Emerging respiratory tract infections 1

Surveillance for emerging respiratory viruses

*Jaffar A Al-Tawfiq, Alimuddin Zumla, Philippe Gautret, Gregory C Gray, David S Hui, Abdullah A Al-Rabeeah, Ziad A Memish**

Several new viral respiratory tract infectious diseases with epidemic potential that threaten global health security have emerged in the past 15 years. In 2003, WHO issued a worldwide alert for an unknown emerging illness, later named severe acute respiratory syndrome (SARS). The disease caused by a novel coronavirus (SARS-CoV) rapidly spread worldwide, causing more than 8000 cases and 800 deaths in more than 30 countries with a substantial economic impact. Since then, we have witnessed the emergence of several other viral respiratory pathogens including influenza viruses (avian influenza H5N1, H7N9, and H10N8; variant influenza A H3N2 virus), human adenovirus-14, and Middle East respiratory syndrome coronavirus (MERS-CoV). In response, various surveillance systems have been developed to monitor the emergence of respiratory-tract infections. These include systems based on identification of syndromes, web-based systems, systems that gather health data from health facilities (such as emergency departments and family doctors), and systems that rely on self-reporting by patients. More effective national, regional, and international surveillance systems are required to enable rapid identification of emerging respiratory epidemics, diseases with epidemic potential, their specific microbial cause, origin, mode of acquisition, and transmission dynamics.

Lancet Infect Dis 2014

Published Online
September 2, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70840-0

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(14)70899-0

This is the first in a Series of five papers on emerging respiratory tract infections

Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, and Indiana University School of Medicine, Indianapolis, Indiana, USA (J A Al-Tawfiq MD); **Division of Infection and Immunity, University College London, London, UK and NIHR Biomedical Research Centre, University College London Hospitals, London, UK** (Prof A Zumla FRCP); **Assistance Publique Hôpitaux de Marseille, CHU Nord, Pôle Infectieux, Institut Hospitalo-Universitaire Méditerranée Infection & Aix Marseille Université, Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), Marseille, France.** (P Gautret MD); **Global Center for Mass Gatherings Medicine, Ministry of Health, Riyadh, Saudi Arabia** (Prof Z A Memish MD, A Zumla, A A Al-Rabeeah MD); **Al-Faisal University, Riyadh, Saudi Arabia** (Z A Memish); **Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida** (Prof G C Gray, MD); **and Division of Respiratory Medicine and Stanley Ho Center for emerging Infectious Diseases, The Chinese University of Hong Kong, Prince of Wales Hospital, New Territories, Hong Kong** (D S Hui MD)

Correspondence to:
Prof Ziad A Memish FRCP, Director WHO Collaborating Center for Mass Gathering Medicine Ministry of Health, and Al-Faisal University, Riyadh 11176, Saudi Arabia
zmemish@yahoo.com

Introduction

The emergence of new human viral diseases affecting the respiratory tract continues to threaten global public health security. On March 12, 2003, WHO issued a global alert for an emerging and yet unknown illness that was subsequently known as severe acute respiratory syndrome (SARS) caused by a novel coronavirus (SARS-CoV).[1] SARS-CoV caused more than 8000 cases and 800 deaths in over 30 countries with a substantial economic impact.[2] Since then, several other viral respiratory pathogens (table 1)[3–19] have emerged including avian influenza (H5N1, H7N9, H10N8), variant influenza A H3N2 virus, human adenovirus-14, and Middle East respiratory syndrome coronavirus (MERS-CoV). Soon after the discovery of SARS, additional coronaviruses were also identified: coronavirus NL63 and coronavirus HKU1.[3,4]

Most influenza A epidemics occur in January, February, and March. However, outbreaks of influenza A Beijing/32/92 H3N2 in 1993 and Fujian/411/2002 H3N2 in 2003 happened in November and December.[20] In an analysis of 335 emerging infectious diseases from 1940 to 2004, most (60%) were zoonoses and 25% were viruses, and the study showed an increase in events over time.[21]

In this Series paper, we review worldwide active surveillance systems for emerging and re-emerging respiratory viruses. We identify the rapid and early identification systems to allow early control measures to be put in place to prevent the spread of these pathogens. We also review the work of WHO Global Influenza Surveillance Network (GISN), Global Influenza Surveillance and Response System (GISRS), and the network of national influenza centres and laboratories.

Severe acute respiratory infection (SARI) is defined as fever of at least 100°F (37·8°C) or self-reported fever, and either a cough or a sore throat, and hospital admission.[22] An influenza-like illness (ILI) is defined as acute illness with fever greater than 38°C, and cough or sore throat.[22]

Global surveillance

Surveillance of emerging and re-emerging respiratory viruses aims for rapid and early identification and control measures, thus preventing spread of pathogens. In 1947, WHO established its GISN, now known as the GISRS.

Key messages

- The emergence of several new viral respiratory tract infectious diseases with epidemic potential threatens global health security.
- Emerging respiratory viruses include severe acute respiratory syndrome cornavirus (SARS-CoV), avian influenza H5N1, H7N9, and H10N8; variant influenza A H3N2 virus; human adenovirus-14; and Middle East respiratory syndrome- coronavirus (MERS-CoV).
- Global surveillance systems for emerging and re-emerging respiratory viruses include active and passive surveillance systems.
- Surveillance systems aim for rapid and early identification of these viruses with epidemic potential, their specific microbial cause, origin, mode of acquisition, and transmission dynamics so that effective intervention and control measures can be put in place.
- Several surveillance systems are in place and include syndromic surveillance and web-based surveillance.
- A good surveillance system would include the whole spectrum of disease presentation from mild to severe cases.
- Future surveillance system should provide real-time early warnings by integrating clinical, laboratory, and automation of collection and dissemination of data.

	Year	Region
Hantavirus pulmonary syndrome, sin nombre virus[16]	1993	USA
Influenza A H5N1[13]	1997	Hong Kong
Influenza A H9N2[15]	1999	Hong Kong
Human metapneumovirus[19]	2001	Netherlands
SARS coronavirus[6,7]	2003	Hong Kong
Human coronavirus NL63[3]	2004	Netherlands
Influenza A H7N7[14]	2004	Netherlands
Human coronavirus HKU1[4]	2005	China
Influenza A, H1 triple reassortant[9,10]	2005	USA
Triple reassortant H3N2 influenza A viruses[11]	2005	Canada
Bocavirus[18]	2005	Sweden
Influenza A H1N1 pdm09[12]	2009	Mexico
Adenovirus 14[17]	2010	USA
MERS-coronavirus[5]	2012	Saudi Arabia
Influenza A H7N9[8]	2013	China

SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome.

