

The burden of childhood tuberculosis: a public health perspective

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SUMMARY

The burden of childhood tuberculosis (TB) reflects recent transmission within a community and the level of TB control achieved within the adult (maintenance host) population. Children contribute little to the maintenance of the TB epidemic, but they may suffer severe TB-related morbidity and mortality. This review describes the main determinants of the burden of childhood TB within a particular community.

Basic infectious disease principles identify the community, and not the individual, as the central entity that sustains an epidemic. The prevalence of TB is determined by the community's exposure to *Mycobacterium tuberculosis*, and their vulnerability to developing disease following exposure. The main variables that influence both exposure and vulnerability are discussed. Multiple variables are linked to poverty, and it is their

cumulative effect, rather than the exact degree of poverty, that seems most important.

Diligent contact tracing and the use of preventive chemotherapy will reduce the TB-related suffering of children. The burden of childhood TB, however, is a reflection of our ability to control the epidemic; this remains the ultimate challenge. Current efforts to control the TB epidemic aim to reduce transmission by treating sputum smear-positive adults, while very little emphasis is placed on reducing the vulnerability of high-burden communities. Successful control of the epidemic is the most effective way to reduce the burden of childhood TB, but this will require a holistic approach that acknowledges the importance of sustainable poverty alleviation.

KEY WORDS: childhood tuberculosis; burden; prevalence; exposure; vulnerability

CHILDHOOD TUBERCULOSIS (TB) is difficult to diagnose accurately, has a low public health priority and its global epidemiology is consequently poorly documented.^{1,2} The lack of public health priority results from the fact that the TB epidemic is maintained by adults with cavitating pulmonary disease, while children contribute little to disease transmission. However, cavitating disease becomes a prominent disease manifestation in children aged over 10 years,³⁻⁵ and these children do pose a high transmission risk.⁶ From an epidemiological perspective, children aged over 10 may be viewed as part of the adult, maintenance host population.

In essence, young children (<10 years of age) who tend to develop non-cavitating, paucibacillary disease, act as a 'spill-over' host for *Mycobacterium tuberculosis* and are an epidemiological dead-end for the organism.⁷ However, children do contribute significantly to the TB caseload (up to 40%) in high-burden settings,^{8,9} and may suffer severe morbidity and mortality.^{3,10}

One of the most striking and intriguing epidemiological observations is the huge variation observed in the prevalence of TB between different communities.¹¹ Previous explanations and debate focused on the contribution of genetic vs. socio-economic factors,¹²⁻¹⁴ while recent emphasis shifted to the profound influence of human immunodeficiency virus (HIV) infection.¹⁵⁻¹⁷ The difficulty with such a multifactorial problem is that research tends to focus on a single aspect at a time, and while individual research reports contribute valuable knowledge, they may also confuse the priorities for public health intervention. Therefore, it is essential to evaluate the public health relevance of these findings within an objective scientific framework, based on basic infectious disease principles.

The aim of this review is to provide a systematic overview of current knowledge, within an objective scientific framework, trying to explain differences in the prevalence of TB, and by extrapolation, the burden of childhood TB between particular communi-

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ties. An improved understanding of the disease dynamics at the community level may guide future research and public health intervention.

Definition of terms

Maintenance host: the population that contributes to disease transmission and maintains the epidemic.

'Spill-over' host: the population that, although they may become ill, rarely contributes to disease transmission.

Community exposure: the combined exposure of all the individuals within a particular community.

Community vulnerability: the combined vulnerability of all the individuals within a particular community to develop disease following *M. tuberculosis* exposure.

BURDEN OF DISEASE

In the absence of preventive chemotherapy, the burden of childhood TB is an accurate reflection of the level of TB control achieved within a particular community, because TB in children results from recent transmission. This is supported by several observations. The natural history of disease in children indicates that more than 95% of children who develop TB do so within 12 months after infection.^{3,18} The incidence of childhood TB rises in tandem with adult incidence when control of the epidemic is lost and the geographical clustering of child and adult TB cases overlap.^{19–21} In addition, the patterns of primary resistance to anti-tuberculosis drugs are similar in recently diagnosed adults and children, which indicates that disease in children reflects recent transmission within the community.^{22,23} Children will continue to suffer from TB as long as adults do,⁷ and the huge burden of childhood TB in developing countries alerts us to the fact that the pandemic remains out of control.

