



# Influence of herd immunity in the cyclical nature of arboviruses

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We review and contrast the evidence for an effect of amplifying host herd immunity on circulation and human exposure to arboviruses. Herd immunity of short-lived West Nile virus avian amplifying hosts appears to play a limited role in levels of enzootic circulation and spillover infections of humans, which are not amplifiers. In contrast, herd immunity of nonhuman primate hosts for enzootic Zika, dengue, and chikungunya viruses is much stronger and appears to regulate to a large extent the periodicity of sylvatic amplification in Africa. Following the recent Zika and chikungunya pandemics, human herd immunity in the Americas quickly rose to ~50% in many regions, although seroprevalence remains patchy. Modeling from decades of chikungunya circulation in Asia suggests that this level of herd immunity will suppress for many years major chikungunya and Zika epidemics in the Americas, followed by smaller outbreaks as herd immunity cycles with a periodicity of up to several decades.

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Current Opinion in Virology 2020, 40:1–10

This review comes from a themed issue on **Viruses in a changing world**

Edited by **Sara Cherry** and **Kellie Jurado**

<https://doi.org/10.1016/j.coviro.2020.02.004>

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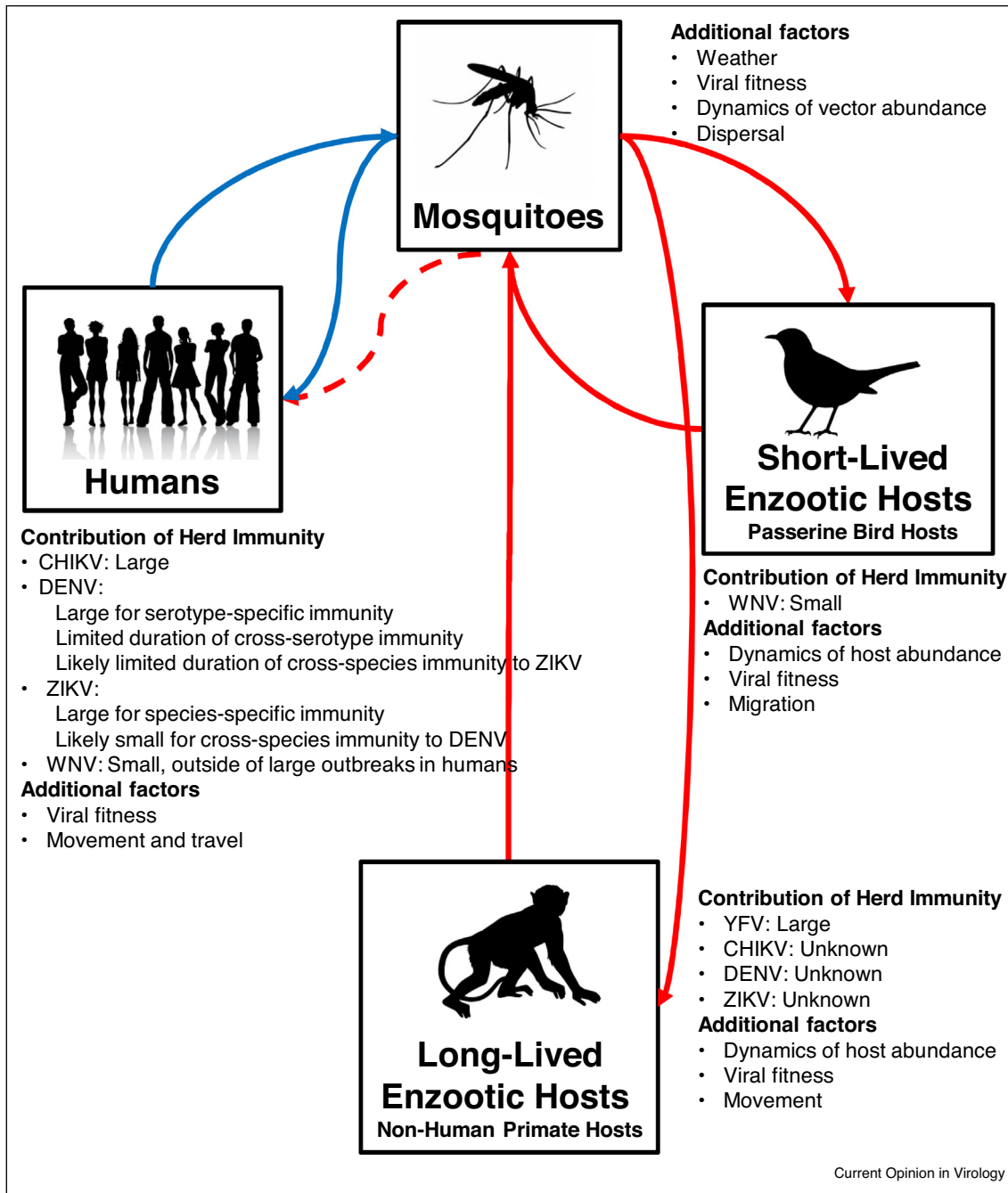
## Introduction to arboviruses and their transmission

