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EXECUTIVE SUMMARY

Background

Increasing concern about the threat of pandemic influenza, emerging infectious diseases and bioterrorism has stimulated efforts to improve infectious disease surveillance and develop greater capacity for early detection and control of outbreaks. Substantial resources have been invested in the development of sophisticated electronic reporting systems, based on non-specific syndromic signs and symptoms. The efficacy and usefulness of syndromic surveillance systems is still being debated. In addition, informal digital resources are characterized by their ability of mining, categorizing, filtering, and visualizing online information regarding epidemics. Examples of such informal digital resources are ProMED-mail, HealthMap and BioCaster. Whether such systems are currently capable of early detection of disease outbreaks remains unclear.

Aim

To review digital resources for infectious disease outbreak detection and control and evaluate to what extent each can contribute to the management of outbreaks, particularly in the area of risk communication.

Methods

A systematic literature review was carried out on both formal and informal digital resources for infectious disease surveillance. We examined the source of information, the manner in which they process and disseminate the information, and whether and to what extent these systems are capable of early detection and management of infectious disease outbreaks. The formal sources are essentially those based on syndromic surveillance. The informal sources reviewed include ProMED-mail, Global Public Health Intelligence Network (GPHIN), HealthMap, MediSys, EpiSPIDER, BioCaster, H5N1 Google Earth mashup, Avian Influenza Daily Digest and Blog, Google flu trends and Argus. The managers of a number of these systems were interviewed with regard to the sources of the information and the screening of the information prior to making it available to the wider public.

Results

The availability of digital resources using both formal and informal methodology for monitoring infectious diseases has grown rapidly during the last decade. The impetus for developing such methodologies was initially driven by the desire to reduce the time taken for detecting infectious disease outbreaks. There is limited evidence to show that such resources actually help to detect outbreaks earlier than conventional methods. However, it has become increasing clear that these resources provide important information for managing

such outbreaks by increasing the situational awareness. They also provide essential information for risk communication.

Conclusions.

Based on the fundamentals of the natural history of the diseases and on simulated outbreaks, both syndromic-type surveillance and non-formal digital methods are unlikely to detect infectious disease outbreaks, prior to clinical and laboratory diagnoses of the early cases. However, there is evidence that they can be useful as decision-support tools for control of the outbreak. They can provide critical, timely information on the location and spread of the outbreak and predictions on its ultimate extent, making them invaluable for managing the epidemic. They can also play a crucial role in providing timely and valid information for risk communication. Emphasis should be placed on this aspect when developing or deploying such systems.

1. INTRODUCTION

During the last few decades, emerging infectious diseases have become an increasingly important global public health problem. Examples of such outbreaks are the Severe Acute Respiratory Syndrome (SARS) originated from Asia in 2003, the Avian influenza H5N1, and the H1N1 2009 pandemic (Morse, 2008). Therefore, effective surveillance systems for early warning are crucial. Surveillance is defined by the US CDC as follows: "Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health" (Morse, 2008). Traditional surveillance systems involve laboratory identification of the pathogen responsible for the disease. Such surveillance systems are passive in their nature, since they require a bottom-up process of noticing of a possible infectious disease by clinicians, reporting to the appropriate authorities, disease confirmation by laboratory tests, and information dissemination by authorities. Another approach is to establish a system whereby public health laboratories report electronic data to a central site. This approach may help public health officials to rapidly identify problems and take actions (Bean & Martins 2001). In addition, such systems are not capable of detection disease outbreaks in real-time.

Traditional surveillance systems are still currently used in all countries, however, due to their limitations, new surveillance systems were developed in recent years. These systems are based on syndromes rather than laboratory identification, without laboratory confirmation (Morse, 2008). On this basis, digital surveillance, or, digital resources for the detection of infection disease outbreaks are evolving and increasing dramatically.

Digital resources can be classified into two types: formal and informal. Formal digital resources are based on data arriving from formal organizations such as hospitals, healthcare clinics, and health agencies, whereas informal digital resources are based on data collected through media sources such as news reports on the Internet, mailing lists, and RSS (Really Simple Syndication) feeds. Informal digital resources are characterized by their ability of mining, categorizing, filtering, and visualizing online information regarding epidemics (Brownstein, Freifeld & Madoff, 2009). Examples of such informal digital resources are ProMED-mail, HealthMap and BioCaster. Whether such systems are currently capable of early detection of disease outbreaks remains unclear.

2. FORMAL INFECTIOUS DISEASE SURVEILLANCE SYSTEMS

During the last decade, there has been a rapid increase in the development of formal infectious disease surveillance systems. This followed a call from the United States CDC to upgrade current surveillance systems to meet the threat of bioterrorism (Khan et al. 2001). They define a number of requirements for upgrading such surveillance systems. The first immediate action was to incorporate surveillance for illnesses resulting from biological and chemical terrorism into the current disease surveillance systems. Secondly, they proposed that partnerships should be created with front-line medical facilities for reporting of unexplained illnesses. Thirdly, they required that the concepts underlying traditional surveillance systems need to be thoroughly revised to adapt to emerging infectious disease crises. Finally, they pointed to the urgent need to expand programs for developing the necessary expertise for investigating unusual outbreaks.

The surveillance systems for infectious disease outbreaks play roles at all levels of prevention. At the level of primary prevention, they can reduce both the actual and perceived efficacy of deliberately caused outbreaks and can have a deterrent effect. For secondary prevention, surveillance systems can make an important contribution to the early detection of infectious disease outbreaks, thus improving the response to the outbreak and limiting its spread. Finally, at the level of tertiary prevention, the information provided by surveillance systems contributes the evidence base for managing the epidemic, and can be especially effective in the area of risk communication. Surveillance systems may be also used for rapid detection of bioterrorist attack. However, detecting a bioterrorism outbreak depends on many factors, including the population characteristics, the attack nature, and the availability and use of health services. Therefore, the capability of such systems to detect bioterrorism-related epidemics remains unknown (Buehler, Berkelman, Hartley, & Peters 2003).

2.1. The goals of surveillance for infectious disease outbreaks

It is possible to identify four main goals for infectious disease outbreak surveillance. They are early detection of cases, monitoring the progress of the outbreak, providing data for risk communication and supplying data to the international health organizations. Thus surveillance is relevant at all stages of the outbreak (Green 2009).

For contagious diseases, such as influenza, early detection would allow for rapid implementation of preventive measures such as developing and distributing vaccines, isolation of cases, quarantine of contacts, social distancing and the use of face masks. For some infectious diseases, early detection can help to institute prompt prophylactic therapy since the response to some of the antiviral therapies deteriorates rapidly following the onset of symptoms. Early detection is also helpful in the logistics of the controlling the outbreak, such as transferring national stockpiles of pharmaceuticals and vaccines to where they are needed.

