PANDEMIC (H1N1) 2009 VIRUS VIEWED FROM AN EPIDEMIOLOGICAL TRIANGLE MODEL

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The cause of atypical respiratory illness in several Mexican states in mid-March 2009 was determined to be a novel pandemic (H1N1) 2009 virus. It has since then spread to six continents, causing illness and death. We review this virus against an epidemiological triangle model for understanding and visualizing communicable diseases that describes the interaction of an agent, host, and environment. We review the agent, i.e., pandemic (H1N1) 2009 virus, hosts focusing on human beings, and the environment, suggesting from this agent-host-environment interaction measures for controlling and preventing infection spread due to pandemic (H1N1) 2009 virus and the related issues.

Keywords: pandemic (H1N1) 2009 virus, epidemiological triangle

1. Introduction

In mid-March 2009, Mexico experienced an outbreak of respiratory illness and increasing reports of patients with influenza-like illness (ILI) in several regions, particularly in a small community in the state of Veracruz [1, 21]. On April 23, several cases of severe respiratory illness in Mexico were confirmed to be caused by a novel strain of influenza A (H1N1) virus (Pandemic (H1N1) 2009 virus) [1, 21, 22]. On April 17, two cases of febrile respiratory illness in children were also reported in California near the Mexican border which the United States' Centers for Disease Control and Prevention (CDC) determined to be caused by pandemic (H1N1) 2009 virus [2, 10]. The rapid spread of infection prompted the World Health Organization (WHO) to declare pandemic alert level six-the highest possible [3]. As of this writing (July 6, 2009), pandemic (H1N1) 2009 virus had spread to six continents resulting in 94,512 confirmed cases and 429 deaths [4].

1.1. Epidemiological Triangle Model and Pandemic (H1N1) 2009 Virus

The epidemiological triangle model for understanding and visualizing communicable diseases, describes the interaction of an agent, host, and environment providing visual aid in controlling and preventing the spread of infectious disease by disrupting the balance in this triangle, shown in **Fig. 1** for pandemic (H1N1) 2009 virus.

2. The Agent

2.1. Influenza A Viruses

Pandemic (H1N1) 2009 is an influenza A virus belonging to family *Orthomyxoviridae* [11, 15, 16, 18]. Structurally, influenza A virions are spherical, (although they may have other shapes and hence are *pleomorphic*); the enveloped particles consist of eight single-strand segments of negative sense ribonucleic acid (RNA) enclosed in a helical protein shell, or nucleocapsid. The virus is enclosed in a lipid envelope with protruding surface proteins consisting of hemagglutinins (HA) and neuraminidase (NA) [10–12, 15, 16, 18, 38] as shown in **Fig. 2**.

The major influenza virus component determining epidemiological dynamics is the predominant surface protein on the viral envelope, the HA antigen, which serves as the hemagglutinin or HA attachment protein determining whether the virus is able to bind to and infect cells of different species by attaching to sialic acid receptors on cells [11, 12, 15, 16]. NA antigen, a second external protein constituting 20-25% [21] to total surface protein, is an enzyme called neuraminidase because it cleaves neuraminic or sialic acid from complex carbohydrates such as mucin [16, 17, 21]. In infection it enables the release of the newly produced virus from surface receptors and digests mucous secretions, giving the virus better access to the surface of susceptible cells and spreading through the respiratory tract [11, 12, 18, 21]. Other structures responsible for virulence include the polymerase complex-consisting of PB2, PB1, and PA, nonstructural proteins NS1 and PB1-F2 [9]. The M protein is further subdivided into a structural matrix M1 protein and an ion channel M2 protein [11, 15, 16]. NS2 is a nuclear export protein responsible for exporting ribonucleoprotein complexes from the host nucleus into the cytoplasm for assembly [15].

