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First case of meningococcal meningitis due to *Neisseria meningitidis* serogroup Z' in Slovenia, December 2010

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We report here on the identification of the first meningococcal meningitis case in Slovenia caused by *Neisseria meningitidis* serogroup Z' in December 2010. The 19-year-old patient had not left the country during the incubation period. The patient was hospitalised and given the antibiotic treatment with cefotaxime very early in the course of the disease. The patient did not develop any complications during hospitalisation and was discharged on 5 January 2011.

Case report

On 27 December 2010, the epidemiologist of the Regional Institute of Public Health of Celje, Slovenia, was informed about a 19-year-old patient hospitalised in the Department of Infectious Diseases and Febrile Conditions of the General Hospital in Celje, with clinical suspicion of meningococcal meningitis.

The patient had been admitted to the Department of Infectious Diseases and Febrile Conditions of the General Hospital on 26 December 2010, with fever (39.9 °C but no chills), headache, mild sore throat and muscular pain since approximately six hours. He had no underlying chronic conditions and had been healthy previously.

When examined, the patient presented meningeal symptoms (nuchal rigidity, Kernig and Brudzinski signs). His throat was mildly reddened, but there were no other symptoms. Laboratory findings showed mild leukocytosis, but neutrophils was predominating (Table). Samples for blood cultures were taken upon admission.

Viral meningitis was suspected and the patient was hospitalised for observation. Despite his generally good condition, the physician repeated the basic laboratory tests four hours after hospitalisation and found a clinically significant increase in the white blood cell count and a small rise of C-reactive protein (Table). Approximately six hours after hospitalisation, discrete petechiae were identified on the patient's hands. Meningococcal meningitis was suspected, lumbar puncture immediately carried out and antibiotic treatment started (2 g cefotaxime every four hours for 10 days) [1]. After 24 hours of antibiotic therapy, the patient no longer had fever or headache, but still showed petechiae and ecchymoses.

Cerebrospinal fluid (CSF) was macroscopically clear with pleocytosis (white blood cell count of 27 per mm^3, predominantly neutrophils), while the protein and glucose levels were within normal range. On 27 December 2010, blood for haemoculture and CSF to test for *N. meningitidis* (Gram staining, antigen detection and culture) were sent to the Department of Medical Microbiology, Institute of Public Health Celje. Gram staining and antigen detection were negative, haemoculture was positive, and CSF remained negative. CSF for rapid molecular diagnostics (real-time polymerase chain reaction, RT-PCR) was sent to the Department of Medical Microbiology, Institute of Public Health of the Republic of Slovenia. RT-PCR was performed on the same day to detect the *ctrA* (capsular transport) gene, which is specific to *N. meningitidis* [2], and using specific primers, we have shown that the isolate did not belong to serogroups B or C.

Meningococci grew from blood cultures after two days, but not from CSF. The isolate from blood cultures was phenotypically typed using slide agglutination with monoclonal antisera (Becton Dickinson, United States of America). On 31 December 2010, we confirmed *N. meningitidis* serogroup Z' as cause of the disease.

The patient did not develop any complications during hospitalisation and was discharged on 5 January 2011. Upon discharge, his skin changes were in regression and he had no other symptoms. He was advised to undergo further tests and to check for possible immunodeficiency, and to be vaccinated against further meningococcal infection. This decision was made although the Slovenian vaccination guidelines do not recommend vaccination of the index case [3]. The patient was vaccinated with quadrivalent polysaccharide meningococcal vaccine on 16 January 2011. The

quadrivalent conjugate meningococcal vaccine is not yet available in Slovenia.

Epidemiological investigation

After microbiological confirmation of meningococcal meningitis on 27 December 2010, we started to identify close contacts for post-exposure chemoprophylaxis (PEP) in accordance with Slovenian methodology [3]. We identified seven close contacts among the family members: six adults who were given one dose (500 mg) of ciprofloxacin and an eight-month-old child who was treated with rifampicin for two days (10 mg/kg two times per day) [3,4].

We also identified 10 student friends of the patient as close contacts, as they had been in contact with him seven days before the onset of symptoms. They were also given 500 mg ciprofloxacin. Until 29 December 2010, all close contacts, from different Slovenian towns, received PEP in various Slovenian regional institutes of public health.

Discussion

N. meningitidis serogroups A, B and C cause 90% of meningococcal meningitis cases and among these, serogroup B is the most common [5]. In 1999, the incidence of meningococcal disease among participating countries in the EU-IBIS network (European Union Invasive Bacterial Infections Surveillance) varied between <1 and 14.3 per 100 000 population. In 2004 serogroup B caused invasive meningococcal diseases in different European countries in various percentage (from 40% in Italy to 95% in Ireland) [6]. Vaccine against serogroup B is still not available. As other countries in Europe, Slovenia registered a substantial increase in the number of invasive meningococcal disease cases caused by serogroup C, after 2002. Serogroup C is most common among adolescents and causes a severe clinical picture [6,7]. After 2000, in Slovenia, the frequency of serogroup W 135 isolates increased, while serogroup A was isolated for the first time in 2007 in a Tunisian tourist [8].

In 2009, 11 sporadic cases of invasive meningococcal disease caused by *N. meningitidis* were confirmed in Slovenia: nine were children under 15 years and two were adults [8]. Meningococci were isolated from blood (five cases), CSF (four cases) and from both blood and CSF (two cases). All isolates were serotyped: in seven cases, the disease was caused by *N. meningitidis* serogroup B, in three cases by serogroup C and in one case by serogroup W 135. Using RT-PCR, we confirmed four cases from CSF, three belonging to serogroup B and one to serogroup C.

According to the literature, serogroup Z' rarely causes meningococcal infections [9,10]. In epidemiological studies investigating the carriage of *N. meningitidis*, this serogroup was confirmed in a low percentage of cases of meningococcal infection (from 5.6% to 5.8%) [9]. The case described here is the first in Slovenia where the invasive meningococcal infection was caused by *N. meningitidis* serogroup Z'. The patient had not left Slovenia during the incubation period.

The Slovenian PEP methodology recommends use of rifampicin, ciprofloxacin or ceftriaxone, for all meningococcal meningitis cases, according to the age or physical condition of the contacts. For instance, ceftriaxone is recommended during pregnancy [3]. For the contacts of the case described here, 16 adults were given ciprofloxacin, while the contact who was eight-months-old was given rifampicin. None of the contacts developed the disease. In 2009, there were no *N. meningitidis* isolates in Slovenia with total or intermediate resistance to third-generation cephalosporins [8].

As there is no vaccine against serogroup Z' and the results of the complement investigation were not known, the patient was vaccinated with quadrivalent polysaccharide meningococcal vaccine.

Table

Results of laboratory tests for the meningococcal meningitis serogroup Z' case, Slovenia, December 2010

Variable	Reference range	On admission	Four hours after admission
White cell count (per mm^3)	4,500–10,000	11,200	17,900
Differential count (%)			
Neutrophils	40–75	86.9	NT
Band forms	<10	0	NT
Lymphocytes	20–50	6.3	NT
Monocytes	2–10	6.3	NT
Basophils	<1	0.2	NT
Eosinophils	<6	0.3	NT
Platelet count (per mm^3)	140,000–360,000	160,000	185,000
C-reactive protein (mg/L)	<5	12.8	40.5
Procalcitonin (µg/L)	<0.5	NT	23.7

NT: not tested.

Conclusion

N. meningitidis serogroup Z' rarely causes invasive meningococcal disease. Before the identification of this case, Slovenia had not registered the disease caused by this serogroup. Even though serogroup Z' infection usually does not result in serious illness, the patient described in this report had fever, headache and petechial bleeding, but his clinical condition was stable after antibiotic treatment.

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Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010

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This report describes one case of verified treatment failure of pharyngeal gonorrhoea using ceftriaxone in Sweden. Previous reports described verified treatment failure of urogenital gonorrhoea using the internationally recommended first-line drug cefixime, but not with ceftriaxone, the last remaining option for empirical treatment of gonorrhoea. Enhanced awareness of clinical failures, pharmacodynamic considerations, follow-up and test of cure, adherence to appropriate case management and treatment guidelines as well as verification/falsification of presumed clinical treatment failures should be emphasised worldwide.

Case report

In late July 2010, a Swedish heterosexual man in his early 20s presented to a primary healthcare clinic in Sweden (on day 1) with symptoms and signs of urogenital and pharyngeal infection (Table). Four days earlier he had had protected vaginal intercourse and unprotected oral sex with a casual female partner in Japan. Polymerase chain reaction (PCR) analysis of DNA obtained from his urine sample was positive for *Neisseria gonorrhoeae* (using Cobas 4800 PCR, Roche Molecular Systems). He was given out-of-date empirical treatment for gonorrhoea (amoxicillin) and referred to a clinic for sexual transmitted infections. On day 12, he presented to this clinic with resolved urogenital symptoms, but pharyngeal inflammation was still present. Although microscopy, culture and PCR analysis of urogenital samples were negative for *N. gonorrhoeae*, a pharyngeal culture was *N. gonorrhoeae* positive and he was therefore given (day 26) ceftriaxone (250 mg), an extended-spectrum cephalosporin (ESC), which is an internationally recommended first-line treatment for gonorrhoea. On day 36, follow-up examination and test of cure showed that the pharyngeal culture remained positive, the pharyngeal inflammation persisted, and he was given 500 mg ceftriaxone on day 43. On day 50, he returned with persisting positive pharyngeal culture and pharyngeal inflammation. He was subsequently administered one dose of 1 g ceftriaxone intraveneously (on day 71) and was also referred to an otorhinolaryngologist, who did not identify any pharyngeal abnormalities. On days 85 and 92, two follow-up examinations showed no visible signs of infection and two pharyngeal cultures were negative for *N. gonorrhoeae*. The patient reported no sexual contacts from day one until the *N. gonorrhoeae* culture results were negative (Table).

Characterisation of *N. gonorrhoeae* isolates (before and after treatment)

All *N. gonorrhoeae* isolates were species-confirmed by sugar utilisation test and Phadebact Monoclonal GC Test (Pharmacia Diagnostics).