During the outbreak, the health authorities will require reliable data on the spread of the disease to monitor the efficacy of quarantine measures and pharmacological prophylaxis. These data also help to estimate the potential size of the outbreak as an aid to allocating resources. This can done by simple methods and more sophisticated mathematical modeling. Surveillance data is used as the input for mathematical models that can be used to predict the likely extent of the outbreak.

Risk communication is an important component of outbreak control. The paucity of factual information during an outbreak creates difficulties for the authorities to develop a trusting relationship with the authorities. High-concern events such as pandemics may evoke strong emotions, and may render the communication environment emotionally charged. In such situation, traditional communication approaches fail, and may even worsen the situation. Therefore a new approach is required (Covello, Peters, Wojtecki & Hyde 2001). Surveillance data can be used to boost trust and improve cooperation with the authorities. In this regard, surveillance data can be used at different stages of the outbreak - prior to the event, on suspicion of an event, on confirmation of the event, during the event and following the event (Green 2009). The questions at each stage can be summarized into: “Will it happen, is it suspected, has it been confirmed, is it under control and has it really ended?” On suspicion of an event, surveillance data can be used to rapidly evaluate whether there is unusual morbidity related in time and place to the suspected cases. On confirmation of an incident, surveillance data can delineate the area of risk. During the outbreak, surveillance data together with confirmed diagnoses could be used to determine the progress of the spread of the outbreak. At the end of the outbreak, surveillance data could be used to respond to rumors of continuation of the outbreak or signs of a new outbreak including addressing reports of the appearance of suspected new exposure foci.

Comprehensive surveillance data from different countries, analyzed by a central body, can greatly strengthen the possibility of identifying international outbreaks and alerting the international community to the dangers of spread of the disease (Bonin, 2007). The WHO International Health Regulations (IHR), were first initiated in 1969 to “prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade.” The regulations were updated and expanded in 2005 and took effect in June 2007.

2.2. Limitations of traditional surveillance

Traditional infectious disease surveillance systems are based on compulsory reporting of specified "notifiable" diseases from community and hospital physicians and from microbiology laboratories. For a number of reasons, they tend to be limited for the early detection and monitoring of rapidly spreading infectious diseases. Firstly, diagnosis of the early cases may either be missed or delayed both due to a failure to suspect unusual diseases (Cosgrove et al. 2005). Secondly, there may be a considerable delay in reporting due to the time it takes for a suspected case to be confirmed by laboratory tests (Nitzan Kaluski, Barak & Kaufman 2006). Thirdly, the flow of information in traditional surveillance systems tends to be relatively slow, delaying alerts to the public health authorities on the beginning of an outbreak and in providing information for monitoring the spread of the outbreak. Finally, the burden on the health services caused by the outbreak is likely to delay access to reports based on confirmed diagnoses.

In order to enhance surveillance for infectious diseases, two components have been addressed. The first is to strengthen early diagnosis and reporting by clinicians. The second is to improve the sensitivity and reporting of more general data on infectious diseases. Emergency room physicians are likely to be among the frontline staff for the early detection of infectious disease outbreaks since it is likely that the first cases to be detected will be those severe enough to present at hospitals. This will require a high level of alert for unusual signs and symptoms and facilities for rapid diagnosis.

2.3. Syndromic surveillance

The collection and reporting of more general data is the second component of surveillance that needs to be enhanced. Most infectious diseases have prodromal periods characterized by non-specific syndromic symptoms and signs, often called "flu-like" symptoms (Kass-Hout et al. 2012). Some years ago, "syndromic surveillance" was proposed as a more sensitive means for early detection of outbreaks. It has been proposed that centrally maintained syndromic surveillance systems can provide early alerts to infectious disease outbreaks and can be used to help to rule out false alarms. Due to large number of cases in epidemics, influenza is rarely diagnosed on the basis of laboratory findings. Thus, surveillance for "influenza-like illness" (ILI) has become an established method of monitoring the incidence of influenza (Brammer et al. 2000).

2.3.1. The role of syndromic surveillance

The ability of syndromic surveillance to detect the first cases in an infectious disease outbreak will depend to a large extent on the biological agent used. Therefore, the system needs to be flexible and designed to detect a number of widely different diseases. During a relatively slowly evolving outbreak, syndromic surveillance is an important tool for detecting the first cases. However, in rapidly evolving outbreaks, it seems more realistic to describe the role of syndromic surveillance as a means of detecting cases at an early stage of the outbreak. This would complement the reporting of early cases diagnosed by front-line physicians , help to confirm the outbreak and estimate its location and extent.

Syndromic surveillance can also play a major role in the management and control of the outbreak. During large infectious disease outbreaks, occurring under emergency conditions, syndromic surveillance will provide data earlier than laboratory diagnosis of individual cases, which is slower and may not be done at all. In addition, the transmission of syndromic surveillance data is much more rapid than that for diagnosed cases. Thus once an outbreak has been confirmed, syndromic surveillance systems would provide timely and detailed surrogate data on the evolution of the outbreak including how it is spreading and it’s likely size (Walden and Kaplan 2004). The system also provides current information on background disease patterns in the general population, and this can help to identify new outbreak foci. The extent of pandemic may also be assessed by the system, by estimating the incidence rates of the syndromes (Fowlkes et al. 2012).

2.3.2. Developing syndromic surveillance systems

The United States CDC guidelines for developing syndromic surveillance systems has required that the goals of the system be defined and include specifications of the kind of information that is expected. Those responsible for the surveillance should be identified and their roles delineated. The system should include procedures to be followed in the event that an incident is suspected, including how and to whom it should be reported (Mandl et al. 2004; Morse 2012; Paterson et al. 2012).

The sources of the data for syndromic surveillance are varied and can include primary care physician visits, attendance at emergency rooms, prescription medication data and requests for blood cultures. Since not every sick person will visit a physician, surrogates of symptoms such as sales of the over-the-counter medications for complaints such as fever, cough and diarrhea may also be used (Jian-Hua et al. 2005). In addition other crude measures of increased disease incidence can include hospital bed occupancy, mortality rates and numbers of blood cultures requested.

Syndromic surveillance systems usually have statistical computing capabilities to determine whether there are unusual changes in syndromes in either time or space or both (Kaufman et al. 2007; Rolka et al. 2007; Green & Kaufman 2005; Peter, Najmi & Burkom 2011; Xing, Burkom & Tokars 2011). A number of analytic tools have been used. Examples are time series analysis and the cusum method, to detect temporal changes in disease patterns (Kulldorff et al 2007), and to detect changes in the usual patterns of morbidity (Fienberg and Shmueli 2005). Geographic Information Systems (GIS) are widely used to detect clusters of cases both in time and place.

