SANDIA REPORT

SAND2014-19373
Unlimited Release
Printed August 2014

Infectious Disease Detection and Control in the Developing World

William Kessler
Reynolds M. Salerno

Prepared by
Sandia National Laboratories
Albuquerque, New Mexico 87185 and Livermore, California 94550

Sandia National Laboratories is a multi-program laboratory managed and operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Corporation, for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

Issued by Sandia National Laboratories, operated for the United States Department of Energy by Sandia Corporation.

Available to DOE and DOE contractors from
U.S. Department of Energy
Office of Scientific and Technical Information
P.O. Box 62
Oak Ridge, TN 37831

Telephone: (865) 576-8401
Facsimile: (865) 576-5728
E-Mail: reports@adonis.osti.gov
Online ordering: http://www.osti.gov/bridge

Available to the public from
U.S. Department of Commerce
National Technical Information Service
5285 Port Royal Rd.
Springfield, VA 22161

Telephone: (800) 553-6847
Facsimile: (703) 605-6900
E-Mail: orders@ntis.fedworld.gov
Online order: http://www.ntis.gov/help/ordermethods.asp?loc=7-4-0#online

SAND2014-19373
Unlimited Release
Printed August 2014

Infectious Disease Detection and Control in the Developing World

William Kessler
Reynolds M. Salerno
Cooperative Threat Reduction
Sandia National Laboratories
P.O. Box 5800
Albuquerque, New Mexico 87185-MS1363

Abstract

Outbreaks of infectious disease threaten the health, economy, and security of every nation on earth. The surveillance and identification of disease outbreaks are critical components in reducing the threat of epidemic diseases. However, current measures are insufficient to address global needs. In the developing world, where many novel and dangerous diseases originate, the need for a robust disease surveillance system is particularly vital, but the costs and effectiveness of most current systems are prohibitory. The two current approaches – single-disease surveillance (vertical surveillance) and multi-disease surveillance (broad-spectrum surveillance) – fail to empower indigenous healthcare systems with the ability to identify infectious diseases. This paper argues that a broad-spectrum surveillance system supplemented with frontline diagnostics tools will enable the healthcare systems in developing countries to identify, and better control, a wide range of known and unknown diseases. In turn, this capacity will significantly assisting the international community reduce the threat of infectious disease.

Outbreaks of infectious diseases (and especially novel, or re-emergent, diseases) have profound effects on local populations, nations, and beyond. Globally, these epidemics can be incredibly disruptive to social, economic, and political stability. In developing countries, sociopolitical stability is notoriously fragile and disease outbreaks often exacerbate current issues. The resulting destabilization is often a security threat to other nations. The impact of epidemic diseases would be significantly minimized if outbreaks could be effectively identified in situ, and responded to before they reached damaging proportions. Though this capacity is severely lacking in much of the developing world, many governments have developed guidelines on how to respond to threats to their national security due to biological hazards. Implementation of reactive response guidelines, however, is not a satisfactory conclusion as disease activity is a dynamic and constantly fluctuating system in the face of social and economic changes. Rather, there needs to be a fundamental policy shift aimed at equipping developing nations with the tools and techniques needed to identify disease outbreaks at their earliest stages so that they may be dealt with proactively.

The US has been slowly making advances in identifying public health as a critical topic in the national security discussion. In 2014, the US and more than 30 partner countries released the Global Health Security Initiative (GHSI) which targets the prevention, detection and response to infectious disease threats. The initiative attempts to address the need for native capabilities and priorities using biosurveillance and diagnostic testing via a regional accredited laboratory. Because US public health is explicitly linked to international public health, the US strategy should bolster other nations' abilities to detect and report disease outbreaks. This initiative is a step in the right direction, but does not do enough to emphasize the identification of novel and re-emergent pathogens. We seek to supplement the current US initiative on global health by advocating indigenous capacity building and POC diagnostics for novel and re-emergent pathogens.

The recent identification of MERS-CoV highlights the inability of many countries to identify novel pathogens indigenously. The first cases of MERS-CoV were documented in Jordan and Saudi Arabia as unidentified coronaviruses in March 2012. However, the United States Naval Medical Research Unit No. 3 (NAMRU-3), the International Committee on Taxonomy of Viruses (ICTV), and other institutions were relied on for analysis and identification, which was not completed until May 2013.[44][45] By October 2013, the number of cases had expanded to between 144 and 161 cases in 9 countries.[44] Although the US and other western countries invest in disease surveillance around the world, these investments are insufficient primarily because they fail to enable indigenous capacities to broadly detect and respond to unknown or reemerging diseases.

This paper scrutinizes the applicability of currently deployed disease surveillance systems and approaches internationally. Much of the debate surrounding these systems focuses on single-disease specificity versus broad-spectrum analysis. In practice, each of these methodologies has strengths and weaknesses, but a gap still exists: empowering the developing world– on their own– to identify destabilizing regional diseases as well as new and emerging diseases that threaten the globe. We seek to supplement current thinking on biosurveillance approaches by advocating the use of front-line, broad-spectrum diagnostic tools that are inexpensive, easy to use, and easy to access. These tools and the corresponding methodologies should additionally empower the local medical and veterinary communities in developing nations.

