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Geographical concentration of falciparum malaria treated in the United Kingdom and delay to treatment with artesunate in severe cases: an observational study.

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Abstract

Objectives: To quantify geographical concentration of falciparum malaria cases in the UK at a hospital level. To assess potential delay-to-treatment associated with hub-and-spoke distribution of artesunate in severe cases.

Design:

Observational study using national and hospital data

Setting and participants:

3,520 patients notified to the Malaria Reference Laboratory 2008-2010, 34 patients treated with intravenous artesunate from a specialist tropical diseases centre 2002-2010.

Main outcome measures:

Geographical location of falciparum cases notified in the UK. Diagnosis-to-treatment times for intravenous artesunate.

Results

Eight centres accounted for 43.9% of the UK's total cases; notifications from 107 centres accounted for 10.2% of cases; 51.5% of hospitals seeing malaria notified 5 or fewer cases in 3 years. Centres that saw <10 cases/year treat 26.3% of malaria cases and 6.1% of cases are treated in hospitals seeing fewer than 2 patients a year. The concentration of falciparum malaria was highest in Greater London (1925, 54.7%), South East (515, 14.6%), East of England (402, 11.4%) and North West (192, 5.4%). The North East and Northern Ireland each notified 5 or fewer cases per year. Median diagnosis-to-treatment time was 1 hour (range 0.5-5) for patients receiving artesunate in the specialist centre; 7.5 hours (range 4-26) for patients receiving it in referring hospitals via the hub and spoke

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system (p 0.02); 25 hours (range 9-45) for patients receiving it on transfer to the regional centre from a referring hospital (p 0.002).

Conclusions

Most UK hospitals see few cases of falciparum malaria and geographical distances are significant. Over a quarter of cases are seen in hospitals where malaria is rare, although 60% are seen in hospitals that see 50 cases or more over 3 years. A hub-and-spoke system minimises drug wastage and ensures it is available in centres that see most cases but is associated with treatment delays elsewhere.

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Introduction

Falciparum malaria remains an important cause of morbidity and mortality in returning travelers. In the UK, there are 1200 to 1600 cases of falciparum malaria annually, most from Africa or Asia, with an overall case-fatality rate of 7.4 per 1000 reported cases[1]. Around 15% of falciparum cases in the UK are “severe” (Malaria Reference Laboratory 2012) based on WHO criteria[2]. Delay to effective treatment and lack of experience of dealing with severe malaria are associated with poor outcome in severe cases[3,4,5].

Worldwide, parenteral quinine has been the mainstay of treatment for severe falciparum malaria for over a century and was first-line treatment in the last UK treatment guidelines (2007[6]). However, two recent large multicentre randomised control trials have demonstrated a significant mortality reduction with intravenous artesunate versus intravenous quinine in severe falciparum infection in African children (AQUAMAT[7]) and Asian adults (SEAQUAMAT[8]). In light of this new evidence, WHO now recommends intravenous artesunate as first-line treatment for severe falciparum infections[2]. It is almost certain the reduced mortality applies also in travellers returning from those regions. Artesunate is also easier to use than intravenous quinine: it can be administered as a bolus rather than an infusion; has no known cardiotoxicity; it is not known to cause hypoglycaemia associated with quinine[8,9]. For these reasons it is likely to replace quinine as the treatment of choice in the United Kingdom and other countries seeing cases of severe malaria once GMP licenced drug is available.

Intravenous artesunate is available in the UK but its use has been limited by restricted availability. Until recently, just one pharmaceutical company, based in Shanghai, was manufacturing the drug for international export. Their product, used in the AQUAMAT and

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SEAQUAMT trials[7,8], only gained WHO pre-qualification status in November 2010[10]. Production is increasing worldwide but parenteral artesunate remains unlicensed for use in the UK. Few hospitals regularly stock intravenous artesunate and national supplies have been limited (June Minton, Hospital for Tropical Diseases, personal communication 2012). Additionally the shelf-life of artesunate (around 18 months) is much lower than for quinine, an operational issue for hospitals which see few cases.

Given the clear outcome advantages of artesunate but its limited availability, two models of drug distribution might be considered: *universal stock in all acute hospitals (blanket coverage)* and a *hub-and-spoke system* where critical stocks are kept in specialist centres and couriered out when needed to hospitals with severe malaria cases. A form of hub-and-spoke system has operated to date.

Minimising delay to effective treatment is essential in severe cases[3,4,11]. Geographical distance is a key consideration for delay. There is existing evidence of geographical clustering of malaria at a regional level[1], but this is too broad brush to help with decisions on a hub-and-spoke compared to blanket coverage distribution for a drug which many centres will use rarely if at all. In this study, we therefore assess the geographical distribution of falciparum malaria in the UK at hospital level, using data from the HPA Malaria Reference Laboratory. We also examine data from a tertiary tropical diseases centre that operates a hub-and-spoke system to distribute artesunate to referring hospitals, specifically reviewing time-to-treatment. These data will inform decisions on the optimal means of distributing intravenous artesunate UK-wide. The geographical concentration of cases is also relevant to training needs for clinical and laboratory staff in the diagnosis and management of malaria. The approach should also help other countries

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with imported malaria which do not currently have universal artesunate coverage (most of them) consider the data they will need for their decisions.

Methods

Malaria is a notifiable disease in the UK: clinicans are required to report all cases by law. The Malaria Reference Laboratory (MRL), part of the UK Health Protection Agency, maintains the national surveillance database of reported malaria cases in the UK. It identifies malaria cases from statutory notification through local authorities; through laboratories sending blood films for diagnostic verification; through clinicians sending standardised malaria reports to the MRL. When a malaria case is notified, the MRL contacts the responsible clinician who is asked to complete a data collection form covering demographic and clinical data, including the notifying hospital's location and the patient's usual place-of-residence.This passive case detection system has been shown to identify at least 66% of cases of falciparum malaria in the UK[12] and it may be higher in areas where malaria is less often seen (over 90% from Scotland[13]).

The MRL database was used to identify the location of every notified case of falciparum malaria in the UK in the years 2008, 2009 and 2010. For Greater London, the notifying hospital's name was recorded given the large number of hospitals; outside Greater London, the notifying hospital's town was recorded.The patient's usual place-of-residence was also recorded. Cases were excluded if there was insufficient information to identify accurately the notifying hospital or town. Where the notifying hospital's location and the patient's usual place-of-residence differed significantly (eg. notified from Liverpool, place-of-residence Cardiff), the notifying hospital's location was recorded as case location.

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Data were anonymised and analysis was performed using EpiInfo and STATA 11. For each notifying site, the annual frequency of falciparum malaria and the total number of cases over 3 years was calculated. Using the decimal geographic coordinates of each notifying site, maps showing the geographical distribution of falciparum malaria within the UK and within each UK region, weighted for caseload, were generated. Cases were also analysed by the UK Government Office Region from which they were reported (North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South East, South West, Greater London, Northern Ireland, Scotland and Wales)[14].

The Hospital for Tropical Diseases (HTD), London has been using intravenous artesunate in cases of severe malaria since 2002 and provides a hub-and-spoke distribution service. It arranges for intravenous artesunate to be couriered from its permanent stocks to referring hospitals via its Tropical Medicine telephone advice service when requested based on clinical need. HTD's Pharmacy records were used to identify inpatients treated with intravenous artesunate at any hospital (including HTD) between 2002 and August 2010. The referring hospitals' pharmacies were contacted and patient identities confirmed. Patients' medical and laboratory records were reviewed after seeking appropriate permission from the hospitals. A standardised proforma was used to record the following for every patient: demographics; parasitaemia; clinical features of severity (based on WHO criteria[2]) initial anti-malarial used; time of malaria diagnosis; time of first treatment with intravenous artesunate. All data were anonymised.

The diagnosis-to-treatment time was calculated for each case (time from the diagnosis of severe malaria as documented in the notes to time of first dose of intravenous artesunate as signed for on the drug chart). Difference between cases treated in a hospital with

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stocks, hospitals where artesunate was couriered and differences with hospitals which transferred patients were calculated by the Wilcoxon Rank Sum test.

Results:

Geographical clustering of cases in the UK

Of 3556 cases of falciparum malaria notified to the MRL between 2008 and 2010: 1096 cases were in 2008; 1185 cases in 2009; 1275 cases in 2010. We excluded 12 cases from 2008 (9 Scotland, 1 Berkshire, 2 London); 11 cases from 2009 (9 Scotland, 2 London); 13 cases from 2010: (8 Scotland, 1 West Yorkshire, 2 London, 1 Surrey, 1 Somerset) due to incomplete geographical data, so in total 3520 cases are included in this study.

Of these cases, 54.7% were notified from London, 14.6% from the South East, 11.4% from Eastern England, 5.5% from the North West. Together, the North East of England and Northern Ireland accounted for just 0.6% of cases, each notifying 5 or fewer cases per year (Table 1). Within all regions, cases were clustered around larger towns and cities and these are plotted out for the UK (Map 1), England (Map 2), the North West and West Midlands (Map 3), the South East and East of England (Map 4) and Greater London (Map 5).

Over the three years studied, eight centres notified more than 100 cases (6 Greater London hospitals, Croydon and Liverpool). Cases from these eight centres made up 43.9% of the UK's total cases. Notifications from 31 centres accounted for 73.7% of the UK's total; 18 of these were Greater London hospitals. In contrast, 140 centres that saw fewer than a case a month saw 26% of cases (924), and 6% of cases were seen in

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centres which saw less than 2 patients a year, many of which were some way from a potential hub (Table 2 and maps).

Intravenous artesunate via hub-and-spoke and time-to treatment.

HTD pharmacy records identified 50 patients who started intravenous artesunate, 22 at HTD. Clinical data were available for 21 HTD cases (one case missing medical records), 14 of whom transferred in from referring hospitals. Records identified 28 patients in referring hospitals treated with intravenous artesunate sent from HTD. Of these 13 could be included in this study (8 cases had incomplete patient identifiers; 7 cases incomplete medical records). 10 patients were in London hospitals, 2 in the South East and 1 in Eastern England. Therefore, 34 patients were included in total: 21 men and 13 women, age range 17- 70 years, median age 41 years. High parasite count was the most common criterion for starting intravenous artesunate: 29 of the 34 had a count greater than 2% on admission; 24 had a count greater than 5%. On presentation, 12 had cerebral malaria (35%), 10 had respiratory distress (29%), 6 had acute renal impairment (18%) and 12 (35%) had 2 or more clinical features of severe malaria (Table 3).

In 23 cases (68%) the diagnosis-to-treatment time could be calculated. For 4/4 patients admitted to HTD with severe malaria, median time was 1 hour, range 0.5 to 5 hours. For 9/13 patients who required artesunate to be couriered to their referring hospital, median time was 7.5 hours, range 4 to 26 hours, difference from the four treated in a hospital with drug stocks (HTD) of p 0.02 (Rank Sum). For 10/14 patients who presented elsewhere but were transferred to and given artesunate at HTD, median time was 25 hours, range 9 to 45 hours, difference from the patients where artesunate was couriered p 0.002. For 25/26 patients admitted to a referring hospital, intravenous quinine was given while they waited

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for intravenous artesunate. One patient did not receive any anti-malarial on initial diagnosis of severe malaria and waited 4 hours before receiving intravenous artesunate (Table 3).

