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Influenza A(H1N1)v in Germany: the first 10,000 cases

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The analysis of the first 10,000 cases of influenza A(H1N1)v in Germany confirms findings from other sources that the virus is currently mainly causing mild diseases, affecting mostly adolescents and young adults. Overall hospitalisation rate for influenza A(H1N1)v was low (7%). Only 3% of the cases had underlying conditions and pneumonia was rare (0.4%). Both reporting and testing requirements have been adapted recently, taking into consideration the additional information available on influenza A(H1N1)v infections.

Introduction

After the first cases of influenza A(H1N1)v in the United States and Mexico became public, the Robert Koch Institute (RKI) established a case-based reporting of cases of influenza A(H1N1)v [1]. In the first weeks of the pandemic, data were reported to the national level by fax, phone and email in parallel with the routine electronic reporting system SurvNet [2]. Thereafter, this changed to exclusive electronic data reporting, including additional information relevant for the assessment of the epidemiological situation.

After the detailed examination of the first 100 cases in the early phase of the pandemic [1], we analyse here data of the first 9,950 cases in Germany, with a focus on information regarding the risk groups, hospitalisation frequency and other factors contributing to the impact this pandemic has on the healthcare system, in order to guide further public health measures.

Methods

As of 30 April 2009 the following information was collected through SurvNet with standardised free-text: classification of cases (possible, probable, confirmed, discarded case), in-country transmission, number of contacts (close as well as wider contacts), antiviral drug used. From 22 June 2009 onwards, the variables were changed in order to collect more detailed data on treatment (start of therapy, antiviral drug), risk groups, presence of pneumonia, hospitalisation and source of infection.

In order to take the age structure of the population into consideration, we calculated the incidence per 100,000 population per age group. From our data, we also calculated the time interval between date of symptom onset and diagnosis and start of therapy, respectively.

Categorical variables were presented as percentages with interquartile ranges when appropriate. Odds ratios were calculated including 95% confidence intervals where appropriate.

Results

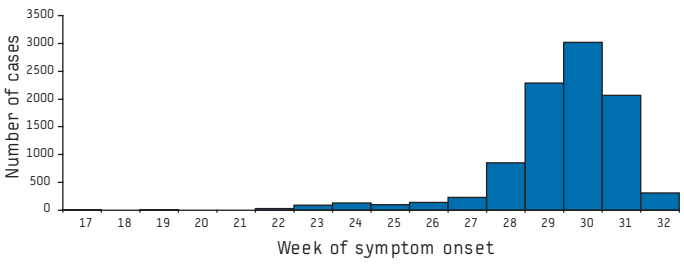
As of 25 August 2009, 14,940 cases of influenza A(H1N1)v have been reported in Germany. For the detailed report below we analysed the first 9,950 cases that were reported to the RKI until 10 August 2009.

The date of symptoms onset of the first German case was 20 April 2009. The person had travelled to Mexico and had already become symptomatic while staying in Mexico. Until the end of May, only sporadic cases were notified, usually associated with travel to North America. Most secondary infections with influenza A(H1N1)v which occurred in this period could be traced back to returning travellers. In June, the number of new cases rose to approximately 10 to 50 cases per day. Since mid-July we saw a considerable increase in cases in Germany (Figure 1) with a peak of up to 500 cases per day and 3,000 cases per week at the end of July. Since then, the number of new cases per day has decreased.

From the 9,950 cases, 54% were male. The median age was 19 years (range: 0-89 years). The majority of cases (77%) were from 10 to 29 years old. Two per cent of the cases were younger than five years, 3% were between five and nine years old, 17% were between 30 to 59 years old and less than 1% of the reported cases were 60 years old and older.

Figure 1

Notified cases of influenza A(H1N1)v by week of symptom onset, Germany, April-August 2009, (n=9,275 cases with available information on symptom onset)



Looking at the incidence (Figure 2), the 15 to 19 year-olds were most affected, with 90 cases per 100,000 population, followed by the 20 to 24 year-olds (43/100,000). In children up to two years old, there were 5.5 cases per 100,000 population. Persons 60 years old and older had less than one case per 100,000 population. The proportion of incidence by age group over the weeks 28 to 32 showed a stable age distribution over this time period (Figure 3).

For 2,141 cases (22%), Germany was indicated as the most likely country of infection. In the first weeks of the pandemic (May and June), most travel-associated cases had been returning travellers from North America. Since the first week in July, the proportion of infections associated with travel to European countries has risen sharply. In July, 80% of travel-associated infections were seen in travellers returning from Spain, followed by the United Kingdom (6%), Bulgaria (3%) and North America (2%). From week

Figure 2

Incidence of notified cases of influenza A(H1N1)v, by age group, Germany, April-August 2009, (n=9,950)

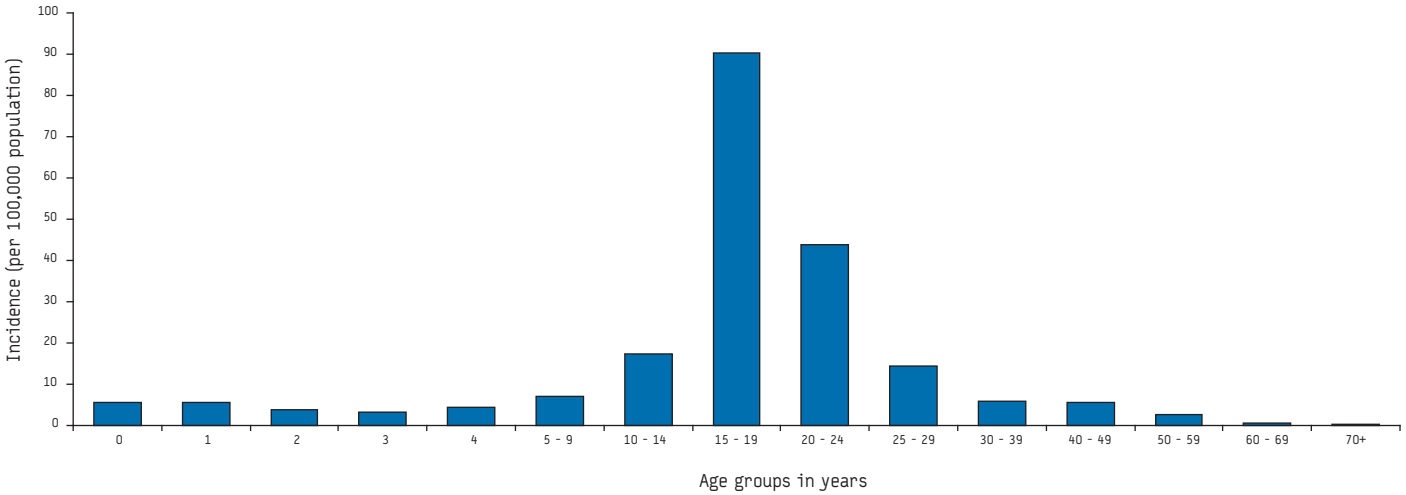
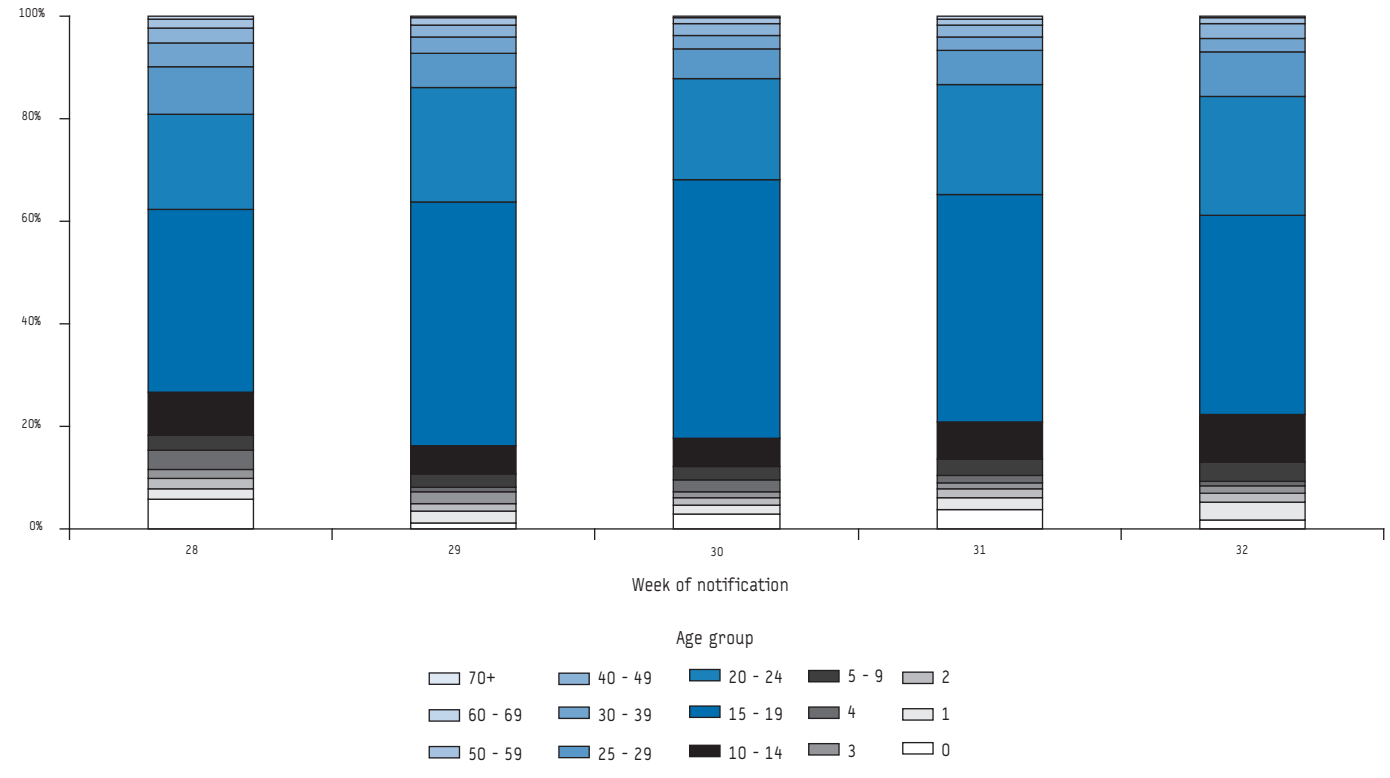


Figure 3

Proportion of incidences by age group and week of notification for notified cases of influenza A(H1N1)v, Germany, July-August 2009, (n=9,341)



29 to 32, the number of cases most likely infected in Germany rose steadily from 16% to 24%. For the cases without travel history, the proportion of infections without a known source increased between weeks 29 and 32 from 38% to 43% (n=1,039).

Symptoms were reported for all 9,950 cases. Cough was the most common symptom, present in 82% of the cases, followed by fever (78%).

Data were also collected on underlying health conditions and risk factors. The results are presented in the table.

The average time interval between date of symptom onset and diagnosis (n=7,955 cases for whom this information was available) was 3.6 days with an increasing trend from week 26 (2.4 days) to week 31 (3.8 days). The average time between date of symptom onset and start of therapy (n=1,810 cases for whom this information was available) was 2.2 days with a decreasing trend from week 28 (4.0 days) to week 32 (2.0 days). Cases with underlying conditions were more likely to receive treatment (72/134: 54%) than cases without underlying conditions (1,679/3,805: 45%; OR=1.44 [1.01; 2.07]). Information on presence of pneumonia at the time of notification was available for 6,460 cases. Pneumonia was reported for 26 cases (0.4%), out of which four belonged to a risk group (two had respiratory, two had unspecified risk factors) and eight were hospitalised.

From 3,630 cases for whom hospitalisation status was available, 263 (7%) persons were admitted to a hospital because of influenza, 122 cases (3%) were in hospital for other reasons, and for 42 cases (1%) the reason of hospitalisation was not known. The influenza hospitalisation rate changed from 11% in week 29 to 5% in week 31. We also looked for cases with information on their risk factors and their hospitalisation status (n=3,270). The proportion of people with risk factors who were hospitalised for influenza was 19% (20/108), while the proportion of people without risk factors that were hospitalised for influenza was 7% (220/3,162; OR = 3.04 [1.78; 5.16]). The median age was 19 years for both groups.