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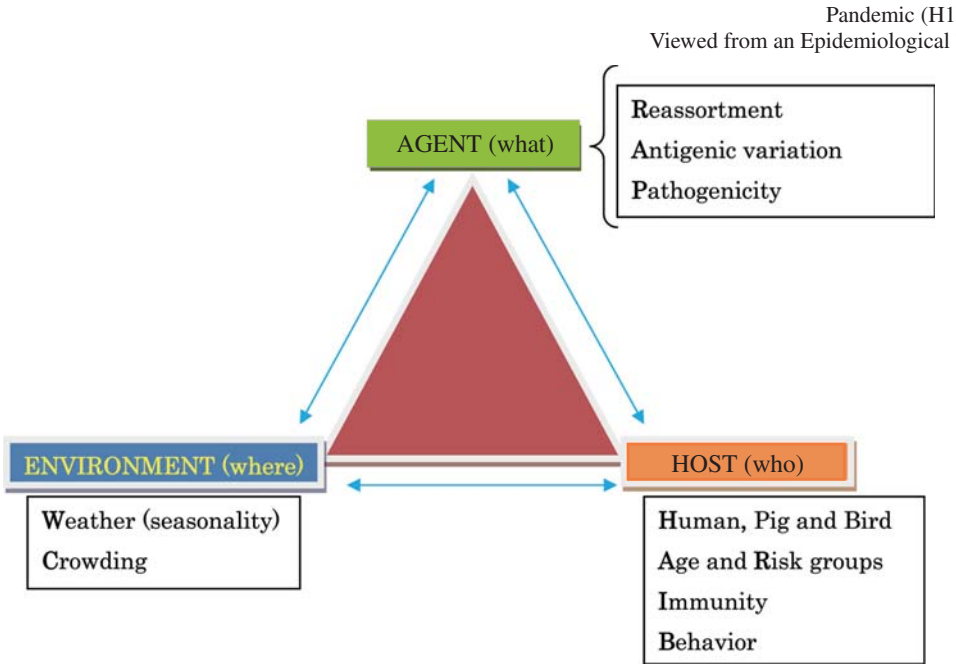

Fig. 1. Epidemiological triangle model showing interaction between pandemic (H1N1) 2009 virus, its hosts, and the environment – factors possibly associated with pandemic influenza disease, including agent reassortment and antigenic variation; host features such as age, high-risk groups, immunity, and behavior; and environmental features facilitating transmission such as weather and crowding.

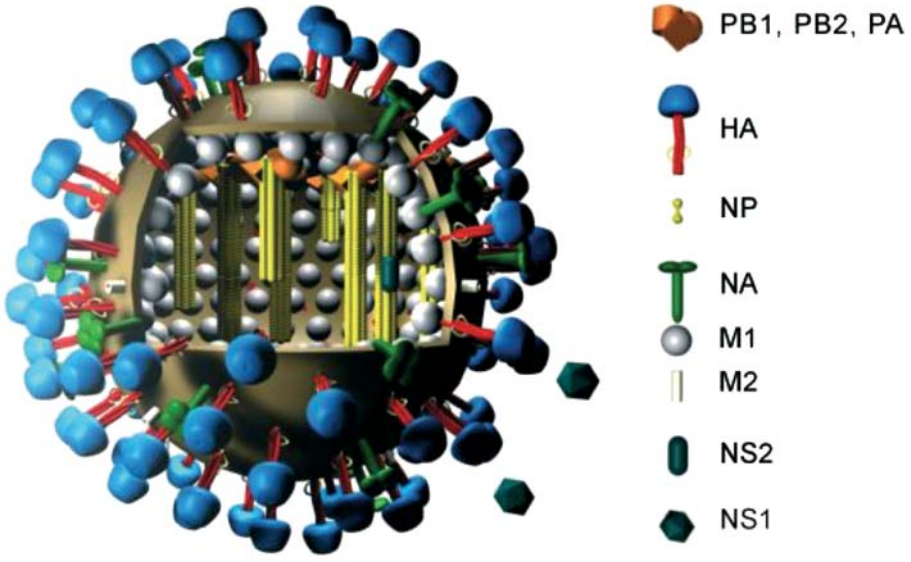

Fig. 2. Influenza A virus showing major structures: The eight segments of single-strand RNA are PB2, PB1, PA, HA, NP, NA, M and NS: where, PB1, polymerase basic 1; PB2, polymerase basic 2; PA, polymerase acidic; HA, hemagglutinin; NP, nucleoprotein; NA, neuraminidase; M, matrix gene; and NS, nonstructural gene. Image copyright by Dr. Markus Eickmann, Institute for Virology, Marburg, Germany. Used with permission, http://www.biografix.de

2.2. Influenza A Classification

Influenza A viruses are subclassified based on the antigenicity of their hemagglutinins (HA) and neuraminidase (NA) molecules [11, 12, 16]. There are currently 16 HA subtypes (H1-H16) and 9 NA subtypes (N1-N9) [12].

