Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level

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A high burden of malaria, tuberculosis, and HIV infection contributes to national and individual poverty. We have reviewed a broad range of evidence detailing factors at individual, household, and community levels that influence vulnerability to malaria, tuberculosis, and HIV infection and used this evidence to identify strategies that could improve resilience to these diseases. This first part of the review explores the concept of vulnerability to infectious diseases and examines how age, sex, and genetics can influence the biological response to malaria, tuberculosis, and HIV infection. We highlight factors that influence processes such as poverty, livelihoods, gender discrepancies, and knowledge acquisition and provide examples of how approaches to altering these processes may have a simultaneous effect on all three diseases.

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Figure 1. Both malaria and tuberculosis have an interaction with malnutrition, but the mechanism for a biological link between them is not well understood.

The overall aim of this two-part review was to identify potential pro-poor disease-control strategies that could simultaneously influence the three Global Fund priority diseases—malaria, tuberculosis, and HIV disease. Our approach involved reviewing the evidence for factors, from the individual level to global policies, that affect vulnerability to these three diseases (figure 1). Common factors were identified and used to suggest synergistic strategies that could be introduced to reduce the pressure of malaria, tuberculosis, and HIV infection on the most vulnerable. A framework that mapped out all potential vulnerability determinants at three levels was devised by the Vulnerability and Health Alliance at the Liverpool School of Tropical Medicine (panel 1). This multidisciplinary team includes clinical, social science, economic, disease control, geographical, health-impact assessment, and mathematical modelling expertise.

In this part of the review we examine the effect of individual, household, and community level factors on disease vulnerability (table 1 and table 2). Part 2, to be published next month, examines the effect of environmental and institutional factors and makes recommendations for future action.

We found information on vulnerability to malaria, tuberculosis, and HIV infection but much of it was disjointed and did not take a holistic approach to the problem. This review presents a synthesis of the information. Rather than being an exhaustive summary of the available information, it is designed to highlight the scope of the evidence available about vulnerability to malaria, tuberculosis, and HIV infection.

Current response to the global burden of malaria, tuberculosis, and HIV disease

In 2001, malaria, tuberculosis, and HIV infection together claimed 5·7 million lives.[1] The effect of these diseases, and the inadequate national and international responses, is a major reason why the poor stay poor. Increasing recognition of the link between the burden of these diseases and a lack of economic growth has galvanised global institutions to renew efforts aimed at reducing the impact of these diseases through both health and non-health approaches.[2] WHO and the Commission of the European Communities have produced reports about the association between these diseases and the "poverty trap". Many donors have contributed to the Global Health Fund initiated at the Okinawa summit of G8 countries in July, 2000. Allocation of these funds between HIV infection, malaria, and tuberculosis is roughly in the ratio of 60/20/20.

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Panel 1. Factors producing vulnerability to progression to disease, progression to severe disease, exposure/infection, severe disease, and effects of disease

Individual level: biological and disease-related factors
Immunity, age, sex, pregnancy, genetics, interactions with other diseases

Household and community levels: social and economic factors
Socioeconomic status/poverty, nutritional status, livelihoods, gender, education, religion, knowledge, behaviour

Meso/macro levels: environmental and institutional factors
Physical/geographical, drug resistance, migration and complex emergencies, health services and policy (including access to health care, quality of care, and health sector reform), development policy

What is "vulnerability"?

Vulnerability is a complex and contested concept, with a variety of definitions arising from different disciplines (panel 2).[3–6] Although vulnerability analyses have been carried out in relation to various settings (eg, disasters, poverty, urban macroeconomic decline, specific health problems such as HIV/AIDS and mental health) some common features emerge (panel 3).[7] Vulnerability encompasses the factors that lead to variation in the impact of disease between different communities and individuals.[8] These factors range from biological (eg, individual immunity) to institutional (eg, inadequate health services). Complicated interactions between these factors, many of which lie outside the health sector, make unravelling of their individual roles and therefore appropriate targeting of interventions difficult.

WHO has identified the 1·2 billion people worldwide living in absolute poverty as those most vulnerable to infectious diseases such as malaria, tuberculosis, and HIV infection.[1] This definition of vulnerability is too broad to enable effective targeting of the most vulnerable when resources are scarce. In an attempt to identify the target groups more precisely, health programmes for malaria, tuberculosis, and HIV infection have focused on biologically vulnerable groups such as infants, children under 5 years old, pregnant women, young mothers, and people of reproductive age. However, this approach ignores other important non-biological features of vulnerability, such as poverty, education, and health-service provision.

