8th National Seminar on Travel Medicine

19 November 2009

FLASHES

17.30-18.00

Flashes from the 11th International Society of Travel Medicine, Budapest 2009 and what's new in travel medicine

Prof B. Vandercam, UCL Brussels - Prof F. Van Gompel, – ITG Antwerpen – Prof F. Jacobs, Hôpital Erasme Brussels

1 - Malaria

A World Malaria Map: *Plasmodium falciparum* Endemicity in 2007

Simon I. Hay[1,2*], Carlos A. Guerra[1,2], Peter W. Gething[2,3], Anand P. Patil[2], Andrew J. Tatem[1,2,4,5], Abdisalan M. Noor[1,6], Caroline W. Kabaria[1], Bui H. Manh[7], Iqbal R. F. Elyazar[8], Simon Brooker[1,9], David L. Smith[5,10], Rana A. Moyeed[11], Robert W. Snow[1,6]

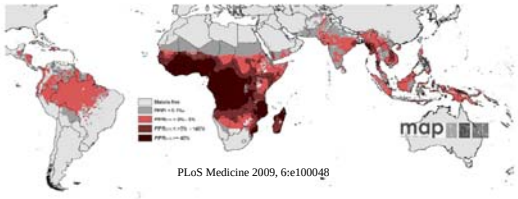
Methods and Findings

A total of 8,938 *P. falciparum* parasite rate (*PfPR*) surveys were identified using a variety of exhaustive search strategies. Of these, 7,953 passed strict data fidelity tests for inclusion into a global database of *PfPR* data, age-standardized to 2–10 y for endemicity mapping. A model-based geostatistical procedure was used to create a continuous surface of malaria endemicity within previously defined stable spatial limits of *P. falciparum* transmission. These procedures were implemented within a Bayesian statistical framework so that the uncertainty of these predictions could be evaluated robustly. The uncertainty was expressed as the probability of predicting correctly one of three endemicity classes; previously stratified to be an informative guide for malaria control. Population at risk estimates, adjusted for the transmission modifying effects of urbanization in Africa, were then derived with reference to human population surfaces in 2007. Of the 1.38 billion people at risk of stable *P. falciparum* malaria, 0.69 billion were found in Central and South East Asia (CSE Asia), 0.66 billion in Africa, Yemen, and Saudi Arabia (Africa+), and 0.04 billion in the Americas. All those exposed to stable risk in the Americas were in the lowest endemicity class ($PfPR_{2-10} \leq 5\%$). The vast majority (88%) of those living under stable risk in CSE Asia were also in this low endemicity class; a small remainder (11%) were in the intermediate endemicity class ($PfPR_{2-10} > 5$ to $< 40\%$); and the remaining fraction (1%) in high endemicity ($PfPR_{2-10} \geq 40\%$) areas. High endemicity was widespread in the Africa+ region, where 0.35 billion people are at this level of risk. Most of the rest live at intermediate risk (0.20 billion), with a smaller number (0.11 billion) at low stable risk.

PLoS Medicine 2009, 6:e100048

Conclusions

- High levels of P. falciparum malaria endemicity are common in Africa.
- Uniformly low endemic levels are found in the Americas.
- Low endemicity is also widespread in CSE Asia, but pockets of intermediate and very rarely high transmission remain.
- There are therefore significant opportunities for malaria control in Africa and for malaria elimination elsewhere.
- This 2007 global P. falciparum malaria endemicity map is the first of a series with which it will be possible to monitor and evaluate the progress of this intervention process.



PLoS Medicine 2009, 6:e100048

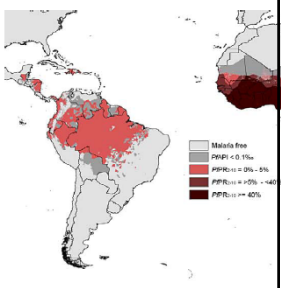
Figure 4. The Spatial Distribution of *P. falciparum* Malaria $PfPR_{2-10}$ Predictions Stratified by Endemicity Class

They are categorized as low risk $PfPR_{2-10} \leq 5\%$, light red; intermediate risk $PfPR_{2-10} > 5\%$ to $< 40\%$, medium red; and high risk $PfPR_{2-10} \geq 40\%$, dark red. The map shows the class to which $PfPR_{2-10}$ has the highest predicted probability of membership. The rest of the land area was defined as unstable risk (medium grey areas, where *PfAPI* < 0.1 per 1,000 pa) or no risk (light grey) [17–19].

doi:10.1371/journal.pmed.1000048.g004

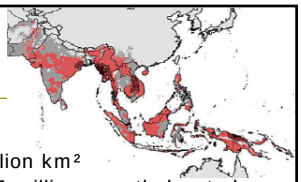
Americas

- Area at risk : 6.03 million km², mostly located in the Amazon basin
- People at risk : 40.64 million
- Endemicity : uniformly low endemic levels



Hay S. et al. A world malaria map. PLoS Medicine 2009

Central SE Asia



- Area at risk : 5.53 million km²
- People at risk : 685.65 million, mostly located in India and Indonesia
- Endemicity : over 4.72 million km² (88.54 %) of this area and 603.61 million (88.03 %) people experience low endemicity. Geographically small but epidemiologically important patches of intermediate and very rarely high risk transmission, for example : Orissa state, eastern India, western Myanmar and the lowlands of New Guinea

Can we rely on epidemiology from travelers ? November 2008

With the reduction in malaria incidence seen in both visitors to and from West Africa,

the most rational explanation for these findings is a fall in malaria transmission in West Africa

which may require a change in chemoprophylaxis policy for UK travelers over the next 5 – 10 years

Malaria Journal 2008, 7: 235

www.ith.int - 2 February 2009

– In recent weeks, several European countries have reported unusually high numbers of cases of P. falciparum infection in holiday travellers to the Gambia (West Africa) who had not taken adequante protective measures against malaria

Severe malaria caused by Plasmodium vivax

Am J Trop Med Hyg
NOVEMBER 2009

Case Report: Histopathology of Fatal Respiratory Distress Caused by *Plasmodium vivax* Malaria

Neena Valecha,* Rock G. W. Pinto, Gareth D. H. Turner, Ashwani Kumar, Savio Rodrigues, Nagesh G. Dubhashi, Edmond Rodrigues, Sidhartha S. Banaulikar, Ruchi Singh, Aditya P. Dash, and J. Kevin Baird*

National Institute of Malaria Research, Delhi, India; Departments of Pathology, Microbiology, Medicine and Forensic Medicine, Goa Medical College and Hospital, Bambolim, Goa, India; Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom; National Institute of Malaria Research Field Unit, Goa, India; Southeast Asian Infectious Diseases Clinical Research Network, Eijkman-Oxford Clinical Research Unit, Jakarta, Indonesia; Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom

Abstract. An otherwise healthy 20-year-old woman in Goa, India, received antibiotics after a diagnosis of upper respiratory tract infection. One week later, vivax malaria was diagnosed at a health center, but the patient developed respiratory distress and lost consciousness. She arrived at emergency department in shock, breathless, and comatose. She died within minutes. Two independent laboratories later confirmed *Plasmodium vivax* by microscopy (140,000/μL) and by nested and real-time polymerase chain reaction methods. Post-mortem examination showed congestion of alveolar capillaries by heavy monocytic infiltrates, along with diffuse damage to alveolar membranes consistent with acute respiratory distress syndrome. Parasites seen in lung tissue were roughly proportionate to both peripheral hyperparasitemia and those seen in other organs without lesions. In this patient, vivax malaria caused a rapidly fatal respiratory distress.

Plasmodium vivax : neglected burden

- 70 – 80 M cases/year
- 80 – 90 % in Asia-Pacific
- 10 – 20 % in Africa (East)
- 110 – 15 % in America
- 40 % of all malaria cases in the world
- > 50 % of all malaria cases out of Africa

Multidrug-Resistant *Plasmodium vivax* Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia

Emiliana Tjitra[1], Nicholas M. Anstey[2], Paulus Sugiarto[3], Noah Warikar[4,5], Enny Kenangalem[4,6], Muhammad Karyana[1], Daniel A. Lampah[4,6], Ric N. Price[2,7]*

1 National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia, 2 International Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia, 3 Mitra Masyarakat Hospital, Timika, Papua, Indonesia, 4 Menzies School of Health Research-National Institute of Health Research and Development Malaria Research Program, Timika, Indonesia, 5 International SOS, Tembagapura, Papua, Indonesia, 6 District Health Authority, Timika, Papua, Indonesia, 7 Centre for Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom

PLoS Medicine 2008, 5:e128

Severe malaria

- 71 % by P. falciparum
  21 % by P. vivax
  5 % by mixed

(N = 2634)	(N = 590)
23 % of PV	- 8,8 % of PV
20 % of PF	- 11,7 % of PF
31 % of mixed	- 17,3 % of mixed

Most < 5 years old

Deaths associated with P. vivax

- Case fatality rate among inpatients
  - P. vivax 1.6 % (46/2,916)
  - P. falciparum 2.2 % (167/7,722)
  - Mixed 2.3 % (29/1,260)

Plasmodium vivax and Mixed Infections Are Associated with Severe Malaria in Children: A Prospective Cohort Study from Papua New Guinea

Blaise Genton[1*], Valérie D'Acremont[1], Lawrence Rare[2], Kay Baea[2], John C. Reeder[2], Michael P. Alpers[2], Ivo Müller[2]
1 Swiss Tropical Institute, Basel, Switzerland, 2 Papua New Guinea (PNG) Institute of Medical Research (IMR), Goroka, Papua New Guinea

PLoS Medicine 2008, 5:e127

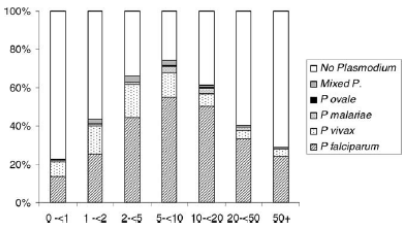


Figure 1. Age-Specific Prevalence of Parasitaemia among Presumptive Malaria Cases
doi:10.1371/journal.pmed.0050127.g001

PLoS Medicine 2008, 5:e127

Plasmodium vivax in pregnancy

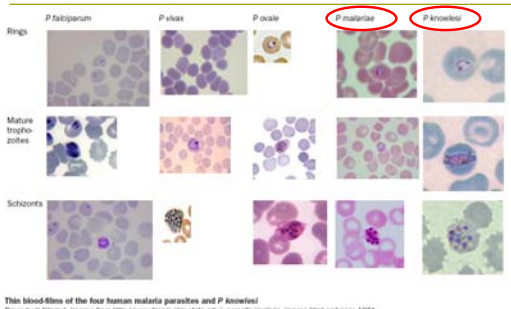
- No documented sequestration
- Unclear if it is more frequent or severe in pregnancy
- Thailand : increased anemia (OR 1-9; CI 1.4-2.6, p<0.001) and decrease in birth weight of 107 gr (95 % CI 61-154)
- Papua : increased anemia (OR 1.8; CI 1.2-2.9; P = 0.1) and decrease in birth weight of 108 gr (95 % CI, 17-199)

Nosten et al. Lancet 1999; Poespoprodjo et al. Clin Infect Dis 2008
Martinez-Espinosa et al. Mem Inst Oswaldo Cruz 2004

Conclusions

- There is a sizeable proportion of severe malaria due to vivax malaria
  - 1/5 of all severe malaria are due to P. vivax in PNG
  - 1 /4 of all severe malaria are due to P. vivax in Papua
- The proportion of severe malaria in mixed Plasmodium infections is higher than in P. vivax or P. falciparum

Severe malaria caused by Plasmodium knowlesi

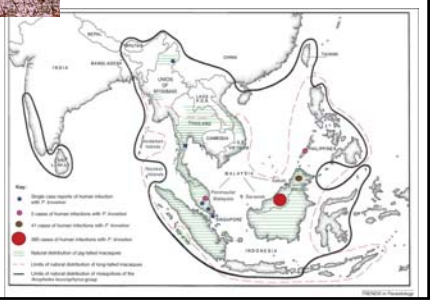


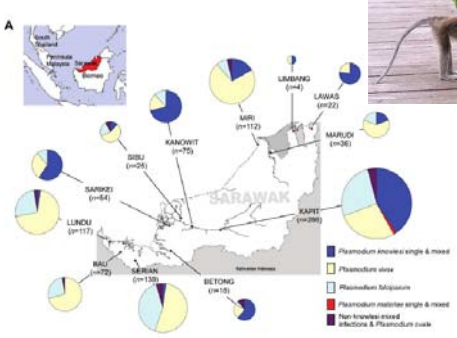
Thin blood-films of the four human malaria parasites and *P knowlesi*
Figure by K Silamut, images from http://www.bioci.ohio-state.edu/~parasite/malaria_images.html and page 1021.

