The background of the slide is a tropical sunset scene. Two palm trees are silhouetted against a vibrant orange and yellow sky. A hammock is strung between the trunks of the two trees, hanging over the ocean. The sun is low on the horizon, creating a warm, glowing light across the sky and water.

Top 10 papers in Travel Medicine

Dr. Maya Hites
Clinic of Infectious Diseases
CUB-Erasme Hospital
October 10, 2019

No conflicts of interest



But....

- No rules to follow
- Personal interpretation
- I am a clinician.... maybe diagnostic tests were less favored.
- I am an infectious disease specialist

Methods

- Articles published in October 2018 or later, only in English
- Search Pubmed with key words:
 - Traveler's diarrhea and 2019
 - Malaria and travel and 2019
 - Dengue and travel and 2019
 - Chikungunya and travel and 2019
 - Zika and travel and 2019
 - Measles and travel and 2019
 - Japanese encephalitis and travel and 2019
 - Arboviruses and travel and 2019 (14)
 - MERS and travel and 2019
 - Typhoid Fever and travel and 2019
 - Schistosomiasis and travel and 2019
 - Leishmaniasis and travel and 2019
 - Chagas disease and travel and 2019
- Systematic review of the table of contents of
 - Lancet Infectious Diseases
 - Clinical Infectious Diseases
 - Int J Infect Dis
 - Journal of Travel Medicine (30)
 - Travel Medicine and infectious Diseases (55)
 - Clin Microbiol Infect



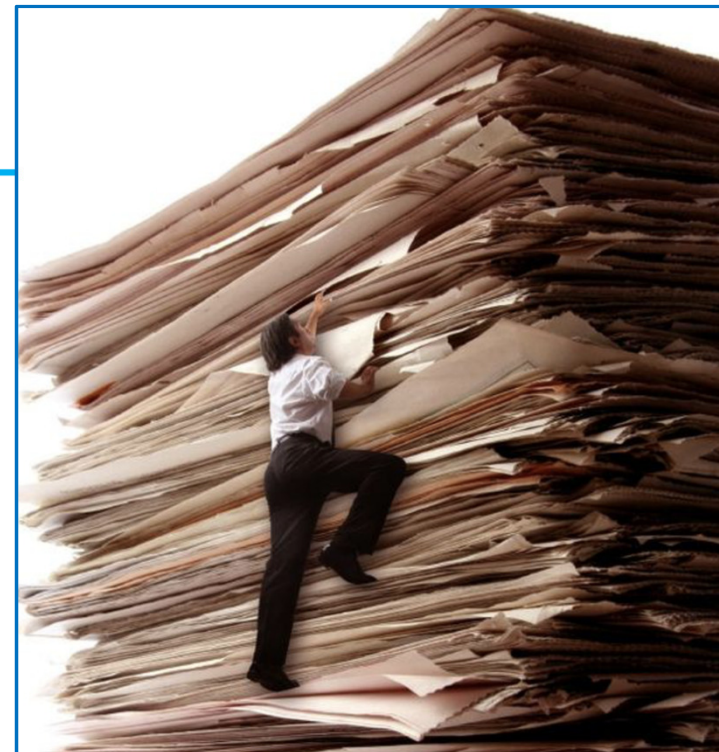
Methods

- Types of articles chosen:
 - Included:
 - Original papers (studies: in-vitro, in-vivo or clinical)
 - meta-analysis or systematic review
 - case reports
 - Excluded: editorials or reviews
- Articles were prioritized based on:
 - Quality of the paper
 - Attempts to answer questions of current clinical interest
 - further questions generated from the research



Results: +/- 100 articles reviewed

- 10 articles chosen
- Not presented in a hierarchical order!



Short Communication

Measles transmission at an international airport — Taiwan,
March–April 2018

1

Hsin-I Huang^a, Ming-Chu Tai^b, Kun-Bin Wu^b, Wan-Chin Chen^a, Angela Song-En Huang^a,
Wen-Yueh Cheng^c, Ming-Tsan Liu^c, Wan-Ting Huang^{a,*}

A 32 year old male with unknown measles vaccination history:

- Travel from Taiwan --> Bangkok (where measles was widespread)--> Taiwan (March 1-->4, 2018)
- Returned to work on March 4th
- Fever and cough on March 14th
- March 17: flight Taiwan --> Okinawa, Japan
- March 19: rash --> hospital: Measles confirmed by RT-PCR testing



Contact tracing/Outbreak investigation

- Screening of:
 - Household contacts
 - Work colleagues
 - Cabin crew
 - Passengers within 2 rows in the plane
 - People who attended the Taiwan Clinic at the same time
- Announcements/ publicity on TV

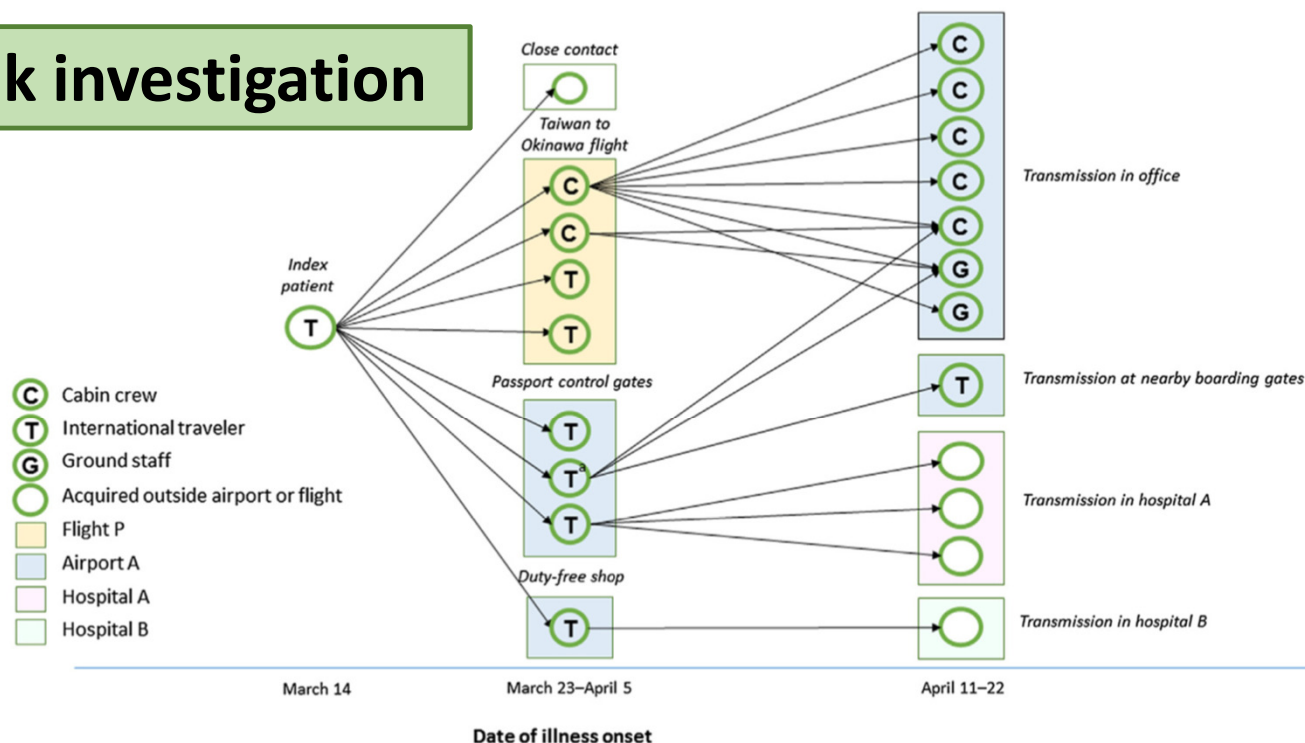


Figure 1. Transmission of measles from an international traveler — Taiwan, March–April 2018.

