Tuberculosis Transmission to Young Children in a South African Community: Modeling Household and Community Infection Risks

Robin Wood,1,2 Simon Johnstone-Robertson,1,3 Pieter Uys,2 John Hargrove,3 Keren Middelkoop,1,2 Stephen D. Lawn,1,2,4 and Linda-Gail Bekker1,2

1Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, and 2Department of Medicine, University of Cape Town Faculty of Health Sciences, and 3Department of Science and Technology/National Research Foundation Centre of Excellence in Epidemiological Modeling and Analysis, University of Stellenbosch, Cape Town, South Africa; and 4Clinical Research Unit, Department of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background. Tuberculosis transmission is determined by contact between infectious and susceptible individuals. A recent study reported a 4% annual risk of child tuberculosis infection in a southern African township. A model was used to explore the interactions between prevalence of adult tuberculosis infection, adult-to-child contacts, and household ventilation, which could result in such a high annual risk of tuberculosis infection.

Methods. Number of residents per household and tuberculosis incidence were derived from a household census and community tuberculosis registers. Using the Wells-Riley equation and probability analyses of contact between infectious adults with tuberculosis and preschool children, we estimated the annual risk of tuberculosis infection within and outside of the home.

Results. There was a mean of 2.2 adults per child-containing household with a 1.35% annual adult smear-positive tuberculosis notification rate. The maximal household annual risk of tuberculosis infection was 3%, which was primarily determined by the number of resident adults. Transmission risk outside the home increased with increasing number of households visited. Transmission probabilities were sensitive to exposure time, ventilation, and period of adult infectivity. The benefits of increased ventilation were greatest when the period of infectivity was reduced. Similar reductions in household transmission could be achieved by increasing ventilation from 2 to 6 air changes/hour or by separating child and adult sleeping areas.

Conclusions. The annual risk of tuberculosis infection of preschool children predominantly results from infectious residents in the home. However, even with limited social interactions, a substantial proportion of transmissions may occur from nonresident adults. The benefits of increased ventilation are maximized when the period of infectivity is reduced by prompt treatment of source cases.

South Africa is now the country with the fifth highest tuberculosis burden in the world, with high rates of both adult and childhood (ages 0–15 years) tuberculosis notifications [1]. The total number of tuberculosis notifications in the South African city of Cape Town, with 3.2 million people, reached 27,000 in 2006 [2]. However, the distribution of tuberculosis cases within the city is very unequal, with unprecedented high burdens in the crowded and socially deprived African townships. In these townships, housing consists largely of informal shack dwellings, in which the annual tuberculosis notification rates exceed 1500 per 100,000 persons [3–5]. Whereas adult tuberculosis disease is caused by a combination of reactivation of remote infection and rapid progression of recent adult-to-adult transmission [6], childhood disease reflects rapid progression from recent adult-to-child transmission [7]. Childhood (ages 0–15 years) tuberculosis notification rates have been reported to be 3.5 times the adult rate in specific highly burdened Cape Town communities, where childhood tuberculosis contributed 39% of the total tuberculosis case load [8]. Recent studies of childhood tuberculosis infection rates in southern Africa townships have reported annual risks...
Table 1. Age Distribution of Residents in All Study Site Households, Households with Adults Residents Only, and Households with Children Aged <15 Years or <5 Years

<table>
<thead>
<tr>
<th>Households</th>
<th>No. of households</th>
<th>No. of children aged &lt;5 years</th>
<th>No. of children aged 5–15 years</th>
<th>No. of adults</th>
<th>No. of adults per household</th>
<th>Total no. of residents</th>
<th>No. of residents per household</th>
</tr>
</thead>
<tbody>
<tr>
<td>All households</td>
<td>6654</td>
<td>1051</td>
<td>1640</td>
<td>12,097</td>
<td>1.82</td>
<td>14,788</td>
<td>2.22</td>
</tr>
<tr>
<td>Households with only adults</td>
<td>4946</td>
<td>0</td>
<td>0</td>
<td>8148</td>
<td>1.65</td>
<td>8148</td>
<td>1.65</td>
</tr>
<tr>
<td>Households with children aged &lt;15 years</td>
<td>1708</td>
<td>1051</td>
<td>1640</td>
<td>3949</td>
<td>2.31</td>
<td>6640</td>
<td>3.89</td>
</tr>
<tr>
<td>Households with children aged &lt;5 years</td>
<td>918</td>
<td>1051</td>
<td>516</td>
<td>2083</td>
<td>2.27</td>
<td>3650</td>
<td>3.98</td>
</tr>
</tbody>
</table>

of tuberculosis infection as high as 4% per annum [9–11]. This annual risk of tuberculosis infection is similar to reported values from 60 years ago, before implementation of national tuberculosis control programs [12].

Childhood tuberculosis infection is quantitatively related to exposure of susceptible children to adults who have sputum smear-positive tuberculosis [13, 14]. The prevalence of infectious adults is determined by the annual incidence rate of smear-positive tuberculosis in adults and the mean time of infectivity, the period between becoming infective and either initiation of effective therapy or death. The prevalence of untreated tuberculosis is therefore primarily determined by the effectiveness of the tuberculosis control program to identify, diagnose, and effectively treat infective tuberculosis cases. The risk of a possible transmission event is related to the number of contacts a child has with infectious adults. The efficiency of transmission, in turn, is determined by the infectiousness of the source, the length of contact, and the environmental characteristics at the site of a contact. Tuberculosis transmission thus results from the interplay between social interactions, environmental factors, and the prevalence of infective adults. The period of infectiousness (Δ) of adults is the only modeled parameter affected by the activities of the tuberculosis control program.