2.3.3. Examples of syndromic surveillance systems

Syndromic surveillance systems are currently operating in a number of centers, particularly in North America (Bravata et al. 2004) and Europe. One of the earliest comprehensive syndromic surveillance systems was developed in the New York City Department of Health. Since 1999, they have been actively monitoring hotline calls (911) on a daily basis to identify temporal or geographic increases in respiratory illnesses that might represent any infectious disease outbreak, including seasonal influenza and potential bioterrorist events. In addition, the Health Department also developed three independent and complementary systems to monitor community-based gastrointestinal outbreaks. These include sales of anti-diarrheal medications, submission of stool samples for laboratory tests and incidence of gastroenteritis in nursing home populations. They employ sophisticated statistical analyses to detect unexpected variation in the data.

In 2000, the United States Department of Defense's developed the ESSENCE system to rapidly identify the occurrence of non-specific syndromes in patients presenting at military health care facilities in the Washington DC area (Kortepeter et al. 2000; Pavlin and Kelley et al.). In the ESSENCE system, daily ambulatory data collected at hospitals and clinics are transmitted to a central database. Daily analyses search for patterns that suggest that an infectious disease outbreak is in its early stages. Once the system detects a significant change in the frequency of reports compared with that expected, military and civilian public health officials are notified. The frequency of outpatient visits for the different syndrome categories are also mapped using geographic information systems (GIS) software (ESSENCE website). Most syndromic surveillance systems operate at a local or state level. However, the United States CDC has developed a national surveillance system called Biosense (Bradley et al. 2005). In addition, the Bio-surveillance program initiative and the BioWatch program were established in 2004 (CIDRAP 2004). In a study carried out in the United States in 2007-8, 83% of public health officials surveyed reported conducting syndromic surveillance (Buehler et al. 2008). Also a new syndromic surveillance system was developed for the London 2012 Olympic and Paralympic Games (Harcourt et al. 2012; Severi et al. 2012).

2.3.4. Operation of syndromic surveillance systems

Classically, syndromic systems have been developed with the goal of continuous active surveillance, continuous, active monitoring of the system, use of complex statistical algorithms and investigation of every significant aberration. The systems require substantial resources including computerized data collection and analysis, manpower for monitoring the system and manpower for investigating alerts. Clearly, the disadvantages of such an approach are the background noise due to incidental illnesses, the non-specific characteristic of the data, multiple false alerts, and the detection of small, local outbreaks, of no public health importance (Reeder, Revere, Olson & Lober 2011). There is also a danger of rapid burnout among the staff, resulting from maintaining continuous vigilance without detecting many important outbreaks.

An alternative approach is to collect syndromic surveillance data, and examine it in detail only periodically (for example on a weekly basis). In the event of a report of a suspicious or confirmed case, the syndromic surveillance data base would be analyzed with a specific goal to determine whether there is a change in the pattern of non-specific disease rates.

2.3.5. Validating syndromic surveillance systems

While some of the biological agents have similarities in the early signs of the disease, each agent behaves differently as regards incubation period, spectrum of signs and symptoms, severity, etc. Thus it's important to assess the surveillance system for each biological agent separately. The success of a surveillance system depends on factors such as simplicity, flexibility, data quality, acceptability, sensitivity, predictive value, representativeness, timeliness and stability (CDC 2000). Technical factors to be considered include method of collecting data, amount of follow-up, method of managing the data, methods for analyzing and disseminating the data, staff training and time spent on maintaining the system. Factors that can affect acceptability include public health importance, acknowledgement of contributions, dissemination of data back to reporting sources, responsiveness of the system, the burden on time, ease and cost of data reporting and assurance of privacy and confidentiality.

Two of the main measures of the efficacy of a surveillance system are the sensitivity and positive predictive value (German 2000). The efficacy of the syndromic systems for early detection of outbreaks, have occasionally been tested on natural outbreaks of influenza and there is evidence that syndromic surveillance will identify influenza outbreaks earlier than surveillance based on laboratory isolates.

There have been a number of studies of the efficacy of syndromic surveillance for early detection of influenza outbreaks (van den Wijnaard, et al. 2008; Singh, et al. 2010, Hope et al. 2010; Westheimer et al. 2012). The results have been mixed. In a study in Ontario, Chu et al. (2012) concluded that "syndromic surveillance had limited use in decision-making during the 2009 H1N1 pandemic". In another study from Ontario (Savage et al. 2012), the authors found that laboratory data were most useful for monitoring outbreaks and making decisions in the control of the outbreak. In a study in North Carolina local health departments, (Samoff et al. 2012) concluded that the use of syndromic surveillance data contributed to useful public health action. In a study in Italy, De Florentiis et al. (2011) concluded that the combination of syndromic surveillance systems with laboratory surveillance yielded a specific and sensitive tool for influenza surveillance. Qian et al. (2011) have demonstrated the potential of using ILI and Unexplained Pneumonia (UP) surveillance data for early detection of outbreaks. A study conducted in the UK has demonstrated the usefulness of syndromic surveillance data for the detection and for the description of a pandemic (Smith et al. 2011). Another study conducted in the Netherlands has suggested that "surveillance clearly has added value in revealing the blind spots of traditional surveillance, in particular by detecting unusual, local outbreaks independently of diagnoses of specific pathogens" (van den Wijngaard 2011). Surveillance systems with different source of data may have different capability of detecting outbreaks. An American study which compared emergency department and ambulatory care syndromic surveillance systems during the 2009 H1N1 pandemic found an earlier increase in ILI in ambulatory care facilities (Plagianos et al. 2011).

2.3.6. Strengths and limitations of syndromic surveillance

The strengths of electronic syndromic surveillance are primarily in the timeliness of the reports and reduced reliance on individual physicians to complete forms. This will be of particular relevance in an emergency situation. Thus the system would provide current information in helping to detect and track the outbreak. During large infectious disease outbreaks, occurring under emergency conditions, laboratory diagnosis of individual cases is likely to be slow and often not done at all. In addition, the transmission of information on diagnosed cases will often be delayed. Thus once an outbreak has been confirmed, syndromic surveillance systems would provide timely and detailed data on the location of the cases and evolution of the outbreak. The system can also provide important, current information on general disease patterns among those exposed, compared with the rest of the population.

Despite the implementation of syndromic surveillance systems in a number of centers, primarily in the United States, their contribution to the early detection of bioterrorism events has been questioned (Reingold 2003; Savage et al. 2012). The main criticism is the danger that there will be an abundance of false reports which could paralyze the system. It is not clear whether such surveillance systems can function efficiently in the long term, without overburdening the public health services.