Table 2. Available evidence about socioeconomic vulnerability factors at household and community level

Vulnerability factor	Malaria	Tuberculosis	HIV/AIDS
Poverty	+	++	+
Poor nutrition	+	+	+
Livelihoods	+	+	+
Gender	++	++	++
Illness conceptualisation	++	++	++

+=weak evidence of association; ++=moderate evidence of association.

Approaches to vulnerability in infectious diseases

Most discussion on vulnerability in infectious disease has been in the context of the HIV epidemic. Initial approaches to dealing with the HIV/AIDS epidemic focused on "high-risk" groups, such as sex workers, long-distance truck drivers, and soldiers, whose behaviour was constructed as "risky". This approach places responsibility for change on individuals; it has been criticised because it ignores the social and economic factors that constrain the ability of an individual to change.[9–13] More recently, attention has shifted towards improved understanding of the many and complex processes that interact to make different individuals and communities vulnerable to infection.[5,6,14–16] Although HIV control programmes have begun to take account of vulnerability in the context of broad social issues, the strategies for malaria and tuberculosis control still tend to concentrate on epidemiological approaches that emphasise biological responses to infectious disease (figure 2).

Epidemiology and transmission of malaria, tuberculosis, and HIV infections

Malaria causes more than a million deaths each year worldwide. 90% of the deaths are in sub-Saharan Africa, predominantly in children under 5 years old.[1] Malaria is a major cause of poverty and slows economic growth by up to 1·3% per year in endemic countries.[17] 42 million people are currently estimated to be living with HIV/AIDS. 95% of them are in less developed countries, particularly sub-Saharan Africa.[18] In 2002 alone, 5 million people were thought to have become infected with HIV (2 million women and 800 000 children). The estimated total number of AIDS deaths in 2001 was 3·1 million.[18] Tuberculosis is the

Table 1. Available evidence about biological and disease-related vulnerability factors

Vulnerability factor	Malaria	Tuberculosis	HIV/AIDS
Age	Under-5s, high endemicity All ages, low endemicity	Under-5s and adults	Young adults
Pregnancy	+++	+	0
Male/female ratio	Equal	Children M=F Adults M>F	Adolescents M<F Adults M=F
Genetic influences on infection or disease vulnerability	Ethnic traits, red-cell abnormalities, HLA/MHC markers	Ethnic traits, genes for vitamin D receptor	Chemokine receptors (eg, CCR5)
Interactions	Coinfection with HIV increases degree and severity of infection	Coinfection with HIV increases disease progression	STDs increase HIV infectiousness

0=no evidence of association; +=weak evidence of association; ++=moderate evidence of association; +++=strong evidence of association. STDs=sexually transmitted diseases.

Panel 2. Examples of definitions of vulnerability

Vulnerabilities refer to the long-term factors that affect the ability of a community to respond to events or that make it susceptible to calamity.[3]

Vulnerability is the degree of susceptibility to a natural hazard; it is the product of sets of prevailing conditions within which disasters may occur.[4]

By "vulnerability" we mean the characteristics of a person or group in terms of their capacity to anticipate, cope with, resist, and recover from the impact of a natural hazard.[5]

Vulnerability describes those features of a social or economic entity that determine the severity of impact likely to be caused by excess morbidity or mortality.[6]

world's second commonest cause of death from infectious disease after HIV/AIDS, killing nearly 2 million people each year. Up to 70% of adults in Africa with tuberculosis are infected with HIV, and there were an estimated 8–9 million new cases of tuberculosis worldwide in 2000.[19]

Individual level: biological and disease-related factors

Age

The degree of malaria immunity acquired by individuals living in endemic areas depends on the amount of exposure to infections and genetically determined immunological responses.[20] In areas of high stable transmission of malaria, the incidence of clinical malaria peaks between 1 and 5 years of age, then declines rapidly as effective immune responses develop.[17,21] In these areas, 25% of all-cause mortality in children aged 0–4 years has been attributed to malaria.[22] Where malaria transmission is less intense, the peak age is later in childhood; and in low-transmission or epidemic-prone regions, vulnerability to infection remains constant across all ages because protective immunity is never acquired.[21,23] Immunity is not long-lasting and is lost in the absence of repeated exposure to infections. Non-immune individuals such as travellers, aid workers, or displaced populations who move into malarious areas are very vulnerable to illness and death from malaria at any age.

