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To contact us:

Western Pacific Surveillance and Response
World Health Organization
Office for the Western Pacific Region
United Nations Avenue
1000 Manila, Philippines
wpsar@who.int
https://ojs.wpro.who.int/

Marking the 1918 influenza pandemic centennial: addressing regional influenza threats through the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies

Erica Dueger,[a] Lisa Peters,[a] and Li Ailan[a]
Correspondence to Erica Dueger (email: wpsar@who.int)

In 1918, near the close of the First World War, pandemic influenza swept across the world. Spread by the movement of troops and fueled by dense military-camp living quarters, the virus caused unusually high mortality rates in people 20–40 years old. An estimated 500 million people were infected, and up to 50 million died. Since then, pandemics caused by newly emerging influenza viruses have occurred every 10–40 years, with each of the pandemics in 1957, 1968 and 1977 taking the lives of roughly one million people.[1] More recently, the 2009 H1N1 influenza pandemic resulted in an estimated half a million deaths and raised concerns about how prepared the global community was to cope with future public health events.[2] Past pandemics can teach us important lessons about preventing and responding to emerging global health threats. This special issue highlights significant achievements across the Western Pacific Region in global pandemic preparedness and response.

The World Health Organization (WHO) Western Pacific Region is a hotspot for significant emerging infectious disease events, including human infections with avian influenza viruses.[3] Home to nearly 1.9 billion people and 6 billion poultry, avian influenza viruses that pass from animals to humans living in close proximity could mutate and rapidly spread through the Region and the world. Since 2003, the Western Pacific Region has experienced the emergence of influenza A(H1N1)pdm09, A(H5N1), A(H5N6), A(H6N1), A(H7N4), A(H7N9), A(H9N2) and A(H10N8) viruses.[4] Member States' abilities to quickly identify emerging infections, determine the pandemic potential of the causative viruses, assess public health risk and event severity, and, when needed, mobilize a public health response is critical to better protecting people from emerging threats in the Region and around the world.

For more than a decade, the *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies* (APSED III) and its earlier versions in 2005 and 2010 have driven joint efforts to build and strengthen national core capacities as required under the International Health Regulations or IHR (2005).[5,6] APSED III envisions a region able to prepare for, detect and respond to public health emergencies through improved regional connectivity and collective responsibility for managing health security. Importantly, APSED III builds on the foundations of the earlier versions to address emerging disease threats and public health emergencies (**Fig. 1**). APSED III provides critical elements for developing public health systems capable of identifying and responding to emerging infectious diseases, events and public health emergencies, including the next influenza pandemic (**Fig. 2**).

Over the last decade, Member States in the Western Pacific Region have substantially strengthened national virological and epidemiological surveillance for influenza.[7] Through these improved capacities, the Region contributes to the continuous global monitoring of seasonal and emerging influenza viruses through the Global Influenza Surveillance and Response System.[8] Event-based surveillance became a regional priority as part of the implementation of IHR (2005) and, through APSED III, is now well

[a] WHO Health Emergencies Programme, WHO Regional Office for the Western Pacific, Manila, Philippines.
[b] Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
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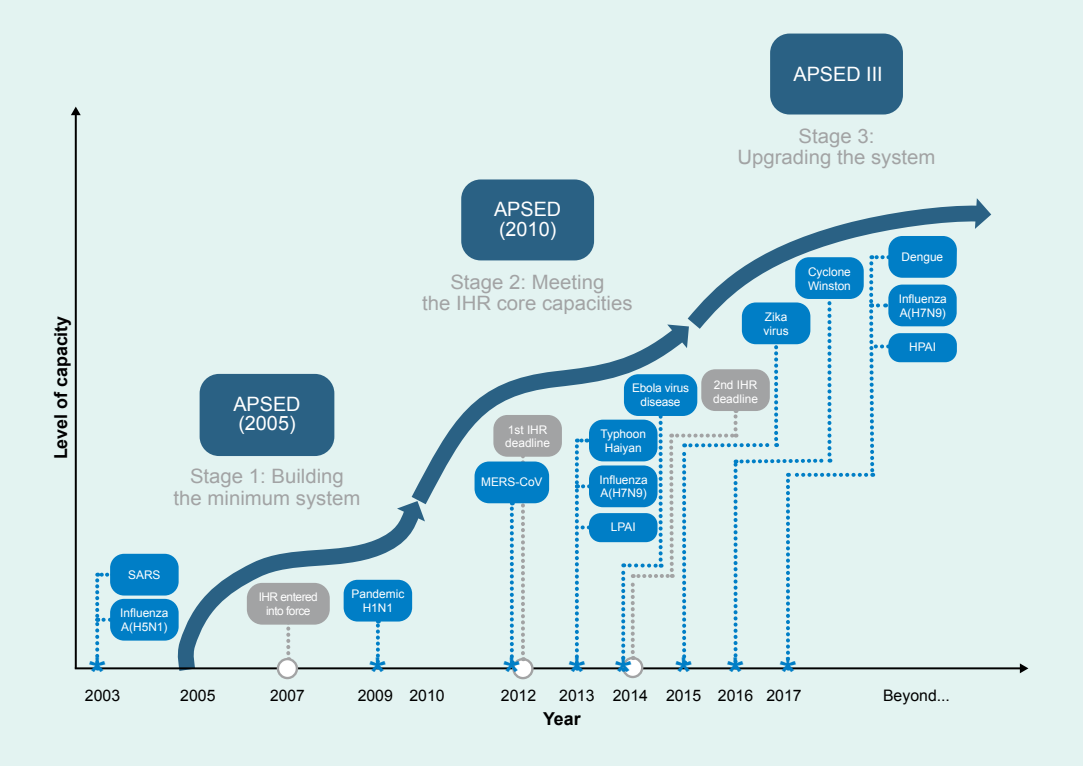
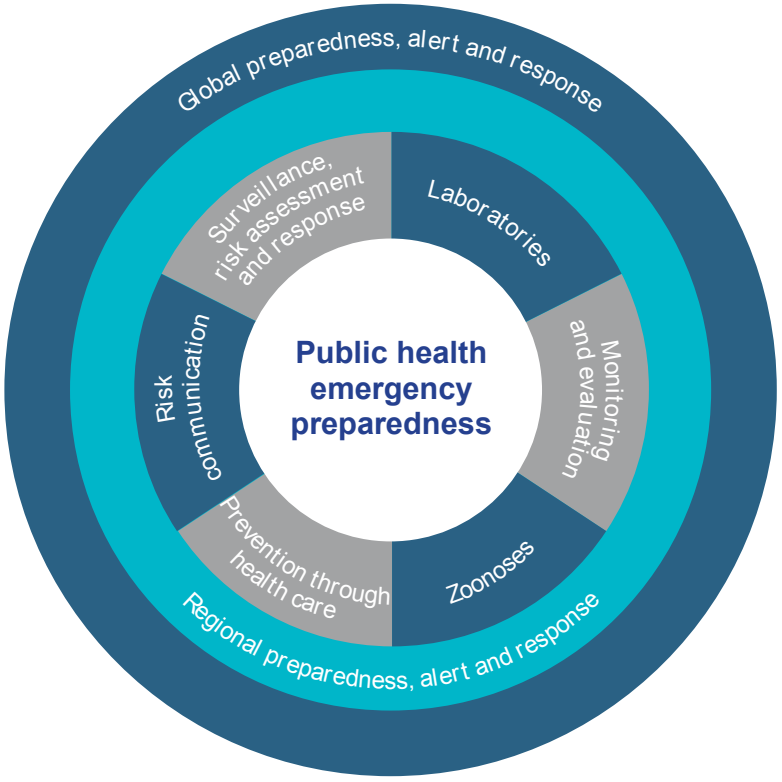
Fig. 1. **APSED development and priorities from 2005 to 2016 and beyond**



APSED, Asia Pacific Strategy for Emering Diseases; HPAI, highly pathogenic avian influenza; IHR, International Health Regulations; LPAI, low pathogenicity avian influenza; MERS-CoV, Middle East respiratory syndrom coronavirus; SARS, severe acute respiratory syndrome.

Fig. 2. **APSED III provides a framework for public health emergency preparedness in the Western Pacific Region, including preparedness for future pandemic influenza**



established in the Western Pacific Region. Outpatient influenza-like illness surveillance across the Asia-Pacific is used to evaluate seasonal severity[9] of influenza and provides isolates to support seasonal influenza vaccine development.[10] These activities are helping countries detect, conduct risk assessments of and respond to influenza outbreaks as well as contribute to biannual recommendations for vaccine composition.

The importance of coordinating pandemic preparedness and response efforts with the animal and environmental sectors cannot be overstated. Zoonotic influenza virus mutations have been associated with pandemics over the last century, and their significance was recognized broadly in 1997, when the first human cases of A(H5N1) were detected in Hong Kong SAR (China). As outlined in the perspective by Peters et al[11] and overview by Hamid et al,[4] infected animals and contaminated environments are often the source of human infection. Close monitoring of domestic animals and wildlife, and any associated human populations, is important for identifying newly emerging influenza viruses. Sharing these data in a timely manner allows policy-makers and public health officials to quickly identify and respond to such emerging threats. In response to this need, the WHO Regional Office for the Western Pacific has developed a set of online interactive influenza dashboards[12] that provide both baseline seasonal and avian influenza data and real-time surveillance information for risk assessments. In addition, the WHO Regional Office has supported national pandemic containment exercises that encourage multisectoral collaboration and improve national pandemic preparedness plans.[13]

Risk communication is essential to moblize an effective public health response to influenza. The 2009 H1N1 influenza pandemic highlighted the importance of comprehensive risk communication strategies; the lessons learnt were applied for timely and transparent risk communication after discovery of the first human case of influenza A(H7N9) in China.[14] Although significant progress has been made in risk communication over the last decade, there is still room for improvement. Efforts under way in Australia highlight improvements in risk communication for in Australian Aboriginal communities[15] and secondary school students.[16]

Lessons learnt from the 2009 pandemic mobilized the World Health Assembly to adopt the Pandemic Influenza Preparedness (PIP) framework in 2011, enabling efficient and equitable access to vaccines and medicines during future pandemics.[17] Critical to these efforts is utilization of national surveillance data to support Member State policies and systems for seasonal influenza vaccination of high-risk groups. Determination of national disease burden, as described in detail for recent efforts in Cambodia[18] and China,[19] is imperative for obtaining national funding to support vaccination of high-risk groups and for influenza vaccination systems that can be scaled up quickly in the face of a pandemic. Collaborative efforts of PIP and the Partnership for Influenza Vaccine Introduction continue to support increased pandemic readiness through the expansion of national seasonal influenza vaccination programmes in low- and middle-income countries.[10]

WHO has been working with partners to ensure strong regional systems are in place to support the rapid detection, identification, reporting and risk assessment of any events with pandemic potential in the Western Pacific Region. As reflected in published influenza profiles[20] of the laboratory, surveillance and vaccination capacities for 37 countries and areas, influenza preparedness is well documented across the Region, including for surveillance and vaccination of high-risk groups. Under the guidance of APSED III, Member States have prioritized regional and global health security, learning from the past, engaging in the present and preparing for the future. This special issue highlights the Region's collective journey in pandemic influenza preparedness and its significant progress over the last decade to improve health security in the Region and the world.

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Planning for and responding to pandemic influenza emergencies: it's time to listen to, prioritize and privilege Aboriginal perspectives

Kristy Crooks,[a,d] Peter D Massey,[a,b] Kylie Taylor,[c] Adrian Miller,[e] Sandra Campbell[f] and Ross Andrews[d,g]

Correspondence to Kristy Crooks (email: kristy.crooks@hnehealth.nsw.gov.au)

Australia's Indigenous peoples account for 3% of the country's population yet continue to experience disproportionately higher rates of mortality and hospitalization for many infectious diseases.[1] The 2009 influenza pandemic had an inequitable impact on Indigenous peoples in Australia,[2] New Zealand,[3] the Americas and the Pacific.[4] Genuine and tangible actions that include Indigenous peoples in the planning and response for pandemic influenza is overdue. This paper will identify some of the strategies to incorporate the perspectives of Australia's Indigenous peoples (hereafter Aboriginal) in planning and responding to infectious disease emergencies.

Historically, infectious diseases have had a major impact on Indigenous peoples internationally. In North America, European contact and ensuing economic developments changed the nature of infectious disease ecology and exacerbated the frequency and severity of the problem for this population.[5] The European invasion of Australia brought new diseases such as varicella, smallpox, influenza and measles to which Aboriginal people had little or no immunity.[6] The influenza pandemic of 1918–1919 had a devastating impact on the Aboriginal population;[7] however, the full impact is unlikely to be known because many Aboriginal deaths went unrecorded.[6] In the 2009 Australian influenza pandemic, the rate ratio comparing Aboriginal people in New South Wales with non-Aboriginal people was 4.2 for hospital admissions, 3.9 for intensive care unit admissions and 5.6 for deaths.[8]

The health science field, dominated by scientific quantitative methods often fails to recognize Aboriginal perspectives[9] as Aboriginal ways of knowing and being are fundamentally different and culturally specific. These differences need to be acknowledged and understood by public health professionals and policy-makers and incorporated into health practice and policy. The omission of Aboriginal people from Australia's pre-2009 pandemic plan[10] is an example of how Aboriginal people have been excluded from the planning and response to infectious disease emergencies. While the current Australian pandemic plan highlights the need for equity and two-way communication with Aboriginal people, there are no recommendations on how to achieve this, and, therefore, the plan inadequately addresses the needs of Aboriginal communities.[11]

Aboriginal people continue to be the subject of health service delivery and policy without the opportunity to be part of the decision-making about their health.[12] Given the historical factors and complexities of contemporary Aboriginal health, a one-size-fits-all approach to pandemic influenza is unlikely to work.[13–15] Measures to reduce the risk of public health emergencies in Aboriginal communities need to be developed with and led by communities to maximize their acceptance, impact and effect. There must be a clear process of engagement and two-way respectful and meaningful communication with Aboriginal communities to identify culturally appropriate and effective public health control strategies.[13]

[a] Hunter New England Local Health District, Population Health, Wallsend, New South Wales, Australia.
[b] College of Medicine and Dentistry, James Cook University, Cairns, Queensland, Australia.
[c] Hunter New England Local Health District, Population Health, Tamworth, New South Wales, Australia.
[d] Menzies School of Health Research, Charles Darwin University, Casuarina, Darwin, Northern Territory, Australia.
[e] Office of Indigenous Engagement, Central Queensland University, Townsville, Queensland, Australia.
[f] Indigenous Health, Research Division, Central Queensland University, Cairns, Queensland, Australia.
[g] National Centre for Epidemiology & Population Health, Australian National University, Canberra, Australian Capital Territory, Australia.
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To ensure cultural appropriateness in pandemic influenza planning and response, management plans and control strategies must appropriately reflect and prioritize the social realities of Aboriginal communities. Families are an intrinsic element in Aboriginal culture; therefore, emphasis on the value of kinship, family structures and social connectedness with a family-centred approach should be adopted.[13] Additionally, pandemic influenza control strategies often include household contacts, but this may or may not encapsulate the risk for Aboriginal families where shared lives and communities are different from mainstream Australia. These differences must be incorporated into pandemic influenza planning so that Aboriginal people are no longer disproportionately affected.

Participatory approaches with Aboriginal communities are becoming a more culturally appropriate and acceptable method for strengthening engagement and building community empowerment.[16] Collaborative engagement processes using qualitative approaches could provide insight into the diverse community perspectives,[16,17] and identify barriers to implementation of disease control strategies.[18] Plans and control strategies need to:

- be developed early with Aboriginal organizations and key stakeholders;
- be flexible to meet local priorities;
- include how to reduce risk in families and at large community events;
- ensure targeted communication strategies are co-developed;
- have flexible models of health care to access vaccinations and other medical interventions, and
- include a stakeholder engagement plan

Including these aspects in pandemic planning are integral to enable Aboriginal people to achieve the level of risk of influenza as the general population and look to a future where Aboriginal people can thrive.

In this period, before the next influenza pandemic, it is the time to listen, prioritize and privilege Indigenous voices internationally. To privilege Aboriginal voices means more than just an equity approach, it is about removing paternalistic approaches to health care and moving beyond listening to and consulting with Aboriginal people about health issues. It is about creating a space where Aboriginal people are at the centre, guiding decision-making processes within a culturally appropriate governance structure that is built on the principles of collaboration, power-sharing, transparent communication, mutual accountability and shared responsibility. Infectious disease emergency plans developed without respectful and meaningful engagement is identified as a barrier to acceptance and implementation.[13] Specific localized plans for Aboriginal communities are needed[13] that are culturally centred, reflect the diverse socio-cultural practices and that can be reassessed and updated in collaboration with public health emergency leaders to meet the changing needs of the community.[16] Infectious disease emergency planners must, with Aboriginal peoples, develop a robust understanding of the issues, be culturally safe, appropriate, inclusive and responsive in the development of disease control strategies. This can happen only if public health approaches are developed in partnership with Aboriginal people, not for them. Aboriginal people need to be engaged in the dialogue, leading the way in the construction of knowledge that is supportive of self-determination. Privileging Aboriginal voices will enable culturally informed strategies and may reduce inequity and the risk of pandemic influenza.

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Strategies for combating avian influenza in the Asia–Pacific

Lisa Peters,[a] Carolyn Greene,[b] Eduardo Azziz-Baumgartner,[b] Suizan Zhou,[b] Socorro Lupisan,[c] Wang Dayan,[d] Aspen Hammond,[e] Filip Claes,[f] Elizabeth Mumford[e] and Erica Dueger[a,b *]

Correspondence to Erica Dueger (email: wpsar@who.int)

Avian, swine and other zoonotic influenza viruses may cause disease with significant impact in both human and animal populations. The Asia Pacific Strategy for Emerging Diseases (APSED), long recognizing the increased global impact of zoonotic diseases on human populations, has been used as the foundation for improving national preparedness and regional coordination for response to zoonotic diseases in the World Health Organization (WHO) Western Pacific Region.[1] APSED encourages multisectoral coordination at the human–animal–environment interface as the primary action required for zoonotic disease control.[2] In this article we emphasize the effectiveness of these multisectoral collaborations in responding to zoonotic diseases at the regional and country level, using avian influenza as an example.

In the 2006 version of APSED, the proposed approach for addressing zoonoses was: to strengthen regional mechanisms to support national-level collaborations between the animal, human and environmental health sectors; and to strengthen national-level capacity for collaboration between the animal and human health sectors.[3] The regional component was achieved through a tripartite collaboration of the Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (OIE) and WHO, which formalized a commitment to coordinate activities and risk reduction strategies at the human–animal–environment interface, taking a One Health approach in 2010.[4,5] The national component was addressed by developing national-level guidelines for establishing collaborations between national human and animal health sectors, providing a step-by-step approach to improve coordination of surveillance, information sharing, response and risk reduction.[3]

During the last five years, the emergence and spread of the H7N9 virus in domestic poultry and the occurrence of human cases in China have illustrated the importance of working at the human–animal–environment interface at the country and regional level. When the first human case of H7N9 virus infection was reported from China in March 2013, pandemic preparedness capacities were quickly tested. First, a swift, multisectoral response was undertaken by the Chinese Government to facilitate early detection and reporting of H7N9 in poultry and humans.[6] Then, the Chinese National Influenza Center shared H7N9 sequences, diagnostic test protocols and viruses with the Global Initiative on Sharing All Influenza Data (GISAID) public database,[11] the WHO influenza collaborating centres and the National Avian Influenza Reference Laboratory in Haerbin. These actions contributed greatly to the global risk assessment and response, including the selection and development of candidate human H7N9 vaccine viruses, vaccine potency and diagnostic reagents, as well as a better understanding of antigenicity, pathogenicity and transmissibility of the virus.[7] The Chinese Government also issued prevention and control guidelines including enhanced surveillance for influenza-like illness and severe acute respiratory infection in humans, improved case investigation and contact tracing and early treatment of human illness.[8] Meanwhile, at the regional level, multisectoral mechanisms were also activated that included increased surveillance in humans and poultry populations at border areas in Viet Nam, the Lao People's Democratic Republic and Myanmar and the sharing of information from China within the region.

Prior to 2017, only the low pathogenic avian influenza (LPAI) form of the H7N9 virus had been detected in poultry in China, with intermittent human

[a] WHO Regional Office for the Western Pacific.
[b] United States Centers for Disease Control and Prevention.
[c] Research Institute for Tropical Medicine, Philippine Department of Health.
[d] National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention.
[e] World Health Organization.
[f] Food and Agriculture Organization of the United Nations.
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cases, usually associated with poultry exposure. LPAI shows little to no clinical signs of infection in poultry, but it is important to monitor and control to prevent the spread to humans. In early 2017, H7N9 viruses that were highly pathogenic avian influenza (HPAI) were detected in poultry and humans in China.[6] Among the 759 human infections of H7N9 identified in China from October 2016 to September 2017, 27 were associated with HPAI H7N9.[13] HPAI often causes illness and death in poultry, facilitating strict control measures to stop the spread of disease among animals and to humans. Responses to this included the promotion of large-scale poultry farming by the Chinese Government (as opposed to higher-risk household or small-holder poultry holdings), centralized slaughtering, improved poultry product cold chain transportation and storage and expanded implementation of the "1110" strategy in live poultry markets. The 1110 strategy involves *1* daily cleaning, *1* weekly disinfection, *1* day of market closure every month and *0* live poultry stock overnight.[9] In September 2017, the Chinese national poultry vaccination programme with bivalent H5/H7 vaccine was launched.[9] In addition to targeted human and animal surveillance and control efforts, regular tripartite risk assessments based on updated national data have informed H7N9 response efforts. These response and control efforts were directly in line with the APSED goal of strengthening coordination at the human–animal interface and underscore the importance of continued regional improvements in this area.

The need for coordinated multisectoral preparedness to respond to acute zoonotic threats was also underscored in April 2017 when the Philippines detected its first outbreak of avian influenza in poultry. Rapid response teams were dispatched and samples were sent to an FAO reference centre laboratory. When avian influenza A(H5N6) was confirmed, the rapid response teams established a 1 km quarantine area and a 7 km control area around infected poultry farms. Strict animal surveillance and movement control measures were implemented and over 500 000 birds were destroyed. Concurrently, intensive surveillance was initiated at both hospital and community levels as well as community awareness campaigns. The acute H5N6 outbreak was resolved in poultry by September 2017 with no human cases detected, highlighting the importance of prioritizing multisectoral collaborations and preparedness efforts, even in countries that have not previously experienced major avian influenza outbreaks.

To continue to support national collaborations between animal, human and environmental health sectors, the WHO, OIE and FAO tripartite has been updating and expanding the tripartite zoonoses guide, entitled: Taking a Multisectoral, One Health Approach: A Tripartite Guide to Addressing Zoonotic Diseases in Countries.[12] The guide addresses coordinating mechanisms, planning and preparedness, surveillance and information sharing, coordinated investigation and response, joint risk assessments, risk communication, community engagement, joint risk reduction strategies and training and workforce development. The Joint Risk Assessment tool,[14] designed to evaluate risks and guide appropriate preparedness and response actions and risk communication, is included in the guide. The tool outlines the multisectoral organizational and technical processes and steps needed to assess the level of risk based on the likelihood and potential impact of zoonotic events. The Joint Risk Assessment tool[14] was designed to guide appropriate preparedness and response actions for zoonotic influenza;, however, it is equally applicable to other emerging zoonotic disease threats.

Successful country response efforts to avian influenza A(H7N9) in China and influenza A(H5N6) in the Philippines exemplify the importance of strong multisectoral collaboration for zoonotic diseases at both national and regional levels. The Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III) and the tripartite zoonoses guide will continue to assist countries in Asia and the Pacific to maintain and improve coordination between the human, animal and environmental health sectors for rapid and effective response efforts to emergent zoonotic influenza viruses.

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Preparedness for influenza vaccination during a pandemic in the World Health Organization Western Pacific Region

Leila Bell,[a] Lisa Peters,[a] James D Heffelfinger,[a] Sheena G Sullivan,[b,c] Alba Vilajeliu,[a] Jinho Shin,[a] Joseph Bresee[d] and Erica Dueger[a,d]

Corresponding author: Erica Dueger (email: wpsar@who.int)

BACKGROUND

Influenza vaccination is a key public health intervention for pandemic influenza as it can limit the burden of disease, especially in high-risk groups, minimize social disruption and reduce economic impact.[1] In the event of an influenza pandemic, large-scale production, distribution and administration of pandemic vaccines in the shortest time possible is required. In addition, monitoring vaccine effectiveness, coverage and adverse events following immunization (AEFI) is important. Since seasonal influenza vaccination programmes require annual planning in each of these areas, establishing and strengthening annual influenza programmes will contribute to pandemic preparedness.[2] This paper presents efforts made in the World Health Organization (WHO) Western Pacific Region to improve seasonal influenza vaccination and pandemic preparedness.

Several initiatives have been established in response to the World Health Assembly goal set in 2003 of reaching 75% influenza vaccination in persons ≥65 years by 2010.[3] In 2006, the Global Action Plan for Influenza Vaccines (GAP) (2006–16 strategy) aimed to increase the use of seasonal influenza vaccines, increase vaccine production capacity and promote research and development for improved vaccines and vaccine production technologies.[3] The goal of GAP was to produce enough vaccine to immunize 70% of the global population with two doses of the influenza vaccine within six months of the identification of a pandemic strain (approximately 10 billion doses) and to develop national vaccine deployment plans for pandemic influenza.

The 2009 pandemic highlighted that there was a lack of existing national influenza vaccination programmes, which was a barrier to rapid deployment of pandemic vaccines. The primary challenges in the WHO Western Pacific Region for vaccination during a pandemic response was the limited experience in many countries in conducting vaccination campaigns, mobilizing financial support for vaccine deployment, refining national planning guidelines and deployment plans and establishing sufficient cold-chain capacities.[4]

In 2011, the World Health Assembly adopted the Pandemic Influenza Preparedness (PIP) framework to address more predictable, efficient and equitable access to vaccines and medicines during future pandemics through establishing antiviral and interpandemic vaccine stockpiles.[5] In 2012, the Partnership for Influenza Vaccine Introduction (PIVI)[6] – a collaboration between the Global Health Task Force, the United States Centers for Disease Control and Prevention, various ministries of health and pharmaceutical and technology industry partners – also supported increased pandemic readiness by expanding national seasonal influenza vaccination programmes in several countries in the Region, including the Lao People's Democratic Republic, Mongolia and Viet Nam.

Production of influenza vaccines

The process and logistics required to manufacture and produce seasonal influenza vaccines can be used for possible pandemic strains when quick action is required on a large scale.[2] The capacity for an effective and timely pandemic vaccine response remains limited by the time

[a] WHO Regional Office for the Western Pacific, Emerging Diseases Surveillance and Response.
[b] WHO Collaborating Centre for Reference and Research on Influenza at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia.
[c] Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia.
[d] Centers for Disease Control and Prevention, Atlanta, Georgia.

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required to manufacture pandemic vaccines and by global vaccine production capacity.[7] Strong systems for detection of new influenza variants are also critical. The Global Influenza Surveillance and Response System is tasked with monitoring influenza strains to detect new variants through a network of laboratories around the world.[8] To ensure adequate production for influenza vaccines during a pandemic, multiple influenza vaccine manufacturers are required so that supply meets demand, vaccine pricing is competitive and manufacturers with capacity and operational plans in place can switch from seasonal to pandemic influenza vaccine production as needed.

In the Western Pacific Region, four countries produce influenza vaccines with three (Australia, China and Republic of Korea) distributing WHO-prequalified influenza vaccines globally. Two (Japan and Republic of Korea) recently built large-scale, cell-based manufacturing plants. Efforts are ongoing to strengthen influenza vaccine supply hubs in Asia and the Pacific, focusing on GAP grantee manufacturers in China, India, Thailand and Viet Nam.[9]

Influenza vaccine regulatory approval and deployment plans

Country vaccination programmes will need policies and effective regulatory pathways in place to rapidly accept, distribute and administer the new pandemic vaccine. Effective mechanisms for seasonal influenza vaccination distribution can be used for distribution during a pandemic.[2,10] WHO encourages optimizing regulatory pathways and the inclusion of a vaccine deployment plan when developing or updating a national pandemic preparedness plan.

