Control Measures for Human Respiratory Viral Infection

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Abstract

Keywords
► influenza
► severe acute respiratory syndrome
► Middle East respiratory syndrome coronavirus
► emerging communicable disease
► influenza A H1N1
► global health
► disease outbreaks

New viral respiratory pathogens are emerging with increasing frequency and have potentially devastating impacts on the population worldwide. Recent examples of newly emerged threats include severe acute respiratory syndrome coronavirus, the 2009 H1N1 influenza pandemic, and Middle East respiratory syndrome coronavirus. Experiences with these pathogens have shown up major deficiencies in how we deal globally with emerging pathogens and taught us salient lessons in what needs to be addressed for future pandemics. This article reviews the lessons learnt from past experience and current knowledge on the range of measures required to limit the impact of emerging respiratory infections from public health responses down to individual patient management. Key areas of interest are surveillance programs, political limitations on our ability to respond quickly enough to emerging threats, media management, public information dissemination, infection control, prophylaxis, and individual patient management. Respiratory physicians have a crucial role to play in many of these areas and need to be aware of how to respond as new viral pathogens emerge.

The increase in rate of emergent respiratory viral infections in the past 15 years is driven by the convergence of various global factors, including growth in the human population, urbanization, changes in the interactions between human and animal populations, climate change, and increases in international travel and trade.1–4 Highly pathogenic strains of influenza viruses are of great concern as potential pandemic threats, although in recent years novel zoonotic coronavirus outbreaks have required new approaches in surveillance and containment.5

The severe acute respiratory syndrome (SARS) outbreak in 2003 exposed major weaknesses in the global capability of coping with an outbreak of a newly emerged infectious disease.6 Since the outbreak, public health authorities and clinicians managing patients with epidemic respiratory infections have learnt some significant lessons about the strengths and weaknesses of international, national, and local responses to emerging epidemics. These will be discussed in this article highlighting the importance of a coordinated global response incorporating surveillance, containment, dependable communication pathways, investigative capacity, early sharing of medical knowledge, and robust strategies designed to manage a national response and assist localities in their plans.

Epidemic Viruses

Influenza is responsible for an average 36,000 deaths annually in the United States, with more than 90% of these occurring in the elderly population.7 There have been four pandemics over the past 100 years due to antigenic shift. The Spanish influenza pandemic of 1918–1919 was the first and was the most severe of these and responsible for an estimated 40 million deaths.8 The 1918 pandemic virus shared properties with swine H1N1 viruses8,9 and is likely to have originated from an avian influenza virus that underwent adaptive mutations to gain the ability to transfer to humans. Later pandemics include those of 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1).10,11
The ability of viruses to jump species barrier and cause severe human infections is not limited to influenza virus as shown in Table 1 which highlights recent emergent respiratory viral pathogens, their potential source, and transmission. In the Guangdong Province in the southern area of China in 2002, a novel coronavirus (SARS-CoV) was reported causing severe viral pneumonia, i.e., SARS.12,13 The intermediate host of SARS-CoV was thought initially to be the masked palm civet cat, but subsequently evidence shifted to the Chinese horseshoe bat.14 This zoonotic virus became a global threat due to an infected physician traveling to Hong Kong in February 2003.12 It spread rapidly worldwide with 8,273 cases and 774 deaths in 1 year in more than 30 countries;15 before it was contained 6 months later.

Nearly 10 years later, in June 2012 in Saudi Arabia, the index case of a new coronavirus, Middle East respiratory syndrome (MERS-CoV), causing severe viral pneumonia emerged. A few days later, the same virus was detected in a Qatari patient receiving intensive care in a London hospital, highlighting the role of air travel in early spread of disease, as was the case in SARS in 2002. Since its discovery in 2012, MERS-CoV has reached 26 countries affecting approximately 1,300 people, including a dozen children, and claiming nearly 500 lives.17 Most MERS-CoV cases (>85%) reported thus far have a history of residence in, or travel to, the Middle East, predominantly confined to six countries: Saudi Arabia, United Arab Emirates, Qatar, Jordan, Oman, and Kuwait, although travel-related cases have been identified in Tunisia, the United Kingdom, France, Germany, and Italy. The zoonotic vector and reservoir of MERS-CoV are dromedary camels, with bats as another possible vector for transmission to humans.18

Surveillance

With our current level of medical knowledge and the existing global political and economic situation, we cannot realistically hope to prevent new pathogens from emerging, as is demonstrated by the emergence of a second highly pathogenic coronavirus within a decade, MERS-CoV. The best opportunities to prevent global spread of a new pathogen are rapid and early identification systems to allow control measures to be put in place to prevent its spread.