P. knowlesi

= zoonosis

Trends Parasitol 08





Thailand, Myanmar, China

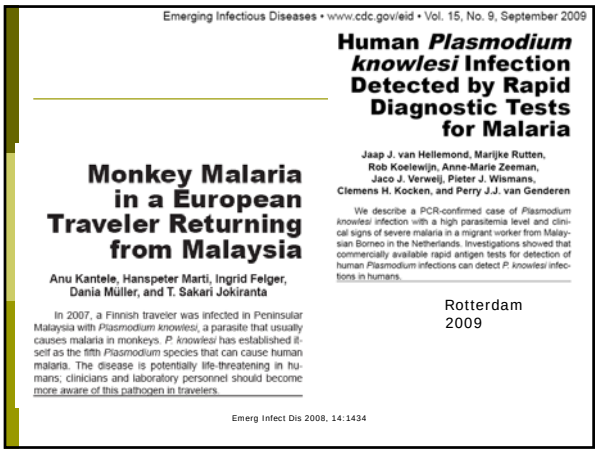
Clin Infect Dis 2008, 46:165-171

Plasmodium knowlesi Malaria in Humans Is Widely Distributed and Potentially Life Threatening

Results. *P. knowlesi* DNA was detected in 266 (27.7%) of 960 of the samples from Sarawak hospitals, 41 (83.7%) of 49 from Sabah, and all 5 from Pahang. Only *P. knowlesi* DNA was detected in archival blood films from the 4 patients who died. All were hyperparasitemic and developed marked hepatorenal dysfunction.

Conclusions. Human infection with *P. knowlesi*, commonly misidentified as the more benign *P. malariae*, are widely distributed across Malaysian Borneo and extend to Peninsular Malaysia. Because *P. knowlesi* replicates every 24 h, rapid diagnosis and prompt effective treatment are essential. In the absence of a specific routine diagnostic test for *P. knowlesi* malaria, we recommend that patients who reside in or have traveled to Southeast Asia and who have received a "*P. malariae*" hyperparasitemia diagnosis by microscopy receive intensive management as appropriate for severe falciparum malaria.

Clin Infect Dis 2008, 46:165-171



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 9, September 2009

Monkey Malaria in a European Traveler Returning from Malaysia

Anu Kantele, Hanspeter Marti, Ingrid Felger, Dania Müller, and T. Sakari Jokiranta

In 2007, a Finnish traveler was infected in Peninsular Malaysia with *Plasmodium knowlesi*, a parasite that usually causes malaria in monkeys. *P. knowlesi* has established itself as the fifth *Plasmodium* species that can cause human malaria. The disease is potentially life-threatening in humans; clinicians and laboratory personnel should become more aware of this pathogen in travelers.

Human *Plasmodium knowlesi* Infection Detected by Rapid Diagnostic Tests for Malaria

Jaap J. van Hellemond, Marijke Rutten, Rob Koelewijn, Anne-Marie Zeeman, Jaco J. Verweij, Pieter J. Wismans, Clemens H. Kocken, and Perry J.J. van Genderen

We describe a PCR-confirmed case of *Plasmodium knowlesi* infection with a high parasitemia level and clinical signs of severe malaria in a migrant worker from Malaysian Borneo in the Netherlands. Investigations showed that commercially available rapid antigen tests for detection of human *Plasmodium* infections can detect *P. knowlesi* infections in humans.

Rotterdam 2009

Emerg Infect Dis 2008, 14:1434

Implications for travelers

- Patients who
  - have traveled to Southeast Asia, especially in the forest areas,
  - and receive a diagnosis of P. malariae hyperparasitemia by microscopy

  should be managed similarly to severe falciparum malaria

Repellents – Pros and cons

Repellent	Advantages	Disadvantages
DEET	Widely used and tested, effective 20 % protects for > 5 hours	May damage fabrics and plastics
Bayrepel® Picaridin KBR 3023	19,2 % preparation similar Protection to DEET Best against An gambiae Less irritating than DEET	Inter-individual variation
EBAAP IR3535	Mean protection 23 minutes Good cosmetic properties	Variation in efficacy
PMD Eucalyptys Citriodora	96 % protection for up to 4 hours Plant based repellent Well tolerated	Inter-individual variation
Natural Oils	« Bio » - High acceptance	(very) short protection duration

Biting times – Important for long-term travel

- An. Gambiae (Africa) – late night indoor feeder – **nets ideal**
- An. Darlingi (Amazon) – early evening biting – peaks 20 and 22.00 – **repellents essential**

Seasonal prophylaxis ?

- Little to no data available
- Unpredictable conditions in many areas
- Possibility for Namibia, Botswana, South Africa
- Seek local advice after 6 months

MEFLOQUINE RESISTANCE

CDC 2004

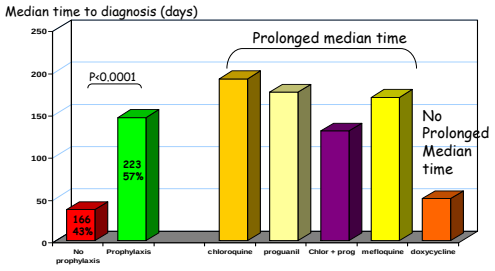
CDC 2007-8

1 - Malaria

Vervolg / suite

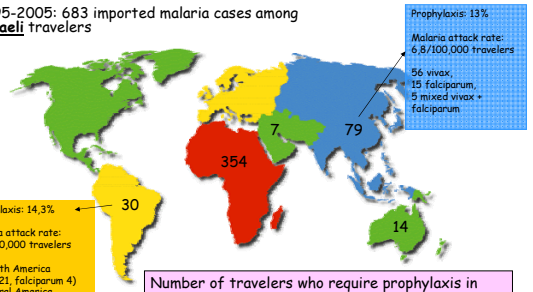
Prevention of vivax malaria: impact of chemoprophylaxis

- 1987-2007: 389 episodes of imported laboratory confirmed *P. vivax* following short-term travel (<2 months). Median time to diagnosis 115days (IQR 22-259)



Very low risk of malaria in Latin America and Asia

1995-2005: 683 imported malaria cases among **Israeli** travelers



Number of travelers who require prophylaxis in order to prevent 1 case of *P. falciparum* malaria
Asia: 50,000Latin America: 110,000

Imported malaria : changing epidemiology in Asia and Latin America

- Malaria endemicity has decreased
- Travel has increased 200-2007
  - Asia & Pacific 109.3 M to 184.3 M
  - Americas 36.7 M to 47.1 M
- Imported malaria has slightly decreased in most countries
- < 20 % Imported from outside Africa
  - Asia : 7 – 16 %
  - Latin America : 2 - 9 %

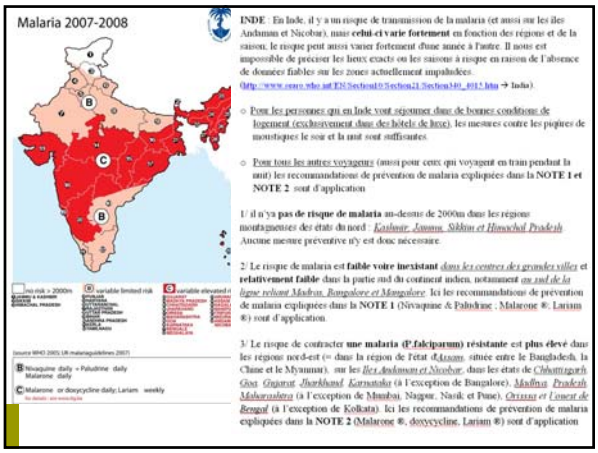
MMWR EEUU, 2006 - BEF France, 2006
HPR UK, 2008 - Smith AD, BMJ 2008 - Milet JP, Mai J 2008

Low risk of malaria in travelers to India

- **1992-2005: imported malaria into 9 countries from India**
  - Decline in number of malaria cases despite constantly increasing travelers numbers :
    93 (1992) → **19** /100,000 travelers (2005)
  - *P. vivax* > 80%, *P. falciparum*: 5-12%,
  - Deaths: 16 deaths
  - High risk: East part of India

- **1999-2004: imported malaria into 8 European countries from Indian subcontinent** (India, Pakistan, Bangladesh, Sri Lanka)
  - Total malaria fell from **317** (1999) to **180** (2004).
  - Only 13% of *P. falciparum*.
  - Risk of malaria <1/1000 per visitor

Non-selective prescribing of chemoprophylaxis for visitors to India, Pakistan, Bangladesh and Sri Lanka should be stopped



INDE : En Inde, il y a un risque de transmission de la malaria (et aussi sur les îles Andaman et Nicobar), mais celui-ci varie fortement en fonction des régions et de la saison. le risque peut aussi varier fortement d'une année à l'autre. Il nous est impossible de préciser les lieux exacts ou les saisons à risque en raison de l'absence de données fiables sur les zones actuellement inpaludées.
(http://www.euro.who.int/EN/Section40/Section21/Section340_4012.htm → India).

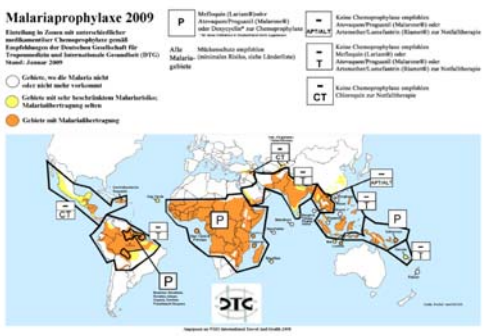
- Pour les personnes qui en Inde vont séjourner dans de bonnes conditions de logement (exclusivement dans des hôtels de luxe), les mesures contre les piqûres de moustiques le soir et la nuit sont suffisantes.
- Pour tous les autres voyageurs (aussi pour ceux qui voyagent en train pendant la nuit) les recommandations de prévention de malaria expliquées dans la **NOTE 1 et NOTE 2** sont d'application

1/ il n'y a **pas de risque de malaria** au-dessus de 2000m dans les régions montagneuses des états du nord : *Kashmir, Jammu, Sikkim et Himachal Pradesh*
Aucune mesure préventive n'y est donc nécessaire.

2/ Le risque de malaria est **faible voire inexistant** *dans les centres des grandes villes* et **relativement faible** dans la partie sud du continent indien, notamment *au sud de la ligne reliant Madras, Bangalore et Mangalore*. Ici les recommandations de prévention de malaria expliquées dans la **NOTE 1** (Nivaquine & Paludrine ; Malarone ®, Lariam ®) sont d'application.

