Disease Control Priorities Project
Working Paper No. 11

The Public Health Burden of *Plasmodium falciparum* Malaria in Africa: Deriving the Numbers

August 2003

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Suggested citation:
The public health burden of Plasmodium falciparum malaria in Africa: Deriving the numbers. by Robert W. Snow, Marlies H. Craig, Charles R.J.C. Newton, Richard W. Steketee. Working Paper No. 11, Disease Control Priorities Project. Bethesda, Maryland: Fogarty International Center, National Institutes of Health. August 2003.

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Robert W. Snow, Marlies H. Craig, Charles R.J.C. Newton,
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1 Introduction

In 2001, malaria was ranked the 8th highest contributor to the global Disability Adjusted Life Year (DALY) and 2nd in Africa (WHO, 2002). The malaria DALY was largely estimated from the combined effects of *Plasmodium falciparum* infection as a direct cause of death and the much smaller contributions of short duration, self-limiting or treated surviving mild morbid events, malaria-specific anemia and neurological disability following cerebral malaria (Murray & Lopez, 1996; 1997). The estimate derives from an assumption that each illness event or death can only be attributed to a single cause that can be measured reliably and for which data do exist. In this review we re-analyze more contemporary evidence on the direct health consequences of malaria infection in Africa and examine the broader contribution of malaria infection to indirect causes of mortality, morbidity and disability.

2 Background to defining the malaria burden in Africa

There have been several historic attempts to provide an estimate of the numbers of deaths that occur each year due to malaria in Africa. Perhaps the most significant and influential was proposed by Leonard Bruce Chwatt of a million deaths each year (Bruce-Chwatt, 1952). His estimate, based upon the civil registration of deaths in Lagos during 1950, provided the basis of the World Health Organization's figure for many years and was a familiar feature of almost all introductions across the entire spectrum of African malaria literature. Since this early estimation others have provided either semi-informed opinion or inquisitive speculation on the numbers of deaths due to malaria in Africa and estimates have varied between 0.5 and 2 million deaths each year (Sturchler, 1989; Greenwood 1990; Schwartlander, 1997; WHO, 1996). Whilst these estimates may have proved useful advocacy tools they equally generated skepticism about their origin and validity. The importance of providing reliable, evidence-based estimates of mortality began with the Global Burden of Disease

study during the early 1990's (Murray & Lopez, 1996). The DALY approach has lead to a renewed effort to better define disease-specific mortality rates. This has been a particular challenge in the high mortality regions of the world where ironically the least comprehensive and reliable vital registration systems exist. Despite the paucity of data, there have been Pan-African extrapolations of specialized survey data on the contributions of acute respiratory tract infections (Williams et al., 2002) and HIV (Walker et al., 2002) to the African mortality burden. In 1998 a more empirical analysis of malaria mortality was undertaken on behalf of the WHO using malaria risk maps and an estimation of mortality, morbidity and disability risks across Africa (Snow et al., 1999; WHO, 1999).

These first iterations of the health consequences of malaria in Africa formed the basis of The Burden of Malaria in Africa (BOMA) project that was established in 1998 and funded by The Wellcome Trust, UK. The aim has been to capture empirical measures of disability, morbidity and mortality associated with *Plasmodium falciparum* infection among African populations (Snow et al., 2001; Snow & Marsh, 2002; Snow et al., 2003a; Korenromp et al., 2003). The project provides a platform to combine empirical evidence of the health impact of *P. falciparum* in relation to age, geographic and intervention determinants of risk and allows a more informed approach to the consequences (human and financial) of control.

3 The spectrum of direct and indirect consequences of malaria infection in Africa

It has long been recognized that the relationships between *P. falciparum* infection and disease outcome are complex. What we do know is that individuals born into areas of stable *P. falciparum* transmission frequently move between periods of being infected with the parasite and states where the individual is uninfected. Most individuals will, at some stage in their lives, develop an overt clinical response to an infection often manifesting as a febrile event. These clinical events may progress to severe clinical states that may naturally resolve or the patient survives through medical intervention. This simplistic view of infection to death provides only part of the overall public health equation. There are morbid and fatal consequences allied to each step of the infection and disease process. Chronic, sub-clinical infections may render an individual anemic or predispose to under-nutrition. These processes in themselves may increase susceptibility to severe clinical outcomes of future infection. It has also been argued that sub-clinical infections predispose to the severity and outcome of other infectious diseases. A far greater body of

evidence supports the view that asymptomatic infection of the placenta of a pregnant woman significantly reduces the weights of their new-born children reducing their survival chances. Patients seek treatment and treatments often carry their own risks of fatal or morbid outcomes. Patients who survive the severe pathological consequences of infection may be left with debilitating sequelae, such as spasticity or epilepsy. More subtle consequences have also been described and include behavioral disturbances or cognitive impairment. To summarize the direct, consequential and indirect health impact of *P. falciparum* infection a crude schematic representation is shown in Figure 1. These broad health impacts will vary between communities and, in the absence of measures aimed to reduce infection risk, will be largely dependent upon the extrinsically driven factors of acquired immunity and access to effective case-management and intrinsic factors such as host genetics. The acquisition of functional immunity depends predominantly upon the frequency of parasite exposure from birth. To capture the intensity or stability of parasite transmission will have attempted to restructure the African continent on the basis of climatic determinants of *P. falciparum* transmission and have ordered disease risks accordingly. In the subsequent sections we consider disease risks as a) directly attributable to a primary infection with the malaria parasite, b) consequential to the direct disease risk, or c) indirectly related to the presence of the parasite.

4 Defining Africa's malaria risk strata

Previously we have used climate-driven models of malaria suitability to characterize the diversity of malaria transmission across the continent (Craig et al., 1999; Snow et al., 1999). These were used in 1998 to classify populations exposed to risk of stable endemic malaria and epidemic malaria (Snow et al., 1999). Details of these climate models are presented elsewhere (Craig et al., 1999). In brief, long-term mean monthly temperature and rainfall data were used to define the limits of distribution of endemic malaria, in terms of suitable climate regimes across Africa at approximately a 5 x 5 km resolution. Temperature and rainfall profiles in sample areas, where malaria endemicity was known, were translated into definitions of "climate suitability". The temperature limits were also related to the requirements for the extrinsic parasite development cycle. The model was structured to define distribution by setting the lower temperature cut-off at 18°C and assuming a saturation of the temperature effect by 22°C; similarly rainfall values between 0 and 80 mm demarcate the range within which transmission is limited. The conditions must coincide on a month-to-

month basis for at least five consecutive months. A frost-factor (mean monthly minimum temperature of less than 5°C for any one month) would eliminate transmission at any point. In north Africa high temperatures combined with a rapid onset of a short duration rainfall allows for a limited transmission period of less than three months. The model provides fuzzy membership, or climate suitability values, ranging from 0 (unsuitable hence malaria absent) to 1 (very suitable, malaria endemic).

In the present analysis we have modified our Pan-African malaria risk criteria and used the fuzzy membership model to delineate four areas of Africa (Figure 2): Class 1 (white: areas) where either there is no human settlement or zero fuzzy climate values for malaria transmission. Class 2 (yellow areas) where populations are exposed to marginal risks of malaria transmission and these risks are uncommon on an average year (fuzzy suitability greater than zero but less than 0.25). Class 3 (orange areas) where populations are exposed to a fuzzy suitability value greater than or equal to 0.25 but less than 0.75 corresponding approximately to acute seasonal transmission with a tendency toward epidemics. Finally, Class 4 (brown areas) represent populations exposed to stable, endemic malaria transmission, which may still vary seasonaly (fuzzy suitability greater than 0.75).

Outside of southern Africa we have assumed that Class 4 areas are represented by endemic conditions able to support a parasite prevalence among childhood populations of >= 25%. This criteria is explained further below and used to classify empirical data on malaria disease outcomes. Class 3 areas correspond to areas subject to low parasite prevalence (less than 25%). Class 2 areas probably do not support transmission and populations are unlikely to be exposed to any indigenous risks of infection although owing to their proximity to at-risk areas and aberrations in climate risks, transmission might occur similar to those in Class 3. As such we have grouped Classes 2 and 3 to represent low risk/potentially epidemic prone. In southern Africa (Namibia, Swaziland, South Africa, Botswana, Zimbabwe), Class 4 areas are those that correspond to conditions where malaria still poses a risk but its extent and transmission potential are determined by aggressive vector control. Class 3 areas have been grouped with Classes 1 & 2 in southern Africa as they constitute historical extents of transmission and do not reflect contemporary distributions of risk (M. Craig, personal communication). All Class 1 areas have been assumed to represent areas unable to support transmission. A number of countries have

only minimal, focal risks of malaria transmission and over 90% of their population resides in Class 1 areas (Western Sahara, Morocco, Algeria, Tunisia, Libya, Egypt, Djibouti and Lesotho). We have assumed that these countries have a negligible malaria burden, and they have been excluded from further computations of quantified health outcomes. The smaller islands were not described during the early malaria risk models. The residents of the Seychelles, Reunion and Comoros have been assumed to be at negligible malaria risk and form part of the excluded African populations during our burden estimations. Conversely it seems reasonable to assume that the islands of Sao Tome & Principal and Cap Verde are subject to stable transmission but they have proven difficult to characterize at effective resolutions using the GIS malaria risk models and their small contribution to populations at-risk (less than 0.5 million people) have not been included.

A Geographic Information System (GIS) population database for Africa was used to define at-risk populations for the continent. Full details of this database are presented elsewhere (Deichmann, 1996). The data were initially constructed using population totals from the last available censuses for administrative units in Africa. To improve the spatial resolution of the population information further, the data by administrative unit were converted into a regular raster grid of population totals and auxiliary information was used to distribute the population total recorded for the administrative unit across the raster grid cells that fall within this unit. This process heuristically incorporated information on where people tend to live: in or close to towns and cities, close to transport infrastructure, and outside of protected areas, water bodies, or very high elevations. Using GIS based information on the location and size of towns and cities, roads, railroads, navigable rivers and uninhabitable areas, a weighted surface was constructed, where a high value implied a high likelihood of high population density and a low or zero value implies low or no population. These weights were then used to proportionately distribute population to grid cells. The digital map extracted population distributions according to each cell in a regular raster grid with a resolution of approximately 5 km at the equator.

The combined malaria-risk and population models were used to identify the proportions of each country's population that are likely to reside within each of the four malaria infection risk classes described above. The total projected population estimates for each country were abstracted from the World Population Prospects Population Database (UN, 2001). The medium variant assump-

tions of changing fertility, mortality and migration on population growth were selected for the year 2000. The database also provided the estimated proportion of the population aged less than 5 years, 5-14 years and 15 years or older and the crude birth rate (CBR). The CBR was used to estimate the approximate number of live-births in 2000. The summed extractions for the continent are shown in Table 1. Since the UN Population Division's figures are based on estimations incorporating assumptions about fertility and mortality in a country, these totals may differ from the total populations in each administrative unit reported by the country. More refined micro-census data or models of population projections below national resolutions are required for future disease burden mapping.

Our malaria mapping efforts have focused on the extrinsic climatic determinants of disease distribution. The inclusion of other spatial determinants of malaria risk have been largely ignored, most notably the effects of population settlement and urbanization, because these parameters (urbanization, as well as land-use and water body distribution) have been harder to define at the same spatial resolution of the climate and elevation data. The most significant for the interpretation of our estimations of malaria burden is urbanization. In Africa it has been estimated that 38% of the 784 million inhabitants were urban dwellers in 2000 and this is estimated to increase to 55% by 2030 (Brockeroff, 2000; UNPD, 2000) There has been little work on the current impact of urbanization on malaria risk and burden estimates and no quantitative consideration of how the "epidemiological transition" will impact on the future malaria burden. There is, however, a growing body of evidence demonstrating the effects of urban settlement reducing the risks of malaria parasite exposure among human populations across Africa. Two recent comparative analyses of urban and rural sites across Africa have highlighted the 100-fold increase in entomological inoculations rates (EIR) from urban centers toward the rural peripheries (Hay et al., 2000; Robert et al., 2003). These effects occur over small distances and are difficult to capture with existing malaria risk maps or public-domain national demographic data. Future iterations of the BOMA program will allow for new models of population settlement and infection risk (SI Hay, personal communication). Meanwhile we must assume that the population-at-risk extents described for stable, endemic transmission (Class 4) will be overestimates: more people will reside in urban areas described as stable, endemic conditions but might more realistically experience a considerably lower risk of indigenous parasite exposure (Classes 2+3).

