



Adult and child malaria mortality in India: a nationally representative mortality survey

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Summary

Background National malaria death rates are difficult to assess because reliably diagnosed malaria is likely to be cured, and deaths in the community from undiagnosed malaria could be misattributed in retrospective enquiries to other febrile causes of death, or vice-versa. We aimed to estimate plausible ranges of malaria mortality in India, the most populous country where the disease remains common.

Methods Full-time non-medical field workers interviewed families or other respondents about each of 122 000 deaths during 2001–03 in 6671 randomly selected areas of India, obtaining a half-page narrative plus answers to specific questions about the severity and course of any fevers. Each field report was sent to two of 130 trained physicians, who independently coded underlying causes, with discrepancies resolved either via anonymous reconciliation or adjudication.

Findings Of all coded deaths at ages 1 month to 70 years, 2681 (3·6%) of 75 342 were attributed to malaria. Of these, 2419 (90%) were in rural areas and 2311 (86%) were not in any health-care facility. Death rates attributed to malaria correlated geographically with local malaria transmission rates derived independently from the Indian malaria control programme. The adjudicated results show 205 000 malaria deaths per year in India before age 70 years (55 000 in early childhood, 30 000 at ages 5–14 years, 120 000 at ages 15–69 years); 1·8% cumulative probability of death from malaria before age 70 years. Plausible lower and upper bounds (on the basis of only the initial coding) were 125 000–277 000. Malaria accounted for a substantial minority of about 1·3 million unattended rural fever deaths attributed to infectious diseases in people younger than 70 years.

Interpretation Despite uncertainty as to which unattended febrile deaths are from malaria, even the lower bound greatly exceeds the WHO estimate of only 15 000 malaria deaths per year in India (5000 early childhood, 10 000 thereafter). This low estimate should be reconsidered, as should the low WHO estimate of adult malaria deaths worldwide.

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Introduction

Malaria still causes many deaths in malaria-endemic countries with limited health-care facilities,^{1,2} but estimation of worldwide and regional malaria mortality has been difficult for three reasons. First, the recorded case fatality from malaria might be misleadingly low even in populations that still have high malaria mortality because the disease can be cured easily if treated promptly, so those episodes that are diagnosed properly will not be those that cause most of the deaths.² Second, where health-care facilities are limited, severe malaria in people who die of it without any medical intervention is easily mistaken in retrospective enquiries for some other life-threatening fever; conversely, other febrile causes of death can be mistaken retrospectively for malaria. Third, in most rural areas where death from malaria is common, proper medical attention at the time of death is uncommon.^{3,4}

India is the most populous country in which malaria is common.¹ The cases and deaths reported by the Indian Government are concentrated mainly in a few states in east and northeast India (the so-called high-malaria states; mainly Orissa but also Chhattisgarh, Jharkhand, and the states in the far northeast of India).⁵ Because the Indian

national malaria programme cures nearly all the cases it treats, it detects only about 1000 malaria deaths each year, and misses most deaths caused by malaria.⁶ WHO estimates that malaria causes only about 15 000 deaths each year in India (5000 children, 10 000 adults), but this too depends indirectly on the low death rates in diagnosed patients.¹ Small studies in specific regions of India or in special subpopulations^{6–14} cannot directly estimate national numbers of malaria deaths.

We provide direct estimates of the range that is plausible for the number of deaths caused by malaria in India, on the basis of structured interviews with non-medical witnesses of the death in a nationally representative study of 122 000 deaths. Written narratives of the deaths were used by study physicians to assign probable causes.^{4,15–17}

Methods

Data collection

Most deaths in rural India take place at home, without prior intervention by any qualified health-care worker, so most causes are not medically certified.^{3–4} Thus, other sources of information are needed to help establish the

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probable underlying causes. The Registrar General of India has, during the past decade, introduced a form of verbal autopsy¹⁵ into the nationally representative Sample Registration System, which monitors all deaths in 1·1 million homes. For narrow age ranges, the proportion of all deaths in 2001–03 that the system attributed to malaria was multiplied by the UN estimate of the number of deaths from all causes¹⁸ to estimate national numbers of malaria deaths.