2.3.7. Response to syndromic surveillance alerts

One of the difficulties in operating syndromic surveillance systems involves dealing with the large number of false alerts. In order to ensure that the system is highly sensitive to changes in disease incidence, the false positive rate tends to dominate. Thus the reporting procedures need to be adapted to syndromic surveillance. In situations when an infectious disease is diagnosed or highly suspected, the procedure to be followed is usually clearly defined. Where indicated, the treating physician should report to the designated public health authority which should initiate an immediate epidemiologic investigation. With syndromic surveillance, the response process is not as clear and it remains problematic which changes in non-specific disease incidence should be reported and investigated. A central question is how large the incidence should deviate from background disease activity in order to justify an epidemiological investigation. Furthermore, since many of the authorities operating the systems use anonymized data, the investigation will require close collaboration with those supplying the data.

In general, there are likely to be three distinct phases of any epidemiological investigation. The first is when an outbreak is suspected without a definitive diagnosis of the disease, the second is when the diagnosis has been confirmed and the third when it is concluded that the outbreak was intentional. Thus in the case of syndromic surveillance, clear, operational protocols should be available for all potential agents, including agreed upon definitions of cases and contacts, and appropriate questionnaires.

2.4. Legal and ethical aspects

Preparedness for epidemic of infectious diseases requires the necessary legislation to enable the public health authorities to carry out measures with adequate legal backing. Issues that require regulation are active surveillance of presumed infected individuals and their contacts. The authorities may have to exercise unusual powers to control the outbreak, and civil liberties may be compromised. There will be a need for ethical review of surveillance procedures, but there is also "an ethical mandate to undertake surveillance that enhances the well-being of the population" (Fairchild and Bayer 2004).

2.5. Conclusions

Surveillance systems for infectious disease outbreaks will need to be flexible and adapted to the characteristics of the potential biological agents. Surveillance systems will also have to be sustainable, without long-term burnout. Furthermore, it is still difficult to define the kind of action that needs to be taken in the event of a signal of an outbreak, especially in order to avoid numerous false alarms. The reporting and follow-up procedures also need to be adapted to syndromic surveillance. It is still not clear which irregularities should be reported and investigated. It is clear that health care professionals at many levels will need to play a much more active role in disease surveillance than in the past.

Despite the increased sophistication of the surveillance systems that have been implemented in many centers, at present, early identification of infectious disease outbreaks will depend largely on the ability of primary care and emergency room physicians to diagnose and immediately report suspected cases. Thus medical personnel, particularly in hospital emergency rooms, should be updated regularly on the clinical manifestations of diseases which may result in large outbreaks.

In summary, syndromic-type surveillance systems, with sophisticated statistical algorithms, are of limited value in the early detection infectious disease outbreaks. The first cases probably will be identified when they are serious enough to be diagnosed by alert physicians. However, syndromic surveillance can play an important support for controlling the outbreak, once it has been detected. It will be most useful in providing timely, valid information for managing the outbreak and for risk communication. Valuable resources should continue to be directed at improving such systems and enhancing clinical and laboratory surveillance. It is possible that some of the resources currently directed at this goal should be redirected towards training primary care and emergency room physicians to recognize the clinical features of infectious diseases with important outbreak potential.

3. INFORMAL INFECTIOUS DISEASE SURVEILLANCE SYSTEMS

3.1. Introduction

Informal digital resources are based on data obtained either from formal organizations or from media sources such as news reports on the Internet, mailing lists, and RSS (Really Simple Syndication) feeds. Informal digital resources are characterized by their ability of mining, categorizing, filtering, and visualizing online information regarding epidemics (Brownstein, Freifeld & Madoff, 2009). Examples of such informal digital resources are ProMED-mail, HealthMap and BioCaster. Whether such systems are currently capable of early detection of disease outbreaks remains unclear.

3.2. Methods

A systematic literature review was carried out to compare the following informal digital systems with regards to their source of information, the manner in which they process and disseminate the information, and whether and to what extent these systems are capable of early detection of disease outbreaks: ProMED-mail, Global Public Health Intelligence Network (GPHIN), HealthMap, MediSys, EpiSPIDER, BioCaster, H5N1 Google Earth mashup, Avian Influenza Daily Digest and Blog, Google flu trends and Argus. In addition, interviews with informal digital systems owners were carried out, in order to answer four main questions: The first is the owners' perception regarding their system's ability to detect disease outbreaks earlier than other surveillance systems and to disseminate of information regarding disease outbreaks. The second one is the owners' perception regarding the system performance during the 2009 influenza pandemic. The third is whether and to what extent the systems are capable of identifying their target users, and to disseminate information adapted to the users' estimated literacy in health-related topics. The fourth is whether the systems are capable of identifying misinformation , and dealing with such misinformation. The interviews were performed in accordance with a structured questionnaire (see Appendix), where some of the questions were multiple choice, and some were open.

3.3. Findings

3.3.1. ProMED-mail

ProMED-mail is "an internet based reporting system aimed at rapidly disseminating information on infectious disease outbreaks and acute exposures to toxins that affect human health, including those in animals and in plants grown for food or animal feed" (ProMED-mail website). ProMED-mail receives information from a number of sources, such as media reports, official reports, online summaries and local observers. The reports are reviewed and investigated by ProMED-mail expert team, and then distributed by e-mail to ProMED subscribers, and published in ProMED-mail website (ProMED-mail website). In addition to filtering the received information, ProMED-mail expert team may also add related information from media, government and other sources (Handbook of biosurveillance, 2006). ProMED-mail was proven as an efficient system during the 2003 outbreak of SARS, where information about points of outbreak, including additional information from a British Medical Journal article, was efficiently disseminated (Handbook of biosurveillance, 2006). It should be stressed that ProMED-mail collects, filters, disseminates and archives it. They do not carry out formal analysis of the information although they provide some evaluation.

3.3.2. Global Public Health Intelligence Network (GPHIN)

The Global Public Health Intelligence Network (GPHIN) is a biosurveillance system developed by Health Canada in collaboration with the WHO. GPHIN receives as input, information about disease outbreaks arriving from news service items, ProMED-mail, electronic discussion groups and selected websites, and disseminates information to subscribers using the following decision algorithm. A relevance score is computed for each information item. Two thresholds are determined, high and low. If the item relevance score is greater than the high threshold, then it is immediately disseminated to subscribers. If the item relevance score is lower than the low threshold, then it is automatically "trashed". Otherwise (if the item relevance score is between the high and the low thresholds), the item goes through human analysis and then disseminated to subscribers (Handbook of Biosurveillance, 2006).