***Table 1*: Emerging respiratory viruses**

The new name followed the adoption of the Pandemic Influenza Preparedness (PIP) framework in May 2011.[23] GISRS is a network of national influenza centres and laboratories. These centres serve as laboratory-based surveillance system to monitor circulating influenza viruses and make annual recommendations on the composition of influenza vaccine for the northern and southern hemispheres. GISRS also detects as early as possible, characterises, and tracks any unusual influenza strains in human populations that could be of pandemic potential. Multiple national influenza centres (NICs) collect virus specimens in their country, do preliminary analysis, and ship representative clinical specimens and isolated viruses to WHO for advanced analysis.[24] The network comprises six WHO Collaborating Centres, four WHO essential regulatory laboratories, and 141 institutions in 111 WHO member states.[25] NICs are concentrated in Europe and the USA, with only a few centres in Africa, the Middle East, and parts of southeast Asia. As a result, there is an absence of knowledge about influenza epidemiology, burden of disease, and patterns of transmission in the tropics and subtropics. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) is a worldwide initiative that involves the gathering of many networks and individuals involved in research related to the outbreaks of diseases such as avian influenza A H5N1, swine influenza A H1N1, and SARS.[26] ISARIC is involved in the collaboration between different scientists to further increase our understanding of emerging respiratory diseases. ISARIC provides a collaborative platform through which worldwide, patient-oriented clinical studies can be developed, done, and disseminated, with shared protocols and a focus on clinical questions and clinical trial expertise.

Surveillance goals

The goals of surveillance are to monitor when the influenza season begins and ends, to characterise the types and subtypes of circulating strains, to monitor the clinical severity of illness, and to detect the emergence of any novel or reassortant viruses. This information also helps in selecting future vaccine strains. The surveillance also monitors the emergence of any viral resistance.[27] The basic goals of influenza surveillance include description of the epidemiology of seasonal influenza and burden of disease, provision of isolates for identification of viruses and monitoring of resistance, and provision of country-specific data for programme planning and preparedness. After the re-emergence of highly-pathogenic influenza A H5N1 in 2004, another objective was to provide an early warning for outbreaks of novel influenza or agents of SARI in human beings or the circulation of a potentially new pandemic pathogen. The main aim of pandemic surveillance is the early recognition of the emergence of a novel virus so that control measures can be instituted. However, once a pandemic has begun, surveillance should switch to monitoring of the epidemiology, the characteristics of the virus, the effect of prevention and control measures, and the progression of the pandemic.[28]

Early warning signs for pandemic

One of the objectives of surveillance for SARI and ILI caused by influenza is the detection of early warning signs for the emergence of any novel influenza virus or respiratory virus with pandemic potential in human beings. The important functions of early warning surveillance systems are many. The early warning system is built to detect events with potential public health threat across international borders, to verify detected events, to assess the risk that an event will have global effect, to report such risk within 48 h of the event determination according to the International Health Regulations, and to work with WHO to establish any public health emergency of international concern.[29] For early warning systems to work, specific triggers or signal criteria are needed for immediate reporting of possible occurrence of a single or multiple cases; such cases might be the initial indicators of the emergence of a novel respiratory virus with a pandemic potential such as H5N1 and Middle East respiratory syndrome coronavirus (MERS-CoV).

SARIs or pneumonia in health-care workers might serve as important signal events that the virus has acquired the ability to spread to human beings, as seen in the SARS epidemic. Examples of events that might signal human-to-human transmission of an emerging respiratory disease include clusters of SARI in people with social connections within a 2 week period, pneumonia in health-care workers, or people with a social or occupational connection. In addition, any change in the epidemiology of SARI cases, with a shift in the age distribution, an increase in mortality, or an increase in

 www.thelancet.com/infection **Published online September 2, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70840-0**

the number of cases, might signal the circulation of a new respiratory pathogen.[30,31]

Monitoring for signals of increased activity

When the weekly influenza rates exceed the seasonal influenza threshold this increase would signal the start of a new influenza season.[32] For signal detection, the model built should have autoregressive components, seasonal trends, other trends, and covariates to predict the number of cases beyond expected for a specific day. However, monitoring of ILI and SARI should take into account the trends in any existing data and not wait to have a definite signal of increased activity.

The adaptation of emerging respiratory viruses to human beings might occur suddenly with widespread infection or more gradually with infection of an at-risk population. The exposure of an at-risk population to a common source results in a spillover of viruses into people. Once these viruses have gained a sustained transmission from human-to-human with an R_0 of 1 or more, in certain conditions an epidemic can result.[33] Monitoring of the rate at which R_0 increases serves as a marker for impending epidemic.[34–36] For accurate estimates of R_0, a detailed outbreak and contact investigation is required.

Early detection

For early detection of new and emerging respiratory viruses, it is important to establish a programme and systems to detect the first evidence of sustained human-to-human transmission of an emerging respiratory pathogen.[37] The occurrence of clusters of SARI in a localised area, the occurrence of an increased mortality or a change in the affected age group, or high sales of specific therapies for upper respiratory tract infections can be evidence of new and emerging respiratory viruses. WHO, through a number of sentinel labs, monitors and coordinates the surveillance activities for any influenza outbreaks as indicated earlier.

Syndromic surveillance

Syndromic surveillance combines cases into syndromes rather than specific diagnoses.[38] Such surveillance depends on the definitions of ILI and SARI that require clinical diagnoses but might not differentiate between different etiological causes. Syndromic surveillance uses data from emergency room visits,[39] discharge diagnosis,[40] ambulance dispatch data that successfully identified the expected annual epidemics of influenza,[41] family doctor surveillance networks,[42] or general population self-reporting networks.[43,44] The use of emergency-services-based surveillance is most sensitive for severe illness and for illnesses affecting elderly individuals.[41,45,46] A systematic analysis of syndromic surveillance for influenza and ILI in emergency departments showed that various data, such as primary complaint, discharge diagnosis, and free text analysis of the entire medical record, were used.[47] Surveillance of paediatric cases with ILI might also facilitate detection of outbreaks 1–4 weeks before the peak of the disease onset.[48]