India was divided into about 1 million areas for the 1991 census, each with about 1000 inhabitants. For the Sample Registration System, the Registrar General chose 6671 such areas randomly in 1993, each with all individuals and their household characteristics then enumerated and with subsequent births and deaths (but not death causes) in those areas reliably enumerated twice yearly.^{4,19} Since 2002, one of 800 non-medical graduates (trained by the Registrar General in appropriate fieldwork methods) has visited each area periodically to record from families (or other informants) a written narrative, usually in the local language, of each death, plus answers to some standard questions about the death.^{4,15–17} Questions included the course of any fever preceding death (ie, whether it was prolonged, severe, intermittent, associated with shivering). Random re-sampling and other fieldwork quality-control methods were used routinely. This survey is part of the Million Death Study (MDS), which seeks to assign causes to all deaths in the Sample Registration System areas during the 13 years 2001–13 (webappendix).^{4,15}

Data interpretation

Individual narratives were scanned as images and emailed randomly to at least two of 130 collaborating

physicians trained in disease coding. Coding physicians were selected randomly from among those who spoke the language in which the narrative was given. Working independently, physicians assessed the probable underlying cause of death, assigning to it an International Classification of Diseases (ICD-10) three-character code.²⁰ Coding physicians knew the state but not the district where the death happened. Any differences between the two coders were resolved either

See Online for webappendix

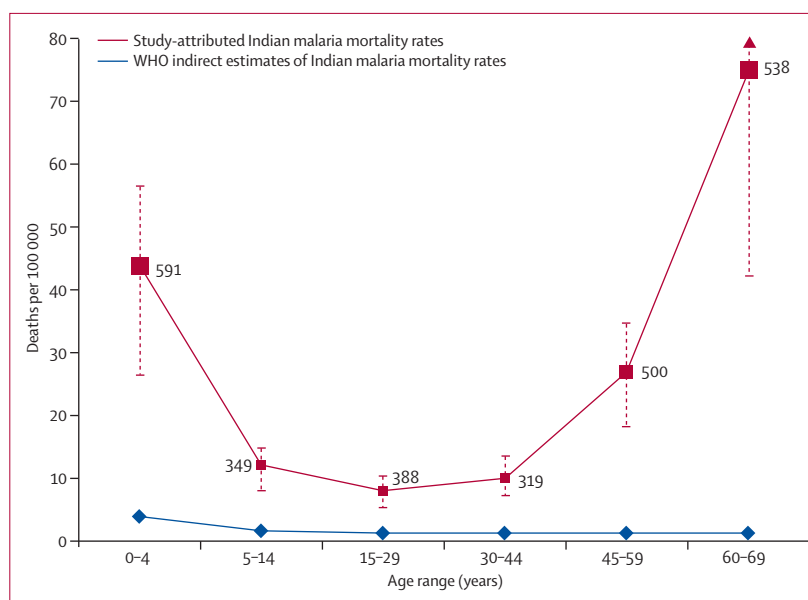


Figure 1: Comparison between malaria mortality rates (per 100 000 person years) in the present study with those estimated indirectly for WHO

Within each age range, the all-India death rates from the present study are standardised in 5-year age groups to the 2005 Indian population.¹⁸ The vertical bars represent the upper and lower bounds on the basis of physician coding.

