

Strengthening the Early-Warning Function of the Surveillance System: The Macedonian Experience

Elisaveta STIKOVA^{1,2}, Dragan GJORGJEV^{1,2}, and Zarko KARADZOVSKI²

¹*National Public Health Institute, Skopje, Republic of Macedonia*

²*Medical Faculty, University "Ss Cyril and Methodius," Skopje, Republic of Macedonia*

Abstract. Epidemics and pandemics can place sudden and intense demands on health systems. The world requires a global system that can identify and contain public health emergencies rapidly and reduce panic and disruption of trade, travel, and society in general. Strengthening public health preparedness requires establishing an integrated global alert and response system for epidemics and other public health emergencies along the lines of the World Health Organization's International Health Regulations. The revised International Health Regulations provide a global framework to address these needs through a collective approach to the prevention, detection, and timely response to any public health emergency of international concern. A standardized approach for readiness and response to major epidemic-prone diseases should be developed. An early-warning and rapid-alert system is one of the possibilities to improve readiness at the local, regional, national, and international level to limit the spread of disease and to reduce health, economic, and social damage. The Republic of Macedonia, with World Health Organization support, has implemented an early-warning system (ALERT) for priority communicable diseases to complement the routine surveillance system that reports individual confirmed cases. ALERT relies on reporting of eight syndromes by primary care facilities. Data are analyzed weekly at the regional level and transmitted to national epidemiologists. It is perceived to be a simple and flexible tool for detecting and triggering timely investigation and control of outbreaks. ALERT was identified as a useful instrument for forecasting and detecting the start of the influenza season.

1. Introduction

We live in a world of new and evolving threats [1-7]. There are six clusters of threats with which the world must be concerned now and in the decades ahead: war between states; violence within states, including civil wars, large-scale human rights abuses and genocide; poverty, infectious disease, and environmental degradation; nuclear, radiological, chemical, and biological weapons; terrorism; and transnational organized crime [8, 9].

In today's world, a threat to one is a threat to all. Globalization means that a major terrorist attack anywhere in the industrial world would have devastating consequences for the well-being of millions in the developing world. Any one of 700 million international airline passengers every year can be a carrier of a deadly infectious disease.

At the beginning of the 21st century, the world still confronts:

- The emergence of new or newly recognized pathogens such as Nipah virus, Ebola virus, Marburg virus, severe acute respiratory syndrome (SARS) corona virus, and influenza A/H5N1 virus
- The recurrence of well-characterized epidemic-prone diseases such as cholera, dengue, influenza, measles, meningitis, shigellosis, and yellow fever
- The accidental release or deliberate use of biological agents such as anthrax [7]

Globally, from 1998 to December 2006, the World Health Organization (WHO) identified 2,031 syndromes and diseases that were potential public health emergencies of international concern. Of these events, 195 subsequently were verified in the WHO European Region [10].

TABLE 1. Syndromes and Diseases Associated with Verified Events That Were Potential Public Health Emergencies of International Concern in the WHO European Region, 1998–2006

Syndrome/Disease	Number of Events	Percent of Total
Foodborne or waterborne diseases	42	22
Acute respiratory syndrome	34	17
Acute hemorrhagic fever syndrome	32	16
Other zoonotic diseases	20	10
Acute neurological syndrome	16	8
Vector-borne disease	11	6
Vaccine-preventable diseases	10	5
Influenza (A/H5 virus)	2	1
Influenza (novel virus, not H5)	2	1
Cholera	4	2
Yellow fever	3	2
Plague	2	1
Others	8	4
Unknown	9	5
Total	195	100

In addition to the events described in [Table 1](#), 10 member states in the European Region reported 34 cases of SARS, including one death, from February through July 2003. This figure corresponds to 4% of the cases reported worldwide over the same period.

Communicable diseases in the European Region account for 9% of the disease burden measured in disability-adjusted life years. This is largely attributable to high rates of tuberculosis and growing rates of HIV infection, particularly in central and eastern European countries and in central Asia, and to emerging and reemerging epidemic-prone diseases. Some of the most prominent public health programs currently being undertaken are the eradication of smallpox, the ongoing efforts to eradicate poliomyelitis and to eliminate measles, the Expanded Programme on Immunization, the Stop TB Partnership, the coordination of the global epidemic response to control SARS, and the ongoing efforts to contain the spread of influenza A/H5N1 virus (avian influenza) and to prepare for pandemic influenza.

We must be aware, however, that widening development gaps, the collapse of public health infrastructure, poverty, urbanization, civil strife, environmental change and degradation, and the globalization of travel and trade can contribute to the new challenges posed by epidemic-prone and emerging communicable diseases worldwide.

These are reasons for public health-capacity building at the local, national, and international level and strengthening of public health preparedness and response systems around the world [11, 12].