2.3. Antigenic Variability of Influenza A Viruses

Influenza viruses have shown marked variations in antigenic properties over the years, most occurring in HA and NA proteins. Mechanisms for producing diversity include antigenic drift – minor antigenic changes in HA and NA proteins occurring annually but not leading to changes in viral subtype and antigenic shift – involving a much more dramatic change in antigenic HA and/or NA protein properties leading to a change in subtype, e.g., from H1N1 to H3N2 [10–12, 15].

3. Pandemic (H1N1) 2009 Virus

3.1. Emergence

Pandemic (H1N1) 2009 virus is a new influenza subtype affecting human beings, that contains gene segments in never-seen-before combinations. Data on genetic composition indicate that pandemic (H1N1) 2009 virus has the following genome composition: a PB2 gene of triple reassortant swine (originally from North American avian), a PB1gene of triple reassortant swine (originally from human H3N2), a PA gene of triple reassortant swine (originally from North American Avian), an HA (H1) gene of triple reassortant swine (originally from classical swine), an NP gene of triple reassortant swine (originally from classical swine), an NA (N1) gene of Eurasian avian-like swine, an M gene of Eurasian avian-like swine and an NS gene of triple reassortant swine (originally from classical swine) [10, 15, 20, 21, 38, 41].

3.1.1. Changes in HA and NA Antigens

Pandemic (H1N1) 2009 virus contains few amino acid substitutions at putative antigenic sites compared to seasonal H1 HA antigen [38]. Amino acid sequence alignment of the HA antigen of Pandemic (H1N1) 2009 virus differs by 27.2% from that of the seasonal (H1N1) virus of 2008 and from the HA antigen of the current influenza vaccine [21]. However, none of these amino acid changes appear to have an antigenic effect, and in fact the antigenic variation among the pandemic (H1N1) 2009 viruses circulating in human beings is currently less than that seen during a typical influenza season in human beings [38]. Also, the HA antigen of Pandemic (H1N1) 2009 is 18% different from that of 1918 pandemic influenza virus and also 12% different from that of 1976 (H1N1) swine flu [21].

The pandemic (H1N1) 2009 NA antigen is significantly novel, differing by 18.2% from seasonal (H1N1) virus of 2008 [21]. Antigenic analysis shows, however, that no genetic markers have been found in NA known to decrease neuraminidase inhibitor sensitivity [38].

Ferret post infection anti-sera raised against the HA antigen of currently circulating seasonal human A (H1N1) viruses did not react to that of pandemic (H1N1) 2009 strains [38]. While some say that means that no cross-protection is likely from the (H1N1) present in the seasonal influenza vaccine of 2008 [21], others argue that this lack of cross-reactivity does not directly equate to a lack of cross-protection in human beings between seasonal A (H1N1) viruses and pandemic (H1N1) 2009 viruses because human beings have a more complex immune profile than the single infection used in ferrets to characterize antigenic aspects [38]. Whether any cross-protection exists, however, remains to be determined.

3.1.2. Pathogenicity Markers

The highly pathogenic avian influenza H5N1 virus which had a case fatality rate (CFR) of 61% [22], is known to have HA sequences recognized by ubiquitous host proteases [8]. This substantial HA cleavage by host protease increases tissue tropism and hence, pathogenicity. The HA of highly pathogenic influenza viruses such as H5N1 strains are thought to have acquired these cleavage sequences by point mutations, but such cleavage sequences have not been observed in the pandemic (H1N1) 2009 virus. We must monitor changes in HA sequences of the pandemic (H1N1) 2009 virus to predict changes in its virulence potential.

Studies have shown that the PB2 protein of all human influenza A viruses have lysine (K) at position 627, and most avian viruses have glutamic acid (E) at this position [9]. E to K mutation in avian viruses is associated with increased virulence in mammalian experimental systems [37]. Pandemic (H1N1) 2009 virus PB2 is avian-originated and has E at position 627. Again, it is important to monitor amino acid sequences at position 627 of the Pandemic (H1N1) 2009 virus to predict changes in virulence.

An important protein translated from another reading frame of the PB1 gene segment due to an alternative translation initiation is the PB1-F2 protein, which is reported to have increased the pathogenicity of the 1918 virus and the highly pathogenic H5N1 [13, 14, 37]. The PB1-F2 gene of pandemic (H1N1) 2009 is incomplete, however, due to the presence of a stop codon at position 12 [38, 41]. A point mutation at position 12 resulting in full-length PB1-F2 protein production may increase pandemic (H1N1) 2009 virus pathogenicity. Changes in the PB1-F2 gene should thus be another focus of genetic surveillance.