Arthropod-borne viruses (arboviruses) are transmitted biologically, involving replication in arthropod vectors and vertebrate amplifying hosts [1]. The development of adaptive immunity, if it prevents secondary infection and viremia, removes hosts from the pool of susceptible amplifiers. Herd immunity can therefore have major impacts on arbovirus circulation and disease, and the temporality and cycling of epidemic and endemic transmission [2].

All arboviruses originated as zoonotic agents that rely on nonhuman animals as amplifying hosts by generating viremia needed for oral infection of the vector (Figure 1). Zika, yellow fever, dengue (DENV), and chikungunya (CHIKV) are four arboviruses with a history of sustained human-mosquito-human transmission in an urban cycle [3]. Here, we refer to these viruses as human-amplified urban arboviruses, although they also occur in more rural areas populated by *Aedes (Stegomyia) aegypti* and sometimes *A. (Stegomyia) albopictus* mosquitoes. However, all originated in sylvatic, enzootic cycles involving nonhuman primates (NHP) and arboreal mosquito vectors in Africa (YFV, CHIKV, ZIKV) or Asia (DENV). The vast majority of human arboviral pathogens remain in enzootic cycles with only dead-end, spillover infections of humans that do not extend the transmission chain; an example we discuss here is West Nile virus (WNV).

The five viruses discussed below are members of the genera *Flavivirus* (YFV, DENV, ZIKV and WNV) and *Alphavirus* (CHIKV). All except CHIKV produce predominantly asymptomatic infections, with most apparent disease presenting initially as a flu-like illness with non-specific signs and symptoms [3–6]. However, all of the flaviviruses have the potential to produce life-threatening disease or severe sequelae: hemorrhagic for YFV and DENV (principally in secondary infections for the latter); congenital birth defects, neurodevelopmental delays and neurological complications as Guillain-Barré syndrome, for ZIKV [5,7]; and neuroinvasive disease, mainly in older age groups, for WNV [6]. In contrast, CHIKV is usually symptomatic with characteristic severe, debilitating, and often chronic arthralgia, but it can be fatal for neonates after peri-natal exposure and for the elderly, mainly those affected by underlying comorbidities [3].

Figure 1



Influence of herd immunity and other factors on the cyclical transmission of arboviruses in humans. Arrows depict transmission pathways where (a) blue arrows illustrate maintenance of human-mosquito transmission observed for DENV, CHIKV and ZIKV; (b) red arrows depict enzootic transmission cycles seen for YFV, WNV, DENV, ZIKV and CHIKV, and (c) the red dashed arrow shows spillover transmission to humans from enzootic circulation of YFV and WNV and less frequently CHIKV, DENV and ZIKV.

Here, we discuss herd immunity for these five arboviruses, with an emphasis on their spread throughout the Americas since 1999. We also compare the human amplified viruses with those amplified only by wild

animals (e.g. WNV), and contrast regions of recent introductions (e.g. CHIKV in the Americas) with others with long-term endemic circulation (e.g. CHIKV in Asia, DENV throughout the tropics and subtropics).