Avian influenza is a major challenge for the international community and a real public health threat. Globally, as of June 19, 2008, 385 laboratory-confirmed human cases of influenza A/H5N1 virus infection, including 243 fatal cases (case-fatality rate about 60%), had been registered in 15 member states. In the European Region in 2006, 20 human cases including nine deaths were reported in Turkey (12 cases and four deaths) and Azerbaijan (eight cases and five deaths) [13].

Many international organizations, including WHO, and experts are working together to coordinate activities regarding key actions, including controlling avian influenza in animals and reducing opportunities for human infection; strengthening the early-warning system; containing or delaying the spread at the source; reducing morbidity, mortality, and social disruption; and conducting research to guide response measures.

The challenges that epidemic-prone diseases, including avian influenza, pose to WHO are:

- How to minimize the risk of international spread
- How to assist countries in preparing for and controlling epidemics
- How to coordinate and focus global resources when no single institution has the necessary capacity [14, 15]

The revised International Health Regulations (IHR) [4], which entered into force in June 2007, provide a legal framework to assist countries in protecting the health of their populations against any potential public health emergency of international concern, implementing the necessary measures, and contributing to making the world more secure [16, 17]. National and international partnerships will maximize the benefit of strengthening surveillance and response [18, 19]. To ensure the timely detection of events that are potential public health emergencies of international concern, the WHO Regional Office for Europe, aside from relying on official reports from national health authorities, systematically screens a wide range of formal and informal sources of information in several languages.

The monitoring and control of communicable diseases are facilitated by well-functioning surveillance systems. Surveillance systems provide information for early detection of potential outbreaks and help to identify disease trends, risk factors, and the need for interventions [20, 21]. They provide information for priority setting, planning, implementation, resource allocation, and for evaluating preventive programs and control measures. Surveillance systems are set up to detect and control communicable diseases in humans regardless of the cause and manner of transmission. Their principal aim is to prevent further transmission of the disease to other persons by epidemiologic investigation [22, 23].

The timely detection of outbreaks at the regional and national level is a priority function of communicable disease surveillance systems. In the process of implementing its IHR [4], WHO included the requirement for member states to maintain an adequate core capacity to detect and respond to significant public health threats. This requires that member states develop effective early-warning systems and strengthen their investigation and response capabilities [24, 25].

Since December 2000, central and eastern Europe and the Baltic countries have worked together to strengthen surveillance and early-warning and response systems [26]. To ensure a rapid and effective response to events (including emergencies) related to communicable diseases, an early-warning and response system has been put in place in Macedonia. This is a Web-based system linking the 10 Regional Public Health Institutes (RPHIs) with the National Public Health Institute (NPHI) and the Ministry of Health.

2. Overview of Syndromic Surveillance

Innovative electronic surveillance systems are being developed to improve early detection of outbreaks attributable to biologic and other causes of threats. A review of the rationale, goals, definitions, and realistic expectations for these surveillance systems is a crucial first step toward establishing a framework for further research and development in this area [27].

Syndromic surveillance has been used for early detection of outbreaks; to follow the size, spread, and tempo of outbreaks; to monitor disease trends; and to provide reassurance that an outbreak has not occurred [28]. Syndromic surveillance systems seek to use existing health data in real time to provide immediate analysis and feedback to those charged with the investigation and follow-up of potential outbreaks. Optimal syndrome definitions for continuous monitoring and specific data sources best suited to outbreak surveillance for specific diseases have not been determined [29, 30]. Broadly applicable signal-detection methodologies and response protocols that would maximize detection while preserving scant resources are being sought [31, 32].

Stakeholders need to understand the advantages and limitations of syndromic surveillance systems. Syndromic surveillance systems might enhance collaboration among public health agencies, health-care providers, information-systems professionals, academic investigators, and industry. However, syndromic surveillance does not replace traditional public health surveillance, nor does it substitute for direct physician reporting of unusual or suspect cases of public health importance [33, 34].

Specific definitions for syndromic surveillance are lacking, and the name itself is imprecise. Diverse names used to describe public health surveillance systems for early outbreak detection include:

- Early-warning systems
- Prodrome surveillance
- Outbreak-detection systems
- Information system-based sentinel surveillance
- Biosurveillance systems
- Health-indicator surveillance
- Symptom-based surveillance

However, syndromic surveillance is the term that has persisted.

The fundamental objective of syndromic surveillance is to identify illness clusters early, before diagnoses are confirmed and reported to public health agencies, and to

mobilize a rapid response, thereby reducing morbidity and mortality. Syndromic surveillance aims to identify a threshold number of early symptomatic cases, allowing detection of an outbreak earlier than would conventional reporting of confirmed cases [35]. The ability of syndromic surveillance to detect outbreaks earlier than conventional surveillance methods depends on such factors as the size of the outbreak, the population dispersion of those affected, the data sources and syndrome definitions used, the criteria for investigating threshold alerts, and health-care providers' ability to detect and report unusual cases [36].

