mann–Whitney U test. Categorical variables were compared using the chi-squared or Fisher exact tests.

To assess the association of different variables with travel-associated gonorrhoea, we performed a multivariable logistic regression using surveillance data and estimated adjusted odds ratios (OR) with their 95% confidence intervals (CI). We adjusted for sex, age, route of transmission, country of residence, origin and year.

Results

During the 2008–2013 period, Denmark, Finland, Norway and Sweden reported 12,645 gonorrhoea cases, of which 11,407 (90.2%) had information on probable country of infection. (Table 1).

Of the 12,645 reported cases, 3,224 (25.5%) were travel-associated. This proportion fluctuated between 27.3% and 28.5% from 2008 to 2011 and then dropped to 22.6% in 2012 and 21.8% in 2013. Over the period, the annual number of cases continuously increased from 1,632 in 2008 to 2,704 in 2013 (+65.7%). This increase was observed for both travel-associated and non-travel-associated cases, but the increase was more pronounced in non-travel-associated cases (+80.5% vs +28.0%). Finland, Norway and Sweden had similar proportions of travel-associated cases (ca 30%) while only 10.6% of Danish cases were related to travel.

Demographics

Of the 3,224 travel-associated cases, 2,755 (85.5%) were male, giving a male-to-female ratio of 5.9:1 (Table 1). Overall, the male-to-female ratio increased with age (1.8:1 below 25 years, 6.7:1 for the 25–34 years and >15 above 35 years). Cases in males were more often travel-associated than cases in females (28.6% vs 15.6%, $p < 0.01$). The proportion of females reported with gonorrhoea infections increased over the study period from below 20% in 2008 to over 25% in 2011–2013. Similarly, the proportion of females among travel-associated cases increased from 10% in 2008 to 15–19% in 2011–2013. Travel-associated cases were older than non-travel-associated cases (median age at diagnosis 33 vs 27 years, respectively, $p < 0.01$). Median ages of both travel-associated and non-travel-associated cases were stable over the study period. The proportion of travel-associated cases increased with age from 17.5% below 25 years to 59.0% at 65 years and above. Of the 3,224 travel-associated cases, 1,722 (53.4%) were young adults below 35 years of age; among non-travel-associated cases, young adults accounted for 73.0% of cases. Information on country of origin was available in Denmark, Finland and Norway. Of the 5,200 cases with known country of origin, 376 (7.2%) were foreign-born.

Table 4

Top destinations for travel-associated gonorrhoea cases, Denmark, Finland, Norway and Sweden, 2008–2013

		Travel-associated cases	
Rank	Destination country	Number	%
1	Thailand	1,006	31.2
2	Philippines	258	8.0
3	Spain	229	7.1
4	Germany	199	6.2
5	Denmark	95	2.9
6	United Kingdom	93	2.9
7	United States	71	2.2
8	Turkey	67	2.1
9	Russia	65	2.0
10	Morocco	63	2.0
11	China	56	1.7
12	Sweden	51	1.6
13	France	50	1.6
14	Greece	47	1.5
15	Greenland	45	1.4
16	Indonesia	45	1.4
17	Brazil	42	1.3
18	Poland	37	1.1
19	Italy	29	0.9
20	Pakistan	27	0.8
	Other	649	20.1
	Total	**3,224**	**100**

Foreign-born cases were more often travel-associated than native-born cases (15.2% vs 5.1%, $p<0.01$).

Transmission

Of the 2,858 (88.6%) travel-associated cases with known probable route of transmission, 2,196 (76.8%) were reported as heterosexual transmission, 652 (22.8%) were due to sex between men, and 10 (0.3%) were through other routes of transmission (Table 1). Of the 2,432 travel-associated cases in males with known transmission status, 652 (26.8%) were MSM, ranging from 19.4% (58/299) in Denmark to 31.7% (230/725) in Norway. The proportion of travel-associated cases was higher in heterosexually transmitted cases compared with MSM (30.7% vs 15.7%, $p<0.01$) and this was observed in all countries. Between 2008 and 2013, the annual number of travel-associated cases with heterosexual transmission fluctuated between 309 (2009) and 425 cases (2011). During the same period, the number of travel-associated cases with MSM transmission continuously increased from 53 in 2008 to 188 cases in 2013. Conversely, the number of travel-associated cases with unknown route of transmission continuously decreased from 84 in 2008 to 19 in 2013. Thus, the proportion of cases with MSM transmission among travel-associated cases with known transmission status increased from 14.1% in 2008 to 33.0% in 2013.

Risk by country of residence, sex, age and destination

During 2008–2013, residents from Denmark, Finland, Norway and Sweden spent ca 1,320 million nights abroad (Table 2).

The most visited regions were the EU (59.8% of all nights spent), Asia (12.5%) and North America (7.1%). The overall risk for travel-associated gonorrhoea was 2.4 cases per million nights spent in outbound destinations (Table 2). The highest risk was found in Swedish travellers (3.1 cases per million nights) followed by Norwegian, Finnish and Danish travellers with 2.5, 2.2, and 1.2 cases per million nights, respectively. In Denmark, where tourism data were available by sex and age group, a higher risk for travel-associated gonorrhoea was observed in males compared with females (1.9 vs 0.3 cases per million nights, respectively) and among persons aged below 45 years, peaking at 2.2 cases per million nights for people aged 25–34 years (Table 3).

Of the 3,224 travel-associated cases, 2,793 (86.6%) had acquired their infection either in Asia or Europe (Table 3). From December to July, Asia was the top destination for travel-associated gonorrhoea (53.4% of all travel-associated cases) peaking in January when Asia accounted for 60.6% of all travel-associated cases. From August to November, the top destination was Europe (48.6%) although the proportion of cases who had travelled to Asia remained substantial (36.5%). Monthly distributions of cases associated with travel to Africa, the Americas or Oceania did not show any obvious seasonal pattern. The highest risk was associated with travel to Asia with 9.4 cases per million nights. Travel to Africa and Central and South America was associated with a risk of ca 3 cases per million nights. Almost a third of all travel-associated cases were associated with a stay in Thailand, and the three destinations with the highest numbers of cases (Thailand, the Philippines and Spain) accounted for nearly half of all cases (Table 4).

