

## Surveillance and outbreak reports

# INTERIM REPORT ON PANDEMIC H1N1 INFLUENZA VIRUS INFECTIONS IN SOUTH AFRICA, APRIL TO OCTOBER 2009: EPIDEMIOLOGY AND FACTORS ASSOCIATED WITH FATAL CASES

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We provide an interim report on pandemic H1N1 influenza activity in South Africa, with a focus on the epidemiology and factors associated with deaths. Following the importation of the virus on 14 July 2009, and the epidemic peak during the week starting 3 August, the incidence in South Africa has declined. A total of 12,331 cases and 91 deaths have been laboratory-confirmed as of 12 October 2009. Age distribution and risk groups were similar to those observed elsewhere. The median age of patients who died (33.5 years) was significantly higher than that of the non-fatal cases (15.0 years,  $p < 0.01$ ). The most common underlying conditions among fatal cases were infection with human immunodeficiency virus (17/32 tested) and pregnancy (25/45 women of reproductive age). Active tuberculosis coinfection was present in seven of 72 fatal cases. These findings should be taken into consideration when planning vaccination strategies for 2010.

### Introduction

The first human cases of infection with the pandemic influenza A(H1N1)v virus were detected in the United States (US) and Mexico during April 2009 [1,2]. Following this, rapid global transmission was observed, prompting the World Health Organization (WHO) to raise the pandemic alert level to the highest phase-6 on 11 June 2009, while noting that the current pandemic may be characterised as moderate in severity [3]. As of 11 October 2009, the WHO has reported over 399,232 laboratory-confirmed cases of pandemic H1N1 influenza and more than 4,732 associated deaths worldwide [4]. Similarities with regards to the epidemiological behaviour of the influenza A(H1N1)v virus have been observed among populations of both the northern and southern hemispheres [5-12]. Further similarities have been observed globally in the risk factors contributing to severe disease and death, with underlying disease recorded in at least half of the fatal cases. Two risk factors appear to be of particular importance based on data already published: pregnancy (30% of the 20-39 year-old women who died) and metabolic diseases (especially severe obesity and diabetes, 30% of fatal cases) [12].

Although much has been published on the epidemiology of pandemic H1N1 influenza infections globally [1,2,5-12], there is little published data from the African continent. The epidemiology of pandemic influenza in South Africa might differ from that described elsewhere for numerous reasons. Firstly, the country is burdened with a high prevalence of other infectious diseases such as human immunodeficiency virus (HIV, approximately 5.2 million infected, 18.8% prevalence in adults 15-49 years of age, 28% antenatal prevalence in 2007 [14]) and tuberculosis (TB, approximately 1% prevalence in 2006 [15]). Secondly, there is a significant burden of non-communicable conditions such as obesity (24% of males and 27% of females in 2008) and diabetes (2.6% of males and 3.9% of females in 2008) [15]. Thirdly, there are large numbers of pregnant women who may be at risk (total fertility rate 2.38 children per woman, general fertility rate 81 per 1,000 women of reproductive age (15-49 years) in 2009) [16]. Finally, importation of the novel influenza virus into South Africa occurred during the winter months, when seasonal influenza epidemics are typically observed (South Africa experiences a temperate climate with the coldest months typically between May and September). The following report provides a preliminary analysis of the epidemiology of laboratory-confirmed pandemic H1N1 influenza cases and deaths in South Africa from 28 April to 12 October 2009.

### Methods

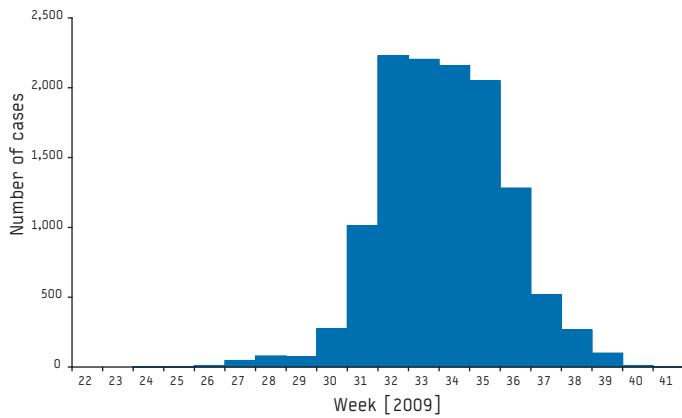
Methods for case finding, surveillance systems, laboratory testing and diagnostic strategies in South Africa have varied considerably with the evolution of the influenza pandemic over the period from April to October 2009. Following the first reports of transmission in the northern hemisphere, South Africa developed local case definitions and a procedure for active case-finding of possible imported cases, which were in place from 28 April 2009. These included the collection of nasal and throat swabs from all individuals who met the interim definition for a suspected-case of recent onset of influenza-like illness (ILI) and a history of travel to an area reporting a confirmed community-wide outbreak, or close contact with a suspected or confirmed case, within the seven days prior to onset of symptoms. Diagnostic testing was initially

