Recent changes in dengue epidemiology in Singapore – the view from outside

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Based on talk given at IMS on 28th Sep 2005
Dengue trends – past and present

Dengue used to be endemic in 60s and 70s; period of quiescence in 80s followed by resurgence in 90s to present

Some have postulated 6-year epidemic cycles, but this present year is the 7th year of sustained increase...

Multiple reasons have been postulated as to the decline and resurgence of dengue in S’pore...

What do we think, what do we know, what can we prove...

Line quoted from “And the Band Played On…”
The view from outside...

- Singapore has often been quoted as a success story for dengue control...
- In the 1998 WHO monograph edited by A/Prof Goh Kee Tai, Duane Gubler suggests 4 key hypotheses proposed for re-emergence of dengue in Singapore:
  - re-emergence of a pre-dominant viral serotype
  - increase in imported cases
  - declining herd immunity
  - changes in vector biology

- So what do we think, and what do we know?

*Adapted and modified from WHO Technical monograph Series No. 2 Dengue in Singapore
The reporter states that: “many neighbouring countries such as Indonesia, Malaysia, Thailand and the Philippines are experiencing a similar surge.”

The reporters report this as a possible reason... but what do we know?

Let’s take a view from outside Singapore... the REGION!
So what is the relationship between local dengue epidemiology, regional trends and importation?

Southeast Asian (SEA) countries account for >90% of all imported cases. Will hence focus on the countries in SEA...


Source: CIA world fact book
While synchronized epidemics did occur in 1998, and possibly in 1987/88, our epidemic in 1992 was certainly not related to regional epidemiology.

Moreover, while the number of imported cases has increased gradually, the proportion of cases which are imported peaks and falls inversely with total cases – this implies our local epidemiology is not driven by importation but internal factors... at least up to 2004.

What of 2005?
Our present outbreak is out of proportion with regional trends...

The region has had it bad, but
- Singapore has had an exceptionally sustained increase for 3 years
- as of Aug 05, only Singapore has exceeded the number of cases for the last year!
Our present increase is out of proportion with regional trends!

<table>
<thead>
<tr>
<th>Year</th>
<th>Singapore</th>
<th>Malaysia</th>
<th>Indonesia</th>
<th>Thailand</th>
<th>Philippines</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003*</td>
<td>4,788</td>
<td>31,000</td>
<td>52,000</td>
<td>63,000</td>
<td>30,000</td>
</tr>
<tr>
<td>2004*</td>
<td>9,459</td>
<td>34,000</td>
<td>69,000</td>
<td>18,000</td>
<td>23,000</td>
</tr>
<tr>
<td>2005-Aug</td>
<td>9,540</td>
<td>24,857</td>
<td>43,509</td>
<td>8,900</td>
<td>17,934</td>
</tr>
<tr>
<td>05 Jan-Aug/04</td>
<td>1.01</td>
<td>0.73</td>
<td>0.63</td>
<td>0.49</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*approximate value read off graphs from WHO
So what else do we think might have happened? More views from the outside – the press, the public, the professionals...

Sept 11, 2005
Three theories on why dengue is out of control

- Fumigation not effective as it does not kill enough mosquitoes
- Foreign workers may have introduced a few strain here
- Because of the successful drive in the 1970s, people now lack immunity

Sept 13, 2005
Changes in physical environment to blame?

A SECOND-TIME dengue victim, I hope my contribution will go some way towards bringing an early end to the near-epidemic.

Sept 21, 2005
Dengue: Fever Pitch

Mozzies go for upgrades too
The enemy adapts to changing conditions - and fast. Lee Hui Chieh and Judith Tan find out more.

The dengue-carrying Aedes mosquito bites only during the day, breeds in clean water and can fly a distance of just 50m to 100m.

True?

Not necessarily so, says Singapore's National Environment Agency (NEA). Research by the agency's Environmental Health Institute has shown that the Aedes mosquito can bite at night under artificial light, can breed in water contaminated by repellent and can fly as far as 740m.
Still more views from the outside... But what do we really know?

