

Finding a new drug and vaccine for emerging swine flu: What is the concept?

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Abstract: Influenza is a well known infection of the respiratory system. The main clinical manifestations of influenza include fever, sore throat, headache, cough, coryza, and malaise. Apart from the well known classical influenza, there are also groups of influenza virus infections that are called “atypical infection”. These infections are usually due to a novel influenza virus infection. In early 2009, an emerging novel influenza originating from Mexico called swine flu was reported. The World Health Organization noted a level VI precaution, the highest level precaution possible, for this newest influenza virus infection. As of June 2009, it is not known if this disease will be successfully controlled. Finding new drugs and vaccine for the emerging swine flu is still required to cope with this emerging worldwide problem.

Keywords: swine flu, drug, vaccine, concept

Influenza infection

Etiology

Influenza is a well known infection.^{1,2} It is classified as a respiratory system infection. The main pathogenic cause of influenza is virus. The influenza virus is a widely studied virus in medicine.^{1,2} As a respiratory tract infection, the influenza virus is mainly transmitted via air as an airborne infectious disease.^{1,2} The pathogenic influenza virus can enter into the human body due to the inhalation of infectious air particles.^{3,4} The contaminated airborne particles can be generated by sneezing and coughing by infected patients.^{3,4} Specific body secretions that are highly contaminated with influenza virus include running nose fluids and saliva. It should also be noted that contaminated secretions can be found in spillage and in any used objects for up to two hours.^{3,4} If someone contacts the contaminated object, there is a possibility of infection and transmission of pathogen can be expected. Recently, Grayson and colleagues said that soap and water hand-washing or alcohol-based hand rub was highly effective in reducing influenza virus on human hands.¹⁵ Hand washing is an important practice to control the spread of influenza.⁵⁻⁸

Clinical manifestations

In general, influenza virus can be classified into three main groups, group A, group B, and group C.^{9,10} All groups can cause disease in human beings. Only group A can also cause infection in animals. Generally, patients usually develop signs and symptoms within two days (range 1–4 days) after contact with the pathogen.^{11,12} However, the isolation of influenza virus may not be seen, hence, transmission of disease can be

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possible before signs and symptoms are manifested.^{11,12} The peak of fever can be usually seen in day 3.^{11,12} The main clinical manifestations of influenza include fever, sore throat, headache, cough, coryza, and malaise. Due to the nature of the virus, the course of illness usually completes within one week or on day 9 after the first contact with the pathogen. Influenza complications usually start after this period.¹³ In general, the disease burden due to influenza is usually low.^{14,15} Hospitalization is usually required for two specific age groups: the infant group aged less than six months and the elderly group aged more than 65 years. Factors relating to the severity of influenza include age and underlying personal illness. The high-risk population for severe clinical manifestation includes the elder group aged more than 65 years,¹⁶ the infant group aged less than two years,¹⁷ patients with human immunodeficiency virus (HIV) infection,¹⁸ patients with chronic obstructive pulmonary disease and asthma,¹⁹ patients with congenital heart disease,²⁰ patients on immunosuppressive drugs, and patients with prolonged usage of aspirin.

In the general low-risk adult population, the signs and symptoms of influenza can be self-limited. There is no need for medication. Serious complications^{21,22} can be seen, such as otitis media, pneumonitis,²³ myocarditis,²⁴ encephalopathy,^{25,26} and Reye's syndrome.²⁷ As previously noted, the prevalence of complication is high in the at-risk groups.^{21,22} For example, up to 10% of infantile cases can develop complications and can end up with influenza encephalopathy. The rate of fatality in influenza encephalopathy is as high as one third of affected cases.^{25,26}

Diagnosis, treatment, and prevention

Clinical diagnosis is generally used for presumptive diagnosis. However, the main problem is due to the similarity between influenza and other respiratory tract infections. Laboratory investigation is required to confirm diagnosis. The basic immunological diagnosis is useful.^{28–38} However, a molecular-based diagnostic tool is usually required in atypical cases.^{39–45} This is because although the immunology-based technique is cheaper and faster in diagnosis, it lacks specificity. New molecular-based diagnostic tools can provide the most specific result since the diagnosis is based on the exact sequence of the viral particle. However, molecular-based diagnosis is expensive and time-consuming to perform. Therefore it might be unavailable and unaffordable for poor settings in developing countries.

Since the influenza viral infection can be self-limiting in otherwise healthy adults, there is no need for specific medication or treatment.⁴⁶ However, in at-risk cases,

an antiviral drug treatment is recommended.^{46–50} The widely used antiviral drugs for influenza are amantadine,⁵¹ rimantadine,⁵² oseltamivir,⁵³ and zanamivir.^{54–56} Oseltamivir and zanamivir are newer drugs with a lower drug-resistant rate. These two drugs are also indicated for atypical cases.

