Lessons Learnt from NMRC and non-NMRC Funded Research: Meningococcal Disease, Dengue and Zika

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Hajj pilgrimage

International W-135 outbreak in 2000 and 2001

[1]Lingappa JR, *et al. Emerg Infect Dis*. 2003;9:665–71; [2]Hahné S, *et al. Lancet* 2002;360:2089–90; [3]Wilder-Smith A, *et al. Clin Infect Dis* 2003;36:679–83

Research ideas

- Where do ideas come from?

Risk factors and at-risk groups

Immature immune system[1]	Impaired immune system[2,3]	Nasopharyngeal irritation[3]	Social factors[3,4]
▪ Infants 	▪ Complement deficiency ▪ Humoral immune deficiency states ▪ Asplenia ▪ HIV/AIDS	▪ Smoking ▪ Respiratory tract infection 	▪ Close contact with a case ▪ Crowding 

- Most cases of meningococcal disease occur in previously healthy persons without identified risk factors. Overcrowding is the MAIN risk risk

[1]Rosenstein NE *et al. N Engl J Med* 2001;344:1378–88; [2]Figueroa JE *et al. Clin Microbiol Rev* 1991;4:359–95; [3]Bilukha OO *et al. MMWR Recomm Rep* 2005;54:1–21; [4]Imrey PB *et al. J Clin Microbiol* 1995;33:3133–7 (copyright-free images)

Carriage rates of W-135 in Singaporean pilgrims and transmission to household contacts in 2001

	Pre-Hajj pilgrims N=204	Post-Hajj pilgrims N=171	Household contacts N=233
W-135 carriage	0	15%	3%

Wilder-Smith A *et al*. *BMJ* 2002;325:365–6

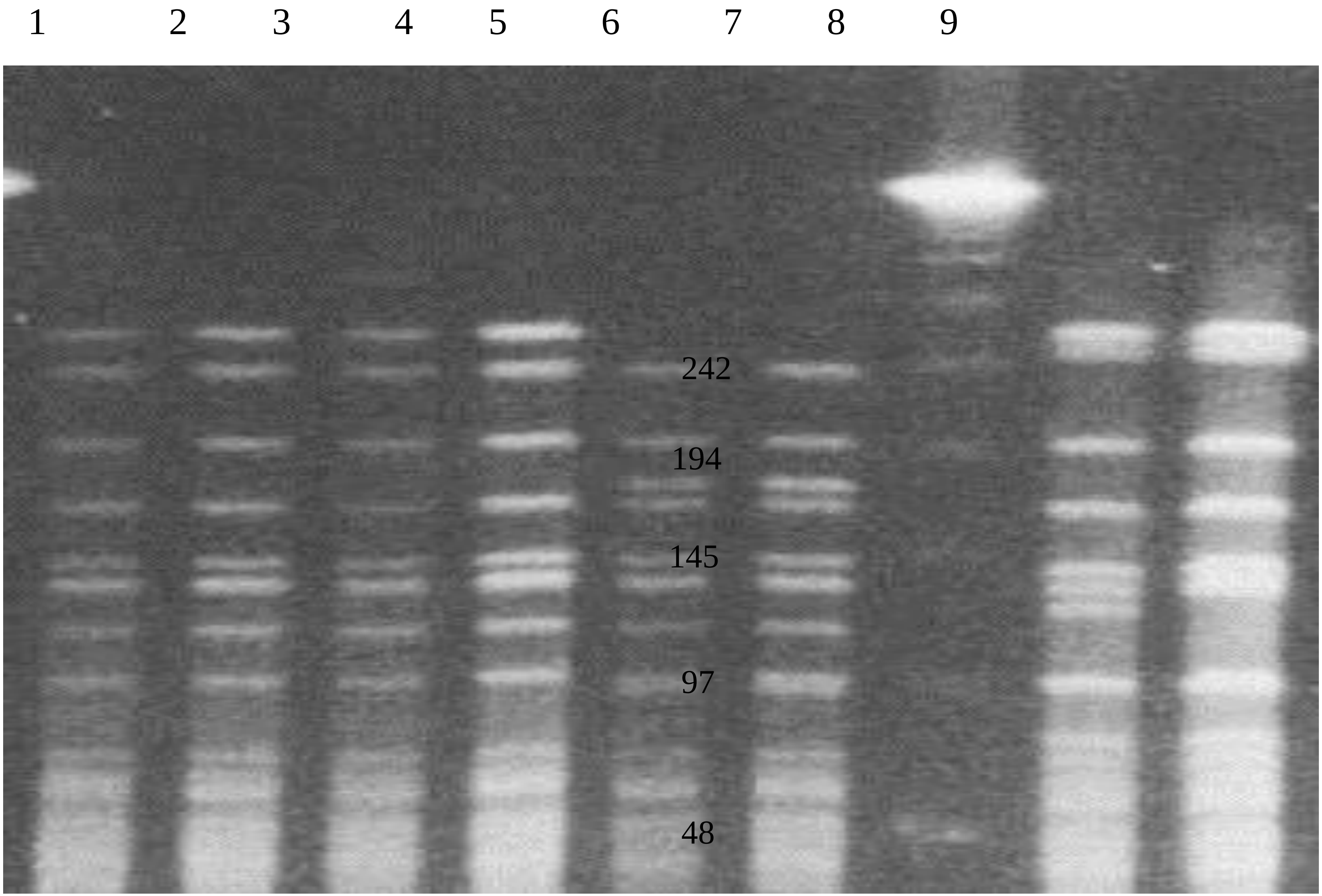


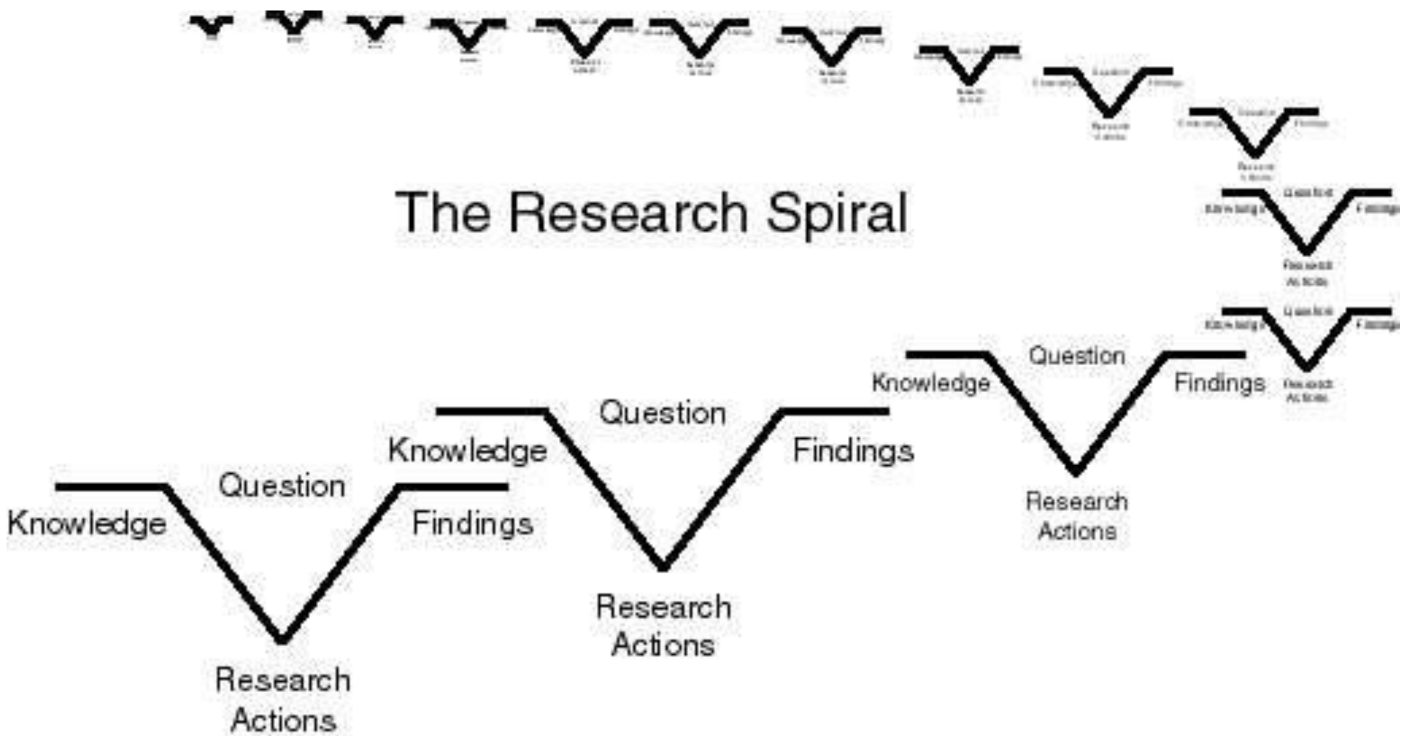
Fig 1. PFGE gel.
Lane 1, W135 from a pilgrim: 2, W135 from the pilgrim's contact: 3, W135 from a clinical case in 2001: 4, a non-groupable pilgrim's isolate: 5 , W135 from a pilgrim: 6, an autoagglutinator from a pilgrim: 7, Lambda ladder in kb: 8, W135 from a pilgrim: 9, W135 from a clinical case in 2000.

