Efficacy of targeted indoor residual spraying (TIRS) in preventing *Aedes-borne* diseases

Gonzalo M. Vazquez-Prokopec, MSc;PhD

Samuel Candler Dobbs Professor

Department of Environmental Sciences
Emory University
Atlanta GA, USA

gmvazqu@emory.edu

www.prokopeclab.org



EMORY
UNIVERSITY

Acknowledgements

Collaborators

Pablo Manrique-Saide (UADY)
Audrey Lenhart (CDC)
Norma Pavia-Ruz (UADY)
Hector Gomez-Dantes (INSP)
Scott Ritchie (James Cook Uni.)
Gregor Devine (QIMR)
Ira Longini (Uni. Florida)
Betz Halloran (Fred Hutch)
Natalie Dean (Uni. Florida)
Thomas Hladish (Uni. Florida)
Donal Bisanzio (RTI)
Fabian Correa-Morales (CENAPRECE)
Azael Che-Mendoza (UADY)
Gabriela Gonzalez-Olvera (UADY)
Solomon Yared (Jigjia Uni, Ethiopia)
Matt Collins (Emory)
Alex Perkins (Notre Dame)
Thomas Scott (UCDavis)
Amy Morrison (UCDavis)
Alun Lloyd (NCSU)

THE PROKOPACK



SAGE (dengue vaccines)

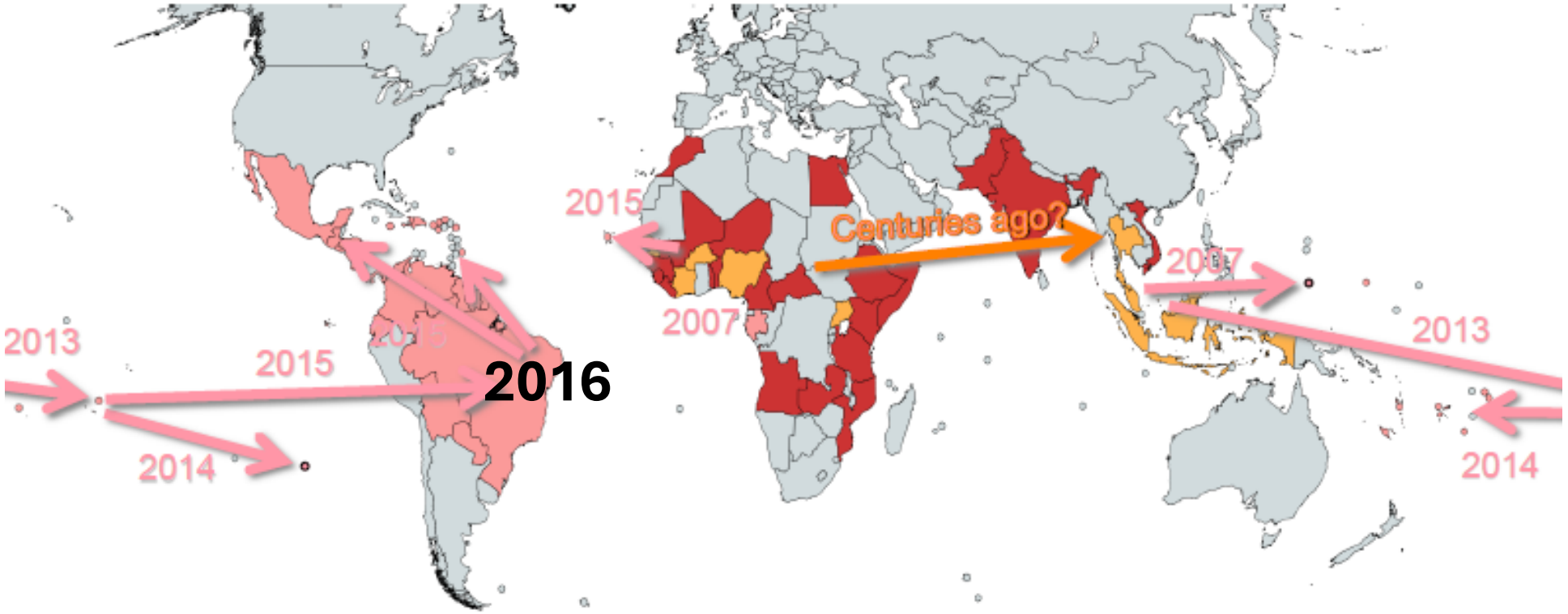
GDG (new)

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Historic and Recent History of Zika Virus Spread and Epidemics



Outbreaks
Serologic evidence
Virus detection or confirmed human case

Global expansion occurred despite intense vector control responses



https://www.channelnewsasia.com/asia/thailand-dengue-mosquito-breeding-climate-change-3654856



Photo Credit: New York Times

CNN Regions | U.S. Politics | Money | Entertainment | Tech | Sport | Travel | Style | Features | Video International Editio

WHO boss: Zika result of 'massive' mosquito control failures

By **Euan McKirdy**, CNN

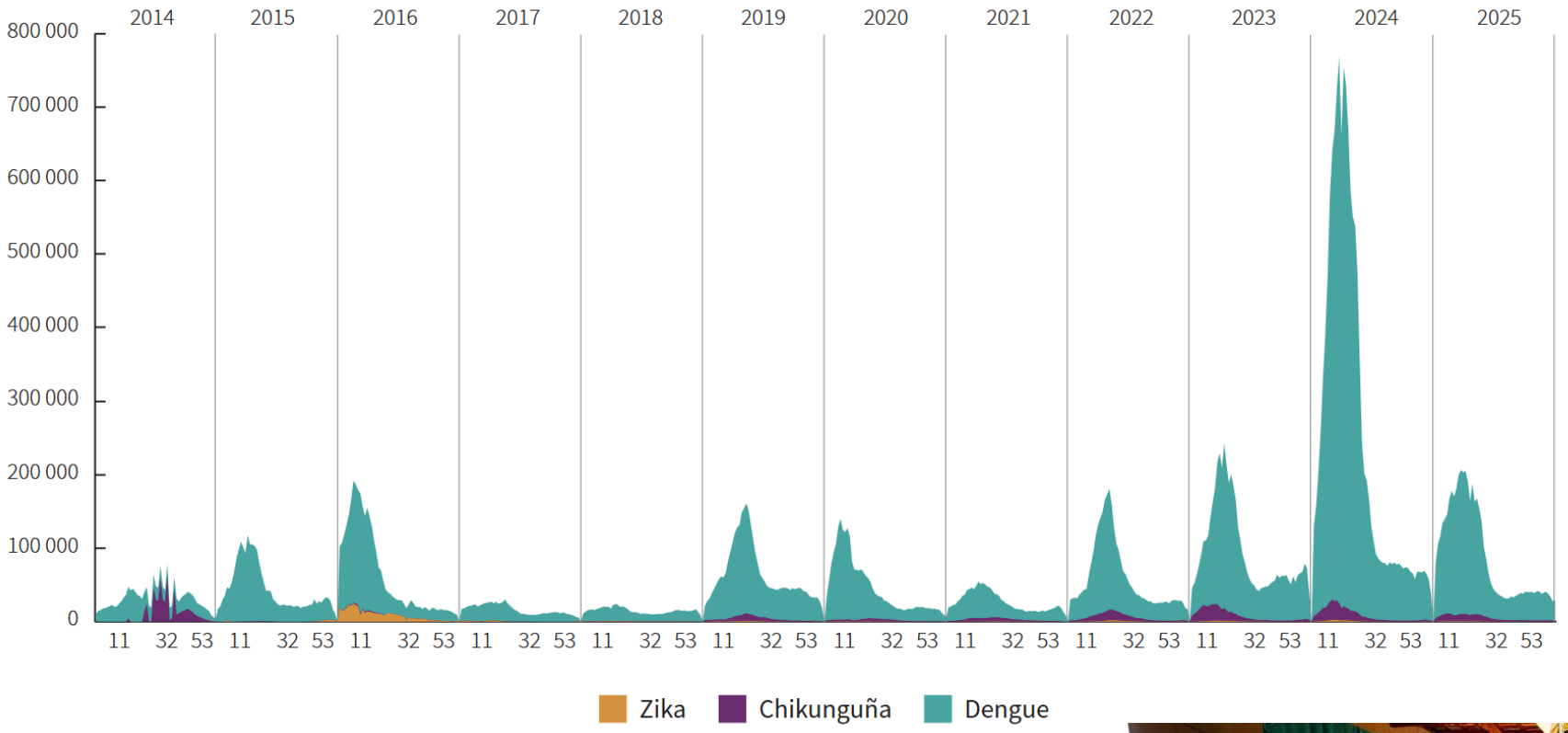
Updated 0652 GMT (1452 HKT) May 24, 2016



Thermal fogging, New Dehli IPL match 2015 (courtesy Bruce Murphy, DFAT)



Zika is out…dengue burden continues increasing



Fuente: Plataforma de Información en Salud de las Américas (PLISA).







Are ineffective vector control tools to blame?

PLOS Neglected Tropical Diseases

About Browse Publish

OPEN ACCESS

REVIEW

A Critical Assessment of Vector Control for Dengue Prevention

Nicole L. Achee, Fred Gould, T. Alex Perkins, Robert C. Reiner Jr., Amy C. Morrison, Scott A. Ritchie, Duane J. Gubler, Remy Teyssou, Thomas W. Scott

… the primary reason for the inability to recommend a specific existing intervention for either sustained management or epidemic mitigation is the absence of data providing clear evidence of a direct, positive health impact, i.e., reduced human dengue cases.

PLOS | NEGLECTED TROPICAL DISEASES



RESEARCH ARTICLE

Is Dengue Vector Control Deficient in Effectiveness or Evidence?: Systematic Review and Meta-analysis

Leigh R. Bowman[1], Sarah Donegan[2], Philip J. McCall[1]*

"we do not have a clear understanding of which of the currently available interventions actually work, where or when they succeed or might work best, and the reasons why they succeed or fail".

A leap forward: 10 years of progress

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Randomized Trial of Targeted Indoor Spraying to Prevent Aedes-Borne Diseases

Authors: Natalie E. Dean, Ph.D., Amy M. Crisp, Ph.D., Azael Che-Mendoza, Ph.D., Oscar D. Kirstein, Ph.D., Gloria A. Barrera-Fuentes, M.D., James T. Earnest, Ph.D., Henry N. Puerta-Guardo, Ph.D., +15, and Gonzalo M. Vazquez-Prokopec, Ph.D. Author Info & Affiliations

Published October 8, 2025 | N Engl J Med 2025;393:1387-1398 | DOI: 10.1056/NEJMoa2501069
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The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Efficacy of Wolbachia-Infected Mosquito Deployments for the Control of Dengue

Authors: Adi Utarini, M.D., Ph.D., Citra Indriani, M.D., M.P.H., Riris A. Ahmad, M.D., Ph.D., Warsito Tantowijoyo, Ph.D., Eggi Arguni, M.D., Ph.D., M. Ridwan Ansari, M.Sc., Endah Supriyati, M.Sc., +17, for the AWED Study Group* Author Info & Affiliations

PNAS

RESEARCH ARTICLE | APPLIED BIOLOGICAL SCIENCES

Efficacy of a spatial repellent for control of *Aedes*-borne virus transmission: A cluster-randomized trial in Iquitos, Peru

Amy C. Morrison, Robert C. Reiner, Jr., William H. Elson, Helvio Astete, Carolina Guevara, Clara del Aguila, Isabel Bazan, Crystyan Siles, Patricia Barrera, Anna B. Kawiecki, Christopher M. Barker, Gissella M. Vasquez, Karin Escobedo-Vargas, Carmen Flores-Mendoza, Alfredo A. Huaman, Mariana Leguia, Maria E. Silva, Sarah A. Jenkins, Wesley R. Campbell, Eugenio J. Abente, Robert D. Hontz, Valerie A. Paz-Soldan, John P. Grieco, Neil F. Lobo, Thomas W. Scott, and Nicole L. Achee -22 Authors Info & Affiliations

