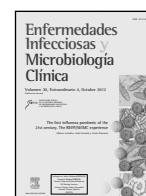




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Influenza A(H1N1)pdm09: beyond the pandemic

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ABSTRACT

Keywords:

Influenza A(H1N1)pdm09
Post-pandemic period
Oseltamivir
Clinical features
Prognosis

On August 2010, the World Health Organization declared the end to the 2009 A(H1N1) pandemic. However, influenza A(H1N1)pdm09 continues to circulate as a seasonal virus. Different viruses have predominated in different parts of the world. To date, influenza A(H1N1)pdm09 has demonstrated little antigenic drift, and its oseltamivir resistance has remained low. In some countries, a higher number of severe cases of influenza A(H1N1)pdm09 infection were documented during the 2010-2011 season than during the pandemic period. In addition, delays in oseltamivir administration, higher ages and comorbidities and low vaccination rates in patients with influenza A(H1N1)pdm09 infection were found during the first postpandemic season. Therefore, physicians should carefully consider the pandemic virus as a possible causative agent in patients with influenza-like illnesses admitted to emergency departments. In addition, surveillance systems and vaccination campaigns should continue after the pandemic period.

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Gripe A(H1N1)pdm09: más allá de la pandemia

RESUMEN

Palabras clave:

Virus de la gripe A(H1N1)pdm09
Período pospandémico
Oseltamivir
Características clínicas
Pronóstico

En agosto de 2010, la Organización Mundial de la Salud declaró el fin de la pandemia de la gripe H1N1. Sin embargo, el virus de la gripe A(H1N1)pdm09 continúa circulando como un virus estacional. Significativamente, diferentes virus han predominado en diferentes partes del mundo en el período pospandémico. Hasta la fecha, el virus de la gripe A(H1N1)pdm09 ha demostrado pocos cambios antigénicos, y la resistencia a oseltamivir se ha mantenido baja. En algunos países se ha documentado un mayor número de casos graves debidos al virus de la gripe A (H1N1)pdm09 durante la temporada de gripe 2010-2011. Además, también se ha reportado durante el primer período de gripe pospandémico: retraso en la administración de tratamiento antiviral, aumento en la edad y la frecuencia de comorbilidades, y tasas bajas de vacunación en los pacientes con infección por gripe A(H1N1)pdm09. Por lo tanto, se debe considerar el virus pandémico como un posible agente causal en pacientes con enfermedad gripal que asisten a los departamentos de emergencia. Además, los sistemas de vigilancia y campañas de vacunación deben continuar después del período pandémico.

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Introduction

The 1918 influenza pandemic occurred in several waves: a mild wave in the spring and summer of 1918, a lethal second wave in autumn of 1918, followed by a less severe third wave in the winter of 1919.^{1,2} Furthermore, the pattern of successive waves of varying severity also occurred in the 1957 and 1968 influenza pandemics.¹ Since its emergence in April 2009, influenza A(H1N1)pdm09 has rapidly affected all countries, with similar epidemiological features

and clinical spectrum of illness. On August 2010, the World Health Organization (WHO) declared an end to the 2009 A(H1N1) pandemic.³ However, influenza A(H1N1)pdm09 continues to circulate as a seasonal virus. This report summarizes the virology, epidemiology and clinical manifestations of influenza A(H1N1)pdm09 during the post-pandemic winter influenza seasons.

Virology of influenza A(H1N1)pdm09 and oseltamivir resistance during post-pandemic influenza seasons

From April 2009 to the present, A(H1N1)pdm09 has been continuously evolving, acquiring new amino acid changes that may

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alter its antigenic characteristics, virulence and antiviral drug susceptibility.

During the early phase of the pandemic, the early diversification of the influenza A(H1N1)pdm09 virus into 7 clades was reported from the results of whole-genome phylogenetic analysis.⁴ Only viruses belonging to clade 7 spread widely to become the predominant variant,^{4,5} a variant from which all latter circulating strains diverged. According to the last ECDC influenza virus characterization report,⁶ the phylogenetic analysis of the hemagglutinin (HA) gene of A(H1N1)pdm09 viruses assigned the viruses to 8 genetic groups defined by specific amino acid substitutions compared with A/California/7/2009, in addition to the new genetic groups reported by regional influenza surveillance networks.⁷ Although these genetic groups showed common amino acid substitutions in the HA protein within the antigenic sites, none are considered antigenically distinct from the vaccine virus A/California/7/2009, which was also recommended for use during the 2012-2013 influenza season in the northern hemisphere.⁸

