

## INVITED REVIEW SERIES: RESPIRATORY HEALTH ISSUES IN THE ASIA-PACIFIC REGION

### Pandemic response lessons from influenza H1N1 2009 in Asia

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#### ABSTRACT

During April 2009, a novel H1N1 influenza A virus strain was identified in Mexico and the USA. Within weeks the virus had spread globally and the first pandemic of the 21st Century had been declared. It is unlikely to be the last and it is crucial that real lessons are learned from the experience. Asia is considered a hot spot for the emergence of new pathogens including past influenza pandemics. On this occasion while preparing for an avian, highly virulent influenza virus (H5N1 like) originating in Asia in fact the pandemic

originated from swine, and was less virulent. This discrepancy between what was planned for and what emerged created its own challenges. The H1N1 pandemic has tested national health-care infrastructures and exposed shortcomings in our preparedness as a region. Key health challenges include communication throughout the region, surge capacity, access to reliable information and access to quality care, health-care worker skills, quality, density and distribution, access to essential medicines and lack of organizational infrastructure for emergency response. Despite years of preparation the public health and clinical research community were not ready to respond and opportunities for an immediate research response were missed. Despite warm words and pledges efforts to engage the international community to ensure equitable sharing of limited resources such as antivirals and vaccines fell short and stockpiles in the main remained in the rich world. This manuscript with authors from across the region describes some of the major challenges faced by Asia in response to the pandemic and draws lessons for the future.

**Key words:** Global outbreak alert response network (GOARN), H1N1, influenza, outbreak, pandemic.

#### INTRODUCTION

On 24 April 2009, The World Health Organization (WHO) informed its member states that a novel H1N1 influenza A virus strain had been identified in Mexico and the USA.<sup>1</sup> It did not take long for the virus to be identified in most continents. Although past pandemics had a global impact, their ability to spread was not as rapid as the 2009 (H1N1) pandemic.<sup>2</sup>

Two days after the initial detection in Mexico and the USA, the virus was documented in Spain, the first country outside the Americas. Four days later, eight deaths had been confirmed (1—USA and 7—Mexico) and six new countries had been infected including

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Austria (1), Canada (19), New Zealand (3), UK (8), Israel (2) and Switzerland (1). Due to the rapid spread, the WHO raised the pandemic alert level from level 3 to level 4 on 27 April and 2 days later moved to level 5.<sup>3</sup> On 1 May 2009, the first imported cases were reported in Hong Kong.<sup>4</sup>

In just 8 weeks after the initial discovery of the novel virus, the WHO announced on 11 June that this outbreak had met their definition of a pandemic with involvement at that stage of 120 countries and with community transmission documented in three continents. Despite the rapid spread, countries including Mongolia, Rwanda, Sao Tome and Principe did not have confirmed cases until mid-October 2009; this may have been due to limited access to laboratory testing.<sup>5</sup> By January 2010, over 209 countries had reported laboratory confirmed cases and 14 141 deaths (Americas: 7094; Europe: 3099; Southeast Asia: 1366; Western Pacific: 1511).<sup>5</sup>

Our response to infectious disease outbreaks is born out of past experience. However, no two outbreaks are the same so an understanding of the infectious agent as well as the environment confronting it is fundamental to the response. This applies whether it is a known or an emerging agent or whether it is a well or under resourced setting. When the agent is a novel virus we are forced to extrapolate from experiences with like-viruses. Health managers quite reasonably prepare for 'worst scenarios'.

Past influenza pandemics such as Spanish Influenza of 1918, the Hong Kong flu and avian influenza H5N1, as well as SARS experiences lent strong support for an aggressive response to prevent the possibility of millions of deaths and social chaos from pandemic 2009 (H1N1). Of course, Armageddon did not happen however, the threat of pandemics will always remain high.<sup>6</sup> In planning for the next pandemic the focus should be on ensuring the response is proportional to the threat and that the impact of unintended consequences is minimized. This will only be possible if the experience gained during the current pandemic, for example the social and economic consequences of isolation and the long-term impact of diverting resources away from other life-threatening illnesses and disease control programs, is evaluated.<sup>7</sup> In addition, the scrutiny of the pandemic response has raised questions about the credibility of decision-making by public health institutions, including WHO and ministries of health. WHO and national governments are undergoing independent reviews of their actions and advice during the pandemic.

