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The use of longitudinal cohorts for studies of dengue viral pathogenesis and protection

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In this review, we describe how longitudinal prospective community-based, school-based, and household-based cohort studies contribute to improving our knowledge of viral disease, focusing specifically on contributions to understanding and preventing dengue. We describe how longitudinal cohorts enable measurement of essential disease parameters and risk factors; provide insights into biological correlates of protection and disease risk; enable rapid application of novel biological and statistical technologies; lead to development of new interventions and inform vaccine trial design; serve as sentinels in outbreak conditions and facilitate development of critical diagnostic assays; enable holistic studies on disease in the context of other infections, comorbidities, and environmental risk factors; and build research capacity that strengthens national and global public health response and disease surveillance.

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Introduction

Although the most well-known prospective cohort studies have focused on predictors of chronic disease [1], cohort studies are also important for understanding infectious diseases. In a cohort study design, individual-level baseline characteristics are measured in a healthy population followed over time as participants naturally acquire disease, thus enabling identification of factors associated with or protective against disease risk. For example, two key findings of such studies include identification of distinct transmission rates of influenza A and B viruses among humans [2] and differential gender-based HIV transmission rates in discordant couples [3]. Prospective community-based, school-based, and household-based cohort studies are particularly useful to study acute viral diseases such as dengue. Dengue virus is comprised of four serotypes, DENV1–4. Infection with one serotype provides long-term protection against disease upon re-infection with the same serotype. However, prior immunity can protect against or enhance disease during secondary heterotypic DENV infection, which is the greatest risk factor for severe dengue disease, Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS). DHF/DSS is thought to be caused in part by antibody-dependent enhancement (ADE): sub-neutralizing antibody titers enhance viremia [4] by enabling infection of monocytes and macrophages via Fcγ receptors [5•,6]; this instigates pathologic immune cell activation and elevated NS1 secretion that result in vascular leak and shock [7]. Because immune history is critical for understanding subsequent disease risk and protection, cohort studies are invaluable for studying protection against and pathogenesis of dengue disease.

Here, we discuss the full value of longitudinal cohorts for: measuring basic determinants and immunological and virological characteristics of dengue disease in populations, estimating correlates of protection and disease risk, providing critical and timely information during outbreaks, enabling rapid development of new assays for diagnosis and surveillance, informing vaccine trial design, studying disease in a broader population context, building research capacity, and informing local and international policy-making (Table 1).

Review of dengue cohort studies

We used PubMed to download all articles with the term 'dengue' in the title and 'cohort' in either the title or abstract (n = 283, January 4, 2018). Titles and abstracts were screened to identify prospective cohort studies of dengue in healthy populations (some reviewed previously in [8–10]; we do not review infant cohorts or index cluster studies here). We identified 28 cohort studies from 1962 to the present (Table 2).

Incidence, burden, and risk factors

Incidence

Dengue cohort studies are used to estimate DENV infection and disease incidence in a given population. Symptomatic disease is measured by active surveillance for febrile illness and testing of acute and convalescent blood samples with molecular biological, virological and/or serological methods. Inapparent infections are measured by rise in antibody titers between pre-epidemic and

Table 1

Ten ways cohort studies promote scientific research and infectious disease control

1. Estimate basic infection and disease incidence, transmission parameters, and risk factors
2. Identify correlates of protection and disease risk
3. Enable scientific studies of well-characterized samples with advanced scientific techniques
4. Provide longitudinal samples to study kinetics of antibody and biomarker levels
5. Inform vaccine trial design and evaluation
6. Serve as sentinels during outbreaks to inform local and international policy decision-making
7. Collect high-quality samples for diagnostic assay development
8. Enable holistic studies of multiple diseases and environmental and socioeconomic factors
9. Increase understanding of individual and intrinsic differences that drive immunity to pathogens
10. Foster infectious disease infrastructure, research, and control in disease-affected countries in close collaboration with Ministries of Health

post-epidemic or annual blood samples. Dengue disease incidence ranges from 0.3 to 4.6 per 100 person-years, exhibiting substantial heterogeneity by year and location. Cohort studies have shown that incidence of symptomatic dengue is higher in Asia than Latin America and that a larger fraction of dengue cases require hospitalization in Asia [11,12,13•]. DENV-attributable incidence among febrile cases was measured as 7.7% in Colombia and in Thailand accounted for 15% of DALYs attributable to febrile illness [14,15]. Estimates of dengue disease incidence in cohort studies have been compared to national-level surveillance data, enabling determination of expansion factors (e.g. from 4.7 to 22 cases identified by active surveillance for every 1 case identified by passive surveillance) [16–19] and estimation of national and global incidence, burden, and mortality [20–22]. DENV infection incidence ranges from 3 to 39.4 per 100 person-years [12,23,24•,25•], with the ratio of symptomatic to inapparent infections (S:I) varying dramatically in cohorts within epidemics, across years [12,49], and by geographic area (e.g. nearby schools) [13•,26,27•]. Analysis has shown that years with high S:I ratio (more symptomatic infections) are often followed by years with low S:I ratio (more inapparent infections) [12,28].

Primary versus secondary infections

The first dengue cohort studies found that DHF/DSS cases were only observed in individuals who had anti-DENV antibodies in pre-infection samples [8,29]. Larger cohort studies proved that pre-existing immunity is a strong risk factor (odds ratio 6.5 in one study, relative risk >50 in another) for DHF/DSS, and DENV2 was most strongly associated with DSS [30•,31,32•]. Cohort studies also showed that the probability of symptomatic disease is lower during primary than secondary DENV infection, particularly when the secondary DENV infection occurred >1 year after primary infection [33].

Age and sex

Cohort studies have not consistently shown differences in DENV infection or symptomatic dengue by sex [12,13•,24•,25•], although differences in DSS by sex have been observed [8]. Age is related to both the probability of exposure and disease incidence. First, younger children have more undifferentiated fever caused by DENV, possibly because they do not describe symptoms as easily as older children [34]. Second, older age is associated with probability of DENV infection, likely due to increased mobility [12,35] and body surface area or mass [36,37]. Third, age of secondary DENV infection is associated with higher probability of severe disease [38], while age of acquisition of post-secondary infection immunity is associated with reduced probability of serologically detectable DENV infection given exposure [24•]. Finally, older age is associated with greater probability of disease, even controlling for anti-DENV antibody titer and number of previous infections [39•].

Spatial heterogeneity

Dengue cohort studies have revealed spatial heterogeneity of circulating serotypes and genetic diversity of viral strains circulating in a given population, including extensive gene flow from larger urban centers into more rural populations as well as between nearby schools [40–42]. Spread of a novel serotype, DENV3, in Iquitos, Peru, was correlated with high pre-existing community seroprevalence, suggesting certain areas had higher risk of transmission [27•,43].

Force of infection

Cohort studies collect age-stratified seroprevalence data, enabling estimation of the force of infection — the rate at which naïve individuals become infected in a population. Age-stratified seroprevalence data from cohort studies have been used to estimate average historical and annual differences in the force of infection, and where serotype-specific neutralizing antibody titers were measured, serotype-specific force of infection [24•,44–46].

Correlates of protection and disease risk

The value of cohort studies for measuring immune correlates

While hospital-based studies are critical for identifying prognostic indicators in acute-phase samples for progression to severe dengue [47] or viral determinants associated with severe dengue outcomes [48], they are limited in that they can only examine individuals who are already sick. Cohorts are essential for evaluating how