Unlike malaria, the greatest mortality and morbidity related to tuberculosis in poorer countries is concentrated in the economically productive 15–59 years age group. Active disease occurs when the host immune response is unable to control replication of the organism, which occurs most commonly in immunosuppressed adults and young children. As occurs in malaria, tuberculosis infection in children is more common at ages 0–5 years than in older children, and this age group carry the highest risk of developing disease after infection.[24,25] However, childhood tuberculosis is likely to have been underestimated because more than 50% of children with tuberculosis in poorer countries do not present to health services.[25] Childhood tuberculosis has commonly been regarded as unimportant because more than 95% of children with tuberculosis have negative sputum smears owing to the low frequency of cavities or cough, but these children do act as a pool from which a large proportion of adult cases will eventually arise.[25,26]

Panel 3. Common features of published definitions of vulnerability

A subject of the vulnerability (eg, person, group, or community).
An external force (ie, hazard) that reveals the vulnerability; in the context of communicable disease, the hazard is the infectious agent.
Factors that create the vulnerability (eg, biological, socioeconomic).
The capacities affected (eg, the ability to anticipate, prepare for, cope with, respond to, and recover from the hazard).

For biological, social, and economic reasons, adolescents and young adults bear the heaviest burden of HIV infection.[27] For example, the rate of heterosexually transmitted HIV infection in South Africa is 18·9% in 17–20-year-olds and 43·1% in 21–25-year-olds.[28] 3·2 million children under the age of 15 years are estimated to be living with HIV/AIDS worldwide.[18] Some individuals have recurrent exposure to HIV but do not become infected, whereas others although infected do not appear to progress to AIDS. In some cases, the lack of progression seems to be due to the presence of protective cytotoxic T-cell and T-helper-cell immune responses.[29,30] However, in most people, HIV infection progresses despite the development of brisk immune responses to HIV.

Sex

Evidence about the prevalence of malaria in male and female populations is inconsistent and varies widely depending on whether the information is derived from studies based in the community or in health facilities. For example, a study in Thailand found that the male to female ratio of malaria prevalence was 6·0 in a clinic and 1·0 in the community.[31] Overall, sex does not seem to be directly related to malaria vulnerability except in pregnancy.

The prevalence of tuberculosis among boys and girls is equal up to age 15 years; thereafter male cases predominate. In adults, notification rates and active case-finding both show a higher prevalence in men than women, with male to female ratios between 1·2 and 4·0.[32,33] By contrast, longitudinal studies show that women have a greater risk than men of progression from infection to disease.[33]

Jenny Hill

Figure 2. Strategies for malaria control generally focus on epidemiological approaches such as increasing the number of children sleeping under insecticide-treated nets.

Whether there is a true disparity in male to female tuberculosis prevalence is not clear because exclusion of confounding factors, such as differences between the sexes in access to treatment and stigmatisation, has been difficult.[34,35] There might also be sex differences in the presentation of symptoms and in response to tuberculin testing, a commonly used method for identifying tuberculosis infections.[36–38]

Women, especially young women, are more vulnerable to acquiring HIV infection than men,[39,40] partly for physiological reasons such as the immature genital tract and high rates of asymptomatic untreated sexually transmitted diseases occurring in young women.[14,41] Women are also more likely than men to be the recipients of blood transfusions because of anaemia and complications during childbirth.

Pregnancy

In malaria-endemic countries, pregnant women have lowered immunity to malaria particularly during first and second pregnancies (figure 3). The low immunity is associated with increased clinical episodes, maternal anaemia, morbidity, and death.[1] The sequestration of parasites in the placenta is associated with low birthweight, adverse effects on lactation, and increased rates of miscarriage and stillbirth.[21] There have been many publications on the adverse implications of low birthweight for the later health and development of the child. The relation between pregnancy and tuberculosis infection is much less pronounced than that for malaria, although there seems to be an increased risk of disease in women during the postpartum period.[42]

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Figure 3. In malaria-endemic countries pregnant women have lowered immunity to malaria especially during first and second pregnancies.

The frequency of vertical transmission of HIV is higher in less developed countries (25–48%) than in more developed countries (14–32%), and it increases with maternal viral load, advanced maternal immunodeficiency, and prolonged rupture of membranes.[43] The risk is higher in poorer countries primarily because of long durations of breastfeeding. Mixed feeding could be associated with a higher risk than exclusive breastfeeding.[44] In resource-poor countries, failure to breastfeed exposes the infant to increased risk of diarrhoeal diseases and is perceived to identify the mother (correctly or incorrectly) as HIV positive.[45,46] Short-course regimens of antiretroviral drugs are effective in reducing the risk of transmission of HIV infection by up to 40% on long-term follow-up, but only about 3% of women at risk in Africa will have access to such treatment before 2005.[47]