Current cost of drugs.

By the standards of emergency life-saving drugs used in high-resource settings, artesunate is not expensive. Drug wastage associated with universal stockage poses an opportunity cost while artesunate supplies are limited, as hospitals seeing many cases may consequently have inadequate drug available.

There are however some cost implications, outlined for illustrative purposes (June Minton, personal communication 2012). A course of 5x 60mg vials (total 300mg) of artesunate at 2012 prices costs £287. A 60kg adult would require 144mg per dose, so would need 1.5 packs in the first 48 hours including loading, costing £381. For IV quinine a pack of 10x 300mg amps (total 3000mg) costs £41. A 60kg adult would require 1200mg loading dose then 600mg per dose thereafter. Assuming it is given tds, this would require 4200mg in total for first 48 hours, so about 1.5 packs, costing £61. Each adult treatment course of artesunate discarded after the expiry date would therefore be around £400 on current prices.

Discussion

This study shows that whilst the majority of UK patients with malaria are seen in centres which see many cases of malaria, a significant minority are seen in centres where malaria

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is rarely seen, and 216 cases (6.1%) were seen in centres which saw fewer than 2 cases a year. Since 5-15% of cases of falciparum malaria probably become severe (although data on this are not reliable)[15] these centres will probably treat a severe case less than once every 5 years. There are 168 acute trusts in the UK and 171 centres reporting malaria over the three years, so it is seen occasionally in the majority of UK hospitals. A hub-and-spoke system for distributing artesunate was unsurprisingly associated with delays in starting treatment- in this study of a relatively limited number of patients of around 7 hours.

The degree of clustering of malaria cases in hospitals has significant operational implications. These include whether rarely used but important drugs, especially parenteral artesunate, are distributed universally or by hub-and-spoke. It also has implications for training needs, and support for hospitals with less experience of severe diseases since mortality is inversely related to experience at least at a regional level[5].

This hospital-level study is consistent with previous studies on the incidence of malaria in the UK regions[1,5] and likely reflects the UK's demographics and travelling patterns. Outside London, the South East and East of England, the frequency of falciparum malaria was low. Together, the North East, Scotland, Wales and Northern Ireland accounted for less than 4% of all cases. The North East of England and Northern Ireland each notified approximately 3 cases of falciparum malaria per year. The MRL capture rate is 66% so we estimate these regions may each see 4 to 5 cases of falciparum malaria per year. Assuming 5-15% of falciparum cases become "severe", we estimate each of these UK regions could expect to use intravenous artesunate once every 1 to 2 years. In Wales and Scotland we estimate it might be used 3 to 4 times per year, with most hospitals using no drug but long geographical distances between hospitals.

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UK intravenous artesunate supplies have been limited for several years for operational and regulatory reasons, and it is unlikely this will be resolved soon. Until supplies improve, the UK and other non-endemic countries will need to distribute and use the drug efficiently and effectively. Intravenous artesunate has a shelf-life of around 18 months. Our data suggest that a universal stock system would lead to substantial drug wastage: more than 50% of UK centres with at least one case notified 5 or fewer cases of falciparum malaria over 3 years and will seldom see severe cases; 2 UK regions notified less than 10 cases over 3 years. On the other hand, as our data shows, a hub-and-spoke system will lead to delays in providing artesunate, and since this has been associated with over 20% reduction in mortality in adults such a delay is likely to be fatal in at least some cases.

Limitations:

The MRL uses a passive case detection system, which relies on the clinician or laboratory to report malaria cases. Therefore under-reporting is inevitable: however a capture-recapture study estimated that 66% of falciparum cases in England are detected by this system[12] which is high by international standards. Case-detection rate may vary by hospital or region and it may be higher in areas where malaria is less often seen (over 90% from Scotland[13]).

Of 34 cases excluded due to incomplete data on case location, 26 were from Scotland. These cases represent a significant proportion of the total number of Scottish cases; they would not have a significant impact on the overall trends described here but make extrapolating results to Scotland difficult. The Royal Liverpool Hospital and the Hospital for Tropical Diseases are national centres for Tropical Medicine, regularly receiving patients and malaria films from throughout the UK. In 98/127 Liverpool cases and 45/266 HTD

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cases included in this study, the notifier's location and the patient's usual place-of-residence were located in different counties or regions, including Greater Manchester, South West England, Scotland and Wales. It was not clear which of these cases represented referrals and which represented temporary visitors so all Liverpool notifications were coded as "Liverpool" and all HTD notifications as "HTD". Some of these patients may have presented elsewhere initially.

HTD operates probably the largest hub-and-spoke distribution system for intravenous artesunate in the UK. Despite this, the number of cases that could be included was small: 34/50 patients receiving intravenous artesunate during this time period could be included in this study. The data we have are retrospective.To calculate the diagnosis-to-treatment time, we used the times as documented in the medical records. Clinicians do not always document decisions or diagnoses immediately, so the diagnosis-to-treatment times may appear shorter in this study, which is therefore conservative on delay which may well in practice be longer than recorded.

Conclusions

If intravenous artesunate becomes first-line treatment for severe malaria in Europe, UK hospitals will require rapid and reliable access to this emergency drug. While artesunate supplies remain limited, a hub-and-spoke system, based around regional infection centres will minimise drug wastage and ensure the drug is available in the centres which see most cases, but will lead to delays, and almost certainly some avoidable deaths in centres which less regularly see cases and are geographically some way from hubs. A system which restricts artesunate to hospitals that see over 100 cases in 3 years would lead to two-thirds of cases being in other centres. Even having artesunate in the 31 hospitals that see more

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than 50 cases in 3 years would leave over 25% of malaria cases being treated elsewhere. When parenteral artesunate becomes more freely available, these data suggest the UK should move rapidly towards universal drug distribution, aiming for all acute hospitals to maintain permanent stocks, to ensure early artesunate treatment for all UK severe malaria cases.

Acknowlegements.

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Table 1

Reported cases of falciparum malaria by UK region, 2008-2010

	2008		2009		2010		All 3 years	
	Number	% of total	Number	% of total	Number	% of total	Number	% of total
North East	1	0.1	4	0.3	5	0.4	10	0.3
North West	49	4.5	58	5	85	6.7	192	5.4
Yorkshire & Humber	19	1.8	26	2.2	53	4.2	98	2.8
East Midlands	15	1.4	18	1.5	34	2.7	67	1.9
West Midlands	27	2.5	45	3.8	53	4.2	125	3.6
East of England	140	12.9	124	10.6	138	10.9	402	11.4
South East	164	15.1	161	13.7	190	15.1	515	14.6
South West	30	2.8	24	2.1	34	2.7	88	2.5
Greater London	614	56.6	682	58.1	629	49.9	1925	54.7
Scotland	13	1.2	18	1.5	22	1.7	53	1.5
Wales	10	0.9	10	0.9	16	1.3	36	1
Northern Ireland	2	0.2	4	0.3	3	0.2	9	0.3
Total	1084		1174		1262		3520	

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Table 2

Number of UK hospitals notifying cases of falciparum malaria, 2008-2010

Number of cases notified in 3 years	Number of centres	Total number of cases	% of UK total cases	Cumulative % of UK cases
>100	8	1547	43.9	43.9
51-100	8	552	15.7	59.6
26-50	15	497	14.1	73.7
11-25	33	565	16.1	89.8
6-10	19	143	4.1	93.9
1-5	88	216	6.1	100

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Table 3

Falciparum cases treated with intravenous artesunate from the Hospital for Tropical Diseases

Age	Gender	Parasitaemia on admission	Number of clinical features of severity	Admitting hospital	Site of first artesunate dose	Diagnosis-to-treatment time (hrs)	Initial anti-malarial
57	M	2.3	1	Elsewhere	Elsewhere	12	iv quinine & doxycycline
41	M	15	6	Elsewhere	Elsewhere	13	iv quinine
34	F	37	1	Elsewhere	HTD	14	iv quinine
45	M	27	0	Elsewhere	HTD	41.5	iv quinine
51	M	15	3	Elsewhere	HTD	13	iv quinine
62	F	17	0	Elsewhere	Elsewhere	5	iv quinine
38	M	8	1	Elsewhere	Elsewhere	26	iv quinine & im artemether
24	F	2.7	0	HTD	HTD	1	iv artesunate
24	M	2.6	0	Elsewhere	HTD	29	iv quinine
39	M	23	3	Elsewhere	Elsewhere	4.5	iv quinine
46	M	8.1	2	Elsewhere	HTD	34	iv quinine
41	M	2.3	2	Elsewhere	HTD	9	iv quinine
47	F	0.2 (recurrence)	0	HTD	HTD	5	iv artesunate
46	M	20	2	Elsewhere	Elsewhere	8	iv quinine
45	F	1.8	1	Elsewhere	HTD	45	iv quinine
42	M	1	0	HTD	HTD	3.5	iv artesunate
36	M	0.3	1	HTD	HTD	1	iv artesunate
49	M	15	1	HTD	HTD	5	iv quinine
17	M	1.1	0	HTD	HTD	11	iv quinine
52	F	50	4	Elsewhere	Elsewhere	Unknown	iv quinine
34	F	22	4	Elsewhere	Elsewhere	4	iv artesunate & clindamycin
52	F	5.2	0	Elsewhere	Elsewhere	Unknown	Unknown

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27	F	5	0	Elsewhere	HTD	Unknown	iv quinine
52	M	10	1	Elsewhere	HTD	33	iv quinine
36	M	17.2	0	HTD	HTD	0.5	iv artesunate
41	F	10	1	Elsewhere	Elsewhere	7.5	iv quinine & doxycycline
35	F	9	0	Elsewhere	Elsewhere	Unknown	iv quinine
70	M	8	1	Elsewhere	Elsewhere	Unknown	iv quinine
51	M	9.2	0	Elsewhere	Elsewhere	5	iv quinine
39	M	30	2	Elsewhere	HTD	Unknown	iv quinine
31	F	4.8	1	Elsewhere	HTD	Unknown	iv quinine
30	M	26.8	2	Elsewhere	HTD	21.5	iv quinine
47	F	12.5	2	Elsewhere	HTD	14.5	iv quinine
43	M	16.4	3	Elsewhere	HTD	Unknown	iv quinine