All pre- and post-treatment isolates were indistinguishable using serovar determination (Bpyvut), full-length DNA sequencing of the *N. gonorrhoeae* porB gene, and *N. gonorrhoeae* multiantigen sequence typing (NG-MAST; ST2958), performed as previously described [1]. Using Etest (AB bioMérieux, Sweden), all isolates displayed a ceftriaxone minimum inhibitory concentration (MIC) of 0.125 or 0.25 mg/L (Table), and overall indistinguishable antibiograms (ampicillin 2 mg/L, cefixime 0.5 mg/L, spectinomycin 12 mg/L, azithromycin 0.5 mg/L, ciprofloxacin >32 mg/L, gentamicin 4 mg/L) and were beta-lactamase negative. According to the ceftriaxone breakpoints stated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [2], the ceftriaxone MICs of these isolates were equal to or slightly above the resistance breakpoint (>0.125 mg/L). Sequencing of the *N. gonorrhoeae penA, mtrR* and *porB1b* alleles, which are known to contribute to the resistance to ESCs, was performed as previously described [3]. All isolates contained an identical *penA* mosaic allele that has been correlated with treatment failure using oral ESCs in Japan and recently in Norway [4-6], and had *mtrR* and *penB* alterations that enhance further the ESC MIC [7,8].

Background

Gonorrhoea remains a public health concern globally. *N. gonorrhoeae* has developed resistance to all

antimicrobials previously used as first-line treatments [4]. Furthermore, susceptibility to the currently internationally recommended first-line ESCs that are the last remaining treatment options – cefixime (oral) and ceftriaxone (injectable) – has rapidly decreased worldwide [4]. Verified treatment failures using cefixime have already been reported from Japan [5] and recently also from Europe [6]. Treatment failures of urogenital gonorrhoea using ceftriaxone have still not been verified, but two cases of clinical failure in the treatment of pharyngeal gonorrhoea were reported in Australia [9]. However, as the ceftriaxone MICs of these gonococcal isolates were low (0.016 and 0.032 mg/L), these clinical failures were unlikely to have been due to bacterial resistance. Rather it was probably due to the known difficulties in treating pharyngeal gonorrhoea compared with urogenital infection. Due to pharmacodynamic parameters, few antimicrobial drugs can reliably cure more than 90% of pharyngeal gonorrhoea infections [4,10-12]. Worryingly, the first *N. gonorrhoeae* strain displaying high-level ceftriaxone resistance has now been isolated in Japan [13].

Discussion and conclusion

This study describes one case of clinical failure of pharyngeal gonorrhoea using internationally recommended first-line treatment ceftriaxone, which is the last remaining treatment option. The treatment failure was rigorously confirmed in accordance with the World Health Organization (WHO) recommendations [4], i.e. a detailed clinical history was recorded and the likelihood of re-exposure and reinfection was excluded as much as possible. Accordingly, the patient reported no sexual contact after his initial one in Japan (place of exposure) and the gonococcal sequence type identified, ST2958, has previously been found only in Australia [14]. Furthermore, pre- and post-treatment isolates were phenotypically and genetically indistinguishable using highly discriminatory genetic epidemiological typing, MICs of ceftriaxone were substantially enhanced, and the isolates contained resistance determinants causing enhanced ceftriaxone MICs.

We may now be reaching the ceftriaxone MICs for which complete bacterial eradication in pharynx, and soon in the urogenital tract, will be impossible in rare cases. According to Monte Carlo simulations [15], a 250 mg dose of ceftriaxone results in median times of free ceftriaxone above the MIC (*f*T>MIC) of only 24.1 h (range: 10.5–52.2 h) and 15.4 h (range: 5.3–34.3 h) for the MICs of 0.125 mg/L and 0.25 mg/L, respectively, which were detected in the present study. Such ceftriaxone MICs may cause rare treatment failures, which most likely will be more frequent when treating pharyngeal gonorrhoea, for which the *f*T>MIC of accessible ceftriaxone will be even shorter. Such treatment failures may already be occurring but not being identified due to rare use of test of cure and also because

Table

Details of verified clinical failure of one case of *Neisseria gonorrhoeae* pharyngeal infection using internationally recommended first-line ceftriaxone treatment of gonorrhoea, Sweden, 2010

Type of healthcare clinic (day of presentation)	Symptoms (signs)	Diagnostic test		MIC (mg/L)[a]		NG-MAST[b]	Treatment (day administered)
		Positive (type of sample)	Negative (type of sample)	*Ampicillin*	*Ceftriaxone*		
Primary (1)	Urethral discharge, dysuria, pharyngeal pain (inflammation in urethra and pharynx)	PCR (urine)	NA	NA	NA	NA	Amoxicillin Two daily doses of 750 mg, for 10 days, oral administration (first administered on day 1)
STI (12)	– (inflammation in pharynx)	Culture (pharyngeal)	Microscopy and culture (urethral) PCR (urine)	2	0.125	ST2958	Ceftriaxone One dose of 250 mg, intramuscular administration (day 26)
STI (36)	– (inflammation in pharynx)	Culture (pharyngeal)	NA	2	0.125	ST2958	Ceftriaxone One dose of 500 mg, intramuscular administration (day 43)
STI (50)	– (inflammation in pharynx)[c]	Culture (pharyngeal)	NA	2	0.25	ST2958	Ceftriaxone One dose of 1 g, intravenous administration (day 71)
STI (85 and 92)	– (–)	NA	Culture (pharyngeal)	NA	NA	NA	NA

MIC: minimum inhibitory concentration; NA: not applicable; PCR: polymerase chain reaction; STI: sexually transmitted infections.

[a] Etest was used and all MIC values were rounded up to whole MIC dilutions.

[b] *Neisseria gonorrhoeae* multiantigen sequence typing of cultured *N. gonorrhoeae* post-treatment isolates.

[c] The patient was also referred to an otorhinolaryngologist, who did not identify any pharyngeal abnormalities.

azithromycin [16] is administered to many gonorrhoea patients, due to suspicion of concomitant chlamydial infection [4,15].

Notably, the current case presented initially to a primary healthcare clinic with urogenital and pharyngeal symptoms. Despite the pharyngeal pain, however, no pharyngeal sample was taken and, in addition, he was given out-of-date treatment. It is therefore crucial that national case management and treatment guidelines are up to date and strictly adhered to at all levels of the healthcare system, including at the primary level.

In conclusion, one case of clinical failure using standard ceftriaxone treatment for pharyngeal gonorrhoea has been verified in Sweden. An increased awareness of future clinical failures (including those using ceftriaxone), more frequent test of cure, and strict adherence to appropriate case management and treatment guidelines as well as verification/falsification of presumed treatment failures should be emphasised worldwide. Importantly, treatment of pharyngeal gonorrhoea poses a considerable challenge as it is harder to treat than urogenital infection, is frequently asymptomatic and acts as a reservoir for infection and emergence of resistance [4]. Accordingly, it is important not only to collect information regarding clinical anamnesis, but also on patients' sexual practices and, if indicated, subsequently take extragenital samples as well. Finally, there is a need for studies on the pharmacokinetics/pharmacodynamics of antimicrobial drugs in the pharynx, and new treatment options (single or in combination) as well as new drug development for gonorrhoea treatment.

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Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11

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This study provides mid-season estimates of the effectiveness of 2010/11 trivalent influenza vaccine and previous vaccination with monovalent influenza A(H1N1)2009 vaccine in preventing confirmed influenza A(H1N1)2009 infection in the United Kingdom in the 2010/11 season. The adjusted vaccine effectiveness was 34% (95% CI: -10 - 60%) if vaccinated only with monovalent vaccine in the 2009/10 season; 46% (95% CI: 7 - 69%) if vaccinated only with trivalent influenza vaccine in the 2010/11 season and 63% (95% CI: 37 - 78%) if vaccinated in both seasons.

Introduction

Following the emergence of pandemic influenza A(H1N1)2009 virus and the development of several monovalent pandemic influenza A(H1N1)2009 vaccines, a number of observational studies have since demonstrated the clinical effectiveness of these vaccines in various settings during the 2009/10 influenza A(H1N1)2009 pandemic [1-3]. Uncertainty exists, however, about their duration of protection.

Vaccination with the 2010/11 northern hemisphere seasonal trivalent influenza vaccine, which includes the influenza A(H1N1)2009 strain, was started in autumn 2010. The United Kingdom (UK) target populations for vaccination were individuals aged six months to under 65 years in clinical risk groups at elevated risk of severe disease (including pregnant women) and individuals aged 65 years and over [4]. Approximately 35% of those under 65 years of age in a clinical risk group had already received monovalent pandemic influenza vaccine in 2009/10 [4].

In the period December 2010-January 2011, the UK experienced widespread influenza A(H1N1)2009 transmission. Using the established swab-negative case-control approach in primary care [5,6], this study sets out to provide in-season interim estimates of the effectiveness of the 2010/11 seasonal influenza vaccine in preventing confirmed influenza infection in the UK in 2010/11 and the potential effect of previous vaccination with monovalent A(H1N1)2009 vaccine.

Methods

Study population and period

This study uses data from four influenza sentinel surveillance schemes in England, Scotland and Wales. Details of the Royal College of General Practitioners (RCGP), Health Protection Agency (HPA) Regional Microbiology Network (RMN) and Health Protection Scotland (HPS) swabbing schemes have been described previously [3]. Public Health Wales operates a sentinel general practitioner (GP) swabbing scheme with 44 practices covering a population of 355,705, 12 per cent of the population in Wales.

This study covers samples collected in the period from 1 September 2010 to 11 January 2011. Cases were individuals presenting with an acute influenza-like illness (ILI) in a participating practice in the study period who were swabbed and tested positive for influenza regardless of type or subtype. ILI was defined as an acute respiratory illness with fever or complaint of feverishness. Controls were individuals presenting with ILI in the same period that were swabbed and tested negative for influenza. A standard specimen request form provided demographic and clinical information on cases and controls including date of birth, sex, risk

group, date of onset of illness, date of specimen collection, influenza vaccination status for the current and previous season and vaccination dates.

Laboratory methods

Samples in England were sent to the HPA Microbiology Services (RCGP scheme) or one of the local HPA Regional laboratories (RMN scheme). Samples in Wales were sent to the Public Health Wales Specialist Virology Centre and in Scotland to the West of Scotland Specialist Virology Centre (HPS scheme) for molecular testing. Laboratory confirmation was undertaken using reverse transcription polymerase chain reaction (RT-PCR) assays for circulating influenza A viruses, influenza B viruses and other respiratory viruses [7,8].

Statistical methods

In order to assess vaccine effectiveness (VE) against influenza A(H1N1)2009 infection, a four-level variable was defined with the following four categories:

1. Unvaccinated in both years (not in receipt of either pandemic influenza A(H1N1)2009 vaccine in 2009/10 or trivalent vaccine in 2010/11);
2. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 but not in receipt of 2010/11 trivalent vaccine;
3. Receipt of either pandemic influenza A(H1N1)2009 vaccine in 2010/11 (provided to certain risk groups) or trivalent vaccine in 2010/11 or both, but not vaccinated in 2009/10;
4. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and trivalent vaccine in 2010/11, or received first dose of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and second dose in 2010/11.