The Global Outbreak Alert and Response Network (GOARN) was established in April 2000 by the WHO and technical partners to improve the coordination of international outbreak responses. Partners agreed on the need for an early alert system to trigger rapid international response, and better response mechanisms to coordinate deployment of multidisciplinary teams to assist countries in investigating and responding to outbreaks.

GOARN has provided an operational framework for partner institutions to contribute technical, operational and logistics expertise and assistance to countries primarily for the investigation and control

of infectious disease outbreaks, including outbreaks of avian influenza, viral haemorrhagic fevers, yellow fever, Nipah virus, SARS, cholera, meningitis and other emerging pathogens. During the past 10 years, GOARN has supported over 139 missions in 75 countries.

Over 50 technical institutions and networks in the Western Pacific are actively participating in GOARN. The network partners were also active in the regional and global response to pandemic 2009 (H1N1), with GOARN missions deployed in Central and Latin America, and Asia. The 'lessons' described in this paper draw on the authors' experiences in international GOARN missions as well as from their home countries.

The 2009 (H1N1) pandemic has tested national health-care infrastructures and exposed shortcomings in our preparedness as a region. Countries in Asia had some weeks lead time and thus an opportunity to learn from what was occurring elsewhere. Resource requirements including isolation and ventilator bed needs could have been anticipated and planned for more effectively.

Asia is the world's largest continent with over 4 billion in population. Key health challenges include communication between and within many countries, the differences in levels of funding for health care between countries, access to quality care, health-care worker skills, quality and density and access to essential medicines. Lack of organizational infrastructure for emergency preparedness and response has also been noted.<sup>8</sup>

The arrival of this pandemic in Asia was inevitable and the first confirmed case was announced on 1 May 2009 in Hong Kong. A traveller staying in a local hotel was the first detected individual resulting in the hotel becoming an immediate quarantine location. Make-shift quarantine, school closures, border controls and travel restrictions were not far from becoming routine protocols enforced by national authorities across Asia. China detected its first three cases in early May and enforced 1 week of quarantine on close contacts.<sup>9</sup> Singapore practised in-hospital-based quarantine for all its early cases where they were kept until PCR negative. In June, the WHO issued interim guidance on public health measures.<sup>10</sup>

By the end of August 2009, 34 026 cases including 64 deaths and 15 771 cases with 139 deaths had been reported in the Western Pacific and South-East Asian regions respectively.<sup>11</sup>

Although the number of confirmed cases quickly increased, accuracy in reporting decreased with the recommendation to 'stop testing, just treat when clinically suspected and indicated'. This was made on 16 July 2009, since most influenza like illness (ILI) was by then the outbreak strain of 2009 (H1N1).<sup>12</sup> In some countries testing was preventing early treatment initiation, which was deemed crucial. It was an unnecessary use of resources and only had around 70% sensitivity.<sup>13</sup>

The Spanish flu pandemic saw a substantial difference in mortality rates reported between high and low income countries.<sup>14</sup> Similarly, the Americas and Europe had more reported deaths rather than

South-East Asia and the Western Pacific for 2009 (H1N1).<sup>11</sup> This is likely to be a result of differences in mortality surveillance across the world. Countries in North America and Europe have established systems for collecting data on influenza-related deaths whereas many developing countries do not have a functioning deaths registration system and are far from having routine ILI mortality surveillance.