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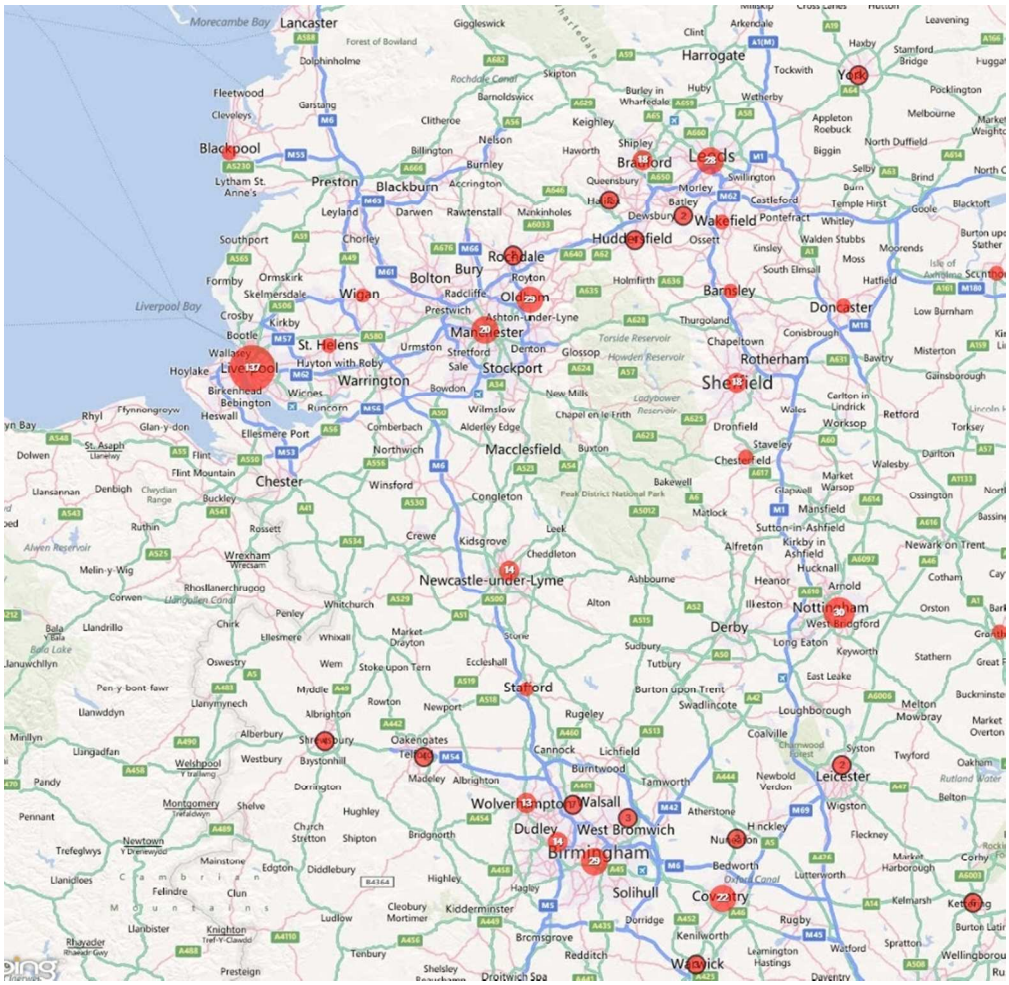
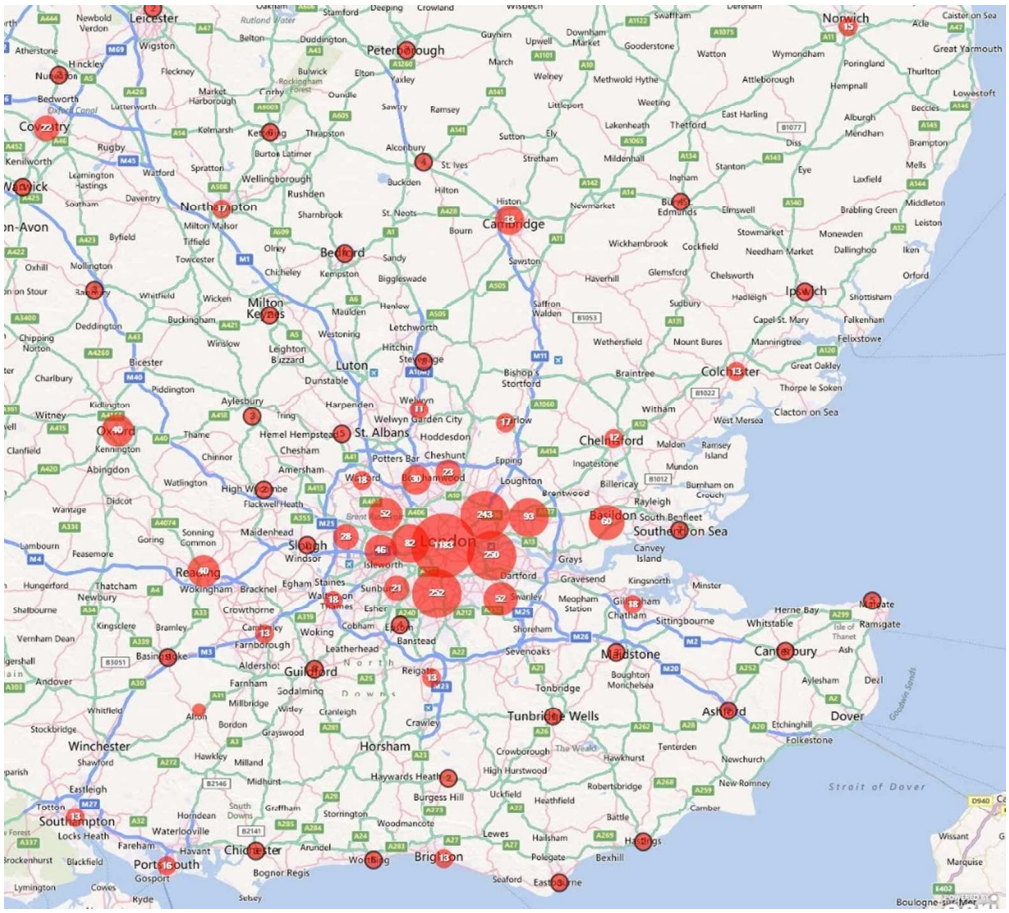
Map 1. Geographical distribution of falciparum malaria notifications in the UK, 2008-2010
143x166mm (96 x 96 DPI)

Map 2. Geographical distribution of falciparum malaria notifications in England, 2008-2010
230x238mm (96 x 96 DPI)

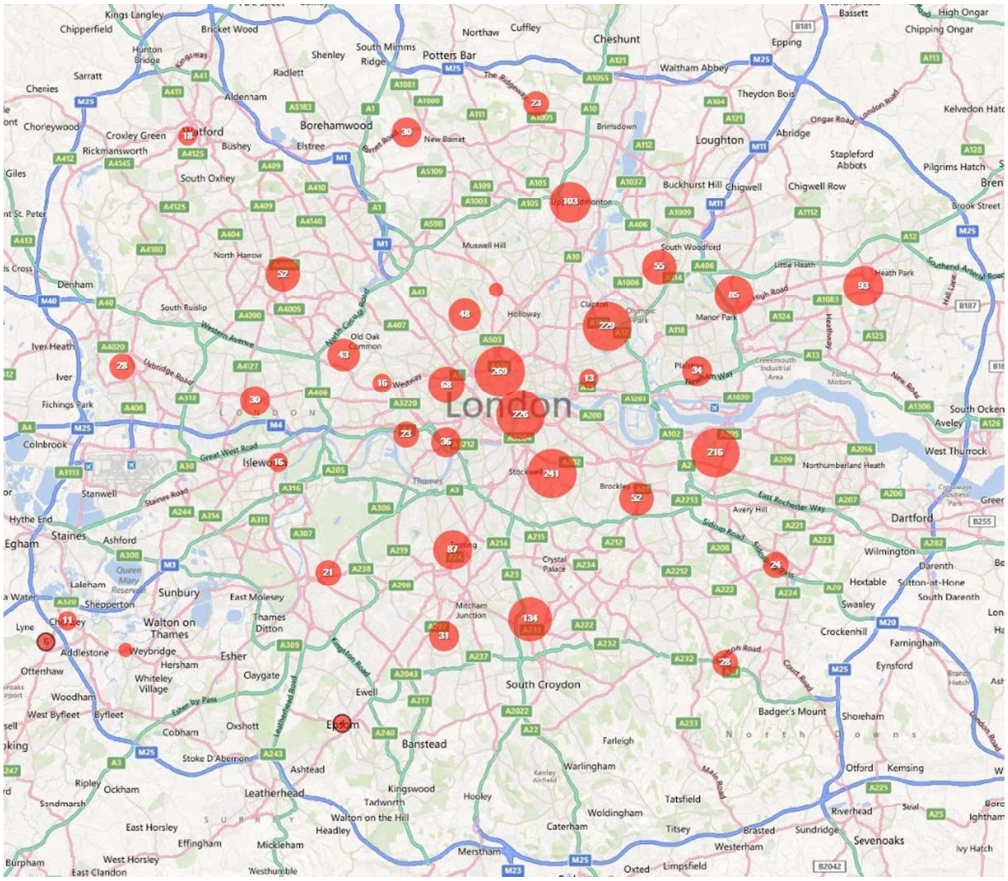


Map 3. Geographical distribution of falciparum malaria notifications in the North West and West Midlands, 2008-2010
262x255mm (96 x 96 DPI)



Map 4. Geographical distribution of falciparum malaria notifications in the South East and East of England, 2008-2010
278x251mm (96 x 96 DPI)

only



Map 5. Geographical distribution of falciparum malaria notifications in Greater London, 2008-2010
274x239mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Geographical concentration of falciparum malaria treated in the United Kingdom and delay-to-treatment with artesunate in severe cases: an observational study.

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Geographical concentration of falciparum malaria treated in the United Kingdom and delay to treatment with artesunate in severe cases: an observational study.

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Abstract

Objectives: To quantify geographical concentration of falciparum malaria cases in the UK at a hospital level. To assess potential delay-to-treatment associated with hub-and-spoke distribution of artesunate in severe cases.

Design:

Observational study using national and hospital data

Setting and participants:

3,520 patients notified to the Malaria Reference Laboratory 2008-2010, 34 patients treated with intravenous artesunate from a tropical diseases centre 2002-2010.

Main outcome measures:

Geographical location of falciparum cases notified in the UK. Diagnosis-to-treatment times for intravenous artesunate.

Results

Eight centres accounted for 43.9% of the UK's total cases; notifications from 107 centres accounted for 10.2% of cases; 51.5% of hospitals seeing malaria notified 5 or fewer cases in 3 years. Centres that saw <10 cases/year treat 26.3% of malaria cases; 6.1% of cases are treated in hospitals seeing < 2 cases/ year. Concentration of falciparum malaria was highest in Greater London (1925, 54.7%), South East (515, 14.6%), East of England (402, 11.4%) and North West (192, 5.4%). The North East and Northern Ireland each notified 5 or fewer cases per year. Median diagnosis-to-treatment time was 1 hour (range 0.5-5) for patients receiving artesunate in the specialist centre; 7.5 hours (range 4-26) for patients receiving it in referring hospitals via the hub and spoke system (p 0.02); 25 hours (range 9-

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45) for patients receiving it on transfer to the regional centre from a referring hospital (p 0.002).

