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Rapid communications

Surveillance and outbreak reports

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Eurosurveillance – keeping an eye on infectious diseases

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2010 will be the 15th year for *Eurosurveillance*, and as always, the editorial team will do their best to provide their readers with timely, relevant and up-to-date information about infectious disease outbreaks, surveillance, prevention and control. The journal is constantly evolving and as in previous years, there were considerable, positive, changes for both editors and readers in 2009. First and foremost, the joint efforts of contributors, editorial board and team have paid off and *Eurosurveillance* has been accepted and is now listed for an impact factor with Thomson Reuters [1]. This development poses obvious challenges for the future and we are convinced that we will be able to present an attractive factor in two years time.

2009 was a special year for all public health experts, physicians and policy makers working with infectious diseases. Since the end of April, the 2009 influenza pandemic has been an overriding priority for all and required considerable resources and efforts. From the start when it was uncertain how this pandemic would evolve, we followed it closely and after the first rapid communication on 28 April, we covered the pandemic in a total of 92 articles with worldwide authorship. The majority of publications on the pandemic were rapid communications, but we also published a special issue in October on the situation of the 2009 influenza A(H1N1) pandemic in the southern hemisphere. The rapid communications on the pandemic, usually published within two to seven days from submission, increased in length and scientific content over time. Most were reviewed by two experts who agreed to support us on short notice while already being under substantial pressure in their day-to-day pandemic work. We are grateful for their valuable input and for the assistance received from all our reviewers in 2009. To acknowledge their help we publish their otherwise invisible names in a list of reviewers in 2009 in this issue.

The ability of *Eurosurveillance* to publish peer-reviewed reports with relevant findings in an exceptionally timely manner created a lot of attention also outside of Europe. During the pandemic, the geographical scope of your journal widened naturally as findings and reports from other continents were obviously relevant for Europe as well. This is reflected in the total of articles with non-European authorship. Also the number of subscribers for *Eurosurveillance* is still rising, and many new readers and contributors are from Asia, Australia, New Zealand, and North and South America.

Even if the 2009 influenza pandemic kept us busy, we had our eyes on other diseases as well. In total, we published 156 peer-reviewed rapid communications, 112 peer-reviewed full articles and a number of editorials, news pieces, letters and meeting reports. The subjects covered ranged from adenovirus infections, gonorrhoea, measles, emerging viruses such as West Nile and Usutu virus and trichnellosis to Salmonella outbreaks. Issues with a special focus were on tuberculosis, hepatitis A and antimicrobial resistance, whereas the topics of our special issues other than pandemic influenza were pregnancy-related infections, capacity building and training in field epidemiology and trends and behavioural surveillance of HIV/AIDS and other sexually transmitted infections in men who have sex with men.

Our achievements in 2009 highlight clear challenges: While we have expanded our geographical scope and will most probably continue to receive papers also from non-European authors, we will need to carefully consider our criteria for inclusion of papers to ensure the European relevance of *Eurosurveillance*. All papers that present interesting, new findings and are important for Europe will be considered for publication. To make our journal more attractive for our readers, we will further develop the scientific content and the visibility of *Eurosurveillance*. From 2010 we will suspend the quarterly print version of *Eurosurveillance* and print only special issues and topical compilations of articles. The design of the print version has been improved and future issues will have a cover image relating to the content.

Looking forward to collaborating with all our supporters in 2010, we would like to thank our Associate Editors and Editorial Board members and those experts and friends who support us behind the scenes by providing advice and guidance whenever we need it. We are also grateful to our readers and authors for their confidence in our journal and will continue to keep an eye on infectious diseases and do our best to provide you with timely, relevant and interesting information in 2010.

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A new decade, a new seasonal influenza: the Council of the European Union Recommendation on seasonal influenza vaccination

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Europe is coming to the end of its autumn-winter wave of the 2009 influenza A(H1N1) pandemic. Transmission has been continuing in the east and south-east of Europe, but the signs from other parts of Europe before Christmas indicated that the circulation of the pandemic influenza A(H1N1) virus was declining. Though as is to be expected the associated burden on hospitals and especially on intensive care, and the number of deaths are declining less quickly and with some delay [1,2]. Worldwide in almost all countries with virological surveillance pandemic viruses are pre-dominating apart from co-circulating influenza B viruses [3]. In Europe, there have hardly been any influenza (AH3) viruses in this season so far, and even fewer of the previous seasonal influenza A(H1) viruses [1].

So what happens next and what needs to be done? The historical pattern of human influenzas is that after pandemics, the world experiences a new mix of viruses referred to as *inter-pandemic influenza* or as *seasonal influenza* in temperate countries. In the three 20th-century pandemics, the new pandemic virus displaced the previous influenza A seasonal viruses, with a variation for the last three decades due to the re-emergence of an A(H1N1) virus (Figure) [4]. Hence, what now has to be done is to determine the characteristics of the coming, new seasonal influenza based first on the growing knowledge of the 2009 pandemic influenza, then on the experiences from the coming influenza season first in the southern hemisphere and then in Europe. These characteristics should then be compared to those of the previous seasonal influenza to be able to determine a rational approach to mitigation, treatment and vaccination [5].

The 2009 pandemic influenza has some similarities with the previous seasonal influenza but there are also a number of important differences. The incidence of severe disease in children and pregnant women from 2009 pandemic influenza seems to be higher than from the previous seasonal influenza. Furthermore, there is residual immunity in many older people, though older people who were not immune had the highest mortality rate of any age group in this pandemic. Another uncommon but striking feature was the prominence of sudden acute illness and deaths due to acute respiratory disease syndrome (ARDS) [5,6]. ARDS had been seen before in association with seasonal influenza, but was even more uncommon. If the features described persist with the new seasonal influenza, this may have an impact on the details of recommendations for seasonal influenza immunisation. To gather the scientific evidence, Europe will need to additionally focus its surveillance on severe cases, so called severe acute respiratory infections (SARI), and especially deaths [7]. Such surveillance has started in the pandemic under a strategy agreed with the European Union Member States, but it now needs to be extended to more countries and to capture more data on deaths [1, 7-9].

Influenza A never stands still. What is true at the moment for the 2009 influenza A(H1N1) will probably not remain so. The virus responsible for the last pandemic in 1968-70 became more transmissible between its first and second winter so that there were more cases and deaths in 1969-70 in at least two European countries [10,11]. The 1957-8 pandemic, declined before Christmas, but then saw a rise in the new year in influenza-related deaths, though not in cases [12,13]. Serological data such as that already gathered by France and the United Kingdom and close epidemiological and virological surveillance throughout the year are essential to determine how likely these scenarios will be in 2010-11 [14,15]. In 2007-8, the seasonal influenza A(H1N1) virus suddenly became resistant to the main oral antiviral oseltamivir, a change that seemingly was not related to the use of antivirals [16,17]. The rule with influenza, pandemic and inter-pandemic, is to maintain vigilance and expect the unexpected.

The most potent countermeasure for any human influenza is vaccination. With prescience the Member States of the European Union (EU) collectively as the Council of the European Union have just adopted under the Swedish Presidency a formal recommendation promoting seasonal influenza vaccination [18].

This has a number of important features (Box), puts responsibilities to Member States to enact vaccination programmes and to monitor coverage. The European Centre for Disease Prevention and Control (ECDC) is to provide technical support from its Seasonal Influenza Immunisation Programme including its work with the Vaccine European New Integrated Collaboration Effort (VENICE) project to monitor policies, practices and coverage. Much is to be done, as uptake in the older age groups varies forty-fold between Member States, some countries cannot provide data at all, and most find it difficult to monitor coverage in the clinical risk groups [19]. A group especially singled out for attention and immunisation by the European Council are healthcare workers (HCW). An article in this week's issue by M. Chironna *et al*. illustrates the necessity for HCW to get vaccinated against influenza [20]. Highly vulnerable patients, hospitalised children with cancer, were probably infected by unimmunised healthcare staff. A number of HCW in Europe choose not to be vaccinated. While the reasons for this may be manifold, what needs to be emphasised with them is that this is not just for their own protection. The most important reason for them to get immunised is to protect their vulnerable patients who often belong to risk groups for influenza.

The question of whether there are also other groups who would benefit from seasonal influenza vaccination, such as young children who have not been exposed to the 2009 pandemic influenza and pregnant women, can only be answered by close European and global epidemiological and virological surveillance in the months to come [7,8]. Results from such common efforts will provide guidance for EU Member States in their decisions for whom to recommend the seasonal influenza vaccine in the autumn of 2010.

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A nosocomial outbreak of 2009 pandemic influenza A (H1N1) in a paediatric oncology ward in Italy, October – November 2009

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A nosocomial outbreak of 2009 pandemic influenza A(H1N1), with eight confirmed cases, occurred in a paediatric oncology ward in Italy, in October/November 2009. The fact that one case was infected despite being isolated and without contact to a symptomatic patient, hints towards potential transmission through a health care worker (HCW) and underlines the importance of vaccination of HCW who are involved in the care of critically ill patients.

Outbreak description

A nosocomial outbreak of 2009 pandemic influenza A(H1N1), with eight laboratory confirmed cases, occurred in a paediatric oncology hospital ward in Italy, in October/November 2009.

For the outbreak the following case definition was applied: A suspected case was defined as a person presenting with a history of acute onset of high fever (≥38 °C) and at least two of the following respiratory symptoms: nasal obstruction, rhinorrhoea, sore throat, cough. This definition did not exclude individuals with negative RT-PCR for 2009 pandemic influenza A(H1N1) virus. A confirmed case was defined as a suspected case with laboratory-confirmed 2009 pandemic influenza A(H1N1), as tested by RT-PCR (Real time ready Influenza A(H1N1), Roche Diagnostics, Mannheim, Germany) [1,2].