An example, albeit on a small scale, of using established seasonal influenza detection, reporting and distribution mechanisms to respond to unusual influenza activity occurred in May 2016 when four pregnant women with severe acute respiratory infection died in Fiji within a five-week period. The laboratory detected an apparent variant of influenza A(H1N1)pdm09 from specimens isolated from two cases.[11] As per testing protocols, the isolates were sent to a WHO Collaborating Centre to confirm that the virus was truly a variant. At the same time, 150 courses of oseltamivir and 20 000 adult seasonal influenza vaccine doses were distributed, targeting pregnant women and health-care workers. The Collaborating Centre determined that neither of the two A(H1N1)pdm09 isolates were novel variants (internal communication). This strong detection and reporting system, aligned with a global response system able to verify laboratory results and assure timely delivery of vaccine and oseltamivir, resulted in an appropriate response to the event. However, had this been a new influenza strain, additional efforts to develop a new vaccine would have been required.

Influenza vaccine policy development and seasonal influenza vaccination programme implementation

Over the past decade, the number of countries and areas with seasonal influenza immunization policies has increased, as has the number of vaccines distributed globally.[12,13] In the Western Pacific Region, the number of Member States that reported having influenza immunization policies increased from 12 in 2011 to 16 in 2014.[13,14] Based on a survey conducted in the Region in 2017, 24 of the 37 countries and areas reported having an influenza immunization policy targeting at least one of the WHO-recommended priority groups (WHO, unpublished data, 2017). However, evidence has also indicated that formal policies or recommendations do not necessarily lead to wider distribution of influenza vaccine as influenza vaccine distribution by pharmaceutical companies per 1000 population decreased between 2011 and 2014.[13,15] Distribution data also cannot account for vaccine wastage or returns and do not provide information on implementation or vaccination rates in high-risk groups. In the Western Pacific Region, improving seasonal influenza vaccination coverage is challenging due to extensive geographic and demographic diversity and varied influenza transmission patterns, burden and vaccination policies.[14,16]

The Lao People's Democratic Republic, one of the countries that receives PIP support and the first country to receive support from PIVI, provides an example of using influenza surveillance data to improve vaccination coverage. As their influenza surveillance data indicated a substantial disease burden, they developed a multiyear introduction plan for influenza vaccine, established systems to evaluate the vaccine programme and are developing a sustainability plan.[17] Since 2014, more than 1.5 million persons have been vaccinated with a focus on high-risk groups such as pregnant women and healthcare workers.[6] The Lao People's Democratic Republic has developed a robust vaccination programme to support timely and efficient vaccine use in response to the next influenza pandemic.

Viet Nam and Mongolia are also working to strengthen their influenza programmes through several initiatives including strengthening the National Immunization Technical Advisory Group and conducting Knowledge, Attitudes and Perceptions surveys to inform their influenza vaccine communication strategies. Viet Nam trained and vaccinated nearly 11 000 health-care workers in 2017, and Mongolia conducted a national survey on AEFI of health-care workers and pregnant women who received the influenza vaccine.[6] These efforts aim to create sustainable seasonal influenza programmes by training health-care workers, developing communication materials, improving vaccine acceptability, establishing monitoring systems for AEFI and assessing influenza vaccine coverage and impact.

CONCLUSIONS

The Western Pacific Region has made improvements to its seasonal influenza vaccination programmes and vaccination planning for pandemic preparedness. This includes improved laboratory capacity to rapidly identify new circulating virus strains, support for development of influenza vaccine regional supply hubs, capacity-building for national regulatory processes and development of vaccine deployments plans. Efforts are also ongoing to strengthen influenza surveillance systems to determine disease severity in order to inform the priority groups to target when designing influenza vaccine policies. Continued political commitment from Member States and support by the global community are needed to ensure that sustainable and robust national seasonal influenza programmes are in place for effective response to the next pandemic.

Conflicts of interest

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Learning from recent outbreaks to strengthen risk communication capacity for the next influenza pandemic in the Western Pacific Region

Lauren J O'Connor,[a] Lisa Peters[a] and Rose Aynsley[b]
Correspondence to Lauren O'Connor (email: oconnorl@who.int)

When an influenza pandemic swept the globe in 1918, it was nicknamed the "Spanish flu" despite evidence of circulation in other countries. This was because the Spanish press were free to publish stories about the outbreak that peers in neighbouring countries were not due to wartime censors.[1] Other governments hid negative news about the pandemic and over-reassured the public. Attempts to prevent panic backfired, and the resulting breakdown in trust "threatened to break the society apart".[1]

The 1918 pandemic illustrates the consequences of failing to transparently and effectively communicate risks to the public during a public health event. This article discusses the lessons learnt in risk communication during the response to recent outbreaks in the World Health Organization's Western Pacific Region. These lessons can inform preparedness for pandemic influenza and other public health threats.

Risk communication is defined as "the real-time exchange of information, advice and opinions between experts, community leaders, or officials and the people who are at risk".[2] The outbreak of severe acute respiratory syndrome (SARS) in China in 2002 in particular highlighted the importance of open risk communication – a lesson that was reiterated once more during the outbreak of Middle East respiratory syndrome in the Republic of Korea in 2015. Effective risk communication during a public health emergency can be difficult, especially in the early stages when many of the facts may be uncertain. Health authorities can be reluctant to proactively communicate as they are apprehensive of saying the wrong thing, creating panic or looking like they do not have all the answers. However, delaying communication can result in the public listening to rumours or relying on less accurate sources of information,[3] or can lead to the very panic authorities were trying to prevent.[4]

Done correctly, however, risk communication can calm fears, facilitate the acceptance of containment measures, curtail the spread of unhelpful rumours and engage affected communities in control measures. In the wake of SARS, risk communication was included as a core capacity required of Member States under the International Health Regulations (2005).[5] Guidance on how to implement and build risk communication capacity has also been part of the Asia Pacific Strategy for Emerging Diseases (APSED) since the first 2005 edition.[6] It has long been recognized that national risk communication plans, supported by trained risk communication personnel, adequate financial allocations, clear internal procedures and mechanisms for coordination, are essential for effective risk communication and should be established before the onset of a public health emergency. Advance preparation, including building an understanding of prevailing cultural practices and establishing relationships with community influencers, is central to ensuring that risk communication efforts are tailored to the local context.

The 2009 influenza A(H1N1) pandemic highlighted some further lessons that apply specifically to influenza and need to be considered ahead of the next influenza pandemic. For example, perceptions of the severity of the disease varied widely. Many people confused it with seasonal influenza and therefore thought the risk to their

[a] WHO Regional Office for the Western Pacific, Division of Health Security and Emergencies.
[b] WHO Regional Office for the Western Pacific, Division of Pacific Technical Support.
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health was low, while others expressed a high level of concern about the virus.[7] Some people also had immense distrust in the vaccine, because of perceived conflicts of interest between pharmaceutical companies and health authorities.[7] Research published following the H1N1 pandemic indicated that countries should be prepared to address rumours and misconceptions about vaccine safety, to carefully communicate the severity of disease and to enlist the support of trusted members of the community.[7] The role of social media also needed to be considered.[8] After the 2009 pandemic, it was recognized that risk communication approaches could be tested and honed during seasonal influenza outbreaks.[9]

Ten years after SARS, China proactively informed the public and international community about human cases of avian influenza (H7N9), demonstrating the benefit of timely and transparent risk communication.[10] Chinese focus group participants were reassured by this increase in transparency, with one participant stating, "I am quite positive that our government absolutely has the capability to control this disease".[11] Another study found that discussion of H7N9 on Sina Weibo, a popular Chinese social media platform, dropped following several formal announcements, potentially indicating reduced public concern about the outbreak.[10]

While social media was used to listen to the public following the discovery of human cases of H7N9, the response to an outbreak of influenza-associated severe acute respiratory infections (SARI) in Fiji in 2016 showed that more traditional means of communication still have a place in effective risk communication. Health authorities worked with religious leaders, women's groups and youth networks to engage vulnerable groups, particularly pregnant women, encouraging vaccination and adoption of protective behaviours.[12,13] For communities in remote areas and outer islands, where communication is often limited, authorities shared health messages via radio, reaching an estimated 90% of the population.[14]

Unfortunately, while much progress has been achieved in risk communication under APSED, other core public health capacities for pandemic preparedness and response continue to be prioritized over risk communication. Results from joint external evaluations of IHR core capacities in the Western Pacific Region show that countries score far higher on traditional public health capacities, such as surveillance and laboratory networks, than they do on risk communication.[15] Countries are encouraged to learn from recent outbreaks and emergencies and to invest in their internal capacity for risk communication as per the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III).[16] This includes integrating risk communication into outbreak preparedness, planning and response, communicating quickly and transparently, using a mixture of channels to best reach their target audience (including social media, where appropriate) and actively engaging communities in the response.

The vision laid out in APSED III is one where risk communication moves from being purely an art to also a science, as risk communication becomes more professionalized and evidence-based. Risk communication professionals should come to be recognized as social scientists conducting work that is as important to the success of emergency preparedness and response as the work of epidemiologists, laboratory experts and other public health personnel. In prioritizing and strengthening risk communication, countries will be better placed to limit the health, social and economic impacts of the next influenza pandemic.

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A severe 2017 influenza season dominated by influenza A(H3N2), Victoria, Australia

Grant KA,[a] Carville KS,[a] Sullivan SG,[b,c,d] Strachan J,[e] Druce J[a] and Fielding JE[a,f]

Correspondence to Kristina Grant (email: kristina.grant@mh.org.au)

Surveillance for influenza-like illness (ILI) and laboratory-confirmed influenza in Victoria, Australia is undertaken jointly by the Victorian Infectious Diseases Reference Laboratory and the Victorian Government Department of Health and Human Services from May to October each year. Surveillance data comprise notifiable laboratory-confirmed influenza and ILI reporting from from two sources – a general practice sentinel surveillance programme and a locum service.

The magnitude of the 2017 influenza season was high in Victoria with widespread circulation of influenza type A(H3N2), which peaked in September. A record number of laboratory-confirmed influenza cases were notified, and the proportion of ILI cases to total consultations from both the general practice and locum service were higher than previous years. Notified cases of influenza A were older than influenza B cases with 25% compared to 17% aged more than 65 years, respectively. The proportion of swabs that were positive for influenza peaked at 58%. Antigenic characterization suggested a good match between the circulating and vaccine strains of influenza A(H3N2).

Most of the increases observed in notified cases of laboratory-confirmed influenza in recent years in Victoria have been attributed to increases in testing. However, that cases of ILI also increased in Victoria in 2017 is suggestive that 2017 was a relatively severe season. The dominance of influenza type A(H3N2), the extended duration of elevated activity, and a potential phylogenetic mismatch of vaccine to circulating strains are likely to have contributed to the relative severity of the 2017 season.

Victoria is Australia's second most populous state and is the mainland's southernmost state. It has a temperate climate with an influenza season usually occurring in the cooler months between May and October. The Victorian Infectious Diseases Reference Laboratory (VIDRL), in partnership with the Victorian Government Department of Health and Human Services (DHHS), coordinates influenza-like illness (ILI) and laboratory-confirmed influenza surveillance in Victoria. There are three data sources included in the influenza surveillance system.

The Victorian Sentinel Practice Influenza Network (VicSPIN) is a surveillance programme of sentinel general practitioners (GPs) that monitors ILI and laboratory-confirmed influenza in the community (previously known as the Victorian General Practice Sentinel Surveillance system).[1] VicSPIN operates annually between May and October.[1] Samples collected from ILI patients that subsequently test positive for influenza by VIDRL are submitted to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza for strain characterization and antiviral drug sensitivity testing.

Notified laboratory-confirmed influenza cases are reported from medical practitioners and laboratory services in Victoria who are required by law to notify DHHS of all laboratory-confirmed cases of influenza within five days of diagnosis. Notifications require identification, demographic and diagnostic data.

The National Home Doctor Service (NHDS) is the largest medical locum service in Australia and provides 24-hour medical services to patients at their residences.[2] The data entered into the NHDS database were analysed to determine the proportion of ILI diagnoses made from all consultations.

In this study, the data from these three surveillance programmes are used to describe the epidemiology of the 2017 influenza season in Victoria, Australia.

[a] Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia.
[b] WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia.
[c] School of Global and Population Health, University of Melbourne, Australia.
[d] Discipline of General Practice, University of Adelaide, Australia.
[e] Communicable Diseases Epidemiology and Surveillance, Health Protection Branch, Department of Health and Human Services.
[f] School of Global and Population Health, University of Melbourne, Australia.
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METHODS

Surveillance data

Victorian Sentinel Practice Influenza Network (VicSPIN)

In 2017, 88 GPs participated in the VicSPIN surveillance programme from 1 May to 4 November. GPs reported the number of ILI cases each week and the total number of consultations as well as age, gender and vaccination status of ILI cases. The definition of ILI was a patient with fever, cough and fatigue/malaise. A nose or throat swab was collected from as many ILI cases as possible, at the GPs discretion, for those patients presenting within four days of symptom onset. Additional data collected on swabbed patients included seasonal influenza vaccination status for the previous year (as well as the current year), date of vaccination/s, fever (reported or measured) and any co-morbidity for which influenza vaccination is recommended.[3]

The samples were submitted to VIDRL where ribonucleic acid was extracted and tested using in-house validated real-time multiplex polymerase chain reaction (PCR) assays to detect type A influenza viruses (matrix gene), type B influenza viruses (nucleoprotein gene) and type C influenza viruses (matrix gene). Influenza A virus-positive samples were further subtyped using individual real-time PCR assays incorporating primers and probes specific for the haemagglutinin gene of A(H1N1)pdm09 and A(H3) strains.[4] Samples positive for influenza were forwarded to the WHO Collaborating Centre for Reference and Research on Influenza for antigenic characterization.

Notifiable diseases surveillance

Cases of laboratory-confirmed influenza notified to DHHS in 2017 were extracted from the DHHS system. Only cases routinely notified were included in the analysis; cases identified and reported as part of an outbreak investigation or from other screening activities were excluded.

National Home Doctor Service (NHDS)

NHDS locums entered consultation data into the NHDS database daily. De-identified data from this database were accessed by VicSPIN staff who applied an algorithm to return records in which the words "influenza" and "flu" were included in the case notes. These records became the ILI cases and, along with total consultations, were aggregated daily and made available to the researchers via a secure website. To avoid inclusion of those immunized prophylactically during the 2009 pandemic, records that contained the terms "Fluvax", "at risk" and "immunization" were excluded.

Strain characterization and antiviral resistance testing

All influenza-positive samples in Victoria, including those from VicSPIN, were sent to the WHO Collaborating Centre for Reference and Research on Influenza for antigenic characterization and antiviral drug sensitivity testing. Samples were first inoculated into Madin-Darby Canine Kidney cells to obtain virus isolates. Those successfully isolated were then analysed by haemagglutination inhibition assay to determine antigenic similarity to the current vaccine strains.[5,6] Isolates were identified as antigenically similar to the reference strain if the test samples had a titre less than an eightfold difference compared with the homologous reference strain. Isolates were also tested in a neuraminidase inhibition assay to determine susceptibility to the antiviral drugs oseltamivir, zanamivir, peramivir and laninamivir.

Data analyses

Descriptive analyses of the surveillance data were conducted in Microsoft Excel. Comparison of proportions were tested using the $\chi 2$ test in Stata (version 14.1; StataCorp LP, College Station, TX, USA) with $P < 0.05$ considered significant.

The WHO method for ILI thresholds[7] was used to assign three threshold levels: seasonal (4–15 ILI cases per 1000 consultations), average (15–24 ILI cases per 1000 consultations) and alert thresholds (>24 ILI cases per 1000 consultations). Data from previous years were compared to evaluate the magnitude of the 2017 season.

RESULTS

Influenza-like illness

During 2017, VicSPIN GPs conducted 151 618 consultations of which 1208 were for patients with ILI – a proportion of 8.0 ILI cases per 1000 consultations. The

NHDS reported 206 833 consultations of which 4512 were for ILI, giving a proportion of 21.8 ILI cases per 1000 consultations.

The proportion of ILI cases reported by VicSPIN was within the average activity thresholds from 25 June to 8 October and peaked in late September at 15.9 cases per 1000 consultations to the alert threshold (Fig. 1). The majority of ILI cases were aged in the working age groups, mostly in the 30–49 age group (29.6%). Only 5.5% were aged 0–4 years and 11.1% were aged over 65 years.

The proportion of ILI cases reported by NHDS peaked in early September at 51.6 per 1000 consultations (Fig. 1). ILI activity was within the above-average activity threshold from mid-August to the end of September; it was above the lower limit for average activity on either side of this peak from mid-July to mid-October. The peaks for both VicSPIN and NHDS were higher than all previous years (Fig. 2).

Notified laboratory-confirmed influenza

There were 47 133 cases of laboratory-confirmed influenza routinely notified to DHHS in 2017 (**Fig. 3**). Of the 2017 cases, 64% were type A and 35% were type B. Ninety-five per cent (n = 44 796) of cases were notified during the usual influenza season of 1 May to 4 November. Notifications of influenza A peaked in August, whereas notifications of influenza B peaked later in September (**Fig. 3**). The number of notifications for 2017 was higher than previous years (**Fig. 4**).

The modal age group of notified influenza A cases was 65 years (n = 6866; 25%); for influenza B it was 30–49 years (n = 4864; 25%) (**Table 1**).

VicSPIN laboratory-confirmed ILI cases

Sixty per cent (n = 725) of the 1208 cases of ILI reported through VicSPIN were swabbed. Of these, 40% were positive for influenza: 12% were influenza A(H1N1) pdm09, 51% were influenza A(H3N2), and 37% were influenza B.

The majority of laboratory-confirmed influenza cases reported through VicSPIN (75%) were of working age (15–65 years) (Table 1). Eighteen of the 28 cases (64%) reported in those aged 65 years or older were type A(H3N2). Most influenza cases were detected between 10 July and 24 September (n = 232; 81%). The percentage of VicSPIN swabs positive for influenza peaked in July and was elevated until early October (Fig. 5) when cases of influenza type A decreased.

Vaccination status was reported for 91% of the 725 swabbed patients; of these, 35% were vaccinated with the proportion vaccinated increasing with age (**Fig. 6**). The difference in the proportion of influenza-positive and influenza-negative ILI cases who were vaccinated was statistically significantly (32% and 40%, respectively; P = 0.02). However, when the data were stratified by age, the difference was only statistically significant for those aged 65 years and older (64% and 88%, respectively; P = 0.01).

Of the 725 swabs received through VicSPIN, 18.2% were from patients reported to have co-morbidities for which influenza vaccine is recommended. Of these, 38.6% were positive for influenza, 22.7% were positive for other respiratory viruses and 38.6% were negative for any respiratory virus. Almost two thirds of these patients with co-morbidities (67%; n = 88) were vaccinated. The most commonly reported co-morbidity was asthma (n = 24; 18%).

Strain characterization and antiviral resistance testing

There were 1675 influenza isolates characterized antigenically in 2017 in Victoria (**Table 2**). A neuraminidase inhibition assay was conducted on 2378 isolates, with two being resistant to oseltamivir, one influenza A(H1N1) pdm09 and one influenza A(H3). One influenza A(H1N1) pdm09 was also resistant to zanamivir.

DISCUSSION

Victoria experienced a relatively severe influenza season in 2017; the seasonal peaks for both the ILI and laboratory-confirmed components of the system were the highest since the pandemic year of 2009. The ILI proportions from both VicSPIN and NHDS showed above-average activity thresholds. Since 2009, large annual increases in notified cases of laboratory-confirmed influenza have been largely attributed to increased laboratory testing, as ILI proportions reported from VicSPIN and NHDS remained

Fig. 1. **VicSPIN and NHDS ILI proportions and WHO thresholds, Victoria, Australia, 2017**

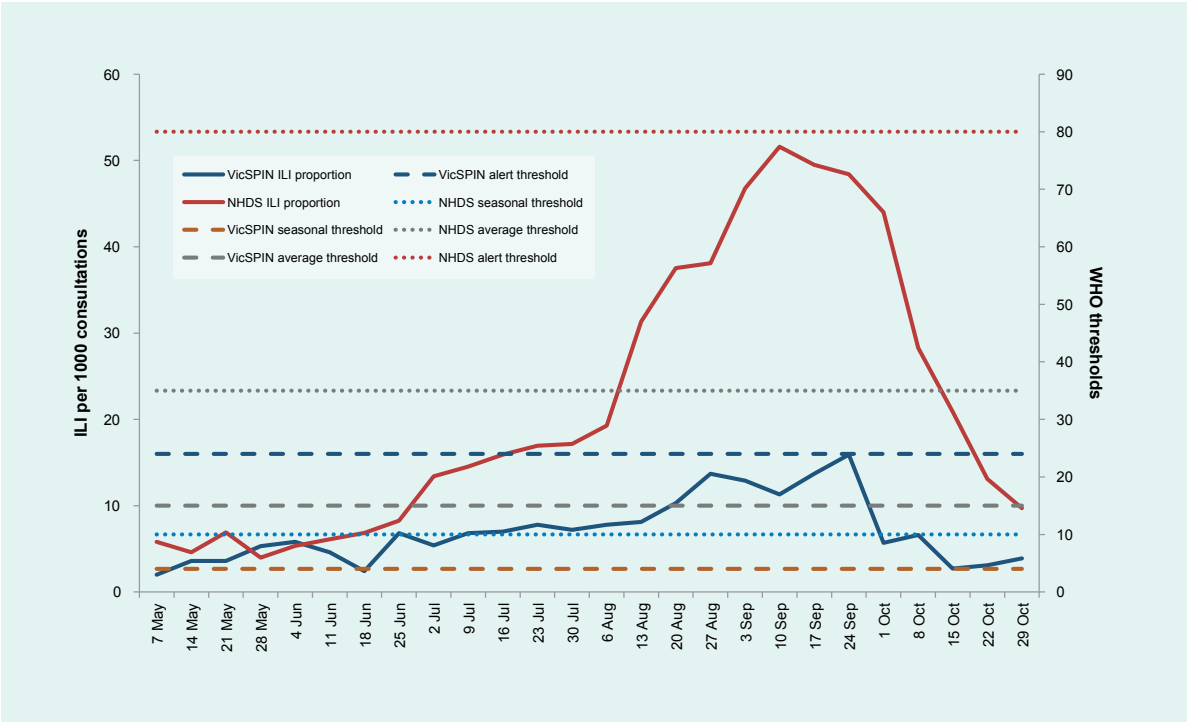


Fig. 2. **VicSPIN and NHDS ILI proportions, Victoria, Australia, 2007 to 2017**

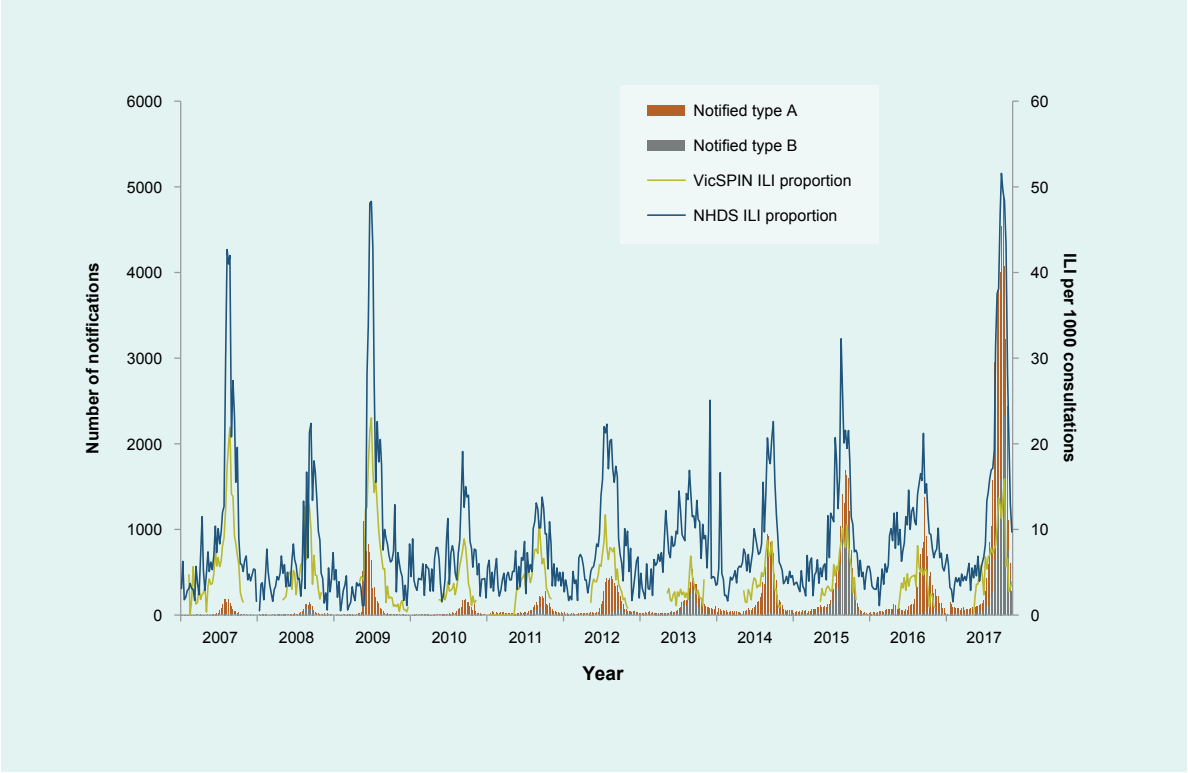


Fig. 3. **Notified cases by influenza type, Victoria, Australia, 2017**

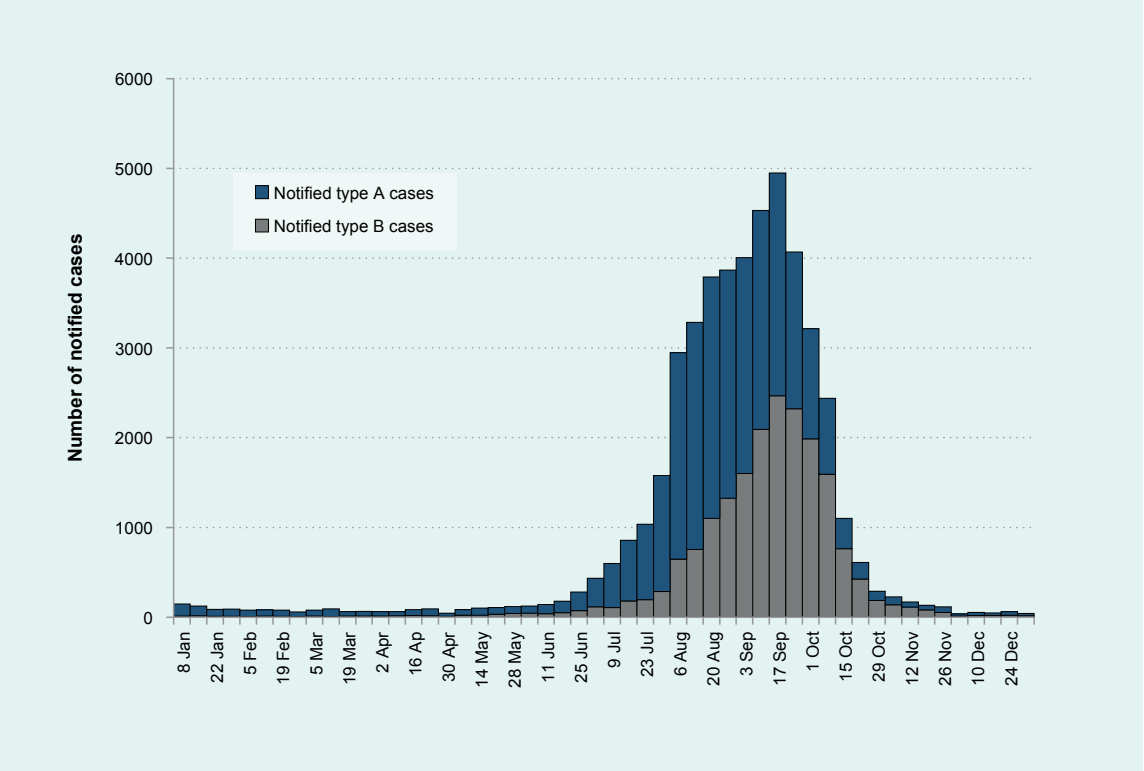


Fig. 4. **Notified cases of laboratory-confirmed influenza by influenza type, Victoria, Australia, 2007 to 2017**