5 Health outcome data searches and abstraction

The BOMA search strategy included the use of electronic databases (Medline®, SilverPlatter International 2000; Embase®, Elsevier Science 1999-2000; and Popline®, Johns Hopkins School of Hygiene and Public Health) using keywords *malaria, Plasmodium falciparum, anemia, morbidity, mortality, Africa, child survival and demography*[1]. In addition, manual searches of pre-electronic English and French tropical and regional biomedical journals were undertaken at archives at the Bodleian Library, University of Oxford and the Wellcome Institute Library in Nairobi. Unpublished Ministry of Health and regional conference material were also reviewed where available at libraries and archives in Kenya, Uganda, Sudan, South Africa and Oxford, UK. References of all publications were checked to identify potential new material missed through initial searches. Authors of published material were contacted if information on precise geographical location, age, duration of follow-up or person-years of exposure to risk were unclear from the original reports.

Each study was geo-positioned using combinations of electronic gazettes (GDE Systems, 1995; World Resources Institute, 1995; ENCARTA (Microsoft, 1997)), reports in published material and 1:50,000 topographical maps. The centriod of the study location was recorded in decimal degrees of latitude and longitude. We have used the prevalence of *Plasmodium falciparum* parasite infection in a given childhood population to represent an approximation to stable endemicity across the continent. The parasite rate is a widely used marker of malaria endemicity (Metselaar & Van Thiel, 1959) and crudely corresponds to the frequency and duration of parasite exposure but does not provide a precise quantification of the number of new infections received by a child each year. Independent data searches were used to locate a time and location specific estimates of infection prevalence for the geographical areas covered by the mortality or morbidity data. Cross-sectional surveys of infection prevalence were included if at least 50 randomly selected children between 0-9 years of age or, if that was not available, 0-15 years. Data were identified primarily through the MARA/ARMA database (http://www.MARA/ARMA.or.sa) or correspondence

[1] During these initial extractions empirical data on pregnancy-related outcomes of malaria infection were not sourced (separate sources of these data are provided in section 8.1).

with authors of original disease burden data. The estimations of malaria risk have been used to provide empirical ecological categorization for each burden description in accordance with the cartography of risk described in section 4.

All data were abstracted, geo-referenced and matched to markers of malaria endemicity onto a pre-coded proforma and entered into a relational database (Access 97, Microsoft®, 1996[2])

6 The direct consequences of *P. falciparum* infection in Africa

In this section we consider the available evidence to define the direct, immediately attributable clinical effects of infection with *P. falciparum*, namely malaria-specific morbidity and mortality. For morbid consequences we have limited the analysis to febrile episodes and whilst acute hemolytic anemia is a direct morbid consequence we consider anemia separately under indirect effects of infection (section 8.2).

6.1 Malaria-specific mortality

Our earlier understanding of the pathophysiology of malaria derived from clinical descriptions among adults in south east Asia and only recently have the mechanisms of death been more precisely defined for pediatric African populations (Marsh et al., 1995; Warrell, 2002). From a series of detailed clinical studies in hospital settings across Africa a number of principal, sometimes overlapping, routes to a fatal outcome have been described. These include cerebral involvement from sequestered infection in the vasculature of the brain, metabolic disturbances, respiratory distress and severe anemia. For epidemiological purposes it is convenient to define two major syndromes, cerebral malaria (CM) and severe malarial anemia (SMA). CM is a condition where patients present in coma which may have a range of underlying causes, ranging from a primarily neurological condition on the one hand to the situation where coma is the result of a systemic metabolic disturbance on the other (Newton & Krishna, 1998; Marsh & Snow, 1999). Severe anemia is a pathology of life-threatening malaria with a complex etiology combining rapid hemolysis during acute infection and/or a slow insidious process compounded by anti-malarial drug resistance. Severe malaria anemia (SMA) is a life-threatening condition in young children and often warrants blood transfusion at a hospital setting. SMA is arbitrarily defined as

[2]Databases and bibliographic sources can be obtained from RWS.

hemoglobin levels of less than 5 gm/dl in association with malaria parasites. There are potential problems in defining SMA in malaria endemic areas as there are many, often interacting, causes of anemia, and that in areas of high intensity transmission it may be the norm to be parasitised. Nonetheless, in many settings children presenting with an acute febrile disease, peripheral parasitaemia and very low hemoglobin concentrations form the majority of inpatient admissions during the malaria season and thus the rather arbitrary definition proves clinically useful.

The relative contributions of CM and SMA to life-threatening presentations of severe, complicated malaria have been described in hospitals under a variety of malaria transmission settings in Africa (see section 7.2). Nonetheless we remain uncertain about their relative contributions to malaria mortality in the community. Most deaths in developing countries occur outside the formal health service and most national government systems of civil registration in Africa are notoriously incomplete.

Epidemiologists interested in defining malaria-specific mortality have established demographic surveillance systems (DSS) of large populations (between 20,000 and 100,000 people) to prospectively monitor population migration, births and deaths. The DSS is a methodology developed, and refined, by French demographers in West Africa and the UN in Bangladesh. The characteristics of DSS studies are provided elsewhere (Smith & Morrow, 1996; INDEPTH, 2002).

The attribution of causes of death during DSS surveys is often performed through a verbal autopsy (VA) interview with bereaved relatives about symptoms and signs associated with the terminal illness. The VA details are either reviewed by a panel of clinicians or subjected to diagnostic algorithms. The sensitivity and specificity of VA diagnosis for malaria as a cause of death have been estimated in seven hospital-based validation studies in Africa (Anker et al., 1999; Korenromp et al., 2003). There is considerable variation in both the specificity (mean: 88%; range: 77% -100%) and the sensitivity (mean: 56%; range 45% - 75%) (Korenromp et al., 2003). The sensitivity of verbal autopsies for malaria will depend on the intensity of malaria transmission: in high-transmission areas where functional immunity is acquired early in childhood, severe malaria is more likely to present as SMA rather than CM. SMA in a young child is often difficult to distinguish from acute respiratory tract infections (ARI) whilst CM among older

children has less ambiguous symptom presentation. Similarly, the sensitivity and specificity of verbal autopsies for malaria will vary with the local spectrum of other diseases, such as ARI, acute gastro-enteritis and meningitis, which share common clinical features including cough, difficulties in breathing, diarrhoea or cerebral dysfunction, with malaria. Despite these limitations the VA-diagnosed risks of malaria mortality represent our only source of information on the direct, fatal consequences of infection in areas of Africa subject to stable transmission.

For the present analysis of mortality outside of southern Africa we have selected only mortality reports that were derived from prospective continuous DSS among communities that employed VA to attribute cause-specific mortality undertaken since 1990. The time restriction has been selected on the basis of recent temporal analysis of paediatric malaria-mortality risks in Africa (Snow et al., 2001; Korenromp et al., 2003). These analyses demonstrate a significant increase in the proportion of childhood deaths attributed to malaria during the 1990's compared to the 1980's and probably related to the spread of antimalarial drug resistance. Where DSS and VA methods were used during community or household randomised intervention trials, only control communities were included. We have also restricted the selection of DSS surveys of malaria-specific mortality to those where there is a congruent estimation of malaria transmission intensity in order to structure risks according to transmission classes described in section 4.

Adult malaria-specific mortality data from DSS sites are rare and VA methods have not been well developed nor widely validated for the description of malaria deaths in this age group. At Kilifi, Kenya, an algorithm was used based upon detailed exclusion criteria (including an exclusion of other well defined deaths or hospital diagnosed conditions) resulting in acute febrile illness in the absence of obvious signs of respiratory disease (RW Snow, unpublished data). In Tanzania a similar rubric was used (Y Hemed, personal communication). Both approaches are likely to over-estimate deaths due to malaria in this age group in malaria endemic areas. Owing to the paucity of empirical data in this age group we have combined these two contemporary estimates with other sources of historical data on adult malaria mortality from detailed pre-independence civil registration systems operating in urban, malaria endemic, colonial protectorate areas of Africa against censused populations. It seems reasonable to assume that under stable transmission conditions adult mortality from malaria is unlikely to have changed much over time due to emerging drug resistance as fatal outcomes would be a result of some ill-defined anomalies in the acquired functional

immune response. However, because we believe that functional immunity is a major limiting factor of malaria mortality in adulthood the consequences of changing HIV prevalence may alter these risks in Africa to an extent as yet poorly defined. The departure from strict selection criteria for adult malaria-specific mortality has been driven by a lack of studies fulfilling DSS criteria in this age-group. During the 1998 iterations of the BOMA malaria mortality data we modelled age-specific risks from childhood malaria mortality data using age-structured severe disease incidence data to estimate adult malaria-specific mortality. This was subject to a large number of assumptions about severe disease versus mortality risks and how these change with increasing age. There are as many limitations to the use of historical data on malaria mortality from civil registration data to inform contemporary mortality risks in adult populations in Africa. We have chosen to present here the empirical data but urge caution in their interpretation.

Twelve independent estimates of malaria mortality among children aged 0-4 years living under conditions of stable transmission (parasite rate >= 25%; Class 4) were available since 1990 representing DSS sites in Burundi, Ghana, The Gambia, Senegal, Sierra Leone, Kenya and Tanzania. The median malaria-specific mortality rate among these communities was 9.33 per 1000 children per annum (p.a.) (Interquartile range (IQR): 7.38, 14.57) and represented 28.2% of all mortality among children aged 0-4 years. Under similar transmission conditions since 1990 the median malaria-specific mortality among older children, aged between 5-14 years, was 1.58 per 1000 p.a. (n = 10; IQR: 0.66, 2.77), representing 52.2% of all deaths in this age group. Among adult populations surveyed as part of colonial administration civil registration systems or more recent DSS sites in stable endemic areas suggests that the median malaria mortality rates are 0.6 per 1000 p.a. (n = 15; IQR: 0.37, 0.94), or 6% of all deaths among populations aged 15 years or older.

DSS or colonial administration civil registration data from low, stable endemic conditions outside of southern Africa are few. Two approximations to the DSS from a tea-estate population in the highlands of Kenya (Shanks et al., 1999; & unpublished data) and a settled refugee camp in the Sudan (Charlwood et al., 2001) provided data on malaria-specific mortality rates among their fixed, known childhood populations at low risk of malaria infection. In addition, the one true DSS site at Hai district in Tanzania provided a VA estimate of malaria mortality (Government of Tanzania, 1997). All three studies covered periods since 1990.

Only the Kenyan and Tanzanian studies provided information on older children and adults. Rather than provide a median estimate from the limited data the combined Person-Years of Observation (PYO) and malaria mortality events have been used to define direct malaria mortality risks under these transmission conditions in Africa. For children aged 0-4 years the overall mortality rate was 2.62 per 1000 p.a. (287/109,412; 3 studies), for children aged 5-14 years the mortality rate was 0.94 per 1000 p.a. (158/167,598; 2 studies) and for adults aged 15+ years the rate was 0.71 per 1000 p.a. (265/372,777; 2 studies).

In South Africa there is one ongoing rural DSS site at Agincourt (Kahn et al., 1999), located at the fringes of malaria risk (Brink, 1958). Between 1992 and 1995 only 2 of the 216 recorded deaths among children aged 0-4 years were attributed by VA to malaria providing a malaria-specific mortality rate of 0.065 per 1000 p.a. Of the 785 deaths recorded in the population older than 5 years only one was attributed to malaria. This single estimate does not provide an adequate representation of the malaria mortality across areas of malaria risk in southern Africa. In southern Africa civil and vital registration systems are significantly more comprehensive compared to systems operating in the more northerly countries of Africa. They will however continue to be under-reporting of events and as such must be viewed as minimum estimates. Data were extracted from reports provided during sub-regional malaria control program meetings and malaria deaths (reported only for all-age groups combined) were expressed per projected population estimates for district, magisterial district or province from areas of known malaria risk (Figure 2). These data were available for the three areas of South Africa in KwaZulu Natal Province, seven areas of Botswana, four areas of Namibia and eight areas of Zimbabwe. The median estimate of malaria-specific mortality among the entire population in these areas was 0.13 per 1000 p.a. (IQR: 0.08, 0.21). Whilst we argue that these estimates represent minimal approximations to the true mortality burden because of their dependence upon civil registration it is interesting to note that they fall within the ranges of mortality described for the single DSS site (Kahn et al., 1999) and those described from a more detailed analysis of vital registered malaria mortality data in two districts of KwaZulu Natal Province between 1996-1999, 0.02-0.52 per 1000 p.a. (Tsoka et al., 2002).

A summary of the estimated numbers of deaths directly attributed to malaria derived from median (IQR) estimates of risks across the diverse transmission conditions of Africa is shown in Table 2.