A prominent limitation of GPHIN efficiency is its reliance on the time in which information about an outbreak or other event if published in one of GPHIN data sources. Nevertheless, GPHIN is considered efficient in providing earlier warning of events of interest to the international community compared with other systems, as 56% of the 578 outbreaks verified by WHO between July 1998 and August 2001 were initially picked up by GPHIN (Handbook of Biosurveillance, 2006).

3.3.3. HealthMap

HealthMap is a freely accessible automated electronic information system aimed at facilitating knowledge management and early detection of infectious disease outbreaks by aggregating, extracting, categorizing, filtering and integrating reports on new and ongoing infectious disease outbreaks. Data on outbreaks are organized according to geography, time, and infectious disease agent (Brownstein et al., 2008).

HealthMap receives as input reports received from variety of electronic sources, including online news sources aggregated in websites such as Google News, reporting systems such as ProMED-mail, and validated official reports received from organizations such as the WHO (Brownstein et al., 2008, Freifeld et al, 2008) . An internet search is performed by HealthMap every hour, 24 hours a day, in order to obtain the required information. Search criteria include disease name (scientific and common), symptoms, keywords, and phrases. After collecting the reports, HealthMap uses text mining algorithms in order to characterize the reports. Characterization includes the following stages: (1) Categorization: reports are categorized according to disease and location and relevance is determined. (2) Clustering: similar reports are grouped together and exact duplicates are removed. Clustering is performed based on similarity of the report's headline, body text, and disease and location categories. (3) Filtering: reports are reviewed and corrected by an analyst, and then filtered into five categories - breaking news, warning, old news, context, and not disease related.

In order to reduce information overload and to focus on disseminating information regarding outbreaks of high impact, only reports classified as breaking news are overlaid on an interactive geographic map located on HealthMap site (Brownstein et al., 2008).

Among the users of HealthMap are the WHO, the US Centers for Disease Control and Prevention, and the European Center for Disease Prevention and Control, which use its information for surveillance activities (Brownstein et al., 2008), (Freifeld, Mandl, Reis, & Brownstein, 2008).

3.3.4. MedISys (Medical Intelligence System)

Medical Information System (MedISys) is an informal automatic public health surveillance system. MedISys is designed and operated by the Joint Research Center (JRC) of the European Commission, in cooperation with the Health Threat Unit at the European Union Directorate General for Health and Consumer Affairs and the University of Helsinki. MedISys collects its information from open-source news media, mainly articles from news pages. MedISys categorizes the collected information according to predefined categories and disseminates it to subscribed users by e-mail. The system also provides its user with features and statistics available on its website, including a world map in which event locations are highlighted, aggregated news count per each geographic location presented on graphs, and the most significant event location for the last 25 hours. MedISys is available in 26 languages (the system collects information in 45 languages, but the website is available in 26 languages). Users can filter the information according to language, disease and location, as well as by outbreaks, treatments and legislations. MedISys users can also select articles into predefined categories, add comments to these articles, add information, and disseminate them to user-defined groups (Hartley et al., 2010).

3.3.5. Argus

Argus is an informal biosurveillance system aimed at detecting and monitoring biological events that may be a global health threat to human, plant and animals. The system is hosted at the Georgetown University Medical Center (Washington, DC, United States), and funded by the United States Government. Argus collects information in 40 native languages from media sources, including printed newspapers, electronic media, Internet-based newsletters and blogs, as well as from official sources (the World Health Organization (WHO) and the World Organization For Animal Health (OIE). The system uses Bayesian analysis tools for selecting and filtering the collected articles. The process is performed by about 40 regional professional analysts, who monitor several thousand internet sources on a daily basis. By using Bayesian analysis tools, the analysts select reports from a dynamic database of media reports. Relevance is determined according to a specific set of terms and keywords applicable to infectious diseases surveillance. After filtering the information, events that may indicate the initiation of an outbreak are disseminated to the system users. Also disseminated are events that may require investigation (Hartley et al., 2010), (Nelson & Brownstein, 2010).

3.3.6. BioCaster

BioCaster is an informal surveillance system aimed to collect information on disease outbreaks, filter the information, and disseminate it to users. The system is a part of a research project developed and managed by the National Institute of Informatics in Japan, which involves five institutes in three countries. BioCaster focuses mainly on the Asia-Pacific region. The system collects information by using Really System Syndication (RSS) feeds from more than 1700 sources. Information is collected mainly from Google News, Yahoo! News, and European Media Monitor, filtered and disseminated in a fully automated manner with no human analysis in any stage. Filtered information (about 90 articles per day) is published in three languages (English, Japanese and Vietnamese). Articles are processed and disseminated every hour. In addition, BioCaster creates an ontology which covers approximately 117 infectious diseases and six syndromes. The ontology is produced in eight languages (English, Japanese, Vietnamese, Chinese, Thai, Korean, Spanish and French), and is used as an input to Global Health Monitor web portal, which offers its users maps and graphs of health-concerning events (Hartley et al., 2010).

3.3.7. EpiSPIDER

The Semantic Processing and Integration of Distributed Electronic Resources for Epidemiology (EpiSPIDER) is a web-based tool which integrates information gathered from electronic media resources containing health information, as well as from informal surveillance systems, such as ProMED-mail. The aim is to enhance the surveillance of infectious disease outbreaks .EpiSPIDER uses ProMED-mail reports as an input, as well as health news sources that provide RSS feeds. By using natural language processing, it extracts location information from the input sources, and geocode them using the Yahoo and Google geocoding services. After a filtering process, the system generates summaries of ProMED reports (on a daily basis). These reports are available in the EpiSPIDER website (Tolentino et al., 2007).

3.3.8. H5N1 Google Earth mashup

Google earth combines satellite images, aerial photography and map data to create a 3D interactive template of the world. This template can be used by anyone to add and share information about any subject that involves geographical elements. Nature (international weekly journal of science) uses Google earth to track the spread of the H5N1 avian flu virus around the globe, and to present a geographic visualization of the spread of H5N1 (Nature website).

3.3.9. Avian Influenza Daily Digest

Avian Influenza Daily Digest is a digest produced by the United States government. The digest collects raw open source content regarding Avian influenza and disseminates it to subscribers. Material is disseminated without any processing. Users are encouraged to provide with updates and/or clarifications that will be posted in subsequent issues of the digest (Avian Influenza Daily Digest website).

