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Monitoring influenza activity in Europe with Google Flu Trends: comparison with the findings of sentinel physician networks – results for 2009-10

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The number of Internet searches has recently been used by Google to estimate the influenza incidence in the United States. We examined the correlation between the *Google Flu Trends* tool and sentinel networks estimates in several European countries during the 2009 influenza A(H1N1) pandemic and found a good correlation between estimates and peak incidence timing, with the highest peaks in countries where Internet is most frequently used for health-related searching. Although somehow limited, Google could be a valuable tool for syndromic surveillance.

Introduction

On 21 April 2009, the Centers for Disease Control and Prevention (CDC) alerted the media regarding the isolation of the 2009 pandemic influenza A(H1N1) virus from humans. The World Health Organization (WHO) made the unprecedented decision to announce a level 4 pandemic alert on 27 April, raising it to level 6 on 11 June given the strong and sustained transmission of the virus around the world [1].

In the northern hemisphere, surveillance of the pandemic was maintained throughout 2009 via the exceptional use of sentinel physician networks (SPNs) during the summer season. The majority of the European countries reported the weekly incidence of influenza-like illness (ILI) or acute respiratory infection (ARI) through this system [2]. Although such networks allow the rapid and precise collection of information, the average delay between receiving it and its dissemination via epidemiological surveillance websites is about two weeks [3]. In addition, for a case to be registered, contact has first to be made with the health system. These problems have led to investigations into the use of alternative surveillance systems capable of registering more cases in the earlier stages of epidemics, such as recording the number of absentees from work or school, the demand for medications, or the use of Internet surveys [3].

The number of Internet searches made using Google (http://www.google.com) employing search terms related to influenza has recently been used to construct a model for the estimation of influenza incidence in the United States (US). The estimates this model provides correlate very well with SPN data, and can be made available one or two weeks earlier than CDC surveillance reports [4], although the correlation of the model with positive influenza tests is somehow weaker [5]. Currently, estimates are available for 20 countries, 14 of which are European, and can be referred to via *Google Flu Trends* (GFT) at http://www.google.org/flutrends [6].

For Australia and New Zealand, a good correlation has been recorded between the incidence estimates of this GFT model and the sentinel physician networks (SPN) data during the 2009–10 influenza season [7,8]. This period falls between influenza seasons in the northern hemisphere, a time during which discrepancies have been noted in GFT and SPN incidence estimates for the US [9]. In this report we aim to examine the correlation between GFT and SPN incidence estimates in different European countries during the 2009 influenza A(H1N1) pandemic, i.e. both before and during the influenza season. The association between online search habits in each country and the correlations observed were also investigated.

Materials and methods

The weekly (23 March 2009–28 March 2010) GFT and SPN (based on ILI or ARI data) estimates of influenza incidence were recorded for 13 European countries. The sources of the SPN information were the European Influenza Surveillance Network of the European Centre for Disease Prevention and Control (ECDC) [10], the World Health Organization [2], the Réseau Sentinelles de France [11], the Spanish Red Nacional de Vigilancia Epidemiológica [12], Robert Koch Institute (Germany)

[13], and Smittskyddsinstitutet (Sweden) [14]. Spearman correlation coefficients between the GFT and SPN estimates were calculated for the periods before and after 31 August 2009 (i.e. before and during the influenza season) for each country. The influence of the percentage of the different populations making health-related Internet searches (obtained from Eurostat) [15] on the strength of the correlation between the GFT and SPN results was also examined by Spearman analysis. Significance was set at $p<0.05$. All calculations were made using Stata 9.1 software.

Results

The Table shows the correlations between the GFT and SPN (ILI or ARI) results for each country and period examined.

Austria was not included in this analysis because the available data were insufficient. In most countries the correlation was stronger during the second period (i.e. after 31 August 2009), the exceptions being Russia and Ukraine. The two systems commonly coincided in terms of registering peak incidence, although the GFT data sometimes identified this to occur one or two weeks earlier, e.g. for Poland and Switzerland. The two notable exceptions to this were Sweden, for which the GFT model estimated peak incidence to have occurred some 11 weeks before that suggested by the SPN system, and Bulgaria, for which the SPN system suggested a peak incidence one week before the GFT estimate.

Figures 1 and 2 show the SPN ILI and ARI results separately in comparison with the corresponding GFT results. In the majority of cases, the graphs are similar.

The graphs compare the weekly proportion of consultations for acute respiratory illness according to sentinel physician networks and incidence estimates obtained from *Google Flu Trends*. The first week of the series was 23–29 March 2009 (epidemiological week 13).

However, the height of the incidence peaks for France and Hungary appears to be overestimated by the GFT model, and underestimated for Switzerland and Spain (preceded by an overestimation during the summer months in Spain).
Figure 3 shows that the greater the proportion of the population that sought health information via the Internet in 2009, the better the correlation between the GFT and SPN ILI results (Rho=0.7545; p=0.0305). This association was maintained after adding the information from countries that record only ARI data (Germany and Bulgaria) (Rho=0.6991; p=0.0245). The graph shows the correlation between the proportion of individuals who used the Internet for seeking health information in 2009 and the Rho coefficient between the SPN ILI per 100,000 population and GFT incidence estimates.

Discussion and conclusions

In general, the GFT and SPN results (both ILI and ARI) showed a strong correlation. This is the first study to relate GFT and SPN estimates in Europe; the only other northern hemisphere study was undertaken by Doornik

Table

Correlation between weekly sentinel physician network data on influenza-like illness or acute respiratory illness and *Google Flu Trends* incidence estimates

COUNTRY	SYNDROME	CORRELATION			
		Overall period[a]	Pre-epidemic[b]	Epidemic[c]	Peak incidence
		Spearman Rho	Spearman Rho	Spearman Rho	(GFT versus SPN)
Belgium	ILI	0.7358	0.6929	0.8533	Same week
France	ILI	0.9124	0.4957	0.9678	Same week
Hungary	ILI	0.8959	0.3931	0.7496	Same week
Netherlands	ILI	0.8597	0.7850	0.9384	Same week
Norway	ILI	0.8769	0.8651	0.8606	Same week
Poland	ILI	0.7157	0.5179	0.5840	1 week before
Spain	ILI	0.7331	0.6443	0.9471	Same week
Sweden	ILI	0.7733	0.5451	0.8704	11 weeks before
Switzerland	ILI	0.8501	0.7800	0.8783	2 weeks before
Bulgaria	ARI	0.8377	0.6263	0.7260	1 week after
Germany	ARI	0.9396	0.7370	0.9029	1 week before
Russian Federation	ARI	0.8479	0.8149	0.6899	1 week before
Ukraine	ARI	0.8144	0.7875	0.5275	Same week

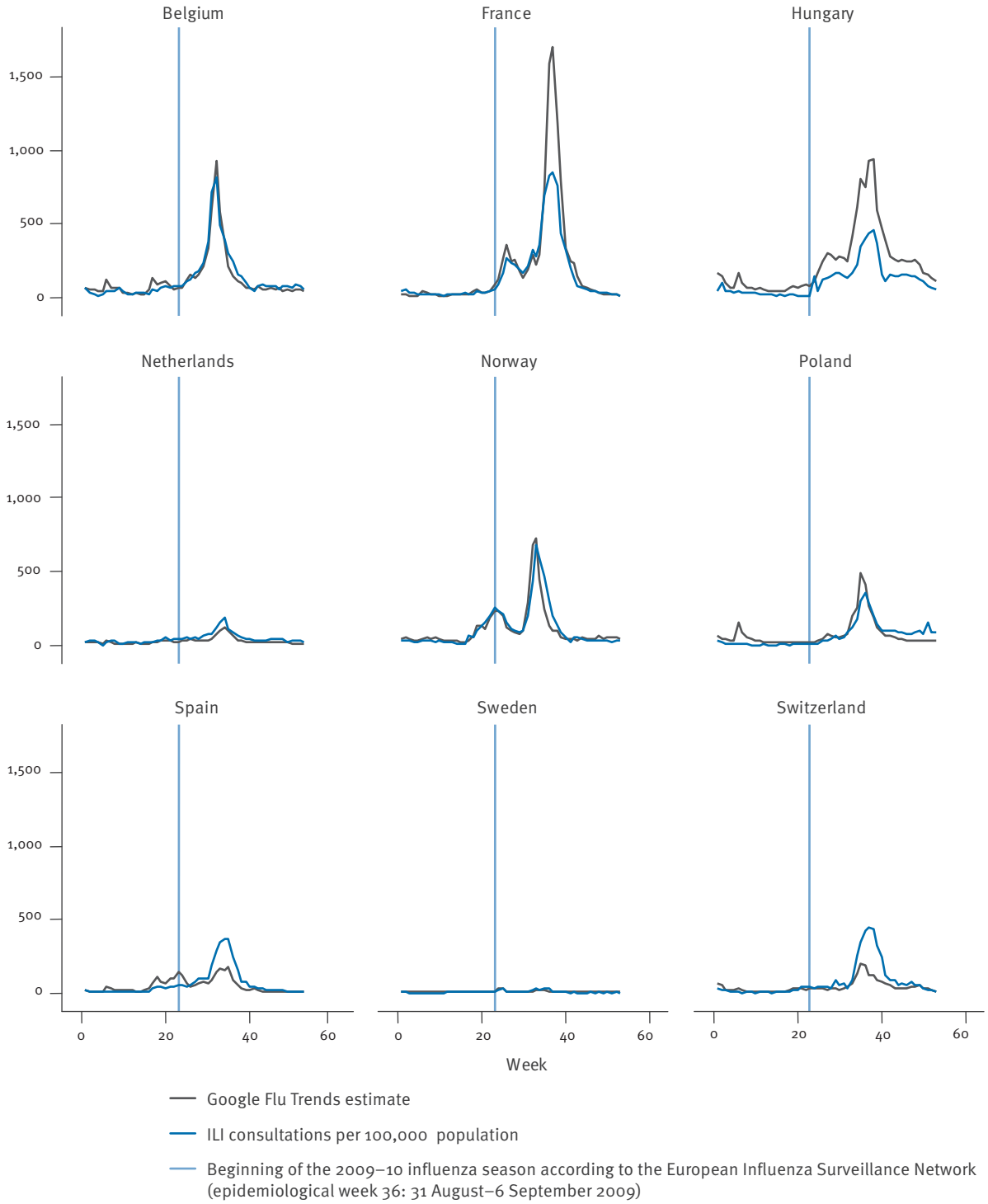
[a] 53 epidemiological weeks: 23 March 2009–28 March 2010.
[b] 23 epidemiological weeks: 23 March 2009–30 August 2009.
[c] 30 epidemiological weeks: 31 August 2009–28 March 2010.
GFT: Google Flu Trends.
SPN: Sentinel Physician Network.

