Indian J. Virol. (January–June 2012) 23(1):12–17
DOI 10.1007/s13337-012-0066-3

REVIEW ARTICLE

Pandemic Influenza A H1N1 (2009) Virus: Lessons from the Past and Implications for the Future

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Received: 20 April 2011 / Accepted: 28 February 2012 / Published online: 25 March 2012

Abstract The recent pandemic by novel influenza A (H1N1) 2009 (pH1N1) virus is an emerging viral infection, being of significant international concern and requires intensive research. The virus spread in pandemic proportions, and continues to be in the post-pandemic phase. Since, the pH1N1 is still circulating in the community, monitoring is required during the post-pandemic period. The pH1N1 defied influenza seasonality and rapidly became dominant over the seasonal influenza viruses. This new strain was antigenically different from the seasonal H1N1 influenza strains due to the genetic re-assortment. Surprisingly, this new reassortant virus emerged at the end of influenza season, caused a sudden toll of mild illness and is now co-circulating with the seasonal strains. The recent outbreak of pH1N1 consolidates the fact that a new reassortant virus may have originated in animal reservoirs and got transferred to human who were in close contact with these animals. There is a continued need for multisite surveillance to detect potentially dangerous influenza strains, which may emerge and establish themselves in human population. This review is an attempt to address the lessons learnt from the recent influenza pandemic and the future implications for prevention and control of influenza.

Keywords Influenza A H1N1 virus · Pandemic · Re-assortment · Antiviral therapy

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Introduction

Acute respiratory illness due to influenza viruses are the major causes of morbidity and mortality in early childhood worldwide. The aggregate numbers of respiratory infections caused by the viruses far exceed the cases accounted by other pathogens in total. Among the respiratory viruses infecting the humans, influenza virus, belonging to the family *Orthomyxoviridae*, can be regarded as the main pathogen which can manifest variously: coryza, rhinitis and other asymptomatic infections of the upper respiratory tract, to fulminate life-threatening conditions, such as pneumonia and acute respiratory failure. Influenza virus has a unique ability to mutate and alter its genetic machinery, rendering itself safe from the pre-existing immunity among humans against the previously circulating strains.

The history has witnessed the dreadful face of influenza virus as cause of pandemics and epidemics, which affects the immunocompromised subjects [1, 20, 23] more than the normal population. A pandemic may occur as a result of antigenic shift and genetic reassortment, in which two different influenza A viruses co-infects the same host cell and new virions are released that contain gene segments from both parental strains [8, 19]. The year 1997 documented the emergence of avian influenza virus H5N1 in human population. This was a reassortant of H5 gene from Guangdong virus and other genes from H9N2 and H6N1 viruses circulating in quail [13]. Since the year 2003, H5N1 virus has been isolated almost every year marking its ability to mutate rapidly and producing a new strain for which the population is not immunized [17]. In nearly less than a decade, mankind has suffered tremendously from the avian influenza H5N1 spread and the pandemic (H1N1) 2009 outbreak. The recent pandemic H1N1 virus which emerged in April 2009 in Mexico and spread worldwide was a reassortant of North

American swine, Eurasian swine, North American avian and human influenza virus strains. The recent H1N1 (2009) virus has demonstrated how rapid an influenza virus can emerge and spread in the population. WHO declared it a pandemic on 11th June 2009 and on 10th August 2010, declared, that the virus has entered its post pandemic period, whereby it is now considered as a seasonal influenza virus.

