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STATE OF THE ART

The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era

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SUMMARY

The pre-chemotherapy literature represents an impressive body of evidence that clarifies important epidemiological concepts in childhood tuberculosis. Reports describe the major transitions in tuberculosis, from exposure to infection and from infection to disease (morbidity and mortality), without the influence of chemotherapy. Children with household exposure to a sputum smear-positive source case experienced the greatest risk of becoming infected and of developing subsequent disease. Household exposure to a sputum smear-negative source case or non-household exposure still posed an appreciable, although greatly reduced, risk. Infection in children less than 2 years of age indicated a probable household source case. The majority of older children who were infected did not have a household source identified, and presumably became infected in the community. The annual risk of infection (ARI) was not constant across all ages, but seemed to increase during periods of widening social contact. Infants and adolescents were the groups at highest risk for disease development and death following primary infection.

KEY WORDS: review; pre-chemotherapy; epidemiology; childhood pulmonary tuberculosis

THE TWENTIETH CENTURY witnessed major advances in the understanding of the pathophysiology of childhood tuberculosis as well as its diagnosis and treatment. In particular, the period from 1920, when chest radiography became available for diagnosis, to 1950, when effective chemotherapy became available, represented an optimal window for the documentation of the natural history of tuberculosis.

During this period tuberculosis was still highly prevalent in Europe and America, where adequate infrastructure permitted the careful diagnosis and follow-up of tuberculosis patients. Detection of infection was possible with the tuberculin skin test (TST), while chest radiography allowed a more accurate diagnosis of pulmonary tuberculosis in children.

The aim of this review is to document the findings from the pre-chemotherapy literature concerning the clinical epidemiology of childhood pulmonary tuberculosis in a critical manner. The relevance of these historic findings is interpreted for the public health challenges faced today.

METHODS AND MATERIALS

Original studies on childhood pulmonary tuberculosis, including the period 1920 to 1950 and published in the English literature, were identified from textbook references and extensive cross-referencing. Only studies reporting on more than 1000 children, with a study duration of at least 10 years, were included.[1–8] The database collected was compared to the International Union Against Tuberculosis and Lung Disease (IUATLD) archive in order to ensure that no major study was excluded. One exception was made with the inclusion of Gedde-Dahl's community-based article on tuberculin conversion. He followed patients for a maximum of 8 years, before the Second World War interrupted the study. However, his unique approach provided valuable insight by documenting tuberculin conversion and subsequent disease development in the community. Hospital-based studies introduced bias by preselection and therefore the inclusion of community-based studies was essential.

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Studies are reported in chronological order to illustrate the progression in knowledge. This review summarises the clinical epidemiological aspects of pulmonary tuberculosis in children. During this same period, basic science studies also improved the understanding of the epidemiology of tuberculosis by the accurate description of droplet airborne infection. These studies have been reviewed previously and are not included.[9]

A brief description of the individual studies and the study design employed in each is provided (Table 1). This is followed by a summary of the key findings and major limitations of each individual study (Table 2). The combined study results summarise the most important findings, with reference to the individual studies described in Tables 1 and 2.

The risk of developing disease (morbidity) or of dying from tuberculosis (mortality), following primary infection within a specific age group, was calculated from the original data reported by Bentley et al. (Table 3).[5] The percentage of children who developed primary infection within a specific age period was calculated by deducting the cumulative percentage of children with a positive TST recorded at entry from the cumulative percentage of children with a positive TST at exit from that age category. Multiplying this percentage with the average number of children who entered that age category annually provided an estimate of the number of children who developed primary infection within that age period. This number was used as denominator. The annual number of notifications for tuberculosis-related disease and death within that age group was used as numerator when calculating the disease and mortality percentages (Table 3).

COMBINED STUDY RESULTS

Exposure to infection

The Mantoux TST using 5 tuberculin units (TU) was the optimal test to identify tuberculosis infection.[6,7] The use of different tuberculin strengths complicated the interpretation of TST results and comparison between studies.[7] Reaction to high dose tuberculin (1 mg or 100 TU) probably represented exposure to environmental mycobacteria and not infection with *Mycobacterium tuberculosis*.[7,8] High-dose tuberculin was used following a negative reaction to standard-dose tuberculin in three of the studies.[3,5,8] Those with a positive reaction to high dose tuberculin were included amongst the infected group without further subanalysis, but they represented a small minority. The degree of induration induced by BCG vaccination was usually <10 mm, compared to natural infection, which was usually >10 mm.[7] BCG-induced hypersensitivity diminished with time and tuberculin responses frequently reverted after variable time periods depending on the BCG strain used. After natural infection, permanent reversion occurred in less than 0.5% of children.[4,6–8] Temporary tuberculin inhibition did occur and was associated with wasting, viral illnesses or severe forms of tuberculosis.[7]