Syndromic surveillance focuses on the early symptom (prodrome) period before clinical or laboratory confirmation of a particular disease and uses both clinical and alternative data sources. Strictly defined, syndromic surveillance gathers information about patients' symptoms (e.g., cough, fever, shortness of breath).

The analytic challenge in using syndromic surveillance for outbreak detection is to identify a signal corresponding to an outbreak or cluster amid substantial "background noise" in the data [37]. However, signal-detection methods have not yet been standardized. Temporal and spatio-temporal methods have been used to assess day-to-day and day and place variability of data from an expected baseline [38, 39].

3. International Health Regulations and Surveillance Systems

The new IHR [4] entered into force on June 15, 2007. The IHR are (1) a legal framework for surveillance of international health threats, (2) a procedure for WHO's recommendations to counteract public health emergencies of international concern, and (3) a set of rules concerning routine measures against international disease spread. Here we will briefly review the first of these features.

In the globalized world, diseases can spread far and wide via international travel and trade. A health crisis in one country can affect livelihoods and economies in many parts of the world. Such crises can result from emerging infections such as SARS or a new human influenza pandemic. The IHR also can apply to other public health emergencies such as chemical spills, leaks, and dumping or nuclear accidents [19]. The IHR aim to limit interference with international traffic and trade, ensuring public health through the prevention of disease spread. The IHR require countries to report certain disease outbreaks and public health events to WHO [5, 6, 40]. Building on the unique experience of WHO in global disease surveillance, alert, and response, the IHR define the rights and obligations of countries to report public health events and establish a number of procedures that WHO must follow in its work to uphold global public health security. Within the framework of the IHR [4], seven areas of work have been identified to achieve the goals described above. The first area of work aims to strengthen global partnerships; the second and third address countries' capacities to meet IHR requirements; the fourth and fifth areas of work focus on surveillance, prevention, control, and response systems at the international level; and the sixth and seventh address awareness of rules and legal aspects and measuring progress (Table 2).

TABLE 2. Seven Areas of Work to Guide IHR Implementation

Area of Work	Goal
Global partnership 1. Foster global partnerships	WHO, all countries and all relevant sectors (e.g. health, agriculture, travel, trade, education, and defence) are aware of the new rules and collaborate to provide the best available technical support and, where needed, mobilize the necessary resources for effective implementation of IHR (2005).
Strengthen national capacity 2. Strengthen national disease surveillance, prevention, control and response systems	Each country assesses its national resources in disease surveillance and response and develops national action plans to implement and meet IHR (2005) requirements, thus permitting rapid detection and response to the risk of international disease spread.
3. Strengthen public health security in travel and transport	The risk of international spread of disease is minimized through effective permanent public health measures and response capacity at designated airports, ports and ground crossings in all countries.
Prevent and respond to international public health emergencies	
4. Strengthen WHO global alert and response systems	Timely and effective coordinated response to international public health risks and public health emergencies of international concern.
5. Strengthen the management of specific risks	Systematic international and national management of the risks known to threaten international health security, such as influenza, meningitis, yellow fever, SARS, poliomyelitis, food contamination, chemical and radioactive substances.
Legal issues and monitoring	
6. Sustain rights, obligations and procedures	New legal mechanisms as set out in the Regulations are fully developed, and upheld; all professionals involved in implementing IHR (2005) have a clear understanding of, and sustain, the new rights, obligations and procedures laid out in the Regulations.
7. Conduct studies and monitor progress	Indicators are identified and collected regularly to monitor and evaluate IHR (2005) implementation at national and international level. WHO Secretariat reports on progress to the World Health Assembly. Specific studies are proposed to facilitate and improve implementation of the Regulations.

There are three groups of events that may constitute public health emergencies of international concern:

Group 1. A case of the following diseases is unusual or unexpected and may have serious public health effects and thus shall be reported:

- Smallpox
- Poliomyelitis due to wild-type poliovirus
- Human influenza caused by a new subtype
- Severe acute respiratory syndrome (SARS)

Group 2. An event involving the following diseases shall always lead to use of the algorithm because these diseases have demonstrated the ability to have serious public health effects and to spread rapidly internationally:

- Cholera
- Pneumonic plague
- Yellow fever
- Viral haemorrhagic fevers (Ebola, Lassa, Marburg)
- West Nile fever
- Other diseases that are of special national or regional concern, e.g., dengue fever, Rift valley fever, and meningococcal disease

Group 3. Any event of potential international public health concern, including those of unknown causes or sources and those involving events or diseases other than those listed above shall lead to use of the algorithm and criteria from Annex 2 of the IHR [4], e.g.:

- Anthrax antimicrobial resistance
- Arboviruses (e.g., Rift valley fever, West Nile fever)
- Dengue
- HIV/AIDS
- Malaria
- Measles and other vaccine-preventable diseases
- Meningococcal meningitis
- Tuberculosis
- Severe emerging zoonoses affecting humans

4. Early-Warning Alert Response System in the Republic of Macedonia – Results

The Republic of Macedonia has population of about two million people. The territory is divided into 123 municipalities. In 1993, in the framework of the new public health system, one national and 10 RPHIs were established. They adopted a previously established system for routine surveillance for registration and notification of communicable diseases, which included 62 diseases. In 2004, new recommendations for protecting the population from communicable diseases were adopted, and a new obligatory list of 48 diseases was introduced.