Most cases with a probable country of infection in south-east Asia were reported with heterosexual transmission (98.3% for the Philippines and 95.9% for Thailand). Conversely, higher proportions of cases with MSM transmission were reported for top European destinations: in decreasing order, Germany (63.8%), the United Kingdom (59.1%), Spain (55.4%) and Denmark (55.2%). A comparable proportion of cases with MSM transmission was observed in people who travelled to the United States (55.9%). Top destinations for travel-associated gonorrhoea were very similar across all four Nordic countries with the exception of Greenland and Russia, which accounted for 12.3% and 9.0% of infections among Danish and Finnish travellers, respectively (Table 5).

The proportion of travel-associated cases with a probable infection in Thailand decreased from ca 40% in

Table 5

Top destinations for travel-associated gonorrhoea cases by country of residence, Denmark, Finland, Norway and Sweden, 2008–2013

Rank	Denmark			Finland			Norway			Sweden		
	Destination country	Travelassociated cases		Destination country	Travelassociated cases		Destination country	Travelassociated cases		Destination country	Travelassociated cases	
		Number	%		Number	%		Number	%		Number	%
1	Thailand	91	24.9	Thailand	217	40.9	Thailand	229	29.0	Thailand	469	30.5
2	Greenland	45	12.3	Russia	48	9.0	Philippines	77	9.7	Spain	119	7.7
3	Philippines	35	9.6	Philippines	40	7.5	Spain	75	9.5	Philippines	106	6.9
4	Germany	14	3.8	Spain	24	4.5	Germany	62	7.8	Germany	102	6.6
5	Spain	11	3.0	Germany	21	4.0	Sweden	31	3.9	Denmark	82	5.3
	Other	169	46.3	Other	181	34.1	Other	316	40.0	Other	660	42.9
	Total	**365**	**100**	**Total**	**531**	**100**	**Total**	**790**	**100**	**Total**	**1,538**	**100**

2008–2009 to 26.0% in 2013. Of the 376 foreign-born travel-associated cases, 154 (41.0%) travelled to their country of birth.

Multivariable analysis

When adjusting for potential confounders, males were nearly three times more likely to have acquired their infection abroad compared with females (OR: 2.96, 95% CI: 2.62–3.34) (Table 6).

The risk of travel-associated gonorrhoea increased with age. Heterosexual transmission of gonorrhoea was four times more likely to be travel-associated compared with MSM (OR: 4.08, 95% CI: 3.66–4.56). Compared with natives, foreign-born cases were eight times more likely to be travel-associated (OR: 8.34, 95% CI: 6.46–10.76). With 2008 as reference, infections acquired in 2012 and 2013 were less likely to be travel-associated.

Discussion

Principal findings

Surveillance data from four Nordic countries suggested that at least 25% of gonorrhoea infections were related to travel, a proportion that slightly decreased over the study period. Half of these cases had a travel history in Asia, a continent that accounted for fewer than 15% of the nights spent abroad by the residents of these countries. Most of the travel-associated cases were observed among persons below 35 years of age. The Danish cases for which denominator information was available suggested that the highest risk for travel-associated gonorrhoea was among the 25–34 year-olds. Danish data also showed that the risk for travel-associated gonorrhoea in men is six times higher compared with women. This is consistent with the finding that younger people and men are more likely to report having a new sex partner while travelling [16]; younger people are also more likely to have a higher number of sex partners in general [17], which is a risk factor for having a new sex partner while overseas [16].

Although the reported number of cases of gonorrhoea decreased with age, the proportion of cases of gonorrhoea which were travel-related increased with age, with a peak of 59% among those aged 65 years or over; almost all of these cases were reported among heterosexual men. Very few cases of travel-related gonorrhoea were diagnosed among people aged 65 years and above and therefore older persons are at lower risk of acquiring gonorrhoea per million bed nights.

During the study period, the number of gonorrhoea and travel-associated gonorrhoea cases increased in all four countries, but the proportion of travel-associated cases decreased most recently in 2012–2013. Overall, this rise in reported cases has been mainly due to increasing numbers of cases among MSM, regardless of travel status [3], which is partly linked to continuing high-risk behaviour in this subpopulation [18], partly to increased testing and use of more sensitive tests such nucleic acid amplification tests [19]. The larger increase among locally acquired cases compared with travel-associated cases is likely to reflect the larger proportion of MSM among locally acquired cases. The increasing number of travel-associated cases with MSM transmission over the study period cannot be explained solely by improved data completeness for transmission status, but should be considered in the context of increasing reports of cases among MSM overall during this time period [3].

A disproportionate number of cases were associated with travel to Thailand and the Philippines. Although some of these cases are likely to be acquired through contact with sex workers, many travellers, particularly backpackers, often find sexual partners among other travellers. The risk of new partner acquisition and overall risk of unsafe sex among backpackers in Thailand has been found to be associated with male gender and longer trip length [20]. Backpackers are also less likely to use condoms when having sex with travel partners compared than with commercial sex workers [21]. Thailand is reported to be the foreign country

Table 6

Adjusted predictors of travel-associated gonorrhoea cases, Denmark, Finland, Norway and Sweden, 2008–2013 (n = 12,643)