## Enzootic arbovirus cycles and the effects of herd immunity on circulation and spillover

### Enzootic cycles of ZIKV, CHIKV, DENV and YFV

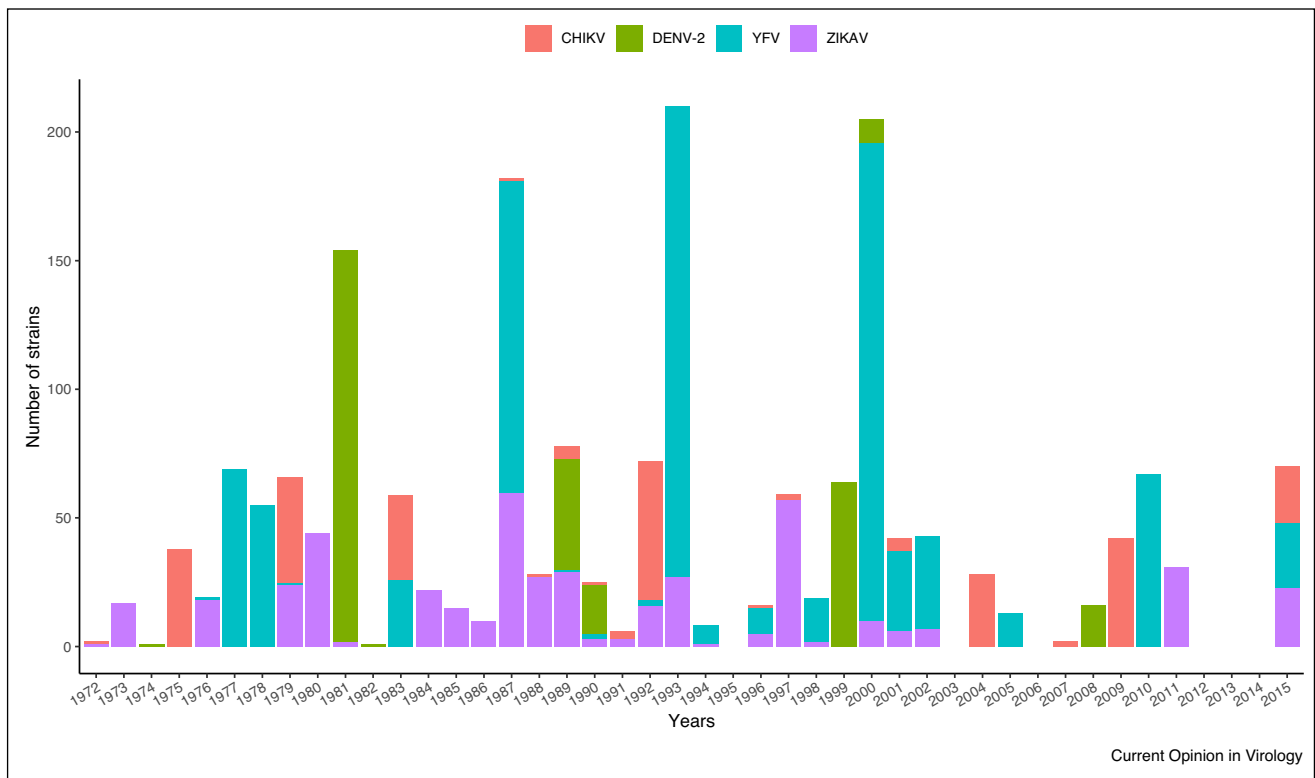
The enzootic, sylvatic cycles of urban, human-amplified arboviruses have received little attention relative to transmission in urban settings. A long-term dataset comes from eastern Senegal, where three NHP species (Guinea baboon, *Papio papio*; patas monkeys, *Erythrocebus patas*; African green monkeys, *Cercopithecus aethiopicus sabaues*) serve as amplifying hosts for these viruses, and several mosquito species transmit. Mosquito surveillance involving hundreds-of-thousands collected annually since the 1970s by the Institut Pasteur and collaborators, as well as NHP sampling, has detected only periodic epizootic amplifications. ZIKV had the highest annual amplification frequency, with detection in mosquitoes during 25 different years from 1972 to 2015, including one period of 8 consecutive years (Figure 2). In contrast, YFV, DENV and CHIKV were detected only during 19, 8 and 13 years, respectively, during the same period [8]. Synchrony is not always detected in these amplification patterns. Thus, although weather patterns that influence mosquito populations have some effect on circulation [9], other factors are also responsible for their periodicity. Age-stratified seroprevalence of NHP amplification hosts suggests that

their herd immunity limits amplification frequency, but that the viruses remain circulating at low levels between epizootics rather than becoming extinct [10<sup>\*</sup>]. The more frequent amplification of ZIKV compared to the other three viruses also suggests that a shorter-lived vertebrate with faster population turnover may be involved in addition to NHPs.

### West Nile virus and short-lived enzootic hosts

An inherent challenge with determining the effects of avian (passerine birds are the main amplifying hosts) immunity on long-term patterns of WNV transmission is the paucity of long-term data on amplification and spillover to humans. Data on West Nile neuroinvasive disease (WNND), the metric of human disease less vulnerable to reporting bias than the more easily misdiagnosed West Nile fever (WNF; [11]), do not necessarily reflect levels of enzootic transmission by *Culex* mosquitoes [12,13]. Although humans are not amplifying hosts, the probability of spill-over disease is complicated by human herd immunity from prior exposure. Humans are long-lived, but the proportion of the population exposed to zoonotic mosquito-borne viruses like WNV is typically a small fraction [14]. However following large outbreaks, locally high levels of human herd immunity may occur

Figure 2



Numbers of chikungunya (CHIKV), dengue serotype 2 (DENV-2), yellow fever (YFV), and Zika virus (ZIKV) isolations from mosquitoes collected in the Kedougou region of southeastern Senegal from similar amounts of annual sampling during the rainy season.