The largest surveillance networks are the USA DiSTRIBuTE network (no longer active) and the European triple "S" system (Syndromic Surveillance Systems in Europe), and these two systems collected large-scale emergency-department-based influenza and ILI syndromic surveillance data.[49,50] Surveillance usually provides the fastest way to identify diseases and is an excellent approach to focus appropriate response measures to any outbreak.[51,52] Syndromic surveillance systems enable a rapid response to outbreak detection.[53] The establishment of the Japanese non-governmental organisation Agency for Cooperation in International Health as a sentinel surveillance system for selected targets of infectious diseases in, Africa, Asia, and South America revealed unreported infectious diseases such as influenza.[54] Syndromic surveillance helps to detect the occurrence of signals of ILI that warrant further investigation. In New York, a rise in the number of cases of respiratory syndrome and fever provided the earliest indication of the occurrence of community-wide influenza activity in 2001–02 seasons.[51] An advantage of sentinel syndromic surveillance is the early detection of syndromes before laboratory confirmation.[51] Syndromic surveillance could depend on the presence of specific symptoms of the ILI and SARI and could also depend on the chief or primary complaints of patients. The accuracy of chief complaint had a good agreement for the syndromes of respiratory infection in reference to discharge diagnosis.[38,51] Syndromic surveillance helped detect the 2009 pandemic influenza H1N1 outbreak in the USA[55] and was used in emergency departments in Canada to predict circulating respiratory viral disease such as influenza and respiratory syncytial virus.[56]

One study compared the Geographic Utilization of Artificial Intelligence in Real-time for Disease Identification and Alert Notification (GUARDIAN) system with the Complaint Coder (CoCo) of the Real-time Outbreak Detection System (RODS), the Symptom Coder (SyCo) of RODS, and an electronic medical record (EMR) system.[57] The study showed that the GUARDIAN surveillance system was more robust in performance compared with standard EMR-based reports and the RODS systems in detection of ILI.[57] Emergency department discharge diagnoses increased surveillance validity for automated and drop-in syndromic surveillance.[58]

The advantages and disadvantages of syndromic surveillance of ILI were discussed by the Provincial Infectious Diseases Advisory Committee.[59] The main disadvantages were that not all patients visit an emergency department as their first step towards treatment, free text entry of data reduces automation of data, and start-up costs are substantial.

For more on **Global Influenza Surveillance and Response System (GISRS)** see http://www.who.int/influenza/gisrs_laboratory/en/

For more on **Influenzanet** see https://www.influenzanet.eu/

For more on **Flu Near You** see https://flunearyou.org/

For more on **FluTracking** see http://www.flutracking.net/

For more on **BioDiaspora** see http://www.biodiaspora.com/

For more on **HealthMap** see http://healthmap.org/

For more on **ProMed** see http://promedmail.org/

For more on **Google Flu Trend** see http://www.google.org/flutrends/

	Websites	Characteristics
Global Influenza Surveillance and Response System (GISRS)	http://www.who.int/influenza/gisrs_laboratory/en/	Monitors evolution of influenza viruses Provides recommendations on antiviral susceptibility Provides global alert
Influenzanet	https://www.influenzanet.eu/	Monitors ILI on a voluntary basis Has volunteers from ten European countries
Flu Near You	https://flunearyou.org/	Website based survey Could be completed by any one older than 13 years Administered by Healthmap of Boston Children's Hospital, the American Public Health Association, and the Skoll Global Threats Fund
FluTracking	http://www.flutracking.net/	Australia In addition to reporting symptoms of influenza provides the participants with sample collection materials for influenza testing
Overcrowd-Severe-Respiratory-Disease-Index	Not available	Simultaneously monitors and informs the demand of required supplies and personnel Generates early warnings of severe respiratory disease epidemic outbreaks
BioDiaspora	http://www.biodiaspora.com/	Customisable, intelligent web application Predicts the impact of infectious diseases worldwide Integrates global data on outbreaks, human populations, animal and insect populations, environmental and climatic conditions, and commercial air travel
HealthMap	http://healthmap.org/	Provides informal sources for disease outbreak monitoring and real-time surveillance of emerging public health threats
ProMED	http://promedmail.org/	ProMed mail provides early warning of outbreaks of emerging and re-emerging diseases
Global Public Health Intelligence Network (GPHIN)	not a public system	Canadian initiative Draws on the capacity of the Internet and global news coverage of health events
Google Flu Trend	http://www.google.org/flutrends/	Estimates ILI incidence based on influenza-related queries done online
Geographic Utilization of Artificial Intelligence in Real-Time for Disease Identification and Alert Notification (GUARDIAN)	http://www.rush.edu/rumc/print-page-1298330251295.html /	Real-time, automated system for detection and diagnosis of infectious agents
Complaint Coder (CoCo) of the Realtime Outbreak Detection System (RODS)	not available	A surveillance system based on data collected routinely for other purposes, such as absenteeism, and over-the-counter sales. RODS is an automated system that classifies complaints (complaints coder) or symptoms coder from all hospital visits into a specified syndrome using Bayesian classifiers

ILI= influenza-like illness.

***Table 2*: Worldwide networks of surveillance and their websites**

Surveillance in emergency departments

Chief-complaint-based emergency department surveillance systems are being used for surveillance of influenza. During the 2009 H1N1 pandemic, influenza activity in emergency departments increased 2 weeks before it did in outpatient sentinel clinics.[60] The use of physician diagnosis in emergency departments proved superior to chief-complaints surveillance in the same setting.[61] However, such surveillance might be influenced by the staff's knowledge of what occurrs in communities.[62] By contrast, another study showed that self-reporting by patients was better than chief-complaint surveillance for prediction of the diagnosis.[63] In emergency departments, increased influenza activity could be assessed by triage nurses recording complaints by categories,[64] syndromic analysis of patients' chief complaints,[39] and patient-based free text grouped into diagnostic groups.[65,66] Similarly, syndromic surveillance is being used in the Hajj pilgrimage for detection of any outbreaks.[67]

Patients' chief-complaint and triage data proved to be a good indicator of respiratory complaints.[38] Information on initial patients' complaint and triage data were used in a few surveillance programmes.[68–70] A computerised triage log was effective in the identification of influenza outbreaks in the first week.[39] Another method of surveillance relies on nurse help-line telephone calls.[71] In a study from England and Wales, surveillance of influenza based on deaths, sickness-benefit claims (SBC), laboratory reports, and observations from general practitioners showed that general practitioners' statistics and respiratory deaths were the most helpful indices for description of both size and timing of the epidemics.[72]

Hospitalisation and laboratory surveillance of respiratory viruses

In addition to syndromic surveillance, laboratory-confirmed influenza hospitalisations and laboratory surveillance depend on identification of the specific cause of respiratory infection; they also rely on good laboratory support for the identification of the causative agent. This conventional disease surveillance that relies on passive reporting of confirmed cases might be slow and insensitive for rapid detection of large-scale infectious disease outbreaks.[73] The goals of the laboratory surveillance are provision of information on geographic distribution and secular patterns of circulating viruses, monitoring of antigenic changes in the viruses for vaccine strain selection, monitoring of antiviral resistance, and detection of novel influenza subtypes of possible pandemic potential.