It is possible to considerably reduce the number of diseased children by diligent contact tracing and the use of preventive chemotherapy. The dramatic effect that may be achieved by the use of active case finding and treatment together with prophylaxis and treatment of latent infection was demonstrated in the Inuit populations of Canada and Alaska during the early 1960s.²⁴ The extreme isolation of these populations enabled this pro-active approach to 'stamp out' active disease and to eliminate all reservoirs of *M. tuberculosis* at the same time. The situation is unfortunately far more dynamic in today's high-burden settings where populations are highly mobile. Taking isoniazid (INH) for 6–9 months eliminates two thirds of the TB risk (with good adherence it may be as high as 90%)¹⁹ in exposed children, while a 3-month course of INH and rifampicin (RMP) has also shown good efficacy.²⁵ However, poor adherence is a major concern, and it is not unusual for less than one third of participants to complete the full course of unsupervised preventive treatment.⁷ Active contact tracing and screening

places an excessive burden on the health care system, and is a luxury that most high-burden countries simply cannot afford. In these settings, it seems appropriate to focus scarce resources only on those children who are at greatest risk of progression to disease following exposure.⁷ This risk is highest in very young (<3 years of age) and immune-compromised children.³ Fifty per cent of infants and 20–30% of 1–2 year olds progress to disease, usually within 12 months after primary infection. It is prudent therefore to give preventive chemotherapy to all infected or recently exposed children under 3 years of age once active disease has been excluded. Immune-compromised children share a similar high risk, irrespective of their age, and the same guideline should apply.³ Immune-competent children older than 3 years of age are at a relatively low risk (less than 5% progress to disease following primary infection),³ and their need for preventive chemotherapy may be reassessed, especially in settings where health care services are already overstretched.

BASIC PRINCIPLES

Conventional herd dynamics describe three factors that determine the ability of an organism to multiply and spread successfully within a community. These include the intensity of exposure to the organism, the virulence of the organism, and the vulnerability of the community to develop disease that will sustain organism transmission following exposure. In this respect, it is essential to view the community, and not the individual, as the central entity.

Genetic variability provides for continuous adaptation by the pathogen to the challenges posed by its environment. Different strains of *M. tuberculosis* have emerged and differences in virulence between strains are well documented.^{26,27} Strain-specific virulence may be an important variable of disease prevalence in a particular community, but geographical isolation has been greatly reduced by the mobility of modern populations. This will encourage the most virulent strains, such as the modern lineage of the Beijing strain, to spread globally over time.^{28,29} Because the geographic localisation of virulent strains is transient, differences in organism virulence are unlikely to explain persistent differences in disease prevalence between communities. This places the focus on the two remaining factors, namely community exposure and vulnerability (Figure).

Community exposure

Basic infectious disease principles indicate that the combined exposure of the community is determined by the number of individuals exposed and the intensity of their exposure. The intensity of individual exposure depends on the exposure duration and the number of infectious particles in the ambient air.³⁰ Using public health terminology, this implies that commu-

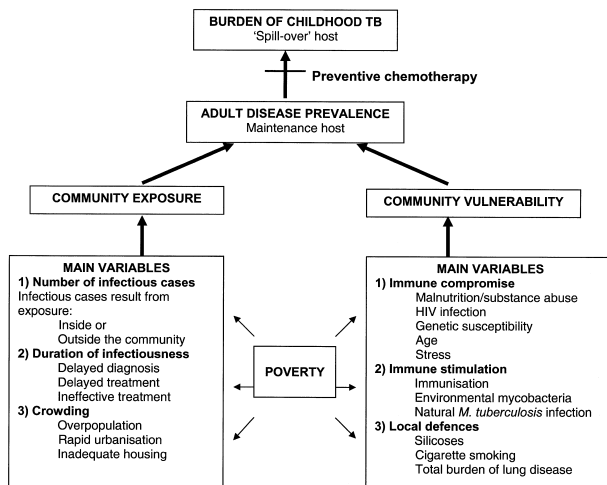


Figure The main variables that contribute to the prevalence of TB in adults and by extrapolation the burden of childhood TB. TB = tuberculosis; HIV = human immunodeficiency virus.

nity exposure is determined by the number of infectious cases, their degree and duration of infectiousness, their mobility within the community and the degree of crowding.

