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Mountains, Melting Pot, and Microcosm: Health Care Delay and Dengue/Zika Interplay on Hawaii Island

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Human history in the Hawaiian Islands offers a sobering study in the population dynamics of infectious disease. The indigenous population numbering an estimated half million people prior to Western contact in 1778 was reduced to less than 24,000 by 1920. Much of the decline occurred in the earliest decades after contact with Western diseases including measles, chicken pox, polio, tuberculosis, and venereal disease. A recent outbreak on the Island of Hawaii (also called the Big Island) of imported dengue fever, an illness endemic in 100 countries affecting an estimated 100–400 million people worldwide, provides insights into the problems and prospects for health care policy in managing mosquito-borne disease in a multicultural setting of geographic isolation and health care provider shortage. This incident represents in microcosm a practice run, applicable in many contexts, for an initial localized appearance of Zika virus infection, with important lessons for effective health care management in a rapidly moving and fluid arena.

Keywords: dengue outbreak; communication; sports competitions; antibody-dependent enhancement; Zika

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The Island of Hawaii, that gave its name to the whole of this unique 1,500-mi chain of land forms traversing the Pacific Ocean, is made of mountains and volcanoes at various stages of life. Five of them are visible; a sixth is still working its way up from the ocean floor. The mountains range up to 14,000 ft in height, directing the paths of moisture-laden winds and affecting how and where people live and travel across the island's many microclimates. Scenery changes from arid brown to lush green within 100 yd along the roadways. Even the lava deserts in "rain shadow" regions have patches of green, trees, and plantings that access deep sources of water percolating through the rock or are fed by man-made resort water systems. Island water supplies throughout thus offer a fertile environment for mosquito breeding.

The history of the Hawaiian Islands' native people, who originated elsewhere in the Pacific, points up the profound impact of infectious diseases on the life outcomes of a populace as well as individuals. Within two years after initial Western contact with Captain James Cook's expedition in 1778 on Hawaii Island, 6% of the overall Hawaiian Islands' native population had died of introduced diseases such

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as measles, polio, and sexually transmitted diseases (STDs). The native death rate further soared, such that 48% of the original population had died within 22 years, and only an estimated 5%–10% of the original indigenous population was extant by 1920. Set against those losses, successive waves of people from other ethnic groups have settled on the Island. Chinese, Japanese, Korean, Thai, Caribbean, Filipino, other Pacific Islanders, Portuguese, and other communities continue today to create the melting pot, the blended family (*ohana* in Hawaiian), that exists today. Now, all Hawaii Islanders are vulnerable to the specter of not just one but successive waves of infectious diseases arriving in the context of a global economy.

A 2015–2016 outbreak of dengue fever on Hawaii Island underscores the issues the health care community faces in managing transmissible diseases in a world made small by rapid global travel. This mosquito-borne illness, carried among humans by *Aedes aegypti* and *Aedes albopictus*, was imported to the Island; dengue fever is not endemic in Hawaii. The outbreak has enhanced recognition of barriers to health care on Hawaii Island, a teachable moment that could inform global health care policy on the looming specter of Zika virus disease with its prospective major world burden of neurological consequences. What can we learn from what has happened on Hawaii Island?

POINT OF ORIGIN

The South Kona coast on the western side of Hawaii Island is a lush green environment dotted with small coffee plantations in Kailua-Kona and Captain Cook, along a steep hillside footed by a lava plain. Prevailing winds bring afternoon clouds that shade the coffee trees as well as rain that accumulates water in exposed tarps, plant crowns, and pots. Featuring water sports, historic sites, and meeting venues, this area melding a tropical countryside with an urban or small-town feel offers numerous occasions for people to congregate, not only island residents, but visitors from all over the world. One such interest group met there in the summer of 2015.