Following prolonged household contact with a sputum smear-positive source case, 60–80% of children became infected.[3,6–8] When the source case was smear-negative, 30–40% of children became infected.[4,7,8] The probability of infection in children depended on the infectivity of the source case together with the proximity and duration of contact with the source case. Local cultural practices may have contributed to different epidemiological patterns of disease spread,[7] e.g., extensive socialisation within rural African villages or the isolation of children and women in certain cultures. Brailey was the only author who related the time of TST conversion in the child contact to the time of symptom onset in the adult source case. More than 60% of the children who became infected did so within 3 months of symptom onset in the adult source case.[3] Infection was often delayed in household contacts under 2 years of age compared to older children, suggesting some protection from their reduced social contact within the family.[3] This delay was not evaluated separately in cases where the primary caregiver was the source case. Viral upper respiratory tract infections may have increased the likelihood of tuberculosis infection and contributed to the observed peak in infection during winter months.[7]

Most children (80%) who became infected before 2 years of age were infected by a household source case.[3,5,7] Additional caregivers outside the household were also important, especially grandparents or extended family members who took care of the children during the day, if both parents worked.[7] The majority of children who became infected after 2 years of age had no household contact identified, and were therefore likely to have been infected in the community.[2,3,5,7,8]

A separate issue raised by these studies was how the contribution of household exposure to primary infection varied according to the prevalence of tuberculosis in a specific community. In high prevalence areas, household exposure contributed to primary infection up until 15 years of age, by which time most children were already infected.[5,8] In low prevalence areas, household exposure remained an important contributor to primary infection until old age.[5,8] The risk of infection following household exposure was reduced under good socio-economic conditions.[5,8] There were no racial differences in the rate of infection following household exposure.[3,8]

The annual risk of infection (ARI) was not constant across all ages.[5,7] There were specific age periods when infection rates increased.[5] These age periods seemed to correlate with times of widening social contact. This occurred with increased mobility after 2 years of age, school entry at 5 to 7 years of age and school exit at 15 to 20 years of age (Table 3).[5,7] Primary

Table 1 Description of the original studies and individual study designs documenting the clinical epidemiology of childhood pulmonary tuberculosis

Individual study reference	Time frame	Study type	Study population	Data collection methods
1 Opie E, McPhedran F M, Putnam P – 1935 Henry Phipps Institute, Philadelphia, PA, USA The fate of children in contact with tuberculosis: the exogenous infection of children and adults[1]	1907–1934 Follow-up period of 1–27 years	Retrospective descriptive, out-patient based	Children <15 years from 1000 families with an adult source case Mortality data for the city of Philadelphia	Adult source cases were self-selected Annual clinical follow-up of all source case contacts Annual CXR (if available)
2 Pope A S, Sartwell M D, Zacks D – 1939 State Department of Public Health (Chadwick Clinics), Boston, MA, USA Development of tuberculosis in infected children[2]	1924–1939 Follow-up period of 5–15 years	Prospective TST survey, school based	400 330 school children 6–16 years TB notification data for Boston	TST survey (Von Pirquet) CXR done if TST positive Annual CXR if the initial CXR was abnormal
3 Brailey M – 1940 Johns Hopkins (Harriet Lane Clinic), Baltimore, MD, USA A study of tuberculous infection and mortality in the children of tuberculous households[3]	1928–1937 Follow-up period of 1–10 years	Retrospective descriptive, out-patient based	1383 children <15 years from 285 families with an adult source case Mortality data for Baltimore	All children from tuberculous households screened Old tuberculin TST (0.1 or 1 mg) Annual CXR if TST positive
4 Gedde-Dahl T – 1951 Kinn district, Bergen, Norway Tuberculous infection in the light of tuberculin matriculation[4]	1937–1944 Follow-up period of 1–8 years	Prospective TST survey, community based	6739 people of all ages 3138 children <15 years	Annual community based TST survey (Von Pirquet) Documented TST conversion/ matriculation Annual CXR once TST positive
5 Bentley F J, Grzybowski S, Benjamin B – 1954 High Wood Hospital for children, Brentwood, Essex, UK Tuberculosis in childhood and adolescence[5]	1901–1952 Notification data used	Audit of TB notifications Mathematical deductions	UK national TB notification data British MRC national TST survey	Reviewed TB notifications for the whole UK and specifically for London (1901–1952) Reviewed TST surveys D'Arcy Hart (1929), Prophit (1935–1944), British MRC (1949–1950)
6 Davies P D B – 1961 Brompton Hospital, London, UK The natural history of tuberculosis in children[6]	1930–1954 Follow-up period of 1–25 years	Retrospective descriptive, out-patient based	2377 children <15 years in household contact with an adult source case	Included all asymptomatic household contacts Different TSTs were compared Annual CXR
7 Miller F J W, Seal R M E, Taylor M D – 1963 Royal Victoria Infirmary, Newcastle upon Tyne Children's Sanatorium, Stannington, Northumberland, UK Tuberculosis in children[7]	1) 1947–1954 2) 1951–1961 Follow-up period of 1–10 years	Retrospective descriptive, out-patient based	1) Children <7 years from 1000 families with an adult source case 2) 1500 children <5 years in household contact with an adult source case	1) 1000 family study Household contacts <7 years Annual CXR + TST (until positive) 2) Household contact study Household contacts <5 years Annual CXR + TST (until positive)
8 Zeidberg L D, Gass R S, Dillon A, et al. – 1963 Tennessee Department of Public Health, USA The Williamson County tuberculosis study: a 24 year epidemiologic study[8]	1931–1955 Follow-up period of 1–24 years	Prospective community cohort study	1746 children <15 years from 828 families with an adult source case Tennessee mortality data	Voluntary inclusion of all household contacts Detailed questionnaire and physical examination Old tuberculin TST (0.1 or 1 mg) 6–12 monthly CXR

