Clinical, geographical, and temporal risk factors associated with presentation and outcome of vivax malaria imported into the United Kingdom over 27 years: observational study

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EDITORIAL by Gill

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STUDY QUESTION Who are the at risk groups for imported vivax malaria in the United Kingdom and their outcomes, and what are the temporal and seasonal trends in imported vivax malaria?

SUMMARY ANSWER Travellers visiting friends and relatives in South Asia are at the greatest risk of acquiring *Plasmodium vivax*; mortality is low and strongly associated with old age. Imported vivax malaria reduced over the study period despite increasing passenger numbers; clinical presentation and latency were highly seasonal with most cases presenting in April to September.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

P vivax is the most widely distributed malaria parasite but much less studied than imported malaria caused by *Plasmodium falciparum*. We found that imported vivax malaria is heavily concentrated in travellers who had visited friends and relatives in South Asia, elderly people (especially those ≥70 years) are most at risk of mortality from vivax malaria, and latency and presentation are highly seasonal.

Participants and setting

All confirmed cases of malaria in the UK (n=50 187) notified to the UK Public Health England Malaria Reference Laboratory from 1987 to 2013. We focused on 12 769 cases of vivax malaria.

Design

We carried out an observational study using prospective national surveillance data, data from the International Passenger Survey (Office for National Statistics), and international climactic data.

Primary outcomes

The main outcome measures were mortality, sociodemographic factors (age, UK region, country of birth and residence, purpose of travel), destination, and latency (time between arrival in the UK and onset of symptoms).

Main results and the role of chance

Of the malaria cases notified, 25.4% (n=12 769) were due to *P vivax*, of which 78.6% were imported from India and Pakistan. Most affected patients (53.5%) had travelled to visit friends and relatives, and 11.1% occurred in tourists. Imported *P vivax* is concentrated in areas with large communities of south Asian heritage. Overall mortality was 7/12 725 (0.05%), but with no deaths in 9927 patients aged under 50 years. Restricting the analysis to those aged more than 50 years, mortality was 7/2798 (0.25%), increasing to 4/526 (0.76%) (adjusted odds ratio 32.0, 95% confidence interval 7.1 to 144.0, P<0.001) in those aged 70 years or older. Annual notifications decreased sharply over the period, while traveller numbers between the UK and South Asia increased. The risk of acquiring *P vivax* from South Asia was year round but was twice as high from June to September (40 per 100 000 trips) compared with the rest of the year. There was strong seasonality in the latency from arrival in the UK to presentation, significantly longer in those arriving in the UK from South Asia from October to March (median 143 days) versus those arriving from April to September (37 days, P<0.001).

Bias, confounding, and other reasons for caution

The Malaria Reference Laboratory operates a passive case detection system, which relies on clinicians and laboratories to notify cases of malaria, so under-reporting is inevitable; capture-recapture suggests that around 60% of cases are notified. International passenger survey data give only approximate number of travellers.

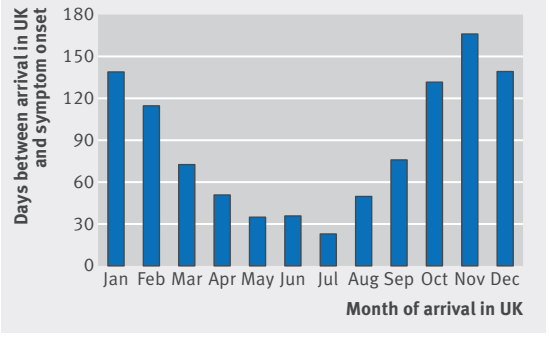
Generalisabilty to other populations

Findings on epidemiological data are generalisable to other non-endemic settings with large South Asian diaspora. Data on seasonality of latency and clinical presentation are of relevance for South Asian countries. Increased mortality in elderly people is likely to be widely generalisable.

Study funding/ potential competing interests

This research was supported by Public Health England (UK Health Protection Agency before 2013). We have no competing interests.