Persons who had received two doses of pandemic influenza A(H1N1)2009 vaccine in 2009/10 were not analysed separately from those who received only one dose as the numbers were low.

Individuals were considered vaccinated if their date of seasonal or pandemic influenza A(H1N1)2009 vaccination was 14 days or more before the date of onset of illness. Persons for whom the interval between vaccination and onset of illness was less than 14 days were excluded, as their immunity status was considered unknown. If a person's trivalent vaccination status was known but not their pandemic influenza A(H1N1)2009 vaccination status or vice versa, they were excluded from the estimation of VE for influenza A(H1N1)2009 vaccine. For the estimation of VE for influenza A(H3) or B, pandemic vaccination status was not considered of interest. If the date of trivalent vaccination was missing, it was assumed that the person was vaccinated more than 14 days before the onset date, and for pandemic influenza A(H1N1)2009 vaccine it was assumed the person was vaccinated in 2009/10.

The same approach was used if date of onset was missing in a vaccinated individual. Respiratory samples with a delay greater than 29 days between onset of illness and sample collection were excluded as the sensitivity of the PCR test reduces for long intervals between onset and sampling. A sensitivity analysis was undertaken censoring at seven days between onset of illness and sample collection.

Vaccine effectiveness was estimated as 1-[odds ratio] using multivariable logistic regression models with influenza A(H1N1)2009 or influenza B PCR results as outcomes and seasonal or pandemic vaccination status

Table 1

Inclusion and exclusion criteria of participants for specimens submitted, United Kingdom, 1 September 2010 –11 January 2011

Criteria	Excluded	Included
1. Original participants		4,554
- Excluded as no PCR results available	538	
- Remaining participants		4,016
2. Influenza A(H1N1)2009 endpoint		
- Excluded as confirmed influenza B or A(H3)	535	
-Excluded as no result for influenza A(H1N1) 2009	1	
- Excluded as missing vaccination history	553[a]	
Interval between onset of illness and sample longer than 29 days	36	
- Final remaining study participants		*2,891*
3. Influenza A(H3)/B endpoint		
- Excluded as confirmed A(H1N1)2009	1,251	
-Excluded as not tested/no result for influenza B	8	
- Excluded as missing vaccination history	236	
Interval between onset of illness and sample longer than 29 days	34	
- Final remaining study participants		*2,487*

[a] Including eight people with sample taken later than 29 days after onset of illness.
PCR: Polymerase chain reaction.

Table 2

Details for pandemic influenza A(H1N1)2009 cases and controls, United Kingdom, September 2010 – January 2011 (n=3,480)[a]

	Number of controls (%) (n=2,229)	Number of cases (%) (n=1,251)
Age group (years)		
<5	224 (10.0)	93 (7.4)
5-14	217 (9.7)	130 (10.3)
15-44	1,030 (46.2)	734 (58.7)
45-64	526 (23.6)	272 (21.7)
≥65	215 (9.6)	16 (1.3)
Missing	17 (0.8)	6 (0.5)
Sex		
Male	843 (37.8)	514 (41.1)
Female	1,324 (59.4)	668 (53.4)
Missing	62 (2.8)	69 (5.5)
Month of sample collection		
September 2010	67 (3.0)	0 (0)
October 2010	436 (19.6)	24 (1.9)
November 2010	629 (28.2)	51 (4.1)
December 2010	934 (41.9)	1,096 (87.6)
January 2011	163 (7.3)	80 (6.4)
Missing	0 (0)	0 (0)
Interval from onset of illness to sampling (days)		
0-1	245 (11.0)	193 (15.4)
2-4	847 (38.0)	598 (47.8)
5-7	462 (20.7)	197 (15.7)
8-14	283 (12.7)	97 (7.8)
15-29	85 (3.8)	18 (1.4)
>29	36 (1.6)	8 (0.6)
Missing	271 (12.2)	140 (11.2)
Vaccination status		
Unvaccinated	1,567 (70.3)	1,022 (81.7)
Vaccinated 2009/10 season only	105 (6.7)	26 (2.1)
Vaccinated 2010/11 season only	78 (3.5)	22 (1.8)
Vaccinated in both seasons	86 (3.9)	21 (1.7)
Vaccination status missing (either 2009/10 season, 2010/11 season or both)	393 (17.6)	160 (12.8)
Surveillance scheme		
RCGP	1,529 (68.6)	775 (34.8)
RMN	239 (10.7)	171 (7.7)
HPS	410 (18.4)	250 (11.2)
Wales	51 (2.3)	55 (2.5)
Missing	0 (0)	0 (0)

HPS: Health Protection Scotland; RCGP: Royal College of General Practitioners' surveillance scheme; RMN: Health Protection Agency Regional Microbiology Network.

[a] Includes those with missing vaccination history and/or interval from onset of illness to sample longer than 29 days.

as the linear predictor. Age (coded into five standard age groups, <5 years, 5-14 years, 15-44 years, 45-64 years and ≥65 years), surveillance scheme (HPS, RCGP or RMN) and date of sample collection (month) were investigated as potential confounding variables.

All statistical analyses were carried out in R version 2.10.1.

Results

This report has information on 4,554 individuals from whom samples were collected during the study period. Of these, 3,204 samples were collected through the RCGP surveillance scheme, 469 through the RMN scheme, 743 through the HPS scheme and 138 through the Public Health Wales scheme.

Those excluded from the study because of missing information (including PCR results and available vaccination history) are summarised in Table 1. Date of onset of illness was missing for 521 persons (11.4%): these were still included in the analyses. In the analyses evaluating VE in preventing influenza A(H1N1)2009 infection, samples positive for influenza A(H3) or influenza B were excluded and vice versa. There were therefore 2,891 persons for whom data on both vaccination status (for both vaccines) and pandemic influenza A(H1N1)2009 infection was available. Similarly, there were 2,487 persons included in the estimation of trivalent vaccine for prevention of influenza B or A(H3).

Table 2 shows the distribution and completeness of the baseline characteristics of the study participants according to whether they were influenza A (H1N1)2009 cases or controls. Age group, surveillance scheme and time period were found to be significantly associated with a confirmed influenza A(H1N1)2009 infection (Table 2).

Vaccine effectiveness in prevention of influenza A(H1N1)2009 infection

Table 3 shows the number and proportion of samples positive for influenza A(H1N1)2009 virus according to vaccination status (three categories). Crude vaccine effectiveness is also shown.

Age group, time period and surveillance scheme were adjusted for in a multivariable logistic regression model. These were all significantly associated with having a positive swab result. Risk group was missing for 1,316 of 4,554 samples (29%), and this variable was therefore not included in the model. The total number of observations included was 2,872.

The adjusted VE estimates (Table 3) increased from 34% (95% CI: -10 - 60%) for vaccination only in 2009/10 to 46% (95% CI: 7 - 69%) for vaccination only in 2010/11 to 63% (95% CI: 37 - 78%) if vaccinated in both seasons. Persons who had received vaccination in both 2009/10 and 2010/11 seasons did not have a significantly higher VE compared to persons who received vaccine only 2009/10 (Wald test p=0.06). Persons vaccinated only in 2010/11 also did not have a significantly different VE compared to those vaccinated only in 2009/10 (Wald test p=0.45). The VE for 2010/11 trivalent vaccination, irrespective of previous pandemic vaccination status, was 51% (95% CI: 29 - 66%). Censoring samples taken more than seven days after symptom onset did not significantly change the VE estimates: the adjusted VE for those vaccinated last season was 44% (95% CI: 0 - 68%), for those vaccinated only this season was 63% (95% CI: 32 - 79%) and for those vaccinated both seasons was 64% (95% CI: 36 - 80%).

The adjustment for month had a large effect on the VE point estimate for the group vaccinated in 2009/10; it decreased from 62% (crude) to 34% after adjustment. This is because the number of people vaccinated in 2009/10 only decreases across months (whilst influenza A(H1N1)2009 incidence is increasing), whereas the number of people vaccinated in 2010/11 is increasing over time.

There was no evidence of significant effect modification of vaccine by age group (using the same five age groups, likelihood ratio test p=0.21), although some of the vaccine-age sub-groups did not have any PCR positive results among them.

Vaccine effectiveness in prevention of H3 or influenza B infection

Twenty-one of 216 persons vaccinated with trivalent influenza vaccine (9.7%) were positive for influenza B or A(H3) compared to 478 of 2,271 persons unvaccinated with trivalent influenza vaccine (21%). This gives a crude VE of 60% (95% CI: 36 - 75%). If adjusted

Table 3

Number and proportion of samples positive for influenza A(H1N1)2009 according to vaccination status, United Kingdom, September 2010 – January 2011

Vaccination status	Influenza A(H1N1)2009 positive/n (%)[a]	Crude vaccine effectiveness	Adjusted vaccine effectiveness
Unvaccinated	1,014/2,554 (39.7%)	-	-
Vaccinated season 2009/10 only	26/130 (20.0%)	62% (95% CI: 41 - 75%)	34% (95% CI: -10 - 60%)
Vaccinated 2010/11 season only	22/100 (22.0%)	57% (95% CI: 31 - 73%)	46% (95% CI: 7 - 69%)
Vaccinated in both seasons	21/107 (19.6%)	63% (95% CI: 40 - 77%)	63% (95% CI: 37 - 78%)

[a] Chi-square test p<0.001 on three degrees of freedom.

for age group, surveillance scheme and time period (month), adjusted VE was reduced to 50% (95% CI: 17 - 70%). There was no evidence of significant age–vaccine interaction (likelihood ratio test p=0.37).

Discussion

The swab-negative case -control study design is an established approach to estimate influenza vaccine effectiveness. A number of studies have recently been published on the methodology [9,10]. The potential limitations of the approach presented in this paper have been outlined previously and relate to convenience sampling; the potential for selection bias; missing data items and lack of information on risk status. The likely impact of each of these on VE estimates has been addressed earlier [3].

This study demonstrates three key findings: vaccination with this current season's trivalent influenza vaccine provides protection against both confirmed influenza A(H1N1)2009 and influenza B infection and immunisation with A(H1N1)2009 vaccine in 2009/10 followed by trivalent influenza vaccine this season provides better protection against confirmed influenza A(H1N1)2009 infection. Finally vaccination only last season with A(H1N1)2009 vaccine, seems to provide the least protection against confirmed influenza A(H1N1)2009 infection.