The South Kona coast is the land of opportunity for another cohort of individuals: an endemic population of *Aedes aegypti* mosquitoes with a preference for urban living, a strong affinity for daytime biting of humans even indoors, and a high efficiency for transmission of dengue virus. The latter was apparently brought in via the group meeting, generating a case cluster beginning September 11, 2015, that spread within a medically underserved area with numerous constraints on access to health care: structural, geographic, cultural, and economic. Hawaii Island's state Sen. Josh Green, MD, an emergency physician, states, "As many as 40% of Big Island residents have difficulty accessing a primary care provider, so many people use the ER or urgent care centers for healthcare. We are 22% short on physicians statewide but much worse on the neighbor islands" (J. Green, personal communication, June, 22, 2016). The end result, as Sen. Green points out, was that "when we first became aware of dengue last October, we were 25 days into the outbreak, and there were 20 cases that hadn't been communicated by professionals" (Yager, 2016, p. A3).

An initially unrecognized transmissible disease outbreak is epidemiologists' ultimate nightmare, postulated to have accounted for the magnitude of the recent Ebola outbreak in West Africa. Infection with dengue virus or its related Zika virus can produce symptoms that are mild, seemingly nonspecific, or in fact nonexistent,

so that some infected persons may not access the health care system at all. Cases identified to public health authorities thus represent part rather than all of an outbreak's scope. Graphic data from the Hawaii State Department of Health (DOH, 2015) shows how reported cases of dengue fever among island residents and visitors grew from a handful in mid-September to approaching 10 new cases per day by November.

PROPAGATION, RESPONSES, AND REPERCUSSIONS

Hawaii Island's county government took the initiative to proclaim a state of emergency on February 8, 2016, when the number of reported dengue fever cases had reached 254. This magnitude exceeded previous imported dengue history in the state of Hawaii, a 122-case outbreak in 2001–2002, three separate introductions from infected travelers from Tahiti, and the most recent four dengue cases on the island of O'ahu in 2011. In the present Hawaii Island outbreak, cases occurred predominantly on the island's western side, with scattered cases elsewhere. The latter likely reflects migration of dengue-infected persons via the mountains to new areas rather than migration of infected mosquitoes, whose range is a bit over 200 yd. The latter parameter establishes the "radius of control" sought in mitigation efforts such as pesticide spraying around a "case house" where dengue infection has been pinpointed.

An interim report by Dr. Lyle Petersen (2015), director of the Division of Vector-Borne Diseases at the Centers for Disease Control and Prevention (CDC), details the scope of the public health response directed by an incident command structure at the Hawaii County Civil Defense Agency and evaluates the efforts at containment in terms of community outreach, surveillance, diagnostic testing, medical care, and vector control. Although the report deems the local response appropriate overall, both the CDC report and Sen. Green have called for significant improvements in immediate communications to overcome barriers to outbreak management (J. Green, personal communication, June, 22, 2016; Petersen, 2015).

The impact of communication deficits within Hawaii Island's melting pot of cultures, a microcosm of global issues affecting health outcomes, is evident in community outreach and vector control efforts that partially created rather than surmounted barriers to health care. For example, a brochure on dengue fever, downloadable from the health department website (DOH, 2015), is available in languages spoken among ethnic groups on the island: Spanish, Samoan, Marshallese, Japanese, Ilokano, Hawaiian, English, Chuukese, Tongan, and Tagalog. However, it is not clear how many people with those as their first languages were regular computer users or technologically able to download this information on mobile phones, or whether paper copies were distributed. Provision of antidengue information to tourist venues was scarce, likely out of fear of harming a heavily tourist-dependent economy already suffering from outbreak-forced closure of shore areas, hiking trails, and access to iconic Waipi'o Valley. The dengue outbreak and controversy over its management garnered substantial media attention. The author's mainland family canceled a Hawaii Island trip planned for mid-January, illustrating the adverse financial impact of the outbreak on tourism.