	Study deaths, 2001–03					All India, 2005			
	Numbers attributed to malaria/all coded deaths	Proportion malarial*	Died in a health facility	Rural area	Two coders immediately agreed	All deaths/population (millions; UN estimates) ¹⁸	Estimated deaths (thousands)	Estimated deaths per 100 000	Period risk†
<1 month‡	4/10 892	0·0%	0	3	3	1·0/27	0	44§	0·22%
1–59 months	587/12 260	4·2%	44	562	354	1·3/101	55	44§	0·22%
5–14 years	349/3876	8·3%	44	328	240	0·3/246	29	12	0·12%
15–29 years	388/9085	3·6%	95	339	261	0·7/313	25	8	0·12%
30–44 years	319/10 863	2·5%	73	279	228	0·9/222	22	10	0·15%
45–59 years	500/18 124	2·6%	83	426	345	1·5/142	37	27	0·40%
60–69 years	538/21 134	2·5%	31	485	304	1·5/49	37	75	0·75%
Subtotal, ages 0–69 years	2685/86 234	2·9%	370	2422	1735	7·2/1100	205	18	1·76%
(lower, upper bounds)	(1735, 3511)	(2·0, 3·7)	(–)	(–)	(–)	(–)	(125, 277)	(12, 25)	(1·02, 2·33)
>70 years	972/36 057	2·7%	36	858	387	2·6/30	71	236	..

Two physicians coded a total of 122 727 deaths, of which 436 were excluded because they were stillbirths or were missing age or sex data leaving 122 291 (86 234 deaths of people younger than 70 years and 36 057 older). See webappendix p 6 for details of deaths assigned to malaria immediately by both physicians and by at least one physician, some of which were eventually assigned to other causes. *Percentages are weighted for state and for urban or rural status (which generally decreases them, albeit only slightly) and for each age range they are then multiplied by the UN-estimated number of all deaths in 2005 to estimate national malaria mortality. †Annual rate multiplied by duration of age range, except for the period risk for ages 0–69 years which was calculated by summation of the age-specific period risks (thereby yielding the probability of death from malaria before age 70 years if there were no other causes of death). ‡Although we do not attribute any neonatal deaths to malaria nationally, review of these four cases found two were neonates with haematological confirmation of malaria; small numbers of neonatal deaths caused by malaria have been reported elsewhere.²⁰ §Combined estimates for all <59 months.

Table 1: Malaria-attributed deaths in the present study and estimated national totals, by age

For the physician coder's guidelines see <http://www.cghr.org/project.htm>

by anonymous reconciliation between them (asking each to reconsider) or, for persisting differences, adjudication by a third physician.^{4,15–17,21}

The training of the physician coders and their written guidelines²¹ instructed them to use their best medical judgment as to whether death was caused by malaria, but advised them to exclude malaria if there was evidence of respiratory infection, diarrhoea, burning sensation during urination, rash, blisters, heatstroke, or evidence of other specific infection. Physicians were advised to consider the course of the fever—eg, acute onset of fever with shivering—and advised that assignment of malaria should generally require, additionally, at least one of jaundice, vomiting, breathlessness, decreased urine output, headache, convulsions, or unconsciousness. Blood tests for malaria were rarely done. Separate guidelines were provided for assigning deaths to each of several other specific infections, including tuberculosis, acute respiratory infection, typhoid, other diarrhoeal disease, meningitis, influenza, dengue, and rabies. The training of the coders advised that these infections would

generally take precedence over a possible diagnosis of malaria.

Mortality attributed to malaria in each of India's 600 districts was compared geographically with three independent measures of malaria. One was the slide *Plasmodium falciparum* rate—ie, the proportion of *P falciparum* positive blood slides from 1995–2005 in the routine blood parasite surveillance data collected in each district by the National Vector-Borne Disease Control Programme (NVBDCP).^{6,22} The second measure was the number of clinically confirmed slide-positive malaria deaths recorded in each state by the NVBDCP from 2000 to 2005. Although most malaria deaths happen outside this programme^{5,6} (because it generally cures those it finds to have malaria), the geographical distribution of the few deaths is informative. For the third measure, we examined the district-specific proportion of households in which any member was reported to have had a fever in the preceding 2 weeks in the District-Level Health Survey, a nationally representative survey of 700 000 households covering about 6000 individuals per district in 2002–03.²³ Simple correlation coefficients were used, excluding districts where our study assigned no deaths to malaria. The geographical distribution of malaria mortality in India as a whole was estimated from the malaria-attributed mortality in the Sample Registration System areas by smoothing (kriging²⁴) the results from the 5335 study areas with some malaria-attributed mortality, mapped to the locations of their coded addresses. Use of the data from all 6671 Sample Registration System areas to estimate district-based mortality yielded similar nationwide patterns.