3/ Le risque de contracter **une malaria (P.falciparum) résistante** est **plus élevé** dans les régions nord-est (= dans la région de l'état d'*Assam*, située entre le Bangladesh, la Chine et le Myanmar), ou les *îles Andaman et Nicobar*, dans les états de *Chhattisgarh, Goa, Gujarat, Jharkhand, Karnataka* (à l'exception de Bangalore), *Madhya Pradesh, Maharashtra* (à l'exception de Mumbai, Nagpur, Nasik et Pune), *Orissa* et *l'ouest de Bengal* (à l'exception de Kolkata). Ici les recommandations de prévention de malaria expliquées dans la **NOTE 2** (Malarone ®, doxycycline, Lariam ®) sont d'application

After stop chemoprophylaxis no increase in malaria coming from Asia & Latin America



After stop chemoprophylaxis no increase in malaria coming from Asia & Latin America

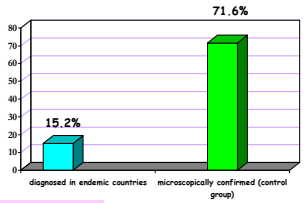
PO01.07
Imported Malaria in Germany 1993 until 2005
K.-H. Herbinger[1], *T. Stingl*[1], *I. Schoeneberg*[2], *D. Altmann*[2], *G. Krause*[2], *H.D. Nothdurft*[1]
[1]University of Munich, Tropical Medicine and Infectious Diseases, Munich, Germany, [2]Robert-Koch-Institute, Berlin, Germany

Background: Germany is the country with the third largest number of reported imported malaria cases in the European region. This study investigated the course of imported malaria from 1993 to 2005 and tries to assess possible impacts of a changed concept of malaria prevention launched in the year 2000.
Method: Data of reported imported malaria between 1993 and 2005 were received from the Robert Koch Institut Berlin. Data on travel frequency from Germany to malaria - endemic countries were received from the Federal Agency for Statistics. Both data were put into relation revealing the incidence of imported malaria per 100,000 travellers per year for selected, frequently visited regions from 1993 to 2005.
Result: No significant increase or decrease of imported malaria cases[IS1] has been recorded from 1993 to 2005. The number of travellers to malaria - endemic countries strongly increased in the vast majority of regions in the same time. Highest malaria incidence rates were found in returnees from West Africa. The incidence of imported malaria per 100,000 travellers per year decreased remarkably over the the years in most of the investigated regions.
Conclusion: With a total 10,490 reported malaria cases and a rate of 800 cases on average per year during the study period 1993 to 2005 malaria remains an important traveller's disease in Germany. The course of the absolute number of malaria imports over the study period remained stable inspite of a strongly increased number of travel frequency. After the year 2000 when the new standby-concept of malaria prevention has been introduced no negative impacts on the number of malaria imports have been recorded. This new concept should be continued weighing the risk of adverse effects of antimalarials against the risk of contracting malaria.

Validity of malaria diagnosis in non-immune travelers in endemic areas

- Sera of 105 non-immune travelers with malaria diagnosed and treated during a stay in endemic countries within the previous 6 months

Antibodies against *P. falciparum* and *vivax* (indirect IF)

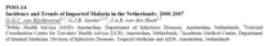


→ Diagnosis of malaria during travel in endemic areas is frequently incorrect

Decline in imported malaria

- Germany: reported imported malaria cases
  - 10,490 cases from 1993 to 2005 (800/y).
  - Highest rates from West Africa
  - Incidence per year decreased remarkably over the years in most of the regions
  - 2000: new stanby-concept of malaria prevention (but chemoprophylaxis still considered in high transmission seasons)
  - No negative impact of the standby concept

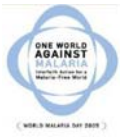
- Netherlands 2000-2007
  - 535 (2000) → 197/y (2007) malaria cases
  - Travelers to endemic countries: 477.000 (2000) → 747.000 (2007)
  - 73% from Sub-Saharan Africa.
  - Prophylaxis: 28% → 44%
    - absolute number of unprotected: 345.000 → 419.000



Malaria decline in Africa: fact or fiction?

- Effective treatment, insecticide-treated nets
- Substantial decline of malaria transmission, morbidity and mortality in more than 15 African countries (also in areas of previously high level of transmission)
  - Children 2-10y: decline from 37% (1985-1999) to 17% (2000-2007)
  - Many areas previously defined as « high stable malaria transmission » → « moderate to low transmission areas »

→ For travelers: shift from chemoprophylaxis to stand-by treatment



D'Acremont, Switzerland SY 07.01

Artemisine resistance in Cambodia

- 2 open randomized trials in uncomplicated falciparum malaria in Pailin (Western Cambodia) and Wang Pha (Northwestern Thailand)
- Children >5y and non-pregnant adults with non complicated

Oral artesumate
2 mg/kg/d for 7 days

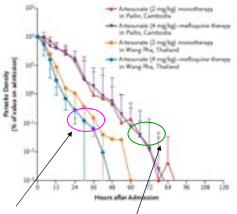
Oral artesumate
4mg/kg/d for 3 days
followed by
mefloquine at 2 doses
totaling 25mg/kg

40 patients in each of the location

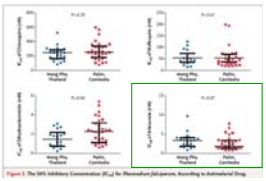
Dondorp NEJM 2009; 361, 455-467

Artemisine resistance in Cambodia

Parasite clearance curve



In vitro sensitivity testing

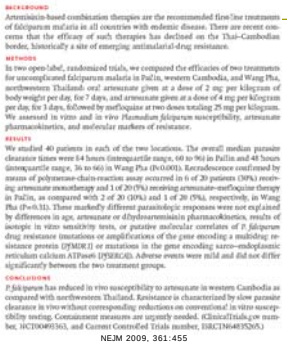


Thailand

Cambodia

Emergence of resistance of P. falciparum
to artesunate in Cambodia
‹ use of artemisine as monotherapy in Cambodia
(combined with mefloquine in Thailand) ?

Artemisinin Resistance in *Plasmodium falciparum* Malaria



BACKGROUND

Artemisinin-based combination therapies are the recommended first-line treatments of falciparum malaria in all countries with endemic disease. There are recent concerns that the efficacy of such therapies has declined on the Thai–Cambodian border, historically a site of emerging antimalarial-drug resistance.

METHODS

In two open-label, randomized trials, we compared the efficacies of two treatments for uncomplicated falciparum malaria in Pailin, western Cambodia, and Wang Pha, northwestern Thailand: oral artesunate given at a dose of 2 mg per kilogram of body weight per day, for 7 days, and artesunate given at a dose of 4 mg per kilogram per day, for 3 days, followed by mefloquine at two doses totaling 25 mg per kilogram. We assessed in vitro and in vivo *Plasmodium falciparum* susceptibility, artesunate pharmacokinetics, and molecular markers of resistance.

RESULTS

We studied 40 patients in each of the two locations. The overall median parasite clearance times were 64 hours (interquartile range, 60 to 96) in Pailin and 48 hours (interquartile range, 36 to 66) in Wang Pha ($P<0.001$). Recrudescence confirmed by means of polymerase-chain-reaction assay occurred in 6 of 20 patients (30%) receiving artesunate monotherapy and 1 of 20 (5%) receiving artesunate–mefloquine therapy in Pailin, as compared with 2 of 20 (10%) and 1 of 20 (5%), respectively, in Wang Pha ($P=0.31$). These markedly different parasitologic responses were not explained by differences in age, artesunate or dihydroartemisinin pharmacokinetics, results of isotopic in vitro sensitivity tests, or putative molecular correlates of *P. falciparum* drug resistance (mutations or amplifications of the gene encoding a multidrug resistance protein [PfMDR1] or mutations in the gene encoding sarco–endoplasmic reticulum calcium ATPase6 [PfSERCA]). Adverse events were mild and did not differ significantly between the two treatment groups.

CONCLUSIONS

P. falciparum has reduced in vivo susceptibility to artesunate in western Cambodia as compared with northwestern Thailand. Resistance is characterized by slow parasite clearance in vivo without corresponding reductions on conventional in vitro susceptibility testing. Containment measures are urgently needed. (ClinicalTrials.gov number, NCT00493363, and Current Controlled Trials number, ISRCTN64835265.)

NEJM 2009; 361:455

Slowing of parasitological response

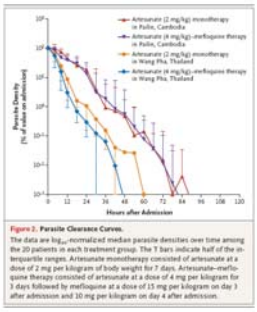


Figure 2. Parasite Clearance Curves.
The data are $\log_{10}$-normalized median parasite densities over time among the 20 patients in each treatment group. The T bars indicate half of the interquartile ranges. Artesunate monotherapy consisted of artesunate at a dose of 2 mg per kilogram of body weight for 7 days. Artesunate–mefloquine therapy consisted of artesunate at a dose of 4 mg per kilogram for 3 days followed by mefloquine at a dose of 15 mg per kilogram on day 3 after admission and 10 mg per kilogram on day 4 after admission.

NEJM 2009, 361:455

Declining Artesunate-Mefloquine Efficacy against Falciparum Malaria on the Cambodia–Thailand Border

Chansuda Wongsrichanalai* and Steven R. Meshnick†

Figure. Map of the Cambodia–Thailand border showing the town of Pailin, Cambodia, and the provinces of Chanthaburi and Trat, Thailand; the areas are collectively known as the epicenter of drug-resistant malaria.

Emerg Infect Dis 2008, 14:716

Declining Artesunate-Mefloquine Efficacy against Falciparum Malaria on the Cambodia–Thailand Border

Chansuda Wongsrichanalai* and Steven R. Meshnick†

Table. Studies that demonstrated poor artesunate-mefloquine efficacy, Cambodia–Thailand border*

Reference	Study site, country, y	ACT	No. patients	Follow-up duration, d	Efficacy, %
Denis et al., 2006 (5)	Pailin, Cambodia, 2002	ATS ≈12 mg/kg in 2 doses on days 0, 1, and 2 + MFQ ≈20 mg/kg in 2 doses on day 0	70 children and adults	28	85.7 (PCR-corrected)
Vijaykadga et al., 2006 (6)	Trat, Thailand, 2003	ATS 12 mg/kg (maximum 600 mg) in 2 doses on days 0 and 1 + MFQ 25 mg/kg (maximum 1,250 mg) in 2 doses on day 0	44, age ≥10 y, mostly adults	28	78.6
Denis et al., 2006 (5)†	Pailin, Cambodia, 2004	ATS 12 mg/kg in 2 doses on days 0, 1, and 2 + MFQ 25 mg/kg in 2 doses on day 0	58 children and adults	42	79.3 (PCR-corrected)

*ACT, artemisinin-based combination therapy; ATS, artesunate; MFQ, mefloquine; day 0, first 24 h of enrollment and start of therapy.
†Also in this study, increased copy numbers of *Plasmodium falciparum* multidrug resistance 1 gene were found to be associated with parasite recrudescence, and as many as 44% of patients did not clear parasites until after 48 hours.

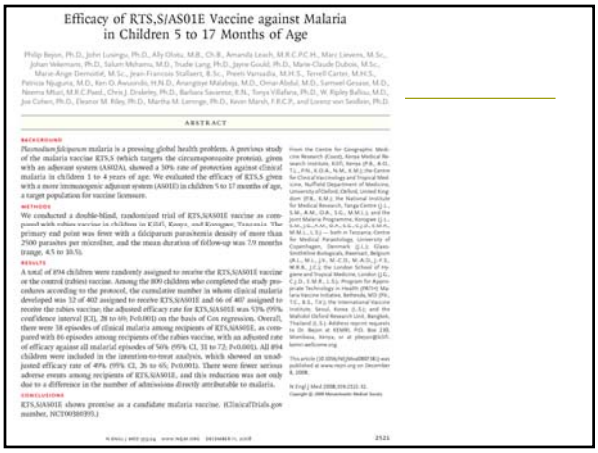
Emerg Infect Dis 2008, 14:717

NB - Malaria

Proguanil will not be available anymore

Malaria vaccine

- No role in travel medicine
- Explanation of adjuvant systems



Efficacy of RTS,S/AS01E Vaccine against Malaria in Children 5 to 17 Months of Age

ABSTRACT

Safety and Immunogenicity of RTS,S/AS02D Malaria Vaccine in Infants

Salim Abdulla, M.D., Ph.D., Rolf Oberholzer, M.D., Omar Juma, M.D., Sulende Kubhoja, M.D., M.M.E.D., Francisca Machera, A.M.D., Christopher Membi, A.D.M.L.S., Said Omari, D.M.L.T., Rivera Urassa, B.P.A., Hassan Mshinda, Ph.D., Ajuza Jumanne, M.D., Nahya Salim, M.D., M.M.E.D., Mwanjia Shomari, B.Sc., Thomas Aello, M.D., David M. Schellenberg, M.D., Ph.D., Terrell Carter, M.H.S., Tonya Villafana, Ph.D., M.P.H., Marie-Ange Demoitié, M.Sc., Marie-Claude Dubois, M.Sc., Amanda Leach, M.R.C.P.C.H., Marc Lievens, M.Sc., Johan Vekemans, M.D., Ph.D., Joe Cohen, Ph.D., W. Ripley Ballou, M.D., and Marcel Tanner, Ph.D., M.P.H.