Case study: international *Neisseria meningitidis* W-135 outbreak 2000

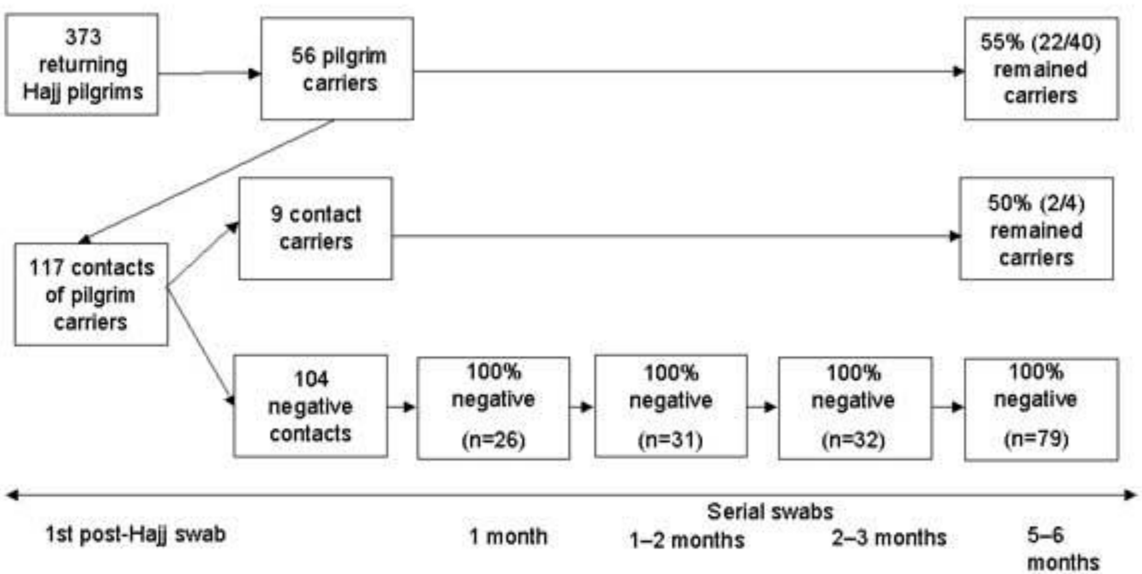
- W-135 carriage in returning pilgrims was 15%[1]
- The rate of transmission to household contacts was 8%[1,2]
- Invasive W-135 disease in contacts occurred in 1 case per 70 acquisitions[1]

[1]Wilder-Smith A *et al*. *Clin Infect Dis* 2003;36:679–83; [2]Wilder-Smith *et al*. *Emerg Infect Dis* 2003;9:123–6 (Copyright free image)

The Research Spiral



Early versus late transmission to household contacts



Wilder-Smith A, Barkham TMS, Ravindran S, Earnest A, Paton NI.
Persistence of W135 *Neisseria meningitidis* carriage in returning Hajj pilgrims: risk for early and late transmission to household contacts. Emerg Infect Dis 2003

Conclusions

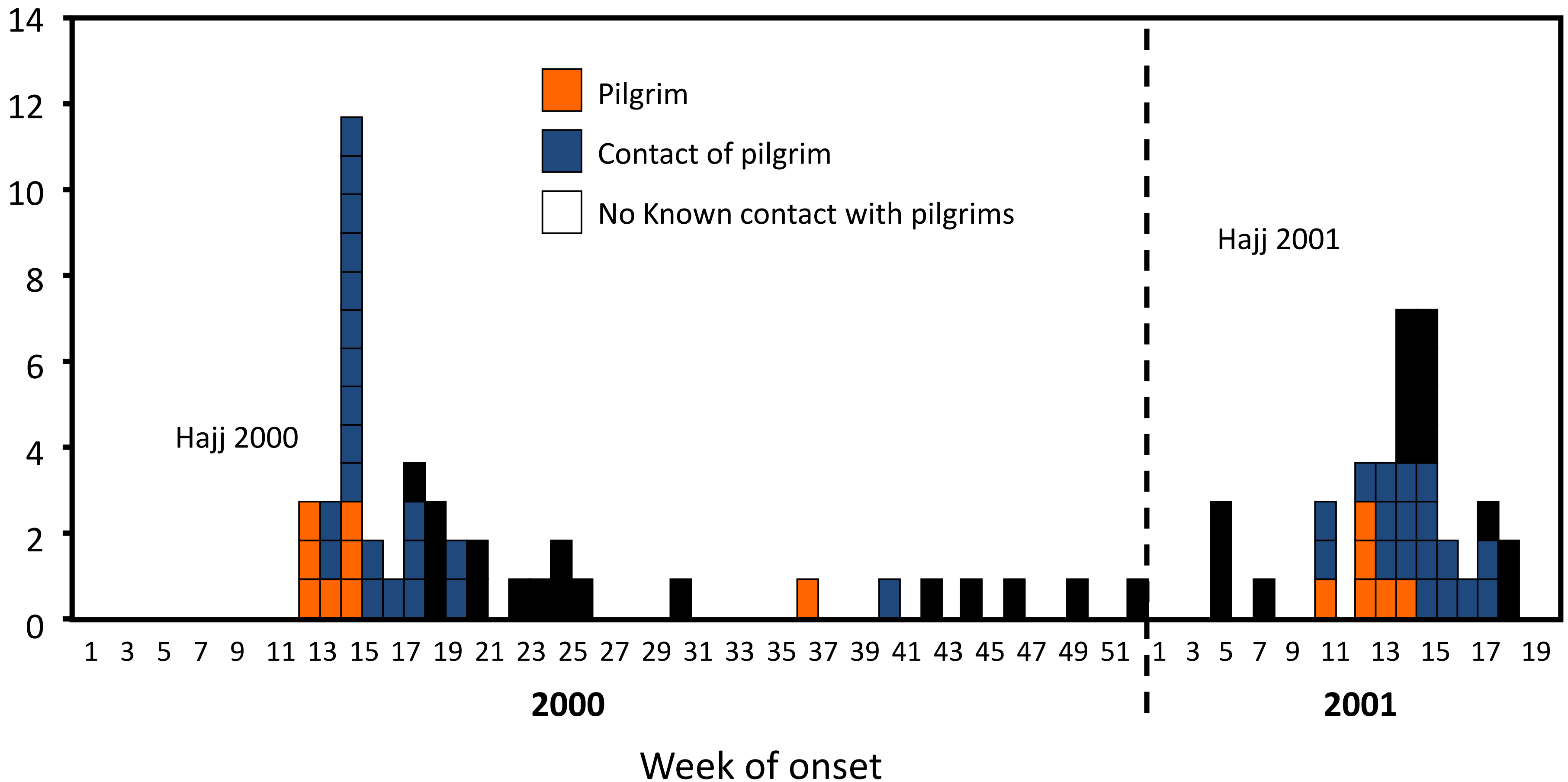
- Returning pilgrims carrying the W135 clone transmitted it to 8 % of their household contacts

- Acquisition only occurred in the first month of contact with the returning pilgrim carriers, and none of the contacts with initially negative results acquired the strain after months of exposure.