done by the National Influenza Centre at the National Institute for Communicable Diseases (NICD), and testing was performed using the real-time PCR protocol distributed by the United States Centers

for Disease Control and Prevention (US CDC) for the detection and characterisation of pandemic influenza A(H1N1)v virus.

**FIGURE 1**

**Laboratory-confirmed cases of pandemic H1N1 influenza by week\*, South Africa, 28 April - 12 October 2009 (n=12,331, of which 25 with unknown date)**

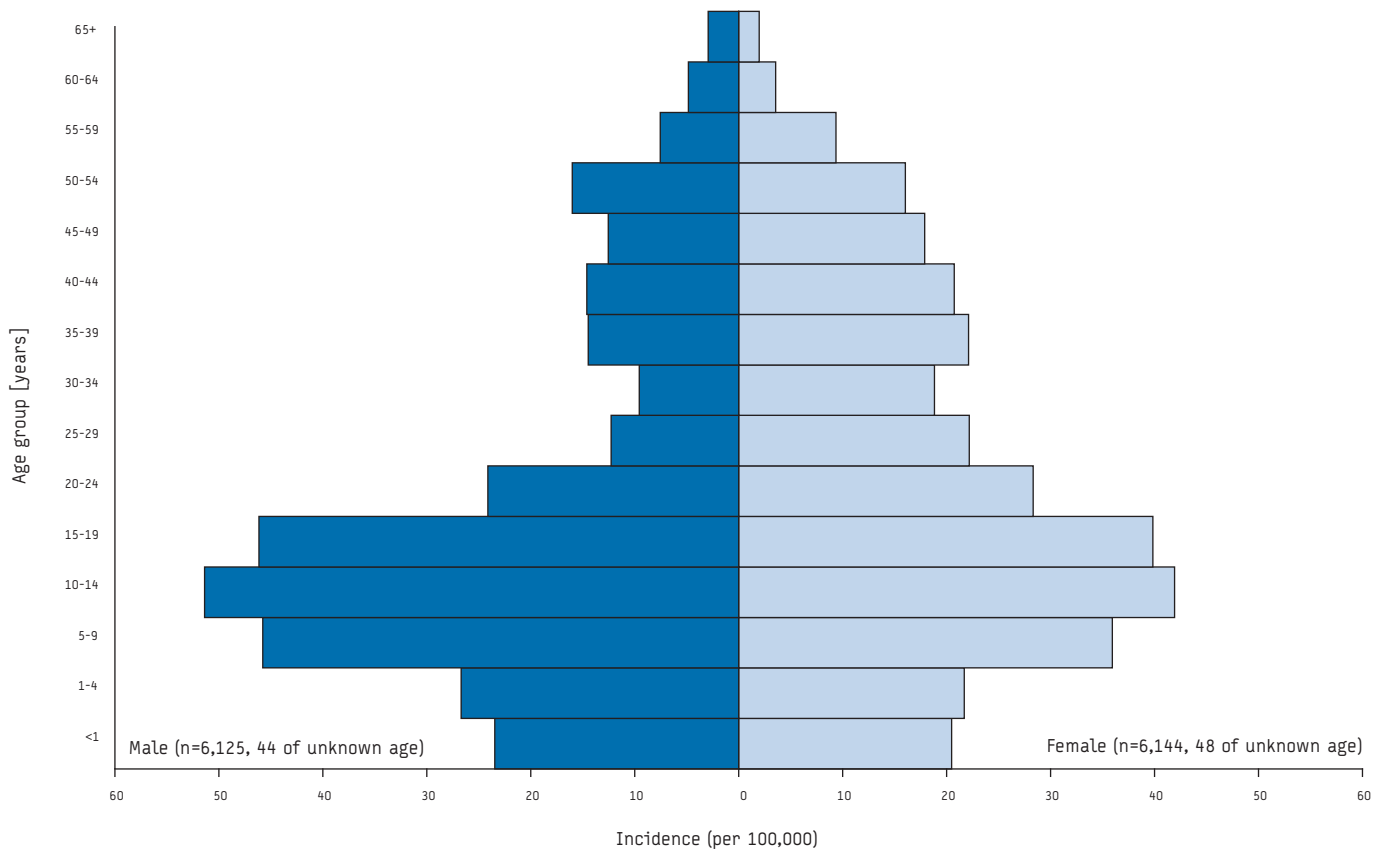


\* Week calculated from date of onset or, if onset was unknown, from date of specimen collection.

