Features of the new pandemic influenza A/H1N1/2009 virus: virology, epidemiology, clinical and public health aspects

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Purpose of review

The emergence of the pandemic A/H1N1/2009 influenza virus has enabled preexisting pandemic influenza plans to be put into action. This review examines the clinical and public health impact of this new virus.

Recent findings

Although early figures suggested that this pandemic virus was causing higher morbidity and mortality than seasonal influenza viruses, subsequent studies have found it to cause milder disease in most cases. Yet, there are some groups with increased risk of serious disease from this new pathogen. The widespread use of antiviral agents, prophylactically and therapeutically, has led to the sporadic emergence of drug resistance, though this is still rare. Nonpharmacological public health interventions for containment and mitigation have been relatively ineffective in limiting the rapid, global spread of this pathogen. Recently, the focus has been on the manufacture and distribution of various specific vaccines against this new virus, and the care of severely ill patients admitted to intensive care.

Summary

As this virus continues to infect new members of the global population, it may eventually become just one of the annual circulating seasonal influenza viruses. Until then, it will be prudent to continue to monitor it closely for any signs of enhanced transmissibility and virulence.

Keywords

epidemiology, H1N1/2009, influenza, pandemic, seasonality

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Introduction

As of October 2009, worldwide the swine-origin influenza A/H1N1 virus (S-OIV) has been implicated in over 318 925 laboratory-confirmed human cases and 3917 deaths, which is an increase of at least 22 454 cases and 431 deaths since September 2009 [1•]. The aim of this review is to summarize and provide interpretations of key aspects of the pandemic influenza situation so far and to indicate areas for further research.

Early emergence

Beginning in April 2009, an unusually high amount of influenza-like illness was noticed in Mexico, resulting in 854 cases of pneumonia and 59 deaths upto 23 April. On 24 April, seven human cases in United States (five in California and two in Texas) were found infected by the same novel influenza A/H1N1/2009 virus, which was later confirmed to be the same causative agent for the influenza-like outbreaks in Mexico occurring just a few weeks before that [2•]. More confirmed human cases of novel influenza A/H1N1/2009 were reported across the United States in the next few days, and the virus soon spread rapidly across the world. Early epidemiological investigations estimated that there were possibly 6000–32 000 Mexicans infected by the novel influenza A/H1N1/2009 by late April [3]. The early infections in other countries were likely exported from Mexico by travelers returning from Mexico, according to the observation of significant correlation between airline passenger flow out of Mexico and the number of confirmed cases worldwide [3].

Origins

This novel influenza A/H1N1/2009 virus is antigenically distinct from the preexisting seasonal human influenza A/H1N1 virus, but shares similar antigenicity and the highest genome sequence similarity (94–97% for different genome segments) with some swine influenza viruses, suggesting it might originate from pigs [4]. Likewise, the phylogenetic analyses found that the neuraminidase and matrix protein genome segments of the novel influenza A/H1N1/2009 virus had originated from Eurasian avian-like H1N1 swine influenza viruses. The other six genome segments had derived from North

American, triple-reassortant, H1N1/H1N2/H3N2 swine influenza viruses [4,5]. This implied that the novel A/H1N1/2009 virus was derived from the reassortment between these two swine lineages that used to circulate in separate continents [6], though they have more recently been found co-circulating in Asia [7,8]. Further molecular clock analyses suggested there is a 7–19-year window period without any sample/sequence data, prior to the emergence of novel influenza A/H1N1/2009, during which a reassortment event may have occurred to give rise to this new virus [9].

Natural drug sensitivities

Similar to its parental Eurasian avian-like A/H1N1 swine influenza lineage, almost all novel influenza A/H1N1/2009 viruses (99.7% observed in GenBank sequences, as of 7 November 2009) possess the S31N mutation (one isolate also has a V27A mutation) on its M2 protein, conferring a natural resistance to adamantine drugs (amantadine and rimantadine) [10]. In addition, the H275Y (N1 numbering) mutation on the neuraminidase protein, which reduces the sensitivity of virus to oseltamivir [11], has also emerged independently and sporadically in some novel influenza A/H1N1/2009 viruses isolated in Asia (2.46%), North America (0.59%) and Europe (0.25%), just within the few months following the emergence of the pandemic. The sporadic emergence of resistance to oseltamivir and natural resistance to the adamantanes (M2 ion channel blockers) creates additional challenges in treating A/H1N1/2009-infected patients.