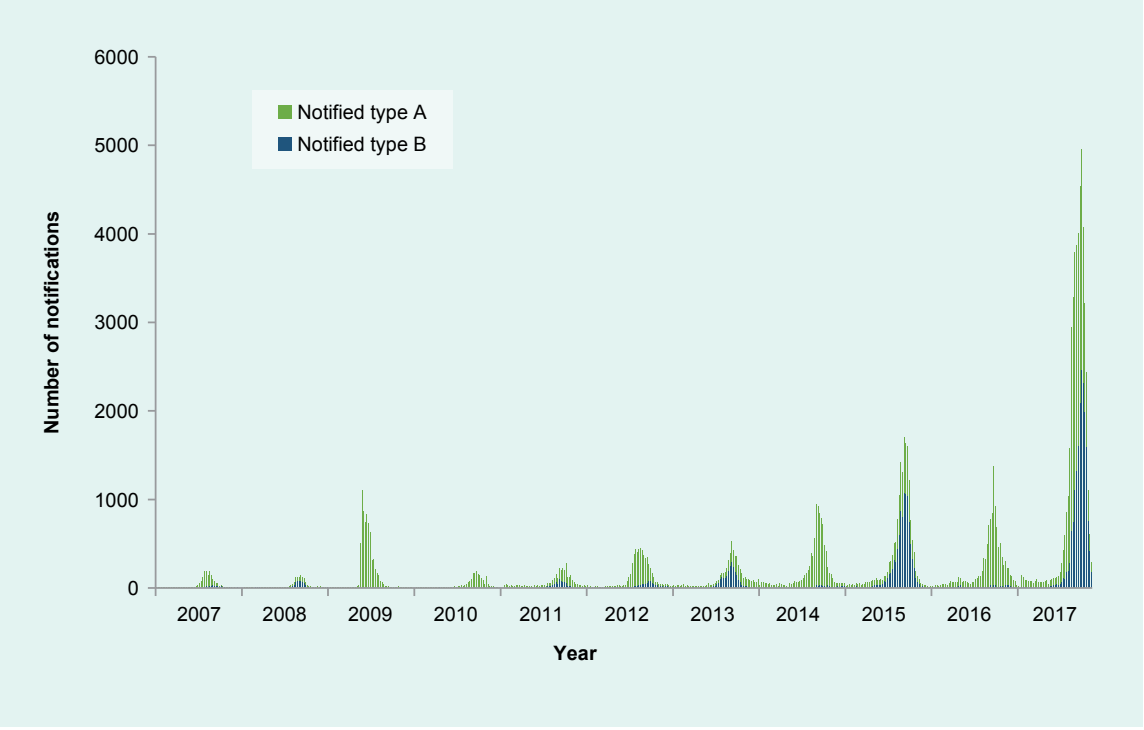
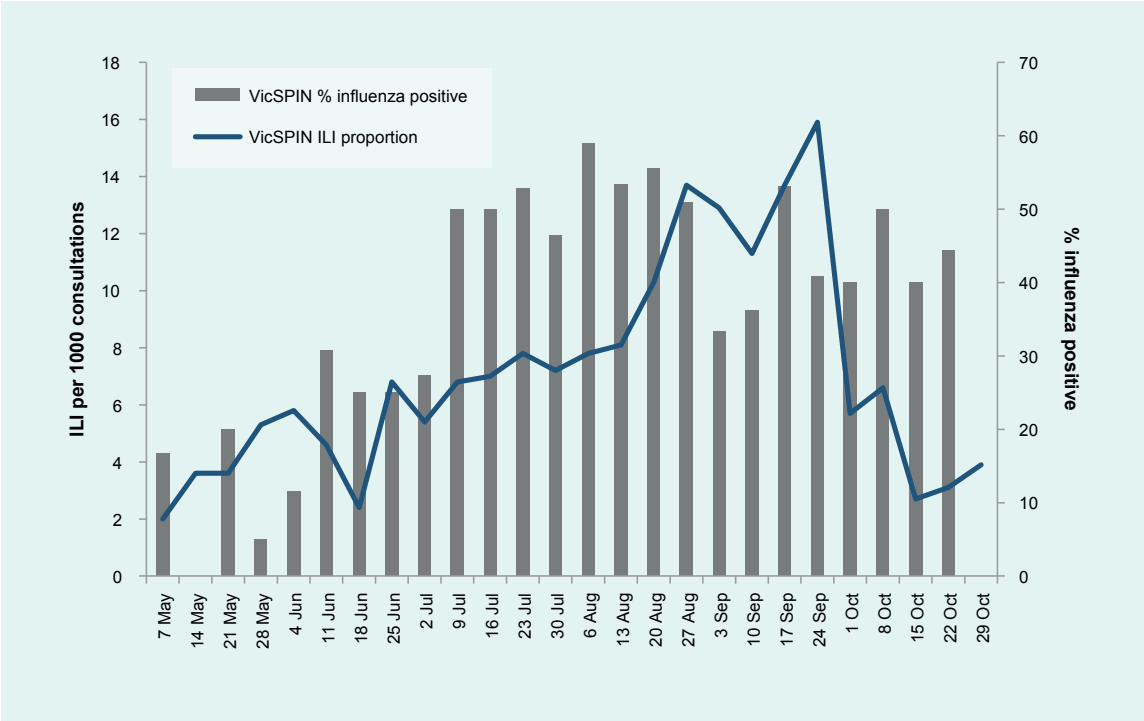


Table 1. **Notified and VicSPIN-detected laboratory-confirmed influenza cases, by age group and type/subtype, Victoria, Australia, 2017**

	Age group (years)	A(H1) n (%)	A(H3) n (%)	A (not subtyped) n (%)	B n (%)
Notified cases	0-4	-	-	2565 (9%)	1352 (7%)
	5-14	-	-	3247 (12%)	4044 (21%)
	15-29	-	-	3945 (14%)	2579 (14%)
	30-49	-	-	6604 (24%)	4864 (25%)
	50-64	-	-	4555 (16%)	3083 (16%)
	≥ 65	-	-	6866 (25%)	3180 (17%)
VicSPIN	0-4	3 (8%)	2 (1%)	-	2 (2%)
	5-14	8 (22%)	12 (8%)	-	17 (17%)
	15-29	6 (17%)	33 (23%)	-	17 (17%)
	30-49	8 (22%)	48 (33%)	1 (50%)	42 (41%)
	50-64	8 (22%)	33 (23%)	1 (50%)	18 (17%)
	≥ 65	3 (8%)	18 (12%)	-	7 (7%)

Fig. 5. **VicSPIN influenza-positive cases, Victoria, Australia, 2017**



comparable in magnitude.[8,9] However, the increase observed for notified cases in 2017 was particularly large at almost three times higher than the next largest year in 2015, and seven times more than the pandemic year of 2009, and was coupled with increases in ILI proportions reported from VicSPIN and NHDS. Similarly, the proportion of swabs positive for influenza in VicSPIN during 2017 was 41%, higher than previous seasons where it ranged from 22% to 39% (median = 34%) from 2010 and 2016.[8] A higher number of cases than usual reported to DHHS during summer 2017 also contributed to the overall increase in notifications. The high magnitude of

Fig. 6. **Percentage of ILI cases vaccinated by influenza status and age group, VicSPIN, 2017**

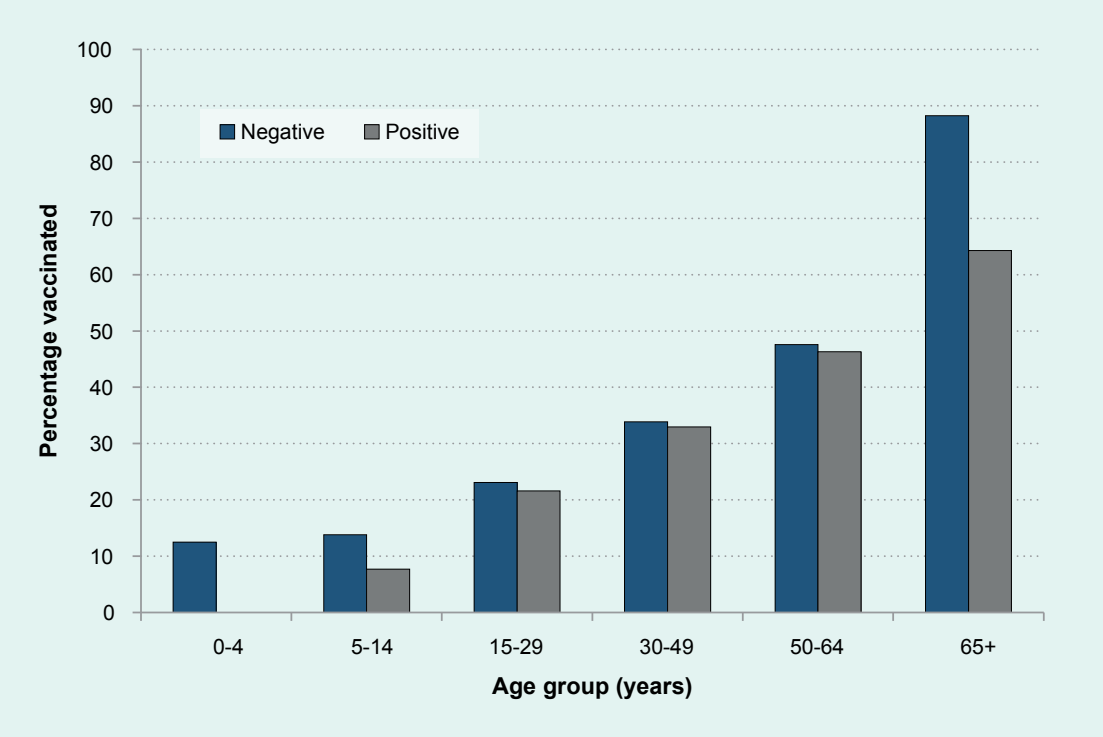


Table 2. **Victorian influenza isolates typed by haemagglutination inhibition assay at the WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, 2017**

Strain	n (%)
A(H3)/Hong Kong/4801/2014	678 (41%)
B/Phuket/3073/2013	606 (36%)
A/Michigan/45/2015 (H1N1)pdm09	347 (21%)
B/Brisbane/60/2008	44 (9%)

the 2017 influenza season was also observed in other states in Australia[10] with a similar increase reported in laboratory-confirmed influenza notifications nationally.[11]

The 2017 influenza season in Victoria was dominated by circulation of influenza A(H3N2) with an increase in influenza B later in the season. This was similar in New Zealand[12] and Western Australia[13] for their 2017 season and the United States of America[14] and Canada[15] for their 2017–18 seasons. The relative severity of the Victoria season could be explained by the dominance of influenza A(H3N2). This subtype disproportionately affects older age groups, while influenza B is more common in younger age groups.[16] While a large proportion of notified cases of influenza A were not subtyped, those aged ≥ 65 years comprised the highest proportion of influenza A notified cases, and the median age of influenza A cases was higher than for influenza B cases. The percentage of VicSPIN influenza cases typed as A(H3N2) was highest in the ≥ 65 years age group compared to A(H1).

The strains included in the 2017 quadrivalent influenza vaccine were A/Michigan/45/2015 (H1N1)pdm09-like virus; A/Hong Kong/4801/2014 (H3N2)-like virus; B/Brisbane/60/2008-like virus; and B/Phuket/3073/2013-like virus.[17] The antigenic characterization datum from the Victorian 2017 season suggested a good match between the influenza A(H3N2) vaccine and these circulating strains; however, interim analysis of Australian data (including VicSPIN data) showed a low effectiveness of the 2017 influenza vaccine against influenza A(H3N2) infection of 10% [95% confidence interval (CI): –16 to 31].[18] This may partially explain the higher number of influenza notifications in Victoria in 2017, but also serves to highlight the limited value of antigenic characterization. Phylogenetic typing of virus isolates may be more useful to assess the degree of match between circulating and vaccine strains.

Low vaccine effectiveness against influenza A(H3N2) is a persisting problem, speculated to be caused by genetic changes in vaccine virus haemagglutinin arising during passage in eggs, resulting in egg-derived viruses that are different from the cell reference strains. In response and to improve vaccine effectiveness in the elderly in 2018, two higher-immunogenicity trivalent influenza vaccine formulations (one a high-dose vaccine and another containing an adjuvant) will be funded in Australia under the National Immunization Program for those aged ≥ 65 years.[19]

Cases presenting with co-morbidities to GPs had a lower proportion positive for influenza than those without co-morbidities. This may be due to the higher influenza vaccination rates in this group at 66.7% as compared to 35.4%. GPs were also encouraged to test as many patients as possible in 2017 through the VicSPIN programme, so those with co-morbidities, such as asthma, may have been swabbed more than in previous seasons.

The influenza surveillance system in Victoria has several limitations including the lack of subtyping in the notifications data, variable age-structures between data sources and variable sensitivity of VicSPIN and NHDS ILI case detection. The NHDS is more sensitive due to the different search algorithms. Most ILI cases that presented to GPs were of working age, especially the 15–29 and 30–49 years old, which may relate to requirements for sick certificates for workplaces and universities. However, the lack of subtyping information for the notifications data limits the ability to determine if subtypes seen in VicSPIN are representative of those seen in the different age groups that are more likely to be notified than those detected in GP sentinel surveillance. While hospital-based surveillance of influenza has not been included in this report, these data are also used by DHHS to further understand influenza epidemiology throughout the season.[20]

The varied data sources used for influenza surveillance in Victoria provide a comprehensive overview of influenza and ILI. The comparison of ILI activity and notifications over time allows a more nuanced understanding of the season than analysing notifications alone and provides the evidence to suggest that the 2017 influenza season in Victoria was more severe compared with previous seasons.

Conflicts of interest

None declared.

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Description of social contacts among student cases of pandemic influenza during the containment phase, Melbourne, Australia, 2009

Caroline van Gemert,[a,b] Emma S McBryde,[c] Isabel Bergeri,[a] Rachel Sacks-Davis,[a,d] Hassan Vally,[e] Tim Spelman,[a] Brett Sutton[f] and Margaret Hellard[a,b]

Correspondence to Caroline van Gemert (email: caroline.vangemert@burnet.edu.au)

Introduction: Students comprised the majority of early cases of influenza A(H1N1)pdm09 in Melbourne, Australia. Students and school settings were targeted for public health interventions following the emergence of pH1N1. This study was conducted to describe changes in social contacts among the earliest confirmed student cases of pH1N1 in Melbourne, Australia, to inform future pandemic control policy and explore transmission model assumptions.

Methods: A retrospective cross-sectional behavioural study of student cases with laboratory-confirmed pH1N1 between 28 April and 3 June 2009 was conducted in 2009. Demographics, symptom onset dates and detailed information on regular and additional extracurricular activities were collected. Summary measures for activities were calculated, including median group size and median number of close contacts and attendance during the students' exposure and infectious periods or during school closures. A multivariable model was used to assess associations between rates of participation in extracurricular activities and both school closures and students' infectious periods.

Results: Among 162 eligible cases, 99 students participated. Students reported social contact in both curricular and extra-curricular activities. Group size and total number of close contacts varied. While participation in activities decreased during the students' infectious periods and during school closures, social contact was common during periods when isolation was advised and during school closures.

Discussion: This study demonstrates the potential central role of young people in pandemic disease transmission given the level of non-adherence to prevention and control measures. These finding have public health implications for both informing modelling estimates of future pandemics and targeting prevention and control strategies to young people.

Initial reports of confirmed cases of pandemic influenza A(H1N1) 2009 (pH1N1) in Australia and internationally suggested that students comprised the majority of early cases.[1–7] This may have been due to numerous and prolonged contacts in classroom settings, heterogeneous mixing across age groups and both casual and sustained social contacts in non-school settings.[8–12] Consequently, students and school settings were targeted by a suite of public health interventions to contain community transmission during the immediate period following pH1N1 detection in Melbourne, the capital city of the Australian state of Victoria (population >3.5 million). Such interventions included school closures, use of antiviral treatment and masks, isolation of cases and quarantine of contacts.[13,14]

An important driver of infectious disease transmission is the contact pattern and subsequent transmission of infection between and within groups of individuals, which may differ among different age groups. However, there is a lack of data for which key parameters, such as the number and frequency of contacts, as well as mixing between people according to age, can be estimated.[8,12,15] Further, decision-making about implementing pandemic influenza management plans are generally guided by mathematical models that compare the potential impact

[a] Burnet Institute, Melbourne, Victoria, Australia.
[b] Department of Epidemiology and Preventative Medicine, Monash University, Alfred Hospital, Commercial Road, Melbourne, Victoria, Australia.
[c] Centre for Biosecurity in Tropical Infectious Diseases, James Cook University.
[d] Department of Medicine, University of Melbourne.
[e] School of Psychology and Public Health, La Trobe University, Melbourne.
[f] Victorian Department of Health and Human Services.
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of prevention and control measures such as school closures, provided there is adequate information on the effect of these interventions on contact and transmission patterns within and across groups involved in the intervention.[12] In this study we collected empirical data to quantify social interactions of students and to describe changes in activity participation and social contacts following symptom onset and during school closures to inform future pandemic influenza policy and infectious disease transmission models assumptions.

METHODS

Study design, recruitment and data collection

A retrospective cross-sectional behavioural survey was conducted. Eligible cases were students notified with laboratory-confirmed pH1N1 between 28 April and 3 June 2009 who attended primary or secondary schools in Melbourne, Australia with 10 or more confirmed cases notified during the same period. This period corresponded to the "Delay" (28 April to 21 May 2009) and "Contain" (22 May to 3 June 2009) phases of the Australian Health Management Plan for Pandemic Influenza. During these phases, the emphasis was on active case-finding and slowing community transmission of pandemic influenza through prevention and control measures.[13,16,17]

Cases were recruited by mail and telephone; up to five calls were attempted. Interviews were conducted either face to face at the students' schools or households or by telephone between 18 November and 21 December 2009. Data collected, described in detail previously,[18] included demographic and case details, as well as specific information on social contacts between 11 May and 14 June 2009. This five-week period included all of the dates of symptom onset reported by the Victorian Department of Health and Human Services and was sufficient to capture activities during cases' exposure and infectious periods.

Participants retrospectively completed a health diary that included information about their illness; the date of symptom onset, symptoms and measures taken to reduce symptoms or prevent transmission; their activities; and group contact. Written consent was obtained from each participant or their parent/guardian if the participant was younger than 18 years.

Measures

Students were asked about their regular extracurricular activities, defined as regularly scheduled activities in addition to school. These included university classes (in Australia, high-achieving students can complete university studies alongside their final year of high school), part-time employment, sporting activities and religious groups. For each group or activity, students reported the number of social contacts (defined as the number of people in the group or activity), number of close contacts (defined as individuals within 1 metre of a case for more than 15 minutes) and the dates that the group or activity took place. Students were also asked to describe additional extracurricular activities, such as social events, private classes (or example, one-on-one classes for music) or school social events.

From this, it was determined if students attended school or participated in extracurricular activities during their potential exposure period (defined as up to seven days before symptom onset), during their infectious period (defined as one day before symptom onset to seven days after symptom onset) or during the period of school closure (including weekends when school closures extended through a weekend).

Data analysis

The mean number of groups and activities reported for each student, the median group or activity size and the number of close contacts per group or activity was calculated. The total number of close contacts per student was calculated by combining the number of unique close contacts at school, university, part-time employment, and sporting, religious and additional extracurricular activities for each individual.

A multivariable model using a generalized estimating equations regression was developed to assess associations between rates of participation in extracurricular activities and both school closures and the students' infectious periods. The model used a negative binomial family function, a log link and an exchangeable within-participant correlation structure. The model was adjusted for school and potential interaction between the effect of school closures and infectious period. Statistical analyses were conducted using STATA version 15 (StataCorp, College Station, Texas, USA) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Ethical approval

Ethical approval was obtained from the Alfred Hospital Ethics Committee and Australian National University Ethics Committee.

RESULTS

There were seven schools in Victoria with more than 10 confirmed cases of pH1N1. The 162 case-patients from these schools were invited to participate; 99 (61%) were interviewed, 38 (24%) were not contactable and 25 (15%) refused or were not available to participate. Students that participated in the study were similar in age structure ($P = 0.62$) and in the schools attended ($P = 0.42$) to non-participants.

Among the 99 respondents, there were more females than males (57% females). Half (49%) were in year 9 or year 10 (aged approximately 14–16 years) (**Table 1**). The earliest date of symptom onset was 16 May 2009 (this case was notified on 31 May 2009) (**Fig. 1**).

Five of the seven schools closed in response to pH1N1, and the earliest date of school closure was 25 May 2009. The number of days that schools closed ranged from three to nine days (not including weekends).

Students reported that they regularly attended or participated in sports ($n = 62$), religious activities ($n = 20$), part-time employment ($n = 18$) and university classes ($n = 10$, **Table 2**). Among students that reported part-time employment, the most common workplaces were shops or department stores ($n = 6$, 33%), followed by supermarkets ($n = 4$, 22%), fast-food restaurants ($n = 4$, 22%) and cafes ($n = 2$, 11%). Among students that reported participating in sports ($n = 62$), the majority (n = 34, 55%) played in indoor settings while the rest played in outdoor settings (n = 27, 44%) or both (n = 1, 2%, data not presented in tables). The majority of students ($n = 81$, 81%) also reported additional extracurricular activities, including attending a school disco ($n = 33$, 41%), private classes ($n = 11$, 14%), school excursions ($n = 8$, 10%), school camps ($n = 6$, 7%), youth groups ($n = 5$, 6%) and a carnival ($n = 2$, 2%). Students reported varying levels of social contact in school and non-school settings. The median class size at school was 20 people. The median group size for non-school setting activities ranged from 12 (university class) to 175 (religious groups).

The median number of close contacts at school was three per class, and the median number of close contacts in non-school settings was similar, ranging from two (university class) to four (religious group, data not presented). The mean number of total close contacts was 45; distribution was highly dispersed and right tailed (**Fig. 2**).

Participation in groups and activities was less during school closures and during the students' infectious periods compared to non-outbreak periods when schools were open and students were participating in regular activities. During their period of infectiousness, nearly all students attended school ($n = 98$, 99% of all students); however, no students attended university classes or work and there was reduced participation in sports ($n = 28$, 45% of the 62 students that regularly had sporting activities), religious ($n = 8$, 40%) and additional extracurricular activities ($n = 35$, 43%) (**Table 2**).

During school closures, there was less participation reported for sports ($n = 14$, 23% of the 62 students that regularly had sporting activities), religious ($n = 1$, 5%) and additional extracurricular activities ($n = 21$, 26%). Compared to non-outbreak periods, the incidence rate for participating in extracurricular activities was approximately one quarter during periods of school closures [incidence rate ratio (IRR) 0.28, 95% confidence interval (CI):0.17–0.46] and approximately one half during the students' infectious periods (IRR 0.56, 95% CI:0.44–0.71, **Table 3**). There was no statistically significant interaction between the effect of infectious period and school closures.

DISCUSSION

Several studies have demonstrated high transmission of pH1N1 in schools.[7,11,19–23] This study provides novel evidence of the potential of pH1N1 transmission within school and non-school settings via student networks and shows that students engaged in multiple activities in a range of settings during the pandemic period, even when public health interventions were implemented. While participation was less, students continued to engage in non-school-based activities during their periods of infectiousness and school closures.

Table 1. **Description of student cases of pH1N1 that were notified between 28 April 2009 and 3 June 2009 and participating in pH1N1 study, Melbourne, Australia**

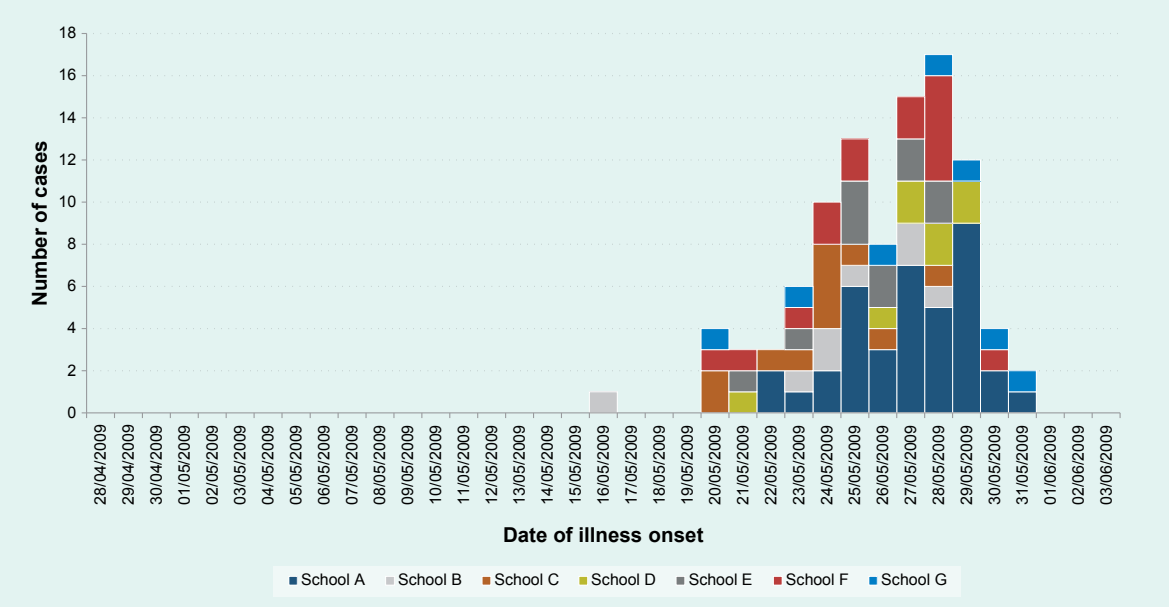
	n	%
Gender		
Male	43	43
Female	56	57
Age group		
6–7 years	4	4
10–11 years	5	5
12–13 years	9	9
14–15 years	48	49
16–17 years	33	33
School attended		
School A	8	8
School B	8	8
School C	11	11
School D	8	8
School E	15	15
School F	11	11
School G	38	38
Year level		
Primary School	9	9
Year 7 (12–13 year olds)	5	5
Year 8 (13–14 year olds)	6	6
Year 9 (14–15 year olds)	25	25
Year 10 (15–16 year olds)	24	24
Year 11 (16–17 year olds)	13	13
Year 12 (17–18 year olds)	17	17

Note: percentages do not equal 100% due to rounding

The structure of Australian secondary schools, in which students move from class to class throughout a single school day, highlights how pandemic influenza can spread in school settings with relative ease. Additional school-based non-curricular activities observed in this study, such as sports groups, choir, excursions, carnivals and school camps, potentially interlink students across year levels, providing additional mechanisms for the transmission of pandemic influenza in young people.

There was a diverse range of social contacts in non-school settings reported by students. That just under one fifth of students reported engaging in regular part-time employment provides a risk factor for exposure of secondary transmission that has not previously been highlighted in studies that explore transmission of pH1N1. This employment resulted in varied social contacts in settings that involved numerous instances of both random and non-random social contacts (i.e. customers versus work colleagues) and included supermarkets, cafes and fast-food restaurants. While comparative data are not currently available to assess the differences in social contacts in workplace settings between teenagers and adults, these findings identify an important non-school setting for pH1N1 transmission for consideration in pandemic planning.