Number of infectious cases

It is self-evident that the level of disease transmission will depend on the number of infectious source cases that spread the disease within a community. New source cases may arise following exposure inside or outside the community. In most low-burden countries, the epidemic is sustained by the constant introduction of new source cases, following exposure outside the community. The introduction of new infectious cases may also fuel the epidemic in high-burden settings. The theoretical risk posed by those who are exposed outside the community can be illustrated using prisons as an example. The risk posed to the community by individuals who are incarcerated is determined by the intensity of their exposure inside the prison (the main variables of exposure remain constant: the number of infectious cases, their degree and duration of infectiousness, and the levels of crowding within the prison),^{31,32} their vulnerability to developing infectious disease and the frequency of their release back into the community. Effective treatment before their release from prison will eliminate the risk they pose, but the concern is that most adult-type disease develops only 1–2 years (up to 5 years) after exposure, and disease may not be present at initial screening.^{3,33} Short-term prisoners are most likely to develop disease only after release back into the community, and therefore prisoners who cycle in and out of prisons with a high prevalence of TB pose a considerable risk to the community. These same principles apply to immigrant populations, tourists and migrant workers who may introduce *M. tuberculosis* into their community.^{29,34–36}

Degree and duration of infectiousness

Early diagnosis and treatment interrupt disease progression and drastically reduce organism transmission.^{37,38} Early intervention is essential to limit the reproductive rate of the organism.³⁹ In the absence of early intervention, transmission represents a self-replicating cycle, and the reproductive rate of the organism will escalate according to the favourability of the circumstances.

DELAYED DIAGNOSIS

Diagnostic delay increases both the degree and duration of infectiousness. Due to the magnitude of the TB pandemic, current guidelines advocate passive case finding. The success of passive case finding depends on early symptomatic presentation, together with adequate diagnostic vigilance and access to sensitive diagnostic tools at the point of presentation.⁴⁰ Diagnostic delay is greatly exacerbated by factors that reduce health awareness and access to health care, such as poverty and discrimination.^{41–43} There is also a need for more sensitive diagnostic tools to detect early disease, as sputum smear microscopy only identifies advanced cavitating disease.

Although most transmission in high-burden settings occurs outside the household,^{44,45} household exposure to a sputum smear-positive source case represents an opportunity for active intervention.^{46–48} Child contacts aged 2–3 years or less and immune-compromised individuals are particularly vulnerable to developing disease,^{3,49} and should receive chemoprophylaxis once active TB has been excluded. Those aged over 10 years, with recent primary infection, are also at high risk of developing disease (10–20% progress to adult-type cavitating disease within 2 years after primary infection),^{3,46} and it may be important to reconsider the use of preventive chemotherapy in such children.^{46,47} The problem is that they are difficult to identify, especially in high-burden settings where many children are already tuberculin skin test (TST) positive by the age of 10 years. A major shortcoming of the TST is its inability to differentiate recent from previous primary infection.

DELAYED TREATMENT

Shortening the duration of infectiousness will reduce the exposure of the community and the reproductive rate of the organism. To achieve this requires not only limiting the diagnostic delay, but also ensuring that effective treatment is instituted as quickly as possible following diagnosis. Treatment may be ineffective due to inappropriate drug regimens, poor drug quality, poor adherence or drug resistance, but with proper implementation the current DOTS and DOTS expansion strategies adequately address most of these treatment-related issues.⁵⁰

Crowding

The degree of crowding and the mobility of source cases within the community influence both the number of individuals exposed and the intensity of their exposure. The transmission of *M. tuberculosis* is strongly

associated with the degree of crowding.^{51,52} Crowding is relevant in all congregate settings, including private homes, public transport systems, institutions such as prisons or health care facilities, and places of socialisation. The worst crowding occurs in urban and peri-urban slum areas, due to rapid urbanisation and overpopulation.⁵³ Paradoxically, crowding may be enhanced within formal housing structures that provide effective protection against the elements, encouraging dense congregation. Transmission is further facilitated by poor ventilation.^{54–55} The seasonal variation observed in the frequency of childhood TB cases may illustrate increased transmission during periods of confinement in poorly ventilated, overcrowded conditions, enforced by harsh weather conditions.^{56,57}

Community vulnerability

Herd immunity, the ability of a particular community to resist the spread of an infectious organism, forms a crucial element of infectious disease control and eradication. Although often restricted to acquired immunity within the immunisation context, this concept may be applied to any communicable disease. Community vulnerability is a more inclusive term, which reflects the combined resistance offered by the full spectrum of defence mechanisms that may limit disease spread within a particular community. In the immunisation model, effective disease containment is achieved by creating a high level of herd immunity within a naturally vulnerable population, using immune stimulation (vaccination). However, the level of natural resistance (without immune stimulation from vaccination or natural mycobacterial infection) offered by immune-competent individuals to *M. tuberculosis* is high, and the vast majority (>90%) of persons infected with the bacillus will never develop any clinical illness.⁵⁸ This high level of natural resistance against *M. tuberculosis* implies that a high degree of 'natural herd immunity' pre-exists in immune-competent communities. It is therefore reasonable to expect that the level of community vulnerability may be affected as much, or even more, by factors that compromise this high level of natural resistance as by those that aim to enhance it.