Animal experiments

Although most human infections with the novel influenza A/H1N1/2009 have been mild, animal experiments on ferrets and mice have suggested novel influenza A/H1N1/2009 has a higher morbidity and replication efficiency than the preexisting seasonal A/H1N1 influenza virus [12,13]. The novel influenza A/H1N1/2009 virus could be recovered from the intestinal tract of intranasally inoculated ferrets and transmitted among ferrets [13], whereas, in comparison, avian A/H5N1 influenza virus has very limited transmissibility among ferrets [14]. The hemagglutinin of novel influenza A/H1N1/2009 retains the receptor-binding specificity to human sialic acid 2,6 receptors, which enables the virus to bind to the apical surface of the human tracheal tissue sections (upper respiratory tract) [13]. Its binding efficiency on the upper respiratory tract is substantially lower than that of 1918 pandemic influenza when the hemagglutinin concentration is low [13], but still considerably higher than most H5N1 avian influenza viruses, which showed more binding to the alveolus (lower respiratory tract) [15].

Severity of clinical disease

Even though it has been questioned as to whether the novel influenza A/H1N1/2009 virus is truly a pandemic virus [16] and whether it causes such serious infection in the majority of people [17], during the early stages of its emergence from Mexico and the United States, great emphasis and concern was put on the case-fatality rate (CFR), as compared to those estimated for previous influenza pandemics. This would allow public health institutions to plan their projected allocation of resources more efficiently. So, would this be a severe 1918-like pandemic (with a CFR of 2%) or a milder 1957/1968-like pandemic (with a CFR 20 times lower, at ~0.1%) [18]?

Despite the uncertainties of case ascertainment (i.e. which flu-like illnesses were really due to the new pandemic virus? For every A/H1N1/2009 infection confirmed, how many more went unidentified?) [19], early estimates of CFRs were published, but with considerable margins of error, for example, 0.08–0.15% up to 0.8–1.5%, depending on which combination of suspected and confirmed cases of H1N1-related deaths from Mexico were used [3]. Another later, crude estimate based on the US cases suggested a CFR of around 2% [20].

As the pandemic progressed, it became clear that the majority of influenza A/H1N1/2009 human infections are mild and indistinguishable from any other seasonal influenza virus infection. Multiple reports have described the clinical features of infection with this novel virus, which are similar to those of seasonal influenza [21•,22,23,24•], with the majority of patients presenting with a combination of fever, cough, shortness of breath, myalgia and fatigue, similar to seasonal influenza. More recently, attention has been focused on the clinical features and management of more serious illness caused by A/H1N1/2009 [25–29].

Intensive care admissions

Although earlier in the pandemic it was suggested that the novel virus may be causing more admissions to intensive care than those by seasonal influenza, this is probably an invalid comparison, as seasonal influenza is rarely tested for in adults with respiratory disease (unlike in children), so the number of adult cases of respiratory failure admitted to ICUs as a result of an initial seasonal influenza infection is mostly unknown. However, given the current hypervigilance with regard to testing patients for A/H1N1/2009, it has been possible to track the patients who would go on to develop secondary bacterial infections severe enough to push them into respiratory failure with admission to ICU. Such secondary bacterial infections have been thought to be a major contributor to the 1918 pandemic influenza mortalities [22,30,31], and

at least one report of ICU patients infected with A/H1N1/2009 has shown that such secondary bacterial infections do occur in these patients, though whether or not these were hospital-acquired or community-acquired could not be determined [32•]. Interestingly, prior to this, earlier reports of influenza A/H1N1/2009 cases did not describe bacterial co-infections in either milder [21•] or more severe [33•] cases.

Risk factors for severe disease

Although other conditions have been associated with severe A/H1N1/2009 disease, for example, pregnancy [22,34•,35] and obesity [22,33•,36], the evidence for this is relatively weak and seems to be based on the outcomes of a small number of patients. Indeed, some teams have not found this association for either of these groups of patients in their patient cohorts [25,26]. However, at least for pregnancy, the potential for severe disease has long been recognized and the immunization of pregnant women in their third trimester has been part of the annual seasonal influenza vaccine recommendations for some time now [37•,38•].

Acquired drug resistance

An additional, potential predisposing factor for more serious disease with A/H1N1/2009 is the sporadic appearance of oseltamivir-resistant viruses that have all, so far, carried the H275 mutation in their neuraminidase gene. These cases have mainly arisen in those given prolonged prophylaxis [39•] or therapy [40•] with this drug. The practice of mass postexposure prophylaxis has now stopped with oseltamivir being used now for mainly treatment purposes [41•]. This should reduce the frequency with which such resistant viruses arise, as well as reducing the inadvertent contamination of rivers with active oseltamivir metabolites (i.e. oseltamivir carboxylate), which are not removed by standard sewage treatments [42•,43–45].