^aThe case was an airline cabin crew member who was traveling off duty at the time.



- Measles is highly contagious!
- Should be a DD in returning travelers (+non-travelers)!
- Importance of verifying measles vaccination coverage in patients going to pre-travel clinic!!





Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid



A cross-sectional analysis of Zika virus infection in symptomatic and asymptomatic non-pregnant travellers: Experience of a European reference center during the outbreak in the Americas

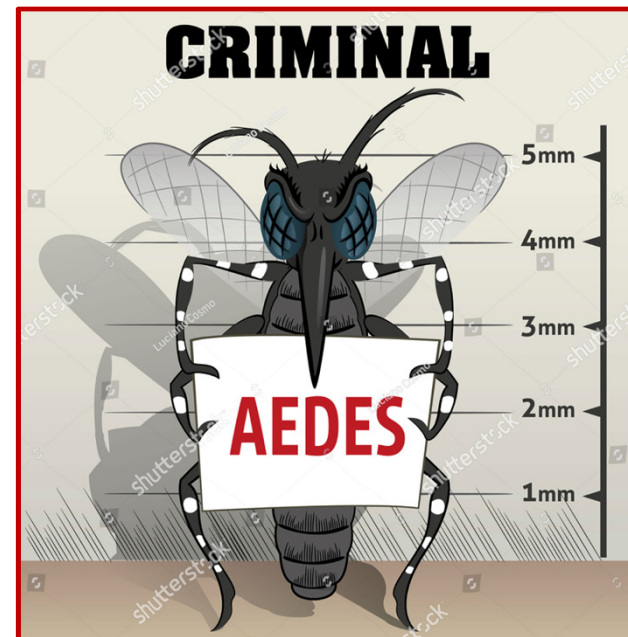
Ralph Huits^{a,*}, Ula Maniewski^a, Dorien Van Den Bossche^a, Erica Lotgering^a, Achilleas Tsoumanis^a, Lieselotte Cnops^a, Jan Jacobs^{a,b}, Marjan Van Esbroeck^a, Emmanuel Bottieau^a

2

Background:

- Travelers to areas with vector-borne Zika transmission are at risk of infection
- Clinical manifestation: mild dengue-like illness
- Exposed travelers perceive ZIKV infection as a serious hazard (ZIKV congenital syndrome, secondary sexual transmission) --> increasing demand for ZIKV diagnostics even if asymptomatic, because +/- 80% of cases in endemic situations were reported to be asymptomatic
- Counseling about risk of sexual transmission + adverse pregnancy outcomes after travel-associated exposure to ZIKV were sought, but data was scarce!

➡ To help travelers take decisions, appropriate tools are needed to assist physicians in translating pre-test --> post-test probabilities.



Main objective: To present the diagnostic approach used at ITM for returning travelers from ZIKV endemic countries



Cross sectional, observational study of all travelers screened for ZIKV at the travel clinic (ITM)

- February –November 2016
- adults who travelled to regions of South or Central America with reported vector-borne transmission of ZIKV

Likelihood ratios were used to calculate Post-test probabilities for travelers of unknown prevalence of ZIKV infection (especially when asymptomatic)!

462 patients screened, 49 cases were diagnosed with ZIKV infection

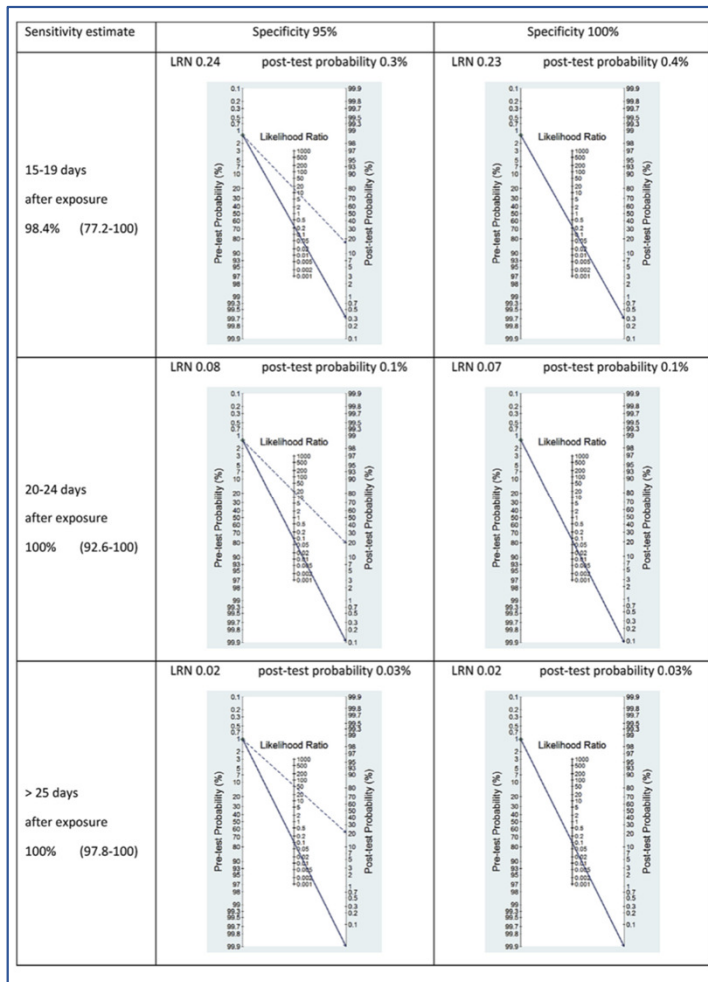


Fig. 1. estimated post-test probabilities for negative Zika virus antibody detection results in asymptomatic adults, at prevalence 1.3% Legend Fig. 1. We calculated the Negative Likelihood Ratio (LRN) using the reported specificity of the anti-ZIKV IgM/IgG Enzyme Linked Immunosorbent Assay (ELISA) (Euroimmun, Lübeck, Germany) was 100% (95%—CI [95.9–100.0]) (ref [18]). We calculated LRN for specificities of 95% and 100%. The sensitivity of anti-Zika antibody detection assays was estimated by adopting lower margins of the 95%-Credible Interval (95%—CrI) for seroconversion in function of the number of days post symptom onset (DPSON) from Lessler et al. and source data [11]. Therefore, with 95% certainty, the true post-test probability is lower than the reported values. The conservative estimates of post-test probabilities of Zika after negative results when tested at 15, 20 and 25 days after travel-associated exposure were calculated and plotted in Fagan nomograms (solid lines). Post-test probabilities of Zika after positive results are plotted only for specificity 95% (dashed lines). The Fagan nomogram consists of 3 vertical axes: the pre-test probability (left axis), the likelihood ratio (middle axis) and the post-test probability (right axis). (Fagan nomograms were created using Stata 14.2 ("FAGAN: Stata module for Fagan's Bayesian nomogram", Statistical Software Components S457060, Boston College Department of Economics), by Ben Dwamena, 2009.)

NLR= negative likelihood ratio

- The frequency of ZIKV infection was high in symptomatic travelers who were exposed during the outbreak in the Americas
- **Negative results** (ELISA IgM/IgG antibody assay) at **20-25 days** after travel-associated exposure allows clinicians to safely rule out ZIKV infection in clinical practice
- Allows for an **acceptable alternative to deferring conception to minimize risk of ZIKV congenital syndrome** in asymptomatic travelers returning to non-endemic areas.