6.2 Mild clinical disease

Given the predominance of fever within the clinical presentation of malaria in a non-immune, this sign has historically dominated the diagnosis and management of the disease. However, where infection and fever are common, the diagnosis of malaria as a distinct clinical entity is fraught with difficulties. For these reasons malaria case-management in Africa largely centers upon presumptive diagnosis and treatment of fever (Gove, 1997; Chandramohan et al., 2002).

Clearly not all fevers are malaria, furthermore not all "febrile events" are true fevers. African communities plagued with infectious disease have developed an elaborate bio-medical and bio-cultural vernacular to describe fever. Anthropological and social-epidemiological studies have examined the ways in which "malaria" fevers are defined in communities (McCrombie, 1996). The common observation across these studies is that specific terms used by communities to describe malaria fevers appear to lack both sensitivity and specificity when compared against subsequent clinically and parasitologically defined malaria.

Demonstrating the presence of malaria infection during a clinical event increases the likelihood that symptoms are directly due to the infection but the high prevalence of asymptomatic infections makes it difficult to exclude other diagnoses. Increasing parasite densities in the peripheral blood increases the statistical chances that a fever is attributable to infection and the sensitivity and specificity of definitions of morbid events are improved by the use of Population Attributable Fractions (PAF) and calculated from cross-sectional, community-based surveys (Schellenberg et al., 1994a; Smith et al., 1994). Given that relative changes in geometric parasite densities occur with increasing age, PAF's ideally should be derived for different age-groupings and afebrile parasite prevalence.

The constraints to defining morbid events attributable to malaria infection make the precise contribution of *P. falciparum* malaria to morbidity in Africa difficult to establish. There is an important distinction between the incidence of perceived fever and the incidence of biologically defined fever. The former is necessary to establish the frequency of drug-patient contacts to estimate subsequent potential frequency of adverse drug reactions (section 7.1). Conversely only estimates of the biologically defined risks of fever attributable to malaria are of value to establish the contribution made by malaria to the DALY.

Measuring the incidence/ prevalence of malaria morbidity usually involves passive and/or active case detection of fevers accompanied by microscopic examination of thick blood smears taken on all fever cases. Biological fevers are measured by axillary or rectal temperature, although the timing of these measurements are subject to diurnal variations (Schellenberg et al., 1994b). Both active and passive case detection usually relate to fixed cohorts of children identified through census enumeration's. The frequency with which active surveillance is undertaken during a year or a malaria season will determine the number of clinical events detected, monthly surveillance tends to detect only one quarter of events detected through weekly surveillance and weekly contacts with cohorts identifies approximately 75% of events detected through daily surveillance (Snow et al., 1989). Prospective studies of fever incidence have been undertaken as part of controlled trials or descriptive studies of malaria since the early 1980's.

The BOMA data search extracted from reports the numbers of observations, the numbers of subjects with a raised body temperature (>=37.5°C axillary or 38.0°C rectal), the numbers of fevers associated with any level of peripheral infection and those with locally defined criteria for attributable levels of parasite density used to distinguish clinical malaria from coincidental associations with infection. Studies of fever were selected for the present estimation of burden if they were: a) undertaken as multi-round cross-sectional studies where at least two separate observations were made on a single cohort to reflect seasonal differences in risk; b) all subjects were randomly recruited from the community and not at clinic; c) cohort members selected to be part of a randomized trial were those allocated to form a control arm; d) studies were undertaken since 1980 (an earlier date than mortality (section 6.1) as disease incidence is less likely to be temporally affected by drug resistance in stable endemic areas); and e) studies described "clinical episodes" by means of attributable infection levels.

Criteria used to distinguish clinical attacks from coincidental infection varied between studies (ranging from 1,000 to 10,000 parasites per μl) and it was not possible to make each study congruent with a single definition. Nor was it possible to correct the data for the mode of body temperature measurement or rigor of microscopic identification of parasites. Precise age criteria was difficult to standardize from original reports and as such the summary measures represent young children (0-6 years - including age groupings such as 1-4 years

but not infants only); older children with age-groupings between 4-14 years and adults. The number of fevers were expressed per number of observations (assumed to represent a single week's observation period) and corrected to an annualized risk per child by expressing each rate per 52 weeks of observation. This correction is likely to underestimate the precise incidence of fever given that weekly observations underestimate the number of events detected through daily surveillance by a factor of 1.333 (Snow et al., 1989). It was also not possible to correct for the seasonal distribution of risks – some studies were undertaken during periods of maximal malaria risk. The following risk estimates should be viewed in the light of these caveats.

In areas of stable endemic risk outside southern Africa (Class 4: parasite prevalence >= 25%) the annual risks of a clinical attack among young children were defined from 28 studies and represent a median risk of 1,424 per 1000 p.a. (IQR 838, 2,167). Among older children (19 studies) the median risks were 587 per 1000 p.a. (IQR 383, 977). Considerably fewer estimates were available for non-pregnant adult populations (n = 7) and the median estimate described for these studies was 107 per 1000 p.a. (IQR: 74, 138).

Only four studies among young children were available to estimate the annualized risks of a clinical attack from areas of low transmission/epidemic fringe risks (Classes 2+3). These studies were undertaken in the highlands of Tanzania (2), The Gambia and Uganda. The median rate was 182 per 1000 p.a. (IQR 125, 216). Empirical, clinical incidence data for older children and adults living under low transmission conditions were not available. In these communities a degree of functional clinical immunity will still be invoked through even low parasite exposure early in life although risks of clinical disease are unlikely to decline much before adulthood (Gupta et al., 1999; Hay et al., 2002). It has therefore been assumed that risks for 5-14 year olds would be similar to those in early childhood and half these risks among adult, non-pregnant populations.

Among the countries of southern Africa, notably South Africa, Botswana, Namibia, Zimbabwe and Swaziland, passive case-reporting of malaria events forms an integral part of the national control strategies. In South Africa this is supplemented by active-case detection in selected areas, prompted by the passive detection of cases. It is not possible to define the precision of these national surveillance data in terms of coverage, however they all represent new, microscopically confirmed cases detected within the formal health system

with, ironically, a higher capacity for decentralized information systems than most other endemic areas of Africa where disease burdens are considerably higher. Data were extracted from reports provided during sub-regional malaria control program meetings and cases expressed per district, magisterial district or province from areas of known malaria risk (Figure 2). Data were available from Botswana (7 areas: 1988-94), Swaziland (4 areas: 1990-92), Namibia (4 areas: 1992-96), South Africa (3 areas of KwaZulu Natal Province: 1988-94) and Zimbabwe (11 areas nationwide: 1997). Data were provided for all age groups combined. Where data were available by age the incidence varied little with increasing age, with only a slightly lower incidence among young children (Kleindschmidt et al., 2002). Population data were obtained from independent national census sources and projected to cover the periods of observation to allow an expression of the case data per 1000 population p.a..

The southern Africa data demonstrated a large spatial variation in risks with some geographical areas experiencing risks similar to endemic conditions common to areas of Africa further north. Another distinguishing feature was the large between year variation in disease burden consequent upon breakdowns in effective control and therapeutics or climate-driven epidemics (Craig et al., 2003; Le Sueur et al., 1993; Kleindschmidt & Sharp, 2002; Kliendschmidt et al., 2002). Despite these limitations to interpreting a limited temporal series, the median rates of passively detected malaria cases in southern Africa was 29.4 per 1000 population p.a. (IQR: 9.7, 129.2).

Applying the estimated median risks (and IQR) to the populations of southern Africa, unstable/epidemic prone and stable endemic Africa the expected numbers of malaria-specific morbid events during 2000 is shown in Table 3.

6.3 Duration of clinical episodes

There are three problems in trying to estimate the duration of clinical events due to *P. falciparum* malaria. First, events detected during active, prospective surveillance are treated promptly by investigators. Second, the majority of retrospectively reported febrile events recorded during demographic and health surveys are not malaria. Finally, precisely defined clinical cases seen at clinics during clinical or drug studies do report duration of fever but not always the length of time taken to resolution of symptoms, and represent only those clinical events which access formal health services, usually those who have failed home

management in Africa. On balance the latter still represent our most reliable source of information on illness duration and if combined with a limited amount of clinical data on symptom resolution provide us with a broad sense of the length of clinical malaria attacks.

19 pediatric study population groups reporting mean symptom duration in days prior to recruitment at clinics in stable endemic areas (parasite rate >= 25%) were identified from nine countries. Among children, of varying age groups within the 0-14 year range, the median of the reported mean duration of symptoms was 3.6 days (IQR: 2.9, 4.4). Mean symptom/fever resolution in days following treatment was reported in nine studies and the median of these reports was 1.5 days (IQR: 1.4, 1.6) after the commencement of treatment. Thus we can assume that clinical events that are managed at formal clinics would last on average 5.1 days (combined IQR: 4.3, 6.0). The selective nature of the data used to define this estimate must be emphasized and it is conceivable that clinical attacks that either spontaneously recover due to acquired immunity or are successfully treated at the household level might well be of shorter duration. Trape et al. (1993) maintained a rigorous daily surveillance among older children (7-11 years) in a very low transmission area of Senegal and suggested (despite investigator intervention with effective drugs) that symptom duration among young children with clinical attacks of malaria was 3.2 days.

Considerably less information is available on adult patients with mild clinical disease. The best details derive from detailed daily surveillance of populations in an asylum in Lagos during the 1950's (Bruce-Chwatt, 1963) and the Dielmo population in Senegal (Rogier et al., 1999) reporting a mean symptom duration of 2.6 and 0.86 days respectively. It seems reasonable to assume that duration of illness is lower in adult populations, although based upon limited observations, by several days and we have assumed that each event in adult populations in stable endemic areas lasts for 2 days. No data are available on symptom duration among populations exposed to transmission conditions that prevail in low risk communities or southern Africa. Here we can assume that all disease events occur among immunologically naïve populations and duration is likely to be similar to those of young children in stable endemic areas. A summary of combined person-days of illness due to *P. falciparum* malaria in 2000 is shown in Table 4.

Of operational interest is the duration of symptoms among patients who develop

severe, potentially life threatening illnesses or die from malaria. Data are available from hospital studies on the duration of presenting symptoms among pediatric patients at admission and the duration of hospitalization. Among 972 children (variously aged between 0-14 years) admitted with cerebral malaria to seven hospitals (9 separate reports), where details were available on mean symptom duration prior to admission, the median number of days these patients were sick was 2 (IQR: 1.95, 3). The median duration of admission varies but is on average 4-5 days for those who survive the first 6 hours of admission (which accounts for over 75% of the cerebral malaria mortality) (Kilifi unpublished data; Biemba et al., 2000; Kilian, 1995). Among two series of clinical studies which defined severe malaria anemia (Hb < 5.0 gm/dl in the presence of high parasite densities) the mean duration of symptoms prior to admission was 7 days and the duration of admission was circa 4 days (Biemba et al., 2000; Kilifi, unpublished data). Details of the duration of illnesses which result in a fatal outcome without contact with formal health services, described by VA, are hard to define with precision and are subject to definition circularity - VA diagnosed deaths are often ascribed to malaria if they are reported to be characterized by "short duration fevers".

Consequential effects of malaria in Africa

7

There are a number of features of the malaria burden equation that have been less well defined in previous estimations of the malaria DALY. In this section we consider the consequences of disease that are related to the clinical event but are consequential to it. These include the consequences of clinical management, such as the immediate effects of adverse drug reactions or the longer-term residual effects of acquired HIV infection through blood transfusion. Non-intervention related consequences of clinical events also include the short and long-term residual impairments consequent upon brain insults during cerebral malaria.

Fever treatments versus adverse drug reactions

7.1

When considering patient-drug contacts to estimate the toxicity burden created through exposure to antimalarial drugs we must revert to estimations of perceived, rather than clinically/epidemiologically defined, malaria. The perception of malaria in many African societies is synonymous with the perception of flu in western biomedical culture. It is the perception of disease that prompts self-

treatment with drugs and to a large extent reported fever serves as the single prompt for most clinically managed patients. The largest source of empirical data on the period prevalence of reported “fever” among pediatric populations in Africa derives from demographic and health surveys.

Since 1984, the Demographic and Health Survey (DHS) has formed an important survey instrument to examine national-level demographic trends (http://www.measuredhs.org/). These surveys were initially designed to collect data on fertility, mortality and family planning program indicators. More recently, new modules have been added to the DHS to capture indicators of interest for other health issues, such as malaria and HIV/AIDS. The data collected by the survey is representative at the national level and can also be disaggregated by urban/rural status. These survey approaches have also been used as part of the UNICEF Multiple Indicator Cluster Surveys (MICS) covering several countries not yet covered by the DHS/Measure project (http://www.childinfo.org/MICS/).