Risk factor	OR	95% CI	p value	Cases exposed (%)
Sex				
Female	1 (Ref)	NA	NA	23.8
Male	2.96	2.62–3.34	<0.01	76.2
Age group (years)				
<25	1 (Ref)	NA	NA	35.3
25–34	1.40	1.24–1.57	<0.01	32.8
35–44	2.38	2.09–2.71	<0.01	18.1
45–54	3.51	3.01–4.10	<0.01	9.3
55–64	4.36	3.47–5.49	<0.01	3.4
≥65	6.04	4.12–8.84	<0.01	1.1
Transmission				
MSM	1 (Ref)	NA	NA	32.8
Heterosexual	4.08	3.66–4.56	<0.01	56.5
Other	2.15	1.03–4.47	0.04	0.4
Unknown	1.85	1.50–2.28	<0.01	10.3
Country of residence				
Sweden	1 (Ref)	NA	NA	42.3
Denmark	0.22	0.18–0.26	<0.01	27.2
Finland	1.37	1.15–1.62	<0.01	12.3
Norway	1.48	1.26–1.73	<0.01	18.2
Origin				
Native	1 (Ref)	NA	NA	38.1
Foreign-born	8.34	6.46–10.76	<0.01	3.0
Unknown	1.28	1.10–1.49	<0.01	58.9
Year				
2008	1 (Ref)	NA	NA	12.9
2009	1.04	0.88–1.23	0.65	13.3
2010	1.09	0.93–1.29	0.27	15.8
2011	0.98	0.83–1.15	0.81	16.7
2012	0.81	0.69–0.95	0.01	20.0
2013	0.83	0.71–0.98	0.03	21.4

CI: confidence interval; MSM: men who have sex with men; NA: not applicable; OR: odds ratio; Ref: reference value.

where the largest number of Swedish males contract HIV and many Swedish men have sex with commercial sex workers while on holiday there, leading to risk of transmission of STI also from the local population [22].

South-east Asian countries are reported to have high levels of multidrug-resistant *N. gonorrhoeae* [23]. Information on the laboratory test used to confirm gonorrhoea is not available within the European surveillance system. This makes it difficult to know how often culture and subsequent susceptibility testing were performed among travel-associated cases. Considering the current concerns on antimicrobial-resistant gonorrhoea in Europe and globally [24], monitoring susceptibility of strains acquired during travel is important.

Over half of gonorrhoea infections acquired in the top European destinations were in MSM. This reflects the high prevalence of MSM having sex abroad, reported to be 25% in the previous 12 months from the European Men-Who-Have-Sex-With-Men Internet Survey (EMIS), and the low proportion of condom use during anal intercourse while abroad [25]. The top destinations for sex abroad reported in EMIS were also Spain and Germany, as in our study. Barcelona and Berlin are both extremely popular sex tourism hotspots in Europe for MSM.

Foreign-born cases were more likely to be travel-associated compared with natives. Approximately 40% of travel-associated foreign-born cases travelled to their country of birth, probably visiting friends or relatives (VFR). VFR travellers are a well-identified risk group for travel-associated illness although the definition may mask a more complex reality [26].

Strengths and weaknesses of the study

The study is based on a relatively homogeneous population in the Nordic European countries. A substantial proportion of Nordic residents travel abroad and this makes the Nordic population very suitable for estimating risk of travel-associated conditions. The surveillance systems for STIs in these countries have been stable during this time, with good case ascertainment and availability of diagnostics. Unfortunately it was not possible to incorporate analysis of Euro-GASP data due to the low completeness of the relevant variables. Improving the completeness of these variables in Euro-GASP should be a priority to allow for better monitoring of the resistance patterns of strains imported into Europe.

The travel behaviour across the included countries is also rather similar: residents of Nordic countries tend to travel to warmer countries during the darkest and coldest months of the year. Travel tourism data were collected mostly via household survey, a method which is prone to memory bias. However, the number of nights spent by destination was fairly stable over the study period suggesting that these data were reliable. Our decision to average the number of nights spent for the study period may have masked annual variations, especially for destinations with fewer nights spent, such as Africa or Oceania. For such destinations the estimated risk may be less accurate.

Unfortunately, tourism data were not available by age group and sex for Finland, Norway and Sweden, limiting enhanced analysis of the data. In Denmark where tourism data were available by age group, there was little variation over 2012–2013. Information on the purpose of travel was not available for cases. Therefore, we were not able to differentiate leisure tourism from business travel or family visits.

Comparison with other studies

The data presented in this paper are consistent with data reported by Steffen et al. who estimated a risk of travel-associated gonorrhoea of 0.06% per month of stay in developing countries [27]. Our findings indicate the highest risk was associated with travel to Asia with 9.4 cases/million nights, which would correspond to an incidence rate of 0.03% per month.

The high proportion of travel-associated cases in older age groups has previously been reported in Sweden where more than 50% of gonorrhoea cases aged 35 years or over were infected abroad during 2007–2011, compared with 20% to 25% for persons below 35 years of age [28]. The Swedish study found that women and MSM were more frequently infected in Sweden than heterosexually infected men. A recent systematic review of casual sex and foreign travel found that people engaging in casual sex while abroad are more likely to be young and males [29].

Possible explanations and implications for clinicians and policymakers

The results presented here highlight the role of young adults below 35 years of age in the epidemiology of gonorrhoea, including travel-associated gonorrhoea. International guidelines recommend specifically addressing STI during pre-travel consultations [7] but a recent systematic review underlined the low level of evidence on the impact of standard STI pre-travel advice on sexual behaviour [30]. The same review also found that motivational pre-travel STI interventions (described as 'a directive, client-centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence' [31]) were not superior to standard STI travel advice [30]. One cohort study identified in this review, however, did find that recall of reading STI information appeared to be related to more consistent condom use [30]. Since a large proportion of travellers do not seek advice in pre-travel consultations [32], other channels of information such as social media including dating apps could be explored. Young adults could be targeted with safe-sex messages related to travel when visiting STI or youth clinics: persons with a history of multiple sex partners and/or an STI are at risk of travel-associated casual sex [29]. The role of social media in targeting prevention messages needs to be considered and further investigated: research suggests that social media plays an increasing role as information sources for travellers [33,34]. Apart from social media, online resources are extensively used by all age groups for travel planning [34]. Targeted online prevention messages could be considered at peak travel periods together with research on their effectiveness.