in the US [9], with which the present results are in general agreement. To our knowledge, data from search queries in Google have also been correlated with SPN estimates for chickenpox [16,17] and gastroenteritis [16], showing a similar or higher correlation than ILI.

We made a division into pre-influenza season and influenza season because in the pre-influenza season Internet interest in influenza is likely to be driven mostly by the global interest in a possible pandemic, which may be unusually high and not related with a real increase in the incidence rate of influenza. According to this hypothesis, the correlation observed in the present work was weaker in the period before 31 August than after this date. This might also be related to a lack of incidence data for the summer. The

Figure 1

Weekly influenza-like illness consultations per 100,000 population compared to *Google Flu Trends* estimates of influenza incidence in nine European countries, 23 March 2009–28 March 2010

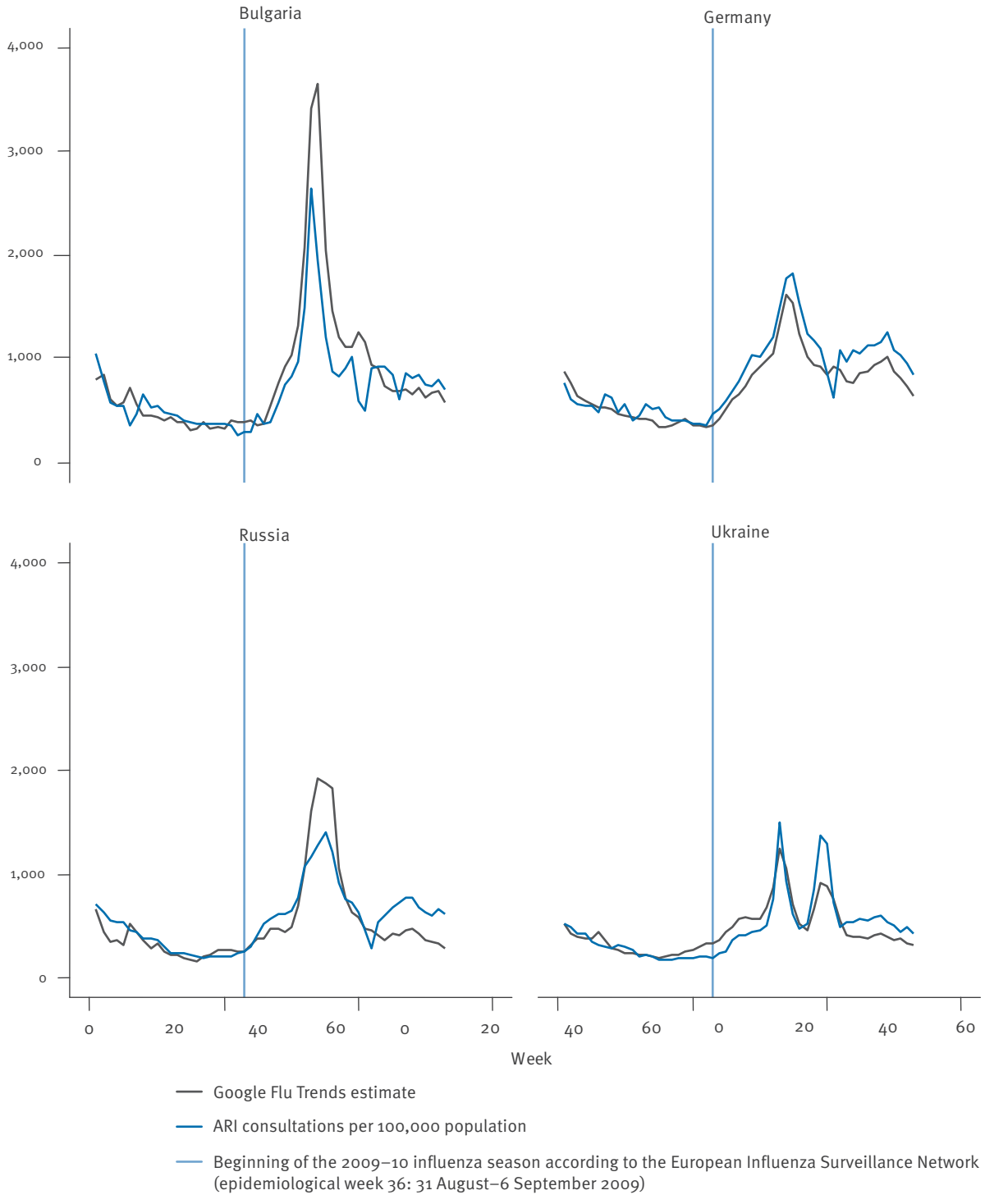


ILI: influenza-like illness.

GFT model is known to provide more robust estimates when incidence rates are higher [4,6]. Nonetheless, in agreement with that indicated by Ginsberg *et al.* [4], the present GFT incidence results were not unduly affected by large numbers of searches for information made before 31 August, i.e. when true influenza incidence was low, probably for the method used by GFT [4]. Google engineers designed an algorithm that detects the search terms most related with ILI, testing the regional variation of Google queries against the regional variations in SPN ILI data. The search fractions for these queries are pooled together in a single search fraction for each week that is used to fit a linear model using the log-odds of an ILI physician visit and the log-odds of an ILI-related search query. The number of top-scoring queries to be pooled together is optimised at estimating out-of-sample points during cross-validation [4]. The Internet Protocol address is used to

Figure 2

Weekly acute respiratory illness consultations per 100,000 population compared to *Google Flu Trends* estimates of influenza incidence in four European countries, 23 March 2009–28 March 2010



ARI: acute respiratory illness.

identify the countries that generate the queries, thus allowing the application of the general method to generate estimates for each single country. This method avoids overfitting using a single explanatory variable and makes the model resilient to variations in only few terms. For instance, at the beginning of the pandemic, there was a massive peak in the search fraction for the term 'influenza' translated in the official languages of each country. This was observed throughout Europe, nonetheless the GFT estimates did not change and continued to be related with the SPN estimates. The only exceptions to this were seen in Belgium, Hungary and Poland (Figure 1).

We used a non-parametric test for the statistical comparison between GFT and SPN estimates. This approach loses information and largely ignores time, but was preferred due to the distribution of the GFT and SPN estimates, significantly different from normal for almost all countries (skewness and kurtosis test, $p<0.05$). In addition, the period considered was too short to justify a multivariate time series approach (e.g. Poisson or binomial negative regression). Thus, we preferred a mixed statistical and graphical approach.