During the first phase of the pandemic, all contacts of cases in Germany were traced back by the local public health authorities and the number of contacts was reported to the national level. The trace back was done for 2,635 cases. On average, three contact persons per case were identified (upper and lower quartile: 2 to 6 contacts, range 0 to 330 contacts).

Table

Frequency of underlying health conditions for cases of influenza A(H1N1)v, Germany, April-August 2009, (n=5,885 cases for whom this information was available)

Underlying conditions*	Number of cases (%)	Proportion of all underlying conditions
No	5,690 (96.7%)	-
Yes	195 (3.3%)	-
Respiratory disease	87 (1.5%)	45%
Cardio-vascular disease	29 (0.5%)	15%
Diabetes	17 (0.3%)	9%
Obesity	11 (0.2%)	6%
Pregnancy	9 (0.2%)	5%
Immunsuppression	5 (0.1%)	3%
Others	34 (0.6%)	17%
Not specified	9 (0.2%)	5%

*Multiple answers were possible.

Discussion

The analysis of the first approximately 10,000 cases of influenza A(H1N1)v in Germany showed that after some sporadic cases and a slow increase in June 2009, a significant increase of newly reported cases was seen starting with July. This trend was also reported from other countries in Europe [3]. There seems to be a downward trend now in Germany, even taking into account a reporting delay of approximately one week. Whether this decrease is a true decline in incidence is not yet clear. A change in health-seeking behaviour might also play a role. The first anxiety about the new infection might have made more people with respiratory symptoms seek medical advice and therefore might have brought the cases to the attention of the of the public health authorities. However, other European countries, like the UK, also report signs that the potential first wave of the pandemic might be coming to an end [4].

The cumulative number of cases by age group clearly shows that there is a peak in the age group 15 to 19 years . Many of these cases were high-school graduates who travelled to Spain in large groups at the end of the school year. The incidence in the under two year old children is relatively low (5/100,000). Data from the United States showed a much higher incidence (22.9/100,000) in children up to five years old [5]. The very low incidence in people over 60 years of age is consistent with other investigations [4-7]. It is still unclear if this is due to a partial immunity from former infections with H1N1 influenza viruses or if this is because the virus has not yet been sufficiently introduced in this subpopulation. Looking at the proportion of affected age groups over weeks, no shift to the older (>60 years) or younger (<5 years) age groups can be seen yet.

The high proportion of cases imported from Spain does not necessarily indicate a relevant epidemic activity there, but probably rather reflects the travel patterns of German holiday makers during summer. The German Federal Office for Statistics reported that from June to August 2008 approximately 1.1 million people travelled every month from Germany to Spain by air [8]. Additionally, there are many organised bus tours to Spain that are especially favoured by high-school students. Closer physical contact, sharing of drinks and special party settings were discussed as possible risk factors, but they need to be validated by further research. Besides the high number of cases in travellers, we could see an increasing proportion of cases that had no travel history and no known source of infection in the last weeks.

Most cases of influenza A(H1N1)v currently seem to have uncomplicated influenza-like illnesses. Our data show that the most common symptoms were cough and fever, similarly to reports from other countries [6-9]. This was one of the reasons why we specified the list of symptoms for the physicians to notify a patient to the local health authorities.

A particular interest for the public health authorities is the protection of the vulnerable groups. These are people with underlying conditions, such as chronic diseases, but also pregnancy, who have a higher risk of developing complications during an influenza infection. From all notified cases in Germany for whom the information was available, only 3% had underlying

conditions. Nearly half of them had chronic respiratory tract diseases. Pregnancy was not often reported among the confirmed cases. Pneumonia at the time of notification was also very rarely reported.

With increasing numbers of cases and laboratory diagnoses, the time interval between date of onset of symptoms and date of diagnosis has increased considerably. In the beginning, both transport of specimens and laboratory testing were done very fast. Now diagnostics have become more routine work and the high number of samples has caused a backlog of samples to be tested. The time interval between onset of symptoms and start of therapy decreased from four to two days. That means physicians start therapy as recommended before the laboratory confirmation of the influenza infection. Treatment is started on average within 48 hours from symptom onset, when the antiviral drugs are supposed to be most effective.

The hospitalisation rate changed considerably over the weeks. During the first weeks, the majority of cases were hospitalised due to infection control measures. Even though that might still be the case for some patients, hospitalisation is now considered as a proxy for the severity of the disease in patients. In the last couple of weeks, the hospitalisation rate due to influenza in the notified cases halved to 5% in week 32. This is a relatively low proportion and does not constitute a high burden for the hospitals at this stage of the pandemic. When we looked closer at those cases with reported underlying conditions we could see that they had a hospitalisation rate more than two times higher than in cases without underlying conditions. Here precaution could have contributed to the referral to a hospital, but it still shows that these known groups with underlying conditions will present an important group when dealing with the pandemic.

Conclusion

As of August 2009, the majority of influenza A(H1N1)v cases reported in Germany are mainly imported from other European countries. However, the proportion of cases with in-country transmission is increasing.

Several factors might influence the characteristics of notified cases in the near future. Firstly, as of 18 August 2009, physicians have to notify possible cases only if the patient presents with cough and fever, therefore it is assumed that the number of cases reported to the national level will decrease. Since 17 August 2009, the costs of the laboratory confirmation have been paid by the statutory health insurances only for cases with severe disease or cases with the risk to develop severe disease. Therefore, the percentage of laboratory-confirmed cases among the notified cases will decrease. However, as long as the sentinel surveillance in Germany does not give a signal, the assessment of the epidemiological situation must rely on routine surveillance.

The public health strategy has changed in Germany from containment (follow-up of all contact persons) to the protection of vulnerable groups. Now, only contact persons who have occupational contacts to persons with a high risk to develop severe disease are followed up (e.g.: healthcare workers).

Until now, no fatalities due to influenza A(H1N1)v have been reported in Germany, which may be partly due to these strategies.

Germany wants to continue the current reporting system until the number of respiratory infections increases significantly, as can be expected in autumn again. Then it is planned to stop the case-based reporting by physicians and get the necessary information from the laboratory-based reporting of confirmed cases as it is done for seasonal influenza viruses and the sentinel surveillance.

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We wish to thank all German local and regional health authorities, who investigated the notified cases, did the trace back and submitted the information to the national authorities. We also want to thank all the physicians who notified their cases to the health authorities.

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Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009

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Following the detection of imported cases of pandemic influenza A(H1N1)v on 25 April 2009, New Zealand implemented containment measures that appeared to slow establishment of the pandemic during May. The pandemic accelerated markedly in June, reaching a peak within four to six weeks, and has been declining since mid-July. By 23 August there had been 3,179 recorded cases (97.8% reported as confirmed), including 972 hospitalisations, 114 intensive care admissions, and 16 deaths. Influenza-like illness (ILI) surveillance in general practice suggests that 7.5% (95% CI: 3.4–11.2) of the population of New Zealand had symptomatic infection, giving a case fatality ratio of 0.005%. Hospitalisations were markedly higher for Māori (age standardised relative risk (RR)=3.0, 95% CI: 2.9–3.2) and Pacific peoples (RR=6.7, 95% CI: 6.2–7.1) compared with Europeans and others. The apparent decline of the pandemic (shown by all surveillance systems) cannot be fully explained. New Zealand remains in the middle of its traditional influenza season, the influenza A(H1N1)v virus appears relatively infectious, and we estimate that only about 11% of the population have been infected by this novel agent.

Introduction

There has been considerable international interest in how the influenza A(H1N1)v pandemic might evolve during the southern hemisphere winter [1]. Initial reports from Australia showed an epidemic increase in influenza-like illness (ILI) reported by general practice (GP) sentinel surveillance from late May and peaking four to six weeks later in June [2]. Another southern hemisphere country, Peru, also observed an epidemic that accelerated rapidly in June, followed by an apparent decline [3]. Here we report the epidemiology of this pandemic in New Zealand based on the experience of the first four months, from late April to late August 2009.

Methods

New Zealand has multiple systems for surveillance of influenza, as listed below. Here we report on key surveillance findings, particularly from the first seven of these systems.

- **Notifiable disease surveillance:** 'Non-seasonal influenza A(H1N1)' was made a notifiable disease on 30 April 2008. Data are entered into a national web-based database (EpiSurv) operated by the Institute of Environmental Science and Research (ESR) and are available for immediate analysis. This system also records hospitalised and fatal cases.
- **General practice (GP) surveillance:** Data on influenza-like illness (ILI) consultations with primary care medical practitioners are collected through two systems: the Sentinel GP Surveillance System (95 general practices covering about 10% of the New Zealand population) and HealthStat (84 computerised general practices with an additional 300 added in 2009, now covering about 40% of the New Zealand population). These systems provide weekly reports of ILI activity.
- **Laboratory-based surveillance:** Nasopharyngeal swabs are collected by practitioners contributing to the Sentinel GP Surveillance System, from a known number of patients seen with ILI every week. These influenza isolates are typed and tested for sensitivity to oseltamivir [4]. Specimens are also collected for diagnostic reasons from outpatients and hospitalised inpatients and as part of public health follow-up and investigation.
- **Healthline:** Reports on telephone calls regarding ILI made by the public to a national free-calling health information service are collated every week. This surveillance records daily counts of calls triaged for ILI, based on a wide set of key terms and clinical syndromes.
- **Hospital intensive care unit (ICU) utilisation:** This additional surveillance was established as part of the situation reporting system used by the Ministry of Health to support its ongoing pandemic management activities. It collects daily reports from all District Health Boards on a number of measures of healthcare utilisation including ICU influenza admissions, total occupancy, and ventilator capacity.
- **Population survey (Flutracker):** A cross-sectional survey was designed by the Ministry of Health and conducted by a market research company to measure the prevalence of ILI in the population and to assess the feasibility of using this form of surveillance on an ongoing basis. This survey used telephone interviewing. The pilot survey in June 2009 used a nationally representative sample of 629 people in 219 households. This full surveillance system was not continued because it was not considered necessary for the scale of the pandemic and was relatively expensive.

- **Mortality:** Data from death certificates and Coroner's reports are provisionally collated within days by the Ministry of Health (but final analysis and reporting of national data take about two years).
- **Hospital morbidity:** All publicly funded hospitals in New Zealand report hospitalisation data to the Ministry of Health with collated data available within three months (consequently these data were not available for this analysis, so notification data were used here to described hospitalisations).
- **Other influenza surveillance systems:** There are also regional systems for syndromic surveillance (based on one hospital emergency department in the capital city) and absenteeism surveillance (recording workplace and school absenteeism in one region of New Zealand).

Rates were calculated using 2008 mid-year population estimates except for ethnicity which used 2006 census data as the denominator. When calculating rates for ethnic groups we used prioritised ethnicity (where individuals record multiple ethnicities, Māori ethnicity takes precedence, followed by Pacific peoples, then Asian, with the remaining people included as European and other). Rates were age-standardised using the age distribution of the 2006 census.

Results

Incidence

Up to 23 August 2009 there had been 3,179 notified cases of influenza A(H1N1)v in New Zealand, a rate of 74.5/100,000. Most cases were reported as confirmed (97.8%), with the rest (2.2%) classified as probable. Of the total cases, 972 (30.6%) were reported to have been hospitalised, 114 admitted to an ICU, and 16 to have died of pandemic influenza as the primary cause of death. Other possible pandemic-associated deaths are still being investigated by the Coroner's office [5].

Over the 11-week period that the pandemic strain has been circulating in New Zealand (from week 24, starting 8 June, to week 34, ending Sunday 23 August), the Sentinel GP Surveillance System detected a cumulative consultation rate of 1,906.2 ILI cases/100,000 population (i.e. 1.9%). During that same period, 382 influenza A(H1N1)v viruses were obtained from these sentinel practices, which was 19.0% of the swabs collected from patients with ILI. These data suggest a cumulative general practice consultation rate for influenza A(H1N1)v of 408.9/100,000, equivalent to a cumulative total of 17,672 patients across New Zealand.

Time course

Epidemic curves for notifications, hospitalisations, ICU admissions and ILI cases (Sentinel GP Surveillance System, HealthStat, and Healthline calls) are shown in the figures below (Figures 1-7). The first known cases in New Zealand were detected on 25 April 2009 following arrival of a flight containing a school group who had travelled to Mexico. Containment efforts (case isolation, quarantine of contacts, and treatment with oseltamivir) appeared to have successfully prevented transmission from that group. No further cases of laboratory-confirmed disease were detected for about 4 weeks from 1 May until 31 May.