CXR = chest radiograph; TST = tuberculin skin test; MRC = Medical Research Council; UK = United Kingdom.

Table 2 Summary of key findings and major limitations of the original studies, documenting the clinical epidemiology of childhood pulmonary tuberculosis

Citation	Features	Key findings	Major limitations
Opie et al.[1]	First to focus on families and children	Sputum positive exposure increased the frequency and severity of disease in childhood contacts The lifetime risk for the development of cavitating disease depended on the age at primary infection, increasing significantly after 10 years of age	TST not recorded Age groups poorly defined Limited CXR availability Sputum positivity not specified (smear or culture)
Pope et al.[2]	TST positivity School survey	Only 30% of infected school children had household contact with a known source case Cavitating pulmonary tuberculosis was seen in children >10 years of age only	TST conversion not recorded Selective follow-up (only those with initial CXR abnormalities were followed) Documented cavitating disease only
Brailey[3]	Focus on children <2 years of age Racial comparison	Infected children <2 years of age indicated an active household source case The majority of household contacts were infected within 3 months of symptom onset in the adult source case No racial difference in infection following exposure Definite racial difference in disease and mortality following infection	Public health entry point selected the poor Response to high dose (1 mg) tuberculin, used in a small minority of patients, is not specific for *M. tuberculosis* infection Sputum positivity not specified (smear or culture) Socio-economic differences were not evaluated
Gedde-Dahl[4]	TST conversion Community survey	The rate of TB infection and TB related mortality was increased in urban areas Radiological abnormalities were visible in 75% of children following primary TB infection	Preschool children were selectively represented (only contacts and symptomatic cases included) Results from this isolated community may be difficult to generalise
Bentley et al.[5]	Tuberculosis disease and mortality specified per age group Concept of relative contribution	The annual rate of infection (ARI) was not constant, but varied between different age groups The majority (90%) of TB-related radiological abnormalities were not detected in routine clinical practice The risk of disease and death following infection was the highest during infancy The relative contribution of TB to age-specific all-cause mortality was the lowest during infancy TB contributed significantly to all-cause mortality throughout childhood	Response to high dose (100 TU) tuberculin, used in 24% of subjects in the British MRC survey, is not specific for *M. tuberculosis* infection Relied exclusively on TB notification data for disease and mortality analysis
Davies[6]	Long-term follow-up Persistence of TST conversion	The Mantoux skin test outperformed other TSTs A positive tuberculin response persisted for >20 years Exposure to a sputum smear-positive vs. a smear-negative source case doubled the risk of infection Infection after exposure to a sputum smear-positive source case doubled the risk for disease and death	Majority of patients were already infected at study entry Selected only asymptomatic children at study entry, to ensure clinical uniformity
Miller et al.[7]	Comprehensive literature review	Clarified the confusion surrounding the interpretation of different TST techniques and doses Described the importance of cultural influences and the extended family Viral respiratory infections might have contributed to the seasonal variation in TB infection	Few deductions were made from own studies Validity of quoted studies was not evaluated Relied extensively on notification data
Zeidberg et al.[8]	Long term follow-up in the community	Identified critical periods of risk for disease development (infancy, puberty) Documented a drastic reduction in TB-related disease and mortality over the 24-year study period in black patients	Age at primary infection was not documented Entry criteria were adapted during the study A controversial finding, not supported by mortality data or results from other studies reviewed, was the delayed progression of disease reported in children infected between 1 and 15 years of age

