The new pandemic influenza A/(H1N1)pdm09 virus: is it really "new"?

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Keywords

Influenza • Pandemic • A/(H1N1)pdm09

Summary

In June 2009, the World Health Organization (WHO) issued a pandemic alert concerning the spread of an influenza A (H1N1) virus that showed distinctive genetic characteristics vis-à-vis both seasonal influenza strains and vaccine strains. The main mutation occurred in the gene coding for hemagglutinin (HA). Mathematical models were developed to calculate the transmissibility of the virus; the results indicated a significant overlap with the transmissibility of previous pandemic strains and seasonal strains. The remarkable feature of A/(H1N1)pdm09, compared with seasonal strains, is its high fatality rate and its higher incidence among younger people. Data provided by the WHO on the number of deaths caused by A/(H1N1)pdm09 only include laboratory-confirmed cases. Some authors suggest that these data could underestimate the magnitude of the event, as laboratory confirmation is not obtained in all cases.

It is important to bear in mind that the A/(H1N1)pdm09 virus is still circulating in the population. It is therefore essential to maintain its epidemiological and virological surveillance.

Influenza pandemics in history

The cyclic occurrence of epidemic and pandemic phenomena attributable to influenza A virus is related to the ability of the virus to modify its two main surface proteins, hemagglutinin (HA) (which allows the virus to adhere to epithelial cells in the upper respiratory tract) and neuraminidase (NA), both of which play a very important role in the pathogenesis of the disease. Antigenic variability of influenza A virus may occur as antigenic drifts (minor variability) or antigenic shifts (major variability). Antigenic drifts (such as nucleotide substitutions, deletions and insertions of HA and NA genes) are responsible for seasonal epidemics of influenza virus, while antigenic shifts cause pandemics. The most important changes are due to the reassortment of viruses of swine and avian origin with viruses of human origin, like those responsible for the pandemics that occurred in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) [1, 2]. The H1N1 virus reappeared in 1977, and is still circulating in humans, while the H3N2 virus was the most common up until 2009 [3, 4].

The "new" pandemic

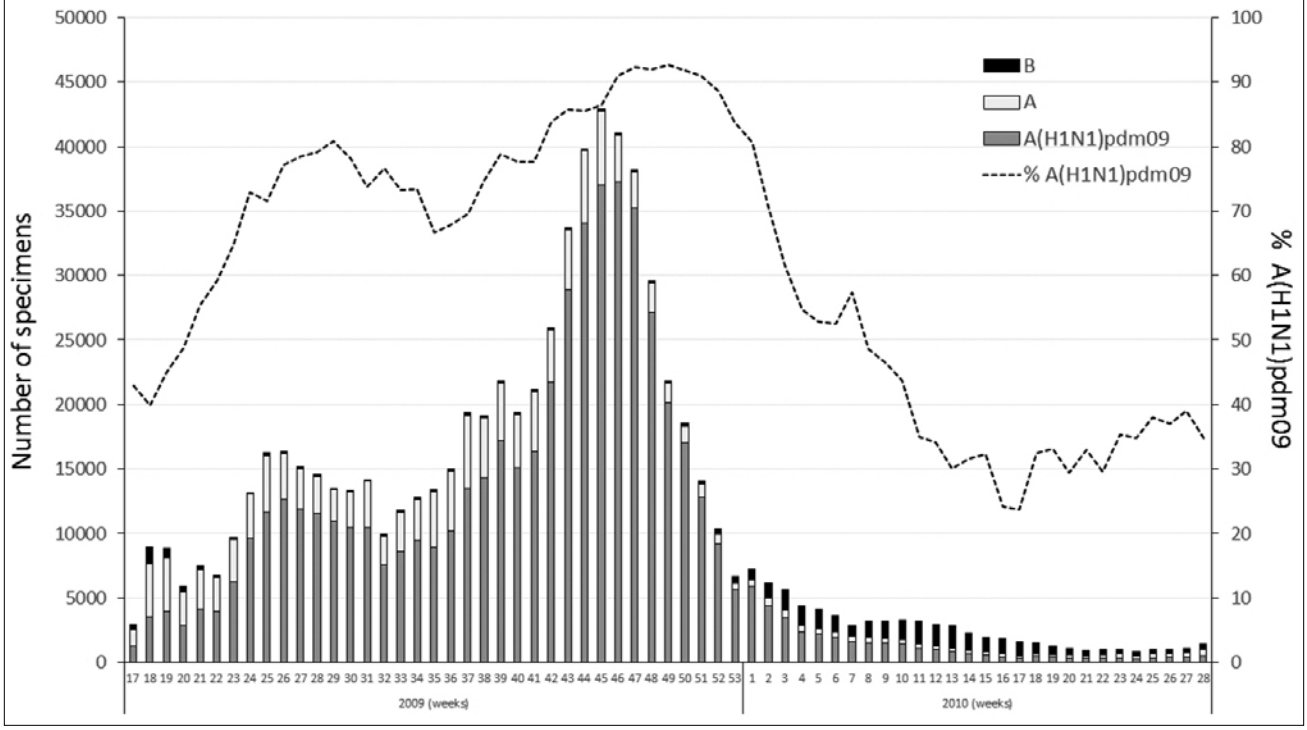
In April 2009, a new virus appeared in Mexico and California (US), and was responsible for the first pandemics of the 21st century. It spreads rapidly from person to person, and is not related to any circulating inter-pandemic viruses. The new virus was labeled A/(H1N1) pdm09. It is a quadruple reassortant virus, consisting of two swine-origin viruses, one avian-origin virus and one human-origin virus. To be more precise, molecular studies have identified the North American H3N2 triple reassortant viruses circulating among swine, a classic swine H1N1 virus, and an "avian-like" swine H1N1 virus circulating in Europe and Asia [5]. This "new" virus has proved remarkably different from the classic seasonal influenza H1N1 viruses and the viruses used to prepare vaccines [6].

