GEOSENTINEL

The Global Surveillance Network of the ISTM and CDC

GeoSentinel: Using Travelers as Sentinels of Worldwide Disease Outbreaks

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CDC

Talk Outline

- Description of GeoSentinel
- Analysis of ill travelers (2007 – 2011)
- GeoSentinel Zika analyses
- Preliminary GeoSentinel AMR data
- Risk of travel-associated acquisition of MDR bacteria

GeoSentinel Surveillance System Overview

- Established in 1995 by CDC and International Society for Travel Medicine (ISTM)
- Clinic-based global surveillance system
  - De-identified patient information
  - International travelers and immigrants
  - Central electronic database
  - Link time and place of exposure
  - Detect new infections and patterns
  - Monitor disease burden and distribution
- Co-funded by CDC (DGMQ), ISTM, and PHAC

Variables Collected in GeoSentinel

Demographics

- Gender
- Age
- Country
  - Birth
  - Citizenship
  - Residence before age 10
  - Current residence
- History of immigration
- Pre-travel encounter with a healthcare provider

Travel History

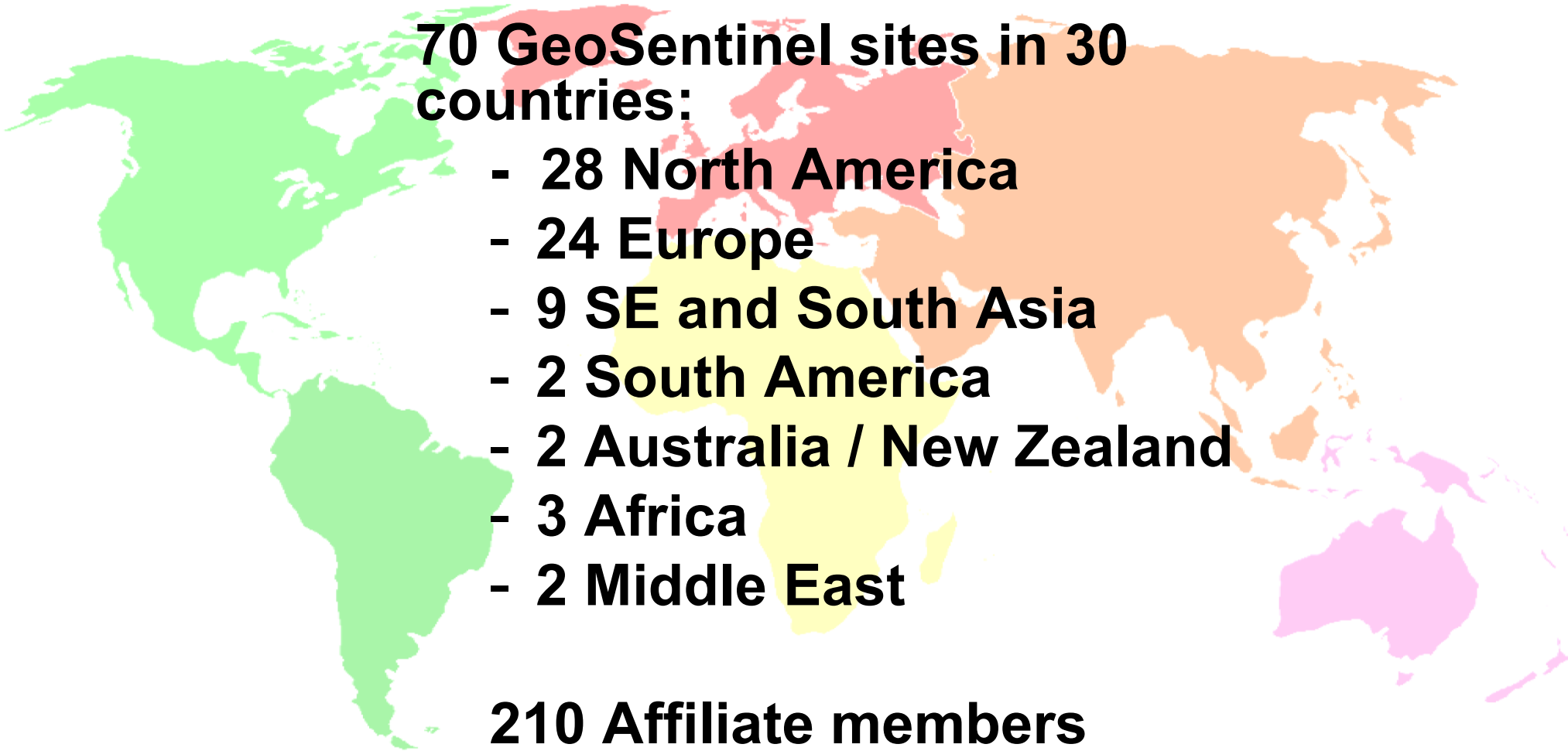
- Recent travel history
- Previous travel history
- Country or countries of exposure to current illness
- Reason for travel related to current illness
- Seen during travel, after travel or after immigration

Clinical Information

- Inpatient/outpatient
- Diagnosis
- Diagnostic method(s)
- Diagnosis status (confirmed/probable)
- Main presenting symptoms
- Underlying conditions
- Active/resolved

Sentinel Sites Contributing Data

(as of Sept 30, 2017)



70 GeoSentinel sites in 30 countries:

- 28 North America
- 24 Europe
- 9 SE and South Asia
- 2 South America
- 2 Australia / New Zealand
- 3 Africa
- 2 Middle East

210 Affiliate members

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GeoSentinel Sites

(dots = sites; shaded areas = affiliate members)

CanTravNet

GeoSentinel
The Global Surveillance Network
of the ISTM and CDC

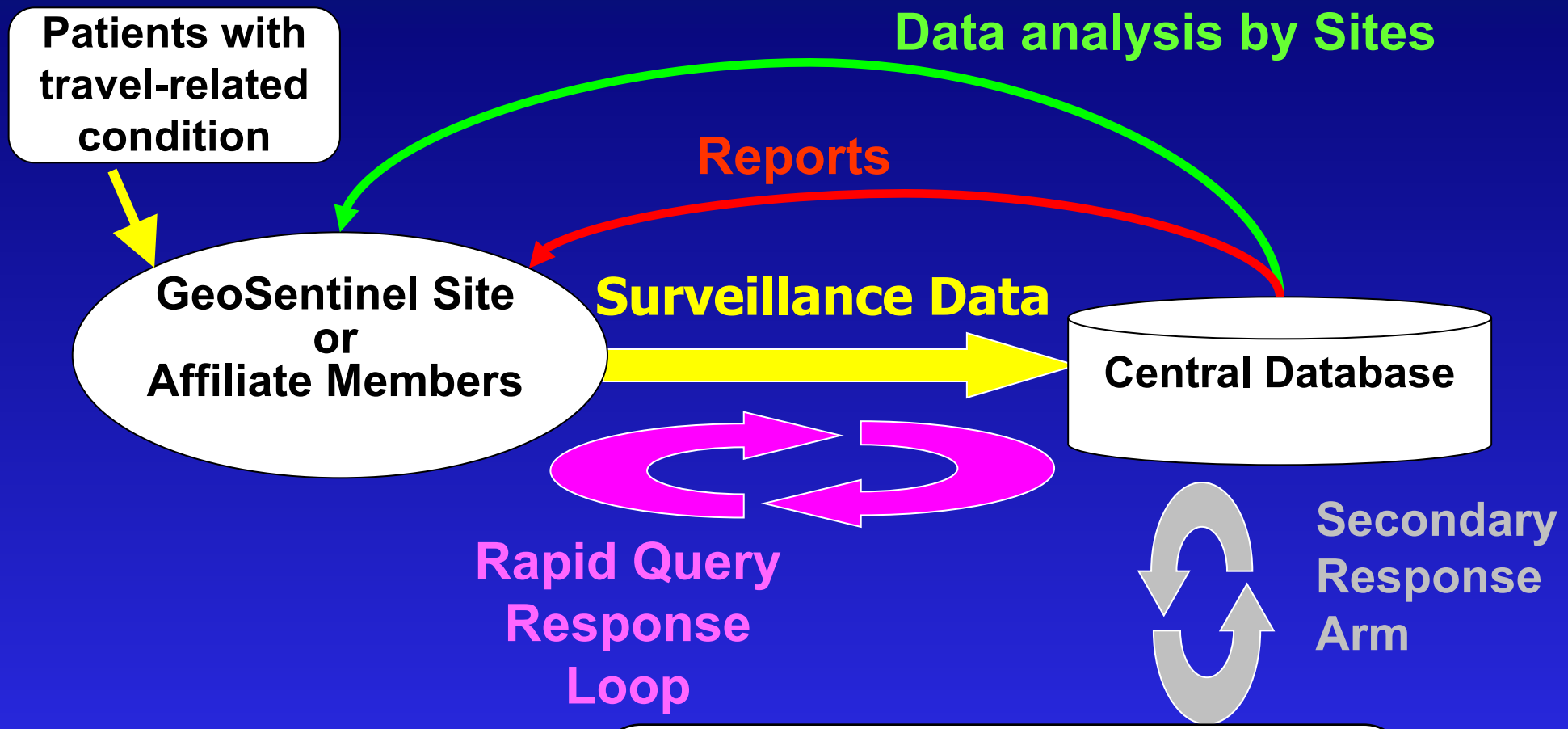
- Consortium of Canadian GeoSentinel sites located across Canada
- Collaboration between the Office of Border and Travel Health of PHAC and CanTravNet
- Contracts between PHAC-CTN and PHAC-GeoSentinel for deliverables including an annual surveillance report

CDC

CanTravNet

GeoSentinel
The Global Surveillance Network
of the ISTM and CDC

How does GeoSentinel work?