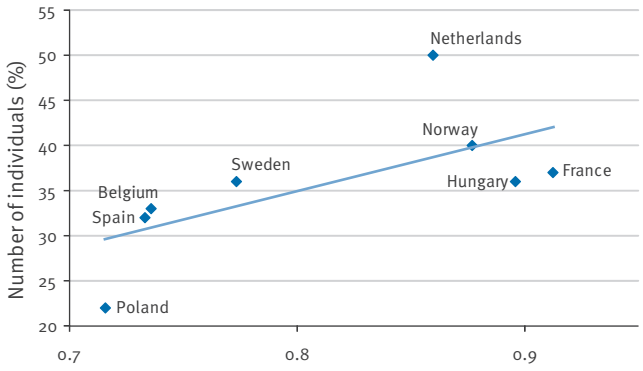
Although the GFT and SPN disease incidence peaks generally coincided or differed by 1-2 weeks (GFT providing an earlier peak in such cases), the GFT peak estimate for Sweden preceded the ILI peak by 11 weeks. This could be related with the sentinel network scheme of Sweden, that presents a lower probability of symptomatic patients to contact a sentinel physician, making ILI estimates less valuable than those from other countries. Large differences were seen in the height of the peaks recorded by each system in France, Switzerland, Hungary and Spain. In addition, in Spain, discrepancies in terms of incidence magnitude appeared during the summer months. This was also reported in the US study, for which correction was made using an autoregression method [9]. This allowed much more robust estimates to be made without losing the capacity to release information one or two weeks before the official CDC reports [9]. The same type of correction might be useful when dealing with European data, in which discrepancies might be the result of different national pandemic control policies or the characteristics of national health and SPN systems. This timely information could be valuable to allocate resources in advance of an epidemic peak, allowing an effective response to sudden changes in the incidence of influenza.

When describing the GFT model, Ginsberg *et al.* [4] indicated that it might be used with good results in any country with a large population of Internet users whose members make regular web searches. The association observed in the present work between the proportion of the population making health-based Internet searches and the strength of the GFT/SPN correlation is in line with the results according to which the strongest GFT/SPN correlations were found in countries where the Internet is more often used as a source for seeking health information. The selected indicator of Internet use in each country (proportion of population that sought health information via the Internet in 2009) describes the health-oriented search habits better than other indirect indicators frequently used (e.g. proportion of households with Internet access, or Internet use at work). The sample (general population of each country) and the period selected (yearly data about Internet use) are representative of the behaviour of European population in the year 2009, and probably highly correlated with the influenza-related searching behaviour during the pandemic.

In conclusion, when disease incidence was high, estimates of the latter based on the GFT model were very similar to those based on SPN data. The GFT model appears robust and could help in epidemiological surveillance by providing more rapid estimates of incidence, i.e. before publication is possible using conventional methods. GFT estimates could well improve in the coming years as actual observations are used to fine-tune the model, and as the use of Internet for finding health information increases. Although the GFT model cannot replace conventional surveillance methods like virological surveillance schemes [5], it may certainly be able to complement them.

Figure 3

Individuals who searched the Internet for health-related information plotted against the correlation between the sentinel physician network/*Google Flu Trends* results, in eight European countries, 23 March 2009–28 March 2010



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The influenza A(H5N1) epidemic at six and a half years: 500 notified human cases and more to come

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Since November 2003, the epidemic intelligence team at the French Institut de Veille Sanitaire has been gathering data on influenza A(H5N1) circulation in poultry and on human cases worldwide. As Indonesia notifies the world's 500th case to the World Health Organization, we discuss the epidemiological situation and trends of A(H5N1) influenza. Although the overall number of cases reported worldwide has decreased, influenza A(H5N1) continues to circulate intensely in some countries and more cases are to be expected, especially in Egypt and Indonesia.

The international and tropical department of the Institut de Veille Sanitaire (InVS) conducts constant monitoring of health events worldwide to provide French health authorities with timely forewarning of public health events of international concern. This process, known as epidemic intelligence (EI), has been described elsewhere [1]. Although topics vary widely, the situation of highly pathogenic influenza A(H5N1) influenza in the world has constantly been monitored since 2003. This paper describes the epidemiological situation six and a half years into the epidemic, as Indonesian authorities notify the world's 500th case since November 2003 [2].

Epizootic

From the end of 2003 to 1 July 2010, 63 countries or territories on the Asian, African or European continents (incl. 15 European Union countries) have notified infections by influenza A(H5N1) virus in poultry or wild birds to the World Organization for Animal Health (OIE) [3]. In 2009, a total of nine countries notified outbreaks in poultry or were considered enzootic by OIE: Bangladesh, Cambodia, China (Tibet and Xinjiang), Egypt, India, Indonesia, Laos, Nepal (first notification) and Vietnam. Six other countries or territories notified cases in wild birds only: China (Qinghai and Hong Kong SAR), Germany, Mongolia and the Russian Federation (Moscow Oblast and Republic of Tyva). In 2010, twelve countries have been affected to date: Bangladesh, Bhutan (for the first time), Cambodia, Egypt, India, Indonesia, Israel, Laos, Myanmar, Nepal, Romania and Vietnam. Furthermore, in 2010, cases were reported in wild birds only by animal health authorities in Bulgaria, China (Tibet and Hong Kong SAR), Mongolia and the Russian Federation (Republic of Tyva). Many other countries, notably in sub-Saharan Africa, have suspected transmission in predominantly backyard flocks, but lack surveillance systems to document it. Table 1 summarises the circulation of the virus in animals in those countries with documented human cases, as assessed by the EI team.

Since 2003, cases of influenza A(H5N1) virus infection have also been occasionally documented in wild (felines, ferrets etc.) or domestic mammals (cats and dogs). No secondary transmission to humans, however, has been described following contacts with animals other than poultry or wild birds.

Wild aquatic fowl constitute the animal reservoir and have occasionally reintroduced influenza A(H5N1) – in European countries along the Danube or in Vietnam for example – leading to sporadic outbreaks in poultry flocks despite previous and successful elimination efforts.

Human epidemic

From 1 November 2003 to 1 July 2010 (by date of symptom onset), a total of 500 confirmed human cases of influenza A(H5N1) including 296 deaths (case fatality rate (CFR) 59%) were notified to the World Health Organization (WHO) by 15 countries [4] (Table 1 and Figure 1).

From 1 January to 1 July 2010, 32 confirmed human cases including 14 deaths (CFR 44%) were notified by seven countries (Tables 1 and 2, Figure 2). During the same period in 2009, 41 confirmed human cases including 12 deaths (CFR 29%) were notified by China, Egypt and Vietnam (Figure 1). Indonesia also reported 18 cases during that period, although data on deaths by date are not available. In 2009, a total of 73 confirmed human cases including 32 deaths (CFR 44%) were notified by these four countries plus Cambodia (Table 1). Five countries, which had notified cases in preceding years,

have notified no new cases since 2006: Azerbaijan, Djibouti, Iraq, Thailand and Turkey. Three additional countries (Laos, Myanmar and Pakistan) have not notified any case since 2007.

Since November 2003, reported human cases seem to follow an overall downward trend and occur mostly during the period from November to April (Figure 1). This variation is due to seasonal patterns described also in poultry [5,6] in the countries which were mainly affected in the northern hemisphere, especially Egypt, Thailand and Vietnam. In Indonesia, however, cases tend to occur throughout the year.

Since the end of 2003, most (366 of 500; 73%) notified human cases of influenza A(H5N1) occurred in

Table 1

Schematic representation of animal outbreaks (colour) and human cases (figures) in 15 countries which notified human cases to the World Health Organization, by date of onset, 1 November 2003- 1 July 2010 (n=500 human cases)

Country / Year	Nov 2003– Dec 2005	2006	2007	2008	2009	To 1 July 2010	Total
Azerbaijan	0	8	0	0	0	0	**8**
Bangladesh	0	0	0	1	0	0	**1**
Cambodia	4	2	1	1	1	1	**10**
China	9	13	5	4	7	1	**39**
Djibouti	0	1	0	0	0	0	**1**
Egypt	0	18	25	8	39	19	**109**
Indonesia	20	55	42	24	21	4	**166**
Iraq	0	3	0	0	0	0	**3**
Laos	0	0	2	0	0	0	**2**
Myanmar	0	0	1	0	0	0	**1**
Nigeria	0	0	1	0	0	0	**1**
Pakistan	0	0	3	0	0	0	**3**
Thailand	22	3	0	0	0	0	**25**
Turkey	0	12	0	0	0	0	**12**
Vietnam[a]	93	0	8	6	5	7	**119**
Total	**148**	**115**	**88**	**44**	**73**	**32**	**500**