Local tempers flared in the face of mosquito mitigation efforts such as insecticide spraying. Early on, a lack of clear and accurate information on how to combat mosquitoes prompted use of soapy water as a spray, an unrealistic approach to

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mosquito control ultimately supplanted by government-mandated spraying with Aqua-Reslin. This insecticide related to chrysanthemum-derived pyrethrin compounds may have aroused less opposition among islanders wary of chemicals and gravitating toward complementary and alternative medicine, had the relationship of such spraying to natural products been appropriately conveyed to them. Along the same lines, targeting mosquito larvae with solid state *Bacillus thuringiensis var israelensis* (Mosquito Dunks/Granules) is highly effective, albeit often costly; little effort was given to expanding this option. Organic agriculture is prominent on Hawaii Island, with attendant concerns about financial losses because of obligatory pesticide use. Signs proclaiming "NO SPRAY!" appeared on farms and roads all over the island. The CDC (Petersen, 2015) notes that such spraying actually has had little success against dengue worldwide; mitigation of breeding loci such as trapped water is the major priority.

A link on the Hawaii State Department of Health website (DOH, 2015), reassuring residents that the need for vector control authorities to enter their property to check for mosquito problems will not lead to citations for "something not related to the outbreak," speaks to other elements of the Hawaii Island living situation as a global microcosm. The link states that DOH personnel are not issuing citations and are not investigating other issues such as plants grown on the property (i.e., marijuana, a popular crop) or immigration status (undocumented persons' fear of detection and deportation) that might prompt citizen refusal to cooperate with mosquito investigation and mitigation. The CDC report (Petersen, 2015) points out that "Hawaii Island has many hard-to-reach populations, including migrant farm workers, homeless, and persons who are deliberately isolated." Islanders may be unable or unwilling to go to a medical facility. Measures to address geographic and/or social isolation, such as mobile capacities for drawing blood, were being developed in early December; the outbreak had been in progress for 3 months.

The daily case rate of dengue fever identified on Hawaii Island began to taper off in February 2016; by March, only a handful of cases were noted, and website updating of outbreak statistics ceased in late April. The cumulative total of 264 confirmed cases reported on the Hawaii State Department of Health website from September 11, 2015, to March 17, 2016, comprised 238 Hawaii Island residents and 26 visitors, distributed among 218 adults and 46 children younger than 18 years old; 33 persons had been hospitalized. One person presented with the severe hemorrhagic form of dengue in an isolated location requiring air evacuation. Further data about gender, numbers of cases at child-bearing age, occupational exposure risks, and so forth is not yet available because of resource limitations in DOH staffing for in-depth analysis; the personnel crunch cited by the CDC raises concerns about slackening surveillance, although an original "Fight the Bite" campaign was relaunched in June 2016. Up to 75% of dengue cases go undetected because of mild or no symptoms, and asymptomatic infected individuals can transmit dengue via mosquito intermediates (Duong et al., 2015). Underreporting of symptomatic cases is a standard feature of such outbreaks (Petersen, 2015) and in this circumstance was exacerbated by failure to provide free testing, thus excluding detection of affected individuals who could not afford to access blood drawing and the $35 testing fee. Thus, the 2015–2016 Hawaii Island dengue outbreak could potentially have affected upward of 1,000 persons, out of an island population of approximately 190,000, with an additional 12,000 visitors each day.

Few people realize the role of competitive sports activities as the vehicle for transnational spread of Zika across vast distances.

SOURCE

The temporal profile of Zika infection and its consequences represents a core set of issues for the field of women's health, including barriers hampering access to care, and individual and institutional views on contraception and abortion.

Where in the world had the Hawaii Island dengue come from? The precise source is not known, but we can infer possibilities from parallels with the spread of Zika virus disease throughout the world since its discovery in Africa in 1947. Because Zika's presence and effects throughout Latin America have drawn public attention because of the 2016 summer Olympic Games in Brazil, few people realize that the virus spread there initially from the South Pacific, nor do they fully grasp the role of competitive sports activities as the vehicle for transnational spread of Zika across vast distances.