Genetics

There is both epidemiological and molecular evidence that genetic background influences the degree of protection an individual develops against malaria infection. Certain ethnic groups, such as the Fulani, have less parasitaemia and malaria illness and higher malaria antibody titres than other similarly exposed groups living in the same region.[48,49] In malaria-endemic regions, there is a high frequency of genes that cause red-cell abnormalities, such as sickle-cell disease and glucose-6-phosphate dehydrogenase deficiency, which confer a selective advantage against malaria mortality.[50] Specific genetic associations such as HLA B53 and MHC antigens have been linked to protection against severe disease and reduced vulnerability to malaria fever, respectively.[51]

Studies on twins and different ethnic groups have shown that host genetic factors are also important in influencing susceptibility to tuberculosis infection and disease.[52,53] Genetic variants of the natural resistance-associated macrophage protein 1 and vitamin-D-receptor genes are associated with smear-positive tuberculosis,[54,55] and there is some evidence that the observed difference in male and female tuberculosis incidence after infection is also due to genetic differences.[56]

Genetic factors have been identified that confer resistance against infection by HIV-1 strains or delay progression of disease.[57] Mutations in the chemokine receptor CCR5 affect susceptibility to HIV infection, and polymorphisms in several other chemokine receptors seem to reduce the rate of progression to AIDS or death in non-African, but not in African, populations.[58] Whether these polymorphisms affect the response to antiretroviral therapy is not clear.[59,60]

Interactions between malaria, tuberculosis, and HIV/AIDS infections and other infections within individuals

Malaria and HIV/AIDS

Despite initial studies suggesting no association between malaria and HIV infection, there is emerging evidence of an important relation, particularly in pregnant women. HIV infection may interfere with pregnancy-specific immunity acquired during first and second pregnancies and increases the chance of parasitaemia and placental malaria.[61,62] The efficacy of intermittent two-dose sulfadoxine/pyrimethamine treatment is decreased in HIV-infected pregnant women, and they may require more frequent treatments.[63,64] Recent studies suggest that antiretroviral drugs alter malaria disease outcomes in coinfected patients.[65] There is also a growing body of evidence that non-pregnant HIV-positive individuals are more vulnerable to malaria infection and to severe disease than those without HIV infection and that this susceptibility is related to the degree of immunosuppression.[66–69]

Tuberculosis and HIV/AIDS

More than 10 million people are estimated to be coinfected with tuberculosis and HIV, and tuberculosis is the leading cause of death in HIV-infected individuals in Africa.[70,71] Up to 70% of HIV-positive sub-Saharan Africans are been estimated to be coinfected with *Mycobacterium tuberculosis*.[72,73] The immunosuppression associated with HIV infection is a strong risk factor for the progression of latent tuberculosis infection to active disease and death.[74,75] HIV infection has contributed to doubling or even trebling of the number of tuberculosis cases in some African countries during the past decade.[76,77] In Kenya, the increasing incidence of HIV/AIDS in the female population is steadily moving the male to female ratio in tuberculosis towards 1·0, and this change is likely to be mirrored in other countries with high prevalence of HIV infection.[78] Coinfection with HIV and tuberculosis can lead to increased difficulties in tuberculosis diagnosis, an increased frequency of treatment side-effects, and higher relapse and reinfection rates.[74,79,80]

HIV and sexually transmitted diseases

Sexually transmitted diseases such as genital ulceration, gonorrhoea, and infections with chlamydia and trichomonas could increase the infectiousness of HIV-positive men and women and the susceptibility of HIV-negative individuals to HIV infection.[81] These effects increase the probability of HIV transmission during unprotected heterosexual contact, independently of risk behaviour.[73] The high prevalence of herpes simplex virus 2 in Africa might be important in contributing to the transmission of HIV.[82]

Malaria and anaemia

Several large trials have shown that use of insecticide-treated bednets is associated with a decrease in anaemia and all-cause mortality that is greater than can be accounted for by the decrease in malaria infections alone. Although the mechanisms underlying this finding are not clear, it suggests that malaria is closely linked to other diseases perhaps by making individuals more susceptible to other infections.[22]

Household and community level: socioeconomic factors

Poverty

Poverty and disease are commonly linked in a downward spiral. Poverty increases vulnerability to malaria, tuberculosis, and HIV infection, and the ill-health and treatment costs associated with the diseases themselves lead to further impoverishment. Although poverty is a complex experience involving a lack of key capital assets (natural, financial, physical, human, and social), it is commonly viewed simplistically in economic terms with low income as a proxy indicator.[83,84] Ideally, information on poverty should be disaggregated into several indicators of deprivation, such as income, food, housing, knowledge, power, and access. This approach would help to unravel confounding relations, but the complex interactions between these factors make disaggregation impracticable.