Time line of events

During the outbreak, 20 children were hospitalised in the paediatric oncology ward. The first case was reported at the end of October in a child who had been admitted three days earlier for chemotherapy. The child presented with acute onset of fever (>38°C), nasal congestion and cough. The source of influenza infection remains unknown. The parents did not report any contact with a confirmed influenza case in the seven days prior to the onset of symptoms. Three days after the first case, another hospitalised child who had been hospitalised for chemotherapy over two weeks earlier, developed fever and acute respiratory symptoms.

On the day after the second child had developed symptoms, a voluntary association organised a Halloween party for the children hospitalised in the ward. All children participated, except one who was isolated because of severe clinical condition. In addition, an outpatient who came to hospital to receive chemotherapy attended the party. During the festivity all children covered their faces with surgical masks.

Three days after the party, in early November, seven hospitalised children presented with a fever of ≥38 °C and acute respiratory symptoms and on the following day, the isolated child and the outpatient presented an influenza-like syndrome (fever and respiratory symptoms) as well (Figure).

Laboratory investigations

At onset of fever, pharyngeal swabs were performed on all symptomatic children and tested for 2009 pandemic influenza. The laboratory results were available two days after the last children had become symptomatic and confirmed the diagnosis in eight of the 11 symptomatic children: the two children who had developed influenza symptoms in October, the child in isolation, the outpatient and four of seven who had developed fever in early November. All cases were laboratory-confirmed by the regional reference laboratory in Bari (Unità Operativa Igiene Policlinico Bari) by real time RT-PCR [2].

The age for the eight confirmed cases ranged from 10 months to 13 years, two children were under one year old, three were between one and five years old, two were between six and 10 years old and one was over 10 years old. All were hospitalised at the same time

for a period between four and 20 days in the paediatric oncology ward, with the exception of a child who had come to hospital during this period to receive chemotherapeutic infusions as an outpatient. Four of seven hospitalised confirmed cases, had acute lymphocytic leukaemia, two had neuroblastoma and one hepatoblastoma, three were neutropenic at admission and all had been hospitalised for chemotherapy. No patient had had any respiratory symptoms before admission to the hospital or prior to the outbreak.

The median duration of illness was 15 days (range 7-25). The attack rate for all hospitalised cases (suspected and confirmed) was 50% and for confirmed cases 35%. Three patients presented evidence of secondary pneumonia. One patient had to be admitted to the intensive care unit and was ventilated for 30 days.

Control measures

When the laboratory results were available, all patients with confirmed 2009 pandemic influenza were treated with 75 mg oseltamivir daily for five days. In addition, they received antibiotic and antifungal prophylaxis for ten days. All symptomatic children were lodged in a separate division of the ward until 48 hours after symptoms had subsided. Contact with other hospitalised children was prohibited and external visits were restricted to a minimum. All health care workers (HCW) used professional protective equipment, such as surgery masks, disposable gowns and gloves until 48 hours after the patients' symptoms had subsided.

Discussion

Since the start of the pandemic in Italy, this has been the first important cluster of 2009 pandemic influenza in a hospital setting involving patients at high risk of complication. Nosocomial transmission of seasonal influenza is well documented, but there are not many reports about nosocomial outbreaks of 2009 pandemic influenza. In the outbreak described, a case of 2009 pandemic influenza occurred in a strictly isolated patient and we can exclude contact with infected patients. Even if no HCW showed influenza-like symptoms during the outbreak, this hints towards an asymptomatic HCW as potential source of infection. To prevent transmission of pandemic influenza in health care settings, HCW should consider influenza early as differential diagnosis, and a high level of awareness of pandemic influenza diagnosis and appropriate infection control practices should be guaranteed. Fever often occurs in oncology patients due to paraneoplastic syndromes, opportunistic infections or chemotherapy [3-7]. This may lead to a delay in diagnosing influenza and consequently to a late application of control measures including restriction of contacts. In fact two symptomatic children were admitted to the Halloween party because clinicians did not consider the diagnosis of influenza.

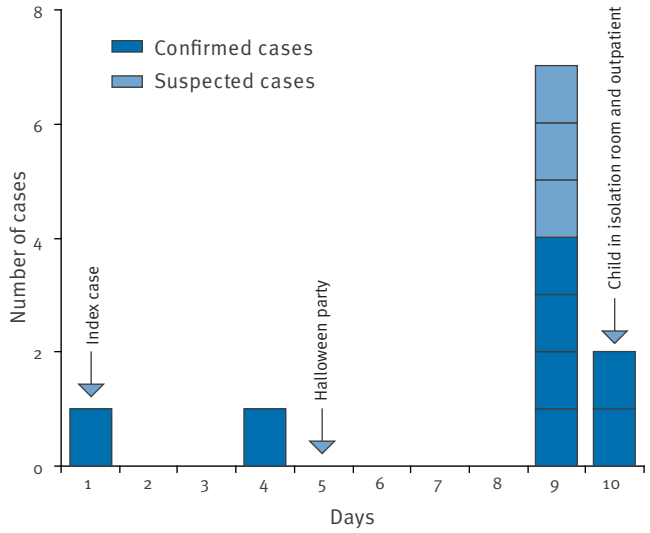
Oseltamivir is effective for prevention of complications associated with pandemic influenza in children. It also reduces the duration of influenza on average by 36 hours, with nausea and vomiting as the primary reported adverse effects [8]. The World Health Organization recommends oseltamivir as first-line treatment for 2009 pandemic influenza, with the use of zanamivir only for cases with suspected or confirmed oseltamivir resistance [9]. Oseltamivir is most effective if given within 48 hours of onset of symptoms. In the outbreak presented, oseltamivir was administered only after the laboratory confirmation, several days after the start of symptoms.

Influenza viruses are transmitted through aerosols, large droplets, or direct contact with secretions (or fomites). Occupational health and infection prevention and control should follow the precautionary principle and the recommendations or findings presented in the scientific literature to ensure staff safety during an influenza pandemic. A comprehensive approach to staff safety should be considered when planning for such an event. This includes implementing routine practices and additional precautions in all healthcare institutions, optimal hand hygiene, fit-tested N95 respirators for staff providing direct care to patients, vaccination of all staff when an effective vaccine is available and chemoprophylaxis in the case of influenza A. Patients will be best cared for when HCW are convinced that everything possible is being done to protect their own health as well [10].

The outbreak described, started before the availability of pandemic vaccine in the particular Region. At present, pandemic vaccine is offered to oncology patients, HCW, relatives and carers of high risk patients such as immunocompromised persons [11]. HCW can be an important source of infection for transmission of influenza, seasonal and pandemic, to patients. HCW may be asymptomatic in the incubation period and

Figure

Epicurve for 2009 pandemic influenza A(H1N1) cases in a paediatric oncology ward by onset of symptoms, Italy, October-November 2009 (n=11)



spread the infection especially in close-contact situations [12-14]. Several randomised clinical trials carried out in long-term care facilities have shown that high influenza vaccination coverage in HCW is associated with reduction in infection rates and decreased mortality for acute respiratory diseases in patients and residents during the winter months [15,16]. Vaccination of HCW against 2009 pandemic influenza is an ethic necessity, especially for those who work with immunocompromised patients. In addition, vaccination of HCW is strongly recommended to avoid interruption of essential care services during an influenza pandemic. Healthcare services are urged to promote activities that increase the uptake of pandemic vaccine of their employees [17-18].

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When should we intervene to control the 2009 influenza A(H1N1) pandemic?

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We simulated the early phase of the 2009 influenza A(H1N1) pandemic and assessed the effectiveness of public health interventions in Japan. We show that the detection rate of border quarantine was low and the timing of the intervention was the most important factor involved in the control of the pandemic, with the maximum reduction in daily cases obtained after interventions started on day 6 or 11. Early interventions were not always effective.

Background

In Japan, the 2009 influenza A(H1N1) pandemic raised questions as to whether the Japanese government's response was adequate. In the early phase, Japan concentrated on onboard quarantine inspection at international airports rather than other public health interventions. From 28 April 2009, the Ministry of Health, Labour and Welfare restricted passenger entry and conducted onboard quarantine inspections to delay the import of influenza cases for as long as possible. At Narita International Airport, the largest international airport in Japan, onboard quarantine inspection was carried out until 18 June 2009, and more than two million passengers from Canada, the United States and Mexico were screened. Ten cases were confirmed by RT-PCR and 60 contacts were quarantined. Other countries also conducted border quarantine inspections. Taiwan, for example, screened 1,328,645 passengers from 29 April to 4 June, and four cases were confirmed [1].

While large amounts of material and human resources were invested in this preventative measure, the first patient infected with the pandemic influenza A(H1N1) virus in Japan, detected on 16 May, had no overseas travel history. This observation indicated that infected individuals had passed the onboard quarantine inspection undetected or had already entered Japan before the inspection was initiated. While some experts suggested that onboard quarantine inspection was not effective, others argued that it delayed the import of pandemic influenza cases and increased the time to prepare for a response. The validity of the Japanese government's early response to the novel type of influenza virus remains controversial.

In this study, we estimated the number of imported cases of pandemic influenza that passed the border quarantine undetected. The domestic pandemic caused by these cases was simulated using mathematical simulation modelling to assess the optimal public health intervention to the influenza pandemic in the early pandemic phase in Japan.