In 1952, the World Health Organization (WHO) established a global network of influenza surveillance; this is now called the WHO Global Influenza Surveillance and Response System (GISRS) and the network includes 142 National Influenza Centres (NICs) in 112 WHO member states, 6 WHO Collaborating Centres, and 4 WHO essential regulatory laboratories.19 GISRS provides real-time virus monitoring and sharing, to rapidly identify and respond to influenza outbreaks including those with pandemic potential. The laboratory-confirmed surveillance information is available real time publicly through FluNet, the web-based database and reporting system since 1996.20 GISRS provides recommendations on the composition of seasonal influenza virus vaccines biannually and on development of vaccines for zoonotic influenza viruses. This network also provides a global mechanism for maintaining an up-to-date inventory of candidate vaccine viruses and potency reagents for seasonal and zoonotic influenza. The majority of NICs are in Europe and the United States, so there is an absence of information about influenza transmission and the burden of disease is the tropics and the subtropics.

The WHO surveillance strategies determine the start and end of the influenza season and characterize the types and subtypes of circulating strains as well as detecting the emergence of novel viruses. It assists with selection of future vaccine strains and monitors for the emergence of viral resistance. Since the reemergence in 2004 of the highly pathogenic influenza A H5N1, GISRS also has a role in the identification of novel influenza or other viruses causing Severe Acute Respiratory Infection (SARI, defined as a fever of at least 37.8 or self-reported fever, and either a cough or a sore throat, and hospital admission)21 and in the identification of a potentially new pandemic pathogen.

### Table 1 Recent emergent respiratory viruses, sources, and transmission patterns

<table>
<thead>
<tr>
<th>Date</th>
<th>Infection</th>
<th>Region</th>
<th>Potential source</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>H5N11189</td>
<td>Hong Kong</td>
<td>Poultry environment</td>
<td>Contact with infected poultry, close contact human to human</td>
</tr>
<tr>
<td>1999</td>
<td>H9N2190</td>
<td>Hong Kong</td>
<td>Poultry (quail)</td>
<td>Direct infection from live poultry</td>
</tr>
<tr>
<td>2003</td>
<td>SARS-CoV14</td>
<td>Hong Kong</td>
<td>Bats</td>
<td>Human to human, sporadic</td>
</tr>
<tr>
<td>2004</td>
<td>H7N7191</td>
<td>The Netherlands</td>
<td>Dutch poultry farms</td>
<td>Direct infection from live poultry</td>
</tr>
<tr>
<td>2005</td>
<td>H3N2192</td>
<td>Canada</td>
<td>Pig, pig farms, turkeys, and swine farm worker</td>
<td>Contact with infected pigs, limited nonsustainable human-to-human spread</td>
</tr>
<tr>
<td>2009</td>
<td>H1N1193</td>
<td>Mexico</td>
<td>Not clear, virus most similar to influenza viruses found in pigs</td>
<td>Human to human</td>
</tr>
<tr>
<td>2012</td>
<td>MERS-CoV7</td>
<td>Saudi Arabia</td>
<td>Camels, bats, camel farms, human patients</td>
<td>Close contact human to human, sporadic</td>
</tr>
<tr>
<td>2013</td>
<td>H7N9196</td>
<td>China</td>
<td>Poultry environment (bird markets, poultry farms, human patients)</td>
<td>Direct contact with live poultry, close limited human-to-human spread</td>
</tr>
</tbody>
</table>
The importance of early identification of a pathogen with pandemic potential in increasing the capability for effective control measures is self-evident. For early warning systems to work, specific triggers are needed for immediate reporting of possible occurrence of a single or multiple cases that might be the first indicators of the emergence of a novel respiratory virus. To assist with this and as part of the global public health response after the SARS epidemic, the WHO established the international health regulations in 2005 (see below). These internationally binding regulations require all countries to report all cases of human influenza cause by new viral subtypes to the WHO.