Current State of Disease Surveillance

Currently the United States, other developed countries, and a variety of private organizations fund an ever increasing number of healthcare initiatives around the world– primarily in under-served and developing nations. According to the World Bank, the official numbers on development assistance have ballooned from US$2.5 billion globally in 1990 to nearly US$21 billion in 2011.[18][47] Of these initiatives, funding for disease surveillance comprise a small fraction of total aid even though surveillance systems can have a major impact on disease control. Take polio eradication as an example: of the $1.052 billion operating budget of the Global Polio Eradication Initiative (GPEI), only 7% goes towards surveillance

and laboratory costs. The majority of funding for polio goes to vaccination efforts, which is effective if surveillance efforts can identify where vaccination efforts are needed.[10] Thus, ensuring disease surveillance systems are working efficiently and effectively is of the utmost importance.

External medical aid has long targeted the major disease problems —Tuberculosis, malaria, and AIDS— to the neglect of many others. This approach can be traced back to the 1978 Alma Ata Conference on Primary Health Care and the introduction of the "Health for All" principle. The "Health for All" principle outlined in the Alma Ata declaration was total primary healthcare for everyone, and encompassed access to curative care, disease prevention, immunization, and health education.[27] Though it was instituted with good intentions, the "Health for All" concept of community-based healthcare proved too cumbersome; the exorbitant cost and the required number of medical personnel were unattainable.[38] To combat shortfalls, healthcare providers were forced to become increasingly selective in what services were provided and what diseases were treated. Thus, the list of targetable diseases was repeatedly shortened. In the US, further selectivity resulted from a series of health goals outlined by the Surgeon General in 1979, and the policy of selecting national health objectives in the US has continued and expanded further to encompass health goals around the world.

In developing nations, this targeted funding is not conducive to strengthening the central healthcare system. This is because the non-governmental organizations (NGOs) and foreign donors pursue a narrow approach for a much broader healthcare coverage problem. Using polio as an example, in regions with the highest incidence, polio only accounts for 2% of years lived with disability, but overwhelmingly polio is the disease most commonly targeted by outside medical assistance. Conversely, developing countries prefer to prioritize other issues such as pneumonia diseases, malaria, diarrheal diseases, and malnutrition.[46] The targeted funding for a single disease ignores many of these other healthcare problems affecting the community. The consequence is mistrust from the local health community. The wariness of local healthcare providers about foreign donors affects collaborative efforts, delivery of care, and further research.[36] If advancements are going to be made in reducing the burden of infectious disease in the developing world, donors need to shift away from a narrow, single-target disease approach, thus reducing the mistrust among local healthcare workers and potentially increasing collaboration and the level of care. To reduce the emphasis on a limited number of predetermined diseases, epidemiological surveillance capacities need to be strengthened in order to shift towards early intervention and regulation of acute and chronic diseases. [12]

Presently, indigenous epidemiologic disease surveillance systems and methodologies in the developing world are fragmented and dysfunctional, at best. In regions that are considered hotbeds for new and emerging infectious diseases, many countries do not have any functioning protocol for reporting and responding to disease outbreaks. The few countries that do have a system in place, such as Ethiopia, are plagued by a lack of funding, budget shortfalls, and operational continuity issues.[33] However, all developing countries, in theory, have the basis for primitive surveillance networks; physicians and laboratories report pertinent information already, but implementation and integration of a standardized methodology has proven unwieldy.[20]

Vertical Surveillance Initiatives

The current biosurveillance systems in many countries focus on a single disease of interest, or consist of an ad-hoc conglomeration of several disease-specific systems operating in parallel.[2these single-disease biosurveillance systems are referred to as "vertical surveillance." These programs are generally a product of healthcare initiatives meant to control or eradicate specific diseases of interest. These initiatives can be characterized by high funding priority focused on a very specific area or disease. Vertical healthcare initiatives have had widespread success in a range of countries and socioeconomic settings, and surveillance has played a crucial role in each case. The eradication of smallpox and rinderpest virus, the only infectious diseases to ever be eliminated, as well as several others in the final steps of eradication, have been accomplished using vertical initiatives. On a global scale, vertical surveillance has undoubtedly proven successful. The initiative to eradicate smallpox required cooperation

from health organizations around the world, as did rinderpest, the only animal disease to be eradicated. Additionally, polio is soon to be eradicated using a similar approach.

A classic example of a vertical initiative's success in a developing-world setting is Yaws surveillance and control. Yaws is a tropical disease closely related to venereal syphilis (treponemes) that can cause a chronic degeneration of bone, muscles, and cartilage. In 1995, the WHO reported 2.5 million cases of treponematoses, of which the majority were Yaws.[43] In Ecuador, for instance, an extensive community-based surveillance program resulted in Yaws prevalence dropping from 96.3% of serological cases in 1993 to only 4.7% in 1998.[3]

Conversely, seemingly successful vertical surveillance initiatives have ended up failing quite spectacularly. In China, disease-specific surveillance systems operating in parallel can perform very differently. In total, there are 47 disease-specific surveillance systems at the province level and 20 at the county level. The systems primarily operate in a vertical management structure alongside the Chinese Center for Disease Control and Prevention (CDC) departments. The issues that arise from this structuring include: insufficient coordination between systems and departments, low efficiency, incompatible methodologies and terminologies, as well as a lack of data sharing across vertical programs.[42][14] Schistosomiasis is classified as a Class B reportable disease in China, and control and elimination efforts are ongoing. In Sichuan, China, Shistosomiasis elimination attained success in 25 counties by 2001. However, there was re-emergence of the disease achieved in several counties roughly 8 years after elimination. The re-emergence was confirmed by epidemiological surveys on humans and the snail vectors. The failed control efforts were attributed in part to a shifting sociopolitical climate that resulted in decreased and inconsistent surveillance and control policies.[14]