ABSTRACT

BACKGROUND

The RTS,S/AS malaria vaccine is being developed for delivery through the World Health Organization's Expanded Program on Immunization (EPI). We assessed the feasibility of integrating RTS,S/AS02D into a standard EPI schedule for infants.

METHODS

In this phase 2b, single-center, double-blind, controlled trial involving 340 infants in Bagamoyo, Tanzania, we randomly assigned 340 infants to receive three doses of either the RTS,S/AS02D vaccine or the hepatitis B vaccine at 0, 12, and 16 weeks of age. All infants also received a vaccine containing diphtheria and tetanus toxoids, whole-cell pertussis vaccine, and conjugated *Haemophilus influenzae* type b vaccine (DTP-Hib). The primary objectives were the occurrence of serious adverse events during a 9-month surveillance period and a demonstration of noninferiority of the responses to the EPI vaccines (DTPwHBV and hepatitis B surface antigen) with coadministration of the RTS,S/AS02D vaccine, as compared with the hepatitis B vaccine. The detection of antibodies against *Plasmodium falciparum* circumsporozoite and efficacy against malaria infection were secondary objectives.

RESULTS

At least one serious adverse event was reported in 31 of 170 infants who received the RTS,S/AS02D vaccine (18.2%; 95% confidence interval [CI], 12.7 to 24.9) and in 42 of 170 infants who received the hepatitis B vaccine (24.7%; 95% CI, 18.4 to 31.9). The results showed the noninferiority of the RTS,S/AS02D vaccine in terms of antibody responses to EPI antigens. One month after vaccination, 98.0% of infants receiving the RTS,S/AS02D vaccine had seropositive titers for anticircumsporozoite antibodies on enzyme-linked immunosorbent assay (ELISA). During the 6-month period after the third dose of vaccine, the efficacy of the RTS,S/AS02D vaccine against first infection with *P. falciparum* malaria was 65.2% (99% CI, 20.7 to 84.3; P=0.01).

CONCLUSIONS

The use of the RTS,S/AS02D vaccine in infants had a promising safety profile, did not interfere with the immunologic responses to coadministered EPI antigens, and reduced the incidence of malaria infection. (ClinicalTrials.gov number, NCT00269191.)

EDITORIALS

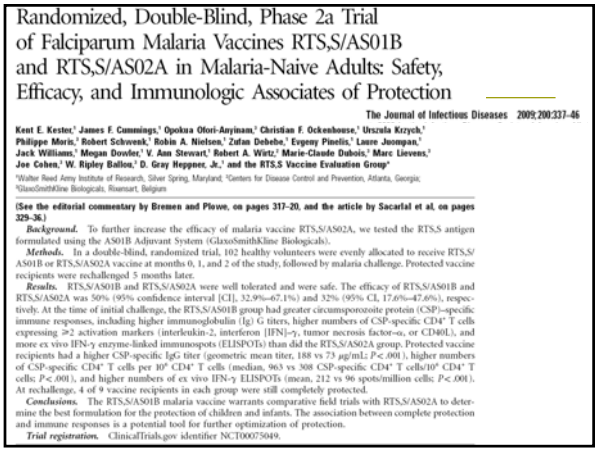
A Hopeful Beginning for Malaria Vaccines

William E. Collins, Ph.D., and John W. Barnwell, M.D.Int., Ph.D.

From the Bagamoyo Research and Training Centre of Ifakara Health Institute, Bagamoyo, Tanzania (S.A., R.O., O.J., F.M., T.M., S.O., A.U., H.M., A.J., N.S., M.S., T.A., D.M.S., M.T.); Swiss Tropical Institute, Basel, Switzerland (R.O., T.A., M.T.); University of Health and Allied Sciences, Ho, Ghana (S.K.); and London School of Hygiene and Tropical Medicine, London (D.M.S.); Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, Bethesda, MD (T.C., T.V.); GlaxoSmithKline Biologicals, Rixensart, Belgium (M.-A.D., M.-C.D., A.L., M.L., J.V., J.C.); and Bill and Melinda Gates Foundation, Seattle (W.R.B.). Address reprint requests to Dr. Abdulla at the Bagamoyo Research and Training Centre, Ifakara Health Institute, Box 74, Bagamoyo, Tanzania, or at sabdulla@ihi.or.tz.

This article (10.1056/NEJMe048277) was published at www.nejm.org on December 8, 2004.

N Engl J Med 2004;351:2333-44



Randomized, Double-Blind, Phase 2a Trial of Falciparum Malaria Vaccines RTS,S/AS01B and RTS,S/AS02A in Malaria-Naive Adults: Safety, Efficacy, and Immunologic Associates of Protection

The Journal of Infectious Diseases 2009;200:337–46

Kent E. Kester,[1] James F. Cummings,[1] Opokua Ofori-Anyinam,[2] Christian F. Ockenhouse,[1] Urszula Krzych,[1] Philippe Moris,[2] Robert Schwenk,[1] Robin A. Nielsen,[1] Zufan Debebe,[1] Evgeny Pinelis,[1] Laure Juompan,[1] Jack Williams,[1] Megan Dowler,[1] V. Ann Stewart,[1] Robert A. Wirtz,[3] Marie-Claude Dubois,[2] Marc Lievens,[2] Joe Cohen,[2] W. Ripley Ballou,[1] D. Gray Heppner, Jr.,[1] and the RTS,S Vaccine Evaluation Group[4]

[1]Walter Reed Army Institute of Research, Silver Spring, Maryland; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]GlaxoSmithKline Biologicals, Rixensart, Belgium

(See the editorial commentary by Bremen and Plowe, on pages 317–20, and the article by Sacarlal et al, on pages 329–36.)

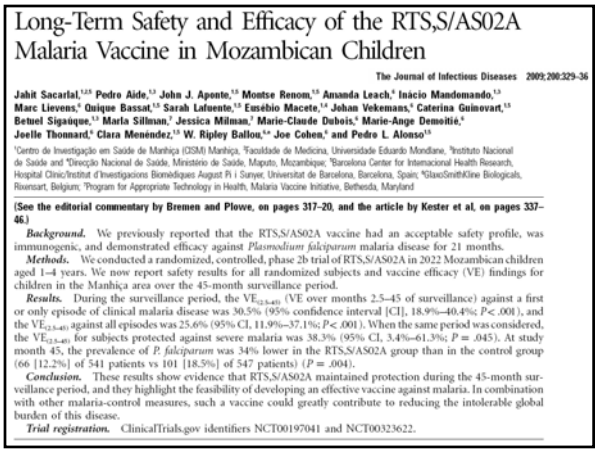
Background. To further increase the efficacy of malaria vaccine RTS,S/AS02A, we tested the RTS,S antigen formulated using the AS01B Adjuvant System (GlaxoSmithKline Biologicals).

Methods. In a double-blind, randomized trial, 102 healthy volunteers were evenly allocated to receive RTS,S/AS01B or RTS,S/AS02A vaccine at months 0, 1, and 2 of the study, followed by malaria challenge. Protected vaccine recipients were rechallenged 5 months later.

Results. RTS,S/AS01B and RTS,S/AS02A were well tolerated and were safe. The efficacy of RTS,S/AS01B and RTS,S/AS02A was 50% (95% confidence interval [CI], 32.9%–67.1%) and 32% (95% CI, 17.6%–47.6%), respectively. At the time of initial challenge, the RTS,S/AS01B group had greater circumsporozoite protein (CSP)–specific immune responses, including higher immunoglobulin (Ig) G titers, higher numbers of CSP-specific $CD4^+$ T cells expressing ≥ 2 activation markers (interleukin-2, interferon [IFN]-γ, tumor necrosis factor–α, or CD40L), and more ex vivo IFN-γ enzyme-linked immunospots (ELISPOTs) than did the RTS,S/AS02A group. Protected vaccine recipients had a higher CSP-specific IgG titer (geometric mean titer, 188 vs 73 μg/mL; $P < .001$), higher numbers of CSP-specific $CD4^+$ T cells per 10^6 $CD4^+$ T cells (median, 963 vs 308 CSP-specific $CD4^+$ T cells/10^6 $CD4^+$ T cells; $P < .001$), and higher numbers of ex vivo IFN-γ ELISPOTs (mean, 212 vs 96 spots/million cells; $P < .001$). At rechallenge, 4 of 9 vaccine recipients in each group were still completely protected.

Conclusions. The RTS,S/AS01B malaria vaccine warrants comparative field trials with RTS,S/AS02A to determine the best formulation for the protection of children and infants. The association between complete protection and immune responses is a potential tool for further optimization of protection.

Trial registration. ClinicalTrials.gov identifier NCT00075049.



Long-Term Safety and Efficacy of the RTS,S/AS02A Malaria Vaccine in Mozambican Children

The Journal of Infectious Diseases 2009;200:329–36

Jahit Sacarlal,[1,2,5] Pedro Aide,[1,3] John J. Aponte,[1,6] Montse Renom,[1,5] Amanda Leach,[4] Inácio Mandomando,[1,3] Marc Lievens,[4] Quique Bassat,[1,5] Sarah Lafuente,[1,5] Eusébio Macete,[1,4] Johan Vekemans,[4] Caterina Guinovart,[1,5] Betuel Sigaúque,[1,3] Marla Sillman,[7] Jessica Milman,[7] Marie-Claude Dubois,[4] Marie-Ange Demoitié,[4] Joelle Thonnard,[4] Clara Menéndez,[1,5] W. Ripley Ballou,[4,*] Joe Cohen,[4] and Pedro L. Alonso[1,5]

[1]Centro de Investigação em Saúde de Manhiça (CISM) Manhiça, [2]Faculdade de Medicina, Universidade Eduardo Mondlane, [3]Instituto Nacional de Saúde and [4]Direcção Nacional de Saúde, Ministério de Saúde, Maputo, Mozambique; [5]Barcelona Center for International Health Research, Hospital Clínic/Institut d'Investigacions Biomèdiques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain; [6]GlaxoSmithKline Biologicals, Rixensart, Belgium; [7]Program for Appropriate Technology in Health, Malaria Vaccine Initiative, Bethesda, Maryland

(See the editorial commentary by Bremen and Plowe, on pages 317–20, and the article by Kester et al, on pages 337–46.)

Background. We previously reported that the RTS,S/AS02A vaccine had an acceptable safety profile, was immunogenic, and demonstrated efficacy against *Plasmodium falciparum* malaria disease for 21 months.

Methods. We conducted a randomized, controlled, phase 2b trial of RTS,S/AS02A in 2022 Mozambican children aged 1–4 years. We now report safety results for all randomized subjects and vaccine efficacy (VE) findings for children in the Manhiça area over the 45-month surveillance period.

Results. During the surveillance period, the $VE_{0.5\text{-}45}$ (VE over months 2.5–45 of surveillance) against a first or only episode of clinical malaria disease was 30.5% (95% confidence interval [CI], 18.9%–40.4%; $P < .001$), and the $VE_{2.5\text{-}45}$ against all episodes was 25.6% (95% CI, 11.9%–37.1%; $P < .001$). When the same period was considered, the $VE_{2.5\text{-}45}$ for subjects protected against severe malaria was 38.3% (95% CI, 3.4%–61.3%; $P = .045$). At study month 45, the prevalence of *P. falciparum* was 34% lower in the RTS,S/AS02A group than in the control group (66 [12.2%] of 541 patients vs 101 [18.5%] of 547 patients) ($P = .004$).