Drug-free Holidays: Compliance, Tolerability, and Acceptability of a 3-Day Atovaquone/Proguanil Schedule for Pretravel Malaria Chemoprophylaxis in Australian Travelers

Colleen L. Lau,^{1,2,3} Lani Ramsey,³ Laura C. Mills,² Luis Furuya-Kanamori,^{1,4} and Deborah J. Mills²

3



Background:

- Malaria= most frequent diagnosis in cases of fever in returning travelers (21% cases, 33% fatalities) (data from 7000 patients from Geo-sentinel clinics)
- Poor compliance= major contributing factor to risk of malaria in travelers
- Standard treatment dose of atovaquone/proguanil 250/100 mg 4 tablets/d for 3 days provides protection against malaria for ≥ 4 weeks



Can 3-day schedule be used for pre-travel chemoprophylaxis?

- Multicentric, prospective, observational study
- Inclusion criteria:
 - Adults ≥ 18 years old
 - Travel to malaria endemic areas in Asia, Pacific Islands, or South/Central America for ≤ 4 weeks
- Exclusion criteria:
 - Concomitant medications
 - Pregnancy
 - Travel to Sub-Saharan Africa

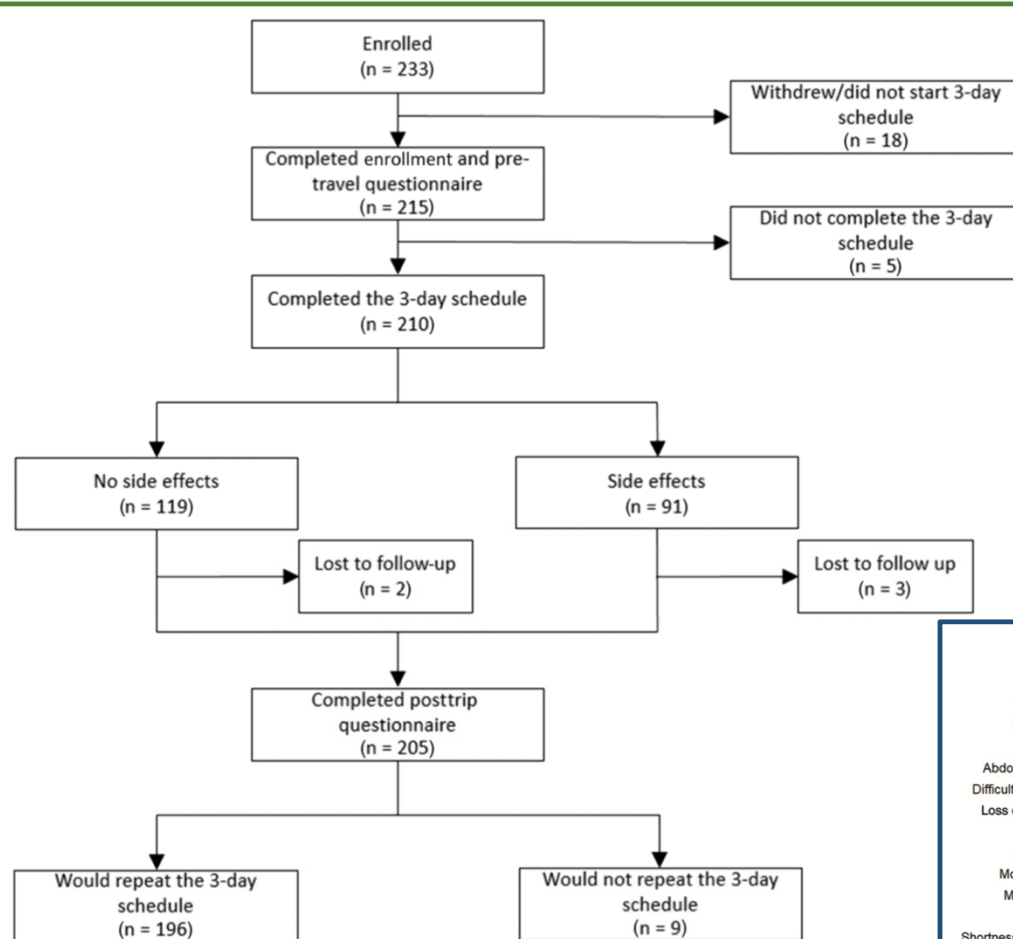


Figure 1. Participant enrollment and follow-up flowchart.

No patients diagnosed with malaria during or after travel!

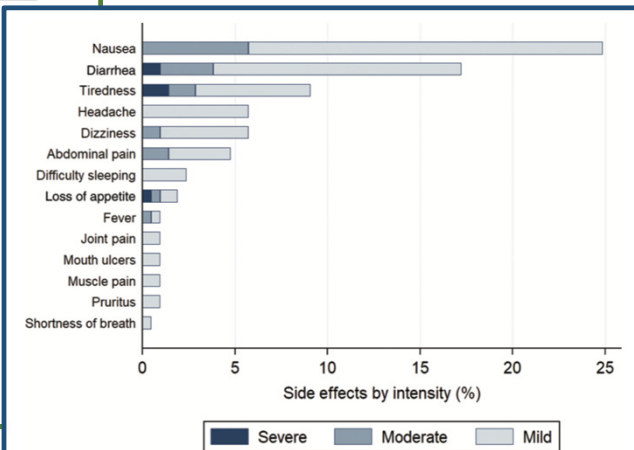


Figure 2. Percentage of participants who reported side effects, stratified by intensity.

Conclusions: 3-day Atovaquone/Proguanil schedule

- High compliance (> 97%)
- Well tolerated
 - Limited, mild side effects: 1-2 days, and resolved before departure
- Well accepted by travelers
- Cheaper than “standard prophylaxis”
- **Nevertheless:**
 - Compliance + acceptability were self reported
 - Study was not designed to study effectiveness of the 3-days schedule for prophylaxis



Further studies, including a larger sample size, + higher risk destinations will be required to confirm effectiveness in nonimmune travelers!

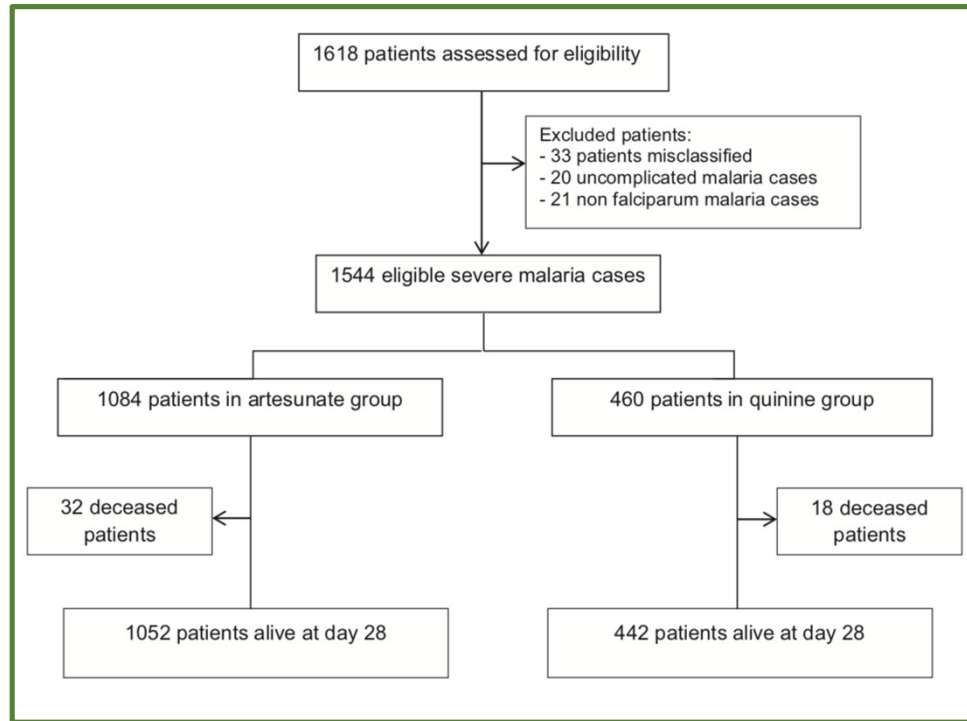
Propensity Score Analysis of Artesunate Versus Quinine for Severe Imported *Plasmodium falciparum* Malaria in France