Apart from the safe-sex message, young adults should be educated to know that a large proportion of gonorrhoea cases are asymptomatic and hence, after risky behaviour, testing is important irrespective of symptoms.

Finally, these data indicate that older males have a higher likelihood of having been infected abroad when presenting with a gonorrhoea infection. This should be taken in consideration by clinicians when treating these patients. Although they represent a lesser burden when compared with younger age groups, this population should not be forgotten by public health interventions.

Conflict of interest

None declared.

Authors' contributions

JB and GS conceived and designed the study. JB, SC, EHB, HK, IV and GS contributed to the data collection. JB ran the analysis. JB and GS drafted the manuscript. All authors contributed to revising the manuscript, providing substantial intellectual input.

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Allergic adverse events following 2015 seasonal influenza vaccine, Victoria, Australia

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Australia was alerted to a possible increase in allergy-related adverse events following immunisation (AEFI) with 2015 seasonal trivalent influenza vaccines (TIV) by the Victorian state vaccine safety service, SAEFVIC. We describe SAEFVIC's initial investigation and upon conclusion of the 2015 influenza vaccination programme, to define the signal event and implications for vaccine programmes. Allergy-related AEFI were defined as anaphylaxis, angioedema, urticaria or generalised allergic reaction. Investigations compared 2015 TIV AEFI reports to previous years as proportions and reporting risk (RR) per 100,000, stratified by influenza vaccine brand. The initial investigation showed an increased proportion of allergy-related AEFI compared with 2014 (25% vs 12%), predominantly in adults, with insufficient clinical severity to alter the programme risk-benefit. While overall TIV AEFI RR in 2015 was similar to previous years (RR: 1.07, 95% confidence interval (CI): 0.88–1.29), we identified a near-doubling RR for allergy-related AEFI in 2015 (RR: 1.78, 95% CI: 1.14– 2.80) from 2011 to 2014 with no difference by vaccine brand or severity increase identified. This increase in generalised allergy-related AEFI, across all used vaccine brands, supports evidence of variable reactogenicity arising from influenza vaccine strain variations. This investigation underlines the importance of effective seasonal influenza vaccine pharmacovigilance.

Introduction

The Australian southern hemisphere seasonal influenza vaccination programme typically runs from March to September, with influenza vaccine funded through the National Immunisation Programme (NIP) for healthcare workers, adults›65 years of age and individuals over 6 months of age with special risk conditions [1]. Adverse events following immunisation (AEFI) are reported to the relevant jurisdictional surveillance system, which in the Australian state of Victoria is via voluntary reporting to the Victoria vaccine safety service, SAEFVIC. SAEFVIC was established in 2007 and comprises a passive surveillance system coupled with clinical services [2]. AEFI reports to SAEFVIC are received primarily as unsolicited reports from immunisation providers or healthcare workers, with direct reporting from vaccinees or their guardians accounting for approximately one fifth of reports [3]. Immunisation nurses review all reports and provide follow-up, including referral for specialist clinical consultation as required.

Influenza vaccines have been subject to additional safety surveillance monitoring in Australia since an episode of increased reactivity of one seasonal trivalent influenza vaccine (TIV) brand occurred in 2010, causing high fever and febrile seizures in children aged under 5 years [4,5].

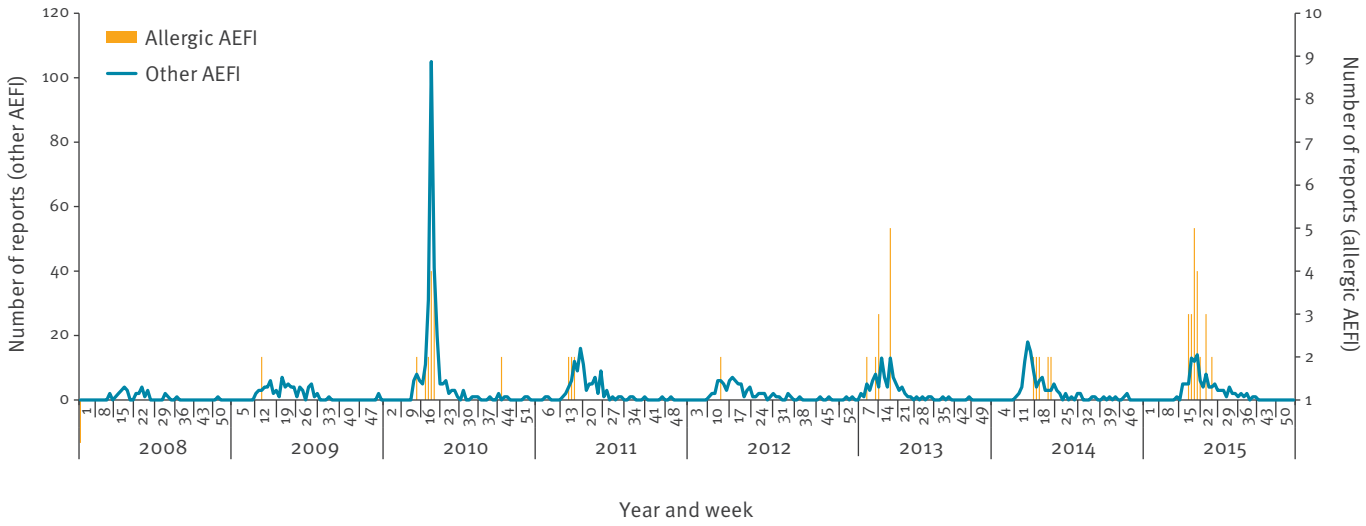
In week 2 of the 2015 TIV Influenza vaccine programme, SAEFVIC nurses receiving AEFI reports were alerted to a possible increase in allergy-related AEFI with TIV. This possible signal was reported to the national regulatory authority, the Therapeutic Goods Administration (TGA) [6]. This paper describes SAEFVIC's investigation initially and upon conclusion of the 2015 influenza vaccination season to define the signal event and provide guidance for future vaccine pharmacovigilance.