Epidemiological and virological surveillance will continue to monitor the changing trends in pH1N1 virus; such surveillance will help health authorities to implement outbreak response measures in future [31]. Timely diagnosis and treatment of influenza is of major importance to check the spread of the virus and decrease the complications in high-risk population. There is an urgent need for pandemic influenza preparedness program to control the influenza outbreaks. The awareness of the disease among general population is equally important as early diagnosis and prompt treatment are prerequisites for controlling the spread of the disease. The pandemic preparedness requires an effective public participation, stringent regulatory policies by the government and active and responsible media. The H1N1 (2009) virus did spread like wildfire across the globe, infecting approximately 491,766 (75.3%) people between 19th April 2009 to 31st July 2010 as per the report from the various National Influenza Centres (NICs) from 26 countries (WHO; weekly updates). According to the World Health Organization and various news reports, cases of H1N1 were reported as late as December 2010 and January 2011 in England, Ireland, Germany, Sri Lanka, Korea, New Zealand and India. The number of cases gradually declined to threshold levels, with no new report of outbreaks in Northern and Southern Hemisphere. The effective control of this new strain of virus could be managed as the precautionary measures given by WHO were already in action in the fear of H5N1 outbreak reported from several countries including India. The preparedness plans made for combating the H5N1 threat became the backbone of initial rapid action during the H1N1 pandemic. The resources and laboratories were well equipped and training were already imparted to healthcare professional and scientists to effectively control the outbreak which ultimately provided great help worldwide in effective management of the pandemic H1N1 virus. It is imperative that lessons learnt during the H1N1 (2009) pandemic may be extrapolated to deal with future pandemics.

Lessons Learnt by the Clinicians from the Recent H1N1-2009 Pandemic

Higher Risk Groups Should be Given Quick Medical Attention on Priority

CDC reiterated the fact that people suffering from asthma are at higher risk of complications by H1N1 influenza. They are prone to secondary bacterial infections, which may further denude their immunity. The National Institutes of Health is preparing to launch the first government-sponsored clinical trial to determine what dose of the H1N1 (2009) influenza vaccine is needed to induce a protective immune response in people with asthma, especially those with severe disease. The study is cosponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute (NHLBI), both part of the NIH.

It was observed that pregnant women had a disproportionately high risk of mortality due to pH1N1 virus [30]. In the post pandemic period, younger age groups, including pregnant women, are expected to continue getting affected disproportionately by severe disease from the novel H1N1 virus, including viral pneumonia. An early antiviral treatment appeared to be associated with fewer admissions to an ICU and fewer deaths. The severe outcomes of the recent pH1N1 outbreak in pregnant women necessitate the study of factors that may account for increased morbidity e.g. effect of physiological changes during pregnancy on the pharmacodynamics and pharmacokinetics of antiviral drugs [12]. The patients in the high risk groups need to be cared more and treated at priority as compared to low risk groups to prevent the loss of life.

Rapid Diagnostic Tests can't be Used for Accurate Detection of Novel Influenza Strain

Various direct antigen detection methods can be used for detecting the pH1N1 infection, but all such tests fail to provide acceptably specific and sensitive results [4]. Although various antigen detection kits available in the market can differentiate between seasonal influenza A and B types, they are unable to detect the pH1N1 virus exclusively. Although a rapid diagnostic method may help in early initiation of empirical therapy but treatment, based on clinical conditions, should not be withheld on negative results [32]. The recent pandemic was realization of the fact that rapid tests are not so accurate and there is a need for alternatives to the costly molecular techniques like real-time PCR assays.

Time of Administration of Antiviral Drugs

In any viral illness, the best clinical recovery is achieved by early diagnosis followed by immediate medication. It was observed that if the antiviral therapy was started within 48 h of the onset of signs and symptoms, the clinical cure rates were higher [11]. There is no rationale to hold the treatment waiting for the laboratory report to arrive. The large number of hospital admitted cases revealed that the antiviral drug treatment must begin within 24 h of infection to effectively control the loss of health.

Rational Use of Antiviral Drugs for Prophylaxis

The few reports on H1N1 (2009) virus being resistant to oseltamivir have proved to be a setback to our defence systems against the virus (WHO; 2009). The risk of resistance is deemed higher in certain group of patients (WHO; 2009): (a) those who are immunocompromised and have prolonged illness, (b) those who have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication, (c) those who receive oseltamivir for "post-exposure prophylaxis" following exposure to another person with influenza, and who then develop illness despite taking oseltamivir.

Resistance to oseltamivir can occur due to a point mutation in any of several regions of the neuraminidase gene of the virus. It was believed that the His274Tyr mutation confered oseltamivir resistance on the currently circulating H1N1 strain [24]. However the recent findings show that His274Tyr attenuates seasonal H1N1 unless there are permissive secondary mutations that maintain adequate surface NA expression. If rapid screening methods be made available to detect the mutation at an earlier stage, clinical failure with antiviral therapy could possibly be averted [26].