Cause of death assignment is particularly difficult in old age, and the proportion of total deaths without a classifiable cause rises sharply after age 70 years.^{4,15,25,26} Thus, the major analyses are of deaths below age 70 years, with those at older ages considered separately. The Sample Registration System enumeration of all deaths slightly underestimates overall Indian adult mortality^{27,28} and, furthermore, we did not interview informants for about 12% of the SRS-enumerated deaths. To estimate absolute numbers of malaria-attributed deaths, we therefore multiplied the 2005 UN estimates of age-specific numbers of deaths in India (irrespective of cause; 9·8 million total deaths in 2005)¹⁸ by the age-specific proportion of all deaths that was attributed to malaria in our study. Because our study included such a large proportion of all deaths in the study areas, no material bias is likely from systematic differences between those included and those not. Similarly, although our age-specific proportions were weighted according to the SRS sampling fractions in the rural and urban parts of each state,¹⁹ this weighting made no material difference.

Role of the funding source

The study was funded by the US National Institutes of Health, Canadian Institute of Health Research, and the

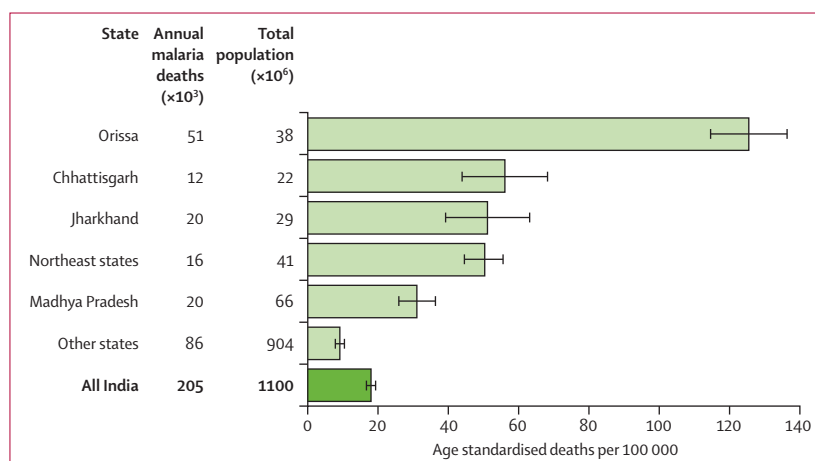


Figure 2: Malaria mortality (absolute number and annual rates) before age 70, by state, India, 2005
Rates are standardised in 5-year age groups to total Indian population (bars depict 99% CIs). The high-malaria states include 12% of national deaths from all causes and 47% of all-India malaria-attributed deaths before age 70 years.

	MDS	NVBDCP
Orissa	823 (31%)	2102 (37%)
Northeast states	468 (17%)	1023 (18%)
Chhattisgarh	131 (5%)	109 (2%)
Jharkhand	118 (4%)	152 (3%)
Madhya Pradesh	217 (8%)	262 (5%)
All other states	928 (35%)	1999 (35%)
All India	2685 (100%)	5647 (100%)

Million Death Study (MDS) malaria-attributed deaths before age 70 years, 2001–03. National Vector-Borne Disease Control Programme (NVBDCP) slide-positive clinically confirmed malaria deaths, 2000–05.