Methods

Reported AEFI with influenza vaccines were extracted by date reported. Data included demographic details as well as information on vaccine administered, reactions experienced and clinical consultations. Reports of drug administration errors not resulting in AEFI were excluded. Allergy-related AEFI were clinically defined as cases of confirmed anaphylaxis, angioedema,

Figure 1

Reports of trivalent influenza vaccine adverse events following immunisation by allergy-related category and week reported, Victoria, Australia, 2008–2015



AEFI: adverse events following immunisation.

The peak in 2010 corresponds to febrile-seizure signal event and increased reporting of febrile AEFI.

urticaria or generalised non-specific allergic reaction. Reports of anaphylaxis were confirmed according to Brighton Collaboration case definitions [7]. All other AEFI reported, including less defined symptom descriptions of itchiness, pruritus or rash with no further description, were categorised as 'Other'. Analyses were conducted using Excel (Microsoft Corporation, Redmond, WA, US) and STATA 13, StataCorp, Texas, US). Research Ethics and Governance of the Royal Childrens Hospital, Victoria granted approval for this study (DA017–2015–07).

Initial investigation

The initial investigation compared the proportion of allergy-related AEFI reported to SAEFVIC with any influenza containing vaccine between 1 January and 3 May 2015 with proportions to similarly categorised data received for the whole of 2014, as convenience comparison data. In addition the Australian regulatory authority, TGA, was notified and publicly accessible data from the national Database of Adverse Event Notifications (DAEN) [8] were accessed for any allergy-related AEFI with TIV with the aim to provide insight on the national distribution of the potential signal.

Monitoring of the proportion of allergy-related AEFI was conducted through the remainder of the influenza season (April–October), with comparison to 2014 using the chi-squared test and alongside individual clinical review of serious AEFI, including anaphylaxis, as a determinant of clinical severity.

Signal investigation

On conclusion of the southern hemisphere seasonal TIV programme on 31 October 2015, additional analysis of all SAEFVIC TIV AEFI reports for the previous eight seasons (since system commencement), 2008–2015, was conducted to define the signal event.

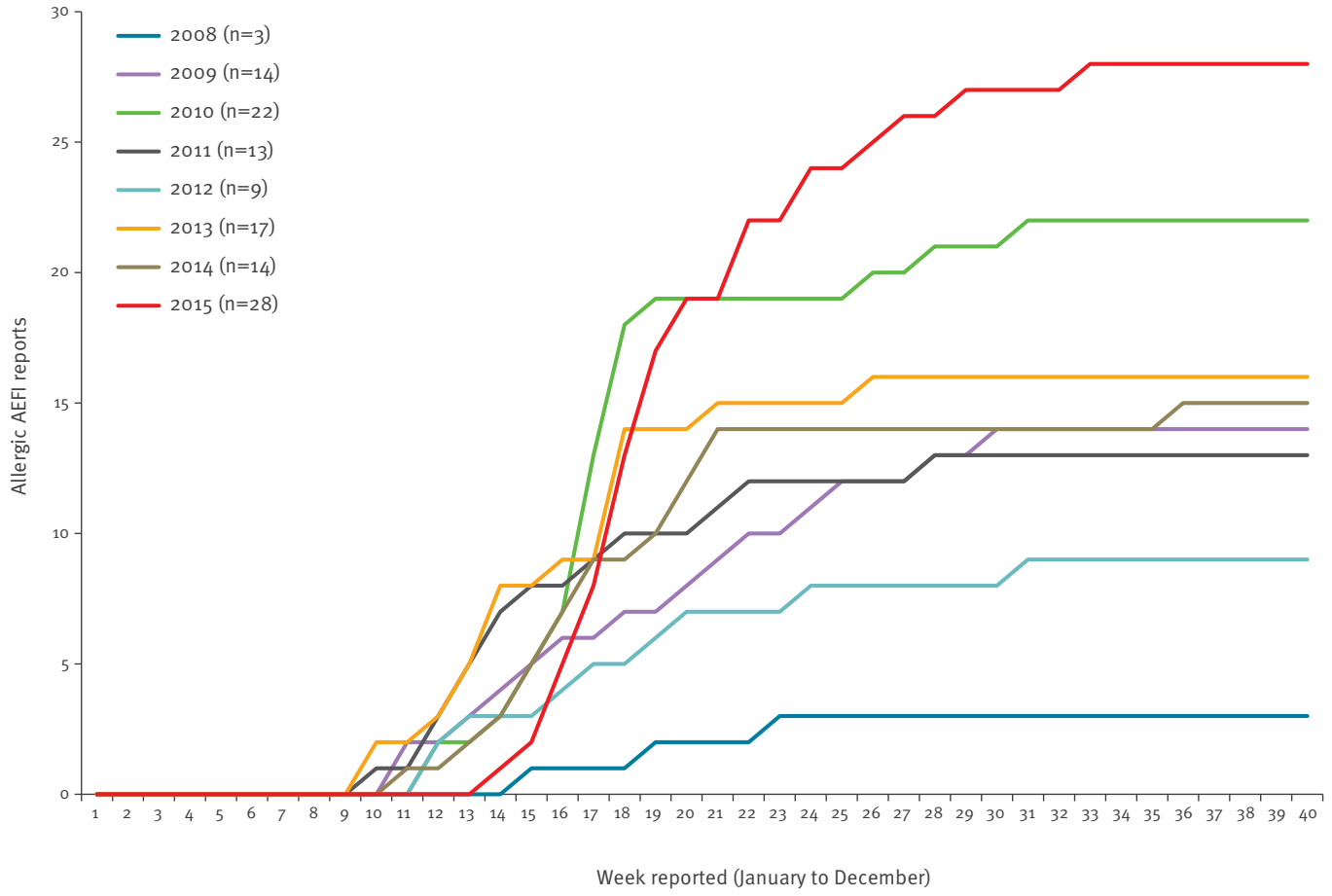
Data included in this analysis were restricted to the TIV brands used in the NIP in Victoria (Fluarix, GlaxoSmithKline; Fluvax, BioCSL; and Vaxigrip/ Vaxigrip Junior, Sanofi Pasteur) and for which dose distribution data were available. AEFI reports received in 2015 were analysed by allergic AEFI categories, vaccinee age, sex, time to symptom onset and TIV brand. The frequency of reporting was assessed by calendar week and also realigned by week of seasonal influenza AEFI reporting commencement, as this varies each year depending on the NIP.

