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 diahrea 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
  • Typhoïd 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!
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
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!!

- 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

**Contact tracing/Outbreak investigation**

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

*The case was an airline cabin crew member who was traveling off duty at the time.*
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


**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.

- 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.
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

No patients diagnosed with malaria during or after travel!
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

Nermine El Ket,1 Eric Kendjo,2,3 Marc Thellier,2,3 Lambert Assoumou,1 Valérie Potard,1 Aïda Taieb,2,4 Ilhame Tantaoui,2,4 Eric Caumes,1,5 Renaud Piarroux,1,3 Camille Roussel,4,6 Pierre Buffet,2,4,6 Dominique Costagliola,1 and Stéphane Jauréguiberry1,2,5, for the French Artesunate Working Group

**Background:**

- Little is known on the use of artemisinin 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
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
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,1 Achilleas Tsoumanis,2 Raffaella Ravinetto,3 Walter Heuninckx,1 Harry van Loen,2 Bernard Brochier,4 Steven Van Gucht,5 Pierre Van Damme,7 Yven Van Herewege,2 and Emmanuel Bottieau1

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

CID. 2019; 68: 607-614
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
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\textsuperscript{a,1}, Callum Taylor\textsuperscript{b,1}, Vattipally B. Sreenu\textsuperscript{a}, Tanya Klymenko\textsuperscript{a}, Ana Da Silva Filipe\textsuperscript{a}, Celia Jackson\textsuperscript{c}, Chris Davis\textsuperscript{a,*}, Shirin Ashraf\textsuperscript{a}, Eleri Wilson-Davies\textsuperscript{c}, Natasha Jesudason\textsuperscript{d}, Karen Devine\textsuperscript{b}, Lisbeth Harder\textsuperscript{a}, Celia Aitken\textsuperscript{c}, Rory Gunson\textsuperscript{c}, Emma C. Thomson\textsuperscript{a,b,*}

\textbf{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, M.D., Ati M. Veurink, M.D., Mariska Leeflang, M.D., René Spijker, M.D., Abraham Goorhuis, M.D., Martin P. Grobusch, M.D.

*Amsterdam UMC, University of Amsterdam, Centre of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Meibergdreef 9, Amsterdam, the Netherlands
*Amsterdam UMC, University of Amsterdam, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam Public Health, Meibergdreef 9, Amsterdam, the Netherlands
*Amsterdam UMC, University of Amsterdam, Medical Library, Amsterdam Public Health, Meibergdreef 9, Amsterdam, the Netherlands
#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

Hannah M et al. Travel Medicine and Infectious Disease, http://doi.org/10.1016/j.tmaid.2019.101479
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?
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
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?

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

Thierry Pistone, Eric Ouattara, Delphine Gabillard, Nathalie Lele, Alexandre Duvignaud, Hugues Cordel, Denis Malvy, Olivier Bouchaud, Sophie Abgrall, ANRS VIHVO Study Group (Michele Bentata, Bruno Fantin, Cécile Goujard, Sophie Matheron, Odile Launay, Vincent Le Moing, Olivier Lortholary, Paul-Henri Consigny, Matthieu Saada, Christine Katlama, Anne Simon, Cédric Arvieux, Pauline Campa, Pierre-Marie Girard, Marie-Aude Khuong, Jean-Michel Molina, Caroline Lascoux-Combe, David Rey, Murielle Rondeau, Gilles Pialoux, Carine Couzigou, Daniel Vittecoq, Olivier Patey, Philippe Morlat, Michel Duong, Pascal Chavanel)

**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

- 38% of 264 HIV-infected SSA 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

**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!