Fig. 1. **Epidemic curve of the date of symptom onset for student cases of pH1N1 that were notified between 28 April 2009 and 3 June 2009 and participating in pH1N1 study, Melbourne, Australia**



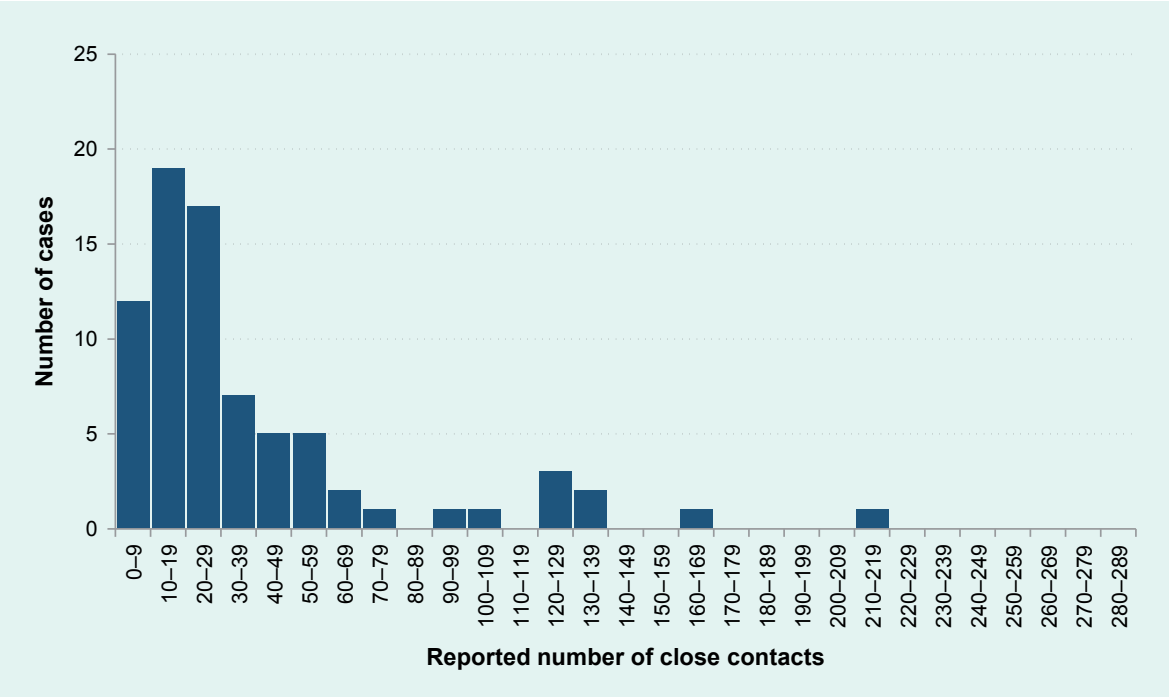
Note: Dates of school closure: School B: 25/05/09–04/06/2009; School C: 26/05/2009–29/05/2009; School E: 01/06/2009–05/06/2009; School F: 31/05/2009–05/06/2009; School G: 01/06/2009–03/06/2009

Table 2. **Number of student cases of pH1N1 that were notified between 28 April 2009 and 3 June 2009 and participating in pH1N1 study that reported participation in school and extracurricular activities and groups and median group size**

	Regular activity	Median size of group or activity	Attended/participated in during potential exposure period		Attended/participated in during infectious period		Attended/participated in during school closure	
	n	*n*	*n*	%	*n*	%	*n*	%
School	99	20	99	100%	98	99%	0	0%
University class	10	12	0	0%	0	0%	2	20%
Part-time work	18	20	0	0%	0	0%	2	11%
Sports	62	16	58	94%	28	45%	14	23%
Religious activity	20	175	20	100%	8	40%	1	5%
Other extra-curricular activity	81	30	81	100%	35	43%	21	26%

Note: The median size of the group relates to the total number of people in attendance at each specific class, group or activity. The median size of school group is based on the reported size of each class that students attended.

Fig. 2. **Frequency of the total number of close contacts reported by student cases of pH1N1 that were notified between 28 April 2009 and 3 June 2009 and participating in pH1N1 study, Melbourne, Australia**



Similarly, information was captured on the level and type of sporting activities in which students engaged. That many students participated in sporting activities during their infectious period and during school closures is similar to that reported in Western Australia where sporting activities were commonly reported by students (cases and non-cases) over a longer period in 2009. This study also found that many team sports were played in an indoor setting, providing opportunities for disease transmission.[6]

Social distancing recommendations, such as the isolation of cases during their infectious period, were poorly adhered to by our sample. Students reported high levels of school attendance after symptom onset and while potentially infectious, thus further contributing to the evidence that schools are effective settings for the spread of pandemic influenza. Anecdotal evidence from some students suggested they did not want to be absent from school because of senior-school examinations during the time period. While this provides some explanation

Table 3. **Adjusted incidence rate ratios for extracurricular participation during students' infectious periods and school closure periods, among 98 students with pH1N1 notification between 28 April 2009 and 3 June 2009**

	Adjusted incidence rate ratio	95% CI for adjusted incidence rate ratio	p-value
Infectious period	0.56	0.44–0.071	< 0.001
School closures	0.28	0.17–0.46	< 0.001

Note: Estimated using a multivariable generalized estimating equation model with a negative binomial family, log link and exchangeable correlation structure. In addition to infectious period and school closures, model was adjusted for school. Possible interactions between infectious period and school closures were assessed but were not statistically significant and were not included in the final model.

for the high level of school attendance, it nonetheless highlights the need for improved communication at the individual level to prevent community transmission. This communication should be aimed at social isolation of symptomatic cases, including while schools remain open and pandemic influenza is potentially circulating within schools.

The participation levels of students in sporting, religious and additional extracurricular activities in the week following symptom onset and while potentially infectious decreased compared to the levels reported as a regular activity. While somewhat helpful, decreased attendance does not meet isolation recommendations during the potentially infectious period. This reduced participation is likely influenced by the presence of symptoms among the samples and possibly because some students were undertaking examinations at this time. Participation in activities, especially while symptomatic, could potentiate transmission within and across social groups and hence be a bridge between young people and the wider community. Other international studies have also documented that social events such as parties and religious activities were implicated in transmission of pH1N1.[5,6] This reinforces the need for improved communication regarding social isolation to include extracurricular groups and activities to maximize the effect of social distancing measures in controlling pandemic influenza.

There was also lower participation in sporting, religious and additional extracurricular activities during school closures. This is similar to a study that compared the social contact patterns of students (pH1N1 cases and non-cases) before and after school closure that found that fewer students visited public places (such as shops, places of worship and playing fields) when school was closed than when open.[22] However, in the Western Australian study, it was reported that almost three quarters of students (influenza cases and non-cases) left home at least once during school closures.[6] This finding reinforces the need for strategies in the revised pandemic plan to ensure that the benefit of school closures – that is, reduced social contact between students – is realized and to prevent students' social contact with potentially broader and unexposed social networks.

The distribution of the total number of close contacts reported by students was highly dispersed and was skewed to the right with the majority of students having a small number of close contacts and a few having much larger numbers of contacts. This has ramifications for the control of disease spread, as containment is more difficult than for a random network of contact between people. Targeted strategies aimed at those more central to the network or with a greater number of social ties may be more efficient than non-targeted strategies. Although impractical to target individuals with many contacts, it may be possible to identify and target activities that lead to the skewed distribution such as religious gatherings or large gatherings.

This study has limitations, some of which have been documented previously,[18] including issues relating to possible selection and recall bias. In addition, the number of social contacts reported here are likely to be an underestimation given that questions were asked about specific planned activities rather than incidental activities and that information was collected retrospectively. Future research to enumerate interactions that are not class or group based would fill this gap in information. Further, the number of contacts in this study was measured by recalling close contacts over a 35-day period, rather than daily, which is the norm in studies of social contacts.[12,24] The relationship between contact ties and interactions is an emerging area of social network research and is likely to be a key determinant in infectious disease transmission.[25]

The results from this study have public health implications for both informing modelling estimates of future pandemics and targeting prevention and control strategies to young people. School closures can only pre-

vent transmission between students that could occur at school or school-based activities such as school camps. Young people participate in numerous activities outside of school hours and continue to engage with other young people via additional extracurricular activities during school closures. This study also identified the possibility of targeted strategies for transmission prevention given the highly dispersed nature of students' contact networks. Young people are not a homogenous group and may play a central role in future influenza pandemics. Therefore it is critical that any response to pandemic influenza considers the mechanisms of transmission through young people.

Conflicts of interest

No author receives any financial support or has any financial involvement or affiliation with any organization whose financial interests may be affected by material in the manuscript or which might potentially bias it.

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Influenza-associated paediatric respiratory hospitalizations in China, 1996–2012: a systematic analysis

Mei Shang,[a,b] Kathryn E. Lafond,[b] Jeffrey McFarland,[a,b] Suizan Zhou,[a,b] John Klena[a] and Marc-Alain Widdowson[b]

Correspondence to Mei Shang (email: pmyvonne@yahoo.com)

Background: The World Health Organization recommends that children aged ≥6 months be vaccinated against influenza. Influenza vaccination policies depend on the evidence of the burden of influenza, yet few national data on influenza-associated severe outcomes among children exist in China.

Methods: We conducted a systematic review of articles published from 1996 to 2012 on laboratory-confirmed, influenza-associated paediatric respiratory hospitalizations in China. We extracted data and stratified the percentage of samples testing positive for influenza by age group (<2, <5 and <18 years old); case definition; test methods; and geographic location. The pooled percentage of samples testing positive for influenza was estimated with a random effects regression model.

Results: Influenza was associated with 8.8% of respiratory hospitalizations among children aged <18 years, ranging from 7.0% (95% confidence interval: 4.2–9.8%) in children aged <2 years to 8.9% (95% confidence interval: 6.8–11%) in children aged <5 years. The percentage of samples testing positive for influenza was consistently higher among studies with data from children aged <5 years and <18 years than those restricted only to children aged <2 years; the percentages were higher in Northern China than Southern China.

Discussion: Influenza is an important cause of paediatric respiratory hospitalizations in China. Influenza vaccination of school-aged children could prevent substantial influenza-associated illness, including hospitalizations, in China.

Young children are at an increased risk of severe disease due to influenza infection compared to older children and young adults.[1–5] Data from temperate northern hemisphere countries indicate that rates of influenza-associated hospitalizations among children aged <5 years range from 0.36 to 5.16 per 1000 children with the highest rate among children aged <2 years.[4,6,7] Therefore, the World Health Organization (WHO) recommends the inclusion of children aged 6 to 59 months as a priority group for seasonal influenza vaccination.[8] WHO also provides global guidance on surveillance for influenza, including influenza-like illness (ILI) among outpatients and severe acute respiratory infection (SARI) among inpatients, to capture influenza epidemiology, including disease burden.[9]

Few nationally representative studies exist on influenza-associated severe disease among children in China. Since 2007, the Chinese Center for Disease Control and Prevention (China CDC) has recommended annual seasonal influenza vaccination for children aged ≥6 months[10,11] based largely on disease burden data from other northern hemisphere countries. However, influenza vaccine uptake among children remains low. A telephone survey in four provinces, representing eastern and central China, found that influenza vaccination coverage among children aged <5 years in urban settings was 21.9% for the 2009–2010 season and 25.6% for the 2011–2012 season.[12]

To better understand the epidemiology of influenza and influenza-associated disease burden, China CDC has implemented national and provincial-level surveillance systems. ILI surveillance, which began in 2009, monitors the predominant influenza virus strains circulating in outpatient settings and covers all provinces in mainland China, but it is not designed to estimate the disease burden. In 2011, China CDC also began inpatient surveillance for SARI in 10 provinces; however, the surveillance only covers a limited geographic area, mostly in the more

[a] China-US Collaborative Program on Emerging and Reemerging Infectious Diseases, Centers for Disease Control and Prevention, Beijing, China.
[b] Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA.
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developed eastern provinces. Furthermore, SARI sentinel site surveillance uses a modified version of the WHO SARI case definition which includes different criteria for patients aged >5 years and ≤5 years and is also more specific.[13] Therefore, SARI surveillance likely underestimates the impact of influenza-associated hospitalizations nationwide, particularly those that do not fall within the strict SARI case definition. The contribution of influenza among respiratory hospitalizations in children aged <18 years remains a key knowledge gap.

To address this gap, we conducted a systematic review of the Chinese and English literature to assess the burden of influenza-associated paediatric respiratory hospitalizations in China. We wanted to better understand influenza-associated hospitalizations, especially during the period when relevant data were not well described. The evidence provided will help to improve estimates of the influenza burden in China, refine influenza vaccination policy and reduce nationwide influenza-associated paediatric morbidity and mortality.

METHODS

Systematic review of the literature

We conducted a systematic search of biomedical reference databases (PubMed, Embase, Web of Science, CINAHL, IndMed, LILACS, WHOLIS, CNKI and Global Health) to identify articles published from 1 January 1996 to 31 December 2012. Keywords that were used for searching were grouped in two categories: respiratory infection and viral etiology (full list of search terms and results are provided in **Supplementary Table 1**). We adopted the same literature search strategy as the one used to assess influenza-associated paediatric respiratory hospitalizations at the global level.[14] Two independent reviewers screened the identified papers to select those that met the following inclusion criteria: (1) presented original data; (2) the study population included Chinese children aged <18 years old; (3) collected data from a minimum of 12 months of continuous surveillance; (4) conducted laboratory testing for influenza; (5) stated a pre-specified case definition or other clear criteria for specimen collection and testing; (6) included hospitalized case-patients (nosocomial infections were excluded); (7) provided both the numerator and denominator for influenza testing; (8) and tested a minimum of 50 children for influenza infection. For papers meeting these criteria, the full-text articles were obtained and re-screened by two reviewers. Key data that were extracted included study duration in years; geographic location of the study (defined as Northern or Southern China; demarcated by the Qinling Mountains-Huaihe River line);[15] total numbers of inpatients tested and total numbers tested positive for influenza; age group; case definition used to screen patients for testing (e.g. community-acquired pneumonia, SARI and acute respiratory infection); type of diagnostic tests used; and publication year. Since distinct age groups in the published data were not standardized for easy comparison, we created three overlapping age groups: <2 years, <5 years and <18 years old. The <18 years old group included the <2 years and <5 years old groups, and the <5 years old group included the <2 years old group. To ensure the disease burden data are associated with seasonal influenza, we excluded results that covered the 2009 influenza A(H1N1) pandemic period.

Quality assessment

Data quality for each eligible article was scored using a modified Newcastle-Ottawa checklist for bias assessment[16] with three standards: (1) representativeness of the sampling process for enrolment; (2) specificity of enrolment criteria; (3) and clarity of reported results. A score of one or zero was given to each item accordingly.

Statistical analyses

We first described eligible studies by age group, study duration, total numbers tested and positive for influenza infection, case definition, type of diagnostic tests used and geographic location. We calculated the percentage of samples that tested positive for influenza (hereafter referred to as per cent influenza-positive). Kruskal–Wallis one-way analysis of variance was used to test the difference among medians.[17] We then calculated pooled estimates of the per cent influenza-positive using a Dersimonian and Laird random effects meta-analysis model[18] for the three age groups stratified by geographic location. Briefly, in the random effect model, we assumed that the per cent influenza-positive estimated in the different studies were not identical. Because of variations in the sensitivity and specificity of different diagnostic tests,[19–27] we also calculated pooled estimates stratified by a different diagnostic approach: (1) diagnosis based on polymerase chain reaction (PCR); (2) any diagnostic test except alkaline phosphatase-anti-alkaline phosphatase technique (APAAP); (3) any diagnostic test except immunoassay;

(4) any diagnostic test except APAAP or immunoassay. All reported tests were two-sided, and *P*-values < 0.05 indicated statistical significance. Data were analysed using Stata, version 12 (StataCorp, College Station, TX).

RESULTS

Study characteristics

The systematic literature search identified 42 456 unique records (4450 Chinese and 38 006 English) from the nine scientific literature databases. A total of 1176 full-text articles (219 in Chinese and 957 in English) were reviewed. After excluding articles that did not meet the inclusion criteria and those with overlapping populations, 79 articles (69 in Chinese and 10 in English) were included in the descriptive analysis (**Fig. 1**). The full list of included articles is provided in **Supplementary Table 2**. The number of available studies published before 2004 was limited (n = 12). The number of studies increased to eight in 2004 and 14 in 2010, reflecting the 2009 influenza A(H1N1) pandemic. The data sets covered 23 provinces and special administrative regions (**Fig. 2**). Of the 79 articles included, 50 studies (63%) were from Southern China and 29 (37%) were from Northern China (**Table 1**). More than 95% of the studies tested at least 100 patients during the study period. More than 40% of the studies used immunofluorescence as the diagnostic test. Most studies differentiated influenza A and influenza B (n = 60 of 79). Over the years, influenza A positivity remained higher than influenza B positivity (median, interquartile range [IQR]: 2.5% [1.2–7.3%] vs 0.5% [0.2–4.1%]).

The most commonly used case definitions for screening were acute respiratory infection (ARI), acute lower respiratory infection and pneumonia. ARI case definitions varied in different settings, but mostly met one or more of the following criteria: (1) symptoms of acute infection; (2) a body temperature >38.0 °C; (3) white blood cell count of >10 000/ml; (4) and signs/symptoms of acute respiratory illness. Only one study used SARI as a case definition. For patients >5 years, SARI is defined as an acute onset of elevated temperature (axillary temperature ≥38 °C), cough or sore throat tachypnea (respiratory rate ≥25/min) or dyspnea (difficulty breathing) either at admission or during stay. For patients aged ≤5 years, SARI is defined as an acute onset of cough or dyspnea either at admission or during stay, and at least one of the following six signs or symptoms: (1) tachypnea (respiratory rate >60/min for those aged <2 months, respiratory rate >50/min for those aged 2 to <12 months, respiratory rate >50/min for those aged 1 to ≤5 years); (2) inability to drink or breastfeed; (3) vomiting; (4) convulsions; (5) lethargy or unconsciousness; (6) and chest in-drawing or stridor in a calm child.

Crude median per cent influenza-positive

The crude median per cent influenza-positive among studies with data from children aged <2 years was 2% (IQR: 1–8%) and from children aged <5 years and <18 years was 6% (IQR: 2–11%, **Table 2**). The crude median per cent influenza-positive was four times lower among the 34 data sets that used immunofluorescence alone as compared to the 44 data sets that used other methods (2% versus 8%, Kruskal–Wallis test $P < 0.05$). The crude per cent influenza-positive was almost four times higher among the seven data sets that used APAAP as compared to the 71 data sets that used other methods (19% versus 5%; Kruskal–Wallis test $P < 0.05$). Stratification by age did not change the patterns. The crude per cent influenza-positive was not associated with case definition, geographic location or study duration (Kruskal–Wallis test $P > 0.05$ for all).

Pooled estimates of per cent influenza-positive

The overall pooled estimates of the per cent influenza-positive among paediatric respiratory inpatients was 4.7% (95% confidence interval [CI]: 4.0–5.4%), 7.3% (95% CI: 6.4–8.1%); and 7.9% (95% CI: 7.1–8.7%) among children aged <2 years, <5 years and <18 years respectively (**Table 3**). Considering the observed low sensitivity of immunoassay tests and the low specificity of APAAP tests, we did three additional analyses that excluded either one or both of them. However, children aged <5 years and <18 years consistently had higher point pooled per cent influenza-positive than children aged <2 years. The 95% CIs of pooled per cent influenza-positive for children aged <5 years and <18 years overlapped considerably (**Table 3**).

In all age groups, per cent influenza-positive in the northern provinces was higher than that in the southern provinces (7.1% vs 3.8%, 10.4 vs 5.9%, 9.8% vs 7.1%). Additional stratified analyses by diagnostic test did not significantly change the pattern. The final pooled

Fig. 1. **Flow diagram for systematic review process**

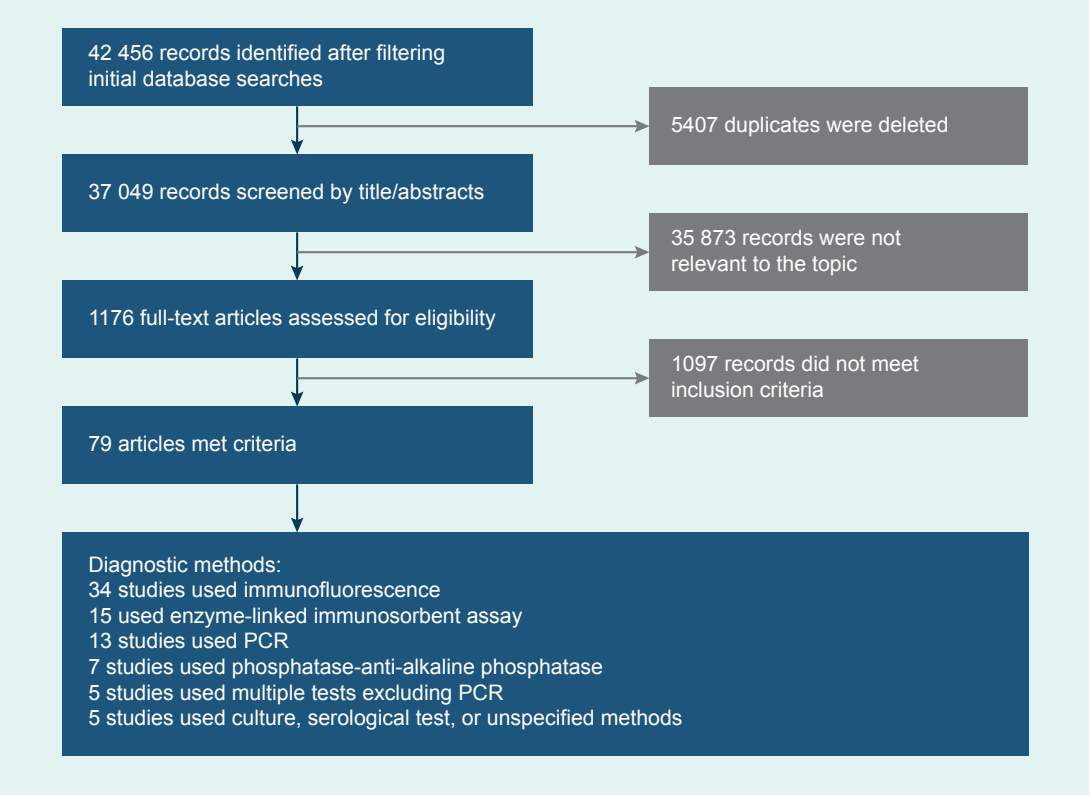
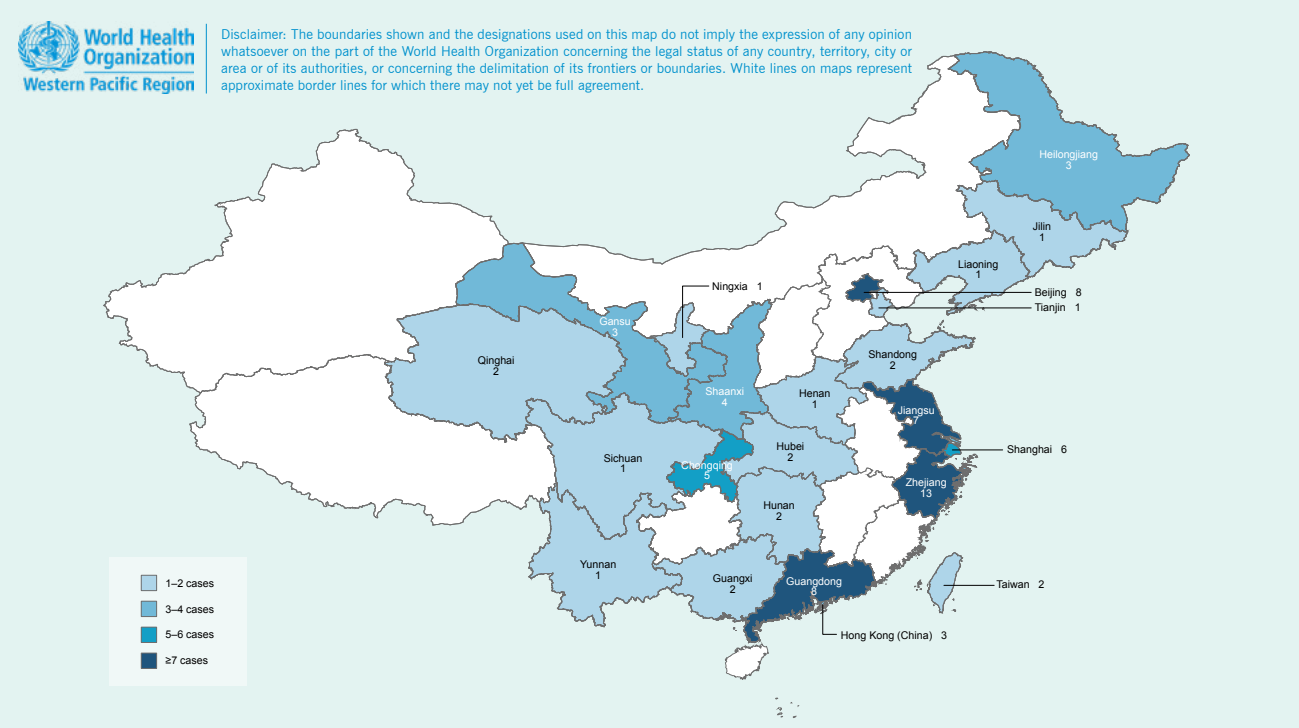


Fig. 2. **The distribution of studies included in the systematic analysis* (n = 79)**



* Demarcated by Qing Mountain and Huai River line; provinces located in Northern China are Shandong, Henan, Shanxi, Shaanxi, Gansu, Qinghai, Xinjiang, Hebei, Tianjin, Beijing, Inner Mongolia, Liaoning, Jilin, Heilongjiang and Ningxia.

Two of the studies were from Taiwan, China.

Table 1. **Characteristics of published studies and data sources about influenza-associated paediatric respiratory hospitalizations in China, 1996–2012 (n = 79)**

Characteristics	Number of published studies (%)
Age group in years	
<2	48 (61)
<5	53 (67)
<18	79 (100)
Study duration in years	
1–2	61 (77)
3–4	14 (18)
≥5	4 (5)
Geographic location*	
Northern China	50 (63)
Southern China	29 (37)
Total cases tested	
0–99	2 (3)
100–499	30 (38)
500–999	13 (16)
≥1000	34 (43)
Diagnostic test	
Polymerase chain reaction (PCR) only	10 (13)
Immunofluorescence only	34 (44)
Multiple diagnostic tests, incl. PCR	3 (4)
Multiple diagnostic tests, excl. PCR	5 (6)
ELISA#	15 (20)
APAAP†	7 (9)
Others‡	4 (5)
Case definition	
Acute respiratory infection	32 (41)
Acute lower respiratory infection	23 (29)
Pneumonia	17 (22)
Others§	7 (9)

* Southern and Northern are defined by national standards, which is Qing Mountain and Huai River line.[15]

† APAAP: Alkaline phosphatase-anti-alkaline phosphatase technique.

ELISA: Enzyme-linked immunosorbent assay

‡ Others included pneumonia & bronchiolitis (n = 1), SARI (n = 1), bronchiolitis (n = 2) and others (n = 3).

§ Others included culture (n = 1), serological test (n = 1), non-classified (n = 2).

analyses of only PCR-confirmed data included 13 data sets; most of them were in the more developed eastern or southern provinces (n = 10 of 13). The point per cent influenza-positive remained higher among children aged <5 years and <18 years, but the 95% CIs of per cent influenza-positive of the three groups overlapped considerably (point per cent influenza-positive and 95% CI: 7% [4.2–9.8%] for <2 years, 8.9% [6.8–11%] for <5 years, and 8.8% [7.0–10.7%] for <18 years).