AEFI reporting risks (RR) were calculated using the number of vaccine doses distributed as the denominator. Doses distributed data were provided on request from the Victorian Department of Health and Human Services for 2011–2015 [9]. RR ratios were calculated, using AEFI reports received per 100,000 doses distributed.

Anaphylaxis AEFI were compared as proportion of all TIV-AEFI and as proportion of allergy-related AEFI as an indicator of clinical severity, with comparisons to combined data 2011–2014 using two-sample test of proportions with 95% confidence intervals.

Figure 2

Cumulative reports of allergy-related adverse events following immunisation with trivalent influenza vaccine, by week reported, Victoria, 2008–2015 (n = 120)



AEFI: adverse events following immunisation.

The numbers in the legend represent cumulative reports per year.

Results

Initial investigation

At 3 May 2015, 11 (25%) of the 44 TIV AEFI reports received were allergy-related; this was an increase from 15 (12%) of 128 reports received by SAEFVIC throughout 2014 (RR: 2.13, 95% confidence interval (CI): 1.00 to 4.56).

The national DAEN database was accessed but was unable to inform the investigation as data were available only to end of January 2015, before season commencement. Personal communication with other jurisdictions and review by the TGA and the Advisory Committee on the Safety of Vaccines (ACSOV) acknowledged the potential signal in Victoria, but agreed there was insufficient evidence of clinical severity to alter the risk-benefit of the ongoing influenza vaccination programme [10].

Ongoing monitoring remained suggestive of above-expected reporting of allergy-related AEFI, although frequency of reporting decreased towards the end of May (Figure 1).

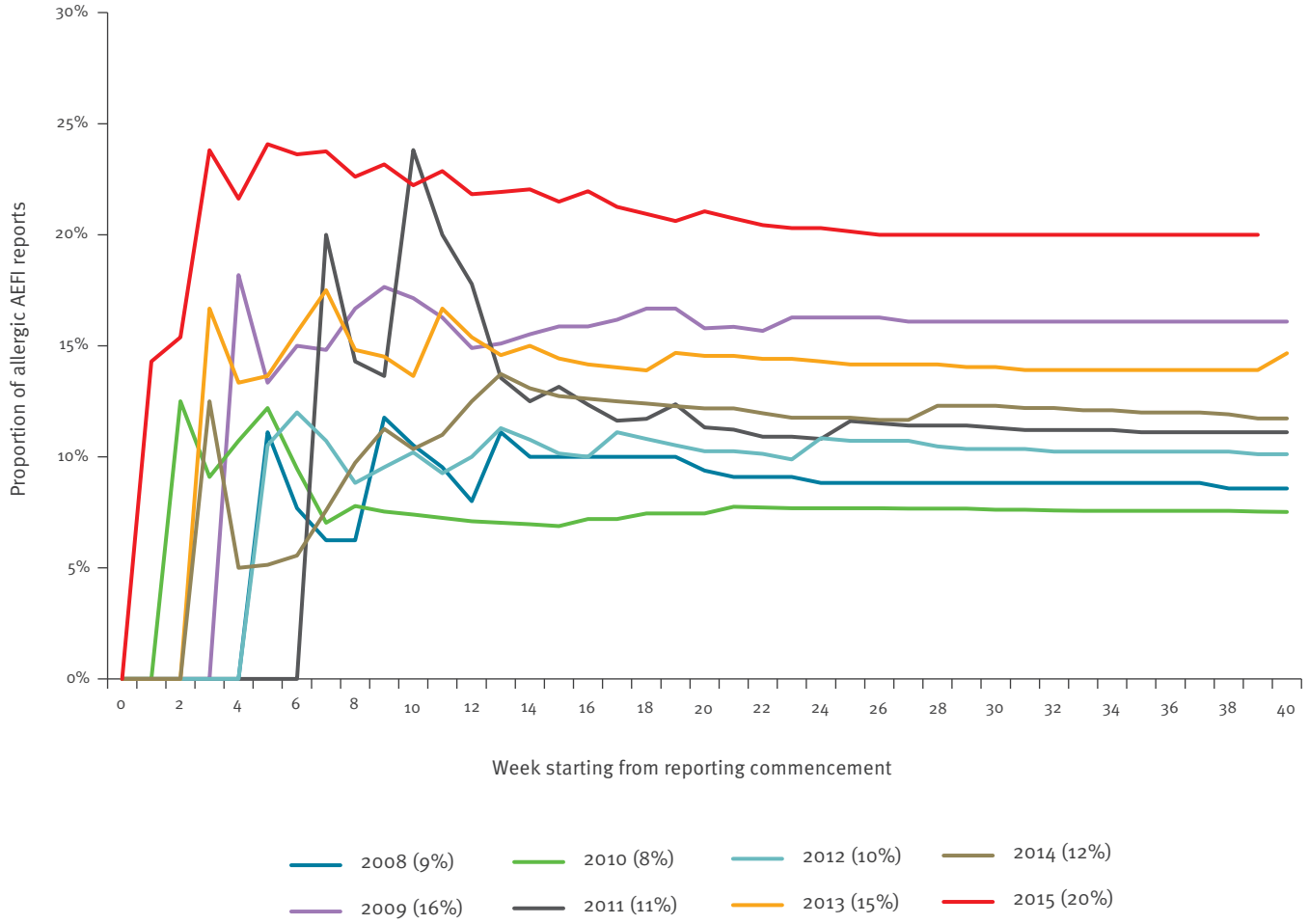
No increase was observed at any time during the 2015 season in the number or proportion of anaphylaxis cases, which peaked at six cases (21% [6/28] of allergy-related AEFI), when compared with four cases (27% [4/15]) reported in 2014 (p = 0.70).