Conclusion. These results show evidence that RTS,S/AS02A maintained protection during the 45-month surveillance period, and they highlight the feasibility of developing an effective vaccine against malaria. In combination with other malaria-control measures, such a vaccine could greatly contribute to reducing the intolerable global burden of this disease.

Trial registration. ClinicalTrials.gov identifiers NCT00197041 and NCT00323622.

Protection against a Malaria Challenge by Sporozoite Inoculation

Meta Roestenberg, M.D., Matthew McCall, M.D., Joost Hopman, M.D., Jonien Wiersma, Adrian J.F. Luty, Ph.D., Geert Jan van Gemert, B.Sc., Marga van de Vegte-Bolmer, B.Sc., Ben van Schaijk, M.Sc., Karina Teelen, Theo Arens, Lopke Spaarman, B.Sc., Quirijn de Mast, M.D., Will Roeffen, Ph.D., Georges Snounou, Ph.D., Laurent Rénia, Ph.D., Andre van der Ven, M.D., Cornelus C. Hermsen, Ph.D., and Robert Sauerwein, M.D.

ABSTRACT

BACKGROUND

An effective vaccine for malaria is urgently needed. Naturally acquired immunity to malaria develops slowly, and induction of protection in humans can be achieved artificially by the inoculation of radiation-attenuated sporozoites by means of more than 1000 infective mosquito bites.

METHODS

We exposed 15 healthy volunteers — with 10 assigned to a vaccine group and 5 assigned to a control group — to bites of mosquitoes once a month for 3 months while they were receiving a prophylactic regimen of chloroquine. The vaccine group was exposed to mosquitoes that were infected with *Plasmodium falciparum*, and the control group was exposed to mosquitoes that were not infected with the malaria parasite. One month after the discontinuation of chloroquine, protection was assessed by homologous challenge with five mosquitoes infected with *P. falciparum*. We assessed humoral and cellular responses before vaccination and before the challenge to investigate correlates of protection.

NEJM 2009, 361:468

RESULTS

All 10 subjects in the vaccine group were protected against a malaria challenge with the infected mosquitoes. In contrast, patent parasitemia (i.e., parasites found in the blood on microscopical examination) developed in all five control subjects. Adverse events were mainly reported by vaccinees after the first immunization and by control subjects after the challenge; no serious adverse events occurred. In this model, we identified the induction of parasite-specific pluripotent effector memory T cells producing interferon-γ, tumor necrosis factor α, and interleukin-2 as a promising immunologic marker of protection.

CONCLUSIONS

Protection against a homologous malaria challenge can be induced by the inoculation of intact sporozoites. (ClinicalTrials.gov number, NCT00442377.)

NEJM 2009, 361:468

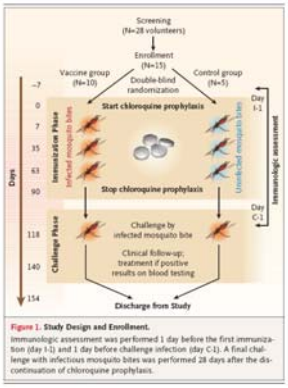


Figure 1. **Study Design and Enrollment.**
Immunologic assessment was performed 1 day before the first immunization (day I-1) and 1 day before challenge infection (day C-1). A final challenge with infectious mosquito bites was performed 28 days after the discontinuation of chloroquine prophylaxis.

NEJM 2009, 361:468

GSK - Adjuvant System

- Adjuvant system **AS01** = MPL and QS21 and liposomes
  - **AS01**-formulated vaccines : RTS,S/AS01 malaria vaccine
- Adjuvant system **AS02** = MPL and QS21 in o/w emulsion
  - **AS02**-formulated vaccines : RTS,S/AS02 malaria vaccine
- Adjuvant system **AS03** = Squaleen & Tocopherol in o/w emulsion & Tween
  - **AS03**-formulated vaccines : Pandemic & prepandemic flu vaccines
- Adjuvant system **AS04** = MPL® adsorbed on aluminum salt (alumunium hydroxide or aluminium phosphate, depending on the vaccine)
  - **AS04**-formulated vaccines : Fendrix ® & Cervarix ®

MPL = Monophosphoryl lipid A, derived from cell wall lipopolysaccharide LPS of *Salmonella Minnesota*

QS 21 = Extracted from the bark of a South American tree (***Quillaja saponaria***)

2- Vaccinations

Yellow Fever

CDC 2009 = WHO 2008

Evidence used for risk mapping

- Human and non-human primates : cases, clusters and outbreaks
- Human serology prior to YF vaccination : most data generated in 1950s and earlier
- Vegetation and altitude
- Vector distribution
- YF vaccination coverage

Historic knowledge of yellow fever distribution

- Determined largely from reports of clinically diagnosed YF cases
- Mild and atypical cases missed
- Confusion with other diaseses (e.g. malaria)
- No laboratory testing available
- No formal surveillance

Recommendations for improvement

- Human serosurveys not feasible
- Modern computer technology required
  - Sophisticated electronic mapping programs
  - Satellite imagery
  - Geographic information systems
- Regular updating
  - Human, monkey and mosquito surveillance data
  - Reflecting changes in ecology (global climate change)

2009

CISTM11, Budapest, Hungary, May 24 - 28, 2009

SY05.04 17:45 - 18:15 Defining Yellow Fever risk in endemic areas
David Hill, London, UK

New Categories of Yellow Fever Risk

• Endemic	Nigeria
• Transitional	East Paraguay
• Low risk	Tanzania, East Kenya, N Zambia
• No risk	
	Colombia = Mix

= near future

2009

CISTM11, Budapest, Hungary, May 24 - 28, 2009

SY05.04 17:45 - 18:15 Defining Yellow Fever risk in endemic areas
David Hill, London, UK

New Categories of Yellow Fever Risk: South America Examples

Colombia

- no risk: areas above 2,300 m
- low risk:
  - ✓ Pacific coast west of Andes
  - ✓ port cities: Cartagena, Barranquilla
- endemic: remainder of country

= near future

CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

SY05.04 Defining Yellow Fever risk in endemic areas
17:45 - 18:15 David Hill, London, UK

New Categories of Yellow Fever Risk: South America Examples

Paraguay

- no risk: western provinces
- transitional: eastern provinces

= near future

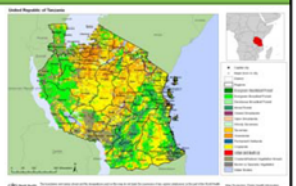
CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

SY05.04 Defining Yellow Fever risk in endemic areas
17:45 - 18:15 David Hill, London, UK

New Categories of Yellow Fever Risk: Africa Examples

Tanzania

- low risk



= near future

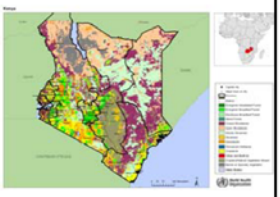
CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

SY05.04 Defining Yellow Fever risk in endemic areas
17:45 - 18:15 David Hill, London, UK

New Categories of Yellow Fever Risk: Africa Examples

Kenya

- low risk: North Eastern zone, Coastal zone and Nairobi
- endemic: remainder of country



= near future

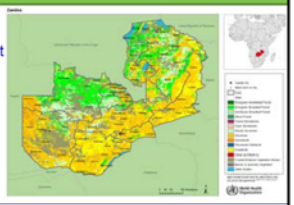
CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

SY05.04 Defining Yellow Fever risk in endemic areas
17:45 - 18:15 David Hill, London, UK

New Categories of Yellow Fever Risk: Africa Examples

Zambia

- low risk: North West and Western provinces
- no risk: remainder of country



= near future

CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

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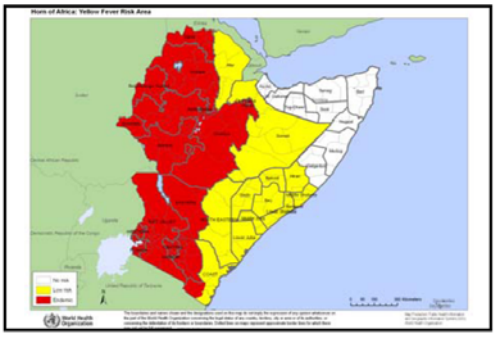
17:45 - 18:15 David Hill, London, UK



CISTM11, Budapest, Hungary, May 24 - 28, 2009 2009

SY05.04 Defining Yellow Fever risk in endemic areas
17:45 - 18:15 David Hill, London, UK

New Categories of Yellow Fever Risk

Practical Implications for Travel Medicine

- Travel to endemic or transitional areas?
  - ✓ vaccinate (≥ 9 months of age)
- Travel to low risk areas?
  - vaccinate only after individual risk assessment: age, duration, itinerary
  - usually longer term, rural exposure

= near future

Enteric Fever

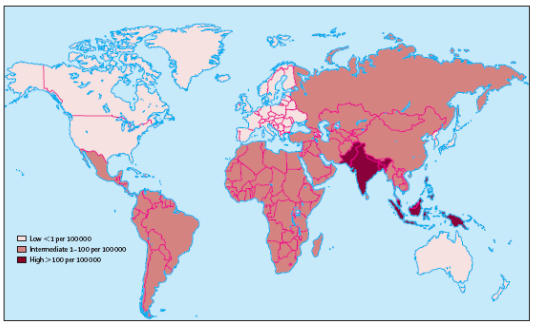


Figure 1: Annual incidence of enteric fever worldwide

Lancet Infect Dis 2005, 5:623-28

Antibiotic resistance among *Salmonella enterica* serovars Typhi and Paratyphi A in Pakistan (2001-2006)

Rumina Hasan[1], Afia Zafar[1], Zohair Abbas[2], Vikram Mahraj[1], Faisal Malik[1], Anita Zaidi[2]

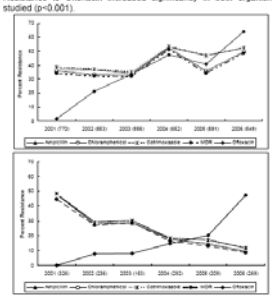
[1]*Departments of Pathology & Microbiology and* [2]*Pediatrics, Aga Khan University Hospitals, Karachi, Pakistan*

S. Typhi = 3671

S. Paratyphi A = 1475

J Infect Developping Countries 2008, 2:289-294

Figure 1. A (upper): Antimicrobial resistance; *S. enterica* serovar Typhi (2001-2006). B (lower): Antimicrobial resistance; *S. enterica* serovar Paratyphi A (2001-2006).
Resistance is expressed as a percentage of the total strains isolated per year. The number of strains tested per year is depicted; (n value). Resistance to individual first-line agents as well as MDR increased in *S. Typhi* ($p < 0.001$), but decreased in *S. Paratyphi* ($p < 0.001$). Resistance to Ofloxacin increased significantly in both organisms studied ($p < 0.001$).



J Infect Developinf Countries 2008, 2:289-294

Cases of typhoid fever imported into England, Scotland and Wales (2000—2003)

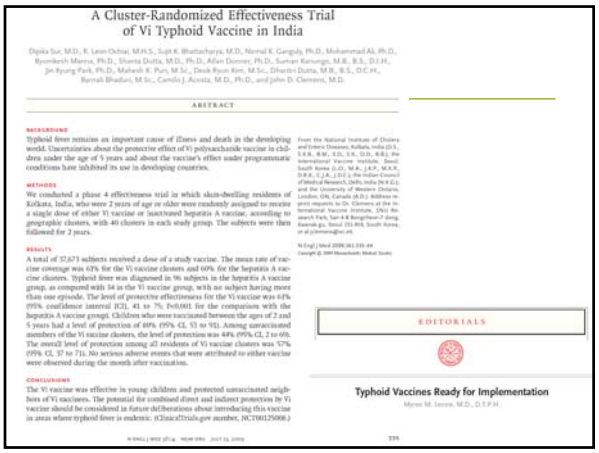
Fiona J. Cooke[a,b,*], Martin Day[a], John Wain[b], Linda R. Ward[b], E. John Threlfall[b]

- N = 692 S. enterica Typhi
- Resistance chloro-ampi-CTX : 22 %
- Resistance quinolone 39 %
- N = 49 Nalidixite acid S but low level cipro-R
- Associated with clinical failure

Transactions of the R Soc Trop Med Hyg 2007, 101:398

Alternative treatments ?