DISCUSSION

Our study of influenza-associated severe hospitalizations from 23 provinces and autonomous administrative areas of China during the period 1996–2012 is the first systematic review of influenza-associated paediatric hospitalizations in China. Findings from this review complement results from China's two influenza surveillance systems that are limited in their ability to capture the true number of influenza-associated paediatric hospitalizations either by using SARI as an overly specific case definition or by excluding many jurisdictions before 2012. Our review covered well-developed provinces as well as the less-developed provinces for which only limited influenza-associated disease burden estimates are available. Using PCR-confirmed outcomes, we found that in addition to the significant burden of influenza in respiratory hospitalizations among children aged <2 years, as observed in other northern hemisphere counties, the relative contribution of influenza was also high among acute respiratory hospitalizations in children aged <5 years and <18 years in China.

The fact that influenza is associated with severe outcomes among younger children as well as among older children is consistent with the SARI surveillance results from China and results from the systematic analysis on respiratory hospitalizations at the global level during similar study periods.[13,14,28] All three studies reported that influenza-associated hospitalization was higher among children of older age groups than among children aged <2 years. Similar percentage of influenza-contributed respiratory hospitalizations among children <18 years was also estimated from the global report[14] with 7.7% in developing countries and 8.5% in the WHO Western Pacific Region. Influenza not only contributes to respiratory hospitalization among children aged <18 years, it also contributes to a significant percentage of outpatient visits. One study conducted in two northern provinces of

Table 2. **Crude proportion of respiratory samples from hospitalized children testing positive for influenza by age group, diagnostic test, case definition, clinical diagnosis and geographic location in China, 1996–2012**

Characteristic	No. studies (*n* = 79)	No. tested, Median (IQR)	No. positive, Median (IQR)	Median percentage influenza-positive samples (IQR)	*P*-value
Age group in years					
<2	48	978 (320–2143)	48 (17–99)	2 (1–8)	‡
<5	53	821 (302–2073)	41 (17–85)	6 (2–11)	
<18	79	796 (280–1908)	39 (15–80)	6 (2–11)	
Diagnostic test					0.09§
PCR	10	482 (340–961)	41 (35–65)	8 (7–12)	
Immunofluorescence only	34	1216 (412–2646)	30 (14–80)	2 (2–6)	
Multiple diagnostic tests including PCR	3	120 (116–469)	12(6–53)	10 (5–11)	
Multiple diagnostic tests excluding PCR	5	1022 (672–1031)	44 (27–85)	6 (2–8)	
ELISA	15	353 (144–837)	25 (7–70)	8 (2–16)	
APAAP	7	1216 (169–5328)	113 (25–494)	19 (8–28)	
Others*	4	1801 (856–7136)	96 (46–180)	6 (3–8)	
Case definition					
Acute respiratory infection	32	1027 (258–2667)	45 (16–116)	3 (2–8)	0.37§
Acute lower respiratory infection	23	961 (412–2073)	41 (22–80)	7 (2–14)	
Pneumonia	17	280 (165–1006)	20 (6–70)	7 (2–9)	
Others†	7	194 (117–469)	15 (8–209)	8 (2–22)	
Geographic location					0.37§
Northern China	29	672 (302–961)	52 (21–78)	7 (3–9)	
Southern China	50	1027 (267–2077)	30 (14–85)	4 (2–11)	

Data are presented as median and interquartile range (IQR).

* One data set did not explain the diagnostic methods used. Others included culture (*n* = 1), serological test (*n* = 1), and not specified (*n* = 3).

† Others included pneumonia & bronchiolitis (*n* = 1), severe acute respiratory illness (*n* = 1), bronchiolitis (*n* = 2), not specified (*n* = 3).

‡ Because the three age groups overlapped with each other, statistical test was not performed to test the difference among them.

§ Values are for children aged ≤ 18 years because only this age group has sufficient data to allow a well powered analysis.

China during 2012–2015 found that influenza was the most commonly detected virus in ambulatory patients across all age groups,[29] though this study used ARI for patient screening.

ARI was also the most commonly used case definition in all articles included in our analysis. This case definition is more sensitive than the strict SARI definition used in the surveillance system during 2011–2013.[13] In most populated developing country hospitals, including hospitals that conduct surveillance associated with severe outcomes of a respiratory virus, busy clinicians examining patients describe the patient's general condition related with ARI rather than list numerous signs and symptoms in detail.[30] For future surveillance on influenza-associated severe outcomes, if clinicians are responsible for case enrolment or if enrolment is based on patient chart review, standardization and simplification of the case definition are encouraged to improve case capture and surveillance quality.

There was a substantial difference in the percentage by diagnostic test, with high positivity in those tested with immunoassay and low positivity in those tested by APAAP assay. Though studies have shown that PCR is more sensitive than other test methods,[31,32] our pooled results from other testing methods (not including APAAP and immunoassay) had higher positivity than PCR. This may be because the use of PCR was largely limited to the resourceful southern provinces that have lower proportions of influenza-associated hospitalizations compared with the northern provinces. Other testing methods were used with similar frequency among studies from southern and northern provinces.

Table 3. **Pooled estimates of per cent influenza-positive of influenza-associated paediatric respiratory hospitalizations, by age group and by diagnostic test method in China, 1996–2012**

	Children aged <2 years		Children aged <5 years		Children aged <18 years	
	Number of data sets	Pooled per cent influenza-positive (95% CI)	Number of data sets	Pooled per cent influenza-positive (95% CI)	Number of data sets	Pooled per cent influenza-positive (95% CI)
Overall pooled per cent positivity	46	4.7 (4.0–5.4)	50	7.3 (6.4–8.1)	77	7.9 (7.1–8.7)
Northern China*	18	7.1 (5.3–8.9)	19	10.4 (8.3–12.4)	27	9.8 (8.2–11.5)
Southern China	28	3.8 (3.1–4.6)	31	5.9 (5.0–6.9)	48	7.1 (6.1–8.1)
Pooled per cent influenza-positive excluding immunoassay	24	6.9 (5.5–8.2)	28	10.0 (8.4–11.7)	45	10.5 (8.9–12)
Northern China	11	8.9 (5.7–12.1)	11	12.2 (8.4–16.1)	18	8.9 (10.5–12)
Southern China	13	6.0 (4.3–7.6)	17	9.0 (7.1–11)	27	8.9 (11.4–13.9)
Pooled per cent influenza-positive excluding APAAP	42	4.4 (3.7–5.1)	46	7.1 (6.2–8.0)	70	6.7 (6–7.4)
Northern China	17	6.7 (4.9–8.5)	18	10 (7.9–12.1)	27	9.5 (7.9–11.2)
Southern China	25	3.5 (2.7–4.3)	28	5.8 (4.7–6.8)	43	5.5 (4.6–6.3)
Pooled per cent influenza-positive excluding APAAP & immunoassay	20	6.6 (5–8.2)	24	10.4 (8.4–12.4)	38	8.8 (7.5–10.1)
Northern China	10	8.1 (5–11.3)	10	11.7 (7.7–15.7)	17	9.0 (6.7–11.4)
Southern China	10	5.7 (3.6–7.7)	14	9.8 (7.1–12.5)	21	9.3 (7.1–11.4)
Overall pooled per cent influenza-positive by PCR	5	7 (4.2–9.8)	9	8.9 (6.8–11)	13	8.8 (7.0–10.7)

*Northern China and Southern China are defined by national standards, which is Qing Mountain and Huai River line.[15]

We also found that the proportion of hospitalizations due to influenza was higher in the northern provinces than the southern provinces. As there were relatively fewer studies in Northern China, we suggest the strengthening of respiratory disease-related surveillance in Northern China to better understand the drivers of the disparity comparing with Southern China (e.g. etiologies, interventions, health seeking behaviours, influenza vaccine and pneumococcal vaccine uptake) to inform local prevention and control strategies.

Our analysis is subject to several limitations. First, the data sets were all from cities (prefectures) or referral hospitals in the provinces. Respiratory disease burden may differ between urban and rural areas, and we may not have adequately captured data from rural populations because of their limited access to city hospitals. Second, many data sets did not use PCR as a diagnostic test, particularly among northern provinces, raising uncertainty regarding the accuracy of their results. Although we attempted to address this limitation by generating a pooled estimate restricted only to PCR-based results, the pooled estimate is less representative of Northern China. Third, although we screened studies for use of clear criteria for influenza testing, it is possible that subjective clinical judgment may have influenced clinician testing practices and therefore our outcomes. Finally, we were not able to exclude 2009 influenza A(H1N1) data from nine data sets because the results were not stratified to allow this separate analysis.

Our study results suggest that influenza was responsible for almost 9% of paediatric respiratory hospitalizations. Though more studies are warranted on the influenza-associated outpatient burdens among these age groups and in Northern China, inclusion of school-aged children in the influenza vaccination priority group and collaborations with other organizations (for instance schools) to improve vaccine uptake may reduce substantial influenza-associated morbidities among children in China.

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National burden of influenza-associated hospitalizations in Cambodia, 2015 and 2016

Vanra Ieng,[*a] M Ximena Tolosa,[*b,c] Bunchhoeng Tek,[d] Borann Sar,[e] Kheng Sim,[d] Heng Seng,[d] Miliya Thyl,[f] Chan Dara,[g] Mey Moniborin,[h] Rebekah J. Stewart,[i] Leila C. Bell,[i] Georgios Theocharopoulos,[a] Savuth Chin,[k] Darapheak Chau,[k] A. Danielle Iuliano,[i] Ann Moen,[i] Reiko Tsuyuoka,[a] Erica L. Dueger,[i,j] Sheena G. Sullivan[c,l,m] and Sovann Ly[d]

Correspondence to M Ximena Tolosa (email: ximena.tolosa@anu.edu.au)

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Introduction: The burden of influenza in Cambodia is not well known, but it would be useful for understanding the impact of seasonal epidemics and pandemics and to design appropriate policies for influenza prevention and control. The severe acute respiratory infection (SARI) surveillance system in Cambodia was used to estimate the national burden of SARI hospitalizations in Cambodia.

Methods: We estimated age-specific influenza-associated SARI hospitalization rates in three sentinel sites in Svay Rieng, Siem Reap and Kampong Cham provinces. We used influenza-associated SARI surveillance data for one year to estimate the numerator and hospital admission surveys to estimate the population denominator for each site. A national influenza-associated SARI hospitalization rate was calculated using the pooled influenza-associated SARI hospitalizations for all sites as a numerator and the pooled catchment population of all sites as denominator. National influenza-associated SARI case counts were estimated by applying hospitalization rates to the national population.

Results: The national annual rates of influenza-associated hospitalizations per 100 000 population was highest for the two youngest age groups at 323 for <1 year and 196 for 1–4 years. We estimated 7547 influenza-associated hospitalizations for Cambodia with almost half of these represented by children younger than 5 years.

Discussion: We present national estimates of influenza-associated SARI hospitalization rates for Cambodia based on sentinel surveillance data from three sites. The results of this study indicate that the highest burden of severe influenza infection is borne by the younger age groups. These findings can be used to guide future strategies to reduce influenza morbidity.

Influenza is a contagious, acute respiratory infection caused by influenza viruses.[1] Globally, seasonal influenza causes significant morbidity, mortality and socioeconomic costs.[2] Accurate figures of the burden of influenza are difficult to estimate. Robust vital statistics and civil registration, well-functioning surveillance systems, hospital discharge databases and the expansion of influenza molecular testing have allowed more countries to complete influenza burden estimations. However, due to data quality and availability issues, the burden of seasonal influenza in low-income, lower middle-income and tropical climate countries is not well documented. Consequently, many countries lack influenza prevention and control policies.[3,4] Limited available data indicate that influenza burden in tropical settings, defined as areas with humid or

[a] World Health Organization, Country Office, Phnom Penh, Cambodia.
[b] National Centre for Epidemiology and Population Health, The Australian National University, Australia.
[c] WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute for Infection and Immunity, Australia.
[d] Communicable Disease Control Department, Ministry of Health, Phnom Penh, Cambodia.
[e] Centers for Disease Control and Prevention, Country Office, Phnom Penh, Cambodia.
[f] Angkor Hospital for Children, Siem Reap, Cambodia.
[g] Svay Rieng Provincial Hospital, Cambodia.
[h] Kampong Cham Provincial Hospital, Cambodia.
[i] Centers for Disease Control and Prevention, Atlanta, USA.
[j] Emerging Disease Surveillance and Response, World Health Organization Regional Office for the Western Pacific, Manila, Philippines.
[k] National Public Health Laboratory, National Institute of Public Health, Phnom Penh, Cambodia.
[l] Department of Epidemiology, University of California, Los Angeles, USA.
[m] School of Population and Global Health, University of Melbourne, Australia.
[*] Joint first authorship.

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arid/semiarid climates with mean temperatures of the coolest month above 18 °C, is higher than in temperate regions, particularly in children.[5] The prolonged circulation of seasonal influenza viruses in tropical areas could explain the higher burden. To address this data gap, the burden of influenza can be estimated using mathematical modelling. Recent estimates for the south-eastern Asian region indicate a considerable burden of influenza (>100 000 deaths per year).[6]

Effective prevention and control strategies for influenza are assisted by routine seasonal influenza burden estimates based on local data. The earliest analysis of influenza-like illness (ILI) and severe acute respiratory infection (SARI) surveillance data available for Cambodia (2009–2011) indicated seasons with a predominance of A(H1N1)pdm09 and with co-circulation of influenza A(H1N1), A(H3) and influenza B.[7] Circulation of influenza A(H1N1)pdm09, influenza B and A(H3N2) was reported by ILI surveillance in 2010–2012 in Cambodia both in urban and rural areas.[8,9] In addition, the threat of avian influenza A(H5N1) in Cambodia[10] demands robust surveillance systems capable of monitoring the impact on hospitalization rates of novel influenza viruses associated with severe disease.

In 2006, the Virology Unit at the Institut Pasteur in Cambodia, the Communicable Disease Control Department of the Ministry of Health and the World Health Organization (WHO) country office jointly established a National Influenza Centre (NIC) in Cambodia. The aim of the NIC was to monitor and characterize circulating strains of influenza virus associated with mild and severe diseases.[7]

Since 2009, Cambodia has conducted hospital- and laboratory-based surveillance for SARI to characterize the epidemiology of severe respiratory illnesses associated with influenza A and B viruses and other common respiratory pathogens.[11] SARI surveillance in Cambodia is conducted throughout the year due to year-round influenza activity.[7] The objective of this study was to estimate the national influenza-associated hospitalization burden using SARI surveillance data.

METHODS

Data sources

SARI sentinel surveillance sites

SARI surveillance in Cambodia includes eight sentinel surveillance sites. For this study, sentinel sites were public health care inpatient facilities (HCFs) where SARI patients were identified and clinical, demographic information and respiratory specimens were collected. A SARI case was defined as measured fever (temperature ≥38 °C) or history of fever, and cough or sore throat, and shortness of breath or difficulty breathing in a hospitalized person with onset of symptoms within 10 days before hospitalization.[12] All data were recorded in a secure online database. Sentinel sites were located in Phnom Penh (two sites), Kandal, Siem Reap, Takeo, Kampong Cham, Svay Rieng and Kampot provinces (**Fig. 1**). New SARI cases were reported weekly by sentinel sites throughout the year. National virological and epidemiological surveillance data were reported in a monthly respiratory bulletin and published online.[13]

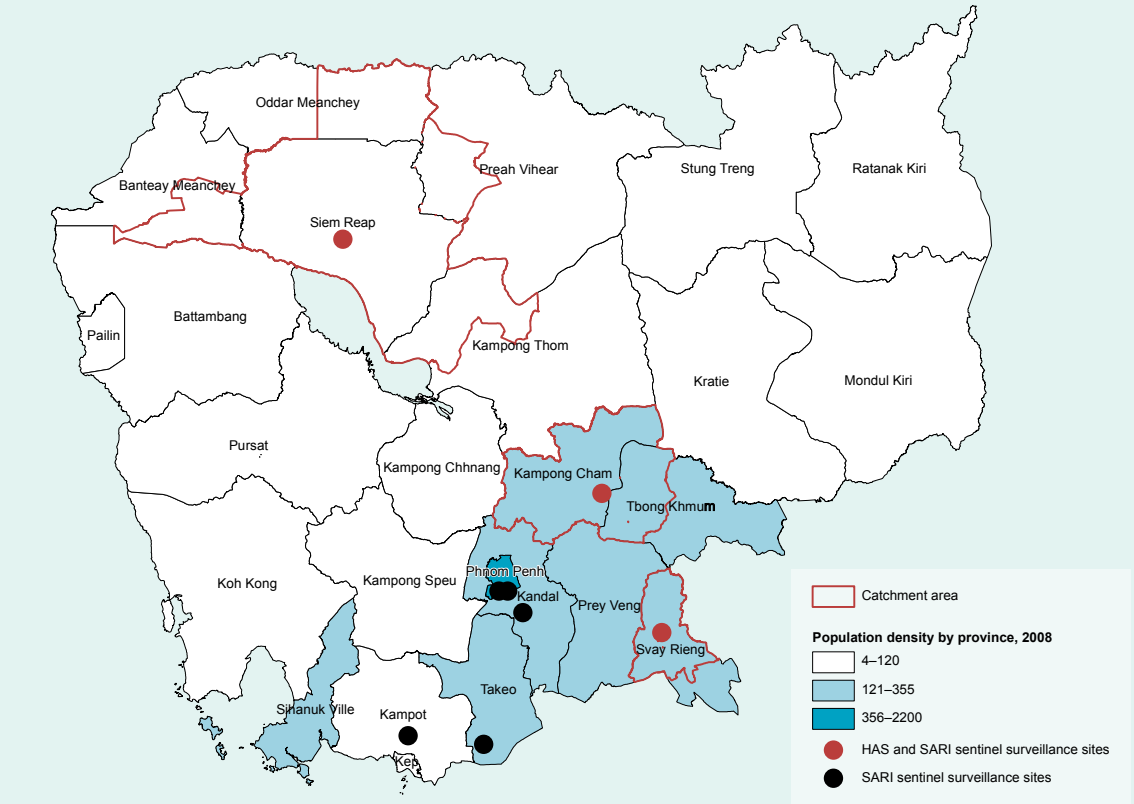
To estimate SARI rates, we used data from the three sentinel sites where Hospital Admission Surveys (HAS) had been conducted (**Fig. 1**). Two sites were rural and one was urban. Only three of the eight sites were included in the HAS due to resource limitations. Criteria used for site selection were site acceptance to participate in HAS and either the perceived quality of their data or availability of medical records in English.

Additional details on sentinel sites, case definitions and laboratory methods are available in **Appendix I** and **II**.

Hospital admission surveys

Hospital admission surveys were conducted in three locations to estimate the catchment population of each sentinel site using methods recommended by WHO[14] and piloted at the Svay Rieng sentinel site.[15,16] First, the addresses of the SARI cases admitted to the sentinel site were reviewed, and the catchment area for each site was defined as the districts from which 80% of the SARI cases admitted to the sentinel hospitals came (**Fig. 1**).

Fig. 1. **Map of Cambodia showing the eight SARI sentinel surveillance sites (black and red circles).***



HAS: Hospital Admission Surveys; SARI: severe acute respiratory infection

* Red circles represent the SARI sentinel surveillance sites that participated in the HAS, and black circles indicate all other SARI sentinel surveillance sites. Red contour lines surrounding HAS sites represent catchment areas for the three sentinel sites that participated in the HAS. Map created with ArcGIS 10.2 software by Environmental Systems Resource Institute (Redlands, CA, USA).

We refer to the catchment area of each site as Svay Rieng, Siem Reap and Kampong Cham.

Second, we listed the non-sentinel health facilities in the catchment areas of the sentinel sites that admitted patients overnight. We visited these health facilities to enumerate respiratory admissions consistent with the following diagnoses: acute pulmonary oedema, asthma, asthma-pneumonia, bronchiolitis, bronchitis, broncho-asthma, broncho-pneumonia, flu/cold, laryngitis, lung abscess/empyema, pharyngitis, pneumonia, pneumopathy, pulmonary tuberculosis, respiratory infection, rhino-pharyngitis, severe pneumonia and tonsillitis. These diagnoses, which were collected from hospital log books, represent a proxy measure for SARI diagnosis. We collected information from 38 privately operated non-sentinel HCFs from 1 January–31 December 2015 (Svay Rieng site) and 1 January–31 December 2016 (Siem Reap and Kampong Cham sites). The data collection team (approximately 12 enumerators and four supervisors) used paper-based forms to collect data from eight non-sentinel HCFs in Svay Rieng, 16 in Siem Reap and 14 in Kampong Cham. Non-sentinel HCFs kept records in Khmer, French, Vietnamese and English. Enumerators captured data recorded in Khmer or English. HAS data were entered in data collection forms and subsequently entered into Epi Info 7 in English.[17]

We calculated the age-specific proportion of SARI cases that sought care at each sentinel site out of all respiratory admissions across all HCFs in the catchment area. Admissions from patients that resided outside the catchment area were excluded from both the numerator and the denominator. We assume the proportion of catchment population of the sentinel site to the total

population is the same as the proportion of SARI cases seeking care in sentinel sites to SARI cases or respiratory admissions in all HCFs. Therefore, this proportion was applied to the age-specific district population (Ministry of Health Management Information System data) to generate an estimated catchment population for each sentinel site to be used as a population denominator for hospitalization rate calculations.

Data validation

We compared the number of SARI cases reported through the surveillance system with the number of cases identified through manual review of paper-based medical records using the same case definition for six weeks both during and out of typical influenza virus circulation periods. In addition, we conducted staff surveys at two sites to explore acceptance and technical aspects of SARI surveillance (**Appendix III**).

Data analysis

Site-specific annual hospitalization rates of influenza-associated SARI and 95% confidence intervals were calculated. For each site, we calculated the number of influenza-associated SARI hospitalizations by multiplying the age-specific influenza positive percentages in each month by the corresponding SARI case count in the same month. For sites with underreporting of SARI cases, we used SARI case counts identified by record review as a numerator in rate calculations by site.

To estimate national influenza-associated SARI hospitalization rates by age group, we used pooled data from the three sites. The count of SARI hospitalization nationally was calculated by multiplying the age-specific rates by the national population in the corresponding age groups.[18]

Ethical approval

The hospital admission review consisted of a retrospective review of health data collected by the SARI sentinel surveillance system, which is a public health activity managed by the Cambodia Ministry of Health. The ethical aspects of this study were approved by the Australian National University Human Research Ethics Committee (Protocol 2017/337).

RESULTS

Counting SARI cases at sentinel sites: findings from SARI surveillance

Overall, 2868 SARI cases were enrolled: 203 cases at Svay Rieng site, 922 cases at Siem Reap site and 1743 cases at Kampong Cham site. The majority of influenza-associated SARI cases in all sites combined were children under 5 years of age (51%) followed by the two older age groups (50–64 years and ≥65 years) representing 21% of SARI admissions (**Table 1**).

Validation of SARI data at three sentinel sites

In Siem Reap, 259 records from patients hospitalized during six weeks in 2016 were reviewed and 98 met the SARI case definition. The surveillance system identified 55 of these cases, indicating that 56% of SARI cases were identified and enrolled in surveillance. In Kampong Cham, we reviewed 99 records from patients hospitalized during six weeks in 2016. Of these, 28 patients met the SARI case definition and only 19 of these were captured by the surveillance system (32% underreporting). In Svay Rieng, we did not find underreporting. Instead we found overreporting by the surveillance system (i.e. 50 SARI cases were reported by the surveillance system compared to 41 identified by medical records review).[15]

Some respondents of the staff surveys reported that surveillance activities represented an acceptable workload. Challenges identified in the survey included difficulties in obtaining consent for specimen collection in children, swabbing distressed children, difficulties in applying the SARI case definition due to incomplete or unclear medical histories, parental misunderstanding regarding the purpose of specimen collection, difficulties in applying the case definition to neonates and fear of reprimand if unable to collect specimens due to lack of parental consent. Through staff surveys we found that SARI surveillance underestimated SARI in infants and children as those without swabs were not counted as SARI.

Influenza viruses circulated year-round with peaks in July and August. Multiple influenza virus types and subtypes were detected in 2015 and 2016; the predominant viruses were influenza A(H3N2) in 2015 and both A(H1N1)pdm09 and B in 2016 (**Fig. 2**).

Table 1. **Number of annual severe acute respiratory infection (SARI) cases and influenza-positive cases by age group and sentinel site, 1 January–31 December 2015 (Svay Rieng) and 1 January–31 December 2016 (Siem Reap and Kampong Cham, Cambodia)**

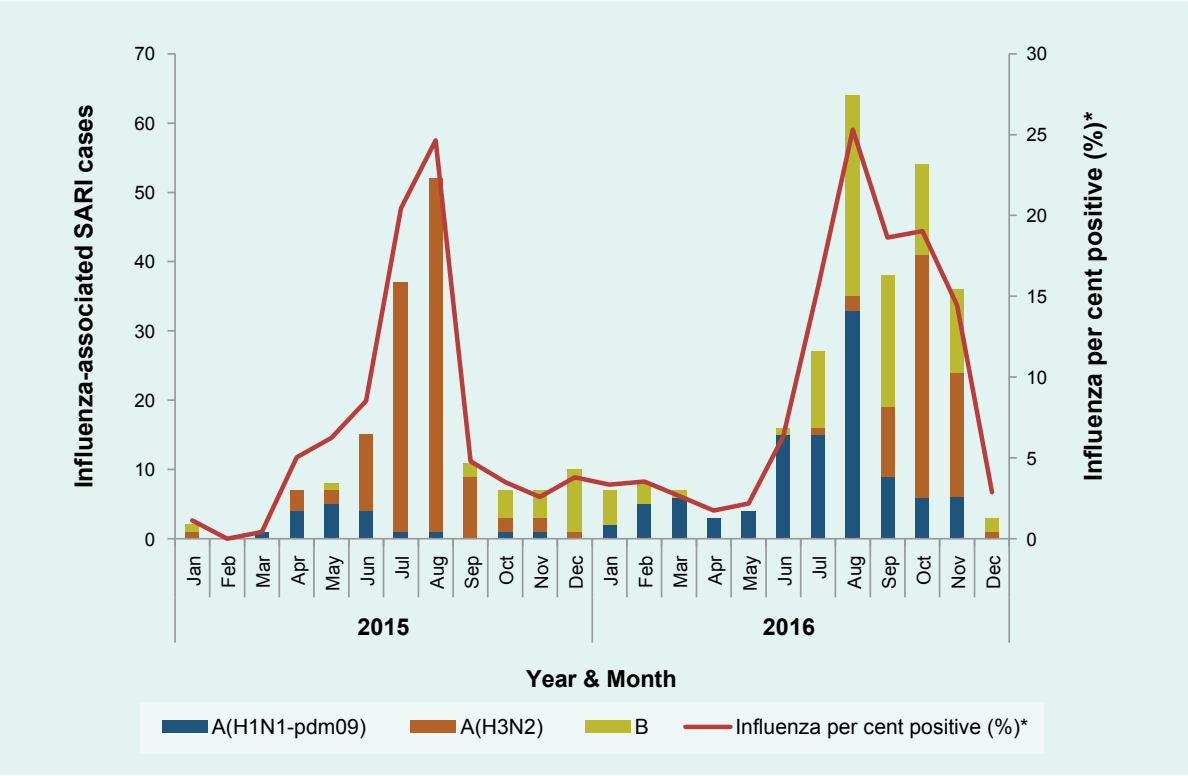
Age group (years)	Svay Rieng			Siem Reap*			Kampong Cham			Total influenza-associated SARI cases
	SARI cases	Per cent positive for influenza‡	Influenza-associated SARI cases†	SARI cases	Per cent positive for influenza‡	Influenza-associated SARI cases†	SARI cases	Per cent positive for influenza‡	Influenza-associated SARI cases†	
<1	8	0% (0/8)	0	455	10.4% (15/144)	47	381	10.0% (2/20)	38	85 (24%)
1–4	18	11.1% (2/18)	2	376	10.9% (19/175)	41	256	20.8% (10/48)	53	96 (27%)
5–15	6	33.3% (2/6)	2	91	10.0% (1/10)	9	157	30.0% (3/10)	47	58 (16%)
16–24	4	25.0% (1/4)	1				91	12.0% (3/25)	11	12 (3%)
25–49	40	7.5% (3/40)	3		NA		244	11.4% (8/70)	28	31 (9%)
50–64	61	6.6% (4/61)	4				280	10.0% (3/30)	28	32 (9%)
≥65	66	7.6% (5/66)	5				334	11.1% (5/45)	37	42 (12%)
Total	**203**	**8.4% (17/203)**	**17**	**922**	**10.6% (35/329)**	**97**	**1743**	**13.7% (34/248)**	**242**	**356 (100%)**

* Siem Reap sentinel site was a paediatric hospital and admitted children <16 years of age.

