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Resurgence of Pandemic A/H1N1 2009 Viruses during Influenza Season 2013-2014

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Authors' contributions

This work was carried out in collaboration between all authors. Author OM participated in the design of the project, carried out the publications' search, participated in the data analysis and drafted the manuscript. Author MEM participated in the conception and design of the project, participated in the data analysis and review the final manuscript. Author AB Participated in the design of the study and review the final manuscript. Authors SL and SEK participated in the conception and design of the project and review the final manuscript. Author AFM conceived the study and participated in the design and coordination of the project and drafted the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

In April 2009, the world has known an emergence of a triple-reasserting influenza virus, pandemic A/H1N1, causing a pandemic around the world. The virus has continued to circulate during influenza seasons from 2010 to 2013, but with low frequencies. However, during the influenza

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season 2013-2014, we have assisted to the resurgence of this same virus worldwide. A comparison of the 2009-2010 and the 2013-2014 influenza seasons revealed a notable change regarding the epidemiology of this virus, in term of hospitalizations and deaths associated with pandemic A/H1N1: A gradual transition of hospitalizations and deaths for older ages related to influenza has been reported.
The resurgence of pandemic A/H1N1 is critical and its explanation is still difficult, but could be related to the viral genetic and/or the host susceptibility. Therefore, the best management of the disease and the effective control of the virus can be attempted by vaccination of all persons without contraindications and strengthening the surveillance systems of influenza.

Keywords: Resurgence; pandemic A/H1N1; hospitalizations; deaths; vaccination.

1. INTRODUCTION

On April 2009, the world has assisted to the emergence of an influenza pandemic, pandemic A/H1N1, causing an estimated 201°200 respiratory deaths [1]. There's evidence that pandemic A/H1N1 is a virus produced from two kinds of porcine influenza, H1N1 Eurasian swine influenza viruses and the North American swine triple re-assortant virus, containing segments originating ultimately in human seasonal H3N2 influenza and in avian influenza as well as porcine influenza, contributing with six gene segments: PB2, polymerase basic 2; PB1, polymerase basic 1; PA, polymerase acidic; HA, hemagglutinin; NP, Nucleoprotein; and NS, nonstructural gene [2-6].

Currently, Ma et al. reported that this re-assorting is a rare event, which probably involved specific strains and some unknown factors. Indeed, the pandemic A/H1N1 could not be re-asserted in cellular model as well as in swine co-infected by the North American triple re-assorting virus and the H1N1 Eurasian swine influenza virus [7]. Genetic analysis conducted by Smith et al. showed that each segment of the pandemic A/H1N1 virus was nested within a well-established swine influenza lineage and the mean time for this re-assorting depended on the gene fragment [4,5].

Worldwide and immediately after the alert, national mandatory notification systems were started for influenza-like illness (ILI) cases and hospitalized persons with pandemic A/H1N1. After the pandemic, A/H1N1 virus continued to circulate with low frequencies and cause critical illness. The follow up of pandemic A/H1N1 infection was more elaborated in United States of America and European countries. In Europe, the prevalence of pandemic A/H1N1has largely reduced, but re-increased during the influenza season, 2012-2013 [8,9]. In United States, and according to the Centre for Disease Control and Prevention (CDC), pandemic A/H1N1 has not predominated until 2013-2014 season, with a corresponding resurgence of influenza-related hospitalizations, critical illness, severe acute respiratory distress syndrome (ARDS) and deaths. Indeed, 96% of subtyped influenza A viruses were characterized as pandemic A/H1N1 and more than 60% of laboratory confirmed influenza associated hospitalizations and deaths reported in adults younger than 65 years have been attributed to pandemic A/H1N1[10].

Mostly, the pandemic A/H1N1 infection will not develop critical illness and appears as a mild and acute upper respiratory tract disease. However, it may lead to sporadic cases of severe pneumonia and (ARDS) in patients with known risk factors and, less frequently, even in patients otherwise healthy. The aim of this paper is to assess the evolution of the pandemic A/H1N1 infection during last years and evaluate associated hospitalization and deaths during influenza season (2013-2014).