End of season signal investigation

For the 2015 season SAEFVIC received 140 reports of AEFI with TIV, of which 28 (20%) were allergy-related. Vaccinee age ranged from 0 to 79 years (mean: 36 years), with all allergy-related cases aged over 5 years (6/28 aged 6–17 years and 22/28 aged ≥18 years, mean: 39 years). While females comprised the majority of reports (104/140, 74%), the proportion reporting allergy-related AEFI was similar in both males (7/36, 19%) and females (21/104, 20%) (p = 0.92; 95% CI: -0.14 to 0.16). Three-quarters (76%) of those experiencing allergy-related AEFI reported symptom onset within one-hour of vaccination and all within 10 hours.

Figure 3

Proportion of allergy-related adverse events following immunisation (AEFI) with trivalent influenza vaccines, by week from reporting commencement, Victoria, 2008–2015 (n = 1,010 total AEFI)



AEFI: adverse events following immunisation.

The y axis shows the proportion of allergy-related AEFI at the end of seasonal vaccination campaign.

The proportion of allergy-related AEFI with TIV of 20% (28/140) in 2015 was higher than in any previous year and significantly higher than the 12% (121/1,010) for all years 2008–2015 combined (p = 0.008; 95% CI 0.01 to 0.15) (Table 1).

The seasonal reporting pattern of overall TIV AEFI reporting in 2015 was similar to that seen in previous years (Figure 1). However, comparison of the number of allergy-related AEFI reported with previous years demonstrated the early steep rise and increased cumulative magnitude in reports (Figure 2), which was more clearly evident when realigned by weekly seasonal influenza AEFI reporting commenced in each annual period (Figure 3).

Final analysis at 2015 seasons end found the overall 2015 TIV AEFI RR of 11.8 reports per 100,000 vaccine doses distributed was no different to the RR of 11.1 per 100,000 for the four years 2011–2014 combined (RR: 1.07, 95% CI: 0.88 to 1.29) (Table 1). However when comparing allergy-related AEFI with TIV, the RR in 2015 of 2.4 per 100,000 vaccine doses distributed was nearly double that of the combined risk of 1.3 in 2011–2014, (RR: 1.78, 95% CI: 1.14 to 2.80).

The observed variation in AEFI reports per 100,000 doses distributed by vaccine brands in 2015 was not significant either comparing individual brands, or when comparing Fluarix to the combined BioCSL Fluvax and Vaxigrip RR (RR: 1.89, 95% CI: 0.79 to 4.48) (Table 2). Anaphylaxis AEFI reports in 2015 did not differ from 2011 to 2014 combined data as a proportion of all AEFI (6/140 (4.2%) vs 9/453 (2.0%); p = 0.13) or proportion of allergy-related AEFI (6/28 (2.1%) vs 9/54, (1.7%); p = 0.60).

Discussion

On conclusion of the 2015 southern hemisphere TIV/ influenza season our study found a near-doubling of

Table 1

Trivalent influenza vaccine adverse events following immunisation reports, by category and comparison of proportion and adverse events following immunisation reports per 100,000 doses distributed, Victoria, Australia 2008–2015 (n = 1,010)

Year	All reports	Allergy reports n	Allergy reports % (95% CI)	Doses distributed	AEFI per 100,000 doses distributed	Allergic AEFI per 100,000 doses distributed
2015	140	28	20 (14–28)	1,186,417	11.8	**2.4**
2014	128	15	12 (7–19)	1,097,024	11.7	**1.4**
2013	116	17	15 (9–22)	1,095,217	10.6	**1.6**
2012	90	9	10 (5–18)	966,393	9.3	**0.9**
2011	119	13	11 (6–18)	932,246	12.8	**1.4**
2010	293	22	8 (5–11)	NA	NA	**NA**
2009	89	14	16 (9–25)	NA	NA	**NA**
2008	35	3	9 (2–23)	NA	NA	**NA**
2008–2015	1,010	121	12% (10–14)	NA	NA	**NA**
2011–2014	453	54	12% (9–15)	4,090,880	11.1	**1.3**

AEFI: adverse events following immunisation; CI: confidence interval; NA: not available.

annual generalised allergy-related AEFI compared with the 4 previous years in this investigation of passive surveillance reports, with no evidence of correlation with any specific vaccine brand or allergic symptom, nor a significant increase in anaphylaxis. Further studies would be required to confirm that the signal was more than a spurious increase in reporting, however we were not aware of any publicity or event that may have stimulated reporting. Our study demonstrated that the longitudinal data availability, combined clinical and epidemiological services of SAEFVIC were well placed to identify and conduct a rapid investigation of a possible signal event early in the influenza vaccination campaign and facilitate evidence-based decision making by the Australian national regulatory authority.

However, vaccine pharmacovigilance in Australia is limited by wide variation in AEFI surveillance systems across Australian health jurisdictions [11]. Data are not consistent in format, categorisation or method of analyses until final collation of jurisdictional reporting and classification according to standardised MedDRA terminology is completed by the TGA. National AEFI data are publicly accessible via the Database of Adverse Event Notifications (DAEN), but there is a 3-month lag in publication. Australia continues to strive towards stronger multi-jurisdictional vaccine pharmacovigilance collaborations and streamlined cohesion between the jurisdictional surveillance models.

Detecting signals as an increase in AEFI frequency from previous years is best achieved by comparing risk of AEFI in the exposed (vaccinated) population. However, in this scenario, cases were predominantly adults for whom there is little available data on the vaccinated (exposed) population as the vaccine register in Australia, the Australian Childhood Immunisation Register (ACIR), is limited to vaccines administered to children aged less than 7 years [12]. Expansion of the Register in 2016 to all age groups for vaccines on the NIP or given in general practice will partially address this gap, but the register will not include vaccines administered in specialist clinics (e.g Bacillus Calmette–Guérin, travel vaccines) [13] thus underlining the importance of spontaneous or passive surveillance collating AEFI reports for all vaccines administered and from all vaccine-recipient sub-groups [14].

