Dengue Fever
A Global Health Challenge

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Overview

- 50 -100 million cases each year and increasing
- One main vector worldwide: *Aedes aegypti*
- Symptoms – Joint/muscle pain ‘Breakbone fever’
- Severe form
  - Dengue Haemorrhagic Fever (DHF)
  - Dengue Shock Syndrome (DSS)
- No medication or vaccine
- Same family (*Flaviviridae*, Genus *Flavivirus*) and same vector as Yellow Fever
Global Trend

Global Trend of Dengue

Number of reported cases

Year

Sources: PAHO/WHO
Reported Cases

World Distribution of Dengue

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Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

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Why is dengue spreading?

Urbanization, population growth and increased international travel

*Anopheles gambiae* is an invasive species in most countries

*Anopheles gambiae* is highly adapted to the urban environment

Very difficult to control with current control measures
Dengue Control Strategies

The application of vector control measures is frequently insufficient, ineffective, or both and is currently failing to reduce the public health burden to an acceptable level

- Chemical Control - larvicide and insecticide
- Biological Control - larvivorous fish
- Community-based interventions - covering the clean water storage container - proper disposal of waste and containers
Dengue Control Strategies

Potential for a Vaccine

Wolbachia Inoculation

Genetically Engineered Mosquitoes
There is currently no safe and effective vaccine for dengue fever due to a range of interrelated problems.

- There are four dengue serotypes circulating globally. Infection with one dengue serotype confers life-long protection against re-infection with the same serotype.
- Moreover, dengue is unique in that sequential infections with different serotypes increase the risk of developing severe and potentially lethal disease.
- As a result, a vaccine is extremely difficult to formulate as it must be able to recognize four different virus types (this is called ‘tetravalent’) and generate an immune response against all four serotypes simultaneously.
- Vaccine development is also hampered by the lack of a suitable animal model, and insufficient knowledge of disease pathogenesis.
- As dengue fever can be contracted by adults and children, the vaccine must be safe for a large age range.
Potential for a Vaccine

According to the Dengue Vaccine Initiative website, since the early 1990s much progress has been made in developing dengue vaccines.

The most advanced candidates include the following approaches:

- Live attenuated vaccines, prepared through advanced genetic techniques, including chimerization or sequence deletion.
- Purified inactivated vaccines.
- Subunit vaccines, which use a portion of the envelope protein of dengue virus.
A vaccination program may not be fully effective over a large geographic area or a long time span.

It will be difficult for a vaccination program to reach all of the 2.5 billion people at risk of contracting the disease.

Even for a smaller target population the cost of a long term vaccination program would reduce its sustainability.

Wolbachia is a bacterium that lives only within insect cells and is passed from one generation to the next through the insect’s eggs.

It is present in up to 70% of insects species including some mosquitoes, but not the dengue carrying mosquito *Aedes aegypti*.

Scientists discovered that the *Wolbachia* can block the dengue virus transmission.
Wolbachia Approach
At one point, 80-90% of the *Aedes aegypti* mosquitoes were infected in the two trials, but the rates dropped to about 45% and 71%, respectively, by May after the last batches were released.

The Wolbachia strain used on the 2 islands in Vietnam blocks dengue 100 percent, but it is also the hardest to sustain in the wild.
Each Wolbachia strain has a different effect on the mosquito’s fitness and consequently affect how easily it will establish in the wild mosquito population once it is released.

Wolbachia strains also differ in terms of their ability to block dengue virus inside the mosquito.

Current strains of Wolbachia available exhibit trade offs between dengue-blocking abilities and ability to thrive in the wild.

Over time scientists hope to select strains that have a strong blocking effect on dengue and yet are easily introduced into mosquitoes in the field and thereby provide a low-cost, long-term solution to dengue control.
Scientists inject thousands of mosquito eggs to obtain just one individual which has the new DNA incorporated into their genome. From this single insect, a new strain of genetically engineered mosquitoes can be made.

The DNA also contains a fluorescent gene to help the genetically engineered (GE) mosquitoes be identified.
Genetically Engineered Mosquitoes

The new male mosquitoes are sterile which means when they mate with a female mosquito, the offspring will die before reaching adulthood.

As long as the GE male mosquitoes are fed a special diet, it is not sterile.
GE Mosquito Trials

The releases are made at predetermined points by hand or from the back of a truck.
Cayman Islands Trial 2010

Graph showing the Ovitrap index and release numbers per hectare over time for different areas.
GE Mosquito Limitations

Regulatory Uncertainty
Regulatory Requirements
Regulatory Costs
Technical Challenges of Continued Release
Synergies

While it is possible that dengue eradication could one day be achieved through the development and dissemination of a fully effective vaccine, that goal does not appear likely in the near term.

Dengue eradication could also occur, in theory, by eliminating the dengue virus or mosquito vector as envisioned by the Wolbachia and genetically engineered mosquito research. However, neither of these approaches alone can ensure that the virus will not return.

A strategy that combined all three approaches could overcome some of the current limitations of each approach.

For example, the genetically engineered mosquitoes could reduce the wild population to nearly zero in a limited geographic area. The subsequent release of Wolbachia inoculated mosquitoes would be expected to achieve much higher infection rates than in previous trials. A vaccine of even limited efficacy could greatly reduce the resurgence of dengue infected mosquitoes.
Conclusion
Backup Slides
Serotypes
World Distribution – 1970

Aedes aegypti Distribution in Americas