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REVIEW ARTICLE

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Potential benefits and limitations of various strategies to mitigate the impact of an influenza pandemic

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Abstract The recent avian influenza outbreaks underscore the importance of improving our preparedness for an impending influenza pandemic. Various strategies, including pharmaceutical interventions (such as vaccines and antivirals) and nonpharmaceutical interventions (such as quarantine, isolation, and social distancing) may be implemented to mitigate the impact of a pandemic. It is necessary to understand the potential benefits and limitations of each strategy to determine the most appropriate strategies to be implemented. In this article, each strategy is reviewed to define its potential benefits and limitations during a pandemic. Vaccines are probably the most effective measure to reduce morbidity and mortality. However, vaccines are not likely to be available at an early stage of a pandemic. The supply of vaccines is most likely to be insufficient due to limited worldwide production capacity. Antivirals, particularly neuraminidase inhibitors, are expected to be effective against a pandemic influenza strain and are the only available pharmaceutical intervention until enough vaccines are produced. Shortage of supply and high cost is still a major limiting factor in amassing large stockpiles of neuraminidase inhibitors. The possible emergence of resistant strains should also be considered. Nonpharmaceutical interventions can be effective in preventing the spread of the virus under certain conditions. The effectiveness of nonpharmaceutical interventions depends on how influenza viruses are transmitted. There are still significant gaps in the scientific evidence of the way in which influenza viruses are transmitted. Further studies should be conducted to define the basic transmission patterns of influenza viruses.

Key words Influenza, Pandemic, Mitigating strategy

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Introduction

An influenza pandemic occurs when a new subtype of influenza A emerges in the human population. In the past, there have been pandemics every 30–40 years. In the twentieth century, there were three pandemics, "Spanish flu" in 1918–1919, "Asian flu" in 1957–1958, and "Hong Kong flu" in 1968–1969.[1] Because a large majority of the human population does not have any immunity to such new subtypes, a pandemic virus can spread rapidly and can have an enormous impact on human health. It is estimated that at least 40–50 million people died during the "Spanish Flu" pandemic. A pandemic is also likely to cause serious economic loss and social disruption in every country in the world. It is impossible to predict when the next pandemic could occur. The current avian influenza outbreaks caused by influenza A (H5N1) underscore the importance of improving our preparedness for the next pandemic. The H5N1 virus has been causing outbreaks of disease in poultry over widespread geographic areas. It started in Asia in 2003 and has already spread to other regions, including Europe, the Middle East, and Africa. Human infections have also been confirmed in many countries, and more than 200 human cases of H5N1 influenza have been reported to the World Health Organization (WHO). This virus may cause the next pandemic, which could have a devastating effect on human health and all other aspects of human life.

Various strategies can be considered to mitigate the impact of a pandemic. These strategies include pharmaceutical interventions (such as vaccines and antivirals) and nonpharmaceutical interventions (such as social distancing, quarantine, isolation, and border control). However, each measure has some limitations, and none of them is likely to have an ultimate effect in controlling a pandemic virus once the virus spreads to large areas. During a pandemic, various measures should be implemented simultaneously to reduce morbidity, mortality, and social and economic impact. It is critical to understand the potential benefits and limitations of all available interventions so that appropriate interventions can be implemented.

Pharmaceutical interventions

Vaccines

Inactivated trivalent vaccines are widely used for preventing seasonal influenza. It has been shown that influenza vaccines are effective in preventing influenza and influenza-associated complications, including deaths.[2,3] Vaccines are also believed to be the most effective intervention for a pandemic.[4,5] Recent studies using epidemiological models have supported the effectiveness of vaccines in reducing transmission of the virus during a pandemic, even if the vaccine strain is poorly matched with the pandemic strain.[5,6]

There are several critical issues to be addressed in relation to pandemic influenza vaccines. First, pandemic vaccines are unlikely to be available at the initial stage of a pandemic. It is not known which strain will cause the next pandemic until the pandemic starts. The H5N1 virus is implicated as a major candidate in causing the next pandemic. But there are also other subtypes with such potential, including H7N7, H9N2, and H2N2.[7,8] Influenza viruses change rapidly, and, even within the same subtype, there are often antigenic variations.[9] It is already known that at least two genetically and antigenically distinct H5N1 strains have been circulating in Asia;[10] however, vaccines developed from the isolate from Vietnam in 2004 may not provide adequate protection against another strain which has been circulating in China and Indonesia.[11] Due to these uncertainties, vaccines will not be produced until an actual pandemic starts. It is likely to take at least 4–6 months to produce pandemic vaccines.[12] The virus may spread widely before vaccines become available.