Table 2: Geographical variation in absolute numbers of malaria deaths in the different populations studied by the MDS and NVBDCP

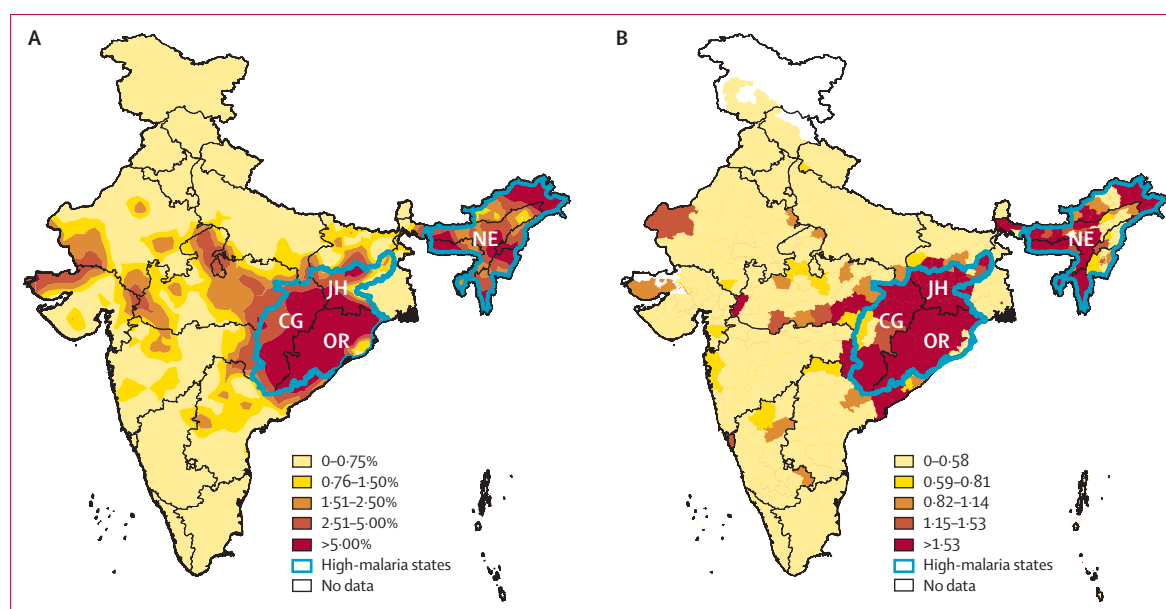


Figure 3: Geographical distributions of malaria-attributed mortality and slide *Plasmodium falciparum* rate

Proportion of 2001–03 mortality attributed to malaria in this study at ages 1 month to 69 years. Mortality is plotted as the smoothed results from the 5335 study areas with some malaria-attributed mortality and is mapped to the locations of their post code (A). District-level 1995–2005 slide falciparum rate from National Vector-borne Disease Control Programme statistics (B).⁵²² High-malaria states comprise Orissa (OR), Jharkhand (JH), Chhattisgarh (CG), and Assam and all the smaller northeastern states except Sikkim (NE).

Li Ka Shing Knowledge Institute. The funding sources had no role in how the study was designed or done, or in data collection, analysis, or interpretation. PJ had full access to all data and final responsibility for the decision to submit for publication on behalf of all authors.

Results

4690 (3.8%) of the 122 291 deaths at all ages available for analyses were initially assigned to malaria by one or other coder. 3657 (3.0%) deaths were eventually accepted as malaria. 2122 (1.7%) deaths had been immediately attributed to malaria by both physician coders, so no subsequent reconciliation or adjudication was needed, and a further 1535 (1.3%) were eventually assigned to malaria after the first two coders had initially disagreed, generally with one coder concluding that malaria was the cause of death and the other assigning fever of unknown origin (webappendix p 4). One of the key symptoms that led coders to assign unattended febrile deaths to malaria rather than to other infectious diseases was fever of sudden onset with chills or shaking (and no other specific diagnosis). More definite evidence was highly desirable²⁹ but not available for many patients, especially for unattended deaths.