Surveillance of influenza through drug sales

There are mixed results from studies looking at sales of over-the-counter drugs as an indicator of influenza activity. The earliest assessment of this indicator of influenza activity dates back to 1979.[74] An increase in sales of these drugs occurred 4 weeks after the first influenza B isolate and 1 week before peak influenza activity.[74] Another study assessed the sale of non-prescription drugs for three consecutive winters 1998–99, 1999–2000, and 2000–01 and did not show any correlation with increased influenza activity nationally.[75] Similarly, in a study from Japan, over-the-counter drug sales did not collate with real-time detection systems for influenza epidemics.[76] In a study from New York, USA, ILI over-the-counter drug sales increased during influenza epidemics and during spring and fall allergy seasons, a finding that was similar to trends in emergency departments for fever and influenza syndrome.[77] In two other studies from France and Slovenia, drug sales correlated with influenza activity.[78,79]

Self-reporting participatory systems

New surveillance systems such as Influenzanet, Flu Near You, FluTracking, and Go Viral are a new frontier in the collection of population symptom data (table 2). Influenzanet monitors ILI on a voluntary basis with 35 180 volunteers from ten European countries including Belgium and the Netherlands (since 2003), Portugal (since 2005), Italy (since 2008), the UK (since 2009), Denmark, France, Ireland, Spain and Sweden. This network obtains information about ILI directly from volunteers from the different countries who enter data in a web-based interphase.[44,80–82]

Flu Near You is a website-based survey about symptoms of ILI that can be completed by anyone older than 13 years of age. The website is administered by Healthmap of Boston Children's Hospital in partnership with the American Public Health Association and the Skoll Global Threats Fund. In Australia, FluTracking is an online health surveillance system for the detection of influenza. In addition to reporting symptoms of influenza, specific websites also provide participants with kits including the sample collection materials so that participants can provide a nasal swab and saliva sample for influenza testing.

One of the challenges in the case of outbreaks is the high demand for specific supplies such as beds, storage areas, haemodynamic monitors, mechanical ventilators, and specialised personnel.[83] An online cumulative-sum-based model named Overcrowd-Severe-Respiratory-Disease-Index was based on the Modified Overcrowd Index. The model simultaneously monitors and informs the demand of required supplies and personnel and generates early warnings of severe respiratory disease epidemic outbreaks through the interpretation of such variables.[83] BioDiaspora is an easy-to-use, customisable, intelligent web application that predicts the effect of infectious diseases worldwide by integration of data on outbreaks, human populations, animal and insect populations, environmental and climatic conditions, and commercial air travel. BioDiaspora has an easy-to-access, web-based, global information system solution that can generate and communicate intelligence about global infectious disease threats in real time and that integrates global epidemic intelligence from HealthMap.[84]

	Description
Syndromic surveillance[38–42, 45–47, 58, 68–70]	The following clinical data was used: chief complaint and presentation, discharge diagnosis, free text analysis of the entire medical record, calls to triage and help lines, ambulance dispatch calls, discharge diagnosis, ambulance dispatch data that successfully identified the expected annual epidemics of influenza
Laboratory surveillance[73]	Slow and insensitive in rapid detection a large-scale infectious disease outbreak
Medication sales[74–79]	Over-the-counter drug sales correlated with influenza activity
Self-reporting participatory systems[81–83]	Online-based surveillance system relying on voluntary participation
Informal surveillance and epidemic intelligence[85–93, 94]	Detect relevant information from the internet, nationally and internationally

***Table 3*: Description of different surveillance system**

Informal surveillance and epidemic intelligence

Epidemic intelligence is a key component of modern surveillance of emerging infectious diseases. Epidemic intelligence is an ad-hoc detection and analysis of unstructured information available on the internet. This information relies on official and informal sources. Epidemic intelligence was developed in the 1990s after the development of the internet,[85] and several systems exist (tables 2 and 3).[85–93] The Program for Monitoring Emerging Diseases (ProMED) mail is an internet-based reporting system designed for rapid distribution of information on infectious disease outbreaks. ProMED mail was started in August, 1994, to monitor emerging infectious diseases worldwide. ProMED mail provides early warning of outbreaks of emerging and re-emerging diseases. ProMED is an event-based, informal surveillance system where information is received from many official and unofficial sources such as WHO, health-care workers, ministries of health, lay public, the media, laboratories, and local health officials. On Feb 10, 2003, a request for information was posted on ProMED in relation to an epidemic in Guangzhou.[95] This epidemic became known as SARS. On Sept 20, 2012, ProMED-mail reported the identification of a novel coronavirus (nCoV), later known as MERS-CoV, from a fatal case of severe respiratory illness with renal failure.[5,96,97]

Search strategy and selection criteria

We did a literature search of the electronic database PubMed and Google Scholar (1980–2014) with the following search terms: "surveillance AND influenza", "influenza", "influenza-like illness", "surveillance" "internet-based surveillance" "syndromic surveillance", "respiratory" "viruses" and "emerging". We complemented the search with publications from WHO, Centre for Disease Control and Prevention, and Google Scholar. We also reviewed studies cited by articles identified in this search. We included only studies in human beings and in the English language.

A team of researchers, epidemiologists, and software developers at Boston Children's Hospital founded HealthMap in 2006. This web-based approach provides informal sources for disease outbreak monitoring and real-time surveillance of emerging public health threats. HealthMap is available as a website, and as a mobile app, Outbreaks Near Me, and both deliver real-time intelligence on a broad range of emerging infectious diseases for a diverse audience, including libraries, local health departments, governments, and international travellers.

For more on **HealthMap** see http://healthmap.org/en/

The Global Public Health Intelligence Network (GPHIN) is a Canadian initiative that draws on the capacity of the internet and worldwide news coverage of health events.[93] GPHIN creates an early warning of outbreaks by monitoring internet media, including news wires and websites, to detect and report disease outbreaks.[94]

Google Flu Trend is a web-based site that estimates ILI incidence on the basis of influenza-related queries made by millions of users around the world online in search for health data related to influenza.[98] Use of Google Flu Trend in emergency departments predicted the 2009 H1N1 outbreak in Manitoba,[99] other emergency rooms,[100] and South Korea.[101] Google Flu Trend results strongly correlated with ILI data from the USA,[98,102,103] Australia,[104] Canada,[99] and China[105] and Google Flu Trend was the only external information system to provided the most accurate influenza predictions with different prediction models.[106] Google Flu Trend results were less reliable during the 2009 influenza H1N1 pandemic in many countries including New Zealand, Singapore, and the USA.[107–109] Such inconsistency might result from a change in internet search behaviour and the change in age-related internet use.[110–112] Google Flu Trend might not provide reliable surveillance for seasonal or pandemic influenza, and the result obtained from this surveillance method should be interpreted with caution.[113] Google Flu Trend also performed poorly compared with laboratory-confirmed influenza.[114] The correlation of Google Flu Trend with influenza incidence was most profound in European countries where the internet is most frequently used for health-related searching.[115]