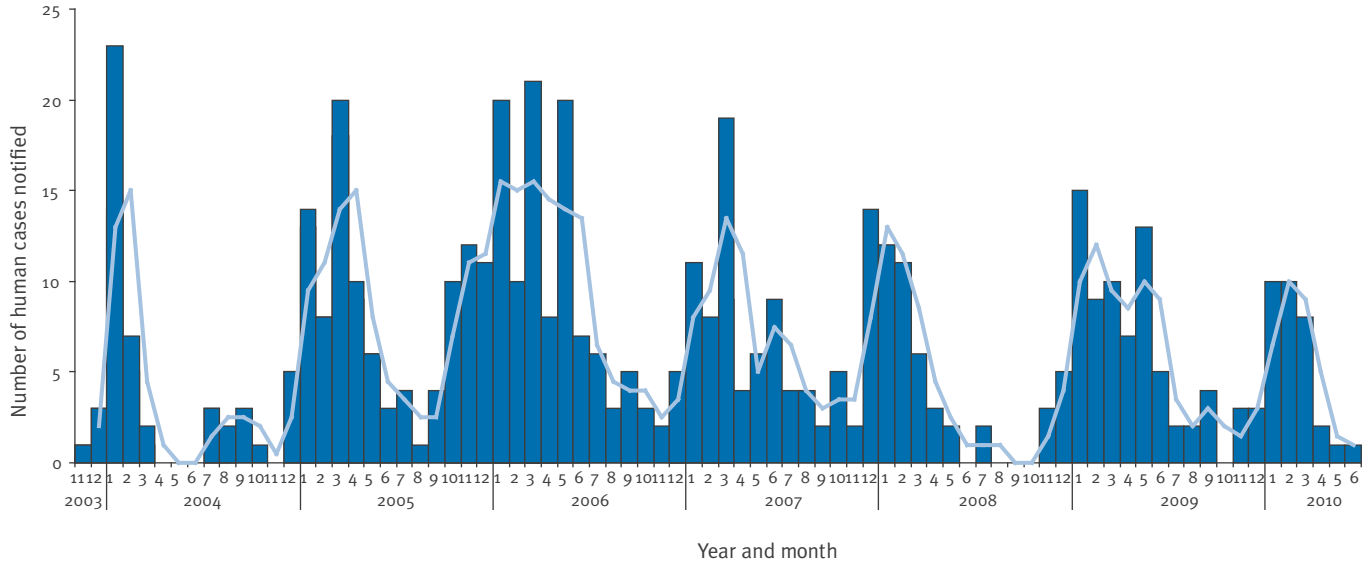
Light blue boxes: sporadic and/or seasonal outbreaks notified in poultry; grey boxes: poultry outbreaks reported throughout the year; white boxes: no avian outbreak reported.

[a]With a high degree of seasonal and geographical variation.

Source: Data collected by the epidemic intelligence team at Institut de Veille Sanitaire from postings on the websites of the World Health Organization, the World Organization for Animal Health and other authoritative national sources in the 15 countries.

Figure 1

Notified cases of human influenza A(H5N1) virus infection in the world, 1 November 2003–1 July 2010, by month and date of symptom onset with moving average over two preceding months (n=500)



Source: Data collected by the epidemic intelligence team at Institut de Veille Sanitaire from postings on the websites of the World Health Organization and other authoritative national sources in the 15 countries.

Table 2

Human A(H5N1) influenza cases and deaths notified to the World Health Organization, 1 November 2003–1 July 2010, by world zone and date of symptom onset (n=500)

	Nov 2003-Dec 2005	2006	2007	2008	2009	To 1 July 2010	
Number of cases by world zone[a]							**Total**
Africa	0	1	1	0	0	0	**2**
Asia	148	73	62	36	34	13	**366**
Near East	0	41	25	8	39	19	**132**
World total cases	148	115	88	44	73	32	**500**
Proportion of world cases for selected countries							**Average**
Indonesia	14%	48%	48%	55%	29%	13%	**33%**
Vietnam	63%	0%	9%	14%	7%	22%	**24%**
Egypt	0%	16%	28%	18%	53%	59%	**22%**
N deaths by world zone[a]							**Total**
Africa	0	0	1	0	0	0	**1**
Asia	79	58	49	29	28	7	**250**
Near East	0	21	9	4	4	7	**45**
World total deaths	79	79	59	33	32	14	**296**
Case-fatality rates in selected countries (%)							**Average**
Indonesia	65%	82%	88%	83%	90%	75%	**83%**
Vietnam	45%	NA	63%	83%	100%	29%	**50%**
Egypt	NA	56%	36%	50%	10%	37%	**31%**

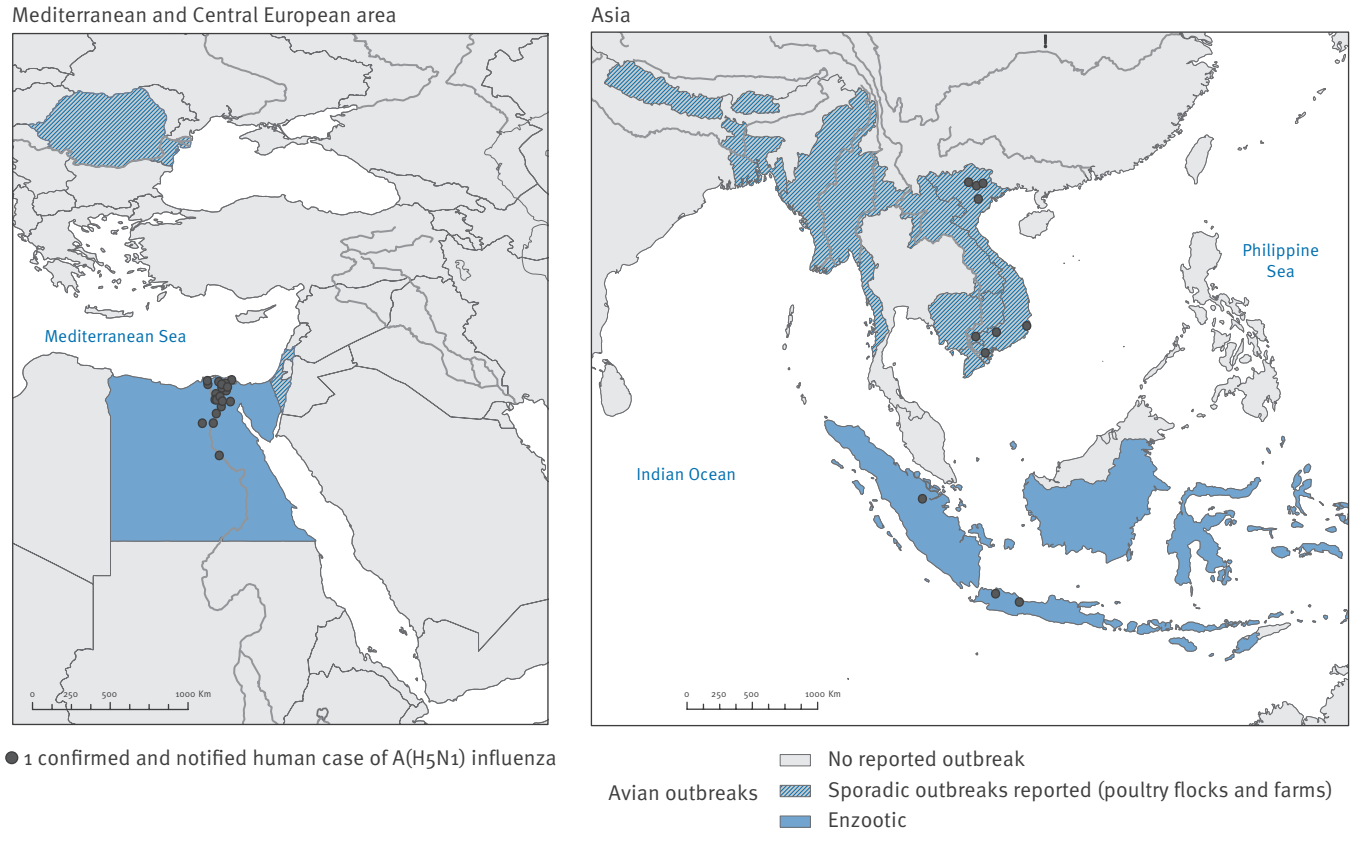
NA: Not applicable.

[a] Africa: Djibouti, Nigeria; Asia: Bangladesh, Cambodia, China, Indonesia, Laos, Myanmar, Pakistan, Thailand, Vietnam; Near East: Azerbaijan, Egypt, Iraq, Turkey.

Source: Data collected by the epidemic intelligence team at Institut de Veille Sanitaire from postings on the websites of the World Health Organization and other authoritative national sources in the 15 countries.

Figure 2

A(H5N1) avian influenza in animals and humans (by date of onset) in affected countries, 1 January–1 July 2010



Source: Data collected by the epidemic intelligence team at Institut de Veille Sanitaire from postings on the websites of the World Health Organization and other authoritative national sources in the 15 countries.

Asia, notably in Indonesia, China and Vietnam (Table 1). Since the start of the epidemic, Indonesia remains the most affected country (33% of cases and 46% of deaths notified worldwide). Indonesia notified 21 cases including 19 deaths (CFR 90%) in 2009 and four cases including three deaths (CFR 75%) in 2010 up to 1 July.

The number of cases has fallen in Asia while it has progressively increased in the Near East (Azerbaijan, Egypt, Iraq and Turkey). Between November 2003 and December 2005, 100% of notified cases occurred in Asia (Table 2). In 2006 and 2007, the annual proportion of cases notified by Asian countries remained somewhat stable at 63% and 70%, respectively. From January 2008 to 1 July 2010, 83 (56%) of 149 notified cases occurred in Asia, the remaining 66 cases worldwide were notified by Egypt (Tables 1 and 2). The percentage of cases notified by Egypt has risen steadily from 18% of worldwide cases in 2008, to 53% in 2009, to 59% of worldwide cases notified to date for 2010.