Another instance of vertical surveillance failing is the case of dengue in Cuba. A passive surveillance system was instituted in 1981 that ran until 1996, at which point there was no indication of dengue transmission in the municipality of Santiago de Cuba. Through vector surveillance and control measures, most, but not all, Cuban municipalities were free from the *A. aegypti* mosquito, the dengue vector. But, after a breakdown of the vector control and surveillance campaign in conjunction with increased immigration from endemic areas, dengue was reintroduced, and efforts to abort the growing epidemic ultimately failed. As a result, almost 3,000 people contracted dengue, including 200 cases of Dengue Hemorrhagic fever/Dengue shock syndrome, during a 1997 epidemic.[13]

Regardless of their track record for success, vertical initiatives come at a hefty price: the total cost for the renewed push to eradicate smallpox between 1967 and 1979 was $300 million (not accounting for inflation) while the annual budget for eradicating polio has been greater than $300 million since the year 2000. For the two year period 2012-2013, the polio eradication budget was $2.182b.[31][10] Part of this increase is attributable to the costs associated with the final steps of disease eradication, in which a huge amount of resources is focused on the last remaining pockets of disease. The rising costs of polio eradication show an obvious upward trend. The price tags on other diseases (HIV/AIDS, Malaria) with substantial vertical initiatives are just as high (malaria control funding topped out at an annual expense of $2.5b in 2012).[48] International funding for malaria control indicates a similar trend, signifying that exorbitant budgets are a necessary part of vertical initiatives. These figures indicate the total cost of the eradication program, and not simply the cost of surveillance. The WHO does not give definitive figures, however, they do indicate that the estimated cost for HIV/AIDS surveillance activities to be up to 10% of a given country's National AIDS budget.[40] This estimation can provide an idea of total global costs for vertical surveillance programs for other major diseases. Polio surveillance in total for 2012-2013, for example, was even substantially less than 10% of the global Poio eradication budget: only $125.19 million went to surveillance activities.[10]

More importantly, it has been shown that funding priorities do not necessarily correspond to diseases with the highest burden. As recently as 2006, Jeremy Shiffman, an expert in health policy, pointed out that "…factors other than developing world need may influence donor behavior…." These factors often include the interests of industrialized states, leaving the vertical health initiative at odds with comprehensive disease control goals.[32] Several other recent papers have highlighted the issues that come with vertical health initiatives.[3][29] Shiffman divides donor behavior into different frameworks based on

various attributes, such as: humanitarian concerns, donor interests, and international peer pressure. He indicated strong historical preferences for what is called a "provider interest framework," i.e. the interests of the donor are of primary concern when allocating funds. Donors with vested interests in disease control and elimination are not just government-funded institutions; NGOs and pharmaceutical companies may also target specific diseases for financial gain.[39]

The moral and ethical implications of this approach have been questioned repeatedly.[39][1] NGOs contribute up to 40% of health expenditures for polio eradication in sub-Saharan Africa. According to public health experts Carl Taylor et al cost-benefit analysis indicates that the savings of polio eradication work will reach upwards of $13 billion by 2040 with the majority of saving going to donors.[34] This is because the majority of associated costs are from rehabilitation and acute care, which are treatment options that are frequently unavailable to patients in developing nations. Therefore donors, rather than recipients, will see the greatest financial gain from its eradication. In addition, the focus on polio forces many recipient nations to defer their own priorities due to decreases in available personnel, or as a result of donor funding being increasingly allotted for polio control.[34] Examples such as this present moral and ethical issues because donors are failing to provide for the best interests of the recipient nations as this funding could be going towards meeting more basic needs, such as clean food and water, shelter, and security– all necessities that, in some instances, would improve living standards more than eradication of a single disease.

Furthermore, physicians and epidemiologists have noted that singular eradication campaigns often divert scarce resources away from other healthcare sectors. Laurie Garrett, a Snior Fellow for Global Health points out that this can result in further tension and increased pressure on over-burdened health systems. In the long term, this may result in a less stable health system. The targeted funding for HIV/AIDS is a conspicuous case as donors have failed to respond to other issues in HIV/AIDS communities, such as malnutrition, sanitation, and healthcare. The large influx of donations to fund aid workers' salaries might have the unintended consequence of exacerbating rampant malnutrition because uncontrolled inflation could push the cost of basic foods out of the reach of a nation's neediest socioeconomic classes.[9] Similarly, the cash pouring into developing countries to combat HIV/AIDS and malaria have unintentionally resulted in a backwards slide of other treatment/control programs, maternal health programs, and prenatal care. Using Ghana as an example, in 2002 a survey found that 72 percent of healthcare facilities could not provide the full range of treatments and services, and that 604 of the 871 medical practitioners trained in Ghana over the last decade had moved their practices overseas for better paying opportunities. A similar picture can be painted for Mozambique, Zambia, Zimbabwe, and other countries across Africa.[9]

Broad-Spectrum Surveillance

The successes of vertical surveillance are easily overshadowed by its shortcomings. The reliance on external funding as well as the limited effectiveness of such systems hinders their usefulness. One solution that many experts are calling for is the implementation of broad-spectrum surveillance systems, including those that can utilize non-traditional data sources. These systems may rely on data that is not specifically clinical data reported by physicians or collected in the field. These systems can extrapolate trending events from a variety of sources in addition to the more traditional disease symptoms reported in clinics and hospitals. More importantly, their capabilities can be extended to detect unknown and novel pathogens. With so many experts clamoring for a change in approach, it seems that the concept of single-disease initiatives will soon fall out of favor.