2. METHODOLOGY

The online English Google scholar and PubMed databases were used to search for articles published from May 2009 to August 2014. The groups of terms that were used for the information retrieval were: Mortality associated with pandemic influenza A/H1N1 virus, Hospitalizations associated with pandemic A/H1N1, critically (Ill) patients with pandemic A/H1N1 virus infection, morbidity and mortality associated with pandemic A/H1N1 Influenza, seasonal influenza vaccine effectiveness and influenza season.

The information was also recovered from the online English and French database WHO (World Health Organization) by consulting the weekly epidemiological record, as well as from

the Weekly Electronic Bulletin of influenza surveillance systems like: EuroFlu (Europe influenza), FLUVIEW (Weekly U.S. Influenza Surveillance Report prepared by The Centers for Disease Control and Prevention's Influenza Division), InVS (Institut de Veille sanitaire, France) and Public Health Agency of Canada.

3. CIRCULATION OF PANDEMIC A/H1N1 VIRUS DURING 2010-2013

During 2010-2011 influenza season, pandemic A/H1N1 was no longer the predominant influenza virus circulating in many parts of the world, but exhibiting the same characteristics as during the pandemic season regarding the age of affected patients and illness clinical pattern. Indeed, the association between the severity of the disease and the age was as reported previously and the infection with pandemic A/H1N1 was more pronounced in young people and middle-aged adults [11]. Of particular interest, in some countries, most notably the United Kingdom (UK), pandemic A/H1N1 was the most predominant viruses and was more marked than the previous season with large numbers of cases requiring ventilatory support in intensive care units [11].

The 2011-2012 influenza season was characterized by the predominance of influenza A (H3N2). Influenza B cases were increased slightly but later in the season. Mexico, as it's the case of the most temperate countries, reported almost exclusively pandemic A/H1N1. Interestingly, the USA reported much more influenza A (H3N2) except in the states bordering Mexico [8].

In the 2012-2013 influenza season, Mexico didn't report any pandemic A/H1N1 infection and relatively few influenza pandemic A/H1N1 viruses were detected throughout the season, accounting for less than 5% in the USA and about 12% in Canada. In contrast, pandemic A/H1N1 has re-emerged in Europe and the majority of influenza viruses characterized belonged to the pandemic A/H1N1 was also the most commonly detected virus in the Middle East and neighboring countries in Asia throughout the season, with relatively few reported cases of A(H3N2) or influenza type B. However, all countries in the Northern Asia have reported more influenza A (H3N2) than the pandemic A/H1N1 [9].

4. CIRCULATION OF PANDEMIC A/H1N1VIRUS DURING 2013-2014 SAESON

The 2013-2014 influenza season was marked by the resurgence of pandemic A/H1N1virus causing substantial morbidity and mortality around the world. In this paper we will focus on countries where influenza A (H1N1) prevailed by reporting data on hospitalizations and deaths associated with pandemic A/H1N1virus.

In North America, pandemic A/H1N1 remained the most commonly detected virus for the 2013/2014 season.

In Canada between August 25th, 2013 and August 9th, 2014, among 5442 cases of Influenza-associated hospitalizations, 68.3% have the influenza A, predominantly pandemic A/H1N1 (56.2%). Moreover, of the most cases of patients admitted to the intensive care units have the pandemic A/H1N1virus. During this influenza season, 64.3% of the 342 deaths registered were infected with influenza A. Distribution of mortality according to patients' age showed that 56.7% patients were ≥ 65 years and 35.4% were aged 20-64 years, One death has been reported this season among children's (≤16 years of age) [12]. In USA, several reports have highlighted the resurgence of influenza-related hospitalizations with serious illness, severe ARDS and death. Moreover, 60% of hospitalizations and deaths attributed to pandemic A/H1N1virus are under 65 years [10,13]. From October 1st 2013 to April 30th, 2014, 9632 laboratory-confirmed influenza-associated hospitalizations were reported. Those aged 18-64 years account for approximately 60% of reported hospitalized cases. Among all hospitalizations, 88.2% were associated with influenza A. Among those with influenza A subtype information, 94.0% were pandemic A/H1N1. On the other hand, 95 Influenza-associated pediatric deaths have been reported during the 2013/2014 season, among them 76 (82.6%) were associated with influenza A [14].