(e.g. >25% in parts of Israel [15]) and could be a significant factor regulating annual variation of human disease [16], independent of the enzootic cycle.

In addition, WNND is often spatially heterogeneous, even within a year. For example, the Dallas-Ft. Worth, Texas region experienced the largest concentration of WNND cases in the U.S. in 2012 [17]. However, the nearby city of Houston in Harris County had relatively few cases in 2012, and instead 2014 was the largest WNV epidemic in its history [18]. Thus, aggregated WNND data at the national and even state levels mask spatial variation in WNV transmission, and are thus less informative for elucidating the role of avian herd immunity in cyclical patterns of circulation and human exposure. Instead, the role of avian herd immunity in modulating inter-annual transmission patterns must be assessed at the local (i.e. county) level, and should ideally combine data on passerine seroprevalence, *Culex* mosquito abundance and infection, and WNND incidence.

The best empirical evidence of avian herd immunity influencing WNV transmission is from a long-term study in Los Angeles County, California [19], which revealed elevated adult and juvenile bird seroprevalence following years with high levels of WNV transmission and human cases. Then, as susceptible bird populations were replaced with recruitment during years of low WNV transmission, herd immunity dropped to <10% [20,21]. The finding that low avian seroprevalence in the spring and summer preceded WNV outbreaks also builds on prior evidence from the same region concluding that a combination of the temperature variation and mosquito abundance, along with low avian herd immunity, drive seasonal variation in transmission and human disease [22]. However, more recent WNND data from Los Angeles County show that the cyclical pattern of transmission observed during the first decade after introduction later diminished (Figure 2), possibly because WNV lineages circulating in California changed their fitness for infection of mosquitoes and birds [23].

Elsewhere in interior regions of the U.S., annual weather can be less stable without buffering from an adjacent ocean. For example, suburban Chicago, Illinois, which has experienced periodic WNV epidemics, shows considerable variation in temperature and precipitation from year-to-year [24–26], as does Houston, Texas, where variation in temperature influences *Cx. pipiens* and *quinquefasciatus* abundance [27]. At the state level, drought conditions were identified as the most important extrinsic factor regulating WNND incidence [16].

Finally, theoretical studies suggest that herd immunity has a stronger influence when its duration equals life expectancy and when transmission levels are high [2,28]. Avian hosts are relatively short-lived, with typical

life expectancies of 1–2 years [20,29,30]. Thus, avian herd immunity tends to remain relatively low given their high birth rates, despite life-long immunity following infection. Furthermore, juveniles, which do not maintain maternally acquired antibodies for more than a few weeks [31], are considered the most important WNV amplifiers [32]. The interaction of seasonal factors such as weather, which drive variation in transmission when reservoir hosts have short-lived immunity or short lifespans, makes it difficult to detect universal patterns of transmission influenced by herd immunity (Figure 3).