Are we barking up the wrong tree?

We need to move from what we think, to what we know...

To review what we know, we look at past data, and describe the present data.

Sept 17, 2005

N Parks steps up pruning of palms

Holes in tree trunks also being sealed to keep water and insects out

By Lee Hui Chieh

TREES like travellers palms are being taken care of to ensure the breeding hotbeds, the National Parks Board (N Parks) said yesterday.
Some insight from past seroepidemiologic studies...

- The proportion of persons in each age-group who have been infected by dengue-2 is lower in successive surveys in later years.
- So while dengue incidence rate did increase between the 1980s and 1998, it would appear that the force of infection was still lower than historical values before the 1980s.
- *But this may have recently changed*...
• The support for a declining herd-immunity theory is not without basis: cases were getting older throughout the years in spite of a rising number of cases
• But there has been a recent change in age distribution which bucks the historical trend; the % aged <35 yrs was lowest in 2000; since then, the trend has been reversed
• We conclude that the shift in age distribution towards younger age groups is recent, since year 2001 or so… and the most recent shift is the most dramatic!

So can we really believe the herd immunity theory? Maybe for earlier years, but I’m inclined to “think” the recent increase in incidence is not due to decreased herd immunity; the increase in younger cases is circumstantial evidence that herd immunity is no longer declining.

Data from serial copies of Communicable Disease Surveillance Reports. Note that 1980-2002 data includes Singapore citizens and permanent residents only; 2003 and 2004 data includes Singapore citizens, permanent residents and temporary residents.
Was at a lecture in London with Prof Eduardo Massad
He had developed a model which explained our epidemic
And the model told us the obvious: within the possible boundaries for present parameter estimates, an increase in mosquito density is the only reasonable explanation for current trends!!!

It was breath of fresh air!!!
Person, place, time...

Or mosquito, place, time?

Let’s start with place...
The total number of HDB flat dwellers has risen steadily over the years.

The overall proportion in HDB flats rose dramatically from the 1960s-1990s and then stayed constant since.

The increase in number of HDB dwellers probably accounted for the decreased dengue incidence in 1980s!

What’s really not recognised is that it probably also accounted for the changes in premise index!
The HDB, the premise index, and the breeding sites...

Premise index in HDB is really low! It is about 1%, and this includes common areas!

Most breeding sites in HDB are probably ornamental, domestic containers, bamboo pole holders. When such small containers are present in such small numbers, can they really sustain mosquito reproduction, let alone mosquito densities above a transmission threshold?

But not all containers are equal!

The ratio of cases from HDB to compound houses was relatively stable in previous years. However, there has been a marked increase in cases from HDB between 2003 and 2004.

2003: 55% of cases are from HDB. 2004: 75% of all Singaporean cases are from HDB...

Let us look at the serial epidemic peaks...
This trend is rather dramatic when looking at the successive epidemic peaks...

- The number of cases for compound houses in 2004 is less than the previous epidemic peak in 1998. The number of cases for condominiums in 2004 is also less than the previous epidemic peak in 1998.

- However, there has been a successive increase in HDB dwellers across epidemic peaks. There is a 275% increase over 1992, and about 100% increase over 1998.

- Taken together, it would appear that something extraordinary may be happening in the HDB estates... But when did most of this happen?

<table>
<thead>
<tr>
<th>Year</th>
<th>Compound houses</th>
<th></th>
<th>HDB flats</th>
<th></th>
<th>Condominiums</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>% increase</td>
<td>No. cases</td>
<td>% increase</td>
<td>No. cases</td>
<td>% increase</td>
</tr>
<tr>
<td>1992</td>
<td>1210</td>
<td>0% (Ref)</td>
<td>1420</td>
<td>0% (Ref)</td>
<td>111</td>
<td>0% (Ref)</td>
</tr>
<tr>
<td>1998</td>
<td>1635</td>
<td>35.1%</td>
<td>2622</td>
<td>84.6%</td>
<td>665</td>
<td>499.1%</td>
</tr>
<tr>
<td>2004</td>
<td>1210</td>
<td>0.0%</td>
<td>5322</td>
<td>274.8%</td>
<td>531</td>
<td>378.4%</td>
</tr>
</tbody>
</table>
A RECENT and DRAMATIC change in epidemiology by housing-type...