‡ Per cent positive for influenza is the proportion of SARI cases that tested positive for influenza.

† Influenza-associated SARI cases were calculated by applying the age-specific influenza per cent positive for each month to the corresponding SARI case count for each month.

Fig. 2. **Number of influenza-positive SARI cases by month and subtype/linage reported by all (eight) SARI surveillance sites, 1 January 2015–31 December 2016, Cambodia**



* Influenza per cent positive is the proportion of SARI cases that tested positive for influenza.

Source: SARI sentinel surveillance system, Cambodia.[19,20]

Estimated annual influenza-associated SARI hospitalization rate

The site-specific influenza-associated SARI hospitalizations rate varied widely. In 2015, the all-age influenza-associated SARI hospitalization rate in Svay Rieng was 7/100 000 population (**Table 2**). In 2016, the all-age rates in Kampong Cham were 72/100 000 population and much higher in the paediatric population (160). The combined influenza-associated SARI hospitalization rate was highest for children <1 year (323/100 000 population) and 1–4 years (196) followed by those aged ≥65 years (91). Influenza-associated SARI hospitalization rates varied by site – with the largest differences seen in the <1 years age group – from 0 for Svay Rieng to 495 per 100 000 in Kampong Cham. Hospitalization rates for Kampong Cham were higher compared with other sites for all age groups. Estimated age-adjusted influenza-associated SARI hospitalizations in Cambodia in 2016 were 7547 with most hospitalizations among children <16 years of age (5328/7547).

DISCUSSION

We present the first national burden estimate of severe influenza in Cambodia using hospital-based influenza surveillance data representing a climatically and demographically representative sample of hospitalizations in Cambodia in both rural and urban areas. Our findings indicate that influenza is an important contributor to hospitalizations in Cambodia particularly among children <5 years of age. In two sites, we observed that infants (<1 year) had the highest influenza-associated SARI hospitalization rates (345 and 495 hospitalizations per 100 000 population) followed by children aged 1–4 years (206 and 338 cases per 100 000 population). Our combined estimates of influenza-associated SARI hospitalizations in children are consistent with findings from African countries[21,22] but higher than those reported for Indonesia and India (82–114 and 118/100 000 children 0–4 years, respectively).[23,24]

When age-specific influenza-associated SARI hospitalization rates could be estimated across all age groups, we observed higher rates in infants and young children, lower rates in working-age adults and higher rates among those >65 years of age. The same patterns of influenza burden have been reported in tropical climate countries. For example, the Lao People's Democratic Republic reported hospitalization rates of 156, 44, 9 and 42 per 100 000 population in 0–4, 5–14, 15–64 and 65 years age groups, respectively.[25] In both Zambia and Rwanda influenza-associated hospitalization rates in infants were highest compared to all other age groups (484 and 295/100 000 children <1 year, respectively), and rates were lowest for the 5–24 years age group (6 and 11/100.000 5–24 years, respectively).[21,22] Compared to the hospitalization rates we estimated for older Cambodian adults, those reported for Zambia and Rwanda were lower (57 and 34/100 000 population >65 years).[21,22]

The combined burden of influenza hospitalizations across all age-groups estimated for Cambodia (56/100 000 population) is similar to that reported for Zambia (44)[21] but higher than Rwanda (35)[22] and Indonesia (19).[23] Influenza hospitalization burden likely varies both within and between countries. This may be explained by virological, geographical, sociological (health care-seeking behaviour), underlying health status of the population and burden estimation approaches.

Consistent with previous reports from Cambodia, countries in the region and globally,[7,23,26] influenza activity was detected throughout the year with peaks between March and December. In 2015 the predominant strain was influenza A(H3N2), whereas in 2016 A(H1N1)pdm09 and B co-circulated. Influenza A(H3N2) typically causes more severe disease in children and older adults compared with other seasonal influenza strains.[1] Therefore, differences in the predominant strain may not entirely explain the lower rates observed in 2015 in Svay Rieng.

Several limitations were identified in this study. The burden of influenza for Svay Rieng was estimated using data from 2015, the first year of operation of surveillance, whereas the other sites used 2016 data, the second year of surveillance. Using data from well-established systems collected in the same calendar year would improve comparability among sites and years. This is particularly important given that the predominant influenza circulating strains usually differ between years, which is associated with specific disease severity and therefore differing impacts on hospitalization rates. Additionally, multiple years of surveillance data are needed to reliably quantify the burden of influenza.

Furthermore, we estimated the burden of influenza based on three of the eight sentinel sites. The

Table 2. **Estimated annual influenza-associated severe acute respiratory infection (SARI) hospitalization rate (and 95% confidence interval) by age group for each sentinel site and nationally, 2015 (Svay Rieng) and 2016 (Siem Reap and Kampong Cham, Cambodia)**

Age group (Years)	Site-specific influenza-associated SARI hospitalization rate (HR) per 100 000 population*			Combined influenza-associated SARI HR per 100 000 population†	Cambodian population	National influenza-associated SARI case count‡
	Svay Rieng§	Siem Reap¦	Kampong Cham	A	B	
<1	0	345.4 (259.8–459.2)	494.9 (360.3–679.9)	323.0 (261.3–399.3)	348 518	1126 (1060–2078)
1–4	14.8 (3.7–59.3)	206.1 (151.6–280.0)	338.2 (258.6–442.3)	196.0 (160.5–239.4)	1 235 655	2422 (2325–4558)
5–15	4.7 (1.2–18.7)	33.2 (17.4–63.6)	195.7 (147.1–260.4)	61.8 (47.8–79.9)	2 880 177	1780 (1697–3327)
16–24	1.9 (0.3–13.4)	NA	16.6 (9.2–30.1)	9.2 (5.1–16.6)	3 334 307	307 (272–534)
25–49	3.6 (1.2–11.2)		22.2 (15.3–32.2)	14.8 (10.4–21.1)	5 066 335	751 (697–1 366)
50–64	12.9 (4.8–34.4)		44.9 (31.0–65.1)	35.4 (25.1–49.7)	1 544 946	546 (501–981)
≥65	36.2 (15.0–86.9)		110.3 (79.9–152.1)	90.8 (67.4–122.4)	677 422	615 (566–1110)
Total	**7.0 (4.4–11.3)**	**159.7 (131.0–194.9)**	**72.4 (63.8–82.1)**	**56.1 (50.6–62.2)**	**15 087 360**	**7547 (7376–14 458)****

* Site-specific HRs were estimated using methodology described in the WHO Manual for Estimating Disease Burden Associated with Seasonal Influenza.[14] We divided A (**Table 2** in **Appendix IV**) by D (**Table 2** in **Appendix IV**) and multiplied by 100 000.

† The combined influenza-associated SARI hospitalization rate was estimated by adding influenza-associated SARI cases from all three HAS sites (i.e. adding column A for each site in **Table 2** in **Appendix IV**), dividing by the sum of the three catchment populations (i.e. adding column D for each site in **Table 2** in **Appendix IV**) and multiplying by 100 000.

‡ The national influenza-associated SARI case count was estimated by applying the combined influenza-associated SARI hospitalization rate (A) to the Cambodian population (B) and dividing by 100 000.

§ The influenza-associated SARI hospitalization rate for Svay Rieng was calculated using 2015 surveillance data (whereas data for Siem Reap and Kampong Cham used 2016 data). The Svay Rieng HR slightly differs from previously published rates[15] due to a different population data source used for their calculation.

¦ The sentinel site in Siem Reap was a paediatric hospital that admitted children under 16 years of age.

** The total national influenza-associated SARI case count was calculated as the sum of all values in the column.

Only two decimal places are displayed, but calculations used >10 decimal places.

associated catchment populations for the sites included represent approximately 4% of the Cambodian population. This presents challenges to the representativeness of our estimates at the national level. We recommend further burden estimations using data from all sentinel sites captured in multiple calendar years, which was not possible in this study. Despite these limitations, our work indicates that the burden of severe influenza in Cambodia, particularly in children and the elderly, deserves consideration as it causes many thousands of hospitalizations annually. The economic costs associated with these hospitalizations, although not estimated in this study, would be substantial and could potentially be mitigated through interventions to reduce the influenza burden.

Through staff surveys at two sentinel sites we found that the surveillance system underestimated SARI in children at an unknown frequency (see **Appendix III**). In some cases parents refused specimen collection for their child. In addition, staff reported that swabbing infants was difficult and sometimes avoided. This would have resulted in a biased estimation of hospitalization rates for children.

We were unable to make a direct comparison between the rate of hospitalizations due to influenza and that of other diseases because of unavailability of complete national morbidity statistics in Cambodia. Challenges in the implementation of International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) have been documented.[27] Training physicians in writing diagnoses and strengthening the implementation of ICD-10 would allow future burden of disease studies to be improved by allowing contextualization with other diseases. Nevertheless, the percentage of those hospital-

ized with severe respiratory illness attributed to influenza in Cambodia (10.9% of all SARI hospitalizations, all-ages average) is comparable to that reported for Thailand (10.4%) and Indonesia (14%).[23,28]

One important strength of the study is the data validation conducted to understand the extent of under-reporting and the potential surveillance operational challenges.

The results of this study can be used by the Ministry of Health in Cambodia to consider the introduction of influenza vaccination to reduce the impact of influenza-associated hospitalizations in the most vulnerable population groups: children and elderly people. Furthermore, this work underscores the value of investing in routine influenza surveillance in low–middle-income countries as key drivers of population health and pandemic preparedness.

Conflict of interest

None.

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From H5N1 to HxNy: An epidemiologic overview of human infections with avian influenza in the Western Pacific Region, 2003–2017

Sarah Hamid,[a] Yuzo Arima,[b] Erica Dueger,[a,f] Frank Konings,[a] Leila Bell,[a] Chin-Kei Lee,[c] Dapeng Luo,[d] Satoko Otsu,[e] Babatunde Olowokure,[a] Ailan Li[a] and WPRO Health Emergencies Programme Team[a]

Correspondence to Erica Dueger (email: duegere@who.int)

Since the first confirmed human infection with avian influenza A(H5N1) virus was reported in Hong Kong SAR (China) in 1997, sporadic zoonotic avian influenza viruses causing human illness have been identified globally with the World Health Organization (WHO) Western Pacific Region as a hotspot. A resurgence of A(H5N1) occurred in humans and animals in November 2003. Between November 2003 and September 2017, WHO received reports of 1838 human infections with avian influenza viruses A(H5N1), A(H5N6), A(H6N1), A(H7N9), A(H9N2) and A(H10N8) in the Western Pacific Region. Most of the infections were with A(H7N9) (n = 1562, 85%) and A(H5N1) (n = 238, 13%) viruses, and most (n = 1583, 86%) were reported from December through April. In poultry and wild birds, A(H5N1) and A(H5N6) subtypes were the most widely distributed, with outbreaks reported from 10 and eight countries and areas, respectively.

Regional analyses of human infections with avian influenza subtypes revealed distinct epidemiologic patterns that varied across countries, age and time. Such epidemiologic patterns may not be apparent from aggregated global summaries or country reports; regional assessment can offer additional insight that can inform risk assessment and response efforts. As infected animals and contaminated environments are the primary source of human infections, regional analyses that bring together human and animal surveillance data are an important basis for exposure and transmission risk assessment and public health action. Combining sustained event-based surveillance with enhanced collaboration between public health, veterinary (domestic and wildlife) and environmental sectors will provide a basis to inform joint risk assessment and coordinated response activities.

Avian influenza viruses occur naturally among wild aquatic birds and cause occasional outbreaks in domestic poultry and other animal species.[1] They do not normally infect humans, though certain subtypes, such as avian influenza A(H5), A(H7) and A(H9) have caused sporadic human infections. Clinical outcomes range from mild illness to death.[2] Co-circulation of influenza A viruses in human and animal reservoirs in shared habitats provides opportunities for these viruses to reassort and acquire a genetic composition that could facilitate sustained human-to-human transmission with potential pandemic consequences.[3,4]

The pandemic potential of avian influenza viruses gained larger recognition in 1997 when the first known human infection with avian influenza A(H5N1) virus was reported in Hong Kong SAR (China).[5] During this event, 18 human infections, including six deaths, were reported.[6] Thereafter, the number of countries reporting human infections with A(H5N1) virus increased, especially between 2003 and 2008. As of September 2017, outbreaks associated with A(H5N1) viruses in domestic poultry and wild birds have occurred in more than 60 countries, and sporadic human infections with A(H5N1) viruses have been reported in 16 countries. A 53% case fatality has been reported among human cases of A(H5N1), which has been associated with severe pneumonia.[7] In addition to A(H5N1), other novel zoonotic influenza viruses infecting humans have emerged, including A(H5N6), A(H7N9), A(H10N8), A(H6N1) and a novel A(H1N2) variant.[1,8]

[a] WHO Regional Office for the Western Pacific.
[b] National Institute of Infectious Diseases, Japan.
[c] WHO Country Office China.
[d] WHO Country Office Lao People's Democratic Republic.
[e] WHO Country Office Viet Nam.
[f] Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA.

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The Western Pacific Region has reported more than one quarter (238/860) of global A(H5N1) cases and is the second most affected region.[9] Moreover, the recently identified zoonotic strains A(H7N9), A(H5N6), A(H6N1) and A(H10N8) emerged in the Western Pacific Region.[10]

Regional and international tools and frameworks have been implemented to address the threat of pandemic influenza and other emerging diseases. Regional and country-specific analyses are important as case fatality, demographic characteristics, seasonality and the clade or subclade of viruses have been observed to vary across regions.[11] In the Western Pacific Region, the *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies* (APSED III) is an action framework to strengthen public health sector capacity to manage and respond to emerging disease threats and to support progress towards implementation of the International Health Regulations (2005) (IHR).[12] APSED III promotes the sharing and use of information from multiple data sources for surveillance and risk assessment and aligns with global initiatives such as the One Health approach for multisectoral collaboration and communication in public health.[13] Member State notification to the World Health Organization (WHO) of zoonotic influenza virus infections in humans is mandated under the IHR, and WHO has maintained an epidemiologic database of human infections with zoonotic influenza viruses reported since 2003. Infections with highly pathogenic avian influenza A virus in birds and low pathogenic influenza H5 and H7 viruses in poultry are notifiable to the World Organisation for Animal Health (OIE) under the Terrestrial Animal Health Code.[14] Data on animal outbreaks are available through OIE and the Food and Agriculture Organization of the United Nations (FAO) Global Animal Disease Information System (EMPRES-i).[15,16] EMPRES-i consolidates disease events worldwide using information from official and unofficial sources including reports by OIE chief veterinary officers.[15] The public availability of these data contributes to the compilation, analysis, interpretation and dissemination of information on avian influenza viruses in humans and animals.

In addition to these international frameworks, the WHO Global Influenza Surveillance and Response System (GISRS) is a laboratory network that collects data on influenza viruses circulating globally to inform vaccine composition recommendations, conduct risk assessments and monitor antiviral susceptibility.[17] In the Western Pacific Region, GISRS includes three WHO collaborating centres, six H5 reference laboratories and 21 national influenza centres (NICs) in 15 countries and areas.[18] WHO regularly produces global and regional updates on avian influenza virus activity and publishes timely information on novel human infections with zoonotic influenza viruses through *Disease Outbreak News*.[7,19–21]

While reports of human infections with A(H5N1) virus have declined since 2013, notifications of human infections with A(H7N9) and other avian influenza viruses have increased, highlighting the continued threat posed by these A(HxNy) viruses. Analyses of avian influenza virus infections in humans and outbreaks in birds can provide a basis for multisectoral risk assessments. This report summarizes the descriptive epidemiology of reported laboratory-confirmed human infection with avian influenza viruses in the Western Pacific Region along with reported outbreaks of these viruses in birds from the resurgence of A(H5N1) activity in November 2003 through the fifth epidemic of A(H7N9) ending on 30 September 2017.

METHODS

Data on human infections with avian influenza virus subtypes were summarized by person, place and time; bird infections were summarized by place and time. The starting date for this analysis was November 2003 when there was a resurgence in reported A(H5N1) activity in both humans and animals across several countries.[22]

Data on human infections with onset dates from November 2003 through September 2017 in the Western Pacific Region were based on official notifications to WHO under IHR. These notifications were primarily reported from National IHR Focal Points to the Western Pacific Regional IHR Contact Point. Notifications included the avian influenza virus subtype, demographic and epidemiologic information available at the time of reporting; information on virus clade was not included in reports. Infections notified and summarized in this analysis were with avian influenza subtypes A(H5N1), A(H5N6), A(H6N1), A(H7N9), A(H9N2) and A(H10N8). For A(H7N9), information regarding clusters of infection and virus pathogenicity in poultry was also included.

Data on infections with these influenza virus subtypes in birds in the Western Pacific Region were

extracted from the EMPRES-i database, which includes reports of avian influenza events involving both low and highly pathogenic viruses—the former cause few or no clinical signs and the latter, severe clinical signs in poultry. The database was queried for confirmed events in domestic, wild and captive birds observed from January 2003 through September 2017. For low and highly pathogenic H5 and H7 viruses notifiable to OIE,[14] records reported by official sources including national authorities, OIE, FAO or laboratories were extracted. For non-H5 and non-H7 low pathogenic viruses not notifiable to OIE, such as A(H6N1), A(H9N2) and A(H10N8), outbreaks and detections reported in publications were also extracted from EMPRES-i. Data were summarized and analysed in SAS (University Edition, Cary, NC, USA) and Microsoft Excel and mapped in ArcGIS (Esri, Redlands, CA, USA) to describe the demographic, temporal and spatial characteristics of avian influenza virus activity in the Region.

RESULTS

From November 2003 through September 2017, 1838 human infections with six avian influenza viruses in the Western Pacific Region were reported to WHO. The majority of infections were with A(H7N9) (n = 1562, 85%) and A(H5N1) (n = 238, 13%) viruses. Infections with A(H5N1) predominated until 2013 when reports of A(H7N9) emerged in China (**Fig. 1**). The majority (n = 1583, 86%) of human infections were reported from December through April. While this seasonality was largely driven by A(H7N9) and A(H5N1) cases, most A(H5N6) and A(H9N2) cases (n = 22, 65%) and all three A(H10N8) cases were also reported during this period (**Fig. 2**). With the exception of A(H5N1) and A(H6N1) viruses, all human infections in the Region were reported from, or associated with history of travel to, China.

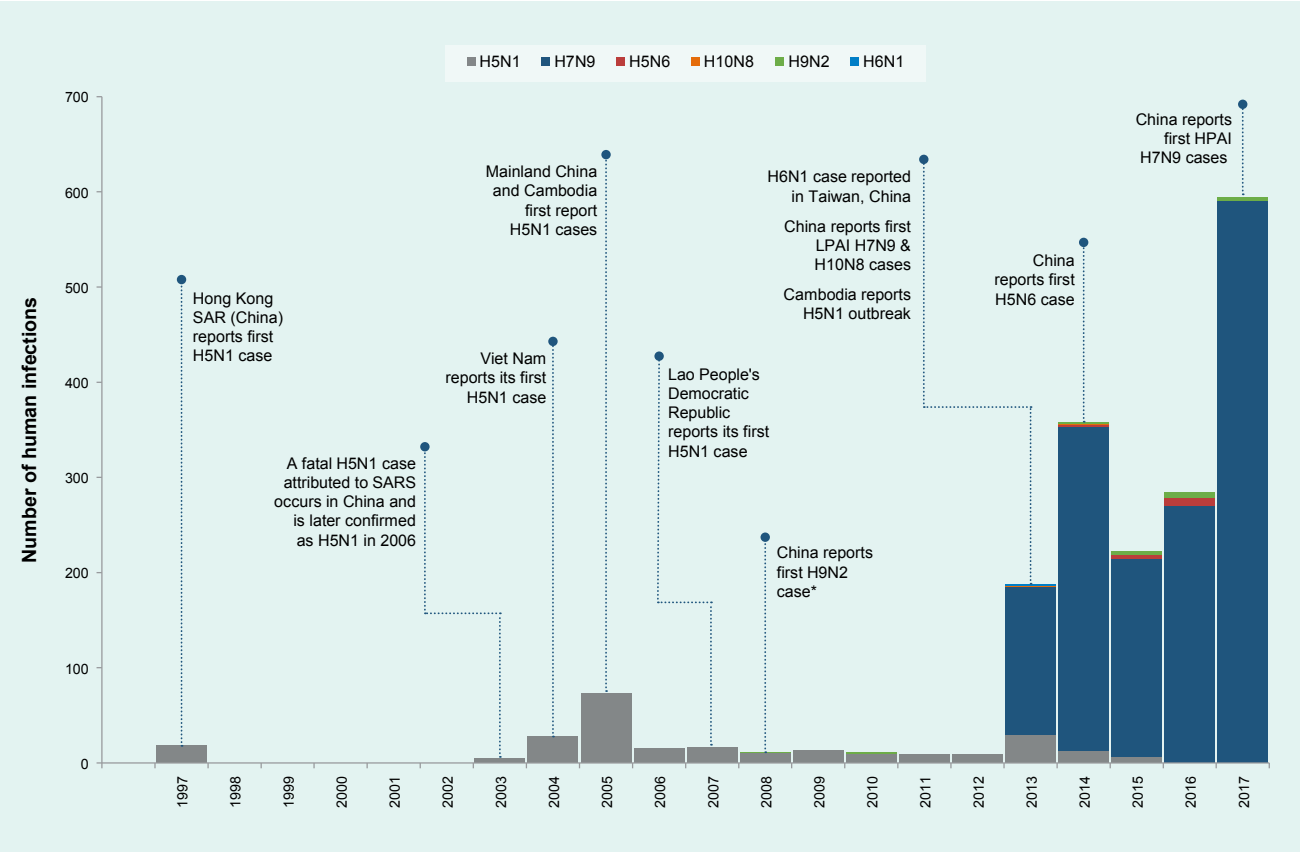
In birds, A(H5N1) and A(H5N6) viruses were the most widely distributed in the Western Pacific Region, and outbreaks were reported from 10 and eight countries and areas, respectively (**Fig. 3**). Low pathogenic avian influenza (LPAI) A(H9N2) viruses have been detected in poultry populations of five Western Pacific Region countries and areas since 2004. As of 30 September 2017, poultry infections with A(H7N9) virus have not been reported in the Western Pacific Region outside of China.

Human infections with avian influenza A(H5N1) viruses

From November 2003 through September 2017, 238 laboratory-confirmed human infections with avian influenza A(H5N1) were reported to WHO from four countries in the Western Pacific Region: Cambodia (n = 56), China (including Hong Kong SAR) (n = 53), the Lao People's Democratic Republic (n = 2) and Viet Nam (n = 127) (**Table 1**). The most recently reported A(H5N1) human infection in the Western Pacific Region had symptom onset in December 2015 and was from China. The overall case fatality rate (CFR) at the time of report was 56% (134/238) with 37 deaths in Cambodia (CFR 66%), 31 deaths in China (CFR 58%) and 64 deaths in Viet Nam (CFR 50%). Both cases in the Lao People's Democratic Republic were reported as fatal. Seasonally, the majority of cases (n = 142, 60%) occurred from January through March (**Fig. 2**). Reports of A(H5N1) infections in humans peaked from November 2003 through December 2005 (n = 106) when notifications from Viet Nam (n = 93) surged and later from January 2013 through March 2014 when there was an outbreak in Cambodia (n = 35) (**Fig. 1**).

Across the Region, 50% (n = 119) of A(H5N1) cases were female; the sex distribution was similar when stratified by country, with females comprising 49% (n = 62) of cases in Viet Nam, 47% (n = 25) in China and 54% (n = 30) in Cambodia. In the Lao People's Democratic Republic both cases were female. The overall median age of cases was 20 years (range: <1–81 years), but age distributions differed by country (**Fig. 4**). The median age of cases in Cambodia (6 years, range: <1–58 years) was considerably lower than that observed in China (27 years, range: 2–75 years), Viet Nam (23 years, range: <1–81 years) and the Lao People's Democratic Republic (15 and 42 years). These differences in age distributions remained when stratified by sex, with a predominance of paediatric cases in Cambodia regardless of sex (**Fig. 4**). For all countries, however, female cases tended to be younger than male cases (**Fig. 4**). Data on poultry exposure were available for 152 of 238 (64%) cases; of these cases, 95% (n = 145) reported contact with poultry.

Fig. 1. **Timeline of human infections with avian influenza virus subtypes in the Western Pacific Region, May 1997–September 2017**



* This refers to the first official report to WHO under the IHR (2005). Human infections with avian influenza A(H9N2) were previously reported in the scientific literature.

HPAI, highly pathogenic avian influenza; LPAI, low pathogenic avian influenza.