This study provides some of the first evidence that this season's trivalent influenza vaccine is effective in reducing confirmed influenza A(H1N1)2009 and B infection in persons consulting in primary care. This level of protection is consistent with several studies undertaken with trivalent influenza vaccines in the pre-pandemic era and is congruent with moderately good matching between the vaccine and the circulating influenza strain [5,6]. We found no evidence that protection was significantly different by age group; however it is likely that the study size was not sufficiently large to address this point specifically.

Although recently published work has demonstrated in several geographical settings, that the pandemic influenza A(H1N1)2009 vaccine was highly effective last season in preventing confirmed influenza A(H1N1)2009 infection that season [2,3], this study indicates that pandemic vaccine protection may not last across seasons. This corroborates recent findings from a longitudinal sero-epidemiological survey, which suggests that population A(H1N1)2009 antibody levels may start to reduce in the post-pandemic period, particularly in the 5-14-years old age-band [11]. Further work needs to be undertaken in this area. Our paper does suggest that within the data available at present there is a dose-response relationship and, that vaccination with this season's trivalent influenza vaccine of individuals who have already received monovalent A(H1N1)2009 vaccine last season produced the highest effectiveness compared to vaccination only in the 2010/11 season or vaccination with A(H1N1)2009 vaccine alone in the 2009/10 season. This reinforces the importance of the UK policy for vaccination of those who had received the monovalent vaccine in the previous season.

In conclusion, this study undertaken mid-season provides evidence that this season's trivalent influenza vaccine does provide protection against infection to both strains of influenza circulating this season (A(H1N1)2009 and influenza B) in Europe. It is important to note that more precision in this estimate will be available at the end of the season. The findings seem to provide some of the first published evidence that protection might wane following vaccination with influenza A(H1N1)2009 vaccine after 12 months and reinforces the recommendation that annual re-immunisation of target groups is required regardless of vaccination the previous season (including those vaccinated with an adjuvanted vaccine).

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Conflicts of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that DM Fleming has received funding to attend influenza related meetings and has received consultancy fees from influenza vaccine manufacturers who might have an interest in the submitted work in the previous 3 years. In addition, The Virus Reference Department of the Health Protection Agency receives funding from a variety of vaccine manufacturers who might have an interest in the submitted work. All other authors declare they have no conflicts of interest.

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The second wave of 2009 pandemic influenza A(H1N1) in New Zealand, January–October 2010

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This paper uses data from multiple surveillance systems to describe the experience in New Zealand with the second complete wave of pandemic influenza A(H1N1)2009 in 2010. Measures such as hospitalisation rates suggest the overall impact of influenza A(H1N1)2009 in 2010 was between half and two thirds that of the first wave in 2009. There was considerable regional and sub-regional variation with a tendency for higher activity in areas that experienced low rates in 2009. Demographic characteristics of the second wave were similar to those in 2009 with highest rates seen in children under the age of five years, and in indigenous Māori and Pacific peoples. Hospital services including intensive care units were not under as much pressure as in 2009. Immunisation appears to have contributed to the reduced impact of the pandemic in 2010, particularly for those aged 60 years and older.

Introduction

Between April and December 2009, New Zealand experienced the first wave of the influenza A(H1N1)2009 pandemic, with 3,211 laboratory-confirmed case notifications, 1,122 hospitalisations and 48 deaths [1]. The numbers from April to August 2009 have been documented in the literature [1-5]. Subsequently, a national seroprevalence survey confirmed that the true extent of infection from the pandemic was much greater than indicated by surveillance data, with an estimated cumulative incidence of over 780,000 infections (18.3% of New Zealanders) [6]. This survey utilised a randomly selected community-based sample from the New Zealand population aged over one year. It obtained 1,156 serum samples from populations enrolled in general practices in selected regions of the country and a further 527 samples from healthcare workers. In addition a baseline survey was conducted using 538 pre-pandemic samples collected for other reasons.

During the early months of 2010 the notifications of pandemic influenza A(H1N1)2009 cases dwindled to zero, until a few cases were notified in July. Influenza activity then increased and peaked in the middle of August 2010 with the pandemic influenza A(H1N1)2009 virus as the predominant strain [7]. The second wave of influenza A(H1N1)2009 again coincided with New Zealand's usual influenza season. This wave was of a similar duration with a lower peak than the first wave, but with significant regional variations – some areas that had relatively low influenza-like illness (ILI) activity or hospitalisations in 2009 experienced higher levels of influenza activity in 2010 [7]. For 2010, as of the middle of October we have seen 1,768 confirmed cases, including 732 hospitalisations and 15 confirmed deaths.

The eligibility policy for the 2010 trivalent influenza vaccine was extended to allow pregnant women, children under five years and obese individuals to receive subsidised vaccine. Individual's over 65 years and those with underlying health conditions were also eligible. A monovalent vaccine (CELVAPAN H1N1; Baxter) was made available for healthcare workers in February 2010. The trivalent (seasonal) vaccine became available in April. The uptake was low for the former while stocks had to be re-ordered for the trivalent vaccine in March 2010. The subsidised influenza immunisation programme ended on 30 September 2010. Since then, influenza vaccines have still been available for people who want to purchase them, but demand has been very low.

This report uses multiple surveillance sources to describe the second wave of pandemic influenza A(H1N1)2009 in New Zealand and compare it with the first wave. These sources are described in a previous publication reporting on the first wave of the pandemic [2]. The aims are to compare incidence and impact of infection as well as timing and shape of the epidemic curve, to identify whether there are persisting or divergent regional patterns and whether vulnerable age and ethnic groups have changed, to assess whether the virus has changed, and to analyse the extent and impact of immunisation. The overall aim is to identify

implications for minimising the public health impact of this virus, particularly for countries in the northern hemisphere in the future.

Methods and data sources

The following surveillance systems provide data on influenza disease burden, characteristics of the virus and immunisation coverage:

Surveillance of influenza-like illness by the Institute of Environmental Science and Research based on data from sentinel general practitioners

There are 90 volunteer sentinel general practitioner (GP) practices distributed throughout the country. Normally sentinel surveillance operates in the winter period, from May to September. However, due to the pandemic, the sentinel system operated continuously from May 2009 to September 2010. The sentinel system defines a case of ILI as *an acute respiratory tract infection characterised by an abrupt onset of at least two of the following: fever* [≥37 °C], *chills, headache, and myalgia* [8]. Each general practice records the daily number of consultations for ILI and also collects three respiratory samples (nasopharyngeal or throat swab) per week from each of the first ILI patient seen on Monday, Tuesday and Wednesday. Consultation numbers and samples were sent to the World Health Organization (WHO) National Influenza Centre at the Institute of Environmental Science and Research (ESR) in Wellington and other hospital laboratories. Sentinel ILI rates are expressed as per population and not per total numbers of consultations. This system has been described in detail previously [2,3].

Surveillance of influenza-like illness by Healthstat based on data from sentinel general practitioners

CBG Ltd, a privately owned company contracted by the New Zealand Ministry of Health (MoH), uses a core of 100 general practices throughout New Zealand to gather computerised information on ILI consultations on a weekly basis (Healthstat). Both the ESR and Healthstat surveillance use practices across the country, providing both a regional and national picture of ILI. However, samples for molecular analysis are not collected in the Healthstat system.

Healthline

Healthline is the national 24-hour triaged telephone health advice service provided by the MoH in New Zealand. All calls are answered by registered nurses with telenursing training and working within the Nursing Council's Professional Standards for Telenursing Practice [2]. The Healthline service uses a computerised triage algorithm for symptomatic callers and an electronic health topic library for general health information. Numbers of monitored ILI calls can be made available on a daily basis.

Notified cases

Influenza A(H1N1)2009 became a notifiable disease in New Zealand on 30 April 2009. Notifications include those made through direct laboratory notification which is a legal requirement in New Zealand. Other sources of notifications are from clinicians in both primary and secondary care. Data are entered into the national database for notifiable diseases (Episurv).
During 2010 and most of 2009, notification has largely been based on laboratory reporting of confirmed cases. Thus although notification data are useful for monitoring trends, they are a substantial underestimate of true community incidence of infection.

Virological surveillance

Virology swabs are collected through the ESR sentinel GP surveillance during the influenza season, as well as through year-round laboratory testing by the four regional virus diagnostic laboratories at Auckland, Waikato, Wellington and Christchurch Hospitals, and by the WHO National Influenza Centre at ESR. Laboratory identification methods include molecular detection by polymerase chain reaction or isolation of the virus [9]. Influenza viruses are typed and subtyped as influenza A, B, seasonal A(H1N1), seasonal A(H3N2), or A(H1N1)2009. Fluorometric neuraminidase inhibition assay is used for monitoring oseltamivir susceptibility [5].

Hospitalisations (including intensive care)

Hospitalisations among confirmed cases of influenza A(H1N1)2009 notified to EpiSurv were reviewed by ESR throughout the second wave. In addition, the National Minimum Data Set (NMDS) that collates all hospital discharges (with diagnoses) was also used. Hospitalisation rates give a good indication of incidence trends for more severe cases nationwide. Such rates, while representing only a small proportion of all cases give a more complete picture of the progression of the pandemic than notifications. Information on cases of influenza A(H1N1)2009 admitted to intensive care units (ICU) and ICU bed occupancy were also obtained directly from ICUs as additional surveillance measures of healthcare utilisation.

Deaths

Mortality data for influenza A(H1N1)2009 are obtained from the standard processes for death certification and case notification, and from deaths referred to the Coroner. In addition, a Pandemic Influenza Mortality Review Committee was established in 2009 to review all deaths linked to the influenza A(H1N1)2009 virus. A death associated with pandemic influenza A(H1N1)2009 was defined as *a person with confirmed pandemic influenza A(H1N1)2009 infection determined from ante-mortem or post-mortem specimens, and who died from a clinically compatible illness or complications attributable to that infection. There should be no period of complete recovery between illness and death, and no alternative agreed-upon cause of death* [10].

We estimated the case fatality and hospitalisation ratios for 2010 by first estimating the number of symptomatic influenza A(H1N1)2009 infections in 2010. The number of symptomatic cases due to influenza A(H1N1)2009 as estimated from the seroprevalence study was adjusted by the ratio of sentinel ILI activity for 2010 and 2009, and the proportion of viruses characterised as influenza A(H1N1)2009 in the two years. This gave an estimate of 176,308 symptomatic influenza A(H1N1)2009 cases in 2010.

School absenteeism

School absenteeism data represent numbers of pupils absent due to sickness or unexplained reasons. These are monitored on a daily basis by region through a database provided by the Ministry of Education using sentinel schools. The system commenced in 2010. 178 schools reported regularly, representing an average daily number of 64,911 students. Overall about 12% pupils are covered nationally. The data for 2010 are available for several regions. These results are not shown in this paper for reasons of brevity, lack of a valid baseline and the inability to compare with previous years.