4. Hosts

Influenza viruses have been collected for over 90 years from many hosts, including human beings, birds (chickens and ducks), pigs, horses, etc and all known influenza A viruses are perpetuated in aquatic birds [10, 16, 19].

For an influenza virus to enter the host cell there must be a functional HA molecule and expression of sialic acid on host cells that are HA receptors. Human and avian species differ in sialyl-transferase expression in mucosal and respiratory tissues. α2,6-linked sialic acid appears abundantly in the human respiratory tract, while α2,3-linked sialic acids tend to be found in avian cells [20]. Swine tissues express both forms of sialic acid enabling cells to be co-infected with avian and human viruses thus increasing the possibilities of genetic reassortment in swine. The pandemic (H1N1) 2009 virus has been reported to infect pigs in Canada and this may lead to reassortment events in swine that may give this novel virus more virulence and enable it to further adapt itself to infecting human beings.

4.1. Pandemic (H1N1) 2009 Virus Pathogenesis in Human Beings

4.1.1. Clinical Pandemic (H1N1) 2009 Virus Symptoms Resemble Seasonal Flu

Studies in the US [26, 27], UK [28] and Japan [29] have reported the following clinical symptoms associ-

ated with the Pandemic (H1N1) 2009 virus infection; fever, headache, tiredness, cough, sore throat, runny or stuffy nose, body aches, diarrhea, and vomiting. Additional symptoms include coryza (nasal mucus membrane inflammation), chills, anorexia, myalgia (muscle pain), sneezing and arthralgia (joint pain). These symptoms are commonly associated with seasonal influenza. Earlier reports of vomiting and diarrhea not commonly associated with seasonal influenza caused an alarm, but such reports are currently gradually decreasing.

4.1.2. High Pandemic (H1N1) 2009 Virus Mortality and Morbidity Among the Young

Past influenza pandemics- A/(H1N1) 1918-1919, A/H2N2 1957-1963, and A/H3N2 1968-1970, were associated with a shift in highest morbidity and mortality to a younger population with peaks at 0-15 years, except for the 1918-1919 outbreak which peaked at 20-40 years [25, 30]. Similar to past influenza pandemics, the pandemic (H1N1) 2009 virus has so far caused more morbidity among the young peaking at 20-30 years. In Japan, 64% of the 401 confirmed pandemic (H1N1) 2009 influenza cases were aged 15-19 years [29]. In a study comparing the age distribution of patients reported to the Mexican Ministry of Health to have severe pneumonia concurrent with pandemic (H1N1) 2009 infection, 71% of patients were 5-59 years old, and the same age group had the highest mortality- 87% [30]. In the UK, a study of 252 confirmed cases showed more morbidity between 0 and 19 years of age [28]. Persons born before 1957 are thought to have been exposed in childhood to influenza A (H1N1) viruses similar to the pandemic (H1N1) 2009 virus and so perhaps better protected against pandemic (H1N1) 2009 virus currently circulating [30]. Observations that most victims are less than 18 years old suggest that children and young adults may be more susceptible than older persons, but differences in social networks that delay transmission to older persons may also be responsible. More time is thus required to clarify the actual age distribution pattern.

4.1.3. Severe Disease in Under-Fives and Those with Underlying Medical Conditions

Information on clinical complications of pandemic (H1N1) 2009 infection is insufficient but studies indicate that most patients confirmed infected with pandemic (H1N1) 2009 do not require hospitalization [28, 29]. An early study in the US showed that among hospitalized patients with severe symptoms, 18% were children under the age of 5, 4% were pregnant women, and 41% had chronic medical conditions such as autoimmune disorder, congenital heart disease and asthma [27]. We argue that risk factors for complications due to pandemic (H1N1) 2009 virus infection are similar to those of seasonal influenza, but this pandemic could be more severe in countries with a high prevalence of underlying conditions such as malnutrition and debilitating diseases.