Changes in the H5 haemagglutinin have determined a phylogeny with clades and sub-clades. Clade 2.2.1 viruses circulate in poultry in Egypt while clade 2.3.2 and 2.3.4 viruses circulate in Asia [7]. There is no conclusive evidence for differences in virulence or resistance to oseltamivir among these viruses. The health outcomes for humans infected with these viruses can be explained by differences in the timeliness and type of medical management and drug treatment.

The overwhelming majority of cases with documented exposure acquired the influenza A(H5N1) virus from sick or dead poultry or wild birds. Many cases lack documented exposure while for some, although this was never definitively proven, there is a strong suspicion of involving environmental sources or human-to-human transmission.

Clustered cases and human-to-human transmission

Since 2003, there have been at least 40 clustered events involving a total of over 100 confirmed cases in 12 countries: Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Laos, Nigeria, Pakistan, Thailand, Turkey and Vietnam. Overwhelmingly, the suspected or documented source was common exposure to sick or dead poultry, although investigation concluded that limited human-to-human transmission occurred in some instances: Most of these clusters involved persons with close familial ties [8]. Although its relevance remains debated [9], at least some degree of genetic susceptibility probably plays a role, as shown by events such as the three-generation transmission cluster described in 2006 in the Karo district [10] or the family clusters described in Turkey [11]. These clusters of limited human-to-human transmission occurred after people had close and repeated contact with cases and did not fully observe standard precautions to prevent infection [12]. Cases of nosocomial influenza A(H5N1) transmission had been described in Hong Kong hospitals in 1997 [13]. Since 2003, however, no confirmed influenza A(H5N1) transmission in the healthcare setting has been documented in studies done to date [14].

Quality of available information

Human case detection and reporting largely depends on the availability and intensity of reliable diagnostic efforts. The global influenza A(H5N1) case count probably vastly underrepresents the true case burden worldwide. Since December 2009, Indonesian health authorities have resumed their collaboration with WHO and notify cases officially. Since January 2009, 25 cases and 22 deaths (CFR 88%) have been notified from the Indonesian archipelago. With the exception of a single case documented in Riau Province (central Sumatra), all notified cases lived on the island of Java. This geographical distribution and the comparatively high CFR suggests that access to diagnosis may be uneven, that severe cases are overrepresented among detected cases and/or that timely clinical management remains a challenge. In China, human cases continue to be reported with no prior notification of influenza A(H5N1) circulation in poultry, pointing to the probable underdetection or underreporting of poultry outbreaks in that country. In an area such as upper Egypt, access to timely diagnosis and care is associated with lower CFR, but suspected human cases occurring in remote locations may not all be officially detected and/or reported and would have contributed to a higher CFR.

Conclusions

All these elements seem to converge and sketch out the following situation: some countries which were heavily affected before 2007 (such as Thailand and Turkey) seem to have controlled the situation and reduced risks to humans. The influenza A(H5N1) virus, however, continues to circulate in poultry elsewhere, especially in Bangladesh, Egypt and Indonesia where the enzootic remains intense. The A(H5N1) influenza virus is one of several which could hypothetically give rise to a pandemic in the future [15]. Although this risk cannot be quantified, poultry outbreaks and human cases now, in contrast to the period from 2003 to 2004, occur in some of the most densely populated urban or suburban areas in the world. Not only might this increase the risk of the virus being transmitted to humans living in close proximity to animals, it may also challenge usual control measures (which are easier to apply to large farms than for instance backyard flocks) and make it more difficult to contain a nascent influenza A(H5N1) pandemic should one arise [16].

Human cases continue and will continue to occur as long as the situation in animals is not brought under control. Authorities and populations face a complex situation in Egypt and Indonesia, but communication in these countries is transparent and constructive and allows for quick reporting of cases, especially if suspected clusters should arise. Although the global CFR reported in 2009 was lower than that observed in 2008,

it varies greatly between countries. Some countries report a greater number of cases and fewer deaths, perhaps due to improved surveillance and access to diagnostic techniques and medical care [17,18]. However, cases occurring in remote locations with no access to healthcare, although having a higher CFR, may still not come to the attention of health authorities or be reported for lack of biological confirmation.

Many clustered events have occurred, some of which are highly likely to have involved human-to-human transmission. To date, this has remained limited with no sustained community transmission. Available data, especially those gathered following clustered events, show that so far the virus shows no sign of 'humanisation', i.e. the ability to transmit easily from human to human. The overall worldwide situation of influenza A(H5N1), however, has not markedly improved since 2003. This fact, and regular reintroduction of the virus by wild birds in countries where foci have been controlled (such as Bulgaria, Romania, Turkey or Vietnam) underscore the importance of maintaining adequate surveillance and response capacities for infections in both animals and humans.

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Alarming spread of vancomycin resistant enterococci in Sweden since 2007

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The total number of persons infected or colonised with vancomycin-resistant enterococci mandatorily reported to the Swedish Institute for Infectious Disease Control increased dramatically during 2007 and 2008. During a period of twenty months from 1 July 2007 to 28 February 2009, a total of 760 cases were reported compared with 194 cases reported during the entire period from 2000 to 2006. This rise was mainly attributed to a wide dissemination of vancomycin resistant enterococci which started in a number of hospitals in Stockholm in the autumn of 2007 and was followed by dissemination in various healthcare facilities (hospitals and homes for the elderly) in a further two Swedish counties in 2008. The majority of the cases (97%) were acquired in Sweden and among these, healthcare-acquired *E. faecium vanB* dominated (n=634). The majority of these isolates had identical or closely related pulsed-field gel electrophoresis patterns indicating clonal dissemination in the affected counties. The median minimum inhibitory concentration of vancomycin was 32 mg/L (ranging from 4 to >128 mg/L) and of teichoplanin 0.12 mg/L (ranging from 0.06 to 0.25 mg/L). Particular emphasis was placed on countermeasures such as screening, contact tracing, cleaning procedures, education in accurate use of infection control practices as well as increasing awareness of hygiene among patients and visitors. With these measures the dissemination rate decreased substantially, but new infections with the *E. faecium vanB* strain were still detected.

Introduction

Enterococci may acquire various types of glycopeptide antibiotic resistance via *van*-associated genetic elements (*vanA/B/D/E/G/L*), of which *vanA* and *vanB* are the most prevalent in clinically relevant species [1,2]. Although vancomycin-resistant enterococci are seldom encountered in serious clinical infections, they occasionally cause invasive infections notably in immunocompromised hosts. Some of these infections, particularly those caused by *Enterococcus faecium*, are often difficult to treat since only few antimicrobial treatment options are available. Vancomycin-resistant *E. faecium* and *E. faecalis* (referred to as VRE throughout this paper) became mandatorily notifiable according to the Swedish Communicable Diseases Act in January 2000, and in 2004 an amendment concerning mandatory contact tracing was added.

According to studies performed in the late 1990s the prevalence of VRE in Sweden was low in the community and in healthcare facilities [3,4] and remained so until the year 2006 with no more than 0.2-0.4 cases per 100,000 inhabitants and year [5]. Only a few minor healthcare -related outbreaks involving less than 20 patients each occurred during that period [6,7]. The prevalence of VRE among invasive *E. faecium* blood isolates in Sweden as reported to the European antimicrobial resistance surveillance system (EARSS; data representing more than 75% of the population) was generally less than 1% for most of the period from 2001 to 2006 [8]. This prevalence is clearly lower than reported from some other European countries [8,9].

In the autumn of 2007, there was a distinct increase in the number of persons infected or colonised with VRE as reported from various hospitals in Stockholm County. During 2008, this increase was also noted in two other counties, Västmanland and Halland, and the total number of reports increased more than 10-fold between 2007 and 2008, showing little or no tendency to decrease during the first months of 2009. The aim of this study was to describe the epidemiology of the dissemination of VRE in the affected counties.

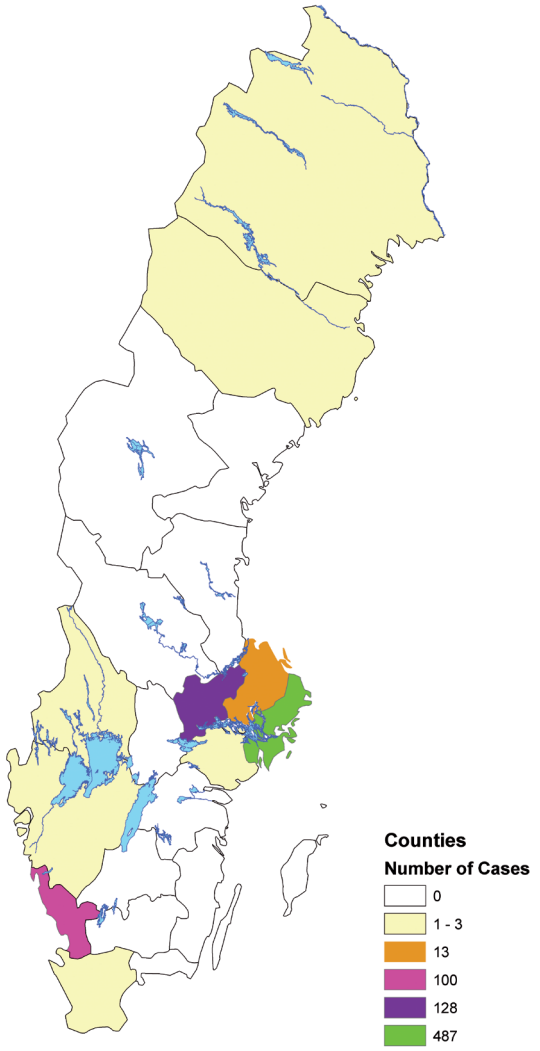
Methods

National surveillance system for vancomycin-resistant enterococci

In Sweden, contact tracing is performed whenever VRE is detected in a clinical sample. Furthermore, screening for VRE is recommended in all patients who have recently received any medical treatment abroad. A case of VRE is defined as a person with a clinical VRE infection or a person colonised with VRE.