<table>
<thead>
<tr>
<th></th>
<th>Compound house</th>
<th>HDB</th>
<th>Condominium</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2003</strong></td>
<td>1124</td>
<td>1937</td>
<td>453</td>
<td>3514</td>
</tr>
<tr>
<td><strong>2004</strong></td>
<td>1210</td>
<td>5322</td>
<td>531</td>
<td>7077</td>
</tr>
<tr>
<td><strong>Relative increase, 2004 vs 2003</strong></td>
<td>1.08</td>
<td><strong>2.75</strong></td>
<td>1.17</td>
<td><strong>2.01</strong></td>
</tr>
</tbody>
</table>

• When we look closely at 2004 vs 2003, the number of cases from compound houses is largely unchanged.
• There has been a slight increase in the cases from condominiums.
• BUT the cases from HDB dwellings has increased 3-fold.

The increase in HDB cases accounts for 95% OF THE INCREASED INCIDENCE IN SINGAPOREAN RESIDENTS FROM 2003 TO 2004!!!

[overall increase from 2003 to 2004 = 7077-3514 = 3563; increase in HDB from 2003 to 2004 = 5322-1937 = 3385; %increase due to HDB = 3385/3563 = 95.0%]

The shift is sustained into 2005, where >70% of S’porean cases to come from HDBs. Well, the overall increased numbers in 2005 means the others have also increased in 2005, but what seems to have happened is that the epidemic profile shifted to a new baseline in 2004, and stayed there! We need to understand the problem, because that’s where most of our cases comes from!
So where are HDB dwellers getting infected? The indoor-outdoor debate...

Are there already studies done which tell us the answer? Yes, and...

- Seroprevalence survey in highly endemic area, Joo Chiat and Geylang East 1994
- Findings of relevance to us underlined:
  - Landed property: prevalence 78.9%, OR 2.9 (vs HDB flat)
  - Ground floor: prevalence 77.6%, OR 4.0 (vs 10+ floors); biological gradient observed (OR for floors 2-9 = 1.9)
- No change in above conclusions after adjusting for confounders. Same findings in a seroepidemiologic follow-up study in school children.

The gradient of infection in the mid-1990s suggests there were more infections in ground-floor dwellers, less in higher floors! Reasonable hypothesis is that breeding habitats are more likely in the ground floors, and there is a diffusion gradient of mosquitos and hence cases on moving upwards! So it’s at least in part indoor biting and outdoor breeding!
So what do we know about the present HDB situation?

- We can repeat Prof Goh’s study – time consuming and expensive, but important for definitive “proof”
- But we can also reanalyse our present case notification data by floor of residence, and then adjust for the denominators (ie. can check how many floors the blocks involved have)
- If we show that those dwelling on lower floors still have a higher risk, then we can reasonably assume that breeding is mostly outdoors, with some indoor biting at lower floors, and a diffusion gradient as we move upwards, and outdoor biting in most instances...
Using other available data to improve our understanding...

- A cluster is defined as 2 persons with onset in 14 days living within 150m of each other
- Older MOH reports (pre-1997) give the listing of all clusters of infection

What do we know from the cluster sizes?
Looking at cluster sizes, we found some interesting things…

Distribution of cluster sizes and cases by cluster size

Distribution of cluster sizes appears similar for the periods 88-92 and 93-97. Analysing 88-97 as a whole, while 70% of clusters are <5 cases, only 30% of clustered cases are in such small clusters. Therefore, preventing large clusters has a much larger effect, and is far more efficient, than preventing small clusters.