The new virus spread rapidly around the world, primarily infecting children, young adults and individuals with lung and heart diseases, though the majority of cases were of low-grade severity and were self-limiting. The first epidemics occurred in Veracruz (Mexico), starting on 12 April 2009, and the virus was isolated by the Centers for Disease Control (CDC) on April 14th. By the end of April, the WHO had declared a phase-5 pandemic alert, and on 11 June this was upgraded to phase 6 (Tab. I), owing to the large number of individuals and na-

Tab. I. A/(H1N1)pdm09 pandemic timeline.

Date	Step
12th April 2009	Epidemic starts in Mexico (Veracruz)
17th April 2009	CDC isolates A/(H1N1)pdm09 virus
25th April 2009	Public health alert is declared
27th April 2009	Pandemic phase-4 alert
29th April 2009	Pandemic phase-5 alert
11th June 2009	Pandemic phase-6 alert
11th August 2010	Post-pandemic phase is declared

Fig. 1. Number of specimens positive for influenza by subtypes (from 19 April 2009 to 24 July 2010).



tions involved. In June 2009, the WHO reported 94,512 cases (including 429 deaths) and 135 nations were involved.

Burden of disease

From April 2009 to August 2010 (when the pandemic was declared to be over) [7], the number of laboratory-confirmed cases amounted to 651,449: 75.4% of these (491,382 cases) attributable to the A/(H1N1)pdm09 virus; 1.4% (35,069 cases) to the A(H1N1) seasonal influenza virus; 12.4% (81,070 cases) to non-typed A viruses; and the remaining 5.3% (34,481 cases) to the influenza B virus. The trend over the period analyzed is shown in Figure 1 [8].

The mean age of the individuals affected was 18.1 years: 64% of the cases occurred in 10- to 29-year-olds, and only 1% were aged 60 and over; 18.4% of the patients had chronic comorbidities.

The clinical manifestations were unexceptional, the most common symptoms being cough (84.9% of cases), high temperature (84.7%), headache (66.5%), runny nose (60.1%), and joint and muscle pain (58.1%). Despite these nonspecific clinical manifestations, some authors recommend considering cough and high temperature as the only parameters for identifying cases [9].