In Mexico, between October 1st, 2013 and January 31st, 2014, a total of 7886 SARI hospitalizations was reported in the national public health care system. Among them, 1203 were confirmed for pandemic A/H1N1.Moreover, of 529 inpatient deaths, 196 were attributed to the pandemic A/H1N1 [15]. Overall, during this influenza season, the rate of hospitalization and death among laboratory-confirmed pandemic A/H1N1 patients aged 30-59 years is significantly

higher as compared to younger people. The illness severity increased with age, and the majority of laboratory-confirmed influenza inpatients were among persons aged 30-59 years (57.4%) followed by seniors' ≥ 60 years (17.4%). Moreover, the rate of death among laboratory-confirmed pandemic A/H1N1patients less than 20 years decreases drastically [15].

In Europe, between September 30th, 2013 and May 11th, 2014, sentinel and non-sentinel surveillance sources have yielded 47 070 Influenza detections: 94% of them were influenza A and among them 56% were pandemic A/H1N1. Eight countries have reported 4755 hospitalized laboratory-confirmed influenza cases: 4696 (99%) were associated to influenza virus type A, and among them 74% were associated to pH1N1. Of particular interest, a higher proportion of pandemic A/H1N1 viruses have been detected in patients in intensive care units. Among European countries, only 5 have reported influenza associated deaths. During the 2013-2014 influenza season, 402 fatal cases were registered: 398 (99%) were associated with influenza virus type A infection and 4 (1%) with type B. Interestingly, among 290 influenza A viruses subtyped from fatal cases, 235 (81%) were pandemic A/H1N1and only 55 (19%) were A (H3N2) [16].

The most affected countries were France and Spain. In France, 647 severe cases were admitted to intensive care units from November 1st, 2013 to April 16th, 2014, and 90 deaths were registered. The majority of these patients were adults; 59% were aged15-64 years and 34% were more than 65 years, younger patients less than 14 years represented only 7%. Moreover, these patients were mostly infected by the influenza type A (95%), pH1N1 representing 41% of them [17].

In Spain, 2402 confirmed hospitalized severe cases were reported during the 2013-2014 influenza season, 99.25% of them were associated with influenza type A and 77% with pandemic A/H1N1. Among hospitalized severe cases of confirmed flu, there have been 280 deaths, 278 (99%) were associated with influenza type A and 179 (64%) were attributed to pandemic A/H1N1. Moreover, 47% of deaths attributed to pandemic A/H1N1 occurred in young and middle-aged adults (14% in 15-44 years and 33% in 45-64 years). Furthermore, since the beginning of the season, 15 outbreaks of flu have been reported and 7 were attributed to the pandemic A/H1N1 [18].

In northern Asia, influenza activity has followed a typical seasonal trend. In northern China, co-circulation of pandemic A/H1N1 and influenza B was reported during the season, with a predominance of pandemic A/H1N1 during the middle of the season. Overall, the numbers of tested samples and influenza-positive samples in China were greater than in previous seasons, but the ILI and test positivity rates were reported to be similar to those in previous seasons. In the Republic of Korea, As the season progressed, similar proportions of pandemic A/H1N1, A(H3N2), and influenza B were detected, although at the end of the season, influenza B was detected most frequently. In Mongolia, reported data showed a high influenza activity in late January 2014, as compared to the national baseline threshold, with predominantly pandemic A/H1N1 detection. Influenza activity remained high through February and March 2014. Moreover, an increased detection of A(H3N2) and Influenza B has been reported late in the season [19].

In Africa, the only available data were from Egypt and showed that among more than 2200 suspected cases, Influenza a virus was detected in 70% of cases with a predominance of pandemic A/H1N1, representing 60% of all positive cases. Infection was most common among young people (median age 47 years). During this season, 44 deaths were reported and 75% of them were aged 25–54 years [20]. It's interesting to note that from December 1st, 2013 to January 17th 2014, an unusual increase of atypical pneumonia cases was reported in Dakahlia Governorate in Egypt, the Egyptian Ministry of Health and Population has reported 24 cases and among them 13 cases (54%) were pandemic A/H1N1 positives. By January 26th, 2014, the total number of laboratory-confirmed cases reported had increased to 75 [20].