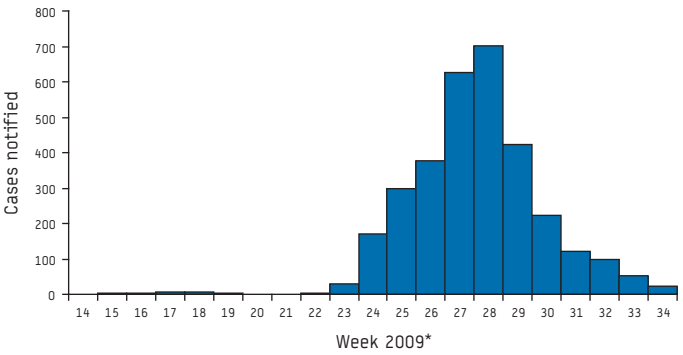
Following the end of May, a marked increase in influenza was detected by all surveillance systems starting in the first or second week of June (depending on the system). All surveillance systems showed that the epidemic reached a peak within four to six weeks (during the weeks starting Monday 27 June to 12 July).

Notifiable diseases

The first cases were notified in the week starting 27 April (student group from Mexico). There was a rapid rise in notified cases of influenza A(H1N1)v in week 23 (starting 1 June), with a peak six weeks later in week 28 (starting 6 July).

Figure 1

Influenza A(H1N1)v cases recorded on notifiable disease surveillance system by week, New Zealand, April-August 2009 (n=3,179)



* Week of onset, hospitalisation or reporting, whichever was earliest

Figure 2

Influenza A(H1N1)v cases hospitalised by week, New Zealand, April-August 2009 (n=972)

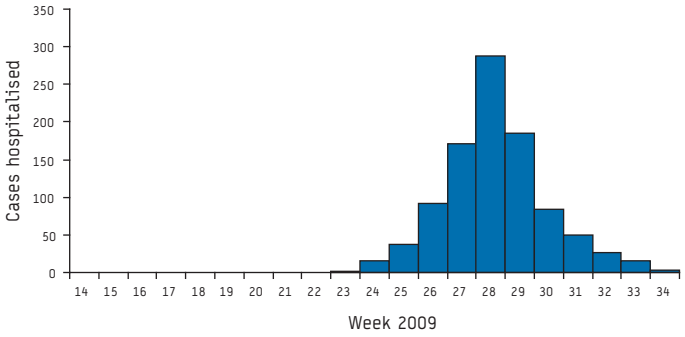
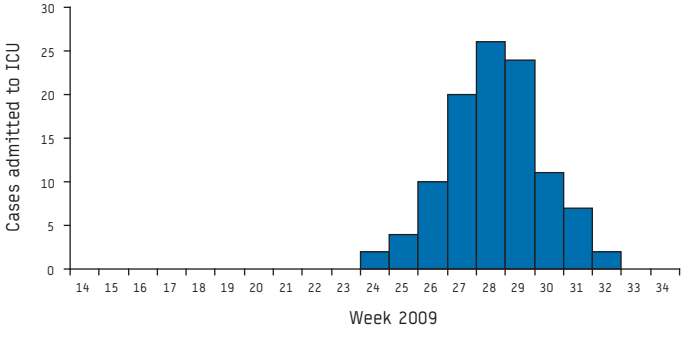


Figure 3

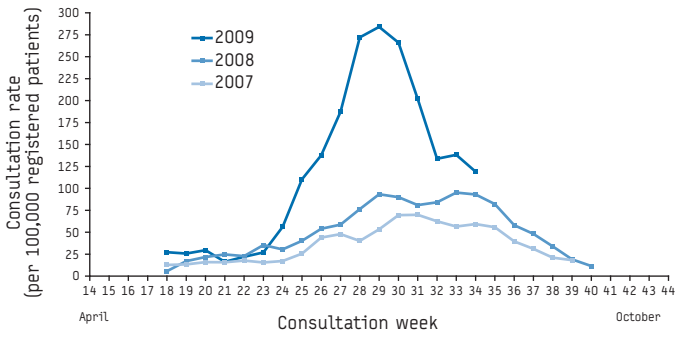
Influenza A(H1N1)v cases admitted to ICU by week, New Zealand, April-August 2009 (n=106*)



*excluding eight cases without reported admission dates

Figure 4

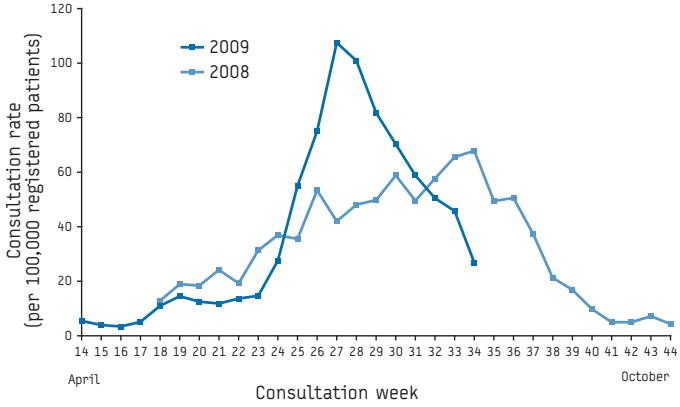
Weekly rate of ILI per 100,000 registered population, all ages, New Zealand, 2007–2009



Source: Sentinel General Practice Surveillance System

Figure 5

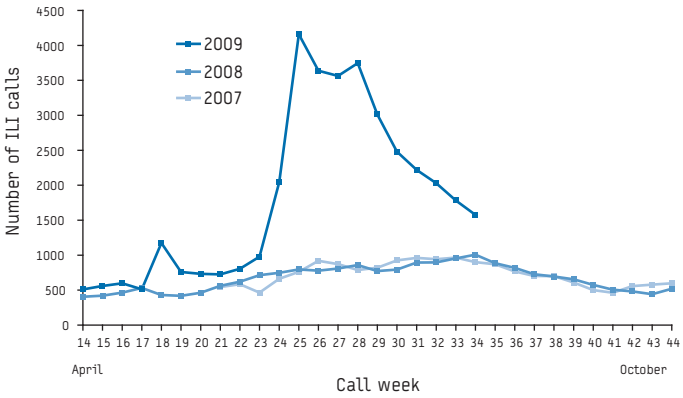
Weekly rate of ILI per 100,000 registered population, all ages, New Zealand 2008–2009



Source: HealthStat General Practice Surveillance System
ILI: influenza-like illness

Figure 6

Weekly ILI calls to Healthline, New Zealand 2007–2009



ILI: influenza-like illness

Hospitalisations (subset of notifications)

The hospitalisation numbers showed the same pattern as the notifications. The first hospitalisations were in week 23 (starting 1 June), with a peak six weeks later in week 28 (starting 6 July).

Hospital intensive care admissions

New admissions to ICU followed a similar pattern to hospitalisations with the first admission in week 24 and a peak in week 28. About 12% of hospitalised cases were admitted to ICU.

Figure 7

Influenza viruses obtained from Sentinel GP Surveillance System by week, New Zealand, April-August 2009 (n=602)

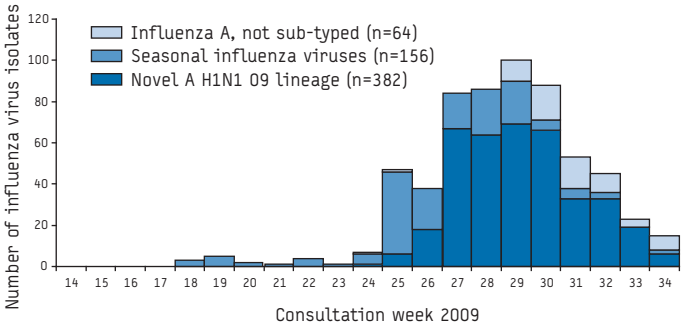


Figure 8

Rates of notified and hospitalised influenza A(H1N1)v cases by age group, New Zealand, cumulative rates for 2009

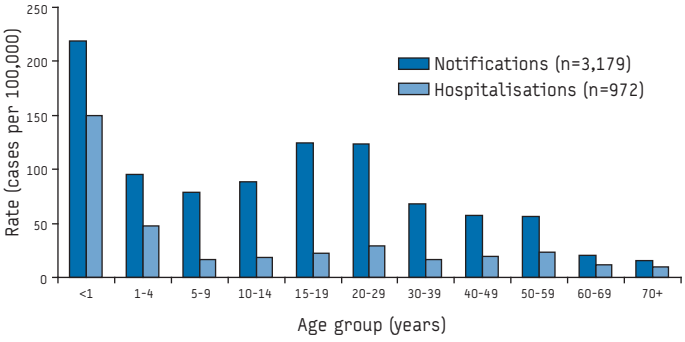
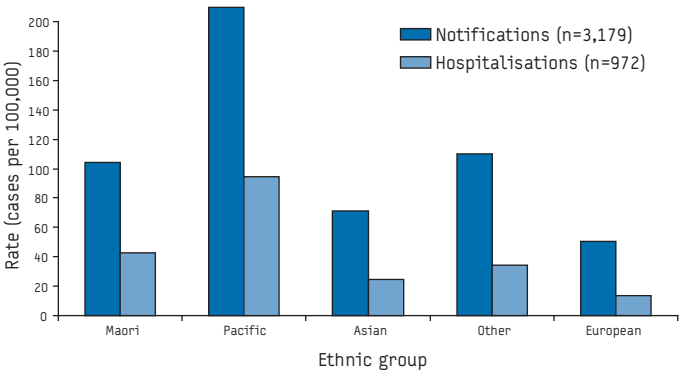


Figure 9

Rates of notified and hospitalised influenza A(H1N1)v cases by ethnic group, New Zealand, cumulative rates for 2009



Sentinel GP Surveillance

This system showed a rapid rise in ILI cases evident in week 24 (starting 8 June), with a peak six weeks later in week 29 (starting 13 July).

HealthStat GP Surveillance

This system showed a rapid rise in ILI cases evident in week 24 (starting 8 June), with a peak four weeks later in week 27 (starting 29 June).

Healthline calls

There was a rapid rise in ILI calls from the public evident from late in week 23 (starting 1 June). The calls peaked two weeks later in week 25 (starting 15 June).

Laboratory surveillance

Influenza A(H1N1)v was first detected by the Sentinel GP Surveillance System in week 24 (starting 8 June). It became the dominant circulating strain after four weeks (week 27 starting 29 June).

Population survey (Flutracker)

For the week of 22–28 June (week 26), ILI was reported by 2.0% (95% CI: 0.9–3.0) in a sample of 619 people. This was an ILI prevalence of 2,000/100,000 population (95% CI: 900–3,000). During that week the Sentinel GP Surveillance System reported a consultation rate of 137.7/100,000 (peaking two and three weeks later at a rate of 272.0 and 284.0/100,000). Also during that week, the expanded HealthStat GPs (n=384 GPs) reported a consultation rate of 80.7/100,000 (peaking one and two weeks later with a consultation rate of 112.0 and 119.6/100,000). Taking the average of these two rates for week 26 (109.2/100,000) implies that only one in 18.3 people with ILI consulted a GP and were also recorded by the ILI surveillance system (95% CI: 8.2–27.5).

Region

The intensity of the epidemic varied widely across New Zealand with some regions experiencing rates markedly higher than others. Across the 21 district health board regions, the cumulative hospitalisation rate ranged from 0.0/100,000 in Wairarapa to 52.9/100,000 in Hutt Health District (Wellington). The national average was 22.8/100,000.

Person characteristics

Notification data were analysed according to the age, sex, and ethnicity of notified and hospitalised cases (see Figures 8 and 9).

Rates of notified disease were highest in the under one year-olds (218.5/100,000) and the 15–29 year-olds (124.6/100,000), with the lowest rates in those over the age of 70 years (15.3/100,000). Hospitalisations showed a similar pattern with markedly higher rates in those under one year of age (149.8/100,000), but with rates falling to a relatively low level for all age groups over the age of five years. Hospitalisation rates for females (24.3/100,000) were slightly higher than for males (20.9/100,000).