Methods

We simulated indigenous transmission of pandemic influenza, caused by cases undetected by the onboard quarantine inspection, in a community of 100,000 individuals. The daily number of undetected cases was estimated by the daily number of detected cases among passengers entering Japan, the distribution of incubation periods, and that of infectious periods [2]. To simulate domestic transmission, we modified the SEIR (susceptible, exposed, infected, recovered) model [3] to take into account undetected cases as exogenous input (SEIRix model). Intervention is also taken into account in the model. Details of the SEIRix model can be found in a document provided on the following website: http://bonsai.ims.u-tokyo.ac.jp/~imoto/suppl_contN1H1.html. We set both incubation time and infectious period to 3.5 days [4-6]. The reproduction number was set as 2.3 obtained from a study conducted in Japan [7].

The simulation settings were as follows: At the border quarantine, some of the symptomatic cases were detected and isolated; undetected cases entered into the country and transmitted the virus to susceptible individuals. The first day on which a case of pandemic influenza was detected in Japan was defined as day 0. To compare the effects of the timing of public health interventions, we examined four different initiation dates, namely, day 1, day 6, day 11, and day 16 after the first case of the virus was detected at the border

quarantine. An intervention was defined as an action aimed at reducing the chances of susceptible individuals having contact with infectious cases, which included school closures or governmental orders to the population to stay at home. The scale of the intervention was described by the compliance rate of staying at home, which was set at three levels in the simulation, i.e. small (10%), medium (30%), and large (50%). Susceptible individuals who stayed at home were assumed to have no contact with infectious individuals. Individuals who stayed at home did so for three, seven or 14 days from the start of the intervention.

The maximum number of symptomatic cases per day and the time of their detection were used to evaluate the effectiveness of the intervention, because the acute capacity of medical institutions would be related to these endpoints, rather than to the total number of cases diagnosed during the pandemic. The total number of individuals who received an intervention was multiplied by the duration of the intervention and the product was called the person-day. The person-day of each intervention was divided by that of the smallest intervention, which was started on day 1 and lasted for three days. We defined this ratio as the standardised person-day ratio. The standardised person-day ratio was used as a surrogate marker for the resources needed for a given intervention. The relationship between effectiveness and required resources was also assessed for each intervention.

Results

In our simulation, border quarantine inspection detected the first case of H1N1 influenza in Japan 56

Table 1

Estimated number of undetected cases of pandemic influenza A(H1N1) among flight passengers entering Japan

	ψ	r	η =1.2	η =1.24	η =1.3
RL-IP	1	0.0000984	16.838	17.094	17.465
	0.7	0.0001405	27.483	27.848	28.379
2-IP	1	0.0001801	31.381	32.169	33.327
	0.7	0.0002572	48.259	49.384	51.038
3.5-IP	1	0.0005703	67.135	70.913	76.763
	0.7	0.0008147	99.336	104.732	113.09

The table shows the number of infected passengers who could not be detected by the entry screening for representative values of η, where η is the growth rate of the numbers of infected individuals on each day, ψ is the detection rate of passengers who make in-flight progression and r is the proportion of the infected passengers estimated by the number of detected infected passengers. We tested three variations of the incubation period: RL-IP has 1.4 days median period, that is the same incubation period as that in Rvachev and Longini (1985) and was used in Pitman *et al.* (2005) [2,8], 2-IP is an incubation period with a median period equal to two days and 3.5-IP has 3.5 days median period. Detailed information on the methods used for the estimation can be found at http://bonsai.ims.u-tokyo.ac.jp/~imoto/suppl_contN1H1.html.

Table 2

Peak reduction and lag by intervention, simulation of pandemic interventions, Japan

Scale	Start date											
	Day 1			Day 6			Day 11			Day 16		
	Duration (days)			Duration (days)			Duration (days)			Duration (days)		
	3	7	14	3	7	14	3	7	14	3	7	14
Small (v=0.1)												
Peak reduction[a]	0.99	0.97	0.90	0.98	0.94	0.84	0.97	0.91	0.88	0.96	0.96	0.96
Peak lag (days)[b]	1	2	3	1	2	3	1	1	−1	0	−1	−1
Standardised person-day ratio	1.0	2.3	4.7	0.9	2.1	4.2	0.8	1.8	3.6	0.6	1.4	2.8
Medium (v=0.3)												
Peak reduction[a]	0.97	0.91	0.78	0.95	0.85	0.64	0.91	0.76	0.73	0.92	0.92	0.92
Peak lag (days)[b]	2	4	9	2	4	9	2	4	−5	−3	−3	−3
Standardised person-day ratio	3.0	7.0	14.0	2.7	6.4	12.7	2.3	5.4	10.8	1.8	4.2	8.3
Large (v=0.5)												
Peak reduction[a]	0.95	0.87	0.73	0.91	0.77	0.56	0.85	0.69	0.69	0.91	0.91	0.91
Peak lag (days)[b]	3	7	15	3	8	17	3	−8	−8	−4	−4	−4
Standardised person-day ratio	5.0	11.7	23.3	4.5	10.6	21.2	3.8	9.0	18.0	3.0	6.9	13.9

v: the compliance rate of staying at home.

a Peak reduction: the reduction rate of the maximum number of cases per a day compared with that of no intervention.

b Peak lag: the lag of the date when the maximum cases were observed compared with that of no intervention; negative values indicate that the peak was achieved earlier than in a scenario with no intervention.

days after the report of the first case worldwide in Mexico. Our estimation suggests that at the time the first case was detected in Japan, more than 100 cases had already entered the country. The detection rate ranged from 7.1% to 22.3% (Table 1).

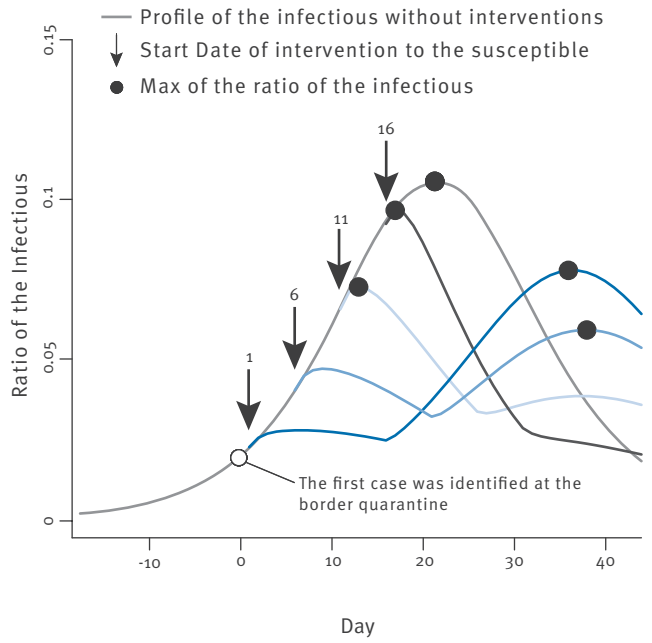
Small interventions were only minimally effective in reducing the maximum number of daily symptomatic cases and delaying the epidemic peak, regardless of the start date and duration of the intervention. When 10% of the susceptible individuals stayed at home for 14 days from day 1, the maximum number of daily symptomatic cases was reduced by only 10% and the epidemic peak was delayed by three days (Table 2). A large-scale intervention for 14 days starting on day 6 was the most effective. This intervention reduced the maximum number of symptomatic cases by 44% and delayed the epidemic peak by 17 days (Table 2). Comparing any combination of intervention scale and duration indicated that the maximum reduction in daily cases was obtained from those interventions that started on day 6 or day 11. Medium interventions for three days starting on day 11 were more effective than those that were started on day 6. Intriguingly, the earliest start date, day 1, did not give the best outcome within the same duration or scale.

Large and long interventions with different starting dates showed differing pandemic curves (Figure). When 50% of susceptible individuals received an early intervention to stay at home for 14 days, a second increase in the pandemic was observed from the end of the intervention. When the intervention was started on day 1 or day 6, the maximum daily number of symptomatic cases was obtained at the second peak, not the first peak that was observed just after the intervention. The last intervention, started on day 16, did not show a second peak, and the curve of the infection rate was attenuated.

The standardised person-day ratio showed that the most effective intervention, which reduced a peak to 56 percent, required the second largest amount of resources (Table 2). The most expensive intervention was a large intervention for 14 days starting from day 1. However, a medium intervention for 14 days starting from day 11 resulted in the same reduction in influenza cases with only half the amount of resources.

Figure

Simulation of pandemic curves after intervention to the susceptible population, Japan



Discussion

We simulated the early phase of the 2009 influenza A(H1N1) pandemic in Japan and assessed the effectiveness of public health interventions. Our estimation of cases undetected in onboard quarantine inspections demonstrated the low detection rate of this technique. A previous study suggested that border quarantine inspection could not prevent importation of the virus completely [2]. Tomba and Wallinga also showed the low detection rate of border quarantine by mathematical modelling [9]. On 28 April 2009, the World Health Organization (WHO) advised that no restriction of regular travel or closure of borders be implemented against the pandemic influenza virus. Our results are consistent with these views. To effectively slow the epidemic curve, the Japanese public health responses to the pandemic influenza virus would have had to shift the emphasis from onboard quarantine inspection to active surveillance and preparation, and such interventions would have been necessary as soon as the first case of the virus was detected by the onboard quarantine inspection. However, the simulation of viral transmission showed that early initiation of an intervention is not always effective in reducing the maximum number of daily cases, as a secondary increase in influenza cases was observed after the implementation of the early intervention. Even if the public health intervention was large and long, the start date was crucial in maximising its effectiveness.

An adequately large and long intervention cannot always be implemented, because of the limitations of human and material resources. Furthermore, interventions against emerging infectious diseases may cause social and economic harm, even if the pandemic does not increase in severity [10]. Therefore, the public health agency and the government must plan a response policy based on scientific data, considering effectiveness, feasibility, and impact on economic or social activities. We used the standardised person-day ratio as an indicator of required resources and showed various patterns of effectiveness versus resources. For example, the most effective intervention required 21.2 times the resources of the smallest intervention. Using such an indicator, the government would have to assess the optimal policy in terms of their ability to implement it and its effect on the spread of the

infection. In Japan, for example, decisions on school closure are taken independently by each school, but scientific forecasts would be able to support a decision for community-wide school closures while taking into consideration the effect on the influenza pandemic and its impact on society and economics. Cauchemez *et al.* reviewed the multiple aspects of school closure as a public health policy [11].