Zika initially spread from Africa to continental Asia after 1947. Throughout this migration as Zika progressed into Indonesia and the Philippines, it was identified with a very mild illness. In 2007, Zika made its appearance on Yap Island in the Federated States of Micronesia, accounting for around 50 cases of an again seemingly mild illness. A key step in our understanding of Zika transmissibility is what happened next: an extensive 2013 outbreak of Zika in French Polynesia that could be traced to canoe paddling competitions involving participants from Yap and other areas of the Pacific Island complement where Zika was present.

Once established in French Polynesia, Zika spread from Tahiti to Brazil via international soccer competitions that were part of the "Confederation Cup" contest, a lead-in to the 2013 World Cup soccer title. The Tahiti soccer team played in six Brazilian cities, supported by a cohort of their fans who had traveled from Tahiti for this event. The six cities later were identified as among the loci of the Zika outbreak in Brazil. This timeline-based scenario for Zika origin and expansion throughout Latin America has been borne out by molecular analysis of the Zika genome in Brazil and throughout Latin America indicating that this Zika is the Polynesian virus, not the version originally identified in Africa (Wang et al., 2016).

An important concern in the Hawaii Island dengue outbreak is thus its temporal parallel with the annual Ironman triathlon competition in the Kona area October 5–12, 2015, drawing worldwide participation. Although public health authorities' formal recognition of the dengue outbreak occurred October 21, 2015, the dengue outbreak itself had clearly begun some weeks earlier. No data is yet available to indicate whether any correlation exists among participants or spectators of Ironman and initial arrival of dengue on the island.

Spread of infectious diseases in post-Western-contact Hawaii, the 2015–16 dengue epidemic, and the Western Hemisphere's explosion of Zika transmission reflect common elements of population density and population vulnerability. The initiation phase occurred under conditions of high population density, either permanent (e.g., living conditions present in precontact Hawaii) or temporary (e.g., present-day congregating for a group event). In the latter case, the nexus of population density reflects, not where people live, but where they gather for purposes of a common interest; the infectious disease that then spills out into where people live can travel very far, very fast. The crash of the Native Hawaiian population because of introduced diseases had an immunological component in terms of lack of resistance to previously unencountered infectious agents. The two modern infectious disease outbreaks may turn out to also have an immunological component, albeit a converse one, based on emerging indications of an interaction between the body's handling of dengue and Zika virus in the course of their respective infections that can potentiate the effects of Zika (Dejnirattisai et al., 2016).

Zika's sociobiological repertoire is substantially increased by its recently identified dual mode of transmission, as an STD as well as a mosquito vector-borne illness.

ZIKA: WAITING IN THE WINGS

Given the worldwide spread of Zika detailed earlier, and its prevalence in Pacific Island nations and other world areas whose residents have occasional contact with Hawaii Island, Zika importation is just a matter of time. This poses serious concerns for the devastating neurological consequences of Zika infection, including the fetal brain malformation of microcephaly and the development of Guillain-Barré syndrome in children and adults. Johansson, Mier-y-Teran-Romero, Reefhuis, Gilboa, and Hills (2016) estimated the statistical risk of microcephaly associated with prenatal Zika infection on a population basis. Most important, the risk was unequivocally associated with Zika infection during the first trimester of pregnancy, supporting the term *congenital Zika* for this and related conditions, in conceptual parallel with congenital rubella and congenital toxoplasmosis. Extrapolating data from the Yap, French Polynesia, and Brazil outbreaks, with allowances for possible problems with levels of reporting, the risk for microcephaly ranges up to 13% of births to mothers infected during the first trimester (Johansson et al., 2016).