Mortality

During the pandemic, a total of 18,631 deaths were reported among the laboratory-confirmed cases, yielding a fatality rate of 2.9% (95% CI 0.0-6.7%), with an estimated fatality rate of 0.02% among all infected individuals [10]. Although this fatality rate cannot be considered a valid indicator, it prompted some to claim that the public health measures taken to deal with the pandemic had been excessive. It is important to bear in mind, however, that these figures are probably underestimated, as not all deaths involved laboratory-confirmed cases (as is usually the case during inter-pandemic periods). A recent study estimated that between 123,000 and 203,000 people died during the pandemics, and 62-85% of these were under 65 years old (and often under 14 years old): these figures suggest that the mortality rate for the 2009 influenza pandemic was in fact 10 times higher than the mortality rate resulting from the laboratory-confirmed cases. If the same method of calculation were applied to seasonal influenza epidemics, the virus would be responsible for 148,000-249,000 deaths, but would involve a larger proportion of elderly people. Indeed, only 19% of deaths involve patients under 65 years old during seasonal influenza epidemics. This epidemiological pattern gives the impression that the 2009 pandemic was more severe than seasonal influenza endemics – an assumption that may be confirmed when it is possible to obtain an estimation in terms of life years lost [10].

The fatality rate during a pandemic is calculated from the number of deaths due to the virus type investigated in relation to the number of cases in a given population. Analysis of the data shows marked heterogeneity in the fatality rates due to the A/(H1N1)pdm09 virus, which range from 1 to 10,000 deaths per 100,000 infections. In other words, the severity of pandemics is unpredictable and hard to estimate on the basis of fatality rates [11].

In-hospital mortality

Among the indicators of a pandemic's severity, the in-hospital mortality rate should be taken into account. In the case of the A/(H1N1)pdm09 pandemic, this rate varied considerably (from 0 to 52%) depending on the type of hospital involved and the gross domestic product of the country considered. In high-income countries, where standards of treatment are higher, the estimated in-hospital mortality rate ranged between 1% and 3%, and did not depend on the type of hospital or the type of ward.
In all countries, the burden of hospitalization was higher among children and younger adults, though the in-hospital mortality rate was always higher among elderly patients, mainly because they often had comorbidities. Despite their lower risk of infection, older people had higher fatality rates than younger patients in the event of hospitalization [12].

The situation in Italy

In Italy, the influenza surveillance network (INFLUNET) actively follows up 2.1% of the Italian population. Comparing data on seasonal influenza epidemics, the network showed, during the 2009 pandemic period, that the infection peaked in the 50th week (while this usually happens in the 4th to 8th week), with an intensity that was similar to other years. The network also found an increase in hospital admissions due to influenza-related complications, with 1,100 hospitalizations, 592 of which were severe cases (admission to intensive care unit, acute respiratory distress syndrome, need for intubation or extra-corporeal membrane oxygenator); 204 patients died [13].
The A/(H1N1)pdm09 virus continued to circulate after the pandemic of 2009. It was estimated that both the A (84%) and the B (16%) influenza viruses were circulating simultaneously during the 2014-2015 seasonal influenza. Specifically, the A/(H1N1)pdm09 virus accounted for 52% of all laboratory-confirmed cases, and for 76% of all severe clinical manifestations. This is the epidemic with the highest number of severe cases reported since the 2009 pandemic [14].

Features related to severity

The severity of influenza epidemics varies, depending on the geographical area involved, and can be measured by estimating the burden of disease at both the individual and community levels. The extent of a pandemic is influenced by several different factors, which depend on the features of the population affected, and severity assessment on a global level is not as straightforward as on the local level. It therefore becomes essential to implement a surveillance system in order to accurately monitor epidemiological trends and detect changes in the pattern of illness, as well as the characteristics of the infectious agent. Surveillance is essential for the prevention and control of influenza illness. Being able to recognize the specific circulating strain and the characteristics of the seasonal epidemic is important in order to identify viruses to be used in vaccines and to detect novel influenza viruses with potential for pandemic spread. Furthermore, combining virological surveillance with epidemiological surveillance gives us the chance to collect useful information for developing severity indicators.