- Extended spectrum cephalosporins
  - Ceftriaxone
  - [Cefixime]
- Azithromycin
- New fluoroquinolones – Gatifloxacin
- Carbapenems
- Combinations ?



A Cluster-Randomized Effectiveness Trial of Vi Typhoid Vaccine in India

ABSTRACT

EDITORIALS

Typhoid Vaccines Ready for Implementation

Jap Encephalitis

Ixiaro ®

- Something new since consensus ? no
- About studies in kids ? no

PO02.03

Kinetics of the Neutralizing Antibody Response to the Vero-cell Culture Derived Japanese Encephalitis Vaccine IC51

K.L. Dubischar-Kastner[1], E. Schuller[1], A. Kaltenboeck[1], C. Klade[1], E. Tauber[2]
[1]Intercell AG, Vienna, Austria, [2]Formerly Intercell AG, Vienna, Austria

Introduction: Japanese Encephalitis is the most common viral encephalitis in Asia. In absence of an active treatment, vaccination is an important control measure. Intercell's vaccine IC51 is a Vero cell-derived, inactivated Japanese Encephalitis vaccine that has proven immunogenic and safe when administered i.m. in a Day 0, 28 schedule in adults and has recently obtained positive opinions by regulators in Europe and Australia to be followed by official approval in due time. Approval is as well pending for the US.
Objectives: To investigate onset and magnitude of neutralizing antibody response of the standard and a rapid immunization schedule of IC51.
Methods: In this observer-blinded phase III study, 374 subjects were randomized to receive either the standard schedule (2x6 mcg, Day 0/28), a single dose (1x6 mcg, Day 0) or the double dose (1x12 mcg, in two injections, Day0) of IC51. Immunogenicity was assessed by measuring neutralizing antibodies on Days 0, 10, 28, 35 and 56. The primary endpoint for non-inferiority of the 1x12 mcg vs 2x6 mcg group was seroconversion rate (neutralizing antibody titer ≥ 1:10) at Day 56.
Summary of results: In the per protocol population, in the 2x6 mcg group, GMTs were 8.4; 11.2; 265.8 and 218.0 on Days 10, 28, 35 and 56 respectively. In the 1x12 mcg group, GMTs were 16.7; 22.8; 17.6 and 11.2., and in the 1x6 mcg group GMTs were 9.3; 13.1; 11.3 and 8.1.
In the 2x6 mcg group SCRs were 21.2; 39.8; 97.3 and 97.3% on Days 10, 28, 35 and 56 respectively. In the 1x12 mcg group, SCRs were 53.9; 65.8; 58.8 and 41.2%. In the 1x6 mcg group, SCRs were 29.4; 42.7; 37.9 and 25.6%. The 2x6mcg group was superior to the 1x12 mcg group for the primary endpoint.
Conclusions: The results of this study confirm the standard schedule with two doses of IC51 (2x6 mcg). While the immune responses in the 1x6 mcg and 1x12 mcg groups were similar in magnitude and kinetics, the second dose administered at day 28 in the 2x6 mcg group led to a rapid increase in antibody response, resulting in seroconversion rates of > 97% already one week after the second dose.

11th Conference of the International Society of Travel Medicine
Budapest, Hungary, May 24-28, 2009

PO02.04

Long Term Immunity Following Vaccination with the Inactivated Japanese Encephalitis Vaccine IC51 and Immune Response to a Booster Dose

K.L. Dubischar-Kastner, S. Eder, A. Kaltenboeck, C. Klade, E. Schuller, G. Woelfl
Intercell AG, Vienna, Austria

Introduction: Intercell's v
been proven immunogenic
obtained positive opinions
Approval is as well pendi
vaccines two years after v
individuals who did not se
Objectives: To investigate
IC51 and to assess safety
titers.
Methods: In this open-lab
IC51 in a previous trial we
PRNT assay at month 6, 1
dose on either month 11 o
booster dose. Systemic and
Summary of results: Resu
Conclusions: To be comp
booster dose in subjects v
immunization; and the im
standard schedule of two d

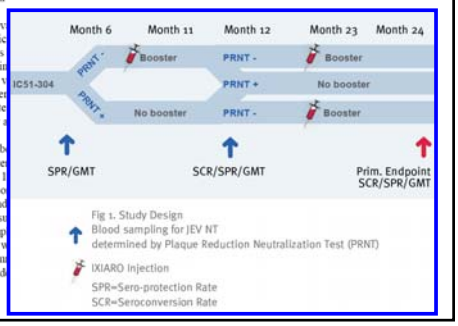


Fig 1. Study Design
Blood sampling for JEV NT determined by Plaque Reduction Neutralization Test (PRNT)
IXIARO Injection
SPR=Sero-protection Rate
SCR=Seroconversion Rate

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Intercell AG, Vienna, Austria

Immunogenicity Results

» SEROPROTECTION RATES AT MONTHS 2, 6, 12 AND 24

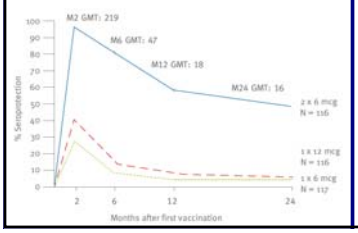

Fig 2.
SPR = Sero-protection Rate

- In the 2x6 mcg group SPRs were 97.4;82.8; 58.3 and 48.3% on Months 2, 6, 12 and 24 respectively.
- In the 1x12 mcg group, SPRs were 41.4; 14.7; 7.8 and 6.0%.
- In the 1x6 mcg group, SPRs were 26.5; 8.5; 4.3 and 4.3%.

GMTs are shown for the 2x6 mcg group.

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PO02.04

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K.L. Dubischar-Kastner, S. Eder, A. Kaltenboeck, C. Klade, E. Schuller, G. Woelfl
Intercell AG, Vienna, Austria

» LATE COMPLETION OF THE PRIMARY IMMUNIZATION SCHEDULE: SCR AFTER A 1X6 MCG DOSE ADMINISTERED 11 MONTHS AFTER A SINGLE 1X6 MCG DOSE

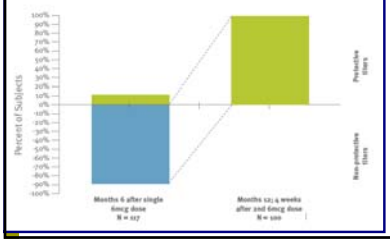

Fig 3. ITT population:

In the 1x6 mcg group, SPR was 10.3% at Month 6.

A booster at Month 11 in unprotected subjects (displayed in blue in the first column) led to a SCR at Month 12 of 99.0% in boosted subjects (displayed in green in the second column).

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PO02.04

Long Term Immunity Following Vaccination with the Inactivated Japanese Encephalitis Vaccine IC51 and Immune Response to a Booster Dose

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Intercell AG, Vienna, Austria

» SEROCONVERSION RATES 28 DAYS AFTER A 1X6 MCG BOOSTER DOSE ADMINISTERED TO UNPROTECTED SUBJECTS

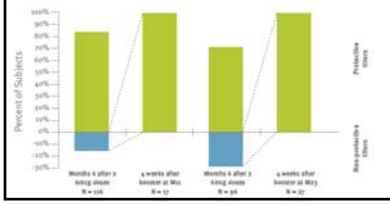

Fig 4. ITT population:
In the 2x6 mcg group, SPR was 83.63% at Month 6.
A booster at Month 11 in unprotected subjects led to a SCR at Month 12 of 100% (displayed in green in the second column).

In unboosted subjects of this group, SPR at Month 12 was 70.8%.
A booster at Month 23 in unprotected subjects led to a SCR of 100%.

2009

IC51: a new investigational Japanese encephalitis vaccine

Dr Christoph Klade speaks to Duc Le, Editor

Expert Rev. Vaccines 7(8), 1139–1140 (2008)

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Pediatric indication is the second target that we are working on. We have carried out a Phase II study in Indian children between 1 and 3 years of age (the IC51–221 study from my presentation [2]). We have demonstrated that IC51 shows comparable immune responses at half the adult dose. We are planning further confirmation studies in India and Southeast Asia. Our partner, Biological E in India, will manufacture the vaccine for the Indian market as well as for the neighboring countries. Our aim is to establish the safety and immunogenicity in children 1–17 years of age and to make IC51 available for childhood vaccination in endemic areas.

= a recent article in JTM

PO02.05
Japanese Encephalitis Vaccine for Travellers: A Critical Analysis
C. Hatz[1], J. Werlein[2], M. Hufnagel[2], R.H. Behrens[2]
[1]Swiss Tropical Institute, Medical Department, Basel, Switzerland, [2]Hospital for Tropical Diseases, Travel Clinic, London, United Kingdom

The Japanese encephalitis (JE) flavivirus is an important public health problem in many rural parts of Asia. JE is transmitted by *Culex tritaeniorhynchus* and other mosquito vectors. The disease has a big toll in endemic populations with one third fatal outcomes and one third permanent neurological sequelae. Fortunately, the risk for travelers to Asia to acquire JE has been very low with only on to two reported cases per year worldwide, although few cases have been observed among short-term travellers in holiday destinations. The risk can, however be up to 1 in 5'000 for persons staying in rural areas with paddy rice farming during the respective transmission seasons. There is no doubt, that people at obvious risk should receive the JE vaccine. This is why the Swiss Expert Committee for Travel Medicine (ECTM) recommends a vaccination for people spending at least 14 nights in endemic villages. Although a safe and efficient vaccine will be available soon, a broader recommendation for this vaccine should be handled with great care, weighing the needs with vaccine safety and cost aspects. Analysis of surveillance reports, numbers of travellers from the UK and Switzerland enabled a critical analysis of prescribing indications for JE vaccine to be examined.