3.3.10. Google Flu Trend

Google Flu Trend is designed by Google Internet Company to be a near real-time tool for detection of influenza outbreaks. Google Flu Trend exploits the fact that millions of people worldwide search online for health-related information on a daily basis. The tool was designed based on the assumption that there is an association between the number of people searching for influenza-related topics and the number of people who actually have influenza symptoms, and therefore, an unusual increase in the number of people searching for influenza-related topic on the web may simulate an increase in influenza syndromes. Studies performed by Google and Yahoo have shown that plotting data on searches using influenza-related keywords has led to an epidemic curve that closely matched the epidemic curve generated by traditional surveillance of influenza (Brownstein, et al, 2009). Google Flu Trends analyzes a fraction of the total Google searches over a period of time, and extrapolates the data to estimate the search volume. The information is displayed in a graph called "search volume index graph". It is claimed by the tool's designers that, according to tool testing, it can detect outbreaks of influenza 7-10 days before it is detected by conventional CDC surveillance (ref).

3.4. Interview with informal digital system owners

We emphasize that all the results and conclusions presented in this chapter are based on the systems owners answers to the interview questions, and therefore they reflect their own perceptions regarding the research questions.

Interviews were conducted with seven owners of six informal digital systems: ProMED-mail, HealthMap, BioCaster, Argus, EpiSpider, GPHIN

All interviewed informal digital systems owners perceived their system's ability to detect disease outbreaks earlier than other surveillance systems (formal and informal), as well as their system's ability to disseminate information regarding disease outbreaks high to very high. The owner of BioCaster has added that some studies performed by BioCaster have shown that automated anomaly detection could detect some outbreaks earlier than ProMED-mail (4 days before ProMED-mail). As for dissemination, all of BioCaster alerts are in the public domain, and are broadcasted in the BioCaster portal and Twitter, and disseminated to public health agencies in the G7's GSHAG project. All interviewed owners believe that their system is intended to function during crisis/emergency, except ProMED-mail owner. HealthMap owner has reported that the system made special focused efforts during emergency, including increased frequency of data collection, increased

frequency of reporting, and new visualization of the data. BioCaster owner has reported that the system has different operational modes, including a routine mode, and a crisis mode, in which the system provides more functionality during crisis. However, this crisis mode is currently not used (demonstration only). All systems owners reported that there is a standardized protocol for deciding what information would be released, except ProMED-mail owner, who reported that it has no such a protocol. The HealthMap protocol is to disseminate breaking news and unique news (not duplicates), based on the International Health Regulations (IHR). The BioCaster protocol is not to limit the published information on one hand, and to control the quality of evidence in accordance with the following protocol: (1) prioritizing what is important according to the IHR. (2) Information is disseminated only if it meets the following conditions: there should be a disease mentioned in the report, there should be a named location, and the time frame for the outbreak should be recent. According to most of the owners, the system is intended to the general public, as well as to health professionals, however, according to the interviews, Biocaster is the only informal digital system that differently appeal to each population in the following manner: Both the general public and the public health agencies receive notifications about the same event, however, public health agencies get a deeper automated analysis of what is happening in the event. Based on this analysis, BioCaster filters the news so that a small subset of the information goes to the public health agencies, which is relevant for their particular work. None of the organizations which owns the systems characterize the system's actual users, in other words, none of the organizations conduct periodic surveys or collect information regarding subscribers in order to characterize the actual users of the systems.
Most interviewed owners have reported that they take measures to screen for misinformation. In ProMED-mail, screening for misinformation is performed by human review, whereas in BioCaster it is performed by trying to get two independent sources which describe the same events. In addition, in case of misinformation published by BioCaster, a mistake message may be sent in the BioCaster portal and in Twitter.

3.5. Are informal digital surveillance systems currently capable of detection disease outbreaks in real-time?

It appears that all the studied digital resources use similar sources of data – official reports, as well as media reports, including global media resources, news aggregators, eyewitness reports, internet-based newsletters and blogs. However, they use different algorithms to create their output, and cover different geographic areas. In addition, existing digital resources are different in the manner they filter and analyze the information and may create different output. Therefore they complement each other with respect to information completeness. There is evidence in the literature on the systems' usefulness in communicating the information during previous outbreaks to public health professionals, as well as to the general public. ProMED-mail and GPHIN had critical roles in updating public health officials about the SARS outbreak in 2002 (Brownstein, et al, 2009). Such systems are also capable to provide officials, clinicians and the general public with guidance to medical decision making, including the importance of vaccination and other preventive actions (Brownstein, et al, 2009).

Some retrospective studies of some systems have shown a theoretical decrease in the time of outbreak detection compared to conventional surveillance, however there is no evidence of such ability in real-time.

Chan et al. (2010) have analyzed the average interval between estimated outbreak start date to the earliest date of discovery and publication, using WHO confirmed outbreak reports, as well as ProMED-mail, GPHIN and Healthmap reports. Analysis showed a decrease in intervals over 14 years, which was partially attributed to the emergence of informal digital resources (Chan et. al, 2010). A retrospective study of Argus reports on respiratory disease in Mexico showed a significant increase in reporting frequency during the 2008-2009 influenza season relative to that of 2007-2008. The authors suggest that, according to these retrospective results, respiratory disease was prevalent in Mexico and reported as unusual much earlier than when the H1N1 pandemic virus was formally identified. However, its connection with the 2009 pandemic is unclear (Nelson, et al, 2010).

The Google Flu Trends tool was also retrospectively tested. According to retrospective testing, influenza outbreaks can be detected by using Google flu trends tool 7-10 days before it is detected by conventional surveillance (Carneiro & Mylonakis, 2013; Carneiro & Mylonakis 2009), however, there are still no prospective evidence to such capability. A retrospective Chinese study reported that Google flu trend search data are correlated with traditional methods of surveillance (Kang, Zhong, He, Rutherford & Yang, 2013). Unlike retrospective evidence, prospective evidence of informal digital systems capability to early detection of disease outbreaks are sparse. The SARS in China (February 10, 2003) is the best known outbreak first reported on ProMED-mail (Morse, 2012).

Informal digital systems may also have an important role in disease surveillance. Incorporating informal digital systems into existing formal systems may improve their performance. A study in the United States showed that combining information gathered from informal digital systems with information received from the Texas Influenza-Like-Illness Surveillance Network (ILINet) improved the ability of predicting hospitalizations due to influenza (Scarpino, Dimitrov & Meyers, 2012). Another study in the United States showed a good correlation between Google flu searches and emergency department influenza-like illness visits (Dugas et. al, 2012).

4. SUMMARY

In summary, there has been impressive progress in the development of informal digital systems for disease surveillance. Informal digital systems are widely used by the general public, as well as by health officials. A good example is the GORAN digital system (the Global Outbreak and Response Network) developed by the WHO, which gather information from number of sources both governmental and informal, including GPHIN and ProMED-mail (Morse, 2012). Currently there is little prospective evidence that existing informal systems are capable of real-time early detection of disease outbreaks. Most systems accumulate a huge mass of information on a large variety of diseases, making it difficult to extract critical information. The challenge is to present critical information clearly and concisely. Another important challenge is to establish a response system to early warnings. With the lack of such a system, early warning is not useful, as no practical action is followed by the publication of the information. Such a response system may include triggers and decision criteria, which would lead to an appropriate and proportionate response to the threat (Morse, 2012).