Neuraminidase inhibitors used as antivirals for prophylaxis may induce drug resistance, hence may aggravate the problem in control of the disease. It has been highlighted in the example of neuraminidase inhibitors that improper use of antiviral prophylaxis may further aggravate the problem [7]. Presently, these drugs can be procured only against a medical prescription for a laboratory diagnosed case. The stockpiling of drugs by hospitals is not a wise strategy because it may hinder the access of the drug in case of an outbreak in a remote area (WHO). These stockpiles of required drugs may result in excess use of a secondary antiviral drug which may not be of benefit [35]. Drug resistance may be of major setback because it may lead to transfer of oseltamivir resistant strain from an infected patient to healthy contacts or persistence of resistant genotype in the environment due to selection pressure [3, 15].

Certain Questions that Need to be Contemplated to Deal with Impending Pandemics

Need for Stringent Hospital Policies

Personal protective equipments are very essential to check the spread of the virus among those who are most exposed to the risk of getting the infection. CDC has laid strict guidelines for collection and transportation of specimens from suspected cases and dealing with infected patients. As is the case with any pandemic, there is an urgent need to devise an algorithm based on the early identification of potential source of infected patients, as well as appropriate selection and adequate use of personal protective equipment [27].

Comparing Deaths from Pandemic and Seasonal Influenza Viruses

Though there is a similarity in signs and symptoms, the pandemic influenza A H1N1 (2009) virus overwhelmed the seasonal influenza virus. It is necessary to report the deaths due to pandemic strains especially in developing countries, where deaths from respiratory diseases, including pneumonia, are common occurrences. According to WHO, 50.7% of subtyped influenza A viruses were 2009 H1N1 as per the global data collected from July 11 to 17, 2010, and reported on July 28. The pH1N1 virus is co-circulating with the seasonal influenza virus and the health authorities need to be more vigilant in countries like India and New Zealand which are still recording significant number of cases infected with pH1N1 virus (WHO-India). Accurate assessments of morbidity and mortality rates will likely be possible only 1–2 years after the pandemic has peaked, and will rely on methods similar to those used to calculate excess mortality during seasonal influenza epidemics.

Reviewing Global Response to Pandemic Influenza A H1N1 (2009) Viruses

The assessment of the global response to the pandemic H1N1 will be conducted by the International Health Regulations Review Committee, a committee of experts with a broad mixture of scientific expertise and practical experience in public health [34]. The International Health Regulations (IHR) is an international legal agreement that is binding on 194 States Parties across the globe, including all of the Member States of WHO. The basic purpose of the IHR is to help the international community prevent and respond to public health risks that have the potential to cross borders and threaten people worldwide. The pandemic influenza A H1N1 (2009) virus is the first public health emergency of international concern to occur since the revised IHR came into force. The IHR played a central role in the global response to the pandemic and so review of the IHR and review of the global handling of the pandemic influenza are closely related. The IHR facilitates coordinated international action by requiring countries to report certain disease outbreaks and public health events to WHO so that global reporting of important public health events is timely and open.

Drug Dynamics and Pharmacokinetics of Oseltamivir in Critically Ill Patients

WHO recommends that hospitalized patients with severe infections (such as those with prolonged infection or who require intensive care unit admission) might require longer treatment courses or higher doses of oseltamivir. The standard dose of oseltamivir in adults is 75 mg twice daily for 5 days for treatment and 75 mg once daily for 10 days for prophylaxis. The recent studies however have refuted the fact that prolonged duration or incremental doses have a role to play in clinical recovery. An increased dosage of oseltamivir for patients with critical illness is unlikely to be required in the treatment of H1N1 (2009) influenza [25].

Need for Alternative Therapeutic Options

Upto August 2010, 302 oseltamivir resistance pH1N1-2009 influenza viruses have been detected worldwide. The crisis of oseltamivir resistance has necessitated an urgent need to discover additional drugs to combat the infection. A new neuraminidase inhibitor, called peramivir was introduced to be used in oseltamivir resistant cases (CDC). Recent reports on peramivir resistant cases indicate a serious need to develop newer drugs and target other pathways of virus machinery [21].