4

Nermine El Ket,¹ Eric Kendjo,^{1,2} Marc Thellier,^{1,2,3} Lambert Assoumou,¹ Valérie Potard,¹ Aida Taieb,^{2,4} Ilhame Tantaoui,^{2,4} Eric Caumes,^{1,5} Renaud Piarroux,^{1,2,3} Camille Roussel,^{4,6} Pierre Buffet,^{2,4,6} Dominique Costagliola,¹ and Stéphane Jauréguiberry^{1,2,5}; for the French Artesunate Working Group

Background:

- Little is known on the use of artesunate compared with quinine for the treatment of imported malaria cases in nonendemic countries with a high level of care
- 2 treatments were compared in France (data from French National Reference Center) in terms of:
 - Mortality
 - Hospital + ICU discharge rates



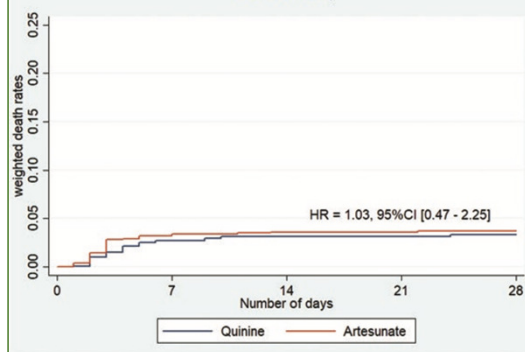
Strengths:

- Large sample size, coming from 110 centers throughout France

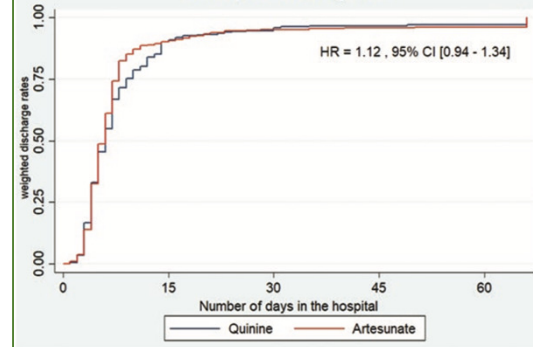
Limitations:

- Imported malaria is not a mandatory notifiable infectious disease in France
- The surveillance system relies on motivation of physicians to report data to the NRC --> available data were not complete
- Safety was not compared between 2 groups either

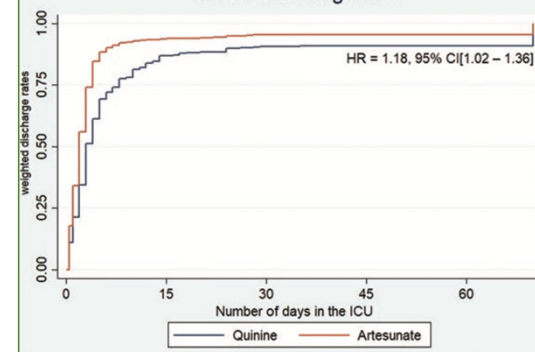
A. Mortality



B. Hospital discharge rate



C. ICU discharge rate



Persistence of Imported Malaria Into the United Kingdom: An Epidemiological Review of Risk Factors and At-risk Groups

5

Qubekani M. Moyo,¹ Martin Besser,² Roderick Lynn,² and Andrew M. L. Lever^{1,3}

Background:

- UK documented a decline of > 30% in imported cases of malaria annually between 1996-2003
- Worldwide: increase in imported and severe malaria cases from 2000-2015
- Still responsible for +/- 1700 cases/year in UK (5-10 deaths each year)
- Much morbidity is attributed to people VFR --> effort has been made to target this population

Objective: To evaluate whether the epidemiology has changed + whether health advice messages are targeting the right population.

- Retrospective review of patients with confirmed malaria seen in Cambridge University Hospital Foundation Trust: 2002 -2016
- Comparison with national data

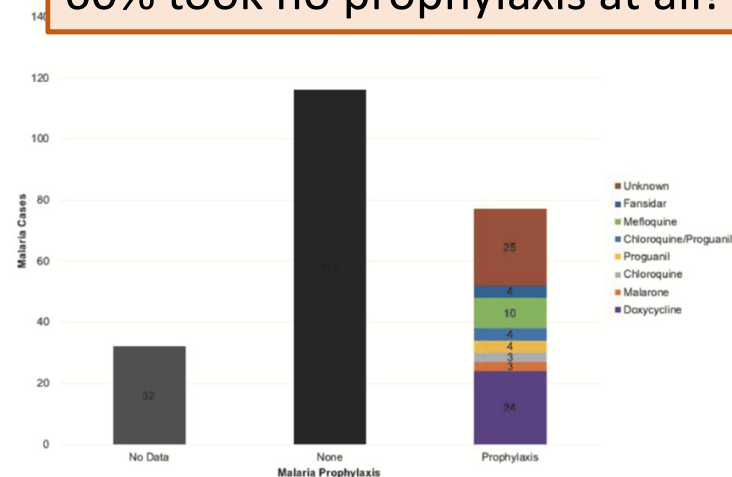
Results:

- 225 patients with confirmed malaria
(67% due to *P. falciparum*)
- 15 cases/year: No decrease in cases/ year since 2004, similar to national trends
- Travel: West Africa (Ghana + Nigeria)

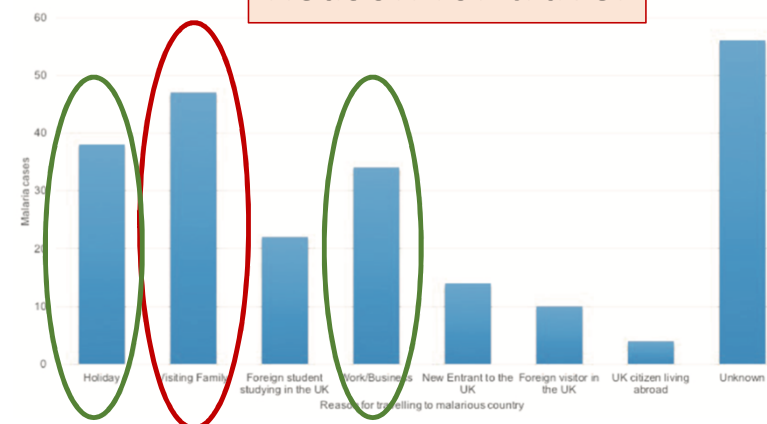
Conclusions:

- Significant number of travelers to countries endemic to malaria still take no chemoprophylaxis!
- Efforts need to be made to give health advice to:
 - VFR
 - Holiday and work

60% took no prophylaxis at all!