Conclusions

Most UK hospitals see few cases of falciparum malaria and geographical distances are significant. Over 25% of cases are seen in hospitals where malaria is rare, although 60% are seen in hospitals seeing over 50 cases over 3 years. A hub-and-spoke system minimises drug wastage and ensures availability in centres seeing most cases but is associated with treatment delays elsewhere. As with all observational studies, there are limitations, which are discussed.

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Introduction

Falciparum malaria remains an important cause of morbidity and mortality in returning travelers. In the United Kingdom (UK), there are 1200 to 1600 cases of falciparum malaria annually, most from Africa or Asia, with an overall case-fatality rate of 7.4 per 1000 reported cases[1]. Around 15% of falciparum cases in the UK are "severe" (Malaria Reference Laboratory 2012) based on World Health Organisation (WHO) criteria[2]. Delay to effective treatment and lack of experience of dealing with severe malaria are associated with poor outcome in severe cases[3,4,5].

Worldwide, parenteral quinine has been the mainstay of treatment for severe falciparum malaria for over a century and was first-line treatment in the last UK treatment guidelines (2007[6]). However, two recent large multicentre randomised control trials have demonstrated a significant mortality reduction with intravenous artesunate versus intravenous quinine in severe falciparum infection in African children (AQUAMAT study[7]) and Asian adults (SEAQUAMAT study[8]). In light of this new evidence, WHO now recommends intravenous artesunate as first-line treatment for severe falciparum infections[2]. It is almost certain the reduced mortality applies also in travellers returning from those regions. Artesunate is also easier to use than intravenous quinine: it can be administered as a bolus rather than an infusion; has no known cardiotoxicity; it is not known to cause hypoglycaemia associated with quinine[8,9]. For these reasons it is likely to replace quinine as the treatment of choice in the United Kingdom and other countries seeing cases of severe malaria once Good Manufacturing Practice (GMP) licenced drug is available.

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Intravenous artesunate is available in the UK but its use has been limited by restricted availability. Until recently, just one pharmaceutical company, based in Shanghai, was manufacturing the drug for international export. Their product, used in the AQUAMAT and SEAQUAMT trials[7,8], only gained WHO pre-qualification status in November 2010[10]. Production is increasing worldwide but parenteral artesunate remains unlicensed for use in the UK. Few hospitals regularly stock intravenous artesunate and national supplies have been limited (June Minton, Hospital for Tropical Diseases, personal communication 2012). Additionally the shelf-life of artesunate (around 18 months) is much lower than for quinine, an operational issue for hospitals which see few cases.

Given the clear outcome advantages of artesunate but its limited availability, two models of drug distribution might be considered: *universal stock in all acute hospitals (blanket coverage)* and a *hub-and-spoke system* where critical stocks are kept in specialist centres and couriered out when needed to hospitals with severe malaria cases. A form of hub-and-spoke system has operated to date.

Minimising delay to effective treatment is essential in severe cases[3,4,11]. Geographical distance is a key consideration for delay. There is existing evidence of geographical clustering of malaria at a regional level[1], but this is too broad brush to help with decisions on a hub-and-spoke compared to blanket coverage distribution for a drug which many centres will use rarely if at all. In this study, we aim to quantify the geographical concentration of falciparum malaria in the UK at hospital level, using data from the Health Protection Agency Malaria Reference Laboratory. We also examine data from a tertiary tropical diseases centre that operates a hub-and-spoke system to distribute artesunate to referring hospitals, aiming to assess potential delay-to-treatment associated with this system.These data will inform decisions on the optimal means of distributing intravenous

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artesunate UK-wide. The geographical concentration of cases is also relevant to training needs for clinical and laboratory staff in the diagnosis and management of malaria. The approach should also help other countries with imported malaria which do not currently have universal artesunate coverage (most of them) consider the data they will need for their decisions.

Methods

Malaria is a notifiable disease in the UK: clinicans are required to report all cases by law. The Malaria Reference Laboratory (MRL), part of the UK Health Protection Agency (HPA), maintains the national surveillance database of reported malaria cases in the UK. It identifies malaria cases from statutory notification through local authorities; through laboratories sending blood films for diagnostic verification; through clinicians sending standardised malaria reports to the MRL. When a malaria case is notified, the MRL contacts the responsible clinician who is asked to complete a data collection form covering demographic and clinical data, including the notifying hospital's location and the patient's usual place-of-residence.This passive case detection system has been shown to identify at least 66% of cases of falciparum malaria in the UK[12] and over 90% of cases in Scotland[13].

The MRL database was used to identify the location of every notified case of falciparum malaria in the UK in the years 2008, 2009 and 2010. For Greater London, the notifying hospital's name was recorded given the large number of hospitals; outside Greater London, the notifying hospital's town was recorded.The patient's usual place-of-residence was also recorded. Cases were excluded if there was insufficient information to identify accurately the notifying hospital or town. Where the notifying hospital's location and the patient's usual place-of-residence differed significantly (eg. notified from Liverpool, place-of-residence Cardiff), the notifying hospital's location was recorded as case location.

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Data were anonymised and analysis was performed using EpiInfo and STATA 11. For each notifying site, the annual frequency of falciparum malaria and the total number of cases over 3 years was calculated. Using the decimal geographic coordinates of each notifying site, maps showing the geographical distribution of falciparum malaria within the UK and within each UK region, weighted for caseload, were generated. Cases were also analysed by the UK Government Office Region from which they were reported (North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South East, South West, Greater London, Northern Ireland, Scotland and Wales)[14].

The Hospital for Tropical Diseases (HTD), London has been using intravenous artesunate in cases of severe malaria since 2002 and provides a hub-and-spoke distribution service. It arranges for intravenous artesunate to be couriered from its permanent stocks to referring hospitals via its Tropical Medicine telephone advice service when requested based on clinical need. HTD's Pharmacy records were used to identify inpatients treated with intravenous artesunate at any hospital (including HTD) between 2002 and August 2010. The referring hospitals' pharmacies were contacted and patient identities confirmed. Patients' medical and laboratory records were reviewed after seeking appropriate permission from the hospitals. A standardised proforma was used to record the following for every patient: demographics; parasitaemia; clinical features of severity (based on WHO criteria[2]) initial anti-malarial used; time of malaria diagnosis; time of first treatment with intravenous artesunate. All data were anonymised.

The diagnosis-to-treatment time was calculated for each case (time from the diagnosis of severe malaria as documented in the notes to time of first dose of intravenous artesunate as signed for on the drug chart). Difference between cases treated in a hospital with

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stocks, hospitals where artesunate was couriered and differences with hospitals which transferred patients were calculated by the Wilcoxon Rank Sum test.

Results:

Geographical clustering of cases in the UK

Of 3556 cases of falciparum malaria notified to the MRL between 2008 and 2010: 1096 cases were in 2008; 1185 cases in 2009; 1275 cases in 2010. We excluded 12 cases from 2008 (9 Scotland, 1 Berkshire, 2 London); 11 cases from 2009 (9 Scotland, 2 London); 13 cases from 2010: (8 Scotland, 1 West Yorkshire, 2 London, 1 Surrey, 1 Somerset) due to incomplete geographical data, so in total 3520 cases are included in this study.

Of these cases, 54.7% were notified from London, 14.6% from the South East, 11.4% from Eastern England, 5.5% from the North West. Together, the North East of England and Northern Ireland accounted for just 0.6% of cases, each notifying 5 or fewer cases per year (Table 1). Within all regions, cases were clustered around larger towns and cities and these are plotted out for the UK (Map 1), England (Map 2), the North West and West Midlands (Map 3), the South East and East of England (Map 4) and Greater London (Map 5).

Over the three years studied, eight centres notified more than 100 cases (6 Greater London hospitals, Croydon and Liverpool). Cases from these eight centres made up 43.9% of the UK's total cases. Notifications from 31 centres accounted for 73.7% of the UK's total; 18 of these were Greater London hospitals. In contrast, 140 centres that saw fewer than a case a month saw 26% of cases (924), and 6% of cases were seen in

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centres which saw less than 2 patients a year, many of which were some way from a potential hub (Table 2 and maps).

Intravenous artesunate via hub-and-spoke and time-to treatment.

HTD pharmacy records identified 50 patients who started intravenous artesunate, 22 at HTD. Clinical data were available for 21 of these HTD cases (one case missing medical records), 14 of whom were transferred in from referring hospitals. Records identified 28 patients in referring hospitals treated with intravenous artesunate sent from HTD. Of these 13 could be included in this study (8 cases had incomplete patient identifiers; 7 cases incomplete medical records). 10 patients were in London hospitals, 2 in the South East and 1 in Eastern England. Therefore, 34 patients were included in total: 21 men and 13 women, age range 17- 70 years, median age 41 years. All were resident in the UK. 23 (68%) had returned from West Africa, 9 (26%) from East Africa, 1 from Central Africa (3%), 1 from Thailand (3%). High parasite count was the most common criterion for starting intravenous artesunate: 29 of the 34 had a count greater than 2% on admission; 24 had a count greater than 5%. On presentation, 12 had cerebral malaria (35%), 10 had respiratory distress (29%), 6 had acute renal impairment (18%) and 12 (35%) had 2 or more clinical features of severe malaria (Table 3).

In 23 cases (68%) the diagnosis-to-treatment time could be calculated (data unavailable for the remaining 11 cases). For 4/4 patients admitted to HTD with severe malaria, median time was 1 hour, range 0.5 to 5 hours. For 9/13 patients who required artesunate to be couriered to their referring hospital, median time was 7.5 hours, range 4 to 26 hours, difference from the four treated in a hospital with drug stocks (HTD) of p 0.02 (Rank Sum). For 10/14 patients who presented elsewhere but were transferred to and given artesunate

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at HTD, median time was 25 hours, range 9 to 45 hours, difference from the patients where artesunate was couriered p 0.002. For 25/26 patients admitted to a referring hospital, intravenous quinine was given while they waited for intravenous artesunate. One patient did not receive any anti-malarial on initial diagnosis of severe malaria and waited 4 hours before receiving intravenous artesunate (Table 3).

Current cost of drugs.

By the standards of emergency life-saving drugs used in high-resource settings, artesunate is not expensive. Drug wastage associated with universal stockage poses an opportunity cost while artesunate supplies are limited, as hospitals seeing many cases may consequently have inadequate drug available.

There are however some cost implications, outlined for illustrative purposes (June Minton, personal communication 2012). A course of 5x 60mg vials (total 300mg) of artesunate at 2012 prices costs £287. A 60kg adult would require 144mg per dose, so would need 1.5 packs in the first 48 hours including loading, costing £381. For IV quinine a pack of 10x 300mg amps (total 3000mg) costs £41. A 60kg adult would require 1200mg loading dose then 600mg per dose thereafter. Assuming it is given tds, this would require 4200mg in total for first 48 hours, so about 1.5 packs, costing £61. Each adult treatment course of artesunate discarded after the expiry date would therefore be around £400 on current prices.

