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REVIEW

Understanding the Influenza A H1N1 2009 Pandemic

Zakariya Al-Muharrmi

فهم وباء أنفلونزا A H1N1 2009

زكريا المحرمي

الملخص: في أبريل سنة 2009 ظهرت في الولايات المتحدة الأمريكية والمكسيك سلالة جديدة من فيروسات أنفلونزا A مع إنتقال حلقي رباعي في الحمض النووي الريبي أدت إلى تفشي وباء، وقد صنفت على إنها إنفلونزا (A H1N1 2009). المادة الوراثية لهذه السلالة ناتجة عن ثلاث سلالات مختلفة من البشر والطيور والخنازير. وفي يونيو 2009 أعلنت منظمة الصحة العالمية هذه السلالة وباءً جائحا ليكون أول وباء عالمي يتم تسجيله منذ 40 عاما. ينتقل فيروس الأنفلونزا من خلال القُطيرات التنفسية، وتنتقل السلالة الجديدة أسرع من غيرها من سلالات الإنفلونزا مما يؤدي إلى صعوبة السيطرة على العدوى. غالبية الحالات المصابة بالسلالة الجديدة كانت خفيفة لكن بعض المرضى حصلت لديهم مضاعفات والبعض الآخر توفى. معظم الفحوص المخبرية لهذه السلالة غير حساسة ما عدا تفاعل البوليميريز المتسلسل وهو باهض الثمن ويتطلب خبرات عالية. السلالة الوبائية الجديدة تستجيب للأدوية المضادة لأنزيم النيورميندیز مثل دواء الأوسيلتامفير والزنمفير، لكن سجلت بعض الحالات المقاومة للأوسيلتامفير. وفي منتصف سبتمبر 2009 تم توفير أول شحنه للقاحات السلالة الجديدة وكانت فعاليتها المناعية عالية جدا دون تسجيل أعراض جانبية تذكر. إن الترصد مهم جدا في جميع مراحل الوباء الجائح لكشف ورصد نزعة العدوى الفيروسية ومنع حدوث الأوبئة في المستقبل، الهدف من هذه المراجعة هو فهم فيروسات الإنفلونزا المسببة للأوبئة الجائحة ودراسة الاستراتيجيات اللازمة لمراقبتها وتخفيف حدتها والسيطرة عليها.

مفتاح الكلمات: الأنفلونزا، الوباء الجائح، تفاعل البوليميريز المتسلسل، اللقاح، الترصد.

ABSTRACT: A new strain of Influenza A virus, with quadruple segment translocation in its RNA, caused an outbreak of human infection in April 2009 in USA and Mexico. It was classified as Influenza A H1N1 2009. The genetic material originates from three different species: human, avian and swine. By June 2009, the World Health Organization (WHO) had classified this strain as a pandemic virus, making it the first pandemic in 40 years. Influenza A H1N1 2009 is transmitted by respiratory droplets; the transmissibility of this strain is higher than other influenza strains which made infection control difficult. The majority of cases of H1N1 2009 were mild and self limiting, but some people developed complications and others died. Most laboratory tests are insensitive except the polymerase chain reaction (PCR) which is expensive and labour intensive. The Influenza A H1N1 2009 virus is sensitive to neuraminidase inhibitors (oseltamivir and zanamivir), but some isolates resistant to oseltamivir have been reported. A vaccine against the new pandemic strain was available by mid-September 2009 with very good immunogenicity and safety profile. Surveillance is very important at all stages of any pandemic to detect and monitor the trend of viral infections and to prevent the occurrence of future pandemics. The aim of this review is to understand pandemic influenza viruses, and what strategies can be used for surveillance, mitigation and control.

Keywords: Influenza; Pandemic; Polymerase Chain Reaction; Vaccine; Surveillance.