Reason for travel

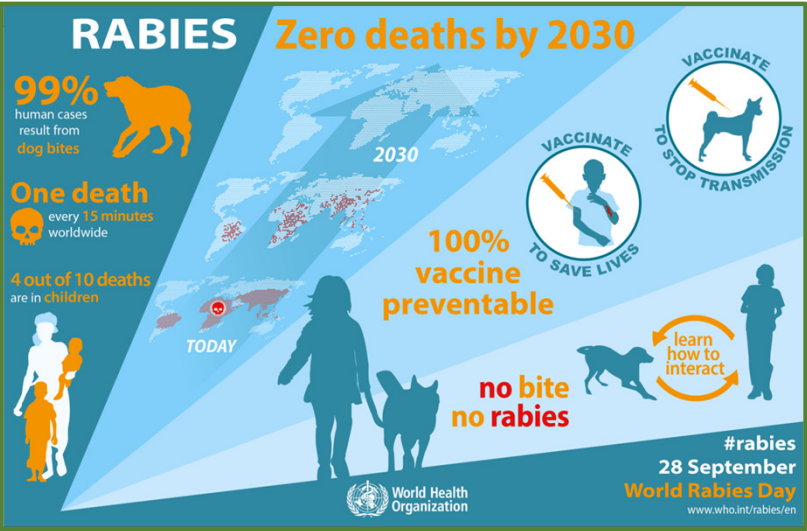
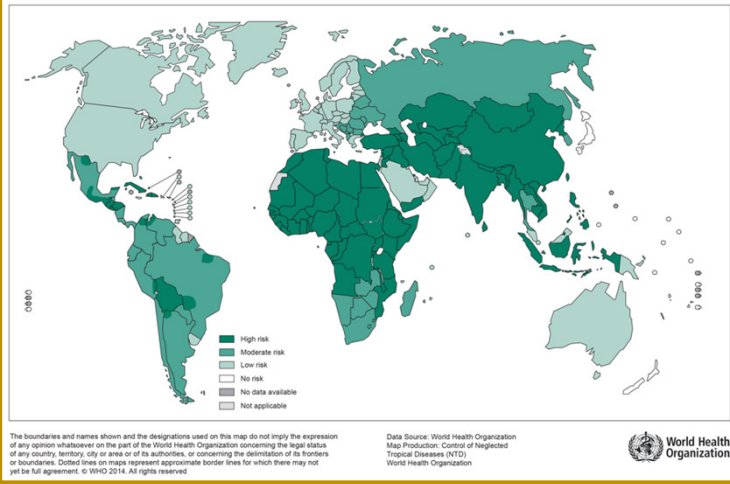


Preexposure Intradermal Rabies Vaccination: A Noninferiority Trial in Healthy Adults on Shortening the Vaccination Schedule From 28 to 7 Days

Patrick Soentjens,^{1,2} Petra Andries,¹ Annelies Aerssens,^{3,4} Achilleas Tsoumanis,² Raffaella Ravinetto,⁵ Walter Heuninckx,¹ Harry van Loen,² Bernard Brochier,⁶ Steven Van Gucht,⁶ Pierre Van Damme,⁷ Yven Van Herreweghe,² and Emmanuel Bottieau²

6

Distribution of risk levels for humans contacting rabies, worldwide, 2013



Background:

- Rabies= neglected tropical disease
- Case-fatality rate= 100%
- Global annual death toll: +/- 61,000 cases (Asia + Africa)
- 40% of all bite exposures occurs in children (Asia + Africa)
- Rabies prevention: Preexposure prophylaxis (PrEP) using rabies vaccine



Main objective: Noninferiority trial to compare immunogenicity 7 days after a single ID booster injection following 2 different priming schedules 1-3 years earlier (to mimic a true PEP situation)

- Double-dose ID 2 visit (D0 + D7), or
- Single-dose ID 3 visit (D0 + D7 + D28)

Assessment with:

- Rabies antibody titers measured with **rapid fluorescent focus inhibition test (RFFIT)**, > 0.5 IU/mL 7 days after booster vaccination injection 1-3 years after primary vaccination
- **Clinical non-inferiority:** loss of $< 10\%$ of subjects who have adequate rabies antibody levels compared to the 3 ID schedule

500 individuals randomized: 183 vs. 185 patients evaluated for immunogenicity on the 2 ID vs. 3 ID schedule

Table 3. Seroprotection Rates, Per-protocol Analysis, Day 7 After Booster Vaccination

Serology	3ID Schedule	2ID Schedule	% Difference (95% CI) ^a
Per-protocol analysis	n = 185	n = 183	
Subjects with serology >0.5 IU/mL	185/185 (100 [98–100])	183/183 (100 [98–100])	0 (–2.1 to 2)
No. of subjects with serology >10 IU/mL	154/185 (83 [78–89])	176/183 (96 [93–99])	13 (7–19)

Conclusions:

Noninferiority was confirmed!

(with 100% adequate antibody response)

- Other secondary endpoints:
 - Greater proportion of Participants with
 - long-lasting protection > 10 IU/mL (96 vs. 83%)
 - Geometric mean titer (GMT): 37 vs. 25
- As safe as 3 ID schedule



New shortened ID schedules aim to be:

- Dose
- Time
- Cost sparing, while maintaining safety + efficacy

+ good news if vaccine shortages!



Metagenomic next-generation sequencing aids the diagnosis of viral infections in febrile returning travellers

Hanna Jerome^{a,1}, Callum Taylor^{b,1}, Vattipally B. Sreenu^a, Tanya Klymenko^a, Ana Da Silva Filipe^a, Celia Jackson^c, Chris Davis^{a,*}, Shirin Ashraf^a, Eleri Wilson-Davies^c, Natasha Jesudason^d, Karen Devine^b, Lisbeth Harder^a, Celia Aitken^c, Rory Gunson^c, Emma C. Thomson^{a,b,*}