At the regional and national levels, malaria can prevent economic development by adversely affecting savings and investments, through the costs of ill-health and reduced productivity.[17] A link has also been described between fever incidence and wealth across regions.[85] At the community and household level, malaria disproportionately affects lower socioeconomic groups.[86,87] There is a strong relation between wealth and treatment-seeking behaviour at this level, with children from richer families being more likely to seek orthodox medical care and appropriate treatment.[85] Poverty also affects the ability to access malaria-prevention services. For example, ownership of bednets used to prevent night-time biting by mosquitoes is more common among wealthy households and is closely linked to socioeconomic status.[88] Poor-quality housing increases exposure to malaria infection because mosquitoes can easily enter through unprotected openings. The poorest in a community are likely to live in the most exposed part of the settlement.[89] Overcrowding might further increase vulnerability to malaria infection because high concentrations of carbon dioxide and other chemicals attract mosquitoes; the chances of mosquitoes infecting more than one person on the same night are higher.[90]

An association between poverty and tuberculosis-infection rates is well established and widespread at national and regional levels. Less clear are the interactions between different features of poverty and the stages of infection at the individual level—vulnerability to infection, progression to disease, and mortality. The prevalence of tuberculosis infections is higher in poor countries but, even within wealthy countries, deprived areas tend to have higher rates of tuberculosis incidence.[91–93] Evidence about the relation between poverty indicators and tuberculosis incidence at the individual level is less clear. A study in the USA found that the risk of developing tuberculosis was 2·3 times higher in the poorest individuals than in the richest.[94] By contrast, studies from Mexico and South Africa found no difference in socioeconomic status between tuberculosis patients and non-tuberculosis patients living in the same community.[95,96]

Poverty is associated with vulnerability to severe disease and death from tuberculosis, through its effect on delaying

access to health care and inhibiting treatment adherence.[91,97,98] The costs incurred while seeking diagnosis and treatment for tuberculosis (such as transport to health facilities, consultation fees, and childcare) are important causes of delays in accessing care, especially for poor women and elderly people.[91,99] The average socioeconomic status of individuals with tuberculosis in Kenya improved significantly at different points along a continuum of care from symptomatic outpatients, through tuberculosis diagnosis, to the completion of treatment. This finding suggests that people with low socioeconomic status who have tuberculosis are more likely to drop out at each stage of the process, though this is not a universal finding.[100]

Because tuberculosis is spread through airborne droplets, overcrowding and lack of ventilation are key factors associated with infection and mortality.[75] Poverty is not the only reason for crowded living conditions. Institutions such as prisons, nursing homes, residential centres for HIV-infected people, and urban homeless centres are also sites for tuberculosis outbreaks.[101,102]

Tuberculosis disease itself has an impoverishing effect because many tuberculosis patients sell assets and take out loans to pay for treatment.[91,103,104] For poor patients in Malawi, the total cost of tuberculosis treatment accounted for 248% of monthly expenditure compared with 124% of the monthly expenditure of better-off patients.[91]

Although poverty can result in increased exposure to the risk of infection (for example, poor women becoming sex workers or taking a "sugar daddy") there is debate about whether poorer individuals and communities are particularly vulnerable to HIV.[14,105] However, having HIV/AIDS is well recognised to be a cause of individual, household, and national poverty, especially because the highest burden falls on the economically active age groups.[106] The contribution of HIV/AIDS to household poverty is substantial and well documented. HIV/AIDS causes spending to rise, particularly on medical care and funerals. In common with malaria and tuberculosis treatment, these expenses are immediate and unpredictable and commonly necessitate borrowing of money or selling of assets. Furthermore, HIV disease can reduce productive labour time and income by 67–83%.[107–109]

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Figure 4. Specific livelihoods, such as logging, can increase vulnerability to malaria infection.