Past work has shown an absence of case definitions, a lack of laboratory confirmation, significant delays in reporting between surveillance levels, delayed and inadequate outbreak response, lack of feedback to reporting level, lack of training, lack of analysis at the peripheral level, under-reporting of unconfirmed cases or outbreaks, and poor motivation of healthcare staff. In 2005, the NPPI, with WHO support, started to develop a syndromic early-warning alert response system (EWARS), called ALERT, with an ultimate goal of strengthening the early detection of outbreaks of epidemic-prone and emerging infectious diseases.

A panel of Macedonian experts in the field of epidemiology and microbiology has assessed the needs and priorities for disease surveillance using a standardized questionnaire. The aim of this assessment was to define what the most important diseases are in Republic of Macedonia, from their point of view. The results of the assessment are shown in [Table 3](#).

TABLE 3. Results of Assessment Performed Among Epidemiologists and Microbiologists Targeted to Define Priorities for Disease Surveillance

Rank	Microbiologist	Epidemiologist
1	HIV ⁺	Influenza
2	Influenza	HIV ⁺
3	Salmonellosis	AIDS
4	<i>Toxoinfectio alimentaris</i>	Enterocolitis
5	AIDS	Hepatitis A
6	Hepatitis A	<i>Toxoinfectio alimentaris</i>
7	Brucellosis	Hepatitis B
8	Hepatitis B	Tuberculosis
9	Shigellosis	Salmonellosis
10	Enterocolitis	Brucellosis
11	Tuberculosis	Hepatitis-nonclassified
12	Hepatitis C	Hepatitis C
13	Hepatitis-nonclassified	Shigellosis
14	SARS	Varicella
15	<i>Hemophilus influenza B</i>	Meningitis epidemica

TABLE 4. Syndromic Events That Are Included in the Early-Warning Alert Response System and Their Case Definitions

Number	Syndromic Event	Case Definition
1	Suspicion of an upper respiratory tract infection	Rhinitis (serious or purulent nose secretions), dry coughing, throat redness and/or throat pain, with or without swelling and painful sensitivity of the lymph glands on the neck
2	Suspicion of a lower respiratory tract infection	Increased body temperature, coughing with or without sputum (productive or nonproductive), acute dyspnea, with or without general exhaustion and chest pains
2-a	Suspicion of acute lower respiratory tract infection in children younger than 5	Every child younger than 5 with the following signs or symptoms: cough or difficult breathing, breathing 50 or more times per minute for infants aged 2 months to 1 year, breathing 40 or more times per minute for children aged 1–5 years
3	Suspicion of rash fevers, excluding varicellae	Acute beginning, increased body temperature and maculopapular-papulose rash, with or without throat redness and/or throat pain, hyperaemia of the upper respiratory tract, cervical lymphadenopathy
4	Suspicion of meningitis/meningo-encephalitis	Acute beginning, increased body temperature, heavy and diffuse headache, vomiting without nausea, painful neck stiffness, with or without photophobia, nausea, pharyngitis with exudate, consciousness disorders, neurological attacks, petechial or purpurial rash
5	Acute watery diarrhea	Dehydration, stomach pains, stomach cramps, with or without vomiting
6	Acute bloody diarrhea	Mucous stools containing (visible) blood in the previous 24 h, with or without dehydration, stomach pain, and cramps
7	Suspicion of acute infective hepatitis	Acute jaundice (yellow skin and sclera colour), weakness and exhaustion, dark urine, light stool, anorexia, nausea, pain below the right rib arch
8	Suspicion of acute hemorrhagic fever	Acute beginning of fever in a period shorter than 3 weeks in a very ill patient and any two of the following signs/symptoms: petechial or purpurial rash, nose bleeding, hematemesis, hemoptysis, oliguria or anuria, bloody stool, any other hemorrhagic manifestation without known cause

A list of eight health events was included in ALERT on the basis of the results of this study. To unify the reporting process for all participants in the system, a case definition is necessary. A case definition is a combination of symptoms and signs that have to be present in a patient for the patient to be placed in a certain category. The list of eight syndromes that are part of the national EWARS are presented in Table 4 with case definitions for each.