Rates of notified disease were highest in Māori (age standardised relative risk (RR)=2.0, 95% CI: 1.9–2.1) and Pacific peoples (RR=4.0, 95% CI: 3.8–4.3), compared with Europeans and others. These inequalities were even more marked for hospitalisations (Māori RR=3.0, 95% CI: 2.9–3.2, Pacific peoples RR=6.7, 95% CI: 6.2–7.1).

Discussion

The virus

The pandemic influenza A(H1N1)v virus became the predominant circulating influenza virus in primary care settings in New Zealand within four weeks of its appearance [6]. It has been genetically very stable, based on testing conducted in New Zealand, and remains sensitive to oseltamivir [7]. The virology of this influenza epidemic was unique in that it was characterised by the co-circulation of three influenza A strains. As of 23 August 2009, there has been virtually no influenza B activity.

The pandemic

The pandemic in New Zealand has been characterised by relatively high transmissibility but low case fatality ratio (CFR). The reproduction number estimated for the early stages of the epidemic was 1.96 (95% CI: 1.80–2.15) [8]. The data from the Sentinel GP Surveillance System imply that about 17,672 patients infected with the pandemic strain have consulted a GP during the initial 11 weeks of the pandemic period. Given that the data from the cross-sectional survey (Flutracker) for week 26 imply that only one in 18.3 of the population with ILI are reported to this sentinel system, these data suggest that a cumulative total of 323,400 New Zealanders (7.5%, 95% CI: 3.4–11.2) have had symptomatic infection with the pandemic strain during this period. Experimental studies suggest about one third of seasonal influenza infections are asymptomatic [9], so these findings would be consistent with about 11% of the population having been infected with the pandemic strain. This result is broadly consistent with one other New Zealand estimate: Using capture-recapture methods and combining data from four sources it was estimated that 3.7% of the population of two Auckland regions (population 0.93 million) were symptomatically infected in a single month (July) [10].

Case fatality ratio

Calculating the CFR is highly dependent on estimates of the total number of people with symptomatic illness [11]. There have been 16 deaths with the pandemic influenza strain recorded as the principal cause (as of 23 August). Using the estimated denominator population of 323,400 symptomatic cases, this suggests a CRF of 0.005% (95% CI: 0.003–0.011). Interestingly, this estimate is in the range found for seasonal influenza in the population under the age of 65 years (according to data from the United States [12] and various assumptions [11]). This impact appears mild compared with the 1918 influenza pandemic in New Zealand, which killed 0.7% of the population [13] and which may have had a CFR of around 2.0% [14]. We can, however, speculate that those people admitted to ICU today (114 so far in New Zealand) would not have survived in 1918. On that basis, the comparable CFR estimate for the current pandemic would be considerably higher at 0.04%. Other interventions, such as use of antivirals (mainly oseltamivir), antibiotics to treat secondary bacterial pneumonia, and public communications have probably also contributed to lowering the CFR. Developing countries without access to such resources might, therefore, experience far more severe health impacts than those seen in a developed country like New Zealand.

Vulnerable groups

Some population groups appear more vulnerable to influenza A(H1N1)v infection than others. A distinctive epidemiological feature of pandemics is the shift in the age distribution to younger people [15], and this feature was clearly evident in New Zealand. In addition, there have been markedly higher rates of severe disease (as reflected by the number of hospitalisations) for Māori (cumulative age-standardised hospitalisation rate of 43.0/100,000)

and Pacific peoples (94.2/100,000) compared with Europeans and others (14.1/100,000). Similar ethnic inequalities between Māori and non-Māori were seen for fatalities in the 1918 influenza pandemic in New Zealand [16]. The reasons for these differences have not been established. However, Māori and Pacific peoples in New Zealand experience marked health inequalities, and these are also manifest for other infectious diseases [17]. Chronic health conditions have been commonly reported for hospitalised cases (notably respiratory disease, cardiac disease, diabetes, and immune suppression) along with some infections in pregnant women.

Impact of school holidays

There is some evidence that the start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic. In New Zealand, the holidays for all schools lasted from Saturday, 4 July to Sunday, 19 July this year (weeks 28 and 29). It is difficult to identify what impact the start of the school holidays had as it coincided with what appears to have been the 'natural' peak of the pandemic. However, following the return to school on Monday 20 July, HealthStat GP consultation rates for school age groups (5–14 years) increased and remained elevated for three weeks (weeks 30–32) before continuing their downward trajectory in week 33. These relationships require further in-depth analysis, but the overall effect on the pandemic appears to have been small.

Public health response

New Zealand has a relatively well developed pandemic plan that includes 'keep it out', 'stamp it out', 'manage it', and 'recover' phases [18]. At the point of writing this article, the country is continuing with the management stage. The first two containment stages were applied from the first detection of imported cases on 25 April until 22 June, when New Zealand formally switched to the 'manage it' phase. The considerable interval without reported cases during May (before the epidemic accelerated in June) provides some suggestive evidence for the success of the containment measures, although this assessment requires further evaluation.

Impact on health care services

The pandemic resulted in a heavy demand for health services in those geographic areas where it was most intense. This demand was experienced by general practices, emergency departments, inpatient paediatric and adult medicine services, diagnostic laboratories, as well as public health services. The impact was particularly marked in ICUs because a relatively large proportion of hospitalised cases were admitted to these units and because many patients stayed there for a relatively long time. The demand on intensive care services peaked at 25% of national ICU occupancy. The health services were not overwhelmed, largely because of considerable additional time and effort by staff, postponing and cancelling of non-urgent work, and also because the numbers of infected people and the morbidity in this pandemic were lower than had been initially expected.

Surveillance

The notifiable disease surveillance system was useful during the containment stage for recording individual cases and supporting control measures aimed at interrupting spread of the disease. Once New Zealand moved into the management phase, this system ceased to provide a meaningful indication of the progression of the pandemic, mainly because routine laboratory testing of ILI patients was discouraged unless clinically indicated. However, this system has increasingly been used for recording hospitalisations and deaths, and the resulting dataset (EpiSurv) therefore provides insights into the more severe end of the disease spectrum. The two GP surveillance systems have provided the most consistent data about the progression of the pandemic. The sentinel GP system with integrated epidemiological and virological surveillance has been particularly valuable in estimating the disease burden as it enables the contribution from different circulating influenza strains to be measured. The pilot testing of the Flutracker cross-sectional survey suggested that this system has good potential for surveillance of more severe pandemics which might overwhelm routine surveillance systems.

Limitations of this analysis

All of these surveillance systems have considerable limitations. The cross sectional survey (Flutracker) in particular was run as a pilot and consequently had a relatively small sample. Consequently, there is considerable uncertainty around the multiplier this study has suggested for estimating ILI in the population based on healthcare events (such as GP visits). It is reassuring that data from a cross-sectional telephone survey in New York City suggested a very similar multiplier (18.2) between physician visits and self-reported ILI (this calculation is based on an estimated emergency department multiplier of 60 and the ratio of 3.3 physician visits per emergency department visit reported in this study) [19]. Sentinel surveillance data themselves were affected by advice discouraging most patients with ILI from attending their GP, which would have lowered the consultation rates compared with previous years. Notification data include only a small proportion of all cases and are unlikely to be representative of influenza A(H1N1)v virus infections in the community. All of the findings presented here require more in-depth analysis based on finalised data following the end of the pandemic.

Persisting uncertainties

All surveillance systems currently show a consistent decline in pandemic disease rates in all areas of New Zealand. This decline cannot be fully explained. New Zealand is still in the middle of its traditional influenza season, the A (H1N1)v virus appears relatively infectious, and we estimate that so far only about 11% of the population have been infected by this novel agent. Similar patterns of a relatively short epidemic have also be reported in other countries in the southern hemisphere, notably Australia [2]. This pattern would be consistent with a range of potential explanations. The lower levels of infections in older age groups may be indicative of some existing immunity in the population. Certain changes in behaviour may also have contributed to reducing the effective reproduction number.

The largest uncertainties relate to the future development of this pandemic. Previous pandemics tended to cause multiple waves over periods between two and five years [15]. This present pandemic is causing widespread illness with low mortality, which would be consistent with the first wave seen in some previous pandemics. In other respects it could be seen as behaving like a typical seasonal influenza strain which usually infects 5–10% of the population over a period of about eight weeks every winter and then largely disappears. It would be prudent for health authorities to plan for a range of pandemic scenarios that might unfold over the months and years ahead. There is also a need to maintain existing surveillance systems and supplement these with an operational research programme including, for example, population sero-surveys to provide more accurate estimates of the pandemic impact to date

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An analysis of a short-lived outbreak of dengue fever in Mauritius

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During the month of June 2009, Mauritius experienced a short-lived outbreak of dengue fever localised in its capital city Port Louis. *Aedes albopictus*, a secondary vector of dengue viruses, was the probable vector. We introduce a method which combines Google Earth images, stochastic cellular automata and scale free network ideas to map this outbreak. The method could complement other techniques to forecast the evolution of potential localised mosquito-borne viral outbreaks in Mauritius and in at-risk locations elsewhere for public health planning purposes.

Introduction

Dengue fever is a mosquito-borne viral disease which affects 50-100 million people every year in tropical and sub-tropical regions of the world. Dengue viruses (DENV) appear in four serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) and can cause dengue fever, dengue haemorrhagic fever and dengue shock syndrome among other illnesses [1]. Sporadic cases of dengue fever occurred in Mauritius [2] at the time of a major dengue virus (DEN-2) epidemic in Réunion Island in 1977-1978 [3]. *Aedes aegypti* mosquitoes are the major vectors of DENV but were eradicated in Mauritius and nearly eradicated in Réunion Island during the anti-malaria campaigns in the early 1950s. *A. albopictus*, a secondary vector of DENV, was the probable mosquito vector during the 1977-1978 Réunion Island epidemic [3].

Dengue fever re-emerged in Mauritius in June 2009 as a mild fever localised in the capital city Port Louis (population of 144,000 and size of 45.6 km2) on the north-west coast of the island, with *A. albopictus* as the probable vector. A first suspected case was detected on 3 June 2009. There were 192 serologically confirmed cases from 3 to 18 June 2009. The number of cases decreased over the next five days with 16, 4, 4, 3 and 0 cases, respectively. Most of these 219 cases were from the Port Louis region. Mosquito fogging and larviciding started on 3 June 2009, covered the whole of Port Louis and were repeated every seven days. Mosquito fogging was carried out outdoors early in the morning, early evenings and sometimes late in the evenings, when wind speeds were less than 15 km/h. The insecticide used was Aqua K-Othrine® and thermal foggers were used for the spraying. Public awareness campaigns on the necessity to search and eliminate mosquito breeding sites at home and in the neighbourhood and to protect oneself against mosquito bites were carried out through radio, television and the press through a public private partnership. Detailed information leaflets were also distributed. Target groups included the public, community groups and school children.

We introduce a method which uses Google Earth images, stochastic cellular automata [4] and scale free network [5] ideas to map the evolution of dengue fever in Port Louis in June 2009, and compare a scenario without mosquito control or behavioural change (Scenario 1) with a scenario with mosquito control and human behavioural change (Scenario 2).

Methods

The outbreak was assumed to have been started by the introduction of a human index case into a completely susceptible human and mosquito population. An area of interest of Port Louis where most of the serologically confirmed dengue fever cases occurred was selected from a Google Earth digital image of Port Louis. The area of interest, an area of 2.9 km x 3.6 km, was divided into cells each 0.1 km x 0.1 km in size. The number of houses in each cell was estimated using colour image analysis, and the human population in a cell was estimated by assuming an average number of five inhabitants per house. The mosquito population in a cell depended on the human population as shown in the Table.

Table

Parameters for the evolution of dengue fever in Port Louis for Scenarios 1 and 2

	Scenario 1					Scenario 2			
Intervention	1	2	3	4	5	1	2	3	4
Day of intervention	1	7	14	21	30	1	7	14	21
Human viraemic period [days]	5	5	5	5	5	5	5	5	5
Human infectious period [days]	5	5	5	5	5	5	3	2	2
DENV latent period in humans [days]	5	5	5	5	5	5	5	5	5
DENV latent period in mosquitoes [days]	6	10	12	15	22	6	10	12	15
Mosquito lifetime [days]	30	25	20	20	20	30	20	15	10
Mosquito infectious period [days]	30	25	20	20	20	30	20	15	10
Ratio vector/humans	3	2	2	2	2	3	2	1.5	1
DENV transmission probability	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mosquito bite rate [per week]	2	2	2	2	2	2	1	1	1

DENV: Dengue virus

The index case was assumed to reside in an index cell. Individuals in a cell were assumed to interact with mosquitoes in the cell following a SEIR (susceptible-exposed-infected-removed) model for human-mosquito interaction [6]. Individuals in a cell were assumed to be able to move locally with equal probability to each of the eight neighbouring cells and to interact with mosquitoes. They were also assumed to move globally on a scale-free network [5]. Only 40% of the human population of a cell was allowed to move globally (and 50% locally) at any time step (one day) and they returned to their original cell at the end of the time step. Mosquitoes were restricted to their cells.