Influenza in Africa

The exact epidemiology of ILI and SARI is not well known in Africa and the Middle East. In a study from several countries, from Madagascar to Senegal, the epidemiology and virology of influenza viruses showed variation in relation to spatiotemporal circulation of the different virus types, subtypes, and strains.[116] In 2008, the sentinel surveillance system in Madagascar showed that of 26 669 fever cases, 11·1% were ILI.[117] The availability of seasonal influenza vaccine in Africa was reported to be 45% of 31 countries who responded to the questionnaire sent by the investigators in one study, and that vaccine coverage data were available for four of 14 countries that reported availability of seasonal influenza vaccine.[118] The importance of having laboratory influenza virus surveillance was highlighted in a study from west Africa where genetic sequencing of 2009 pandemic influenza A H1N1 viruses during 2009–13 showed persistence of two viral lineages.[119]

Challenges for emerging respiratory viruses surveillance

The challenges for the surveillance of any emerging respiratory viruses, especially at the beginning of any outbreak, are the difficulties in the identification of the causative agent and the large number of samples received. Ideally, routine cultures might provide the answer for any emerging virus identification; such techniques would require additional safety measures. Comprehensive multiplexed PCR reactions might help in the identification of various agents without the use of biosafety level 3 laboratories.[120] The combined use of culture, rapid antigen detection assays, and molecular assays are often effective.[121,122] The use of a combination of these techniques will decrease the number of samples from patients being tested at one time.[123]

Further improvement of surveillance systems to cover diverse areas of the world including developed and developing countries is clearly needed. Such an objective could be accomplished by capacity building. The experience in Laos is an excellent example.[124] There was a clear coordination and collaboration between multisector interests such as human and animal health, the Government of Laos, and the international partner community through the Lao National Avian and Human Influenza Coordinating Office (NAHICO) resulting in the translation of experience into practical steps to deal with emerging viral infections.[124] The collateral impact of the influenza investment in advance of overall public health capacity in Laos has been pronounced, and this could also happen to other resource-limited countries. Real-time data should be displayed on the internet to allow immediate access. The immediate availability of data would help health-care policy makers in the preparation for any epidemics.

Contributors

ZAM and AZ initiated *The Lancet Infectious Diseases* respiratory tract infections series. ZAM, AZ, DH, and JAA-T developed the series articles outlines and assigned lead authors. ZAM and JAA-T coordinated the

writing of this Series paper and wrote the draft outline, subsequent and final drafts of the manuscript. All authors contributed relevant text and tables on their expert sections and contributed to finalisation of the manuscript.

Declaration of interests

All authors declare no conflicts of interest.

Acknowledgments

AZ is supported by the UK European Union FW7 Rid-RTI programme grant; European Developing Countries Clinical trials Partnership (EDCTP) TB NEAT, PANACEA and REMox grants; UBS Optimus Foundation, Switzerland; and NIHR Biomedical Research Centre, University College London Hospitals, London, UK.

References

1 WHO. WHO issues a global alert about cases of atypical pneumonia. 2003. http://www.who.int/csr/sars/archive/2003_03_12/en/index.html (accessed March 28, 2014).

2 World Bank. People, pathogens and our planet. The economics of One Health. Washington (DC). The Bank; 2012. https://openknowledge.worldbank.org/handle/10986/11892 (accessed March 28, 2014).

3 van der Hoek L, Pyrc K, Jebbink MF et al. Identification of a new human coronavirus. *Nat Med* 2004; **10:** 368–73.

4 Woo PC, Lau SK, Chu CM et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol* 2005; **79:** 884–95.

5 Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367:** 1814–20.

6 Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361:** 1319–25.

7 Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; **348:** 1953–66.

8 Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; **368:** 1888–97.

9 Newman AP, Reisdorf E, Beinemann J, et al. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. *Emerg Infect Dis* 2008; **14:** 1470–72.

10 Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med* 2009; **360:** 2616–25.

11 Olsen CW, Karasin AI, Carman S, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. *Emerg Infect Dis* 2006; **12:** 1132–35.

12 WHO. www.who.int/csr/don/2009_05_25 (accessed June 2, 2014).

13 Subbarao K, Klimov A, Katz J, et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. *Science* 1998; **279**: 393–96.

14 Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *Lancet* 2004; **363:** 587–93.

15 Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. *Lancet* 1999; **354:** 916–17.

16 Outbreak of acute illness— south western United States, 1993. MMWR *Morb Mortal Wkly Rep* 1993; **42:** 421–424.

17 Kajon AE, Lu X, Erdman DD, et al. Molecular epidemiology and brief history of emerging adenovirus 14-associated respiratory disease in the United States. *J Infect Dis* 2010; **202:** 93–103.

18 Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA* 2005; **102:** 12891–96.

19 van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; **7:** 719–24.

20 Räty R, and National Institute for Health and Welfare. Laboratory diagnosis and surveillance of acute respiratory tract infections caused by certain common viruses and mycoplasma pneumonia. Helsinki, Finland 2013. http://www.julkari.fi/bitstream/handle/10024/110666/THL_RES115_2013_web.pdf?sequence=1 (accessed March 28, 2004).

21 Jones K, Patel G, Levy M, et al. Global trends in emerging infectious diseases. *Nature* 2008; **451:** 990–994.

22 WHO Regional Office for Europe guidance for sentinel influenza surveillance in humans. http://www.euro.who.int/__data/assets/pdf_file/0020/90443/E92738.pdf (accessed June 1, 2014).

23 WHO. Available at: http://www.who.int/influenza/gisrs_laboratory/en/ (accessed June 3, 2014).

24 WHO. Available at: http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/en/ (accessed May 28, 2014).

25 WHO. Available at: http://www.who.int/influenza/gisrs_laboratory/en/. (accessed May 28, 2014).

26 ISARIC. https://isaric.tghn.org/about/ (accessed May 28, 2014).

27 WHO Interim Global Epidemiological Surveillance Standards for Influenza (July 2012) http://who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1 (accessed May 28, 2014).

28 Epidemic, Alert & Response. WHO checklist for influenza pandemic preparedness planning. http://www.who.int/influenza/resources/documents/FluCheck6web.pdf. (accessed May 30, 2014).

29 WHO. International Health Regulations (2005). www.who.int/ihr/9789241596664/en/. (accessed May 25, 2014).

30 Armour PA, Nguyen LM, Lutman ML, Middaugh JP. Evaluation of the novel respiratory virus surveillance program: pediatric early warning sentinel surveillance (PEWSS). *Public Health Rep* 2013; **128** (suppl 2)**:** 88–96.