TST = tuberculin skin test; CXR = chest radiograph; MRC = Medical Research Council; TU = tuberculin units.

Table 3 The calculated risk of developing primary tuberculosis (TB) infection, compared to the calculated risk of being notified with TB-related disease or death following primary TB infection, within specific age groups

Age group, years	Calculated risk to develop primary TB infection* %	Calculated risk to be notified with TB-related disease, following primary TB infection† %	Calculated risk to be notified with TB-related death, following primary TB infection‡ %	Relative TB-related mortality§ %
<1	<1	11.9	6	0.6
1–4	10	5.6	1	12.1
5–9	20	3.8	0.3	9.1
10–14	10	6.4	0.5	9.1
15–24	30	10 (males) 13 (females)	1.5 (males) 2.6 (females)	16.7 (males) 39.4 (females)

* Indicates the calculated percentage of children who develop primary infection (tuberculin conversion) within a specific age group.
† Indicates the number of children notified with TB, as a percentage of the total number expected to have developed primary TB infection, within a specific age group.
‡ Indicates the number of children notified with death due to TB, as a percentage of the total number expected to have developed primary TB infection within a specific age group.
§ Indicates the percentage of TB-related mortality compared to all-cause mortality within a specific age group.
Data on primary TB infection were collected from the British MRC tuberculin skin test survey for London (1949–1950).[5] This was converted into the number of children expected to develop primary infection within a specific age group, using national census data for London (1951). Data on TB-related disease and death were collected from TB notifications and death certificates for London (1945–1949).[5] Absolute notification numbers were converted into percentages, using the number expected to develop primary infection within a specific age group as denominator and accepting that all notifications result from recent primary infection. Relative TB-related mortality was calculated from death certificates for England and Wales (1950), comparing TB-related mortality with all-cause mortality.[5]

infection occurred at a younger age in high-density, low-income, urban areas.[4–7] The age-specific infection rate was the single most important public health indicator of the prevalence of disease in a given community.[5,7,8]

Infection to disease (morbidity)

To describe the progression from infection to disease accurately, a clear case definition of disease is required. Definitions of disease were not consistent across studies and disease was not well defined. Notification data were routinely used, reflecting passive case finding where any radiological abnormality attributed to tuberculosis was reported as tuberculous disease.

With constant community surveillance and active case finding it was found that a high percentage of children (50–70%) developed radiological abnormalities following primary infection. This was most common (60–80%) following primary infection before 2 years of age.[3–5] On comparison with notification data, it was clear that only 5–10% of children who developed radiological abnormalities during the natural course of the disease were notified as diseased (Table 3). This implied that more than 90% of radiological abnormalities passed undetected in routine clinical practice.[5,7]

The risk of radiological abnormality in children with household exposure to a sputum smear-positive source case and a positive TST was 30–50%.[1,4,6–8] This risk was reduced by 50% when the source case was sputum smear-negative or not a household member.[1,4,6–8] Duration since primary infection and age at primary infection determined the risk for disease development.[4,5,7] Most disease developed in the first year following primary infection.[1,3,4,5,7] Children with primary infection before 2 years or after 10 years of age[5,7] and black children[1,3,7,8] were at increased risk for disease development. The increased susceptibility of black children declined drastically as socio-economic conditions improved during the Tennessee study.[8]

The risk of developing cavitating pulmonary tuberculosis depended on the age at primary infection. The highest risk for cavitating disease (10–20%) occurred in children who were first infected after 10 years of age, with perimenarchal girls being most vulnerable.[1,2,5–8]

Mortality

Tuberculosis-related mortality following infection from a sputum smear-positive household source case was twice as high as when infection occurred from an unknown source case.[6–8] All-cause mortality was similar in both these groups, indicating that the difference was not due to general increased mortality in the households of sputum smear-positive patients.[1,3,7,8]