However during the pandemic, a number of countries in Asia did aggressively pursue deaths data by undertaking PCR on lung tissue of any possible infection-related death. Highly sensitive mortality surveillance was in some instances linked to media and political fallout, and became a disincentive to maintain accurate case fatality data.

As a result of these confounding factors, the quantitative impact of this pandemic is truly difficult to calculate. Socioeconomic status of the country was also a factor in the accuracy of reported cases. It is these countries where surveillance is arguably more crucial given the often routine exposure between poultry and humans and therefore the risk of genetic assortment of influenza viruses higher.

## LESSONS LEARNT IN ASIA

**1** An emerging influenza pandemic irrespective of severity places a huge burden on health-care services and will expose any weaknesses in a system.

The 2009 (H1N1) pandemic spread through communities faster than that normally seen with seasonal influenza.<sup>2</sup> The majority of the population was susceptible and despite most of the cases presenting with mild symptoms, the speed of spread and number of infections meant that health facilities were quickly overwhelmed. In many countries, pandemic plans for health-care services were poorly implemented or were not developed. Capacity could not easily be created and often poor central coordination meant underutilization of the resources that were available. For instance, hospitals with no available ICU beds were managing severe patients in emergency rooms or general wards while in nearby hospitals ICU beds were available. In some countries the ability to share resources (particularly beds and manpower) between the public and the (often underutilized) private health sectors was not surmountable.

National and subnational health authorities can better prepare and utilize available resources if there are practical and tested hospital and inter-hospital level response plans for public health emergencies and mass casualty events. Authorities should have a system in place, which allows for coordinated management of beds and other finite resources including equipment and manpower. This should operate above the hospital level and involve financial compensation where the private sector is needed. During an emergency, normal referral practices are unlikely to work and central proactive coordination is needed.

**2** All national authorities need to consider pandemic threats in advance in order to establish sustainable preparedness in the context of endemic day-to-day health issues.

A variety of responses can be established based upon risk assessment of transmissibility, susceptible populations and severity of illness. Pandemic 2009 (H1N1) had a particularly interesting twist for Asia as there was a lead time of several weeks between the first identification and local transmission being established. This was an opportunity for further preparation. Hong Kong and Singapore have among Asia's best resourced health systems and had experienced SARS. It is therefore not surprising that they delivered aggressive and very proactive responses.<sup>15</sup> In China a comprehensive alert and response system built up by government agencies after SARS was also in place and aimed at delaying the onset of local transmission to further the lead time for vaccine production.

All countries had to manage the 2009 (H1N1) pandemic irrespective of resource limitations or endemic national health problems including malaria, tuberculosis and HIV. Despite views that it is wrong to divert resources towards preparedness or even management of influenza, public and media pressures made it impractical to try to ignore the pandemic.<sup>16,17</sup>

**3** Containment measures did little to prevent or delay entry of influenza into countries.

Containment is an attractive intervention; however, this outbreak showed how impractical it is in reality. Mathematical models have suggested potential effectiveness.<sup>18–20</sup>

Since the SARS outbreak and with the modern day skills of geographic tracking of a pandemic, it seems that border controls with thermal scanners is the first 'showpiece' of choice. Their international roll out was swift. Such a containment measure may work where infectivity is low and where the infection is only contagious after the onset of the febrile phase but this is not the case with influenza.<sup>21</sup>

Entry screening is an easy measure and can be used by governments to portray a sense of control. Entry screening (consisting of temperature check on board, health declaration forms, watching for flu symptoms, thermal scanner for travellers) may lead to short-term delays (7–12 days) in local transmission of a novel strain of influenza virus but the resources required for implementation should be balanced against the expected benefits of entry screening.<sup>22</sup>

Unpublished data from Singapore and Vietnam suggest that countries with just one or two international airports may realize delayed community transmission by a few weeks although epidemiological models suggest that border controls are ineffective unless they actually stop travel.<sup>23</sup>

