Dengue: a trilogy of people, mosquitoes and the virus. Current epidemiology and pathogenesis in (non-)endemic settings

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CHAPTER 5

GEOGRAPHICAL HETEROGENEITY
OF DENGUE TRANSMISSION
IN TWO VILLAGES
IN SOUTHERN VIETNAM

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This study was performed to test the hypothesis that there are "hotspots", i.e. geographical heterogeneity, of dengue transmission. Data from two repeat sero-surveys in two villages in Vietnam were used to identify incident infections and to relate these to prevalence at baseline and thus assess geographical heterogeneity, i.e. clustering, in dengue transmission. A total of 400 households were surveyed; serological data from 521 children at baseline and from 119 children at follow-up were included in a spatial analysis. Geographical heterogeneity of dengue transmission was explored using a permutation null distribution test. This showed for the first time evidence of clustering of dengue virus transmission at the household level among asymptomatic children. Risk areas could be identified by sero-prevalence surveys combined with mapping. Control of dengue virus transmission could be supported by identification and control of hotspots.

1. INTRODUCTION

Recent estimates indicate that approximately 3.5 billion people, ~55% of the world's population live in countries at risk for dengue.16 Dengue ranks among the most important infectious diseases with a major impact on public health in Vietnam and many other countries in the tropics and subtropics. Dengue virus transmission primarily takes place through bites by the mosquito vectors, *Aedes aegypti* and *Aedes albopictus*, which feed preferentially on human blood, and are often found in and around human dwellings.112,245 Infection with dengue virus results in either (almost) asymptomatic infection, undifferentiated febrile illness, dengue fever (DF) or even life-threatening manifestations such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).235

To date, no vaccine or chemotherapy is yet available. Prevention and control of dengue transmission therefore depend on vector control (larvicide treatment, insecticide sprays and elimination of breeding sites) and avoidance of bites. The national dengue control program in Vietnam recommends vector control by larvae elimination. However, these measures are usually only implemented after notification of severe cases (DHF and DSS).527 This local policy is based on the assumptions that such cases reflect locally increased vector densities with higher infection rates. It remains unclear to what extent this approach controls further transmission, because the majority of dengue virus infections (~80%) are mild/atypical or even asymptomatic.27 It is therefore likely that such measures are not adequate to prevent sustained transmission, because the majority of dengue virus infections (~80%) are mild/atypical or even asymptomatic.27 It is therefore likely that such measures are not adequate to prevent sustained transmission, because the majority of dengue virus infections (~80%) are mild/atypical or even asymptomatic.27

This study used available data from a cross-sectional, a follow-up study and a household survey in two communes, Ham Kiem and Ham Hiep, among primary school children.272-274 Briefly, we conducted a cross-sectional study in two communes in 2003, in which all primary school children at two primary schools in the two communes were included and their prevalence of antibodies to dengue measured. Additionally, a household survey was carried out in 400 houses. All children who had no dengue virus-specific IgG serum antibodies in a sero-survey of 2003 were retested in a follow-up study which was conducted in 2005. From 2002 census data, the total populations in Ham Kiem and Ham Hiep were 6,467 and 11,131. The population densities of the two communities were approximately 109 people/km² and 322 people/km² for Ham Kiem and Ham Hiep, respectively. It has a tropical climate with a mean temperature of 27 °C, an average monthly rainfall of approximately 100 mm and a rainy season that lasts from May until October.

2. METHODS

2.1. DATA SOURCES, STUDY SITES AND POPULATION

This study used available data from a cross-sectional, a follow-up study and a household survey in two communes, Ham Kiem and Ham Hiep, among primary school children.272-274 Briefly, we conducted a cross-sectional study in two communes in 2003, in which all primary school children at two primary schools in the two communes were included and their prevalence of antibodies to dengue measured. Additionally, a household survey was carried out in 400 houses. All children who had no dengue virus-specific IgG serum antibodies in a sero-survey of 2003 were retested in a follow-up study which was conducted in 2005.

To explore the hypothesis that dengue virus transmission is spatially focal, we used available data from a cross-sectional sero-epidemiological study in 2003, a two year follow-up study and a household survey in two communes, Ham Kiem and Ham Hiep in southern Vietnam.272-274

2.2. GEOGRAPHIC MAPPING

During the household visits in 2003, geographic coordinates were recorded. The latitude and longitude of household visits were recorded using a hand-held global positioning system (eTrex®, Garmin International Inc., USA). The coordinate system and datum used were degree decimal and WGS-84, respectively. MapInfo Professional (MapInfo Corp., 1998) was used to display the distribution of dengue serum specific IgG cases per household.

2.3. STATISTICAL ANALYSIS

We hypothesized that there is geographical heterogeneity in dengue transmission within communities with the occurrence of "hotspots". If so, new infections, as indicated by observed seroconversion during follow-up, would occur near places where dengue IgG seroprevalence was highest at baseline (2003). If not (the null hypothesis) new infections would occur randomly.

