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Commentary

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Background

On 31 August 2016, the Singapore Ministry of Health and the National Environment Agency confirmed a cluster of new infections related to the Zika virus. As of 11 October 2016, 404 cases of Zika virus infections, including 8 cases among pregnant women, were confirmed by the Singapore authorities (1,2). Further, the first pregnant woman in Singapore to be infected with Zika has been identified, living in the south-east part of the state, where other Zika cases had already been identified. Malaysia documented its first Zika infection the next day, Thursday 1 September 2016, indicating the virus had already crossed the border. The Malaysian woman infected had recently visited her daughter, a resident in Singapore, who also tested positive for Zika infection. As Zika is surging at this key international hub, the wider region of Asia is on high alert for potential transmission of the virus to the Arabian Peninsula.

Certainly Singapore, a tropical island, is well acquainted with mosquito-borne infections, most notably dengue fever, which shares the same vectors as Zika, Aedes aegypti and Aedes albopictus (3). Recognition is growing that dengue-affected areas can expect and indeed should plan for unfolding Zika outbreaks. Particularly worrisome for Singapore is that over the first 9 months of 2016 a cumulative total of 12 032 cases of dengue fever were notified to the Ministry of Health, suggesting Zika numbers could be equally high, both adding to morbidity and mortality, but also confounding the diagnosis of both conditions.

Zika virus and Saudi Arabia

In Saudi Arabia the situation is being very closely watched. Global travel of an infected person is a likely mechanism for spreading the pathogen to new territories. In Saudi Arabia dengue virus (DEN-1, DEN-2, DEN-3) was first detected in Jeddah in 1994 and Aedes aegypti was implicated (4,5). After a large outbreak of dengue in Mecca in 2009 the disease became endemic in the city (6). Saudi Arabia is host to tens of millions of Muslims for religious tourism at Mecca, and 6 weeks ago, with the completion of the 2016 annual Hajj pilgrimage, the country

had received a total of 1 325 372 international travellers, including from Singapore, Malaysia and neighbouring Indonesia, the most populous Muslim-majority nation in the world. Should Zika impact Indonesia, Saudi Arabia will be particularly threatened.

Certainly the numbers of pilgrims traveling to Saudi Arabia from these countries are sobering: while only 100 pilgrims travel from Singapore to Hajj, over 15 000 arrive from Malaysia, and Indonesia sends almost 200 000 to every Hajj, where approximately 2–3 million Muslims gather. A further 6 million Muslims attend Umrah, the minor pilgrimage, most often performed in the months leading up to Hajj (the Hajj season), among whom many tens of thousands of Indonesians can also be expected.

For these reasons, should Zika make the leap to Indonesia, the world's fourth most populated country (247 million), Saudi Arabia can expect significant outbreaks of Zika virus infection within a short time frame. In some ways, although the Hajj Healthcare and Emergency Management System is seasoned at managing epidemics, outbreaks and even national effects of global pandemics which coincide with Hajj season, we are certainly fortunate that this year Hajj was a huge success. Next year we may not be so lucky.

Zika poses particular challenges to Indonesia: first the assumed lack of population immunity among Indonesians can be expected to lead to significant widespread acute infections among all ages groups. In Indonesia, other arboviral infections (e.g. dengue and chikungunya) are commonly encountered, distinguishing Zika infection may be difficult or delayed and matters could be further complicated by co-infection. Similarities to these other pathogens could be one reason why Zika has not been so frequently reported in Asia in the past when Zika expanded from equatorial Africa to Equatorial Asia between 1969 and 1983. Added to the mild and nonspecific nature of symptoms during most acute infections, it is easy to see how even today Zika infection can progress rapidly within this populous country undetected. Saudi Arabia also shares this challenge. More troubling still is that, unlike Saudi Arabia, Indonesia lacks the economic resources that a Zika outbreak would demand. All these factors together suggest that an Indonesian Zika outbreak is set to develop rapidly and explosively, posing an enormous risk to the region and also to Saudi Arabia, where so many Indonesians travel for work, Umrah and Hajj.

Saudi Arabia is also home to Aedes aegypti and Aedes albopictus, as previous dengue outbreaks have shown. Aedes aegypti is a formidable vector: its high vectorial capacity (the ability of a vector species to transmit a pathogen in a specific location at a specific time) lies in its ability to feed predominantly on human beings, bite almost imperceptibly and feed on multiple humans in a single blood meal, transmitting the virus as it goes (7,8). It also lives in

close proximity to human habitation being found both external to and inside impacted dwellings. However, globalization and air travel affords Zika enormous transmission capabilities, with travel and the ability for human-to-human transmission to occur becoming a game changer as is already becoming apparent in Brazil and 33 other territories in the Americas (9).