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Discussion

This study shows that whilst the majority of UK patients with malaria are seen in centres which see many cases of malaria, a significant minority are seen in centres where malaria is rarely seen, and 216 cases (6.1%) were seen in centres which saw fewer than 2 cases a year. Since 5-15% of cases of falciparum malaria probably become severe (although data on this are not reliable)[15] these centres will probably treat a severe case less than once every 5 years. There are 168 acute trusts in the UK and 171 centres reporting malaria over the three years, so it is seen occasionally in the majority of UK hospitals. A hub-and-spoke system for distributing artesunate was unsurprisingly associated with delays in starting treatment- in this study of a relatively limited number of patients of around 7 hours.

The degree of clustering of malaria cases in hospitals has significant operational implications. These include whether rarely used but important drugs, especially parenteral artesunate, are distributed universally or by hub-and-spoke. It also has important implications for clinical care standards and training since malaria mortality is inversely related to experience at least at a regional level in the UK[5], a pattern which is almost certainly seen in other non-endemic countries. Idenitifying training needs and providing support for hospitals with less experience of malaria is important for minimising delays in diagnosis and improving clinical outcomes.

This hospital-level study is consistent with previous studies on the incidence of malaria in the UK regions[1,5] and likely reflects the UK's demographics and travelling patterns. Outside London, the South East and East of England, the frequency of falciparum malaria was low. Together, the North East, Scotland, Wales and Northern Ireland accounted for less than 4% of all cases. The North East of England and Northern Ireland each notified

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approximately 3 cases of falciparum malaria per year. The MRL capture rate is 66% so we estimate these regions may each see 4 to 5 cases of falciparum malaria per year. Assuming 5-15% of falciparum cases become “severe”, we estimate each of these UK regions could expect to use intravenous artesunate once every 1 to 2 years. In Wales and Scotland we estimate it might be used 3 to 4 times per year, with most hospitals using no drug but long geographical distances between hospitals.

UK intravenous artesunate supplies have been limited for several years for operational and regulatory reasons, and it is unlikely this will be resolved soon. Until supplies improve, the UK and other non-endemic countries will need to distribute and use the drug efficiently and effectively. Intravenous artesunate has a shelf-life of around 18 months. Our data suggest that a universal stock system would lead to substantial drug wastage: more than 50% of UK centres with at least one case notified 5 or fewer cases of falciparum malaria over 3 years and will seldom see severe cases; 2 UK regions notified less than 10 cases over 3 years. On the other hand, as our data shows, a hub-and-spoke system will lead to delays in providing artesunate, and since this has been associated with over 20% reduction in mortality in adults such a delay is likely to be fatal in at least some cases.

Limitations:

The MRL uses a passive case detection system, which relies on the clinician or laboratory to report malaria cases. Therefore under-reporting is inevitable: however a capture-recapture study estimated that 66% of falciparum cases in England are detected by this system[12] which is high by international standards. Case-detection rate may vary by hospital or region as some units may disproportionately under-report cases. For example, the same study found that London had a higher detection rate than the rest of England.

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Hospitals that rarely see malaria may be less familiar with reporting systems; so this study may underestimate the proportion of the UK's malaria cases seen in these centres. Scotland has been shown to have a very high case detection rate (over 90%[13]).

Of 34 cases excluded due to incomplete data on case location, 26 were from Scotland. These cases represent a significant proportion of the total number of Scottish cases; they would not have a significant impact on the overall trends described here but make extrapolating results to Scotland difficult. The Royal Liverpool Hospital and the Hospital for Tropical Diseases are national centres for Tropical Medicine, regularly receiving patients and malaria films from throughout the UK. In 98/127 Liverpool cases and 45/266 HTD cases included in this study, the notifier's location and the patient's usual place-of-residence were located in different counties or regions, including Greater Manchester, South West England, Scotland and Wales. It was not clear which of these cases represented referrals and which represented temporary visitors so all Liverpool notifications were coded as "Liverpool" and all HTD notifications as "HTD". Some of these patients may have presented elsewhere initially.

HTD operates probably the largest hub-and-spoke distribution system for intravenous artesunate in the UK. Despite this, the number of cases that could be included was small: 34/50 patients receiving intravenous artesunate during this time period could be included in this study. The data we have are retrospective.To calculate the diagnosis-to-treatment time, we used the times as documented in the medical records. Clinicians do not always document decisions or diagnoses immediately, so the diagnosis-to-treatment times may appear shorter in this study, which is therefore conservative on delay which may well in practice be longer than recorded.

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Conclusions

If intravenous artesunate becomes first-line treatment for severe malaria in Europe, UK hospitals will require rapid and reliable access to this emergency drug. While artesunate supplies remain limited, a hub-and-spoke system, based around regional infection centres will minimise drug wastage and ensure the drug is available in the centres which see most cases, but will lead to delays, and almost certainly some avoidable deaths in centres which less regularly see cases and are geographically some way from hubs. A system which restricts artesunate to hospitals that see over 100 cases in 3 years would lead to two-thirds of cases being in other centres. Even having artesunate in the 31 hospitals that see more than 50 cases in 3 years would leave over 25% of malaria cases being treated elsewhere. When parenteral artesunate becomes more freely available, these data suggest the UK should move rapidly towards universal drug distribution, aiming for all acute hospitals to maintain permanent stocks, to ensure early artesunate treatment for all UK severe malaria cases.

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Table 1

Reported cases of falciparum malaria by UK region, 2008-2010

	2008		2009		2010		All 3 years	
	Number	% of total	Number	% of total	Number	% of total	Number	% of total
North East	1	0.1	4	0.3	5	0.4	10	0.3
North West	49	4.5	58	5	85	6.7	192	5.4
Yorkshire & Humber	19	1.8	26	2.2	53	4.2	98	2.8
East Midlands	15	1.4	18	1.5	34	2.7	67	1.9
West Midlands	27	2.5	45	3.8	53	4.2	125	3.6
East of England	140	12.9	124	10.6	138	10.9	402	11.4
South East	164	15.1	161	13.7	190	15.1	515	14.6
South West	30	2.8	24	2.1	34	2.7	88	2.5
Greater London	614	56.6	682	58.1	629	49.9	1925	54.7
Scotland	13	1.2	18	1.5	22	1.7	53	1.5
Wales	10	0.9	10	0.9	16	1.3	36	1
Northern Ireland	2	0.2	4	0.3	3	0.2	9	0.3
Total	1084		1174		1262		3520	

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Table 2

Number of UK hospitals notifying cases of falciparum malaria, 2008-2010

Number of cases notified in 3 years	Number of centres	Total number of cases	% of UK total cases	Cumulative % of UK cases
>100	8	1547	43.9	43.9
51-100	8	552	15.7	59.6
26-50	15	497	14.1	73.7
11-25	33	565	16.1	89.8
6-10	19	143	4.1	93.9
1-5	88	216	6.1	100

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Table 3

Falciparum cases treated with intravenous artesunate from the Hospital for Tropical Diseases

Age	Gender	County of residence	Country of travel	Parasitaemia on admission	Number of clinical features of severity	Admitting hospital	Site of first artesunate dose	Diagnosis-to-treatment time (hrs)	Initial anti-malarial
57	M	UK	Nigeria	2.3	1	Elsewhere	Elsewhere	12	iv quinine & doxycycline
41	M	UK	Gambia	15	6	Elsewhere	Elsewhere	13	iv quinine
34	F	UK	Nigeria	37	1	Elsewhere	HTD	14	iv quinine
45	M	UK	Gambia & Liberia	27	0	Elsewhere	HTD	41.5	iv quinine
51	M	UK	Nigeria	15	3	Elsewhere	HTD	13	iv quinine
62	F	UK	Ghana	17	0	Elsewhere	Elsewhere	5	iv quinine
38	M	UK	Nigeria	8	1	Elsewhere	Elsewhere	26	iv quinine & im artemether
24	F	UK	Uganda	2.7	0	HTD	HTD	1	iv artesunate
24	M	UK	Thailand	2.6	0	Elsewhere	HTD	29	iv quinine
39	M	UK	Kenya	23	3	Elsewhere	Elsewhere	4.5	iv quinine
46	M	UK	Nigeria	8.1	2	Elsewhere	HTD	34	iv quinine
41	M	UK	Uganda	2.3	2	Elsewhere	HTD	9	iv quinine
47	F	UK	Mozambique	0.2 (recurrence)	0	HTD	HTD	5	iv artesunate
46	M	UK	Sudan	20	2	Elsewhere	Elsewhere	8	iv quinine
45	F	UK	Uganda	1.8	1	Elsewhere	HTD	45	iv quinine
42	M	UK	Nigeria	1	0	HTD	HTD	3.5	iv artesunate
36	M	UK	Nigeria	0.3	1	HTD	HTD	1	iv artesunate
49	M	UK	DR Congo	15	1	HTD	HTD	5	iv quinine
17	M	UK	Sierra Leone	1.1	0	HTD	HTD	11	iv quinine
52	F	UK	Ghana	50	4	Elsewhere	Elsewhere	Unknown	iv quinine
34	F	UK	Ghana	22	4	Elsewhere	Elsewhere	4	iv artesunate & clindamycin

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52	F	UK	Sierra Leone	5.2	0	Elsewhere	Elsewhere	Unknown	Unknown
27	F	UK	Tanzania	5	0	Elsewhere	HTD	Unknown	iv quinine
52	M	UK	Kenya	10	1	Elsewhere	HTD	33	iv quinine
36	M	UK	Gabon	17.2	0	HTD	HTD	0.5	iv artesunate
41	F	UK	Ghana	10	1	Elsewhere	Elsewhere	7.5	iv quinine & doxycycline
35	F	UK	Ghana & Ivory Coast	9	0	Elsewhere	Elsewhere	Unknown	iv quinine
70	M	UK	Nigeria	8	1	Elsewhere	Elsewhere	Unknown	iv quinine
51	M	UK	Nigeria	9.2	0	Elsewhere	Elsewhere	5	iv quinine
39	M	UK	Uganda	30	2	Elsewhere	HTD	Unknown	iv quinine
31	F	UK	Nigeria	4.8	1	Elsewhere	HTD	Unknown	iv quinine
30	M	UK	Sierra Leone	26.8	2	Elsewhere	HTD	21.5	iv quinine
47	F	UK	Sierra Leone	12.5	2	Elsewhere	HTD	14.5	iv quinine
43	M	UK	Ghana	16.4	3	Elsewhere	HTD	Unknown	iv quinine

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Geographical concentration of falciparum malaria treated in the United Kingdom and delay to treatment with artesunate in severe cases: an observational study.