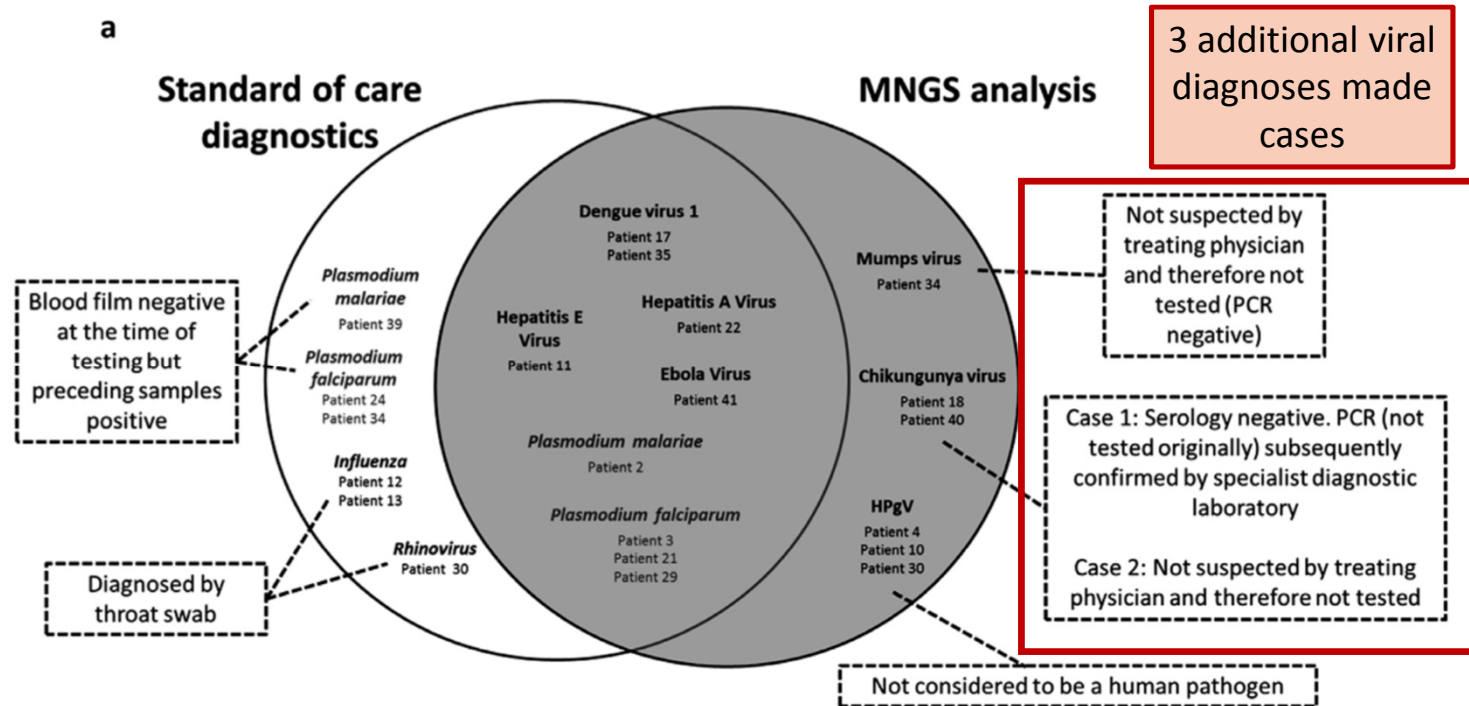
Background:

- The increase in international travel has increased the potential for transmission of a wide range of viruses
- Traditional diagnostic tests:
 - require a priori knowledge of pathological agents
 - Are often batched
 - Sent to a reference laboratory
- Metagenomic next-generation sequencing (MNGS) may help:
 - Identify new or emerging infections (+ those not considered by the treating physician)
 - Resistance screening
 - Detect multiple pathogens in a single sample

Objective: Proof-of-concept study to use MNGS to identify viral pathogens in clinical samples from returning travelers in a single center to explore suitability as a diagnostic tool

Methods: Retrospective use of samples from patients admitted with a febrile illness following overseas travel within 12 weeks of presentation to hospital from 2013- 2016

- MSNG analysis was performed
- Diagnoses made by 2 blinded physicians (ID physician + laboratory scientist with expertise in NSG data analysis) prior to comparison with clinical data
- Confirmatory testing carried out by PCR or serology in the West of Scotland Specialist Virology Center



Conclusions:

- MNGSs has the potential to improve diagnostic yield of viral, bacterial + parasitic infectious diseases
- The requesting physician does not need to consider all DD possibilities

Limitations:

- The method is designed to detect RNA viruses --> it is likely to detect DNA viruses with an RNA stage in the life cycle, but with reduced sensitivity!
- CSF, respiratory + urine samples were not often tested
- Sensitivity of MSNGs for detection of each pathogen identified in this study has not been performed

Hepatitis A vaccine immunogenicity in patients using immunosuppressive drugs: A systematic review and meta-analysis

Hannah M. Garcia Garrido^{a,*}, Ati M. Veurink^a, Mariska Leeftang^b, René Spijker^{c,d}, Abraham Goorhuis^a, Martin P. Grobusch^a

8

^a Amsterdam UMC, University of Amsterdam, Centre of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Meibergdreef 9, Amsterdam, the Netherlands

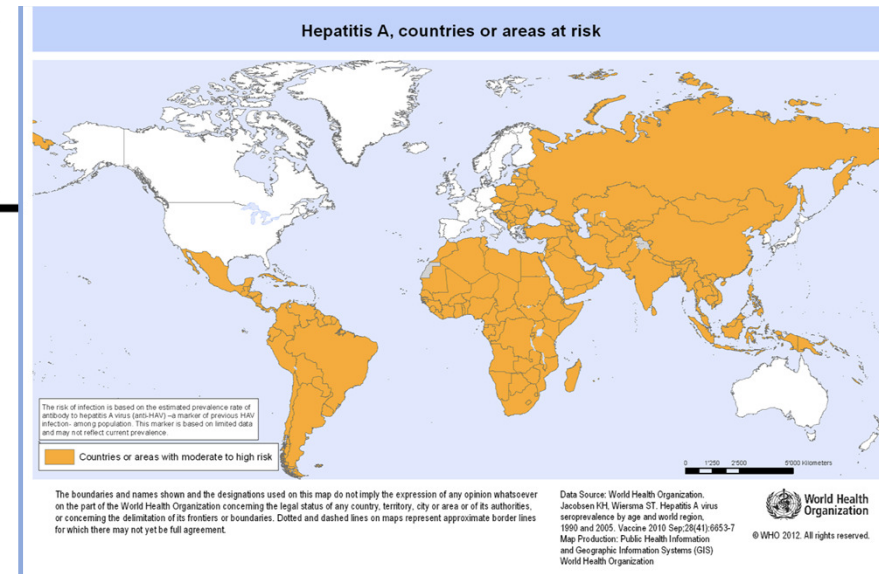
^b Amsterdam UMC, University of Amsterdam, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam Public Health, Meibergdreef 9, Amsterdam, the Netherlands

^c Amsterdam UMC, University of Amsterdam, Medical Library, Amsterdam Public Health, Meibergdreef 9, Amsterdam, the Netherlands

^d Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht University, Utrecht, the Netherlands

Background:

- Patients taking immunosuppressive treatments are more likely to travel to exotic destinations
- HAV is a common vaccine-preventable disease in travelers
- Reasons for looking at IS travelers:
 - Many IS travelers are > 40 years old --> increased case-fatality rate compared to younger individuals
 - Prolonged viral shedding upon HAV infection --> risk of outbreaks
 - Inactivated HAV vaccines:
 - Safe
 - Highly immunogenic, response rates of 100% after a single dose in immuno-competent individuals
- Immune response following HAV vaccination involve cellular + humoral pathways, but antibodies alone are protective against infection



Objectives:

- What are the seroconversion rates after 1 and 2 doses of HAV vaccine?
- What is the strength of the humoral immune response in geometric mean antibody concentration
- Are there differences in SCRs between IS regimens?
- Are alternative vaccination regimens superior to the established 2 dose regimen?
- What is the duration of protection after successful vaccination?