While Saudi Arabia has advanced surveillance and serological testing capabilities and a sophisticated epidemiology workforce and Biosafety Level 3 (BSL3) laboratories (a legacy of past outbreaks, most recently the outcome of the MERS-CoV challenge), first-responding physicians and local health facilities are yet to be formally educated in detecting, reporting and mitigating Zika virus infection (10,11). Without comprehensive public health education of Saudi Arabian physicians and aggressive education campaigns to raise public awareness of Zika symptoms that are easily overlooked, and necessary precautions for limiting vector exposure, the potential for unreported cases to develop into clusters in Saudi Arabia remains high. Worse, with its formidable human-to-human transmission capacity, vertical transmission of Zika is of particular concern in Saudi Arabia, where maternal fertility rates are high.

Without definitive tests and only a fleeting viral load, confirming infection will continue to be difficult and cases can continue to progress at a startling rate as we have seen elsewhere in the world for reasons which are still unclear but are certainly underpinned by globalization and urbanization. The situation in Saudi Arabia is further complicated because of the coexistence of other flaviviruses which confound the picture. Flavivirus antibody cross reactivity complicates the serological evaluation where dengue is present. Saudi Arabia may therefore have a head start as the previous dengue outbreaks have allowed for careful mapping of affected areas and these regions should be particularly targeted for Zika prevention.

The presentation of Zika infection on delivery of a baby with microcephaly or other birth defects is the most feared of its manifestations. With a maternal fertility rate of 2.75 in Saudi Arabia, and 3.1 in the wider Muslim-majority world (12,13), it can be expected that microcephalic children will be born. Caring for 1 child with microcephaly over its lifetime in the United States has been estimated at a staggering US$ 10 million (14). Most troubling is the fact that the Zika virus appears to target the neural stem cells, devastating central nervous system development in utero and potentially throughout early childhood and later life. Rather like rubella infection, the sequelae could be potentially undetected at birth, only to become manifest well into childhood as serious morbidity. Real concerns exist as to how Zika will affect these children with long-term health consequences decades after presentation. The full spectrum of Zika ramifications may go unknown for decades. At this time the unknown adds tremendously to the public health pressures governments and health agencies face as well as escalating public fears concerning travel to Zika-impacted areas and to family planning itself. Lipkin astutely makes the observation that further racial and ethnic stigmatization could add to other barriers to impacted patient populations, magnifying the challenges and suffering (14).

International response

A silver lining in this epidemiological storm is the remarkable international response which is rallying to address Zika worldwide. This commitment, unlike that for almost any other recent global outbreak, can be credited to the world's experience with recent outbreaks that later developed into epidemics or pandemics. The world's experience with SARS, H1N1, H5NI avian influenza, MERS-CoV, and most recently Ebola, while resulting in devastating impacts, including deaths, also led to the foundation of what is today's international response to Zika.

On 1 February 2016 the World Health Organization declared Zika a public health emergency of international concern (PHEIC). This recognition has lent enormous responsibility to many agencies to collaborate towards prevention, treatment and cure. Political and financial will has been globally focused and aligned. Soon after this declaration, President Obama asked the Congress in the United States of America for US$ 1.8 billion in emergency financial aid to combat Zika (14). The WHO Global Emergency Response has forecast budgetary needs at US$ 122 million (15,16). This Zika-specific funding is in addition to existing underlying frameworks to support rapid response to pathogen outbreaks, including vaccine development, preparedness, epidemic monitoring capacity and laboratory and personnel development. Such unusually focused and cohesive international and political will, triggered by the first major infectious disease to result in human birth defects in over half a century, while unprecedented, is both reassuring and responsible.

Saudi Arabia, with its unique experience in the management of infectious disease and infection control of transmission of 3 viral infections with high morbidity and mortality in the recent past: Ebola (EBOV), MERS (MERS-CoV), and pandemic Influenza A H1N1 in the Hajj season. Because of its expertise in mass gathering medicine through Hajj, the country is well positioned to meet the needs of the Zika threat, both for the domestic population and the international visitors hosted every year. Informed by the Hajj experience, Saudi Arabia is among 16 nations who developed the Global Health Security Agenda (GHSA) which helped focus international efforts in combating global infectious disease threats. Both the GHSA and the responses to Zika will be vitally tested in these difficult times. The country will also share the insights gained in studying Hajj, both this year and in the future, for evidence of the Zika natural history here in the region and in the mass gathering setting as we work together in preserving global health security in our highly mobile world. While Zika is certainly an imminent threat to Saudi Arabia and the wider region, as Zika establishes a foothold in Singapore, Saudi Arabia is ready to respond and to help its neighbours do the same.

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