### Human-amplified urban arboviruses

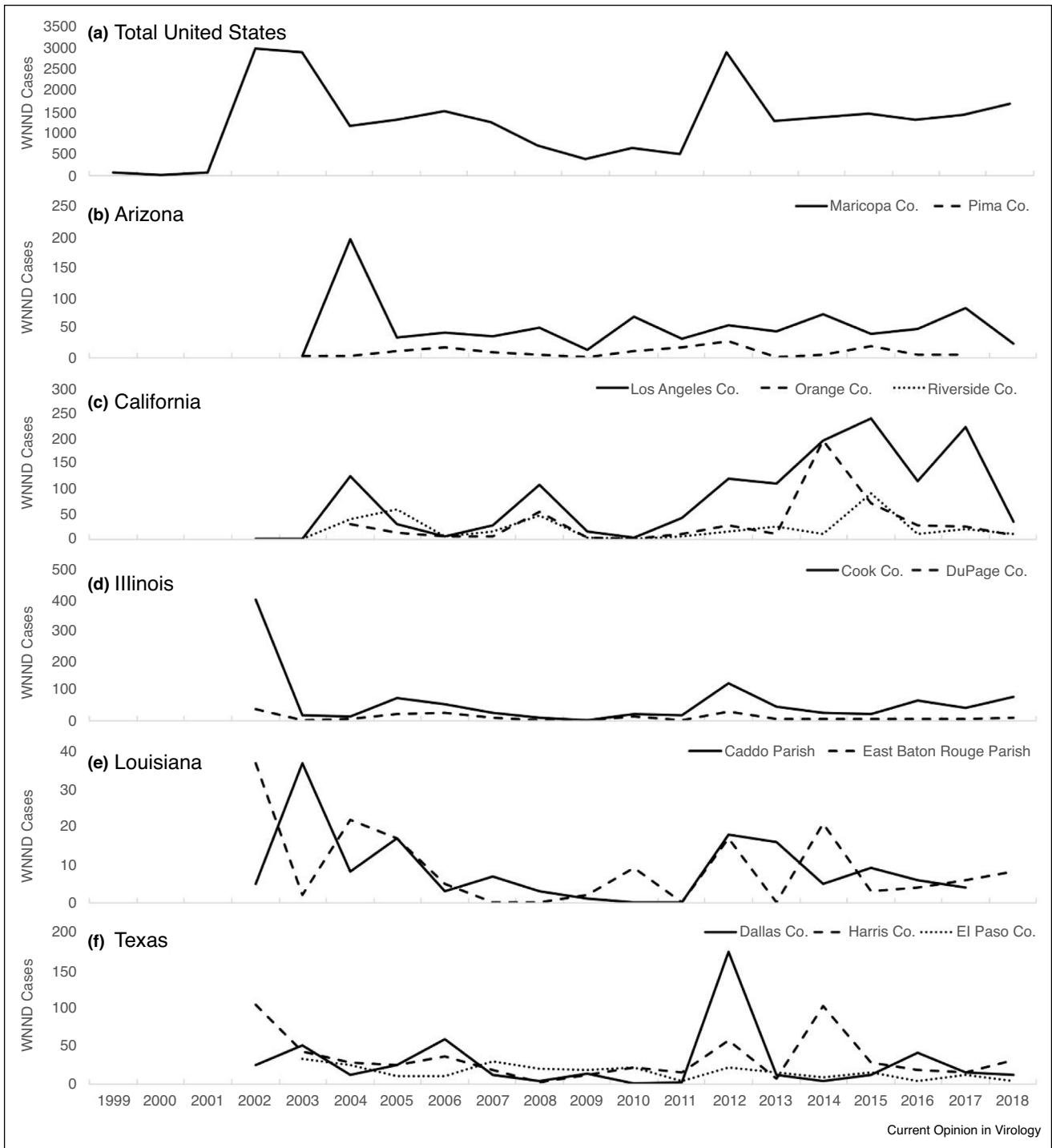
Compared to enzootic arboviruses, herd immunity for human-amplified arboviruses has greater influence on fluctuations in DENV, ZIKV, and CHIKV transmission. This reflects the long duration of human immunity, longer human lifespans, and relatively low birth rates compared to enzootic hosts, which in turn limit the proportions of individuals who are newly susceptible to infection.

#### Zika virus

ZIKV transmission was first recognized in the Americas in April 2015 during a large epidemic in northeastern Brazil, and spread throughout Latin America by 2016 (or earlier, but without initial recognition) [5,33]. At that time of ZIKV introduction, surveillance and diagnostics were not prepared to detect and report cases. Nevertheless, ~650 000 cases were reported to PAHO in 2016 [34]. This number greatly underestimates the true burden of ZIKV infection, given the deficits in the surveillance and their largely asymptomatic nature. Investigations performed in the city of Salvador, Brazil found that 63%–73% of the population was exposed by the end of the 2015 outbreak [35,36], and provided empiric evidence that the resulting herd immunity drove ZIKV transmission to extinction [36].

Early modeling investigations projected that ZIKV infection rates during the pandemic in the Americas will provide sufficient herd immunity to mitigate the risk of another large epidemic for at least another decade [37]. However, the extent of ZIKV transmission remained patchy and widely variable in the Americas; for example, in French Guiana, overall seroprevalence was estimated at 23.3%, ranging from 0% to 45.6% in different municipalities [38]. In addition, more than 31 000 suspected and 3500 confirmed Zika cases were reported to the Pan American Health Organization (PAHO) in 2019 [34], indicating that on-going transmission is occurring, primarily in Central and South America. While pockets of susceptible populations that have not been infected may continue to drive low-level transmission, the consensus is that significant levels of herd immunity have accumulated in many parts of Central and South America [39].