During the course of an anti-influenza and cytotoxicity screening program on natural products, it was found that a $CHCl_3$ extract of *Ferula assa-foetida* was active against H1N1 influenza virus and various human cancer cell lines [6]. A new pyrazole-based compound BPR1P0034, which acts during viral uncoating or viral RNA import into the nucleus has shown promising results as an antiviral drug [29]. DAS181 is a sialidase fusion protein which in early clinical development with in vitro and in vivo preclinical activity against a variety of seasonal influenza strains and highly pathogenic avian influenza strains (A/H5N1), has also shown satisfactory results with the recent pandemic H1N1 strain [33].

A broad acting antiviral therapy is the need of the hour because influenza virus can elude immune system through mutation. The protective effect of a human monoclonal antibody termed A06 has been shown against two isolates of the 2009 H1N1 pandemic influenza virus [16]. Such novel therapies may be a useful addendum in our armamentarium against H1N1 (2009) virus.

Virulence Markers in Pandemic Influenza A H1N1 (2009) Virus

It has been documented that certain genes are consistently associated with the pandemic influenza strains. Reverse genetic studies have identified several genes as virulence markers in both 1918 pandemic and H5N1 avian influenza pandemic, which accounted for the high levels of viral replication and strong pro-inflammatory responses [2, 22]. The HA gene, the polymerase complex and non-structural proteins NS1 and PB1-F2 significantly contributed to the virulence of these pandemic strains. Recent studies have shown that PB1-F2 gene, responsible for mediating apoptosis in influenza virus is truncated in the novel pandemic strain [9]. Therefore, PB1-F2 is of questionable significance as a virulence marker in the pandemic influenza A H1N1 (2009) virus [14]. Further studies are necessary to search for the additional factors that may account for the high virulence of the novel virus.

A study of the genetic signatures of H1N1 (2009) virus is essential to reveal information for promoting medical diagnosis, drug-resistance monitoring, clinical and basic research, and vaccine development [5]. Studies have shown that H1N1 (2009) virus was circulating in the environment 3 months prior to the outbreak [28]. If more such studies be planned, the pandemic virus may be recognized at the time of their inception.

Other Factors to Combat a Pandemic Situation

Social Distancing

Social distancing may prove to an effective measure during outbreak situations [10]. It can be enacted in two ways, firstly by cancelling all events like concerts, movies, plays etc. that require gathering of general public and secondly by closing or restricting access to certain buildings, schools, youth clubs and gymnasiums that gather crowd. Further avoiding public transport as far as possible may also help in controlling the spread of the virus. Many people who visit hospitals for illness due to other pathogens may acquire infection with pandemic H1N1.

Eating Habits

Nutritious food has been proved to be an effective means of combating infection. WHO has developed an approach to the integrated management of sick children in which the patient's illness is addressed as a combination of problems including malnutrition, rather than only as a single disease.

Public Awareness

Public should be educated for the modes of transmission of the pandemic virus, their methods of prevention and general etiquettes (like cough etiquettes) by television, newspapers, road side plays and local announcements.

Preparedness Plan for Pandemic Influenza A H1N1 (2009) Virus in India

Through influenza surveillance, India has been continuously monitoring the antigenic changes of seasonal influenza viruses that are circulating in the community. The major research objectives were to detect new and potentially dangerous strains of influenza viruses so that measures can be implemented in the event of a pandemic. Influenza surveillance in India gained momentum soon after the emergence of novel pandemic strain of influenza virus H1N1 in Mexico and USA [18]. Nine surveillance centers, funded by the Center for Disease Control and Prevention, USA and Indian Council for Medical Research, across the country were operational to study the epidemiology and disease burden due to influenza. Scientists from all the regional centers (All India Institute of Medical Sciences, New Delhi; Vallabhbhai Patel Chest Institute, Delhi; National Institute for Cholera and Enteric Diseases, Kolkata; King Institute of Preventive Medicine, Chennai; Regional Medical Research Center, Dibrugarh; Indira Gandhi Medical College, Nagpur; Christian Medical College and Hospitals, Vellore and Haffkine Institute, Mumbai) were trained by referral centre, National Institute of Virology, Pune to cope up with the pandemic situation and the efforts proved to be successful in controlling virus infection, its spread and also prevent chaos in the community.