The coders eventually accepted as malaria 2681 (3.6%) of all 75 342 deaths after the first month of life but before age 70 years. Nationally, this would suggest 205 000 malaria deaths per year before age 70 years (55 000 in early childhood, 30 000 at ages 5–14 years and 120 000 at ages 15–69 years; table 1). The 99% CI based on random variation for the national total before age

70 years would be 195 000–215 000, although random variation is not the main source of uncertainty. Although the malaria-attributed death rate was high in young children, it became high compared with younger ages from 45 years (figure 1). The age-specific rates suggest an overall probability of 1.8% of dying from malaria before the age of 70 years, in the absence of other causes. About half of the 205 000 malaria-attributed deaths before age 70 years happened in a few states with high malaria burden (figure 2), with just one such state, Orissa, accounting for more than 50 000 (overall probability of death of 12.5% in Orissa; webappendix p 7). Of the malaria-attributed deaths before age 70 years, 2422 (90%) of 2685 were in rural areas and 2315 (86%) were not in any sort of health facility (table 1). Even at ages 15–59 years, only 251 (21%) of 1207 malaria-attributed deaths happened in a health facility (where diagnosis might have been reliable), and at younger or older ages even a smaller proportion did so.

To suggest plausible lower and upper national estimates, we included only those deaths that were immediately coded by both physicians as malaria (1735 deaths of people younger than 70 years) and, at the other extreme, all deaths with malaria as the initial diagnosis by at least one coder (3511 younger than 70 years), a quarter of which were eventually reassigned to other causes. For ages 0–70 years, this results in a lower bound of 125 000 malaria-attributed deaths (99% CI 117 000–133 000, cumulative probability of malaria death by age 70 years 1.0%) and an upper bound of 277 000 (99% CI 265 000–289 000; cumulative probability 2.3%; webappendix).

Proportional distribution across the major states was similar to that reported by the national malaria control programme for the few slide-positive, clinically confirmed, malaria deaths (5647 deaths at all ages during 2000–05; table 2). Number of deaths varied seasonally (being higher some time after the wet season began, typically in June), although perhaps not as extremely as might be expected for *P. falciparum* malaria (webappendix p 9). Malaria mortality correlated geographically with the district-level

P. falciparum transmission rates indicated independently by the Indian malaria control programme^{5,22} (figure 3; $r=0.59$, $p<0.0001$) and with self-reported fever rates from nationwide district-level surveys of 700 000 households²³ in which a household informant was asked if any member had had any fever, malarial or not, in the preceding 2 weeks (data not shown; $r=0.57$, $p<0.0001$). By contrast, the rates of death our coders attributed not to malaria but to fever of unknown origin (ICD-10 code R50) did not correlate with