- The absence of late transmission is an important new finding

Wilder-Smith A, Barkham TMS, Ravindran S, Earnest A, Paton NI.
Persistence of W135 *Neisseria meningitidis* carriage in returning Hajj pilgrims: risk for early and late transmission to household contacts. Emerg Infect Dis 2003

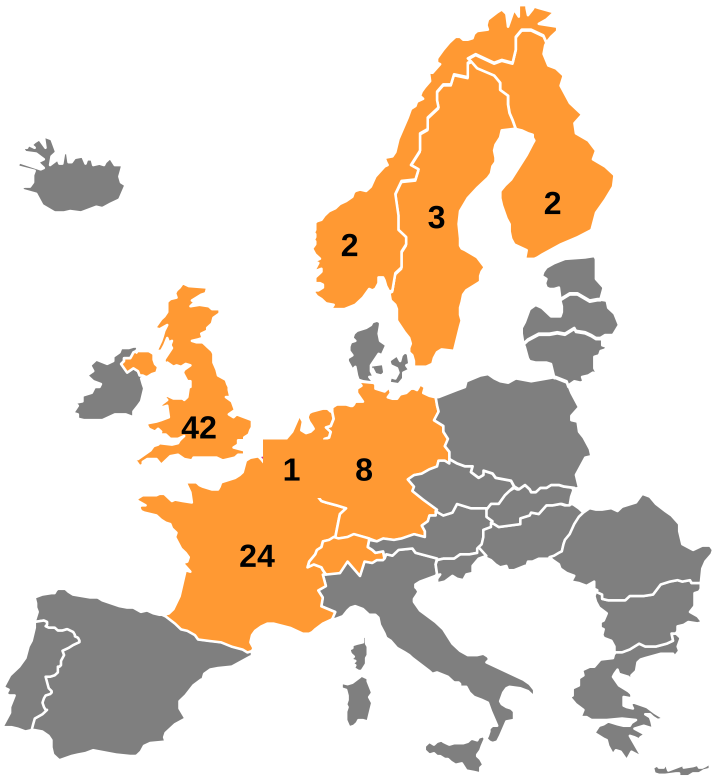
Cases of invasive W135 disease, in England and Wales by onset



Hahne, et al. *Lancet* 2002 February 16, 359.

Case study: international *Neisseria meningitidis* W-135 outbreak 2000

Distribution of 90 cases

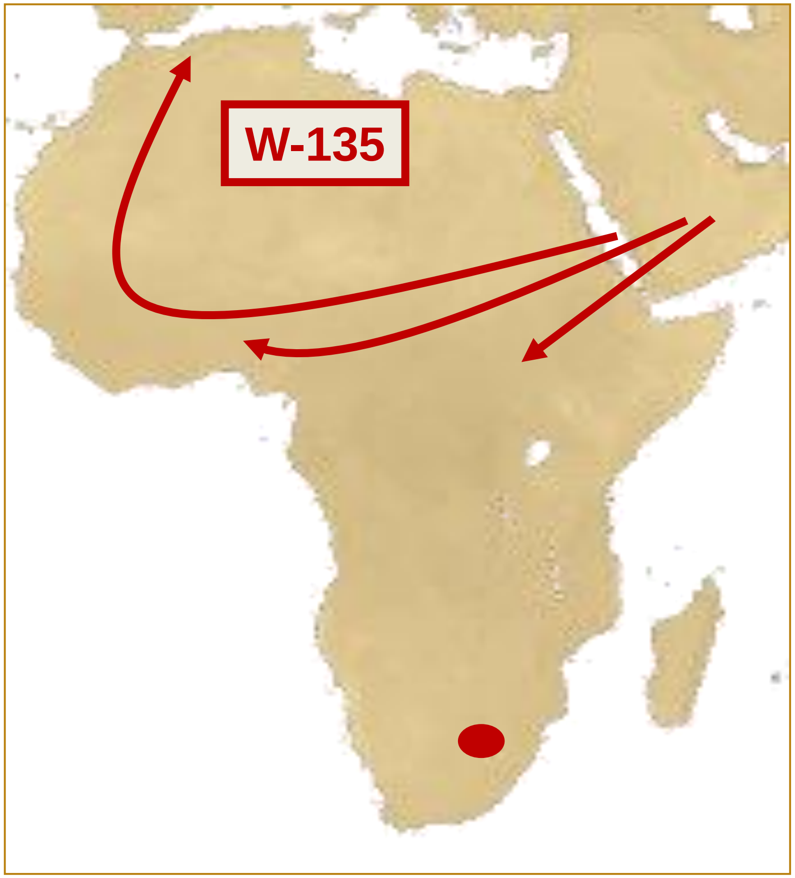


- Of 90 confirmed cases of W-135 disease throughout Europe
  - Only 12 (13%) cases were pilgrims
  - 31 (34%) infected through contact within same household
  - 21 (23%) infected outside household
  - No pilgrim contact identified for 26 cases (29%)
- The infection spread rapidly
  - 45 (50%) cases occurred during the first 4 weeks after the first return of pilgrims

Not only may travelers themselves be at risk of contracting IMD, but their close contacts (family and friends) may be at risk too

Aguilera J-F, Perrocheau A, Meffre C, Hahné S. Outbreak of serogroup W135 meningococcal disease after the Hajj pilgrimage, Europe, 2000. Emerg Infect Dis [serial online] 2002 Aug [cited 2012 June 7]. Available from: http://wwwnc.cdc.gov/eid/article/8/8/01-0422.htm