After the decision was made about the syndromic diseases that would be included in the EWARS, the next challenge facing the expert panel was to make a decision about the threshold limits. Two different approaches have been used for threshold definition. Regarding the severity of the disease and expecting threats for three of the syndromic diseases, the fixed number of cases was used. For the other five syndromic diseases, threshold limits were established on the basis of previous epidemiologic data and already-registered cases. Using these two methodologies, threshold limits were established for all ten surveillance units. They are shown in Table 5.

TABLE 5. Threshold Limits for All Syndromic Diseases Included in the Early-Warning Alert Response System

	URTI	LRTI	RF	M&ME	AWD	ABD	AVH	AHF
Stip	470	100	3	1	90	1	9	1
Strumica	305	102	2	1	90	1	6	1
Bitola	520	122	6	1	75	1	11	1
Ohrid	700	200	3	1	80	1	6	1
Prilep	330	56	4	1	35	1	4	1
Veles	930	450	5	1	215	1	8	1
Kocani	580	140	5	1	55	1	7	1
Skopje	2,800	300	20	1	700	1	8	1
Kumanovo	870	234	5	1	176	1	7	1

URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; RF, rash fever; M&ME, meningitis/meningo-encephalitis; AWD, acute watery diarrhea; ABD, acute bloody diarrhea; AVH, acute infective hepatitis; AHF, acute hemorrhagic fever.

Anytime the defined number of syndrome cases listed in Table 5 is exceeded, the alert will go out automatically. For three groups of syndromic events – meningitis and meningoencephalitis, acute bloody diarrhea, and acute hemorrhagic fever – an alert will be declared after every registered case. For the other five syndromic events, an alert will be declared after the defined number of cases specific for each region of surveillance is exceeded.

5. Reporting and Surveillance Units

Reporting units all are comprised of primary care physicians who work in different segments of the health system in the Republic of Macedonia. Currently there are 1,014 primary health units, but only 30–40% of them are included in EWARS. Through a written, standardized surveillance form, they report weekly the aggregated number of new cases in four age groups to the corresponding collecting units at the municipality level or directly to the local and regional surveillance units. They send aggregated data by mail or fax. There are ten regional surveillance units equipped and trained to process

data from the reporting units. The regional surveillance units are RPHIs and their epidemiologic departments. At the regional level, data are computerized and electronically transmitted to the NPHI. The NPHI prepares a report and sends it to the Ministry of Health and initiates and performs all requested interventions and additional activities. Feedback is sent electronically from the NPHI to the regional institutes. In addition, the RPHIs can send information to the reporting units. Epidemiologists from the RPHIs and the NPHI are responsible for data control and regularity, reporting any unusual changes and undertaking urgent activities.

A program has been developed using public-domain software for relational data entry (EpiData) and production of interactive reports (EpiInfo). It includes features for data entry (with quality checks) at the RPHI level and electronic transfer of records to the NPHI. It provides links with Excel and Word. The application produces a weekly epidemiologic bulletin in Word and allows interactive browsing of tables, charts, and maps in HTML format. The system generates alert reports based on disease-specific thresholds. The communicable diseases surveillance system in the Republic of Macedonia is shown in Fig. 1.

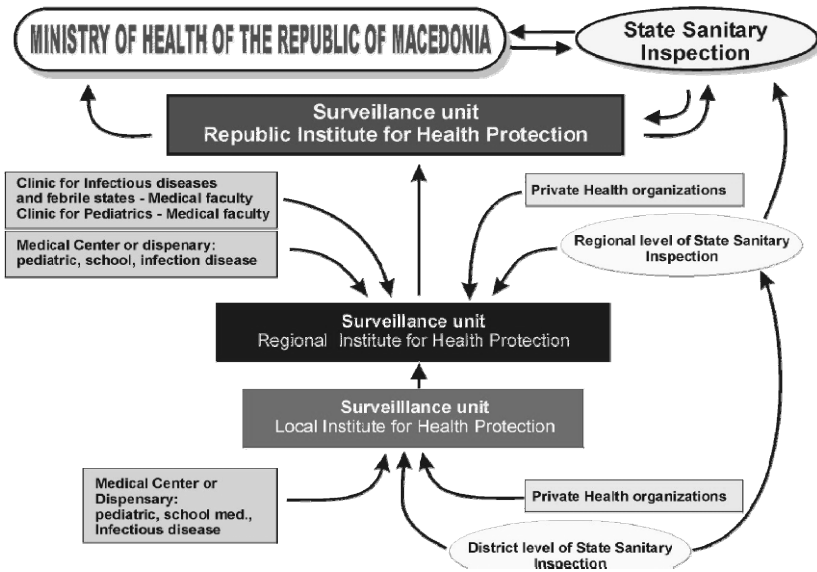


Figure 1. Early-warning alert response surveillance system in the Republic of Macedonia.