31 Qian YH, Su J, Shi P, et al. Attempted early detection of influenza A (H1N1) pandemic with surveillance data of influenza-like illness and unexplained pneumonia. *Influenza Other Respir Viruses* 2011; **5:** e479–86.

32 WHO. Epidemiological surveillance standards for influenza. http://www.who.int/influenza/resources/documents/INFSURVMANUAL.pdf (accessed May 28, 2014).

33 Antia R, Regoes RR, Koella JC, Bergstrom CT. The role of evolution in the emergence of infectious diseases. *Nature* 2003; **426:** 658–61.

34 Lloyd-Smith JO, George D, Pepin KM, et al. Epidemic dynamics at the human-animal interface. *Science* 2009; **326:** 1362–67.

35 Ferguson NM, Fraser C, Donnelly CA, Ghani AC, Anderson RM. Public health risk from the avian H5N1 influenza epidemic. *Science* 2004; **304:** 968–69.

36 Yang Y, Halloran ME, Sugimoto JD, Longini IM. Detecting human-to-human transmission of avian influenza a (H5N1). *Emerg Infect Dis* 2007, **13:** 1348–53

37 Western Pacific Regional Office: A guide to establishing event-based surveillance.:http://www.wpro.who.int/internet/resources.ashx/CSR/Publications/GuideToHarmonizingInfluenzaSurveillance-revised2302.pdf (accessed May 28, 2014).

38 Begier EM, Sockwell D, Branch LM, et al. The National Capitol Region's Emergency Department syndromic surveillance system: do chief complaint and discharge diagnosis yield different results? *Emerg Infect Dis* 2003; **9:** 393–96.

39 Irvin CB, Nouhan PP, Rice K. Syndromic analysis of computerized emergency department patients' chief complaints: an opportunity for bioterrorism and influenza surveillance. *Ann Emerg Med* 2003; **41:** 447–52.

40 Lober WB, Trigg LJ, Karras BT, et al. Syndromic surveillance using automated collection of computerized discharge diagnosis. *J Urban Health* 2003; **80** (suppl 1)**:** i97–106.

41 Mostashari F, Fine A, Das D, Adams J, Layton M. Use of ambulance dispatch data as an early warning system for communitywide influenza-like illness, New York City. *J Urban Health* 2003; **80** (suppl 1)**:** i43–49.

42 Turbelin C, Souty C, Pelat C, et al. Age distribution of influenza like illness cases during post-pandemic A(H3N2): comparison with the twelve previous seasons, in France. *PLoS One* 2013; **8:** e65919.

43 Debin M1, Turbelin C, Blanchon T, et al. Evaluating the feasibility and participants' representativeness of an online nationwide surveillance system for influenza in France. *PLoS One* 2013; **8:** e73675.

44 Paolotti D1, Carnahan A, Colizza V, et al. Web-based participatory surveillance of infectious diseases: the Influenzanet participatory surveillance experience. *Clin Microbiol Infect* 2014; **20:** 17–21.

45 Greenko J, Mostashari F, Fine A, Layton M. Clinical evaluation of the Emergency Medical Services (EMS) ambulance dispatch-based syndromic surveillance system, New York City. *J Urban Health* 2003; **80** (suppl 1): i50–56.

46 Josseran L, Nicolau J, Caillere N, Astagneau P, Brucker G. Syndromic surveillance based on emergency department activity and crude mortality: two examples. *Euro Surveill* 2006; **11:** 225–29.

47 Hiller KM1, Stoneking L, Min A, Rhodes SM. Syndromic surveillance for influenza in the emergency department-A systematic review. *PLoS One* 2013; **8:** e73832.

48 Lemay R, Mawudeku A, Shi Y, Ruben M, Achonu C. Syndromic surveillance for influenza like illness. *Biosecur Bioterror* 2008; **6:** 161–70.

49 Olson DR, Paladini M, Lober WB, Buckeridge DL, ISDS distribute working group. Applying a new model for sharing population health data to national syndromic influenza surveillance: DiSTRIBuTE Project Proof of Concept, 2006– 2009. Version 2. *PLoS Curr* 2011; **3:** RRN1251.

50 Triple S Project. Assessment of syndromic surveillance in Europe. *Lancet* 2011; **378:**1833–34.

51 Heffernan R, Mostashari F, Das D, Karpati A, Kulldorff M, Weiss D. Syndromic surveillance in public health practice, New York City. *Emerg Infect Dis* 2004; **10:** 858–64.

52 Lewis MD, Pavlin JA, Mansfield JL, et al. Disease outbreak detection system using syndromic data in the greater Washington DC area. *Am J Prev Med* 2002; **23:** 180–86.

53 Wu TS, Shih FY, Yen MY et al. Establishing a nationwide emergency department-based syndromic surveillance system for better public health responses in Taiwan. *BMC Public Health* 2008; **8:** 18.

54 Arita I, Nakane M, Kojima K, Yoshihara N, Nakano T, El-Gohary A. Role of a sentinel surveillance system in the context of global surveillance of infectious diseases. *Lancet Infect Dis* 2004; **4:** 171–77.

55 Bellazzini MA, Minor KD. ED syndromic surveillance for novel H1N1 spring 2009. *Am J Emerg Med* 2011; **29:** 70–74.

56 Hall G, Krahn T, Van Dijk A, et al. Emergency department surveillance as a proxy for the prediction of circulating respiratory viral disease in Eastern Ontario. *Can J Infect Dis Med Microbiol* 2013; **24:** 150–54.

57 Silva JC, Shah SC, Rumoro DP, et al. Comparing the accuracy of syndrome surveillance systems in detecting influenza-like illness: GUARDIAN *vs* RODS *vs* electronic medical record reports. *Artif Intell Med* 2013; **59:** 169–74.

58 Fleischauer AT, Silk BJ, Schumacher M, et al. The validity of chief complaint and discharge diagnosis in emergency department-based syndromic surveillance. *Acad Emerg Med* 2004; **11:** 1262–67.

59 Provincial Infectious Diseases Advisory Committee (PIDAC). Syndromic surveillance discussion paper. http://www.publichealthontario.ca/en/eRepository/PIDAC_SyndromicSurveillance_DiscussionPaper_ENG_2013.pdf (accessed May 28, 2014).

60 Shimoni Z, Rodrig J, Dusseldorp N, Niven M, Froom P. Increased emergency department chief complaints of fever identified the influenza (H1N1) pandemic before outpatient symptom surveillance. *Environ Health Prev Med* 2012; **17:** 69–72.