Immune compromise

The analogy of acquired herd immunity illustrates that a relatively small reduction in 'natural herd immunity' may cause a considerable increase in the vulnerability of a particular community to sustain the TB epidemic. On a public health scale, the biggest influence may be exerted by the cumulative effect of minor factors that affect large numbers of people within the community, even though their individual effect is small.

NUTRITION

Both macro- and micro-nutrient deficiency may reduce cellular immunity and the natural resistance against

TB.^{59–62} The effect of malnutrition is best quantified for severe protein-calorie deficiency,^{62,63} while evidence for moderate nutrient deficiencies often lacks scientific rigour. However, the large numbers of people who are affected by moderate degrees of malnutrition⁶⁴ probably contribute more to the overall vulnerability of a particular community than the few who suffer from severe malnutrition.⁶² In this regard, the combined effects of malnutrition and alcohol (or other drug) abuse may be especially relevant in poverty stricken areas where large numbers of people are dually affected. Alcohol abuse does damage the immune system and seems to increase the vulnerability to develop TB,⁶⁵ but it is difficult to separate its independent effect due to the multiple comorbidities and increased exposure within the social context. People with drug and/or alcohol problems frequently congregate and their exposure is increased by prolonged diagnostic delay and poor compliance with therapy among their companions.⁶⁶

HIV

HIV infection has a devastating effect on the immune system,⁶⁷ which explains the increased incidence of TB amongst HIV-infected individuals.^{15–17} Rapid disease progression in severely immune-compromised individuals may reduce their duration of infectiousness and their contribution to transmission, as suggested by reports that TB incidence rates amongst non-HIV-infected adults remain stable in HIV-affected areas.⁶⁸ However, the widespread use of antiretroviral therapy in high-burden settings may increase the number of people in the community who are mildly immune-compromised, thereby increasing transmission and the incidence of TB at the community level.⁶⁹ Children from HIV-affected households may be particularly vulnerable, because TB cases tend to cluster within these households, and they may be immune-compromised themselves.

HOST GENETICS

The influence that infectious diseases exert on population genetics is well documented for many diseases, such as malaria and leprosy.^{70,71} However, in TB it remains extremely difficult to differentiate between the impact of genetic and environmental influences. The fact that individual vulnerability is partly influenced by genetic variability is illustrated by adult adoptee studies,^{72–74} and by the vulnerability of individuals with mutations or specific polymorphisms of the interferon-gamma (IFN- γ) receptor gene.^{75,76} Host genetics certainly play an important role at the individual level, but the majority of genetic influences result from the complex interaction of multiple genes,^{72–74} and their effect on vulnerability at the population level remains uncertain. The fact that TB incidence rates have plummeted wherever social upliftment succeeded argues strongly for the overriding influence of

the environment in the nurture vs. nature debate. This is best illustrated in the African-American population, where TB was nearly eliminated within a single generation (same gene pool) after their standard of living improved dramatically.⁷⁷ If genetic susceptibility is an important variable at the individual level, it implies that successful treatment will return these susceptible individuals to the community. This is of particular relevance in high-burden settings where the risk of future re-infection is high, and it is demonstrated by the fact that the rate of re-infection TB is higher in successfully treated individuals than the rate of new TB in individuals without previous TB.⁷⁸

AGE

Both the innate and acquired immune response show prominent age-related variation. Young children under 2–3 years of age in whom the immune system is still immature are highly susceptible to developing disease following primary *M. tuberculosis* infection.³ At the other end of the age spectrum, elderly people are often considered at high risk for reactivation disease, because they are over represented among cases in industrialised countries with a historic high prevalence of TB.^{79,80} However, it is extremely difficult to demonstrate the contribution of old age, independent from the cohort effect, in such a setting. The ontogeny of the immune response is an important variable, as demonstrated by the fact that adult-type cavitating disease, which is responsible for continued disease transmission within the community, only emerges after 8–10 years of age.