Most interventions to control pandemics were based on pessimistic scenarios [10]. Indeed, the onboard quarantine inspection in Japan was based on the response policy against the highly pathogenic avian influenza A(H5N1) and attempted to block all cases of the pandemic influenza A(H1N1) virus from entering the country. However, this method was ineffective in preventing the spread of the infection, and scientific policy-making would have been needed to minimise the adverse effects of this intervention [12, 13]. In the current study, we have highlighted a method of accomplishing evidence-based public health policy making for emerging infectious diseases.

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Genesis of a KPC-producing Klebsiella pneumoniae after in vivo transfer from an imported Greek strain

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We document here the *in vivo* transfer of bla_{KPC-2} between intensive care unit-acquired and a commensal strain of *Klebsiella pneumoniae* in a French patient after his repatriation from Greece. This first report of *in vivo* transfer of a bla_{KPC-2} between two *K. pneumoniae* strains raises further concerns about the spread of carbapenem resistance among *Enterobacteriaceae*.*

Introduction

Carbapenems are the cornerstone of therapy against multidrug-resistant (MDR) enterobacteria, notably those expressing extended-spectrum β-lactamases (ESBL). To date, enterobacterial strains producing Ambler class A *Klebsiella pneumoniae* carbapenemases (KPC) remain very scarce in western European countries and correspond almost exclusively to imported clones from endemic areas, namely, the United States, Israel and Greece [1]. The *bla*KPC genes are located in a set of plasmid-borne Tn*4401*-type transposons [2], with recent evidence of interspecies conjugative transfer [3,4]. Here, we provide the first evidence of *in vivo* transfer of bla_{KPC-2} between two *K. pneumoniae* strains from a single patient, one imported from Greece and the other from the commensal flora, leading to the emergence of a new KPC-2-producing strain in France.

Case report and study

A French man in his 70s who was travelling in Greece was admitted to the intensive care unit (ICU) of a hospital in Athens on 30 April 2009 (day 0) for intestinal bleeding complicated by haemorrhagic shock and multiple organ failure. Several nosocomial infections occurred during his five-week long ICU stay in Athens, including a catheter-related bloodstream infection (BSI, day 25) due to a carbapenem-resistant *K. pneumoniae* strain that was also resistant to fluoroquinolones, co-trimoxazole, and aminoglycosides except gentamicin. This episode resolved after catheter removal and a one-week course of intravenous colistin. Subsequent clinical improvement allowed medical repatriation in France, and the patient was transferred to the ICU of a hospital in Paris (day 42). Intestinal carriage of MDR enterobacteria was routinely screened at admission by plating a rectal swab on ChromID ESBL medium (BioMérieux). One carbapenem-resistant *K. pneumoniae* strain (CHA-1) was isolated, and expressed the same co-resistances as the one involved in the BSI episode (Table). As the patient had never been hospitalised previously, we assume that he acquired the CHA-1 in the ICU in Athens.

The patient was discharged to a general medical ward on day 62. He did not receive carbapenems or other β-lactams after his transfer from Greece. On day 92, a second rectal swab was cultured on ChromID ESBL medium. Overnight growth yielded *K. pneumoniae* for which subsequent antibiotic susceptibility testing showed two distinct phenotypes. Subculturing recovered CHA-1 and another *K. pneumoniae* strain designated as CHA-2 (Table). According to the latest breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [5], CHA-2 was resistant to ertapenem, intermediate susceptible to doripenem, and susceptible to imipenem and meropenem (Table).

Strains CHA-1 and CHA-2 were PCR-tested for all major β-lactamase-encoding genes, with subsequent sequencing of the PCR products. Both CHA-1 and CHA-2 carried bla_{KPC-2} and bla_{TEM-1}. In addition, the Ambler class B carbapenemase-encoding gene bla_{VIM-1} was detected in strain CHA-1 (Table).

We suspected that the strain CHA-2 had emerged by an *in vivo* co-transfer of bla_{KPC-2}/bla_{TEM-1} from the ICU-acquired strain CHA-1 to a recipient wild-type commensal strain of *K. pneumoniae*. This hypothesis was supported by several facts: Firstly, conjugation assays in mixed broth cultures using the rifampicin-resistant Escherichia coli J53 strain as recipient and either CHA-1 or CHA-2 as donors resulted in bla_{KPC-2}/bla_{TEM-1}-positive J53 transconjugants (conjugation frequency: 10^{-7} to 10^{-8}), suggesting co-transfer of a plasmid carrying both genes. After extraction using the CompactPrep Plasmid Midi Kit (Qiagen), plasmids from both transconjugants yielded identical *Eco*RI-digestion patterns, arguing that CHA-1 and CHA-2 strains harboured the same bla_{KPC-2}/bla_{TEM-1}-carrying plasmid. bla_{VIM-1} could not be transferred from CHA-1, as already experienced elsewhere [6]. Secondly, the swab from day 92 was re-plated on Drigalski agar. Twenty-five suspected *K. pneumoniae* were isolated, and those that did not grow on subcultures on ChromID ESBL medium were identified and tested for β-lactam susceptibility. Sixteen wild-type isolates of *K. pneumoniae* were thus collected and all yielded identical patterns in an enterobacterial repetitive intergenic consensus (ERIC)-PCR, suggesting that they were duplicates of a single wild-type *K. pneumoniae* strain, designated as BW1 (Table). Pulsed-field gel electrophoresis (PFGE) patterns of strains CHA-1, CHA-2 and BW1 were then compared to those of all KPC-2-producing pulsotypes of *K. pneumoniae* isolated to date in Greece (Figure).

The result indicated that (i) strain CHA-1 belonged to a KPC-2/VIM-1-coproducing pulsotype that is currently spreading in Greek hospitals (pulsotype C) in parallel with the pulsotype A that is the predominant KPC-2-producing pulsotype in Greece [6,7], (ii) CHA-2 did not match with any of the described Greek pulsotypes and (iii) KPC-2-producing strain CHA-2 and

Table

Antibiotic resistance phenotypes and acquired *bla* gene contents of enterobacterial strains described in this study

	K. pneumoniae strain CHA-1	*K. pneumoniae* strain CHA-2	*K. pneumoniae* strain BW1	*K. pneumoniae* strain TcBW1m[a]	*E. coli* strain J53	*E. coli* strain TcJ53-1	*E. coli* strain TcJ53-2
Origin	Acquired in Athens ICU	Commensal flora	Commensal flora (putative precursor of strain CHA-2)	Conjugation assay (donor: CHA-1 / recipient: BW1m)	Collection	Conjugation assay (donor: CHA-1 / recipient: J53)	Conjugation assay (donor: CHA-2 / recipient: J53)
Date of isolation since hospital admission	Day 42 and day 92	Day 92	Day 92	NA	NA	NA	NA
Acquired *bla* genes	bla_{VIM-1b}, bla_{KPC-2}, bla_{TEM-1}	bla_{KPC-2}, bla_{TEM-1}	None	bla_{KPC-2}, bla_{TEM-1}	None	bla_{KPC-2}, bla_{TEM-1}	bla_{KPC-2}, bla_{TEM-1}
MIC values, mg/L[c]							
Amoxicillin	>256	>256	>256	>256	2	>256	>256
Amoxicillin + CLA[d]	>256	32	1.5	32	2	24	24
Piperacillin	>256	>256	6	>256	0.75	256	256
Piperacillin + TZP[e]	>256	32	1	64	0.75	32	48
Cefotaxime	>32	2	0.047	2	0.023	4	4
Ceftazidime	>256	2	0.094	2	0.032	4	4
Aztreonam	>256	8	0.032	6	0.016	4	4
Ertapenem	>32	2	0.006	2	0.006	0.75	0.75
Meropenem	>32	2	0.012	0.75	0.006	0.25	0.38
Doripenem	>32	1.5	0.016	0.75	0.006	0.25	0.25
Imipenem	32	2	0.125	2	0.19	0.5	0.75
Tobramycin	16	0.25	0.25	0.19	0.064	0.064	0.064
Amikacin	16	1	1	1	0.38	0.25	0.25
Gentamicin	1.5	0.5	0.5	0.5	0.094	0.094	0.094
Ciprofloxacin	>32	0.032	0.032	0.032	0.047	0.047	0.047
Cotrimoxazole	>32	0.064	0.064	0.064	0.004	0.004	0.004
Tigecycline	0.5	1	1	1	0.5	0.5	0.5
Colistin	0.125	0.125	0.125	0.125	0.19	0.125	0.19

bla: beta lactamase; ICU: intensive care unit; NA: not applicable.

[a] Obtained by conjugation assays using a rifampin-resistant mutant of BW1 selected on Szybalski gradients (BW1m, MIC of rifampin > 250 mg/L) as recipient and CHA-1 as donor, and subsequent isolation on Drigaslki agar supplemented with cefotaxime (1mg/L) plus rifampin (250mg/L).