The presence of known specific molecular markers in A(H1N1)pdm09 viruses associated with high pathogenicity, increased transmissibility and virulence in avian and mammalian species was ruled out early in the first A(H1N1)pdm09 genomic analysis.^{9,10} A D222G amino acid substitution in the HA1 subunit of HA was the first potential virulence marker of A(H1N1)pdm09 viruses associated with severe clinical outcomes.¹¹⁻¹³ The substitution causes a reduction in the binding avidity to SA α 2,6Gal receptors, which are mainly found on the epithelial cell surface of the human upper respiratory tract, and it causes an increase in binding to SA α 2,3Gal receptors,^{14,15} which are localized on human lung alveolar cells, thus explaining the severe viral pneumonia.

Antiviral resistance in influenza viruses has been well described and evolves through mutations or by reassortments that result in the acquisition of mutations that confer antiviral resistance.¹⁶ A(H1N1)pdm09 is naturally resistant to M2 inhibitors, amantadine and rimantadine due to presence of S31N in its M2 protein.^{10,17} To date, the vast majority of influenza A(H1N1)pdm09 viruses tested in the WHO-GISRS (Global Influenza Surveillance and Response System) laboratories were sensitive to neuraminidase inhibitors drugs (NAIs), which include oseltamivir, zanamivir and peramivir. From September 2010 to March 2011, approximately 1.5% of tested strains in the WHO Collaborating Centers were resistant to oseltamivir, all of which were associated with the H275Y mutation in the NA protein sequence, which confers resistance to oseltamivir and peramivir but not to zanamivir. Zanamivir resistance has been rarely documented in surveillance viruses.¹⁸

During the 2011-2012 influenza season, the resistance to neuraminidase inhibitors remained low (1%) in the United States and undetectable in Europe, but this data may be biased due to the scarce global circulation of A(H1N1)pdm09 viruses.¹⁹ The majority of resistance cases were reported in people with severe conditions who were on antiviral therapy, such as immunocompromised patients undergoing oseltamivir treatment. However, a small number of cases were detected in patients who were not receiving oseltamivir and were not in known contact with others receiving treatment,^{18,20,21} which suggests low-level community transmission of resistant viruses.²⁰

Current in vitro and in vivo studies of the fitness of resistant influenza A(H1N1)pdm09 strains carrying the H275Y mutation are producing conflicting results. There are ongoing studies to better understand the role of other potential resistance mutations and compensatory amino acid substitutions that can counteract the loss of fitness conferred by specific drug resistance-conferring substitutions.

In addition to the H275Y substitution, a few other amino acid substitutions in A(H1N1)pdm09 viruses isolated from patients receiving treatment have been shown to confer resistance or reduced

susceptibility to one or more NAIs in phenotypic assays. These substitutions include N295S, E119V/G, I117V, D199G, I223K/R/V and S247N.²¹ However, it should be noted that the lack of known mutations associated with antiviral resistance is not a guarantee of susceptibility to the corresponding drug, and viruses can only be designated resistant or sensitive to the neuraminidase inhibitors by phenotypic NA enzyme-inhibitor assays. The variation in the prevalence of resistance to the limited antiviral medications available for influenza has important public health and clinical implications for the future,²² and therefore continuous monitoring of A(H1N1)pdm09 viruses for antiviral resistance is essential.¹⁷

Epidemiology of influenza viruses during post-pandemic influenza seasons

2010-2011 influenza season

Active influenza transmission in North America was first noted in Mexico in July 2010 and overlapped with the start of the winter season. In the United States and Canada, influenza activity began in November 2010. Influenza A (H3N2) was the most common virus circulating in Canada and the United States throughout this season, although the United States had more transmission of type-B influenza and influenza A(H1N1)pdm09.²³

In contrast with North America, the influenza A(H1N1)pdm09 virus was the predominant virus causing illness in Europe and the Middle East; type-B influenza was less common, and influenza A (H3N2) was rare. The 2010-2011 influenza season in Europe became evident in December 2010 in England and Scotland. In Western Europe, transmission peaked during late January and early February 2011 and peaked 2-3 weeks later in Eastern Europe.²³ The United Kingdom Severe Influenza Surveillance System Steering Group documented that among 1668 hospitalized cases of confirmed influenza during this season, 1260 (75.5%) were due to influenza A(H1N1)pdm09, 4 (0.2%) were influenza A (H3N2), 49 (2.9%) were influenza A/unknown subtype and 355 (21.3%) were type-B influenza.²⁴ In Greece, of the 13279 specimens tested during week 40 of 2010 and week 20 of 2011, 98.2% were influenza A, with (H1N1)pdm09 as the predominant strain, and 1.8% were influenza B viruses.²⁵ In Spain, there were 4747 detections of influenza viruses during the 2010-2011 winter season, of which 52% came from sentinel sources and 48% came from non-sentinel sources. Of the total virus detections, 71.9% were influenza A viruses, of which 97.7% were influenza A(H1N1)pdm09, 27.8% type-B influenza and 0.3% type-C influenza.²⁶