In Hong Kong the public approved of government policies including the quarantining of hotel guests. However, misconceptions were prevalent and the public avoided visiting crowded places, as many people wrongly believed that this was a government recommendation. Clear communication, updated scientific information and transparency on government decision-making were insufficient.<sup>23</sup>

The criticism over the failure to isolate individuals after their exposure on board a cruise ship in Australia highlighted public and health department concerns and problems of communication in that country.<sup>24</sup>

School and workplace education and reminders relating to prevention measures and staying home if sick were widespread. While some school closures were subjective and apparently excessive, it was estimated that transmission was reduced by approximately 25% when secondary schools were closed in Hong Kong.<sup>25</sup> Closing schools is political and emotive. The early concerns over virulent influenza supported any intervention to protect children.<sup>26</sup> As concerns were downgraded; however, it seemed often politically unpalatable to deescalate the will to close schools.

In Singapore, oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of 2009 H1N1 in a military barracks.<sup>27</sup> However, this is not generalizable to the point of being of use in this pandemic setting. Indeed, attempts at ring prophylaxis in school settings have been shown to be detrimental.<sup>28,29</sup>

In conclusion, it is likely that some containment measures were useful in slowing the spread and preventing large numbers of coinciding infections to facilitate the continuity of services and business. When the limited impact of containment measures was evident, the challenge became one of risk communication so as to wind back the approaches.

**4** National antiviral policies and stockpiles were over-reliant on one oral formulation, which had poorly conceived distribution plans.

For many years oseltamivir has been a world's top seller.<sup>30</sup> The medication was central to mitigation and possible containment strategies in most national guidelines yet its long anticipated utilization was sub-optimal in Asia.<sup>19,21,31</sup> In countries with limited stocks of the drug, there were often delays in identifying distribution plans to health-care facilities and guidelines for utilization. Supplies needed to be devolved to primary care or else the use of the antiviral was effectively reserved for hospitalized patients who presented beyond the time frame for which its use is recommended. Future planning needs to consider much greater support of general practitioners if they are to fulfil such roles.

Stockpiling needs to consider the likelihood of resistance which for oseltamivir was reported on 8 July 2009.<sup>32</sup> Furthermore, the lack of intravenous antivirals was a major shortcoming for the management of severe disease. Attempts to circumvent this using inhalational zanamivir on ventilated patients had tragic outcomes and a subsequent recommendation against the practice.<sup>33</sup> Future preparedness plans should consider more than one antiviral and intravenous preparations.

Shortages of antivirals and vaccines in much of Asia were exacerbated by the hoarding by wealthy countries where stockpiles of drug were underutilized and vaccines were returned and orders cancelled.<sup>34,35</sup> Only at that point were they offered to the less resourced.

**5** Health Practitioners were reluctant to follow the recommendation of the empiric use of oseltamivir.

Increasing the capacity of the health system to rapidly process and communicate test results was a key measure in response to the pandemic. Once there

was widespread community transmission and that most ILI (based on sentinel site surveillance) was 2009 (H1N1), it was appropriately decided that testing was wasteful and only delaying treatment.<sup>36</sup> Oseltamivir, however, was often in short supply, so once laboratories stopped testing many doctors were reluctant to use it empirically. Furthermore, doctors with the medication in the community did not feel comfortable using it on mild cases but at 'high risk' as they did not see or accept that such an intervention was warranted. These policies were discordant with the belief held by primary practitioners. For a policy to be implemented it needs to be concordant with experiences or else be linked to strong communications.

**6** In some countries there was a failure to empower and engage local clinical experts.

In an outbreak of a novel virus a clinician focal point is a very useful resource for tertiary advice, policy matters and the like. This was generally quite well done in the largest and capital cities but in the provinces often no clinicians either as individuals or groups were promoted as champions for the issue. Such a person or small group can also act as a point from which up-to-date information can be channelled either from the ground to management or else for the purposes of dissemination out to the clinical workforce.<sup>37,38</sup>

**7** Managing surveillance data is a crucial function that is also vulnerable to stress in an outbreak setting and needs surge capacity.