The scale free network was set up as follows:

1. Four most frequently visited places (hubs) in the area of interest were chosen.
2. Each hub was represented by one cell.
3. The index cell was randomly linked to two of the hubs.
4. Another cell was chosen that was allowed to link itself with the hubs or with the index cell using the Barabási–Albert algorithm [5].
5. Steps 3-4 were repeated for the remaining cells to generate a scale-free network.

The evolution of the outbreak was computed for the two scenarios for the parameter values given in the Table. It was assumed that the mosquito latent period increased with falling temperatures as the month of June passed, accompanied by a decrease in the mosquito lifetime. The decrease in mosquito lifetime was assumed to be greater for Scenario 2 with vector control measures. The human infectious period decreased in Scenario 2 because confinement of affected humans and protection against mosquito bites led to a decrease in the bite rate.

Results

The human population size for the area of interest was computed as 82,580. Figure 1 shows the evolution of the number of infected cases over time for the two scenarios averaged over 100 runs. The average final epidemic size 3,662 cases for Scenario 1 was and 549 cases for Scenario 2.

A histogram of the final epidemic size for 1,000 runs for Scenario 2 is shown in Figure 2.

Figure 3 shows an example of the spread of infected humans over the region of interest in Port Louis 21 days after the first intervention. The outbreak is well-developed and spread over Port Louis with maximum incidence at and around the index cell.

Discussion

We have introduced a method which combines Google Earth images, stochastic cellular automata and scale-free network ideas to yield quantitative estimates for the outcome of a localised dengue fever outbreak. An average of about 550 infected people was computed in Scenario 2 for the period in June 2009 when cases were reported. This number compares well with the actual number about 220 serologically confirmed cases. However, the histogram indicates that larger epidemics can occur, although

FIGURE 1

Temporal evolution of the number of infected humans (averaged over 100 runs) for Scenarios 1 and 2

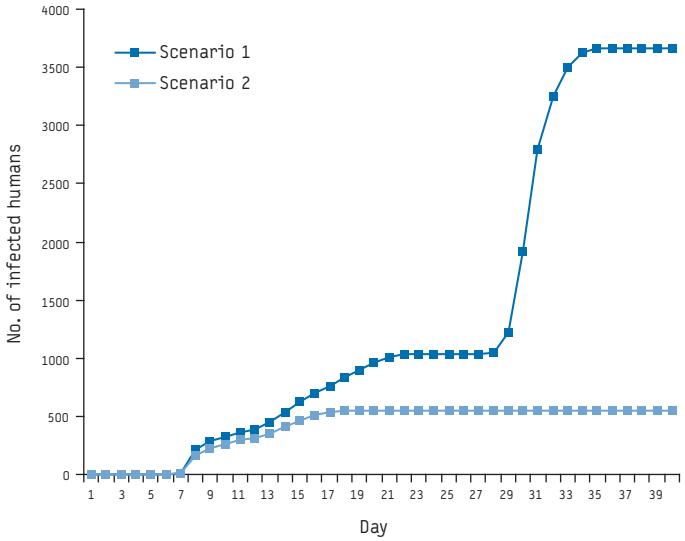


FIGURE 2

Histogram for the final epidemic size for 1,000 runs for Scenario 2

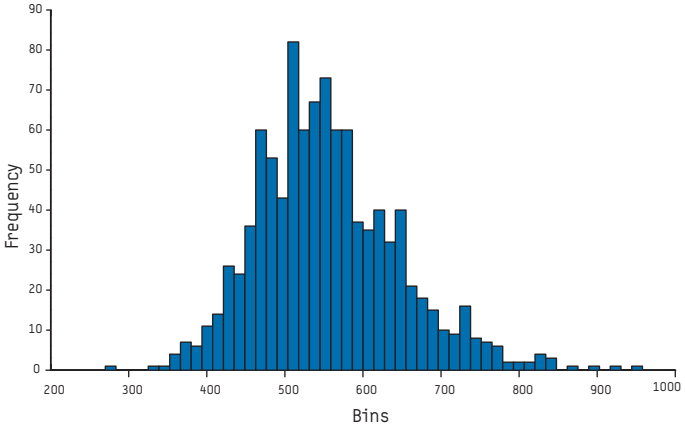
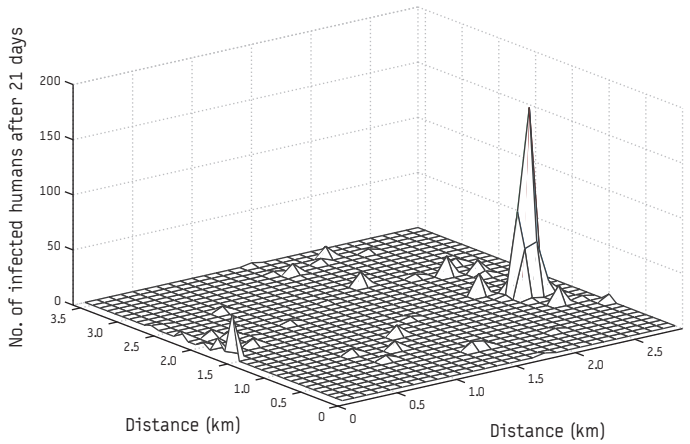


FIGURE 3

Example of the spread of infected humans over the region of interest in Port Louis 21 days after the first intervention for Scenario 2



with lower probability. Computations for Scenario 1 indicate that, without the intense mosquito fogging campaign and – to a lesser extent – the public awareness campaign carried out by Mauritius authorities in June 2009, the number of cases could have been in the thousands. Larviciding is unlikely to have played a major role in controlling the outbreak, given the very short duration of the outbreak.

The localised nature of the dengue virus outbreak in Mauritius in June 2009 suggests an isolated event limited by by falling temperatures, by the fact that only one secondary vector (*A. albopictus*) for DENV was present, and by the fact that infected mosquitoes outside of the outbreak area did not generate additional cases. The occurrence of the outbreak is not surprising considering the recent resurgence of dengue fever in many countries [7] and global air travel. However, the timing of the outbreak at the beginning of winter in Mauritius is surprising and highlights the risk of an emergence of dengue fever in those countries in the north temperate zone which have established populations of *A. albopictus* and where climatic conditions favourable for the propagation of dengue viruses may prevail in the summer [7]. The modelling technique described here could complement other techniques to forecast the evolution of potential localised mosquito-borne viral outbreaks in Mauritius and in at-risk locations elsewhere for public health planning purposes.

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Struggling with recurrent Clostridium difficile infections: is donor faeces the solution?

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Patients with recurrent *Clostridium difficile* infections (CDI) in hospitals and the community constitute an increasing treatment problem. While most patients with a first infection respond to either metronidazole or oral vancomycin, therapy in recurrent *C. difficile* infections tends to fail repeatedly. Lack of alternative treatment options can be a tremendous burden, both to patients and their treating physicians. Most guidelines recommend prolonged oral vancomycin pulse and or tapering schedules, but evidence-based treatment strategies are lacking. The role of immunoglobulins, whey prepared from vaccinated cows, probiotics or other antibiotics is unclear. Since 1958 several case series and case reports describe a treatment strategy where faecal infusions are successfully given for the treatment of recurrent CDI. Restoring intestinal flora has been historically thought of as the mechanism responsible for cure in these patients. In the literature, more than 150 patients have received faeces from a healthy donor, either infused through an enema, or through a nasoduodenal or nasogastric tube. We summarise the literature regarding treatment with donor faeces for recurrent CDI, and introduce the FECAL trial, currently open for inclusion.

Introduction

Described as a commensal bacterium in 1935, it took until the late seventies, before *Clostridium difficile* was recognised as the most important causative agent of antibiotic-associated diarrhoea and colitis [1-3]. *C. difficile* infection (CDI) nowadays is a common nosocomial disease with substantial morbidity and mortality. The increasing incidence, partly due to the recent epidemics caused by the hypervirulent toxinotype III, ribotype 027 strain, and recent reports of community-associated infection in patients without predisposing conditions, illustrate the changing epidemiology of CDI [4-7]. Asymptomatic intestinal carriage of *C. difficile* in the normal population is estimated at 3-15%, but is much higher in hospitalised patients [8]. A prerequisite for the development of clinical *C. difficile* infection (CDI) is a disturbed homoeostasis of the normal intestinal flora, most often caused by previous antibiotic use or gastrointestinal surgery. Toxins produced by *C. difficile* disrupt the colonic epithelium, leading to an inflammatory response and clinical symptoms varying from mild diarrhoea to severe life-threatening pseudomembranous colitis [9].

Although most patients with a first episode of clinical infection respond either to withdrawal of prescribed antibiotics or to additional treatment with metronidazole or oral vancomycin, about 15–30% experience recurrent episodes [10]. Recurrent CDI can be defined as recurrence of symptoms within 8-10 weeks after cessation of specific antibiotic therapy, with exclusion of other enteropathogens and a positive diagnostic test for CDI. A subset of patients with recurrent CDI get into a spiral with several subsequent recurrences. In these cases, *C. difficile* becomes the largest hurdle for recovery, it contributes to increased mortality and morbidity and leads to prolonged isolation measures and additional costs [11,12]. Relapses or reinfections occur due to prolonged disturbance of intestinal flora, persistence of spores, incapacity to mount specific antibodies against *C. difficile* toxin, or an immunocompromised

Box 1

Treatment schedule for recurrent *C. difficile* infection

First recurrence
- Mild to moderate infection
  Metronidazole at a dose of 500 mg orally three times daily for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole
  Vancomycin at a dose of 125 mg orally four times daily for 10 to 14 days

Second recurrence
Prolonged vancomycin orally in tapered and pulsed doses, for example:
125 mg four times daily for 14 days
125 mg twice daily for seven days
125 mg once daily for seven days
125 mg once every two days for eight days (four doses)
125 mg once every three days for 15 days (five doses)

Third recurrence
Vancomycin at a dose of 125 mg orally four times daily for 14 days, combined with any of the other options for recurrent infection (not evidence based):
- Intravenous immunoglobulin at a dose of 400 mg per kg body weight once every three weeks, for a total of two or three doses depending on effect.
- Vancomycin, followed by rifamycin at a dose of 400 mg twice daily for 14 days
- Healthy donor faeces installation*

* We feel that there is at this point not enough evidence to recommend the optimal time to introduce the procedure.

Adapted from Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med. 2008;359(18):1932-40 [9]; Copyright© 2008 Massachusetts Medical Society. All rights reserved.

state [13,14]. Few studies have addressed treatment strategies for recurrent CDI. In general practice, oral vancomycin is prescribed, with limited efficacy. Restoring intestinal flora has been historically thought of as a logical mechanism to repair the host-defense against CDI. Infusion of faeces from healthy donors in patients with severe antibiotic-associated colitis was first described in 1958 [15]. We summarise the treatment options for recurrent CDI and give an overview of literature reports about the use of donor faeces as unconventional therapy in patients with recurrent CDI.

Treatment options for recurrent *C. difficile infection*

Antibiotic treatment

Vancomycin or metronidazole

Results of randomised clinical trials uniquely designed for treatment of recurrent CDI are lacking. Prospectively collected data can be derived from subgroup analysis of placebo-controlled studies comparing the combination of probiotics (or placebo) with oral vancomycin for treatment of CDI. Antibiotic treatment of a first recurrence in observational studies shows a success rate of 67%, both for metronidazole and vancomycin [16]. For additional recurrences, success rates as low as 35% are reported [10]. A subset of patients experience numerous recurrent episodes, and repeated antibiotic courses can be required for treatment of CDI, which may even persist for years [17]. Oral vancomycin is preferred for recurrent CDI because of the neurotoxic side effects of longstanding metronidazole therapy [18]. For a second recurrence, vancomycin taper and/or pulse schedules are commonly advised (Box 1) [19]. The aim of these interrupted regimens is to eradicate germinating *C. difficile* spores. In a stratified analysis including 136 patients with recurrent CDI derived from different study groups, tapered or pulsed therapy seemed with a recurrence rate of 14.3% more successful than a short course with vancomycin (recurrence rate 31%) [19].