Other important signal events in early recognition of respiratory viral infections with a pandemic potential are SARI or pneumonia in health care workers that indicates the development of human-to-human transmission (as occurred in the SARS epidemic) and clusters of SARIs in social or occupational connected individuals. Other surveillance triggers are a shift in age distribution, increase in mortality, or increase in number of cases.

**Containment and Limiting Initial Spread**

With effective surveillance, pathogens are identified early, but the mitigating actions to contain and limit spread are a scientific and political challenge. Following the global threat of an infected physician traveling from China to Hong Kong in February 2003, Chinese authorities received international criticism for not revealing the extent of the epidemic earlier, prior to SARS spreading internationally, when it could have potentially been contained. The delay in the Chinese communicating the extent of the epidemic to the international community was a combination of political considerations as well as significant deficiencies in the structure of its public health service that severely limited its ability to recognize and track potential epidemics.

The SARS pandemic highlighted that few countries possessed the necessary surveillance and response capacities to rapidly detect and control emerging infectious diseases. The deficiencies of the 1969 International Health Regulations (IHR) at the global level had been acknowledged, and attempts to revise them were ongoing before 2003, but the SARS outbreak added new urgency and momentum for change. These were updated in close consultation with WHO member states, international organizations, and other relevant partners, and were adopted by the 58th World Health Assembly on May 23, 2005 and the adoption began from June 15, 2007. Global acceptance of the 2005 IHR has improved international vigilance and collaboration and should provide the framework for cooperation between countries so that effective public health actions can be initiated.

In parallel to the WHO IHR 2005, international and national planning has improved with the recognition of Global Surveillance Systems and epidemic intelligence systems such as the Global Public Intelligence Network and ProMed. ProMed mail was the forum used by a Saudi Arabian physician on September 20, 2012, to report the isolation of a novel coronavirus from a patient with pneumonia (subsequently identified as MERS-CoV). New monitoring and information initiatives have been established to provide important insights into laboratory-confirmed cases and clinical manifestations of disease, such as the Early Alert and Response System established by the Global Health Security Initiative member states and the Connecting Organizations for Regional Disease Surveillance. The increased use and availability of social media has further driven transparency or informally increased awareness where there is a lack of collaboration.

Since 2003, international and national authorities have recognized the importance of more effective animal health surveillance. Limited resources in most countries have resulted in investments in surveillance capacity predominantly in those countries affected by major outbreaks, such as the case with an outbreak of influenza A H5N1 virus infection in Thailand, China, Vietnam, and Indonesia. The response to the H7N9 infection by the Chinese authorities in 2013 demonstrates the substantial improvements made in international surveillance compared with the SARS outbreak in 2002. On March 31, 2013, China notified the WHO of the first recorded human infections with avian H7N9 virus. The poultry markets were rapidly identified as a major source of transmission of H7N9 to humans and were quickly closed down in the affected areas. The health authorities collaborated with the WHO in risk assessments and communication, with heightened surveillance in humans and poultry and prompt reporting of new cases. As a result, the infection was contained to China with 139 cases (82% had a history of exposure to live animals, including chickens) and 34% death rate.

The Global Health Security Agenda launched in the United States in 2014 is a program to link the U.S. government, other nations, international organizations, and public and private stakeholders. This initiative aims to overcome barriers to sharing information, samples, protocols, and to develop a more integrated global laboratory for diagnostic and vaccine development, as well as addressing specific capacity-building activity to further progress the community of trust within the global public health system.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) was launched in December 2011 and is a global initiative aiming to ensure that clinical researchers have the protocols and data-sharing processes needed to facilitate a rapid response to emerging diseases that may turn into epidemics or pandemics. The consortium brings together over 70 networks and individuals involved in research related to the outbreaks of diseases such as H5N1, H1N1, and SARS. It is working to discover how severe acute respiratory diseases develop and progress in patients, and identify the most efficient treatments and the best way to prevent further transmission.