Alarming Diagnoses Strategy

- Updated list of flagged diagnoses
  - Any record with an alarming diagnosis entered in the central database triggers an immediate alarm
  - Immediate notification of Site Director, PI, CDC Epi team, and T+C WG Chair for decision on response

GeoSentinel

CDC

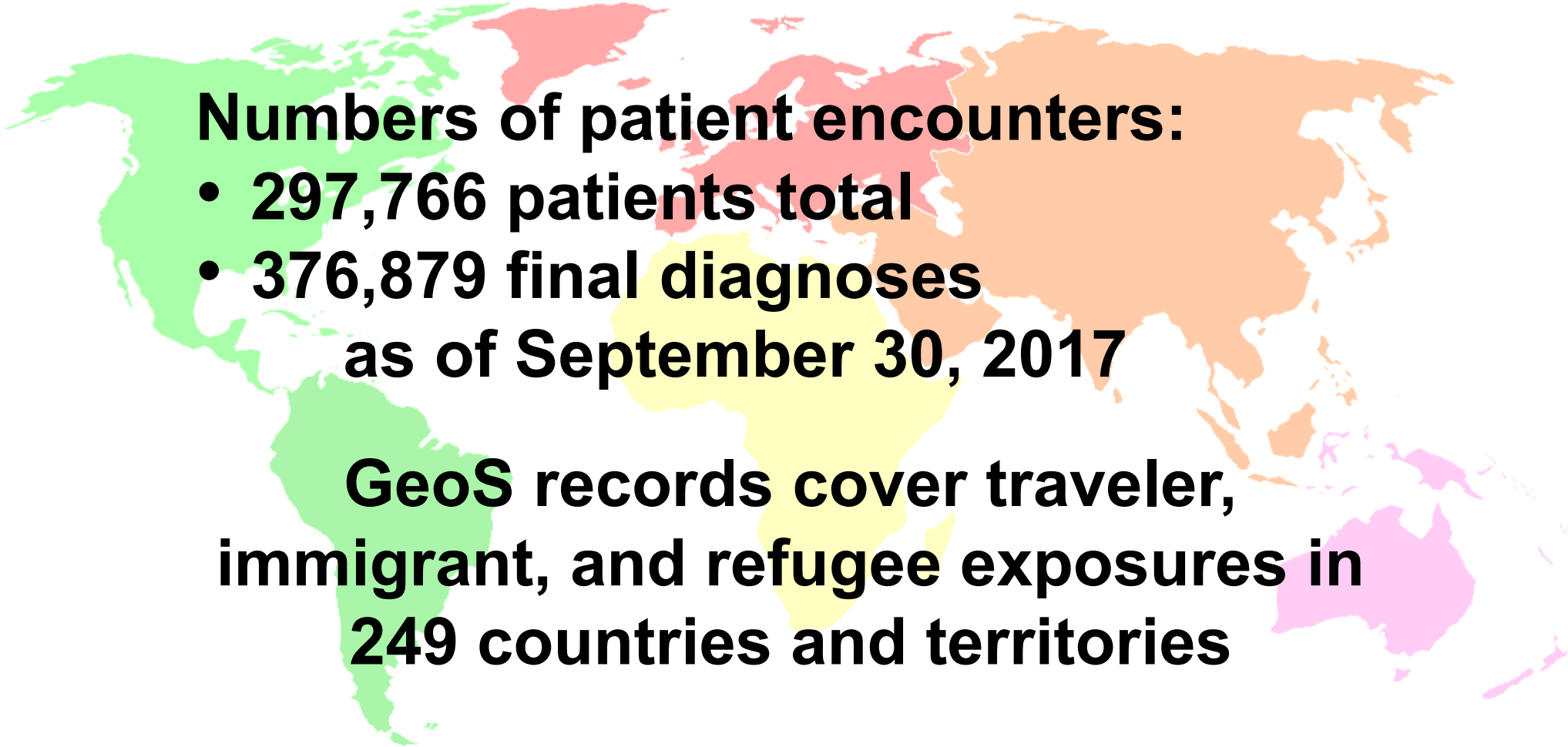
Rare Alarming Events

- Anthrax, pulmonary/cutaneous
- Botulism
- Chagas disease, acute
- Cholera (toxigenic *V. cholerae*)
- Death
- Dengue (complicated)
- Diphtheria
- Ebola virus
- *E. coli* Shiga toxin producing
- Encephalitis, acute specific etiology
- Encephalitis, acute, unspecified
- Guillain-Barré syndrome
- Hemolytic uremic syndrome (Shiga toxin associated)
- Hemorrhagic fever syndrome, acute
- Influenza, avian
- Lassa fever
- Malaria – atovaquone, mefloquine, quinine-resistant, or treatment failure
- Mayaro virus
- Meningococcal meningitis
- MERS CoV
- TB (MDR, pre-XDR, XDR)
- Plague (all forms)
- Poisoning, shellfish
- Polio
- Q fever (*Coxiella burnetii*)
- Rabies
- *Rickettsia prowazeki* (epidemic typhus, louse borne)
- Rift Valley fever
- Sarcocystosis, muscular
- Serious adverse event (drug or vaccine)
- SARS
- Smallpox (variola major)
- Trypanosomiasis, African
- Tularemia
- Yellow fever
- Zika virus (non-vector-associated)

GeoSentinel

CDC

Data Summary



Numbers of patient encounters:

- **297,766 patients total**
- **376,879 final diagnoses**

as of September 30, 2017

GeoS records cover traveler, immigrant, and refugee exposures in 249 countries and territories

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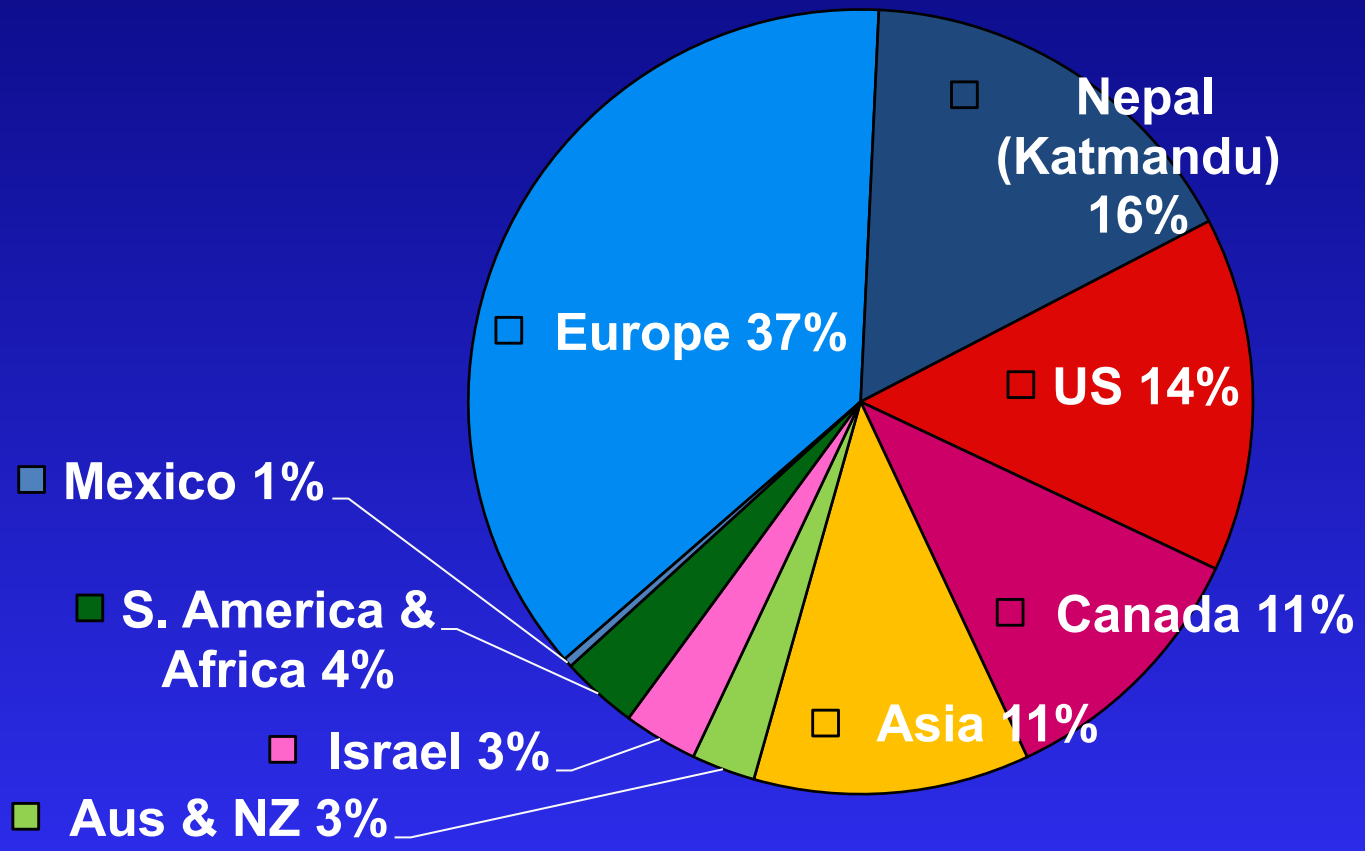
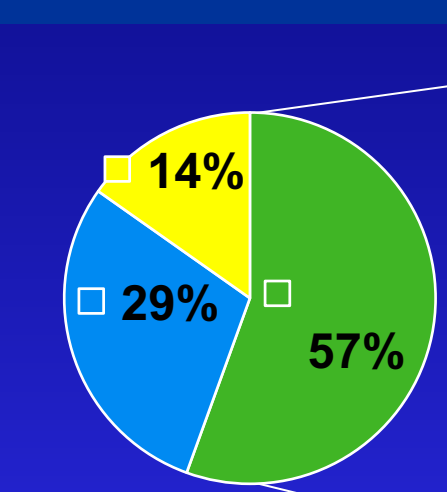
CDC

GeoSentinel Contributions by Site
(as of September 2017)

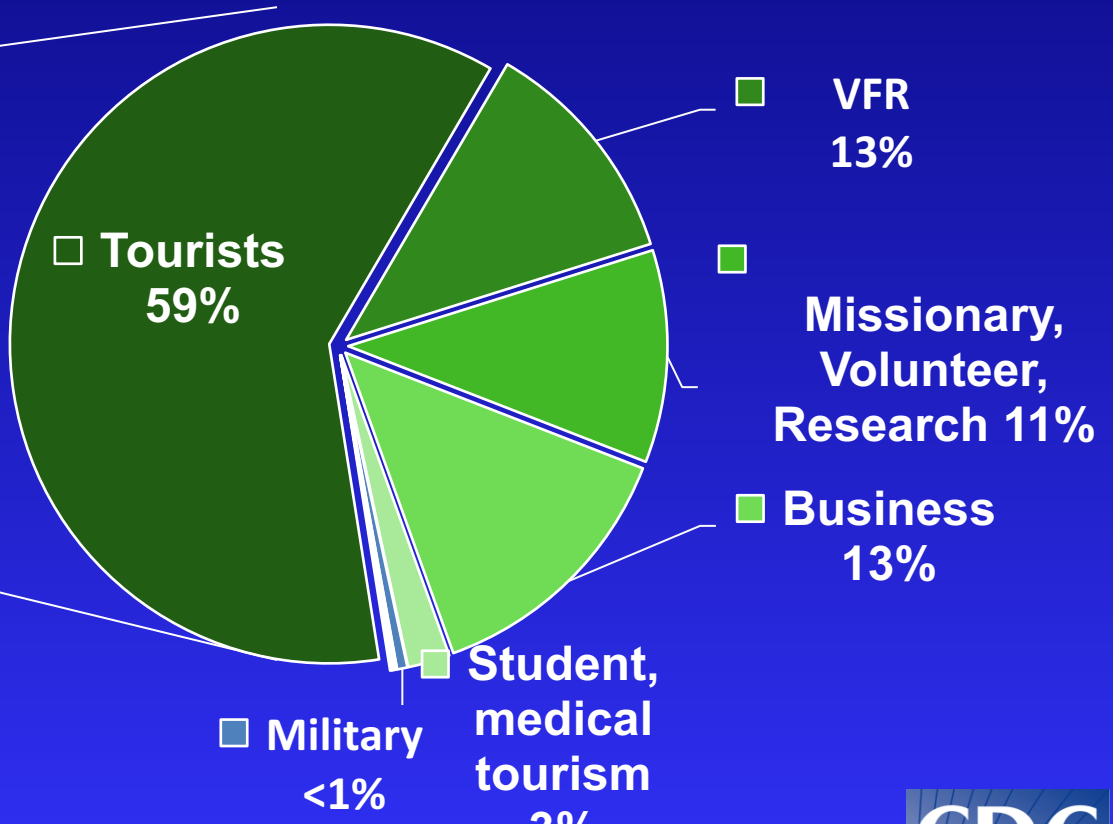


Who are GeoSentinel Patients?
(as of September 2017)