Other antibiotic therapies

According to case reports and case series, rifamycin appeared effective for initial episodes of CDI. Rifamycin was also reported to be successful in 18 of 21 patients with recurrent CDI, in three different dosing regimens [20]. Of concern are reports about rifamycin-resistance of *C. difficile* after treatment failure [21,22] and the spreading of rifampicin–resistant *C. difficile* clones in hospitals with frequent use of rifamycins [23].

Table 1

Faecal therapy for recurrent *C. difficile* infections: overview of the literature

Year	Patients (male/ female)	Mean age	No. of relapses	Entry diagnosis	Cured (%)	Follow-up	Donor related to recipient?	Prepared with whole bowel lavage	No of faecal infusions	Amount of faeces	Route of installation		Reference
											Upper GI	Lower GI	
1958	4 (3/1)	56	*	PMC	4 (100)	10 days	Md	No	1-3	Md	0	4 (e)	[15]
1981	16 (7/9)	56	*	PMC	13 (81)	5 days-3 years	If possible	No	1-24	Md	1	15	[34]
1984	1 (0/1)	65	6	CDI	1 (100)	9 months	Spouse	No	2x2	Md	0	1	[35]
1989	2 (1/1) i	60	3	CDI	1 (50)	6 months	Spouse/ daughter	No	1	50 g	0	2	[36]
1991	1 (0/1)	64	7	CDI	1 (100)	3 days	Spouse	No	1	10 g	1	0	[37]
1994	7**	56	1-4	CDI	7 (100)	2 years	Spouse/ relative	No	3	200 ml	0	7	[38]
1998	18**	Md	Md	CDI	15 (83)	Md	No	Md	1	Md	1	17	[39]
1999	32 (14/18)	27-89	Md	AAD	32 (100)	4-6 weeks	No	Md	1-2	5-10 g	0	32	[40]
2000	1 (0/1)	60	>5	CDI	1 (100)	1-6 months	Spouse	Yes	1	500 ml	0	1	[41]
2002	6 (1/5)	53	2-6	CDI/PMC	6 (100)	9-50 months	Yes	no	1	30 ml	0	6	[42]
2003	18 (5/13)	73	2-7	CDI	15 (83)	90 days	15 yes/3 no	No	1	30 g	18	0	[43]
2003	24 (11/13)	19-59	Md	CDI	20 (83)	Nd	Related and non-related donors	Yes	1-10	200-300 g	8	16	[44]
2006	5 (0/5)	82	>2	CDI	5 (100)	2,5-21 months	No	No	1	30 ml	0	5	[45]
2007	16 (5/11)	11-87	Md	CDI	15 (94)	4-6 weeks	Related and non-related donors	Yes	1-24	200-300 g	0	16	[46]
2008	7 (4/3)	67	3	CDI	7 (100)	30 days-1 year	6 yes/1 no	Yes	1-3	50-100 g	3	4	[47]
2008	1 (1/0)	69	1	CDI	1 (100)	2 days	Yes	No	1	45 g	0	1	[48]
	159				144/159 (91)						32	127	Total

AAD: antibiotic-associated diarrhoea; CDI: C. difficile-associated disease; GI: gastrointestinal tract; Md: missing data; Nd: not determined; PMC: pseudomembranous colitis

*unclear, since C. difficile at that time was not identified as the causative organism, so adequate antibiotics where not given.

** Sex unknown.

i = two patients treated with a faecal enema of which one failed. The failing patient and four others were treated with a new enema, consisting of a bacterial culture.

Teicoplanin (although not widely available and expensive) is another antibiotic with high reported efficacy against CDI, and limited data suggest that it may be effective in recurrent CDI [24,25]. A new and specific antibiotic against *C. difficile* is OPT-80 (PAR-101), which belongs to a new class of antibiotics, the macrocycles [26]. Data from a phase 3 study are awaited, and its role in recurrent disease is yet to be determined.

Non-antibiotic treatment modalities for recurrent CDI

Toxin targeted therapy

Binding of the pathogenic toxins (A and B) of *C. difficile* may contribute to clinical improvement and subsequent regression of CDI. However, toxin-targeted therapy (e.g. cholestyramine) has not been investigated for recurrent disease. Tolevamer, a non-antibiotic toxin-binding polymer appeared less successful for treatment of an initial episode of CDI than metronidazole or oral vancomycin [27]. Future studies should address the efficacy of combination regimens of tolevamer and antibiotics for treatment of (recurrent) CDI.

A whey product (mucomilk) isolated from cows inoculated with *C. difficile* and inactivated *C. difficile* toxin, containing high amounts of secretory IgA seems to prevent recurrence of CDI if given as adjuvant therapy in patients treated with metronidazole or vancomycin [28]. However, a randomised placebo-controlled study is lacking and the value for recurrent CDI is unknown. Vaccines containing formaldehyde-inactivated toxins A and B have been developed and some promising initial experience has been gained in a few patients with recurrent CDI [29].

Intravenous immunoglobulins

Intravenous administration of immunoglobulins (IVIG) can be considered a last resort for recurrent disease, in particular for patients with a suspected impaired immune response to *C. difficile.* Although case series suggest a beneficial effect of IVIG at a dose of 300-400 mg/kg body weight once every three weeks, a case control study did not show a reduction in recurrences [30,31].

Probiotics treatment for recurrent CDI

Several randomised trials have compared probiotics (containing *Lactobacillus* species or *Saccharomyces*) to placebo as an additional treatment to antibiotics in patients with CDI. Although the results are not uniformly negative, a recent Cochrane systematic review concludes that there is insufficient evidence to recommend the addition of probiotics to antibiotics in recurrent disease [32]. Furthermore, the occurrence of *Saccharomyces* fungaemia in patients treated with *Saccharomyces* strains merits attention [33].

Donor faeces infusion

In 1958, the surgeon Eiseman successfully treated four patients with severe antibiotic-induced colitis with an enema that consisted of donor faeces [15]. Following this initial publication, more than 150 patients with recurrent CDI have been described, the vast majority of whom was cured by the infusion of faeces. Recovery of normal intestinal flora was (and is) postulated to be the mechanism for cure.

Literature review and experiences with fecal infusions

Publications that contained original data (case reports, case series, uncontrolled studies) were selected in Pubmed and Embase. From references and through Google, additional publications were collected. A total of 16 publications (two abstracts, 14 full publications) were found (Table 1).

Success rate of faecal therapy

Taken together, 91% of all reported patients with recurrent CDI treated with donor faeces (n=159, see Table 1) were cured after one or more infusions. Clinical improvement can be noticed within a few days following donor faeces infusion. Follow-up rates vary from one week to two years. Many patients had a reported follow-up of less than one month, which implies that definite success rates are often lacking.

Necessity of donor screening

Early reports on faecal installation only mention that donors who had used antibiotics in the preceding months were excluded [15]. Although transmission of infectious diseases has not been reported after faecal infusions, most publications from the past decade report extensive screening of donors [40,43]. Our protocol for screening of (healthy) donors is summarised in Table 2. Most donors are sought in relative proximity of the patient (partners, relatives, household members). However, there is no rationale to exclude healthy volunteers. Many reports fail to mention the exact origin of the donors and an investigation of patient preferences is lacking. We do not apply any restrictions concerning the food intake of donors prior to donation. Although there can be potential important differences in the quality of the microbiota present in donor faeces from different individuals, historically their intestinal flora has not been analysed prior to use for faecal infusion. Information is lacking with regard to the specific groups and amount of bacteria necessary for optimal restoration of intestinal flora, thereby preventing *C. difficile* to become clinically significant.

Route of instillation

Of the reported patients, 80% were given a faecal installation through enema or colonoscope, and 20% received the faeces through a nasogastric or nasoduodenal/jejunal tube [43]. From our own experience, infusing faeces through colonoscopy is more difficult and strenuous, whereas (slow) infusion through a nasoduodenal tube seems safe and time-efficient [47]. To our knowledge, no other authors have discussed their experiences with different routes of administration. A disadvantage of a nasoduodenal/jejunal tube is that donor faeces may be difficult to install if patients have signs of diminished passage of fluids through their intestines. On the other hand, infusing faeces using this route has the advantage that the infused flora reaches the whole bowel. In the reported cases, no specific side effects were reported related to installation of faeces in the upper or lower tract. With the limited numbers available it is not possible to predict which route of installation is more successful in curing patients from CDI.

Virtually all publications report diluting or homogenising the faeces in saline or water, prior to infusion either in the upper gastrointestinal tract through a tube, or in the colon through enema or colonoscopy. Gustafsson et al. report homogenising faeces in pasteurised cow's milk [40]. Almost all faecal preparations are processed in a normal aerobic environment. Only Schwan et al. specifically describe preparing enemas in an anaerobic cabinet [35]. In several reports it is stated that faeces are processed and infused as quickly as possible following production by the donor, in order to preserve faecal flora. Due to lack of detailed data it is not possible to establish a relationship between a prolonged time that has passed between production and infusion, and failure of therapy.

Pre-treatment

Most early reports fail to mention antibiotic usage directly preceding the treatment. Aas et al. gave a protocolised antibiotic

regimen of 500 mg vancomycin orally four times a day during four days preceding faecal installation [43]. In addition to antibiotics, four publications describing 48 patients report pre-treatment with a laxative directly prior to donor faeces infusion [41,44,46,47]. Most publications do not report any other preparation, apart from Aas et al. who gave patients an oral proton pump inhibitor before intragastric installation of donor faeces [43].

We pretreat patients with 500 mg orally four times a day during four days and oral whole bowel lavage with a macrogol solution in an attempt to remove the pre-existent (pathological) flora and *C. difficile* spores prior to donor faeces installation. It is not known, however, whether this contributes to the efficacy of donor faeces infusion for recurrent CDI.

Table 2

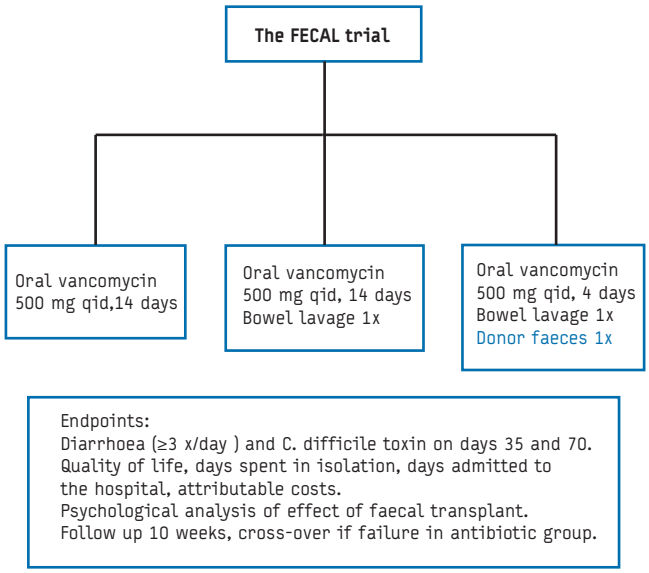
Screening of donors*

Donor	Faeces	Blood
Parasitology	Stool ova and parasites test ("Triple faeces test"[49] *Cryptosporidium* *Microsporidium*	*Strongyloides* *Entamoeba*
Microbiology	Faecal culture for common enteropathogens and *Clostridium difficile*	*Treponema pallidum*
Virology		Cytomegalovirus, Epstein-Barr virus, hepatitis A/B/C viruses Human immunodeficiency virus, human T-lymphotropic virus

*Prior to screening of faeces and blood, potential donors have to fill in an extensive questionnaire. Donors with abnormal bowel motions, abdominal complaints, symptoms indicative of irritable bowel syndrome, an extensive travel history or predisposing factors for potentially transmittable diseases are excluded. If they are considered eligible after completing the questionnaire, they are screened using the protocol above.

Figure

Design of the FECAL trial



qid: four times a day.