Immunisation coverage

Estimations of total immunity prior to the onset of the second wave were based on the results of the seroprevalence study and estimated immunisation uptake levels [6]. These levels were taken as baseline levels for 2010, and estimated immunisation uptake levels were then included in the final estimate. Assuming that the immunisation uptake before the second wave was similar across age groups and independent of previous immune status, we estimated the age-specific immunity prior to the onset of the second wave as follows:
Total immune = Immune (following first wave) + Immune (vaccinated) – Immune (first wave and vaccinated)

Results

Epidemic curves

Following a substantial increase in July 2010, the number of influenza A(H1N1)2009 notifications peaked in mid-August and declined rapidly after that.

Figure 1 summarises the epidemic curves of the second wave of influenza A(H1N1)2009 in 2010 based on surveillance data from sentinel ILI, notifications, Healthline, hospitalisations and virological reporting systems in comparison with previous years. Results from these surveillance systems suggest that the pandemic in 2010 commenced one month later than in 2009 and had a significantly lower incidence.

Community surveillance of influenza-like illness (sentinel surveillance by the Institute of Environmental Science and Research)

The overall national ILI consultation rates in 2010 in the GP sentinel surveillance system show less influenza activity compared to 2009 (Figure 1a). As of the week 39 (ending 3 October 2010), the 2010 cumulative incidence rate of 1,019.9 per 100,000, was lower than that of 2,695.6 per 100,000 in 2009 (Table 1). The 2010 peak consultation rate of 152 per 100,000, which was lower than that of 284.0 per 100,000 in 2009, occurred in week 33 (ending 22 August), four weeks later than the 2009 peak.

During this period from May to 3 October 2010 the highest ILI consultation rates were recorded among children and young adults. ILI consultation rates per 100,000 were 1,982.2 for infants, 2,163.7 for children aged one to four years, and 1,092 for children aged five to 19 years.

Community surveillance of influenza-like illness (Healthstat)

Healthstat returns show some major differences compared to most other surveillance results. The epidemic curves for 2009 and 2010 in Figure 1b are of equal intensity. This might be a result of low sensitivity of the coding during 2009 (Table 1). It is known that in 2010 there was a concerted effort to improve the sensitivity of the data being collected with particular attention to coding by each of the practices involved.

Notified cases

Figure 1c shows the epidemic curves based on notifications for 2009 and 2010. These are all cases that have been notified and entered into the Episurv database from January to October 2010. The sharp increase in notifications during the second wave of influenza A(H1N1)2009 commenced four weeks later than during the first wave. Following a substantial increase in July 2010, the number of influenza A(H1N1)2009 notifications peaked in week 33 (ending 22 August) with 367 cases, and then declined to less than 10 per week by the first week in October 2010. From January to 24 October 2010, a total of 1,782 cases of influenza A(H1N1)2009 were notified, including 1,758 confirmed cases and 24 probable cases (Table1).

Healthline

The number of calls to Healthline for ILI during 2010 were lower than for 2009 (Figure 1d). The total number of triaged calls that were symptomatic for ILI gave the best indication of the impending second wave. Healthline calls increased in mid-June, two to three weeks before the other surveillance systems.

Hospitalisations and admissions to intensive care

Hospitalisation rates in 2010 were considerably below the peak national rates for 2009, and declined rapidly (Figure 1e). As of 15 October the total number of hospital admissions with confirmed influenza A(H1N1)2009 (n=732) was just over 72% of the total for the same period in 2009 (n=1,011) while the number of ICU admissions was 87.4% of 2009 admissions (n=104 and 119). The ICUs did not report unusually high levels of bed occupancy during the 2010 influenza wave. The hospitalisation ratio in 2010 (number hospitalised per symptomatic infections) was 415.2 cases per 100,000. This

was much higher than the ratio of 287 per 100,000 in 2009. Using total hospitalisations as the denominator from the NMDS, the ICU ratios in 2010 and 2009 were 14.5% and 10.6%, respectively, of all hospitalisations.

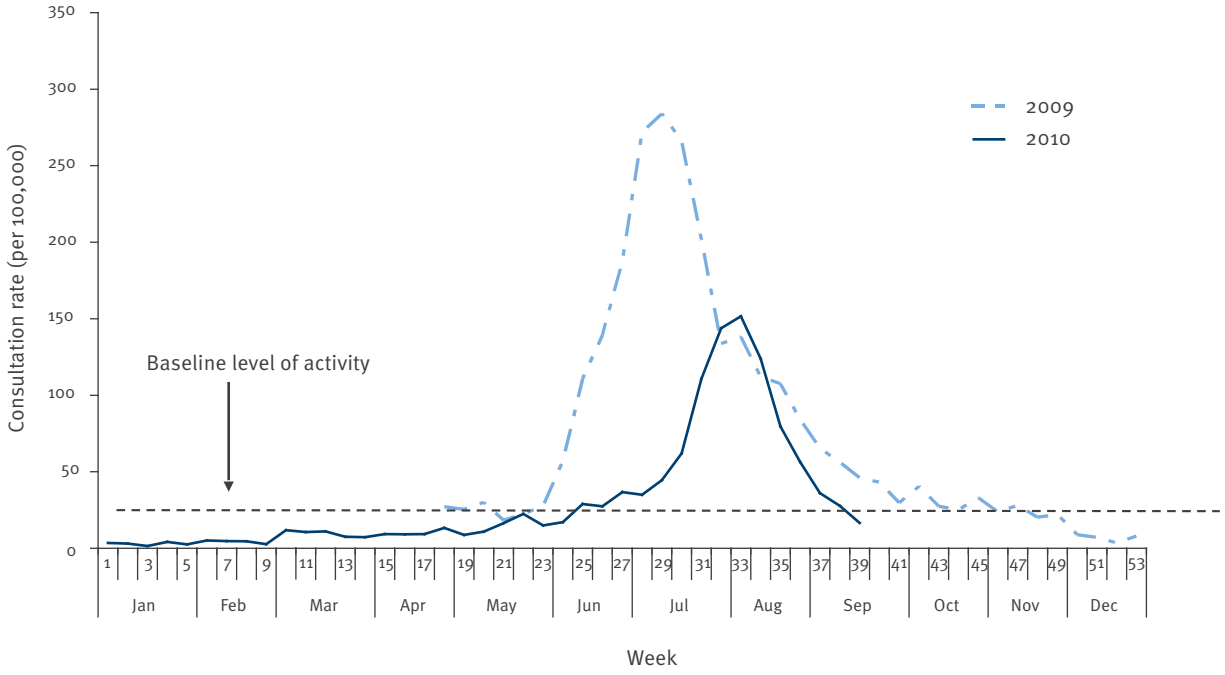
Deaths

From 1 January to 15 October 2010, 20 deaths were reported as *linked to* pandemic influenza A(H1N1)2009 [8]. Fifteen of these deaths have so far been confirmed as being *due to* influenza A(H1N1)2009. Most deaths occurred in the age group 20 years and older. The 15 confirmed deaths due to influenza A(H1N1)2009 in 2010 give a case fatality ratio of 8.5 per 100,000 (15 of 176,308). This is similar to the one calculated for 2009: 9.0 per 100,000. The median age of the fatal cases was 50 years in 2010 and 40 years in 2009.