Figure 3



West Nile neuroinvasive disease (WNNND) cases in humans reported to ArboNET between 1999 and 2018 for the United States (a), Arizona (b), California (c), Illinois (d), Louisiana (e), and Texas (f). Selected counties and states included in this figure had among the highest numbers of cases reported, providing more opportunity to consider the influence of herd immunity on longitudinal patterns. Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado.

The contribution of prior infection and herd immunity to the transmission dynamics of ZIKV in Africa and Asia is entirely unknown [5]. ZIKV has been circulating in these continents for decades or more, yet large outbreaks have not been reported. Although there is evidence suggesting that seroprevalence to ZIKV in certain regions of Asia may be sufficient to confer herd immunity [40], several studies have documented only low seroprevalence (<10%) in populations where endemic dengue occurs [41]. Surveillance for Zika is now being established in Asia and has identified small outbreaks, which will provide future insights on the role of herd immunity and other potential factors, such as cross-species protection conferred by DENV exposure, in the timing of Zika epidemics and transmission cycles.

### Dengue virus

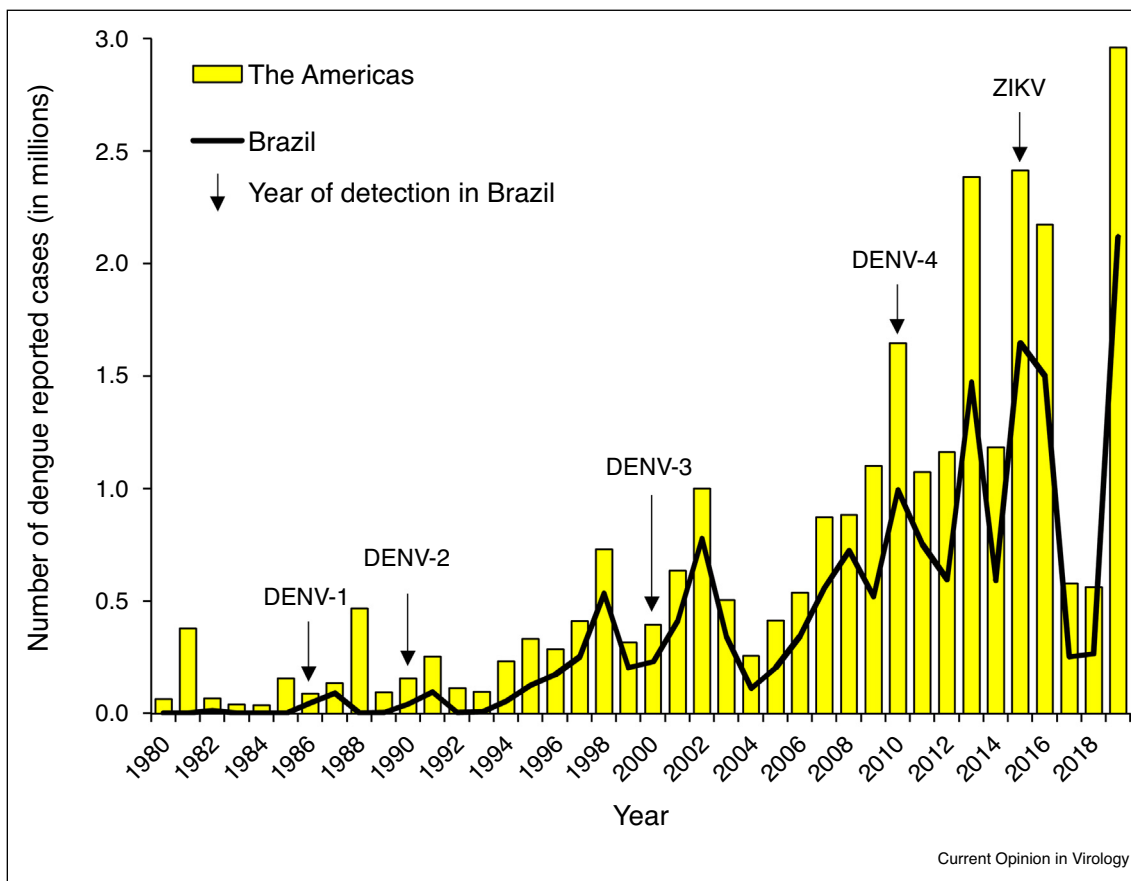
Four different serotypes cause human infection (DENV-1 to DENV-4). Immunity against the infecting serotype is usually lifelong, but heterotypic protection against other

serotypes tends to be short (<1–3 years) [42]. Consequently, DENV is characterized by cyclical epidemics, followed by periods of lower transmission due to the resultant herd immunity that reduces the susceptible population for efficient amplification. In general, this period of interepidemic transmission lasts 3–5 years; then, when heterotypic immunity declines and a new DENV serotype is (re)introduced, another epidemic occurs. This pattern has been seen repeatedly throughout the DENV range (Figure 4).