Identification
Screening
Eligibility
Included

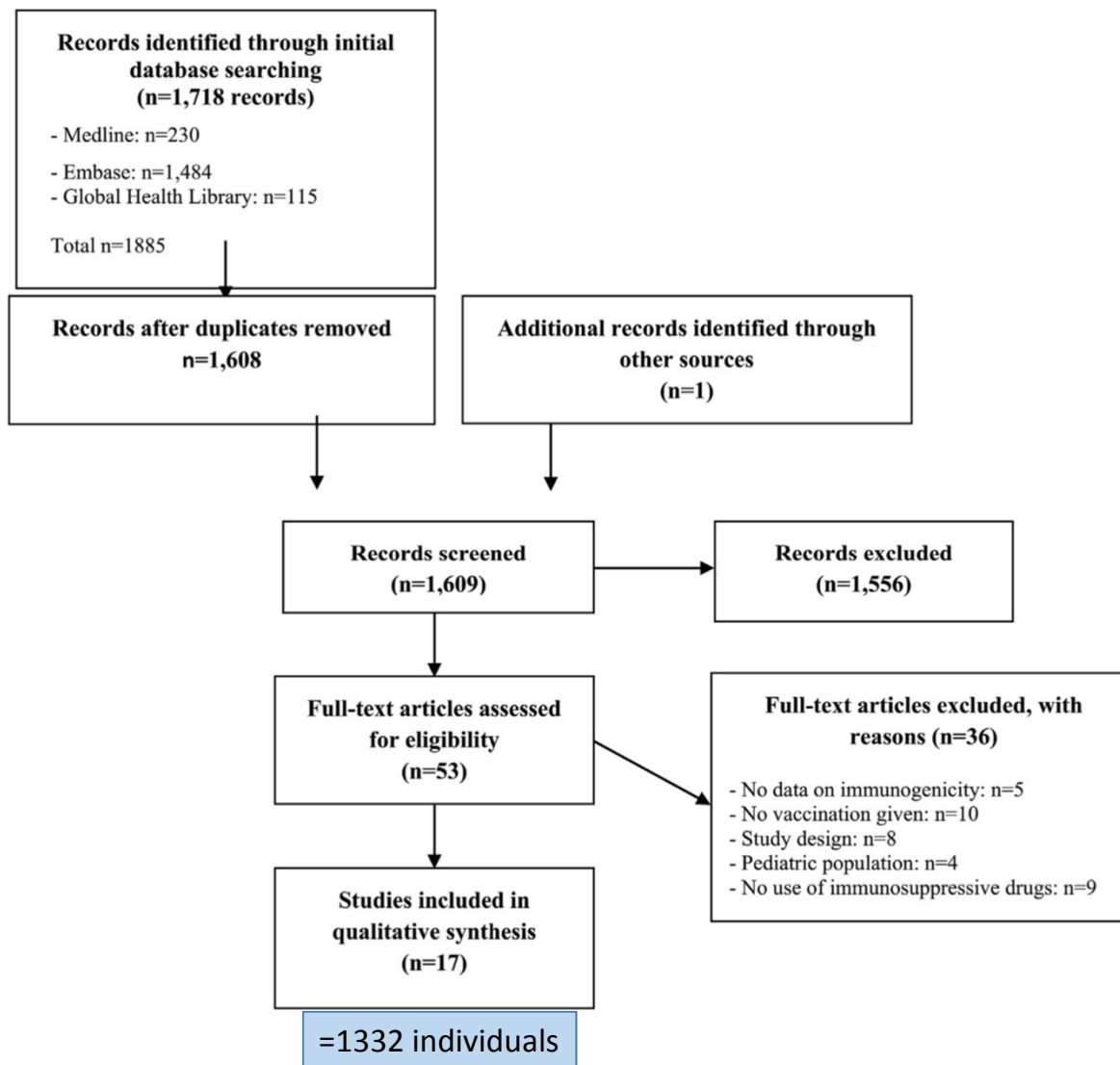


Fig. 1. PRISMA flowchart of study selection process.

Results:

- Differences in IS regimens:
 - Anti-TNF > conventional immunomodulatory (cIM) > organ transplant patients
 - No data on other non anti-TNF biologicals
- Seroconversion rates:
 - Rituximab: 0--> 47%
 - Anti-TNF + cIM: 6-100%; 48-100%
 - SOT: 0-67%; 0-97%
- Alternative vaccination regimens?
 - 1 single study in RA patients: 2 doses + 1 vs. 1-1-1 schedule, but no control group of IS patients receiving standard regimen
- Duration of protection after successful vaccination?: no conclusions because too few data

Limitations: Great heterogeneity of SC rates between studies: 0--> 100%

- Age
- Different IS regimens (dose, number of IS drugs)
- The serological assay used
- Serological cut-offs: from 10 --> 40 mIU/mL
- Different vaccines used across studies (Havrix[®], Vaqta[®], Epaxal[®]), different SCRs have been reported for different vaccines



Conclusions: overall, evidence is of low quality

- Impaired immune response to the 2 dose vaccination regimen in patients receiving IS therapy , especially after 1 single dose
- Vaccination before start of IS therapy! (long term serological protection after is not guaranteed!
- Antibody measurement after vaccination is needed before travel to endemic regions
- Protective antibodies after vaccination in IS patients may take longer --> 6-8 weeks between antibody assessment + vaccination
- Alternative vaccination regimens: Extra doses of vaccines: only 1 study in 54 patients!
 - Well tolerated
 - Generate excellent short-term seroconversion rates in RA patients with mild IS regimens
 - More studies needed in other patient categories

Microbiome and Antimicrobial Resistance Gene Dynamics in International Travelers

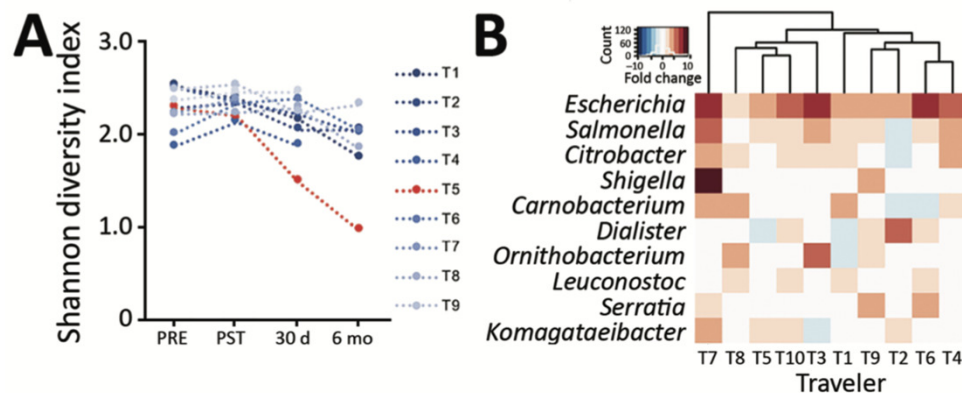
9

Charles Langelier, Michael Graves,¹
Katrina Kalantar,¹ Saharai Caldera,
Robert Durrant, Mark Fisher, Richard Backman,
Windy Tanner, Joseph L. DeRisi, Daniel T. Leung

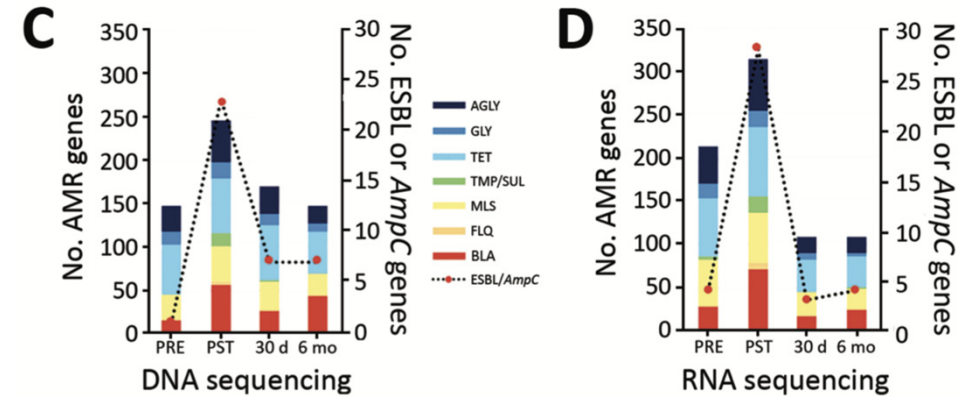
Main objective: To clarify AMR exchange during global travel using metagenomic next generation sequencing (mNGS) to assess composition of gut microbiota + the antimicrobial resistome

Background:

- Intl travel is a known contributor to the emergence of organisms with antimicrobial resistance (AMR)
- Colonization with resistant pathogens acquired during travel can persist for extended periods of time --> transmission into environment + susceptible populations
- Mechanisms underlying acquisition of AMR bacteria are not completely understood
- Hypothesis: changes in the microbiota may play a role?