REFERENCES

Avian Influenza Daily Digest website: http://aidailydigest.blogspot.co.il/2008/10/dni-avian-influenza-daily-digest_09.html

Bean N. H. & Martin S. M. (2001). Implementing a network for electronic surveillance reporting from public health reference laboratories: an international perspective. *Emerging Infectious Diseases*, 7, 773-779

Bonin S. (2007). Book: International Biodefense Handbook. An inventory of national and international biodefense practices and policies; Center for Security Studies at ETH Zurich

Bradley C. A., Rolka H., Walker D. & Loonsk J. (2005). BioSense: Implementation of a national early event detection and situational awareness system. *Morbidity and Mortality Weekly Report*, 54, 11-19

Brammer T. L., Izurieta H. S., Fukuda K., Schmeltz L. M., Regnery H. L., Hall H. E. & Cox N. J. (2000). Surveillance for influenza – United States, 1994-95, 1995-96, and 1996-7 seasons. *Morbidity and Mortality Weekly Report CDC Surveillance Summary*, 49, 13-28

Bravata D. M., McDonald K. M., Smith W. M., Rydzak C., Szeto H., et al. (2004). Systematic review: surveillance systems for early detection of bioterrorism-related diseases. *Annals of Internal Medicine*, 140, 910-922

Brownstein J. S., Freifeld C. C., & Madoff L. C. (2009). Digital disease detection – harnessing the web for public health surveillance*. New England Journal of Medicine*, 360, 2153-2157

Brownstein J. S., Freifeld C. C., Reis B. Y., Mandl R. K. (2008). Surveillance Sans Frontieres: Internet-based emerging infectious disease intelligence and the HealthMap project. *PLoS Medicine*, 5

Buehler J. W., Berkelman R. L., Hartley D. M. & Peters C. J. (2003). Syndromic surveillance and bioterrorism-related epidemics. *Emerging Infectious Diseases*, 9, 1197-1204

Buehler J.W., Sonricker A., Paladini M., Soper P. & Mostashari F. (2008). Syndromic surveillance practice in the United States: Findings from a survey of state, territorial, and selected local health departments. *Advances in Disease Surveillance*, 6, 1-20

Carneiro H. A. & Mylonakis E. (2009). Google trends: a web-based tool for real-time surveillance of disease outbreaks. *Clinical Infectious Diseases*, 49(*10*), 1557-1564

Carneiro H. A. & Mylonakis E. (2013). Google Trends: A web-based tool for real-time surveillance of disease outbreaks. *Surfing The Web*, 2009(*49*)

Centers for Disease Control and Prevention (CDC). (2011). Assessment of ESSENCE performance for influenza-like illness surveillance after an influenza outbreak--U.S. Air Force Academy, Colorado, 2009. *Morbidity and Mortality Weekly Report*, 60(*13*), 406-409

Centers for Disease Control and Prevention. (2001). Updated guidelines for evaluating public health surveillance systems. *Morbidity and Mortality Weekly Report*, 50 (*13*), 1-35

Chan E. H., Brewer T. F., Madoff L. C., Pollack M. P., Sonricker A. L., Keller M., Freifeld C. C., Blench M., Mawudeku A., & Brownstein J. S. (2010). Global capacity for emerging infectious disease detection. *Proceedings of the National Academy of Sciences*, 107(*50*), 21701-21706

Chu A., Savage R., Willison D., Crowcroft N. S., Rosella L. C., Sider D., Garay J., Gemmill I., Winter A. L., Davies R. F., & Johnson I. (2012). The use of syndromic surveillance for decision-making during the H1N1 pandemic: A qualitative study. *BMC Public Health*, 12,929

Covello V. T., Peters R. G., Wojtecki J. G., & Hyde R. C. (2001). Risk communication, the West Nile virus epidemic, and bioterrorism: responding to the communication challenges posed by the intentional or unintentional release of a pathogen in an urban setting. *Journal of Urban Health*, 78,382-391

De Florentiis D., Parodi V., Orsi A., Rossi A., Altomonte F., Canepa P., Ceravolo A., Valle L., Zancolli M., Piccotti E., Renna S., Macrina G., Martini M., Durando P., Padrone D., Moscatelli P., Orengo G., Icardi G., & Ansaldi F. (2011). Impact of influenza during the post-pandemic season: epidemiological picture from syndromic and virological surveillance*. Journal of Preventive Medicine and Hygiene*, 52(*3*), 134-136

Dugas A. F., Hsieh Y. H., Levin S. R., Pines J. M., Mareiniss D. P., Mohareb A., Gaydos C. A., Perl T. M., & Rothman R. E. (2012). Google Flu Trends: correlation with emergency department influenza rates and crowding metrics. *Clinical Infectious Diseases*, 54(*4*), 463-4

ESSENCE – Electronic Surveillance System for the Early Notification of Community-Based Epidemics, Website: http://www.geis.ha.osd.mil/

Fairchild A. L. & Bayer R. (2004). Public health. Ethics and the conduct of public health surveillance. *Science*, 303, 631-632

Fowlkes A., Dasgupta S., Chao E., Lemmings J., Goodin K., Harris M., Martin K., Feist M., Wu W., Boulton R., Temte J., Brammer L., & Finelli L. (2012). Estimating influenza incidence and rates of influenza-like illness in the outpatient setting. *Influenza and Other Respiratory Viruses*, 10, 12014

Freifeld C. C., Mandl K. D., Reis B. Y. Brownstein J. S. (2008). HealthMap: Global infectious disease monitoring through automated classification and visualization of internet media reports. *Journal of the American Medical Informatics Association*, 15, 150-157

German R.R. (2000). Sensitivity and predictive value positive measurements for public health surveillance systems. *Epidemiology*, 11, 720-727

Green M. S. & Kaufman Z. (2005). Syndromic surveillance for early location of terrorist incidents outside of residential areas. *Morbidity and Mortality Weekly Report*, 54, 189, http://www.cdc.gov/mmwr/preview/mmwrhtml/su5401a35.htm ,Internet accessed on July 14 2007

Green M. S. (2009). Book: Public Health Aspects of Bioterrorism. Oxford Textbook of Public Health, 5th Edition

Harcourt S. E., Fletcher J., Loveridge P., Bains A., Morbey R., Yeates A., McCloskey B., Smyth B., Ibbotson S., Smith G. E., & Elliot A. J. (2012). Developing a new syndromic surveillance system for the London 2012 Olympic and Paralympic Games. *Epidemiology and Infection*, 140(*12*), 2152-2156