The web-access DHS and MICS databases provide details on the age-structured period prevalence of fever among the pediatric populations sampled in randomly selected households across the country. During the survey mothers of children born within the last 3 or 5 years are asked whether their child had a fever during the last 14 days. These data have been abstracted and corrected to annualized estimates of fever risk by multiplying the period prevalence by 26. It has not been possible to correct the single-round, period prevalence estimate of fever to reflect seasonal patterns of risk. Many of the surveys were undertaken during dry periods of the year to facilitate easier community access for survey teams.

It seems reasonable to assume that under stable endemic conditions clinical immunity to malaria is acquired during childhood and the risks of disease decline significantly during this period. However, the reported prevalence of locally defined “fever” has been shown to be as common among older children and adults as among their younger household members (McCombie, 1996). In settings where data is available from stable endemic areas of Africa the common pattern is of equivalent numbers of out-patient malaria diagnoses in adults and children (Snow et al., 2003b) and this is reflected in DHS-type questions on perceived fever (Ettling et al., 1994).

It has been assumed that fever and treatment-seeking patterns are similar in low

endemic and high endemic areas (supported by a more sub-national analysis in Kenya (Amin et al., 2003) and similarities between urban and rural comparisons (DHS data). The empirical estimates of pediatric fever period prevalence from the 33 predominantly stable endemic countries outside southern Africa among 375,064 children suggests a median annualized "fever rate" of 9.1 per child p.a. (IQR: 7.4, 10.8). Data from southern Africa (Namibia, Zimbabwe, Botswana and Swaziland) suggests a much lower period prevalence (median 0.4 per child p.a.: IQR: 0.1, 0.7).

Assuming perceived fever frequency was similar across all age groups and similar in high (Class 4) and low stable transmission (Classes 2+3) in Africa this computes to approximately 4.9 billion febrile events signaling patient treatment each year in sub-Saharan African countries. In southern Africa the corresponding number of fever-treatment prompts would be 5.7 million. Recently Monash et al. (submitted) analyzed the results from 24 DHS or MICS surveys undertaken in non-southern African, mainland countries to examine the frequency of reported anti-malarial drug use during reported fevers among pediatric populations. Their results suggest that reported anti-malarial drug-exposures range from only 3% in Ethiopia to 66% in the Central African Republic. The median across these studies of anti-malarial drug use among pediatric fevers was 54% (IQR: 31.8, 60.3%). Although these data refer only to young children there is reason to believe that these frequencies would be similar among older children and adults (Figure 3: Spencer et al., 1987; Guyatt & Snow, submitted). In all areas of malaria risk outside of southern Africa there might be as many as 2.7 billion anti-malarial treatment exposures each year or 4.93 per person per year.

The toxicity of many anti-malarial drugs has been poorly described among African populations repeatedly exposed to these compounds. Most data derive from an examination of chemoprophylactic drug use among non-immune travelers (Philips-Howard & West, 1990; Philips-Howard & Bjorkman, 1990). Almost no post-marketing surveillance (PMS) data were generated at a time of introducing chloroquine, (CQ), amodiaquine (AQ), quinine (QN) or sulphadoxine-pyrimethamine (SP). More PMS data are available for much less widely used drugs in Africa (e.g. Mefloquine, Halofantrine and the artesunate combinations). It is thought that the majority of adverse reactions due to sulphonamides and 4-aminoquinalones are idiosyncratic. However, there is some evidence that risks are increased with repetitive dosing, particularly important in Africa where

patients self-medicate and access similar treatments from formal sectors or soon after with further informal sector drugs. Severe adverse events to the commonly available antimalarial drugs in Africa (CQ, AQ, QN and SP), when used largely as recommended doses, include severe cutaneous reactions (Stevens-Johnson and Lyell syndromes), aplastic anemia, severe neutropenia, thrombocytopenia, keratopathy, agranulocytosis and hepatic failure (Jaeger et al., 1987; Reynolds, 1993). Milder allergic type conditions such as pruritus, muscle fatigue, headaches, tinnitus, and gastric disturbances have not been considered here. Empirical population data on exposure versus in utero effects of CQ, AQ, QN and SP are rare and as such no estimation is made here on the effects of inadvertent exposure to these compounds during early pregnancy on birth outcomes and interuterine deaths and defects. Our current knowledge of the safety of anti-malarial drugs during pregnancy is reviewed by Philips-Howard & Wood (1996).

Among UK travelers exposed to SP prophylaxis serious ADR were reported in 1:2,100 prescriptions and fatal events were 1: 11,100 (Philips-Howard & West, 1990). No serious events occurred in 36,673 patients receiving single-dose sulphadoxine although 10 ADR-skin related deaths occurred in 72,500 taking multiple doses (1:7,250) (Bergoend et al., 1968). The often cited severe ADR risks for SP is 1:50,000 patients receiving single dose sulphomnamide increasing by a factor of 10 to 1:5,000 for repeated dosing (Miller et al., 1986; Hernborg, 1985).

For UK travelers exposed to AQ prescriptions the serious ADR risks were 1:2,100 and fatal outcomes were 1:31,000 (Philips-Howard & West, 1990). In the meta-analysis of AQ therapy 66 probable or possible ADRs were reported among 1,071 drug exposures for treatment and half recovered without sequelae (Olliario et al., 1996). Data submitted to the UK Committee on the Safety of Medicines suggested that the frequency of adverse reactions to amodiaquine was about 1:1,700 for serious reactions, 1:2,200 for agranulysotosis, 1:30,000 for aplastic anemia, 1:15,500 for hepatotoxicity, and 1 in 15,650 for fatal reactions (P. Philips Howard cited in Olliario et al., 1996; Reynolds, 1993).

There are many caveats to using the available data on ADRs to commonly used antimalarials in Africa. Data are scantly and fatal outcomes, if they were reliably monitored, would be hard to distinguish from the pathology caused by malaria. Clearly the ADR profiles differ between anti-malarial drugs and the most widely

used drug on the continent, CQ, seems to have the least documented ADR risk description (although this drug can be highly toxic with poor prognosis when taken in excessive doses). At a continental level most patients during 2000 will have been exposed to CQ rather than SP or AQ. Multiple dosing is a likely occurrence in many endemic settings where patients seek branded generic named drugs of the same compounds. Examining the risks so far reported in special groups we have selected a conservative estimate of severe ADR risk and applied this to the total pediatric population only living in malaria risk areas of Africa. This makes three assumptions, a) the ADR responses will be idiosyncratic; b) all children will have a drug exposure at least once each year and c) if children do not experience an ADR on first exposure they will not do so upon subsequent exposures (i.e. risks in later life). The later assumption again will be drug specific particularly in the light of differences in ADR responses assumed for HIV infected patients exposed to sulphonamides. If we assume a minimum risk of 1:20,000 exposures will result in a severe ADR and that 50% are fatal we might expect circa 4,700 ADRs and 2,350 deaths associated with treatment each year among the childhood populations outside of southern Africa. The types of surviving ADRs might include hepatotoxicity, agranulocytosis and aplastic anemia that could last with effective management between 28 days and 6 months. These consequential deaths are presented here to demonstrate the potential delicate public health balance between toxicity and the curative value of drugs in reducing the risks of a fatal outcome due to infection. Clearly the risks and assumptions we have used are conservative and these will only increase with new, more efficacious but more toxic drug combinations and exposure for the first time among all age groups.

Severe disease and residual sequelae

7.2

Most hospital settings in malaria endemic areas have a system of recording patient's admission diagnosis. Invariably these diagnoses are made in the absence of microscopy or strict clinical criteria and rarely altered on discharge. Over the last 10 years a number of rigorous prospective clinical descriptions have been undertaken at hospital settings across Africa. These studies have included upgraded systems of admission surveillance which capture all demographic details of the patient including residence, strict clinical examination protocols, blood film examination for malaria infection, hematology and additional laboratory investigations. These studies have been linked to population data from defined catchment populations of known size within easy access of the

in-patient facility to define rates of severe disease presentation and a more thorough investigation of pathology (Marsh et al., 1995; Snow et al., 1997a; Slutsker et al. 1994; Brewster & Greenwood, 1993; Modiano et al., 1998).

Seven estimates of annualized CM have been abstracted from previously published (Snow et al., 1997a) and unpublished data constructed in a similar fashion (Marsh & Snow, 1999) - three areas of The Gambia, three in Kenya, one in Tanzania and one in Malawi. Surveillance covered various periods between 1991 and 1996 and reflected a total of 219,441 person-years exposure to risk among children resident within the hospital catchment area aged between 0 and 9 years. During this period a total of 246 CM cases presented to hospital from the combined sites (1.121 per 1000 p.a.). The rates of CM varied considerably between settings with the highest rates in areas of low-to-moderate malaria transmission and the lowest rates in areas of intense malaria transmission. The malaria conditions prevailing across the sites included in this analysis broadly represent the spectrum of transmission across much of stable, endemic malaria in SSA and a single point estimate has been used to describe these risks.

The case-fatalities of CM, even under optimal management conditions, are high. Similarly, given the pathogenesis of CM its seems reasonable to assume that clinical conditions which progress to severe cerebral involvement would not survive in the absence of intensive clinical management and as such CM cases surviving hospital admission probably reflect most of the surviving CM cases in a community, and hence exposed to the risk of seqeulae. Those who do not reach hospital would contribute to the mortality component of the malaria burden. To define the proportions of survivors of CM admission the BOMA project identified temporally or spatially discrete studies describing pediatric CM case-fatalities in hospitals settings located in stable, endemic areas since 1990 (selected to allow for changing impacts of drug resistance upon clinical presentation and prognosis) and where patients were not part of interventions of improved case-management strategies. Among 5,639 CM admissions described in the 34 studies there were 989 deaths (17.5%: Median 17.0%; IQR 13.0, 21.7%). As such one can assume an annual incidence of surviving CM among children aged 0-9 years within easy reach of a hospital setting of between 0.874 per 1000 p.a. to 0.975 per 1000 p.a.

The populations exposed to residual sequelae are likely to be those located

within reach of hospital. Previously we have tried to define the population access component of the sequelae derivations using DHS survey data which provide the proportions of the population living within 15 km of hospital care (Snow et al., 1999). During these iterations we used a median estimate of 36% (ranging from 22-65%) derived from DHS studies in seven countries (Uganda, 1995; Kenya, 1995; Tanzania, 1991/92; Mali, 1995/96; Central African Republic, 1994/95; Chad, 1996/97; and Cameroon, 1991). Given the approximations used in deriving surviving risk this figure continues to serve as a reasonable approximation.

Prolonged coma and seizures are associated with neurological impairment following CM. 14 studies have described the immediate and prolonged sequelae associated with CM among African children. The studies described a range of neuro-cognitive impairments including hemiparesis, quadriparesis/severe deficit, hearing and visual impairments, speech/language and non-verbal construction difficulties, behavioral problems and epilepsy. The overall rate of neurological damage recorded at discharge for 1,780 surviving CM admissions from 14 reports was 9.7%. However, these studies are extremely difficult to compare owing to either different criteria used for complex assessment or too little information on how residual damage was assessed. Behavioral and learning deficits are difficult to measure and most studies have been difficult to compare owing to major differences in endpoints and neuro-psychological assessment tools (Holding & Snow, 2001; Holding & Wekulo, submitted). Very few studies validated batteries of assessment tools for local cultural environments. Furthermore, most studies did not follow patients up for long enough periods to define recovery rates from discharge seqeulae. Newton & Krishna (1998) reviewed studies for consistency in diagnosis, performance measures and duration of post-discharge follow-up. They presented a series of proposed immediate and residual risks of neuro-cognitive sequelae following CM from five congruent studies (Molyneux et al., 1989; Brewster et al., 1990; Bondi (1992); Murphy et al., 1996; van Hensbroek et al., 1997) [for summary see Table 5]. Since these data were reviewed new and more epidemiologically rigorous data have been collected as part of on-going clinical investigations of CM and malaria seizure patients at Kilifi on the Kenyan Coast (Carter et al., submitted). These new observations provide a more precise estimation of the impact of brain insults early in life upon the long-term residual impact on the incidence of epilepsy, behavioral difficulties and language deficits. To this end these data have been used in Table 5 rather than earlier presentations by Newton & Krishna (1998).