The influenza season in Asia began during late October 2010. During the early weeks of the season, nearly all influenza cases were caused by influenza A (H3N2). However, the influenza A(H1N1)pdm09 virus became the most commonly detected subtype during January 2011. Only a small number of cases were caused by type-B influenza.²³ In Taiwan, 2767 specimens were laboratory-confirmed during the 2010-2011 influenza season. There were 1264 (45.7%) influenza A(H1N1)pdm09 cases, 1010 (36.5%) influenza A (H3N2) cases, and 489 (17.7%) type-B influenza cases.²⁷

2011-2012 influenza season

Different viruses predominated in different parts of the world in the 2011-2012 influenza season. The virus most frequently identified during this winter season in the northern hemisphere was influenza A (H3N2), although in Canada there was a predominance of type-B influenza (53% of influenza virus detection), and in Mexico, influenza A(H1N1)pdm09 was predominant.²⁸ Of the cases with the influenza A virus detected in Canada since the start of the season, 40.5% were influenza A (H3N2), 18.9% were influenza A(H1N1)pdm09, and 40.6% were untyped influenza.²⁹ In contrast to Canada, there was a predominance of influenza A (H3N2) in the United States.²⁸

In Europe, the large majority of influenza viruses were influenza A (H3N2), with only small numbers of cases of influenza A(H1N1) pdm09 and type-B influenza. Asia reported mostly type-B influenza early in the season, with influenza A (H3N2) appearing later. Since the beginning of the season, 41,844 influenza viruses from sentinel and non-sentinel sources across Europe and Central Asia have been typed; 91% were influenza A and 9% were influenza B. Of the influenza A viruses, 96% were influenza A (H3N2) and 4% were influenza A(H1N1)pdm09.²⁸ In Spain, 4,151 cases of influenza virus were reported during the 2011-2012 influenza winter season. Of these, 91.5% were cases of influenza A 8.4% were type-B influenza, and 0.1% were type-C influenza. Among the cases of influenza A viruses, 99.8% were influenza A (H3N2) and 0.2% were influenza A(H1N1)pdm09.³⁰

Clinical features and prognosis of the influenza A(H1N1)pdm09 infection during post-pandemic influenza seasons

2010-2011 influenza season

When compared with the pandemic period, a higher number of severe cases during the 2010-2011 season were reported in some countries. The risk groups for severe disease during the first post-pandemic influenza season were similar to those during the pandemic period.²³

In the Novel Influenza A (H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI), we compared hospitalized adults who had confirmed influenza A(H1N1)pdm09 pneumonia during the pandemic period (234 patients) with adults hospitalized during the first post-pandemic influenza season (114 patients).³¹ Hospitalized adults with influenza A(H1N1)pdm09 pneumonia during the 2010-2011 post-pandemic influenza season were older and were more likely to have certain comorbid conditions than those in the pandemic period. They also had more severe disease at hospital admission. Intensive care unit (ICU) admission and the need for mechanical ventilation were also more frequent among hospitalized patients during the post-pandemic period. Importantly, in-hospital mortality was 4-fold higher in the post-pandemic period than during the pandemic. The frequency of pregnancy, obesity and bacterial co-infection were not significantly different between the 2 study periods. In another Spanish multicenter study on patients requiring ICU admission,³² 648 patients hospitalized during the pandemic period were compared with 349 patients hospitalized during the post-pandemic period. Researchers found that influenza A(H1N1) pdm09 infection during the post-pandemic period targeted patients with a poorer baseline condition than those of the pandemic period. Patients from the post-pandemic period were older and had more comorbidities, more advanced clinical presentations on admission, higher severity scores and increased incidences of bacterial co-infection, septic shock and requirements for mechanical ventilation. In addition, patients from the post-pandemic period had higher mortality rates. Delayed antiviral administration was more frequently documented during the post-pandemic period in the 2 previous Spanish studies, a factor that has been related with poorer prognoses.³³