61 May LS, Griffin BA, Bauers NM, et al. Emergency department chief complaint and diagnosis data to detect influenza-like illness with an electronic medical record. *West J Emerg Med* 2010; **11:** 1–9.

62 Moore K, Black J, Rowe S, Franklin L. Syndromic surveillance for influenza in two hospital emergency departments. Relationships between ICD-10 codes and notified cases, before and during a pandemic. *BMC Public Health* 2011; **11:** 338.

63 Bourgeois FT, Porter SC, Valim C, Jackson T, Cook EF, Mandl KD. The value of patient self-report for disease surveillance. *J Am Med Inform Assoc* 2007; **14:** 765–71.

64 Silka PA, Geiderman JM, Goldberg JB, Kim LP. Demand on ED resources during periods of widespread influenza activity. *Am J Emerg Med* 2003; **21:** 534–39.

65 Olson DR, Heffernan RT, Paladini M, Konty K, Weiss D, Mostashari F. Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. *PLoS Med* 2007; **4:** e247.

66 Brillman JC, Burr T, Forslund D, Joyce E, Picard R, Umland E. Modeling emergency department visit patterns for infectious disease complaints: results and application to disease surveillance. *BMC Med Inform Decis Mak*. 2005; **5:** 4.

67 Memish ZA, Zumla A, Alhakeem RF, et al. Hajj: infectious disease surveillance and control. *Lancet* 2014; **383:** 2073–78.

68 Jorn LR, Thackway SV, Churches TR, Hills MW. Watching the Games: public health surveillance for the Sydney 2000 Olympic Games. *J Epidemiol Community Health* 2003; **57:** 102–08.

69 Gesteland PH, Gardner RM, Tsui FC, et al. Automated syndromic surveillance for the 2002 Winter Olympics. *J Am Med Inform Assoc* 2003; **10:** 547–54.

70 Muscatello DJ, Churches TR, Kaldor J, et al. An automated, broad-based, near real-time public health surveillance system using presentations to hospital Emergency Departments in New South Wales, Australia. *BMC Public Health* 2005; **5:** 141.

71 Rodman JS, Frost F, Jakubowski W. Using nurse hot line calls for disease surveillance. *Emerg Infect Dis* 1998; **4:** 329–32.

72 Tillett HE, Spencer IL. Influenza surveillance in England and Wales using routine statistics. *J Hyg Camb* 1982; **88:** 83–94.

73 Miller B, Kassenborg H, Dunsmuir W, et al. Syndromic surveillance for influenzalike illness in ambulatory care network. *Emerg Infect Dis* 2004; **10:** 1806–11.

74 Welliver RC, Cherry JD, Boyer KM, et al. Sales of nonprescription cold remedies: a unique method of influenza surveillance. *Pediatr Res* 1979; **13:** 1015–17.

75 Davies GR, Finch RG. Sales of over-the-counter remedies as an early warning system for winter bed crises. *Clin Microbiol Infec* 2003; **9:** 858–63.

76 Ohkusa Y, Shigematsu M, Taniguchi K, Okabe N. Experimental surveillance using data on sales of over-the-counter medications—Japan, November 2003–April 2004. *MMWR Morb Mortal Wkly Rep* 2005; **54** (suppl): 47–52.

77 Das D, Metzger K, Heffernan R, et al. Monitoring over-the-counter medication sales for early detection of disease outbreaks—New York City. *MMWR Morb Mortal Wkly Rep* 2005; **54** (suppl): 41-46.

78 Vergu E1, Grais RF, Sarter H, et al. Medication sales and syndromic surveillance, France. *Emerg Infect Dis* 2006; **12:** 416–21.

79 Socan M, Erculj V, Lajovic J. Early detection of influenza like illness through medication sales. *Cent Eur J Public Health* 2012; **20:** 156–62.

80 Vandendijck Y1, Faes C, Hens N. Eight years of the Great Influenza Survey to monitor influenza-like illness in Flanders. *PLoS One* 2013; **8:** e64156.

81 Debin M, Turbelin C, Blanchon T, et al. Evaluating the feasibility and participants' representativeness of an online nationwide surveillance system for influenza in France. *PLoS One* 2013; **8:** e73675.

82 de Lange MM, Meijer A, Friesema IH, et al. Comparison of five influenza surveillance systems during the 2009 pandemic and their association with media attention. *BMC Public Health* 2013; **13:** 881.

83 Polanco C, Castañón-González JA, Macías AE, Samaniego JL, Buhse T, Villanueva-Martínez S. Detection of severe respiratory disease epidemic outbreaks by CUSUM-based overcrowd-severe-respiratory-disease-index model. *Comput Math Methods Med* 2013; **2013:** 213206.

84 The Centre for Research on Inner City Health. The bio.diaspora project. http://www.biodiaspora.com/ (accessed June 19, 2014).

85 Barboza P, Vaillant L, Mawudeku A, et al. Evaluation of epidemic intelligence systems integrated in the early alerting and reporting project for the detection of A/H5N1 influenza events. *PLoS One* 2013; **8:** e57252.

86 Madoff LC. ProMED-mail: an early warning system for emerging diseases. *Clin Infect Dis* 2004; **39:** 227–32.

87 Brownstein JS, Freifeld CC. Health Map: the development of automated real-time internet surveillance for epidemic intelligence. *Euro Surveill* 2007; **12:** E071129.

88 Collier N, Doan S, Kawazoe A, et al. Bio Caster: detecting public health rumors with a web-based text mining system. *Bioinformatics* 2008; **24:** 2940–2941.

89 Keller M, Blench M, Tolentino H, et al. Use of unstructured event-based reports for global infectious disease surveillance. *Emerg Infect Dis* 2009; **15:** 689–695.

90 Bohigas PA, Santos-O'Connor F, Coulombier D. Epidemic intelligence and travel-related diseases: ECDC experience and further developments. *Clin Microbiol Infect* 2009; **15:** 734–39.

91 Rotureau B, Barboza P, Tarantola A, Paquet C. International epidemic intelligence at the Institut de Veille Sanitaire, France. *Emerg Infect Dis* 2006; **13:** 1590–92.

92 Linge JP, Steinberger R, Weber TP, et al. Internet surveillance systems for early alerting of health threats. *Euro Surveill* 2009; **14:** 19162.

93 Kaiser R, Coulombier D. Different approaches to gathering epidemic intelligence in Europe. *Euro Surveill* 2006; **11:** E060427.1.

94 Mykhalovskiy E, Weir L. The Global Public Health Intelligence Network and early warning outbreak detection: a Canadian contribution to global public health. *Can J Public Health* 2006; **97:** 42–44.