Complete Database



After Travel Visits Only (~57%)



GeoSentinel

Top 10 Diagnoses: Travelers
(Previous 2 Years)

Diagnosis	Number of Diagnosis	Percent
DIARRHEA, ACUTE UNSPECIFIED	4137	12.3%
RESPIRATORY INFECTION, ACUTE	3515	10.4%
DIARRHEA ACUTE BACTERIAL	1956	5.8%
DIARRHEA, CHRONIC	1831	5.4%
VIRAL SYNDROME (WITH/WITHOUT RASH)	1589	4.7%
ZIKA (includes screening)	1495	4.4%
DENGUE, UNCOMPLICATED	1183	3.5%
DIARRHEA ACUTE parasitic	1148	3.4%
BITE, ANIMAL	1122	3.3%
MALARIA (ALL SPECIES)	1067	3.2%

Top 10 Diagnoses: Immigrants & VFRs
(Previous 2 Years)

Diagnosis	Number of Diagnosis	Percent
CHAGAS DISEASE, CHRONIC	170	19.6%
LATENT TUBERCULOSIS, POSITIVE IFN-RELEASE ASSAY (e.g. Quantiferon or T-SPOT) (NOT ACTIVE DISEASE)	97	11.2%
NEMATODE INFECTIONS, INTESTINAL	95	10.9%
SCHISTOSOMIASIS	70	8.1%
MYCOBACTERIUM TUBERCULOSIS	69	7.9%
EOSINOPHILIA	63	7.2%
HEPATITIS (VIRAL- CHRONIC)	49	5.6%
AIDS, HIV, SYPHILIS, GONORRHEA	25	2.9%
ECHINOCOCCOSIS	18	2.1%
DIARRHEA ACUTE parasitic	17	2.0%

Core Function – "ALERTS"

Plague in Madagascar	5-Oct-17
Locally Transmitted Plasmodium falciparum and P. vivax Malaria Cases in Southern Europe	21-Sep-17
Locally acquired P. vivax malaria in Greece	11-Sep-17
Oropouche Virus	29-Aug-17
Non-tuberculous mycobacteria infections among medical tourists to the Dominican Republic	18-Jul-17
Increased hantavirus transmission in parts of Central, Eastern, and South-eastern Europe	11-Jul-17
P. falciparum malaria cases ex Dar es Salaam, Tanzania	26-Jun-17
UPDATE - Haff Disease outbreak in Salvador, Brazil	20-Jun-17
CASE - Japanese Encephalitis	7-Jun-17
UPDATE - Severe febrile rhabdomyolysis in refugees from West Africa	1-Jun-17
Outbreak of Dengue in Israeli travelers returning from the Seychelles	26-May-17
Trypanosomiasis - The Netherlands ex Tanzania	24-May-17
Severe febrile rhabdomyolysis in refugees from West Africa	24-May-17
Malaria in Southern Africa	16-May-17
Increase in Angiostrongylus cases in Hawaii	25-Apr-17
Sindbis and West Nile fevers in South Africa	23-Feb-17
Cluster of Acute Schistosomiasis in Belgian Travellers Returning from Kwazulu-Natal, South Africa	16-Feb-17
Expanded geographic areas of yellow fever transmission in Brazil	30-Jan-17
Yellow Fever in Brazil	16-Jan-17

GeoSentinel Sentinel Case – Reclassification of Maldives

Two tourists test positive for Zika after visiting Maldives

October 01 17:05 2016 by Ahmed Naish

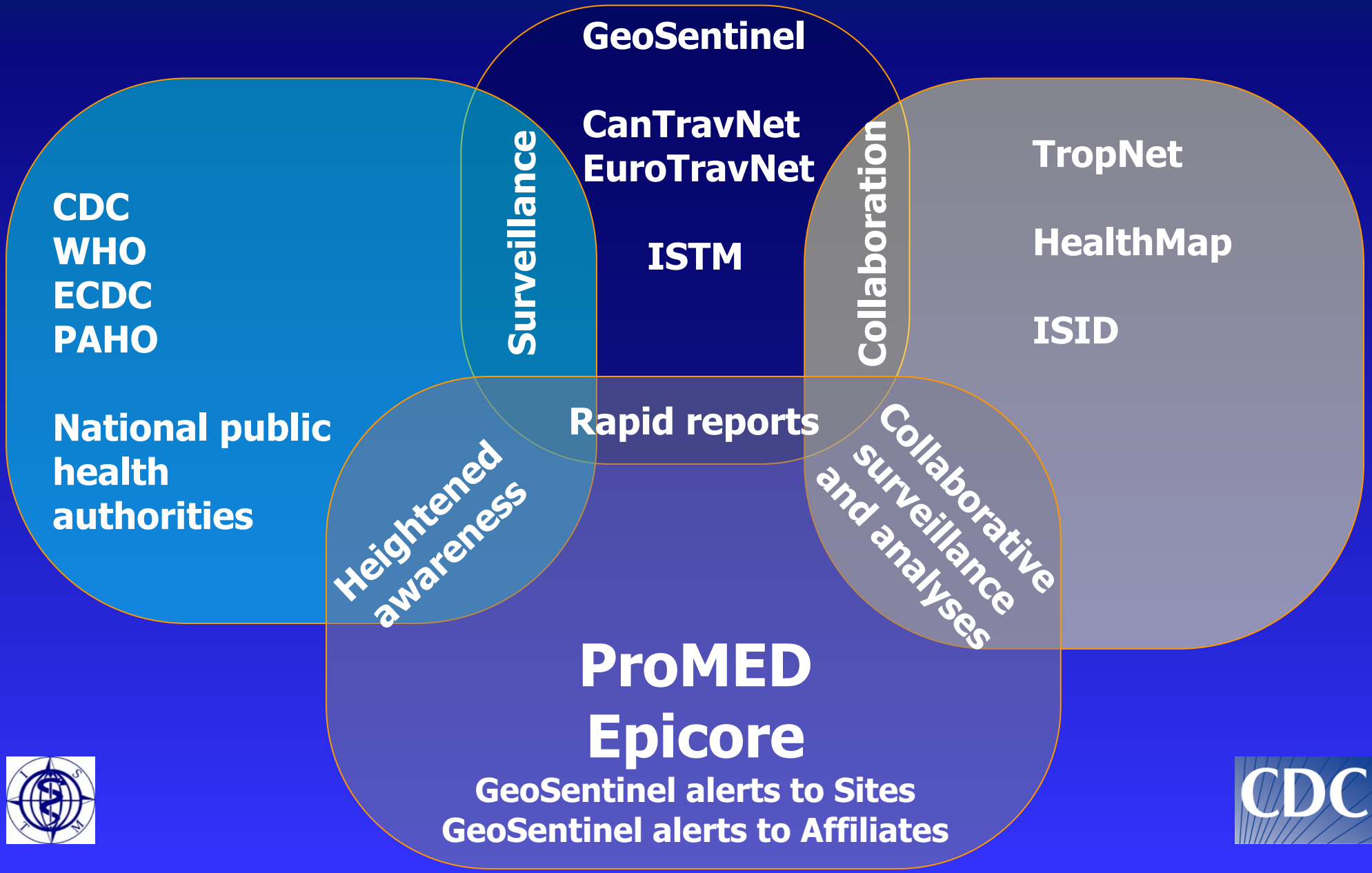
The Health Protection Agency revealed Friday night that two European tourists who visited the Maldives this year have tested positive for the Zika virus.

The virus infection was detected upon their return to their countries but was "possibly acquired in Maldives," the HPA said in a press statement last night.

"The cases were linked to travels to Maldivian in February and June this year. Therefore, [the World Health Organisation] has classified Maldives as category 2, indicating possible endemic transmission in the country."

The HPA said it was informed by the WHO about the cases on September 28 and 29

GeoSentinel Synergies



Strengths of GeoSentinel

- Physician-confirmed diagnoses
- Network sites include many top tropical medicine sites and investigators
- Geographic coverage
- Ability to identify sentinel events (new foci of emerging infections)
- Capacity to describe characteristics of specific diseases among travelers
  - Country of exposure, timing, etc.

Limitations of GeoSentinel

- Data not necessarily representative of all international travelers
  - Severity and frequency of illness among returned travelers may be underestimated
- Lack of denominator data
  - GeoSentinel data cannot be used to calculate travel-related disease rates and risks

Limitations of GeoSentinel

- Despite use of standard diagnosis codes, data coding and entry practices may vary by site and over time
- Direct comparisons over time may not be valid
  - GeoSentinel data system has undergone numerous changes over time and number of sites has changed

ORIGINAL RESEARCH | Annals of Internal Medicine

GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011

Karin Leder, MBBS, MPH, PhD; Joseph Torresi, MBBS, PhD; Michael D. Libman, MD; Jakob P. Cramer, MD, MSc; Francesco Castelli, MD, PhD; Patricia Schlagenhauf, PhD; Annelies Wilder-Smith, MD, PhD, MIH; Mary E. Wilson, MD; Jay S. Keystone, MD, MSc; Eli Schwartz, MD; Elizabeth D. Barnett, MD; Frank von Sonnenburg, MD, PhD; John S. Brownstein, PhD; Allen C. Cheng, MBBS, PhD, MPH; Mark J. Sotir, PhD, MPH; Douglas H. Esposito, MD, MPH; and David O. Freedman, MD, for the GeoSentinel Surveillance Network*

Ann Intern Med. 2013;158:456-468.