The concept of non-traditional broad-spectrum surveillance, often referred to as syndromic surveillance, has taken on a life of its own, outgrowing its original definition to encompass a wide variety of surveillance systems. Syndromic surveillance, as indicated by the name, catalogs outbreaks grouped by broad syndromic diagnoses. By identifying clusters of syndromes, researchers can test for specific diseases that match those syndromes. This definition has been further broadened recently to encompass biosurveillance systems that operate off of non-traditional data sources, such as school and work absenteeism, OTC drug purchases, and web search queries. They have been instituted to some extent in a

variety of countries and settings; both developed and developing countries have deployed systems focused on both human and animal pathogens. [41][29]

In Sri Lanka, for instance, the Infectious Disease Surveillance and Analysis System (IDSAS) was implemented in 2009 to "[track] syndromes and clinical diagnoses in cattle, buffalo, and poultry…" across the country.[29] Front line veterinarians armed with cell phones were instructed to submit a simple yes/no answer on whether a syndrome was present, identify a syndromic group, and provide a clinical diagnosis.[29] The IDSAS system allows for the rapid identification of clusters of similar illnesses without the need for an exact medical identification. This allows a faster response time to outbreaks of disease. In Indonesia, a collaboration between the Ministry of Health and the US Naval Medical Research Unit-2, created the Early Warning Outbreak Recognition System (EWORS), which has successfully detected outbreaks of dengue, diarrhea, and flu syndromes among others. The provincial hospitals collect 29 signs and symptoms, which are then reported and analyzed on a daily basis.[6] Using these signs and symptoms, the US navy can rule out specific diseases without having to waste precious resources on clinical tests, while also identifying outbreak loci and concentrations. Programs based on EWORS have also been implemented in Lima, Peru. The Peruvian system has the capacity for real-time data reporting using text messaging and telephones; these capabilities have proven successful as well, facilitating outbreak confirmation of *Cyclospora cayetanensis* on several occasions.[6]

Not all broad-spectrum systems are effective, however. In China, the Notifiable Disease Reporting System (NDRS) is a multi-disease-specific system that extends to central, province, and county administrative levels. The system aggregates reports of 39 diseases and syndromes from across the country and generates reports which the Department of Health then investigates. As well structured as it may seem, the NDRS suffers from a lack of coordination amongst the reporting levels.[42] Additionally, the various levels of reporting in the NDRS system utilize different methodologies and procedures that further complicate the system. Xiong et al found the lack of communication to be an issue in upwards of 60% of cases between the lower level China CDC (CCDC) departments and health administrative departments. Compromised communications not only result in an ineffective system, they can also increase overall expenses to operate the system.

Keeping operating costs low is an important requirement for surveillance systems in the developing world. The cost for effective syndromic surveillance programs can be significantly lower than that of a single-disease initiative approach. Due to the nature of syndromic surveillance programs, the majority of reporting is collectively generated by many primary healthcare providers, and consists of data currently required by many health departments. The additional manpower and operating costs can be kept very low. A prime example of the low costs achievable by these systems is a National Health Service Direct based syndromic surveillance program in the United Kingdom, which was operated at an estimated cost of only $280,000 annually.[7] This system successfully detected outbreaks of Influenza-like illnesses and other syndromes.[7] Other syndromic systems, such as the Global Disease Detection Program (GDD) or the Global Public Health Intelligence Network (GPHIN), have annual budgets in the $3.5-$10m range.[11] In comparison to the $125 million surveillance budget of polio, broad-spectrum surveillance systems are exceptionally inexpensive to operate. Obviously costs will increase as the complexity of the system increases, but even if the costs increase exorbitantly, the price tag could remain significantly lower than the surveillance budget for a single disease approach.

Though Experts are calling for the continued development and implementation of syndromic surveillance systems, there are still, however, widespread disputes in the literature over the efficiency and applicability of broad-spectrum programs, as well as their feasibility in developing countries due largely to the underdevelopment of current healthcare systems.[28][21][42] The characteristics that all these systems have in common are also their limiting factors. These programs all utilize a limited, defined list of reportable diseases with little room for identification of unknown or un-included pathogens.[38][1] However, the origins of the majority of emerging and novel infectious diseases are traced back to developing regions of the world, where these systems have a limited reach. In order to take full advantage of what these systems can offer, they need to be adapted to work with the current healthcare systems in

developing nations. These systems must have the capacity to recognize novel pathogens inexpensively and with little external support.

Necessary Policy Advances

While both vertical surveillance and broad-spectrum surveillance have been shown to be effective under certain circumstances, the wide range of identifiable diseases and other advantages of broad-spectrum and syndromic surveillance systems make them an ideal choice for the future direction of disease surveillance. The many challenges with current disease surveillance strategies, including limitations on targeted diseases, increased burden on healthcare systems, unsustainable approaches, and the lack of self-empowerment, need to be addressed, however. So what can be done to address these shortcomings of biosurveillance? The regional immunization program of the Americas is often cited as a well-functioning system that is heavily reliant on its surveillance system. Some key factors that are recognized as contributing to its success are international cooperation, sustainability of the program, an effective network of diagnostic resources, and technical cooperation across national borders.[2] Thus, effective systems in the developing world should seek to emulate the successful characteristics of the Americas system in order to better empower their medical communities.