In the last few years, the world has faced two major disasters. The first was economical recession; the second was the pandemic spread of a new reassortant influenza virus that spread all over the world in few weeks. Economic recession is clearly man-made, with economic mismanagement leading to the collapse of international banks, but pandemic viruses occur naturally and man has to struggle with nature for his survival. On 17th April 2009, the Center of Disease Control and Prevention (CDC), in the USA, reported a new Influenza A H1N1 strain with quadruple segment translocation in its RNA.[1] Since then this strain has spread worldwide and on 11th June 2009 it was declared by the World Health Organization (WHO) to be a Phase 6 pandemic virus (maximum threat).[2] Influenza pandemics have many effects on people, health care services and countries. The pandemic spread of influenza viruses is characterised by a high attack rate and

Department of Microbiology & Immunology, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman
Email: almuharrmi@gmail.com

an increased level of mortality particularly in young adults. Therefore, it necessary to understand influenza viruses that cause pandemics and what strategies can be used for surveillance, mitigation and control.

The Virus

The influenza virus belongs to *Orthomyxoviridae* family. It has three classes: A and B which only infect humans and C which is uncommon. Its genetic material is made up of eight separate segments.[3] The virus is enveloped with two important projections on the surface, these are haemagglutinin that binds to cell receptors in target tissues and neuraminidase that cleaves to the sialic acid in the cell wall to release the progeny viruses. Influenza A has 16 different haemagglutinins and 9 different neuraminidases.[4] It is classified according to the types of haemagglutinin and neuromindase on its surface, e.g. H1N1, H3N2 and H5N1. It infects not only humans, but also other mammals mainly pigs, birds and horses.[3] Two types of genetic mutations occur in the influenza A virus. First, genetic drift which is a point mutation leading to a mild changes on surface antigens, leading to new variant of the same virus which causes the recurrent epidemic influenza infections. Second, genetic shift which occurs when genetic segments are translocated among Influenza A viruses from different species e.g. human, birds and pigs leading to a completely new strain not previously existing in nature.[3] Such strains can cause pandemic infections if they have the ability to infect humans and the ability to be transmitted from one person to another.

The current Influenza A H1N1 2009 strain is a result of genetic translocation from three different species: one genetic segment from human Influenza A H3N2, two segments from avian Influenza A H1N1 and five segments from swine H1N1.[5] In 1998, a new triple reassortant swine influenza virus was identified in North America. Genetically it was made up of five segments derived from the North American classical A/H1N1swine virus, while the polymerase gene segments derived from either birds or humans. Genetic analysis of the influenza A H1N1 2009 showed that it was derived from a new reassortment of six gene segments from the known triple reassortant swine virus.[6] The genes encoding neuraminidase and the M protein were most closely related to those in influenza A viruses circulating in swine populations in Eurasia.[5] Within a few months, the A H1N1 2009 virus became the predominant influenza strain worldwide.[7] Compared to seasonal strains, A H1N1 2009 replicates more efficiently and produces different cytokines resulting in more lung damage in animal models.[8]

History and Phases of Pandemic Influenza

Influenza pandemics occur in waves. The WHO uses a six-phased approach to guide national preparedness plans against pandemics.[9] Phases 1–3 correlate with preparedness while phases 4–6 signal the need for mitigation efforts. In Phase 1, no viruses circulating among animals have been reported to cause human infection. In Phase 2, an animal influenza virus is known to have caused infection in humans. In Phase 3, an animal or human-animal influenza reassortant virus has caused small clusters, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks. Phase 4 occurs when such viruses cause human-to-human transmission at community-level. In Phase 5, the human-to-human spread of the virus attacks at least two countries in one WHO region. If the outbreak is recorded in more than one WHO region, the final "pandemic phase", or Phase 6, is declared.[9] In the post-pandemic period, influenza disease activity returns to levels normally seen for seasonal influenza.[9] The Influenza A H1N1 virus was declared Phase 6 by the WHO on 11th June 2009.[2]