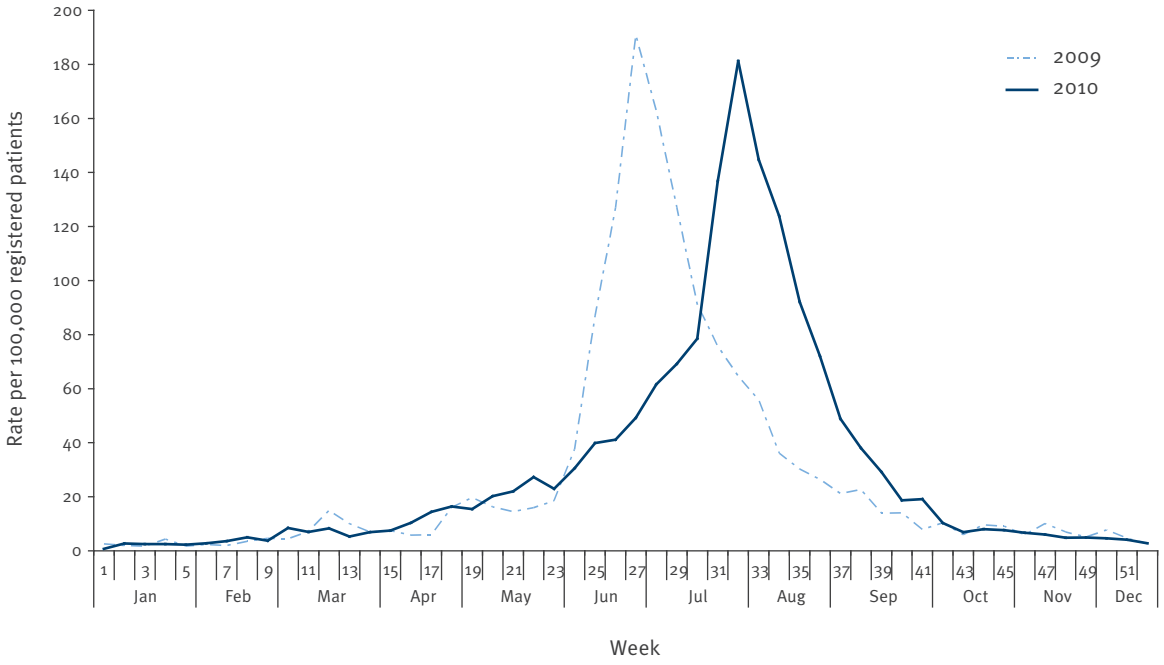
Figure 1

National influenza surveillance data, New Zealand, 2008–10

A. ILI consultation rates (ESR) 2008-10

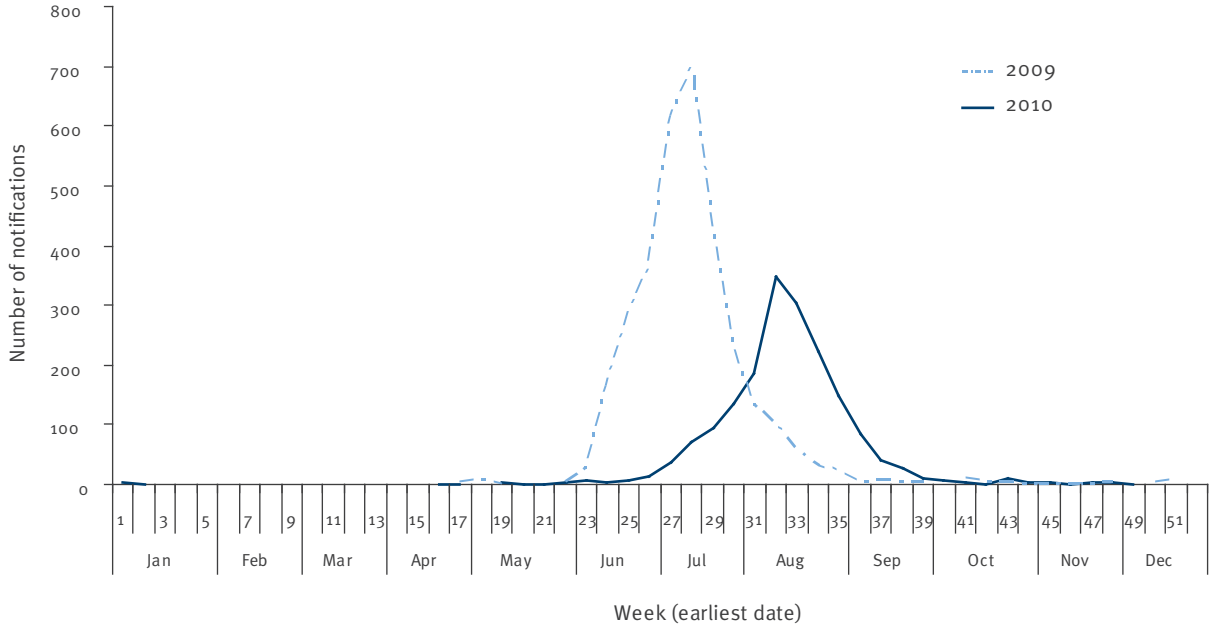


B. ILI consultation rates (Healthstat) 2008-10

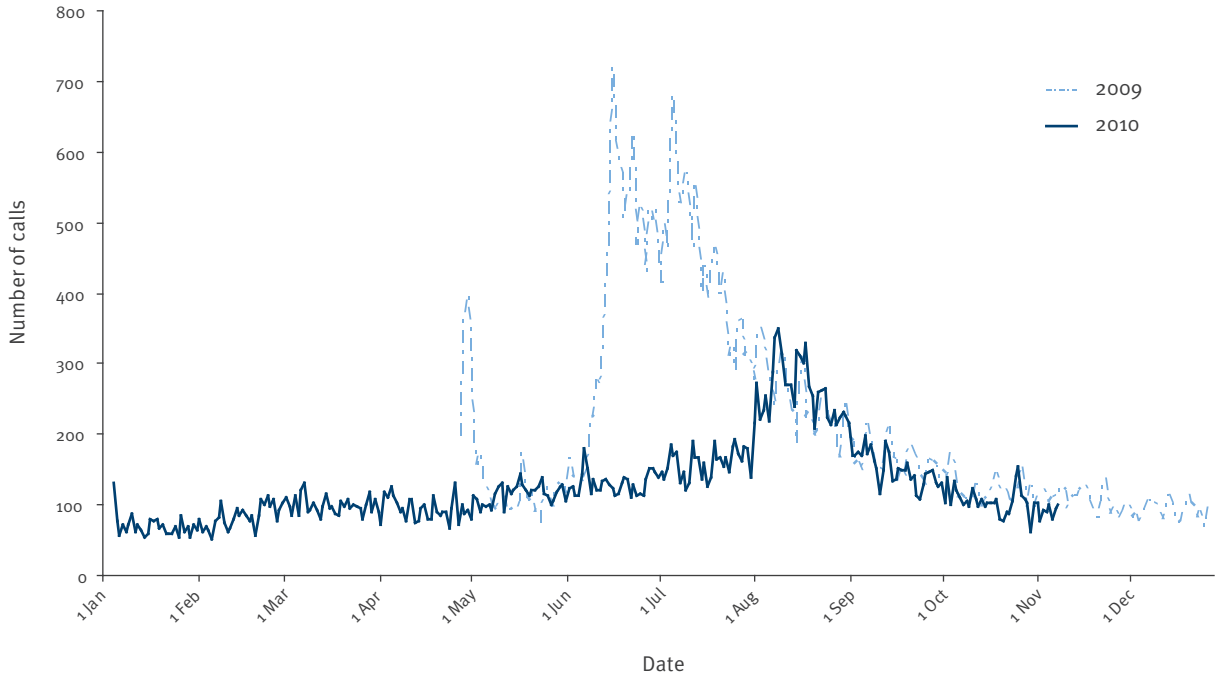


Data source: From responding practices of Original HealthStat GP practice panel.

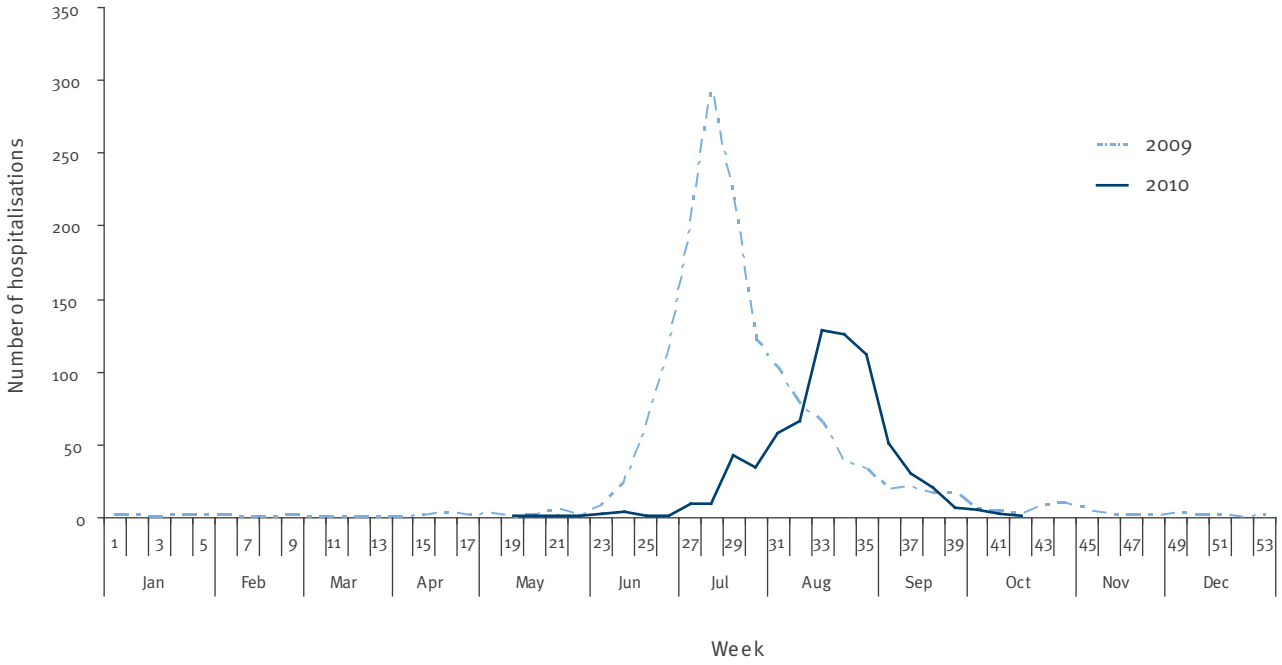
C. Influenza A(H1N1)2009 notifications 2009–10



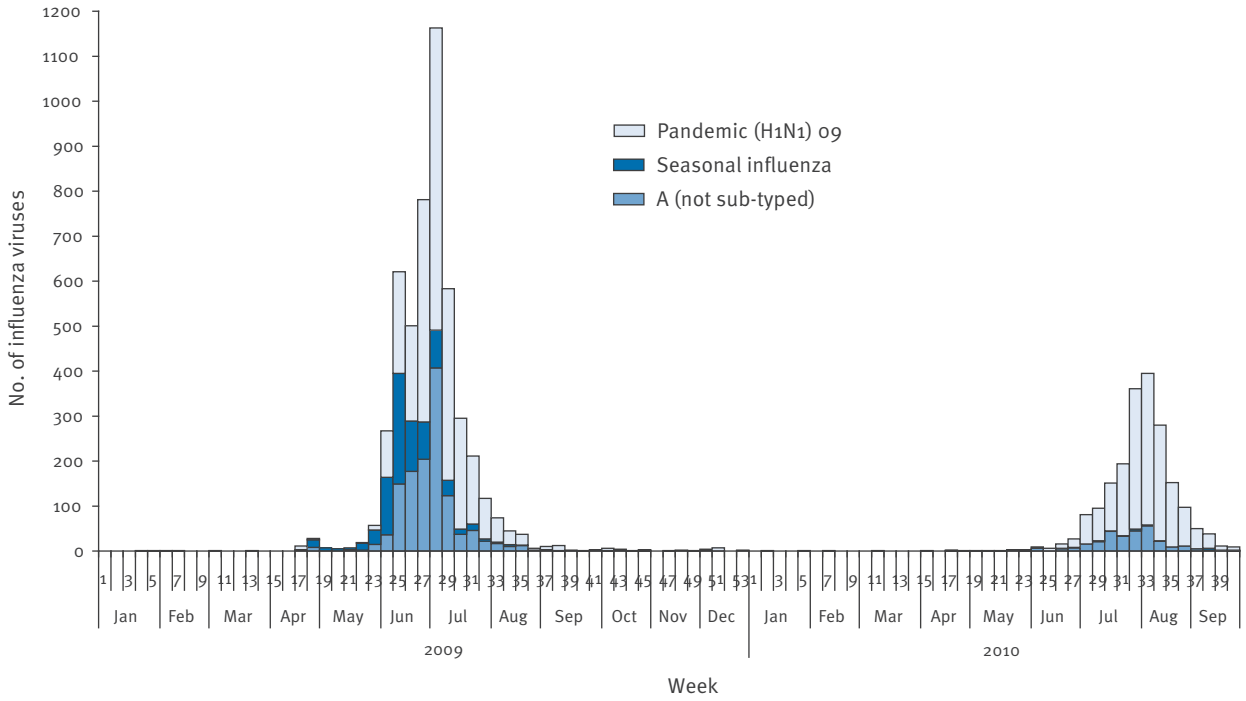
D. Healthline ILI calls, 2009–10



E. Hospitalisations 2009–10



F. Virological surveillance 2009–10



2010 data only up to week 39 (sentinel surveillance only).