[b] The co-expression of VIM-1 and KPC-2 contributes to explain the higher MICs of β-lactams in strain CHA-1 when compared to the blaVIM-1-egative/blaKPC-2-positive strain CHA-2;

[c] MIC: minimal inhibitory concentrations, as defined by E-test

[d] CLA: clavulanic acid (2 mg/L)

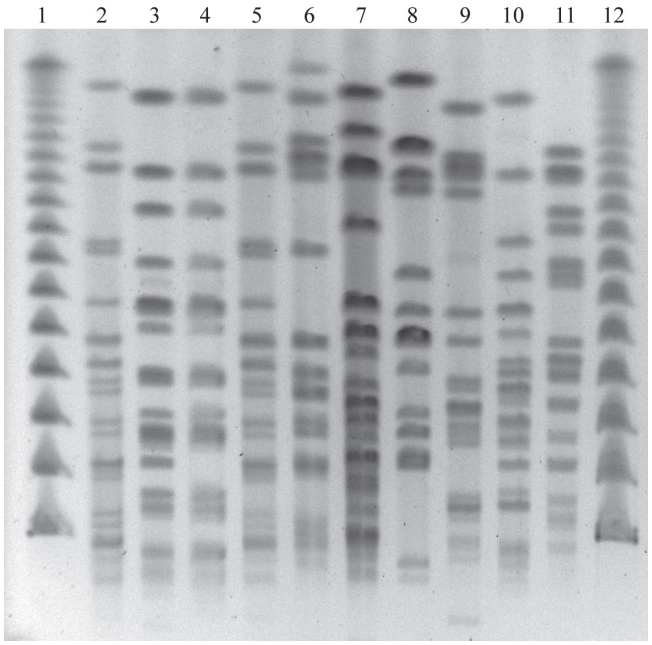
[e] TZP: tazobactam (4 mg/L)

wild-type strain BW1 displayed strictly identical XbaI-fingerprints, except for one band of approximately 100 kb also observed in CHA-1 that may correspond to the bla_{KPC-2}/bla_{TEM-1}-carrying plasmid. These data supported the role of BW1, the dominant wild-type *K. pneumoniae* strain within the digestive flora, as the bla_{KPC-2}-negative precursor of CHA-2. Lastly, we confirmed that the bla_{KPC-2}/bla_{TEM-1}-carrying plasmid was transferable from CHA-1 to a rifampicin-resistant BW1 strain obtained on a Szybalski gradient (Table). Some limitations are yet to be considered since we cannot strictly exclude that CHA-2 could have been acquired in Greece and could have been missed in the swab taken on day 42 at admission in France. Likewise, we cannot exclude that acquisition of CHA-2 could have occurred in France although reports on KPC-producing strains remain scarce to date.

This report raises further concerns about the diffusion of carbapenem resistance among enterobacteria. Indeed, that imported strains from endemic areas are able to spread *bla*KPC genes – even in the absence of β-lactam selective pressure, as in this patient – is worrisome, most notably for western European countries where the incidence of KPC-producing pathogens is still low.

Figure

*Xba*I-PFGE of *K. pneumoniae* strains CHA-1, CHA-2, BW1 and KPC-producing clones disseminated in Greek hospitals



Lanes 1 & 12: Lambda Ladder (New England Biolabs)
Lane 2: strain CHA-1 bla_{VIM-1} + bla_{KPC-2}
Lane 3: strain CHA-2 bla_{KPC-2}
Lane 4: strain BW1 wild type
Lane 5: strain 1780 bla_{VIM-1} + bla_{KPC-2} Greek pulsotype C
Lane 6: strain 1797 bla_{VIM-1} + bla_{KPC-2} Greek pulsotype G
Lane 7: strain 1504 bla_{KPC-2} Greek pulsotype A
Lane 8: strain 1370 bla_{KPC-2} Greek pulsotype B
Lane 9: strain 1433 bla_{KPC-2} Greek pulsotype D
Lane 10: strain 1516 bla_{KPC-2} Greek pulsotype E
Lane 11: strain 1643 bla_{KPC-2} Greek pulsotype F

* CHA-2 and BW1 pulsotypes only differ by a ~100-kb band deemed to match the bla_{KPC-2}-carrying plasmid (also harboured by strains CHA-1 and 1780) [6].

PFGE: pulsed-field gel electrophoresis.

Acknowledgements

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*Erratum: This sentence was replaced on 14 January 2010

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Outbreak of 2009 pandemic influenza A(H1N1), Los Lagos, Chile, April-June 2009

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On 17 May 2009, the first two cases of 2009 pandemic influenza A(H1N1) were confirmed in the Metropolitan region (Santiago, Chile). On 6 June 2009, Chile reported 500 confirmed cases, seven severe and two fatal. Because six of the severe cases and the two deaths occurred in the region of Los Lagos in southern Chile, a retrospective study was conducted using data on emergency room visits as well as laboratory viral surveillance, during the period from 1 April to 31 May, in order to establish the date of the beginning of the outbreak. From 1 to 27 June, data were collected in real time, to establish the real magnitude of the outbreak, describe its transmission, clinical severity and secondary attack rates. Confirmed cases, their household contacts and healthcare workers were interviewed. This analysis showed that the outbreak in Los Lagos started on 28 April. By 27 June, a total of 14,559 clinical cases were identified, affecting mostly 5-19 year-olds. The effective reproduction number during the initial phase (20 days) was 1.8 (1.6–2.0). Of the 190 confirmed cases with severe acute respiratory infection, 71 (37.4%) presented a risk condition or underlying illness.

Introduction

On 24 April 2009, the United States (US) Centers for Disease Control and Prevention (CDC) reported eight confirmed cases of a novel strain of influenza A(H1N1) in Texas and California, and Mexico confirmed the same virus in 16 samples [1-5]. That same day, the Ministry of Health of Chile alerted all regions of the country, so they could strengthen their surveillance of respiratory viruses and maximise infection control measures.

On 17 May, the first two cases of the 2009 pandemic influenza A(H1N1) were confirmed in the Metropolitan region of Santiago, in a person returning from Punta Cana (Dominican Republic) and another with no history of travel outside Chile. The first case in Puerto Montt (Region of Los Lagos) was laboratory-confirmed on 26 May. One week later, Chile reported 500 confirmed cases throughout the country, among those seven cases with severe acute respiratory infection (SARI) and two fatalities. Because six of the SARI cases and the two deaths occurred in the region of Los Lagos, the Ministry of Health formed a field team on 1 June to investigate the outbreak in Puerto Montt. This team conducted a retrospective study from 1 April to 31 May, in order to establish the date of the beginning of the outbreak, and a follow study until 27 June to establish its real magnitude, and to describe its transmission and clinical severity.

The Los Lagos region, in the south of the country, has 825,000 inhabitants and is one of the 15 regions in Chile. The capital Puerto Montt with 230,855 inhabitants has the second most important airport in the country in terms of air traffic. This city receives many foreign travellers for business or tourism. The climate is cold, with temperatures fluctuating between 0 ºC and 8 ºC during the period of this study (1 April to 27 June).

The surveillance of influenza-like illnesses (ILI) in the region is carried out through sentinel units in ambulatory care centres and hospitals.

Until 6 October, Chile reported 12,254 confirmed cases of pandemic influenza, of which 1,585 (9.4 per 100,000 inhabitants) were cases with SARI including 134 fatalities (0.8 per 100,000 inhabitants); only one fatality was a pregnant woman. Los Lagos had the third highest rate of severe cases of the country (30.8 per 100,000 inhabitants) and the fourth highest mortality rate (1.33 per 100,000 inhabitants).

It is noteworthy that Chile indicates treatment with oseltamivir with a doctor's prescription for anybody older than five years of age whose symptoms comply with the case definition.

Methods

In order to establish the date of the beginning of the outbreak, its magnitude, transmission and clinical severity, we carried out a retrospective study using data on emergency room visits, from 1 April to 31 May 2008 and for the same period in 2009 at the two main health facilities in Puerto Montt. The following diagnoses were included: respiratory viral disease, influenza, severe acute respiratory infection, pneumonia, pneumonitis, obstructive bronchial syndrome, bronchitis, rhinopharyngitis, common cold and febrile syndrome. In addition, for the same period, a review of viral surveillance was conducted in the local laboratory registers.

From 1 June, case follow-up was implemented: In all healthcare facilities, in the public and private sector, people who fulfilled the following definition of a suspected case were notified: "any person presenting

Figure 1

Distribution of clinical (n=14,559) and laboratory-confirmed cases (n=301) of pandemic influenza A(H1N1) by date of symptom onset, Los Lagos, Chile, 28 April- 27 June

