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Perspective

Does public perception of exposure risks and transmission mechanisms drive antiviral vaccine awareness? What if cytomegalovirus was transmitted by mosquitoes?

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There exist many high-priority areas for development of improved preventive and therapeutic antiviral vaccine strategies. In a set of reviews in this issue of *Current Opinion of Virology*, several of these important areas for antiviral vaccine research are considered in details, as noted in the introductory editorial commentary. What do these viral infections have in common? Importantly, each of these viruses is well-known by both health care practitioners and the general public alike. Under many circumstances, considerable media and public attention is focused on these infections. Genital HSV disease was the focus of a cover story in *Time* magazine in the early 1980s, when it was asserted that that the 'incurable' herpes infection threatened to '. . .undo the sexual revolution'. Although media attention was quickly refocused on HIV disease with the advent of the burgeoning HIV epidemic in the mid-1980s, both infections still remain the focus of extensive attention and, unfortunately, considerable stigma. One of the major driving forces for an improved influenza vaccine is the widely held view — again, often promulgated by misinformation and unfounded myth — that flu vaccines are unsafe, unreliable, and unnecessary. Clearly, the performance of influenza vaccines has been suboptimal [1], but there is no question about the considerable morbidity and mortality conferred by this infection on society. Few infections in recent memory garnered a storm of media attention as extensive as that of the Ebola epidemic in west Africa in 2014, with much of the attention being focused not on the disease itself, but on the missteps, mistakes and mismanagement associated with the initial public health response to the outbreak [2]. Even misinformation is still information, and the media and public discussion surrounding these infectious diseases is an important force driving the social and political pressure needed to promote vaccine research and discovery.

All of the virus vaccines and immunotherapies reviewed in this issue are focused on infections that are transmitted by person-to-person contact. Although the 'natural hosts' of influenza virus are aquatic birds, the virus can infect pigs and humans — an aspect of flu biology that can lead to generation of dangerous re-assortant viruses when pigs are infected with an avian and a human virus, facilitated in settings where pigs, humans and birds share living space. Ultimately, human strains during influenza outbreaks are transmitted by close personal contact. Ebola virus, similarly, has its origins in an as-yet uncertain nonhuman host (although bats are likely a reservoir), but the terrifying Ebola outbreak in west Africa was promulgated by person-to-person transmission, not vectored transmission. HIV and genital HSV disease, of course, require the most intimate form of person-to-person contact — sexual contact — to be passed from one individual to another. A new infectious disease threat with different transmission mechanisms, Zika virus, has emerged. Substantial evidence suggests that this virus is a major cause of both disabling fetal infection [3–5] and Guillain–Barre syndrome [6]. Although sexual transmission of Zika virus has been described [7], the majority of infections are transmitted by mosquito bites, via *Aedes aegyptii* and, potentially, *Aedes albopictus*. The magnitude of the human tragedy engendered to date by Zika infection, particularly for the developing fetus, almost defies description. The spectrum of fetal brain injury includes profound microcephaly, polymicrogyria, agyria, hydrocephalus, chorioretinitis, and intracranial calcifications. As with the viruses discussed in this issue of *Current Opinion of Virology*, Zika virus has been the target of enormous media attention and attendant high public awareness. Certainly the high level of public awareness will drive the perception that a vaccine is urgently needed. Will the fact that the route of transmission is intrinsically different also impact public

perceptions regarding the urgency of vaccine development? It may be perceived that, in contrast to the close interpersonal contact required to transmit infections such as HIV and HSV, that the ubiquitous nature of mosquitoes and the shared risk confronting anyone exposed to the insect — irrespective of interpersonal exposures or behavioral variables — may cast the Zika vaccine argument in a different, and more urgent, light.

Although the Zika epidemic is an international health emergency demanding urgent attention, it is nonetheless of interest to compare and contrast the impact of this virus on reproductive health with that caused by another agent that causes fetal infection — human cytomegalovirus (CMV). As of this writing, nearly 5000 cases of microcephaly have been reported in Brazil to date. Although most have been attributed to Zika infection, most cases are unconfirmed. It is of considerable interest to compare this to the 'silent' burden of congenital CMV infection [8], which causes up to 6000 cases of permanent neurologic and neurodevelopmental injury in newborn in the United States every year [9]. The neuropathogenesis of fetal CMV brain infection has many apparent similarities to that exhibited by Zika infection [10]. There are important differences in the epidemiology and transmission of the two viruses (Table 1). Although it is not immediately intuitive, the risk of congenital infection actually *increases* in populations where women of reproductive age have high CMV seroprevalance rates [11]. This is in striking contrast to Zika, a new and emerging infection in the Western hemisphere that appears to pose a major risk at least in part because serologically naïve women in populations have no herd immunity to the infection. CMV, in contrast to Zika, is an endemic infection that is not undergoing rapid spread, but at baseline it causes severe neurological morbidity in newborns every year, with little media or public attention devoted to the problem. It remains to be elucidated whether re-infection with Zika can occur in women with pre-conception immunity to the virus, or whether infants who appear normal at birth may nonetheless have congenital Zika infection and, with it, a risk of more subtle neurodevelopmental abnormalities (such as sensorineural hearing loss or mild learning disabilities) that become evident only later in life. Both of these clinical scenarios are features of congenital CMV infection.

Against the backdrop of this issue focusing on high-priority areas of antiviral vaccine research, what can we expect with respect to development of vaccines designed to protect reproductive health? A vaccine for prevention of congenital Zika virus infection is a major priority, and already the race is on in both academia and pharma to identify a safe and effective vaccine strategy [12] — and, importantly, a vaccine that does not confer a risk of Guillain–Barre syndrome. The justifiable urgency to develop a Zika vaccine should remind us, however, that a vaccine against congenital CMV infection has been recognized as an urgent public health priority for 45 years [13], and yet no vaccine has been licensed. The disease burden of congenital CMV is large, and yet there is disappointingly little knowledge or awareness of modes

Table 1

Comparison of Zika and cytomegalovirus: virology, modes of transmission, pathogenesis, and fetal outcome

	Cytomegalovirus	Zika Virus
Virus	*Herpesvirinae* (double-stranded DNA)	*Flaviviridae* (Plus sense, single-stranded RNA virus)
Genome	~245,000 base pairs	~11,000 bases
Insect vector	No	Yes; *Aedes* mosquitoes
Person-to-person transmission	Yes; infectious secretions (urine, saliva, breast milk); blood; sexual transmission	Yes; sexual transmission
Trans-placental infection	Yes	Yes
Fetal infection	Yes	Yes
Brain injury	Microcephaly; lissencephaly; polymicrogyria; calcifications; loss of neuronal migration; CNS inflammation	Microcephaly; lissencephaly; polymicrogyria; calcifications; loss of neuronal migration; CNS inflammation
Pathogenesis	Infection/loss of neuronal progenitor cells; developmental stage-specific	
Central Nervous System Sequelae	Microcephaly; neurological deficits; retinitis; neurodevelopmental delay; sensorineural hearing loss	Microcephaly; neurological deficits; retinitis; neurodevelopmental delay; sensorineural hearing loss
Role of Immunity	Risk of fetal transmission highest in high-seroprevalance populations; reduced disease severity and transmission in setting of maternal preconception immunity but re-infections lead to transmission	Risk of fetal transmission highest in serologically naïve populations? Protective role of preconception maternal antibody?
Animal models	Yes; guinea pigs, rhesus macaques models of vaccines, fetal pathogenesis	Unknown
Knowledge and awareness	Low	High