Health authorities generally ask for the submission of surveillance data from primary care and hospital providers relating to ILI, hospitalization, mortality, etc. It is essential that a rapid risk assessment is carried out on all incoming information and that the outcome is used to inform public health action. In addition, this needs to be rapidly fed back to service providers and all stakeholders including the public through the media. Poor data management, failure to carry out systematic risk assessments and risk communications were responsible for misleading media reports which at times influenced decisions.<sup>16,38</sup>

The timeliness of the data management and risk assessments is also essential in identifying unusual clusters (e.g. high death rates) and initiating appropriate responses.<sup>19</sup> Only in this way can a rapid response to viral change be identified during the course of the outbreak. The speed with which H1N1 spread means that unusual reports and clusters need to be identified in real time.

**8** The coordination of protocol dissemination and the resources to implement them was a regular issue further highlighting the importance of two-way communication between administration and clinical providers.

Guidelines created centrally often had poor application at the clinic level. Advice on the use of antivirals may have been confounded by lack of access, while infection control procedures were often unrealistic in practice. Widespread dissemination of guidelines to clinicians in hospitals and in primary care is very difficult in all but a few countries. Guidelines written carry expectations but these are without chance if not

linked to appropriate dissemination, basic resources and stakeholder engagement and feedback.

**9** Pre-existing suboptimal infection control practices were exposed in the form of influenza outbreaks in Asian hospitals and this could be a focus for future efforts, which will benefit day-to-day hospital care as well as future pandemic responses.

Personal protective equipment (PPE) was required in volumes far exceeding supply.<sup>21</sup> Prevention of nosocomial 2009 (H1N1) infection of staff and existing inpatients was not uniformly achieved although there does not seem to have been major consequences as a result. Some apparent clusters were confounded by the possibility of community transmission. The seropositive rate of antibodies against the pandemic 2009 (H1N1) virus in hospital staff was higher than that in the general population in a study conducted in Taiwan, reflecting a higher contact risk and suggesting that hospital staff should have been vaccinated early.<sup>39</sup> However in Singapore the rate of exposure, measured serologically in health workers was lower than the general population, suggesting that isolation, PPE and visitor policies may have been beneficial. Sero prevalence studies have even shown a protective effect in being a health-care worker where collaborative efforts were made to standardize and regulate the use of PPE.<sup>40,41</sup>

**10** The planning and hierarchy of intensive care and high dependency units need development in much of Asia.

Oxygen supplies in some countries were quickly depleted. Make-shift plumbing failures resulted in deaths in ICU patients. In many countries of Asia, 'critical care' including intensive care and high dependency units is still an emerging specialty. Countries should have strategic plans for their development.<sup>42</sup> In some, it is very appropriate not to allocate resources to these services, thereby maintaining a focus on primary care and public health. Some countries were found to have an ad hoc system with ventilated beds in quite inappropriate settings. Intensive care units are much more than ventilators alone. Resources and expertise need to be focused in to a small number of institutions first. While the issue is significant outside of the outbreak setting, once again the effects are exaggerated during stressed times such as during the H1N1 period.

**11** An opportunity for important clinical research has been under-utilized (again).

Despite millions of cases in over 200 countries and over 17 000 deaths the clinical research response was cumbersome and slow despite years of global preparations for a potentially devastating influenza pandemic of avian origin or the next SARS-like outbreak. Although observational and descriptive studies were undertaken, initiatives to launch randomized controlled trials or more sophisticated pathogenesis studies generally missed the initial waves of the 2009 H1N1 pandemic and in many cases failed to enrol sufficient numbers of patients across the clinical spectrum of disease into studies, even during subsequent waves. During the 2009 H1N1 virus pandemic the efforts to prepare for a respiratory disease outbreak allowed a reasonably rapid and coordinated