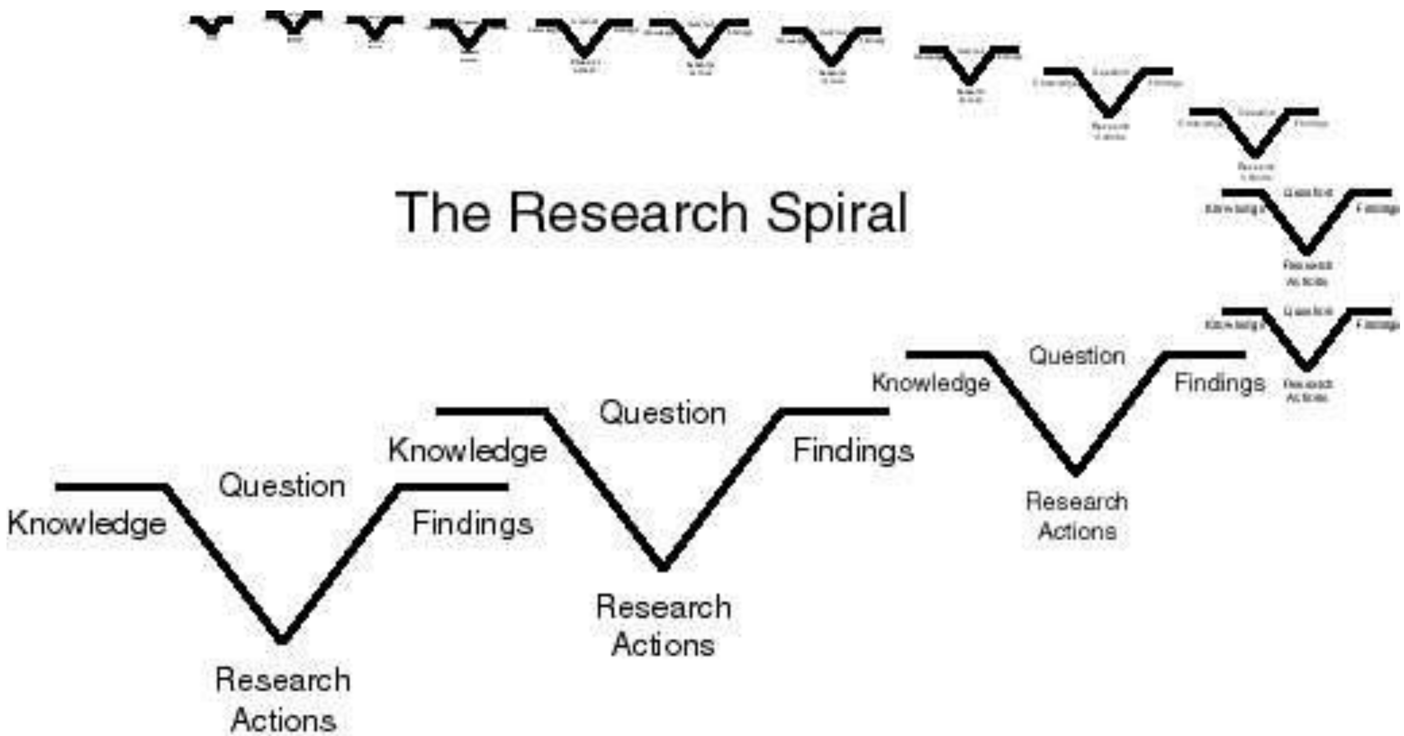
Spread of W-135



- Amplified in Saudi Arabia during 2000 Hajj pilgrimage[1,2]
- Spread to Africa[2,3]
- Caused a major outbreak in Burkina Faso in 2002 with >14000 cases[4]

[1]Cohn A and Jackson M. Travelers' Health: CDC Travelers' Health: Yellow Book 2012. http://wwwn.cdc.gov/travel/yellowbookCh4-Menin.aspx; [2]Lingappa JR, *et al. Emerg Infect Dis*. 2003;9:665–71; [3]von Gottberg A, *et al. Clin Infect Dis* 2008;46:377–86; [4]Caugant *et al. Vaccine* 2007;25:A8–A11

The Research Spiral



Same study for 2002

	Pre Hajj N=193	Post Hajj N=153 (79%)
Carriage	2%	1.3%
W135 Carriage	0	1.3%

Wilder-Smith A, Barkham TMS, Chew SK, Paton NI.
Absence of *Neisseria meningitidis* W-135 electrophoretic type 37 during the Hajj, 2002.
Emerg Infect Dis 2003

After the introduction of compulsory quadrivalent meningococcal vaccination for pilgrims attending the Hajj in 2001, no pilgrims developed W-135 disease[1,2]