5. HOSPITALIZATIONS AND DEATHS ASSOCIATED WITH PANDEMIC A/H1N1 FROM THE PANDEMIC YEAR TO 2013/2014 SEASON

During the influenza season 2009-2010, and in most countries, the majority of confirmed pandemic A/H1N1 cases has occurred in younger age groups. In Hong Kong, almost half of pandemic A/H1N1 confirmed cases were school-aged children (5 - 14 years) [21]. In France young age was considered as the principal mortality risk factor due to the pandemic A/H1N1 [22]. In Washington, Kwan-Gett et al.

have reported that 60% of pandemic A/H1N1 confirmed cases were less than 18 years [23]. Moreover, 88.5% of pH1N1 infected cases were reported in persons less than 20 years of age [24]. Furthermore, children under 16 years were more susceptible to infection with pandemic A/H1N1 in United Kingdom and Mexico [25,26].

The population based surveillance conducted by the influenza hospitalization surveillance network, regrouping more than 70 countries, have reported a change in the epidemiology and distribution of hospitalized cases with Pandemic A/H1N1between influenza seasons 2009-2010 and 2013-2014. An analysis of hospitalization rates in 13 states from USA, between 2009/2010 and 2013/2014 influenza seasons, clearly illustrate the gradual change in the age distribution observed elsewhere (Fig. 1). Notably, a decrease of hospitalization rate among younger population was reported in 2013-2014 influenza season, whereas a more pronounced rates were observed among elderly people and those over 65 years old [14].

Change in the epidemiology of Influenza outbreak has been noted in hospitalizations and deaths associated with pandemic A/H1N1. A gradual shift of influenza-related hospitalizations and deaths towards older ages has been reported. Dàvila et al. [15] have reported that the gradual change in the age distribution of pH1N1 infections observed in Mexico suggests a slow reinforcement of immunity among younger populations, as it was the case in the past pandemics. The shift to older ages in the age distribution of hospitalized and fatal patients have started during the winter period of the 2010/2011 influenza season, as reported by Bolotin et al. [27] in United Kingdom, Athanasiou et al. [28] in Greece, Chuang et al. [29] in Taiwan.

Incidence rates are calculated using the national center for Health Statiscits '(NCHS)' population estimates for the counties included in the surveillance catchment area.

6. REASONS FOR THE RESURGENCE OF PANDEMIC A/H1N1

Worldwide, there's a resurgence of pandemic A/H1N1influenza but the reasons for this recrudescent trend remain to be explained, it'd look to antigenic drift to explain this resurgence. According to Skowronski and Coll., they have reported that the vaccine is substantially effective and pH1N1 viruses remain genetically and antigenically similar to the A/California/07/2009 vaccine strain, thus they related that "Neither antigenic drift nor homologous vaccine failure can account for resurgent pandemic A/H1N1activity this season in Canada". Other factors involved in agent–host interaction, including pre-existing antibody, should be considered in explaining the current epidemiology of this virus [30]. They suggest that the lack of previous exposure and vaccination have probably combined to create a "pocket of residual susceptibility [30].

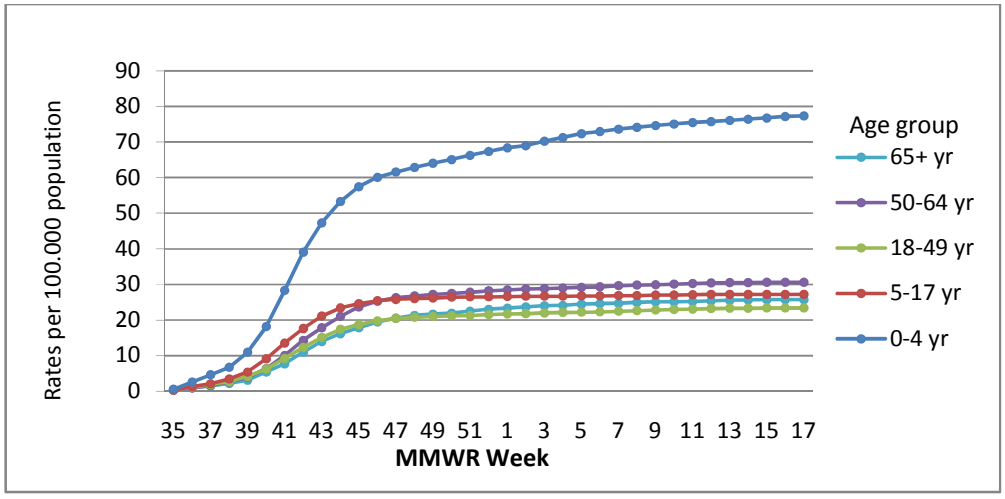
Moreover, protection against influenza has shown a U-shaped pattern by age [31]. Indeed, the high rates of protection was founded on people over 80 years of age, this could be due to the previous exposure to a similar virus that circulated in the 1930s whereas middle-aged adults have only a 30% seroprotection rate. Interestingly, children have high seroprotection rates, probably as a result of high rates of exposure and vaccination in 2009 [30].