response on epidemiologic and diagnostic aspects of disease but failed in the timely conduct of clinical research aimed at improving patient management and understanding pathogenesis. Interventions including school closures, masks, hand-washing, social distancing and screening at ports of entry were not critically assessed.<sup>43</sup> The optimal antiviral regimen remains unclear particularly in the critically ill, in pregnant women, in obese patients and in the very young. Many commonly debated adjunctive and new therapies were not prospectively assessed. Despite years of apparent preparation and talk, the clinical research community and funding agencies were not ready to respond and missed the opportunity.<sup>44</sup> During the 2009 H1N1 virus pandemic the efforts to prepare for a respiratory disease outbreak allowed a reasonably rapid and coordinated response on epidemiologic and diagnostic aspects of disease but failed in the timely conduct of clinical research aimed at improving patient management and understanding pathogenesis. Indeed, we do not even know precisely why we continue to fail. In almost all recent epidemics (Nipah, SARS, H5N1, outbreaks of VHF or rapid development of drug resistance) very little research aimed at improving clinical management through prospective clinical trials or understanding pathogenesis has been conducted. Poor Institutional Review Board responsiveness and the politics and bureaucracy of research play a role. These experiences have shown that unless something is done, now to change the approach to clinical research in severe acute respiratory infections (SARI) and other rapidly evolving public health emergencies the next influenza (or other) epidemic will result in a similar missed opportunity to save lives and advance medical knowledge. We currently have no framework for ensuring research is built into epidemic responses and in fact our present research culture often prevents against a rapid response. Furthermore, from recent epidemics no integrated analyses exist combining microbiological/virological, immunological, clinical, epidemiological, and genetic data for comprehensive assessment of host-emerging pathogen interactions. This is the only real way to best inform prevention and control activities as well as guide clinical management.<sup>45,46</sup> This will be challenging as there are major clinical, ethical, administrative and organizational constraints. A new paradigm is required to prepare for and respond to rapidly emerging health threats and ensure we build a framework that incorporates and facilitates prospective clinical research and clinical trials during these epidemics. This will need to be done before epidemics and pandemics develop and will require development of agreed protocols with pre-approval from ethical review boards and networks of clinical sites willing to undertake such research. Such protocols should be available freely on line to encourage research. We do not underestimate the challenge of developing such a framework but given the increasing occurrence of these threats and threat to lives we need to do this as a matter of urgency. The Virology, Epidemiology, Emergency Response Groups and Public Health communities have developed much better coordinated systems

and collaborative approaches since the epidemics of SARS, H5N1, and these were of great help during the 2009 H1N1 pandemic. The clinical research community needs to learn the lessons from these other disciplines and develop similar collaborative approaches.

## CONCLUSION

Efforts engaging international cooperation where limited resources such as antivirals and vaccines are prioritized to the neediest countries still fall short. It is in these countries with suboptimal (or even non-existent) intensive care units where the highest mortalities will arise. Understanding our shortcomings in the approach to the management of the 2009 (H1N1) outbreak can better equip us to manage the next inevitable emerging infection.

After April 2009, the world's health managers and the broad medical community rose to a potentially extreme threat. Viral sequences were rapidly shared and laboratories adapted with in-house tests and prioritized their work to the clinical need. Intensivists, infectious disease, respiratory and general physicians grasped the new information to make themselves expert. Information sharing internationally has clearly improved over the last decade. It is a success story from which international organizations especially the WHO can claim credit.

It is essential, however, that outbreak periods be recognized as a time to identify the weaknesses of health systems at an international, national, regional or even individual facility level. The excess demands necessarily associated with an infectious disease outbreak invariably expose areas, which were failing or close to it in the non-outbreak phase.

Influenza pandemics have been on the public health agenda for nearly a century. The major lesson on reflection of the 2009 (H1N1) outbreak is that we were only saved because the infection turned out to be relatively mild. For all the apparent preparation we did not really alter the natural history significantly.

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