No data are available on the risks of residual sequelae among adults exposed

to cerebral malaria in Africa, nor the risks of CM among populations in southern Africa and low endemic areas of sub-Saharan Africa. The differences in the denominators used to calculate risk (0-9 years) and the application to continental populations at risk (0-15 years under class 4 * 0.36) might allow for the residual numbers of cases in older age groups and thus could be viewed as the complete sequelae burden estimate. Assuming a risk of exposure to sequel of between 0.874 and 0.975 per 1000 p.a. and a total at-risk population aged 0-15 years living within 15 km of a hospital of 67,900,379 (188,612,165*0.36) then the total numbers of at-risk CM survivors is likely to be between 59,344 and 66,203 each year. As such the numbers of children impaired each year following CM brain insult will be between 2,700 and 3,000 for epilepsy; 7,000 to 7,800 for learning difficulties; and 770 and 860 with severe deficits including quadriparesis (Table 5). Most long-term residual neuro-cognitive sequelae are probably life-long impairments (CRJC Newton, personal communication). Many children with severe physical impairments are unlikely to attend school particularly when household resources for education are scarce and choices have to be made between siblings. Furthermore those with severe deficits are likely to have a higher mortality risk during their early years of living with the disabilities (Mung'ala et al., submitted). Increased mortality rates have been described among Africans with epilepsy (Jillek-All & Rwiza, 1992; Coleman et al., 2002; Snow et al., 1994; Versteeg et al., 2003). In western countries, the risk of premature mortality could be as high as 2-3 times that described in age-comparable groups without epilepsy (Hauser et al., 1980; Cockerell et al., 1994; Zielinski, 1974), but in Africa this could be as high as 9 times (Coleman et al., 2002). This is likely to be caused by poorly managed epilepsy resulting from status epilepticus or accidents (such as drowning or burns) (Snow et al., 1994).

There is a growing body of evidence to suggest that neuro-cognitive sequelae not only occur after CM, but also after other forms of severe malaria, in particular children with complicated seizures (focal, repetitive or prolonged) who do not fulfill the definition of CM (Carter et al., 2003; Carter et al., submitted). This last group may make a significant contribution to the burden of disease. During recent long-term follow-up studies on the Kenyan coast it has been determined that the odds ratio of developing epilepsy by the age of 6-9 years following CM was 4.4 (95%CI: 1.42 – 13.69) and severe malaria including complicated seizures but not CM was 6.1 (95%CI: 2.02 – 18.25) (Carter et al., submitted). This study also highlights that the incidence of epilepsy following malaria may well rise with a longer follow up. It is much harder to define the

true incidence of complex seizures at a community-level, where many events may not seek hospital treatment and do survive. As such we must assume that the incidence of neuro-cognitive sequelae following severe malaria presented from our descriptions of surviving CM is only a fraction of the true residual burden.

7.3 Risks of HIV from blood transfusions during episodes of severe malaria anemia

To estimate the numbers of SMA admissions warranting a transfusion we began with an estimate of the annualized risk of admission to hospital with SMA derived from detailed prospective clinical surveillance linked to discrete catchment populations-at-risk (as per CM calculations described above). Among the five sites where hemoglobin was measured on all admissions, 617 SMA cases were identified amongst a resident population of 152,215 (4.053 per 1000 p.a.).

The assumptions used for case-fatalities in the absence of hospital intervention for CM cannot be made for SMA that is a life-threatening complication of malaria but is more likely to have a better prognosis under treatment modalities available outside the in-patient setting. Thus the SMA risks are valuable only as entry point into the definition of risks associated with blood transfusion, usually available only at the referral, hospital level. However, the duration of morbidity is often much longer for SMA than CM (section 6.2) and as such a greater degree of "access" (spatial and timing combined) is likely to apply to SMA treatment than was selected for CM. To allow for this we have used the upper range of 65% "catchment access" defined from DHS surveys rather than the average estimate resulting in an exposed to risk population aged 0-15 years of 122,597,907 (188,612,165*0.65) living under stable endemic conditions (Class 4) and 496,889 SMA admissions each year.

To define the proportions of survivors of SMA admission we used temporally or spatially discrete studies describing pediatric SMA case-fatalities in hospital settings located in stable, endemic areas since 1990 and where patients were not part of interventions of improved case-management strategies. Among 5,624 SMA admissions aged variously between 0-15 years described in 17 studies there were 486 deaths (8.6%: Median 8.0%; IQR 4.7, 13.8%). Thus between 428,320 and 473,540 children with SMA would survive admission each year.

Transfusion is a common pediatric practice in Africa. Criteria for transfusion

vary between clinical settings, however, we have identified nine reports where transfusion rates were provided for children presenting to hospital with malaria and a hemoglobin of less than or equal to 5.0 gm/dl. The median transfusion rate among 12 studies was 80.1% (IQR: 64.3, 93.4%). Combining the ranges in estimates for transfusion we might expect between 275,400 and 442,290 surviving SMA admissions aged 0-14 years to have been “exposed” to blood transfusion each year.

Greenberg et al. (1988) examined the HIV and malaria status of 167 pediatric admissions to an emergency ward at the Mama Yemo Hospital in Kinshasa, Democratic Republic of the Congo (DRC). Of 112 malaria diagnoses, 68 were transfused and 44 were not. HIV infection rates on discharge were 15% among the transfused group compared to 2% among the non-transfused group. The authors propose an unadjusted odds ratio for acquired HIV infection of 3.5 for malaria patients transfused once rising to 21.5 and 43.0 for those transfused twice and three times during a single admission. At Kinshasa HIV infection rates at the blood bank were 6.3%. In a study of transfusion practices in 1994 at six government hospitals in Kenya, Moore et al. (2001) calculated a 2% risk of transmission of HIV antibody positive blood from screened donations through blood transfusion to HIV negative patients. The prevalence of HIV among blood donors was 6.4%. Reasons for this high risk included irregular laboratory practices, record keeping errors and inaccuracy of testing. The Kenyan study did not include the risk from pre-seroconversion donations, nor did it allow for the sensitivity of test-kits or the use of unscreened blood. The probability that an HIV antibody negative unit of blood is HIV infected (pre-seroconversion and sensitivity of test) has been estimated to be between 0.5 and 1.1% in Côte d’Ivoire where HIV prevalence among blood donors was 11% (Savarit et al., 1992). The probability of seroconversion following HIV contaminated blood is assumed to be 96% (study in Zaire, Colebunders et al., 1991).

In our estimations we have selected a conservative risk of 2% of exposure to HIV from blood transfusion and 0.96 probability of seroconversion. This will clearly depend on the prevalence of HIV among blood donors in a given population which varies considerably across the continent, with west African populations probably having lower sero-prevalence rates compared to east and southern Africa in 2000. We have no data on the risks of SMA in adults, or any age group in southern or low endemic/epidemic areas of Africa and we have not

attempted to derive these estimates. The numbers of children aged 0-14 years living in stable endemic areas of Africa likely to acquire an HIV infection because of exposure to blood transfusion to manage SMA we estimate to be between 5,300 and 8,500 each year. This figure is lower than estimated earlier owing to the selection of a more contemporary estimate of risk (Moore et al., 2001) rather than a reliance upon a risk factor defined during the early years of the epidemic in Kinshasa (Greenberg et al., 1988). The prognosis of HIV infected infants is poor in most African settings. During a recent review of the literature Dabis & Ekpini (2002) suggest that 26-45% of children infected at birth will die before their first birthday and a further 35-59% at 2 years. The acquired infections through blood transfusion might therefore be expected to survive only a further two years from the time of inadvertent infection contributing to non-malaria mortality components of the DALY.

8 Indirect and co-morbid risks of infection

The DALY model does not allow sufficiently for malaria as an indirect cause of broader morbid risks, for example anemia (unless linked to acute high-density parasitaemia), low-birth weight or growth retardation/ under nutrition or the role of malaria infection in enhancing severity of other comorbid infectious diseases through immune suppression or enhanced invasive capacities across compartments. The assumption within the DISMOD model used to compute the DALY is that malaria is a distinct clinical entity that can be measured reliably and fitted into a fixed disease-mix matrix. It has been observed during a number of randomized controlled intervention trials aimed at reducing the incidence of infection, but were not 100% protective, that all-cause pediatric mortality is often reduced more that would be attributed by VA diagnosis. For example, in Kilifi the proportion of deaths 0-4 years attributed to malaria by VA was 34% (RW Snow, unpublished data) and during a randomized controlled trial of insecticide-treated nets (ITN) the incidence of malaria infection was reduced by 50% (Snow et al., 1996) which was sufficient to reduce all-cause mortality by 33% (Nevill et al., 1996). More dramatically, in The Gambia, ITN reduced all-cause mortality by over 60% and yet the VA-diagnosed contribution of malaria to all-cause mortality among control populations was only 16% (Alonso et al., 1993). This has led some to speculate that malaria infection per se is a contributor to broad causes of mortality beyond the direct fatal consequences of infection (Molineaux, 1997).

In this section we review the evidence in support of some of the most plausible mechanisms of indirect effects of malaria infection upon health outcomes in Africa. We have tried to distinguish between factors that enhance the direct outcomes of malaria infection (risk factors for the direct malaria burden) and the effects of malaria infection upon the outcome of other health burdens (malaria infection as the risk factor for indirect burden). This is particularly important when considering the interaction between malaria and HIV or under-nutrition and our emphasis is on the role malaria infection plays as a risk for the extended, indirect burden. We end this section with a summary of a recent model which has related infection prevalence to all-cause pediatric mortality outcomes in Africa to demonstrate the differences between the direct estimation of malaria's contribution to mortality versus an approach which views malaria infection as a risk factor.

8.1 Malaria during pregnancy

Despite a poor understanding of the precise mechanisms of pathology (Menendez, 1995), the morbid outcomes of malaria infection during pregnancy have been well described (Brabin, 1983; Brabin et al., 1990; Guyatt & Snow, 2001a, 2001b; Luxemburger et al., 2001; Schultz et al., 1994; Shibuya & Murray, 1998; Steketee et al., 1996a; 2001).

In endemic settings in Africa pregnant women experience relatively little malaria-specific morbidity (e.g. fever illness) but do have increased risk of infection and higher density parasitemia leading to anemia and placental sequestration of the parasite. These effects operate across a broader range of endemicities used to describe morbid and fatal risks among non-pregnant populations. For this reason we have regarded the at-risk maternal populations to be those residing in category 3 & 4 areas shown in Table 1. Maternal anemia has been shown to be an important contributor to maternal mortality (Brabin et al., 2001) with elevated relative risks of mortality from moderate anemia (1.35; 95% confidence interval: 0.92-2.00) and from severe anemia (3.51: 95%CI: 2.05 – 6.00); and malaria contributes a modest portion to this depending on the prevalence of severe anemia (e.g., at a Hb <7 g/L conservative prevalence of 5%, malaria contributes to 9% of the anemia-associated maternal mortality). The investigators summarize the mean all-cause maternal mortality in sub-Saharan Africa as approximately 640 per 100,000 live births and 40.7% of maternal mortality is associated with anemia; thus, malaria-associated anemia is estimated to

contribute to 3.7% of maternal mortality – or approximately 5,300 maternal deaths annually attributable to malaria anemia in category 3 & 4 areas of Africa excluding southern Africa.

The prematurity and low birth weight (LBW; <2500 grams) associated with maternal malaria (including the contribution from both malaria-associated maternal anemia and placental infection) has been reported by 2 different groups of investigators to range from 3% to 8% of infant mortality (Greenwood et al., 1992; Steketee et al., 1996a; summarized in Steketee et al., 2001). If this range is applied to the expected numbers of live births in 2000 in category 3 & 4 areas outside of southern Africa and one assumes an approximate infant mortality rate of 105 per 1000 live births (UNICEF, 1998), one might have expected between 71,000 and 190,000 infant deaths attributable to malaria in pregnancy during 2000 (Table 6). There is the possibility that prematurity and LBW contribute to infant morbidity as well; however, in the literature, there is only evidence of substantial morbidity associated with very low birth weight infants – the vast majority of whom do not survive in the African setting (Greenwood et al. 1992).

Effective antimalarial treatment has been shown to prevent adverse effects of malaria in pregnancy. Since most women with placental malaria may be asymptomatic in areas of stable endemic transmission, a preemptive preventative, rather than curative, approach has been adopted. Provision of regular prophylaxis with chloroquine, from early pregnancy to delivery, intermittent presumptive treatment (IPT) with two or more doses of sulfadoxine-pyrimethamine (SP) administered in the second and third trimesters and sleeping under insecticide-treated nets (ITN) have consistently shown protection against peripheral and placental infection and anemia during pregnancy and variously against the incidence of LBW, intrauterine death and neonatal mortality. A summary of the available empirical evidence from randomized control trial data and cross-sectional data has been provided by Steketee et al. (2001) [Table 6].