Although there have been substantial improvements in worldwide preparedness for emerging infections and potential pandemics, establishing trust and overcoming tensions generated by political differences remain a challenge. An example of this occurred following the H1N1 pandemic in 2009, when the Council of Europe highlighted potential conflicts of interest of individual members of the WHO emergency pandemic committee (membership of which was secret) linking them to industry. Shortfalls and delay in
the H1N1 vaccine distribution in low- and middle-income countries also added to the controversy around the 2009 H1N1 response.\textsuperscript{39,40}

**Containment at International Borders**

As more than 700 airlines transport over 2.5 billion travelers between 4,000 airports each year, local infectious disease outbreaks have the opportunity to transform quickly into international epidemics. As an epidemic emerges and the threat is recognized, the vast majority of public health authorities and governments across the world will be trying to prevent infection of their own population employing the strategies of quarantine and screening at points of entry into the country. Neither of these ineffectual strategies is recommended by the WHO,\textsuperscript{41} and it is generally accepted that exit screening is a more effective intervention although there is often less political motivation for this approach.

**Exit Screening**

Exit screening appears to be more effective than entry screening, perhaps primarily related to the reduced numbers of infected passengers on board the aircraft and therefore decreased transmission.\textsuperscript{41,42} The screening method used determines the effectiveness and resource implications of exit screening for the detection of infectious cases. As with any screening measure, the impossibility of detecting asymptomatic cases or people who are incubating the infection limits its implementation,\textsuperscript{41,43} particularly with influenza, where cases are infectious during incubation and when asymptomatic.\textsuperscript{44}

Although SARS did spread to 28 countries,\textsuperscript{45} it is likely that exit screening with quarantine helped to contain the epidemic.\textsuperscript{41} On this background, exit screening was recommended by the WHO during the H1N1 2009 pandemic,\textsuperscript{46} while entry screening was not recommended. Arguments for the choice of exit screening over entry screening included the possible impact on passengers’ behaviors by discouraging ill passengers from traveling abroad, the decreased risk of global transmission due to the reduced numbers of travelers, and being most effective in containing a disease at the source.\textsuperscript{6,41,46} Arguments against exit screening include passenger concerns about the cost of accessing affordable health care in the country of departure if they are not allowed to leave,\textsuperscript{47} resulting in failure to disclose possible infections.

Despite the implementation of exit screening, throughout March and April 2009, international air travelers departing from Mexico were unknowingly transporting the H1N1 virus to cities around the world. In Australia, for example, just 20 days after quarantine measures were enacted for H1N1, public health authorities conceded defeat in the face of widespread infection in the general population.\textsuperscript{48} The difference in effectiveness of control measures in containing SARS and H1N1 are due to the differences in the infectivity of the viruses and the speed of onset of infectivity after initial exposure. The fact that SARS continued to be viewed as a serious mortality threat whereas H1N1 rapidly became regarded as a predominantly non lethal disease may also have reduced public compliance with public health measures for the latter.\textsuperscript{49,50}

Unfortunately, many countries are more focused on preventing new cases of infection from entering their borders rather than preventing established cases from leaving. As this is the more commonly adopted approach, the WHO suggests that entry screening should be considered in passengers arriving from countries where there are concerns about the presence or thoroughness of exit screening.\textsuperscript{41}

**Entry Screening**

There is substantial evidence confirming that entry screening at international borders for controlling influenza and other epidemics is ineffective.\textsuperscript{41,51} Infrared thermography (IRT) involves the quantification of emitted radiation to measure temperature and provides a quick noninvasive means to measure body temperature.\textsuperscript{52} It was implemented as a border control strategy during the SARS epidemic with the advantages of its ability to screen mass numbers of individuals and reduce close contacts with infected individuals. Unfortunately, no cases were detected for over 35 million travelers screened.\textsuperscript{53} There was a similar story with H1N1 where IRT was found to be both ineffective and inaccurate.\textsuperscript{54} IRT may be influenced by several confounding factors including age and outdoor temperature, and in addition, results from studies looking at IRT as a tool to detect fever tend to have small positive predictive values due to the small prevalence of febrile passengers.\textsuperscript{25}

The use of quarantine and entry screening at international borders is costly and in some countries its use has created considerable debate about the legality and ethical basis for this approach.\textsuperscript{55–58} The IHR 2005 specifically addresses issues of human rights related to quarantine and travel restrictions,\textsuperscript{22} stating travelers’ dignity and fundamental freedoms should be respected as well as minimizing any discomfort or distress and providing food, accommodation, and interpreter services. A review of experiences from the H1N1 pandemic revealed that compliance with these sections was far from universal.\textsuperscript{59} The cost and time taken for additional screening measures are also predicable not popular with airlines.\textsuperscript{60}