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Abstract

Objectives: To quantify geographical concentration of falciparum malaria cases in the UK at a hospital level. To assess potential delay-to-treatment associated with hub-and-spoke distribution of artesunate in severe cases.

Design:

Observational study using national and hospital data

Setting and participants:

3,520 patients notified to the Malaria Reference Laboratory 2008-2010, 34 patients treated with intravenous artesunate from a tropical diseases centre 2002-2010.

Main outcome measures:

Geographical location of falciparum cases notified in the UK. Diagnosis-to-treatment times for intravenous artesunate.

Results

Eight centres accounted for 43.9% of the UK's total cases; notifications from 107 centres accounted for 10.2% of cases; 51.5% of hospitals seeing malaria notified 5 or fewer cases in 3 years. Centres that saw <10 cases/year treat 26.3% of malaria cases; 6.1% of cases are treated in hospitals seeing < 2 cases/ year. Concentration of falciparum malaria was highest in Greater London (1925, 54.7%), South East (515, 14.6%), East of England (402, 11.4%) and North West (192, 5.4%). The North East and Northern Ireland each notified 5 or fewer cases per year. Median diagnosis-to-treatment time was 1 hour (range 0.5-5) for patients receiving artesunate in the specialist centre; 7.5 hours (range 4-26) for patients receiving it in referring hospitals via the hub and spoke system (p 0.02); 25 hours (range 9-

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45) for patients receiving it on transfer to the regional centre from a referring hospital (p 0.002).

Conclusions

Most UK hospitals see few cases of falciparum malaria and geographical distances are significant. Over 25% of cases are seen in hospitals where malaria is rare, although 60% are seen in hospitals seeing over 50 cases over 3 years. A hub-and-spoke system minimises drug wastage and ensures availability in centres seeing most cases but is associated with treatment delays elsewhere. As with all observational studies, there are limitations, which are discussed.

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Introduction

Falciparum malaria remains an important cause of morbidity and mortality in returning travelers. In the United Kingdom (UK), there are 1200 to 1600 cases of falciparum malaria annually, most from Africa or Asia, with an overall case-fatality rate of 7.4 per 1000 reported cases[1]. Around 15% of falciparum cases in the UK are "severe" (Malaria Reference Laboratory 2012) based on World Health Organisation (WHO) criteria[2]. Delay to effective treatment and lack of experience of dealing with severe malaria are associated with poor outcome in severe cases[3,4,5].

Worldwide, parenteral quinine has been the mainstay of treatment for severe falciparum malaria for over a century and was first-line treatment in the last UK treatment guidelines (2007[6]). However, two recent large multicentre randomised control trials have demonstrated a significant mortality reduction with intravenous artesunate versus intravenous quinine in severe falciparum infection in African children (AQUAMAT study[7]) and Asian adults (SEAQUAMAT study[8]). In light of this new evidence, WHO now recommends intravenous artesunate as first-line treatment for severe falciparum infections[2]. It is almost certain the reduced mortality applies also in travellers returning from those regions. Artesunate is also easier to use than intravenous quinine: it can be administered as a bolus rather than an infusion; has no known cardiotoxicity; it is not known to cause hypoglycaemia associated with quinine[8,9]. For these reasons it is likely to replace quinine as the treatment of choice in the United Kingdom and other countries seeing cases of severe malaria once Good Manufacturing Practice (GMP) licenced drug is available.

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Intravenous artesunate is available in the UK but its use has been limited by restricted availability. Until recently, just one pharmaceutical company, based in Shanghai, was manufacturing the drug for international export. Their product, used in the AQUAMAT and SEAQUAMT trials[7,8], only gained WHO pre-qualification status in November 2010[10]. Production is increasing worldwide but parenteral artesunate remains unlicensed for use in the UK. Few hospitals regularly stock intravenous artesunate and national supplies have been limited (June Minton, Hospital for Tropical Diseases, personal communication 2012). Additionally the shelf-life of artesunate (around 18 months) is much lower than for quinine, an operational issue for hospitals which see few cases.

Given the clear outcome advantages of artesunate but its limited availability, two models of drug distribution might be considered: *universal stock in all acute hospitals (blanket coverage)* and a *hub-and-spoke system* where critical stocks are kept in specialist centres and couriered out when needed to hospitals with severe malaria cases. A form of hub-and-spoke system has operated to date.

Minimising delay to effective treatment is essential in severe cases[3,4,11]. Geographical distance is a key consideration for delay. There is existing evidence of geographical clustering of malaria at a regional level[1], but this is too broad brush to help with decisions on a hub-and-spoke compared to blanket coverage distribution for a drug which many centres will use rarely if at all. In this study, we aim to quantify the geographical concentration of falciparum malaria in the UK at hospital level, using data from the Health Protection Agency Malaria Reference Laboratory. We also examine data from a tertiary tropical diseases centre that operates a hub-and-spoke system to distribute artesunate to referring hospitals, aiming to assess potential delay-to-treatment associated with this system.These data will inform decisions on the optimal means of distributing intravenous

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artesunate UK-wide. The geographical concentration of cases is also relevant to training needs for clinical and laboratory staff in the diagnosis and management of malaria. The approach should also help other countries with imported malaria which do not currently have universal artesunate coverage (most of them) consider the data they will need for their decisions.

Methods

Malaria is a notifiable disease in the UK: clinicans are required to report all cases by law. The Malaria Reference Laboratory (MRL), part of the UK Health Protection Agency (HPA), maintains the national surveillance database of reported malaria cases in the UK. It identifies malaria cases from statutory notification through local authorities; through laboratories sending blood films for diagnostic verification; through clinicians sending standardised malaria reports to the MRL. When a malaria case is notified, the MRL contacts the responsible clinician who is asked to complete a data collection form covering demographic and clinical data, including the notifying hospital's location and the patient's usual place-of-residence.This passive case detection system has been shown to identify at least 66% of cases of falciparum malaria in the UK[12] and over 90% of cases in Scotland[13].

The MRL database was used to identify the location of every notified case of falciparum malaria in the UK in the years 2008, 2009 and 2010. For Greater London, the notifying hospital's name was recorded given the large number of hospitals; outside Greater London, the notifying hospital's town was recorded.The patient's usual place-of-residence was also recorded. Cases were excluded if there was insufficient information to identify accurately the notifying hospital or town. Where the notifying hospital's location and the patient's usual place-of-residence differed significantly (eg. notified from Liverpool, place-of-residence Cardiff), the notifying hospital's location was recorded as case location.

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Data were anonymised and analysis was performed using EpiInfo and STATA 11. For each notifying site, the annual frequency of falciparum malaria and the total number of cases over 3 years was calculated. Using the decimal geographic coordinates of each notifying site, maps showing the geographical distribution of falciparum malaria within the UK and within each UK region, weighted for caseload, were generated. Cases were also analysed by the UK Government Office Region from which they were reported (North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South East, South West, Greater London, Northern Ireland, Scotland and Wales)[14].

The Hospital for Tropical Diseases (HTD), London has been using intravenous artesunate in cases of severe malaria since 2002 and provides a hub-and-spoke distribution service. It arranges for intravenous artesunate to be couriered from its permanent stocks to referring hospitals via its Tropical Medicine telephone advice service when requested based on clinical need. HTD's Pharmacy records were used to identify inpatients treated with intravenous artesunate at any hospital (including HTD) between 2002 and August 2010. The referring hospitals' pharmacies were contacted and patient identities confirmed. Patients' medical and laboratory records were reviewed after seeking appropriate permission from the hospitals. A standardised proforma was used to record the following for every patient: demographics; parasitaemia; clinical features of severity (based on WHO criteria[2]) initial anti-malarial used; time of malaria diagnosis; time of first treatment with intravenous artesunate. All data were anonymised.

The diagnosis-to-treatment time was calculated for each case (time from the diagnosis of severe malaria as documented in the notes to time of first dose of intravenous artesunate as signed for on the drug chart). Difference between cases treated in a hospital with

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stocks, hospitals where artesunate was couriered and differences with hospitals which transferred patients were calculated by the Wilcoxon Rank Sum test.

Results:

Geographical clustering of cases in the UK

Of 3556 cases of falciparum malaria notified to the MRL between 2008 and 2010: 1096 cases were in 2008; 1185 cases in 2009; 1275 cases in 2010. We excluded 12 cases from 2008 (9 Scotland, 1 Berkshire, 2 London); 11 cases from 2009 (9 Scotland, 2 London); 13 cases from 2010: (8 Scotland, 1 West Yorkshire, 2 London, 1 Surrey, 1 Somerset) due to incomplete geographical data, so in total 3520 cases are included in this study.

Of these cases, 54.7% were notified from London, 14.6% from the South East, 11.4% from Eastern England, 5.5% from the North West. Together, the North East of England and Northern Ireland accounted for just 0.6% of cases, each notifying 5 or fewer cases per year (Table 1). Within all regions, cases were clustered around larger towns and cities and these are plotted out for the UK (Map 1), England (Map 2), the North West and West Midlands (Map 3), the South East and East of England (Map 4) and Greater London (Map 5).

Over the three years studied, eight centres notified more than 100 cases (6 Greater London hospitals, Croydon and Liverpool). Cases from these eight centres made up 43.9% of the UK's total cases. Notifications from 31 centres accounted for 73.7% of the UK's total; 18 of these were Greater London hospitals. In contrast, 140 centres that saw fewer than a case a month saw 26% of cases (924), and 6% of cases were seen in

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centres which saw less than 2 patients a year, many of which were some way from a potential hub (Table 2 and maps).

Intravenous artesunate via hub-and-spoke and time-to treatment.

HTD pharmacy records identified 50 patients who started intravenous artesunate, 22 at HTD. Clinical data were available for 21 of these HTD cases (one case missing medical records), 14 of whom were transferred in from referring hospitals. Records identified 28 patients in referring hospitals treated with intravenous artesunate sent from HTD. Of these 13 could be included in this study (8 cases had incomplete patient identifiers; 7 cases incomplete medical records). 10 patients were in London hospitals, 2 in the South East and 1 in Eastern England. Therefore, 34 patients were included in total: 21 men and 13 women, age range 17- 70 years, median age 41 years. All were resident in the UK. 23 (68%) had returned from West Africa, 9 (26%) from East Africa, 1 from Central Africa (3%), 1 from Thailand (3%). High parasite count was the most common criterion for starting intravenous artesunate: 29 of the 34 had a count greater than 2% on admission; 24 had a count greater than 5%. On presentation, 12 had cerebral malaria (35%), 10 had respiratory distress (29%), 6 had acute renal impairment (18%) and 12 (35%) had 2 or more clinical features of severe malaria (Table 3).