Figure 1

County distribution of domestic cases with vancomycin-resistant enterococci, Sweden, 1 July 2007–28 February 2009 (n=738)



Green: Stockholm County; purple: Västmanland County; pink: Halland County; orange: Uppsala County.

Table

Distribution of genotype for domestic cases with *Enterococcus faecium*, Sweden, 1 July 2007–28 February 2009 (n=738)

County	Number of cases	*E. faecium vanA*	*E. faecium vanB*	Incidence 2008[a]
Stockholm	487	98	387	20.9
Västmanland	128	2	126	33.2
Halland	100	-	100	29.3
Other (n=7)	23	-	21	0.06 - 4.0
Total	**738**	**100**	**634**	

VRE: vancomycin-resistant *E. faecium* and *E. faecalis*.

[a] Number of domestic VRE cases per 100,000 inhabitants in the year 2008.

All cases of VRE are mandatorily reported via the national internet-based reporting system SmiNet2 [10]. Case reports are created in this system combining information from the laboratory notification on species and *van* gene with the clinical notification from the treating physician which contains epidemiological information on country of acquisition, route of transmission and reason for sampling. The descriptive epidemiology of the cases presented in this report is based on data from SmiNet2 covering the period from 1 July 2007 to 28 February 2009. The primary information from the clinical notifications was reviewed and complemented with additional information collected during our investigation in collaboration with the County Departments of Communicable Disease Control, infection control teams and the regional clinical microbiological laboratories.

Identification and susceptibility testing of vancomycin-resistant enterococci

A preliminary diagnosis of VRE in a clinical sample is based on standard methods for culture, species identification and susceptibility testing. Guidelines for susceptibility testing are provided by the Swedish Reference Group for Antibiotics and are followed by the clinical laboratories [11]. It is recommended that all enterococci are tested for susceptibility to vancomycin and that results are reported back to the clinician for treatment guidance. The preliminary diagnosis of VRE is subsequently verified using genotypic (PCR-based) methods identifying the *van* genes [12]. Phenotypic detection of vancomycin-resistant *E. faecium* or *E. faecalis*, combined with detection of genetic resistance markers in the isolate constitutes the Swedish case definition for notifiable VRE infections and colonisations.

Contact tracing and screening are done by sampling from faeces and, if applicable, from insertion sites of indwelling catheters and catheter urine, and sometimes also from apparent infection sites on skin and soft tissue. The samples are cultured over night in broth containing vancomycin 4 mg/ L [13], followed by detection through phenotypic or genotypic (PCR-based) methods. Before 2009 some Swedish laboratories used selective broth containing higher vancomycin concentrations 32 mg/L, designed for detection of enterococci with the *vanA* gene.

During the present investigation, all VRE isolates (with the exception of the majority of isolates from Stockholm County) were submitted to the Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet, SMI) for genetic confirmation of *van* genes and species-specific *ddl* genes [12]. VRE isolates from Stockholm were investigated using identical methods at the Department of Clinical Microbiology and Infection

Control, Huddinge, and representative isolates were also analysed at SMI.

Epidemiological typing

Epidemiological typing was performed using pulsed-field gel electrophoresis (PFGE). Mapping of *Sma*I-digested DNA was performed according to standard procedures for PFGE [14], using the CHEF Mapper XA system (Bio-Rad Laboratories) set at 6 V/cm. PFGE patterns, comprising bands within the size range 48–400 kb, were analysed and compared using BioNumerics software (version 5.01, Applied Maths). The Dice coefficient was used for pair-wise comparisons of patterns, and the unweighted pair group method with arithmetic mean (UPGMA) for pattern groupings. Position tolerance and optimisation were both set at 1%. PFGE band patterns were defined as identical (100% pair-wise Dice similarity), closely related (›90% pair-wise Dice similarity) or unrelated (‹ 90% pair-wise Dice similarity).

Results

During the period from 1 July 2007 to 28 February 2009, a total of 760 VRE cases were reported nationally via SmiNet2 from 13 of 21 Swedish counties, including 493 from Stockholm, 128 from Västmanland and 100 from Halland. The majority of the persons (n=738, 97.1%) had acquired VRE in Sweden. These 738 domestic cases were notified from 10 counties, and *E. faecium vanB* was the most commonly reported strain (n=634, 85.9%). (Figure 1 and Table).

Of the 634 *E. faecium vanB* cases reported, 610 (96%) were healthcare-related. The epidemic curve for these 610 healthcare-related cases is shown in Figure 2. Spread of *E. faecium vanB* was reported in several hospitals in the affected counties as well as homes for the elderly. The mean age of the 610 domestic healthcare-related cases with *E. faecium vanB* was 72 years for females (range 1-98 years, n=291) and 68 years for males (range 22-96 years, n=319).

Reason for sampling and site of isolation

Of the 610 healthcare-related domestic *E. faecium vanB* cases reported, 52 (8.5%), had clinical infections and 494 were colonised. Of these 494, 410 (67%) were identified through contact tracing and 84 (14%) through screening. In 64 (10.5%) of the 610 cases there were miscellaneous, or unknown, reasons for sampling.

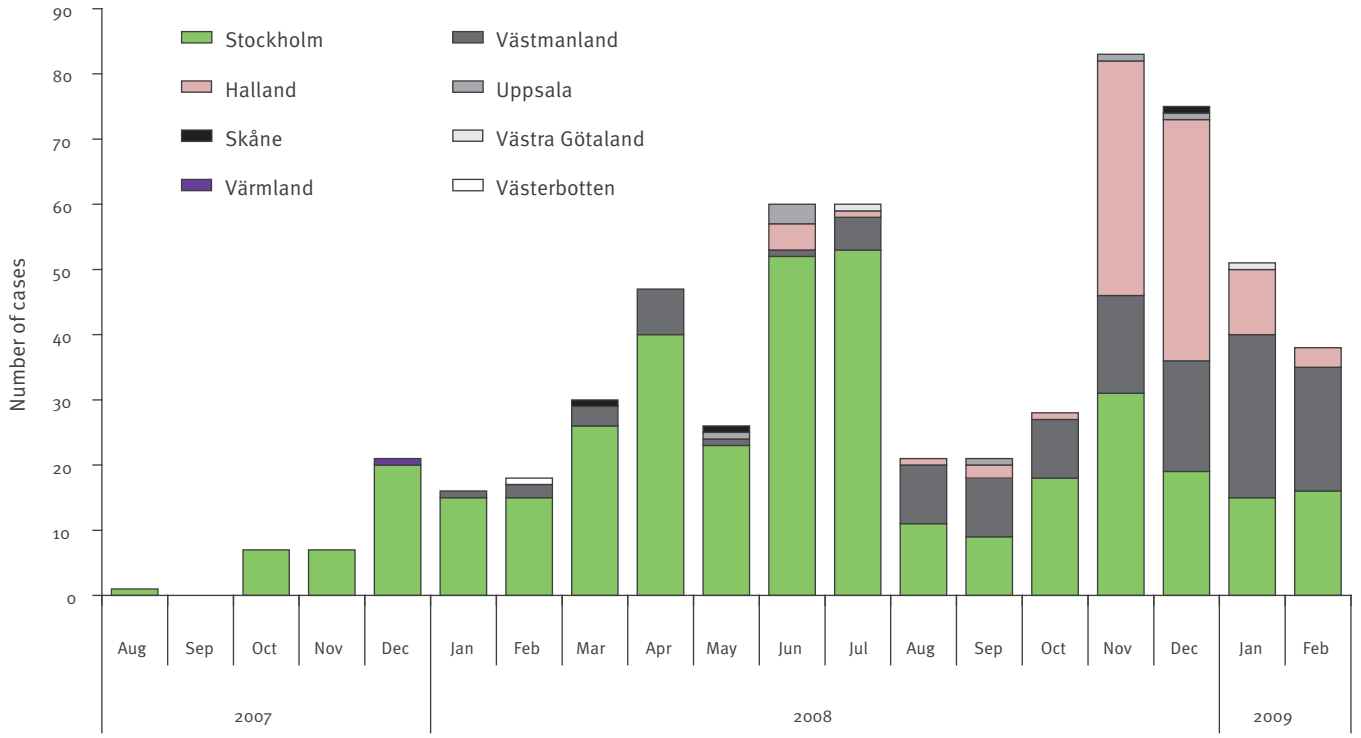
According to the first laboratory notifications for each case, the majority of VRE (85%) were isolated from faecal samples, and 5% each from wound and urine samples. The remaining 5% were collected from various other sampling sites. Blood-stream infections caused by VRE were reported for 15 cases during the period from 1 July 2007 to 28 February 2009.