Avian influenza A(H5N1) virus in birds

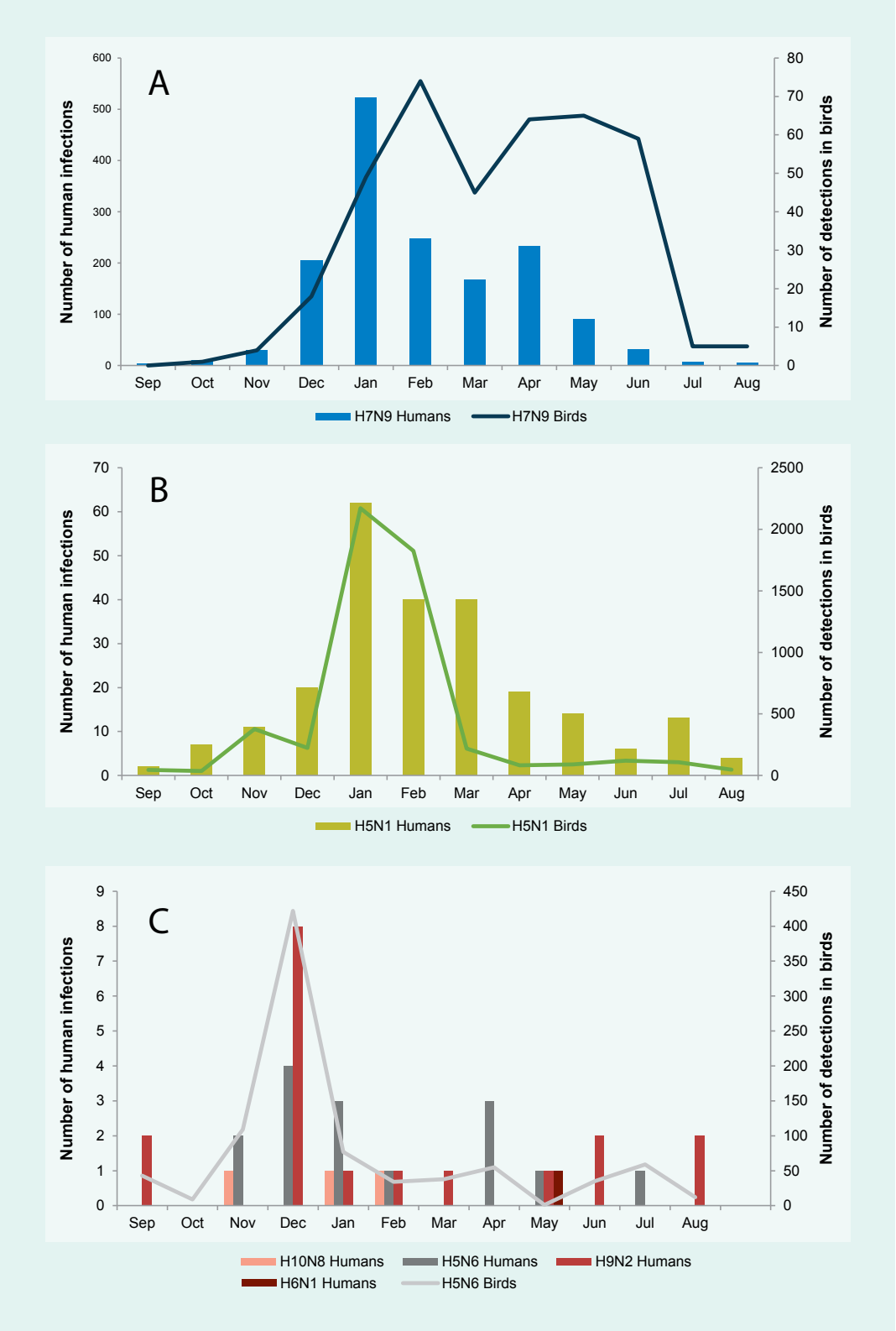
Since late 2003, high mortality associated with A(H5N1) virus has been observed in poultry and wild birds in the Western Pacific Region. All reported viruses were highly pathogenic. Events (n = 5344) were reported from 10 countries and areas (**Table 1**, **Fig. 3**). The majority (n = 4037, 76%) were reported in Viet Nam during 2004 and 2005. The reported number of events in avian populations decreased steadily from 2004 to 2006, rose slightly in 2007 and has since declined. In March 2017, however, Malaysia reported its first A(H5N1) poultry outbreak since 2006. Events were reported year-round but most frequently (n = 4597, 86%) from November through February, coinciding with the months when A(H5N1) infections in humans were most frequently reported (**Fig. 2**).

Human infections with avian influenza A(H5N6) viruses

As of 30 September 2017, 16 laboratory-confirmed human infections with avian influenza A(H5N6) virus had been reported to WHO from China. At the time the cases were reported, four (25%) cases had died. The first human case was reported in May 2014 in Sichuan province and was associated with infected poultry.[23] Subsequent infections were detected between December 2014 and November 2016 from the eastern province of Anhui (n = 1), the southern provinces of Hunan (n = 3), Guangdong (n = 7), Guangxi (n = 1), Yunnan (n = 2) and the central province of Hubei (n = 1) (**Fig. 3**).

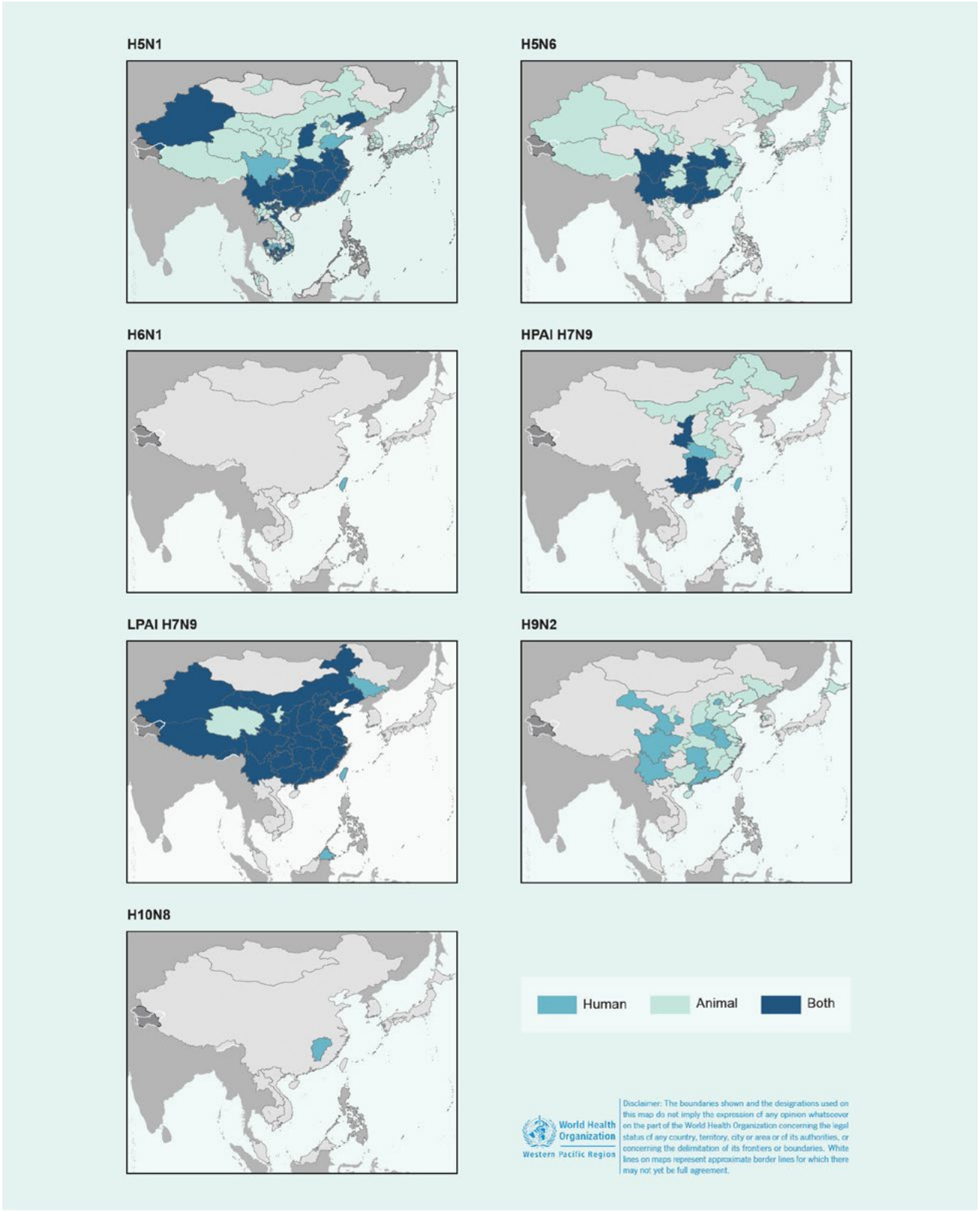
Ages ranged from 11 to 65 years (median 40 years). Males (7 of 16 cases) were older compared to females (**Table 1**). Contact with poultry or wild birds was reported in all 13 cases for whom exposure history was known.

Fig. 2. **Reported human infections with avian influenza viruses and events in birds in the Western Pacific Region by month, November 2003–September 2017***



* Scales differ between graphs A, B and C. Events in birds are only plotted for viruses notifiable to OIE (i.e. highly pathogenic influenza A infections in birds and low pathogenic H5 and H7 in poultry).

Fig. 3. **Map of avian influenza virus detections reported in humans and birds in the Western Pacific Region, November 2003–September 2017***



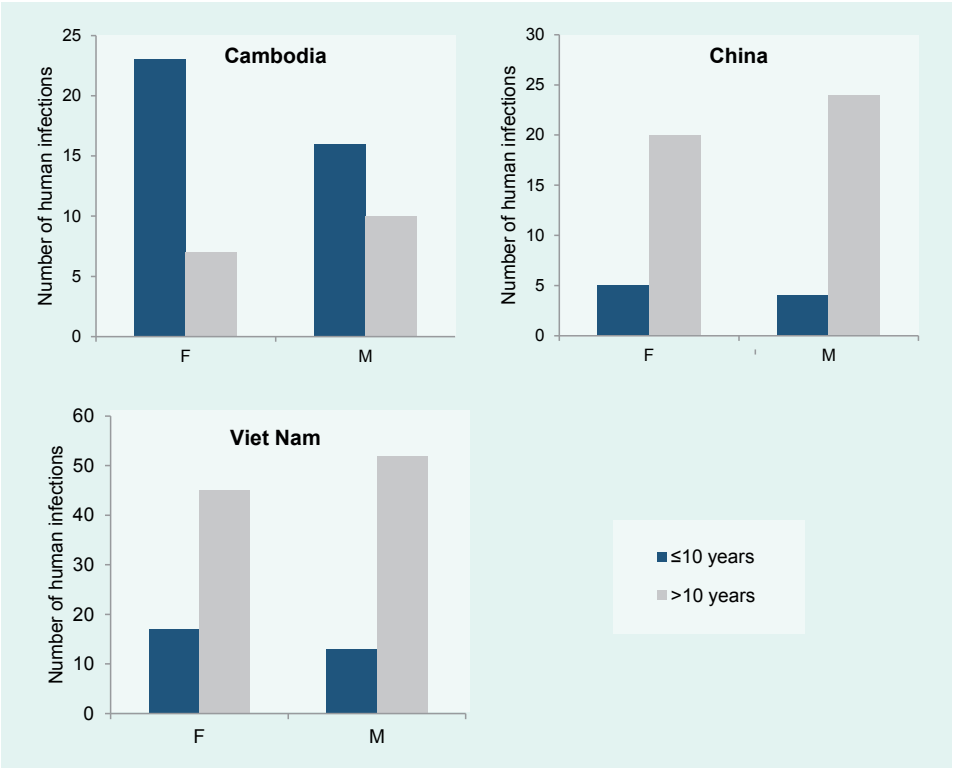
* This map displays human infections with avian influenza viruses reported to WHO and detections and outbreaks of these viruses in animal populations recorded in the EMPRES-i system based on place of report. Detections reported through other channels are not included. Low pathogenic H6N1, H9N2 and H10N8 are not notifiable to OIE.

HPAI, highly pathogenic avian influenza; LPAI, low pathogenic avian influenza.

Table 1. **Demographic, geographic and temporal characteristics of avian influenza virus subtypes reported in the Western Pacific Region, November 2003–September 2017**

	Influenza A virus subtype					
	H5N1	H7N9	H5N6	H9N2	H10N8	H6N1
Human infections, *n*	238	1562	16	18	3	1
Median age (range), years	20 (<1–81)	57 (<1–91)	40 (11–65)	3 (<1–86)	73 (55–75)	20
Male	23 (<1- 81)	57 (1–91)	44 (25–58)	2 (<1–86)	75	–
Female	18 (<1–75)	56 (<1–85)	37 (11–65)	4 (<1–57)	55, 73	20
Geographic spread*						
Countries/areas affected (humans)	Cambodia, China, Lao People's Democratic Republic, Viet Nam	China, Malaysia (travel history to mainland China)	China	China (including Hong Kong SAR with travel history to mainland China)	China	China, Taiwan, China
Countries/areas affected (birds)	Cambodia, China (including Hong Kong SAR and Taiwan, China), Japan, Lao People's Democratic Republic, Malaysia, Mongolia, Republic of Korea, Viet Nam	China (including Hong Kong SAR, Macao SAR and Taiwan, China)	China (including Hong Kong SAR and Taiwan, China), Japan, Lao People's Democratic Republic, Philippines, Republic of Korea, and Viet Nam	China (including Hong Kong SAR), Japan, Republic of Korea and Viet Nam	No reports in EMPRES-i	No reports in EMPRES-i

Fig. 4. **Reported cases of human infections with avian influenza A(H5N1) virus in Cambodia, China and Viet Nam by age and sex, November 2003–September 2017**



Avian influenza A(H5N6) virus in birds

The first outbreaks of A(H5N6) virus in poultry were reported in March 2014 in Xayabury, Lao People's Democratic Republic and in Sichuan, China in May 2014. However, the virus had been isolated in December 2013 from an environmental sample collected in a live poultry market in Jiangsu Province.[24] Since then, the geographic distribution of reported events gradually expanded, affecting eight countries and areas by September 2017 (**Table 1**, **Fig. 3**). All events involved highly pathogenic avian influenza (HPAI) A(H5N6), except for two events involving LPAI A(H5N6) in Hunan Province, China and Louangphabang, Lao People's Democratic Republic. A(H5N6) events in birds were widespread in most of the affected countries (**Fig. 3**).

The majority of events were reported from the Republic of Korea (n = 386, 43%) followed by mainland China (n = 260, 9%). Across the Region, events were reported year-round with some variation in circulation among countries. In mainland China, Japan and the Republic of Korea, the largest number (n = 417, 46%) of events occurred in December. The Lao People's Democratic Republic reported three events in March, July and October. In Viet Nam events were reported every month of the year with no clear seasonality. The Philippines reported its first A(H5N6) outbreaks in July and August 2017.

Human infections with avian influenza A(H7N9) viruses

Between 31 March 2013 and 30 September 2017, 1564 laboratory-confirmed human infections with avian influenza A(H7N9) virus were reported to WHO, occurring in five annual epidemics (defined as reported case onset from 1 October to 30 September of the following year). The outbreak began in China in March 2013 with two patients from Shanghai and one from Anhui. The geographic distribution of reported cases has shifted and expanded over time with cases reported from 27 mainland China provinces and municipalities, several of which are along international borders, as well as from Hong Kong SAR, Macao SAR and Taiwan, China (**Fig. 5**). In addition, cases associated with travel to China were reported in Malaysia (n = 1) and Canada (n = 2).[7]

The majority (n = 1381, 88%) of cases occurred from December to April each year with a few sporadic cases occurring during the summer months (**Fig. 2**). The peak of A(H7N9) infections was in January, with the exception of 2013 when notifications peaked in April. The majority of cases were reported from Zhejiang (n = 310, 20%), Guangdong (n = 258, 16%) and Jiangsu (n = 252, 16%) provinces on China's eastern coast (**Fig. 5**).

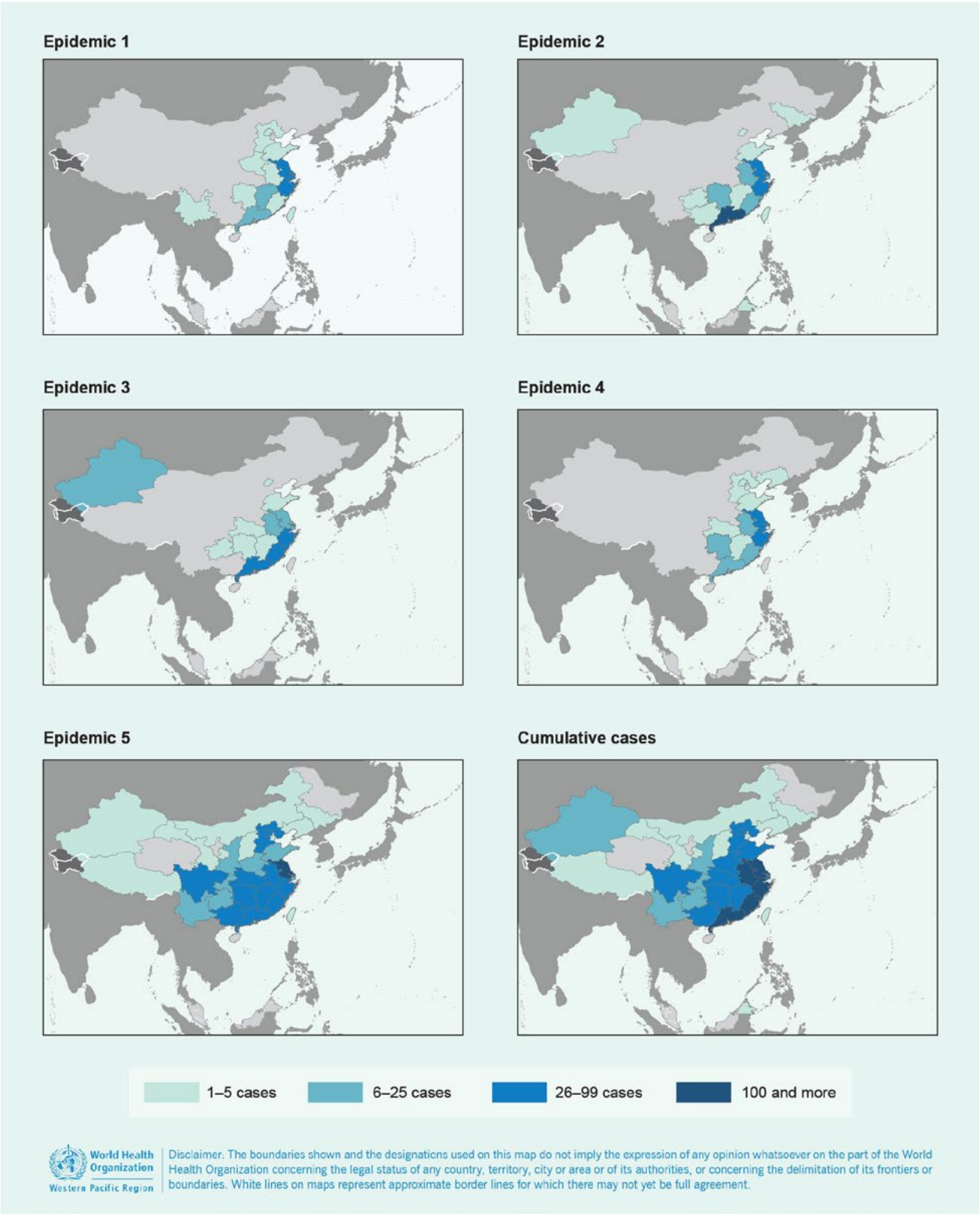
The median age of cases was 57 years (range: <1–91 years), and 67% (n = 1054) of cases were aged 50 years and older. Overall, approximately 70% of A(H7N9) cases were male (**Table 2**), but the proportion differed by age; among those aged 0–24 years, males comprised 49% (n = 38) of cases, but among those 25 years of age and older, 67% (n = 1055) were male. Among the latter, further age group stratification (25–34, 35–44, 45–54, 55–64, 65+ years) indicated that the predominance of males was similar across these age groups (range: 68% to 72%).

The sex and age distribution of cases were similar across epidemics with infections in men reported more frequently than in women (**Table 2**). However, shifts in the frequency as well as temporal and geographic distribution of cases were observed (**Table 2**, **Fig. 5**). The second epidemic year (1 October 2013–30 September 2014) was considerably higher in amplitude compared to the first and peaked in January rather than April. During the third (1 October 2014–30 September 2015) and fourth (1 October 2015–30 September 2016) epidemic years, the number of human infections reported declined, but there was no major change in the temporal distribution of cases compared to the second epidemic year (**Table 2**).

The fifth epidemic year of A(H7N9) activity in humans saw an epidemic that surpassed all previous years in amplitude and number of cases reported (n = 766), with peak activity observed in January 2017 consistent with trends observed in the second to fourth epidemic years. However, the increase in notifications started earlier than in previous years and expanded to the north and west with Jiangsu reporting the greatest number of cases (n = 148, 19%) and nine administrative regions (Chongqing, Gansu, Inner Mongolia, Shaanxi, Shanxi, Sichuan, Tibet, Yunnan provinces and Macao SAR) reporting cases for the first time.

As of 30 September 2017, WHO received reports of 39 clusters, three of which involved multiple provinces: two from Beijing and Hebei and one from Fujian and

Fig. 5. **Geographic distribution of reported cases of human infections with avian influenza A(H7N9) virus in the Western Pacific Region, March 2013–September 2017***



* Epidemics are defined as 1 October to 30 September of the following year with the exception of the first epidemic that started in April 2013. Maps are based on the provinces where the cases were reported.

Table 2. **Characteristics of A(H7N9) epidemics, March 2013–September 2017**

	Epidemic (year)*				
	2013	2013–2014	2014–2015	2015–2016	2016–2017
Human infections, *n*	135	320	224	119	766
Male, *n* (%)	97 (72)	218 (68)	154 (69)	78 (66)	546 (71)
Median age (range), years	61 (2–91)	57 (<1–88)	56 (1–88)	58 (13–91)	57 (3–91)
Clusters, *n*	4	9	6	6	14
Month of peak notifications	April	January	January	January	January
Provinces** reporting human infections, *n*	13	17	15	15	30
Provinces** reporting detections in birds, *n*	11	12	14	10	27

* Epidemics are defined as 1 October to 30 September of the following year with the exception of the first epidemic that started in April 2013.

** Within China, provinces refer to China's provincial administrative units, which include province, autonomous region, municipality and special administrative region. Information on detections in birds is based on data in the EMPRES-i system as of November 2017.

Zhejiang. Most were two-person clusters (n = 35, 90%), but three-person clusters also occurred (n = 4, 10%). With the exception of four clusters in health-care settings, all clusters involved household or family contacts. Clusters often involved cases that had exposure to live poultry or their environments; thus, it was not always possible to determine whether human-to-human transmission or common poultry exposure was the source of infection. Clusters increased in number but not in the size in the fifth epidemic (**Table 2**) with no apparent change in human-to-human transmission risk.[25]

While IHR notifications do not typically include virus pathogenicity, on 18 February 2017, the National Health and Family Planning Commission of China notified WHO of two previously reported human infections with viral sequences with changes at the haemagglutinin gene cleavage site that are associated with a transition from low to high pathogenicity in poultry. Since this announcement, 28 human cases have been identified with HPAI A(H7N9) from Guangdong, Guangxi, Hunan, Shaanxi and Hebei provinces, and Taiwan, China. Viral sequencing from one person in a family cluster of two sisters in Guangdong during the fifth epidemic was found to have these HPAI genetic markers. However, no viral samples from the other sister were available to determine if these markers were present in both cases.

Avian influenza A(H7N9) virus in birds

Poultry surveillance for LPAI A(H7N9) has relied on targeted sampling because, by definition, infected poultry show little to no clinical signs of infection. In 2017, HPAI A(H7N9) was reported for the first time through active surveillance in a live bird market in Guangdong province and on a layer farm in Hunan province. Subsequent outbreaks were reported in nine other provinces in China. While the majority of A(H7N9) detections are LPAI viruses, recent viral changes found in human, poultry and environmental samples are associated with high pathogenicity in poultry.[26] Since it was first detected in 2013, low and/or highly pathogenic A(H7N9) viruses have been detected in poultry in 31 administrative areas of China, including Hong Kong SAR and Macao SAR. The number of provinces reporting virus detections has gradually increased over time (**Table 2**). However, some provinces that reported A(H7N9) detections in earlier years did not report infections in subsequent years.

Detections of LPAI A(H7N9) have been most frequent in the southern and eastern provinces, but reports have stemmed from 26 mainland administrative areas, from the northern province of Liaoning to the southern province of Hainan and the western provinces of Qinghai, Ningxia and Sichuan (**Fig. 3**). As of September 2017, the strain of A(H7N9) virus circulating in China has not been detected in poultry in other countries. Virus detections were most frequently reported between January and June.

Other avian influenza A virus subtypes infecting humans and poultry

Other avian influenza viruses infecting humans in the Western Pacific Region include A(H9N2), A(H10N8) and A(H6N1).

Between December 2008 and September 2017, 18 human infections with avian influenza A(H9N2) virus were officially notified to WHO from China. Cases were reported from nine administrative areas: Hong Kong SAR (n = 3; all with travel history to Guangdong Province), Anhui (n = 1), Beijing (n = 1), Gansu (n = 1), Guangdong (n = 4), Henan (n = 1), Hunan (n = 5), Sichuan (n = 1) and Yunnan (n = 1) provinces. Cases had a median age of 33 years (range: <1–86 years) and seven (39%) were male. At the time of notification, nine (50%) patients had been hospitalized and three manifested serious illness; none was fatal at the time of reporting.

LPAI A(H9N2) viruses circulate endemically among poultry in Asia. Since 2004, they have been detected in China (including Hong Kong SAR), Japan, the Republic of Korea and Viet Nam. A(H9N2) infections in poultry have been widespread in China (the EMPRES-i database includes international reference laboratory reports of detections from 23 of 34 administrative units from 2010 through 2014), but they have been found predominantly in eastern provinces. As of September 2017, no avian events had been reported in the Western Pacific Region since 2014.

Avian influenza A(H10N8) was responsible for three human infections in the Region as of March 2017. The first human infection was reported in a 73-year-old female in Jiangxi, China in December 2013; it was followed by two cases in the same province: a 55-year-old woman in January and a 75-year-old man in February 2014. All cases had poultry exposure and required hospitalization.

As a low pathogenic virus in birds, A(H10N8) is not notifiable to OIE and no events were recorded in the EMPRES-i system. However, isolation of A(H10N8) viruses from poultry and environmental samples, including in Jiangxi Province following detections in humans, has been reported in the scientific literature.[27–29]

In June 2013, a case of human A(H6N1) infection was reported to WHO from Taiwan, China. This was the first reported human infection with the virus. The case was a 20-year-old female hospitalized with mild pneumonia in May 2013. She had no known exposure to poultry and fully recovered.

Avian influenza A(H6N1) is an LPAI virus in birds and commonly circulates in the domestic bird population.[30–32] It is not a notifiable disease in animals, and no events were recorded in the EMPRES-i system.

DISCUSSION

Our regional analysis of human infection with avian influenza viruses reported from November 2003 through September 2017 revealed common patterns as well as variations in epidemiology across countries, age and time that may not be apparent from pooled global summaries or isolated country reports. In addition, assessing surveillance data from both the human and animal sectors provided a more complete overview of zoonotic influenza virus activity that can inform regional risk assessment and response efforts.

Temporal trends

During the analysis period, notifications of human A(H5N1) infections followed similar temporal trends to those of A(H5N1) poultry outbreaks with initial increases in reports followed by declines by 2005. Reports of human A(H5N1) infections have remained low despite enhanced surveillance, awareness and reporting following the detection of other avian influenza virus subtypes. Declines in reported human and poultry infections despite enhanced surveillance activities indicate that a surveillance or reporting artefact is unlikely to explain the observed decline in A(H5N1).

While the incidences of human and animal A(H5N1) infections have likely declined, A(H7N9) has emerged as a new threat. The fifth A(H7N9) epidemic had the largest number of reported human infections to date with an earlier start and longer period of activity than previous seasons.[33] Human A(H7N9) infections occurred seasonally, coinciding with peak influenza detection in poultry as observed with A(H5N1) in other regions,[4,14] and similar to A(H5N1), A(H5N6), A(H9N2) and A(H10N8) in the Western Pacific Region. While the temporal correlation between human infections and poultry events may be due to increased influenza virus activity in birds that increases transmission potential to humans, surveillance bias could play a role (i.e. if surveillance is enhanced in humans once a poultry outbreak occurs

or vice versa). Given the predominantly low pathogenic nature of A(H7N9) and the systematic targeted poultry sampling, this bias is unlikely. Enhanced surveillance and control measures at live bird markets, particularly during the cooler, drier months, could potentially reduce the risk of coinfection and reassortment.

HPAI A(H7N9) viruses have been detected recently; preliminary analyses based on eight cases indicated similar epidemiologic characteristics among humans infected with both low and highly pathogenic A(H7N9).[34] Animal studies have shown that HPAI A(H7N9) viruses can be transmitted through respiratory droplets,[35] but additional research is needed to determine the likelihood of this mode of transmission in humans.

Geographic trends

Despite the extensive regional distribution of both A(H5N1) and A(H5N6) events in birds, only A(H5N1) has been reported in humans outside of China, excluding travel-associated A(H7N9) cases.[36] The absence of reported human or animal A(H7N9) infections in neighbouring countries that trade live poultry with China suggests that the A(H7N9) virus is currently limited to China. Based on live-bird trade patterns, the likelihood of A(H7N9) virus entry is considered moderate for the Lao People's Democratic Republic and Viet Nam and negligible for Cambodia, which has no known live poultry trade with China.[37] Nevertheless, the spatial distribution of reported A(H7N9) cases within China across epidemics and the presence of provinces in which only human cases have been detected may suggest undetected poultry infections.