With the spread of infection among local communities, a strategy of laboratory testing and diagnosis of all ILI cases became unsustainable and unnecessary. In accordance with the WHO recommendations to cease universal laboratory testing of all suspected cases once the 100 case mark had been reached (100 cases had been confirmed in South Africa on 15 July 2009), the country reverted to testing only selected cases where a clinical decision warranted laboratory investigations. The new recommendation provided to South African clinicians was to collect specimens only from patients with moderate to severe illness or in case of unusual events such as: cases of severe or fatal ILI, clusters of respiratory illness requiring hospitalisation, or unexplained or unusual clinical patterns associated with serious or fatal cases. Furthermore, in response to the critical situation regarding molecular diagnostics capacity with the increased demand for testing, there was an active effort from 15 July 2009 to decentralise laboratory testing from NICD and to include a network of private and public health diagnostic laboratories throughout the country. Systematic surveillance systems administered by the NICD for detection and characterisation of ILI and severe acute respiratory infections (SARI) were maintained and strengthened (data from the individual surveillance programmes will be reported elsewhere but are summarised on the NICD website: <http://www.nicd.ac.za>).

**FIGURE 2**

**Incidence of laboratory-confirmed pandemic H1N1 influenza cases by age-group and gender, South Africa, 28 April - 12 October 2009 (n=12,331, of which 113 of unknown age and 62 of unknown gender)**

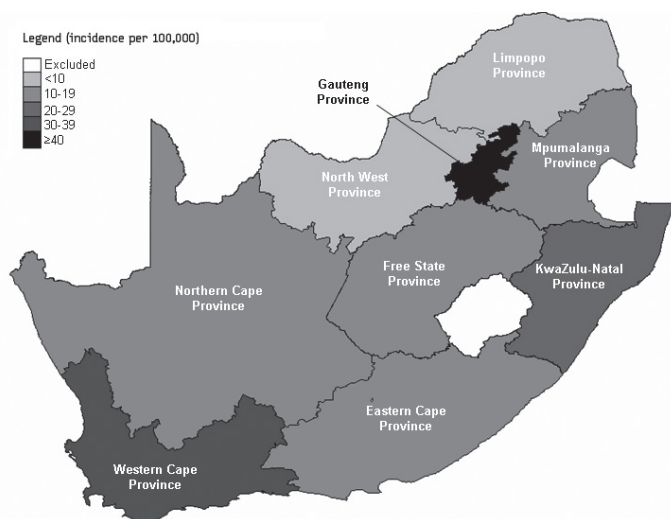


In response to the pandemic, the NICD has maintained an ongoing collective national database of all pandemic H1N1 influenza cases confirmed within the country by the various private and public diagnostic laboratories. This database contains basic demographic, spatial and temporal data about each case. Clinical data were not available. Although routine testing of mild cases was discouraged following 16 July 2009, it can be assumed that the cumulative data collated within this national dataset and reported here includes a mixture of ILI and SARI clinical presentations. Further investigations of all pandemic H1N1 influenza-associated deaths were conducted using a standardised case investigation form to collect detailed information on the patients' past medical history, clinical presentation and development of complications from the attending physicians. A pandemic H1N1 influenza-related death

was defined as any person for whom H1N1 influenza infection was confirmed in an ante mortem or post mortem specimen, and who died from a clinically compatible illness or complications attributable to that infection, with no period of complete recovery between illness and death and no alternative cause of death. Case investigations into all confirmed deaths are ongoing, with information on underlying risk factors currently available for 76 patients who died; however, basic demographic data are available for all 91 deaths.

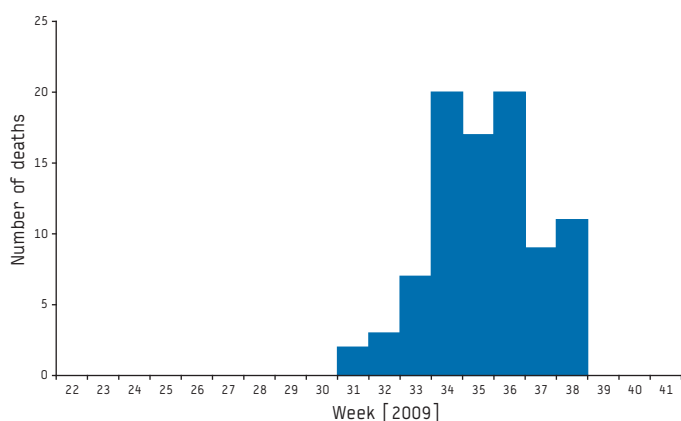
**FIGURE 3**

**Map of South Africa showing the incidence of laboratory-confirmed pandemic H1N1 influenza cases by province, 28 April - 12 October 2009 (n=12,331, of which 43 of unknown province)**