Objectives:

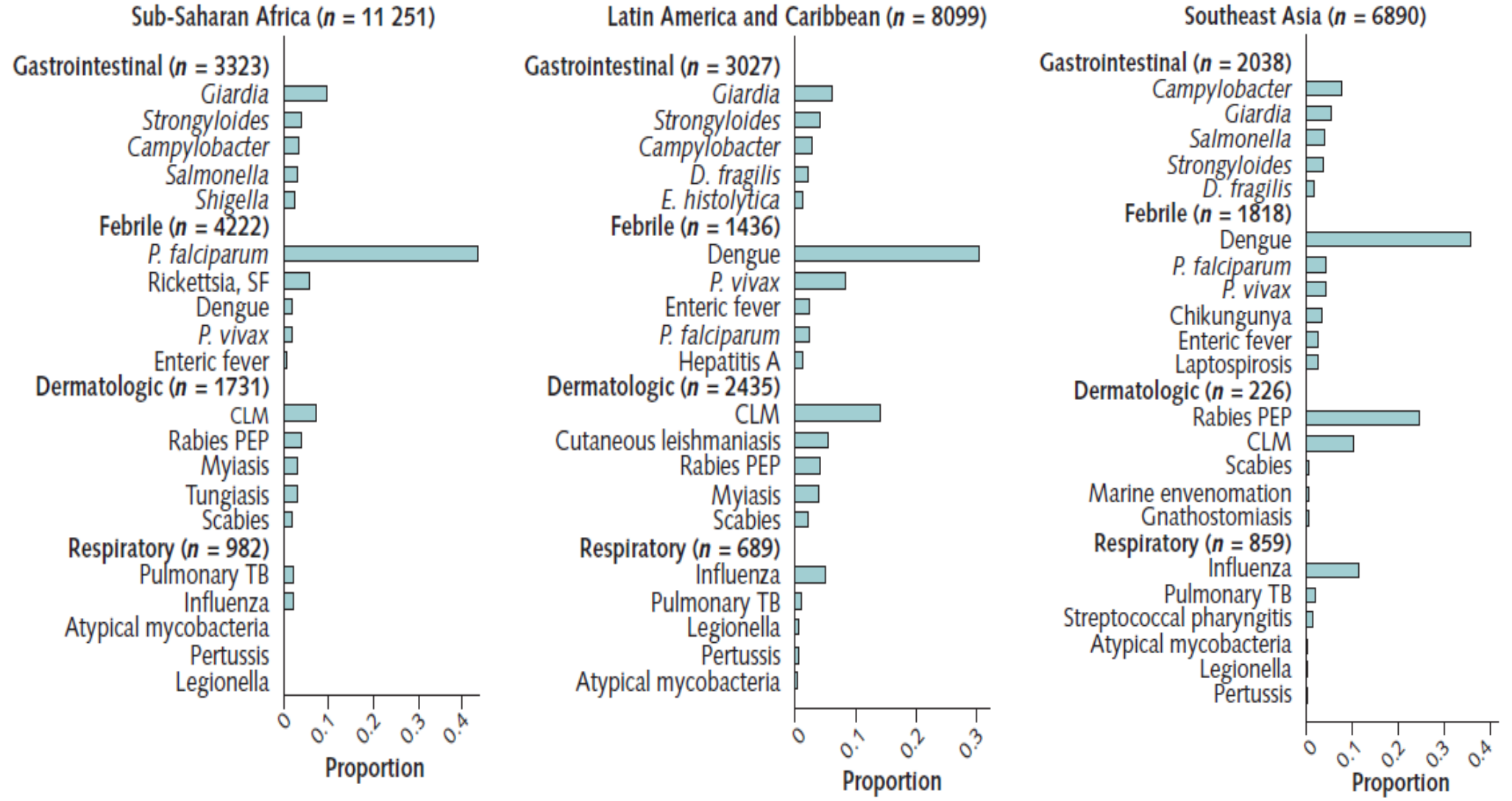
- To describe typical diseases in returned travelers according to region, travel reason, and patient demographic characteristics
- To describe pattern of low-frequency travel-associated diseases
- To refine key messages for care before and after travel

CDC

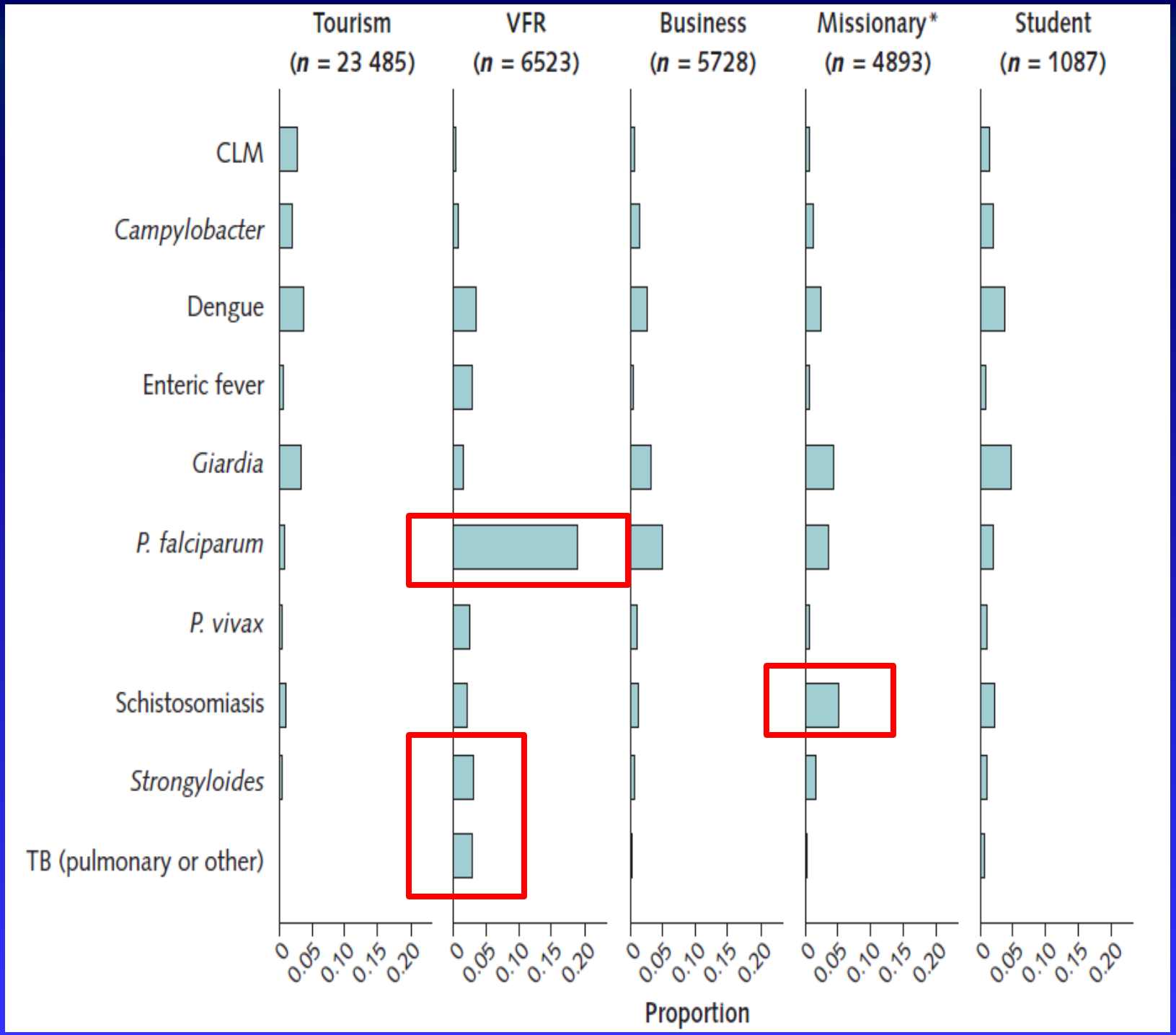
Results – 2007-2011 Returning Travelers

- 42,173 ill returned travelers
  - Asia (32.6%) and sub-Saharan Africa (26.7%)
- Illnesses: GI (34.0%), fever (23.3%), and dermatologic (19.5%)
- Only 40.5% reported pre-travel medical visits
- Relative frequency of many diseases varied with both travel destination and reason for travel

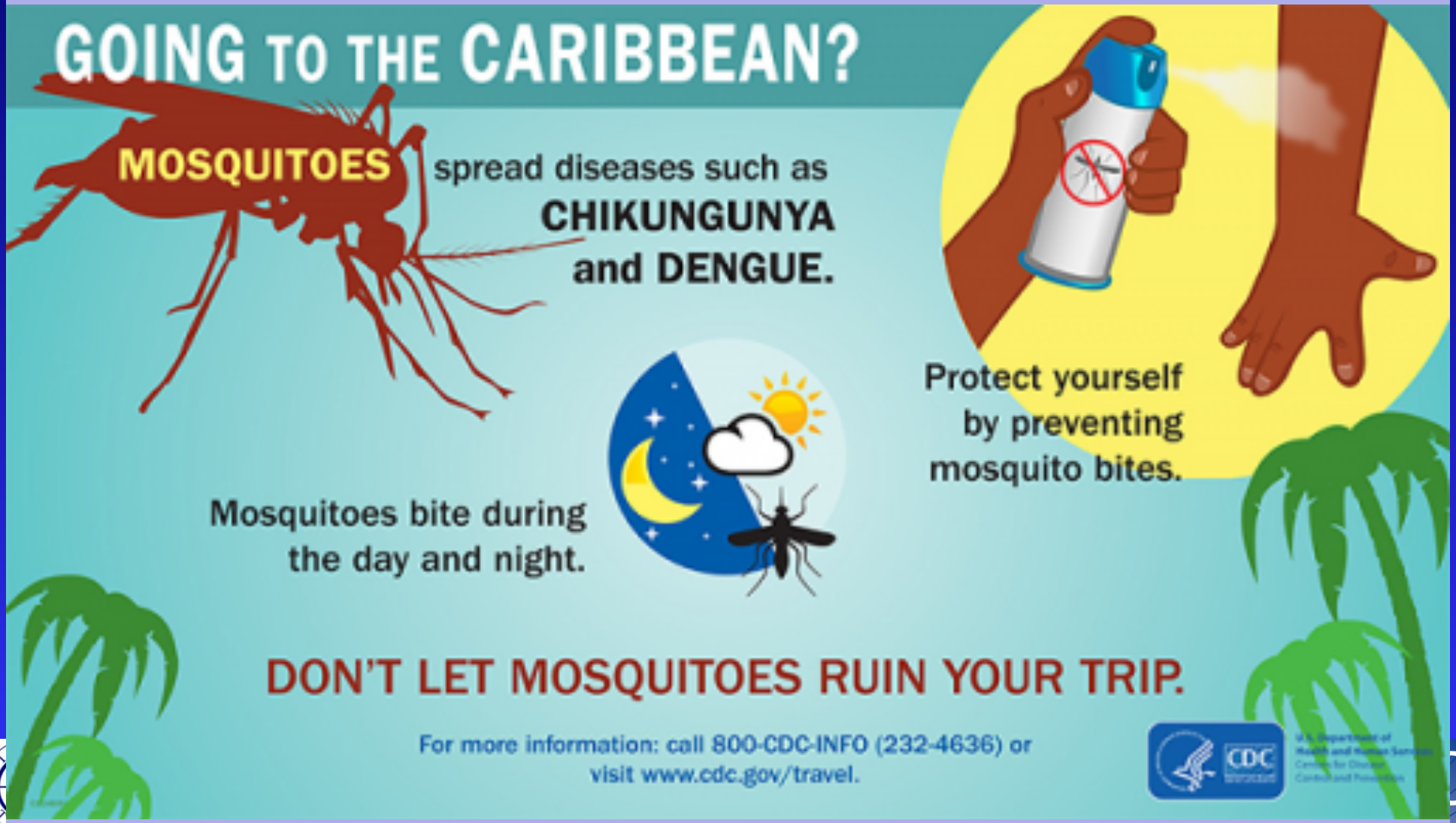
Top identified specific causes for GI, fever, dermatologic, and respiratory illnesses by region among ill returned travellers