In conjunction with shifting responsibilities to the medical communities of developing countries, ensuring that the system being implemented is simplistic enough to use and maintain, and yet robust enough to identify a broad range of diseases, including unknown or emerging infections, is of the utmost importance. Simplicity will ensure sustainable use in fragile healthcare systems, reducing developing nations' reliance on external aid, while a robust system should give developing nations the ability to detect the majority of important disease outbreaks. Accomplishing these objectives is beneficial to nations in both the developing and developed world; it will strengthen the health security of all parties involved.

Current Solutions

Surveillance Methodologies

There are several current systems that, with a little modification, would address the shortcomings of many syndromic and broad-spectrum surveillance systems. The United States Department of Defense's (DOD's) Global Emerging Infections Surveillance and Response System (now the Armed Forces Health Surveillance Center Global Emerging Infections Surveillance and Response System, or AFHSC-GEIS) is one such system. Created in 1997, the system has worked to reduce infectious disease threats through surveillance and response via a network of overseas laboratories. AFHSC-GEIS relies on several predictive components to pinpoint potential disease outbreaks: animal-host interaction to detect vector and pathogen exposure from human-human, animal-to-human, and animal-to-animal transmission; arthropod-vector observation to determine potential for vector-borne diseases; and GIS information for environmental, ecological, and geographical information.[41] The system also incorporates direct disease surveillance, utilizing a network of reference laboratories around the world. The system of labs reaches every heavily populated region on the planet with efforts coordinated over 80 regional government institutions in 74 countries. Utilizing advanced techniques, such as real-time reverse transcriptase polymerase chain reaction (rRT-PCR), the labs can conduct clinical diagnosis of samples for a wide range of pathogens, though their focus is primarily on influenza and other respiratory infections, malaria, dengue, other vector borne diseases, and acute diarrheal diseases.[30]

The system's primary objective is to protect U.S. forces abroad, though some effort is taken to address regional medical priorities as well. The emphasis on region-wide capacity building efforts is what separates AFHSC-GEIS from most other surveillance systems, and identifies it as a potential solution to the current shortcomings of broad-spectrum disease surveillance systems. AFHSC-GEIS has its limitations, of course, namely that the system is DOD-centric with the best interests of DOD forces at the

top of the list of priorities. The time required to send samples to regional labs for processing is another stumbling block.

Although AFHSC-GEIS purportedly reaches every heavily populated region on the planet, the system's reliance upon regional laboratories for clinical confirmation of samples is one point that could be improved. While precise, the need to ship samples in order to identify a pathogen wastes resources and is time consuming; often this process can take days or weeks, dramatically increasing the response time to an outbreak. During the initial SARS outbreak in 2003, laboratories of the WHO Global Influenza Surveillance Network were sent samples taken from patients with severe atypical pneumonia from China with the task of analyzing them. The WHO finally had enough clinical information to release an alert one month later. During that time the number of cases had already begun spreading along busy international travel routes.[49] Although AFHSC-GEIS played only a limited role in the identification of SARS, the Global Influenza Surveillance Network's reliance on transported samples highlights the shortcomings of such a practice.

Any system that seeks to improve on AFHSC-GEIS should work to remove the DOD centricity and the reliance on regional reference laboratories while further emphasizing the importance of indigenous capacity building.

Diagnostic Technologies

One of the major obstacles to implementing effective biosurveillance systems is the lack of diagnostics labs in developing regions that have the human and technical capacities to test a multitude of samples. The majority of infectious agents can be identified using currently available tests, and can be done so with a high level of sensitivity. Yet even in regions that have the laboratory capacities, many of these facilities are plagued by intermittent supplies of materials, reagents, equipment, and electricity.

Many of the diagnostic tests are laboratory dependent, and well-trained clinicians and expensive equipment are often required to run them.[14] Currently, many primary care clinicians rely on bacteria culture for diagnosis, which is time-intensive, costly, and dependent on reagents, electricity, and operational equipment. More importantly, these conventional methods can take days to perform.[23][6] As a result, many of the tests, chemicals, and reagents necessary for diagnosis are not readily available in a developing country setting.

However, the rise of genomic and proteomic diagnostics may reduce our dependence on decades-old culture techniques.[19][16] Protein-based microarrays can be used to identify pathogens using techniques such as ELISA, via antigen/antibody interactions such as immunochromatography, or by direct observation using direct agglutination tests (DATs) or rapid plasma reagin (RPR) tests.[17][19] The inclusion of a field assay test employing one of these technologies in a syndromic or other broad-spectrum surveillance system would greatly expand the applications for developing countries around the world.