Side effects or potential adverse effects

Side effects are absent or not mentioned in all but one study which mentions (transient) side effects such as a sore throat following placement of the nasoduodenal tube, rectal discomfort following colonoscopy, flatulence, nausea and bloating [46]. We did not notice side effects in our patients treated with donor faeces infusions [47]. A possible complication could be bacterial overgrowth in the small intestine after intragastric or duodenal installation of faeces. In patients who have signs of diminished intestinal passage, infusion of faeces via the upper gastrointestinal tract should be avoided.

Faecal therapy to Eliminate *Clostridium difficile*-Associated Longstanding diarrhoea: the FECAL trial

To investigate the efficacy of faecal installations for recurrent CDI, a randomised trial comparing donor faeces infusion to conventional antibiotic treatment with oral vancomycin has been initiated in 2008 in the Netherlands. The trial follows a pilot study in which seven consecutive patients with recurrent CDI were successfully treated with one or more infusions of donor faeces [47]. Patients (over 18 years of age) are eligible if they have a proven relapse of CDI and are able to give informed consent. They are excluded if they are severely immunocompromised, have a life expectancy of less than three months, are admitted to the intensive care unit, need vasopressive therapy or if they are using antibiotics other than for the treatment of *C. difficile* for a prolonged period of time. The primary endpoint is response to treatment at 10 weeks after initiation of therapy. Secondary endpoints are response at five weeks, time nursed in isolation, and quality-adjusted life-years.

Response is defined as: absence of diarrhoea (diarrhoea is defined as ≥3 loose or watery stools per day for at least two consecutive days or ≥8 loose or watery stools in 48 hours), or persisting diarrhoea (due to other causes) with repeating (three times) negative stool tests for toxins of *C. difficile*. Treatment failure is defined as persisting diarrhoea with a positive *C. difficile* toxin stool test.

Eligible patients who have signed informed consent are randomised to one of three different treatment arms (Figure).

The conventional treatment arm (the control arm) consists of 500 mg vancomycin, given orally four times a day, for 14 days. The second treatment arm consists of 500 mg vancomycin, given orally four times a day for 14 days, combined with a whole bowel lavage by drinking four litres of a macrogol solution, taken on day four or five after initiation of the antibiotics. This arm serves as a second control arm to assess the role of whole bowel lavage in the treatment of recurrent CDI [50], since patients randomised to donor faeces infusion are also pre-treated with a bowel lavage. The

Box 2

Amsterdam protocol used for the preparation of donor faeces

1. Faeces are collected and weighed (ca. 60-120 g, depending on production);
2. 300-400 cm3 Saline (0.9% NaCl) is added and mixed until a smooth suspension is created;
3. Faeces are poured through a double gauze and put in a glass bottle;
4. Within six hours after production by the donor, the faeces are installed through a nasojejunal tube

third (experimental) arm consists of treatment with a suspension of faeces. Patients are pre-treated with vancomycin given orally for four days and a whole bowel lavage on the fourth day. In the period before randomisation and faecal infusion, treatment is often necessary to prevent spread and deterioration of the clinical condition. Furthermore, it is logistically difficult to give a faecal infusion directly after verifying the diagnosis. We believe it may be beneficial to prepare the bowel with a short course of vancomycin for the above mentioned reasons. In the protocol, a standardised preparation period of four days prior to the faecal infusion was chosen. On the fifth day, donor faeces (Box 2 and Table 2) are infused through a nasoduodenal tube. The nasoduodenal tube is placed radiologically or endoscopically. If there is any doubt regarding the position, an abdominal X-ray will be performed. Faeces are installed within six hours after production by the donor. After this treatment, all antibiotics are stopped. Patients will be followed for 10 weeks after randomisation by a weekly telephone assessment of diarrhoea and by *C. difficile* culture and toxin stool tests (ELISA) done four times, on days 14, 21, 35 and 70.

Outpatients from the Netherlands as well as from outside the Netherlands are eligible for the trial if they are willing to travel to Amsterdam for inclusion and donor faeces installation. Patients who fail in one of the antibiotic arms (i.e. the vancomycin arm or the arm which combines vancomycin with a whole bowel lavage) are offered a treatment with a faecal infusion following their proven failure.

Conclusion

Recurrent *C. difficile* infections are a growing burden and a therapeutic challenge for patients and physicians. Current therapy consists of repeated courses of antibiotics with limited success rates and new therapeutic options are urgently needed. Faecal installations from healthy donors for the treatment of recurrent CDI seem a promising approach, restoring a normal bowel flora and preventing further outgrowth of *C. difficile* and its spores. To date, more than 150 patients treated with donor faeces have been reported in the literature. A 91% success rate is reported in case series and case reports. Due to a lack of clinical trials, faecal installations often are offered only to patients with more than two relapses, since it is still considered a last, uncommon, and rather distasteful rescue therapy. Currently, adult patients with proven recurrent CDI can be included in the first randomised controlled study comparing donor faeces installation with antibiotic therapy (FECAI trial).

Competing interest and funding

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Increase in reported gonorrhoea cases in Sweden, 2001 - 2008

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Gonorrhoea is on the rise in Sweden and in many other European countries. The present report describes and evaluates the gonorrhoea trends in Sweden from 2001 to 2008 when an increase of 32% was reported. Up to 86% of the cases were reported in men, with the highest proportion among heterosexually infected men (41-59% during these years). Heterosexually infected men more often acquired gonorrhoea abroad, especially in Thailand, whereas women and men who have sex with men were more likely to acquire the infection within Sweden. The recent increase in gonorrhoea cases in Sweden is most likely due to adoption of more risky sexual behaviour (e.g. an increase in the number of sexual partners and the number of new/casual sexual partners and/or low use of condoms) in the Swedish population. Further research regarding more effective identification and description of sexual transmission chains and sexual networks is needed in order to follow the spread of infection and to recognise more effective interventions to prevent the spread of gonorrhoea and also other sexually transmitted infections.

Introduction

Gonorrhoea is a bacterial sexually transmitted infection (STI) that showed a steady decline in incidence during the 1970s, 1980s and early 1990s in Sweden. This epidemiological trend was also seen in many other, especially high- and middle-income, countries worldwide [1]. However, after an all-time low incidence in 1996 (2.4 per 100,000 population) with most of the cases acquired abroad, the gonorrhoea incidence in Sweden started to increase again (Figure 1) [2].

A similar increase has also been described from many other high- or middle-income, industrialised countries since the mid- or late 1990s. In north-western Europe, this re-emergence of gonorrhoea was primarily due to outbreaks among men who have sex with men (MSM), but also due to increased transmission among young heterosexuals of both sexes [2-4]. In 2005, it was estimated that 95 million gonorrhoea cases among adults occurred worldwide, with the majority of cases in Sub-Saharan Africa, South and South-East Asia, Latin America and the Caribbean [5].

Resistance of the aetiological agent of gonorrhoea, the bacterium Neisseria gonorrhoeae, to antimicrobials used in the traditional treatment (penicillin, tetracycline, and fluoroquinolones) of the infection is now prevalent worldwide. Most worrying, the level of resistance and/or reduced susceptibility of *N. gonorrhoeae* also to newer treatment alternatives, such as azithromycin and extended-spectrum cephalosporins (cefixime and ceftriaxone), has increased worldwide [6-8].

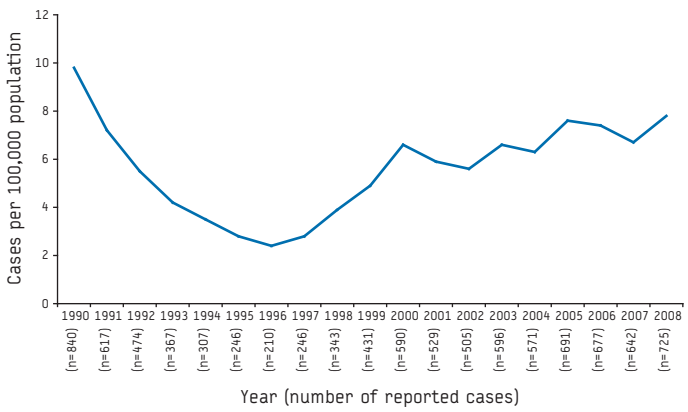
This report summarises the gonorrhoea surveillance data in Sweden for the last eight years (2001-2008).

Methods

Gonorrhoea is a notifiable infection in Sweden, in accordance with the Swedish Communicable Diseases Act, and the present surveillance system has been described elsewhere [2,9]. The gonorrhoea case definition used in Sweden since 1997 includes any person meeting the laboratory criteria. The laboratory criteria are as follows: a) *N. gonorrhoeae* has been isolated from a clinical specimen using culture, b) *N. gonorrhoeae*-specific antigen or nucleic acid has been demonstrated in a clinical specimen, and/or c) *N. gonorrhoeae* Gram-negative intracellular diplococci have been identified in a urethral smear from a symptomatic male. The Swedish laboratory confirmation also requires use of appropriate diagnostics. Quality-assured culture remains the recommended diagnostic method and accounts for most of the reported cases during each year. Positive nucleic acid amplification tests (NAATs) are recommended to be confirmed (using other method or a NAAT targeting another suitable gene). The Swedish gonorrhoea case

Figure 1

Incidence of reported gonorrhoea cases in Sweden, 1990–2008



definition is identical to the case definition of the European Union (EU) [10,11].

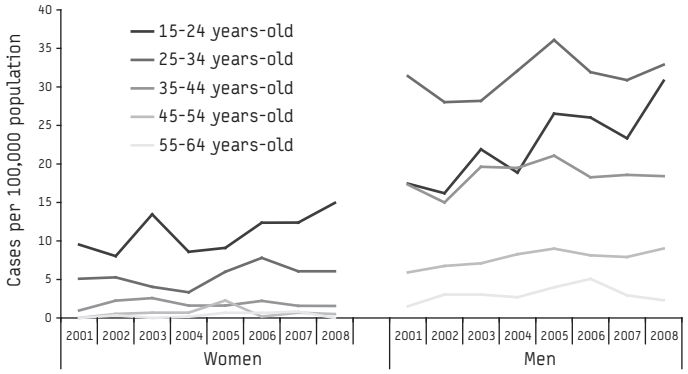
Data from the national computer-based surveillance system SmiNet was used to describe epidemiological trends for the period from 2001 to 2008. In this system, gonorrhoea cases are described by age, sex, reporting county, self-reported route of transmission (divided into heterosexual transmission, homosexual transmission and vertical transmission (mother to child), and country of acquisition (consistent with incubation period and anamnesis). Unfortunately, the electronic database can contain only one laboratory notification, and notifications from other sites for the same case are disregarded, which makes it impossible to draw any conclusions from the site of infection (therefore these data are not presented).

In this paper, we present data on the self-reported sexual route of transmission (not on sexual identity) when we are referring to homosexually infected men (MSM) and heterosexually infected men. Furthermore, the number of people tested and the number of people positive for *N. gonorrhoeae* are reported on a voluntary basis to the Swedish Institute for Infectious Disease Control, by the 29 laboratories in Sweden performing diagnostics for *N. gonorrhoeae*. These data are presented as number of people tested (by sex) and as positivity rate (proportion of people positive for *N. gonorrhoeae*). The annual incidence was calculated using all reported gonorrhoea cases per 100,000 population/men/women (population data from Statistics Sweden, www.scb.se).

The presented antimicrobial resistance data are from the Swedish Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital, Örebro, which annually reports trends and characteristics including antimicrobial resistance data of all examined Swedish *N. gonorrhoeae* isolates [12,13]. It is recommended by the Swedish Reference Laboratory that all gonococcal isolates should be examined for antimicrobial resistance. Although most isolates are actually tested, the results from a few laboratories are not available for this report.

FIGURE 2

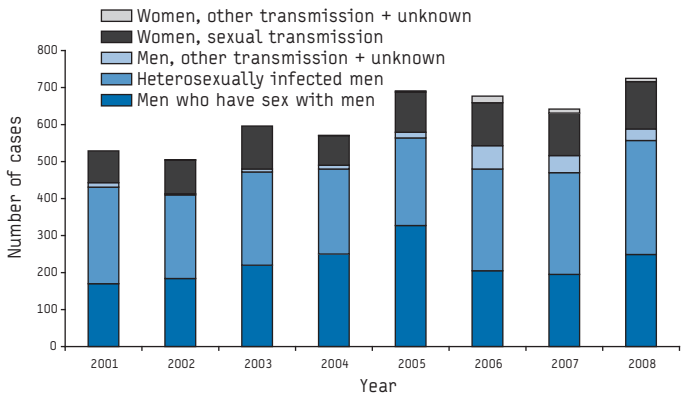
Gonorrhoea incidence in women (n=877) and men (n=4,020) by age group in Sweden, 2001–2008*



* Cases under 15 years and over 64 years (n=39) are not included in the figure.