Global pandemics have been observed for several hundred years. The best documented pandemic occurred in 1918 (A (H1N1), Spanish flu).[10] It was estimated to have infected 50% of the world's population, with an estimated mortality of 40–50 million (mortality rate of 2–2.5%). The attack and mortality rates were highest among healthy adults (20–40 years old). The second was in 1957 (A(H2N2), Asian flu) which affected around 40–50% of people during two waves, with a mortality rate of 1 in 4000 and the total death toll probably exceeding 1 million. The third was in 1968 (A(H3N2), Hong Kong flu) with similar morbidity and mortality to Asian Flu.[11] Aspirin use which is known to cause hyperventilation and pulmonary oedema in high doses, was the major factor in the high death rate

from Spanish flu.[12] Other possible factors could be the unavailability of antibiotics which were not yet discovered to treat bacterial superinfection; primitive infection control practices and the destruction of health care facilities as a result of World War I.

The first cases of the new pandemic influenza A H1N1 2009 infections were identified in April 2009 in the United States.[1] By August 2009, the cumulative number of infections in the United States alone was estimated to be at least 1 million.[13] However, there were only 556 confirmed deaths,[14] i.e. the mortality rate was only 0.056%.

Infection Control and Mitigation Strategies

Influenza viruses are transmitted by respiratory droplets, which do not normally travel more than one metre distance although coughing and sneezing can increase this distance by a few more metres. The virus can survive for 6 hours on a dry surface; when touched by hands it can be retransmitted. Transmissibility of the A H1N1 2009 strain is higher than that of seasonal influenza strains.[15]

Controlling the spread of influenza in a hospital setting is difficult and should include the following: isolating patients with suspected or documented influenza; sending home health care workers (HCW) with influenza-like illnesses and advising visitors showing symptoms of influenza not to come to hospital.[16] Hand washing with water and soap or alcohol-based hand sanitiser should be universal policy although some reports claim soap and water to be more effective than alcohol.[17] It is recommended to keep one metre distance between sick and healthy people and the patient should cover his/her mouth and nose when sneezing or coughing. If the patient is admitted in to hospital, a droplet isolation policy should be followed; this requires a side room with normal pressure ventilation. HCW should wear surgical face masks when caring for patients with influenza. Respirators, e.g. N95 masks, are indicated for HCW doing invasive procedures in the respiratory tree, e.g. intubation or bronchoscopy.[18] Some researchers claim surgical face masks to be as effective as N95 masks in the prevention of seasonal influenza.[19] Others claim they are ineffective against A H1N1 2009.[20] The patient is considered infectious from one day prior to illness onset until the resolution of fever or until 5 to 7 days after the onset of symptoms.[5] The attack rate of A H1N1 2009 was estimated to be between 20–30%.[21]

In a community setting the mitigation strategies for a pandemic depend on its level of severity and this is determined by the infectivity and case fatality rates. For low-severity pandemics with case fatality rates <0.5% and infectivity of 1.6 or below, such as the current pandemic, the preferred policy is a combination of social distancing with the use of antivirals for treatment and prophylaxis without school closure.[22] School closure is a debatable option; the main reason for closure would be a high level of transmission leading to focal outbreaks and staff absenteeism.[23] The greatest benefits of school closures are achieved when schools are closed very early on during an outbreak, ideally before 1% of the population falls ill;[24] however, school closure have not shown benefits in previous outbreaks.[23] Regulations taken by national and international authorities to control the A H1N1 2009 pandemic need to address human rights according to Siracusa Principles. These principles states that social restriction should be: 1) in accordance with the law; 2) in the interest of a legitimate objective; 3) strictly necessary; 4) using the least intrusive or restrictive means available; 5) neither arbitrary nor discriminatory, and 6) subject to review.[25] Each country should have a complete preparedness plan for pandemic control. However, this is lacking in most countries which respond to such disasters out of fear or from economic and political self-interest rather than with policies based on scientific fact; even the WHO and the CDC lack key powers and resources to control pandemic viruses efficiently.[26]