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Dengue Suppression by Male Wolbachia-Infected Mosquitoes

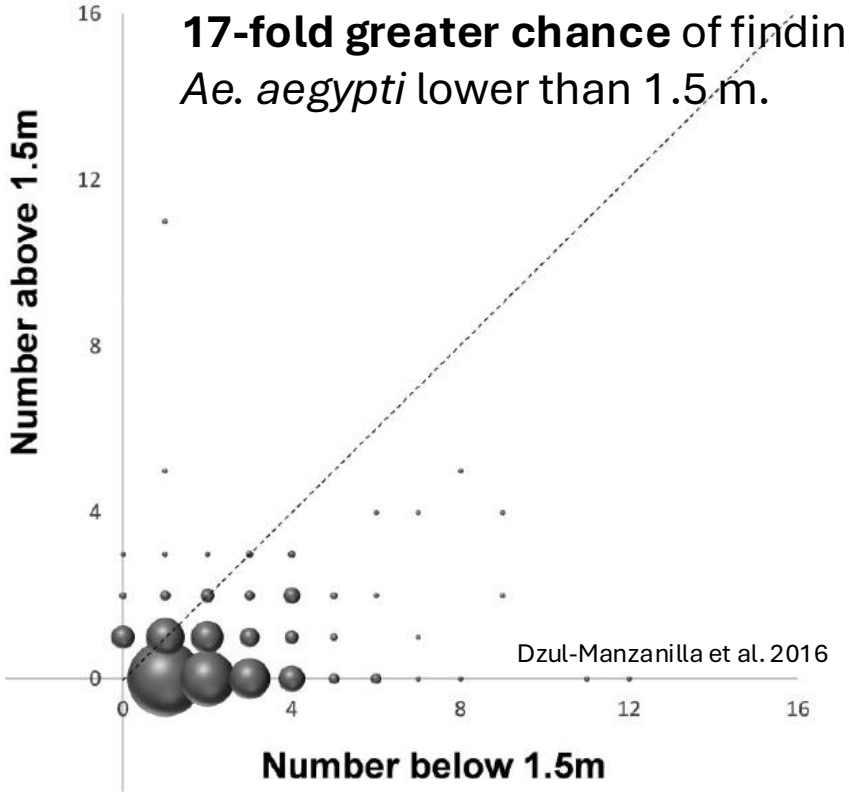
Authors: Jue Tao Lim, Ph.D., Chee-Seng Chong, Ph.D., Chia-Chen Chang, Ph.D., Diyar Mailepessov, M.P.H., Borame Dickens, Ph.D., Yee Ling Lai, B.Sc., Lu Deng, B.Sc., +13, for the Project Wolbachia–Singapore Consortium* Author Info & Affiliations



Aedes aegypti flight and resting behaviors



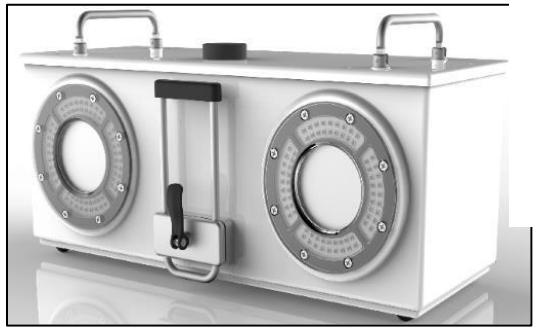




17-fold greater chance of finding *Ae. aegypti* lower than 1.5 m.

Dzul-Manzanilla et al. 2016

Similar low-height resting behavior: Iquitos (Peru), Acapulco (Mexico), Panama City (Panama).



OPEN

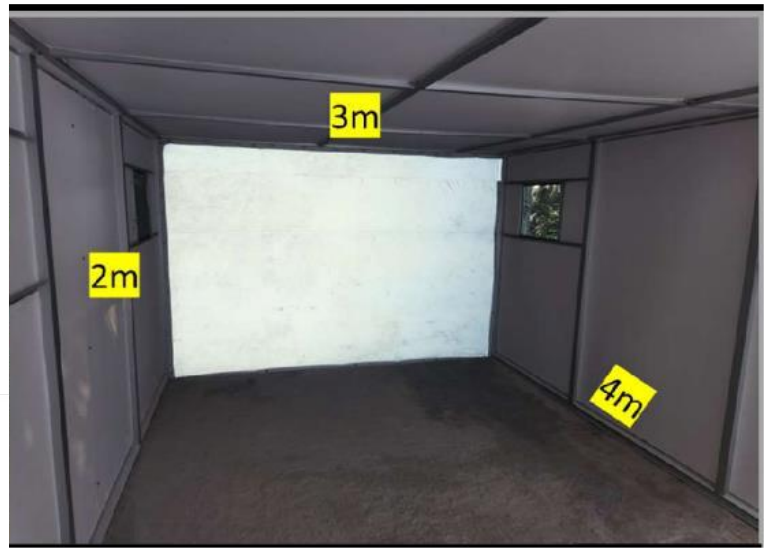
Check for updates

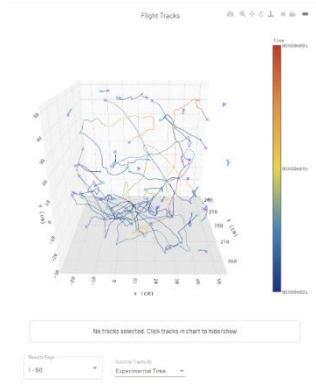
Optical tracking and laser-induced mortality of insects during flight

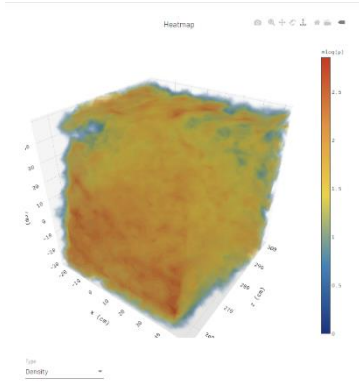
Matthew D. Keller, Bryan J. Norton, David J. Farrar, Phil Rutschman, Maclen Marvit & Arty Makagon









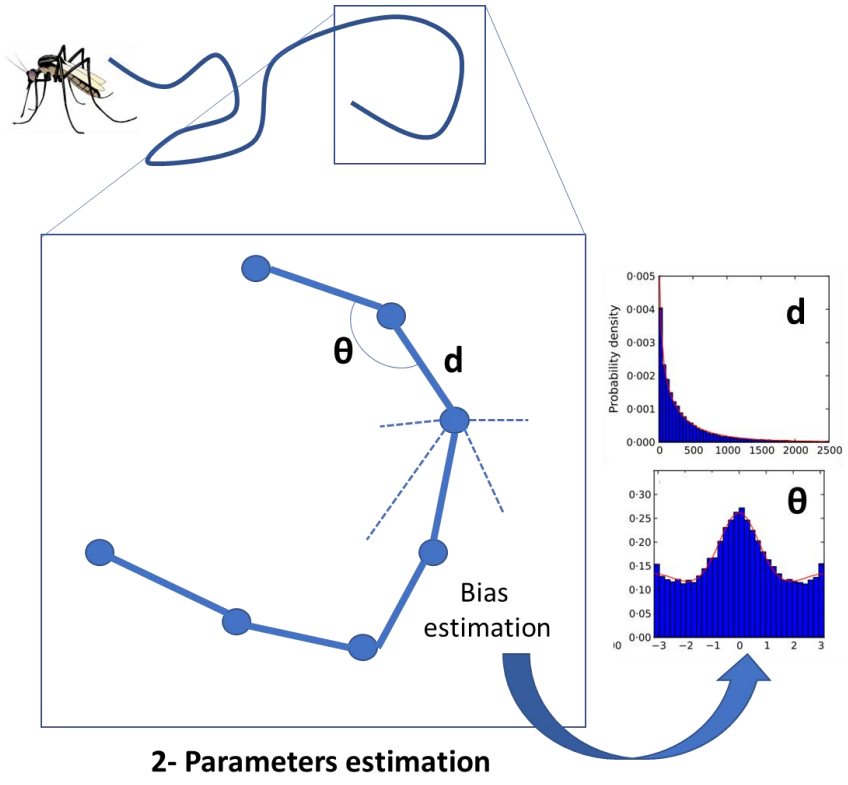


Jimenez-Vallejo et al. in rev.

What is a good ‘null model’ for mosquito flight?

- Quantifying behaviors requires knowing what is ‘normal’ or at least ‘expected’ if mosquitoes showed no preference to anything (randomness).