### Dengue-Zika cross-immunity

ZIKV and DENV are antigenically similar as closely related flaviviruses, and elicit highly cross-reactive immune responses [5], which has hampered development of specific serodiagnostics to differentiate these infections. ZIKV infection can boost cross-neutralizing and cross-protective antibody responses in individuals previously exposed to DENV [43]. Two prospective studies provide evidence that pre-existing DENV

Figure 4



Annual number of dengue cases reported in the Americas and Brazil, and years of first detection of DENV and ZIKV in Brazil, 1980–2019. Source of data: Pan-American Health Organization (available at: <http://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en.html>) Data for 2019 accessed on November 12, 2019.

immunity confers reciprocal cross-protective immunity to ZIKV. In a Nicaraguan pediatric cohort, children with prior DENV infection had a decreased risk of symptomatic ZIKV infection compared to those without DENV immunity, but this protection did not affect the overall (symptomatic plus asymptomatic) rate of ZIKV infection [44]. Another cohort study from Salvador, Brazil found that participants with preexisting, high-titer DENV antibodies had a reduced risk of symptomatic as well as of overall ZIKV infection [35<sup>\*\*</sup>]. Given the large Zika epidemics in the Americas after decades of intense DENV circulation, pre-2015 DENV herd immunity may not have played a major role in preventing ZIKV infections. More likely, prior DENV exposure reduced the risk for the development of symptoms after ZIKV infection.

Conversely, exposure to ZIKV may elicit cross-protective immunity, and possibly cross-protective herd immunity to DENV. In rhesus macaques, ZIKV infection modulates the magnitude of both antibody and T cell responses against subsequent DENV infection, supporting the hypothesis of herd cross-immunity against DENV after ZIKV infection [45]. Following the Zika epidemic in Salvador, Brazil in 2015 [46], a major reduction in dengue was observed during longitudinal surveillance for acute febrile illnesses. Before the epidemic, between 2009 and March, 2015, 25% of the 1937 enrolled patients had PCR-confirmed DENV infections. However, after the Zika epidemic, between April, 2015 and May, 2017, DENV infections decreased to 3% of the 1334 tested subjects [47<sup>\*\*</sup>]. Consistent with this local reduction in Salvador, reductions in annual dengue case reports were observed throughout Latin America (from >2.1 million cases in 2015–2016 and always >500 000 from 2006 to 2015, to ~570 000 in 2017–2018) [34]. A panel of experts considered alternative hypotheses (such as changes in surveillance and/or density and competency of *Ae. aegypti* vectors) and concluded that the most likely explanation for this dengue decline was cross-reactive immunity established by Zika epidemics [48]. However, the resurgence of dengue epidemics in the Americas in 2019 (2.9 million cases as of November) suggests that cross-protective immunity is short-lived (Figure 4), in accordance with simulations of surveillance data for reported dengue and Zika cases from Brazil and Colombia [49<sup>\*</sup>]. The models not only supported the hypothesis that cross-protection suppressed dengue incidence following Zika outbreaks, but also concluded that dengue resurgence should be expected.

#### Chikungunya virus

The Asian CHIKV lineage arrived in the Americas in 2013, then quickly swept through the Americas. This introduction was followed closely by an East/Central/South African (ECSA) lineage strain imported into Brazil from Africa. Both strains generated massive epidemics in

completely naïve human populations. Compared to DENV and ZIKV, CHIKV seroprevalence is easier to measure due to fewer problems with cross-reactions in diagnostic assays, so seroprevalence data are in some cases more conclusive.

Following the 2013–2014 CHIKV epidemics in the Caribbean, seroprevalence in blood donors was 48.1% in Guadeloupe, 41.9% in Martinique [50], and 23.5% in Puerto Rico in 2015 [51]. On Saint Martin Island, seven months after CHIKV introduction, a convenience serosurvey of subjects >6 months of age found a combined IgG/IgM seroprevalence of 20.7% (age-adjusted and sex-adjusted: 16.9%) [52]. In Haiti, a seroprevalence study including 62 urban and 92 rural sites found IgG prevalence of 57.9%, <1 year after CHIKV was first detected. Interestingly, the differences between rural and urban areas were pronounced (mean 44.9% versus 78.4%, respectively) [53].

