Leveraging Pacific Laboratories to Boost Global Health Security

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Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Contributing Editors Tetine L. Sentell PhD from the Office of Public Health Studies at the University of Hawai'i at Manoa and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Associate Editors Ranjani R. Starr MPH and Lance K. Ching PhD, MPH from the Hawai'i Department of Health.

Introduction

Just as the Ebola virus was claiming its first West African victims, world leaders gathered in Washington, DC, and Geneva, Switzerland, to inaugurate the Global Health Security Agenda (GHSA)—an ambitious framework intended to accelerate progress toward a world secure from infectious disease threats, particularly those with potential to spread across national borders. The GHSA was launched in February 2014, endorsed by the G7 (United States, Canada, France, Germany, Italy, Japan and the United Kingdom) in June 2014, and supported by 53 nations, as of August 2016.[1] All three core GHSA goals—preventing avoidable epidemics, detecting threats early, and responding rapidly and effectively to biological threats[2]—depend on adequate laboratory expertise to identify and characterize infectious pathogens in support of public health surveillance and response.

By virtue of its strategic location and access to sophisticated, reference-level laboratory services, Hawai'i is in a unique position to further GHSA goals in the Asia-Pacific region. The Hawaiian Islands lie about 2,500 miles southwest of the mainland United States, almost 4,000 miles east of the US territory of Guam and about 3,900 miles east of Tokyo, Japan. As a midway point between Asia and the continental US, Hawai'i attracts a large number of domestic and international visitors: 4.36 million air travelers and 56,555 out-of-state cruise ship passengers from January through June 2016, coming from Alaska and the US mainland (over 2.7 million), Japan (693,057), Australia (157,744), China (91,781), and other parts of the world.[3] In fact, in 2015, Honolulu was the port of entry for more non-US residents than any other domestic port, excepting New York City, Miami, and Los Angeles.[4] Hawai'i also engages in a robust maritime trade. In 2015, Hawai'i consumers purchased $2.27 billion worth of goods from the state's top five foreign import markets: (1) Indonesia, (2) Russia, (3) France, (4) Japan and (5) China.[5] Altogether, 85-90% of Hawai'i's food is imported from out of state.[6]

The mixing of international citizens and goods in Hawai'i's remote 6,422 square miles of land area makes the state a natural sentinel jurisdiction, well-positioned to monitor emerging (eg, Zika virus), re-emerging (eg, measles), and endemic (eg, leptospirosis) pathogens in the Asia-Pacific region. For example, the first US cluster of multi-drug resistant *N. gonorrhoeae* with enhanced cefixime resistance was detected here and associated with sex partners from Asia.[7] Similarly, 2009 H1N1 pandemic influenza was confirmed in a student and teacher from the same O'ahu school just 21 days after the Centers for Disease Control and Prevention (CDC) reported the first cases in the continental US.[8]

The Role of the Hawai'i State Laboratories

Of course, these disease investigations and ensuing interventions, were predicated on the existence of a strong, multidisciplinary Hawai'i public health infrastructure. Of particular relevance for this article are the services provided by the State Laboratories Division (SLD) of the Hawai'i State Department of Health. The SLD— which includes biosafety level 3 containment—tests over half a million air samples, 10,000-12,000 environmental samples, and 40,000 human specimens each year, licenses clinical laboratory scientists, conducts research, provides adjunct faculty to local colleges and universities, and participates in a range of activities for emergency preparedness and response. Importantly, the SLD leads the Hawai'i Laboratory Response Network, made up of several clinical (mostly hospital-based), veterinary, food testing, and military laboratories in the Hawaiian Islands. This network offers a highly trained workforce, proficient in classical and molecular disease testing; capability to test for priority bioterrorism agents, such as smallpox, *Bacillus anthracis* and *Brucella* species; surge capacity for high-volume outbreak response; and a platform for secure laboratory report-

Keywords
GHSA, USAPI, PIHOA, Hawai'i SLD, APHL, Specimen Transport, influenza, Zika

Abbreviations
GHSA: Global Health Security Agenda
SLD: Hawai'i State Laboratories Division
CDC: Centers for Disease Control and Prevention
APHL: Association of Public Health Laboratories
USAPI: US-affiliated Pacific Islands
PIHOA: Pacific Island Health Officers Association
LRN: Laboratory Response Network

ing and data exchange. The SLD is also a member of the US Laboratory Response Network (LRN) founded by the Centers for Disease Control and Prevention (CDC), the Association of Public Health Laboratories (APHL), and the Federal Bureau of Investigation. The LRN is integrated with the US Postal Inspectors, Department of Homeland Security, and other federal law enforcement agencies, and is considered a national security asset. As a member, the SLD has access to specialized training and standardized testing reagents and protocols for certain biological select agents and toxins monitored by the CDC Select Agent Program, as well as for emerging and re-emerging pathogens of public health significance.