How does Zika virus cause brain malformation that is selective for infection during the first trimester? Current evidence indicates that Zika in maternal blood is quite facile at not only crossing into the placenta but replicating extensively once it gets there. One recently postulated culprit in this process of transplacental Zika transmission is a long-recognized but poorly understood macrophage cell type called Hofbauer cells, which are especially prominent during the first trimester within the villi of the placenta, in close proximity to the capillaries of the fetal circulation. Zika has been shown to replicate in Hofbauer cells at high efficiency (Quicke et al., 2016). As a next step, from its placental locus, Zika can just as readily enter fetal blood for transport to the fetal brain, where it settles in to replicate, killing neuronal progenitor cells at key points in the brain developmental program. The lost cells cannot be replaced because the programmed sequence of progenitor maturation steps has been disrupted (Cugola et al., 2016). No remedy for this situation exists at present.

Why has this Zika effect on fetal development appeared across the world now? This phenomenon has been variably ascribed to mutation of the virus or differential vulnerabilities of the populations now being infected, without clear-cut further indications of the mechanism. Whatever the mechanism may be, it was clearly evident in viral behavior by the time Zika reached French Polynesia in 2013; the population sample was too small to ascertain whether this congenital Zika had occurred by 2007 in Yap.

Johansson and colleagues (2016) indicate that it is prudent "for health care systems to prepare for an increased burden of adverse pregnancy outcomes in the coming years" (p. 4). The temporal profile of Zika infection and its consequences represents a core set of issues for the field of women's health, including barriers hampering access to care, and individual and institutional views on contraception and abortion. Microcephaly can only be detected by ultrasound imaging later than the first trimester, approaching the time frame for later, higher risk abortion. Decision making on this matter portends to be more complex in the face of the risk numbers. Would women readily terminate pregnancies if faced with a 13% risk of microcephaly? They may view this landscape differently than a 100% or even a 30% risk, in which the choice to terminate may be more likely if possible, depending on local laws and/or personal or religious proscriptions.

Zika's impact extends more broadly, to the male population as well, in such realms as sex education at the secondary school level and conduct of personal relationships. Zika's sociobiological repertoire is substantially increased by its recently identified dual mode of transmission, as an STD as well as a mosquito vector-borne illness. Its observed persistence in semen and the role of the testes as a viral reservoir (McNeil, 2016) underscore how Zika seems to settle in somewhat immunologically privileged territories such as the brain, placenta, and testis. This immunological privilege of certain tissues may become a human health liability when Zika has entered the scene, for host defenses cannot readily access and counter the virus.

ZIKA ON THE HEELS OF DENGUE: A ONE-TWO PUNCH?

Dengue virus infection triggers an initial immunoglobulin M (IgM) and subsequent immunoglobulin G (IgG) antibody response that may persist long term even in blood of persons who were never symptomatic. Early studies (Dejnirattisai et al., 2016) report that this behavior may augment the magnitude of subsequent Zika infection by 100-fold, an effect termed *antibody-dependent enhancement* (ADE). Dengue and Zika viral particles share in common an exposed surface region called the E-loop. This region in Zika virus is recognized by antidengue antibodies left from previous dengue infection, promoting a formation of Zika virus complexed with antidengue antibodies. This combination can interact with cell types that neither partner alone would necessarily target. One recruited cell type is the macrophage, which has cell surface sites able to bind the tails of antibody molecules within the complex and take up both partners wholesale into itself (Dejnirattisai et al., 2016). Placental Hofbauer cells that strongly support Zika multiplication are in fact a macrophage cell type (Zaccheo, Pistoia, Castellucci, & Martinoli, 1989). It is notable that French Polynesia and Brazil, areas where microcephaly has appeared in recent years concurrent with establishment of Zika, are places where dengue has preexisted for some time. This raises concerns about how such a potential tandem virus interaction could impact health outcomes on Hawaii Island, in consequence of the dengue outbreak followed by a potential future arrival of Zika virus.

An official MosquitoMobile could be equipped with facilities to draw and process blood or other samples, communications capability via mobile devices/ hotspots, and paper and a printer to provide appropriate-language brochures or notices.