In the continental Americas, CHIKV seroprevalence ~1.5 years following its introduction ranged from 45.7%–57.1% in two urban areas of northeastern Brazil [54], and 20.0% in a rural area [55]. In central Mexico, 29.5% of tested subjects were seropositive 18–20 months after CHIKV's arrival [56]. In Nicaragua, a national serosurvey of subjects >2 years of age found overall seroprevalence of 32.8% in October, 2015, about one year after the first autochthonous cases [57]. Another Managua study following the first epidemic peak found seroprevalences of 6.1% and 13.1% among 2–14 and ≥15 year-old participants, respectively [58]. Following a second, larger epidemic wave, seroprevalence among 2–14 year-olds increased to 24.9%, peaking at 45.6% in those 14 years of age [59].

In the Philippines, age-stratified CHIKV serological data were collected from 1973 to 2012 to reconstruct transmission dynamics [60<sup>\*\*</sup>]. In 1973, 22% of the tested subjects were plaque-reduction neutralizing test (PRNT)-seropositive, ranging from 6% (<10 years of age) to 42% (40–49 years). In 2012, overall seroprevalence was 28% but no children <14 years of age were positive, suggesting the absence of CHIKV transmission during this 14-year period. Modeling implied that, between 1952 and 2012, 3.1 outbreaks (95% CI, 3.0–4.0) occurred, with a probability of infection among susceptibles of 23% per outbreak (95% CI, 16%–37%). Importantly, the analyses suggested that the susceptible proportion of the population after outbreaks always remained >50%, with seroprevalence preceding outbreaks ranging from 5 to 28%. This is in accordance with most seroprevalence data from the Americas, indicating that after intense CHIKV transmission, seroprevalence reaches up to ~50%, but remains spatially heterogeneous. Thus, the level of herd immunity now seen throughout much of the Americas will likely limit the occurrence of major new epidemics until a new birth cohort provides additional amplifying hosts. With an identical transmission cycle, a single serotype, similar  $R_0$  values, and similar patterns of spread in the Americas, ZIKV

will likely exhibit similar trends in the region. Finally, recent trends of major DENV epidemics indicate that ZIKV cross-protection has waned, suggesting that DENV will return to its formerly preeminent status among urban arboviruses in the Americas.

### Summary and research needs

Overall, the impacts of herd immunity on the enzootic and endemic/epidemic transmission of arboviruses vary greatly based on the lifespans and population turnover of their amplification hosts, with the short-lived avian hosts of WNV being typical of many zoonotic arboviruses. Herd immunity of these hosts with rapid population turnover probably has only limited impact on levels of circulation and the associated risks of human spillover infections. Longer-lived enzootic hosts such as NHP with slower population turnover have much more impact on the periodic nature of enzootic amplification of YFV, DENV, ZIKV and CHIKV, with risks for human spillover exemplified by the recent YFV epidemic in Brazil. However, for the few human-amplified arboviruses such as YFV, DENV, ZIKV, and CHIKV, human herd immunity has a major impact on both circulation and risk, with major, explosive outbreaks produced when these viruses are introduced into naïve populations (e.g. ZIKV and CHIKV recently in the Americas) and smaller, periodic outbreaks or no transmission once herd immunity limits transmission efficiency or drives transmission to extinction thereafter. Time-limited cross-protection between DENV and ZIKV appears to further complicate this pattern of periodic outbreaks.

Despite these general conclusions, further research remains critical to better understanding herd immunity and its impacts on arbovirus circulation and risk. Levels of enzootic WNV circulation vary dramatically across time and space despite similar levels of avian immunity, probably the result of complex interactions between weather and climate, mosquito vector populations, and avian host populations that remain enigmatic. Enzootic transmission cycles of YFV, DENV, ZIKV, and CHIKV in Africa vary in their periodicity despite the use of the same repertoire of vectors and NHP hosts, suggesting the possibility of other enzootic hosts yet to be incriminated and possibly interactions among these viruses. Knowledge of the temporal patterns of circulation of all of these viruses is extremely limited due to the lack of surveillance in most parts of their enzootic ranges and outside of apparent outbreaks for human-amplified transmission. The lack of cost-effective, point-of-care diagnostics for most arbovirus further complicates surveillance challenges, especially for the flaviviruses where cross-reactivity in serologic tests remains problematic. Our ability to increase our understanding of spatial and temporal patterns of human risk to improve predictions and interventions will ultimately progress in all of these areas through research efforts sustained during interepidemic periods [61]. The boom-and-bust support for surveillance and research programs, driven by the latest outbreak and public health emergencies,

and media attention, must be replaced by concerted and consistent efforts to understand the transmission dynamics of arboviruses.

### Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

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