At present, a specific influenza vaccine is available for prevention and is recommended for the at-risk population, especially the elderly.^{57,58} Jefferson and colleagues noted in a Cochrane review that influenza vaccines were effective in reducing cases of influenza, but were less effective in reducing cases of influenza-like illness.⁵⁹ Jefferson and colleagues also noted that influenza vaccines had a modest impact on lost working days but there was no sufficient evidence on complications.⁵⁹ In the scenario of an influenza pandemic, vaccination is the main hope for disease control.⁶⁰

Novel influenza virus infection: What is it?

Apart from the already mentioned classical influenza virus infection, there are also a group of influenza virus infections that are called “atypical infection”. These infections are usually due to a novel influenza virus infection.^{61,62} Those new pathogenic viruses, which usually result from genetic mutations, correspond to atypical infection. The new infection is usually recognized as a new emerging infectious disease.⁶³

Zoonosis is usually mentioned for any novel influenza virus infection. “Why is zoonosis usually mentioned?” is an interesting question. As previously noted, influenza group A can infect both human beings and animals. When animals live near human beings, the exchange of viruses that each side carries can be expected and the final result can be a new, emerging zoonosis. This viral transmission scenario is a big problem for medicine since new emerging infections are new diseases that human beings have never experienced before.

The lack of immunity can be seen since present data indicate that only some older individuals have immunity against the current novel influenza A (H1N1).⁶⁴ At present, most physicians are already aware of this ongoing pandemic.

Examples of emerging influenza are well known. The case of avian flu^{65–71} which emerged in the few recent years is the best example (Table 1). Avian flu is a novel influenza virus infection (owing to H5N1 influenza virus infection). This bird-borne disease is still a problem worldwide.^{65–72} No specific treatment has been developed yet. Luckily, only sporadic cases occurred around the world without pandemic. However, another emerging novel influenza originated from Mexico in early 2009.^{73–85} This new infection is called swine flu (Table 1). Swine flu is caused by the novel influenza virus,

Table 1 Details of important novel influenza

Aspects	Avian flu ⁶⁵⁻⁷²	Swine flu ⁷³⁻⁸⁵
1. Pathogenic virus	H5N1 influenza virus.	Atypical H1N1 influenza virus.
2. Related animal	Avian.	Swine.
3. Disease burden	High fatality.	No high fatality.
4. Pandemic	No.	Yes (in 2009).
5. Human to human transmission	No evidence.	Strong evidence.
6. Vertical transmission	No evidence.	No evidence.
7. Clinical manifestation	Similar to classical influenza with some interesting atypical manifestations (such as diarrhea).	Similar to classical influenza with some interesting atypical manifestations (such as nonfebrile illness).
8. Viral receptor in human beings	Can be seen in lower respiratory tract.	Can be seen in upper respiratory tract.
9. Vaccine	Not available.	Has been manufactured and approved by the US FDA. ⁸⁶
10. Treatment by antiviral drug	Needed, usually with oseltamivir, but there are few good outcomes.	Suggested, usually with oseltamivir, good outcomes.

Abbreviation: FDA, US Food and Drug Administration.

H1N1 influenza virus. The novel H1N1 influenza virus that causes swine flu is the result from genetic reassortment of gene segments from not only human H1N1 virus, but North American swine flu, Asian swine flu, and avian flu.⁸⁷ This new recombinant virus causes the current pandemic and leads to generalized infection worldwide.⁸⁵ In early June 2009, the

swine flu, which is now called influenza 2009 is pandemic in many countries worldwide (more than 70 countries and more than 25,000 infected cases).⁸⁵ The World Health Organization (WHO) noted a level VI precaution, the highest level precaution possible, for this newest influenza virus infection (Table 2). As of June 2009, it is not known if this