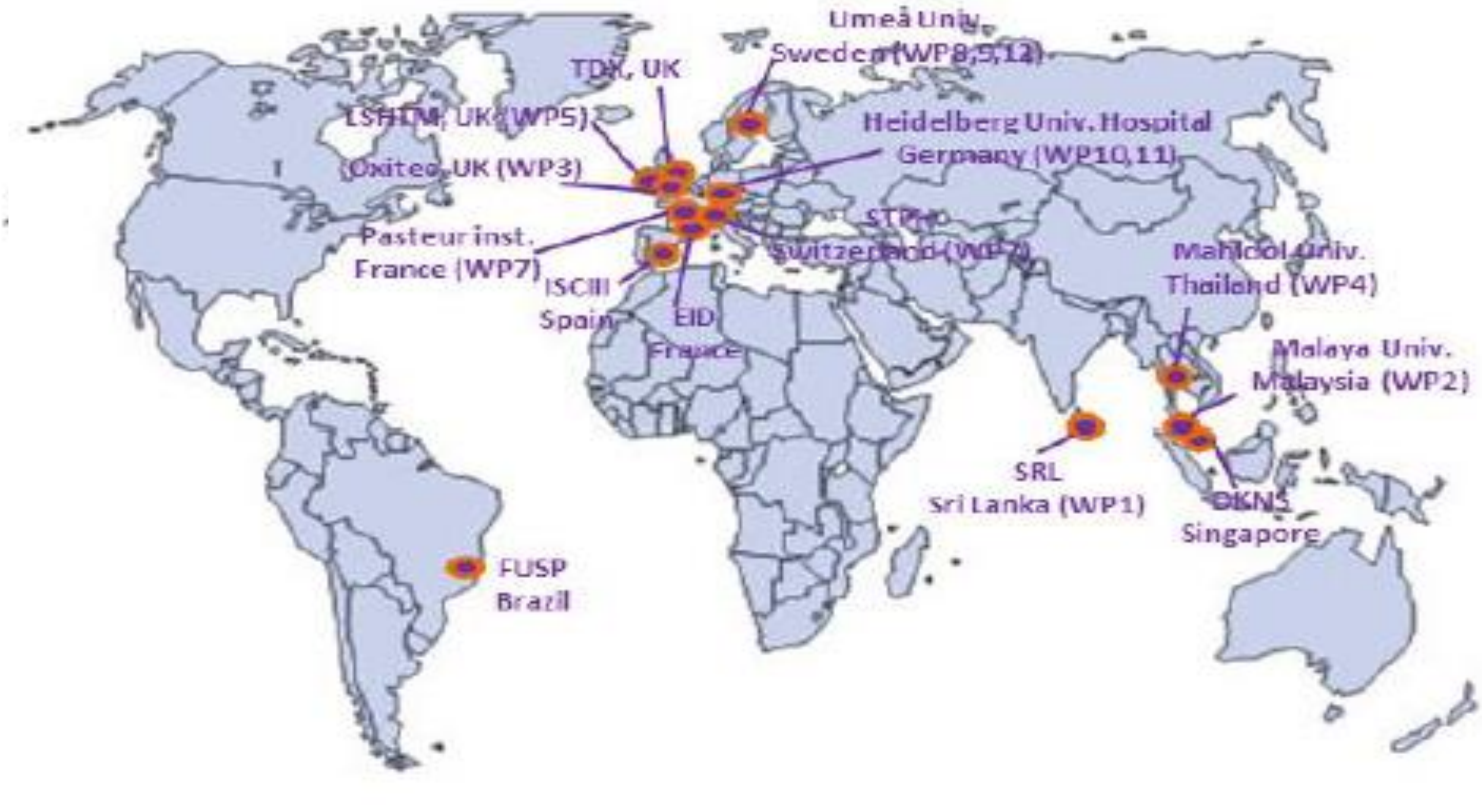
STUDY DESIGN ARTICLE

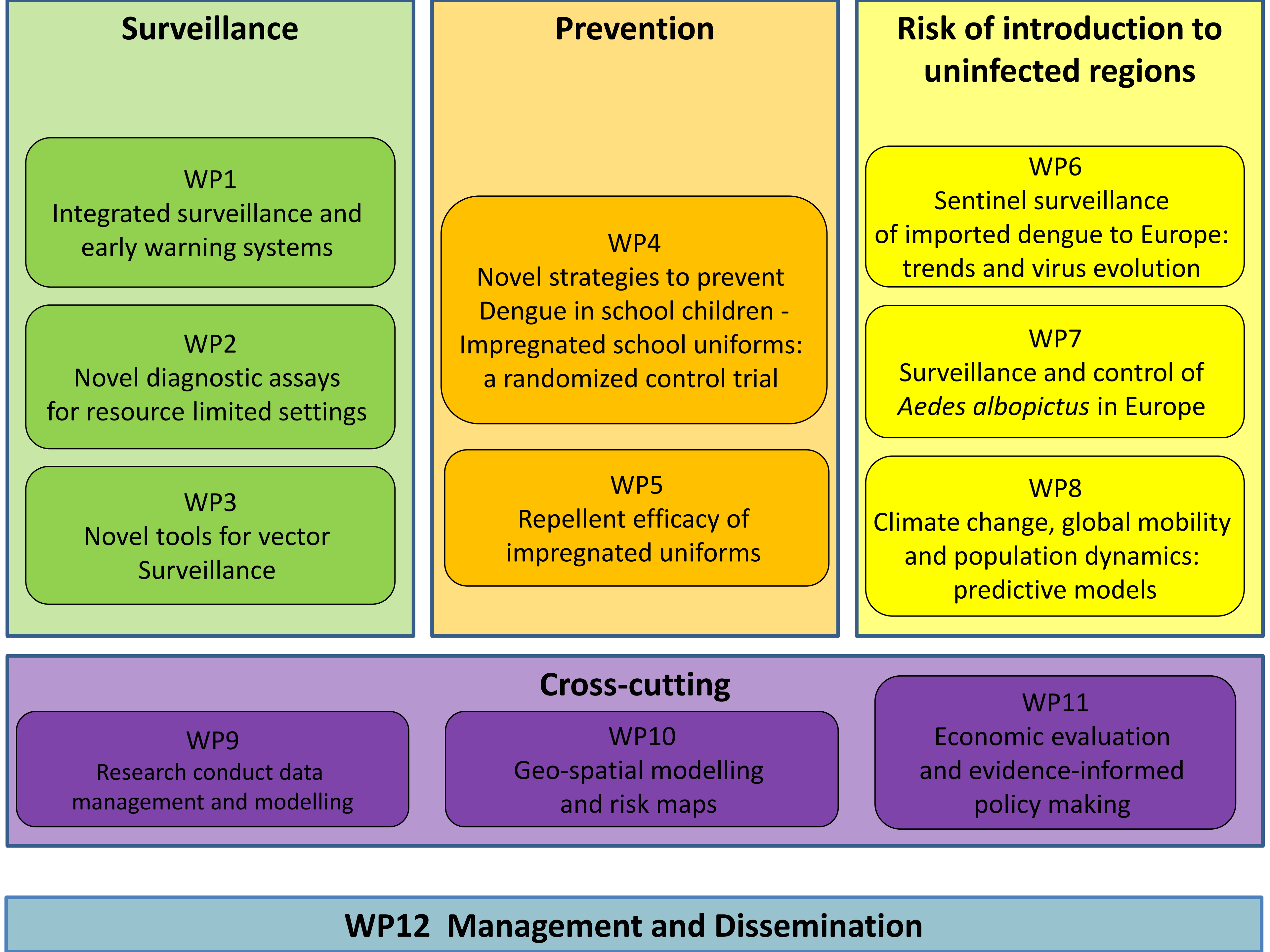
DengueTools: innovative tools and strategies for the surveillance and control of dengue

Annelies Wilder-Smith[1,9*], Karl-Erik Renhorn[1], Hasitha Tissera[2], Sazaly Abu Bakar[3], Luke Alphey[4], Pattamaporn Kittayapong[5], Steve Lindsay[6], James Logan[6], Christoph Hatz[7], Paul Reiter[8], Joacim Rocklöv[1], Peter Byass[1], Valérie R. Louis[9], Yesim Tozan[9,10], Eduardo Massad[11], Antonio Tenorio[12], Christophe Lagneau[13], Grégory L'Ambert[13], David Brooks[14], Johannah Wegerdt[1] and Duane Gubler[15]

Sri Lanka

DengueTools Consortium – 14 partners worldwide, funded by the European Commission with 5.6 million Euro




Surveillance
WP1
Integrated surveillance and early warning systems
WP2
Novel diagnostic assays for resource limited settings
WP3
Novel tools for vector Surveillance
Prevention
WP4
Novel strategies to prevent Dengue in school children - Impregnated school uniforms: a randomized control trial
WP5
Repellent efficacy of impregnated uniforms
Risk of introduction to uninfected regions
WP6
Sentinel surveillance of imported dengue to Europe: trends and virus evolution
WP7
Surveillance and control of *Aedes albopictus* in Europe
WP8
Climate change, global mobility and population dynamics: predictive models
Cross-cutting
WP9
Research conduct data management and modelling
WP10
Geo-spatial modelling and risk maps
WP11
Economic evaluation and evidence-informed policy making
WP12 Management and Dissemination

EU experts in Sri Lanka to study dengue

EXPERTS from the European Union have arrived in Sri Lanka to conduct a study on the dengue epidemic, the Health Ministry said Thursday (16).

According to an official, the team led by J. Gubler of the Duke-NUS Graduate Medical School in Singapore, includes specialists from Heidelberg University in Germany, Umea University in Sweden, and Boston University in the US.

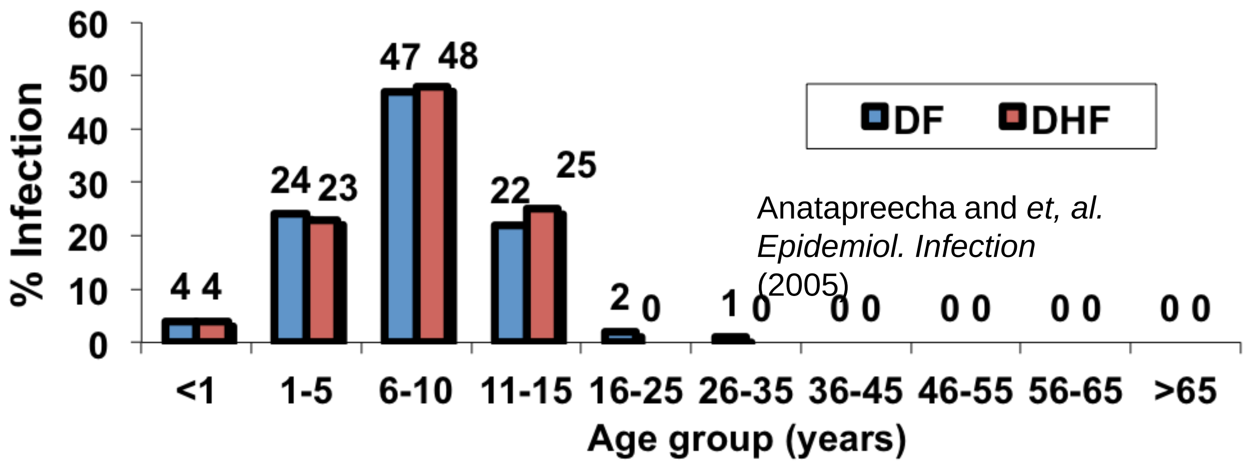
The specialists held discussions with the ministry on the EU-funded Dengue Disease Surveillance Project (DDSP), Ministry Spokesman W.M.D. Wanninayake told reporters.

The EU has agreed to provide 1.1 million euros over the next four years to implement the project, Xinhua reported.

Due to the increasing spread of dengue in the world, the European Commission has decided to provide funding aid to set up a multi-country project in the developing countries.

The project aims to detect and identify areas with a high risk of dengue spread and identify dengue patients early. In January, over 3,000 dengue cases were reported in Sri Lanka.