ESR: Institute of Environmental Science and Research; ILI: influenza-like illness.

Virological surveillance

Results of virological surveillance using samples from sentinel GPs and hospitals for 2010 and 2009 are shown in Figure 1e. As of the week ending 3 October 2010, pandemic influenza A(H1N1)2009 was the predominant strain (84.5%, 1,684 of 1,992) including 392 pandemic influenza A/California/7/2009(H1N1)-like strains, followed by not subtyped influenza A (n=290), influenza B (n=9) including four B/Brisbane/60/2008-like strains,

Table 1

Cumulative incidence of influenza-like illness and influenza A(H1N1)2009 cases, and viruses, New Zealand, 2009–10 (mid-October)

Surveillance system	Event	Cumulative incidence per 100,000 (number of cases)	
		2009	2010
Sentinel GP (ESR)[a]	ILI case	2,695.6	1,019.9
Sentinel GP (Healthstat)[a]	ILI case	462.9	521.9
Healthline	ILI call	987.9	820.4
Notifications[b]	Influenza A(H1N1)2009 case	74.5 (3,214)	40.4 (1,768)
Hospitalisations (notification data)[b]	Influenza A(H1N1)2009 case hospitalised	23.5 (1,016)	16.7 (732)[c]
Hospitalisations (NMDS)	Influenza A(H1N1)2009 case	26.0 (1,122)	16.4 (717)
ICU admission	Influenza A(H1N1)2009 case	2.8 (119)	2.4 (104)
Deaths (mortality reporting system)	Influenza A(H1N1)2009 case	1.1 (48)	0.34 (15)
Surveillance system	Virus type	Percentage of total influenza viruses (number of viruses)	
Virological surveillance – influenza A(H1N1)2009[d]	Influenza A(H1N1)2009 virus	63.6% (395)	75.9% (274)
Virological surveillance – seasonal influenza (A and B)[d]	A(H1N1) virus	15.8% (98)	0% (0)
	A(H3N2) virus	7.6% (47)	0.8% (3)
	B virus	0.5% (3)	0.3% (1)

ESR: Institute of Environmental Science and Research; GP: general practitioner; ICU: intensive care unit; ILI: influenza-like illness; NMDS: National Minimum Data Set.

[a] Data for surveillance week ending 6 May to week ending 30 September.

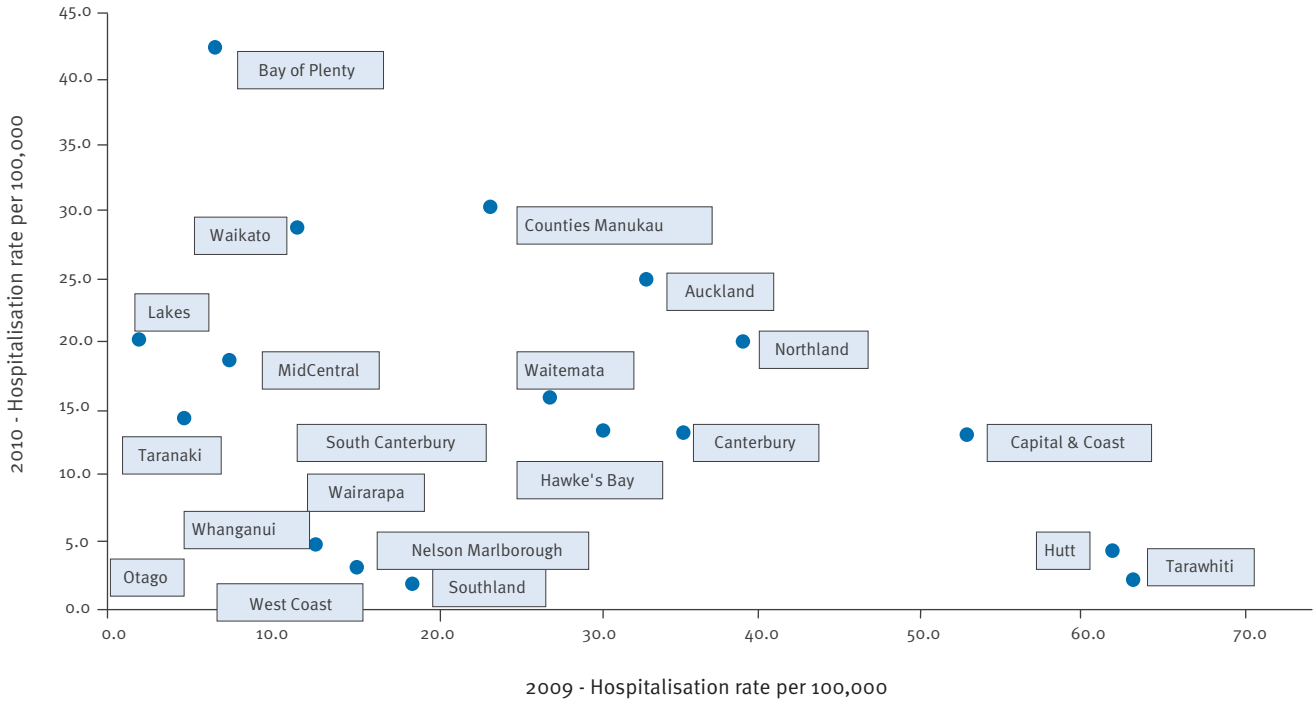
[b] Notified to Episurv for 2010 up to 15 October 2010.

[c] 65 hospitalised of 97 cases in pregnant women.

[d] The percentages represent proportions of the total number of viruses identified. These figures are ESR sentinel data, and do not include non-sentinel sources.

Figure 2

Laboratory-confirmed pandemic influenza A(H1N1)2009 hospitalisation rates per 100,000 by District Health Board of domicile, New Zealand, 2009 versus 2010[a]



[a] The full year 2009 (first pandemic wave) is compared with 2010 until 14 October (second pandemic wave).

and seasonal influenza A(H3N2) (n=9) including two A/Perth/16/2009 (H3N2)-like strains. No non-pandemic influenza A(H1N1) virus has been isolated in 2010, in contrast to 2009 when it was the dominant virus before influenza A(H1N1)2009 became established.

Most of the New Zealand isolates were antigenically and genetically closely related to the pandemic influenza A(H1N1)2009 vaccine candidate A/California/7/2009–like strain. In addition, 280 influenza A(H1N1)2009 isolates were subjected to the fluorometric neuraminidase inhibition assay and the results showed that they were all sensitive to oseltamivir.

Cumulative incidence of influenza A(H1N1)2009

Table 1 reports the cumulative incidence of ILI and influenza A(H1N1)2009 cases for 2010 up to the end of October and compares this with the total year 2009. Both periods cover the complete pandemic waves. The data show that the proportion of hospitalised cases admitted to ICUs has been higher in 2010 (14.5%) compared with 2009 (10.6%).

Regional patterns

We observed heterogeneous distribution of pandemic influenza A(H1N1)2009 among different geographical locations in New Zealand. In particular, some regions (mainly small urban and rural areas) that had relatively low ILI activity in 2009 experienced higher levels of activity during the second wave in 2010. For example, eight of the 20 District Health Boards (DHBs) reported weekly GP ILI consultation rates higher than those seen last year: Waikato, Bay of Plenty, Tairawhiti, Taranaki, Hawke's Bay, Wairarapa, West Coast and South Canterbury. Six DHBs hospitalised more cases with pandemic influenza A(H1N1)2009 this year than for the whole of the 2009 year: Counties Manukau, Waikato, MidCentral, Bay of Plenty, Taranaki and Lakes.

Figure 2 compares the DHBs' hospitalisation rates in 2010 with such rates in 2009. The scattergram gives a correlation coefficient of −0.20 indicating that in general DHB's with high rates in 2009 had low rates in 2010 and vice versa. The scattergram is included as a descriptive qualitative visual display only, with confidence intervals for each point not shown.

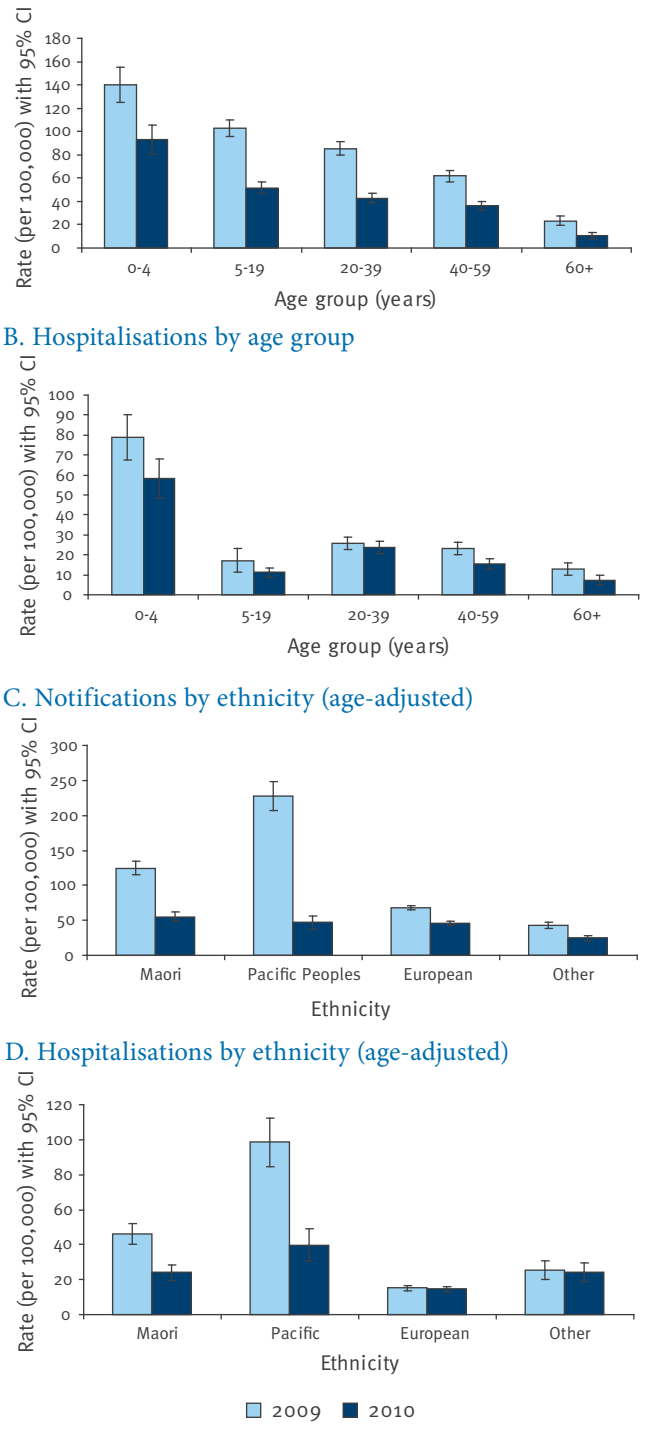
Notification and hospitalisation rates by age and ethnicity

Based on Episurv data, the age distribution of notifications and hospitalisations for influenza A(H1N1) infections in 2010 was very similar to 2009 (Figure 3). As in 2009, the highest cumulative rates of notification and hospitalisation were in children under five years of age (92.9 and 58.2 cases per 100,000 population respectively). The overall hospitalisation rates were about a third lower in 2010 compared with 2009. The overall notification rate in 2010 was just over half of the 2009 rate. Notification and hospitalisation rates declined from 2009 to 2010 in all age groups, with relatively greater reductions in the age group of 0-19 year-olds.