Table 2 Summary of some problematic points of swine flu infection⁷³⁻⁸⁵

Points	Descriptions
1. Mode of transmission	Human-to-human transmission is confirmed. This raises serious concerns and leads to a high level of precaution set by WHO.
2. Natural history	A similar natural history to classical influenza can be seen. However, there is a notification on nonfebrile cases, which can be a big problem for detection and surveillance processes.
3. Epidemiology	Presently swine flu is worldwide. Thousands of infected cases can be seen. Of interest, in the early stage (April–May 2009) the disease was confined in Mexico and nearby countries. Some sporadic cases were observed from distant countries. The main infected group was adults with a history of traveling to/from the infected areas. This reflects the importance of traveler medicine. However, after the first period, human-to-human transmission becomes an important emerging issue. New infectious cases in distant countries with no history of traveling to the problematic infected areas could be detected (such as in Japan and Thailand).
4. Diagnosis	Diagnosis by clinical manifestation shows difficulties in separating swine flu from classical influenza and other common respiratory tract infections. This is a serious problem for clinical diagnosis. The basic immunological diagnostic tool can confirm only H1N1 infection, but not typical or atypical. Molecular-based detection is required. A real-time PCR for diagnosis is available. However, the problems of over-register or under-diagnosis in setting due to lack of a gold standard can be expected.
5. Treatment	Pharmacological treatment with oseltamivir is the present treatment, although it can not yet be confirmed if it is the best measure. With the present sign of emerging pandemic, there are several problems with the use of oseltamivir. These problems include the development of drug-resistant virus and availability as well as affordability for sufficient amounts of the drug in developing countries. Overlapping treatment of the classical strain to the new atypical strain can still be expected.
6. Vaccine	Isolation, although possible, is not the best way to prevent contagion. Vaccination might be a more proper method. However, the present vaccine for classical influenza is not applicable to the new mutation of atypical swine flu. The development of a new vaccine specific for swine flu is needed and is the present focus of vaccinologists worldwide. As of early June 2009, there were some positive signals from some pharmaceutical companies on forthcoming specific vaccines for swine flu.
7. Complication	The complications of swine flu are similar to those of classical influenza. This is the main problem that leads to some cases resulting in death, although not highly prevalent. Pneumonitis and respiratory failure are the most problematic and can cause poor outcome in complicated cases.

Abbreviations: PCR, polymerase chain reaction; WHO, World Health Organization.

disease will be successfully controlled. Finding new drugs and vaccine for emerging swine flu is still required to cope with this emerging problem worldwide. This review focuses on the search for new drugs and a vaccine for swine flu. Data from searching all available publications from PubMed, Scopus, and ISI databases were included, and non-English language papers were excluded.

Concepts on finding new drug for swine flu

As previously noted, swine flu is an emerging disease. Treatments for swine flu are suggested and the general practice guideline for dealing with influenza is applied (Table 3). A routine antiviral for influenza is applied. Since amantadine and rimantadine are confirmed for drug-resistant strains of influenza,^{88–90} the recommended drugs are oseltamivir and zanamivir. In current general practice (Table 4), oseltamivir is routinely used in cases with swine flu with good efficacy.^{88–90} Focusing on the pharmacological reaction, oseltamivir blocks the M2 protein and blocks viral penetration and uncoating.^{91,92} According to an US report, no resistance to oseltamivir in the emerging swine flu was observed.^{88–90}

However, new drugs for swine flu need to be sought. This need is due to several reasons. First, although oseltamivir is still effective, drug resistance is expected to develop in the near future due to a high volume of use in the pandemic scenario. Second, we can expect a genetic instability in the swine flu virus. In addition to new drugs, there is also a need for the local production of generic drugs of oseltamivir in developing countries. This issue needs to be carefully considered as drug patent concerns may be an obstacle for the local production of oseltamivir in many developing countries.

As previously mentioned, this paper will focus in the pharmacological dynamic issue of drug development and this paper does not discuss the current treatment process of swine flu. In order to find new drugs for swine flu, the recommended steps are listed below:

1. The viral sequence of the novel influenza virus must be mapped. Luckily, plenty of data are already loaded into public databases such as PubMed. At present, a diagnostic tool with real-time polymerase chain reaction (PCR) for influenza A is available and recommended as a diagnostic test by the US Food and Drug Administration (FDA). This provided several data on the genomics of the new emerging virus and helps further clarifies its viral structure. The data on sequence and structure of swine flu are useful not only for drug development, but also for diagnostic tool development.
2. The next focus should be on proven drugs. The reaction between the presently used drug, oseltamivir, and swine flu virus has to be clarified. This reaction has to be shown at the molecular level. Study by crystallization technique is suggested. Simulation by a molecular-docking technique can be helpful at this point. There are some present researches on this stage.^{93,94} According to the homology modeling of the neuraminidase, it can be seen that novel mutations are not likely to interfere with the active site hence the currently used neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) will still be effective against the new virus strain.⁹⁴ The same mechanism of pharmacological reaction, blocking M2, can be seen in either classical or novel viruses. However, the drugs do not have the same effect in both viruses. This might be explained by the difference in required energy for drug–virus binding reaction.⁹² More required energy can be seen in case of the novel H1N1 influenza virus, which, based on the new viral genomic sequence, is larger than that of the classical virus.⁹²
3. Possible genetic variation at the reaction site should also be predicted. This is useful for further calculation on optimum pharmacological binding energy between antiviral drug and virus. The mutated resistant portion should be the specific favorable site for our pharmacological target. Although a big genetic shift of the new virus has not yet been reported, it can be expected. Modification of previously used drugs into new drugs can be done based on the described data.
4. The derived drug needs to be tested *in vitro* and *in vivo* with a special focus on possible adverse effects including toxicity, mutagenesis, teratogenesis, and carcinogenesis. All drugs must pass and follow WHO recommendations with the four complete drug trial stages before becoming commercially available. This is needed to confirm that the drug is actually effective and pose no unwanted adverse effects.