Clinical Presentation

The majority of cases of influenza A H1N1 2009 were mild and self limiting.[8] The clinical presentation of influenza A H1N1 2009 is similar to those seen in seasonal influenza, with fever in 94% of patients, cough in 92% and sore throat in 66%.[27] In admitted patients, the prevalence of symptoms is as follows: fever (95%); cough (88%); shortness of breath (60%); fatigue/weakness (43%); rhinorrhoea (38%); myalgias (36%); headache (34%); sore throat (31%); vomiting (29%); wheezing (26%) and diarrhoea (24%).[28] The time between onset of symptoms and

admission to the hospital ranged from 4 to 25 days.[29] In Australia and New Zealand, the rate of ICU admission was 28.7 cases per million inhabitants.[30] The major determinants of ICU admission are: a) shortness of breath, which was seen in (87%) of admitted patients, and b) chest radiograph results consistent with pneumonia (seen in 73%), compared with 51% and 28% in those not admitted to the ICU.[28] Major complications of influenza include viral pneumonia, peripheral neuropathy, encephalitis, myocarditis and myositis.[31] These are mainly seen in people with chronic respiratory diseases, chronic cardiac diseases, immune suppression, neurological disorders, chronic haemoglobinopathies, diabetes and obesity.[32] The immunoglobulin subclass, mainly IgG2 deficiency, has been also associated with severe H1N1 infection. Patients taking aspirin are at high risk for complications and development of fatty hepatitis with encephalopathy (Ray's syndrome).[33]

Children less than 5 years old are at higher risk,[33] and paediatric presentations of A H1N1 2009 can be atypical; severity is often associated with underlying disease, and rates of secondary bacterial infections are low.[34] There were some case reports of children presenting with pneumomediastinum as a complication of A H1N1 2009.[35] There are other case reports of children presenting with signs of influenza-like illness and seizures or altered mental states.[36] The rate of hospital admission among pregnant women during the first month of the Influenza A H1N1 2009 outbreak was higher than it was in the general population (0.32 per 100,000 pregnant women, versus 0.076 per 100,000 of the population at risk).[37] In seasonal influenza, most hospitalisations occur among children less than 2 years of age, the elderly ≥65 years of age and patients with certain medical conditions.[29] For pandemic A H1N1 2009, most admissions were in young adults; in the USA 38% of admitted patients were young adults aged from 18–49 years.[29]

Mortality

Annually around 3 to 5 million people suffer from severe seasonal influenza epidemics worldwide, the number of fatalities being around 250,000 to 500,000.[38] In USA, the estimated annual mortality caused by seasonal influenza is 23,710 or 0.91% of all deaths.[39] The high pandemic Influenza A H1N1 2009 mortality in Mexico was mainly due to delayed care-seeking. The main reason for delayed care-seeking and mortality of Influenza A H1N1 2009 in USA was the lack of health insurance.[40] In comparison with seasonal influenza, the paediatric mortality caused by pandemic A H1N1 2009 occurred mainly in children with known co-morbidities including chronic lung disease or immunodeficiency. The median age was higher than that for seasonal influenza (9 versus 2.7 years).[41] Compared to seasonal influenza, the proportion of deaths in the USA was below the epidemic threshold.[42] Some people believe that secondary bacterial infections were the main cause of high mortality in past influenza pandemics.[43] These infections have not been shown to be responsible for deaths in the current pandemic, except in 29% of cases.[44]