IXIARO represents an advance in JE vaccines

Characteristics	Mouse-brain derived vaccines	IXIARO
Live/inactivated	Inactivated	Inactivated
Virus substrate	Mouse brain	Vero cells
Adjuvant	None	Aluminimu hydroxi
Stabilizers	Porcine gelatin	None
Preservative	Thimersal	None
Format	Lyophilized	Liquid, pre-filled syringe
Dosing schedule	3 doses (days 0, 7, 28)	2 doses (days 0, 28)

Summary

- IXIARO is a new Vero-cell-derived JE vaccine for travelers
- Highly immunogenic, providing protective antibody titers in 98 % after two doses
- Protective antibody response lasting for at least 12 months
- Well tolerated
- Can be co-administered with hepatitis A vaccine

Tauber E et al. Lancet 2007, 370:1847-1853
Schulier E et al.Vaccine 2008, 26:4382-86
Tauter E et al. J Infect Dis 2008, 198:489-99
Lehner C et al. Abstracts of the 56th American Society of tropical Medicine and Hygiene

Expert opinion on vaccination of travelers against JE

- Advise
  - Advise all travelers to areas of Asia where JE virus is transmitted in an enzootic cycle (including Japan) about the risks and consequences of JE and characteristics of available vaccines
- Recommend JE vaccination to
  - All expatriates
  - Repeat travelers who return frequently to the region or who cumulatively have prolonged duration of exposure
  - Any individual with a prolonged duration of stay, independent of itinerary
  - Any individual with a travel itinerary including rural areas
  - Travelers wishing maximum protection

Expert opinion on vaccination of travelers against JE

- Consider vaccination for
  - All other travelers visiting regions with enzootic transmission during a transmission period, particularly
    - Those with greater outdoor exposure
    - Individuals $\geq$ 50 years of age
    - Individualswith chronic conditions, such as
      - History of solid organ transplant
      - History of chochlear implants, ventriculoperitoneal shunts and other devices impinging the CNS or history of or medical conditions associated with CSF leakage
      - Hypertension
      - Daibetes melitus
      - Chronic renal disease
      - Anti-TNF therapy

Meningococcal meningitis

Vaccine strategies in travelers : comparative risks

	Incidence per 100,000
Travelers to developping countries	0,4 month
General US population	1
General UK population	1-3
Close contacts US (household)	420
Africa meningitis belt epidemics	200-800
1987 Haji pilgrims (US)	640
2000 Haji pilgrims (UK, Singapore)	25-30
Pilgrim contacts (Singapore)	18-28

Polysaccharide vaccine (Mencevax ACWY)

- Quadrivalent polysaccharide meningococcal vaccine
  - Safe and protection of approximately 90 %
  - No protection for age < 2 years
  - Duration of protection is short (3-5 years)
  - Immune hyporesponsiveness after repeated vaccination
  - Do not reduce colonization and do not prevent carriage (unprotected close contacts)

Experience with conjugate vaccines

- MenC conjugate vaccination in the UK in 1999 has led to a dramatic decline in the incidence of serogroup C disease
- 66 % reduction in serogroup C carriage : Herd immunity
- Broader protection beyond serogroup C needed
- Quadrivalent meningococcal vaccines against A, C, Y and W135. ACIP recommends the quadrivalent conjugate vaccine to all adolescents and those in high-risk groups – licensed for 2-55 year old

Lancet 2002, 359:1829-31

MenACYW-CRM : conclusion

- Protection against 4 serogroups
- Well tolerated
- Immunogenic in all age groups including infants
- Immunogenicity in adolescents is similar or higher compared to the polysach vaccine

Advantages of conjugate vaccines

Property	Polysaccharide	Conjugate
Effective in infants	No	Yes/No
Immune memory	No	Yes
Prolonged duration of protection	No	Yes
Booster effect	No	Yes
Reduction of carriage	No	Yes
Contributes to herd effect	No	Yes
Hyporesponsiveness with repeated dosing	Yes	No

Harrison LH. Clin Microbiol Rev 2006, 19:142-64

Menactra ® - US

From now on boosters are advised !!!

- After 3 year for children vaccinated at 2-6 years
- After 5 years for those older than 6 years & adults

CDC Immunization Works Monthly Immunization Update 23 July 2009

Summary : meningococcal vaccine strategies for travelers

- Vaccination is required for Haji and Umrah pilgrims
- Vaccination is recommended
  - For travelers to the meningitis belt (dry season)
  - For travelers to countries where outbreaks are known to occur
  - For travelers with high risk factors
- Vaccination should be considered when traveling to other endemic countries because of the unpredictability of meningitis outbreaks and severity of the disease

Polio

Vaccine 27 (2009) 3700–3703

Why polio has not been eradicated in India despite many remedial interventions?

Yash Paul*

Maharaja Agrasen Hospital, Vidhyadhar Nagar, Jaipur 302023, India

ARTICLE INFO

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Polio eradication
Polio eradication failure
Polio eradication strategy

ABSTRACT

Oral polio vaccine has reduced the incidence of polio in India and many states have been polio free for a long time while occasional polio cases are occurring in some states. On the other hand more than 96% of polio cases being reported in India are occurring in Uttar Pradesh and Bihar. The current polio scenario indicates that oral polio vaccines cannot eradicate polio from Uttar Pradesh and Bihar because some children from these two states show poor response to OPV. There is an urgent need for re-appraisal of polio eradication strategy.

In Brief: Burundi health officials act to check polio

BUJUMBURA, 28 October 2009 (IRIN) - Following two reported cases of polio in Burundi's northwestern province of Cibitoke, the Health Ministry and UN World Health Organization have begun a three-day immunization campaign, targeting at least 1.5 million children under five, officials said.

"By [27 October], initial estimates indicated that at least 75 percent of the children targeted were immunized in the first two days," Olivier Kagabo, head of the national immunization department, said. "But we expect [to immunize] more children on [28 October] as parents generally come on the last day."

Kagabo said local administration officials were assisting health officials to mobilize parents to take their children for immunization. Kagabo stressed that even vaccinated children should get the new vaccine since "it is different from the routine vaccine they were getting".

Burundi had eradicated polio for 10 years but two children caught the disease in September following contamination from neighbouring Democratic Republic of Congo. "The virus, wild polio type 1, originated from India and contaminated Angola and DR Congo and reached Burundi last month," Kagabo said. A second immunization campaign will be held in November.

jb-bn/js/mw

Theme(s): (IRIN) Health & Nutrition

[ENDS]

TBE

SY04.01

Climate Change and Evolution of Ticks

Jochen Süss
Friedrich-Loeffler-Institute, National Reference Laboratory for Tick-borne Diseases, Jena, Germany

Interactions between ticks, competent hosts and various pathogens are complicated and only partially understood. As ticks are ectoparasites which spend most of their life cycle in the environment, their development is influenced by many individual elements of the complex climate system. Humidity of the air and ground temperature are of particular importance, but other factors must not be neglected either. We have seen that the current climate change improves the living and developmental conditions of ticks. Increased mean temperatures induce changes in the developmental cycle, e.g. the spring and fall season may be prolonged which increases the time span for host search and moulting. The microclimate in the tick habitat in terms of an 'ecological niche' is of importance in this respect. Factors which protect the tick from extreme climatic influences are of crucial significance. Questing and diapausing ticks are especially susceptible to outside influences and are better protected in milder winters. The availability of hosts is another important factor. Within the framework of the vector-host interactions the so-called cofeeding phenomenon is of utmost significance. Individual scientifically firm observations have been made in ticks in Europe which can be associated with the climate change, e.g. the northward spread of *Ixodes ricinus (I.r.)* in Sweden and the first occurrence of TBE cases at the southern tip of Norway. Milder winters and a prolonged spring and fall season have produced similar effects in Denmark. In Latvia, the numbers of both, *I.r.* and *I. persulcatus (I.p.)* have increased. The northernmost TBEV focus in the world is located in Finland, where the classical European tick (*I.r.*) occurs alongside *I. p.* throughout the country. The results presented over the past years show that *I.r.* has expanded its range from approx. 800 m above sea level to 1200 m (Czech Republic) and 1560 m above sea level (Austria) and are also able to transmit TBEV at these higher altitudes. A significant increase in the host-questing activity of *I.r.* in the winter (Germany) and a northward spread of other tick species, e.g. *Dermacentor reticulatus* (Germany, The Netherlands), must also be mentioned.These facts lead to a (climate-induced) increased incidence of tick-borne diseases. In addition, there are other social, political, economic, demographic and ecological factors which produce similar effects, but which are associated with the term „exposure to tick-bites".

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 10, October 2009

SY04.01

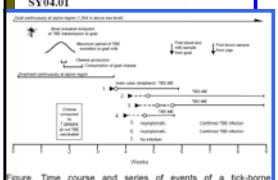

Figure. Time course and series of events of a tick-borne encephalitis (TBE) outbreak from cheese made with goat milk. Week 0, transport of goat to high altitude; ►, onset of disease; O—I, hospitalization period; TBEV, tick-borne encephalitis virus; ME, meningoencephalitis.

Tick-borne Encephalitis from Eating Goat Cheese in a Mountain Region of Austria

Heidemarie Holzmann, Stephan W. Aberle, Karin Stiasny, Philipp Werner, Andreas Mischak, Bernhard Zainer, Markus Netzer, Stefan Koppi, Elmar Bechter, and Franz X. Heinz

We report transmission of tick-borne encephalitis virus (TBEV) in July 2008 through nonpasteurized goat milk to 6 humans and 4 domestic pigs in an alpine pasture 1,500 m above sea level. This outbreak indicates the emergence of ticks and TBEV at increasing altitudes in central Europe and the efficiency of oral transmission of TBEV.

Norway. Milder winters and a prolonged spring
Latvia, the numbers of both, *I.r.* and *I. persulc*
world is located in Finland, where the classical
The results presented over the past years show
level to 1200 m (Czech Republic) and 1560 m
these higher altitudes. A significant increase in
northward spread of other tick species, e.g. *Dermacentor reticulatus* (Germany, The Netherlands), must also be mentioned.These facts lead to a (climate-induced) increased incidence of tick-borne diseases. In addition, there are other social, political, economic, demographic and ecological factors which produce similar effects, but which are associated with the term „exposure to tick-bites".

3- Varia

Human Ebola Outbreak resulting from direct exposure to fruit bats

- May to November 2007: Ebola outbreak in the Occidental Kasai province of Congo:
  - 260 human cases,
  - 186 deaths
- Epidemiological investigations:
  - Massive annual fruit bat migration toward the southeast, up to Lulua River

Ebola outbreak 2007

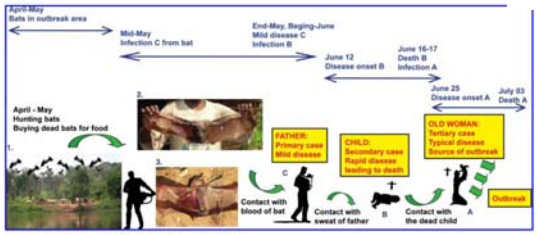

FIG. 2. Schematic diagram of the putative chain of Ebola virus transmission from bats to the initial human cases in the 2007 outbreak in Luebo, DRC. The first picture shows a village near the islands where migrating bats settle during April and May. The second picture shows the main migratory bat species (*H. monstrosus*) hunted by villagers during April to May. The third picture shows how villagers handle the bats they kill and eat, which underlines the direct contact with blood and other potentially infected bat body fluids.

VECTOR-BORNE AND ZOONOTIC DISEASES
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DOI: 10.1089/vbz.2008.0167

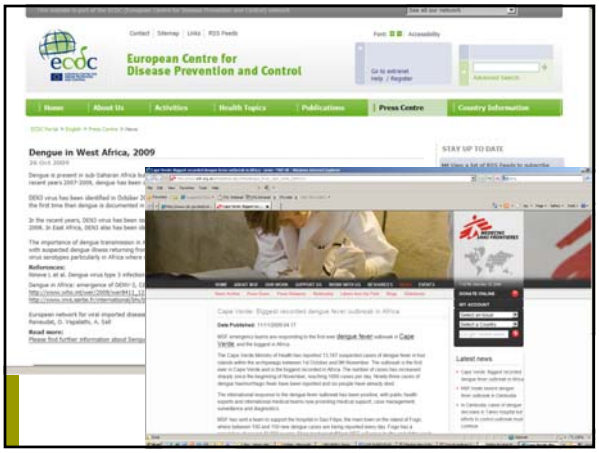
Human Ebola Outbreak Resulting from Direct Exposure to Fruit Bats in Luebo, Democratic Republic of Congo, 2007

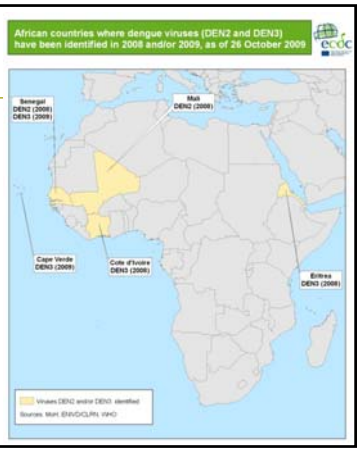
Eric M. Leroy,[1,2] Alain Epelboin,[3] Vital Mondonge,[4] Xavier Pourrut,[1,2] Jean-Paul Gonzalez,[1] Jean-Jacques Muyembe-Tamfum,[5] and Pierre Formenty[6]

Abstract

Twelve years after the Kikwit Ebola outbreak in 1995, Ebola virus reemerged in the Occidental Kasaï province of the Democratic Republic of Congo (DRC) between May and November 2007, affecting more than 260 humans and causing 186 deaths. During this latter outbreak we conducted several epidemiological investigations to identify the underlying ecological conditions and animal sources. Qualitative social and environmental data were collected through interviews with villagers and by direct observation. The local populations reported no unusual morbidity or mortality among wild or domestic animals, but they described a massive annual fruit bat migration toward the southeast, up the Lulua River. Migrating bats settled in the outbreak area for several weeks, between April and May, nestling in the numerous fruit trees in Ndongo and Koumelele islands as well as in palm trees of a largely abandoned plantation. They were massively hunted by villagers, for whom they represented a major source of protein. By tracing back the initial human-human transmission events, we were able to show that, in May, the putative first human victim bought freshly killed bats from hunters to eat. We were able to reconstruct the likely initial human-human transmission events that preceded the outbreak. This study provides the most likely sequence of events linking a human Ebola outbreak to exposure to fruit bats, a putative virus reservoir. These findings support the suspected role of bats in the natural cycle of Ebola virus and indicate that the massive seasonal fruit bat migrations should be taken into account in operational Ebola risk maps and seasonal alerts in the DRC.