Table 3 Presently available antiviral drugs for influenza treatment

Drugs	Specific site of reaction	Route of administration	Resistance to swine flu
Amantadine	M2 protein	Oral	Yes
Rimantadine	M2 protein	Oral	Yes
Oseltamivir	Neuraminidase	Oral	No
Zanamivir	Neuraminidase	Inhaled	No
Peramivir	Neuraminidase	Oral, intravenous	No

Table 4 Recommended dosage of oseltamivir and zanamivir in treatment and prevention for swine flu (adapted from World Health Organization recommendations, see <http://www.cdc.gov/swineflu/recommendation.htm>)

Drugs	Treatment	Prevention
Oseltamivir*	2 mg/kg bid × 5 days	2 mg/kg bid od × 10 days
Zanamivir**	10 mg bid × 5 days***	10 mg od × 10 days***
	10 mg bid × 28 days****	10 mg od × 28 days****

Notes: *Either in cases with close contact to the patients or during the pandemic period; maximum dosage not more than 75 mg; **For patients aged more than 7 years; ***In cases with close contact to the patients; ****During the pandemic period.

Concepts on finding new vaccine for swine flu

Although there are several measures for prevention for swine flu including basic sanitation practice (hand-washing and mask use), isolation, chemoprophylaxis, and vaccination, vaccination is expected to be the most effective tool. Although there is evidence on the finding of immunity to the new virus in some elderly adults,⁶³ this might be a cross-protective immunity since there are some antigenic similarities to currently or previously circulating strains of influenza.⁹⁴ There is currently no effective vaccine for swine flu. The classical influenza vaccine is not applicable. Finding a new vaccine for swine flu is the current hot topic in medicine.⁹⁵ The current question is how to produce an effective pandemic influenza vaccine.^{96,97} Focusing on classical influenza, the problem of the genetic shift highlights the problem of the efficacy of the in-use influenza vaccine. In the case of the novel influenza swine flu, the problem remains. For production of pandemic influenza vaccine, the similar process to that of seasonal (regular) influenza vaccine can be followed. Nevertheless, adding to the basic two major focuses, safety and efficacy, for seasonal influenza vaccine, the other two major focuses, immunogenicity and timely availability, are also needed for pandemic influenza vaccine.^{94,95} However, the original seed virus must be the new virus. This raises the problem of production because it is hard to make the new virus available in huge amounts. The problem might be solved by present biotechnology, but the limitation of technology in developing countries also prevents success in local production of new vaccine in those settings. There are also post-production concerns: “How to test the new vaccine in the shortest period?” “How to register the new vaccine in each country?” “How to administer the vaccine to the at-risk population in each country?”

To find a new vaccine for swine flu, the recommended steps are listed below:

1. It will be necessary to completely map the genome of the novel influenza virus. This is the main requirement because any new vaccine has to be based on the genomic information of the new virus. Luckily, this data is presently available. The genomics data of the novel influenza virus is freely available on public databases such as PubMed.⁸⁷ According to the recent study by Maurer-Stroh and colleagues, the antigenic regions of the neuraminidase relevant for vaccine development, serological typing, and passive antibody treatment was totally different from those of classical influenza.⁹⁴ This is the main reason for asking why the vaccine for classical influenza cannot be applied for the novel strain and this is also the reason for the need for finding a new vaccine specific to the novel virus.
2. The immunological aspect of the new emerging virus must be known by finding the immunogenic part of the new virus. The use of immunomics technology might help shorten this period. The finding of the epitope is the basic primary step to find a new vaccine.
3. The application of new recombinant biotechnology to produce sufficient amount of new original seed virus for production of pandemic influenza vaccine must be completed.^{92,93}
4. Post-production testing to assess both safety and efficacy of the derived vaccine is required. On one hand, the new vaccine has to be well verified before real world use. On the other hand, this process has to be as fast as possible to cope with the fast emerging pandemic.
5. Post-marketing surveillance to follow up the effectiveness and adverse effect of the new vaccine is needed, similar to the routine practice for all new vaccines.

As already noted, a new vaccine has just been manufactured and approved by the US FDA.⁸⁶ However, it should be noted that there is still no report on the clinical and epidemiological aspect of the new vaccine is only in the trial phase. It is not possible to present the data on these aspects in this review. This information will be provided by future studies.

Disclosure

The author reports no conflicts of interest in this work.

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