STRESS

Stress has deleterious effects on the immune system, but the causal link between stress, immune function and TB requires further clarification.⁸¹ The existence of a psychoneuro-immunological network is well described, and although it is still poorly understood, it represents a possible mechanism for increased community vulnerability.⁸² The fact that TB incidence rates increase during times of war may be attributed to a combination of malnutrition, overcrowding, disruption of medical services and increased levels of stress.⁸³

Many other factors may cause immune compromise, but these affect few individuals and will not influence the disease prevalence at a population level. These factors, which include rare immunodeficiency syndromes and iatrogenic immune deficiency caused by corticosteroid treatment or cancer chemotherapy, remain very important from an individual perspective.

Immune stimulation

Immune stimulation in the form of vaccination has practically eradicated some of the world's most devastating infectious diseases. However, compared to these highly virulent diseases, *M. tuberculosis* is a rather innocuous organism to which the vast majority

of immune-competent people exhibit a high level of natural resistance.

The effect of immune stimulation in the form of bacille Calmette-Guérin (BCG) vaccination has shown variable protection in different settings. This may be due to variations in strain-specific immunogenicity, timing or technique of vaccine administration, genetic factors and the presence or absence of environmental mycobacteria.^{84,85} Neonatal BCG vaccination protects mainly against disseminated forms of TB during early childhood and confers no protection against adult-type TB.^{84,85} BCG vaccination may offer improved protection against adult-type TB when administered to older children/adolescents who are TST-negative in locations with a low prevalence of environmental mycobacteria.^{86–88} In the presence of exposure to environmental mycobacteria, the additional protection provided by BCG is negligible,⁸⁹ but without environmental mycobacterial exposure the protection provided by BCG vaccination seems to be of the same order (around 60%) as that afforded by previous natural infection that failed to progress to disease.⁹⁰ The possible deleterious effect of repeated exposure and multiple re-infections, as may occur in high-burden settings, requires further elucidation.^{91,92} Novel vaccines are currently under development to try and improve the degree of protection provided by immune stimulation.⁹³ The provision of additional protection would be of particular value in high-burden settings, where exposure is nearly universal.

Local defences

Compromised local defences may contribute to the vulnerability of particular communities. Poor organism clearance, decreased mucosal immunity and a favourable micro-environment at the point of organism deposition may increase the risk of pulmonary infection and disease.⁹⁴ This is demonstrated by the comorbidity that exists between pulmonary silicosis and TB,⁹⁵ and by the increase in *M. tuberculosis* infection, subsequent disease and ultimate death from TB associated with cigarette smoking.^{96–98} Passive smoking is also associated with a greatly increased risk (odds ratio 5.29, 95% confidence interval [CI] 2.33–12.82) in children to develop TB following recent infection.⁹⁹ The cumulative effect of smoking, environmental airborne pollutants, recurrent chest infections and previous TB all contribute to the total burden of lung disease within a community, which may be an important variable that contributes to the vulnerability of a particular community.

CONCLUSION

Although children rarely contribute to the maintenance of the TB epidemic, they do suffer severe morbidity and mortality. Their suffering can be greatly reduced by diligent contact tracing and pre-

ventive chemotherapy. In resource-limited settings, it may be necessary to target high-risk groups (children <3 years of age and immune-compromised individuals exposed to a sputum smear-positive household source case) for preventive chemotherapy. The accurate diagnosis of TB in children remains a major obstacle, and the development of new diagnostic tools is anxiously awaited. However, the burden of childhood TB results from recent transmission, and in the absence of preventive chemotherapy it represents a barometer of TB control within a particular community.

Basic infectious disease principles identify the exposure and the vulnerability of the community as the main determinants of TB prevalence. Multiple factors affecting both community exposure and vulnerability are linked to poverty, which explains why, on a global scale, TB reflects the plight of poverty stricken populations. It is the cumulative effect of these factors, rather than the exact degree of poverty, that seems most important. Exposure is increased by the large number of infectious cases and their prolonged duration of infectiousness due to poor health education, inaccessible health care, co-morbidity and the all-absorbing daily struggle for survival. Exposure is further enhanced within overcrowded, poorly ventilated living conditions that children share with adults. Poverty also increases the vulnerability of a community, due to the cumulative effect of factors such as malnutrition, substance abuse, stress and the total burden of lung disease, while the triangular shape of the population pyramid reflects the large number of very young and vulnerable children. Like TB, poverty represents a self-replicating cycle that requires active intervention. As stated by J Kevany, 'the world's biggest killer and the greatest cause of ill health and suffering across the globe is listed almost at the end of the International Classification of Diseases. It is given the code Z59.5—Extreme poverty.'¹⁰⁰