OUR OBJECTIVE: A BETTER TOOL FOR DENGUE PREVENTION IN CHILDREN



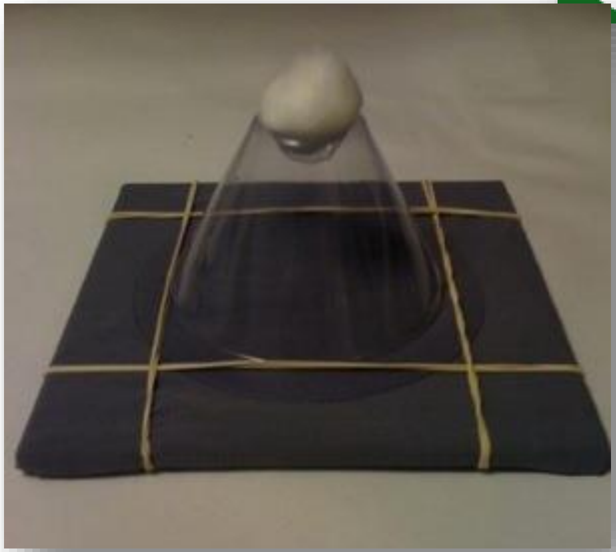
Our study, which is part of the EU/FP7-funded DengueTools Consortium, aims at finding an alternative solution for dengue prevention and control in the most vulnerable school-age children

Sri Lanka

Labotoratory based efficacy

– WHOPES cone tests

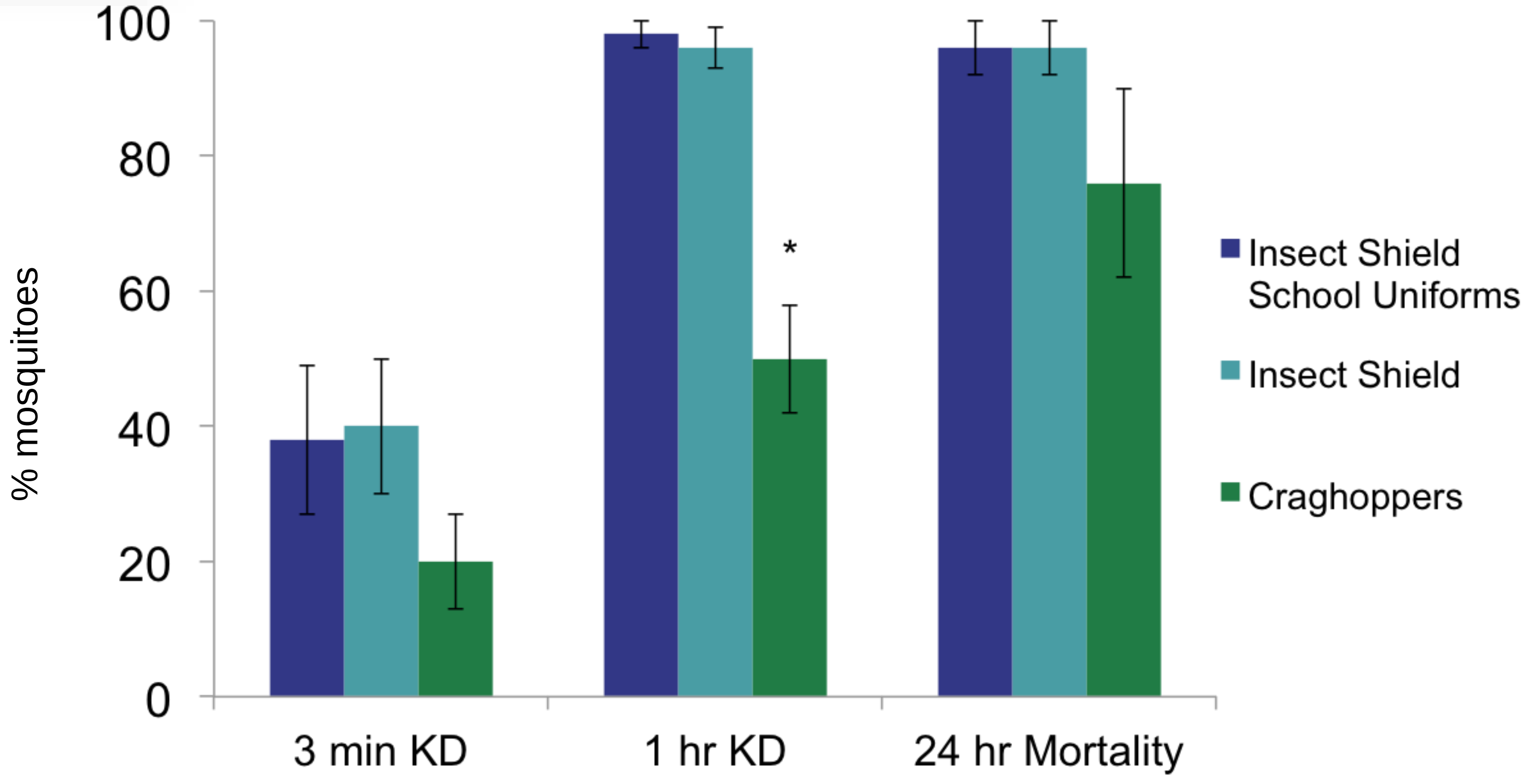
- 3 min exposure
- 1 hour knockdown (KD)
- 24 hour mortality
- 100, 70, 50, 20, 5, 0 washes



– Repellency arm-in-Cage test

- 30 *Stegomyia aegypti* (susceptible and resistant)
- 1.5 min exposure to arm covered by treated material
- Landing and biting recorded