To determine AEFI RR, we therefore used a proxy denominator of vaccine doses distributed. This is an approximation of the exposed population as usage (and wastage) is unknown and may therefore lead to underestimation of RR. Reports of AEFI with non-NIP TIV brands were excluded from the final investigation in all years as numbers were small and vaccine doses distributed data were not readily available. Exclusion of these non-NIP TIV reports and non-specific potential allergy-related symptoms such as itchiness or undefined rash means that this summary is a conservative approach to the signal magnitude.

Non-specific AEFI such as the allergy-related reactions reported in 2015 can give rise to subjective variations in categorisation, although these would be consistent in inter-year comparisons. Brighton Collaboration definition criteria were applied for the serious AEFI of anaphylaxis [15], which showed no significant increase from previous years. The observed increased proportion of allergy-related AEFI may equally indicate a decrease in non-allergic reports; although there is no specific reason that non-allergic reporting would be depressed and no drop in the number of non-allergy-related reports was observed. Furthermore our analysis does not consider temporal co-circulation of environmental or infective allergic triggers; however,

Table 2

Reports of trivalent influenza vaccine adverse events following immunisation, by symptom and reports per 100,000 doses distributed, by influenza vaccine brand, Victoria, Australia 2015 (n = 140)

Brand	All reports	Allergic reports (n)	Allergic reports (%)	Anaphylaxis	Angiodema	Urticaria	Allergic reaction generalised	Vaccine doses distributed	AEFI reports per 100,000 doses distributed	Allergic AEFI reports per 100,000 doses distributed	Comparison of Fluarix to other brands RR (95% CI)
Fluarix[a]	36	7	19%	2	1	1	3	212,605	16.9	3.3	Reference
bioCSL Fluvax	44	8	18%	2	1	4	1	586,250	7.5	1.4	2.41 (0.90–6.44)
Vaxigrip (including Jnr)	43	9	21%	2	1	5	1	387,562	11.1	2.3	1.42 (0.53–3.79)
Brand unknown	17	4	24%	0	1	1	2	NA	NA	NA	NA
Total	**140**	**28**	**20%**	**6**	**4**	**11**	**7**	**1,186,417**	**11.8**	**2.4**	

AEFI: adverse events following immunisation; NA: not available.

[a] Fluarix was the National Immunisation Programme- funded vaccine for Victoria.

there was no indication that either parameter was in variance to previous years.

Any analysis by vaccine brand should be interpreted with caution. Vaccine brands are targeted to different vaccinee demographics and propensity to report AEFI cannot be assumed to be similar. In Victoria, Fluarix was the main brand of TIV for healthcare workers and BioCSL Fluvax the main brand of TIV used in the community with Vaxigrip used in children aged less than 5 years. It is possible that healthcare workers were more aware of SAEFVIC and likely to report an AEFI than the general population, giving rise to reporting bias for Fluarix brand. It should also be noted that low numbers limited the comparision between brands.

In 2015 there was a delay in vaccine supply and distribution due to manufacturing delays to accommodate a two-strain change in the seasonal formulation [16]. The early non-specific signal was initially hypothesised as an anomaly of timing of administration reflecting changes in uptake [10], in particular in the healthcare worker demographic where vaccination delivery was concentrated into a shorter-than-usual timeframe. However, our analysis showed that even with realignment for season commencement, the overall proportion of allergy-related AEFI was still observed to be higher than in previous years.

TIV reactogenicity has been shown to change dramatically despite a stable manufacturing process and within a single manufacturer [17-19]. The apparent increase in allergic-type AEFI reports in 2015 did not suggest that one single brand employed in the Australian-funded TIV programs was responsible, suggesting that, if real, the incorporation of one or both of the new influenza strains for 2015 season may have carried a higher allergen component in the manufacturing processes. However, these data are from a single jurisdiction and need to be confirmed by national and international data for vaccines incorporating the same strain changes before broader hypotheses can be drawn.

The recognised limitations of passive surveillance, including unquantifiable under-reporting, potential reporting biases, unascribed causality and lack of information on the exposed population, align to the benefit of multi-faceted approaches for signal detection [14,20]. The growing number of active surveillance initiatives using targeted solicited systems or interrogation of healthcare databases have the benefit of increased sample size and can also facilitate data-linkage and hypothesis-testing studies [21-23]. However, especially in the absence of a pre-specified AEFI of interest, even large-scale active surveillance systems are unlikely to consistently detect all signals. Specific target-group restrictions may also hinder detection of unanticipated signal events. For example, Australian short message service (SMS)-stimulated reactogenicity reporting surveillance systems [24] primarily target the paediatric population and so could not inform on this predominantly adult event. An increasing number of statistical signal detection methodologies have been described, but most studies demonstrate the methodological utility retrospectively and few describe the evolution of a signal detection and investigation in real time as we describe [25].

Variation in influenza vaccine strain is a regular, if not annual, occurrence depending on wild-type virus circulation. In 2016, Australia's immunisation programme adopted quadrivalent influenza vaccines; therefore demonstrations of effective vaccine pharmacovigilance are paramount for ensuring the safety of vaccination programs. The cross-hemispheric sharing of possible signals, even if relatively minor, may aid in early alertness and stimulated monitoring to ensure vaccine pharmacovigilance is able to accurately inform the risk profile of routine immunisation programs.

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Conflict of interest

None declared.

Authors' contributions

HJC contributed to the study design, conducted data analysis and interpretation of results and drafted the manuscript. NWC contributed to the study design and reviewed and contributed to the manuscript draft. MAR contributed to the data analysis, result interpretation and reviewed and contributed to the manuscript draft. JPB contributed to the study design and reviewed and contributed to the manuscript draft.

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