- Developed a 3D ‘random’ model for mosquito flight: Random Walk3D

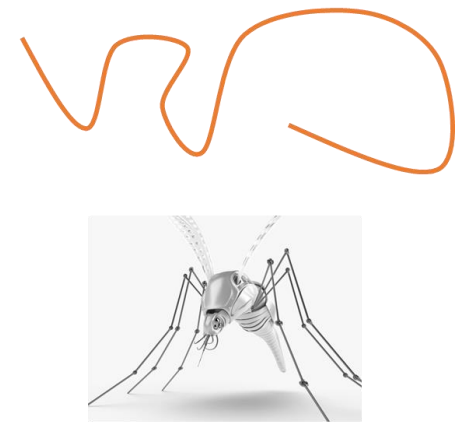


2- Parameters estimation

$$x_{n+1} = x_n + s \cdot \sin(\theta_n) \cdot \cos(\phi_n)$$

$$y_{n+1} = y_n + s \cdot \sin(\theta_n) \cdot \sin(\phi_n)$$

$$z_{n+1} = z_n + s \cdot \cos(\theta_n)$$

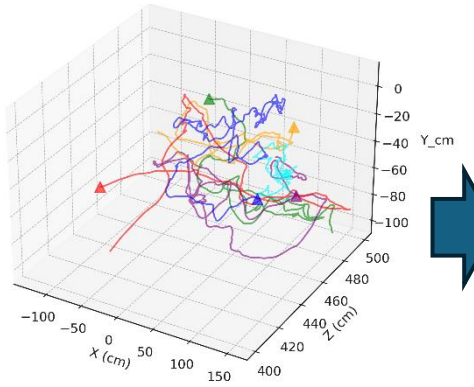


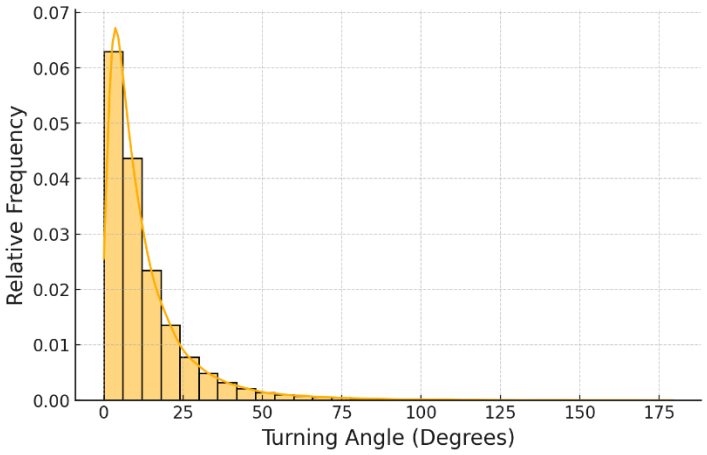
3- Simulation

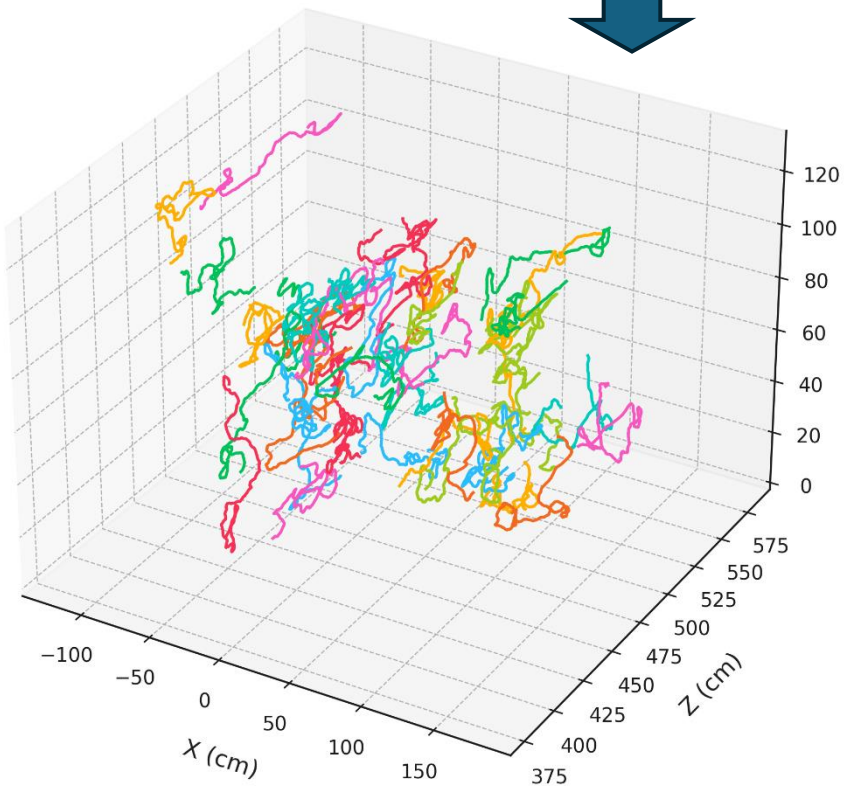
Random Walk3D uses 2 parameters from the PFMD to generate simulations of mosquito movement in 3D space.



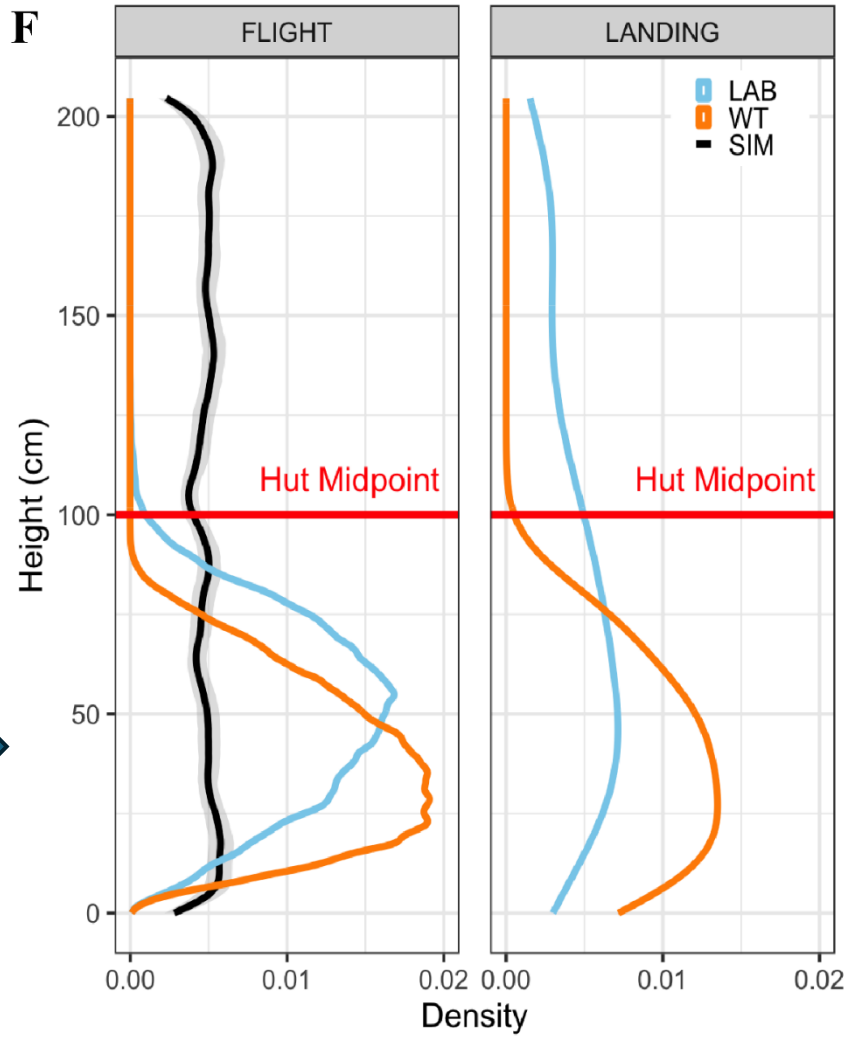
Innate free-flight behavior: flight and resting preferences







100K trajectories simulated to capture 'expected' behavior under randomness



Ae. aegypti shows an innate behavior focused on low (<1m) flight and resting.

Microclimatic conditions, visual cues and genetic factors jointly influence such behaviors.

Jimenez-Vallejo et al. in rev.

Accounting for resting behavior: Targeted Indoor Residual Spraying (TIRS)

Targets the resting behavior of *Aedes aegypti*



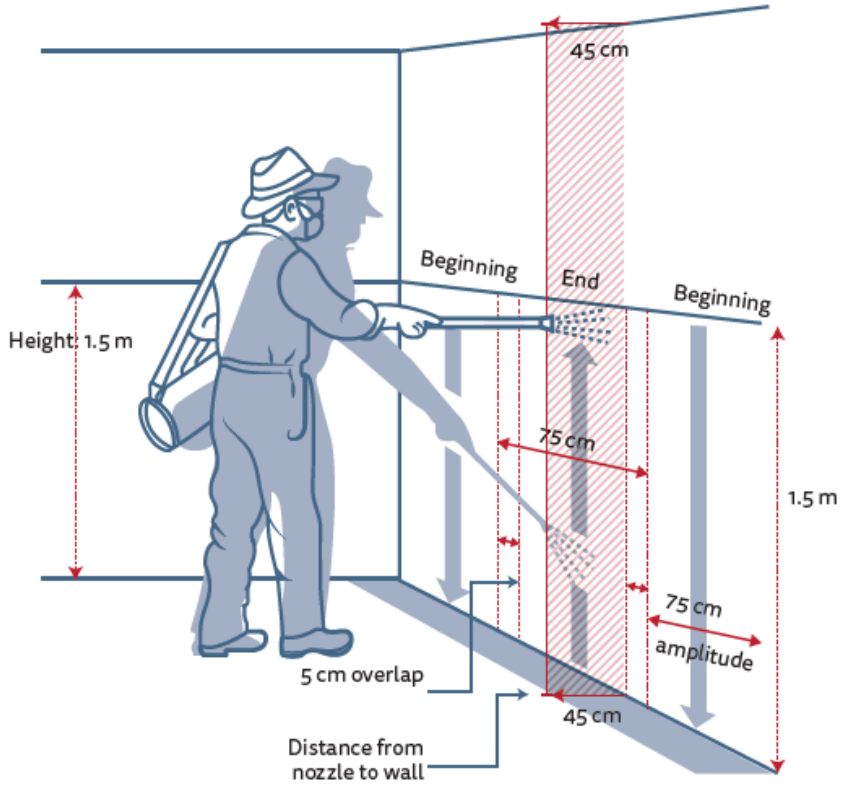


Figure 5. Illustration of the IRS technique for urban *A. aegypti* control (adapted from WHO, 2015).

Spraying residual insecticides in walls below 1.5m and in key resting sites such as under or behind furniture.
Excludes kitchens and bathrooms.

https://iris.paho.org/handle/10665.2/51637

Climbing the public health evidence ladder: 15 years of research

RESEARCH ARTICLE

Efficacy of novel indoor residual spraying methods targeting pyrethroid-resistant *Aedes aegypti* within experimental houses

Mike W. Dunbar[1]*, Fabian Correa-Morales[2], Felipe Dzul-Manzanilla[2], Anuar Medina-Barreiro[3], Wilbert Bibiano-Marín[3], Evaristo Morales-Ríos[3], José Vadillo-Sánchez[2], Beatriz López-Monroy[4], Scott A. Ritchie[5], Audrey Lenhart[6], Pablo Manrique-Saide[3], Gonzalo M. Vazquez-Prokopec[1]

Preventive residual insecticide applications successfully controlled *Aedes aegypti* in Yucatan, Mexico

Gonzalo M. Vazquez-Prokopec[1,2], Azael Che-Mendoza[2], Oscar D. Kirstein[1], Wilberth Bibiano-Marin[2], Gabriela González-Olvera[2], Anuar Medina-Barreiro[2], Hector Gomez-Dantes[3], Norma Pavia-Ruz[4] & Pablo Manrique-Saide[2]

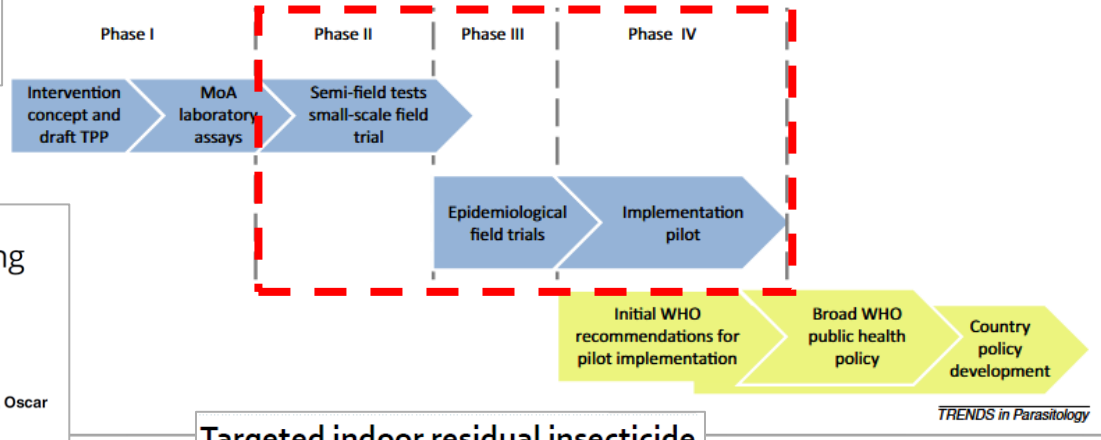
STUDY PROTOCOL Open Access

The TIRS trial: protocol for a cluster randomized controlled trial assessing the efficacy of preventive targeted indoor residual spraying to reduce *Aedes*-borne viral illnesses in Merida, Mexico

Pablo Manrique-Saide[1], Natalie E. Dean[2], M. Elizabeth Halloran[3,4,5], Ira M. Longini[2,6], Matthew H. Collins[7], Lance A. Waller[8], Hector Gomez-Dantes[9], Audrey Lenhart[10], Thomas J. Hladish[6,11], Azael Che-Mendoza[1], Oscar D. Kirstein[12], Yamila Romer[12], Fabian Correa-Morales[13], Jorge Palacio-Vargas[14], Rosa Mendez-Vales[14], Pilar Granja Pérez[14], Norma Pavia-Ruz[15], Guadalupe Ayora-Talavera[15] and Gonzalo M. Vazquez-Prokopec[12]