In 23 cases (68%) the diagnosis-to-treatment time could be calculated (data unavailable for the remaining 11 cases). For 4/4 patients admitted to HTD with severe malaria, median time was 1 hour, range 0.5 to 5 hours. For 9/13 patients who required artesunate to be couriered to their referring hospital, median time was 7.5 hours, range 4 to 26 hours, difference from the four treated in a hospital with drug stocks (HTD) of p 0.02 (Rank Sum). For 10/14 patients who presented elsewhere but were transferred to and given artesunate

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at HTD, median time was 25 hours, range 9 to 45 hours, difference from the patients where artesunate was couriered p 0.002. For 25/26 patients admitted to a referring hospital, intravenous quinine was given while they waited for intravenous artesunate. One patient did not receive any anti-malarial on initial diagnosis of severe malaria and waited 4 hours before receiving intravenous artesunate (Table 3).

Current cost of drugs.

By the standards of emergency life-saving drugs used in high-resource settings, artesunate is not expensive. Drug wastage associated with universal stockage poses an opportunity cost while artesunate supplies are limited, as hospitals seeing many cases may consequently have inadequate drug available.

There are however some cost implications, outlined for illustrative purposes (June Minton, personal communication 2012). A course of 5x 60mg vials (total 300mg) of artesunate at 2012 prices costs £287. A 60kg adult would require 144mg per dose, so would need 1.5 packs in the first 48 hours including loading, costing £381. For IV quinine a pack of 10x 300mg amps (total 3000mg) costs £41. A 60kg adult would require 1200mg loading dose then 600mg per dose thereafter. Assuming it is given tds, this would require 4200mg in total for first 48 hours, so about 1.5 packs, costing £61. Each adult treatment course of artesunate discarded after the expiry date would therefore be around £400 on current prices.

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Discussion

This study shows that whilst the majority of UK patients with malaria are seen in centres which see many cases of malaria, a significant minority are seen in centres where malaria is rarely seen, and 216 cases (6.1%) were seen in centres which saw fewer than 2 cases a year. Since 5-15% of cases of falciparum malaria probably become severe (although data on this are not reliable)[15] these centres will probably treat a severe case less than once every 5 years. There are 168 acute trusts in the UK and 171 centres reporting malaria over the three years, so it is seen occasionally in the majority of UK hospitals. A hub-and-spoke system for distributing artesunate was unsurprisingly associated with delays in starting treatment- in this study of a relatively limited number of patients of around 7 hours.

The degree of clustering of malaria cases in hospitals has significant operational implications. These include whether rarely used but important drugs, especially parenteral artesunate, are distributed universally or by hub-and-spoke. It also has important implications for clinical care standards and training since malaria mortality is inversely related to experience at least at a regional level in the UK[5], a pattern which is almost certainly seen in other non-endemic countries. Idenitifying training needs and providing support for hospitals with less experience of malaria is important for minimising delays in diagnosis and improving clinical outcomes.

This hospital-level study is consistent with previous studies on the incidence of malaria in the UK regions[1,5] and likely reflects the UK's demographics and travelling patterns. Outside London, the South East and East of England, the frequency of falciparum malaria was low. Together, the North East, Scotland, Wales and Northern Ireland accounted for less than 4% of all cases. The North East of England and Northern Ireland each notified

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approximately 3 cases of falciparum malaria per year. The MRL capture rate is 66% so we estimate these regions may each see 4 to 5 cases of falciparum malaria per year. Assuming 5-15% of falciparum cases become “severe”, we estimate each of these UK regions could expect to use intravenous artesunate once every 1 to 2 years. In Wales and Scotland we estimate it might be used 3 to 4 times per year, with most hospitals using no drug but long geographical distances between hospitals.

UK intravenous artesunate supplies have been limited for several years for operational and regulatory reasons, and it is unlikely this will be resolved soon. Until supplies improve, the UK and other non-endemic countries will need to distribute and use the drug efficiently and effectively. Intravenous artesunate has a shelf-life of around 18 months. Our data suggest that a universal stock system would lead to substantial drug wastage: more than 50% of UK centres with at least one case notified 5 or fewer cases of falciparum malaria over 3 years and will seldom see severe cases; 2 UK regions notified less than 10 cases over 3 years. On the other hand, as our data shows, a hub-and-spoke system will lead to delays in providing artesunate, and since this has been associated with over 20% reduction in mortality in adults such a delay is likely to be fatal in at least some cases.

Limitations:

The MRL uses a passive case detection system, which relies on the clinician or laboratory to report malaria cases. Therefore under-reporting is inevitable: however a capture-recapture study estimated that 66% of falciparum cases in England are detected by this system[12] which is high by international standards. Case-detection rate may vary by hospital or region as some units may disproportionately under-report cases. For example, the same study found that London had a higher detection rate than the rest of England.

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Hospitals that rarely see malaria may be less familiar with reporting systems; so this study may underestimate the proportion of the UK's malaria cases seen in these centres. Scotland has been shown to have a very high case detection rate (over 90%[13]).

Of 34 cases excluded due to incomplete data on case location, 26 were from Scotland. These cases represent a significant proportion of the total number of Scottish cases; they would not have a significant impact on the overall trends described here but make extrapolating results to Scotland difficult. The Royal Liverpool Hospital and the Hospital for Tropical Diseases are national centres for Tropical Medicine, regularly receiving patients and malaria films from throughout the UK. In 98/127 Liverpool cases and 45/266 HTD cases included in this study, the notifier's location and the patient's usual place-of-residence were located in different counties or regions, including Greater Manchester, South West England, Scotland and Wales. It was not clear which of these cases represented referrals and which represented temporary visitors so all Liverpool notifications were coded as "Liverpool" and all HTD notifications as "HTD". Some of these patients may have presented elsewhere initially.

HTD operates probably the largest hub-and-spoke distribution system for intravenous artesunate in the UK. Despite this, the number of cases that could be included was small: 34/50 patients receiving intravenous artesunate during this time period could be included in this study. The data we have are retrospective.To calculate the diagnosis-to-treatment time, we used the times as documented in the medical records. Clinicians do not always document decisions or diagnoses immediately, so the diagnosis-to-treatment times may appear shorter in this study, which is therefore conservative on delay which may well in practice be longer than recorded.

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Conclusions

If intravenous artesunate becomes first-line treatment for severe malaria in Europe, UK hospitals will require rapid and reliable access to this emergency drug. While artesunate supplies remain limited, a hub-and-spoke system, based around regional infection centres will minimise drug wastage and ensure the drug is available in the centres which see most cases, but will lead to delays, and almost certainly some avoidable deaths in centres which less regularly see cases and are geographically some way from hubs. A system which restricts artesunate to hospitals that see over 100 cases in 3 years would lead to two-thirds of cases being in other centres. Even having artesunate in the 31 hospitals that see more than 50 cases in 3 years would leave over 25% of malaria cases being treated elsewhere. When parenteral artesunate becomes more freely available, these data suggest the UK should move rapidly towards universal drug distribution, aiming for all acute hospitals to maintain permanent stocks, to ensure early artesunate treatment for all UK severe malaria cases.

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Table 1

Reported cases of falciparum malaria by UK region, 2008-2010

	2008		2009		2010		All 3 years	
	Number	% of total	Number	% of total	Number	% of total	Number	% of total
North East	1	0.1	4	0.3	5	0.4	10	0.3
North West	49	4.5	58	5	85	6.7	192	5.4
Yorkshire & Humber	19	1.8	26	2.2	53	4.2	98	2.8
East Midlands	15	1.4	18	1.5	34	2.7	67	1.9
West Midlands	27	2.5	45	3.8	53	4.2	125	3.6
East of England	140	12.9	124	10.6	138	10.9	402	11.4
South East	164	15.1	161	13.7	190	15.1	515	14.6
South West	30	2.8	24	2.1	34	2.7	88	2.5
Greater London	614	56.6	682	58.1	629	49.9	1925	54.7
Scotland	13	1.2	18	1.5	22	1.7	53	1.5
Wales	10	0.9	10	0.9	16	1.3	36	1
Northern Ireland	2	0.2	4	0.3	3	0.2	9	0.3
Total	1084		1174		1262		3520	

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Table 2

Number of UK hospitals notifying cases of falciparum malaria, 2008-2010

Number of cases notified in 3 years	Number of centres	Total number of cases	% of UK total cases	Cumulative % of UK cases
>100	8	1547	43.9	43.9
51-100	8	552	15.7	59.6
26-50	15	497	14.1	73.7
11-25	33	565	16.1	89.8
6-10	19	143	4.1	93.9
1-5	88	216	6.1	100

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Table 3

Falciparum cases treated with intravenous artesunate from the Hospital for Tropical Diseases

Age	Gender	County of residence	Country of travel	Parasitaemia on admission	Number of clinical features of severity	Admitting hospital	Site of first artesunate dose	Diagnosis-to-treatment time (hrs)	Initial anti-malarial
57	M	UK	Nigeria	2.3	1	Elsewhere	Elsewhere	12	iv quinine & doxycycline
41	M	UK	Gambia	15	6	Elsewhere	Elsewhere	13	iv quinine
34	F	UK	Nigeria	37	1	Elsewhere	HTD	14	iv quinine
45	M	UK	Gambia & Liberia	27	0	Elsewhere	HTD	41.5	iv quinine
51	M	UK	Nigeria	15	3	Elsewhere	HTD	13	iv quinine
62	F	UK	Ghana	17	0	Elsewhere	Elsewhere	5	iv quinine
38	M	UK	Nigeria	8	1	Elsewhere	Elsewhere	26	iv quinine & im artemether
24	F	UK	Uganda	2.7	0	HTD	HTD	1	iv artesunate
24	M	UK	Thailand	2.6	0	Elsewhere	HTD	29	iv quinine
39	M	UK	Kenya	23	3	Elsewhere	Elsewhere	4.5	iv quinine
46	M	UK	Nigeria	8.1	2	Elsewhere	HTD	34	iv quinine
41	M	UK	Uganda	2.3	2	Elsewhere	HTD	9	iv quinine
47	F	UK	Mozambique	0.2 (recurrence)	0	HTD	HTD	5	iv artesunate
46	M	UK	Sudan	20	2	Elsewhere	Elsewhere	8	iv quinine
45	F	UK	Uganda	1.8	1	Elsewhere	HTD	45	iv quinine
42	M	UK	Nigeria	1	0	HTD	HTD	3.5	iv artesunate
36	M	UK	Nigeria	0.3	1	HTD	HTD	1	iv artesunate
49	M	UK	DR Congo	15	1	HTD	HTD	5	iv quinine
17	M	UK	Sierra Leone	1.1	0	HTD	HTD	11	iv quinine
52	F	UK	Ghana	50	4	Elsewhere	Elsewhere	Unknown	iv quinine
34	F	UK	Ghana	22	4	Elsewhere	Elsewhere	4	iv artesunate & clindamycin