In very low endemic settings or areas where malaria is epidemic prone (class 2 areas), or southern Africa there is limited information showing that malaria in these essentially non-immune pregnant women can be devastating and leads to maternal death and abortion. For example, in urban Mozambique, 15.5% of all maternal deaths in one hospital over a 5 year period were attributed directly to malaria (Granja et al., 1998). In an epidemic-prone setting of Ethiopia, maternal malaria carried an approximate 8-fold increased risk of abortion (R Newman,

unpublished data). Similarly, in a low endemicity setting in south east asia even single malaria infections were associated with increased risk of LBW (Luxemburger et al., 2001). However, because true epidemic malaria in non-immune populations is relatively rare, it is impossible to extrapolate risk estimates to a larger population to then estimate malaria-associated DALYs in these settings. Thus, current estimates do not include these risks and, again, our summary DALY estimates presented here remain conservative.

8.2 Malaria and anemia

Anemia among African children is a haematological state determined by combinations of nutritional deficiencies (iron, folic acid, other micronutrients and protein-calorie malnutrition), iron loss through helminth infection, red cell destruction, decreased red cell production by infectious diseases and the genetic constitution of red cell haemoglobin (Menendez et al., 2000; Stolfus et al., 2000; Nussenblat & Semba, 2002). Malaria has long been recognised as a major contributor to pediatric anemia. Malaria contributes to reduce haemoglobin concentrations through a number of mechanisms, principally increasing rates of destruction and removal of parasitised and non-parasitised red cells and decreasing the rate of erythrocyte production in the bone marrow. Some of the mechanisms of anemia during malaria are associated more with the acute clinical states (e.g. hemolysis or cytokine disturbances) whereas chronic or repeated infections are more likely to involve dyserythropoiesis (Menendez et al., 2000).

The WHO defines mild anemia as a hemoglobin of <= 11.0 gm/dl (DeMaeyer & Adiels-Tegman, 1985). Furthermore, this is the criteria used to define anemia burden during the 1995 estimations of the DALY (Murray & Lopez, 1996). What remains unclear is the extent to which children or adults with a hemoglobin of 9-10 gm/dl experience any significant physiological or morbid disability. More appropriate morbid distinctions include hemoglobin concentrations less than 7-8 gm/dl (moderate) and less than 5 gm/dl (severe). In many African settings a reduced hemoglobin concentration and malaria infection are both common occurrences and defining precise attributable risks of malaria for anemia is problematic.

Despite these definition constraints we have recently compared the prevalence of mild anemia (as defined by WHO and the DALY of Hb <= 11.0 gm/dl) with the

prevalence of malaria infection among pediatric communities in three countries of Africa (Korenromp and Snow, in preparation). For childhood populations located in areas with a low prevalence of *P. falciparum* infection (less than 25%) the median prevalence of mild anemia was 31.7% (n = 26; IQR 26.5, 42.3%). Children residing in areas of where the prevalence of infection was in excess of 25% the median prevalence of anemia was 75.3% (n=32; IQR 62.6, 83.0%). By modelling the relationship between mild anemia and parasite prevalence mild anemia could rise by on average 6% with every 10% increase in the prevalence of infection and parasite prevalence explained 71% of the variation in anemia prevalence between studies. This contrasts the DALY estimations for SSA for 1990, where malaria-anaemia (Hb <= 11.0gm/dl) accounted for only 18% of all anaemia DALY descriptions for children aged 0-4 years (Murray & Lopez, 1996). The ecological analysis is supported by evidence from community or individually randomised controlled trials of malaria-specific interventions aimed at reducing the incidence of new infections through insecticide-treated nets (ITN) or the prevalence of blood-stage infections through chemoprophylaxis or intermittent presumptive treatment – all suggesting a halving of anemia risks through intervention (Korenromp and Snow, in preparation).

As described above the relative importance of mild anemia to morbidity remains uncertain. It can be assumed from studies where the prevalence of mild, moderate and severe anemia have been presented that approximately 25% of all anemia descriptions are moderate-to-severe (Hb <= 7-8.0 gm/dl) and less than 10% are severe (Hb <= 5.0 gm/dl). To better define the morbid consequences of malaria-related anemia requires a more detailed analysis of empirical data on hemoglobin concentrations among childhood populations to examine the relationships between the proportional distributions of mild versus severe anemia. Furthermore only a few studies have prospectively monitored the incidence of anemia, the best descriptions being provided from children living in Asembo Bay, Kenya (McElory et al., 1999). Modelling the various assumptions regarding the dynamics and “recovery” of hemoglobin concentration in the face of sub-clinical and clinical malaria infections is particularly important to distinguish between burden estimates derived from prevalence and the incidence of new events attributable to *P. falciparum*. This work is important to provide a more complete understanding of the contribution of anemia to the DALY (R Steketee, personal communication).

8.3 Malaria and under-nutrition

There have been persuasive studies and proposed mechanisms relating nutritional status to individual and community-level responses to broad threats from infection and disease and the role of infectious disease in perpetuating under nutrition (Pelletier, 1994; Pelletier et al., 1995; Chandra, 1991; Nussenblatt & Semba, 2002). However, studies have generally focused on severe malnutrition, specific nutrient deficiency and only a few have examined the role of malaria. One striking feature of the global distribution of anthropometric markers of under-nutrition is its congruence with the distribution of endemic malaria. Although *P. falciparum* malaria and malnutrition are both highly prevalent in sub-Saharan Africa the existence of any precise synergistic interaction has not been well established. In The Gambia susceptibility to mild malaria was not correlated with prior anthropometric status, serum albumin or markers of iron deficiency (Snow et al., 1991). Others have observed an outbreak in *P. falciparum* malaria in re-fed famine victims (Murray et al., 1987), a finding that supported the prevailing view that malnutrition may actually protect against clinical malaria (Edirisinghe, 1986). However, recent studies conducted in Kenya (K Marsh, unpublished data) and The Gambia (Deen et al., 2002) show that signs of chronic malnourishment (stunting) is associated with increased parasite prevalence and higher parasitaemias and act as risk factors for the development of severe malaria (Kenya) and mild clinical attacks (The Gambia).

With respect to the role malaria infection might play in the growth of African children, evidence from intervention trials aimed at reducing the frequency of new infections provides stronger support of a synergistic relationship. An early study in Nigeria of chemoprophylaxis showed reductions in the incidence of infection, clinical attacks and a reduction in the incidence of malnutrition (Bradley-Moore et al., 1985). Improved growth among young children has more recently been demonstrated in The Gambia and Kenya comparing those protected and unprotected by ITN (D'Allessando et al., 1995; Snow et al., 1997b; Ter Kuile et al., 2003). Pelletier et al., (1993) estimated that mortality increases by a compound risk of 5.9% with each percentage point loss of weight-for-age representing relative risks of 8.4, 4.6 and 2.5 for severe, moderate and mild malnutrition respectively. However, there is a need to be cautious in making any extrapolations from the results of the ITN trials and growth velocities because of the acute effects of weight loss during clinical attacks of malaria (McGregor, 1982). Measures of weight-for-age or weight-for-height might simply

represent coincidental reductions in clinical attacks rather than any intrinsic improvements in growth. Despite the biological plausibility of synergism and the somewhat contradictory evidence, the precise relationship between undernutrition and severe malaria continues to remain difficult to empirically quantify within disease burden frameworks.

8.4 Malaria and HIV interactions

In sub-Saharan Africa, the HIV epidemic has been superimposed on the long-standing malaria pandemic. The wide geographical overlap and the concurrent high prevalence of both HIV and malaria mean that even modest interactions could lead to substantial public health impacts among populations exposed to both (Chandromohan & Greenwood, 1998; French & Gilks, 2000).

Early in the HIV epidemic it was clearly demonstrated that malaria-associated anemia treated with unscreened blood transfusions contributed to HIV transmission (Greenberg, 1992). With the inception of the Global Roll Back Malaria partnership, there was a recognition that the initial decline in malaria mortality in Africa, observed from the 1960s onwards, had reversed in the 1990s, when an apparent increase was seen (Snow et al., 2001). While there were other likely contributors, such as increasing chloroquine resistance, the concurrent worsening of malaria as the HIV epidemic evolved in Africa led to a re-examination of potential interactions between these two infections.

In the 1990s, investigators observed that malaria infection was more common and of higher parasite density in HIV-positive than in HIV-negative pregnant women in a range of malaria endemic settings, and in women of all gravidity, with multigravidae most affected (Schulman, 1999; Steketee et al., 1996b; Parise et al., 1998; Verhoeff et al., 1999; van Eijk et al., 2001a). In western Kenya, where one-quarter to one-third of pregnant women are HIV-infected, HIV accounts for approximately 35%-42% of placental malaria (van Eijk et al., 2001b). Additionally, two longitudinal cohort studies in Uganda and Kenya and one hospital based case-control study in Uganda have demonstrated that HIV-infection approximately doubles the risk of malaria parasitemia and clinical malaria in non-pregnant adults, and that increasing HIV-immunosuppression is associated with higher density parasitaemias (French et al., 2001; Whitworth et al., 2000; Francesconi et al., 2001). Thus HIV infection increases the incidence and severity of clinical malaria in both pregnant and non-pregnant adults.

The potential impact of placental malaria on mother to child HIV transmission (MCHT) has also been investigated, and results from a recent study suggest that, while overall MCHT is not increased, there may be a complex interaction whereby malaria-stimulated immune responses protect against MCHT, except in a small sub-group of women with higher density placental malaria infections, who are at increased risk of MCHT (Ayisi JG, personal communication).

It remains uncertain whether or not the high intensity of exposure to infections increases the rate of progression of HIV disease in sub-Saharan Africa compared to more developed countries (Bentwich et al., 2000), but, if there is an effect, then malaria could be an important component. In a recent study in Malawi, HIV blood viral levels were found to be seven-fold higher in HIV-infected adults with acute uncomplicated malaria than in HIV-infected blood donors without malaria (Hoffman et al., 1999). As with other acute infections, the increased viral burden was reversed by effective malaria therapy (Hoffman et al., 1999). These findings are consistent with in vitro laboratory studies in which HIV-1 replication was increased 10-100 fold in peripheral blood mononuclear cells exposed to soluble malaria antigens or malaria pigment (Xiao et al., 1998).

The increasing incidence of HIV-associated febrile illnesses may thus lead to increased use of antimalarials above and beyond that anticipated from the direct effects of HIV on malaria incidence. This is likely to fuel the increasing problem of resistance to antimalarial drugs, a concern that is heightened by recent evidence that HIV infection may contribute to inadequate clearance of parasites that escape drug action in pregnant women (Parise et al., 1998; Verhoeff et al., 1999) and possibly in children as well (Kamya et al., 2001). In this context, however, surprisingly little is known about the impact of HIV on response to treatment of malaria.

Finally, despite the potentiation of malaria by HIV or HIV by malaria, currently, there is insufficient information to quantify the specific HIV-malaria interaction risks in a way that would allow for inclusion in DALY calculations.

8.5 Malaria infection and cognitive performance

Between 0.001 and 0.021 days are suggested to be lost from school due to malaria per child each year, accounting for between <3% and 8% of all reasons and 13-15% of medical reasons for absenteeism (Brooker et al., 2000). There

are no reports in the literature on the role of school children as caretakers of younger siblings sick with malaria during school terms. Furthermore there is very little information on the performance of parasitized school children whilst at school (Holding & Wekulo, submitted). A randomized placebo control study of chloroquine prophylaxis in Sri Lankan school children, demonstrated an improvement in mathematic and language scores in those who received chloroquine, despite the fact there was no difference in absenteeism (Fernando, 2001). Whether these results are applicable to endemic areas in Africa is unknown. The only empirical demonstration in Africa of chemoprohylaxis among school children during the 1950's in Accra, Ghana that failed to show any tangible improvements in school performance associated with infection suppression (Colbourne, 1955).

There is a body of evidence linking LBW and a range of persistent impaired outcomes, predominantly behavioral difficulties, cerebral palsy, mental retardation, blindness and deafness that are detected in late childhood and may last through to adulthood (McCormick et al., 1990; Wood et al., 2000; Hille et al., 2001). Those most at risk of long-term impairments appear to be those born of exceptionally or extremely low birth weight (< 750gm or 1000 gm) and these risks have only been defined among pre-term or ELBW babies born in the developed north. In most endemic areas of Africa it seems unlikely that many of these ELBW babies would survive beyond the neonatal period. More importantly is the role infection plays during early infancy. During this period of a child's life there is maximal brain growth and coincidental development of functional immunity to disease. Citing long-term follow-up studies in The Gambia, Holding & Wekulo (submitted) refer to Jukes & colleagues recent observations of infant populations under chemoprophylaxis or placebo 12 years previously who now exhibit differences in mental functions. The recently launched studies of IPT during infancy should provide a more powerful platform to examine the consequences of infection early in life upon performance latter in life.