Tools which can predict the formation of large clusters should be developed, and resources should be focussed on identifiable factors predisposing to the formation of large clusters.

This analysis should be repeated on present cluster data!
More on a possible underlying scale-free network, using data up to 1997

Log-log plot of the number of clusters larger than size $X$ versus $X$: R-squared for all the data is 0.95. Does the distribution suggests an underlying scale-free network?
Scale-free network theory was developed to explain the connectedness of the internet. The network is organised around hubs. The distribution of connections resembles the distribution on the previous slide.

In our case, could the dengue clusters be part of a dynamic scale-free network? Big clusters are the hubs, which then connect the epidemic to other hubs over space and time, hence allowing its perpetuation! If so, it would be far more important to take out the hubs than go chasing the smaller nodes!
But still, what do we know about the recent increase?

- Easier to start with what we know it is NOT likely to be due to:
  - changes in serotype (but we had 100% increase in cases, and present Den-3 cases is insufficient to account for the surge!)
  - increased importation
  - declining herd immunity

- What we do know:
  - model outputs suggest increase in mosquito densities are necessary to explain trends
  - increase in HDB cases (in spite of low premise indices)
  - clusters follow a distribution that suggests most of the problem is in a few of the areas
  - and there is a suggestion that an underlying scale-free network is responsible; but even if so, what can we do?

- Unfortunately, the view outside is a view without data...
What do we think, what do we know, *what can we prove...*
Good old basic shoe-leather epidemiology

- Decided that I would drive to 16 selected HDB clusters that were still active and take a look at the view outside
- Common environmental features at the sites may then help us generate some hypotheses for further investigation
- Sample pictures follow...
Hougang St 12

- Carpark works for Blocks 150 to 157
A nice clean cluster of flats in Bishan St 12

- Construction in the blocks across the road from the flats within the cluster...
Major construction is ongoing at Shunfu Road, and also on the main road near Shunfu Road, within Aedes flying distance.
Lorong 7 Toa Payoh

- Extensive construction works present at Lorong 7 Toa Payoh
Ang Mo Kio Ave 10

- Re-roofing works to several blocks in progress
- Container HQ and construction materials in background
- Also the infamous rubbish skip was in the carpark... This structure is cleared only once in about 2 weeks. It traps water under bigger rubbish items; the water may not evaporate, but is accessible to mosquitoes as breeding grounds. Are these structures regularly inspected, or when combing for breeding sites? Can they be inspected if there are big pieces of rubbish above?
In summary, 14 out 16 assessed (88%) have evidence of nearby construction works.
- 8 of 16 (50%) have blocks directly involved in some form of upgrading works
- 3 of 16 (19%) are within 200m of nearby upgrading works (to other blocks)
- 3 of 16 (19%) involve other construction work nearby within 200m

But the above does not constitute proof that any of the construction sites are involved; it could just be that, with the high prevalence of improvement works in Singapore, any cluster of flats would be close to a construction site.

Moreover, in many of the clusters, there was more than one single construction project in the surrounding the area, and therefore we cannot pin the cause on any single site!

However, it does raise the hypothesis that construction sites may in some way be related to some of the outbreaks, and to bridge the gap between association and causality, what is needed is to see if sites positive for breeding have been found in the residential clusters!
But is there an increase in construction workers getting dengue fever?

Due to changes in format of annual report, have to use data on male foreigners to make inferences

In 2002, about 55% of male foreigners were construction workers

Probably quite valid to say that there has been a sharp increase in 2004 of such cases; this was above the general increase in cases

The increase has been sustained into the 2005 epidemic (estimated figure for construction workers up to Sept 05 based on Channel News Asia report on 30th Sep 05)

MOM data shows that the total number of workers in construction has fallen from 2000-2004; it is hence reasonable to deduce that there has been an increase in the incidence rate amongst construction workers.
But the premise index in construction sites has fallen...

News article by Channel News Asia listed all the measures adopted by the sites... the concluding lines are as below.