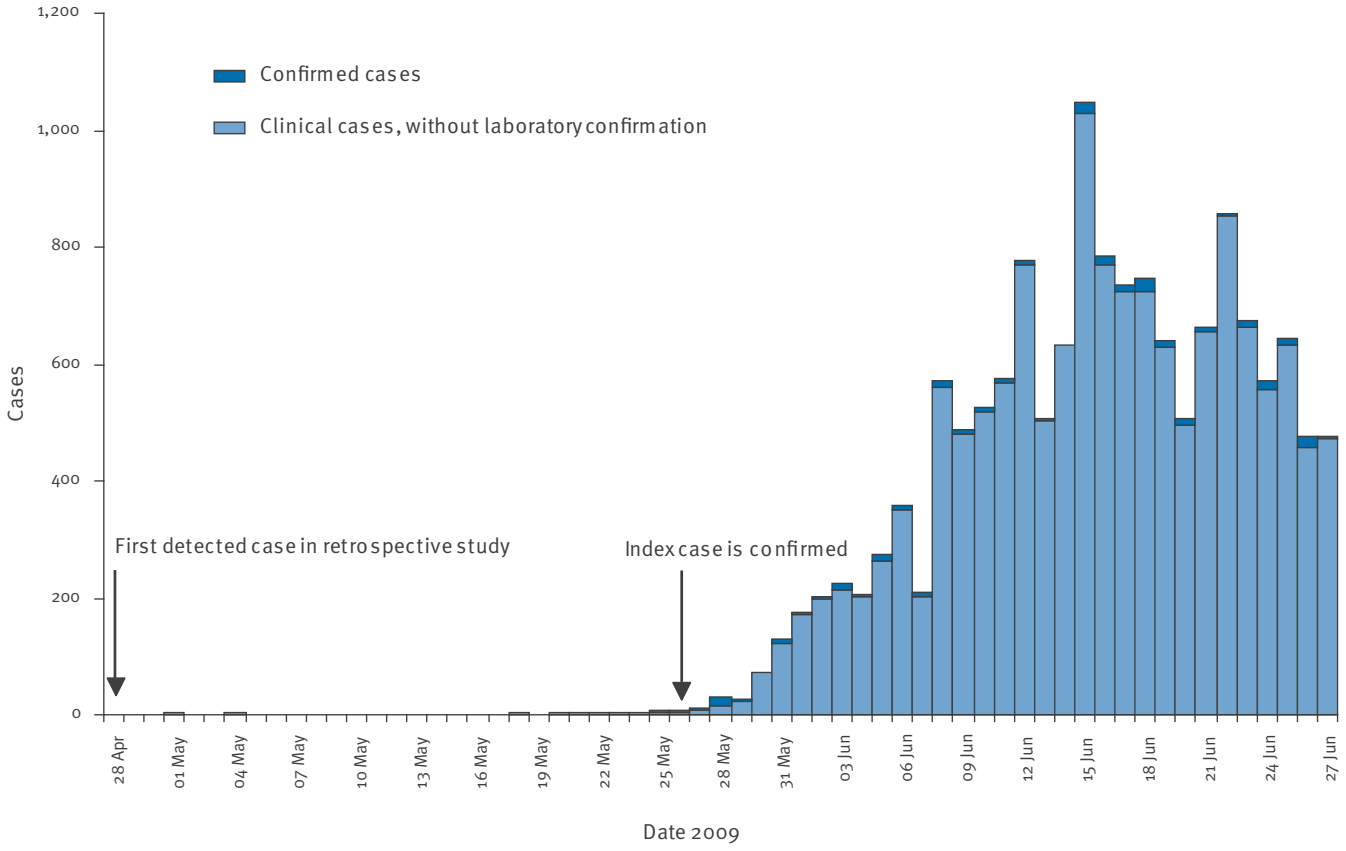


Table 1

RT-PCR results for influenza A by age group, Los Lagos, Chile, 1 April-27 June 2009

Age groups (years)	Total samples processed	RT-PCR results		
		Negative	Positive	
			Seasonal influenza	Pandemic H1N1 influenza
0 to 4	112	39.29%	2.68%	57.14%
5 to 14	78	21.79%	1%	78.21%
15 to 29	75	20.00%	0%	80.00%
30 to 59	135	36.30%	0.74%	62.96%
60 and older	63	73.02%	0.00%	26.98%
Not specified	10	0.00%	0%	100.00%
Total	**473**	**36.15%**	**1.06%**	**62.79%**

a fever of 38.5 °C or higher accompanied by coughing and any of the following symptoms: headache, myalgia, arthralgias, and/or sore throat". In order to identify suspected cases with SARI, the presence of dyspnoea, tachypnoea, cyanosis, or hypoxaemia was added to the previous case definition, and dehydration or food rejection was added for cases involving infants.

In addition, household visits were carried out to conduct in-depth interviews with laboratory-confirmed cases and their contacts at home, in order to determine the secondary attack rate. A symptomatic contact of the index case was defined as anyone developing ILI within 14 days following the date of onset of symptoms of the confirmed case. Interviews were also conducted with family members and with healthcare personnel who personally provided patient care, to establish the date of symptoms onset, the date of first medical attention and hospitalisation, risk factors and clinical evolution of severe and fatal cases. Clinical files of hospitalised patients and fatal cases in the two facilities were also reviewed.

All respiratory samples (nasopharyngeal aspiration) were analysed by direct and indirect immunofluorescence and by the real-time RT-PCR distributed by the US CDC to all national influenza centres.

The reproduction number R was estimated using the Wallinga and Lipsitch linearisation method based on the intrinsic growth rate r of the epidemic curve in its initial phase, which was assumed exponentially by visual inspection of the epidemic curve. The assumption was that its initial phase corresponded to the first 20 days of consecutive transmission (between 15 May and 3 June) and that the intrinsic growth rate corresponded to the beta (slope) of the curve. The merit adjustment was estimated using the exponential regression coefficient for ascertainment. As the average latent period, 1.0 days was chosen and for infectiousness, 1.5 days [6-9].

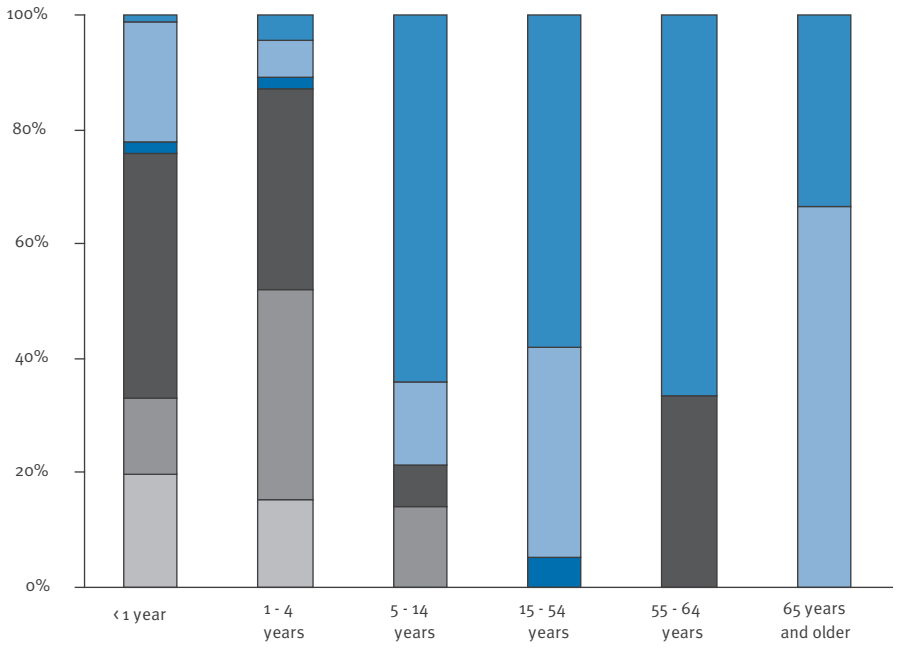
Results

Identification and general characteristics of the cases

A 23% increase in pneumonias was observed in 2009 from 1 April onwards, compared with 2008; however, this increase was not significant (p=0.159). The first case of pandemic influenza was confirmed on 26 May.

Figure 2

Distribution of circulating viruses by age group, Los Lagos, Chile, weeks 1 to 21, 2009 (n=176 for whom age was known)



	< 1 year	1 - 4 years	5 - 14 years	15 - 54 years	55 - 64 years	65 years and older
Influenza A(H1N1)	1	2	9	11	2	1
Non-subtyped influenza A	19	3	2	7	0	2
Influenza B	0	0	0	0	0	0
Seasonal influenza A	2	1	0	1	0	0
Parainfluenza	39	16	1	0	1	0
Adenovirus	12	17	2	0	0	0
Respiratory syncytial virus	18	7	0	0	0	0

However, the retrospective study showed that the first case had occurred on 28 April. After that date, the comparative analysis of 2008 and 2009 showed a significantly higher number in 2009 of common colds ($p<0.001$), ILI and influenza ($p<0.001$), pneumonia ($p=0.008$), obstructive bronchial syndrome ($p<0.001$), and febrile syndrome ($p<0.001$). This increase was first observed in emergency rooms during week 19 (10-16 May), reaching its peak by week 23 (7-13 June). The age groups in which the increase in pneumonias was observed were school children (5-19 years), young adults (20-29 years) and the elderly (over 65 years).

From 1 April to 27 June, a total of 14,559 clinical cases of pandemic influenza were identified, 301 (2.1%) of them were laboratory-confirmed for pandemic influenza. Also, 190 (1.3%) of the clinical cases had SARI laboratory-confirmed for pandemic influenza, including 10 deaths (0.06%). From 26 May, the date of confirmation of the first case in Los Lagos and its notification, an abrupt increase in the number of cases was observed, according to the date of onset of symptoms and consultation (Figure 1). For the cases observed before 26 May, the average period between the date of onset of symptoms and the first consultation was three days. After that date, the average period fell to 0.91 days.

The most affected age groups were the 5–19-year-olds (12.6 per 100,000 inhabitants) and the 20–29-year-olds (11.9 per 100,000 inhabitants). No significant differences were observed by sex. The main clinical characteristics were fever (96.2%), cough (78.0%), myalgia (69.8%), sore throat (57.4%), vomiting (35.0%), diarrhoea (28.2%) and conjunctivitis (21.4%).

Laboratory surveillance

Of a total of 473 respiratory samples (nasopharyngeal aspiration) processed by the Chilean Institute of Public Health (Instituto de Salud Pública), 297 (62.79%) were positive for pandemic influenza A(H1N1), five (1.06%) were positive for seasonal influenza (H1 and H3), and 171 (36.15%) were negative for both. The highest percentage of pandemic influenza infections was found in the age groups between five and 29 years (Table 1).