In recent years, the SLD substantially increased its public health reach, serving as a hub of laboratory expertise for the six US-affiliated Pacific Islands (USAPI) jurisdictions, which include the US flag territories of American Samoa, Commonwealth of the Northern Mariana Islands, and Guam, plus the Compact of Free Association nations of the Federated States of Micronesia (includes the islands of Chuuk, Pohnpei, Kosrae, and Yap), the Republic of the Marshall Islands (includes the island atolls of Majuro and Ebeye), and the Republic of Palau. These are resource-poor states with limited laboratory infrastructure; for example none has a Biosafety Level 3 "containment room" with one-way, filtered air flow to enable safe handling of highly infectious pathogens. With the exception of Guam, all send clinical infectious disease specimens off-island for any testing other than routine bacteriology. Before 2009, however, specimens were referred to laboratories in Australia, Hawai'i, Puerto Rico, or the US mainland on an ad hoc basis entailing complicated logistical arrangements and high costs. In 2009, the influenza A (H1N1) pandemic exposed the need for a more economical and efficient transport system. This article describes the USAPI's transition to a unified specimen transport mechanism, coordinated by the Pacific Island Health Officers Association (PIHOA), and the subsequent working relationship among USAPI, PIHOA, APHL, and the Hawai'i SLD. This partnership is boosting disease surveillance in the Asia-Pacific region, improving health outcomes, and advancing the GHSA vision of a world secure from infectious disease threats.

USAPI Laboratories and Off-island Specimen Shipment

Of the six USAPI, only one, Guam, has a dedicated public health laboratory; all other USAPI laboratories serve a dual role, providing both clinical testing for individual patient diagnosis and testing to support public health surveillance and outbreak response within their jurisdictions. The Commonwealth of the Northern Mariana Islands has a unique arrangement: instead of a freestanding public health department, the islands use the Commonwealth Healthcare Corporation, a combined 86-bed municipal hospital/public health department organized as a public corporation. The hospital laboratory offers the only biosafety level 2 testing available in the Northern Mariana Islands and primarily performs standard metabolic test panels for hospital patients and limited tests for priority public health pathogens, such as tuberculosis, chlamydia, and gonorrhea. None of the USAPI public health laboratories are able to test for agents of bioterrorism, and only Guam is able to perform influenza typing and molecular detection of some arboviruses (eg, Zika, dengue, and chikungunya) via the US Food and Drug Administration Emergency Use Authorization-approved Trioplex assay developed by CDC. All USAPI jurisdictions routinely ship specimens off-island for specialized analytical services, including confirmatory testing for measles, leptospirosis, and foodborne disease pathogens.

As the most advanced public health laboratory among the USAPI, the Guam Public Health Laboratory has assisted other USAPI laboratories in various capacities, including confirmatory testing for syphilis and a few other pathogens, outbreak response testing for a 2014 measles outbreak in Chuuk, and routine specimen packing and shipping to distant reference laboratories, such as CDC in Atlanta and the World Health Organization Regional Measles Reference Laboratory in Melbourne, Australia. Guam has the only daily supply of dry ice needed for long-distance specimen shipping, and the Guam Public Health Laboratory is hopeful that an ambitious renovation/construction project (funded in large part by the US Department of Defense[9]) will substantially increase its reference microbiology capabilities.

Yet, as stated in a PIHOA training document, "The USAPI are resource-limited and face significant challenges developing public health infrastructure, especially laboratory testing capacity for infectious diseases… The USAPI are truly a weak link in the global network for the prevention and mitigation of pandemic influenza and other infectious diseases. This fact underscores the need for a coordinated, region-wide approach to upgrading the USAPI lab network and increasing the capacity of the USAPI to provide timely and effective epidemiological surveillance and [disease] notifications."[10]

Pandemic Response Changes Public Health Practice

Before 2009, USAPI public health laboratories referred relatively few specimens to the Hawai'i SLD. During the 2009 influenza A (H1N1) pandemic, however, CDC included resources for virologic surveillance in its cooperative agreement with APHL, which, in turn, enabled SLD to test hundreds of specimens from USAPI patients over the next four years. This emergency response support strengthened the relationship between the SLD and the USAPI laboratories and highlighted the advantages of working with Hawai'i, including fewer shipping days compared with other reference laboratories used by the USAPI, negating the need for packing specimens with dry ice; faster reporting of positive test results (24-48 h from SLD specimen receipt), via line list or a password-protected electronic information system; and lower costs. For example, a shipment from the USAPI to Honolulu costs about $250 per 50 mL package for a Category A (highest risk) specimen and $100 per 4 kg/4L package for a Category B (lower risk) specimen, compared with $800 and $500, respectively, to ship the same specimens, with dry ice, to Melbourne, Australia.