Clonal dissemination of *E. faecium vanB*

All examined isolates (n=226) of *E. faecium vanB* from the counties of Västmanland and Halland and 93% of the isolates from Stockholm County gathered during the study period, had identical or closely related PFGE patterns indicating a clonal dissemination (Figure 3). Ten isolates of this *E. faecium vanB* were identified as the cause of invasive bloodstream infections. The isolates had a MIC of vancomycin ranging from 4 mg/L to

Figure 2

Domestic healthcare-related cases with *E. faecium vanB*, Sweden, 1 July 2007–28 February 2009 (n=610)



>128 mg/L (median value: 32 mg/L, with 80% of the isolates in the range 16–64 mg/L) and a median MIC for teichoplanin of 0.125 mg/L (range: 0.064–0.25 mg/L). The isolates were resistant to ampicillin, ciprofloxacin and macrolides and exhibited low-level resistance to gentamicin. Susceptibility testing for linezolid, tigecycline, daptomycin and quinupristin/dalfopristin was performed on a few of the isolates. However, resistance to linezolid and tigecycline was never recorded, while varying susceptibility profiles were recorded for the other two compounds.

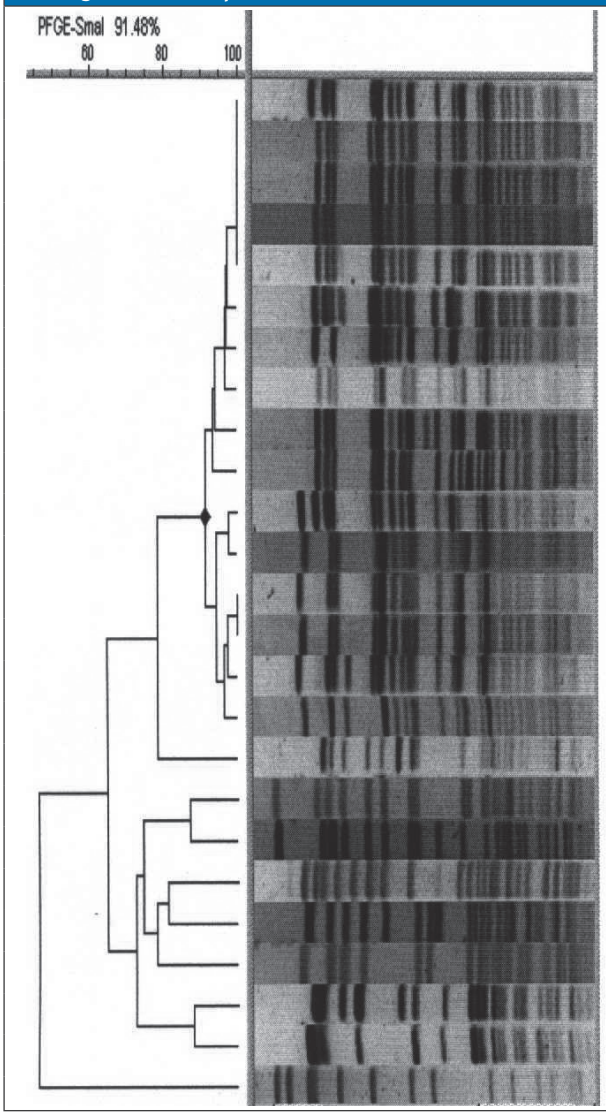
Discussion and conclusion

Our report describes a current strong increase in mandatorily reported cases of VRE in healthcare facilities in three geographically separate regions of Sweden, i.e. the counties of Stockholm, Västmanland and Halland. This increase was largely characterised by clonal dissemination of an *E. faecium vanB* strain as revealed by contact tracing and screening performed in connection with VRE infections detected in healthcare facilities in these counties. The cause of the dissemination is unknown, and no major changes in the general hospital infection control policies such as changes of nurses per bed ratios or antibiotic policies had been introduced that could explain the increased VRE prevalence.

The three counties accounted for the majority of all domestic cases of VRE reported to the SMI during a period of 20 months from July 2007 to February 2009.

Figure 3

PFGE patterns of *Enterococcus faecium* with *vanB* gene isolated in Sweden, 1 July 2007–28 February 2009



Lane	Year of isolation	Swedish county
1	2007	Stockholm
2	2007	Stockholm
3	2008	Västmanland
4	2008	Västmanland
5	2008	Västmanland
6	2007	Stockholm
7	2007	Stockholm
8	2008	Uppsala
9	2008	Västmanland
10	2008	Västmanland
11	2007	Stockholm
12	2008	Halland
13	2008	Halland
14	2008	Halland
15	2008	Halland
16	2008	Halland
17	1997	Västra Götaland
18	1997	Västerbotten
19	2001	Stockholm
20	2002	Stockholm
21	2003	Stockholm
22	2004	Örebro
23	2004	Skåne
24	2004	Skåne
25	Normalisation standard	

PFGE: pulsed-field gel electrophoresis.
Lanes 1–16 show the closely related band patterns (91.5% pair-wise Dice similarity as indicated by ◊ in the dendrogram) of representative isolates of the current *E. faecium vanB* strain from Stockholm County (green), Västmanland County (purple) and Halland County (pink), including one isolate from Uppsala County. Lanes 17–24 show band patterns of representative isolates from various minor healthcare-related disseminations of vancomycin-resistant enterococci in Sweden 1997–2004. In lane 25 is the normalisation standard from *Staphylococcus aureus* NCTC 8325.

Despite the marked geographical separation between these counties, the *E. faecium vanB* isolates were apparently genetically closely related according to the typing results of the isolates. The PFGE pattern of the current strain is seemingly new and has not been seen previously among vancomycin-resistant *E. faecium* isolates in Sweden. Moreover, when compared to PFGE-patterns of a large collection of VRE isolates in Germany, a pattern corresponding to that of this Swedish strain could not be identified (G Werner, personal communication, 2009). Investigations to find possible links to vancomycin-susceptible *E. faecium* isolates are ongoing, including MLST-typing, since such connections have been described in other outbreak situations [15].

No apparent epidemiological link between the three major affected counties has been identified. Still, some patient exchange does take place between the involved counties, hence a possible epidemiological link involving patients whose VRE-positive status was undetected cannot be excluded.

More than 80% of the healthcare-associated cases with *E. faecium vanB* were identified through contact tracing or screening, and only 9% had a clinical infection. This proportion of clinical infections versus colonisations is in accordance with that reported in a previous outbreak report in Finland [15]. During the study period, 15 of our patients were reported to have a bloodstream infection caused by VRE, ten of which had *E. faecium vanB*. This compares to a total of 19 bloodstream infections caused by VRE notified in SmiNet2 during the entire period from 2000 to 2006.

The methods used for microbiological processing of the samples obtained from contact tracing and screening for VRE were optimised during the study period (unpublished data). The reference methodology previously endorsed in Sweden, published by the Swedish Society of Medicine and SMI [16], was designed for the selective isolation and identification of the *vanA* phenotype and therefore included an enrichment broth containing 32 mg/L of vancomycin. Since MICs of vancomycin for the present *E. faecium vanB* isolates ranged between 4 mg/L and >128 mg/L, laboratories using this methodology for VRE screening might have failed to detect some of the strains belonging to the currently spreading *vanB* strain, especially in samples with low numbers of VRE. However, as the majority of the isolates (approximately 80%) had MICs ranging between 16 mg/L and 64 mg/L, it is most likely that only few isolates remained undetected due to an unsuitably high vancomycin concentration. Low sensitivity of the laboratory screening method may, however, contribute to the maintenance of undetected dissemination of moderately resistant strains. As a consequence, all Swedish microbiological laboratories have been advised since January 2009 to decrease the vancomycin concentrations in the enrichment broth to 4 mg/L.

The present situation regarding healthcare-associated dissemination of VRE urged the SMI, the Swedish Strategic Programme against antibiotic resistance (Strama) and the National Board of Health and Welfare (NBHW) to initiate a working group with representatives from the County Departments of Communicable Disease Control, infection control teams, and the regional clinical microbiological laboratories in the spring of 2008. The group organised a workshop in December 2008, in which also the National Veterinary Institute participated. They discussed the countermeasures taken so far as well as additional steps needed to stop the spreading of VRE in Swedish healthcare facilities. The workshop was followed by a national one-day educational VRE conference arranged by the SMI. In December 2008, the NBHW commissioned their Central Field Epidemiology Group (CFG) to review the outbreaks, to map the VRE-screening capacities of the microbiological laboratories during an outbreak situation and to suggest actions in order to improve the national coordination of actions to be taken in order to contain the ongoing dissemination of VRE. The report of the CFG formed the basis for a national action plan which is in preparation.