As of 31st October 2010, 45101 laboratory confirmed positive cases with 2,679 registered deaths due to the pandemic H1N1 has been reported all over the country as per the MOHFW, Govt. of India. Delhi has recorded the maximum number of positive cases while the Maharashtra has maximum number of registered deaths in the country. States like West Bengal, Bihar and Jharkhand, in spite of huge population, have managed well with zero death record due to this pandemic influenza infection. A sudden rise in the number of positive cases has been observed in Kerala in the month of June 2010 probably due to rise in humidity.

The influenza research must be in pace as the H5N1 virus has already become endemic in Asia and in the wake of currently prevailing situation of pandemic H1N1, it might not be an unanticipated scenario if the two deadly viruses swap their genes to further give rise to a lethal virus. The current H1N1 pandemic taught few lessons about how the accurate diagnosis of influenza can lead to quick management of the outbreak. The death rate during the 2009 pandemic was low as compared to the previous pandemics (Table 1) since the new strain was not as pathogenic as the previous ones. The currently ongoing multi-site influenza surveillance programs in India may serve as the best precautionary measure for management of any future outbreaks. With well trained staff, various laboratories in India are already equipped with advanced diagnostic facilities.

Table 1 Year wise pandemic data showing the causative influenza strain type and associated mortality

Year	Name of pandemic	Strain	Mortality
1889–1890	Asiatic (Russian) Flu	H2N2	1 million
1918–1920	Spanish Flu	H1N1	50 million
1957–1958	Asian Flu	H2N2	1.5–2 million
1968–1969	Hong Kong Flu	H3N2	1 million
2009–2010	Pandemic H1N1-2009 Flu	H1N1	Over 18,209

The pandemic influenza A (H1N1) 2009 is a new chapter in the history of human influenza. It blew out of proportions in such a short duration of time that WHO had to raise its pandemic alert to level 6. This review article will provide an insight to gather additional data about the ever-changing genetic structure of influenza virus and need to target additional genes for antiviral therapy.

References

1. Barry JM. The great influenza. The story of the deadliest pandemic in history. London: Penguin Books; 2005.
2. Basler CF, Aguilar PV. Progress in identifying virulence determinants of the 1918 H1N1 and the Southeast Asian H5N1 influenza A viruses. Antiviral Res. 2008;79:166–78.
3. Baz M, Abed Y, Papenburg J, Bouhy X, Hamelin M, Boivin M. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. N Eng J Med. 2009;361:2296–7.
4. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) virus—United States, 2009. MMWR Morb Mortal Wkly Rep. 2009;58:826–9.
5. Chen GW, Shih SR. Genomic signatures of influenza A pandemic (H1N1) 2009 virus. Emerg Infect Dis. 2009;15:1897–903.
6. Chia-Lin L, Chiang LC, Cheng LH, Liaw CC, El-Raze MAH, Chang FR, et al. Influenza A (H1N1) antiviral and cytotoxic agents from *Ferula assa-foetida*. J Nat Prod. 2009;72:1568–72.
7. Eichner M, Schwehm M, Duerr HP, Witschi M, Koch D, Brockmann SO, Vidondo B. Antiviral prophylaxis during pandemic influenza may increase drug resistance. BMC Infect Dis. 2009;9:4.
8. Garten RJ, Davis CT, Russel CA, Shu B, Lindstrom S, et al. Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) influenza viruses circulating in humans. Science. 2009;325:197–201.
9. Gibbs AJ, Armstrong JS, Downie JC. From where did the 2009 'swine-origin' influenza A virus (H1N1) emerge? Virol J. 2009;6:207.
10. Glass RJ, Glass LM, Beyeler WE, Min HJ. Targeted social distancing design for pandemic influenza. Emer Infect Dis. 2006;12:1671–81.
11. Glezen WP. Containing the novel influenza A (H1N1) virus. Clin Infect Dis. 2010;50:869–70.
12. Goldkind SF, Sahin L, Gallauresi B. Enrolling pregnant women in research—lessons from the H1N1 influenza pandemic. N Engl J Med. 2010;362:2221–3.