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52	F	UK	Sierra Leone	5.2	0	Elsewhere	Elsewhere	Unknown	Unknown
27	F	UK	Tanzania	5	0	Elsewhere	HTD	Unknown	iv quinine
52	M	UK	Kenya	10	1	Elsewhere	HTD	33	iv quinine
36	M	UK	Gabon	17.2	0	HTD	HTD	0.5	iv artesunate
41	F	UK	Ghana	10	1	Elsewhere	Elsewhere	7.5	iv quinine & doxycycline
35	F	UK	Ghana & Ivory Coast	9	0	Elsewhere	Elsewhere	Unknown	iv quinine
70	M	UK	Nigeria	8	1	Elsewhere	Elsewhere	Unknown	iv quinine
51	M	UK	Nigeria	9.2	0	Elsewhere	Elsewhere	5	iv quinine
39	M	UK	Uganda	30	2	Elsewhere	HTD	Unknown	iv quinine
31	F	UK	Nigeria	4.8	1	Elsewhere	HTD	Unknown	iv quinine
30	M	UK	Sierra Leone	26.8	2	Elsewhere	HTD	21.5	iv quinine
47	F	UK	Sierra Leone	12.5	2	Elsewhere	HTD	14.5	iv quinine
43	M	UK	Ghana	16.4	3	Elsewhere	HTD	Unknown	iv quinine

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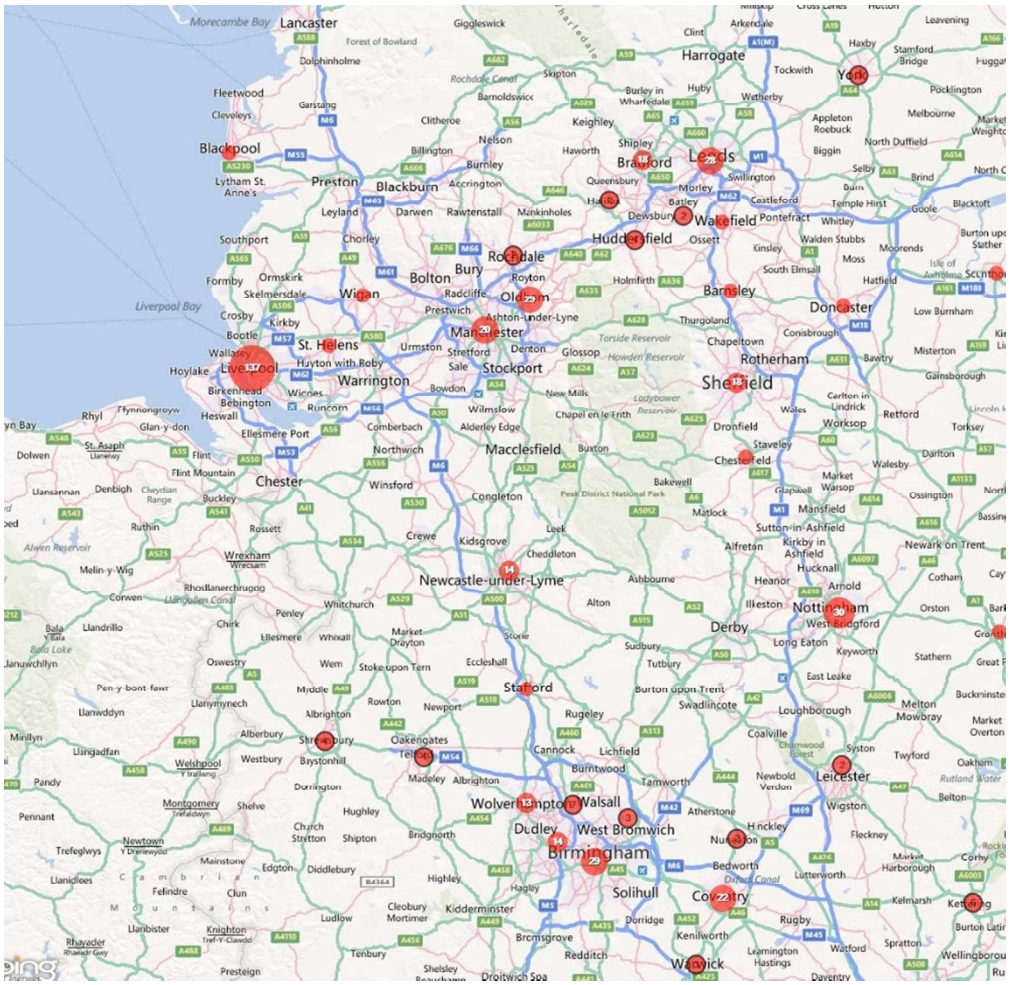
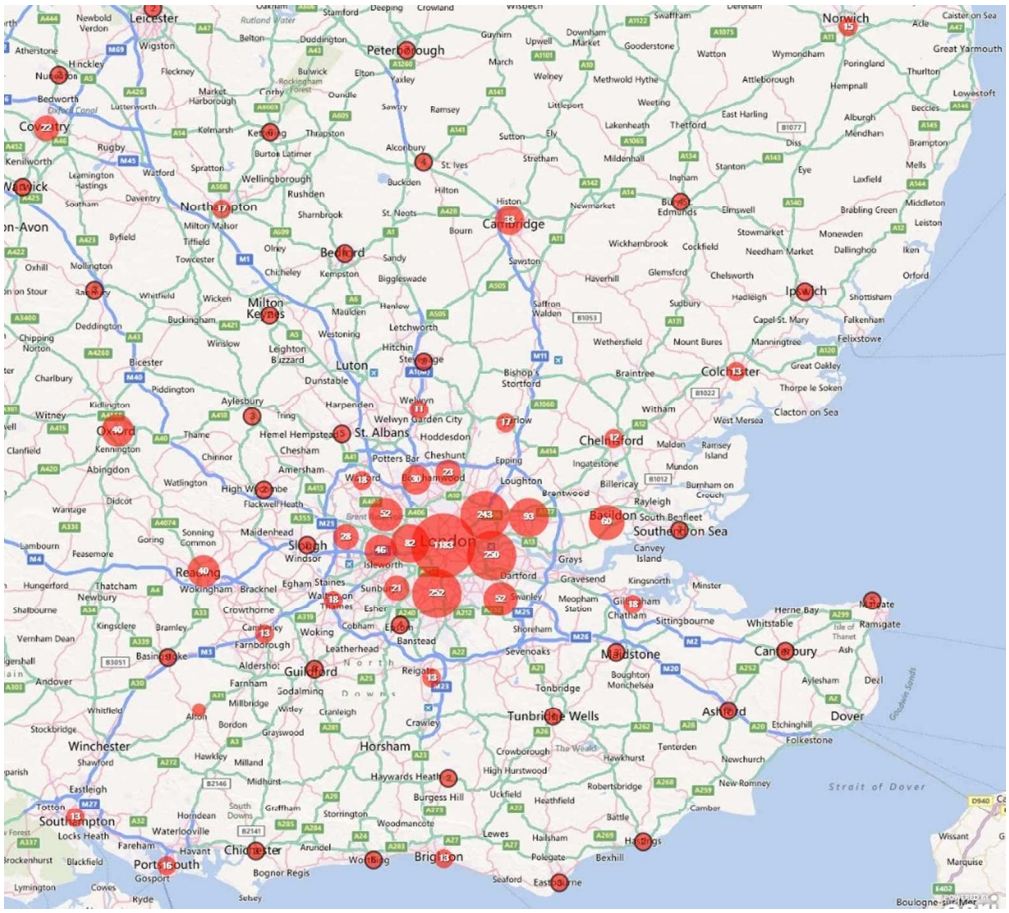
Map 1. Geographical distribution of falciparum malaria notifications in the UK, 2008-2010
143x166mm (96 x 96 DPI)

Map 2. Geographical distribution of falciparum malaria notifications in England, 2008-2010
230x238mm (96 x 96 DPI)

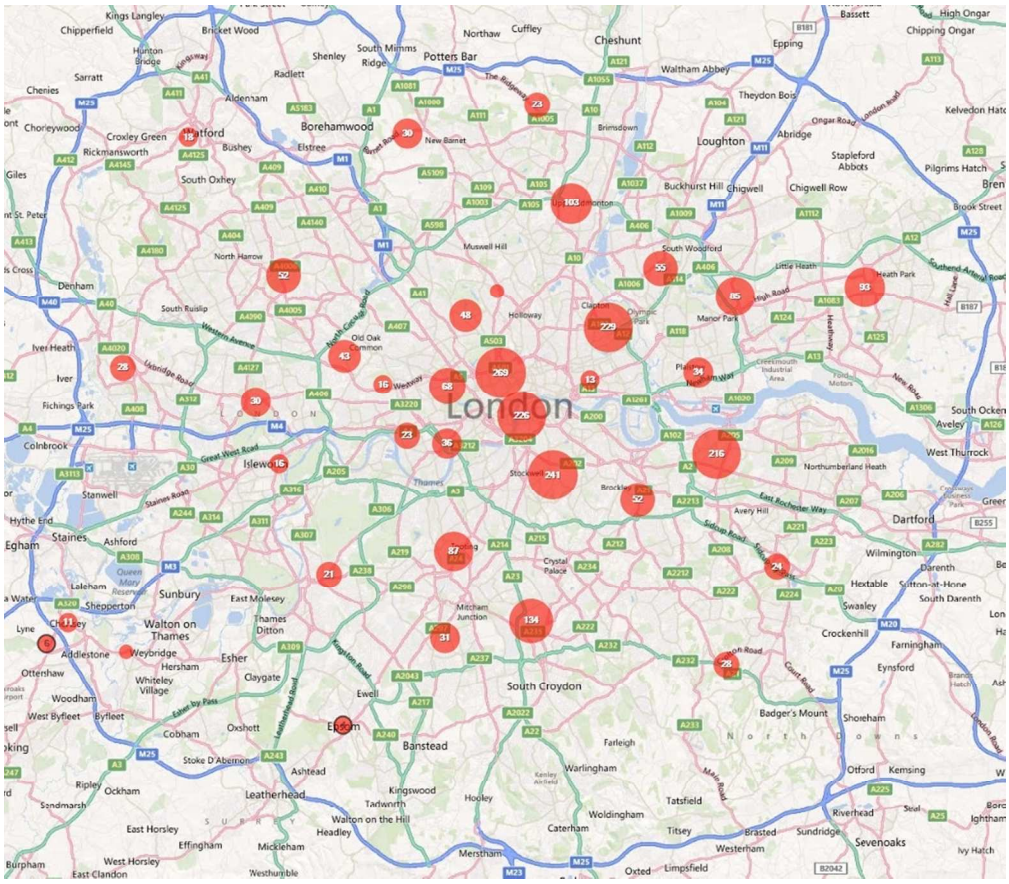


Map 3. Geographical distribution of falciparum malaria notifications in the North West and West Midlands, 2008-2010
262x255mm (96 x 96 DPI)



Map 4. Geographical distribution of falciparum malaria notifications in the South East and East of England, 2008-2010
278x251mm (96 x 96 DPI)

only



Map 5. Geographical distribution of falciparum malaria notifications in Greater London, 2008-2010
274x239mm (96 x 96 DPI)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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