Latency of vivax malaria between arrival in United Kingdom and onset of symptoms, by month of arrival in UK, 1987-2013



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- Investigation and treatment of imported malaria in non-endemic countries (*BMJ* 2013;346:f2900)
- Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan (*BMJ* 2012;349: e4389)
- Imported malaria and high risk groups: observational study using UK surveillance data 1987-2006 (*BMJ* 2008;337:a120)

Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials

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STUDY QUESTION What is the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with the implantation of drug eluting stents?

SUMMARY ANSWER Discontinuation of dual antiplatelet therapy before 12 months yields reduced bleeding without increasing ischaemic complications, while continuation of therapy beyond 12 months reduces ischaemic and thrombotic events but at the price of greater risk of major bleeding and all cause death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Dual antiplatelet therapy is currently recommended after implantation of drug eluting stents, but the optimal duration is a matter of debate. The increase in all cause but not cardiovascular death seen with therapy beyond 12 months also requires further investigation.

Selection criteria for studies

PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, Cochrane Library, and major congress proceedings were searched from 1 January 2002 to 16 February 2015. Randomised controlled trials comparing two durations of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stent implantation were selected: short term (<12 months) versus 12 months; and extended (>12 months) versus 12 months.

Design

Meta-analysis of randomised controlled trials.

Main outcomes

	Odds ratio (95% CI)	
	Short term *v* 12 month dual antiplatelet therapy	Extended *v* 12 month DAPT
All cause mortality	0.91 (0.71 to 1.18)	1.30 (1.02 to 1.66)*
Cardiovascular mortality	0.95 (0.68 to 1.33)	1.09 (0.79 to 1.50)
Myocardial infarction	1.11 (0.87 to 1.43)	0.53 (0.42 to 0.66)†
Stent thrombosis	1.32 (0.83 to 2.08)	0.33 (0.21 to 0.51)†
Major bleeding	0.58 (0.36 to 0.92)*	1.62 (1.26 to 2.09)†

*P<0.05.
†P<0.001.

Outcomes

Primary endpoints were cardiovascular mortality, myocardial infarction, stent thrombosis, major bleeding, and overall mortality; secondary endpoints were repeat revascularisation, cerebrovascular accident, and the combination of cardiac and cerebrovascular accidents.

Main results and role of chance

Ten randomised controlled trials (n=32 287) were included. Compared with 12 month dual antiplatelet therapy, short term therapy was associated with a significant reduction of major bleeding (odds ratio 0.58 (95% confidence interval 0.36 to 0.92); P=0.02) with no significant differences in ischaemic or thrombotic outcomes. Extended versus 12 month therapy yielded a significant reduction in myocardial infarction (0.53 (0.42 to 0.66); P<0.001) and stent thrombosis (0.33 (0.21 to 0.51); P<0.001) but more major bleeding (1.62 (1.26 to 2.09); P<0.001). All cause but not cardiovascular death also increased significantly in the comparison between extended and 12 month therapy (1.30 (1.02 to 1.66); P=0.03).

Bias, confounding, and other reasons for caution

The results were analysed on trial level data and not on patient level data; individual patient information would have added further insights to the analysis.

Study funding/potential competing interests

Part of this study was supported by the Collaborative Research Center 1116 Masterswitches in Myocardial Ischemia, funded by the German Research Council (Deutsche Forschungsgemeinschaft). EPN has received honorariums for lectures from Eli Lilly; MV has received fees for lecturing from or has served on the advisory board of Abbott Vascular, Alvimedica, AstraZeneca, Correvio, The Medicines Company, Medtronic, and Terumo; FA has received honorariums for lectures and advisory boards from Amgen, Bayer, Boehringer Ingelheim, BMS-Pfizer, and Daiichi Sankyo-Eli Lilly; all the remaining authors do not have any conflicts relevant to this contribution.

Immunogenicity of reduced dose priming schedules of serogroup C meningococcal conjugate vaccine followed by booster at 12 months in infants: open label randomised controlled trial

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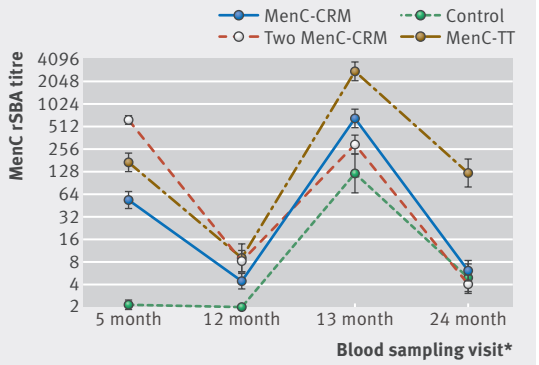
STUDY QUESTION Is the immunogenicity of one infant priming dose of serogroup C meningococcal (MenC) conjugate vaccine non-inferior to two doses when followed by a booster at 12 months of age?