Yet, despite this, there are recent reports of an increasing number of oseltamivir-resistant viruses being isolated from individuals infected with influenza A(H1N1/2009) who have had no history of oseltamivir treatment [46•]. If such resistant viruses become more transmissible from person-to-person, the use of oseltamivir as early treatment to prevent the progression to more serious disease will become more ineffective. The other licensed member of the neuraminidase inhibitors (NAIs), zanamivir (administered via an inhaler), is still effective against such oseltamivir-resistant viruses. A new member of the NAIs, peramivir (that can be given intravenously), is still undergoing licensing clinical trials (at this time of writing), though meanwhile emergency use authorization (EUA) has been granted recently for this drug by the US Centers for Disease Control and Prevention (US CDC) [47,48•]. Hence, there are therapeutic alternatives to oseltamivir (given orally) to prevent serious or fatal cases of influenza A(H1N1/2009), and these alternatives should be used wisely.

Serological cross-immunity

Although there is evidence for the existence of some cross-reactive protective antibodies against A(H1N1/2009) in the older population in the United States [49], this has not been found elsewhere [50]. There is also evidence that long-term T-cell-mediated immunity may exist in older populations exposed to A/H1N1 viruses similar to the current pandemic strain (e.g. in those born before 1957) [51], but in the younger population, there is still clearly a need for an A/H1N1/2009-specific vaccine. Hence, recently, multiple A/H1N1/2009-specific vaccines have been developed [52,53], some of which have been recently licensed and (at the time of writing) are currently being distributed worldwide [38•,54•].

Public health aspects

It is becoming evident that the 2009 H1N1 influenza virus is now the predominant influenza virus in circulation in most countries worldwide (Fig. 1). The epidemiology of disease caused by influenza A/H1N1/2009 in the Southern Hemisphere has been very similar to that described in the United States in the spring of 2009. So far, there have been no significant changes detected in the pandemic influenza A/H1N1/2009 viruses isolated from persons in the Southern Hemisphere as compared to viruses isolated from persons in the Northern Hemisphere. According to the WHO, the majority of influenza A/H1N1/2009 isolates tested worldwide remain sensitive to oseltamivir. Only 39 of the A/H1N1/2009 isolates tested worldwide have been found to be resistant to oseltamivir – 14 of these isolates were detected in the United States [1•].

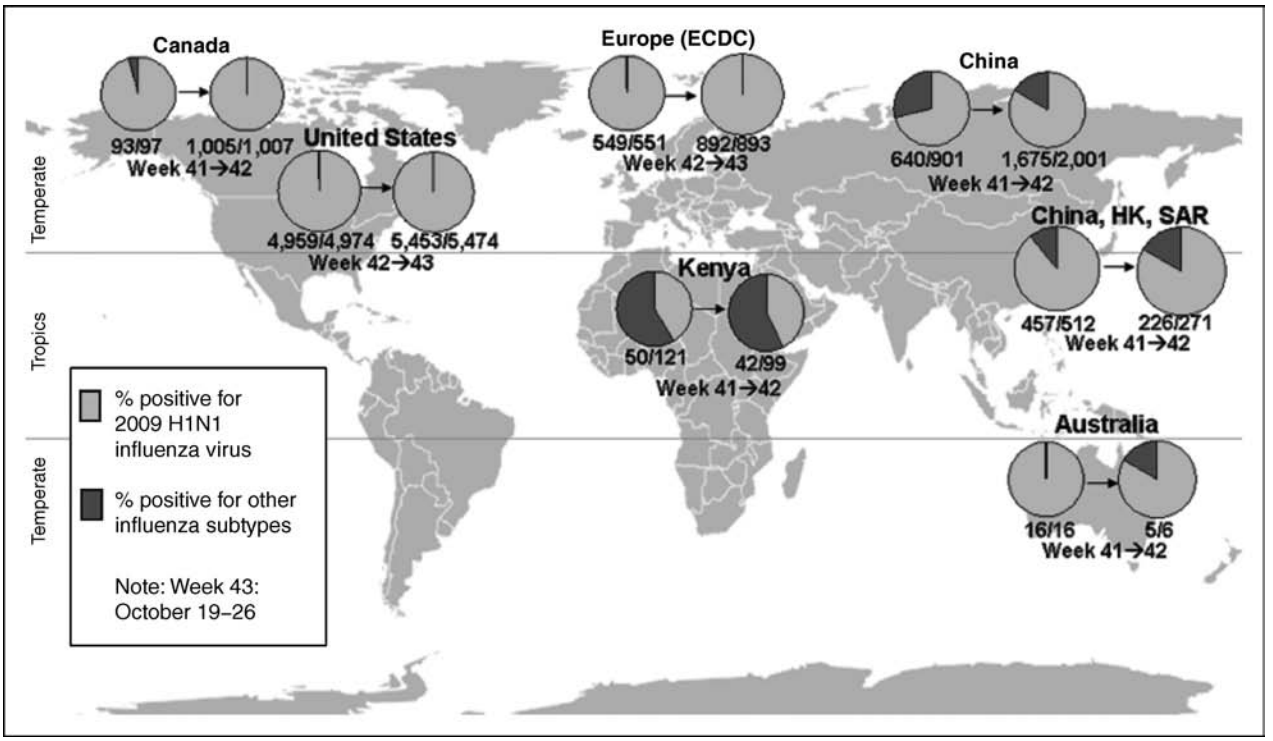
Estimates of basic reproductive number (R_0)