Nutritional status

Although malaria and malnutrition influence each other and frequently occur together in less developed countries, the evidence for a biological link between them is not clear[110] (figure 1). Malaria adversely influences nutrition by restricting food intake through anorexia and vomiting; young children who experience frequent attacks of malaria fail to gain weight and have retarded growth and impaired cognitive development.[21,111] Nutritional status also affects responses to antimalarial drugs.[89] There are complex interrelations between nutrition, malaria, and anaemia that are difficult to disentangle. About two-thirds of cases of anaemia in children in malaria-endemic countries are thought to be the result of malaria, but poor nutrition, particularly deficiencies of iron and other micronutrients, is a contributory factor.[21] Studies of the interaction between micronutrients such as iron, zinc, and vitamin A, and malaria are beset by technical difficulties associated with assessment of micronutrient status during acute infections.[112] After much debate, evidence is now accumulating that supplementation with oral iron does not increase the prevalence of clinical or slide-positive cases of malaria.[113] International guidelines now recommend that iron and folate supplements should be given to all children aged 6–24 months and to pregnant women.[114]

Poor nutritional status is associated with vulnerability to progression from tuberculosis infection to disease. Low body mass and food shortages have both been associated with increases in tuberculosis infection and mortality.[115] There have been suggestions of links with specific deficiencies of vitamin D, iron, and zinc.[116–118]

Although poor nutrition is associated with adverse outcome in HIV/AIDS, evidence of clinical benefit from supplementation is scarce, with the exception of severe malnutrition and vitamin A supplementation in children.[119,120] Multi-vitamin supplementation in HIV-1-infected pregnant women substantially decreases adverse pregnancy outcomes such as low birthweight and preterm birth, and increases maternal T-cell counts. Despite suggestions that poor nutritional status in mothers is associated with increased risk of vertical transmission, vitamin supplementation does not reduce transmission in utero but may lower breastfeeding-related transmission.[121,122]

Livelihoods

Vulnerability to malaria, tuberculosis, and HIV/AIDS can be affected by an individual's livelihood, and the illnesses themselves may necessitate a change in livelihood. Work based on payment of a daily wage and occupations without sickness benefits or with inflexible schedules are more likely to be disrupted by illness and treatment, rendering such individuals and households particularly vulnerable to the effects of illness.

Specific livelihoods increase vulnerability to malaria infection. For example, malaria occurs frequently among forest workers in Thailand because the forest is the mosquitoes' preferred breeding site (figure 4).[123] Depending on which species of mosquito causes malaria transmission locally, animal husbandry practices can also influence

malaria vulnerability, because some species prefer feeding on animals such as cattle rather than human beings. Individuals living or working in close proximity to these animals may therefore have altered risk of infection. Knowledge about the biting preferences of local vectors is essential for effective control programmes.[123] Malaria infections increase during the rainy season owing to better availability of water for breeding sites for female mosquitoes. This season coincides with the time of increased agricultural work; for the poorest farmers, malarial illness and the lost productivity at this crucial time can be especially devastating.[124]

Vulnerability to tuberculosis infection and disease has also been associated with specific livelihoods. Workers with high exposure to silica and other dusts are at greater risk of tuberculosis infection and disease progression.[125,126] Individuals diagnosed as having tuberculosis are vulnerable not only to loss of wages but also the possibility of dismissal from work.[91,98,104,115]

Certain occupations, such as long-distance truck drivers and female sex workers, are widely recognised to be associated with vulnerability to HIV infection (figure 5). Even within these groups there are subgroups who are particularly vulnerable, such as sex workers with low socioeconomic status.[127] Individuals employed in mobile workforces (eg, construction, mining, trucking, agriculture, industry, forestry, fishing, and shipping) have an increased risk of HIV infection because they often purchase commercial sex. Sexually transmitted infections may be overlooked by occupational health services associated with large industries during the process of health and safety regulation.[83]

Gender

The term "gender" refers to the different behaviour, roles, expectation, and responsibilities all women and men learn in the context of their own societies. Women and men of different ages, marital staus, and socioeconomic status have different vulnerabilities influenced by a complex interaction of social, economic, and institutional factors. Gender can therefore affect disease exposure as well as treatment-seeking behaviour and adherence to treatment. Stereotyped gender roles can also influence how women and men are treated by the health-care system during diagnosis and treatment processes and therefore their vulnerability to progressing to severe disease.

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Figure 5. Illuminated signs in a "truckers" bar in Thailand aim to discourage sex workers. Although this occupation is associated with vulnerability to HIV infection, such a focus on "high-risk" groups risks making scapegoats of these groups and detracting attention from vulnerability to HIV infection in the broader population.

Stop TB/WHO

Figure 6. Women are generally the carers of sick family members. This responsibility can prevent them from working and carrying out household tasks and can negatively affect their livelihoods.