Key Words: Bat—Ebola—Emerging disease—Outbreak—Pathogenicity—Virus—Zoonotic disease.





TD & post TD

FC03.01

Irritable Bowel Syndrome among a Cohort of European Travelers to Low Income Destinations

R. Pitzurra, A. Tschopp, C. Hatz, R. Steffen, M. Mutsch
University of Zurich, Institute of Social and Preventive Medicine (ISPM), Zurich, Switzerland

Objectives: Previous studies have detected rates of 4 to 11% of irritable bowel syndrome (IBS) among travelers to low income countries. So far no survey investigated this risk in Europeans, none used the Rome III criteria.
Methods: Adult travelers were invited to participate in a cohort study before leaving to a high risk traveler's diarrhea (TD) destination for a maximum of 8 weeks when consulting our travel clinic for pre-travel health advice between July 2006 and June 2008. Exclusion criteria included pre-existing functional gastrointestinal disorders and antibiotic prophylaxis. Volunteers were investigated about demographics, travel and health characteristics by means of questionnaires pre-travel (Q1), immediate post-travel (Q2) and 6-months post-travel (Q3). IBS and related symptoms were assessed pre-travel and 6-months post-travel according to Rome III criteria.
Results: Among 3,100 travelers enrolled (Q1), 2,800 (90.3%) concluded Q2 and 2,440 (78.7%) were eligible for the final analysis. Classic TD was reported by 837 returning travelers (34.3%). Rates over 35% were found among those who had visited Central and West Africa and South Asia. Symptoms compatible with IBS were recorded in Q3 in 31 (1.3%) travelers and a 2-weeks-of-stay incidence of 0.9% was estimated. In a preliminary multivariate analysis classic TD was an independent risk factor of IBS (RR 4.8, 95%CI 2.2 - 10.4). Additionally, age, newcomers to tropics and subtropics and reported consumption of potentially contaminated food and beverages significantly increased the risk of IBS. No significant difference was found for gender, travel duration, travel destination and education.
Conclusions: Among Europeans the incidence of travel-related IBS is lower than the one in other populations.

FC02.02

Symptoms of Infectious Diseases in Travellers with Diabetes: A Prospective Study with Matched Controls

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Objective: Diabetic travellers to the (sub)tropics are thought to have symptomatic infectious diseases more often and longer than non-diabetics. Evidence for this is lacking. Nevertheless, several guidelines advise to prescribe diabetics stand-by antibiotics in case of traveller's diarrhoea. This study evaluates whether diabetic travellers are at increased risk of symptomatic infectious diseases, and how often diabetics use their stand-by antibiotics for diarrhoea.

Methods: A prospective two-centre study with matched controls was performed between October 2003 and February 2008. All adult medication-dependent diabetics planning to travel to the (sub)tropics with a non-diabetic, non-immune-suppressed travel companion were eligible. Thus, participating diabetics and controls were assumed to have comparable exposure to infection. They recorded data using a structured diary.

Results: Among 70 insulin-dependent diabetics, the incidence of travel-related diarrhoea was 0.99 per person-month, and the median number of symptomatic days 1.54 per month. For their 70 controls, figures were 0.74, and 1.57, respectively ($p>0.05$). Among 82 non-insulin-dependent diabetics, incidence was 0.75, and the median number of symptomatic days was 1.57. For their 82 controls, figures were 0.70, and 1.69, respectively ($p>0.05$). As for vomiting, fever, cough, rhinitis, and signs of skin infection, no significant travel-related differences were found between diabetics and controls.

Only 17% of diabetic travellers with diarrhoea used their standby-antibiotics, although all were specifically advised to do so. Some simply forgot, others preferred oral rehydration solution or loperamide.

Conclusions: Diabetic travellers to (sub)tropical destinations do not have symptomatic infectious diseases more often or longer than non-diabetics. Their use of antibiotics for self-treatment of travel-related diarrhoea is minimal. They should therefore not be routinely prescribed.

Prize winning poster

PO07.07

Are Incidences of Faecal-orally Transmitted Diseases among Travellers Changing due to Better Hygienic Standards in the (Sub) Tropics or to Pre-travel Vaccination?

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Objective: Incidences of faecal-orally transmitted infections among travellers to the (sub)tropics are declining. Whether decreases can be attributed to pre-travel vaccinations, better hygienic standards at travel destinations, or both, is unknown.

Methods: National surveillance data on laboratory-confirmed cases of travel-related hepatitis A and shigellosis diagnosed in The Netherlands from 1995 through 2006 were analysed. Data on numbers of Dutch travellers to the (sub) tropics were used as a denominator to calculate region-specific annual attack rates. Thus, trends in incidences of non-vaccine preventable shigellosis were compared with those of vaccine preventable hepatitis A. Human Development Indices (HDI) from the United Nations Development Program were used to evaluate region-specific trends in hygienic standards.

Results: From 1995 through 2006, overall annual attack rates per 100.000 travellers from the Netherlands declined: from 22 to 6 for hepatitis A, and from 27 to 8 for shigellosis. For Latin America rates declined from 6 to 1, and from 20 to 9, respectively; for North Africa & the Middle East from 62 to 7 and from 31 to 7. For Asia, hepatitis A rates remained stable (median 6 per 100,000), whereas shigellosis rates declined (from 22 to 7). The rates for Sub-Saharan Africa did not decline: the median hepatitis A rate was 10, the shigellosis rate 39. Sub-analysis for popular tourist destinations showed low and stable rates for the Caribbean. For Turkey and Egypt all rates dropped dramatically. Rates for East Africa were lower than for West Africa. Median rates for the Indian subcontinent were highest: 34 per 100,000 for hepatitis A and 84 for shigellosis. Rates for Thailand & Malaysia were stable and the lowest: 1 per 100,000 for hepatitis A and 5 for shigellosis. Trends in these incidences correlated with HDI baseline level and degree of increase. All regions showed an HDI increase (median 2.4% per 5 years). Baseline HDIs for Latin America, Turkey, and Thailand & Malaysia were the highest. HDI increase was highest for Egypt (+4.8%). The HDI for Sub-Saharan Africa was the lowest, the HDI increase the smallest (+1.2 %). HDI for the Indian subcontinent was the second lowest.

Conclusion: The decline in travel-related shigellosis shows that the decline in hepatitis A cases can not only be attributed to pre-travel vaccination. Incidences of faecal-orally transmitted diseases among travellers are related to hygienic standards at travel destination.

Extra

Cerebral Malaria
BVDC

CM in travelers : clinical features

- Severe malaria in adult travelers (Paris, France; N = 93)
  - Chemoprophylaxis not given/inappropriate : 98 %
  - Long median time to adequante treatment : 5 days
  - Bacterial illness : 13 %
  - Increased risk of death with CM, pulmonary edema, shock, metabolic acidosis
- Within this case series, CM patients (N = 34)
  - Case fatality rate of 26,5 %
  - 9 of 10 who died from severe malaria (90 %) had CM

Can we improve CM definition ?

- Malaria retinopathy
  - Retinal heporrhages
  - Macular and/or peripheral whitening
  - Vessel changes
- In Malawi children, sensitivity 95 %, specificity 90 % for CM (vs autopsy-proven brain blood vessel sequestration)
- Malawi study : 23 % of CM cases had another diagnosis

Malaria retinopathy in adults

- Bangladesh study
  - Retinopathy had 70 % sensitivity and 70 % specificity for CM (compared to sepsis, healthy malaria)
  - Also frequently seen in uncomplicated malaria
- Case reports in travelers
  - Findings fairly specific, sensitivity in travelers not established

Mortality and morbidity

- Mortality in African and Asian studies, 5–40%
- Morbidity
  - Neurologic
  - Cognitive
  - Neuropsychiatric

Neurologic morbidity

- Acutely, significant morbidity
  - African studies - ± 25 % gross neurologic deficits at discharge
  - Two indian studies 3-14 % neurologic deficitis at discharge
  - No prospective evaluation in travelers
- Long term, most gross neurologic deficits resolve
  - African studies – 6 months after discharge 1-4 %
  - One Indian study – 6 months after discharge 1 %
- Kenya : high erythropoeitin levels associated with less frequent neurologic deficits

Cognitive morbidity

- Long-term (2 y after episode) cognitive impairment in 25 % of children with CM
- Primary areas affected : attention, language, working memory
- Asia, adults, travelers
  - No prospective or case-control studies
  - Case series – memory impairment

Neuropsychiatric morbidity

- African children
  - Ghana study : increased subclinical mixed anxiety-depression
- Asia
  - Case report, some symptoms resolve, others remain
- Vietnam war veterans
  - Higher frequency of abnormalities in depression, personality change in veterans with CM 25-30 years earlier
- No research on risk factors for psychiatric morbidity

CM treatment : anti-malarials

- Artesunate : treatment of choice in Asia (lower mortality than quinine)
- Trials ongoing in Africa
- Available in the US only through CDC; Europe available through IDIS Pharma, GMP available ? 2009
- Need longer-acting partner drug to prevent recrudescence
  - Doxycycline
  - Clindamycin
  - Mefloquine
  - Atovaquone-proguanil

CM treatment : anti-malarials

- Quinine or Quinidine
- Generally also used with second drug to decrease recrudescence
  - Doxycycline
  - Clindamycin
  - Atovaquone-proguanil

Adjunctive therapy in CM

- Made no difference
  - Mannitol
  - Pentoxifylline
- Made outcomes worse
  - Dexamethasone
  - Anti-TNF monoclonal Ab
- Might help
  - Exchange transfusion, for high-level parasitemia
  - Iron chelators : desferrioxamine or dferiprone

New adjunctive therapies in CM ?

- Nitric oxide
  - Clinical trials of arginine in Indonesia show improved endothelial function and increased NO levels in children and adults with severe malaria
  - Other methos – inhaled NO ?; meds that inhibit NO breakdown ?
- Erythropoeitin
  - Clinical trial in Mali to assess safety
- Rosiglitazone
  - Immunomodulator, decreased mortality in murine model even 5 days after infection
- Statins
  - Suppression of endothelial activation, anti-parasitic effect

Conclusions 1

- Cerebral malaria (CM) remains a major problem worldwide
- CM is an uncommon but often deadly problem in travelers
- CM in travelers is largely avoidable with appropriate chemoprophylaxis
- Investigate bacterial illness in travelers with CM (13 % France)
- Malaria retinopathy may be a uselful clinical sign in CM

Conclusions 2

- Cognitive morbidity occurs in 25 % of children with CM (2 years follow up)
- Cognitive and psychiatric morbidity in adults and travelers is largely unknown (Vietnam war vet)
- Factors that relate to cognitive and neurologic morbidity may differ from those relating to mortality
- CM pathogenesis is complex, involves multiple pathways
- New insights into the pathogenesis of CM may lead to better adjunctive treatment of CM