In a recent study in England, Bolotin et al.²⁴ documented that from December 2010 to January 2011, there was a sharp rise in the number of hospitalized cases of confirmed influenza. The 2010-2011 season was also marked by an increase in the number of influenza-related fatalities in the United Kingdom compared with the 2009-2010 season. This was also reflected in an excess of all-cause mortality and by a higher number of ICU admissions.²³ The majority of severe cases were due to influenza A(H1N1)pdm09, with a minority due to type-B influenza. An important shift was noted in the age distribution for severe influenza infection during the 2010-2011 influenza season compared with the pandemic period.²⁴

Moreover, it was documented in Greece that the severity of clinical illness (as measured by the number of patients admitted to the ICU, the overall population mortality rate and the impact on the

healthcare system) in the first postpandemic influenza season was comparable or even higher than during the pandemic period.²⁵ The results of the comparison of the age distribution of cases between the pandemic and the post-pandemic season suggested a shift to older ages. The age group with the highest mortality rate was adults aged 45 to 64 years, followed by the age group of over 65 years. Metabolic disease (including diabetes) and chronic respiratory disease were the most commonly reported long-term underlying conditions among patients admitted to the ICU, while immunosuppression and chronic cardiovascular disease were the most commonly reported comorbidities among fatal cases during the post-pandemic period. The total number of ICU admissions was higher during the post-pandemic influenza season. The overall population mortality rate was also higher during this period.

Moreover, a national surveillance study²⁷ of infection caused by influenza A(H1N1)pdm09 during the first post-pandemic winter season in Taiwan found a higher number of hospitalizations and deaths compared with the pandemic period. In addition, the average age of patients with influenza A(H1N1)pdm09 infection during the post-pandemic period was consistently higher than that of patients during the pandemic period. Of the patients whose death was related to influenza, 85.9% had underlying diseases, mainly diabetes mellitus and cardiovascular diseases, and most of these patients did not receive the influenza season vaccine.

Finally, the proportion of hospitalizations and the number of deaths in Mongolia and China were lower during the post-pandemic period than they were during the pandemic period.²³

2011-2012 influenza season

Currently available data suggest that the 2011-2012 season has been milder than previous seasons. Comparative studies between the seasons have not been reported; however, information is still emerging.

During the 2011-2012 influenza winter season in Spain, there were 601 severe cases requiring hospitalization in 16 regions. The largest group of patients consisted of those over 64 years of age (41%), and the second largest group consisted of children under 5 years of age (28%). In addition, 79% had comorbidities, primarily chronic pulmonary disease, chronic cardiovascular disease and diabetes mellitus. The most frequent complication among hospitalized patients was pneumonia (62%). In terms of the influenza virus, 95% of patients had influenza A infection—99.3% influenza A (H3N2) and 0.7% influenza A(H1N1)pdm09—and 5% had type-B influenza. Forty-seven (7.8%) patients with influenza infection died, of whom 30 (64%) were elderly (>64 years old), 45 (95.7%) had influenza A (H3N2) and the other 2 patients had type-B influenza. The majority of patients who died had comorbid conditions.³⁰

Since the start of the season in the United States, 20 influenza-associated pediatric deaths have been reported, which is markedly fewer than the 122 pediatric deaths reported during the 2010-2011 season. Among adults hospitalized with laboratory-confirmed influenza, the most frequent comorbidities were chronic lung disease, obesity and metabolic disorders.²⁸ In Canada, 1674 influenza-associated hospitalizations have been reported. The largest proportion of cases was observed in those >64 years of age (33.7%). Type-B influenza (56.1%) was predominant among hospitalized cases, while the predominant subtype among patients with influenza A was H3N2 (60.5%). There were 70 hospitalizations requiring ICU admission and 88 influenza-associated deaths. Of the adult deaths, 80.2% were in patients >64 years of age.²⁹

Conclusions

Influenza A(H1N1)pdm09 continues circulating as a seasonal virus after the pandemic period, along with other influenza viruses

such as type-B influenza and influenza A (H3N2). Different viruses have predominated in different parts of the world. All circulating influenza viruses demonstrated little antigenic drift during the postpandemic period, and oseltamivir resistance remains low. A higher number of severe cases during the 2010-2011 season than during the pandemic period were documented in some countries. Although the reasons for this difference are unclear, delays in the administration of oseltamivir, higher age, comorbidities and low vaccination rates were possible causes. Therefore, during influenza seasons following a pandemic period, physicians should carefully consider a pandemic virus as a possible causative agent when ordering microbiological tests and selecting treatment for patients with influenza-like illness at emergency departments. In addition, surveillance systems and vaccination campaigns for patients considered at high risk should continue after the pandemic period.

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Conflicts of interest

All authors declare that they have no conflicts of interest in this article.

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