6. Discussion

The system is considered simple and flexible. Users emphasized that ALERT has improved communication between reporting and surveillance units and strengthened the surveillance network. The acceptability of the system is higher at the national level mainly because data from ALERT are received in a timely fashion, which allows the surveillance department at RIPH to monitor potential outbreaks at the national level.

Using syndromic case definitions allows remote areas that do not usually report, because of lack of confirmation capacity, to report, thereby providing valuable early-warning information. Moreover, for some rare and serious diseases such as those targeted by the hemorrhagic fever syndrome, ALERT is used as zero reporting.

Syndromic surveillance is simple and often the only available surveillance tool at the primary health care level when laboratory confirmation of disease is not possible [41]. It allows detection of potential outbreaks of targeted diseases earlier than with the diagnosis-based routine surveillance system and leads to field investigations for confirmation and control [19, 20]. Experience has shown that reporting units at the primary health care level are not the most appropriate source of notification for early detection of some epidemic-prone diseases. Some specific syndromes may be seen first in emergency departments, private clinics, or pharmacies [21].

Syndromes such as hemorrhagic fever, as an indicator for hantavirus or Crimean-Congo hemorrhagic fever, are sensitive and specific enough to detect outbreaks. Because it is a serious and uncommon syndrome, each individual case reported is an alert and triggers an action. For other diseases, such as influenza, targeted by acute respiratory illness, the alert for action is a rise in reported syndrome cases, indicating the onset of the influenza season. ALERT was able to detect this increase during the 2008 season. However, other categories of syndromes have not been sensitive or specific enough to detect outbreaks in a timely fashion. Timely detection of public health threats relies on proper analysis of early-warning data at each level. ALERT software produces automated tables, charts, and maps highlighting increases. Epidemiologists should use those resources to trigger actions when individual confirmed cases are reported.

The evaluation of the effects of implementation of the pilot project for the EWARS have shown us that sensitivity and usefulness should be increased. There are many possible ways to do this, such as adding emergency departments as notification sources for some syndromes, better defining the role of the laboratory to confirm the suspicion of outbreaks, revising the list and definition of syndromes to adjust their sensitivity and specificity for detecting the targeted diseases, and strengthening data analysis through training.

Our experience shows that the role of training should not be overlooked. It is a change of paradigm, which is impossible to induce by simply implementing new surveillance tools, difficult to induce by short training, and best induced by coaching programs such as field-epidemiology training programs.

Although the process for implementing the EWARS was piloted by the ministry of health, the ALERT reporting procedures were not incorporated into public health laws. ALERT does not interrupt the continuity of the existing reporting system, regulated by law. All obligations and responsibilities prescribed by it still remain. The final goal is, by comparing the advantages and disadvantages of both systems, to enable the creation (establishment) of a new, combined system that would be more functional, safer, and more economically sustainable. On the basis of our experiences, the obligation for syndromic reporting through EWARS will be laid down in our national law. Some additional measures, such as financial copayment for reporting units, should be discussed.