EVALUATION AND COMPARISON OF SPRAY EQUIPMENT FOR INDOOR RESIDUAL SPRAYING

FABIAN CORREA-MORALES,[1] MIKE W. DUNBAR,[2,4] FELIPE DZUL-MANZANILLA,[2] ANUAR MEDINA-BARREIRO,[3] EVARISTO MORALES-RÍOS,[3] WILBERT BIBIANO-MARÍN,[3] AZAEL CHE-MENDOZA,[3] PABLO MANRIQUE-SAIDE[3] AND GONZALO M. VAZQUEZ-PROKOPEC[2]



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Randomized Trial of Targeted Indoor Spraying to Prevent Aedes-Borne Diseases

Authors: Natalie E. Dean, Ph.D., Amy M. Crisp, Ph.D., Azael Che-Mendoza, Ph.D., Oscar D. Kirstein, Ph.D., Gloria A. Barrera-Fuentes, M.D., James T. Earnest, Ph.D., Henry N. Puerta-Guardo, Ph.D., +15, and Gonzalo M. Vazquez-Prokopec, Ph.D. Author Info & Affiliations

Published October 8, 2025 | N Engl J Med 2025;393:1387-1398 | DOI: 10.1056/NEJMoa2501069

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RESEARCH ARTICLE

Efficacy of targeted indoor residual spraying with the pyrrole insecticide chlorfenapyr against pyrethroid-resistant *Aedes aegypti*

Azael Che-Mendoza[1], Gabriela González-Olvera[1], Anuar Medina-Barreiro[1], Carlos Arisqueta-Chablé[1], Wilberth Bibiano-Marin[1], Fabián Correa-Morales[2], Oscar D. Kirstein[3], Pablo Manrique-Saide[1], Gonzalo M. Vazquez-Prokopec[3]*

Targeted indoor residual insecticide applications shift *Aedes aegypti* age structure and arbovirus transmission potential

Oscar David Kirstein[1,6], Carlos Culquichicon[1,6], Azael Che-Mendoza[2,6], Juan Navarrete-Carballo[2], Joyce Wang[1], Wilberth Bibiano-Marin[2], Gabriela Gonzalez-Olvera[2], Guadalupe Ayora-Talavera[3], James Earnest[1], Henry Puerta-Guardo[2], Norma Pavia-Ruz[4], Fabian Correa-Morales[5], Anuar Medina-Barreiro[2], Pablo Manrique-Saide[2] & Gonzalo M. Vazquez-Prokopec[1,2]

Residual efficacy of the neonicotinoid insecticide clothianidin against pyrethroid-resistant *Aedes aegypti*

Azael Che-Mendoza,[a] Gabriela González-Olvera,[a] Anuar Medina-Barreiro,[a] Carlos Arisqueta-Chablé,[a] Josue Herrera-Bojórquez,[a] Wilberth Bibiano-Marín,[a] Oscar Kirstein,[b] Gonzalo Vazquez-Prokopec[b]* and Pablo Manrique-Saide[a]

Direct and Indirect Entomological Efficacy of Targeted Indoor Residual Spraying in Iquitos, Peru

RESEARCH ARTICLE

Forecasting the effectiveness of indoor residual spraying for reducing dengue burden

Thomas J. Hladish[1,2]*, Carl A. B. Pearson[3], Diana Patricia Rojas[2,4], Hector Gomez-Dantes[5], M. Elizabeth Halloran[6,7,8], Gonzalo M. Vazquez-Prokopec[9], Ira M. Longini[2,7,10]

Designing effective control of dengue with combined interventions

Thomas J. Hladish[a,b,1,2], Carl A. B. Pearson[c,d,e,1], Kok Ben Toh[f], Diana Patricia Rojas[g,h], Pablo Manrique-Saide[i], Gonzalo M. Vazquez-Prokopec[i], M. Elizabeth Halloran[k,l,m], and Ira M. Longini Jr[b,g,l]

Phase II: showing selective applications 'work'

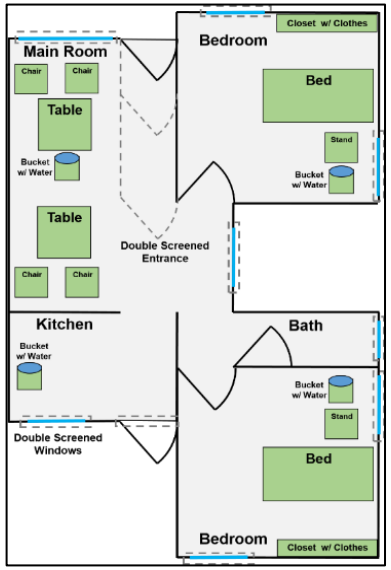
PLOS NEGLECTED TROPICAL DISEASES February 28, 2019

RESEARCH ARTICLE

Efficacy of novel indoor residual spraying methods targeting pyrethroid-resistant *Aedes aegypti* within experimental houses

Mike W. Dunbar[1]*, Fabian Correa-Morales[2], Felipe Dzul-Manzanilla[2], Anuar Medina-Barreiro[3], Wilbert Bibiano-Marín[3], Evaristo Morales-Ríos[3], José Vadillo-Sánchez[2], Beatriz López-Monroy[4], Scott A. Ritchie[5], Audrey Lenhart[6], Pablo Manrique-Saide[3], Gonzalo M. Vazquez-Prokopec[1]

- **How fast and effective is TIRS?**
- Trials in 9 rented (real) houses in Merida and releases of resistant mosquitoes.
- Houses are typically 120 – 140 m^2: 2 bedrooms, 1 bathroom, 1 or 2 living spaces
- Windows and doors were screened and experiments conducted in temperatures of 28 - 32C

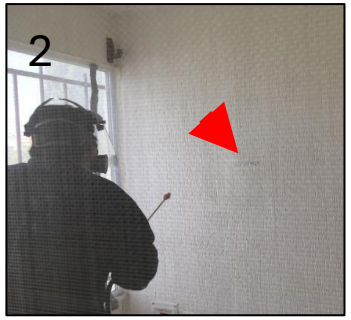










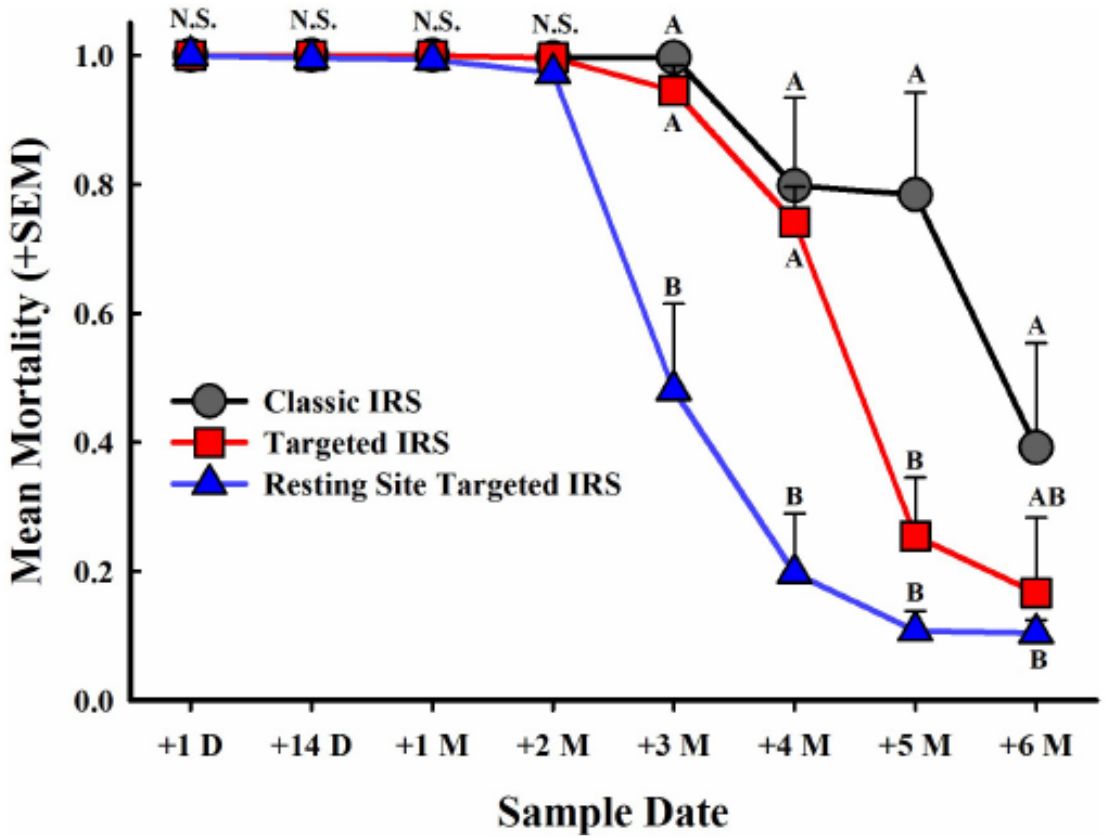




Whole wall and all furniture ("classic IRS")

Wall < 1.5m and all furniture ("Targeted IRS")

Only furniture (Resting Site TIRS")

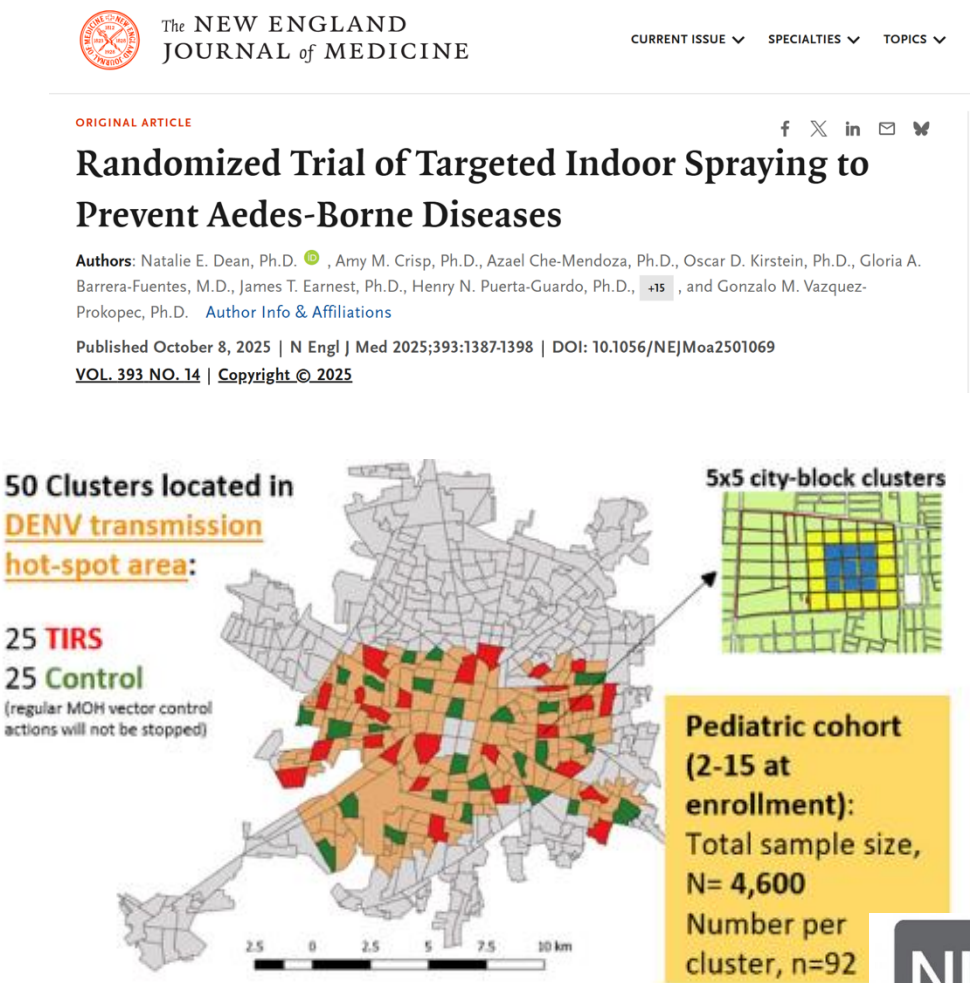


Can behavioral targetting through TIRS work?