95 ProMED. Pneumonia- China (Guandong): RFI. Archive number: 20030210.0357. http://www.promedmail.org/direct.php?id=ph17223 (accessed May 20, 2014).

96 ProMED-mail, novel coronavirus—Saudi Arabia: human isolate 2012;. Archive number: 20120920.1302733. Sept 20, 2012. http://www.promedmail.org/?p=2400:1000. (accessed May 20, 2014).

97 Pollack MP, Pringle C, Madoff LC, Memish ZA. Latest outbreak news from ProMED-mail: novel coronavirus— Middle East. *Int J Infect Dis* 2013; **17:** e143–44.

98 Ginsberg J, Mohebbi MH, Patel RS, Brammer L, Smolinski MS, Brilliant L. Detecting influenza epidemics using search engine query data. *Nature* 2009; **13:** 1012–14.

99 Malik MT, Gumel A, Thompson LH, Strome T, Mahmud SM. "Google flu trends" and emergency department triage data predicted the 2009 pandemic H1N1 waves in Manitoba. *Can J Public Health* 2011; **102:** 294–97.

100 Thompson LH, Malik MT, Gumel A, Strome T, Mahmud SM. Emergency department and "Google flu trends" data as syndromic surveillance indicators for seasonal influenza. *Epidemiol Infect* 2014; **20:** 1–9.

101 Cho S, Sohn CH, Jo MW, et al. Correlation between national influenza surveillance data and google trends in South Korea. *PLoS One*. 2013; **8:** e81422.

102 Patwardhan A, Bilkovski R. Comparison: Flu prescription sales data from a retail pharmacy in the US with Google Flu trends and US ILINet (CDC) data as flu activity indicator. *PLoS One* 2012; **7:** e43611.

103 Dugas AF, Hsieh YH, Levin SR, et al. Google Flu Trends: correlation with emergency department influenza rates and crowding metrics. *Clin Infect Dis* 2012; **54:** 463–69.

104 Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. *Euro Surveill* 2009; **14:** 19288.

105 Kang M, Zhong H, He J, Rutherford S, Yang F. Using Google Trends for influenza surveillance in South China. *PLoS One* 2013; **8:** e55205.

106 Dugas AF, Jalalpour M, Gel Y, et al. Influenza forecasting with Google Flu Trends. *PLoS One* 2013; **8:** e56176.

107 Wilson N, Mason K, Tobias M, Peacey M, Huang QS, Baker M. Interpreting Google flu trends data for pandemic H1N1 influenza: the New Zealand experience. *Euro Surveill* 2009; **14:** 19386.

108 Cook AR, Chen MI, Pin Lin RT. Internet search limitations and pandemic influenza, Singapore. *Emerg Infect Dis* 2010; **16:** 1647–49.

109 Cook S, Conrad C, Fowlkes AL, Mohebbi MH. Assessing Google flu trends performance in the United States during the 2009 influenza virus A (H1N1) pandemic. *PLoS One* 2011; **6:** e23610.

110 buka Y, Chapman GB, Meyers LA, Li M, Galvani AP. The dynamics of risk perceptions and precautionary behavior in response to 2009 (H1N1) pandemic influenza. *BMC Infect Dis* 2010; **10:** 296.

111 Timpka T, Eriksson O, Spreco A, et al. Age as a determinant for dissemination of seasonal and pandemic influenza: an open cohort study of influenza outbreaks in Östergötland County, Sweden. *PLoS One* 2012; **7:** e31746.

112 Timpka T, Spreco A, Dahlström Ö, et al. Performance of eHealth data sources in local influenza surveillance: a 5-year open cohort study. *J Med Internet Res* 2014; **16:** e116.

113 Olson DR, Konty KJ, Paladini M, Viboud C, Simonsen L. Reassessing Google Flu Trends data for detection of seasonal and pandemic influenza: a comparative epidemiological study at three geographic scales. *PLoS Comput Biol* 2013; **9:** e1003256.

114 Ortiz JR, Zhou H, Shay DK, Neuzil KM, Fowlkes AL, Goss CH. Monitoring influenza activity in the United States: a comparison of traditional surveillance systems with Google Flu Trends. *PLoS One* 2011; **6:** e18687.

115 Valdivia A, Lopez-Alcalde J, Vicente M, Pichiule M, Ruiz M, Ordobas M. Monitoring influenza activity in Europe with Google Flu Trends: comparison with the findings of sentinel physician networks— results for 2009–10. *Euro Surveill* 2010; **15:** 19621.

116 Heraud JM, Njouom R, Rousset D, et al. Spatiotemporal circulation of influenza viruses in 5 African countries during 2008–2009: a collaborative study of the Institut Pasteur International Network. *J Infect Dis* 2012; **206** (suppl 1)**:** 5–13.

117 Randrianasolo L, Raoelina Y, Ratsitorahina M, et al. Sentinel surveillance system for early outbreak detection in Madagascar. *BMC Public Health* 2010; **10:** 31.

118 Duque J, McMorrow ML, Cohen AL. Influenza vaccines and influenza antiviral drugs in Africa: are they available and do guidelines for their use exist? *BMC Public Health* 2014 Jan; **14:** 41.

119 Nelson MI, Njouom R, Viboud C, et al. Multi-year persistence of two pandemic A/H1N1 influenza virus lineages in West Africa. *J Infect Dis* 2014; **210:** 121–25.

120 Brice GT1, DrewsSJ, Low DE. Respiratory virus panels for global surveillance of emerging infectious diseases. *J ClinVirol* 2007; **40** (suppl 1)**:** 58–60.

121 Dunn JJ, Woolstenhulme RD, Langer J, Carroll KC. Sensitivity of respiratory virus culture when screening with R-mix fresh cells. *J Clin Microbiol* 2004; **42:** 79–82.

122 Zitterkopf NL, Leekha S, Espy MJ, Wood CM, Sampathkumar P, Smith TF. Relevance of influenza A virus detection by PCR, shell vial assay, and tube cell culture to rapid reporting procedures. *J Clin Microbiol* 2006; **44:** 3366–67.

123 Khanna M, Fan J, Pehler-Harrington K, et al. The pneumoplex assays, a multiplex PCR-enzyme hybridization assay that allows simultaneous detection of five organisms, Mycoplasma pneumoniae, Chlamydia (Chlamydophila) pneumoniae, Legionella pneumophila, Legionella micdadei, and Bordetella pertussis, and its real-time counterpart. *J Clin Microbiol* 2005; **43:** 565–71.

124 Phommasack B, Moen A, Vongphrachanh P, et al. Capacity building in response to pandemic influenza threats: Lao PDR case study. *Am J Trop Med Hyg* 2012; **87:** 965–71.