The current DOTS and DOTS expansion programmes are aimed at reducing community exposure to *M. tuberculosis*, but it seems as important to reduce the vulnerability of communities if we aim to control the TB pandemic. Basic infectious disease principles emphasise the need to break the cycle of poverty in high-burden settings and to achieve sustainable social upliftment. The fight against TB serves as a prime example of the interdependence of the millennium development goals and the need for global political commitment to achieve these goals.

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R É S U M É

Le fardeau de la tuberculose (TB) infantile est le reflet d'une transmission récente au sein d'une collectivité et du niveau de contrôle de la TB obtenu au sein de la population adulte (hôtes de persistance). Les enfants contribuent peu à la persistance de l'épidémie de TB mais peuvent souffrir d'une morbidité et d'une mortalité sévères liées à la TB. Cette revue générale décrit les déterminants principaux du fardeau de la TB infantile au sein d'une collectivité particulière.

Les principes de base en matière de maladies infectieuses identifient la collectivité et non l'individu comme étant l'entité centrale de persistance d'une épidémie. La prévalence de la TB est déterminée par l'exposition à *Mycobacterium tuberculosis* dans la collectivité et par la sensibilité de cette dernière au développement d'une maladie à la suite de cette exposition. Les variables principales influençant à la fois l'exposition et la vulnérabi-

lité ont été discutées. De multiples variables sont liées à la pauvreté, et c'est leur effet cumulatif plutôt que le degré exact de pauvreté qui semble le plus important.

Un dépistage attentif des contacts et l'utilisation de la chimiothérapie préventive permettront de réduire les atteintes d'enfants liées à la TB. Le fardeau de la TB infantile est toutefois un reflet de notre capacité de contrôler l'épidémie ; celle-ci reste le défi final. Les efforts actuels pour lutter contre l'épidémie de TB visent à réduire la transmission en traitant les adultes à bacilloscopie positive alors que l'on attribue peu d'importance à la diminution de la vulnérabilité des collectivités à haute prévalence. Un contrôle couronné de succès de l'épidémie est la manière la plus efficace de réduire le fardeau de la TB infantile, mais ceci exigera une approche holistique prenant en compte l'importance d'une réduction persistante de la pauvreté.

RESUMEN

La carga de morbilidad por tuberculosis (TB) infantil refleja la transmisión reciente dentro de una comunidad y también el grado de control de la TB alcanzado dentro de la población adulta (huéspedes de mantenimiento de la epidemia). Los niños contribuyen en poca medida al mantenimiento de la epidemia de TB, pero pueden padecer en forma considerable la mortalidad y morbilidad causadas por la TB. En el presente análisis se describen los principales determinantes de la carga de morbilidad por TB infantil dentro de una comunidad particular.

Los principios fundamentales de las enfermedades infecciosas designan la comunidad, y no el individuo, como la entidad central que sostiene la epidemia. La prevalencia de TB está determinada por la exposición de la comunidad a *Mycobacterium tuberculosis* y la vulnerabilidad de la misma a la aparición de enfermedad tras la exposición. Se analizan aquí los principales factores que influyen en la exposición y la vulnerabilidad. Entre ellos,

los factores relacionados con la pobreza son múltiples y parecen más importantes sus efectos acumulados que el grado exacto de la pobreza.

El seguimiento cuidadoso de los contactos y el uso de la quimioprofilaxis reducirá el padecimiento de los niños por causa de la TB. Sin embargo, la carga de morbilidad por TB infantil refleja la capacidad del sistema para luchar contra la epidemia de TB, y esta sigue siendo la esencia del desafío. Las iniciativas actuales para controlar la TB tienen como objetivo reducir la transmisión mediante el tratamiento de los adultos con baciloscopia positiva, y hacen poco hincapié en la reducción de la vulnerabilidad de las comunidades con alta carga de morbilidad. El control exitoso de la epidemia constituye el medio más eficaz para reducir la carga de morbilidad por TB infantil, pero exigirá un enfoque integral que reconozca la importancia de un alivio sostenible de la pobreza.