Top 10 specific diagnoses, by main reasons for travel



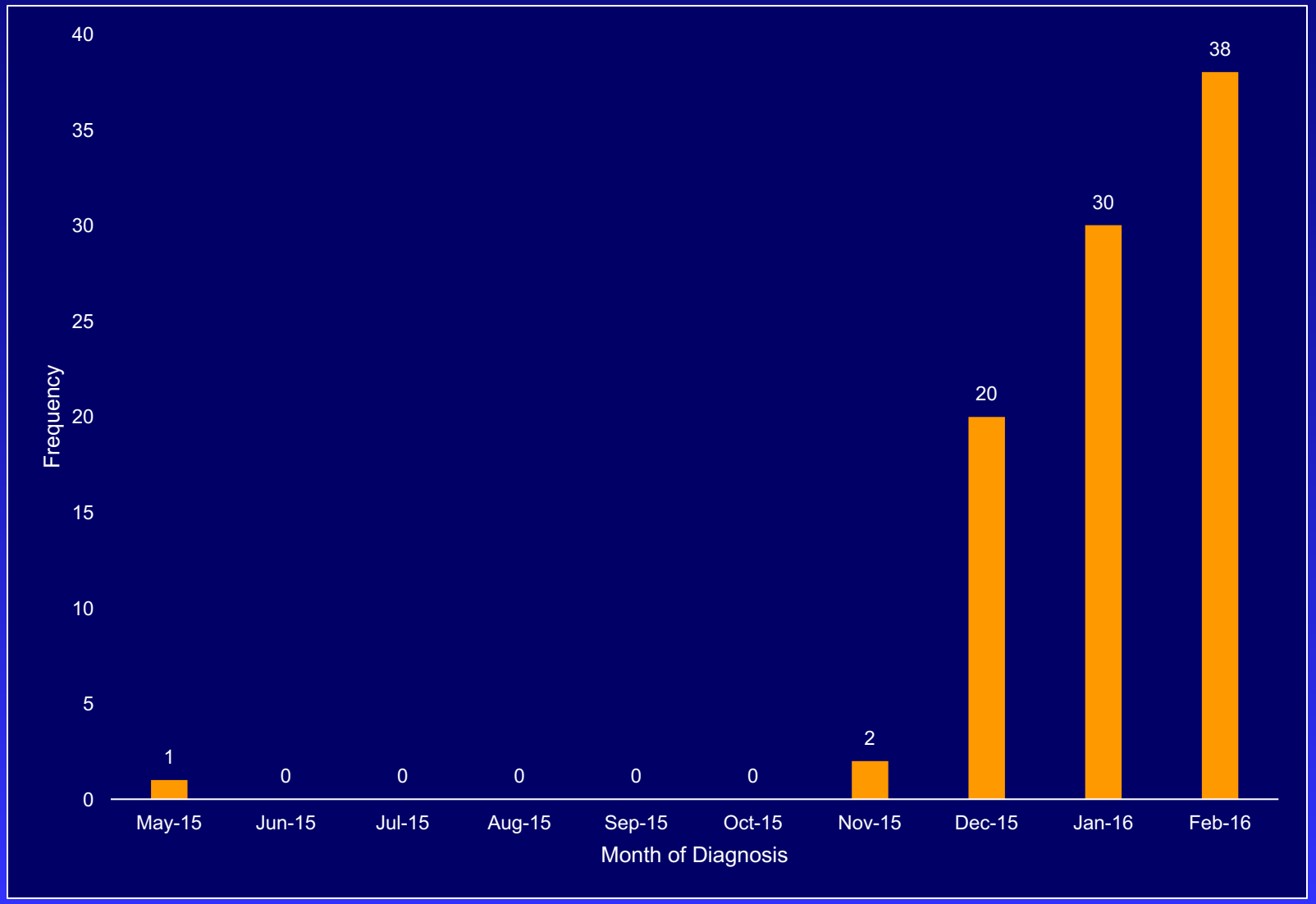
Zika and the Americas



GeoSentinel Zika in the Americas Analysis

- Cases entered by all sites between Jan 1, 2013 and Feb 29, 2016
- Limited to patients who had traveled to the Americas
- Standard GeoSentinel data collected plus supplemental information on exact destinations, symptoms and laboratory testing
  - Hamer DH et al. Ann Int Med 2017

Month of clinic visit for 93 Zika-infected patients evaluated at GeoSentinel sites



GeoSentinel Zika in Americas: Results

- 93 patients: 62% women
  - 69% confirmed; 14% probable; 17% clinically suspect
- Age distribution: mean 41 y, range 3-77 y
- Reason for travel: 48% tourism; 40% VFR; 8% business
- 96% of patients managed as outpatients
- Sentinel cases: Costa Rica, Danish traveler
  - Chen LH. Ann Int Med 2016

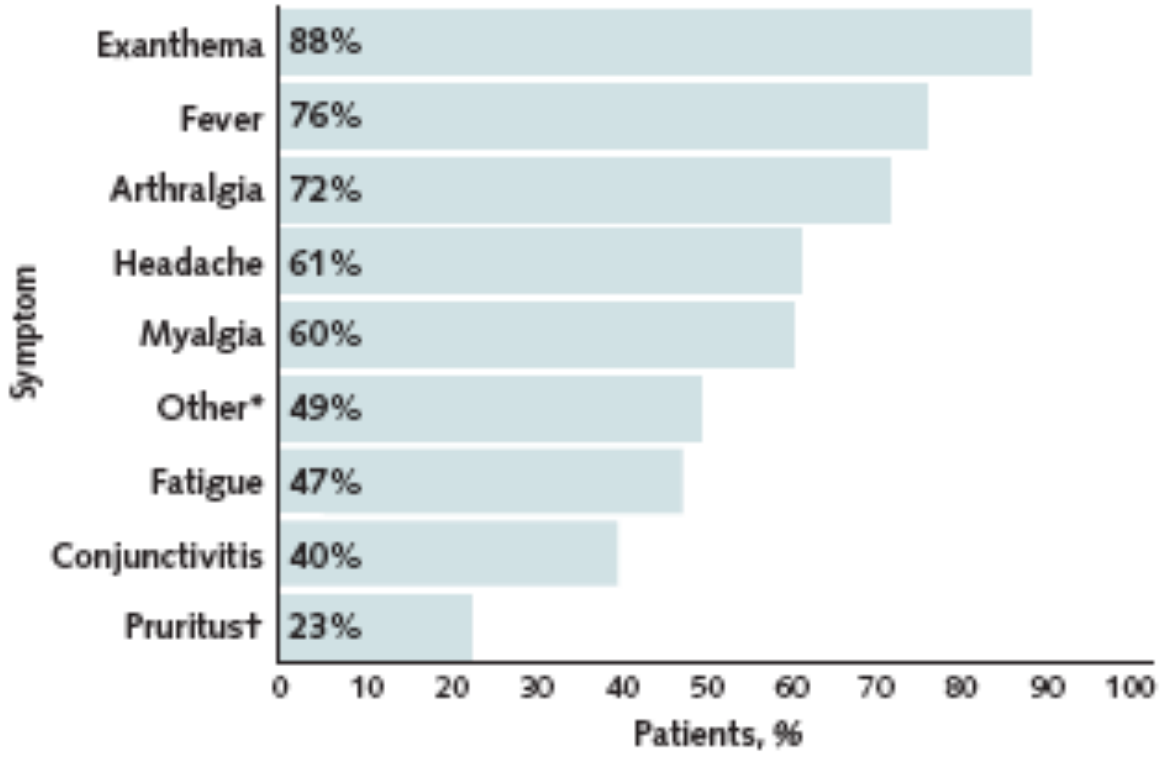
Region/Country of Exposure*

- South America: 59%
  - Suriname, Colombia, Brazil, Venezuela
- Caribbean: 24%
  - Martinique, Haiti, DR, Guadeloupe, Dutch Antilles
- Central America and Mexico: 16%
  - Honduras, Mexico, Costa Rica, El Salvador

*More than one region and country of exposure possible

Symptoms at Time of Presentation to GeoSentinel Site (n = 93)

Figure 2. Clinical symptoms and signs among 93 patients diagnosed with Zika virus disease acquired in the Americas.



* 46 persons reported a total of 71 additional symptoms and signs in the form of comments in this category. Those observed in ≥3 patients (≥3%) included diarrhea (12%), joint swelling/arthritis (9%), abdominal pain (8%), nausea (6%), anorexia (4%), retro-orbital pain (3%), pharyngitis (3%), and dysgeusia (3%).

Annals of Internal Medicine ORIGINAL RESEARCH

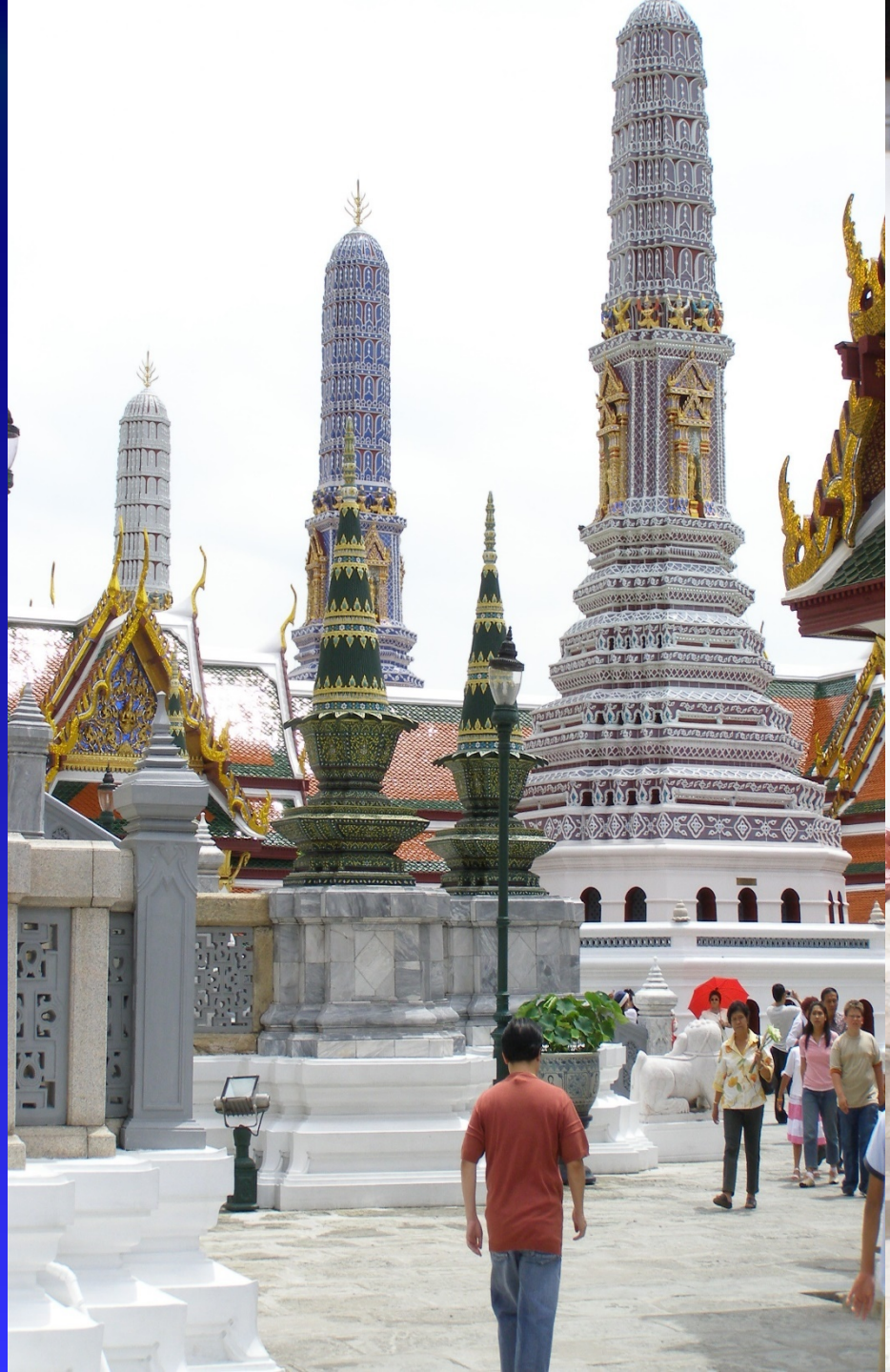
Travel-Associated Zika Virus Disease Acquired in the Americas Through February 2016