A potential technological solution to the inadequacies of current surveillance systems has been suggested from several sources, in varying forms. W. Ian Lipkin of Columbia University has called for the use of molecular technologies to identify bacteria and viruses in real time. His perspective is that further advances in nucleic acid analysis will result in faster, more sensitive, and far cheaper methods for identifying infectious agents.[15] The technology being advocated by Lipkin is currently being developed by others. These approaches are a form of microarray that use fluorescent dyes or discrete mass tags to simultaneously test for and detect 20-100s of pathogens simultaneously. Microarray platforms reduce the time and biocontainment requirements associated with pathogen culture.[24] Other similar technologies that are promising for broad-spectrum disease surveillance include integrated capillary electrophoresis microsystems, which could be suitable for point-of-care diagnostic applications.[35] The very small quantities of sample used in these systems, as well as the detection method themselves (probe type, target molecules, etc.), have some inherent drawbacks. There is often a trade-off between having a high level of sensitivity, meaning the microarray can detect very minute amounts of a pathogen, and having high specificity, meaning the tests can have difficulty distinguishing between targets. In most cases a microarray can have one or the other, but not both.[50] Current work on microarray technology is rapidly

advancing the sensitivity and specificity of these diagnostics tools so that both high sensitivity and specificity can be achieved on the same chip.

Another Approach

While surveillance of a wide range of diseases is a step in the right direction, systems need to go further. Broad-spectrum surveillance systems should be able not only to identify disease outbreaks in real time, but they also need to have the capacity to detect outbreaks of previously unknown pathogens. One approach to the problem is to supplement syndromic or other broad-spectrum surveillance approaches with front-line clinical diagnosis. Clinical diagnostic tests have been cited as a means for improving disease surveillance. Under syndromic surveillance conditions, a diagnostic test could be used to rapidly rule out specific diseases from a syndromic cluster via a specific order of elimination. Thus, such tests could serve dual purposes: extending the capabilities of the surveillance system, while also improving case-finding and case-management of identified diseases.

A system utilizing frontline diagnostics, such as microassay tests, would need to be implemented by primary healthcare personnel in a manner that was minimally disruptive to the current healthcare structure. These tests could be implemented in a system based on an identified syndromic cluster where: 1) a sample from a sick individual is taken, 2) that sample is immediately tested against the broad panel of pathogens using a microassay test, 3) the initial result would be able to swiftly rule out potential culprits or indicate likely pathogens, and 4) if need be, the sample would then be passed to the regional lab for a confirmatory diagnosis, especially in cases where the pathogen could not be identified (potentially indicating a novel infection). A stepwise process like this or something similar has the advantage that it provides three intervention points for a response/control initiative to be implemented: 1) steps can be taken to contain an identified syndromic cluster, 2) If the primary assay result is indicative of an agent of interest, preliminary control measures can be taken, and 3) alternatively, if the confirmatory diagnosis from a regional lab is worrisome, then a full response can be initiated at a regional level. One important result of this process is that it addresses the need to rapidly identify novel agents. The two-step process of identifying a syndromic cluster followed by a focused assay panel is less resource-intensive than broadly testing for every possibility, and allows healthcare workers to systematically eliminate known pathogens using the broad-spectrum assays.

Both the US's GEIS platform and current work on microassays are steps in the right direction. This GEIS system, with its network of biomedical laboratories around the world, gives DOD researchers the opportunity to develop drugs to combat diseases that are not endemic to the US, but are a threat to DOD personnel. In addition, its laboratory capacity also allows the DOD to identify, and respond to, outbreaks. However, the system has its limitations; in the case of emerging diseases this system is dependent on sending samples to one of the participant labs for diagnosis, which wastes valuable time in identifying a new or novel disease. If a system such as GEIS were to implement a primary broad-spectrum assay test, the system would be far more effective.

Conclusion

The largest hurdle confronting US national health is our continued efforts to focus on responding to current disease outbreaks. Instead, the US and our global partners need to concentrate on confronting future pandemics, biological attacks, or novel outbreaks. In other words, our efforts must be increasingly proactive instead of reactive. The health of a nation and the global state of health and healthcare is a national security issue. To accomplish this goal, current preferences on healthcare aid allocation and focus should favor an approach to disease detection and control that is effective, inexpensive, and sustainable for indigenous healthcare providers. Currently, disease detection approaches on a global scale that utilize primary assay diagnosis and secondary laboratory confirmation are lacking, and thus limiting the investment in such systems.

Because funding for surveillance programs often comes from outside an unindustrialized nation's borders, an ideal system would provide the developing world with a means of improving the quality of life within its own borders, while reducing the need for continuous assistance from the donor. We contend that future systems should include animal and human syndromic surveillance programs, and clinical diagnosis affirmation, using a standardized procedure and reporting methodology. The use of a low-cost, broad-spectrum microassay by primary healthcare workers in developing countries would help to enhance infectious disease surveillance globally. Implementation of an international surveillance system based on broad-spectrum diagnostic tests would enable individual countries to better investigate and control disease outbreaks from within their own borders, and from abroad. Broad-spectrum disease surveillance needs to be directed towards a global syndromic surveillance system that has flexibility to meet the needs of all member countries, while still maintaining continuity in reporting standards and methods.

Citations

1. Allotey, Pascale, Daniel D. Reidpath, and Subhash Pokhrel. "Social Sciences Research in Neglected Tropical Diseases 1: The Ongoing Neglect in the Neglected Tropical Diseases." Health Research Policy and Systems 8.1 (2010): 32. Print.

2. Andrus, Jon K., Carlos C. Solorzano, Lucia De Oliveira, M. C. Danovaro-Holliday, and Ciro A. De Quadros. "Strengthening Surveillance: Confronting Infectious Diseases in Developing Countries." Vaccine 29 (2011): n. pag. Print.