In May 2010, APHL—whose members include the SLD and some USAPI public health laboratories—provided PIHOA with a year of funding support to subsidize further shipments of USAPI influenza specimens to the SLD for ongoing public health surveillance. PIHOA provided training in specimen packaging and shipping to all USAPI shippers, developed influenza specimen shipping protocols, and secured an agreement with the Honolulu-based Diagnostic Laboratory Services Inc, (DLS) to transport USAPI influenza specimens to Honolulu along with the tuberculosis specimens it tests for USAPI laboratories under its own contract with CDC. Unfortunately, the cost structure prohibited DLS from continuing this arrangement past December 2012. Instead, PIHOA drew from a revolving fund established in 2007 with $20,000 of seed money from the US Department of Interior. The intent was for PIHOA to front shipping costs, to avoid delays, and for laboratories to reimburse the fund afterward. In addition, fund reserves were supplemented with 17 months of financial support for influenza shipments to the SLD from the Secretariat of the Pacific Community. However, support from the Secretariat ceased in December 2014, and, by January 2015, the revolving fund was depleted due to delayed and incomplete reimbursements. At this time, the Association of USAPI laboratories devised the current funding mechanism for off-island shipments of infectious disease specimens (not limited to influenza specimens): a revolving account managed by PIHOA and funded by initial and periodic contributions of $2,000-$3,000 from each of the ten USAPI laboratories. Thus, instead of reimbursement after-the-fact, laboratories draw down the prefunded account. This mechanism remains in use today.

Altogether, from 2009 to 2016, between 700 and 800 shipments have been sent from USAPI public health laboratories to the Hawai'i SLD for either routine surveillance testing or emergency response testing during infectious disease outbreaks, including an ongoing Zika virus outbreak on Majuro, Republic of the Marshall Islands and American Samoa. During this period, SLD has tested 2,641 USAPI specimens for one or more disease agents, including, but not limited to, influenza virus, dengue virus, chikungunya virus, Zika virus, foodborne disease bacteria, measles virus, and *Leptospira* bacteria. The SLD has also provided viral transport media and other shipping supplies to PIHOA public health laboratories, as well as technical support, as requested, to improve USAPI laboratory services. For its part, PIHOA has established accounts with various airlines serving the Pacific-Asia corridor and with courier services in Honolulu and Guam; developed shipping protocols outlining the roles of the public health partners and transport providers; and managed the revolving fund. PIHOA also ensures that each USAPI public health laboratory has at least three staff members certified to package infectious disease specimens in accord with International Air Transport Association requirements and provides periodic training in specimen packaging and shipping.

Boosting Global Health Security

Enhanced SLD testing for USAPI laboratories since 2009 has had a strong, positive public health impact in the region. A few notable SLD accomplishments include the following:

- Performing chemistry and microbiological testing of seawater used for thawing frozen tuna, so the American Samoa StarKist® factory could reopen after a major submarine earthquake and tsunami in 2009 threatened seawater quality.

- Determining the causative agent—Staphylococcal enterotoxin—of two 2011 food poisoning outbreaks in Guam, one of which affected five schools and sickened over 300 children.

- Confirming measles as the pathogen responsible for outbreaks in 2014 in Chuuk, Guam, Kosrae, and Pohnpei.

- Determining that Chikungunya virus, and not measles, was the cause of a 2014 outbreak of acute fever and rash in American Samoa that coincided with the measles outbreaks occurring elsewhere in the region. This was the first confirmation of Chikungunya virus in American Samoa.

- Providing testing support for a large dengue 3 outbreak in American Samoa in summer 2015.