**Air Travel**

A controversial area with viral epidemics is the extent to which air travel itself is responsible for infecting passengers. Modern high-efficiency particulate air filters in aircraft recirculate air within very localized cabin areas,\textsuperscript{60} in theory containing most of the risk to within two rows of the infective individual. Of course, pathogens vary in their innate infectivity; however, even for a highly contagious virus like H1N1, there is considerable debate. Modeling from Wagner et al based around a single individual infected by H1N1 suggested that in long-haul flights from 7 to 17 people may be infected during the flight.\textsuperscript{61} Analysis of a group of students suffering inflight exposure to H1N1 found the risk to be approximately 3.5% for those seated within two rows of the index case.\textsuperscript{42} It is not safe, however, to assume that there is no risk beyond the two-row limit, with one case of SARS leading to infection of 22 of 120 passengers and crew dispersed throughout the aircraft.\textsuperscript{52}

In an ideal world, passengers should be responsible and not travel when symptomatic, which, combined with effective exit screening, should significantly reduce the risk to fellow
from other serious lower respiratory tract infections. Capability to deliver rapid microbiological testing is essential, as delays in confirmed diagnosis result in difficulties with quarantine advice, contact tracing, and the use of medications.

**Pandemic Plans**

Another lesson from H1N1 in 2009 is that our pandemic plans need to be flexible and the public health response needs to be able to adapt quickly to nuances of individual pathogens. Virtually all pandemic influenza plans were based around an assumption that the vast majority of infected individuals would be febrile, leading to initiatives such as fever clinics and quarantine of febrile patients until a diagnosis was established. With H1N1, many infected individuals were not febrile, nor were there any specific clinical characteristics that made it possible to define infected versus noninfected patients. Well after it was recognized by clinicians that fever was often not present with H1N1, public health officials were still discussing establishing fever clinics in Australia. These types of communication breakdowns between clinicians and public health officials are another area that needs to be improved so that the whole process of responding to epidemics is substantially more flexible.

**Isolation**

SARS highlighted the central role of health care facilities as hubs of dissemination. Most cases of SARS outside of China were acquired in a health care setting, health care workers representing 21% of cases with a mortality rate of 9.6%. In the hospital setting, it is critical to treat all patients with respiratory tract infections as contagious and have appropriate protective measures in place to protect staff and other patients. The psychological impact on health care workers of dealing with an epidemic should not be underestimated and needs to be addressed as part of any response plan.

While SARS severely tested the quarantine capacity of most hospitals, H1N1 overwhelmed them. Few, if any, hospitals have been built with the capacity to isolate all patients individually, which led to cohorting of suspected cases and potentially spread between them to originally uninfected individuals. Again the capability to be able to rapidly make a diagnosis is critical to managing the quarantine situation. Basic measures such as limiting or preventing visitors, keeping the number of hospital staff having contact with infected patients to a minimum, strict infection control with basic measures of handwashing, and proper fitting masks that are fit for purpose are all critical.

All public health pandemic plans advise that where possible infected individuals should be kept at home. Infected individuals need to be told not to go to work or other public areas and employers need to be educated to enforce these guidelines. This is particularly important with hospital staff, with some health authorities instigating regular temperature checks of staff during the SARS epidemic. School closures are likely to be highly effective when the epidemic is severe.
and highly transmissible,\textsuperscript{71} as school-age children have been shown to amplify the spread of epidemics.\textsuperscript{68}

**Personal Protection Measures**

Basic measures such as handwashing and cough hygiene have an important role, as demonstrated by the experience in Hong Kong during the SARS epidemic, with substantial reductions observed for all respiratory infections during the period of increased public vigilance.\textsuperscript{72} Communication and education are clearly important in obtaining maximum compliance with public health measures;\textsuperscript{73} however, the reality is that without a high level of perceived threat most individuals stop being vigilant about personal protection measures.\textsuperscript{72,74–76}

Health care organizations and countries have different policies and guidelines around mask and respirator use for influenza, SARS, and MERS. These policies vary regarding not only the choice of product used, but also the application and specifications, reflecting the relative lack of level-one evidence available to inform policy development. For the health care worker, the availability of conflicting guidance about mask use from different sources (such as the WHO and in-country guidelines) is confusing and reflects the major gaps around the modes of transmission of respiratory viruses, the efficacy of cloth masks, and the impact of extended and reuse of masks/respirators.\textsuperscript{77}