A GeoSentinel Analysis

Davidson H. Hamer, MD; Kira A. Barbre, MPH; Lin H. Chen, MD; Martin P. Grobusch, MD, PhD; Patricia Schlagenhauf, PhD; Abraham Goorhuis, MD, PhD; Perry J.J. van Genderen, MD, PhD; Israel Molina, MD, PhD; Hilmir Asgeirsson, MD, PhD; Phyllis E. Kozarsky, MD; Eric Caumes, MD; Stefan H. Hagmann, MD, MSc; Frank P. Mockenhaupt, MD; Gilles Eperon, MD; Elizabeth D. Barnett, MD; Emmanuel Bottieau, MD, PhD; Andrea K. Boggild, MSc, MD; Philippe Gautret, MD, PhD; Noreen A. Hynes, MD, MPH; Susan Kuhn, MD; R. Ryan Lash, MA; Karin Leder, MBBS, MPH, PhD; Michael Libman, MD; Denis J.M. Malvy, MD, PhD; Cecilia Perret, MD; Camilla Rothe, MD; Eli Schwartz, MD; Annelies Wilder-Smith, MD, PhD, MIH; Martin S. Cetron, MD; and Douglas H. Esposito, MD, MPH; for the GeoSentinel Surveillance Network*

Conclusions

- Substantial regional variation in diagnostic testing for Zika
- Symptom data in travelers similar to case series from outbreak countries
- Assumed vector-borne transmission for all infected travelers

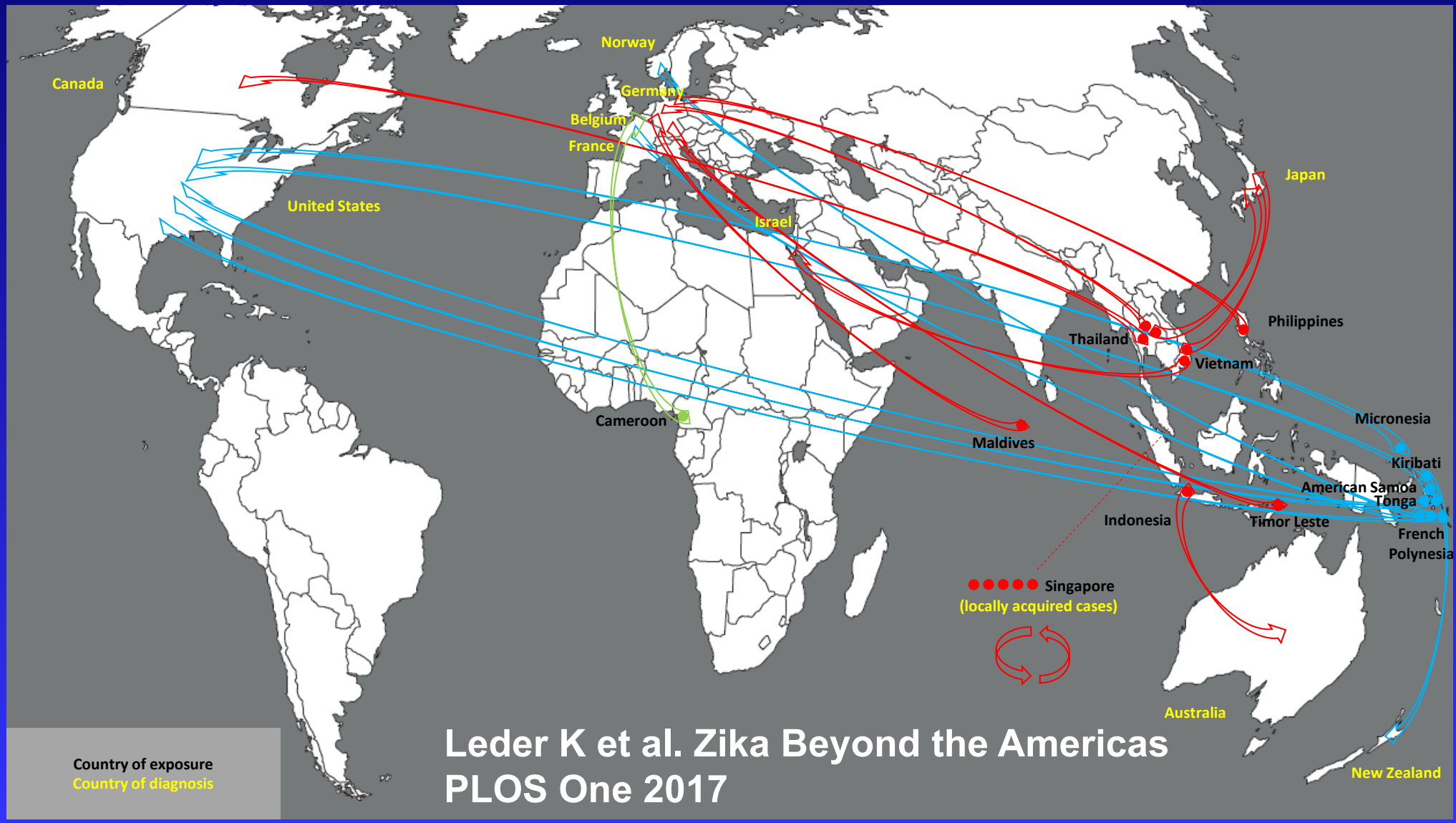



NGÂN HÀNG CÔNG THƯƠNG VIỆT NAM
INCOMBank
ATM
ATM

Zika in SE Asia, South Pacific and Africa: GeoSentinel Analysis

- Database reviewed for reported Zika cases from 1995 to December 2016
- Cases classified using modified CSTE definitions – confirmed and probable
- Comprehensive search of PubMed, ProMED and other outbreak sites to identify reported cases and timing of reporting

Zika Countries of Exposure and Diagnosis



Possible Sentinel Cases

- 2012: Indonesia (diagnosed in Australia)
  - Kwong JC et al. AJTMH 2013
- 2013: Thailand (dx in Canada)
  - Serological data in Thailand from the 1950s
    - Fonseca C et al. AJTMH 2014
- 2015: Kirabati (dx in New Zealand)
  - First known report
- 2015: Vietnam (dx in Israel)
  - Serological data in Vietnam from the 1950s
    - Pond WL. Trans R Soc Trop Med Hyg 1963
- April 2016: East Timor (dx in Germany)
  - First known report (diagnosis - probable)

Conclusions

- Travelers may serve as sentinels of local Zika transmission and potentially impending outbreaks
- Sentinel surveillance can complement local surveillance activities
- Travelers represent potential source for local introduction (if competent vector) or through sexual transmission
- Sentinel surveillance data can be used by international authorities for country risk categorization

GeoS: Nine Organisms of Interest for Tracking AMR

- *Campylobacter* spp.
- *E. coli*
- *K. pneumoniae*
- *S. aureus*
- *S. pneumoniae*
- *Salmonella* spp.
- *S.* Typhi
- *S.* Paratyphi
- *Shigella* spp.

S. Typhi N=58 isolates

- Records entered from 10/28/16-10/28/2017

- Diagnostic code 108: Bacteremia 3 (5%)
- Diagnostic code 193: *S.* Typhi 55 (95%)

- ND/NR: 10 (19%) – all stool

S. Typhi: AMR Results

Antibiotic	#(S) Isolates	#I/R Isolates	% Resistance
3rd generation cephalosporin	44	0	0%
Carbapenem	21	0	0%
Cotrimoxazole	35	5	12.5%
Macrolide	12	2	14%
Fluoroquinolone	11	33	75%

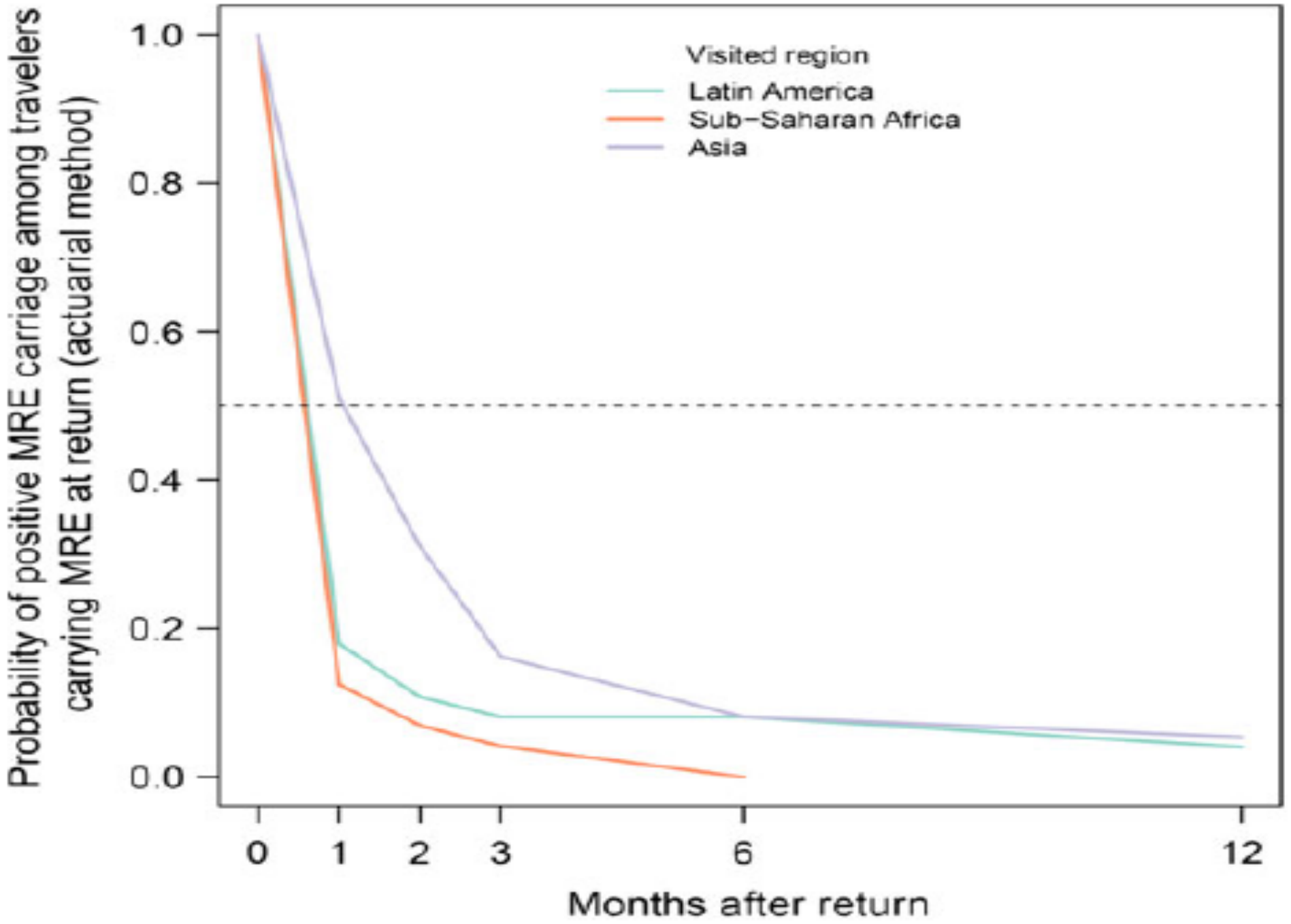
S. Typhi: # Resistant Isolates (for those with AMR data) by Regions