Similarly, the Vaccine effectiveness (VE) against the predominant influenza pandemic A/H1N1 virus was 62% in the USA. This VE was calculated for all ages and showed similar protection from medically attended illness across age groups. Moreover, no significant antigenic changes in circulating pandemic A/H1N1 virus strains compared to vaccine strains have been detected since 2009 [32]. However it was also reported that a very high number of otherwise healthy individuals with critical illness requiring care in the Intensive care unit (ICU) in the USA were not previously vaccinated and the vaccination rate in hospitalized patients appears lower (23.6%) than the CDC-reported early-season vaccination rate of 39.5% for the 2013–2014 season [33] . On the same way, Napolitano has reported that the relative effect on young and middle-aged adults might be partially due to their low influenza vaccine coverage and cross-reactive immunity to pH1N1 virus that elderly individuals have acquired during past exposure to antigenically related viruses [13]. There's evidence that vaccination is sometimes not effective and not all prior influenza vaccinations or infections leading to preexisting influenza antibodies may be beneficial [34]. Indeed, Kim et al. have shown that the presence of cross-reactive antibodies to one influenza virus strain can reduce production of B cell antibodies to a second encountered strain [35]. Moreover, low-affinity influenza antibodies have been detected in patients with severe concurrent bacterial pneumonia leading to higher disease severity

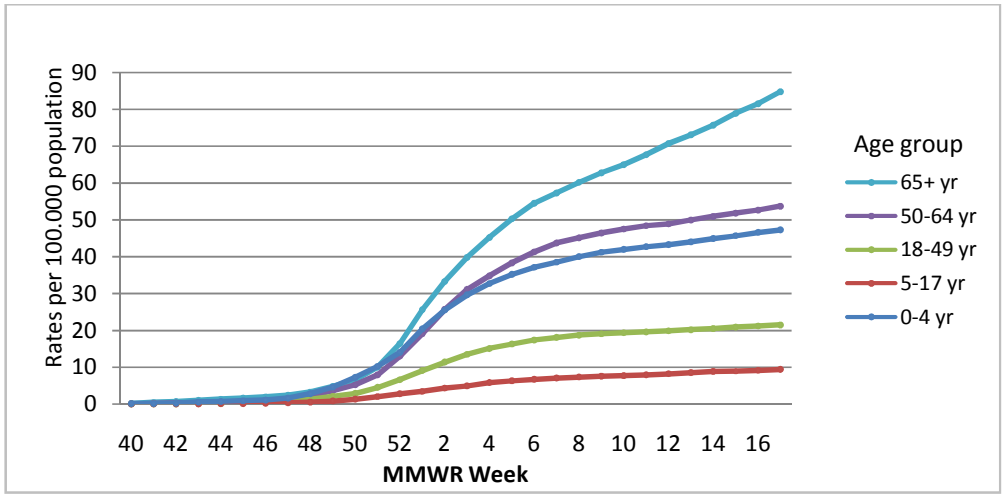
[36]. Severe diseases were also observed in middle-aged adults presenting preexisting serum antibody that cross-reacts with, but does not protect against pandemic A/H1N1 influenza virus [36].

7. INFLUENZA TREATMENTS AND NEW DRUG DEVELOPMENT

Worldwide, a success of influenza management program rests on an early detection of the viral strains and an effective for short-term defense against influenza. At the beginning of the pandemic, many studies have reported that the pandemic A/H1N1 virus was resistant to adamantanes drugs (amantadine and its derivative rimantadine), that are M2 inhibitors which block the ion channel activity of the M2 protein of most influenza A viruses [37,38]. Unfortunately, the pandemic A/H1N1 virus was reported that it has gained drug resistant for oseltamivir, which is a neuraminidase inhibitor [39]. To overcome this problem, USA and Japan have allowed the use of peramivir (another neuraminidase inhibitor) [40,41]. However, Memoli et al. have reported the H275Y mutation in the neuraminidase gene (NA) confer a significant reduction in sensitivity to oseltamivir and peramivir [42,43].