To test this hypothesis we looked at the geographical distance between old infections (i.e. children who were seropositive for dengue) at baseline and new infections observed during follow-up using a permutation analysis.

Consider a child *i* at baseline living at coordinates $Q_i = (x_i, y_i)$. Let $P_i = 1$ if the child was seropositive and -1 otherwise. Similarly, let consider a child *j* observed at follow-up, and let,
again, \( l_j = 1 \) if the child was seropositive and \(-1\) otherwise. The coordinates of this child are 
\[ Q_j = (x_j, y_j). \]

Now consider the statistic:
\[
T = \sum_{i=1}^{N} \sum_{j=1}^{M} w_i P_i d(Q_i, Q_j)
\]

where \( d(Q_i, Q_j) = 1/(0.001 + \text{distance}(Q_i, Q_j)) \) where the (Euclidean) distance is measured 
in degrees (i.e. approximately 110 km) so that \( d(Q_i, Q_j) \) of sites a hundred meters (flying 
distance of vectors) apart is about half that of the \( d() \) between a spot and itself.

Further, let \( w_i \) (the “weight” of a baseline child) be taken \( = \text{age} \) for \( P_i = -1 \) and \( = 1/ \text{age} \) for \( P_i = 1 \). This weighting was done because age is an important predictive factor 
for seropositivity since the seroprevalence increases strongly with increasing age. \(^{272}\)

The permutation null distribution (with separate permutations for the two communities 
in the study) was generated using a specially written computer program. Large values 
(relative to the permutation null distribution) reflect the existence of hotspots. A total of 
100 draws from the permutation null distribution were generated using this program.

2.4. ETHICAL CONSIDERATION

The protocols for recruitment, testing and follow-up were approved by the Provincial Health 
Services, the community stations of Ham Kiem and Ham Hiep and the Scientific Committee 
of Cho Ray Hospital, Ho Chi Minh City. In cooperation with the People’s Committee of the 
villages, the health post-staff and school teachers, all children of the primary school and 
their parents were informed about the study and consent was obtained from all.

3. RESULTS

3.1. BASELINE SERO-PREVALENCE

The study design and data sources are shown in figure 1. Figure 2 shows the map of Binh 
Thuan province, Vietnam and location of the study areas. During the household survey in 
2003, a total of 400 households, home to 533 children, were visited for obtaining geographical 
coordinates. Serological data were available for 521 children of which 339 (65%) were positive 
for dengue serum specific IgG. This was taken as background sero-prevalence in this study. 
The spatial distributions of the households of these 521 children in the villages are shown in 
figure 3 and 4.

3.2. GEOGRAPHICAL HETEROGENEITY

All children \((n = 216)\) who had no dengue virus-specific IgG serum antibodies (dengue naïve) in 
a sero-survey of 2003 and who had been followed-up for 23 months were eligible for inclusion 
to exploring the heterogeneity of dengue transmission excluding 97 children whose geographical 
coordinates had not been recorded in 2003. Because only dengue naïve were included, any 
seroconversion of IgG was due to dengue infection during the 23 months of follow-up. In the 
permutation analysis, we considered 119 children, 65 and 54 from Ham Kiem and Ham Hiep, 
respectively. These children were living in 111 households. All children who have been followed-
up lived in the same house as two years previously. Figure 5 shows the permutation null 
distribution of \( T_{\text{observed}}/T_{\text{null}} \). The null distribution values exceeded 1 for every permutation, i.e. the 
observed clustering exceeded random draws from the null distribution 100/100 times. Clearly, 
this provides cogent evidence for the existence of geographical heterogeneity, i.e. that new 
infections occurred near places where prevalence was highest at baseline.

4. DISCUSSION

Results in this study showed that new dengue virus infections occurred near places where 
sero-prevalence was highest at baseline, suggesting important spatial heterogeneity in the 
transmission of dengue. This study overcomes methodological problems of earlier studies 
which looked at clustering of symptomatic cases. \(^{17;183}\)

There are several plausible explanations for the nearby simultaneous appearance of dengue 
cases at household level. First, entomological studies have shown that \textit{Ae. Aegypti} has a multi-
feeding behaviour on multiple people during a single gonotrophic cycle. \(^{50;246;247}\) The implications of
Figure 1: Data sources overview

Figure 2: Map of Bình Thuan province, Vietnam and location of the study areas.
Figure 3. Distribution map of children per household in Ham Kiem, Binh Thuan, Vietnam.

Figure 4. Distribution map of children per household in Ham Kiem, Binh Thuan, Vietnam.
this behaviour may include the occurrence of clusters of dengue cases in or nearby the same household and the rapid and sometimes explosive spread of dengue. However, this is unlikely to account for our observations in view of the probable (long) time lag between “baseline” infections and follow-up infections. Second, local occurrence of dengue clusters could also be due to locally elevated vector density. Cluster investigations in Thailand showed significant differences in the *Ae. aegypti* pupae/person ratio among dengue cases in comparison with non-dengue cases. However, no significant differences were shown for adult *Ae. aegypti* population density. Abundance of pupae or adult female mosquitoes may be informative for routine surveillance or as an eradication measure, but these measures lack correlation between indices and dengue disease. Detection of DENV-infected adult *Ae. aegypti* female mosquitoes that can potentially infect multiple individuals may be more relevant for DENV transmission.