Investigation

People infected with Influenza A H1N1 2009 are assumed to be shedding the virus and potentially infectious one day prior to illness onset until resolution of fever.[45] Some reports have shown that viral shedding may continue for at least 7 days.[46] Some patients might shed the virus for longer periods, for example young infants and the immunocompromised.[45] Upper respiratory tract specimens are the most appropriate samples for laboratory testing of pandemic Influenza A H1N1 2009. Samples should be taken from the nasopharynx (a nasopharyngeal swab), nasopharyngeal aspirates, throat swabs and transbronchial aspirates. Swab specimens should be collected using swabs with a synthetic tip (e.g. polyester or Dacron®), but not calcium alginate or cotton tips; the shaft should be made of aluminum or plastic, but not of wood. Specimens should be placed into sterile viral transport media. All respiratory specimens should preferably be sent immediately to the laboratory, but if a delay is expected they should be kept at 4°C for no longer than 4 days. Clinical specimens should be shipped on wet ice or cold packs in appropriate packaging.[45] Influenza A H1N1 2009 virus can be detected in respiratory specimens by different tests. These tests differ in their sensitivity, specificity and ability to distinguish between influenza A subtypes (e.g. 2009 H1N1 versus seasonal H1N1 versus seasonal H3N2 viruses).[47]

Rapid influenza diagnostic tests (RIDTs), have variable sensitivities and specificities, some experts

having reported sensitivity of 47%, and specificity of 86%.[48] Others have reported sensitivity of 51%, and specificity of 99%.[49] Direct immunofluorescence (DIF) has variable sensitivities (47–93%), but high specificity ≥96%.[49] Some reports claim that the DIF has a sensitivity of 93%, specificity of 97%, positive predictive value of 95% and negative predictive value of 96%.[50] Viral culture was the gold standard for influenza virus testing; however, it is only 88.9% sensitive for Influenza A H1N1 2009.[51] Therefore, a negative viral culture does not exclude infection with influenza A H1N1 2009.[45] Some researchers have described detection of the virus using microarray techniques.[52]

PCR testing is highly sensitive (lower limit of detection, 1–10 infectious units).[53] Real-time PCR is the test of choice for influenza A H1N1 2009.[54] It is more rapid and sensitive than cell culture.[55] However, PCR is expensive and labour intensive; therefore, it is impractical to investigate all affected patients because of the large number of people infected.[56] It is recommended to test hospitalised patients with suspected influenza or patients for whom a diagnosis of influenza will change decisions regarding clinical care, infection control, or management of close contacts. Patients dying of an acute illness, where influenza was suspected, should also be tested.[47]

Treatment

Influenza A H1N1 2009 virus is resistant to M2 inhibitors (amantadine and rimantadine), but sensitive to neuraminidase inhibitors (oseltamivir and zanamivir).[57] Oseltamivir is an oral agent, while zanamivir comes in puffs for inhalation. Unlicensed intravenous formulation of zanamivir has been used successfully in treatment of ventilated patient not responding to oral oseltamivir.[58] As of 4th October 2009, the WHO declared the isolation of 31 influenza A H1N1 2009 isolates resistant to oseltamivir, but sensitive to zanamivir. These were from patients taking prolonged courses of oseltamivir prophylaxis.[59]

A meta-analysis has shown that neuraminidase inhibitors shorten the duration of illness in children with seasonal influenza and reduce household transmission.[60] The same positive effects were reported in adults.[61] These effects prompted people to use oseltamivir sooner leading to the emergence of oseltamivir resistance; therefore, WHO guidelines have discouraged prescribing antivirals to patients with mild disease forms unless they have risk factors for complications.[62] The antiviral drug of choice is oseltamivir; zanamivir is only indicated in patients with oseltamivir resistant strains. Oseltamivir is also the drug of choice in treatment and chemoprophylaxis for pregnant women; zanamivir may also be used, but there are less data available about its safety in pregnant women.[57] Antibiotic chemoprophylaxis is not recommended in patients with H1N1 2009; however, when pneumonia is present, treatment with antibiotics should follow the recommendations from published evidence-based guidelines for community-acquired pneumonia.[63]