4.1.4. Pandemic (H1N1) 2009 Virus Case-Fatality Rate (CFR) and Reproductive Number R_0

Fraser et al analyzed the pandemic (H1N1) 2009 outbreak in Mexico using early data on international spread and viral genetic diversity to assess transmission and severity. Their estimates suggested that between 6,000 and 32,000 individuals were infected in Mexico by late April, with the estimated case fatality rate (CFR) 0.4% (range, 0.3-1.5%). In the same analysis, the CFR for a community outbreak in La Gloria, Veracruz had a CFR of 0.6% [24]. While uncertainty is substantial, we can argue for now that pandemic (H1N1) 2009 clinical severity appears less than that seen in 1918 (which had a CRF as high as 2.5 %) [15].

5. The Environment

5.1. Suitable Environment

Influenza viruses are highly resilient in the environment [31]. Low temperature and low humidity favor aerosol transmission, explaining the seasonal nature of influenza in temperate climates [20]. In tropical climates influenza infections are associated with increased rainfall [39], perhaps because the increased need to stay indoors increases human-to-human contact leading to a high incidence of infections. Nonetheless, the best environment for a novel virus is a population without pre-existing immunity to it, enabling it to spread pandemically as is the case with the pandemic (H1N1) virus.

5.2. Seasonality and Multiple Waves

In temperate countries, influenza epidemics are more common in the winter. Evidence suggests that influenza infection in the tropics is also seasonal and associated with rainfall [39]. The introduction of a new strain of a virulent virus in a susceptible population spreads widely regardless of the season [40], as is being seen now in the spread of the pandemic (H1N1) 2009 virus.

Another signal feature of influenza pandemics is that they demonstrated multiple waves; each wave had increased mortality for 2 to 5 years [25]. The lethal wave in the autumn of 1918 was preceded by a first wave in the summer that led to substantial morbidity but relatively low mortality in both the USA and Europe. The 1957 pandemic had three winter waves during the first five years. The 1968 pandemic had a first mild wave in Britain, followed by a severe second wave the following winter [25]. The pandemic (H1N1) 2009 virus is now spreading in the southern hemisphere as it enters the cool winter season and may return to the northern hemisphere from September as a potentially more severe infection. While it cannot be predicted how Pandemic (H1N1) 2009 virus infection will behave in subsequent waves. We should learn from history by strengthening and implementing preparedness plans.