Demographic characteristics

Demographic characteristics of reported human infections varied. Aggregated age and sex distributions of human infections with A(H5N1) viruses in the Western Pacific Region were similar to global averages,[7] but epidemiologic patterns differed among countries. Accounting for sex, younger age groups were reported in Cambodia compared to China, the Lao People's Democratic Republic and Viet Nam; these differences were too large to be explained solely by differences in population age distributions. In addition, age distributions differed by sex; male cases tended to be older than their female counterparts. Such differences could arise from differential poultry exposure, health-care-seeking behaviour, case ascertainment or illness severity.

For non-A(H5N1) avian influenza virus infections in humans reported from China, the age and sex distributions also varied. Relative to A(H5N1) cases, A(H7N9) cases tended to be skewed towards older males, and, although numbers were small, A(H5N6) cases also tended to be older while A(H9N2) cases tended to be younger with more females. Explanations proposed for the difference in age and sex distribution of human A(H5N1) and A(H7N9) in China include differences in exposure patterns, increased susceptibility to serious disease after infection with A(H7N9) and case ascertainment bias.[38–40] Serological and epidemiologic data indicate that A(H5N1) infections may be more severe than A(H7N9) infections; A(H7N9) illness severity increases with patient age, and mild A(H7N9) infections in younger people may be underascertained.[41–43] While further studies are required to understand the factors and exposure patterns driving the epidemiology and to inform targeted prevention activities, basic surveillance data and descriptive epidemiology will continue to inform operational research and response. Population-level observations, particularly those related to poultry rearing and purchasing practices, will help generate preliminary hypotheses regarding risk factors for infection.

Limitations

Interpretations based on surveillance data represent an important limitation in our assessments. While H5 and H7 serosurveys suggest limited asymptomatic illness,[41,44–46] even a low seroprevalence may indicate a substantial number of undetected cases and underestimations of the true burden and spectrum of zoonotic influenza infections. Surveillance and laboratory capacities vary among countries and between human and animal sectors; thus, country-level comparisons require caution. Moreover, within each country, the capacity to detect influenza viruses has evolved through national and partner support for influenza surveillance strengthening.[47] Surveillance biases may have affected the observed geographic distribution of cases as previously affected areas may have more complete surveillance and reporting. For example, regional variations in China in surveillance for pneumonia of unknown etiology led to increased surveillance in areas in which A(H7N9) cases had been detected relative to areas in which they had not.[48] While recognizing the role of possible ascertainment bias, surveillance and reporting enhancements have led to a more comprehensive understanding of the epidemiology of various influenza viruses circulating in the Region.

Event notification through IHR facilitates timely information sharing, greater understanding of an event as it unfolds and collaborative risk assessment to reduce the potential for international disease spread. Similarly, reporting to OIE is designed to facilitate information sharing and early warning and response to transboundary animal diseases. Thus, official IHR/OIE notifications include information available at the time of reporting that may not include sufficient exposure or outcome history to allow for an in-depth assessment.

Another limitation is potential missing data. Reports to WHO or OIE might not include all cases of detected human infections and poultry outbreaks. IHR (2005), which mandates the reporting of human infections with novel influenza viruses, did not come into effect until 2007. Thus, cases occurring before 2007 may not have been officially reported to WHO.[49–54] There are also human infections with avian influenza viruses after 2007 that are reported in the literature that have not been confirmed by national authorities or officially reported under the IHR.[55,56]

Duplicate event reports in the EMPRES-i database are another possibility. We did not include EMPRES-i records from publications for H5 and H7 viruses, which are notifiable to OIE, to avoid possible duplication of events officially reported by OIE, FAO or national authorities. As a result, events involving notifiable subtypes reported in scientific publications but not through official reports are not included in our summary.

CONCLUSIONS

Despite these limitations, disseminating regional analyses can improve Member States' situational awareness, knowledge of the epidemiology in neighbouring countries as well as of the broader regional perspective, and risk assessment and response efforts. This analysis specifically demonstrates the usefulness of combining multiple sources of surveillance data for better informed risk assessments, including those based on the WHO Tool for Influenza Pandemic Risk Assessment.[57] Moreover, using multiple sources of information helps to assess potential surveillance biases, thereby improving decision-making.

Further sporadic human infections with avian influenza viruses are likely to occur. Although A(H5N1) incidence may have declined, A(H7N9) virus has emerged, and other avian influenza viruses have been detected in recent years. In China, country of the origin of recently identified avian influenza virus strains, the poultry industry has expanded greatly in the past two decades.[58] In many areas, the close proximity of humans and animals increases the risk of human exposure to zoonotic influenza viruses.[3] As infected animals or contaminated environments are the primary sources for human infection, risk assessments should incorporate a One Health approach and gather information from all relevant sectors. Continued surveillance at the human–animal interface is imperative for all avian influenza viruses. Every sporadic human infection provides a virus with an opportunity to change its genetic makeup, increasing the possibility of an influenza virus with pandemic potential to arise. Strengthened communication and collaboration between animal and human health sectors at subnational, national, regional and global levels are necessary to monitor the dynamics of influenza virus activity. An APSED approach that aligns with One Health initiatives combining sustained event-based surveillance with enhanced collaboration between the human, animal (domestic and wildlife) and environmental sectors will provide a basis to inform joint risk assessment and coordinate response capacities.

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Influenza virus detection: driving change in public health laboratories in the Western Pacific Region

Raynal C Squires,[a] Patrick C Reading,[b] Sheena G Sullivan,[b] Ian G Barr[b] and Frank Konings[c]
Correspondence to Frank Konings (email: koningsf@who.int)

As we observe the 100th anniversary of the 1918 influenza pandemic, we are reminded of the importance of preparedness for and adequate response to influenza, and the critical role of influenza surveillance through laboratory detection. Influenza virus detection has helped drive the development of diagnostic and virology laboratories in the World Health Organization (WHO) Western Pacific Region over the last 10–15 years, at the same time strengthening their capacity to detect and respond to infectious threats beyond influenza. Such cross-cutting approaches are advocated under the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III),[1] which continues to guide Member States in advancing implementation of the International Health Regulations, 2005[2] and has a dedicated focus on strengthening laboratory capacities.

For over 65 years, worldwide surveillance of influenza has been conducted through the WHO Global Influenza Surveillance and Response System (GISRS) laboratory network.[3] National Influenza Centres (NICs, usually national or provincial diagnostic or reference laboratories) report in-country influenza activity to WHO and refer a subset of clinical specimens or virus isolates to WHO collaborating centres (WHO CCs) for detailed antigenic and genetic characterization, antiviral drug susceptibility testing and other analyses. WHO CCs, H5 Reference Laboratories, Essential Regulatory Laboratories and other experts meet twice-yearly to review laboratory and epidemiological data to assist WHO in making recommendations on suitable virus strains for seasonal and pandemic influenza vaccines.[3]

In 2017, GISRS laboratories in the Western Pacific Region tested nearly 800 000 specimens for influenza (**Fig. 1**). GISRS monitoring of circulating influenza viruses in humans enables timely detection and reporting of significant changes in seasonal influenza viruses such as the emergence of the influenza A(H1N1) pandemic virus in 2009 and the rapid global spread of oseltamivir-resistant seasonal H1N1 viruses in 2007–2008.[4] It also increases the speed with which novel influenza A subtypes with pandemic potential can be detected, like avian influenza A(H7N9). Through the Pandemic Influenza Preparedness Framework, vaccine, antiviral and diagnostics manufacturers benefitting from the sharing of viruses and data collected through GISRS return a monetary contribution to WHO to help strengthen surveillance in the laboratory network, particularly in countries with lower capacity.[3] The system does have limitations, however, that reflect country capacities and priorities. For instance, the resources needed to maintain NICs and surveillance are primarily concentrated in larger Western Pacific Region Member States rather than small Pacific islands, and countries with unusual numbers of cases are more likely to prioritize sharing. Nevertheless, sharing is key to the success of GISRS, and attention, support and advocacy should be invested into enhancing country participation.

Fast, accurate and reliable methods for the diagnosis of influenza virus infection are needed for surveillance of emerging viruses, outbreak management, early antiviral treatment, prophylaxis and infection control. The traditional method of influenza virus detection by isolation in eggs or cell culture followed by antigenic typing is labour-intensive and time-consuming, particularly in

[a] WHO Regional Office for the Western Pacific, Manila, Philippines.
[b] WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
[c] WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt.
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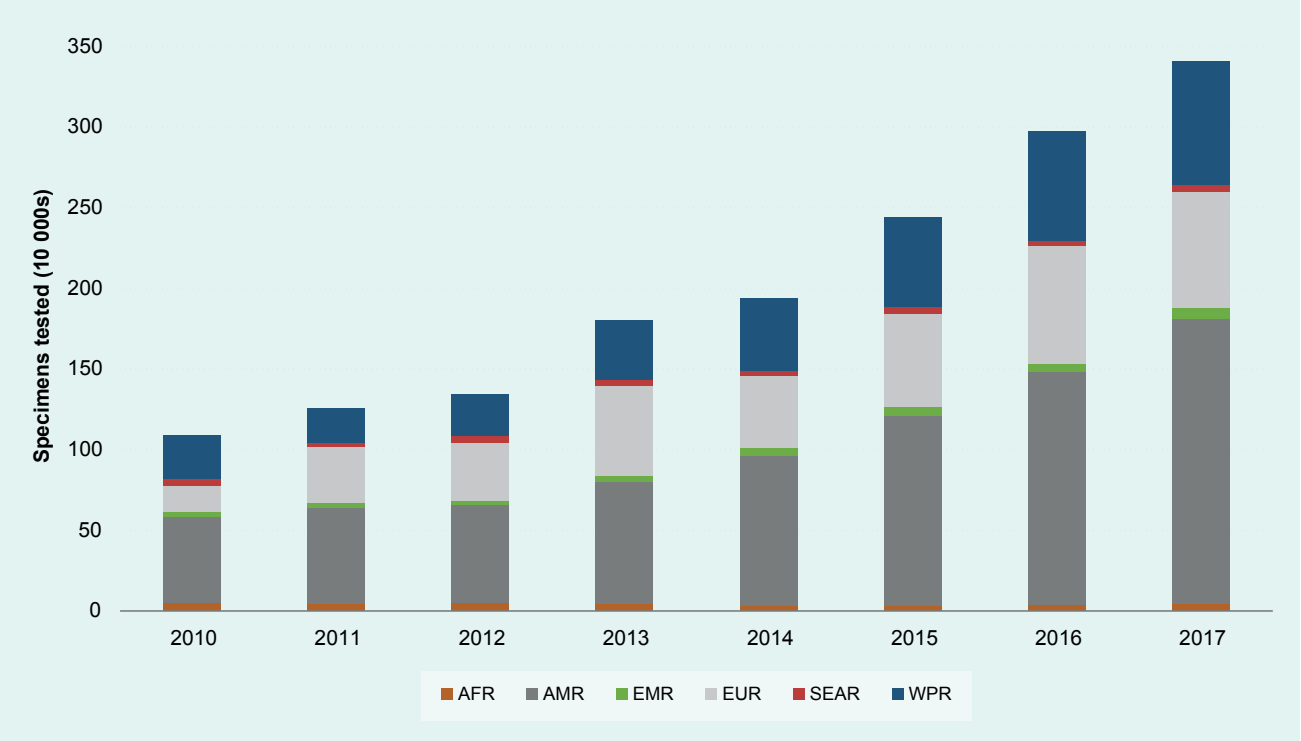
Fig. 1. **Number of clinical specimens tested for influenza by the GISRS laboratory network in the six WHO regions from 2010 to 2017**



AFR, African Region; AMR, Americas Region; EMR, Eastern Mediterranean Region; EUR, European Region; GISRS, Global Influenza Surveillance and Response System; SEAR, South-East Asia Region; WHO, World Health Organization; WPR, Western Pacific Region.

Data obtained from FluNet (http://www.who.int/influenza/gisrs_laboratory/flunet/en/), a global web-based tool for influenza virological surveillance and provided by National Influenza Centres (NICs) in the WHO GISRS network. NICs in the Western Pacific Region are located in: Australia (three laboratories), Cambodia, China, Fiji, Hong Kong SAR (China), Japan, the Lao People's Democratic Republic, Malaysia (two laboratories), Mongolia, New Caledonia (France), New Zealand (two laboratories), Papua New Guinea, the Philippines, the Republic of Korea, Singapore and Viet Nam (two laboratories).

the context of an outbreak. Polymerase chain reaction (PCR) techniques developed in the past 25 years enabled the rapid and specific detection of viral nucleic acid sequences, becoming the gold standard for diagnosis and surveillance. Since 2004, PCR has been instrumental in the early detection of various zoonotic influenza viruses in humans, including A(H5N1), A(H5N6), A(H7N9), A(H9N2) and others in the Western Pacific Region.[5] NICs worldwide now routinely perform conventional, real-time and/or multiplex PCR for molecular detection of influenza viruses. In addition to PCR, some NICs in the Western Pacific Region have introduced other molecular tests (e.g. sequencing, pyrosequencing, next-generation sequencing) as well as serological assays (e.g. haemagglutination inhibition, virus neutralization) and testing for sensitivity to antiviral drugs. Nevertheless, serological and drug-sensitivity assays require influenza viruses to be amplified from clinical material, meaning that laboratories performing these tests must still maintain good capacity for traditional methods.

NICs are mandated to maintain high technical capacity for influenza testing[3] and are evaluated on the quality of their testing through external quality assessment (EQA). Following several outbreaks of human infection with avian influenza A(H5N1), WHO initiated an EQA programme in 2007 to monitor the quality of PCR detection of influenza virus, and to identify gaps in testing and potential areas of support to NICs. The programme has since grown in sophistication and now includes seasonal influenza A, influenza B and other non-seasonal influenza A viruses responsible for human infections, as well as drug susceptibility analysis. In the Western Pacific Region, the percentage of NICs scoring fully correct results for the detection of influenza virus by PCR increased from 57.1% in 2007 (Frank Konings, WHO, personal communication, 2018) to 84.2% in the 2017 round of the EQA programme.[6] In a related first-run EQA to evaluate performance in the isolation and identification of influenza viruses in cell culture, over two-thirds of regional NICs had 80% or more correct results.[7]

As the majority of NICs in the Region actually test a broad range of infectious diseases or are housed in institutions that do, the benefits of technical and human resource strengthening through GISRS have been cross-cutting. Annual NIC meetings bring together experts to discuss progress, obstacles and best practices, helping to strengthen countries' laboratory technical capacity through better coordination, a key strategic action in APSED III. Molecular testing available in the GISRS laboratory network has also formed the basis of regional preparedness for detection of emerging pathogens, including Middle East respiratory syndrome coronavirus[8] and Zika virus.[9] Similarly, drawing on the established EQA programme for PCR detection of influenza virus, WHO worked with WHO CCs to develop and distribute an EQA for arboviruses to the network, starting with dengue virus in 2013 and now including chikungunya, Zika and yellow fever viruses.[10] Not solely an evaluation of performance, EQA helps to reveal problems in general laboratory practices, improves the reliability of delivering accurate test results in a timely manner and is usually required for laboratory accreditation.[11] Finally, there has long been strong focus on NIC staff development through training in data management and analysis, virus isolation, sequencing and bioinformatics, drug susceptibility testing, infection prevention and control and shipping of infectious substances. These skills are clearly applicable beyond influenza work, multiplying the benefits of the initial investment manyfold.

Since the 1918 pandemic and the later introduction of GISRS, regional NICs have been maintaining traditional methods, incorporating new technologies and building human resource capacity to help strengthen preparedness and response to influenza. The cross-cutting advantages generated and the benefits of sharing and collaboration through GISRS contribute to better preparedness for future outbreaks of influenza and other infectious diseases.

Conflicts of interest

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PanStop: a decade of rapid containment exercises for pandemic preparedness in the WHO Western Pacific Region

Edna Moturi,[a] Katherine Horton,[a] Leila Bell,[a] Lucy Breakwell,[a] Erica Dueger[a,b]
Correspondence to Erica Dueger (email: wpsar@who.int)

Rapid containment (RC) is one of the five priority interventions of the World Health Organization (WHO) Strategic Action Plan for Pandemic Influenza;[1] it relies on the concept that mass prophylactic administration of antiviral drugs, combined with quarantine and social distancing measures, could contain or delay the international spread of an emerging influenza virus.[2,3] During a RC operation, mass antiviral prophylaxis treatment and non-pharmaceutical interventions are rapidly implemented within a containment zone surrounding the initial cases; active surveillance and additional activities are extended to a broader buffer zone where cases are most likely to appear based on the movements of cases and contacts.[2,4] The strategy is dependent on the rapid (within three to five days) detection, investigation and reporting of initial cases; the efficacy and availability of antivirals and vaccines; and timely risk assessment and decision-making. In the Western Pacific Region, a stockpile of antiviral medication and personal protective equipment acquired through donations from the Government of Japan is warehoused in Singapore under the auspices of the Association of Southeast Asian Nations (ASEAN),[5] and is managed under contract by the Japan International Cooperation System (JICS).[5] These supplies are reserved for early intervention when initial signs of increased human-to-human transmission of a highly contagious influenza virus occur.

Advanced planning is required for RC to ensure that all relevant partners and sectors work together in a coordinated manner within a short time frame. Simulation exercises are recognized as a crucial component of pandemic preparedness, and many different types of exercises have been conducted in the Asia–Pacific region.[6] In this paper, we describe the PanStop exercises conducted by the WHO Regional Office for the Western Pacific to show how they have contributed to pandemic preparedness in the Region.

In 2007, the WHO Regional Office for the Western Pacific conducted the first simulated exercise known as PanStop that aimed to determine the validity of procedures developed in the Asia–Pacific Region for RC of a new, highly contagious influenza virus.[5] The exercise took 11 hours over one and a half days, and was conducted in six sites, at the WHO Regional Office for the Western Pacific, the WHO Country Office in Cambodia, JICS and the Japanese Ministry of Foreign Affairs in Tokyo, the ASEAN Secretariat in Jakarta, and the offices of Singapore Technologies Logistics (STL) in Singapore.[5] Since then, the WHO Regional Office for the Western Pacific has conducted nine PanStop exercises on RC to identify strengths and opportunities to improve planning activities for containing pandemic influenza. PanStop is designed to test pandemic influenza response plans through a simulated real-world event and is not designed to evaluate individual participant performance.

PanStop exercises typically involve artificial but realistic scenarios where human infections of a novel influenza A virus are reported from a Member State. Participants, who may include WHO staff, ministry of health officials and people from other government agencies potentially involved in pandemic response, work through and discuss the decision-making process and actions necessary to implement RC based on their current pandemic preparedness plans. Each year, Member States or WHO country offices may request that a PanStop exercise be conducted in their country to test their levels of preparedness. The Regional Office has also been the

[a] WHO Regional Office for the Western Pacific, Manila, Philippines.
[b] Influenza Division, Centers for Disease Control and Prevention, Atlanta, United States of America.
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main player in two exercises to test and evaluate the roles and responsibilities of Regional Office staff for regional RC, particularity in logistics and communication.

Both modified functional and table-top exercises have been employed for PanStop exercises (**Table 1**). A modified functional exercise is an interactive process where multisectoral participants receive simulated outbreak information through email, telephone or actions and then respond as they would within actual designated roles. Participants may carry out tasks in response to outbreak information (e.g. prepare a line list of cases, develop talking points for a press conference, calculate required doses of prophylaxis) or, when time is constrained, they may be asked to describe the actions they would take. These functional exercises have been conducted in Cambodia (2007),[5] the Philippines (2008),[7] Malaysia (2009),[8] Mongolia (2010),[9] Viet Nam (2013),[11] and at the WHO Regional Office of the Western Pacific (2011),[10] 2014[12] and 2015[13] (**Table 1**). All the exercises involved fictional scenarios of diseases of unknown etiology or occurrence of novel avian influenza with evidence of human-to-human transmission which necessitated the launch of a RC exercise. With the exception of PanStop 2007 and 2010, all the exercises were conducted within two days. PanStop exercises conducted at the WHO Regional Office of the Western Pacific have typically included JICS and ASEAN to test their transportation protocols when they ship items in the regional stockpile from Singapore to the requested country.

A table-top exercise comprises the same stakeholders, but a facilitator guides a discussion about a simulated series of events that prompts discussion of response actions from participants. Table-top exercises provide an opportunity for moderated interactions of multiple sectors in addition to the ministry of health. In 2017, a table-top PanStop exercise was held in Fiji at the request of the Fiji Ministry of Health to test the readiness of organizations involved in the national pandemic preparedness plan, including ministries of agriculture and transportation.[14] The exercise, which lasted one and a half days, highlighted the importance of good multisectoral collaboration in ensuring a successful response. A similar table-top exercise was conducted this year in Mongolia involving a fictional outbreak of novel avian influenza A(H10N8) in Choibalsan province with multi-sectoral participation from the WHO Regional Office, WHO Country Office in Mongolia, JICS and various ministries and authorities.

As for all simulation exercises, PanStop is a relatively inexpensive way of assessing operational readiness and is more feasible than full-scale exercises that require extensive financial and human resource investment. PanStop exercises typically last one or two days with simulated deployment of human and physical resources rather than actual movement of these resources. The exercises provide an opportunity for multisectoral engagement as RC requires involvement from both animal and human health sectors as well many other stakeholders, including administration, communication and logistics specialists (**Table 1**). PanStop exercises are overseen by evaluators who are pandemic preparedness experts. They assess the participants' actions in terms of their appropriateness and alignment with the exercise's goals and objectives. Through consultation with participants, they also recommend improvements for operational readiness for RC. A final report is published for each conducted PanStop exercise that includes the evaluation results, lessons learnt and recommendations (**Table 1**).

Lessons learnt from PanStop exercises include the need to (1) update national pandemic preparedness plans; (2) clarify specific sector roles during both RC and pandemic response efforts; (3) emphasize concepts to senior officials from different government agencies that may be involved in pandemic response; and (4) allow stakeholders to identify knowledge and planning gaps, such as lack of standardized operating procedures for RC initiation and availability of trained staff to execute the plans. A lesson learnt from the exercise at the regional level in 2014 was the need to improve Emergency Operations Centre activation plans. As a result, the improved plans were developed, implemented and successfully tested in the 2015 PanStop exercise (**Table 1**). Recommendations for improvements to the PanStop exercise have been made so that future exercises are more effective and can potentially evolve beyond RC to test broader national systems.

Many national governments within the Western Pacific Region have developed national pandemic response plans for RC to prepare for the next influenza pandemic.[15] It is critical that these plans have the ability to be operationalized efficiently to mitigate the consequences of the next pandemic. PanStop exercises provide an opportunity to test the RC mechanisms of these pandemic plans in the participating countries and at the regional level in a simulated environment that imitates pandemic events as they unfold. By participating in these exercises and sub-

Table 1. **PanStop exercises on influenza pandemic responses in the Western Pacific Region, 2007–2018**

Year	Country	Objectives	Scenario summary	Type of exercise	Duration	Participating agencies	Lessons learnt
2007	WHO Regional Office and Cambodia[5]	Practise decision-making and communication with partner agencies to launch and manage a RC operation; train staff in RC; develop a replicable model exercise for training other jurisdictions.	Fictional discovery of cases of novel strain of avian influenza in a village with evidence of human-to-human transmission.	Modified functional	1½ days	WHO Regional Office, WHO Country Office in Cambodia, ASEAN, JICS, STL, Cambodia Ministry of Health, and the Cambodian National Centre for Disaster Management	It is safer to be proactive and deploy resources in waves, despite the consequences of lacking data, than to respond too late.
2008	Philippines[7]	Assess the preparedness of the Philippines to implement a RC operation; gain a better understanding of operational capacity for RC in the country.	Fictional outbreak of a potential pandemic strain of the avian influenza virus in the Philippines.	Modified functional and table-top	2 days	WHO Regional Office, JICS, ASEAN, Philippine Department of Health, and various agencies and authorities, including the Armed Forces and Police	Philippine Government and nongovernmental agencies now understand a RC operation from a national perspective.
2009	Malaysia[8]	Identify strengths and opportunities for improvement in planning activities for pandemic influenza; gain better understanding on the operational capacity for RC activities in Malaysia.	Fictional outbreak of a potential pandemic strain of avian influenza in a village in Johor State.	Modified functional	2 days	WHO Country Office in Malaysia, WHO Regional Office and various health and disaster management ministries and authorities	Ministry of Health to take lead in strengthening the management processes or emergency operations at state, district and field levels.
2010	Mongolia[9]	Test WHO decision-making processes during a routine rapid response and before launching a RC operation.	Fictional outbreak of a potentially pandemic strain of influenza virus in a district in Mongolia.	Modified functional	Six hours	WHO Country Office in Mongolia, WHO Regional Office, Ministry of Foreign Affairs, Japan, JICA	Exercise led to a deepened understanding of RC protocol and identified need to clarify stakeholders' roles and responsibilities in the RC protocol.
2011	WHO Regional Office and, Philippines[10]	Test the responses of the WHO Regional Office during RC in a Member State to evaluate roles and responsibilities of response logistics, validate risk communication; assess operational issues and processes to establish, maintain and close the containment zone.	Fictional outbreak of a disease occurring in a hypothetical country in WPR.	Functional table-top	2 days	WHO Country Office in the Philippines, WHO Regional Office, JICS	There was a need for a RC plan to serve as an outline for planning future exercises. High staff turnover requires frequent training exercises.
2013	Viet Nam[11]	To practise and strengthen processes within the health ministry in Viet Nam before a decision to initiate a RC for an outbreak of influenza with pandemic potential.	Fictional outbreak of a disease of unknown etiology in a northern province in Viet Nam.	Modified functional	2 days	Viet Nam Health Ministry, WHO Country Office for Viet Nam, JICS, ASEAN, Asia-Europe Foundation, CDC	Health ministry should take the lead in developing guidelines, decision-making tools and RC logistics plans, including those to be involved in the process.
2014	WHO Regional Office[12]	For WHO staff to become familiar with RC decision-making process and to understand their RC roles.	Fictional outbreak of a novel avian influenza virus in a hypothetical country.	Modified functional	2 days	WHO Regional Office, JICS	There is a need for expanded guidance for RC, training on the role of JICS in RC, and improvement to EOC activation plans.
2015	WHO Regional Office[13]	For WHO staff to evaluate the need for RC and initiate an operation; provide training on roles and responsibilities within an active EOC as developed in previous PanStop exercise.	Fictional outbreak of a novel avian influenza virus in a hypothetical country.	Modified functional	2 days	WHO Regional Office, JICS	RC briefing and training documents should be updated and expanded, EOC procedures maintained and validated, and status board templates developed.
2017	Fiji[14]	For health ministry and partner staff to evaluate roles, responsibilities and decision-making for a RC operation, including response logistics and risk communication.	Fictional outbreak of a novel avian influenza virus in a district in Fiji that escalates into a national emergency.	Table-top	2 days	WHO Country Office in Fiji, WHO Regional Office, various ministries and authorities, including health, police and military	Strengthened multisectoral collaboration is key to the success of a RC operation.
2018	Mongolia	For health ministry and partner staff to evaluate roles, responsibilities and decision-making for a RC operation, including response logistics and risk communication.	Fictional outbreak of a novel avian influenza virus in Choibalsan city.	Table-top	1½ days	WHO Country Office in Mongolia, WHO Regional Office, and various health and disaster management ministries and authorities	Exercise identified a need for improved coordination within the health sector and promotion of intersectoral preparedness and response planning.

ASEAN: Association of Southeast Asian Nations; CDC: Centers for Disease Control and Prevention; EOC: Emergency Operations Centre; JICA: Japan International Cooperation Agency; JICS: Japan International Cooperation System; RC: rapid containment; STL: Singapore Technologies Logistics; WHO: World Health Organization.

sequently adapting national preparedness plans based on exercise outcomes, the readiness capacity of participating governments, WHO and other partners in the Region improves for the next influenza pandemic.

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