Vaccine

Universal influenza immunisation is known to reduce the rate of seasonal influenza and to decrease influenza-associated respiratory antibiotic prescriptions by 64%.[64] WHO experts promised that the vaccine for influenza A H1N1 2009 would be available within 5–6 months from the date of discovery of the new pandemic virus.[65] They estimated that first shipment would start in mid-September and this took place. It was expected that vaccine manufacturing capacity would not meet the demand of all countries, given the fact some experts recommend two doses of the vaccine for each individual.[66] The WHO estimated that 3 billion doses of vaccine would be produced within a one year period.[67] Other experts claim that 4.9 billion could be produced within a year.[68]

Thirty-three influenza A H1N1 2009 vaccine formulations were reported, most of them based on whole-virion or split-virion antigens, and 12 products would be adjuvanted (in most cases with aluminum hydroxide or as an oil-in water emulsion).[68] The USA Food and Drug Administration gave approval to four influenza A H1N1 2009 monovalent vaccine manufacturers in mid-September 2009. None of them contained adjuvants.[69] The approval was made on the basis of standards developed for vaccine strain changes for seasonal influenza vaccines; adherence to manufacturing processes; product quality testing, and lot release procedures developed for seasonal vaccines.[69] Preliminary data indicate that the immunogenicity and safety of these

vaccines are similar to those of seasonal influenza vaccines.[69] All influenza vaccines available in the United States for the 2009–10 influenza season are produced using embryonated hen's eggs and contain residual egg protein.[69]

There are concerns that the vaccine might cause Guillain-Barré syndrome (GBS) causing peripheral nerve damage. In 1976, the USA withdrew an influenza vaccine after a spike in cases of this neurological disease.[70] Experts have disputed that decision, based on the argument that people would be more likely to get GBS as a result of the influenza itself rather than from the vaccine. The other argument against the association of the vaccine with GBS was that in 1976 science was less well developed. All influenza vaccines in the 30 years since 1976 have shown excellent safety records. In any case, a link between GBS and vaccination is basically impossible to demonstrate at this stage.[70]

A preliminary report from a randomised control trial in Australia for the safety and immunogenicity of 15 µg dose of an inactivated, split virus 2009 H1N1 vaccine in healthy adults between the ages of 18 and 64 years showed immunogenicity in 96.7%. Local discomfort (e.g. injection-site tenderness or pain) was reported in 46.3%. Systemic symptoms (e.g. headache) were reported in 45%. No deaths or serious adverse events were reported.[71] Another study from UK showed that a 7.5 µg dose of inactivated vaccine with adjuvant was immunogenic to 92%, while the adjuvanted dose was only 76% immunogenic. The most common side effects were pain at the injection site in 70% and muscle aches in 42% of subjects.[72] Live seasonal influenza vaccines have been associated with increased respiratory diseases, e.g. bronchitis in children.[73]

Surveillance

Surveillance is very important at all stages of any pandemic. It provides information about the change of incidence, severity of infection, risk in specific groups, types of complications, appearance of new strains and monitors drug sensitivity. Such information is important for the development of policies regarding control measures, resource allocation and responses to other public health needs.[56] The WHO suggested case-based reporting at the start of the pandemic, rather than shifting to a qualitative assessment of pandemic influenza activity, combined with virological sampling of a representative number of isolates. It also recommended keeping continuous records of influenza-like illnesses with laboratory testing for pandemic H1N1 in a subset of cases. The general population perceptions of disease magnitude, risk and severity are very much influenced by surveillance data.[56] Because the world has become a global village, every country should implement a surveillance system to detect and monitor the trends of their viral infections to prevent the occurrence of future pandemics.

Conclusion

The pandemic influenza A H1N1 2009 is currently the most prevalent influenza virus. Most of the cases are mild, but there are high incidences in children and young adults. The presentation and complications are similar to those caused by seasonal influenza strains, but the mortality rate to date seems to be lower compared to seasonal strains. A vaccine against the pandemic strain has already been distributed in the markets with a very good safety profile. A major lesson learned from this pandemic is the establishment of surveillance systems to detect new viruses and track the trends of outbreaks.

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