WHOPES cone test

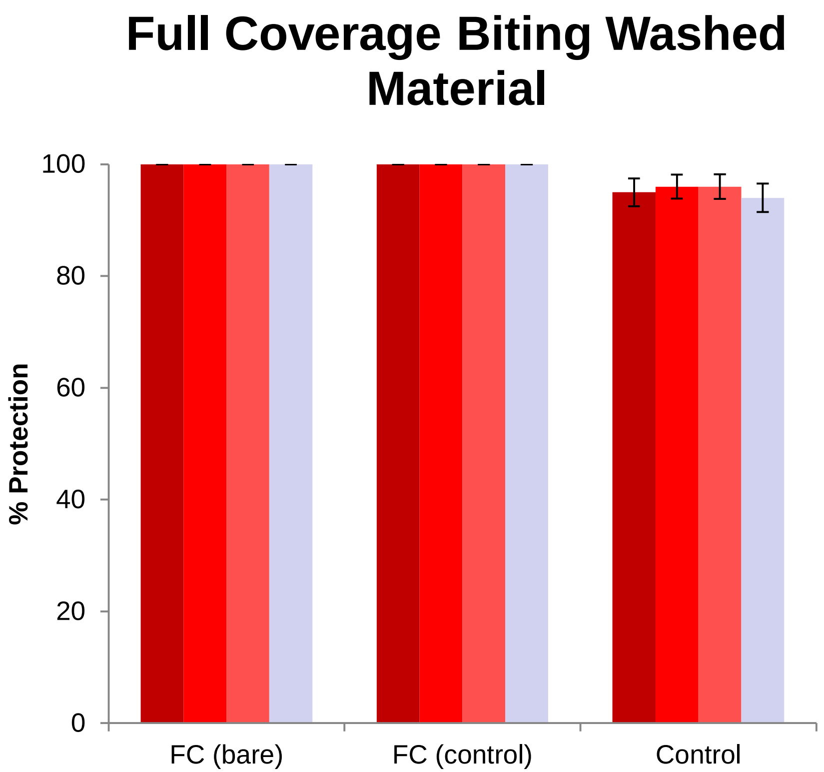


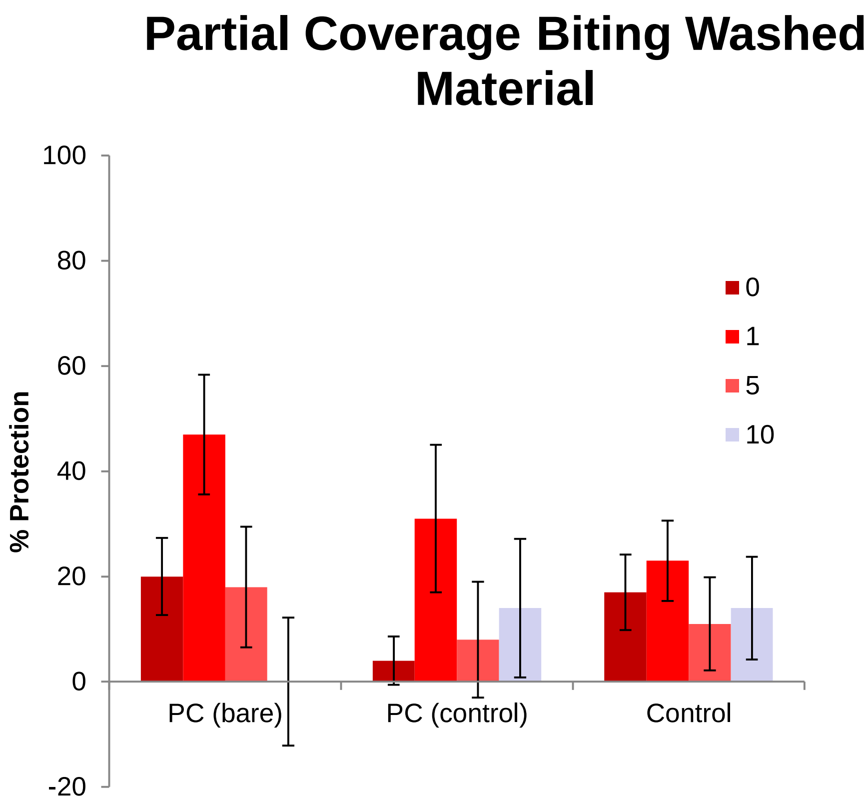
Factory dipping Insect Shield yielded higher KD and mortality

Craghoppers microencapsulation technique significantly lower at the 1 hour KD ($p<0.0005$)

Sri Lanka

Repellency





- Treated clothing gave 100% protection; untreated clothing gave~96% protection

- Treated partial coverage gave ~47% protection after 1 wash; untreated partial coverage gave 20% protection

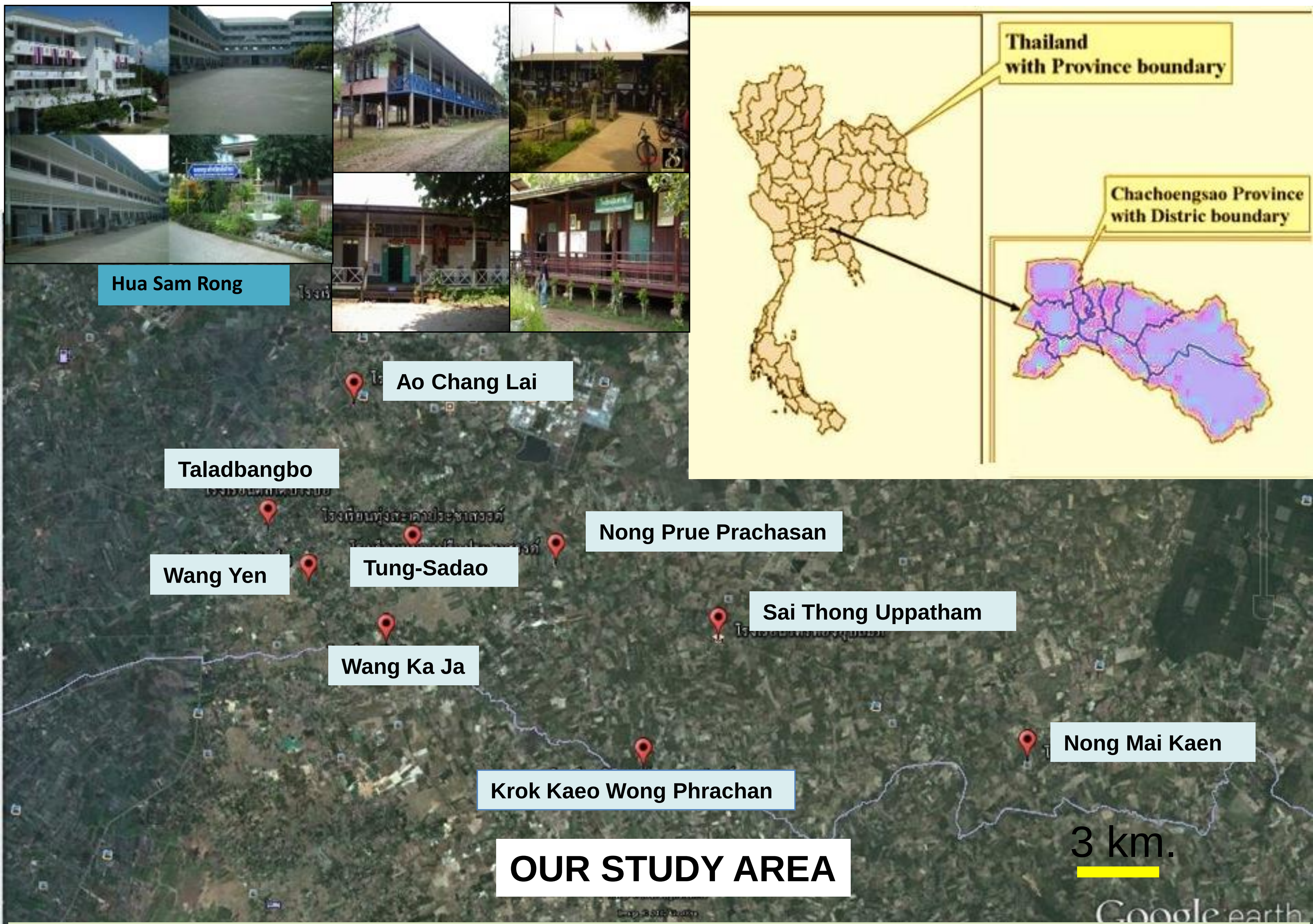
Sri Lanka

Study design

- Cluster Randomized placebo-controlled school based trial
- 10 schools
- 2000 children aged 5-13
- Cross-over design

schools	first 6-month transmission season	washout/crossover period during non-transmission season	second 6-month transmission season
1	intervention	Crossover	control
2	control	Crossover	intervention
3	intervention	Crossover	control
4	control	Crossover	intervention
5	intervention	Crossover	control

Sri Lanka



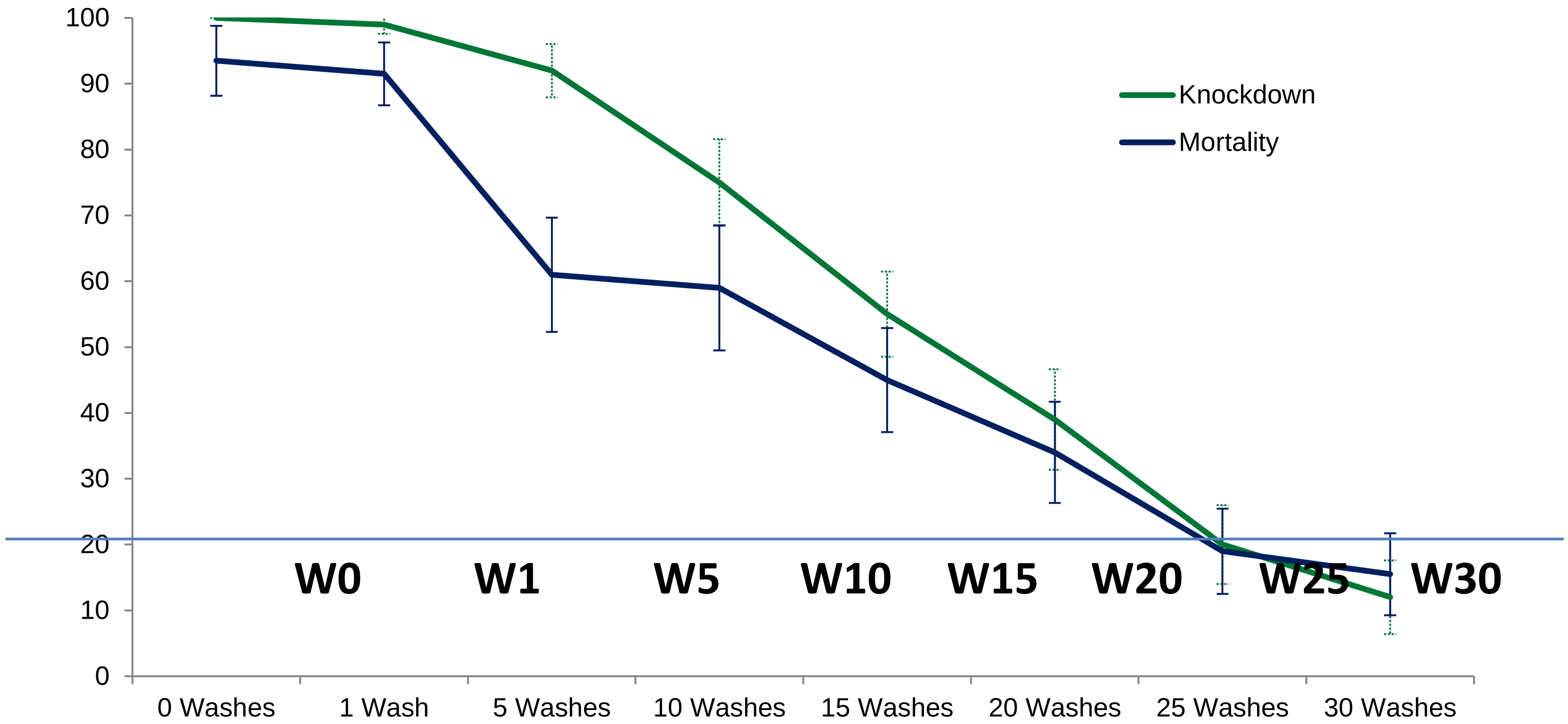
A double-blind randomized trial in 10 schools with 1,825 enrolled students in Chachoengsao Province, eastern Thailand.
Sri Lanka