The highest risk for TB-related mortality following primary infection (5–10%), occurred during infancy.[1,3–5,7,8] This risk declined to 1% between 1 and 4 years of age, with the lowest levels maintained at less than 0.5% from 5 to 14 years of age, before rising to more than 2% from 15 to 25 years of age (Table 3).[5,7] Most deaths from tuberculosis occurred within the first year following primary infection in children under 10 years of age,[1,3,4,5,7] but mortality lagged 5–10 years behind the onset of cavitating disease in older children.[8]

All-cause mortality exhibited an age-related pattern similar to that of tuberculosis-related mortality.[5] Therefore, the relative tuberculosis-related mortality best described the impact of tuberculosis on all-cause mortality within a specific age group.[5] Tuberculosis contributed significantly to all-cause mortality in all

age groups, except in infancy.[3,5] The low rate of infection and the high mortality from other causes during infancy explain this contradiction (Table 3).[3,5,8] Urbanised, densely populated areas suffered increased mortality from both tuberculosis and other causes.[4,6]

Black children suffered double the tuberculosis-related mortality and four times the all-cause mortality experienced by white children.[3,7,8] The tuberculosis-related mortality in black children declined by 80% during the Tennessee study.[8] A 10-fold decline in tuberculosis-related mortality occurred in Britain between 1900 and 1950, without a comparable decrease in tuberculosis infection.[5,7]

DISCUSSION

The combined studies represent an impressive body of evidence and clarify some important epidemiological concepts in childhood tuberculosis. Household exposure to a sputum smear-positive source case posed the greatest risk to children. Household exposure to a sputum smear-negative source case or non-household exposure to a sputum smear-positive source case posed a reduced, but still appreciable risk.

It is a public health priority to identify and treat all sputum smear-positive source cases in the community. Therefore, prudent public health policy should encourage active case finding amongst household members of children infected before 2 years of age, as part of an expanded ('reverse') contact investigation. In low prevalence areas this active case finding may be extended to household members of all recently infected or diseased children, irrespective of age.

After 2 years of age, the majority of children from high prevalence areas became infected in the community. However, household exposure to a sputum smear-positive source case remained an important contributor to primary infection up to 5–10 years of age. Children with primary infection at 5–10 years of age had the lowest risk of disease development and death. In low-prevalence areas household exposure remains an important contributor to primary infection throughout life, and all household contacts, irrespective of age, require screening. These findings provided the scientific basis for classical contact investigation practices, which focus on children less than 5 years of age in most developing countries and all household contacts in most industrialised countries.

Another public health priority is the identification of children at risk of disease development and death. The calculated risk for disease development and death following primary infection within a specific age group represents a reinterpretation of original data, as outlined under methods (Table 3). Infants were at highest risk of disease development and death following primary infection. However, the use of accumulated tuberculin positivity as denominator in the original publication,[5] instead of tuberculin converters within a specific age group, obscured the emergence of the second high-risk period around puberty. Children who were uninfected at 10 years of age were at considerable risk of developing adult-type cavitating disease following primary infection. This marked increase in risk may be obscured by analysis of notification data, due to the delay in disease notification that results from passive case finding in adult-type disease. Disease and mortality data for the age group 15–25 years probably contain a significant contribution from delayed disease notification following primary infection in the 10–14 year age group (Table 3).

Previously uninfected adolescents are a particularly vulnerable group, especially in high-prevalence communities where the risk of future infection is high. Mantoux skin testing at 7–9 years of age may aid in the identification of children who are still uninfected. Effective immunisation or active case finding may be warranted in this vulnerable group to reduce individual morbidity and disease transmission in the community. Children with a significant Mantoux reaction without prior anti-tuberculosis treatment may be offered treatment of latent infection to reduce the possible risk of future reactivation.

The relative tuberculosis-related mortality indicates that tuberculosis contributes significantly to all-cause mortality in high-burden areas throughout childhood. The relative contribution to all-cause mortality is lowest in infancy, but it does not detract from the important observation that infected infants represent the group at highest risk of death from tuberculosis.

It is difficult to separate racial and genetic factors from socio-economic and cultural influences. However, the dramatic decline in disease and mortality documented within a single generation, without a comparable decrease in infection,[5,8] emphasises the considerable influence of socio-economic improvement. This is contrary to the natural selection view proposed by Grigg in his influential article, 'The arcana of tuberculosis'.[10] The nature versus nurture issue is complex, and is far from resolved,[11] but improvement in the environment rather than genetic selection seems to be the main contributor to the dramatic reduction in tuberculosis witnessed in the developed world during the 20th century.