Gender differences in social customs (eg, men in India sitting outside in the evenings) or occupations (eg, male loggers in Thailand) can lead to increased exposure to malaria.[31,123,128] Routine health-systems data from Mexico, Ghana, and Uganda suggest higher use of government services for malaria symptoms by women of reproductive age than their male counterparts, although the reasons for this difference are not fully understood.[129–131] Women may be more willing than men to invest in malaria-prevention measures (such as insecticide-treated bednets) but many lack the financial and decision-making power to act on this desire.[132,133] Although it is generally women who care for children who become sick with malaria (figure 6), many women have a subordinate role to men in the household and have little control over resources. Their ability to seek malaria prevention or care for themselves and their children is therefore hindered.[124,134–136] In addition, the time that women have to spend looking after sick relatives can also negatively affect their livelihoods. This combination of factors tends to make women more vulnerable than men to the consequences of malaria.[137–139]

Gender differences in the social and economic effects of being diagnosed as having tuberculosis vary with age and position. For example, in Asia women with tuberculosis infection were concerned about its effect on marriage prospects or employment opportunities, whereas men were more concerned about implications for their daily wages.[115,140] The effect of a parent's having tuberculosis is likely to be greater for girls than boys, because daughters take on a greater proportion of the extra workload.[91]

The timing and method of accessing tuberculosis care can be affected by gender. In southeast Asia, tuberculosis is perceived as a largely male disease and this perception might prevent women from recognising and seeking care for tuberculosis-related symptoms.[141] Women fear social

isolation and tend to self-medicate at an early stage of the symptoms, whereas men are more worried about the cost, seek help late, and prefer to use formal health services.[99,140] Women are more inhibited by poor-quality services and lack of confidentiality than men; these feelings could account partly for their preference for traditional healers and self-medication, which delays diagnosis and treatment.[99,142,143] Even within the orthodox health service, diagnosis seems to be more efficient for men than for women. In Vietnam, a mean delay of 2 weeks for women compared with men was associated with increased morbidity and rates of transmission.[141]

Gender also influences adherence to treatment. In India, married men and single women seem to find it easier to receive and complete treatment than married women, who try to keep their illness secret owing to fear of blame or rejection.[112] Many families are more willing to support and pay for treatment for men than women because men are the major wage earners.[98,144]

Women's subordinate role in the household, their fear of abandonment by their partners, and the expectation that women will become mothers cause difficulties in negotiation with their partners over HIV-prevention strategies, such as condom use.[105] In societies where a high social and economic value (including a bride price) is placed on the virginity of unmarried girls, they are kept ignorant of sexual matters and are therefore unable to seek information about sexual health services.[14,145] Women's general lack of education and information means that they may be unaware of their right to access family-planning services or care for HIV/AIDS symptoms.[146] In most countries, women and girls, and to a lesser extent grandparents, have taken on the role of carers for the sick and orphaned.[147–149] Caring is an economic and emotional drain on the carer and can be associated with an increased risk of contracting HIV infection, because carers do not always have the knowledge or resources to take the necessary precautions.[150]

The risk of HIV infection in women is strongly related to the age of their last partner, and relationships between younger women and older men appear to be a major factor in the spread of HIV in young women.[151,152] Sexual violence experienced by women, and less commonly by men, can exacerbate vulnerability to infection with HIV/AIDS because of extreme barriers to acknowledging these events and their repercussions on survivors and communities.[105,153,154] Societal and cultural expectations can also increase men's vulnerability to infection with HIV by pressurising them to behave in risky ways (eg, having multiple sexual partners, use of drugs and alcohol).[105,155] Sex between men can carry a social stigma and in some countries is illegal, which discourages access to HIV diagnostic and support services.[105]

Influence of education, religion, knowledge, and behaviour on societies and individuals

An understanding of the transmission and clinical features of malaria, tuberculosis, and HIV infection is important to encourage individuals to seek prompt and appropriate prevention measures and treatment. Preventive and treatment-seeking behaviour is influenced by perceptions, personal and religious beliefs, and knowledge about the illness.[156] The precise mechanisms through which education affects health-related behaviour are much debated because education does not necessarily translate into effective behaviour changes. The constraints that individuals face in moving from knowledge to behaviour change are complex and involve power relations that are affected by many factors including gender, age, and poverty.