BLUEPRINT FOR ACTION

What could have been done differently in the Hawaii Island dengue outbreak? What resources are needed to mount a highly effective response to vector-borne illness in the future? Identifying these needs and their most realistic means of fulfillment is critical to allowing us to project and plan better. Exploration of these issues with Hawaii Island thought leaders has outlined some common themes, whose successful implementation requires careful thought, personnel, funds, and approaches that should be under construction *now*.

In the Near Term

Enhance communication to provide immediate dispersal of information:

- Rapid electronic communication among Hawaii Island health care professionals and the responsible agencies. Sen. Green has urged legislation

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creating an email database able to inform these parties quickly of key developments in health care status on the Island.

- Rapid, accurate, and effective conveyance of information to the public by a wide variety of means, including e-communications and social media as well as paper brochures, posters, and so forth, addressing the language needs of stakeholders.

Promote immediate response via a mobile approach (J. Green, personal communication, June 22, 2016), delivering health services such as no-cost blood draws and testing, along with health information and environmental assessment, for example, of potential mosquito breeding loci.

These two goals could be accomplished together in a single vehicle . . . literally. An official MosquitoMobile or two need not require an expensive custom design but could employ a simple used van, with a recognizable appearance such as a distinctive color and logo, run by health care and vector control staff. Equipping the MosquitoMobile with facilities to draw and process blood or other samples, communications capability via mobile devices/hotspots, and paper and a printer to provide appropriate-language brochures or notices could easily be accomplished via on-island big box store items or Amazon. Another necessary attribute is tolerance for the island's steep *ad hoc* tertiary local roads and driveways of asphalt, concrete, and even lava applied by Madame Pele herself.

Dispel the silos in favor of joint efforts across local, national, and international venues that transcend the boundaries and barriers of space, time, and turf. Continue and expand to all administrative levels, reaching out to other agencies early and often to learn from their experiences. For example, the population of Puerto Rico, an island which has some similarities to Hawaii Island in terms of isolation and mountainous geography, socioeconomic profile, and multilingual communication, has a known 80% dengue infection rate, a projected 20% Zika infection rate, and a report of congenital Zika (Sifferlin, 2016). The developing Puerto Rico experience may help to model Hawaii's future responses.

Support islanders in their state-mandated individual efforts against vector-borne illnesses, with accurate information and advocacy. For example, major mosquito abatement and precautions have become a fact of life across the continental United States with the advent of West Nile virus. Humans vary widely in their attractiveness to mosquitoes as a function of each person's chemical signature encompassing scents, heat, and carbon dioxide (McMeniman, Corfas, Matthews, Ritchie, & Vosshall, 2014). Measures such as permethrin treatment of fabrics and clothing are highly effective as a long-term repellent strategy but are expensive. Official subsidy or price negotiation for these supplies may benefit lower income groups, as would cost support for supplies of *Bacillus thuringiensis israelensis* for the home environment.

In the Longer Term

Work to remedy the shortage of health care professionals, in primary care as well as specialties that address the health needs of Hawaii Island, by creatively expanding ongoing efforts such as those depicted at https://www.youtube.com/watch?v=VGbZD48uR_0 that **explore recruitment strategies** for attracting more

health care providers and seek to **identify incentives** that would make Hawaii Island a desirable site for a health care career.

PERSPECTIVE

The Hawaii Island–based arts and culture journal *Ke Ola* (*The Life* in Hawaiian) speaks of "people who love Hawaii Island" (https://keolamagazine.com). Hawaii's entire history is one of travelers who came here and stayed, whether they were plant and animal species who colonized these far-flung lands, or people who found they loved this place. Certainly, unwelcome agents have come as well, leaving a wake of destroyed health, lives, and heritage. But Hawaii's resurgence of language, culture, and ancient knowledge conveyed in a spirit of openness and cooperation is now showing the world, through the *Mālama Honua* Worldwide Voyage of the traditionally navigated sailing canoe *Hokule'a* (http://www.hokulea.com), how to rebuild, nurture, and protect both people and values. With proper support and resources, the health system caring for Hawaii's people can surely do the same.

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