8.6 The combined indirect effects of malaria infection upon all-cause mortality

The effects of malaria infection upon LBW and anemia seem conclusive, the overall role of malaria infection and under-nutrition and HIV is at present less persuasive. Some authors have further proposed that the presence of malaria infection increases the risks of poor outcomes from other infectious agents, for example bacteraemia, although there is little empirical data to define these potentiating or co-morbid risks. However, combined any additional risks might

contribute to all-cause mortality beyond that described from estimates of the directly malaria-attributed causes of death.

To examine this further we recently analyzed data on all-cause mortality among under fives derived from DSS studies undertaken across a broad range of malaria transmission settings in Africa against the prevalence of *P. falciparum* infection. To model the contiguous relationships between all-cause mortality and parasite prevalence rates, weighted least squares regression was applied allowing for the square of parasite prevalence (for possible saturation of parasite prevalence), timing, location and the sampling precision of each study (Snow et al., in press). The unadjusted median mortality rate for areas represented by a low-prevalence of infection in childhood (less than 25%) was 10.9 per 1000 children aged 0-4 years p.a. (9 DSS studies; IQR 7.8, 17.6). This rose dramatically to 39.1 per 1000 children p.a. (36 DSS studies; IQR 32.8, 52.2) among populations exposed to childhood parasite prevalence risks >= 25%. In the regression model, mortality increased significantly with parasite prevalence (p=0.0001), but this effect leveled off at higher prevalence rates. The models suggest that, in rural DSS sites throughout sub-Saharan Africa, all-cause mortality increases by more than two-fold (25-30 deaths per 1000 under-five years) over the range of prevalences of malaria infection covered by the DSS sites, and parasite prevalence explained 64% of the variation between sites in all-cause under-five mortality. By contrast, during the global burden of disease estimations for 2000 malaria accounted for 20.2% of under-five deaths based upon VA derivations (WHO, 2002).

These comparisons of direct versus indirect contributions of malaria infection to child survival must be viewed with some caution. A perennial constraint to ecological analyses is that multiple possible confounders that might bias associations, notably influences such as socio-economic status, access to and effectiveness of health services, prevalence of HIV, exposure to other parasitic diseases, nutrition and the genetic make-up of the population. These data are often not available for analysis, if they were it is plausible that the proportion of under-five mortality or disease explained by malaria infection would be less. Nevertheless we believe that malaria's contribution to child mortality in Africa lies somewhere between the estimates provided through VA diagnoses and the possible indirect contributions defined within the ecological models and this difference from direct estimation is likely to be explained by indirect mechanisms operating through the effects of malaria during pregnancy upon low birth weight and to a lesser extent from nutritional and hematological influences of malaria infection.

9 Summary of risks and concluding remarks

The precise number of fatal and morbid events due to *P. falciparum* infection in Africa will never be known. Even with the most sophisticated of disease surveillance systems malaria remains an elusive diagnosis. What characterises malaria in Africa is that infection is common and death directly attributed to the parasite is comparatively rare, largely a consequence of acquired immunity. Unlike HIV/AIDs or tuberculosis, infection with the malaria parasite is, in most settings of Africa, universal and the presence of the pathogen is not a sufficient marker of disease. Those who do die from malaria represent the public health costs of developing immunity at a population level. These deaths are concentrated among the immunologically naïve and across much of Africa it is the newborn and young children who bear the brunt of the mortality burden.

Estimating the malaria public health burden continues to be driven by informed approximations, in part because of the paucity of reliable and accurate data but also due to the inherent difficulties of unique diagnosis. There are a number of ways in which health consequences can be predicted and enumerated. We have selected an approach which employs empirical epidemiological measures of disability, morbidity and mortality risks and structured these according to age and malaria transmission. In this paper we have laid out our assumptions, data extraction methods and caveats and presented, where possible, the summary risks within a descriptive range of the data. This approach is similar to one previously used to define the malaria burden in Africa (Snow et al., 1999) but is cognisant of new data, broader health consequences and the temporal effects associated with changing anti-malarial drug sensitivity and HIV.

Other approaches are equally valid and these include estimating malaria mortality from the frequency of heterozygotes for distinct human polymorphisms which protect against malaria death, such as sickle cell trait; meta-analysis of health outcomes described during randomised controlled trials of malaria-specific interventions; ecological analyses of malaria infection risk (an example provided in section 8.6); or the modelling of proportional mortality with a method that ensures that the sum of the disease-specific components do not exceed total deaths. The relative merits and contributions of each approach to our understanding of disease burdens are currently being considered by the Child Health Epidemiology Reference Group (CHERG) of the World Health Organisation (A Rowe, personal communication). These alternative approaches may have

comparative advantages over our methods, particularly proportional modelling, as they should allow the malaria burden to be considered simultaneously with other diseases, often equally difficult to diagnose. However, it is probably fair to conclude that no one method will provide the definitive answer to the relative burdens of individual diseases.

Through our analysis of available information we estimate that there may have been as many as 213.5 million clinical events of *P. falciparum* malaria, or 0.8 billion person-days of illness, in Africa during 2000 among 557 million people exposed to any risks of infection with the parasite. Over 48% of these events would have been experienced by children aged 0-4 years living under stable, endemic conditions. During 2000 we estimate that approximately 1.14 million people might have died as a direct result of infection with *P. falciparum* (IQR: circa 703,000 – 1.61 million). 88% of these deaths would have occurred in areas of stable, endemic malaria and of these 68% were among children aged less than 5 years of age. Adult malaria mortality remains poorly defined and represents an area worthy of future empirical investigation, particularly in then light of the changing HIV prevalence on the continent.

Consequential or indirect mortality contributions to the malaria DALY are harder to define. In our presentations we estimate that adverse drug reactions consequent upon managing febrile illness in areas of stable, endemic malaria might contribute a minimum of 2,350 additional deaths. These might easily subsumed within the direct "malaria-specific" mortality component as many of the deaths will occur temporally close to the precipitating clinical event for which treatment was sought. Likewise the management of SMA with blood transfusion might contribute a further 5,300 to 8,500 HIV related deaths in endemic Africa each year. These consequential deaths will probably all occur within two years of the inadvertent exposure to HIV through blood transfusion. Epilepsy, an important sequelae of brain insult during severe malaria, has a poorer prognosis in Africa compared to western societies and poorly managed epilepsy can result in premature mortality. The precise consequential mortality burden of epilepsy or paralysis has not been quantified. The indirect effects of malaria in pregnancy upon mortality outcomes are significant. We estimate that between 71,000 and 190,000 newborn children will not survive their first birthday because they were born of low-birth weight as an indirect result of their mother's being infected by *P. falciparum* during pregnancy in 2000. The majority of these deaths will have occurred during the first 4 weeks of life. There are few detailed studies of the

causes of maternal mortality in Africa however extrapolating the assumptions of the role of malaria induced anemia (Brabin et al., 2001; Steketee et al., 2001) we suggest that there may have been 5,300 malaria related maternal deaths in areas of low-to-high transmission in Africa during 2000.

If one accepts the assumptions made during our analyses of epidemiological and intervention trial data to estimate indirect or consequential mortality, this additional mortality component may explain an additional 10% of mortality above that defined as direct attribution. This would be consistent with observations made during randomised controlled trials which suggest that reducing the risks of infection in a community has an impact beyond what might readily be described by direct malaria mortality through verbal autopsies. More recently ecological analyses of all-cause pediatric mortality imply that the difference between direct and indirect attribution might be higher than 10% (Snow et al., in press). There are a number of pathological processes for which there remains fragmented or incomplete evidence, including the effects upon growth, HIV replication and disease progression and anemia. We have not quantified these additional risks but each might contribute in different ways to the indirect mortality consequences of *P. falciparum* infection. Whether one regards malaria infection as a risk factor for all-cause mortality or as a distinct directly attributable cause of death remains a moot point. What is clear is that the contribution of *P. falciparum* to mortality in Africa is larger than can be described by verbal autopsy diagnosis alone.

The malaria burden envelope continues to be dominated by the mortality component, however, the consequences of morbidity from febrile events or, albeit far less well defined anemia, is substantial. Other disabilities also deserve attention, not least because they are disguisable from morbid events in their duration: the neurocognitive disabilities. Many of these are life-long residual effects of early clinical experiences and have a high disability weighting. Evidence on the epileptogenic effects of cerebral malaria suggest that at least 3,000 new pediatric epileptic cases may arise each year following prolonged coma during a severe clinical episode of malaria managed through their crisis period in hospital. This is likely to be a gross underestimate of the true consequential epilepsy burden owing to our inability to articulate the incidence of complex seizures not fulfilling the cerebral malaria criteria. The effects upon learning abilities and performance require further investigation in order to reliably define the contributions of early childhood severe disease or infection upon educational attainment.

Such reviews of available evidence reveal as much about what we do know as about what we do not know. A number of areas of the malaria burden in Africa require further modeling and empirical investigation. In the continued absence of wide-area, reliable coverage of morbidity and mortality data there is a need for increased research effort to understanding of the spatial determinants of risk. Assuming urban versus rural, East versus West African, or poor versus affluent populations experience similar risks of poor health outcomes following malaria infection is clearly a gross oversimplification of complex interactions. The precise cartography of risk requires improved population distribution maps. The emphasis within the literature upon measuring childhood risks of malaria disease and death would seem justified from our understanding of immunity but we remain comparatively ignorant of the true public health consequences of malaria among older children and adults. The impact of infection and disease upon cognition, under-nutrition, anemia and HIV remain at best speculative and require further investigation before these composite risks can be defined. This review has attempted to lay out our current empirical evidence of the combined risks of disease, disability and death [Table 7]. How these risks change from birth through adulthood according to the dependent factors of infection, immunity and control and the gaps in our knowledge of the complete disease burden continue to represent the most significant challenges facing the malaria epidemiologist as this millennium begins.

Acknowledgements

The authors are grateful to a variety of individuals who have supplied additional information in order to provide more reliable age-structured mortality and infection risk data as presented in this paper. These include Gilly Maude & the late Nicola Dollimore (Navrongo, Ghana VAST Program), Hugh Reyburn and Chris Drakeley (Gates Malaria Program, London School of Hygiene & Tropical Medicine), Caroline Maxwell, Chris Curtis and Ilona Carneiro (London School of Hygiene and Tropical Medicine), Salim Abdulla (Ifakara Research Centre, National Medical Research Institute, Tanzania), Yusuf Hemed (AMMP, Tanzania), Don de Savigny (MARA data co-ordination in Tanzania), John Chilumba (National Malaria Control Program, Zambia), Tabitha Mwangi, Victor Mung'ala Odera, Judy Omumbo, Helen Guyatt and Penny Holding (KEMRI-Wellcome Trust Program, Kenya), Dennis Shanks (Walter Reed Research Programme at Kericho, Kenya), Uwe Deichman (Development Research group, World Bank for his earlier inputs into methodologies for defining populations exposed to malaria risk), Jean-Francois Trape (Institut de Recherche pour le Development, Senegal), and Eline Korenromp (RBM/WHO). The authors are also grateful to Kevin Marsh and Joel Breman for their comments on the completed manuscript. Finally, the authors wish to thank Linda Goldstone, Lydiah Mwangi and Lucy Muhunyo for their technical assistance. Financial support for the Burden of Malaria in Africa (BOMA) was provided by the Wellcome Trust, UK, The Bill & Melinda Gates Foundation & the Kenya Medical Research Institute. RWS & CRJC are supported as Wellcome Trust Senior Research Fellows (# 058992 & 050533 respectively).