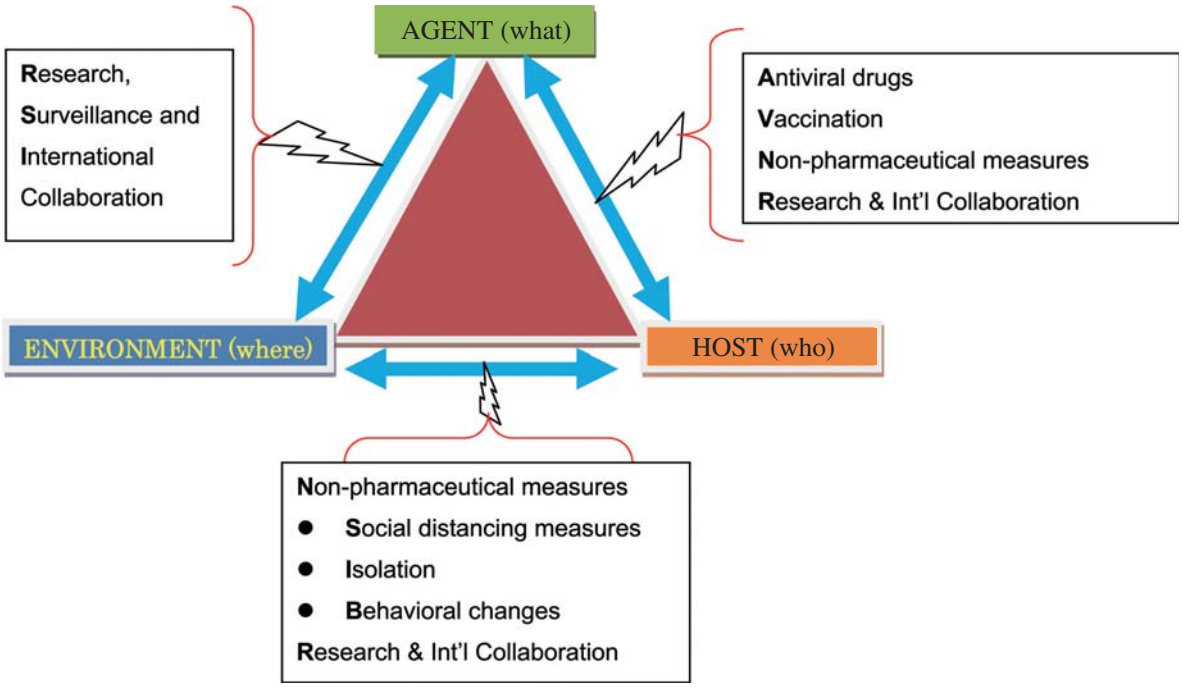

Fig. 3. Measures for controlling pandemic (H1N1) 2009 influenza using the epidemiological triangle model. The disease depends on equilibrium in the epidemiological triangle and hence measures for controlling and preventing influenza target disrupting this balance. Success in the fight against pandemic influenza calls for a multifaceted strategy better visualized using the epidemiological triangle model. Preventing and controlling the pandemic (H1N1) 2009 virus in the host (human) requires judicial antiviral use, vaccination, and non-pharmaceutical measures that keep infection from spreading. Preventing environmental transmission requires more non-pharmaceutical measures, while research, continuous surveillance and international collaboration are important in all aspects of the epidemiological triangle. These measures must be applied simultaneously and with nearly equal weight.

5.3. Transmission and Spread

The main route of transmission in human beings is via inhalation of infected respiratory droplets after coughing and sneezing. Formites such as infected surfaces and materials also transmit the virus between human beings [31]. Studies in the UK [28] and Japan [29] showed that most infections were more pronounced in close contact between human beings, such as schools and workplaces.

6. Pandemic (H1N1) 2009 Virus Control and Prevention

Strategies – long-term action plans – and tactics – immediate actions to achieve strategies – can be used to disrupt the balance between agent, host and environment to prevent and control pandemic (H1N1) 2009 virus infection, as shown in **Fig. 3**.

6.1. Nonpharmaceutical Measures

Preventing human-to-human transmission is successful when nonpharmaceutical approaches are maximized. Measures include behavioral changes, social distancing and isolation.

6.1.1. Personal Hygiene and Behavioral Change [32-34]

Healthy persons must continue practicing behavior that ensures that they remain healthy, including wearing masks, observing cough etiquette, and covering the mouth and nose with a tissue while sneezing, then immediately discarding the tissue. This should be followed by washing the hands with soap and/or running water. Individuals should avoid touching the nose, mouth, and eyes because droplets from these spread easily and cause infection. Contact with sick persons should be avoided because infection spreads by droplets from sneezing or coughing. Those with respiratory infections are advised to stay home and restrict social contacts. Care should be sought by those having symptoms typical of influenza, such as fever, cough, sore throat, rhinorrhea (runny nose) or nasal obstruction, fatigue, joint or muscle pain, headache and nausea [29].

All those with underlying diseases and children under 5 years old should seek immediate medical attention when they have these symptoms. Other behavior for those with upper respiratory infection or any of the above symptoms is to avoid healthy persons because the virus can be transmitted while symptoms are subsiding and possibly up to 7 days following the onset of illness.

6.1.2. Isolation and Social Distancing

6.1.2.1. Home Quarantine

Those caring for persons suspected of having pandemic (H1N1) 2009 virus infection or diagnosed with such infection and being cared for at home should promptly isolate themselves and patients until patients are symptom-free. Patients should be isolated in a separate room with the door closed and not be allowed to leave home. If they must go out, they should practice preventive behavioral strategies stated above. This applies even when leaving the sickroom, using common household areas, or going to the bathroom. House should be adequately ventilated by keeping windows open for long periods [34].

6.1.2.2. School Closure and Cancellation of Mass Gathering

During rapid spread of infection, as at the beginning of a pandemic, governmental authorities should limit spread of infection by closing schools and cancelling mass gathering. In response to the pandemic (H1N1) 2009 outbreak, for example, hundreds of schools in the US and elsewhere were closed [20], including nearly 4200 schools in Japan [29]. For similar reasons, officials in Mexico, against all economic odds, closed schools and commercial establishments to decrease infection, as shown by Shimada *et al* that, after school closure by local governments in Kobe City and Osaka prefecture for one to two weeks from May 16, 2009, the number of new confirmed cases decreased significantly [29].