The ethnicity distribution of notifications and hospitalisations due to influenza A(H1N1)2009 infection in 2010 was markedly different from the one in 2009. Although highest rates in both years were seen in Pacific and Māori populations, their rates dropped relative to the

Figure 3

Notification and hospitalisation rates for influenza A(H1N1) by age group (A,B) and ethnicity (C,D), stratified by year, New Zealand, 2009 and 2010



CI: confidence interval.

groups European and Other (Figure 3). In comparison to the European ethnic group, the rate ratio for Pacific Peoples in 2010 was 1.6 (95% confidence interval (CI): 1.3–1.9) for hospitalisation and 1.0 (95% CI: 0.8–1.2) for notification. This is much lower than the hospitalisation rate ratio of 4.6 (95% CI: 4.2–5.1) and notification rate ratio of 3.4 (95% CI: 3.0–3.7) in 2009. The Māori hospitalisation rate ratio of 1.8 (95% CI: 1.6–2.0) and notification rate ratio of 1.2 (95% CI: 1.1–1.4) in 2010 showed a lesser reduction compared with those of 2.5 (95% CI: 2.3–2.7) and 1.8 (95% CI: 1.7–2.0) in 2009, respectively.

Immunisation coverage and immunity

Data are based on the results of the influenza A(H1N1)2009 seroprevalence study conducted in 2009–10 [6] and claims received by the Ministry of Health from GPs for immunisations given on the subsidised programme. These are likely to be underestimates as the number of claims yet to be received and the number of people who purchased the vaccine privately is unknown.

A minimum of 1,046,000 doses of the seasonal trivalent influenza vaccine were distributed in New Zealand in the 2010 season. Over 624,000 claims have been received up to end of October 2010 for the subsidised programme. In that year a considerable number of doses must have been purchased privately to explain that stocks were exhausted and had to be replenished. Table 2 shows numbers of persons with estimated levels of immunity and immunisation for five age groups.

Discussion

Impact of the 2010 influenza pandemic

The second year of pandemic influenza A(H1N1)2009 in New Zealand produced an epidemic curve similar in shape to the first wave, of about half to two thirds the size, and starting one month later in the winter. Multiple surveillance systems showed that the influenza A(H1N1)2009 incidence increased markedly in July 2010, peaked in mid-August and then declined. The national influenza wave lasted 15 weeks in 2009 as well as in 2010. It comprised multiple waves of activity at the district level that had a duration of about five weeks.

The second year of pandemic influenza A(H1N1)2009 again showed marked geographic heterogeneity. There was a weak negative correlation of infection rates in 2010 relative to 2009. This finding supports the hypothesis that areas that were more affected in 2009 were protected to a certain extent in 2010. If this was not the case, we would expect (as we see for most diseases) that rates from one year to the next would be highly positively correlated because patterns of vulnerability tend to persist. Regional variations of influenza A(H1N1)2009 infections were also observed in 2009 in clinical surveillance as well as an influenza A(H1N1)2009 serosurvey [2,3,6]. It is possible that this variability allowed areas (mainly rural and small urban areas) with low pandemic influenza A(H1N1)2009 activity to maintain more susceptible populations and to sustain more influenza A(H1N1)2009 infections and transmission in 2010 than in 2009.

While the hospitalisation rates for influenza in 2010 (16.7 per 100,000) were lower than in 2009 (23.5 per 100,000), the proportion of hospitalised influenza cases was higher in 2010 than in 2009. In addition, the proportion of hospitalised cases admitted to ICUs was higher in 2010. The reasons for these differences are not clear. There has been no obvious change in the severity of pandemic influenza A(H1N1)2009 disease or the thresholds for hospital and ICU admission. However, there was less pressure on hospital and ICU bed availability this year. It is also possible that there was a greater awareness of pandemic influenza A(H1N1)2009 as a contributing factor to severe respiratory disease, and therefore higher likelihood of laboratory testing, hospitalisation and ICU admission.

The age distribution of influenza A(H1N1)2009 infections in 2010 was broadly similar to 2009 with highest rates in children under the age of five years. Hospitalisation rates declined significantly for most age groups, except for the 20-39-year-olds. This decline was particularly marked for children of 5-19 years although notification rates were still higher in

Table 2

Influenza immunity levels by age group, New Zealand, 2010

Age group (years)	Baseline immunity[a] n (% of population)	Immunity following 2009 H1N1[a] n (% of population)	Immunisation 2010 (pre-second wave)[b] n (% of population)	Total immunity 2010[c] (pre-second wave)[b] n (% of population)
1-4	18,303 (6.1%)	88,515 (29.5%)	30,023 (10.0%)	109,818 (36.6%)
5-19	127,665 (14.0%)	425,853 (46.7%)	27,523 (3.0%)	440,443 (48.3%)
20-39	86,485 (7.5%)	255,995 (22.2%)	44,089 (3.8%)	290,589 (25.2%)
40-59	75,026 (6.5%)	233,159 (20.2%)	105,968 (9.2%)	317,419 (27.5%)
60+	169,401 (22.6%)	185,891 (24.8%)	416,832 (55.6%)	499,207 (66.6%)

[a] Seroprevalence study.

[b] Immunisation claims 2010.

[c] Estimated total immunity assuming vaccination independently distributed in age group.

children aged 5 19 years. This probably reflected a feature of the 2009 pandemic which caused relatively mild disease in children aged 5-19 years. By contrast, the ethnicity distribution of influenza A(H1N1) infections in 2010 changed markedly compared with 2009. Rates for Pacific and Māori populations remained significantly higher than for the groups European and Other, but the disparity was far less pronounced. These changes in the age and ethnicity distribution of the disease may reflect immunity from a combination of sources, including immunisation and natural infection (see impact of interventions below).

Reasons for ethnic differences in hospitalisation may include a higher incidence of infection in Pacific and Māori peoples, a higher prevalence of co-morbidities (such as asthma and diabetes), unfavourable environmental factors (such as household crowding and poor quality housing), behavioural differences in responding to influenza, differences in socio-cultural-economic status, differences in health service utilisation and increased genetic susceptibility [12]. Further study on the contributing factors to ethnic differences in the risk of influenza A(H1N1)2009 infection and severe disease is underway in New Zealand.

New Zealand experience compared with other southern hemisphere countries

When the experience with the 2010 winter influenza season in New Zealand was compared to other temperate southern hemisphere countries such as Australia, South Africa and South America, they shared the common features that the influenza season started later and overall influenza activity was lower in 2010 than in 2009, with regional variation observed [13].

Most of the New Zealand isolates were antigenically and genetically closely related to the pandemic influenza A(H1N1)2009 vaccine candidate A/California/7/2009–like strain. However, a genetic variant with the dual haemagglutinin mutations E391K and N142D emerged in Singapore in early 2010 and has subsequently spread through Australia and New Zealand in the 2010 winter period [11]. As of mid-October 2010, it appears that this genetic variant has not resulted in significant antigenic changes that would make the current vaccine less effective.

The pandemic influenza A(H1N1)2009 strain predominated with some seasonal influenza A(H3N2) and B viruses in New Zealand and Australia. In Chile, the most frequently detected virus has been seasonal influenza A(H3N2) and in South Africa influenza B.

Impact of interventions

Community-based interventions to reduce the impact of pandemic influenza A(H1N1)2009 included immunisation and continuing promotion of respiratory and hand hygiene. Parallel interventions included the provision of free antiviral drugs as well as asking sick persons to stay away from school or work and seek early medical advice. Uptake of the seasonal vaccine in 2010 was higher than in previous years although the proportions estimated to have been immunised remain low at around 24%. The age distribution of influenza A(H1N1)2009 in 2010 was consistent with estimated patterns of immunity in the population with higher disease rates in 20-39-year-old adults corresponding to their relatively low levels of immunity [14]. High levels of immunisation of those aged 60 years and older probably contributed to the large decline in disease rates in this age group in 2010 relative to their already low risk in 2009 [14]. The overall impact of these interventions requires further evaluation.

Implications for northern hemisphere

Many of the lessons from the first pandemic wave in the southern hemisphere in 2009 still apply[14] . While careful monitoring is required for emerging new antigenic variants the current circulating virus is now a familiar virus and we also have the benefits of an effective vaccine. The description of the second wave of the pandemic in New Zealand, a temperate southern hemisphere country, has some implications for the influenza season in the northern hemisphere. Although the second wave affected smaller numbers in New Zealand overall, it had a higher impact in some regions and populations with less immunity (from the first wave). Vulnerable populations continue to include indigenous people, the young, pregnant woman, and those with serious chronic health conditions [14]. There was no indication of a change in virulence of the virus.

The New Zealand experience also raises the question as to whether the phenomena we have seen with this virus in 2010 are best described as the second wave of a pandemic or the first year of a new seasonal influenza virus. In past pandemics (certainly in 1918), the second and subsequent waves of infection were often characterised as out of season and with markedly higher virulence compared with seasonal viruses [15] The pandemic influenza A(H1N1)2009 virus has not shown those pandemic features in 2010. It appears to have completely displaced seasonal influenza A(H1N1) virus in 2010 in New Zealand.

Strengths and limitations of New Zealand surveillance data

The influenza surveillance systems in New Zealand provide information on disease, hazards, determinants and interventions related to this infectious agent [16] Several of these systems have been particularly effective at providing strategy-focused information to characterise the pandemic, notably GP sentinel surveillance (which includes virological surveillance), hospitalisation data, and the national serological survey. A full investigation is still needed to assess the overall adequacy of influenza surveillance in New Zealand, particularly control-focussed surveillance aimed at supporting the containment phase of pandemic management, but overall the systems stood up well to the challenges posed by the pandemic.

Acknowledgements

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