- Two arm, parallel, Cluster Randomized Controlled Trial evaluating the epidemiological impact of TIRS in Merida, Mexico.
- Two paradigms were evaluated:
  - TIRS
  - Preventive application
- Covariate-constrained randomization.

Table 1 Outcome measures for the trial

Endpoint	Name	Population	Brief description
Primary	Laboratory-confirmed *Aedes*-borne disease	2–15-year-olds at enrollment	Laboratory-confirmed (virologically [RT-PCR testing of acute samples] or serologically [IgM and IgG ELISA testing of paired acute and convalescent samples]) symptomatic DENV, CHIKV, or ZIKV
Secondary	Laboratory-confirmed *Aedes*-borne infection	2–15-year-olds at enrollment	Laboratory-confirmed (serologically, [IgG ELISA and neutralization testing of annual surveillance samples]) DENV, CHIKV, or ZIKV infection. A FRNT50 for one DENV serotype ≥ 4-fold the FRNT50 to the other 3 serotypes is considered DENV mono-immune seroconversion
Secondary	*Aedes aegypti* infection with *Aedes*-borne viruses	Female *Ae. aegypti* collected in central 3 × 3 blocks of each cluster	*Ae. aegypti* mosquito infection rates with DENV, CHIKV, and ZIKV (assessed by RT-PCR) from 10% of households
Secondary	*Aedes aegypti* infestation	*Ae. aegypti* collected in central 3 × 3 blocks of each cluster	*Ae. aegypti* indoor entomological indices (adult presence and abundance, female presence and abundance, blood-fed female and abundance) from 10% of households
Secondary	Community acceptability of TIRS	Head of household in clusters receiving TIRS	Households receiving the intervention will be asked about their response and issues with TIRS. Conducted on same houses where entomology occurs.
Secondary	Community impact of TIRS	All ages	Number of symptomatic ABV cases reported to the passive surveillance system, including children and adults, distributed in treatment and control clusters
Secondary	Safety profile	All houses in 5 × 5 block treatment clusters	Percentage of households receiving the intervention that had evidence of a reaction to the insecticide (assessed and confirmed by study doctors). All sprayed households are eligible.



ClinicalTrials.gov NCT04343521. Registered on 13 April 2020

National Institutes of Health

Numbers of residential premises treated

2021	2022	2023
13,683 residential premises	13,703 residencial premises	13,965 residential premises
8,241 treated with TIRS	9,170 treated with TIRS	10,472 treated with TIRS:



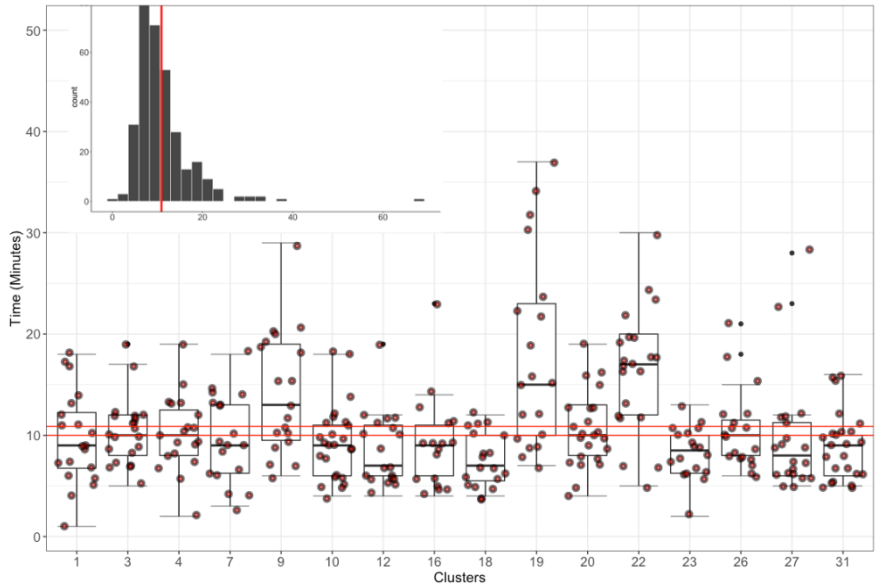
Pirimiphos-methyl (Actellic 300CS)





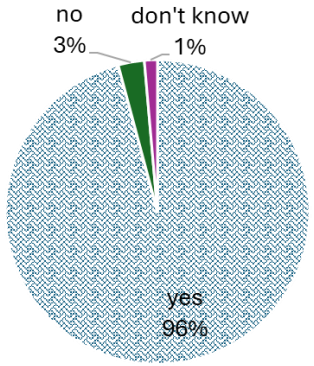


Two cases of multisymptom adverse events (e.g., nausea, watery eyes, diarrhea, and vomiting) were associated with the intervention.



Average application time was 11 min per house.

Recommend the intervention?



Very high community acceptance

Initial evidence: ABV illness

Positive entomological impact (70%)

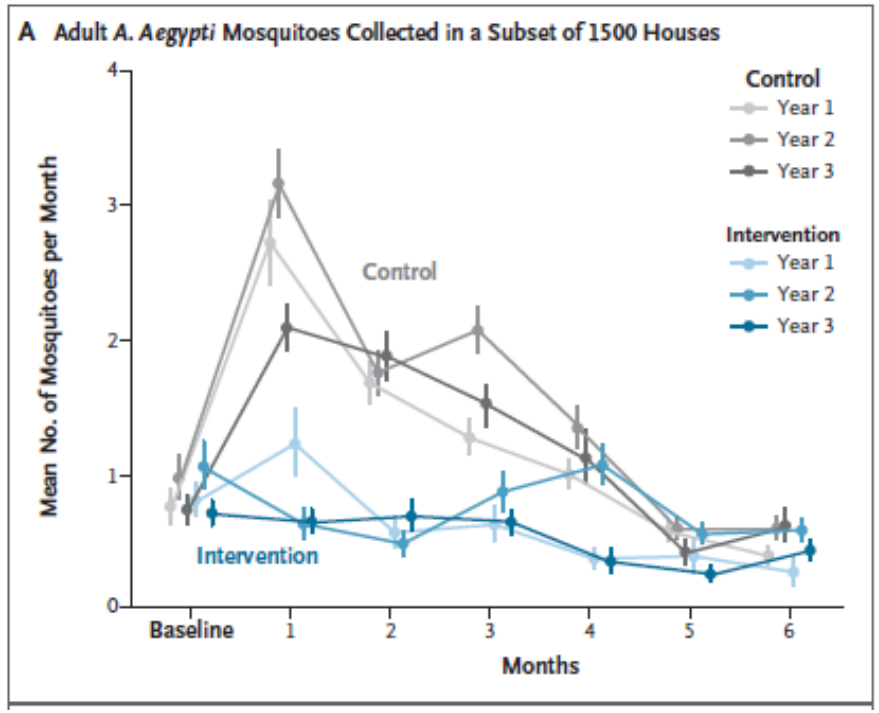


Table 1. Epidemiologic Efficacy Estimates.

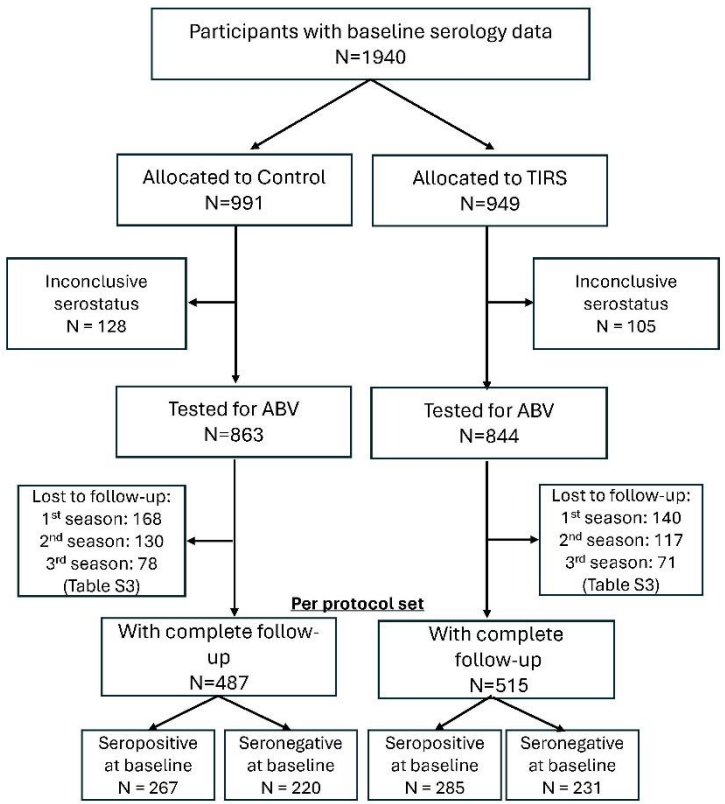
Analysis	Targeted Indoor Residual Spraying			Control			Efficacy*
	No. of Participants	No. of Cases	Cumulative Incidence (95% CI)† %	No. of Participants	No. of Cases	Cumulative Incidence (95% CI)† %	Point Estimate (95% CI) %
Primary analysis							
Per-protocol analysis of cluster centers	1038	91	11.5 (8.4 to 14.5)	1037	89	10.1 (7.8 to 12.3)	−12.8 (−60.7 to 23.0)
Secondary analyses							
Intention-to-treat analysis of entire clusters	2239	198	10.1 (8.4 to 11.8)	2222	199	10.5 (8.6 to 12.3)	3.9 (−28.1 to 26.7)
Community effect analysis	—	150		—	202		24.0 (6.0 to 38.6)

Lower mosquito levels.

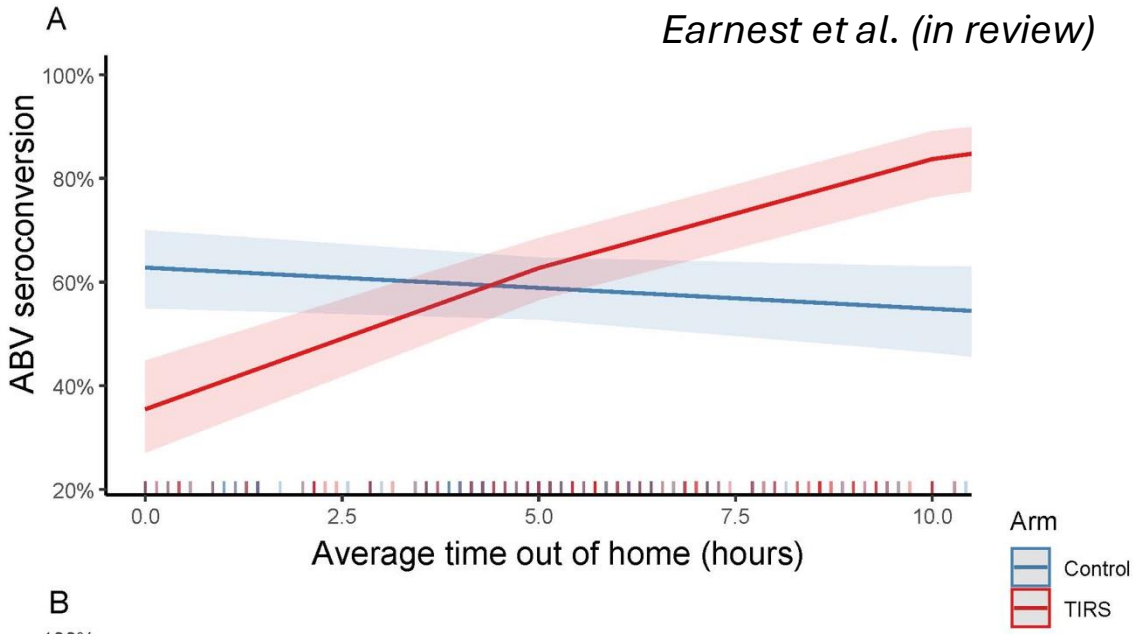
A significant community effect (across all ages): Test-negative: Overall DENV reduction of 24%.