Experiences from the affected healthcare facilities demonstrated that VRE may be found at scattered places in the environment of the wards. It has also proved important to meticulously follow the local cleaning instructions to eradicate VRE from the environment. Intense educational efforts have been taken to persuade the ward personal to follow the basic infection control practices stated by Swedish law [17]. In addition, local educational efforts to increase awareness of hygiene among patients and hospital visitors have been made. Food buffets in the affected hospitals have been removed, and probiotic treatment using yoghurt supplemented with *Lactobacillus rhamnosus,* has been offered to patients in affected wards [18].

This report describes the, to date, largest known dissemination of VRE in healthcare settings in Sweden. Although occurring in geographically separate counties, the bacteria share the same PFGE pattern indicating a clonal origin. Vigorous counter measures were taken in order to prevent further local and national spreading of these bacteria. Owing to these measures the rate of new cases decreased substantially, but new cases carrying the *E. faecium vanB* strain were still detected.

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Estimation of the reproduction number for 2009 pandemic influenza A(H1N1) in the presence of imported cases

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To the editor: Paine *et al.* recently reported an estimate of the reproduction number (R) for 2009 pandemic influenza A(H1N1) in New Zealand [1]. Given that early epidemiological assessments of pandemic potential (i.e. transmission potential and severity of the disease) were limited in accuracy and precision, identifying technical pitfalls in relevant past studies is of the utmost importance. While we enjoyed reading Paine *et al.*'s contribution [1], we believe more emphasis on the estimation framework and relevant data needs is essential for improving future studies. Namely, constructing an epidemic model involving imported cases requires particular attention to the estimation of the number of secondary cases generated by a single imported case relative to the time since immigration (i.e. arrival of the imported case into the country).

Compared with an earlier study estimating R of the pandemic influenza in New Zealand [2], a new aspect of Paine *et al.*'s study [1] is the method used to account for imported cases. It should be noted, however, that an earlier study in Japan, cited in [1], did not involve any imported cases and thus did not ignore this aspect [3]. Despite the improvement reported in [1], the estimate of R obtained should not be regarded as correct or as a revised estimate, as compared with [2], for the reasons given below.

To demonstrate our concerns, we have used a renewal equation (which captures the birth process of infected individuals) to describe the time dependent increase in incidence $j(t)$ (i.e. the number of new local infections) at calendar time t. With generalisation, the modelling approach taken by Paine *et al.* [1] is identical to a classical branching process model with immigration [4], i.e.

$$j(t) = R\int_0^\infty \left[j(t-\tau)+i(t-\tau)\right]g(\tau)d\tau \qquad \text{(Equation 1)}$$

where R is the reproduction number, $i(t)$ is the number of new imported cases (incidence of imported cases) at time t and $g(\tau)$ is the probability density function of the generation time of length τ. Of course, the corresponding estimator of R is given by

$$\hat{R} = \frac{j(t)}{\int_0^\infty \left[j(t-\tau)+i(t-\tau)\right]g(\tau)d\tau} \qquad \text{(Equation 2)}$$

Direct application of Equation 2 to the epidemiology of influenza results in an underestimation of R for three reasons. Here we propose a more appropriate equation than Equation 1 to describe the observed epidemiological dynamics:

$$j(t) = R\left(\int_0^\infty j(t-\tau)g_1(\tau)d\tau + \alpha\int_0^\infty i(t-\tau)g_2(\tau)d\tau\right) \qquad \text{(Equation 3)}$$

where α is the relative contribution of imported cases to secondary transmission (as compared with local cases), $g_1(\tau)$ is the probability density function of the generation time (i.e. identical to $g(\tau)$ in Equation 1), and $g_2(\tau)$ is a truncation of the generation time distribution, i.e.

$$g_2(\tau) = \begin{cases} 0 & \text{for } \tau < \tau_0 \\ g_1(\tau) & \text{for } \tau \geq \tau_0 \end{cases} \qquad \text{(Equation 4)}$$

where τ_0 represents the time elapsed from infection of imported cases to their entry into New Zealand.

The first of our concerns is that the relative infectiousness, α, not only rescales $g_2(\tau)$ but also reflects both the intrinsic and extrinsic dynamics of imported cases (e.g. international travellers may have a smaller number of contacts than local cases and, moreover, may have been more likely to be tested than local febrile cases), which would have changed the estimate obtained in [1]. Given that the early epidemic period of interest corresponds to the containment phase, it is natural to assume that α was smaller than one. This was the case in Japan, where α = 0.15 was estimated, ignoring the difference between g_1 and g_2 [5]. If α were

zero, employing Equation 3 would have the same effect as removing imported cases from the analysis, as in [2]. Second, failing to account for Equation 4 led to an underestimation of R in [1], although an explicit estimation of $g_2(\tau)$ would require substantial epidemiological and statistical effort. Third, Paine *et al.* [1] adopted an exponential distribution for $g(\tau)$ in Equation 1, which is known to yield a smaller estimate of R compared with that from a more realistic distribution with an identical mean [6]. Although Paine *et al.* [1] emphasised the importance of imported cases and obtained a smaller R compared with the earlier study [2], none of the three key issues mentioned above were discussed. Without addressing these, the modelling approach of Paine et al. [1] could be interpreted as arbitrarily scaling down the magnitude of R.

Although we agree that the early estimate of $R = 1.96$ in New Zealand is now regarded as an overestimate, due to the observed final size of the epidemic (i.e. the proportion infected in a population by the end of first epidemic wave) and when compared with estimates of R in other countries, we believe that the underlying reasons for the overestimation have not been clarified by Paine *et al.* [1], leading to concerns about the modelling method. An important implication that can be drawn from this letter is that an explicit modelling approach to immigration requires us to know at least the times of infection and arrival of imported cases. In addition, understanding the frequency of contacts of travellers (in comparison with non-travellers) and empirically observing the number of secondary cases arising from imported cases would add great value when attempting to obtain a precise estimate of R. Critical assessment of early naive studies of pandemic potential must be based on a firm analytical understanding.

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Author's reply: Estimation of the reproduction number for 2009 pandemic influenza A(H1N1) in the presence of imported cases

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To the editor: We thank Nishiura and Roberts for their interest in our paper [1]. They raise important issues concerning the accuracy of estimates of the reproduction number (*R*) and the need for early and comprehensive data to ensure such accuracy. We agree that this is one of the main points of our article and something that needs to be addressed further in the future.

Nishiura and Roberts draw particular attention to the need to adjust estimates of *R* early in an outbreak when the imported cases are external to the susceptible population. The key issue here, as noted by Nishiura and Roberts, is the need for early and accurate assessments of *R* to aid public health policy and planning. Clearly, as we noted in our article [1], quite different conclusions can be reached through overestimating *R* early in an epidemic, without adjustment for importations when imported cases are the predominant transmitters. In their calculation of the early estimation of *R* in New Zealand [2], the authors removed the imported cases from the dataset before estimating *R*, obtaining an estimate of 1.96. This is entirely consistent with our estimate of *R* when imported cases are removed, as seen by the upper curve in Figure 3 in our paper [1] – we estimated R to be between 1.82 and 1.94 over a similar time frame of 8–14 June 2009.

We agree that the issues highlighted by Nishiura and Roberts of not truncating the generation time for imported cases and using exponentially distributed generation time both lead to underestimates of *R*. Hence our estimates when allowing for imported cases in [1] are most likely underestimates of the true *R*. Tests that we have conducted with simulated data have shown that even moderate levels of imported cases can lead to a sizeable overestimation of *R* that is larger than the effect of the underlying generation time distribution used in standard methods (unpublished data). For the New Zealand data, the overestimate of *R* by removing the imported cases was approximately 25% whereas the underestimate due to using an exponentially distributed generation time was approximately 5% when compared with a more realistic distribution such as the gamma distribution. Unfortunately, with current data collection it is rare to have accurate information that can be used to assess the truncation of the infectivity period of imported cases. This is clearly an area that needs addressing in the future.

Other issues may lead to overestimates of *R* early in an outbreak and these should also be considered when drawing conclusions from the calculations. For example, if the initial cases are in a subpopulation with an intrinsically higher *R*, for example children in Japan [3,4] or Pacific Peoples in New Zealand [1,2], then care must be taken when extrapolating *R* to whole population level.

Recent criticism of overzealous public health responses to the 2009 influenza A (H1N1) pandemic in New Zealand and elsewhere [5,6] highlights even further the need for responses that are modified to appropriately reflect the severity of newly emerged infectious diseases, including pandemic influenza [7]. A crucial element needed to allow appropriate policy decisions is accurate assessment of disease transmissibility and severity. Both of these rely on the rapid gathering, sharing and analysis of accurate and relevant data. Our method, with further refinements as suggested by Nishiura and Roberts, provides an important step forward in such early analysis of transmission dynamics. We recommend that this modelling approach, and data collection to support it, should be considered by those currently charged with revising pandemic plans in the light of events in 2009 and that our proposed methods should be tested in a variety of other settings to further demonstrate their validity.

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