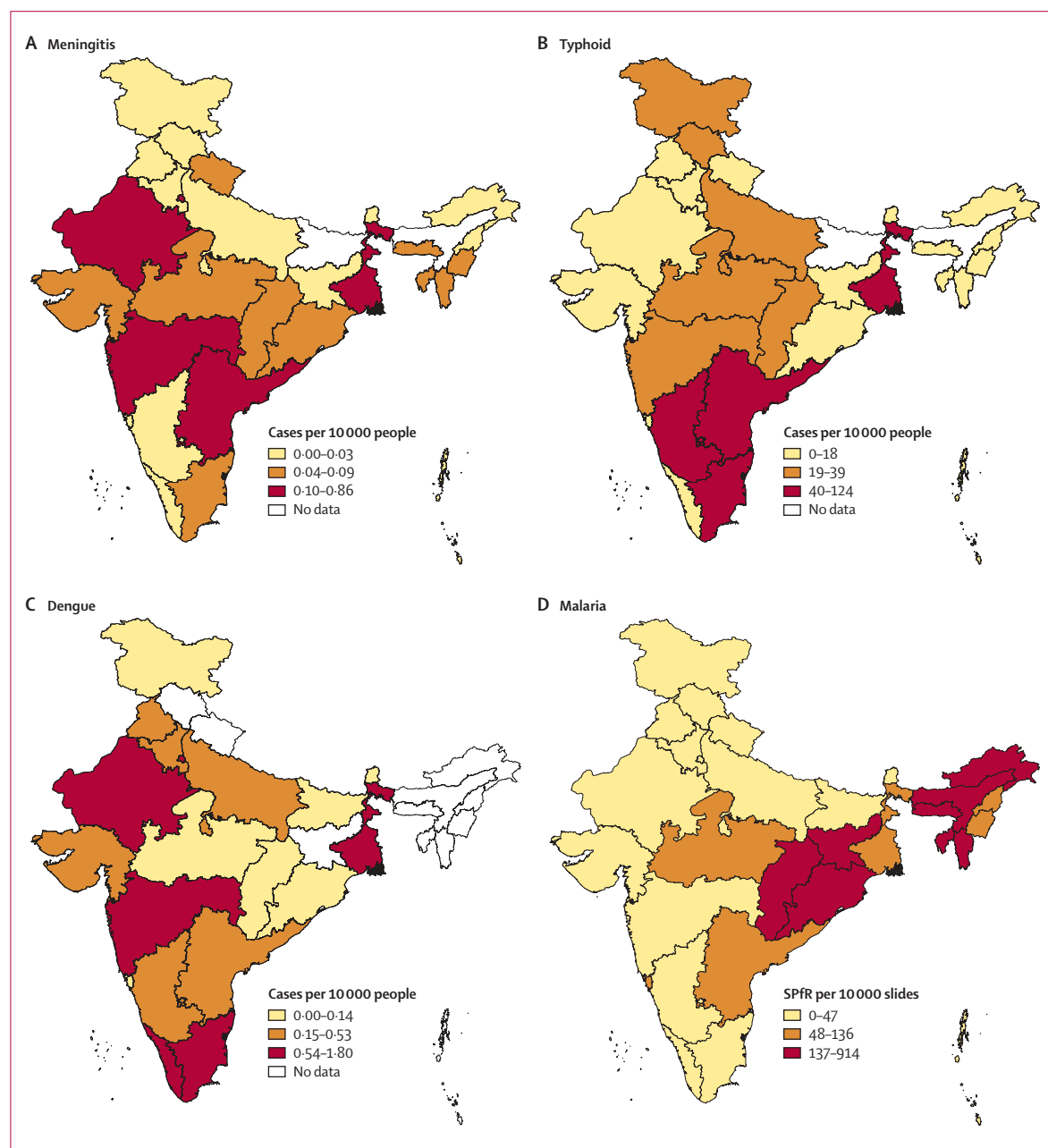


Figure 4: Reported cases of meningitis, typhoid, and dengue infections, 2006, and estimated malaria infections, 1995–2005, per 10 000 population, by state. Total cases reported to the Government of India programme of meningitis, typhoid, and dengue are divided by total population for 2005 for that state and malaria cases are divided by total slides tested for malaria. Similar results are seen if reported deaths are plotted for each disease. Note that the scales differ for each disease. SPfPR=slide *Plasmodium falciparum* rate.

these independent indicators (data not shown; $r < 0.1$, $p > 0.25$). Malaria mortality did not correlate with national data for dengue, typhoid, and meningitis, which, in retrospective enquiries, might be confused with malaria (figure 4).³¹ In the high-malaria states, our coders attributed more deaths to malaria than to the aggregate of all three of these diseases.³¹ Malaria deaths were a substantial minority of about 1.3 million unattended deaths attributed to infectious diseases in people younger than 70 years in which fever was the key symptom (webappendix p 8).

Discussion

Our study of written narratives of a large, nationally representative, sample of all deaths suggests that malaria might be a cause of about 200 000 deaths per year before the age of 70 years in India (including 120 000 deaths per year at ages 15–69 years), which is an order of magnitude greater than the WHO estimates.¹ The range of reasonable uncertainty on both sides of our estimate is inevitably wide, because the main contributor is febrile deaths of people who were never properly diagnosed or treated.