**Antivirals**

With H1N1, it was fortunate that neuraminidase inhibitors had been shown to reduce the transmission of influenza and at least for the majority of the pandemic, resistance rates were quite low. These drugs were clearly effective in reducing the spread of H1N1; however, diagnostic delays reduced the potential impact.\textsuperscript{78} Most developed countries had sufficient stocks of these drugs to meet demand, but this was not the case in many developing countries despite significant efforts over the past 5 years to improve the situation.\textsuperscript{79} Novel non-influenza pathogens such as SARS and MERS are unlikely to be affected by existing antiviral drugs.

**Vaccine Development and Distribution**

A significant positive result from the H1N1 pandemic was the speed at which an effective vaccine was developed.\textsuperscript{80} A major factor in the quick success with the H1N1 vaccine is that it was a relatively straightforward adaptation of the usual seasonal influenza vaccine production process. There were, however, problems with the uptake of the vaccine, driven by a variety of factors including perceptions about the likelihood of developing a severe illness if infected and problems with the H1N1 vaccine in the 1970s.\textsuperscript{81–83} These factors, however, are not likely to be an issue if we are faced with a highly virulent pandemic. What is a much more significant problem is the production and distribution of vaccine,\textsuperscript{84,85} particularly to developing countries.\textsuperscript{85,86} These logistical issues remain a priority for the WHO to address ahead of future epidemics.

The existence of established protocols for manufacturing influenza vaccine was clearly an advantage with H1N1. Much more problematic is the production of a safe and effective vaccine in the setting of the novel, noninfluenza pathogens, such as the recent coronavirus infections SARS and MERS. Indeed, nearly a decade later, research is still defining the appropriate vaccine targets for SARS.\textsuperscript{87,88} The timeline from bench research to approved vaccine use is 10 years or longer, and vaccine development in these conditions is further hindered by the lack of a suitable animal model, which complicates the in vivo testing of candidate vaccines. Due to the low number of cases worldwide, pharmaceutical companies have little incentive to pursue vaccine production as the costs of clinical trials are high. Research is underway to look at genetically engineered vaccines to expedite cost-effective vaccine development against these emerging diseases.\textsuperscript{4}

**Summary**

The SARS epidemic highlighted the weaknesses in national and global capabilities to detect and respond to emerging infectious diseases. As such, it had a transformative effect on global laboratory and surveillance networks and accelerated the revision of the WHO IHR. Global surveillance and response capacity for public health threats have been strengthened with coordination of the sharing of diagnostic and clinical information across the Global Health Community. This framework is support by the revised International Health Agreement that endorses international vigilance and collaboration.

Despite the SARS and MERS outbreak, influenza remains the respiratory viral pathogen with the most significant global impact. Via the coordinating functions of the WHO, the infrastructure is in place for real-time, web-based virus monitoring and sharing to quickly identify potential pandemic strains. This framework also provides a global network for early identification of zoonotic influenza with heightened surveillance in humans and poultry and prompt reporting of new cases as occurred with H7N9 in 2013.

It seems unlikely that we can prevent new pathogens from arising, as has been shown recently with MERS-CoV, so enhanced syndromic surveillance to provide rapid and early identification to prevent spread is critical. Once a pandemic is suspected, exit screening offers the most effective solution for containment within a country although the political incentives are low. Experience from previous pandemics has taught us that health care institutions are major foci of disease transmission and all institutions need to have the facility to isolate infected patients as well as have maximal protection for staff. There is no doubt that personal protective measures such as handwashing and avoidance behaviors are effective, and the general public also needs to act responsibly by staying at home when unwell and not traveling when potentially infective. Mechanisms for early international communication around clinical features such as infectivity, disease course, and treatment responsiveness are becoming more robust, with trust improving between countries.
Recent history has shown that further respiratory epidemics not only are likely to happen, but also will occur with increasing frequency. No single measure will be effective in stopping the mortality, morbidity, and cost from future epidemics. Not only are likely to happen, but also will occur with increasing frequency. No single measure will be effective in stopping the mortality, morbidity, and cost from future.

Conflict of Interest
Neither author has any conflict of interest related to the preparation or publication of this manuscript.

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