Second, worldwide vaccine production capacity is still limited. Most countries do not have any capacity to produce seasonal influenza vaccines, and it is impossible to establish such capacity in a short time period. It is estimated that a global total of 300 million doses of vaccines are produced annually.[13] In 2000, 85% of influenza vaccines were produced by nine vaccine manufacturers in developed countries.[14] This means that vaccine production capacity in developing countries is very limited. The current level of vaccine production is definitely not enough to meet the massive global need that would be generated during an influenza pandemic.

Third, the required level of antigen in pandemic vaccines is not known. Seasonal influenza vaccines are normally trivalent, containing 15 μg each of H1N1, H3N2, and B antigens. The total content of antigen is therefore 45 μg. Pandemic vaccines are likely to be monovalent, containing only one antigen, which means that up to 45 μg of pandemic virus antigen can be included in each vaccine. More antigens are required to induce enough protective immunity, because the whole human population is immunologically naïve to a pandemic strain. For pandemic vaccines, two doses per person are likely to be required to achieve seroconversion.[15] But a two-dose schedule has significant implications for vaccine supply, because an additional vaccine dose per person is required. The appropriate level of antigen and the number of doses required should be decided with carefully designed clinical trials. A recent clinical trial with H5N1 vaccine confirmed that a two-dose schedule with higher antigen content would be required to achieve enough seroconversion.[16] Adjuvant may be used to overcome the problem of low immunogenicity and to maximize the use of limited antigens. H5 vaccines with adjuvant gave a significantly higher antibody response.[17]

Antivirals

Because of the likely delay in producing a large quantity of pandemic vaccines, antivirals may be the only available pharmaceutical intervention in the early phase of a pandemic. There are two groups of antiinfluenza drugs that are available, M2 inhibitors (amandatine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir).[4,18] M2 inhibitors, particularly amantadine, are widely available and are much cheaper than neuraminidase inhibitors. However, there is a critical limitation in the use of M2 inhibitors, which is drug resistance. It is known that strains resistant to M2 inhibitors are common,[19] and a recent report indicated that there was an increasing rate of resistance to M2 inhibitors among seasonal influenza viruses, possibly associated with increasing usage of the drugs.[20] It has also been reported that some H5N1 strains are resistant to M2 inhibitors.[10] Neuraminidase inhibitors are, therefore, considered to be a better option for an influenza pandemic, and many countries have already started to stockpile neuraminidase inhibitors, mainly oseltamivir, as part of national pandemic preparedness. But the limited supply and high cost of oseltamivir is a significant barrier for the large-scale stockpiling of the drug. Stockpiles of drugs may not be enough to meet increasing demand during a pandemic. Another critical decision to be made is how to use the available antivirals. It has been shown that antivirals are effective for the prophylaxis of influenza.[21] But if these drugs are given as long-term prophylaxis during a pandemic, larger quantities of the drugs will be required. There are also some key issues with antiviral treatment, such as the selection criteria for patients who are to receive treatment, and problems with the distribution of the drugs.

There have been some new findings, which may have implications for the use of oseltamivir during a pandemic. Oseltamivir-resistant strains of H5N1 were isolated from patients in Vietnam who had received oseltamivir treatment.[22,23] There were also some fatalities in spite of the patients having been treated with oseltamivir,[24] which may indicate that the currently recommended dosage of oseltamivir may not be enough to treat patients with H5N1 infection. A study in animals has suggested that an increase in dosage and duration may be needed to treat humans infected with highly pathogenic H5N1.[25]

Nonpharmaceutical interventions

As noted in the above section, pharmaceutical interventions such as the use of vaccines and antivirals are expected to be effective for reducing the impact of a pandemic, but both interventions have some critical limitations. Therefore, nonpharmaceutical interventions, such as isolation and quarantine, social distancing, attention to personal hygiene, hospital infection control, and border control measures have important supplementary roles during a pandemic. But the effectiveness of these measures during a pandemic has not been properly evaluated during past pandemics, and scientific evidence for the effectiveness of these measures is also limited.[26,27]

Isolation and quarantine

Isolation is defined as "the removal of symptomatic individuals from the general population" and quarantine as "the removal of individuals who have had contact with an infected individual but are not displaying symptoms".[28] This is the conventional approach that has been used for the control and containment of disease outbreaks for hundreds of years. These measures were also used as the main strategy to contain the spread of severe acute respiratory syndrome (SARS).[29,30] Whether or not isolation and quarantine are effective depends on several factors. The most important factor is the time at which an infected individual becomes infectious. If most of the infected individuals are not infectious until they develop apparent clinical symptoms, isolation and quarantine are more likely to be effective in controlling the disease. Most SARS patients were not infectious until they developed severe lower respiratory infections, such as pneumonia and respiratory distress syndrome (WHO Consensus report). On the other hand, if infected individuals become infectious before the onset of clinical symptom (i.e., during the incubation period) or immediately after the onset, containment by isolation and quarantine is more difficult.[28] The shedding of influenza viruses starts even before patients develop clinical symptoms such as fever. Therefore, quarantine and isolation are considered to be less effective for influenza than for SARS.[31] Implementation of quarantine measures is also associated with many legal, ethical, and psychological issues.[32,33]