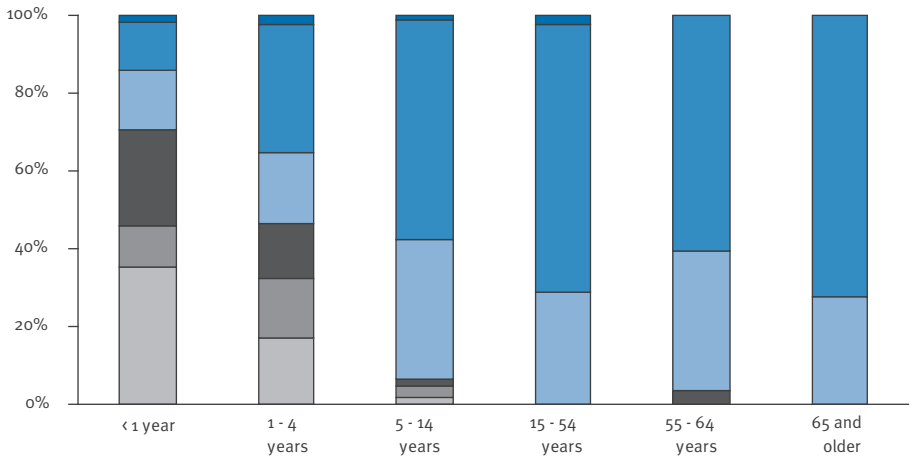
The viral surveillance (Figures 2: weeks 1-21 and Figure 3: weeks 1-25) showed an increase in the circulation of pandemic influenza and untyped influenza over week 21, especially in children under five (from 18.25% to 37.05%). Also observed was an increase in the circulation of respiratory syncytial virus (RSV, 32%), affecting in particular children under the age of one year.

Geographical spread

The first cases were detected in week 17 in the city of Puerto Montt (where the airport is located), spreading at a rate between one and two new communes per week during the first three weeks (from one commune in week 17 to six communes in week 19) and between six and seven new communes per week during the following three weeks (from six communes in week 20 to 26 in week 23). Six weeks after the first case detection

Figure 3

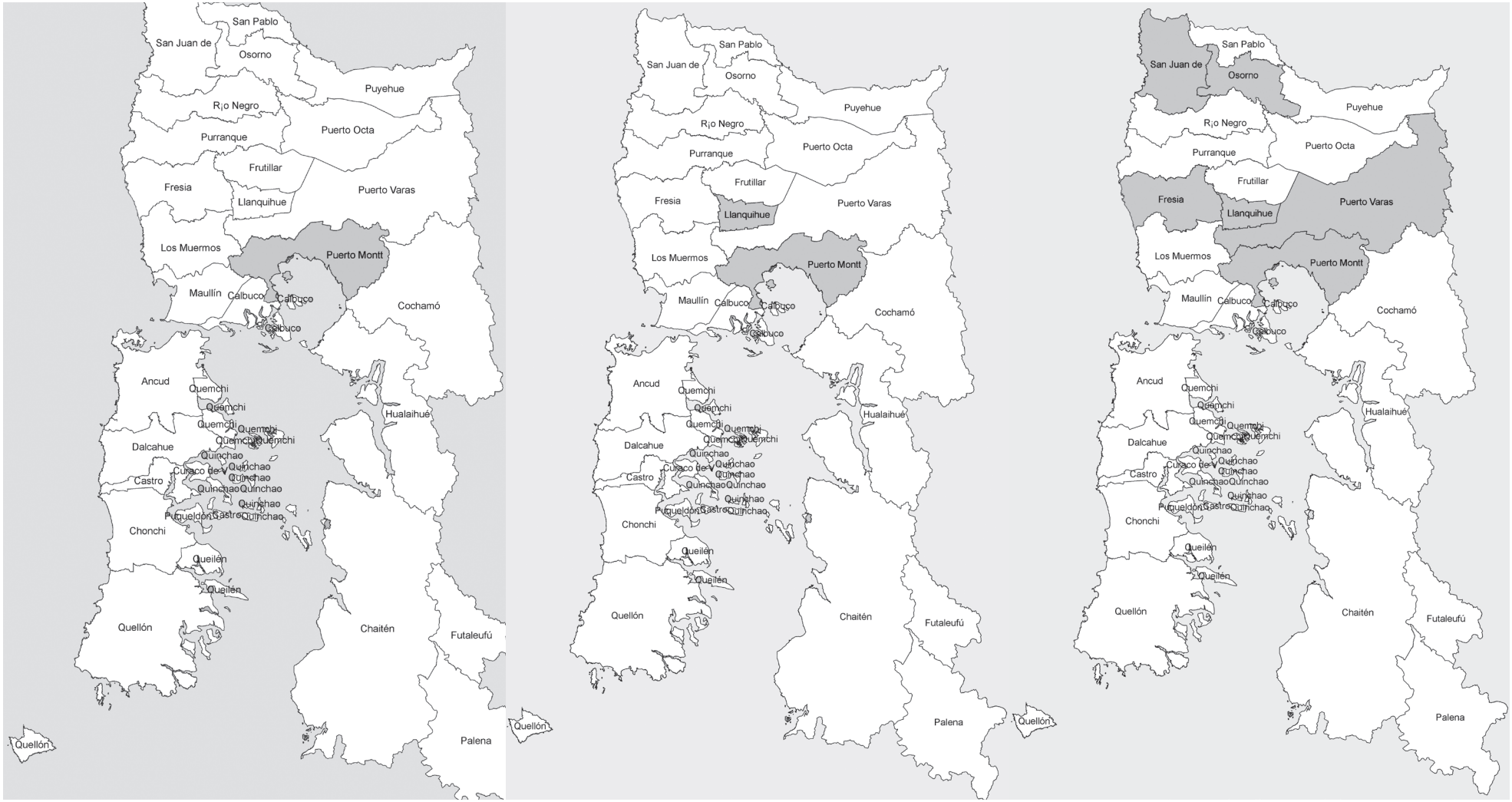
Distribution of circulating viruses by age group, Los Lagos, Chile, weeks 1 to 25 2009 (n=646 for whom age was known)



	< 1 year	1 - 4 years	5 - 14 years	15 - 54 years	55 - 64 years	65 and older
Seasonal influenza A	3	3	1	5	0	0
Influenza A(H1N1)	20	44	61	132	17	13
Non-subtyped influenza A	26	24	39	56	10	5
Influenza B	0	0	0	0	0	0
Parainfluenza	41	19	2	0	1	0
Adenovirus	17	20	3	0	0	0
Respiratory syncytial virus	59	23	2	0	0	0

Figure 4

Geographical spread of pandemic influenza, Los Lagos Region, Chile, weeks 16 to week 23, 2009



Source: Centro Nacional de Enlace, Depto. Epidemiología, Ministerio de Salud – 2009.

(week 23), 26 of the 30 communes had been affected. Those with the highest rates per 100,000 inhabitants were Hualaihué (27.3), Osorno (7.8), Puyehue (6.2), Río Negro (4.5) and Llanquihue (4.6), while the overall rate for the region was 1.2. The communes that did not present any cases up to week 23 were Futaleufú, Chaitén, Queilén, and Quinchao (the latter two on the island of Chiloé), see Figure 4.

Analysis of transmission

Initial estimate of transmission reproduction number R)

The exploratory analysis for a complete series of 20 days (15 May–3 June) showed an effective reproduction number (R) equal to 1.8 (confidence interval (CI):1.6–2.0); for 15 days (20 May–3 June) the R was 1.9 (CI:1.7–2.2), for 10 days (24 May–3 June) R was 2.0 (CI:1.7–2.3), and for the last five days (30 May–3 June) R fell to 1.6 (CI: 1.5–1.8).

Transmission among household contacts

On 3 June, the field team started interviewing confirmed cases and their household contacts. At that point, 59 cases were laboratory-confirmed for pandemic influenza. From those, 57 cases were interviewed and only two cases could not be contacted. For the 57 interviewed cases, 245 persons living in the same households were identified (average: 3.3 household contacts per case; range: 0–8), with an average age of 29 years (ranging from 0 to 76 years) and 54.8% female cases (134 of 245). Besides the 57 interviewed cases, 89 of their household contacts presented ILI (complying with the case definition) from 24 April onwards, representing a household prevalence of 59.6% (146 of 245 cases).