Dean et al. N.Engl.J.Med 2025

Secondary endpoint: infection



2021-2023: 568 ABV seroconversions (N=1002). FRNT confirmed majority DENV3



Earnest et al. (in review)

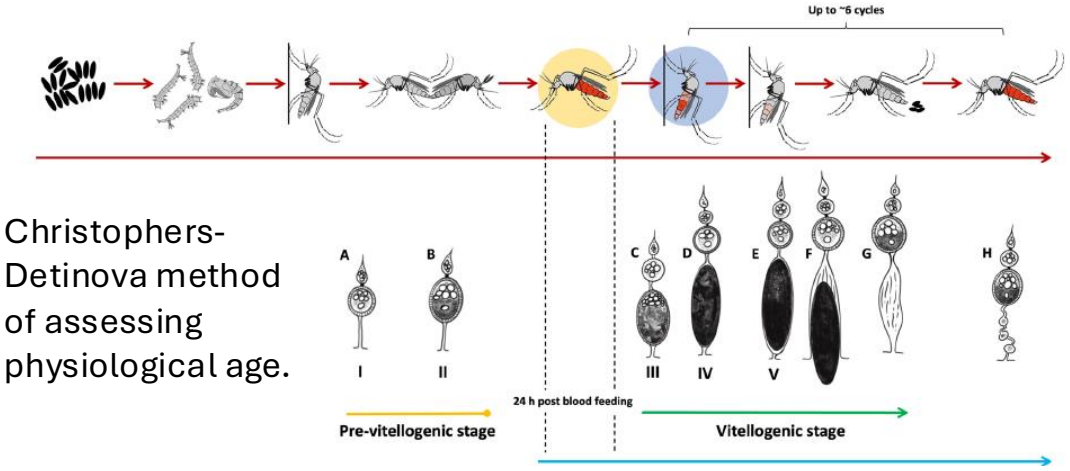
Significant interaction between arm and mobility (hours out of home during weekdays). Re-analyzed trial for less mobile participants.

Efficacy increased as time in home increased.

Analysis population / model	TIRS (cases / total)	Control (cases / total)	Effect estimate (OR, 95% CI)	Efficacy (%) (95%CI)	p value
Per-protocol, unadjusted	300 / 516	268 / 487	1.14 (0.79-1.64)	-14% (-64 to 21)	0.477
Sensitivity analysis, adjusted*					
TIRS vs Control at up to 2h/day outside	38 / 80	58 / 87	0.40 (0.18 – 0.92)	60% (8 to 82)	0.030
TIRS vs Control at up to 3h/day outside	48 / 105	73 / 111	0.42 (0.22 – 0.81)	58% (19 to 78)	0.009
TIRS vs Control at up to 4h/day outside	85 / 184	115 / 198	0.62 (0.38-0.99)	38% (1 to 62)	0.048
TIRS vs Control at up to 5h/day outside	174 / 294	123 / 257	0.64 (0.41-1.00)	36% (0 to 59)	0.052

* Odds ratios (OR) were estimated using a mixed-effects logistic regression as the unadjusted model, but on a subset of participants in the PP set that matched the specified number of hours outside the house.

Effect of TIRS on mosquito parity and age



Christophers-Detinova method of assessing physiological age.

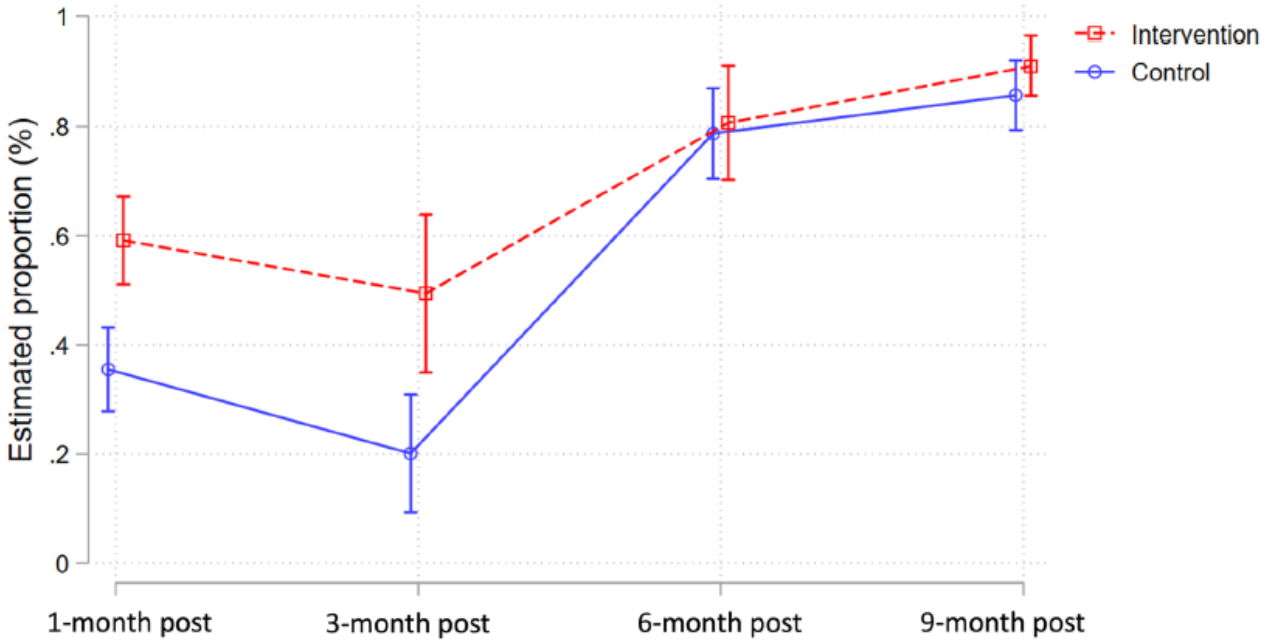
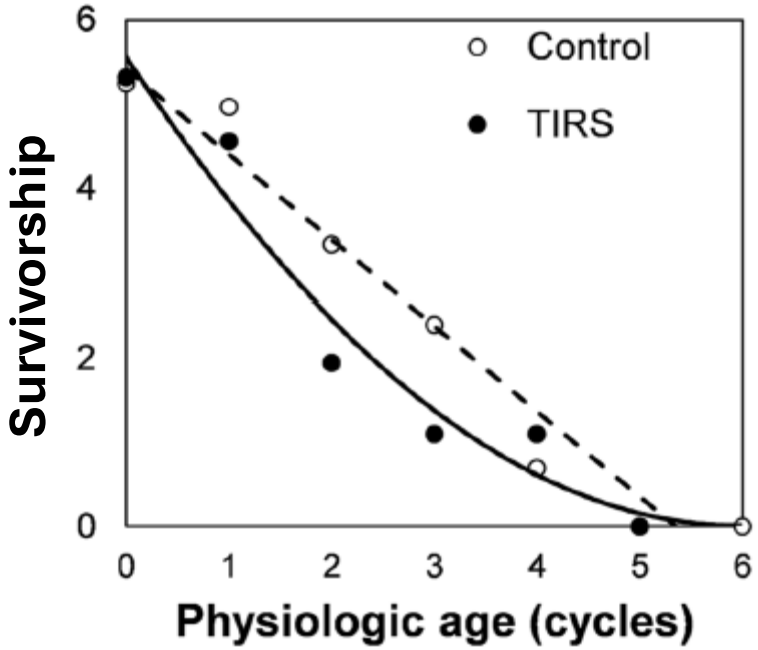


Figure 3. Proportion of nulliparous females over time in TIRS and control arms, with 95% CI estimates expressed as error bars.



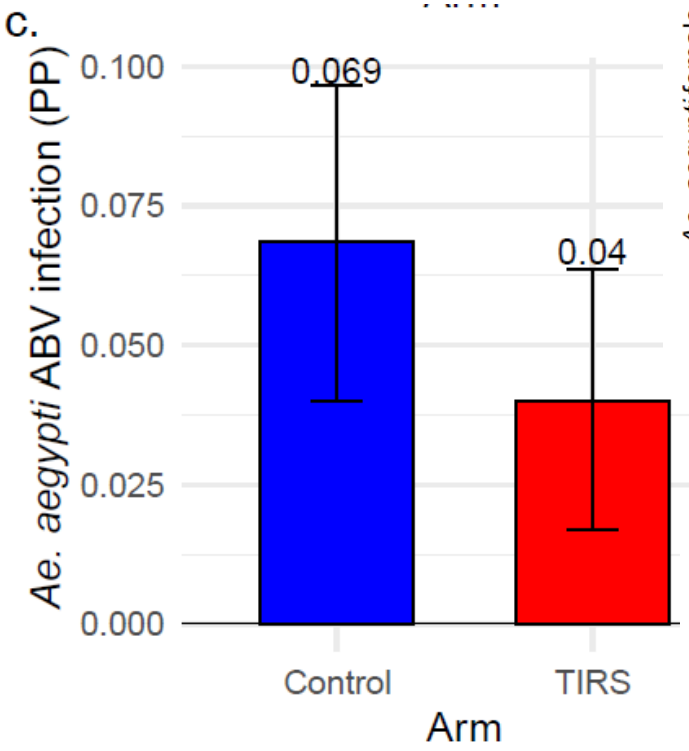
Up to 3 months post-TIRS significantly higher nulliparous females in TIRS.

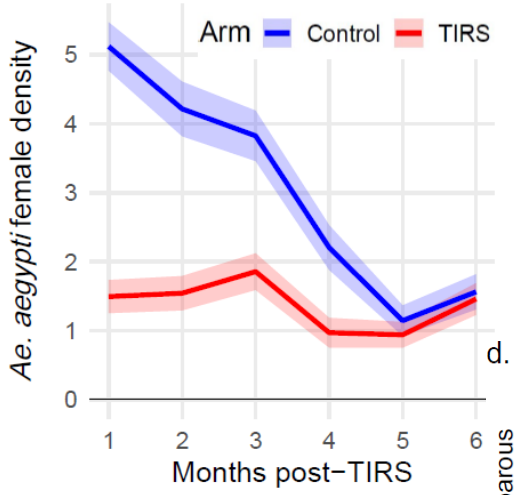
When looked by physiologic age (number of follicular dilatations), TIRS increased the mortality of younger females, leading to non-linear mortality hazard rate.