SUMMARY ANSWER After a 1 year *Haemophilus influenzae* type b (Hib)-MenC-TT booster dose, the immunogenicity of one priming dose of MenC-CRM at 3 months was not only non-inferior but was superior to two MenC-CRM doses given at 3 and 4 months of age.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Different prime and boost schedules for MenC glycoconjugate vaccines are effective in controlling MenC disease. The functional MenC antibody response offered by one Hib-MenC-TT dose at 12 months of age is not sustained but should prime for a strong boost after vaccination offered later in childhood to maintain individual and herd immunity. Only the single MenC-TT, rather than one/two MenC-CRM prime and boost schedule induced persistent immunity in most until 24 months of age.

MenC rSBA geometric mean titres (95% confidence intervals) by visit according to MenC priming schedule



*5 month visit: 28-42 days after last vaccinations administered at 4 months of age; 12 month visit: at 51-58 weeks of age; 13 month visit: 28-42 days after Hib-MenC-TT vaccination at 51-58 weeks of age; 24 month visit: 11-12 months after Hib-MenC-TT vaccination

Design

A phase IV open label randomised controlled trial with stratified block randomisation.

Participants and setting

509 healthy infants aged 6-12 weeks were recruited in the United Kingdom and in Malta. In the priming phase infants were randomised to receive either one MenC-CRM dose at 3 months (single MenC-CRM Group); two doses of MenC-CRM at 3 and 4 months (two MenC-CRM Group), one MenC-TT dose at 3 months (single MenC-TT Group), or no MenC doses (control group), respectively. All participants received Hib-MenC-TT vaccine at age 12 months. Blood samples were taken at age 5, 12, 13, and 24 months.

Primary outcome

MenC serum bactericidal antibody using rabbit complement (rSBA) one month after the Hib-MenC-TT vaccine.

Main results and the role of chance

After a Hib-MenC-TT booster dose the MenC rSBA geometric mean titres in infants primed with one MenC-CRM dose were non-inferior to those primed with two MenC-CRM doses (660 (95% confidence interval 498 to 876) *v* 295 (220 to 398)). The difference in mean $\log_{10}$ MenC rSBA of 0.35 (0.17 to 0.53) shows superiority of the single over the two infant dose MenC-CRM schedule. One month after Hib-MenC-TT vaccination, MenC rSBA ≥1:8 was observed in >96% (95% confidence interval 92% to 100%) of those primed with any infant MenC vaccine schedule and in 83% (71% to 92%) of controls. Only priming with MenC-TT induced robust post-boost MenC bactericidal antibody that persisted until 24 months of age. MenC rSBA geometric mean titres (percentage of participants with MenC rSBA ≥1:8) were 123 (82%) for the single MenC-TT group; 6 (31%) for the single MenC-CRM group; 4 (20%) for the two MenC-CRM group; and 5 (27%) for the control group.

Harms

One infant, who developed a haematoma at the MenC-CRM injection site, had previously unrecognised factor VIII deficiency.

Bias, confounding, and other reasons for caution

Future studies of antibody persistence in children aged over 2 years would show if the differences between the MenC-TT and MenC-CRM priming schedules or the control group are sustained.

Generalisability to other populations

90% of the participants were white. Results cannot be generalised to other populations.

Study funding/potential competing interests

The study was funded by the NIHR Oxford Biomedical Research Centre, UK, the NIHR Medicines for Children Network South West and London (now NIHR Clinical Research Network: Paediatrics), the Southampton NIHR Wellcome Trust Clinical Research Facility and NIHR Respiratory Biomedical Research Unit, GlaxoSmithKline Biologicals, Belgium, and the European Society of Paediatric Infectious Diseases.