Tuberculosis and HIV infection both require a definitive laboratory diagnosis before treatment is started, but most malaria illness is treated presumptively on the basis of fever. The success of this approach depends crucially on an individual's understanding of the need to treat malaria promptly with the correct dose of effective antimalarial drugs. Misperceptions, such as beliefs that exposure to the sun causes malaria and that convulsions indicate spiritual "possession", can adversely affect treatment-seeking behaviour and increase the malaria vulnerability of those with poor understanding of malaria transmission.[133,157]

The provision of information on appropriate use of antimalarial drugs can influence treatment-seeking behaviour. For example, mothers with low educational attainment were able to make a significant reduction in mortality among children under 5 years old in their community in Ethiopia when given information about appropriate antimalarial drugs.[158] There is also some evidence that educated parents are more likely to seek formal treatment when their child gets malaria symptoms, which will reduce the risk of progression to severe disease.[85] Although concern about malaria mortality is often focused on children under 5 years old, older children are also significantly affected by malaria. 15–50% of fevers and absences in schoolchildren in endemic countries are due to malaria.[159,160] Malaria itself therefore contributes to poor educational attainment by causing anaemia and absence from school.

Tuberculosis is widely perceived as a dangerous, infectious, and incurable disease leading to stigmatisation and social isolation of patients and their families.[140] Traditional beliefs (eg, tuberculosis is associated with sorcery and witchcraft) encourage secrecy around a diagnosis of the disease because the individual fears stigmatisation, and this secrecy affects adherence to treatment.[129] The belief that tuberculosis is incurable engenders a sense of fatalism, which deters discussion and treatment-seeking.[98,129] A low educational attainment is associated with delayed treatment-seeking for tuberculosis and failure to complete treatment.[91,161,162] Conversely, maternal literacy is associated with better rates of case notification of tuberculosis and early treatment-seeking.[25]

Low general educational attainment and lack of knowledge about HIV transmission are both linked to higher rates of risky behaviour and HIV infection.[163,164] HIV/AIDS education programmes have improved awareness about avoidance of infection, but the greater awareness has generally not translated into changes in practice.[105,165] Voluntary counselling and testing programmes have had some success in improving rates of safe sex even though only 1–10% of individuals in less developed countries are aware

of their HIV status.[27,166] HIV infection itself restricts opportunities for formal education, demonstrated by falls in school enrolment of up to 36% in some parts of Africa.[109,167] The reasons are multifactorial but include sickness among teachers and students, adoption of the role of family carers by children, and reduced ability to pay.[168]

Muslim Africa generally has lower rates of HIV/AIDS than other parts of the continent. In mixed communities, Muslims have HIV rates 25–50% of those in non-Muslims.[8] This difference could be due to the practice of circumcision among Muslims, although there may also be other factors such as sanctions against promiscuity and the effect of abstinence from alcohol on high-risk behaviour. Polygamous behaviour has been considered one of the major factors promoting the spread of HIV/AIDS in Africa, where higher rates of HIV infection are found in areas with high rates of polygamy. However, the evidence supporting this notion is inconsistent. In Ghana, the prevalence of HIV infection was lowest in the north, where 44% of marriages are polygamous.[8] Polygamy may provide a closed sexual network, with a lower chance of the introduction of HIV. More recent evidence from Ghana shows that women belonging to Christian churches had lower risks and more knowledge about HIV/AIDS than non-Christian groups, possibly because they were more likely to be monogamous and to stick to church tenets about sexuality.[130]

Although there is debate about the relation between tuberculosis and tobacco smoking,[169,170] abuse of illicit drugs and alcohol has been clearly associated with an increased incidence of tuberculosis, possibly through effects on the immune system.[171] These factors have also been associated with increased HIV infection, which is partly explained by the associated increase in high-risk sexual practices such as unprotected and anal sex.[127] Drug use has been particularly important in the rapid escalation of the HIV epidemic in several countries in Asia and eastern Europe.[172–174]

Search strategy and selection criteria

Quantitative, qualitative, and anecdotal evidence, predominantly since 1980 and relevant to less developed countries, was gathered from key informant interviews and hand and web-based literature searches. Web-based academic search engines used were: Bids, Ingenta, ISI Web of Science, Medline/PubMed, and BIDS-Psychinfo. Initial search terms included: "malaria", "tuberculosis", "HIV/AIDS", and "vulnerability", "malnutrition", "poverty", "gender", "risk or risk factor", "susceptibility", "equity", "inequity", "access to healthcare". Further specific terms were used as the search progressed, including: "mental illness", "sexually transmitted disease* or sexually transmitted infection", "refugee", "multi-drug resistance", "pastoralis*", "polygamy", and "sickle cell". References from key papers identified through these searches were then followed up. Existing reviews of susceptibility, risk factors, and vulnerability to malaria, tuberculosis, and HIV infection were also consulted. The framework was used to guide the collection of data and to identify gaps in knowledge and was revised in the light of additional factors revealed during the review. Since vulnerability to disease is not just an issue for the health sector, evidence from other sectors was also sought to inform intersectoral and broader development policies.

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Conflicts of interest

None declared.

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