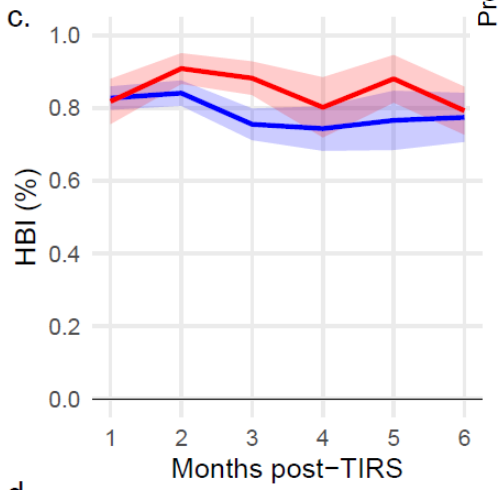
Kirstein et al. 2023

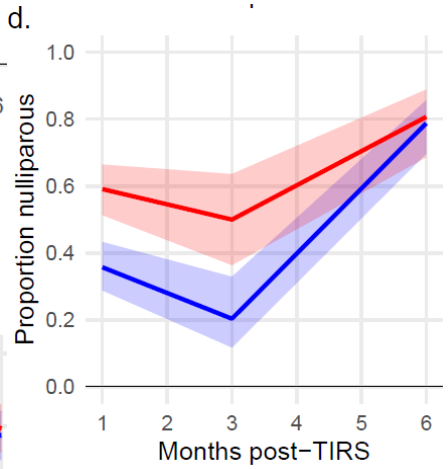
Phase III: Secondary endpoint (entomological impact)

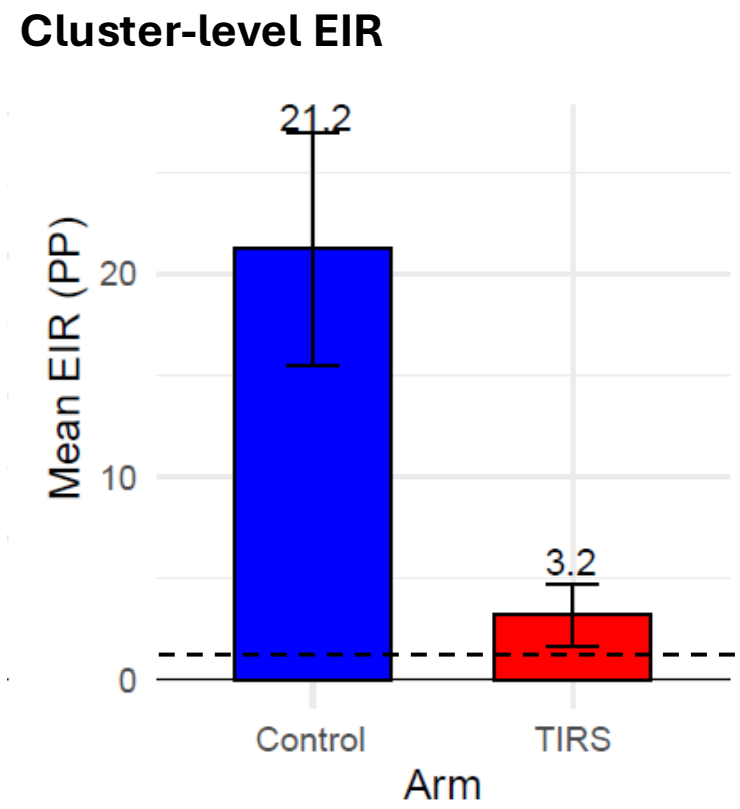
- 2023 only. A total of 600 pools (300 TIRS, 300 Control).
- Trioplex rtPCR.







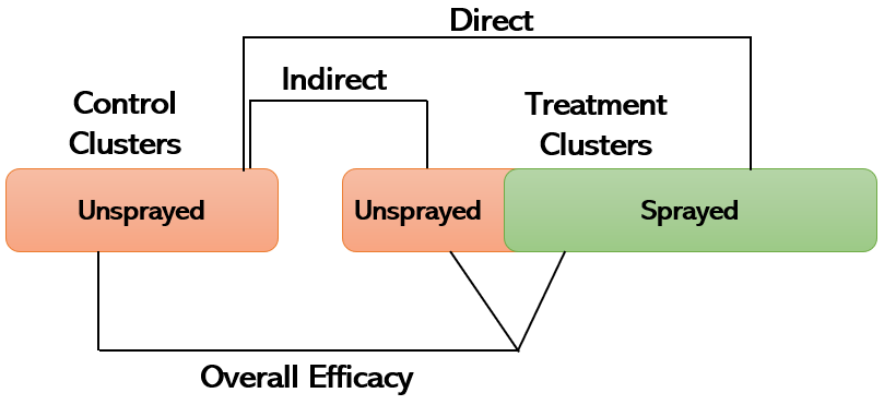


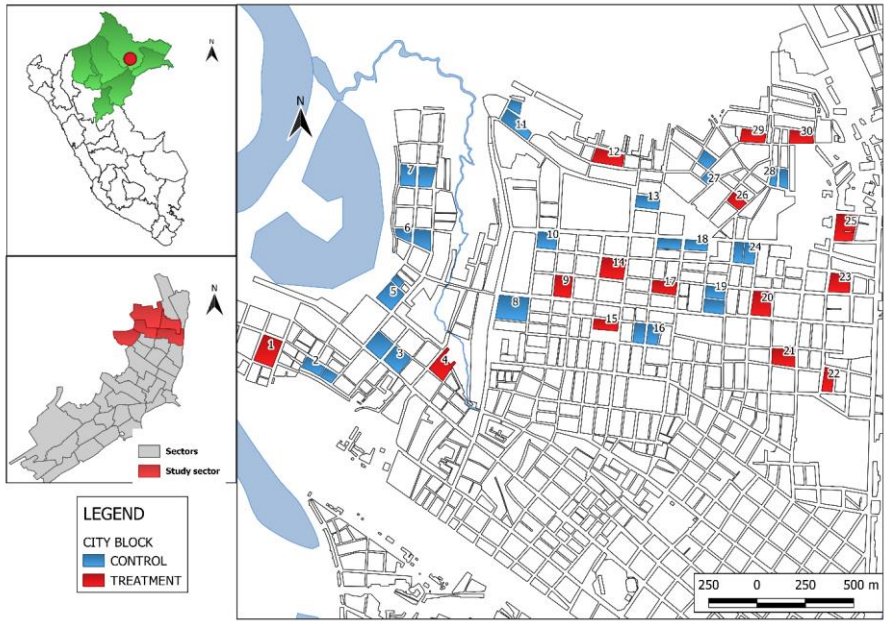


Number of potentially infectious ABV bites per host per 6-months

Che-Mendoza et al. in prep.

Phase II: direct and indirect efficacy in Iquitos

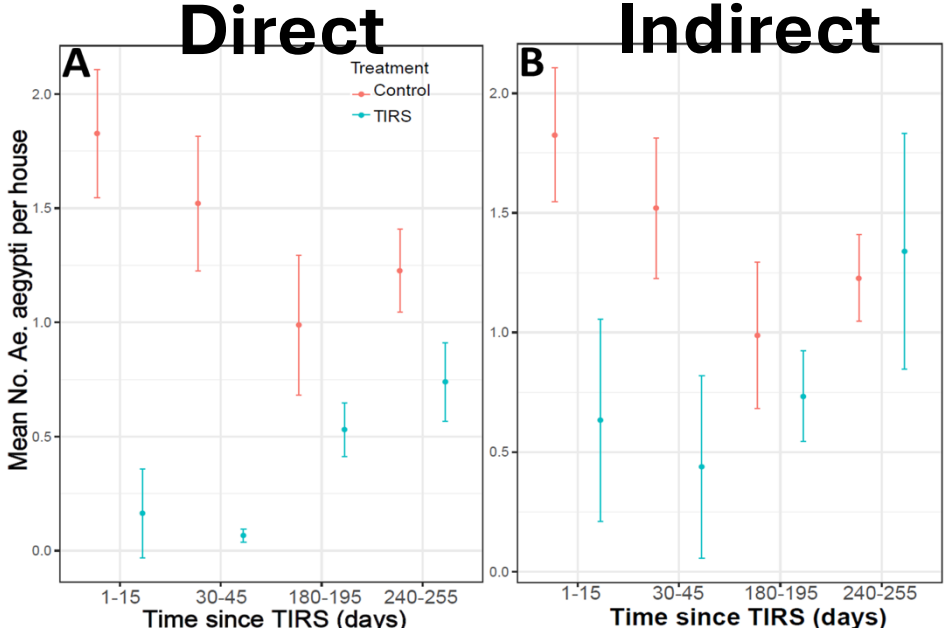


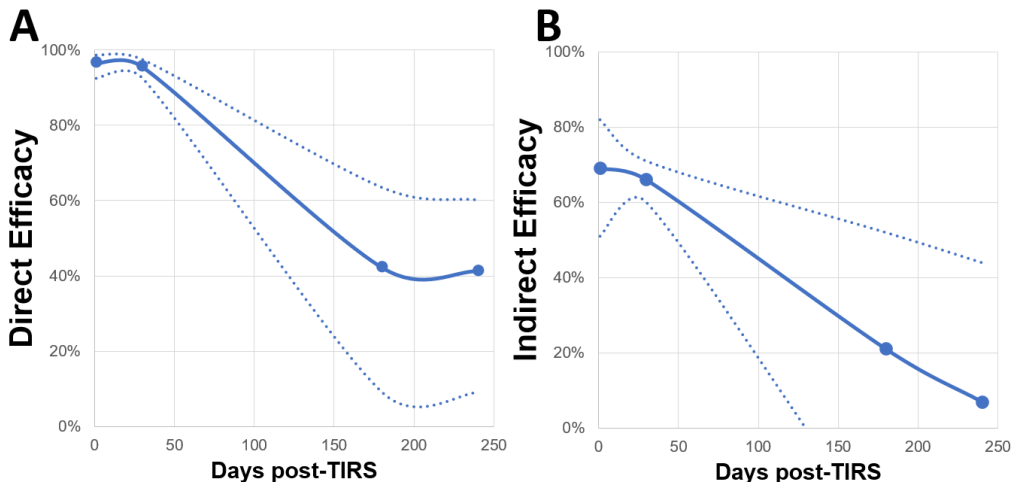


Actellic 300CS

Direct efficacy was highest during the first 45 days post-spraying (96%) but sharply reduced.

Up to 45 days, indirect efficacy ranged between 66% and 69%.





Morrison et al. unpublished

Country adoption and integration of TIRS

Ministério da Saúde
Secretaria de Vigilância em Saúde e Ambiente
Departamento de Doenças Transmissíveis
Coordenação-Geral de Vigilância de Arboviroses

NOTA TÉCNICA Nº 6/2025-CGARB/DEDT/SVSA/MS

1. **ASSUNTO**

1.1. Orientação técnica para a implementação da Borrifação Residual Intradomiciliar para o controle do *Aedes aegypti* e *Aedes albopictus* (BRI- Aedes) em imóveis especiais.

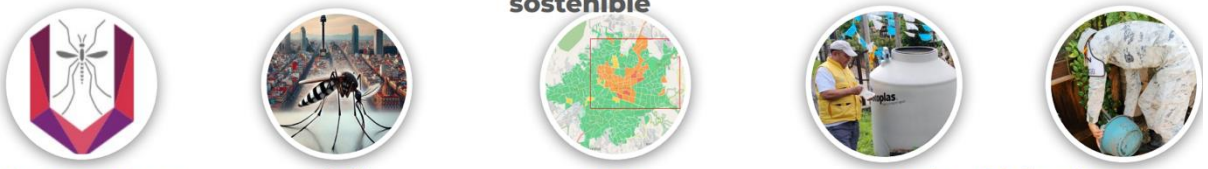
2.4. A utilização da BRI-*Aedes* é indicada para imóveis especiais (IE), locais com grande fluxo ou permanência de pessoas, tais como unidades básicas de saúde, lares de idosos, residência de recicladores, rodoviárias, universidades e escolas, além dos pontos estratégicos. Esta estratégia deve ser utilizada tanto em áreas prioritárias como nas áreas não prioritárias, no entanto, deve ser iniciada sempre pelas áreas prioritárias do município.