The virus transmits successfully even during a period that is not the conventional influenza season in a particular region; the basic reproduction number (R_0) has been estimated to be 1.4–1.6 and 2.2–3.1 in different analyses of the Mexican data [55•]. Epidemiological data indicate that the outbreak of influenza-like respiratory illness started in the Mexican town of La Gloria, Veracruz, in mid-February of 2009. Secondary attack rates in this well-defined outbreak were 61% in those under 15 years and 29% in people above that age [3].

School closures

School closure has been repeatedly seriously considered as an important intervention for mitigating influenza

Figure 1 International co-circulation of pandemic A/H1N1/2009 and seasonal influenzas, October 2009 [Accessed from http://www.cdc.gov/h1n1flu/updates/international/map.htm]



pandemics, largely because children are thought to be important vectors of transmission, they constitute a larger (as compared with adults) susceptible pool for infection by most influenza strains and high contact rates in schools favor transmission [56••]. However, the benefits of school closure are unclear when other interventions such as influenza vaccination are used, which is very likely. Other factors, unrelated to disease transmission, such as economic, social and educational impact, need to be considered, some of which are difficult to predict using the mathematical modeling approach, and the interplay between such factors changes during the course of the pandemic. For example, when illness was reported as being very severe, the US CDC initially recommended school closure. As reports of a minor illness in a majority of children emerged, early identification and isolation of ill students and staff became the primary method to reduce the spread of influenza in schools [57•]. Panic-induced school closures fueled by adverse media reports will cause an unnecessary burden on the economy. Decisions regarding school closures should be based on age-specific estimates of severity and local morbidity indicators [56••], and also should take into consideration the overall mitigation strategy, including the reliability and consistency of home treatment and isolation of infected individuals to reduce further contacts [58].

Other nonpharmaceutical interventions

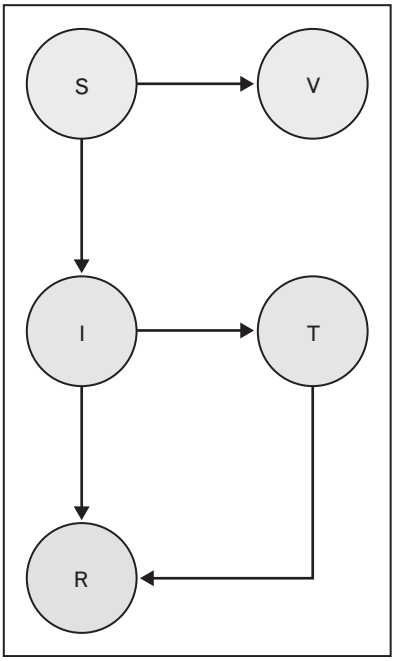
A meta-analysis of six case–control studies has reported that nonpharmaceutical measures are highly effective in preventing the spread of respiratory viruses: hand washing more than 10 times daily [odds ratio (OR) 0.45, 95% confidence interval (CI) 0.36–0.57]; wearing masks (OR 0.32, 95% CI 0.25–0.40); wearing N95 masks (OR 0.09, 95% CI 0.03–0.30); wearing gloves (OR 0.43, 95% CI 0.29–0.65); wearing gowns (OR 0.23, 95% CI 0.14–0.37); and hand washing, masks, gloves and gowns combined (OR 0.09, 95% CI 0.02–0.35). The highest quality cluster randomized trials suggested that spread of respiratory viruses can be prevented by hygienic measures in younger children and within households. Evidence that the more uncomfortable and expensive N95 masks were superior to simple surgical masks was limited. That the N95 masks were uncomfortable was a significant issue. The incremental effect of adding virucidals or antiseptics to normal hand washing was also uncertain. Global measures, such as screening at entry ports, were not properly evaluated. Evidence was limited for social distancing being effective, especially if related to risk of exposure, that is, the higher the risk, the longer the distancing period [59].