An ongoing focus of SLD support for USAPI is testing for influenza virus and other respiratory pathogens. In 2013, for example, the Hawai'i SLD tested 345 specimens from the region for influenza virus, including 121 from the Commonwealth of Northern Mariana Islands in the single month of June. Subsequent subtyping of positive specimens revealed an upsurge of influenza A (H1N1) in the region. In 2014, the SLD tested 165 USAPI specimens for influenza (50 received in a single month from Republic of Palau), and determined that influenza A (H3) was the predominant strain. Circumstances in both Palau and the Marianas raised concerns of potential avian influenza transmission to humans, and laboratory results alleviated those fears. In addition, the SLD performed pyrosequencing on a subset of 21 USAPI influenza specimens—including both H1 and H3 strains from 2013-14—to assess the presence of mutations associated with resistance to one of the most common, first-line anti-influenza drugs, oseltamivir (a neuraminidase inhibitor marketed under the trade name, Tamiflu), and found all specimens to be wild type with no oseltamivir resistance.[11]

Such information is of critical importance to inform patient care management, as well as public health interventions to stop the spread of disease. The virulence and drug-resistance profiles of different seasonal influenza strains vary greatly, and CDC estimates that between the 1976-77 flu season and the 2006-07 flu season, US influenza-associated deaths ranged from a low of about 3,000 to a high of about 49,000 people, mostly adults aged 65 years and older.[12] Additionally, CDC reports an average of more than 200,000 US influenza-related hospitalizations each year.[13]

The SLD selected 175 influenza-negative USAPI specimens from 2013-14 for additional testing by a molecular respiratory viral panel that simultaneously detects and identifies multiple respiratory virus nucleic acids. Among the 85 specimens positive for various non-flu viruses, 49 were positive for rhinovirus, 21 for respiratory syncytial virus, 5 for adenovirus, 4 for human

metapneumovirus, and 5 for a combination of these. These data were similar to viral panel results from Hawai'i surveys indicating minimal difference in the types of respiratory viruses causing illness in the Pacific region.

Battling Zika Virus in the Pacific

More recently, in 2015 and the first half of 2016, the SLD performed over 1,000 analyses of USAPI patient specimens for a range of endemic and emerging pathogens. Even as the SLD was in the midst of seasonal influenza testing and also responding to a dengue outbreak detected in October 2015 on the Big Island of Hawai'i, the laboratory began the process of bringing two new diagnostics tests on-line: one for molecular detection of Zika virus (via real-time reverse transcriptase polymerase chain reaction) and one for detection of IgM antibodies to the Zika virus. By March 2016, SLD was one of few US laboratories with capability for both molecular and antibody testing for the Zika virus. Subsequent SLD testing provided the first laboratory evidence that Zika had emerged in American Samoa, the Marshall Islands (Majuro), and Micronesia (Kosrae and Chuuk). CDC and local epidemiologists responding to the large American Samoa outbreak collected specimens from 50 pregnant women to rule out Zika virus exposure, and SLD's IgM tests demonstrated presumptive evidence of exposure in about half the women.

The interpretation of confirmatory serological testing by the plaque reduction neutralization test (PRNT) of Zika IgM screen positives, performed at CDC's Fort Collins, Colorado, facility is very complex, and suffers from cross-reactivity in patients from areas with active dengue transmission. Consequently, SLD convened several conference calls with health officials in American Samoa and Guam to help health officials understand the test reports. By spring 2016, the turn-around-time for CDC Zika testing on the US mainland was at least six weeks, making the availability of Zika testing in Hawai'i even more valuable to inform patient diagnoses and timely public health interventions, such as travel advisories, mosquito control activities, and outreach to pregnant women. In addition, SLD data provided Hawai'i and CDC health officials with situational awareness of Zika risks in the USAPI, which is necessary for evaluating potential imported cases.

Summary

In conclusion, PIHOA, Hawai'i SLD, CDC, and APHL have partnered to strengthen health security in the Pacific by providing or assuring access to testing services, providing technical support, improving specimen transport systems, and nurturing the fragile USAPI laboratory network. This work continues and will expand with resources allocated through the GHSA. Future projects include a potential laboratory "twinning" relationship between SLD and Vietnam public health laboratories—in which Vietnamese scientists will train on-site at the SLD, and SLD scientists will provide on-site support in Vietnam—and activities to achieve Hawai'i Department of Health recognition of clinical training rotations to enable state licensure of medical technologists/clinical laboratory scientists trained in the Philippines. Rigorous laboratory data are critical to enhance our understanding of health issues in the vast Pacific region and, thus, to protect Hawai'i and the US mainland from health threats we may not otherwise even know exist.

Conflict of Interest

None of the authors identify any conflicts of interest.

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