Third, focal spreading can also be explained by the movement of the infected mosquitoes with its restriction of the flying range of approximately 100 metres. The transmission through a neighbourhood is most likely caused by the activities, daily movements and social networks of infected people as cluster sizes often exceed the flying range of the mosquitoes. Apparently, undiagnosed asymptomatic dengue virus infections or unrecognized dengue cases with mild symptoms play a more predominant role for the spread of dengue virus and undetected persistence of transmission locally.

Though this study gives insight in the transmission dynamics of dengue virus within communes and at household level, there are some limitations: (1) it must be noted that it is impossible to ascertain whether these children were infected at home, at school, or somewhere else. Only household geographical coordinates were considered but children living close together often attend the same school, and make use of the same playgrounds etc. However, the likely role of households is suggested by observations from a prospective spatial cluster study in Thailand. Absenteeism of children due to fever tended to cluster in small geographical areas where dengue transmission was active, whereas those who were absent for other reasons were always from areas where dengue was not active. Other reports also showed that household members of dengue sero-converters had a higher relative risk for dengue virus infection. (2) While our study established geographical clustering, it was not designed to identify the key factors accounting for this clustering, such as environmental or entomological factors (water source, water storage, vector density), which have been known to contribute to dengue virus transmission.

Despite these limitations, results from spatial analysis provide insight in dengue virus transmission and control. Based on these data, we believe that sero-surveillance should play a role in identifying hotspots of transmission and that strategies that are centered only on severe clinical dengue cases will be ineffective in controlling transmission, as only a very small proportion (~5%) of dengue cases will develop severe disease. Such population based sero-prevalence surveillance among children combined with geographical information systems (GIS), is a rapid, easy-to-perform and affordable tool for identification of possible high exposure areas at community level. Where possible, identification of dengue risk areas should also be accompanied with vector surveillance and more importantly with the identification of DENV-infected mosquitoes in field settings. Presently, tools for detection of dengue virus in vectors are not yet available for field application. Thus in addition to infection hotspot identification, control measures should be guided by measurement and control of vector density, e.g. through breeding sites elimination with perifocal spraying in identified risk areas. However, the effectiveness of insecticidal treatments in open areas is limited by insufficient residual effect when applying spraying of ultralow volume of insecticides formulation per unit area, and insecticides application inside house where DENV-infected mosquitoes rest may be more cost-effective. Nevertheless, the success of dengue control cannot only rely on intermittent surveillance and insecticide spraying alone, and involvement of the community seems key. However, the best approach to this involvement is still unclear. Education campaigns have been used to increase awareness of dengue in Vietnam, but their effects on source reduction have never been studied.

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SUPPORTING INFORMATION

RANDOMIZE TIMER
rep = 100
iter = 100
loops = 0
OPEN "gis3.txt" FOR INPUT AS #1
OPEN "gis4.dat" FOR OUTPUT AS #2
DIM x(521, 7)
FOR i = 1 TO 521
   INPUT #1, x(i, 1), x(i, 2), x(i, 3), x(i, 4), x(i, 5), x(i, 6)
   PRINT x(i, 1), x(i, 2)
NEXT i
n1 = 1: n2 = 261: n3 = 262: n4 = 521
10 dist2 = 0
   FOR k = 1 TO 2
      IF k = 1 then m1 = n1: m2 = n2 else m1 = n3: m2 = n4
      FOR i = m1 to m2
         IF (x(i, 5) <> 9) then GOSUB 1000
      NEXT i
   NEXT k
   PRINT #2, dist2
   loops = loops + 1: PRINT loops
   IF (loops <= iter) then GOSUB 2000: GOTO 10
CLOSE #1
CLOSE #2
STOP
1000 REM subroutine
FOR j = m1 TO m2
   dist = (ABS(x(i, 5) = x(j, 5)) - ABS(x(i, 5) <> x(j, 5))) / (.001 + SQR((x(i, 1) - x(j, 1)) ^ 2 +
   (x(i, 2) - x(j, 2)) ^ 2)))
dist2 = dist2 + dist
   REM PRINT i; j; ABS(x(i, 5) = x(j, 5)); ABS(x(i, 5) <> x(j, 4)); dist; dist2
NEXT j
RETURN
2000 REM permute
FOR m = 1 TO rep
   FOR j = n1 TO n2
   x = RND
   IF (x(i, 5) <> 9 AND x(j, 5) <> 9) THEN IF x > .5 THEN c = x(i, 5): x(i, 5) = x(j, 5): x(j, 5) = c
   NEXT i
   NEXT j
FOR j = n3 TO n4
   FOR i = n3 TO n4