Virological characteristics

Virological surveillance is essential in order to detect changes in the viral genome that may have an impact on the pathogenicity of the virus and on the effectiveness of influenza vaccines. Vaccine effectiveness decreases when the viral strains in the vaccine and the circulating viruses do not perfectly match [15, 16].
Mutations may be irrelevant; alternatively, they may modify the structure of epitopes (antibody-binding sites), thus giving rise to new serotypes and becoming critical in causing clinically relevant symptoms.
Critical mutations are those occurring in hemagglutinin (HA), the non-structural proteins (NS1), and polymerase (PB2). If these mutations occur simultaneously, increased virulence can be expected. Amino acids 187 and 222 in HA are involved in determining receptor-binding affinity and tissue-specific tropism: D187/D222 for α(2,6) in receptors on the human respiratory tract, D187/G222 for α(2,6) and α(2,3) in swine, and E187/G222 for α(2,3) in avian species. The new pandemic virus was characterized by major genomic mutations. Two have been identified: the so-called D222G and D222N, in which aspartic acid (D) is substituted by glycine (G) or asparagine (N), respectively. The D222G mutation is responsible for a change in receptor-binding affinity; this change enables the virus to bind to sialic acid receptors α(2,6), located on the ciliated epithelial cells in the upper respiratory tract, and to sialic acid receptors α(2,3), located on the ciliated epithelial cells in the lower respiratory tract [17]. A recent review showed a correlation between the D222G mutation in HA and the most severe and fatal cases of influenza. It also established that viral strains isolated during the pandemic did not carry other mutations in genes associated with increased virulence [18].

Epidemiological characteristics

Transmissibility is an important aspect of a pandemic. It is related both to intrinsic features of the agent causing the disease and to the public health measures adopted to deal with it. It can be measured by calculating the R0, i.e. the ability of an index case to infect other susceptible individuals. This indicator depends on the risk of transmission by contact (β), the average number of contacts per unit of time (κ), and the duration of the virus's infectiveness (D), which is agent-specific. R0 is calculated by means of the formula: $R0 = \beta * \kappa * D$. All possible public health measures may modify the R0, in which case the R0 is replaced with a Reproduction Control (RC) number. The RC depends on both the R0 and the public health measures taken, and is obviously always lower than the R0. If the RC is lower than 1, the epidemic will stop; if it is higher than 1, the epidemic will only decline

in intensity. The R0 value calculated for influenza viruses varies: in the case of the viral strain responsible for the pandemic in 1918-1919, for instance, it was about 2 (ranging from 1.4 to 2.8), while for a strain responsible for a seasonal influenza epidemic it is 1.3 (ranging from 0.9 to 2.1). These values do not differ greatly from the R0 value calculated for the A/(H1N1)pdm09 virus, which was 1.4-1.6. Since all these values overlap significantly, it is reasonable to assume a similar transmissibility among the strains considered [19].

Conclusions

The influenza A/(H1N1)pdm09 virus revealed some unique features in comparison with other circulating influenza viruses. These characteristics, combined with the state of immunity of the populations affected, accounted for the first pandemic of the 21st century. The viral and infectivity characteristics of A/(H1N1)pdm09 were entirely comparable to the characteristics of seasonal influenza strains, but the virus affected a larger proportion of children and young adults. It was consequently responsible for a heavier burden of disease, despite its similar virulence.
The picture was much the same in Italy, where the influenza epidemic peaked earlier than usual in 2009-2010.
It is important to bear in mind that the A/(H1N1)pdm09 virus is still circulating in the population. It is therefore essential to maintain its epidemiological and virological surveillance.
In conclusion, A/(H1N1)pdm09 is a new virus which is similar to seasonal influenza viruses in terms of disease incidence and transmissibility, but different in terms of its sudden appearance, rapid spread and severity of clinical manifestations in young people.

Acknowledgments

No funding declared for this overview.

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■ Received on January 22, 2016. Accepted on February 16, 2016.

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