Important limitations of the individual studies were identified, and although the combined study results compensate for many of the individual study deficiencies, major limitations remain. Different methods of tuberculin administration were used, with the Mantoux intradermal technique established as the best method. Different strengths of tuberculin were used, with 5 TU providing the best sensitivity whilst retaining specificity. The sensitivity of the TST could not be measured due to lack of a gold standard, but it correlated well with exposure and radiographic proof of infection. The Mantoux skin test remains the accepted

method of documenting infection. Even with the advent of more sensitive and specific T-cell based assays (e.g., ELISPOT),[12] the skin test's sensitivity and specificity remain favourable and its simplicity unsurpassed.

The most important limitation to this analysis was the absence of a clear definition of disease. To gain a better understanding of the crucial transition from infection to disease, it is important to accurately define disease. Pulmonary tuberculosis represents a whole spectrum of pathology, and different disease entities need to be separated. Notification data often provide unreliable information due to under- or over-reporting of disease and inaccurate cause of death identification. Under-reporting of primary pulmonary tuberculosis in children was a particular problem.[7] In addition, the reported rate of infection varied considerably among studies, especially within the important younger age groups. The rate of primary infection accepted at a specific age influences the calculated risk of subsequent disease and mortality. Due to these limitations, risk calculations may vary widely. The optimal way to define risk and to describe exact disease entities is by prospectively following an unselected cohort of children with recent primary infection for subsequent disease development and death. Studies that documented the natural history of disease achieved this.

Despite the limitations of the articles reviewed, valuable epidemiological information is provided, which may assist with the formulation of evidence-based public health policies. The recent emergence of human immunodeficiency virus (HIV) infection in many high-prevalence areas, and its influence on morbidity and mortality, establish the need for new epidemiological data and the global epidemiological surveillance of tuberculosis in children.

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RÉSUMÉ

La littérature pré-chimiothérapique représente un ensemble de faits impressionnants qui permettent de clarifier un important concept épidémiologique au sujet de la tuberculose de l'enfant. Elle décrit les transitions majeures dans la tuberculose : de l'exposition à l'infection et de l'infection à la maladie (morbidité et mortalité) en dehors de toute influence de la chimiothérapie. Les enfants exposés à leur domicile à un cas-source à bacilloscopie positive des expectorations ont le risque le plus élevé de développer une infection et une maladie ultérieure. L'exposition à domicile à un cas-source à bacilloscopie négative ou l'exposition en dehors du domicile comporte toujours un risque appréciable quoique fortement réduit. Les enfants chez qui l'on découvre une infection avant l'âge de 2 ans suggèrent la probabilité d'un cas-source dans le ménage. Chez la majorité des enfants plus âgés qui ont été infectés, on n'a pas pu identifier une source au sein de ménage ; ils ont probablement été infectés dans la collectivité. Le risque annuel d'infection (RAI) n'est pas constant au fil des âges mais semble augmenter au cours des périodes d'élargissement des contacts sociaux. Les nourrissons et les adolescents ont été les groupes où le risque de développement de la maladie et celui de décès sont les plus élevés dans les suites de la primo-infection.

RESUMEN

La literatura de la era prequimioterapia representa un conjunto impresionante de evidencias que clarifican importantes conceptos epidemiológicos de la tuberculosis infantil. Ella describe las transiciones más importantes de la tuberculosis, desde la exposición y desde la infección hasta la enfermedad (morbilidad y mortalidad), sin la influencia de la quimioterapia. Los niños expuestos en el domicilio a casos índices con baciloscopia positiva tenían el mayor riesgo de desarrollar la infección y la enfermedad subsecuente. La exposición en el domicilio a casos índices con baciloscopia negativa o la exposición fuera del domicilio tenía un riesgo apreciable, aunque considerablemente reducido. La constatación de una infección en un niño menor de 2 años indicaba la existencia probable de un caso índice en el domicilio. En la mayoría de los niños mayores de 2 años que estaban infectados no se identificaba un caso índice en el domicilio y presumiblemente habían sido infectados en la comunidad. El riesgo anual de infección (ARI) no era constante a través de las edades, sino que parecía aumentar durante los períodos en los que los contactos sociales se multiplicaban. Los lactantes y los adolescentes eran grupos de alto riesgo para el desarrollo de la enfermedad y muerte después de la infección primaria.