References

1. World Health Organization. The World Health Report 2007 – a safer future: global public health security in the 21st century. Geneva: World Health Organization; 2007. Available at: <http://www.who.int/whr/2007/en/index.html>.
2. World Health Organization. Enhancing health security: the challenges in the WHO European region and the health sector response. Copenhagen: World Health Organization Regional Office for Europe; 2006. Available at: euro.who.int/Governance/RC/RC56/20060623_29.
3. Stikova, E. Public health threats and disaster management. In: Donev, D., Pavlekovic, G., Kragelj, L., editors. Health protection and diseases prevention. Hellweg Lage, Germany: Hans Jacobs Publishing Company; 2007. pp. 746–772.
4. World Health Organization. Fifty-Eighth World Health Assembly. Resolution WHA58.3. Revision of the International Health Regulations. Geneva: World Health Organization; 2005. Available at http://www.who.int/gb/ebwha/pdf_files/WHA58/WHA58_3-en.pdf.
5. Baker, M.G., Fidler, D.P. 2006. Global public health surveillance under the new international health regulations. *Emerg. Infect. Dis.* **12**:1058–1065.
6. Gill, N. 2002. Public health emergencies of international concern and the revision of the International Health Regulations – latest update. *Eurosurveillance*. Available at <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2136>.
7. Rockenschaub, G., Pukkila, J., Profili, M.C., editors. Towards health security. A discussion paper on recent health crises in the WHO European Region. Copenhagen: World Health Organization Regional Office for Europe; 2007. Available at: http://www.euro.who.int/InformationSources/Publications/Catalogue/20070427_1.
8. Multi-hazard identification and risk assessment. Washington, DC: Federal Emergency Management Agency; 1997. Available at: <http://www.fema.gov/library/viewRecord.do?id=2214>.
9. Risk reduction and emergency preparedness. WHO six-year strategy for the health sector and community capacity development. Geneva: World Health Organization; 2007. Available at: http://www.who.int/hac/techguidance/preparedness/emergency_preparedness_eng.pdf.
10. Hoyois, P., Below, J.-M., Guha-Sapir, D. Annual disaster statistical review: numbers and trends 2006. Brussels: Center for Research on the Epidemiology of Disasters; 2007. Available at: <http://www.em-dat.net/documents/Cred%20Crunch%209.pdf>.
11. Cummings, C.E., Stikova, E. Strengthening national public health preparedness and response to chemical, biological and radiological threats. Amsterdam: IOS Press; 2007.
12. Copola, D.P. Introduction to international disaster management. Burlington, MA: Butterworth-Heinemann; 2007. Available at: <http://books.google.com/books?id=s6oxEraqWWwC&pg=RA1-PA23&ots=Ok9au7c-j&dq=OFDA/CRED+International+Disaster+Database&ei=UyHxRrigPfI26wKpp9HrBg&sig=1dLUfv-xyoIXOxsdBnI93eiPnPk#PRA1-PA23,M1>.
13. Global alert and response (GAR). Cumulative number of confirmed cases of avian influenza A/(H5N1) reported to WHO. Geneva: World Health Organization; 2008. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_06_19/en/index.html.
14. Van Loock, F., Gill, O.N., Wallyn, S., Nicoll, A., Desenclos, J.C., Leinikki, P. 2002. Roles and functions of European Union Public Health Centre for Communicable Diseases and other threats to health. *Euro-surveillance*. Available at: <http://www.eurosurveillance.org/em/v07n05/0705-225.asp>.
15. World Health Organization. Fifty-Fourth World Health Assembly. Resolution WHA54.14. Global health security: epidemic alert and response. Geneva: World Health Organization; 2001. Available at: http://apps.who.int/gb/archive/pdf_files/WHA54/ea54r14.pdf.
16. World Health Organization. Fifty-Ninth World Health Assembly. Resolution WHA59.2. Application of the international health regulations. Geneva: World Health Organization; 2006. Available at: http://www.who.int/gb/ebwha/pdf_files/WHA59/WHA59_2-en.pdf.
17. Rodier, G., Hardiman, M., Plotkin, B., Ganter, B. 2006. Implementing the international health regulations (2005) in Europe. *Eurosurveillance*. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=664>.
18. Buehler, J.W., Hopkins, R.S., Overhage, J.M., Sosin, D.M., Tong, V., CDC Working Group. 2004. Framework for evaluating public health surveillance systems for early detection of outbreaks: recommendations from the CDC Working Group. *MMWR Recomm. Rep.* **53**:1–11.