Country Region	#FQ N (%)	#Mac N (%)	#3GC N (%)	#Carb N (%)	#CTX N (%)
Southeast Asia	1/3 (33)		0/2 (0)		0/2 (0)
South Asia	22/25 (88)	1/11 (9)	0/27 (0)	0/15 (0)	3/23 (13)
Central America	2/5 (40)		0/5 (0)	0/1 (0)	0/5 (0)
Sub-Saharan Africa	2/3 (66)	1/1 (100)	0/3 (0)	0/2 (0)	2/3 (66)

Risk of Acquisition of MDR Bacteria During Travel

Paris Traveler Study

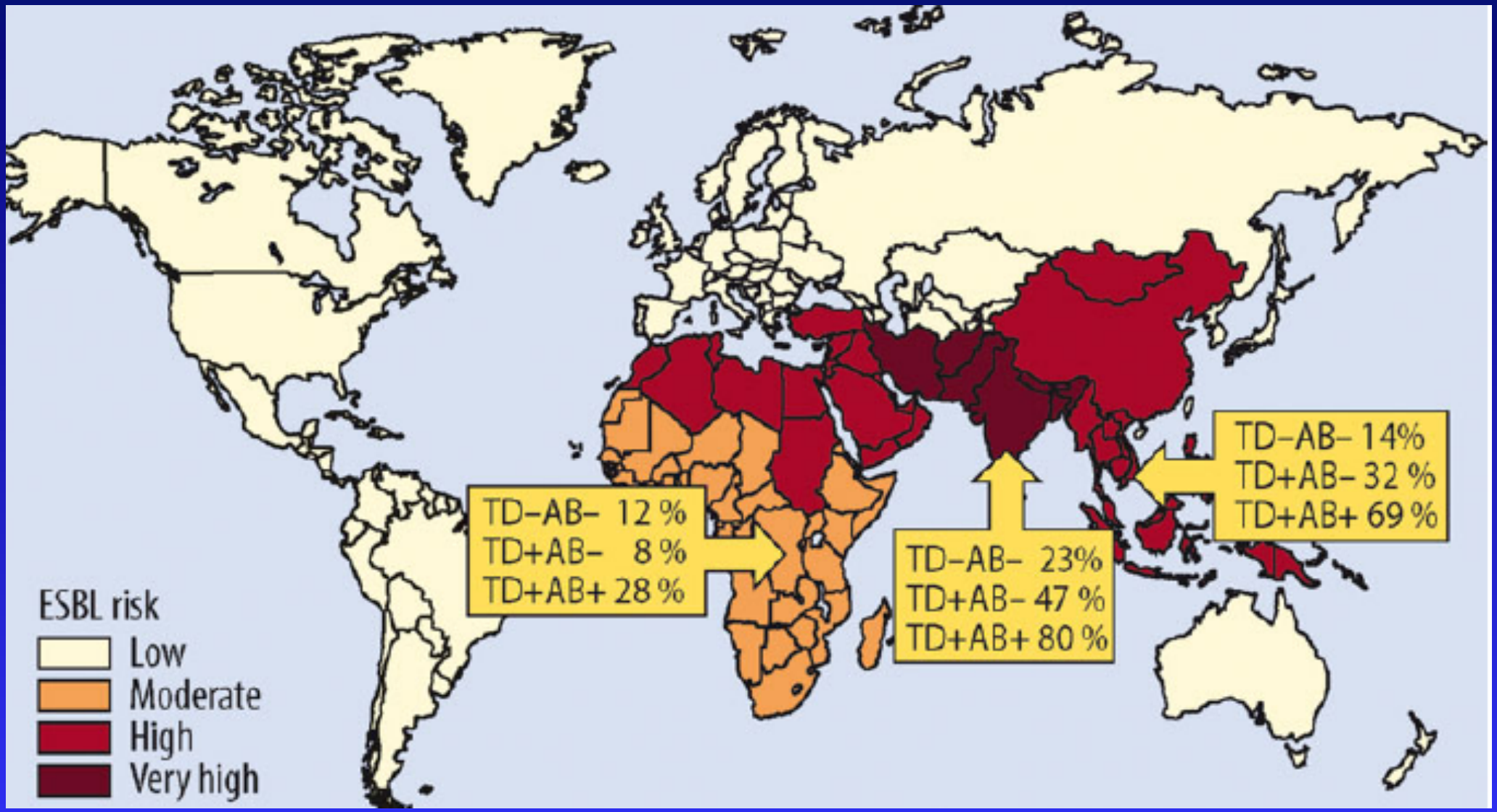
- February 2012 – April 2013
- 574 travelers provided pre- and post-travel specimens
- 51% acquired MDR Enterobacteriaceae (mean 1.8 organisms per traveler)
  - ESBL main resistance mechanism (92%)
  - 0.6% had carbapenemase-producing Enterobacteriaceae (CRE) (all from India)
- MDR-E most common after travel to South Asia (72%) followed by SSA (48%) and Latin America (31%)
  - Ruppe E et al. Clin Infect Dis 2015


Probability of positive MRE carriage among travelers carrying MRE at return (actuarial method)
1.0
0.8
0.6
0.4
0.2
0.0
Visited region
Latin America
Sub−Saharan Africa
Asia
0
1
2
3
6
12
Months after return

Finnish Traveler Study

- March 2009 – February 2010
- Stool pre- and post-travel specimens from 430 Finns
  - 5/430 ESBL+ before travel (1 new strain post-travel)
- 21% acquired ESBL MDE
  - None had CRE
- Risk factors included region of travel (esp. South Asia), age, travelers' diarrhea, and antibiotic use
  - Protective factors: meals with locals
  - No impact of malaria prophylactic drugs
    - Kantele A et al. Clin Infect Dis 2015

Risk of Acquisition of ESBL-PE



Kantele A et al. Clin Infect Dis 2015

Finnish Traveler Study
Loperamide and ESBL Risk

- Same cohort as above except limited analysis to 288 who reported TD
  - Kantele A et al. Emerging Infect Dis 2016

Study group	ESBL positive (%)	Multivariate analysis aOR (95% CI)
LO- AB- (n = 139)	21%	1.0
LO+ AB- (n = 90)	20%	0.8 (0.4-1.7)
LO- AB+ (n = 45)	40%	2.9 (1.2-7.4)
LO+ AB+ (n =14)	71%	7.4 (1.7-32.6)

Finnish Traveler Study Co-Resistance Analysis

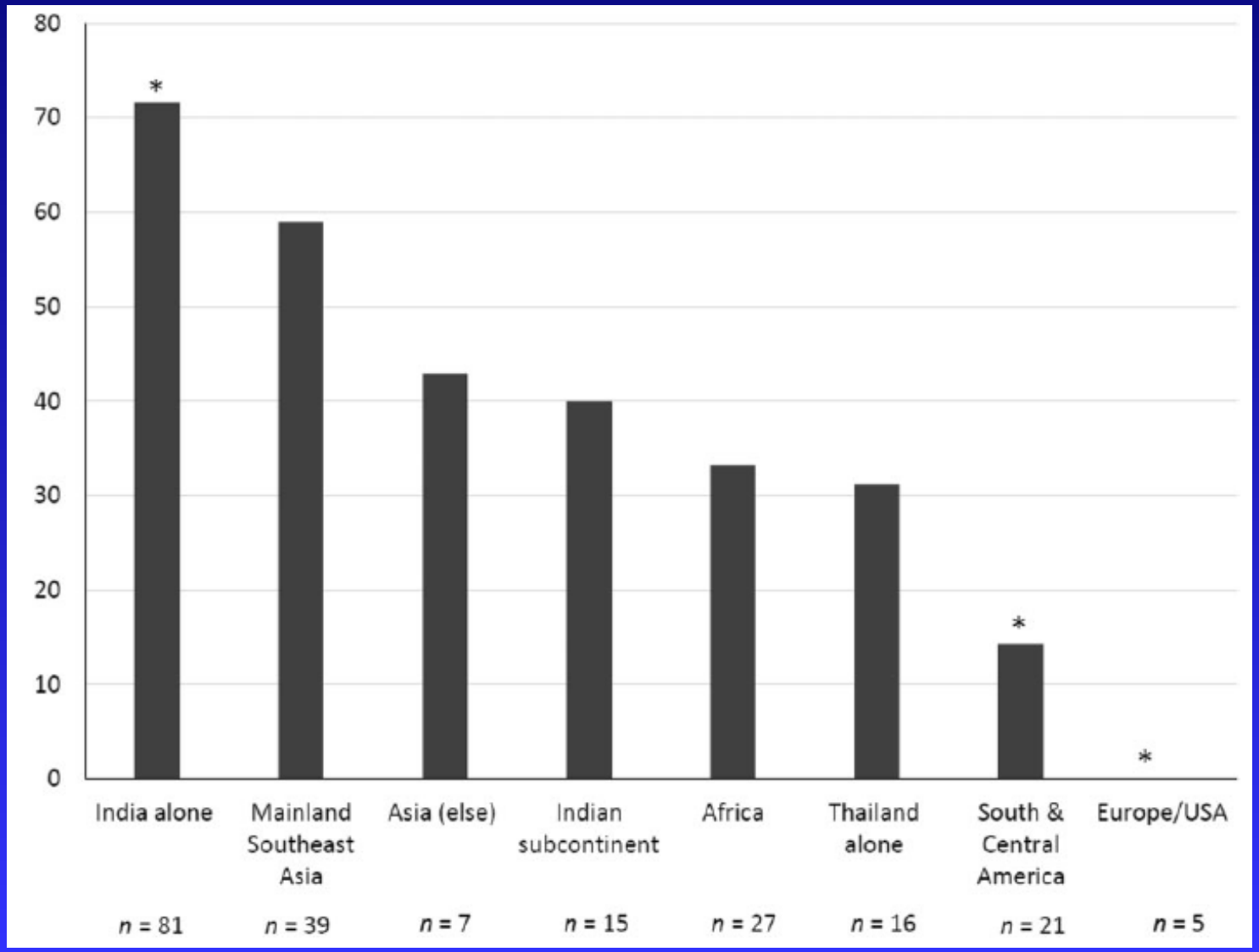
- Focused on 90 travelers who acquired ESBL-PE
- Co-resistance of ESBL strains to ciprofloxacin and CTX associated with increasing age
- Proportion with Cipro R was 37% among those who refrained from taking antibiotics
- Proportion with Cipro R was 95% among those who took antibiotics
- FQ use associated with increased proportion of ESBL-PE R to tobramycin (85% vs 32%)
  - Kantele A et al. Trav Med Infect Dis 2017