FIGURE 3

Reported gonorrhoea cases by sex and self-reported route of transmission in Sweden, 2001–2008 (n=4,936)



Results

In the period from 2001 to 2008, a total of 4,936 gonorrhoea cases were reported to the national electronic surveillance system SmiNet. The gonorrhoea incidence during this period increased by 32% from 5.9 to 7.8 cases per 100,000 population (notably, this corresponds to a 225% increase since 1997) with several smaller incidence peaks in 2000 (6.6/100,000), in 2003 (6.6/100,000), in 2005 (7.6/100,000) and in 2008 (7.8/100,000). Overall during the study period, a steady upward trend in the incidence was observed (Figure 1).

Age

During 2001-2008, the median age for infected women was 27 years (range: 14-61 years), for heterosexually infected men 34 years (range: 15-80 years), and for MSM 32 years (range: 15-77 years). The highest incidences as well as the largest increase in incidence in both sexes were observed in the age groups of 15-24 year-olds and 25-34 year-olds, and were consistently higher among men (Figure 2).

Sex and self-reported route of transmission

Between 2001 and 2008, the male-to-female ratio varied from 4.1 to 6.2. The mean proportion of men in general and MSM was 83% (range: 80-86%) and 44% (range: 38%-56%), respectively (Figure 3). The proportion of female cases increased from 16% in 2001 to 20% in 2008.

Geographic spread

The majority of the gonorrhoea cases between 2001 and 2008 were reported from the counties with the highest number of population. Accordingly, Stockholm county (21% of Sweden's population) reported a mean of 68% of all gonorrhoea cases per year (range during 2001-2008: 61-73%), Skåne county (13% of Sweden's population) reported 10% (range: 6-16%), and Västra Götaland county (17% of Sweden's population) reported 10% (range: 5-16%).

Country of acquisition of the infection

In the period from 2001 to 2008, a mean of 60% of the cases had acquired the infection in Sweden, 34% abroad, and for 6% this information was not available. Women and MSM more often acquired gonorrhoea in Sweden (71% of the female cases and 79% of MSM). In contrast, heterosexually infected men more often acquired infection abroad (56%). No major longitudinal trends were identified regarding the country of acquisition of

gonorrhoea and way of transmission (Figure 4). For men who had acquired gonorrhoea abroad by heterosexual transmission, the most common countries of infection were Thailand (22-32% of these cases over the years) and the Philippines (3-5% of these cases). The other heterosexually infected male cases acquired gonorrhoea in countries worldwide that were implicated less frequently, e.g. 1-2% in northern European countries (Denmark, Finland, Iceland, Norway and Sweden), 1-4% in western European countries (United Kingdom, Spain, France, Germany, Portugal, Italy), and 0-1% in eastern European countries (Baltic States, Poland, Bulgaria) (range for 2001-2008). MSM who acquired gonorrhoea abroad most frequently acquired it in Denmark (1-8% of the cases), Spain (1-4% of the cases) and Germany (0.5-3% of the cases). Among men with unknown route of transmission, the majority had acquired gonorrhoea in Sweden (range for 2001-2008: 5-67%) and in Thailand (range: 0-33%).

Laboratory-based reporting of test volumes (voluntary)

According to the voluntary reporting from the laboratories, the number of persons tested for *N. gonorrhoeae* in Sweden increased by 15% from 48,925 in 2001 to 56,084 in 2008. The peak in the number of people tested in 2007 was likely due to the reports in late 2006 of the new variant of *Chlamydia trachomatis* (nvCT), which resulted in high numbers of false-negative results. In 2007, when new genetic assays detecting the nvCT had been introduced, many people were re-tested (testing volumes for *C. trachomatis* significantly increased in 2007), and were most probably also tested for gonorrhoea at the same time. All 29 laboratories performing testing for *N. gonorrhoeae* reported most of the requested data and, accordingly, the coverage was as high as 97-100% in the period from 2001 to 2008, although reporting was voluntary. Of those tested, 60-64% were women. Despite the fact that more women were tested for *N. gonorrhoeae*, only 0.3-0.4% were found to be positive. In contrast, 2.2-2.9% of the tested men were positive (Figure 5), which may also reflect that gonorrhoea is more commonly symptomatic in men than in women. In general, no major trends were seen in the positivity rates for women or men from 2001 to 2008. Furthermore, during the study period, there has not been any major change in the laboratory methods used for diagnosis.

FIGURE 4

Gonorrhoea reported to be acquired in Sweden and abroad by sex and route of transmission, 2001–2008 (n=4,936)

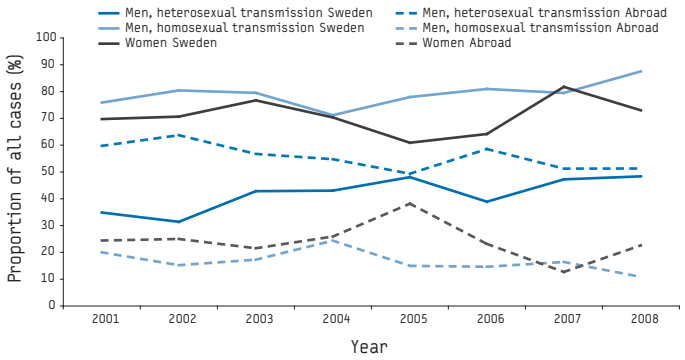
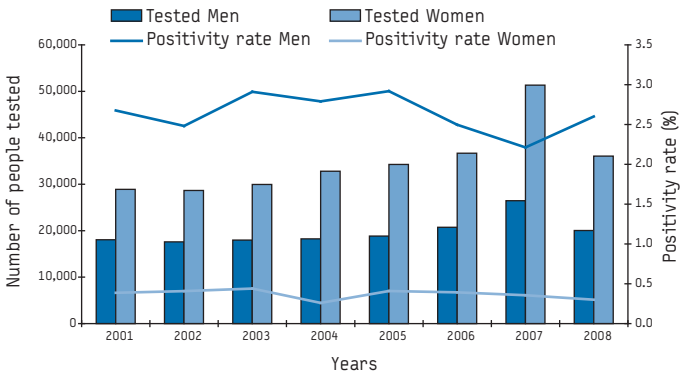


FIGURE 5

Number of persons tested and positivity rate for *Neisseria gonorrhoeae* among men and women in Sweden, 2001–2008



Antimicrobial resistance of Swedish *Neisseria gonorrhoeae* isolates

Between 2001 and 2008, all Swedish isolates reported by the Swedish Reference Laboratory (n=2,242) were susceptible to spectinomycin (100%), 99.96% to ceftriaxone (i.e. only one isolate in 2008 displayed an intermediate susceptibility/resistance in vitro), 98.7% to cefixime, and 94.8% to azithromycin. However, the level of intermediate susceptibility to cefixime increased from 0% to 4% and the resistance to azithromycin increased from 0% to 3% (0-10% intermediate susceptibility), over the years. The level of beta-lactamase production, intermediate susceptibility and resistance to ampicillin, and intermediate susceptibility and resistance to ciprofloxacin varied from 22% to 39%, 66% to 82%, and 50% to 71%, respectively, over the study period [12,13].

Discussion

The incidence of reported gonorrhoea cases in Sweden has increased by 32% over the last eight years (2001-2008), from 5.9 to 7.8 cases per 100,000 population, an increase of 225% compared to the all-time low incidence in 1996 (2.4 per 100,000 population) [2]. Similar increasing patterns have also been observed in other Nordic countries such as Denmark and Norway [4,14] as well as in other EU countries [3,15,16]. The main contributors to the recent increasing trend in Sweden, in particular in the period form 2005 to 2008, were heterosexually infected men but also women: the proportion of heterosexually infected men increased from 41% to 59% and the proportion of female cases increased from 16% to 20% during these years. MSM also contributed to the increase in gonorrhoea cases. However, the proportion of these cases decreased from 56% to 42% in the past four years (2005-2008).

The majority of the heterosexually infected men acquired gonorrhoea abroad, with the majority of cases acquired in Thailand, sometimes through sexual contacts with female commercial sex workers (FCSWs; it is occasionally but not consistently possible to collect these data). This is most worrying because Thailand has a high prevalence of human immunodeficiency virus (HIV) infection and many other STIs among commercial sex workers. For instance, recent estimates among FCSW in Thailand revealed an HIV prevalence of 4.7% among venue-based FCSW and of 43% among street-based FCSW [17]. Accordingly, the heterosexual Swedish men may, in addition to gonorrhoea, also acquire HIV and other STIs that they could transmit to others after their return to Sweden. A similar pattern has also been observed in Norway [4]. This provides support for targeted prevention interventions

among Swedish men going abroad, especially to Thailand and the Philippines.

The high proportion of MSM (38-56% during the study period) among the men gonorrhoea cases in Sweden is also a reason for concern. Some MSM have not consistently adopted safe sex practices and therefore maintain continuous possibilities for transmission of STIs and HIV [3]. An increasing number of casual sexual partners, anonymous sexual partners, and non-use of condoms are likely to have contributed to the recent increases in STIs among MSM [3,18]. Preventive programmes with adapted educational messages tailored specifically to MSM would be beneficial.

From 2001 to 2008, gonorrhoea cases were reported from all over Sweden with a higher number of cases reported from the counties with the largest cities, such as Stockholm county, Skåne, and Västra Götaland. This correlates well with the reported syphilis cases in Sweden [9], suggesting that cities with a large population provide an environment where free sexual behaviour is more readily accepted. In addition, sexual networks tend to be larger in the cities and the chances of contact with risk groups for STI transmission are higher.

The increase in gonorrhoea and other STIs in Sweden could be due to several reasons. One of the most important reasons might be the adoption of more risky sexual behaviour which has been observed in studies among MSM in Sweden [19]. For example, practise of unprotected anal sex during the last 12 month was reported by 59% of responding MSM with an average number of three to four partners during the last 12 month, as well as practise of unprotected anal sex with a partner with unknown HIV-status (during the last sexual contact) [19]. The present study observed more risky sexual behaviour not only among MSM but also among heterosexually infected men and women. The increase in the number of sexual partners overall and in the number of new/casual sexual partners combined with an insufficient use of protection is certainly one of the factors contributing to the spread of gonorrhoea. Regular assessments and studies of sexual knowledge, behaviour, attitudes, and the risks of HIV/AIDS and STIs that have been performed in Sweden since 1989 provide comprehensive and valuable insights into these factors [20,21]. These studies showed that in the years from 1989 to 2003, the prevalence of casual sexual contacts (unspecified type of sexual contacts) without condom use rose significantly, especially in the age groups under 35 years (both men and women) [20]. Furthermore, the proportion of 18-19 year-old men and women who had more than three sexual partners during the last 12 months increased between 1989 and 2007 from 17% to 23% in men and from 13% to 26% in women [21]. These studies, as well as surveillance data for gonorrhoea (and other STIs), support the need for targeted prevention interventions in vulnerable groups of the Swedish population.

The upward trend of gonorrhoea in Sweden during the period analysed in this study cannot be explained by changes in the national gonorrhoea case definition or the diagnostic methods. Nevertheless, another possible contributing factor is a rise in the number of people tested for *N. gonorrhoeae* (by 59% in 2001-2008), which is partly a result of an improved access to health care.

Gonorrhoea is on the rise in many European countries [3,4,14,22,23]. There are also major concerns worldwide regarding the high level of antimicrobial resistance in *N. gonorrhoeae*, and it is crucial for effective treatment to perform antimicrobial resistance surveillance locally, nationally and internationally. Accordingly, gonorrhoea needs special attention from health care professionals, health promoters, surveillance facilities and diagnostic laboratories. Further research regarding more effective identification and description of sexual transmission chains and sexual networks is needed in order to follow the spread of infection and to recognise more effective interventions to prevent the spread of gonorrhoea as well as other STIs.

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