Sri Lanka

SCHOOL MEETINGS TO INFORM TEACHERS, PARENTS AND STUDENTS

Sri Lanka

Mortality and KD



Knockdown	100%	99%	92%	75%	54.5%	39%	20%	11.5%
Mortality	93.5%	91.5%	61%	59%	45%	34%	19%	15.5%

Sri Lanka

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Mitigating Diseases Transmitted by *Aedes* Mosquitoes: A Cluster-Randomised Trial of Permethrin-Impregnated School Uniforms

Pattamaporn Kittayapong[1,2]*, Phanthip Olanratmanee[3], Pongsri Maskhao[4], Peter Byass[5], James Logan[6], Yesim Tozan[7,8], Valérie Louis[7], Duane J. Gubler[9], Annelies Wilder-Smith[5,6,10,11]*

Conclusions

Entomological assessments showed that the intervention had some impact on the number of *Aedes* mosquitoes inside treatment schools immediately after impregnation and before insecticidal activity declined. However, there was no serological evidence of protection against dengue infections over the five months school term, best explained by the rapid washing-out of permethrin after 4 washes. If rapid washing-out of permethrin could be overcome by novel technological approaches, insecticide-treated clothes might become a potentially cost-effective and scalable intervention to protect against diseases transmitted by *Aedes* mosquitoes such as dengue, Zika, and chikungunya.

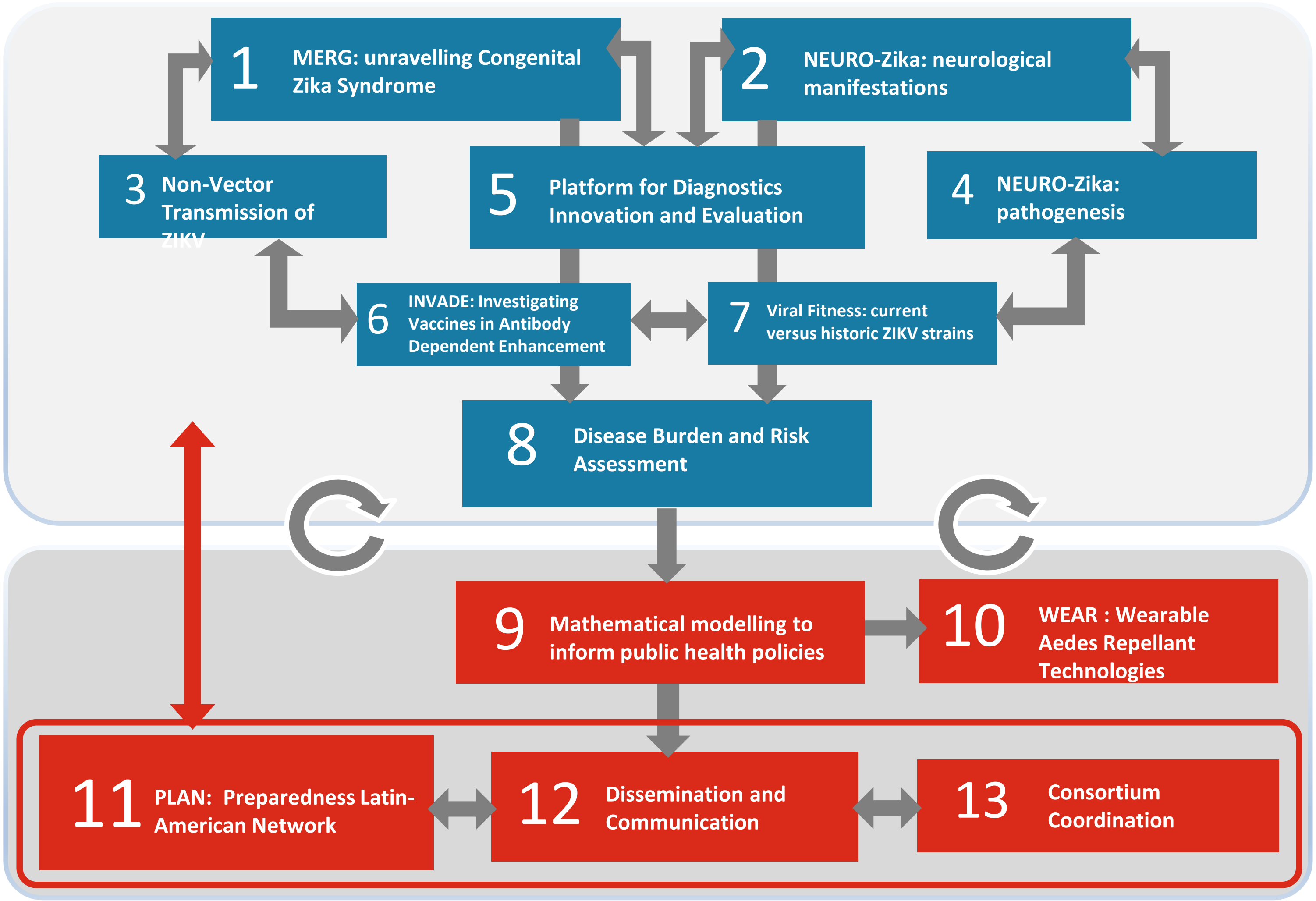
Outcome from these 2 research areas?

- Publications:
- From W-135 meningococcal disease: 15
- From DengueTools: 53

- Lessons learnt:
- Ideas create new ideas. Timing is of essence in emerging infectious diseases and outbreak situations
- Consortium approach is not additive, but synergistic


Rio de Janeiro

ZikaPLAN



1 MERG: unravelling Congenital Zika Syndrome
2 NEURO-Zika: neurological manifestations
3 Non-Vector Transmission of ZIKV
5 Platform for Diagnostics Innovation and Evaluation
4 NEURO-Zika: pathogenesis
6 INVADE: Investigating Vaccines in Antibody Dependent Enhancement
7 Viral Fitness: current versus historic ZIKV strains
8 Disease Burden and Risk Assessment
9 Mathematical modelling to inform public health policies
10 WEAR : Wearable Aedes Repellant Technologies
11 PLAN: Preparedness Latin-American Network
12 Dissemination and Communication
13 Consortium Coordination