Use of masks

With regard to respiratory protection, some groups, including the WHO and Society for Healthcare Epidemiology of America, recommend the use of medical masks for most patient care activities, and others, most notably the CDC, recommend N95 respirators [60•]. In a study of 478 nurses randomly assigned to receive either surgical masks or N95 respirators, influenza infection occurred in 50 nurses (23.6%) in the surgical mask group and in 48 (22.9%) in the N95 respirator group (absolute risk difference, −0.73%; 95% CI −8.8–7.3%; $P = 0.86$), the lower confidence limit being inside the noninferiority limit of −9%. This single study, alone, cannot be definitive, but did suggest that the use of surgical masks compared with an N95 respirator resulted in noninferior rates of laboratory-confirmed influenza [61•].

Mask wearing acts as a mechanical barrier to reduce self-inoculation as well as inhalation of airborne infectious agents. There is increasing evidence for the significance of the airborne transmission route for influenza [62•], against which the wearing of masks alone will not be sufficient protection. For this reason, the use of such personal protective equipment (PPE) should be considered the 'last line of defense' in a hierarchy of infection control measures in hospitals, with immunization being considered as a priority wherever possible [60•]. Also important are procedures to exclude ill visitors (and staff), effective isolation strategies and the implementation of respiratory hygiene/cough etiquette programs. For example, one study showed that hand hygiene and face masks played a part in preventing household transmission of influenza virus when implemented within 36 h of index patient symptom onset, though delays in initiating such interventions and their variable adherence almost certainly limited their effectiveness [63].

Figure 2 SIR compartmental model of disease transmission incorporating vaccination and treatment

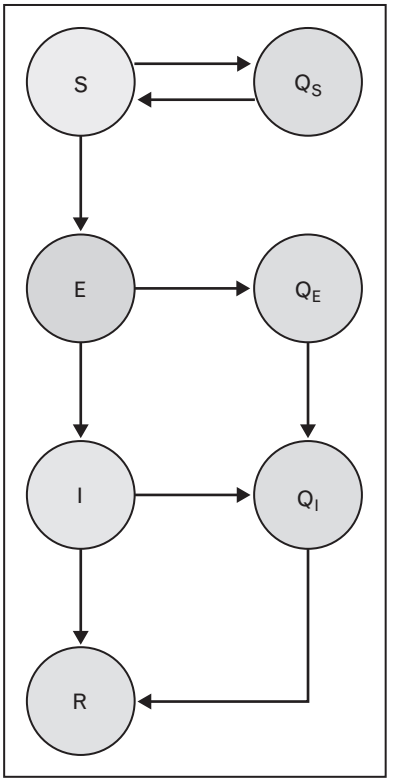


Susceptible individuals (S) who are vaccinated proceed to class V (immune). After treatment, infectious individuals (I) proceed to class T; they then join the class R (recovered) [64••].

Mathematical models

Although mathematical models have been used to understand the spatial–temporal transmission dynamics of influenza and to provide health policy tools in the absence of clinical trials, a detailed discussion is outside the scope of this review, though Figs. 2 and 3 show some simple formulations and interested readers are referred to an excellent review [64••].

Figure 3 SEIR compartmental model of infection incorporating quarantine and isolation measures



The class E represents a latent class during which an individual who has been exposed to the pathogen is not yet infectious and is asymptomatic. Individuals who might have been exposed (S and E) are quarantined and proceed to the respective Q classes: Q_S and Q_E. When susceptible individuals in quarantine (Q_S) are determined not to have been infected, they are returned to the susceptible class (S). Those in quarantine who develop infection (Q_E) are isolated and proceed to class (Q_I), as do infected individuals (I) [64••].

Conclusion

Many questions still remain about how this pandemic and the novel virus will evolve in a global human population with differing natural exposure and vaccination histories. However, only 6 months after the appearance of this new pathogen, clinical management and diagnostic testing algorithms are becoming more routine and outcomes less unexpected. Studies to track the evolution of the virus in real time (as well as its effects on the human host) are now possible (and may already be ongoing) with modern technologies and internationally networked clinical and basic research teams. Results from such studies are eagerly awaited and will be useful for informing public health policy, which will, hopefully, optimize clinical outcomes for those infected as well as streamline some of the already huge costs expended in dealing with this pandemic.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 290–291).

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