CDC

German Traveler Study

- 211 returning travelers with GI symptoms seen in Berlin
- 51% had ESBL-PE (mainly *E. coli*)
  - No carbepenem resistance identified
- Risk factors included:
  - Region of travel (India highest at 72% followed by SE Asia, 60%)
  - Age (highest in ≤ 30 y)
  - Shorter time period since return from travel
    - Miranda IB et al. J Trav Med 2016

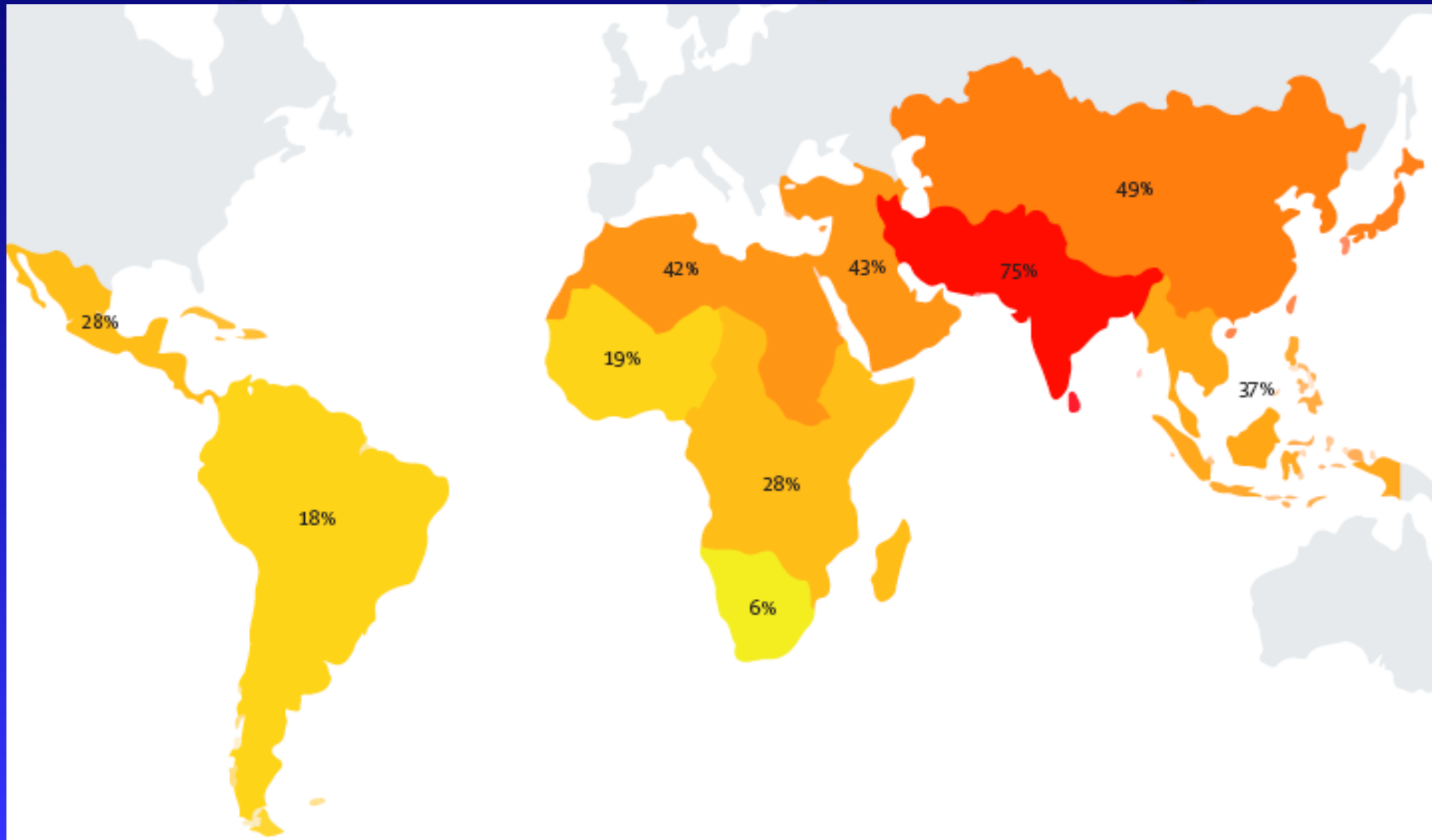
Carriage of ESBL-PI According to Travel Destination



Dutch Traveler Study (COMBAT)

- Multi-site study 2001 Dutch travelers and 215 non-travelling household members
- 6% carried ESBL-PE before travel
- 34% acquired ESBL-PE during travel
  - Acquisition was highest in India (89%)
  - Relatively high in Uganda (44%)
  - Lowest in Suriname (3.6%)
- Median duration of colonization post-travel was 30 days
  - 11% remained colonized at 12 mo
    - Arcilla MS et al. Lancet Infect Dis 2016

Percentages of Travelers Who Acquired ESBL-PE per Subregion

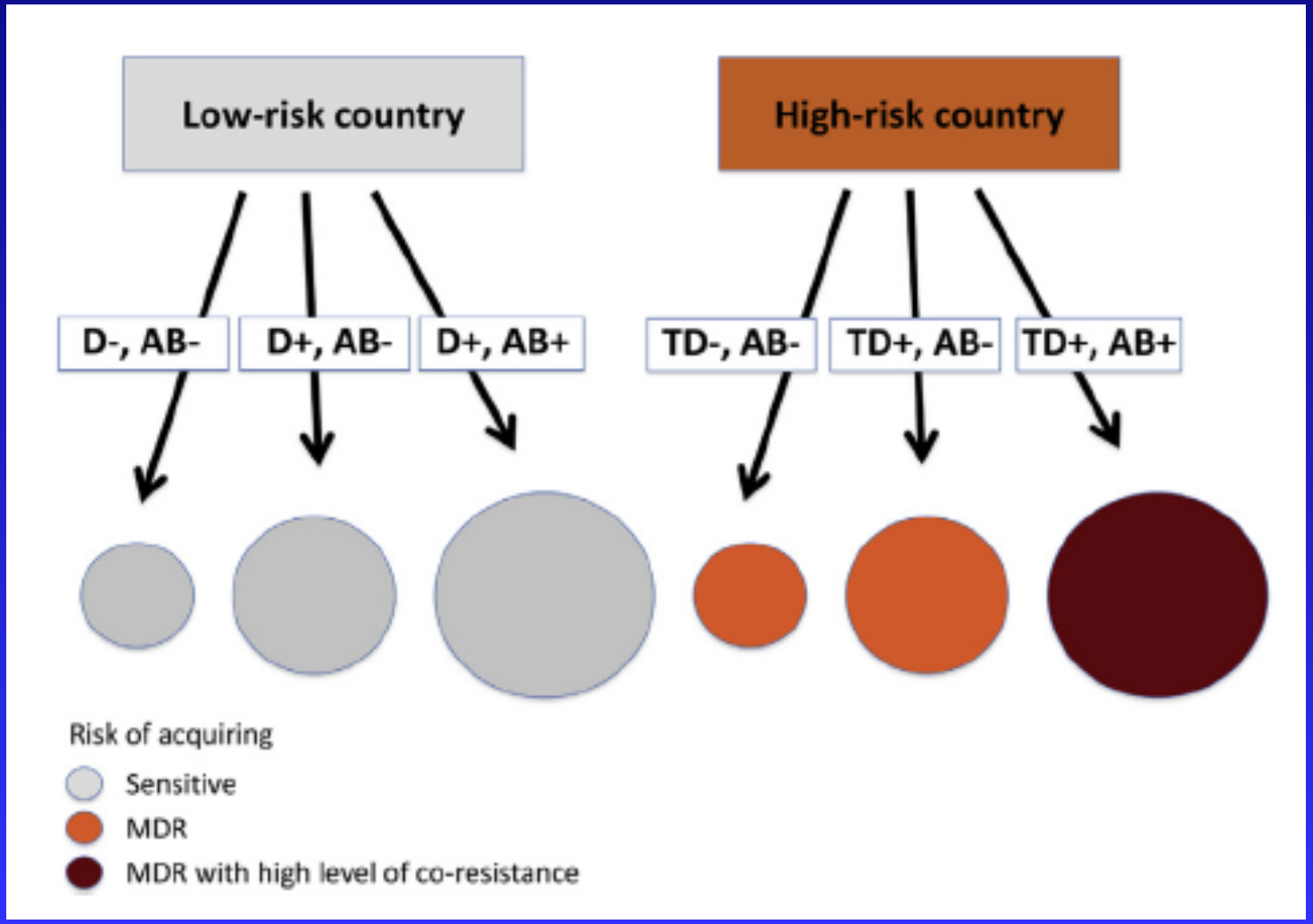


COMBAT Results (2)

- Risk factors for ESBL-PE acquisition:
  - Pre-existing bowel disease (aOR 2.1)
  - Traveler's diarrhea (aOR 2.3)
  - Antibiotic use during travel (aOR 2.69)
  - Attendance mass gathering (aOR 0.57)
  - Clean hands with soap before meals (aOR 0.77)
  - Daily consumption meals at street food stalls (aOR 1.78)
- Onward transmission found in 13/168 (7.7% household members
  - Arcilla MS et al. Lancet Infect Dis 2016

Hypothetical Model

from Kantele A. et al. TMID 2017



Traveling Expands the Mind…
And Loosens the Bowel

Abraham Verghese

And now appears to facilitate acquistion of MDR-E!

Discussion

- Acquisition ESBL-PE relatively common but CRE rare
- Risk factors for acquiring ESBL-PE include age, TD, and antibiotic use, especially fluoroquinolones
- Mixed results on protective efficacy of good personal hygiene
- Carriage declines relatively rapidly post-travel
- Potential onward transmission to family members

ISTM Travelers' Diarrhea Guidelines

- New ISTM TD guidelines recommend:
  - Limiting self-Rx to severe diarrhea
    - Preferably with single dose azithromycin
  - Consider self-Rx for moderate diarrhea
  - Given increasing evidence of association between travel, TD, and antibiotic use and acquisition of MDR bacteria, should include risk-benefit discussion in pretravel counselling
    - Riddle MS et al J Travel Med 2017

Acknowledgments

Any Questions?

STATEMENT ON TRAVELLERS' DIARRHEA

AN ADVISORY COMMITTEE STATEMENT (ACS)

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

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Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report

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