Social distancing

Various social distancing measures, such as the closure of schools and workplaces, home confinement, and cancellation of social gatherings were used to prevent the transmission of the virus during past pandemics. Some of these measures were implemented as official policy, but in many cases, they were implemented as voluntary behavior changes due to a fear of infection in crowded places. Similar behavioral changes were also seen during the SARS epidemic.[34] There is little scientific evidence for the effectiveness of these interventions in reducing influenza transmission during periods of seasonal and pandemic influenza.[26] Schools often play an important role in spreading the virus to the community. It was suggested that school closures were associated with a reduced incidence of influenza.[35] Recent studies, using epidemiological models, have concluded that social distancing measures alone would have little impact on the overall number of cases, although they might have some effect in delaying the peak of an epidemic.[5,6] Therefore, social distancing may only be effective in gaining time to produce sufficient vaccines or as a supplemental strategy in addition to pharmaceutical interventions.

Personal protection

Several personal protective measures, such as hand washing, the use of face masks in public places, and respiratory hygiene have been recommended by health authorities for protecting against seasonal influenza, pandemic influenza, and outbreaks of other respiratory infections, such as SARS. Influenza viruses are believed to be transmitted by contaminated hands and other surfaces. But there is no data on what proportion of influenza infections are attributable to such modes of transmission. It has been shown that hand washing reduced the incidence of respiratory infections in children[36] and young adults,[37] but these studies did not include virological analysis, and they provide no direct evidence of the protective effect of hand washing against influenza infection. In another study, it was shown that influenza viruses could be recovered from the hands for only 5 min after exposure and only when the hands were contaminated with a high virus titer.[38] It is necessary to accumulate more data to evaluate the effectiveness of hand washing for protecting against influenza infection.

Masks were used by many individuals during past pandemics.[39] No controlled studies have been conducted to assess the use of masks in preventing influenza infection. Epidemiological studies showed that the use of masks in public places in Beijing and Hong Kong was associated with a lower incidence of SARS.[40,41] In Hong Kong, the influenza isolation rate dropped during the SARS epidemic, possibly due to various public health measures, including the wearing of masks in public.[42] But these results should be validated by further studies.

Hospital infection control

Healthcare workers who have an important role during a pandemic can be also at higher risk of infection at such times. It is extremely important to provide maximum protection to healthcare workers to maintain healthcare services during a pandemic. The selection of appropriate preventive measures depends on the viral mode of transmission, particularly whether the virus is transmitted by droplet or by airborne (or droplet nuclei) transmission. If the virus is transmitted mainly by droplet transmission, transmission can be prevented by so-called droplet precautions, such as the isolation of the patient in a private room and the use of

ordinary surgical masks. But if the virus can also be transmitted by airborne transmission, additional precautions, such as isolation of the patient in a negative pressure room and the use of high-efficiency masks (e.g., N95 masks) are required.[43,44] Strict implementation of these precautions against airborne transmission are unlikely to be feasible during a pandemic, when large numbers of patients visit health-care facilities. It is believed that the majority of influenza infections occur through droplet transmission, but there has been some evidence of the airborne transmission of influenza viruses.[43,45] However, the proportion of influenza infections that can be acquired by airborne transmission is largely unknown. This is one of the most important questions to be addressed to decide which control measures should be implemented in healthcare facilities during a pandemic.

Border control

During past pandemics, various border control measures, such as the quarantine of incoming passengers and the complete shutdown of borders were implemented, but these had inconsistent results in preventing importation of the virus.[27] Border control measures, including exit screening and travel restriction, were believed to be effective in preventing further international spread in the SARS outbreak in 2003.[46] Various border control measures, including travel advisories, travel restrictions, passenger screening, and the complete shutdown of international borders are considered to help in preventing the importation of cases of the pandemic virus. These measures may be able to reduce the speed of international spread. However, epidemiological models suggest that border control measures are unlikely to be effective unless virtually all travel is stopped at the early stage of a pandemic.[6,47]

Conclusions

Many possible interventions have potential in mitigating the effect of an influenza pandemic, but there is no magic bullet that can be effective under any scenario. Specific pharmaceutical interventions, such as the use of vaccines and antivirals, are expected to have a central role in mitigating the impact of a pandemic. However, these interventions have critical limitations and we can not rely on these interventions alone. Other, nonpharmaceutical, interventions should have an important supplementary role, particularly in delaying the spread of a pandemic virus.

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