Since April 2001, construction sites with a contract value of more than $10 million must employ a trained Environmental Control Officer to ensure such measures are taken and the site is free from mosquitoes.

The sites are also checked regularly by National Environment Agency officers.

Now less than 9 percent of all construction sites inspected are found breeding the Aedes mosquito, compared to 30 percent in 2000.

The most common places mosquitoes breed are actually in the home. - CNA/de

We need data of better resolution than this – we need to see if the 9% are in critical areas, like near schools or within HDB estates...
So what can we prove?

- Prof Goh KT in his 1998 monograph already pointed out based on local data that living less than 200m away from a construction site puts a person at increased risk of infection.
- In spite of the falling premise index, the link with construction activities must be thoroughly investigated before it is ruled out as a possible cause of the present outbreak, because of:
  - the historical association
  - some of the big clusters at present are near ongoing construction activities
  - all the recent school clusters have such activities along their transport route
  - the estimated number of construction workers infected has been increasing
- Yes, we’ve always had these construction activities – but could it be that there is:
  1. more intra-residential construction
  2. changes in legislation / policing / inspections
  3. a change in construction methods / equipment (eg. more rubbish skips!!!)
  4. new mosquito with affinity for construction sites, and hard-to-find breeding areas within the sites (highly speculative)
  5. formation of the scale-free networks linking the sites (highly speculative)

Occam’s Razor states: pluralities ought not be supposed without necessity …
We need to check out the simple reasons first (i.e. 1 to 3)!
How can we prove or disprove the involvement of construction activities?

- Use the spatial methodologies suggested by Arul Earnest (eg. on opposite slide)
  - If the construction works coincide with areas of higher incidence rates, we would have stronger evidence that this may be a cause

- Alternatively, the 2005 Q1 ENB article states that NEA has about 2,000 ovitraps deployed in surveillance; if start and end dates of construction activities are known, we can analyse data from ovitraps near these sites to see if changes in larval density are observed in relation to construction activities!

If an association is established, then pre-emptive action can be taken:
eg. more frequent site inspections, etc
Other views from the outside...

Yes, fine town councils that breed mosquitoes

I AGREE with Health Correspondent Salma Khalik ('Fine way to get town councils to clean up act'; ST, Sept 22) that 'town councils should be fined like any other property owner found breeding mosquitoes'.

Aug 30, 2005
Puddles pose a danger

This story was printed from channelnewsasia.com

Title : NEA targets landed homes in dengue prevention efforts
By : 
Date : 28 August 2005 2003 hrs (SST)
URL : http://www.channelnewsasia.com/stories/singaporelocalnews/view/165385/1.html

SINGAPORE : The number of landed homes found breeding mosquitoes has seen a dramatic fourfold increase.

Shoddy aircon ledges a hazard

Sept 2, 2005
Conduct checks on households

MORE blocks Environment

This happened weeks. This

I have two suggestions for NEA and the town council:

• Conduct mandatory checks on households in the affected areas. Thermal fogging is done only outside the house while there may be breeding grounds inside.

Aug 30, 2005
Get to root of the problem


All unlabelled articles from Straits Times.
Concluding remarks

Regardless of my attempt at a scientific analysis, my opinion may be viewed as one more opinion from the outside, amongst many others.

The reason why there are so many opinions is because there has been so little data!

While I didn’t talk much on this, Prof Massad’s model helped me tremendously in focusing my efforts! If there are more mosquitoes, then there must be a source; it follows that we must identify this source!

And ultimately, models cannot substitute for field investigations.

So…

- Are there more mosquitoes?
- What are the MOST IMPORTANT breeding sites?
- Are some of the construction activities involved in some way?
- Is there a scale-free network?

The above remain as hypotheses, and we are unable to prove or disprove the above with just the data from outside!

More data, but more importantly, better analysis of existing data, is required to answer the above questions…

And we hope the people from “inside” can look inside their data, analyse it with the best available methods, and give us the answers soon!