3. Anselmi, Mariella, Juan-Martin Moreira, Cinthia Caicedo, Ronald Guderian, and Gianni Tognoni. "Community Participation Eliminates Yaws in Ecuador." Tropical Medicine and International Health 8.7 (2003): 634-38. Print.

4. Bond, Katherine C., Sarah B. Macfarlane, Charlanne Burke, Kumnuan Ungchusak, and Suwit Wibulpolprasert. "The Evolution and Expansion of Regional Disease Surveillance Networks and Their Role in Mitigating the Threat of Infectious Disease Outbreaks." Emerging Health Threats Journal 6.0 (2013): n. pag. Print.

5. Calain, Philippe. "From the field side of the binoculars: a different view on global public health surveillance." Health Policy and Planning 22 (2007) 13-20.

6. Chretien, Jean-Paul, Howard S. Burkom, Endany R. Sedjaningsih, et al. "Syndromic Surveillance: adapting Innovations to Developing Settings." PLoS Medicine 5.3 (2008): 0367-0372. Print.

7. Doroshenko, Alexander, et al. “Evaluation of Syndromic Surveillance Based on National Health Service Direct Derived Data– England and Wales.” In: Syndromic Surveillance: Reports from a National Conference, 2004. MMWR 2005; 54(Suppl): 117-122.

8. Foudeh, Amir M., Tohid Fatanat Didar, Teodor Veres, and Maryam Tabrizian. "Microfluidic Designs and Techniques Using Lab-on-a-chip Devices for Pathogen Detection for Point-of-care Diagnostics." Lab on a Chip 12.18 (2012): 3249. Print.

9. Garrett, Laurie. "The Challenge of Global Health." Foreign Affairs 86.1 (2007): n. pag. Print.

10. Global Polio Eradication Initiative. Financial Resource Requirements 2012-2013. Geneva, CH: World Health Organization. 2012. Print.

11. Hitchcock, Penny, Allison Chamberlain, Megan Van Wagoner, Thomas V. Inglesby, and Tara O'Toole. "Challenges to Global Surveillance and Response to Infectious Disease Outbreaks of International Importance." Biosecurity and Bioterrorism 5.3 (2007): 206-27. Print.

12. Jamison, Dean T, and Henry Mosle. “Disease Control Priorities in Developing Countries: Health Policy Responses to Epidemiological Change.” American Journal of Public Health 81.1 (1991) 15-22. Print

13. Kouri, Gustavo, Maria Guadalupe Guzman, et al. "Reemergence of Dengue in Cuba: A 1997 Epidemic in Santiago De Cuba." Emerging Infectious Diseases 4.1 (1998): n. pag. Web.

14. Liang, Song, Changhong Yang, Bo Zhong, and Dongchuan Qiu. "Re-emerging Schistosomiasis in Hilly and Mountainous Areas of Sichuan, China." Bulletin of the World Health Organization 84.2 (2006): 139-44. Print.

15. Lipkin, W. Ian. "Pathogen Discovery." Ed. Marianne Manchester. PLoS Pathogens 4.4 (2008): E1000002. Print.

16. Liu, Yuanli. (2004). China's public health-care system: facing the challenges. Bulletin of the World Health Organization, 82(7), 532-538. Retrieved April 03, 2014, from http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862004000700011&lng=en&tlng=en. 10.1590/S0042-96862004000700011.

17. Mabey, David, Rosanna W. Peeling, Andrew Ustianowski, and Mark D. Perkins. "Diagnostics for the Developing World." Nature Reviews Microbiology 2.3 (2004): 231-40. Print.

18. Mccoy, D., S. Chand, and D. Sridhar. "Global Health Funding: How Much, Where It Comes from and Where It Goes." Health Policy and Planning 24.6 (2009): 407-17. Print.

19. Morens, David M., Gregory K. Folkers, and Anthony S. Fauci. “The Challenge of Emerging and Re-emerging Infectious Diseases.” Nature. 430. (2004)242-249. Print

20. Morse, Stephen S. “Global Infectious Disease Surveillance and Health Intelligence.” Health Affairs 26.4 (2007) 1069-1077.

21. Mostashari, Farzad, and Jessica Hartman. “Syndromic Surveillance: A Local perspective.” Journal of Urban Health: Bulletin of the New York Academy of Medicine 80.2 (2003).

22. Niemz, Angelika, Tanya M. Ferguson, and David S. Boyle. "Point-of-care Nucleic Acid Testing for Infectious Diseases." Trends in Biotechnology 29.5 (2011): 240-50. Print.

23. Pai, Nitika Pant, Caroline Vadnais, Claudia Denkinger, Nora Engel, and Madhukar Pai. "Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries." PLoS Medicine 9.9 (2012): E1001306. Print.

24. Palacios, Gustavo. "Panmicrobial Oligonucleotide Array for Diagnosis of Infectious Diseases." Emerging Infectious Diseases 13.1 (2007): 73-81. Print.

25. Panisset, U. "Informed Choices for Attaining the Millennium Development Goals: Towards an International Cooperative Agenda for Health-systems Research." The Lancet 364.9438 (2004): 997-1003. Print.

26. Park, Seungkyung, Yi Zhang, Shin Lin, Tza-Huei Wang, and Samuel Yang. "Advances in Microfluidic PCR for Point-of-care Infectious Disease Diagnostics." Biotechnology Advances 29.6 (2011): 830-39. Print.