Hartley D. M., Nelson N. P., Walters R., Arthur R., Yangarber R., Madoff L., Linge J. P., Mawudeku A., Collier N., Brownstein J. S., Thinus G., & Lightfoot N. (2010). Landscape of international event-based biosurveillance. *Emerging Health Threats Journal*, 3

Hope K. G., Merritt T. D., Durrheim D. N., Massey P. D., Kohlhagen J. K., Todd K. W., & D'Este C. A. (2010). Evaluating the utility of emergency department syndromic surveillance for a regional public health service. *Communicable Diseases Intelligence*, 34(*3*), 310-318

Kaluski D. N., Barak E., Kaufman Z., et al (2006). A large food-borne outbreak of group A streptoccocal pharyngitis in an industrial plant: potential for deliberate contamination. *Israel Medical Association Journal*, 8,824

Kang M., Zhong H., He J., Rutheford S., & Yang F. (2013). Using google trends for influenza surveillance in south China. *PLoS One*, 8(*1*)

Kass-Hout T. A., Buckeridge D., Brownstein J., Xu Z., McMurray P., Ishikawa C. K., Gunn J., & Massoudi B. L. (2012). Self-reported fever and measured temperature in emergency department records used for syndromic surveillance*. Journal of the American Medical Informatics Association*, 19(*5*), 775-776

Kaufman Z., Wong W. K., Peled-Leviathan T. et al. (2007). Evaluation of a syndromic surveillance system using the WSARE algorithm for early detection of an unusual, localized summer outbreak of influenza. Implications for bioterrorism surveillance. *Israel Medical Association Journal*, 9, 3-7

Kortepeter M. G., Pavlin J. A., Gaydos J. C., Rowe J. R., Kelley P. W., Ludwig G., McKee K. T. Jr., & Eitzen E. M. (2000). Surveillance at US military installations for bioterrorist and emerging infectious disease threats. *Military Medicine*, 165, 2-3

Mandl K. D., Overhage J. M., Wagner M. M., Lober W. B., Sebastiani P., et al. (2004). Implementing syndromic surveillance: a practical guide informed by the early experience*. Journal of the American Medical Informatics Association*, 11, 141-150

Morse S. S. (2012). Public health surveillance and infectious disease detection. Biosecurity and Bioterrorism: Biodefence. *Strategy, Practice, and Science*, 10(*1*)

Nature website: www.nature.com/avianflu/google-earth

Nelson N. P., Brownstein J. S., & Hartley D. M. (2010). Event-based biosurveillance of respiratory disease in Mexico, 2007-2009: connection to the 2009 influenza A (H1N1) pandemic? *EuroSurveillance*, 15(*30*)

Paterson B. J., Kool J. L., Durrheim D. N., & Pavlin B. (2012). Sustaining surveillance: evaluating syndromic surveillance in the Pacific. *Global Public Health*, 7(*7*), 682-694

Peter W., Najmi A.H., & Burkom H.S. (2011). Reducing false alarms in syndromic surveillance. *Statistics in Medicine*, 30(*14*), 1665-1677

Plagianos M. G., Wu W. Y., McCullough C., Paladini M., Lurio J., Buck M. D., Calman N., & Soulakis N. (2011). Syndromic surveillance during pandemic (H1N1) 2009 outbreak, New York, New York, USA. *Emerging Infectious Diseases*., 17(*9*), 1724-1726

ProMED-mail website: http://www.promedmail.org/

Qian Y. H., Su J., Shi P., He E. Q., Shao J., Sun N., Zu R. Q., & Yu R. B. (2011). Attempted early detection of influenza A (H1N1) pandemic with surveillance data of influenza-like illness and unexplained pneumonia. *Influenza and Other Respiratory Viruses*, 5(*6*), 479-486

Reeder B., Revere D., Olson D. R., & Lober W. B. (2011). Perceived usefulness of a distributed community-based syndromic surveillance system: a pilot qualitative evaluation study. *BMC Research Notes*, 14(*4*), 187

Reingold A. (2003). If syndromic surveillance is the answer, what is the question? *Biosecurity and Bioterrorism*, 1,1-5

Rolka H., Burkom H., Cooper G. F., Kulldorff M., Madigan D., & Wong W. K. (2007). Issues in applied statistics for public health bioterrorism surveillance using multiple data streams: Research needs. *Statistics in Medicine*, 26, 1834-1856

Samoff E., Waller A., Fleischauer A., Ising A., Davis M. K., Park M., Haas S. W., DiBiase L., & MacDonald P. D. (2012). Integration of syndromic surveillance data into public health practice at state and local levels in North Carolina. *Public Health Reports*, 127(*3*),310-317

Savage R., Chu A., Rosella L. C., Crowcroft N. S., Varia M., Policarpio M. E., Vinson N. G., Winter A. L., Hay K., Davies R. F., Gemmill I., Willison D., & Johnson I. (2012). Perceived usefulness of syndromic surveillance in Ontario during the H1N1 pandemic*. Journal of Public Health: Oxford*, 34(*2*), 195-202

Scarpino S. V., Dimitrov N. B. & Meyers L. A. (2012). Optimizing provider recruitment for influenza surveillance networks. *PLOS*, 8(*4*)

Severi E., Heinsbroek E., Watson C., & Catchpole M. (2012). Infectious disease surveillance for the London 2012 Olympic and Paralympic Games. *EuroSurveillance*, 17(*31*)

Smith S., Smith G. E., Olowokure B., Ibbotson S., Foord D., Maguire H., Pebody R., Charlett A., Hippisley-Cox J., & Elliot A. J. (2011). Early spread of the 2009 influenza A(H1N1) pandemic in the United Kingdom--use of local syndromic data, May-August 2009. *EuroSurveillance*, 16(*3*) van den Wijngaard C. C., van Pelt W., Nagelkerke N. J., Kretzschmar M., & Koopmans M. P. (2011). Evaluation of syndromic surveillance in the Netherlands: its added value and recommendations for implementation. *EuroSurveillance*, 16(*9*)

Wagner M. M., Moore A. W., & Aryel R. M. (2006). Book: Handbook of Biosurveillance, 301

Westheimer E., Paladini M., Balter S., Weiss D., Fine A., & Nguyen T. Q. (2012). Evaluating the New York City Emergency Department Syndromic Surveillance for Monitoring Influenza Activity during the 2009-10 Influenza Season. *PLoS Currents*, 4

Xing J., Burkom H., & Tokars J. (2011). Method selection and adaptation for distributed monitoring of infectious diseases for syndromic surveillance. *Journal of Biomedical Informatics*, 44(*6*), 1093-1101