The U-shaped age-specific pattern of malaria-attributed mortality (table 1, figure 1), with high rates not only in early childhood but also in later middle age, is consistent with the age relations previously reported for malaria mortality in selected urban hospitals in India,³² in family-reported causes of death from a national household demographic survey in 1998–99,³³ and in a network of demographic mortality studies by use of physician adjudication in rural Africa,^{34,35} but not with WHO mortality estimates.^{1,36}

Most of the malaria-attributed deaths were in rural areas and involved an acute fever that was never seen or diagnosed by any health-care worker, so assignment of the pathogen is inherently uncertain. In retrospective enquiries to families about the symptoms, and hence the probable causes, of such deaths, malaria and other infectious diseases are easily confused, although untreated fatal malaria can have distinct symptoms.^{25,29,37–41} Because treated malaria is rarely fatal, the distribution of pathogens in untreated fevers that cause rapid death in the community might be very different from the distribution of pathogens in fevers that cause death in hospital, and from the distribution of pathogens in fevers that do not cause death.⁴² This makes it difficult to use hospital-based studies to assess the reliability of community-based verbal autopsies or to predict the proportion of febrile deaths due to malaria.^{37,40} Physicians coding in Oriya, the main language of rural Orissa, were slightly more likely to assign febrile deaths to malaria, and this excess accounts for about 5% of national malaria-attributed mortality in this study; but, some or all of the excess appropriately reflects the high malaria mortality in rural Orissa. Other mosquito-borne diseases such as dengue or Japanese encephalitis can share the seasonal transmission patterns of malaria, but they differ substantially from malaria in clinical symptoms and geographical distribution³¹ and are not common enough

to account for a large proportion of all Indian deaths, particularly in the high-malaria states.^{31,43,44}

There are about 1.3 million deaths from infectious diseases before age 70 in rural areas in which fever is the main symptom. If there are large numbers of deaths from undiagnosed and untreated malaria in some parts of rural India then any method of estimating overall malaria deaths must rely, directly or indirectly, on evidence of uncertain reliability from non-medical informants and, although our method of estimating malaria mortality has weaknesses, indirect methods may be even less reliable.^{45,46} The major source of uncertainty in our estimates arises from the possible misclassification of malaria deaths as deaths from other diseases, and vice versa. There is no wholly satisfactory method to quantify the inherent uncertainty in this, and indeed the use of statistical methods to quantify uncertainty can convey a false precision.⁴⁷ However, even if we restrict our analyses to deaths immediately classified by both physician coders as malaria, WHO estimates (15 000 deaths per year at all ages)¹ are only one-eighth of our lower bound of malaria deaths in India (125 000 deaths below the age of 70 years; of which about 18 000 would have been in health-care facilities).

Our study suggests that the low WHO estimate of malaria deaths in India (and only 100 000 adult malaria deaths per year worldwide)¹ should be reconsidered. If WHO estimates of malaria deaths in India or among adults worldwide are likely to be serious underestimates, this could substantially change disease control strategies, particularly in the rural parts of states with high malaria burden. Better estimates of malaria incidence⁴⁶ and of malaria mortality in India, Africa, and elsewhere will provide a more rational foundation for the current debates about funding for preventive measures, about the need for more rapid access to malaria diagnosis, and about affordable access in the community to effective antimalarial drugs for children and adults.^{1–2,48}

Contributors

PJ and the academic partners in India (MDS Collaborators; webappendix p 11) planned the Million Death Study in close collaboration with the Office of the Registrar General of India. ND, VPS, and PJ planned the analyses. AAC, DGB, PJ, PSR, RP, and WS did the statistical analyses. All authors were involved with data interpretation, critical revisions of the paper, and approved the final version; PJ is its guarantor.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

The Registrar General of India established the SRS in 1971, has continued it ever since, and is collaborating with several of the authors on the ongoing Million Death Study. External funding is from the Fogarty International Center of the US National Institutes of Health (grant R01 TW05991–01), Canadian Institute of Health Research (CIHR; IEG-53506), Li Ka Shing Knowledge Institute and Keenan Research Centre at St Michael's Hospital, University of Toronto (CGHR support), and UK Medical Research Council (CTSU support). Additional support was provided by the Disease Control Priorities Network, University of Washington. PJ is supported by the Canada Research Chair programme. The opinions expressed in this paper are those of the authors and do not

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