**FIGURE 4**

**Deaths associated with laboratory-confirmed pandemic H1N1 influenza by week\*, South Africa, 28 April - 12 October 2009 (n=91, of which three with unknown date)**



\* Week calculated from date of death.

For the purposes of this paper, incidence rates were defined as the total number of new laboratory-confirmed pandemic H1N1 influenza cases detected in South Africa from 28 April to 12 October 2009 per 100,000 persons within the same population group, calculated utilising the 2009 mid-year population estimates published by Statistics South Africa [16]. Sub-population estimates for 2008 were substituted where 2009 estimates were unavailable. Sustained local transmission was defined as the detection of four or more laboratory-confirmed cases without epidemiological links to a confirmed case or a history of international travel. Underlying factors and comorbidities (diabetes mellitus; obesity, cardiovascular disease (excluding hypertension) or active TB (including pulmonary and extrapulmonary TB)) were defined as presence or absence of the condition as diagnosed and reported by the attending clinician. HIV infection was defined as documented evidence of a laboratory-confirmed HIV-positive or negative status. We note that HIV testing was not mandatory and was likely conducted based on clinical indications of HIV infection (if conducted during the acute phase of influenza infection). Documentations of HIV results conducted prior to influenza infection were also included. Pregnancy and puerperium included patients within 42 days post delivery.

Univariate analysis was performed using the Fisher's exact test or the Mantel-Haenszel test for categorical variables, and the Kruskal-Wallis test for continuous variables. Analysis was performed with EpiInfo 2000 (version 3.5.4) software. Two-sided p-values of <0.05 were considered as significant throughout.

## Results

The first pandemic H1N1 influenza virus infection in South Africa was confirmed on 14 June 2009. Over a period of the next

**TABLE**

**Selected clinical characteristics of pandemic H1N1 influenza-associated deaths, South Africa, 28 April - 12 October 2009 (n=91\*)**

Factor	Frequency of factor / Number of cases with data available	%
HIV infection	17 / 32	53
Pregnancy or puerperium	25 / 88	28
Obesity	16 / 73	22
No co-morbidities identified	16 / 76	21
Diabetes	11 / 72	15
Cardiac disease†	9 / 71	13
Active tuberculosis (TB)	7 / 72	10

† Cardiac disease includes: previous stents, mitral stenosis, cardiomyopathy, congestive cardiac failure, previous valvular replacement, recent myocardial infarction, and previous cardiac bypass surgery; excludes hypertension.  
\* Patients may have had multiple factors.  
HIV: human immunodeficiency virus.

one month (until 15 July), the number of confirmed cases rose to over 100, a large proportion of whom were associated with a history of international travel within the seven days before onset of symptoms (42 of the first 100 cases). The establishment of sustained local transmission within this same period resulted in a rapid increase in the reported number of cases (Figure 1), with the epidemic peaking during week 32 (the week starting 3 August) with 2,229 new confirmed cases reported. A case frequency of over 2,000 cases per week was maintained for a period of four weeks (week 32 starting 3 August to week 35 ending 30 August), and was followed by a rapid decrease in the number of newly reported cases.

By 12 October 2009, a total of 12,331 laboratory-confirmed cases of pandemic H1N1 influenza had been recorded in South Africa, an incidence rate of 25 per 100,000 population. Overall, males and females were equally affected, with 6,125 male and 6,144 female cases among the 12,269 cases with known age, Figure 2). The age of all confirmed cases ranged from under one month to 90 years, with a median of 15.5 years. Sixty-four percent of cases (7,759/12,213) were under 20 years-old. The incidence of confirmed pandemic H1N1 influenza infections varied by geographical administrative region, with the provinces Gauteng (52 per 100,000) and Western Cape (38 per 100,000) reporting the highest rates (Figure 3).

A total of 91 pandemic H1N1 influenza-associated deaths were confirmed between the beginning of the outbreak and 12 October 2009. The frequency of deaths over time follows a similar pattern to that observed for cases (Figure 4).