A: season 2009-2010



B: season 2013-2014

Fig. 1. Laboratory confirmed influenza hospitalizations by age group [14]

Hence, regarding the increasing frequency of resistance to available antiviral drugs, new drugs are required the pandemic A/H1N1, to combat this virus, stop its dissemination and control the disease.

The traditional way of drug discovery, based on the experimental screening of large libraries of chemicals against the biological target (high-throughput screening or HTS) for identifying new lead compounds, is time and budget consuming. The application of *rational*, structure-based drug design is proven to be more efficient than the traditional way of drug discovery since it aims to understand the molecular basis of a disease and utilizes the knowledge of the three-dimensional (3D) structure of the biological target in the process. In this field, Chen et al. [44] have screened 365 602 compounds from NCI database by docking study of N1 and H1. Molecular modeling has shown 9 potent dual-target candidate drugs for H1N1 that have to be evaluated on the pandemic A/H1N1.

Structure-based drug discovery was also used for development of drugs against pandemic A/H1N1. This approach, based on modeling techniques for predicting binding sites, protein-ligand interaction, quantitative structure-activity relationships (QSAR) and simulation of molecular dynamics, is central to the efficient development of therapeutic agents and to the understanding of metabolic processes [45,46]. In this field, Tambunan et al. [47] have used the molecular docking method to design ligands able to inhibit the M2 channel protein of influenza virus, and the molecular dynamic simulation to evaluate the interaction of ligands with the hydrated protein. Results clearly showed that 3 lignads, AML6R6, TR6L6 and TL6R12, exhibited high interaction activities with M2 channel, with small free binding energy, and therefore could be proposed as a potential inhibitor to inhibit interaction of M2 channel in H1N1 virus [48].

8. CONCLUSION

The lack of data in some countries of the world does not exclude the presence of this virus, but self-medication and unsystematic use of laboratory virology diagnosis of ILI cares are the main causes of the lack of data on this flu season.

The resurgence of pandemic A/H1N1 influenza is critical and its explanation is still delicate, but we believe that the best management of the disease and the efficient control of the virus remain the vaccination of all individuals without contraindications and strengthening surveillance systems.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. The Lancet Infectious Diseases. 2012;12(9):687-695.
2. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, Donis R. Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) influenza viruses circulating in humans. Science. 2009;325(5937):197-201.
3. Gibbs AJ, Armstrong JS, Downie JC. From where did the 2009 swine-origin 'influenza A virus (H1N1) emerge. Virol J, 2009;6(207):19930669.
4. Smith GJ, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, Rambaut A. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature. 2009a;459(7250):1122-1125.
5. Smith GJ, Bahl J, Vijaykrishna D, Zhang J, Poon LL, Chen H, et al. Dating the emergence of pandemic influenza viruses. Proceedings of the National Academy of Sciences. 2009b;106(28):11709-11712.
6. Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. New England Journal of Medicine. 2009;361(2):115-119.
7. Ma W, Liu Q, Qiao C, del Real G, García-Sastre A, Webby RJ, Richt JA. North American Triple Reassortant and Eurasian H1N1 Swine Influenza Viruses Do Not Readily Reassort to Generate a 2009 Pandemic H1N1-Like Virus. mBio. 2014;5(2):e00919-13.
8. WHO. Review of the 2011-2012 winter influenza season, northern hemisphere Weekly epidemiological record. 2012;87:233-240. Available:http://www.who.int/wer/en/