Total number of AMR genes identified with $\geq 20\%$ allele coverage by DNA and RNA sequencing



Conclusions: the enteric microbiota and resistomes of returned travelers were analyzed:

- a marked increase in AMR genes that was associated with an increased proportion of *Escherichia spp.* Bacteria
- Persistent ESBL colonization was observed after 6 months --> travel can induce long-term changes in the antimicrobial resistome
- mNGS identified a number of other AMR gene classes that increased in abundance after travel
- Changes in microbiome diversity were not associated with ESBL positivity at 30 D or 6 months post-travel--> **disruption of the antimicrobial resistome can occur in the setting of a preserved microbial community structure!**
- Limitations: small sample size



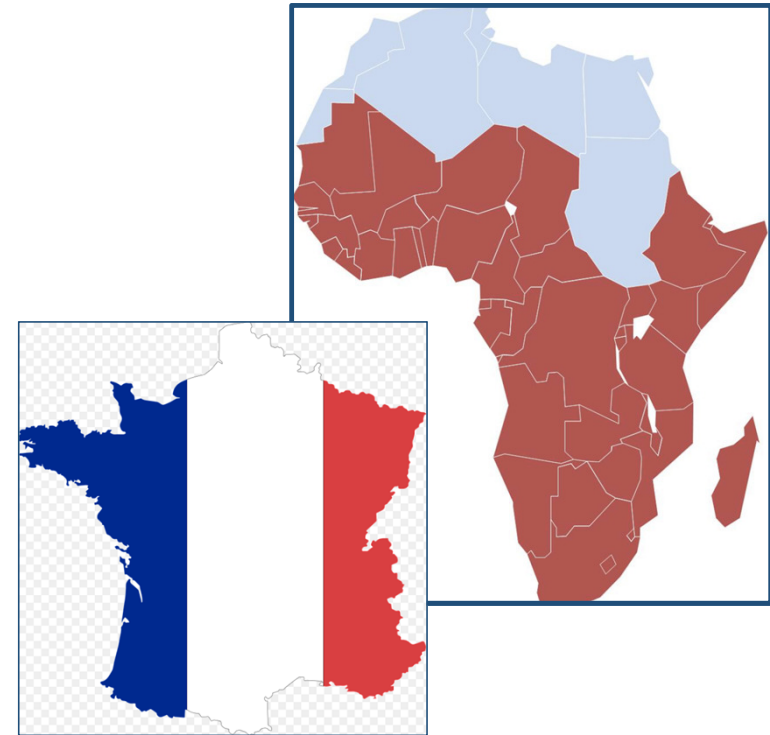
Travel-related health events and their risk factors in HIV-infected sub-Saharan migrants living in France and visiting their native country: The ANRS VIHVO cohort study

10

Thierry Pistone^{a,b,*}, Eric Ouattara^{a,b}, Delphine Gabillard^b, Nathalie Lele^{c,d}, Alexandre Duvignaud^{a,b}, Hugues Cordel^{c,d}, Denis Malvy^{a,b}, Olivier Bouchaud^{c,d}, Sophie Abgrall^{e,f}, ANRS VIHVO Study Group (Michele Bentata^g, Bruno Fantin^h, Cécile Goujardⁱ, Sophie Matheron^j, Odile Launay^k, Vincent Le Moing^l, Olivier Lortholary^m, Paul-Henri Consignyⁿ, Matthieu Saada^o, Christine Katlama^p, Anne Simon^p, Cédric Arvieux^q, Pauline Campa^r, Pierre-Marie Girard^r, Marie-Aude Khuong^s, Jean-Michel Molina^t, Caroline Lascoux-Combe^t, David Rey^u, Murielle Rondeau^u, Gilles Pialoux^v, Carine Couzigou^w, Daniel Vittecoq^w, Olivier Patey^x, Philippe Morlat^y, Michel Duong^z, Pascal Chavanet^z)

Background:

- +/-5.8 million migrants live in France
- 670,000 were born in sub-Saharan Africa (SSA)
- Migrants of SSA constitute 23% of the HIV-infected individuals in France
- Quality of life of HIV-infected individuals has markedly improved since introduction of cART
- HIV-infected SSA migrants travel more frequently to their native countries for long travel duration
- Data on travel-related health problems of HIV-infected persons that visit tropical regions are scarce
- No studies have focused on HIV-infected SSA migrants living in a Western country who visit their country of origin



Main objective: To describe travel-related health events and their risk factors in HIV-infected SSA migrants included in the ANRS VIHVO study

- Prospective study from July 2006 --> June 2009
- Patients enrolled: 268 HIV-infected migrants (natives of SSA) who travelled within 8 weeks of their visit to their native country for > 2 week, but < 6 months

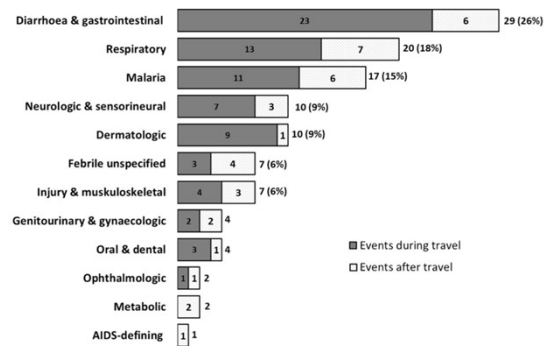


Fig. 1. Travel-related health events according to the timing of occurrence during or after travel in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

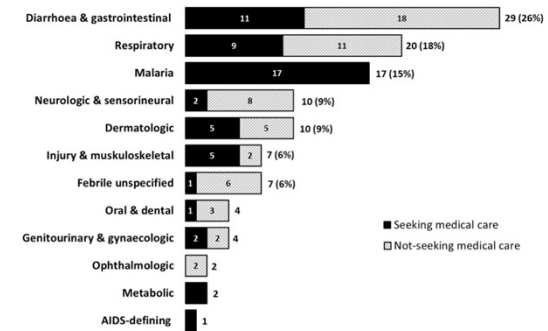


Fig. 2. Travel-related health events according to medical-care-seeking behaviour in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

- 38% of 264 HIV-infected SAA migrants living in France experienced > 1 travel-related event during travel to their native country, lower than the 64-87% of health events reported in the general population of Intl travelers to resource-limited countries
- Medical care was sought in 50% of the events
- Most common events: diarrhea > respiratory symptoms > malaria –related events

Results:

- Low reported adherence rates to vector control measures + malaria chemoprophylaxis
- Patients at greatest risk for a travel-related health event:
 - low-level pre-travel viremia
 - No pre-travel medical advice on diarrhea + vector-borne diseases
- 11% decrease in cART adherence during travel:
 - Lower socio-economic conditions
 - Negative perception about cART effectiveness
 - Prolongation of the stay
 - Unexpected traumatic events during stay

4x more frequent than if undetectable pre-travel viremia + pretravel advice

Conclusions: counselling needs to focus on adherence to pre-travel medical advice regarding prophylactic measures for:

- diarrhea and
- vector borne diseases



Thank you for
your attention!

Bon Voyage!