19. European Center for Disease Prevention and Control. Surveillance of communicable diseases in the European Union, a long-term strategy 2008–2013. Available at: http://www.ecdc.europa.eu/en/activities/surveillance/Pages/StrategiesPrinciples_Long-termStrategy.aspx.
20. Krause, G., Benzler, J., Reiprich, G., Görden, R. 2006. Improvement of a national public health surveillance system through use of a quality circle. *Eurosurveillance*. Available at: <http://www.Euro-surveillance.org/ViewArticle.aspx?ArticleId=659>.
21. Krause, G., Ropers, G., Stark, K. 2005. Notifiable disease surveillance and practicing physicians. *Emerg. Infect. Dis.* **11**:442–445.
22. Kaiser, R., Coulombier, D., Baldari, M., Morgan, D., Paquet, C. 2006. What is epidemic intelligence, and how is it being improved in Europe? *Eurosurveillance*. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2892>.
23. Reingold, A. If syndromic surveillance is the answer, what is the question? 2003. *Biosecur. Bioterror.* **1**:1–5.
24. Green, M.S., Kaufman, Z. 2002. Surveillance for early detection and monitoring of infectious disease outbreaks associated with bioterrorism. *Isr. Med. Assoc. J.* **4**:503–506.
25. Mykhalovskiy, E., Weir, L. 2006. The Global Public Health Intelligence Network and early warning outbreak detection: a Canadian contribution to global public health. *Can. J. Public Health* **97**:42–44.
26. Valenciano, M., Bergeri, I., Jankovic, D., Milic, N., Parli, M., Coulombier, D. 2004. Strengthening early warning function of surveillance in the Republic of Serbia: lessons learned after a year of implementation. *Eurosurveillance*. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=465>.
27. Wagner, M.M., Tsui, F.C., Espino, J.U., Dato, V.M., Sittig, D.F., Caruana, R.A., McGinnis, L.F., Deerfield, D.W., Druzdzal, M.J., Fridsma, D.B. 2001. The emerging science of very early detection of disease outbreaks. *J. Public Health Manag. Pract.* **7**:51–59.
28. Mostashari, F., Hartman, J. 2003. Syndromic surveillance: a local perspective. *J. Urban Health* **80**(Suppl 1):1–7.
29. Henning, K.J. Syndromic surveillance. In: Smolinski, M.S., Hamburg, M.A., Lederberg, J., editors. *Microbial threats to health: emergence, detection, and response*. Washington, DC: National Academies Press; 2003. pp. 309–350.
30. Buehler, J.W., Berkelman, R.L., Hartley, D.M., Peters, C.J. 2002. Syndromic surveillance and bioterrorism-related epidemics. *Emerg. Infect. Dis.* **9**:1197–1204.
31. Das, D., Weiss, D., Mostashari, F., Treadwell, T., McQuiston, J., Hutwagner, L., Karpati, A., Bornschlegel, K., Seeman, M., Turcios, R., Terebuh, P., Curtis, R., Heffernan, R., Balter, S. 2003. Enhanced drop-in syndromic surveillance in New York City following September 11, 2001. *J. Urban Health* **80**(Suppl. 1):i76–88.
32. Duchin, J.S. Epidemiological response to syndromic surveillance signals. 2003. *J. Urban Health* **80**(Suppl. 1):i115–116.
33. German, R.R., Lee, L.M., Horan, J.M., Milstein, R.L., Pertowski, C.A., Waller, M.N., Guidelines Working Group Centers for Disease Control and Prevention (CDC). 2001. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *MMWR Recomm. Rep.* **50**(RR13):1–36.
34. Paquet, C.L., Coulombier, D., Kaiser, R., Ciotti, M. 2006. Epidemic intelligence: a new framework for strengthening disease surveillance in Europe. *Eurosurveillance* **11**:212–214.
35. Pavlin, J.A. 2003. Investigation of disease outbreaks detected by syndromic surveillance systems. *J. Urban Health* **80**(Suppl 1):i107–114.
36. Heffernan, R., Mostashari, F., Das, D., Karpati, A., Kullendorff, M., Weiss, D. 2004. Syndromic surveillance in public health practice, New York City. *Emerg. Infect. Dis.* **10**:858–864.
37. Heymann, D.L., Rodier, G. 2001. Hot spots in a wired world: WHO surveillance of emerging and re-emerging infectious diseases. *Lancet Infect. Dis.* **1**:345–353.
38. Kluger, M.D., Sofair, A.N., Heye, C.J., Meek, J.I., Sodhi, R.K., Hadler, J.L. 2001. Retrospective validation of a surveillance system from unexplained illness and death: New Haven County, Connecticut. *Am J Public Health* **91**:1214–1219.
39. Centers for Disease Control and Prevention. Syndrome definitions for diseases associated with critical bioterrorism-associated agents. Atlanta: Centers for Disease Control and Prevention. Available at: <http://www.bt.cdc.gov/surveillance/syndromedef/index.asp>.
40. Guglielmetti, P., Coulombier, D., Thinus, G., Van Loock, F., Schreck, S. 2006. The early warning and response system for communicable diseases in the EU: an overview from 1999 to 2005. *Eurosurveillance* **11**:215–220.
41. Epidemic alert and verification: summary report for 2005. 2006. *Wkly. Epidemiol. Rec.* **81**:357–362.

Additional Reading

- Biological and chemical terrorism: strategic plan for preparedness and response. Recommendations of the CDC Strategic Planning Workgroup. *MMWR Recomm. Rep.* 2000;**49**(RR-4):1–14.
- Centers for Disease Control and Prevention (CDC). 2002. Syndromic surveillance for bioterrorism following the attacks on the World Trade Center–New York City, 2001. *MMWR Morb. Mortal. Wkly. Rep.* **51**(Spec. No.):13–15.
- Hutwagner, L., Thompson, W., Seeman, G.M., Treadwell, T. 2003. The bioterrorism preparedness and response early aberration reporting system (EARS). *J. Urban Health* **80**(Suppl. 1):89–96.
- Kaiser, R., Coulombier, D. Different approaches to gathering epidemic intelligence in Europe. *Eurosurveillance*. Available at: <http://www.eurosurveillance.org/ew/2006/060427.asp#1>.
- Ostroff, S.M. 2001. The epidemic intelligence service in the United States. *Eurosurveillance* **6**:34–36.
- Pavlin, J.A., Mostashari, F., Kortepeter, M.G., Hynes, N.A., Chotani, R.A., Mikol, Y.B., Ryan, M.A., Neville, J.S., Gantz, D.T., Writer, J.V., Florance, J.E., Culpepper, R.C., Henretig, F.M., Kelley, P.W. 2003. Innovative surveillance methods for rapid detection of disease outbreaks and bioterrorism: results of an interagency workshop on health indicator surveillance. *Am. J. Public Health* **93**:1230–1235.