9. WHO. Review of the 2012-2013 winter influenza season, northern hemisphere. Weekly epidemiological record. 2013;88:225–232. Available:http://www.who.int/wer/en/
10. Carmen S. Arriola, Lynnette Brammer, Scott Epperson, et al. Update: Influenza activity-United States, september 29, 2013-february 8, 201 4. MMWR. Morbidity and mortality weekly report. 2014;63(7):148-154.
11. WHO. Review of the 2010-2011 winter influenza season, northern hemisphere. Weekly epidemiological record. 2011; 86(22):221-232. Available:http://www.who.int/wer/en/
12. Public Health Agency of Canada (PHAC). Fluwatch week 33, 34. Fluwatch; 2014. (August 10, 2014 to August 23, 2014).
13. Napolitano LM, Angus DC, Uyeki TM. Critically ill patients with influenza A(H1N1) pdm09 virus infection in 2014. Jama. 2014;311(13):1289-1290.
14. United States Centers for Disease Control and Prevention (CDC). 2013-2014 Influenza Season Week 20 ending May 17, 2014. Flu View; 2014.
15. Dávila J, Chowell G, Borja-Aburto VH, Viboud C, Muñiz CG, Miller M. Substantial Morbidity and Mortality Associated with Pandemic A/H1N1 Influenza in Mexico, Winter 2013-2014: Gradual Age Shift and Severity. PLoS currents. 2013;6.
16. WHO. Influenza season 2013-2014: week 19/2014 EuroFlu - Weekly Electronic Bulletin. 2014;(530). Available:https://www.isirv.org/cgi-files/bulletin_v2.cgi?season=2013&menu=y (Accessed 30 November 2014).
17. In Vs (Institut de veille sanitaire: France). Bulletin hebdomadaire grippe, 16/4/2014; 2014. Available:http:// www.invs.sante.fr › download › version › file › Bulletin_grippe_160414 (Accessed 16th May 2014).
18. Instituto de Salud Carlos III. Annual and weekly reports Influenza Surveillance in Spain. System Influenza Surveillance in Espa -a. [Annual and weekly national influenza reports. Spanish Influenza Surveillance System]. Madrid: National Epidemiology Center Instituto de Salud Carlos III; 2014; Semana 19. Accessed 16th May 2014. Available:http://www.isciii.es/cne-gripe-infsemanal
19. WHO. Review of the 2013-2014 winter influenza season, northern hemisphere. Weekly epidemiological record. 2014;89(23):245–256. Avialable:http://www.who.int/wer/en/
20. WHO. Severe atypical pneumonia outbreak associated with influenza A(H1N1)pdm09 in Egypt, 2013–2014 season. Weekly epidemiological record. 2014;89(16):161–164. Available:http://www.who.int/wer/2014/wer8916.pd
21. Wu JT, Ma ES, Lee CK, et al. The infection attack rate and severity of 2009 pandemic H1N1 influenza in Hong Kong. Clinical infectious diseases: An official publication of the Infectious Diseases Society of America. 2010;51(10):1184-1191.
22. Lemaitre M, Carrat F. Comparative age distribution of influenza morbidity and mortality during seasonal influenza epidemics and the 2009 H1N1 pandemic. BMC infectious diseases. 2010;10:162.
23. Kwan-Gett TS, Baer A, Duchin JS. Spring 2009 H1N1 influenza outbreak in King County, Washington. Disaster Med Public Health Prep. 2009;3(2).
24. Kamigaki T, Oshitani H. Epidemiological characteristics and low case fatality rate of pandemic (H1N1) 2009 in Japan. PLoS Curr. 2009;20(1).
25. Ghani A, Baguelin M, Griffin J, et al. The Early Transmission Dynamics of H1N1pdm Influenza in the United Kingdom. PLoS Curr. 2009;16(1).
26. Rogelio Perez-Padilla, Daniela de la Rosa-Zamboni, Samuel Ponce de Leon, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. New England Journal of Medicine. 2009;361(7):680-689.
27. Bolotin S, Pebody R, White PJ, et al. A new sentinel surveillance system for severe influenza in England shows a shift in age distribution of hospitalised cases in the post-pandemic period. PloS one. 2012;7(1):e30279.
28. Athanasiou M, Baka A, Andreopoulou A, et al. Influenza surveillance during the post-pandemic influenza 2010/11 season in Greece, 04 October 2010 to 22 May 2011. Euro Surveill. 2011;16(44):20004.
29. Chuang JH, Huang AS, Huang WT, et al. Nationwide surveillance of influenza during the pandemic (2009-10) and post-

pandemic (2010-11) periods in Taiwan. PloS one. 2012;7(4):e36120.

30. Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Dickinson J, Winter A, Fonseca K, Gubbay J, Charest H, Petric M, Krajden M, Mahmud S, Van Caeseele P, Kwindt T, Eshaghi A, Bastien N, Li Y. Interim estimates of 2013/14 vaccine effectiveness against influenza A (H1N1) pdm09 from Canada's sentinel surveillance network, January 2014. Euro Surveill. 2014;19(5).
31. Brown C. Low rates of immunity in adults behind H1N1 resurgence. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. Apr 1 2014;186(6):410.
32. Flannery B, Thaker SN, Clippard J, Monto AS, Ohmit SE, Zimmerman RK, Nowalk MP, Gaglani M, Jackson ML, Jackson LA, Belongia EA, McLean HQ, Berman L, Foust A, Sessions W, Spencer S, Fry AM. Centers for Disease Control and Prevention (CDC).Interim estimates of 2013-14 seasonal influenza vaccine effectiveness-United States, february 2014. MMWR Morb Mortal Wkly Rep. 2014;63(7):137-142.
33. Catania J, Que LG, Govert JA, Hollingsworth JW, Wolfe CR. High Intensive Care Unit Admission Rate for 2013–2014 Influenza Is Associated with a Low Rate of Vaccination. American journal of respiratory and critical care medicine. 2014;189(4):485-487.
34. Haran JP, Hoaglin DC, Chen H, Boyer EW, Lu S. Antigen-specific H1N1 influenza antibody responses in acute respiratory tract infections and their relation to influenza infection and disease course. Journal of clinical virology: The official publication of the Pan American Society for Clinical Virology. 2014;60(4):367-373.
35. Kim JH, Skountzou I, Compans R, Jacob J. Original antigenic sin responses to influenza viruses. J Immunol. 2009;183(5):3294-3301.
36. Monsalvo AC, Batalle JP, Lopez MF, et al. Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes. Nature medicine. Feb 2011;17(2):195-199.
37. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009;325:197-201.
38. Centers for Disease Control and Prevention. Update: Drug susceptibility of swine- origin influenza A (H1N1) viruses, April 2009.MMWR Morb Mortal Wkly. Rep. 2009;58:433-435.
39. Gubareva LV, Trujillo AA, Okomo-Adhiambo M, Mishin VP, Deyde VM, Sleeman K, et al. Comprehensive assessment of 2009 pandemic influenza A (H1N1) virus drug susceptibility in vitro. Antiviral therapy. 2010;15:1151–1159.
40. Centers for Disease Control and Prevention. Termination of the Emergency Use Authorization (EUA) of Medical Products and Devices; 2010. Available:http://www.cdc.gov/h1n1flu/eua/peramivir.htm (Accessed 23 September 2010).
41. Castillo R, Holland LE, Boltz DA. Peramivir and its use in H1N1 influenza. Drugs Today (Barc). 2010;46:399-408.
42. Memoli MJ, Hrabal RJ, Hassantoufighi A, Eichelberger MC, Taubenberger JK. Rapid selection of oseltamivir and peramivir resistant pandemic H1N1 during therapy in two immunocompromised hosts. Clin Infect Dis. 2010;50:1252-1255.
43. Yamashita M, Tomozawa T, Kakuta M, Tokumitsu A, Nasu H, Kubo S. CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. Antimicrob Agents Chemother. 2009;53:186–92
44. Chen CY, Chang YH, Bau DT, Huang HJ, Tsai FJ, Tsai CH, Chen CYC. Ligand-based dual target drug design for H1N1: swine flu--a preliminary first study. Journal of Biomolecular Structure & Dynamics. 2009;27(2):171–8.
45. Huang HJ, Yu HW, Chen CY, Hsu CH., Chen HY, Lee KJ, et al. Current developments of computer-aided drug design. Journal of the Taiwan Institute of Chemical Engineers. 2010;41(6):623–635.
46. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52:447–56.
47. Tambunan USF, Parikesit AA, Dephinto Y, Sipahutar FRP. Computational design of drug candidates for influenza A virus

subtype H1N1 by inhibiting the viral neuraminidase-1 enzyme. Acta Pharmaceutica (Zagreb, Croatia). 2014;64(2):157–72.

48. Tambunan USF, Rahdiansyah MR, Parikesit AA. In Silico Design of the M2 Proton Channel Inhibitors of H1N1 Virus. OnLine Journal of Biological Sciences. 2013;13(1):1–12.

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