Trial registration

Eudract No: 2009-016579-31; NCT01129518; study ID: 2008_06 (http://clinicaltrials.gov).

Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial

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STUDY QUESTION In patients with rheumatoid arthritis, is disease activity guided dose reduction of the tumour necrosis factor (TNF) inhibitors adalimumab or etanercept non-inferior to the continuation of usual care?

SUMMARY ANSWER Dose reduction of adalimumab or etanercept was non-inferior to usual care in the occurrence of major flare, while resulting in successful dose reduction or stopping in two thirds of patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Tapering or stopping the use of costly TNF inhibitors adalimumab and etanercept in rheumatoid arthritis is possible in some patients, but no clinically feasible pragmatic strategy has been tested yet. Our study shows that disease activity guided tapering results in clinical outcomes comparable to usual care and a sizable reduction in inhibitor use.

Design

Pragmatic, open label, randomised controlled, non-inferiority trial undertaken from December 2011 to May 2014, with block randomisation and computer generated allocation.

Participants and setting

In two rheumatology outpatient clinics in the Netherlands, consenting patients with rheumatoid arthritis and low disease activity using adalimumab or etanercept were allocated to disease activity guided dose reduction (advice to stepwise increase the injection interval every three months, until flare of disease activity or discontinuation, n=121) or usual care (no dose reduction advice, n=59). Flare was defined by the composite DAS28-CRP score. In case of flare (DAS28-CRP increase >1.2, or increase >0.6 and current score ≥3.2), TNF inhibitor treatment was restarted or escalated.

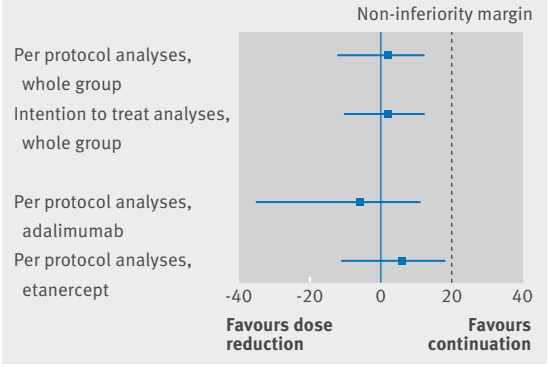
Primary outcomes

Between group difference in proportions of patients with major flare (flare >three months) at 18 months, compared against a non-inferiority margin of 20%.

Main results and the role of chance

The figure compares the cumulative incidence of major flare at 18 months between groups, against a 20% non-inferiority margin. Dose reduction was non-inferior to usual care (proportion of patients with major flare, 12% *v* 10%; difference 2%, 95% confidence interval −12% to 12%). Inhibitor use was successfully stopped in 20% (13% to 28%) of patients, and the treatment interval successfully increased in 43% (34% to 53%). In 37% (28% to 46%) of patients, no dose reduction was possible. Mean disease activity at study end, functional status, quality of life, and relevant radiographic progression did not differ between groups.

Primary outcome analyses



Harms

Short lived flares and minimal radiographic progression (Sharp-van der Heijde score increase >0.5) were significantly more frequent in the dose reduction group than in the usual care group (73% *v* 27%; 32% *v* 15%). Adverse events did not differ between groups.

Bias, confounding, and other reasons for caution

The study's open nature could have led to underestimation rather than overestimation of the patients' ability to taper.

Generalisability to other populations

Owing to non-restrictive inclusion criteria, generalisability seems realistic to patients with rheumatoid arthritis who have had low disease activity for some time and using TNF inhibitors. However, the prerequisite of good quality, disease activity guided care for the disorder might not be easily achieved in more rural regions or other healthcare systems.

Study funding/potential competing interests

This investigator driven study received no external funding. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JB received grants and personal fees from Pfizer and AbbVie, during the conduct of the study; and grants and personal fees from Roche, Bristol Myers Squibb, Union Chimique Belge, outside the submitted work. RvV received grants from AbbVie, BMS, GlaxoSmithKline (GSK), Pfizer, Roche, and UCB, and personal fees from AbbVie, Biotest, BMS, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, and Vertex, outside the submitted work. The other authors declare no conflicts of interest.

Trial registration number

Dutch trial register (www.trialregister.nl), NTR 3216.