27. Primary Health Care: Report of the International Conference on Primary Health Care, Alma-Alta, USSR, 6-12 September 1978. Geneva: World Health Organization, 1978. Print.

28. Reingold, Arthur. "If Syndromic Surveillance Is the Answer, What Is the Question?" Biosecurity and Bioterrorism 1.2 (2003): 77-81. Print.

29. Robertson, Colin, Kate Sawford, Walimunige S. N. Gunawardana, Trisalyn A. Nelson, Farouk Nathoo, and Craig Stephen. "A Hidden Markov Model for Analysis of Frontline Veterinary Data for Emerging Zoonotic Disease Surveillance." Ed. Corinne Ida Lasmezas. PLoS ONE 6.9 (2011): E24833. Print.

30. Sanchez, Jose L., Matthew C. Johns, et al. "Capacity-building Efforts by the AFHSC-GEIS Program." BMC Public Health 11.Suppl 2 (2011): S4. Print.

31. Seymour, Jane. Eradicating Smallpox. Case Study. Washington, D.C.: Center for Global Development, 2007. Print.

32. Shiffman, J. "Donor Funding Priorities for Communicable Disease Control in the Developing World." Health Policy and Planning 21.6 (2006): 411-20. Print.

33. Strengthening Infectious Disease Prevention, Control and Response in Amhara National Regional State. 18 Jan. 2013. Project Summary. Japan International Cooperation Agency.

34. Taylor, Carl E., Felicity Cutts, and Mary E. Taylor. "Ethical Dilemmas in Current Planning for Polio Eradication." American Journal of Public Health 87.6 (1997): 922-25. Print.

35. Thaitrong, Numrin, and Peng Liu. "Integrated Capillary Electrophoresis Microsystem for Multiplex Analysis of Human Respiratory Viruses." Analytical Chemistry 82.24 (2010): 10102-0109. Print.

36. The Millennium Development Goals Will Not Be Attained without New Research Addressing Health System Constraints to Delivering Effective Interventions Report. Geneva: World Health Organization (WHO), 2005. Print.

37. Thomas, Steff. "Next-Generation Bio-Surveillance Program's Costs Questioned; Future Remains ..." National Defense Magazine. National Defense Industrial Association, 15 July 2013. Web. 24 July 2013.

38. Walsh, Julia A., and Kenneth S. Warren. "Selective Primary Health Care: An Interim Strategy for Disease Control In Developing Countries." New England Journal of Medicine 301 (1979): 967-74. Print.

39. Webber, David, and Michael Kremer. "Perspectives on Stimulating Industrial Research and Development for Neglected Infectious Diseases." Bulletin of the World Health Organization 79.8 (2001): 735-41. Print.

40. "WHO | Second Generation Surveillance for HIV/AIDS." WHO | Second Generation Surveillance for HIV/AIDS. World Health Organization, 07 Apr. 2006. Web. 02 July 2013.

41. Witt, Clara J., Allen L. Richards, et al. "The AFHSC-Division of GEIS Operations Predictive Surveillance Program: A Multidisciplinary Approach for the Early Detection and Response to Disease Outbreaks." BMC Public Health 11.Suppl 2 (2011): S10. Print.

42. Xiong, Weiyi, Jun Lv, and Liming Li. "A Survey of Core and Support Activities of Communicable Disease Surveillance Systems at Operating-level CDCs in China." BMC Public Health 10.1 (2010): 704. Print.

43. "Yaws." Media Center Fact Sheets. World Health Organization, Oct. 2012. Web. 05 Aug. 2013.

44. The WHO MERS-CoV Research Group -. State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. PLOS Currents Outbreaks. 2013 Nov 12. Edition 1. doi: 10.1371/currents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8.

45. Groot, R. J. De, S. C. Baker, R. S. Baric, C. S. Brown, C. Drosten, L. Enjuanes, R. A. M. Fouchier, M. Galiano, A. E. Gorbalenya, Z. A. Memish, S. Perlman, L. L. M. Poon, E. J. Snijder, G. M. Stephens, P. C. Y. Woo, A. M. Zaki, M. Zambon, and J. Ziebuhr. "Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group." Journal of Virology 87.14 (2013): 7790-792. Web. 17 June 2014.

46. World Bank. World Development Report 1993: Investing in Health. Oxford, England: Oxford University Press Inc; 1993.

47. OECD. Aid to Health data to 2010-2011. October, 2013: http://www.oecd.org/dac/stats/documentupload/Aid%20to%20Health%20data%20to%202010-11%20%28pdf.%20Oct.%202013%29.pdf

48. WHO. *World Malaria Report 2013*. Publication. N.p.: World Health Organization, 2013. Print.

49. Heymann, D. L. "The International Response to the Outbreak of SARS in 2003." *Philosophical Transactions of the Royal Society B: Biological Sciences* 359.1447 (2004): 1127-129. Web. 5 Aug. 2014. <http://rstb.royalsocietypublishing.org/content/359/1447/1127.full.pdf+html>.

50. Miller, M. B., and Y.-W. Tang. "Basic Concepts of Microarrays and Potential Applications in Clinical Microbiology." *Clinical Microbiology Reviews* 22.4 (2009): 611-33. Web. 5 Aug. 2014.


Sandia National Laboratories