Gobierno de México | Salud Secretaría de Salud | CENAPRECE

Plan nacional para el control del dengue y otras arbovirosis

Plan Anual contra el Dengue

Reducir el número de casos nuevos de Dengue, Zika, Chikungunya y otras arbovirosis en un 50% en el periodo 2025-2030 de forma coordinada y sostenible



Febrero - Marzo
- Implementación del Plan Nacional para el Control del Dengue y Otras Arbovirosis

Abril
- Dotación de insecticidas a entidades.
- Transferencia de recurso para adquisición de equipamiento

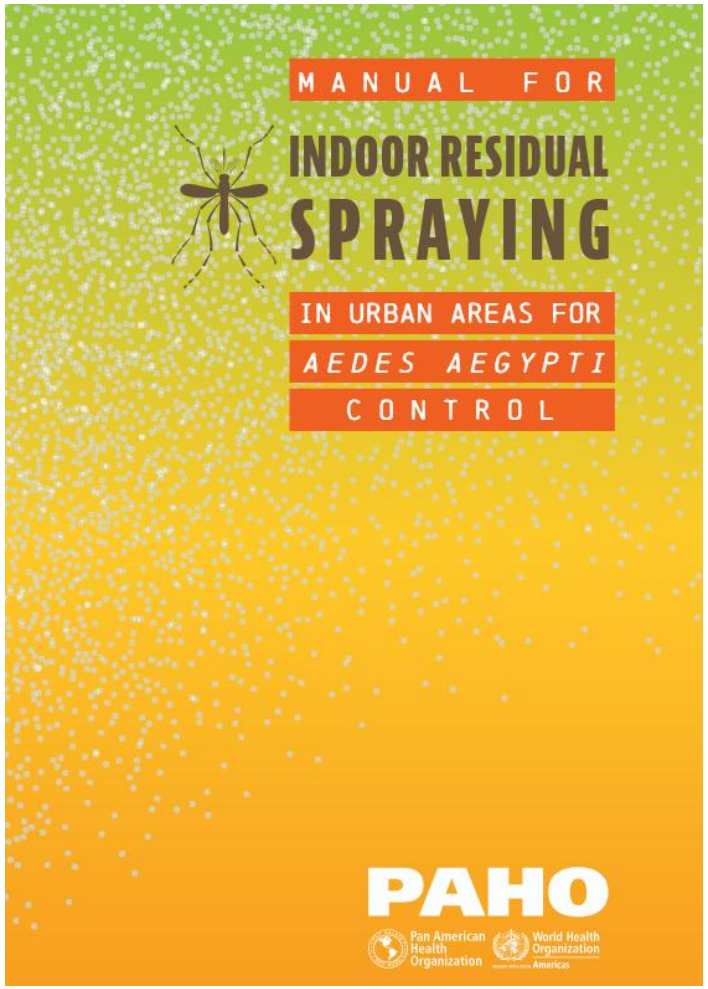
Mayo
- Implementación focalizada en puntos calientes y riesgo entomológico
- Larvicidas
- Rociado intradomiciliar
- Nebulizaciones

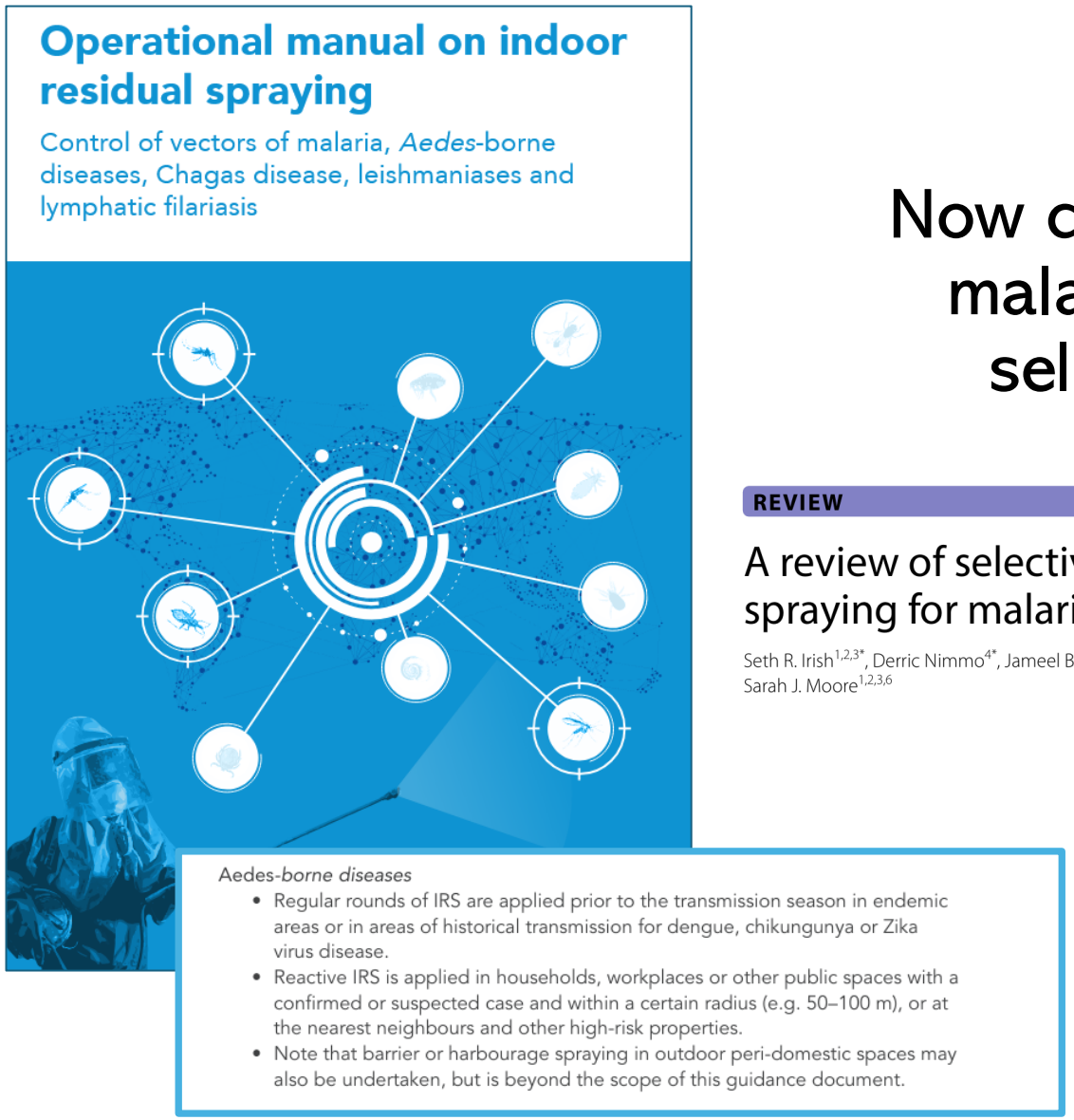
Junio - Diciembre
- Liberación de mosquitos con Wolbachia
- Proyectos de investigación para vacuna de dengue

Acciones comunitarias
- Difusión de los Programas de Participación Comunitaria.
- Casa segura y libre de dengue donde haya personas vulnerables (embarazadas, adultos mayores recién nacidos)
- Escuela y hospitales libres de criaderos de mosquitos

TIRS has been programmatically adopted: focused on 'priority premises' and hot-spots. Brazil is leading the way

Global Policy supporting TIRS



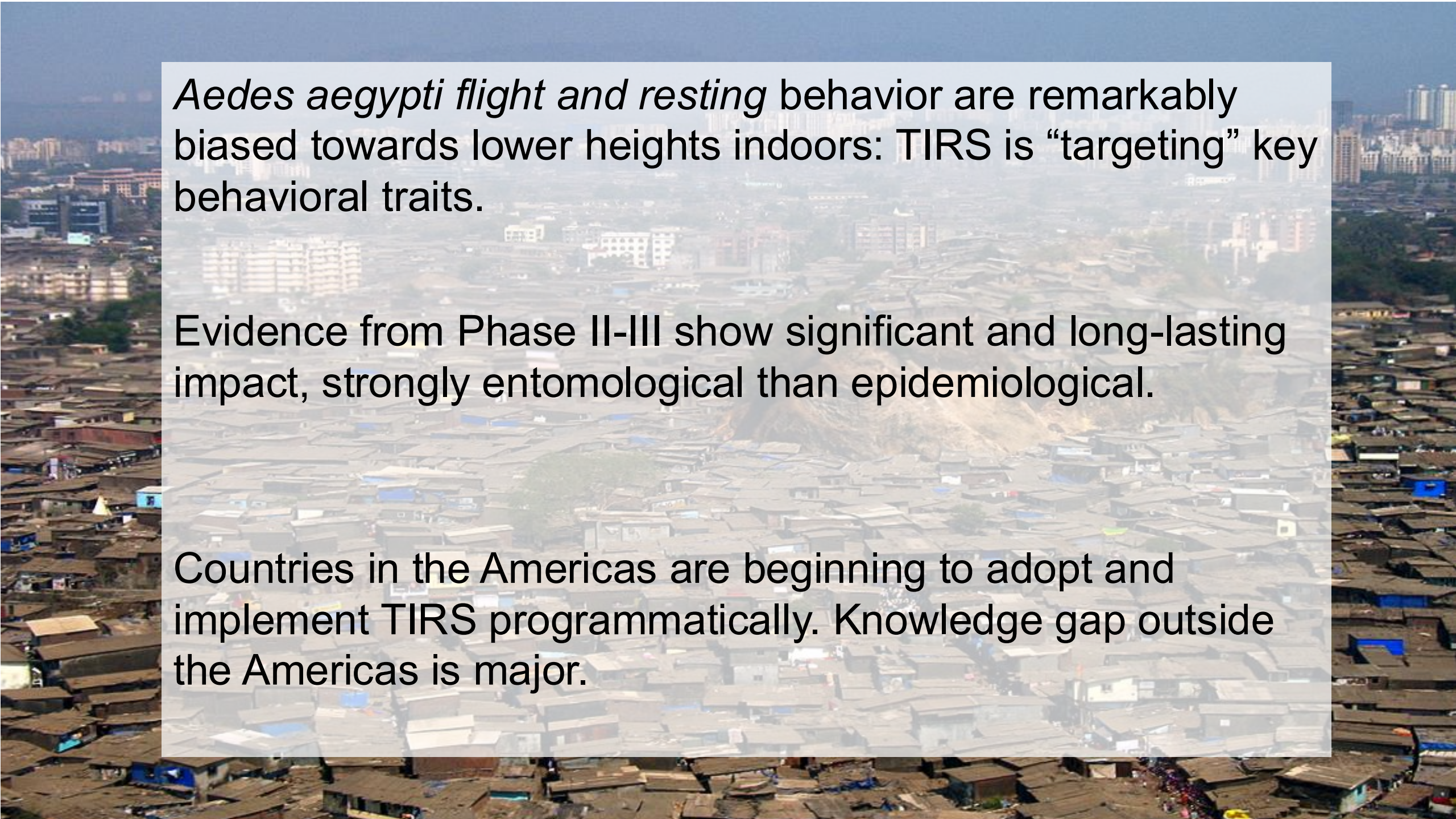


Now considered for malaria vectors: selective IRS.



A review of selective indoor residual spraying for malaria control

Seth R. Irish[1,2,3*], Derric Nimmo[4*], Jameel Bharmel[4], Frederic Tripet[1,2], Pie Müller[1,2], Pablo Manrique-Saide[5] and Sarah J. Moore[1,2,3,6]



Aedes aegypti flight and resting behavior are remarkably biased towards lower heights indoors: TIRS is “targeting” key behavioral traits.

Evidence from Phase II-III show significant and long-lasting impact, strongly entomological than epidemiological.

Countries in the Americas are beginning to adopt and implement TIRS programmatically. Knowledge gap outside the Americas is major.

Questions?