The age distribution of fatal cases ranged from three days to 70 years, with a median of 33.5 years. This is significantly older than for the non-fatal cases that had a median of 15.0 years (range under one month to 90 years,  $p$ -value < 0.01). Fifty-nine percent (54/91) of fatal cases were female. HIV infection (17 HIV-positive of 32 tested) and pregnancy (25 of the 88 pregnant or puerperal woman and of the 45 women of reproductive age who died) were the most frequently reported underlying factors among patients who died (Table). Twenty-five of the 76 fatal cases were reported as having no underlying disease or risk factors, and seven of 72 were reported as having an active TB coinfection. Among the 21 deaths associated with pregnancy with data available for the stage of pregnancy, 18 were within the third trimester, one was in the second trimester, and two in the puerperium. Ten of 14 tested pregnant or puerperal woman had an HIV infection, and four of 21 had active pulmonary TB.

### Discussion and conclusions

Laboratory-based surveillance for pandemic H1N1 influenza in South Africa has recorded a total of 12,331 confirmed cases to 12 October 2009. The first reported cases were associated with travel; however, the virus quickly established itself locally with sustained transmission occurring within one month of the first case, which was followed by an exponential increase in case numbers. While the establishment of a network of both public and private sector laboratories was critical in providing data on laboratory-confirmed cases, the frequencies of new cases per week reported through these systems were likely affected by a time lag in the implementation of testing, followed by a high demand for testing that stretched both sectors to capacity. These factors, combined with the change to a strategy testing only the more severe cases, implemented from the middle of the epidemic until its end, may have resulted in the plateaued epidemic curve presented here

(see Figure 1). Although sporadic cases of confirmed influenza A(H1N1)v virus infection continue to be reported in South Africa, all testing laboratories are currently reporting a significant decline in the number of new positives, coinciding with the change from winter to spring in South Africa.

Infections have primarily been detected among younger age groups. The median age of cases was 15.5 years, which appears to be younger than the median age of seasonal influenza A(H1N1) cases recorded in 2008 (median age 27 years, range one month to 73 years [17]). Relatively higher incidence rates were noted in provinces containing the three largest metropolitan areas, and the highest incidence was noted in Gauteng Province. This province includes the primary hub for international travel to and from South Africa and has the highest population density of the country. In addition, patients in large metropolitan areas are more likely to access healthcare and be tested for influenza.

The median age of patients who died (33 years) was higher than that of non-fatal cases (15.0 years), suggesting that adults appear to be at higher risk of death associated with pandemic influenza virus infection as compared to children or teenagers. The high prevalence of HIV infection (53% of those tested), pregnancy (56% of woman of reproductive age), and TB (10% of deaths and 19% of pregnancy-associated fatal cases), in comparison to the overall prevalence of these conditions observed in South Africa, suggests that these comorbidities are possible risk factors associated with fatal pandemic influenza infections. Other comorbidities such as metabolic conditions were also identified.

Although there was a significant underestimation of the incidence of disease and the true number of deaths, laboratory-based surveillance became critical during the outbreak to allow counting of cases and collection of epidemiological information to describe the outbreak. Limitations of the data presented here include the possible introduction of bias due to: differences in laboratory testing practices between subpopulations, changes in the surveillance and recommended testing strategy during the pandemic, and the addition of laboratories offering testing with commercially available kits that had varying policies on testing. Information on underlying factors associated with fatal cases may also be biased by currently missing data. The prevalence of HIV among deaths is also limited in that only 32 of the 91 fatal cases are currently recorded to be tested, and furthermore the practice of HIV testing is known to be more likely in individuals with clinical evidence of HIV infection. Data are currently pending on important factors including: outstanding HIV status, level of immunosuppression and antiretroviral treatment history in HIV infected patients, as well as details of concurrent TB and anti-TB treatment. Such information will be important in gaining insight into possible interactions between pandemic influenza and HIV or TB.

Many important questions remain unanswered for South Africa and the southern hemisphere. For example: whether the pandemic will recur during the summer, or what the risk factors are for severe disease and death in developing and middle income countries on the African continent. The epidemiology of pandemic influenza documented here is similar to that observed elsewhere [1,2,5-12]; however, our data suggests that common infectious conditions such as HIV and TB may be associated with increased mortality risk. Even if this elevated risk is found to be relatively small, with the large numbers of HIV and TB infected people in sub-Saharan Africa, this

may translate into a substantial public health impact. Nonetheless, further studies that utilise a representative comparison group are required to explore these hypothesised risks. With limited resources to conduct vaccinations in 2010, emerging data on risk groups for severe illness in South Africa and other countries will be critical for planning targeted campaigns.

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