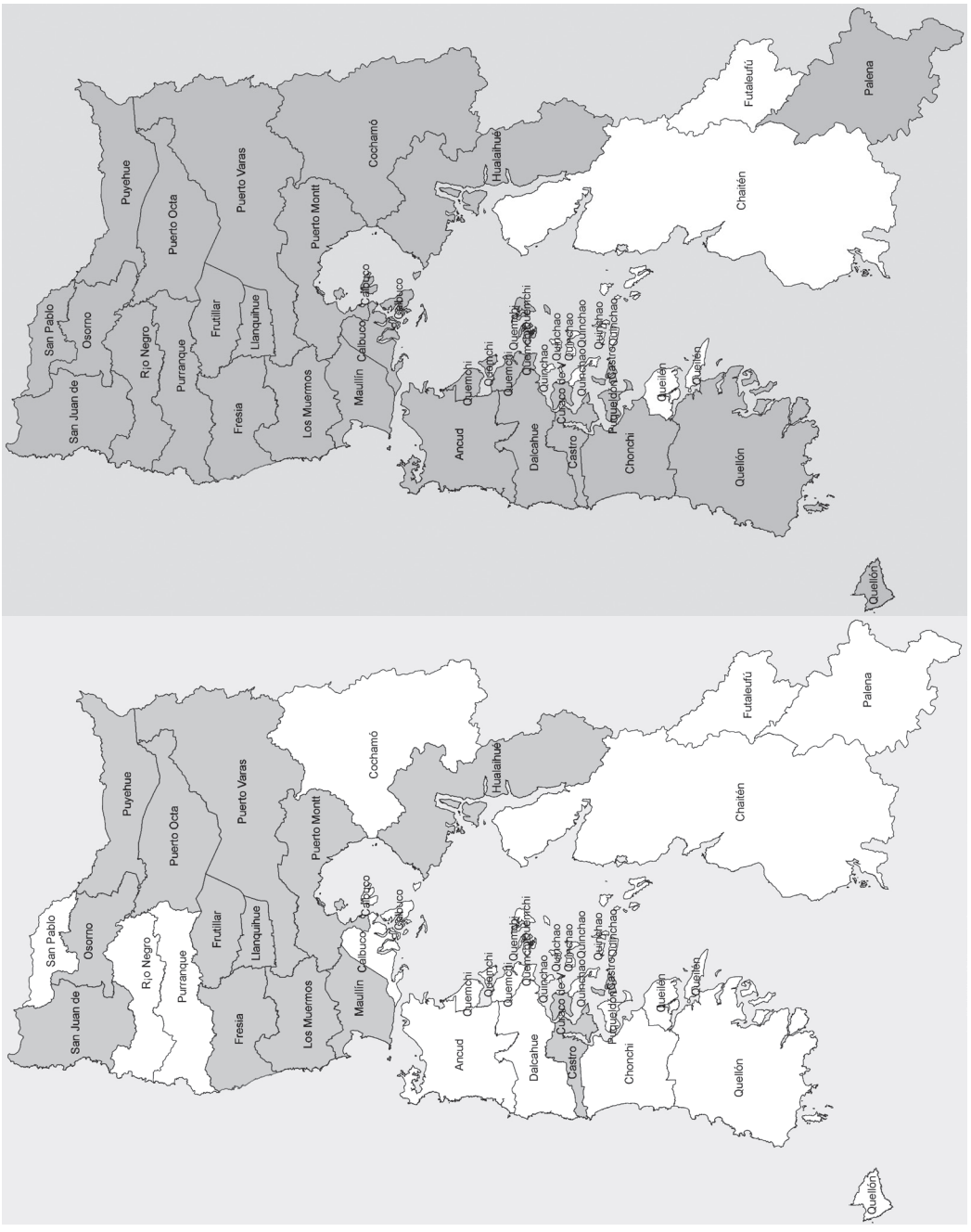


Figure 4 Continued
Geographical spread of pandemic influenza, Los Lagos Region, Chile, weeks 16 to week 23, 2009

Source: Centro Nacional de Enlace, Depto. Epidemiología, Ministerio de Salud – 2009.

Of all 89 symptomatic contacts studied, 35 presented symptoms before the household index case and 54 were classified as secondary cases of the index case, representing a secondary attack rate of 35.0% (54 out of 146).

With the available information on the 54 secondary cases, the average time between the date of onset of symptoms of the index case and the date of onset of symptoms of the contact (generation interval) was 3.61 days (median: three days, ranging from less than 24 hours to nine days).

Transmission among healthcare workers

Forty-one healthcare personnel were interviewed, 20 presented respiratory symptoms within the four weeks prior to interview (48.7%); and 34 (82.9%) staff members indicated that they had had contact with

Table 2

Symptoms, interventions and laboratory results for hospitalised cases of pandemic influenza A(H1N1), Los Lagos, Chile, 1 May-27 June 2009 (n=20)

Signs and symptoms			n	Proportion
Dyspnoea			17	85.00%
Tachypnoea			13	65.00%
Crepitations			12	60.00%
Tachycardia			10	50.00%
Cyanosis			5	25.00%
Wheezing			5	25.00%
Hypotension			4	20.00%
Seizures			2	10.00%
Confusion			2	10.00%
Interventions			**n**	**Proportion**
Needed oxygen upon admission			11	55.00%
Needed mechanical ventilation during hospitalisation			5	25.00%
Were admitted to ICU			8	40.00%
Received antibiotic therapy			16	80.00%
Received steroid therapy			9	45.00%
Laboratory results upon admission	**Mean**	**Minimum**	**Maximum**	**Normal values**
Total white blood cell count/mm^3	9,168	4,100	22,800	4,000-10,000
% Neutrophils	69.16	6.7	91	55-65
% Lymphocytes	18.29	5.3	43	25-35
Haemoglobin (g/dl)	13.74	10.4	20.4	12 - 17
% Haematocrit	41.27	33.1	57.3	37-52
Platelets/mm^3	262,706	123,000	533,000	150,000-450,000
Erythrocyte sedimentation rate (mm)	31	6	84	1-15
C-reactive protein (mg/dl)	8.8	1.2	26.5	‹ 1
Na^+ (meq/l)	135.1	130.7	140	135 a 146
K^+ (meq/l)	4.04	3.2	4.63	3.5 a 5
Cl^- (meq/l)	101.2	98.6	106	98 a 106
Urine urea nitrogen (mg/dl)	19.5	8.4	49	7 a 18
Creatinine (mg/dl)	1.34	0.5	4.6	0.6 a 1.4
Glucose (mg/dl)	130.4	90	234	70 a 105
SGOT(U/l)	321.5	60	583	up to 37
SGPT (U/l)	104.7	19	354	up to 41
Creatine kinase (U/l)	189.5	122	257	38 a 210
PT (%)	74	51	89	70 a 100
PTT(seg)	47	42	52	25 a 38
pH	7.29	6.79	7.46	7.35 a 7.45
pCO_2 (mmHg)	47.6	27.5	131.3	35 a 45
HCO_3^- (meq/l)	18.9	2.6	30.6	22 a 26
paO_2 (mmHg)	73.9	45.6	111.5	80 a 100
FiO_2 (%)	51.6	28	100	21

Meq: milliequivalents; PT: prothrombin time; PTT: partial thromboplastin time; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

suspected or confirmed cases in the community. Of the symptomatic healthcare workers, 47.2% had been vaccinated, but only 25% of the asymptomatic healthcare workers. An evaluation of the compliance with treatment guidelines for symptomatic healthcare workers (with oseltamivir) showed that only two cases received treatment with oseltamivir.

Severity analysis

General characteristics

The proportion of cases who developed a SARI and required hospitalisation was 1.3% (190 of all 14,559 cases). The first cases with SARI were hospitalised from the middle of May (week 22) onwards, 20 days after the first case had been detected in the retrospective search, and eight days before the first case in Puerto Montt's (index case) had been detected (see Figure 1). A gradual increase in hospitalised cases was observed up to 23 June, when the number of cases with SARI rose to twelve on that day alone.

Among the 190 cases of SARI with a confirmed diagnosis, the median age was 27 years (0–85), 47.4% being male (90 of 190). The age group most affected were children under five years (73 per 100,000 inhabitants), followed by those over 60 years of age (22 per 100,000), 40-59 years (20.3 per 100,000), 20-39 years (18 per 100,000), and finally those between five and 19 years of age (17 per 100,000 inhabitants).

As of 27 June 2009, 10 deaths have been reported (a fatality rate of 0.19%) eight male and two female: a six-year-old boy, seven young adults between 18 and 64 years of age, and two elderly adults aged between 65 and 85.

Co-morbidity in severe cases

Of the 190 cases with confirmed SARI, 71 (37.4%) presented an underlying risk condition or illness.

The interviews with the 57 confirmed cases (37 mild cases and 20 cases with SARI) and the review of the clinical files showed that presenting some underlying evidence of co-morbidity increased the risk of presenting SARI (14.3% in the mild cases versus 57.9% in the cases with SARI (odds ratio (OR)=8.25; CI: 2.22 to 30.60; p=0.0013). The underlying risk factors in the acute cases were pulmonary disease (six), obesity (three), heart disease (three), diabetes (one), alcoholism (one) and smoking (two). Of these cases, three presented two or more underlying conditions. Of the 10 deaths, five showed between one and three risk factors: obesity (two), heart disease (three), hypertension (one), diabetes (one), chronic obstructive pulmonary disease (one), pulmonary fibrosis (one), and heavy smoking (two).

Clinical and laboratory characteristics in severe cases

The main results from the 20 hospitalised cases studied in depth are shown in Table 2. The characteristics at the beginning of the clinical profile did not differ between the group of people with mild disease and those with severe disease. With respect to chest X-rays performed at the time of admission, seven presented images compatible with pneumonia, 11 presented interstitial infiltrate, and in two cases the X-rays were not available.

Of the severe cases, 11 were admitted with evidence of hypoxia, for which they required oxygen at that time; however, all patients required oxygen at some point during their hospitalisation.

The serum glutamic oxaloacetic and glutamic pyruvic transaminases at the time of admission reached average values of 321 U/L (range: 60–583) and 105 U/L (range: 19–354), respectively. The rest of the laboratory tests performed at the time of admission were found to fall within the reference values.

Discussion

As a result of this study, it was possible to determine that the outbreak of pandemic influenza A(H1N1) in Los Lagos started on 28 April 2009 (week 17), before the confirmation of the first case in the country (17 May, week 20). It probably originated due to the high level of international commercial activity in that region.

By week 23, the virus had spread to 26 of 30 communes in Los Lagos, reaching a total of 14,559 cases. Regarding transmission, the preliminary reproduction number for the initial phase (1.6–2.0) was higher than estimated for the outbreak in Mexico (1.4–1.6) and lower than estimated for the outbreak in Japan (2.0–2.6) [7,8]. Household prevalence was higher, at 59.2%, probably due to lifestyle factors related to the low temperatures during the period of investigation; while the secondary attack rate (35.0%) and the generation interval (3.61 days) were similar to the values found in Mexico (31% and 3.9 days, respectively (10). Although high levels of transmission were found among healthcare personnel (48.7%), no link with hospitalised patients could be established, because 83% of the staff had had contact with suspected or confirmed cases in the community.

The highest rates of SARI were in small children and elderly people, while mild disease was more frequent in school children and young adults.

One of the main limitations of this study was the small number of patients with SARI who were studied in depth. Further analysis will include all cases that occurred in Los Lagos during the winter season, which will give us more information on the clinical presentation and serious risk factors.

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