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Figure 1

The direct, indirect and consequential public health effects of *Plasmodium falciparum* malaria in Africa (Snow & Gilles, 2002)

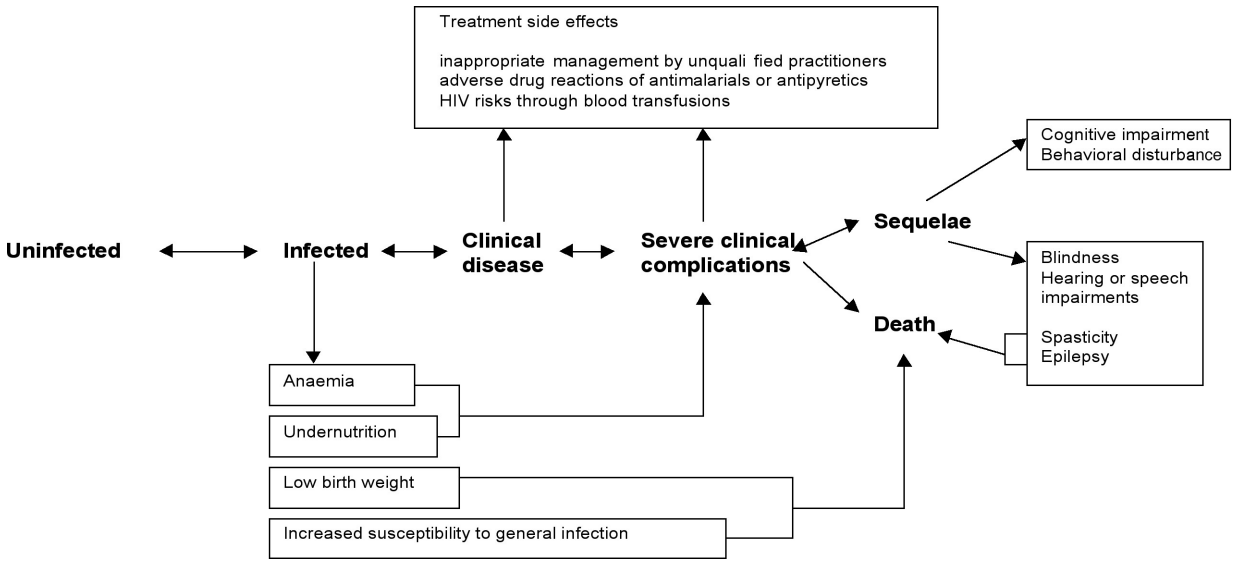

Figure 2
Fuzzy climate suitability membership for malaria

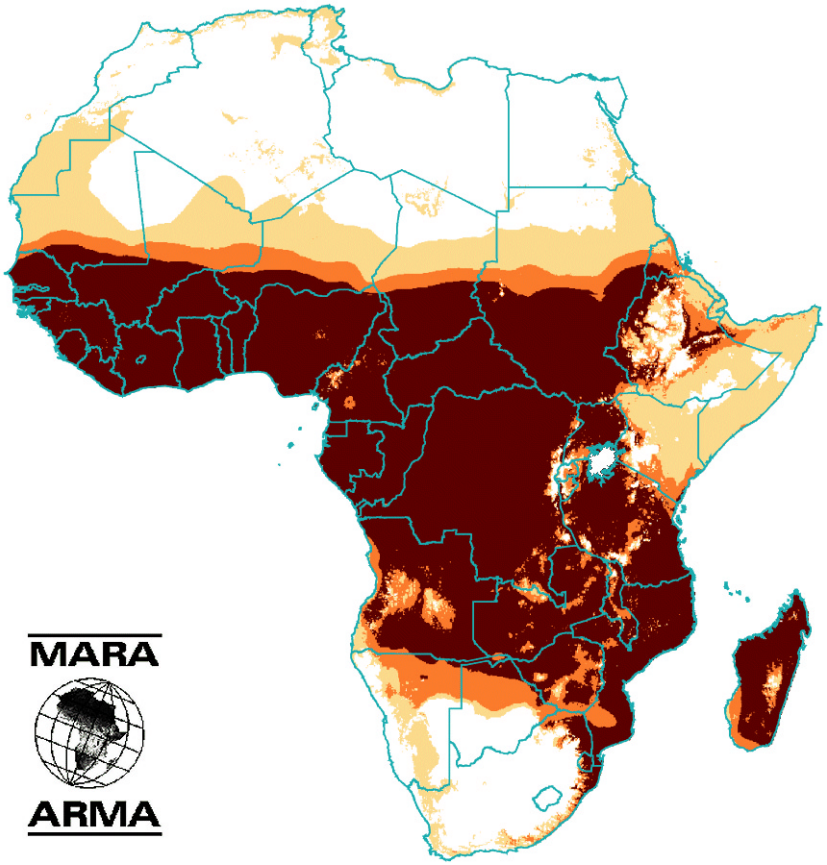

Figure 3
Age-pattern of annual chloroquine treatments per person in Saradidi, Kenya [Spencer et al., 1987].

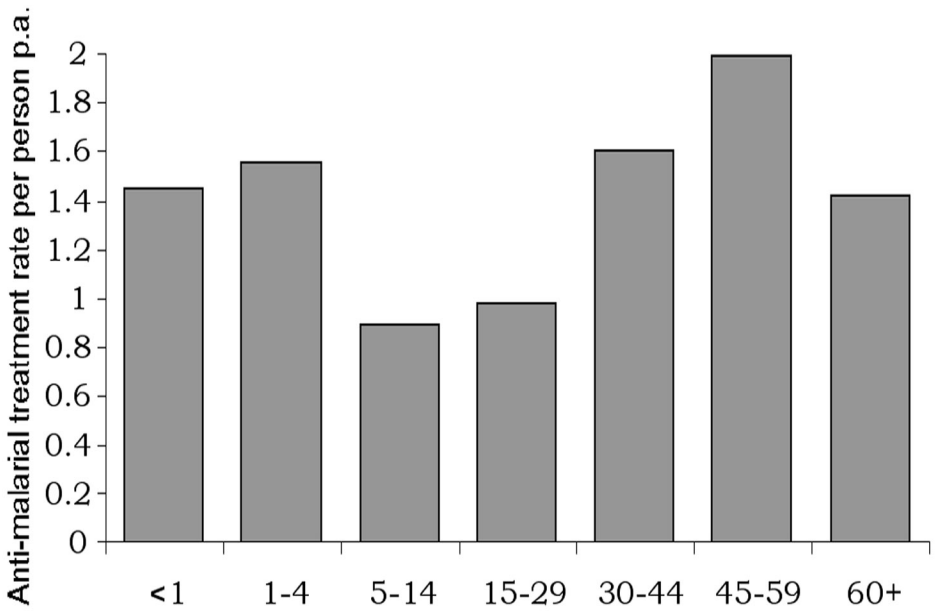

Table 1

Populations at risk (thousands) during 2000.

	Births	0-4 years	5-14 years	15+ years	Total
North Africa Exclusion	3,450	17,020	33,663	95,038	145,721
Southern Africa					
At no malaria risk (Classes 1-3) — no risk	1,212	4,190	10,682	29,195	44,067
At malaria risk (Class 4)	435	2,049	3,709	8,687	14,445
Rest of Africa					
At no malaria risk (Class 1) — no risk	1,778	7,366	11,680	23,033	42,079
At low stable/epidemic risk (Classes 2+3)	5,280	22,018	34,668	69,126	125,812
At stable endemic risk (Class 4)	17,330	73,351	115,261	228,105	416,717

Table 2

Estimated malaria specific mortality [IQR range] during 2000

	0-4 years	5-14 years	15+ years	Total
Southern Africa malaria risk (Class 4)	266 [164 — 430]	482 [297 — 779]	1,129 [695 — 1,824]	1,877 [1,156-3,033]
Rest of Africa - low stable/ epidemic risk (Classes 2+3)	57,688	32,588	49,079	139,355
Rest of Africa - stable endemic risk (Class 4)	684,364 [541,330 — 1,068,723]	182,113 [76,072 - 319,274]	136,863 [84,399 — 214,419]	1,003,340 [701,801-1,1602,415]
Total	742,318 [541,494 — 1,069,153]	214,701 [76,369 — 320,053]	187,071 [85,094 — 216,253]	**1,144,572 [702,957 — 1,605,448]**

Table 3

Estimated number [IQR] of clinical attacks (thousands) of malaria during 2000.

	0-4 years	5-14 years	15+ years	Total
Southern Africa malaria risk (Class 4)	60 [20 — 265]	109 [36 — 479]	255 [84 — 1,122]	424 [140 — 1,866]
Rest of Africa - low stable/ epidemic risk (Classes 2+3)	4,007 [2,752— 4,756]	6,310 [4,333 — 7,488]	6,291 [4,320 — 7,466]	16,608 [11,405 — 19,710]
Rest of Africa - stable endemic risk (Class 4)	104,452 [61,468 — 158,952]	67,658 [44,145 — 112,610]	24,407 [16,880 —31,479]	196,517 [122,493 — 303,041]
Totals	108,519 [64,240 – 163,982]	74,077 [48,514 — 120,577]	30,953 [21,284 – 40,000]	**213,549 [134,322 — 324,617]**

Table 4

Estimated number [IQR] of person-days of malaria illness (thousands) during 2000.

	0-4 years	5-14 years	15+ years	Total
Southern Africa malaria risk (Class 4)	306 [102 — 1,352]	556 [184 — 2,443]	1,301 [428 — 5,772]	2,162 [714 — 9,517]
Rest of Africa - low stable/ epidemic risk (Classes 2+3)	20,436 [14,035 — 24,256]	32,181 [22,098 — 38,189]	32,084 [22,032 — 38,077]	84,701 [58,166 — 100,521]
Rest of Africa - stable endemic risk (Class 4)	532,705 [313,487 — 810,655]	135,316 [88,290 — 225,220]	48,814 [33,760 — 62,958]	716,835 [435,537 — 1,098,833]
Totals	553,447 [327,624 — 836,263]	168,053 [110,572 — 265,852]	82,199 [56,220 — 196,757]	**803,699 [494,416 — 1,298,872]**

Table 5

Percent immediate and persistent neuro-cognitive impairments following Cerebrai Malaria (Newton & Krishna, 1998; Carter et al., submitted*)

Deficit	On discharge (%)	Long-term residual (%)	Events 0-15 years p.a.
Hemiparesis	2.5	0.6	360-400
Quadriparesis/Severe deficit	4.1	1.3	770-860
Hearing impairment	1.9	1.1	650-730
Visual Impairment	2.3	0.5	300-330
Behavioral difficulties	1.3	2.6*	1,540-1,720
Language deficits	1	11.8*	7,000-7,800
Epilepsy	0.8	4.6*	2,700-3,000

Table 6

Summary of population attributable risk (PAR) estimates for *P. falciparum* malaria in pregnant women (modified from Steketee et al., 2001) and applied to expected numbers of pregnancies in 2000 in areas outside southern Africa in risk areas 3 & 4 to estimate the indirect mortality.

Adverse event	Prevalence / incidence	Risk estimate	PAR (%)	Fatal events 2000 Attributed to malaria
Moderate or severe anemia	1-20%	1.5-2.5	2-15	-
Low birth weight	12-20%	1.4-1.8	8-14	-
Pre-term LBW	3-8%	2.2-3.5	8-36	-
IUGR LBW	8-15%	1.7-5.5	13-70	-
Infant mortality	105 %	NA	3-8	71,000-190,000

Table 7

A summary of the burden of P. falciparum malaria - Africa during 2000 [IQR].

	0-4 years	5-14 years	15+ years	Total
Malaria specific mortality	742,318 [541,494 — 1,069,153	214,701 [76,369 — 320,053]	187,071 [85,094 — 216,253]	1,144,572 [702,957 — 1,605,448]
Maternal mortality attributed to malaria-anemia	--	--	5,300	5,300
Infant mortality attributed to malaria during pregnancy	71,000 — 190,000	--	--	71,000 — 190,000
Fatal adverse drug events	2,350	Unknown	Unknown	2,300
Fatal HIV risks from blood transfusion used to manage SMA	5,300 — 8,500		Unknown	5,300-8,500
Premature mortality of poorly managed epilepsy developed through cerebral malaria or complex seizures	--	Unknown	Unknown	Unknown
Role of infection on anemia, under-nutrition and HIV as indirect mortality effects	Unknown	Unknown	Unknown	Unknown
Malaria morbid attacks (thousands)	108,519 [64,240 — 163,982]	74,077 [48,514 — 120,577]	30,953 [21,284 — 40,067]	213,549 [134,322 — 324,617]
Estimated number of morbid days (thousands)	553,447 [327,624 — 836,263]	168,053 [110,572 — 265,852]	82,199 [56,220 — 196,757]	803,699 [494,416 — 1,298,872]
Neuro-cognitive sequelae following cerebral malaria	Numbers			
Hemiparesis	360-400		Unknown	360-400
Quadriparesis/ Severe deficit	770-860		Unknown	770-860
Hearing impairment	650-730		Unknown	650-730
Visual impairment	300-330		Unknown	300-330
Behavioral difficulties	1,540-1,720		Unknown	1,540-1,720
Language deficits	7,000-7,800		Unknown	7,000-7,800
Epilepsy	2,700-3,000		Unknown	2,700-3,000
Effects of infection on cognitive performance	Unknown	Unknown	Unknown	Unknown