13. Guan Y, Shortridge KF, Krauss S, Webster RG. Molecular characterization of H9N2 influenza viruses: were they the donors of the ''internal'' genes of H5N1 viruses in Hong Kong? Proc Natl Acad Sci USA. 1999;96:9363–7.
14. Hai R, Schmolke M, Varga ZT, Manicassamy B, Wang TT, et al. PB1-F2 expression by the 2009 pandemic H1N1 influenza virus has minimal impact on virulence in animal models. J Virol. 2010;84:4442–50.
15. Hill A, Guralnick R, Wilson M, Habib F, Janies D. Evolution of drug resistance in multiple distinct lineages of H5N1 avian influenza. Infect Genet Evol. 2009;9:169–78.
16. Kashyap AK, Steel J, Rubrum A, Estelles A, Briante R, et al. Protection from the 2009 H1N1 pandemic influenza by an antibody from combinatorial survivor-based libraries. PLoS Pathog. 2010;6:1000990.
17. Khanna M, Kumar P, Choudhary K, Kumar B, Vijayan VK. Emerging influenza virus: a global threat. J Biosci. 2008;33:475–82.
18. Khanna M, Kumar B, Gupta N, Kumar P, Vijayan VK, Kaur H. Pandemic swine influenza virus (H1N1): a threatening evolution. Indian J Microbiol. 2009;49:365–9.
19. Lindstrom SE, Cox NJ, Klimov A. Genetic analysis of human H2N2 and early H3N2 influenza viruses, 1957–1972: evidence for genetic divergence and multiple reassortment events. Virology. 2004;328:101–19.
20. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog. 2007;193(10):1470–4.
21. Memoli MJ, Hrabal RJ, Hassantoufighi A, Eichelberger MC, Taubenberger JK. Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. Clin Infect Dis. 2010;50:1252–5.
22. Merler S, Ajelli M, Rizzo C. Age-prioritized use of antivirals during an influenza pandemics. BMC Infect Dis. 2009;9:117.
23. Mishra AC, Chadha MS, Choudhary ML, Potdar VA. Pandemic Influenza (H1N1) 2009 Is Associated with Severe Disease in India. PLoS One. 2010;5:e10540.
24. Moscona A. Global transmission of oseltamivir-resistant influenza. N Engl J Med. 2009;360:953–6.
25. Ariano RE, Sitar DS, Zelenitsky SA, Zarychanski R, Pisipati A, Ahern S, Kanji S, Rello L, Kumar A. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ. 2010;182:357–63.
26. Operario DJ, Moser MJ, St.George K. Highly sensitive and quantitative detection of the H274Y oseltamivir resistance mutation in seasonal A/H1N1 influenza. J Clin Microbiol. 2010;48:3517–24.
27. Poalillo FE, Geiling J, Jimenez EJ. Healthcare personnel and nosocomial transmission of pandemic 2009 influenza. Crit Care Med. 2010;38:98–102.
28. Rambaut A, Holmes E. The early molecular epidemiology of the swine-origin A/H1N1 human influenza pandemic. PLoS Curr. 2009;1:RRN1003.
29. Shih SR, Chu TY, Reddy GR, Tseng SN, Chen HL, Tang WF, et al. Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity. J Biomed Sci. 2010;17:13.
30. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303:1517–25.
31. Tandale BV, Pawar SD, Gurav YK, Chadha MS, Koratkar SS, et al. Seroepidemiology of pandemic influenza A (H1N1) 2009 virus infections in Pune, India. BMC Infect Dis. 2010;10:255.
32. Torres JP, O'Ryan M, Herve B, Espinoza R, Acuna G, Manalich J, et al. Impact of the novel influenza A (H1N1) during the 2009 autumn-winter season in a large hospital setting in Santiago, Chile. Clin Infect Dis. 2010;50:860–8.
33. Triana-Baltzer GB, Gubareva LV, Nicholls JM, Pearce MB, Mishin VP. Novel pandemic influenza A (H1N1) viruses are potently inhibited by DAS181, a sialidase fusion protein. PLoS One. 2009;4(11):7788.
34. Wilson K, Brownstein JS, Fidler DP. Strengthening the international health regulations: lessons from the H1N1 pandemic. Health Policy Plan. 2010;25:505–9.
35. Wu JT, Leung GM, Lipsitch M, Cooper BS, Riley S. Hedging against antiviral resistance during the next influenza pandemic using small stockpiles of an alternative chemotherapy. PLoS Med. 2009;6:1000085.