6.2. Pharmaceutical Approaches

6.2.1. Vaccination

Immunization provides the best prevention against influenza virus but no vaccine currently protects human beings against the pandemic (H1N1) 2009 influenza virus. While vaccines are being produced, this will take 3-6 months. Vaccine production itself faces issues, the first of which is outdated production methods developed in the 1930s to 1950s that use massive amounts of embryonated chicken eggs, with each flu vaccine dose requiring 1.2 live eggs, or about 600 million embryonated eggs to produce 500 million doses of vaccine for 6.77 billion people (current capacity) [21]. Clearly in pandemics, eggs may be in short supply and more efficient programs are needed to produce effective and safe influenza vaccines to ensure that this and future pandemic influenza threats can be met. The use of cell lines is important, e.g., the purity and immunogenicity of influenza vaccines produced using Madin-Darby Canine Kidney (MDCK) or African Green Monkey kidney cells match those of vaccines produced in embryonated eggs [15] and such production should be promoted. Cell-culture-based influenza vaccines have been approved for use in human beings in Europe [15].

Since vaccine development for pandemic (H1N1) 2009 virus takes time, nonpharmaceutical prevention with timely and judicial use of antiviral therapy are the only sure way to prevent and control pandemic (H1N1) 2009 virus infection.

6.2.2. Antiviral Drugs and Resistance

Two classes of antiviral medication are available for treating seasonal human influenza – NA inhibitors (oseltamivir and zanamivir) and adamantanes (rimantadine and amantadine) [10, 15, 30].

6.2.2.1. NA Inhibitors

NA plays an essential role in influenza virus replication and has highly conserved active sites that are the main target for drugs against influenza viruses [5]. NA inhibitors include oseltamivir (tamiflu) and zanamivir (relenza). While oseltamivir can be taken orally, zanamivir must be inhaled. Oseltamivir-resistance viruses with an H274Y mutation in the NA gene and that show a considerable (1000-fold) experimental increase in 50% inhibitory concentration (IC50%) of oseltamivir are common with seasonal influenza viruses [6, 42]. A study of 13 specimens of pandemic (H1N1) 2009 viruses tested earlier in the outbreak showed that they did not have mutation at residue 274 making pandemic (H1N1) viruses generally sensitive to NA inhibitors [5, 6]. On July 8, 2009, the WHO released a note stating that pandemic (H1N1) 2009 viruses resistant to oseltamivir (tamiflu) had been identified in Denmark, Japan and the Special Administrative Region of Hong Kong, China. It added that while those viruses were resistant to oseltamivir, they remained sensitive to zanamivir [36]. So, constant systematic surveillance and information sharing is needed to better understand oseltamivir resistance evolution and spread.

6.2.2.2. M2 Channel Blockers

Adamantanes are a class of antiinfluenza drugs targeting the M2 proton channel protein within the virus membrane. Examples include amantadine and rimantadine [5, 6]. Pandemic (H1N1) virus is resistant to adamantanes because it has the S31N mutation in the M2 protein which confers cross-resistance to the adamantanes [5–7, 34].

6.3. Research, Surveillance and International Collaboration

Influenza research and development must be expanded because priority of influenza research had decreased in the absence of a pandemic coupled with the availability of drugs and what seemed to be adequate vaccine technology. Research will help improve the prediction of which influenza viruses may potentially cause serious outbreaks. Research will also help determine molecular markers that predict virus transmission. Preventative medicine and vaccine development depends on progress in basic research.

International collaboration is important because influenza pandemics have multiple waves making global real-time viral disease surveillance important. Transnational collaboration is crucial for effectively exchanging genomic, clinical, and epidemiological data enabling vaccines and treatment protocols to be developed and to identify optimal population-based prevention and control strategies and tactics.

7. Conclusions

Influenza viruses are an ongoing threat to society due to their significant genetic change capability forming antigens new to human populations. Influenza A viruses have been especially responsible for pandemics killing large numbers of people.

The emergence of the pandemic (H1N1) 2009 virus is yet another reminder of the constant threat influenza viruses pose. We have reviewed pandemic (H1N1) 2009 virus status in terms of the epidemiological triangle model to help visualize the pandemic as an infectious disease and see how to control and prevent it. We have also reviewed the issues we face in these efforts. Lacking a pandemic (H1N1) 2009 virus vaccine, we must rely on prudent and timely use of antiviral therapy and on non-pharmaceutical prevention and control requiring behavioral change. Developments in research, surveillance and global collaboration are important in controlling the current pandemic and those likely to arise in future.

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