We modeled tuberculosis transmission among preschool children (aged 0–5 years), both in and outside of their primary residence, using the distribution of resident adults per household and the prevalence of adult infectious tuberculosis. The modeled transmission probabilities were adjusted for length of exposure time and variable household ventilation characteristics. We also explored decreased periods of adult infectivity and increased household ventilation, which would be required to achieve significant reductions in transmission.

METHODS

Study design. The study aim was to explore probabilities of transmission from adults to preschool children within and outside of households in a South African township. The Wells-Riley equation is a well-known transmission model that has been used to describe airborne transmission probabilities of a single enclosed room or space with defined ventilation [14].

The Wells-Riley equation, which has been applied to a wide range of transmission scenarios [15–19], was used in combination with the distribution of adults per household and their probability of being infectious, to explore adult-to-child tuberculosis transmission probabilities.

Study community. The study site used to provide data inputs to these modeling analyses is a periurban township (Site-M) near Cape Town, South Africa, which was established in 1992 and has grown to a 2008 population of 14,788 people. The township is home to an almost exclusively African population, the adult human immunodeficiency virus (HIV) prevalence in 2005 was 23%, and the majority of persons have low socioeconomic status [3]. Unemployment exceeds 50%, and housing predominately consists of closely aggregated, formal and informal structures. The township has clearly demarcated boundaries and constitutes a well-defined population for research studies and community health interventions.

Figure 1. The proportions of households with preschool children (aged <5 years) in which different numbers of adults are resident. A total of 2083 adults and 1051 preschool children were resident in 918 households. Data were derived from a 2008 household survey performed at the study site.
Table 2. Tuberculosis Notifications at the Study Site Reported in 2004–2008, Stratified by Age

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total population</th>
<th>Adults aged &gt;15 years</th>
<th>Children aged 5–15 years</th>
<th>Children aged ≤5 years</th>
<th>Adults with smear-positive tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tuberculosis notifications</td>
<td>1289</td>
<td>1158</td>
<td>48</td>
<td>86</td>
<td>670</td>
</tr>
<tr>
<td>Population years of exposure 100,000</td>
<td>67,747</td>
<td>53,056</td>
<td>9181</td>
<td>5510</td>
<td>53,056</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

Tuberculosis control program. The study community is served by a single government primary health care clinic with a dedicated tuberculosis service. All patients with tuberculosis in the community are treated at this facility. The program adhered to the South African National TB Control Program guidelines and included the World Health Organization Directly Observed Treatment Short Course (DOTS) strategy [20]. DOTS coverage in this community was complete, and treatment completion rates for smear-positive disease exceeded 80% [13]. Adult pulmonary sputum-positive tuberculosis was diagnosed on the basis of at least 1 sputum culture positive for Mycobacterium tuberculosis or 2 sputum smears containing acid-fast bacilli in the context of a compatible clinical illness. Childhood tuberculosis diagnosis was made with a scoring system using a combination of clinical and radiological features [20]. A score ≥7 indicated a high likelihood of tuberculosis, using the features length of illness (1–3), nutritional status (1–3), family history of smear-positive disease (3), tuberculin skin test reactivity (3), enlarged lymph nodes (3), abdominal mass (3), central nervous signs (3), chest radiography (3), and spinal angling (4). All sputum testing was performed at the National Health Laboratory Services facilities in Cape Town.

Data sources. Tuberculosis definitions used for notification data were as defined by the South African TB Control Program [20]. Tuberculosis is a notifiable condition in South Africa, and each tuberculosis clinic is required to maintain and report tuberculosis statistics. The numbers of tuberculosis notifications, demographic characteristics, history of previous tuberculosis, sputum microbiologic test findings, and tuberculosis classification data were obtained from the community tuberculosis clinic register. Tuberculosis program data were collected for the years 2004–2008, to cover the period of potential tuberculosis exposure for children aged ≤5 years in 2008. Demographic data for the community were derived from household censuses performed in 2004, 2006, and 2008 as part of an ongoing health research program. This research was approved by the Research Ethics Committee of the University of Cape Town.

Mathematical transmission model. The number of childhood tuberculosis infections (\(C\)) within a household with susceptible children (\(S\)) was assumed to be a function of the number of infectious adults (\(I\)), their infectivity (\(q\)), the time of exposure (\(t\)), the susceptible respiration rate (\(p\)), and germ-free ventilation (\(Q\)) as given by the Wells-Riley equation: \(C = S(1 - e^{-ptq})\). The number of infectious adults at any time is given by the smear-positive incidence rate (\(M\)) and the period of infectivity (\(\Delta\)). The risk of contact with an infectious adult is given by the Poisson distribution \((\lambda/\lambda)e^{-\lambda}\), where \(\lambda = MA\) is the expected number of infectious adults in a household with \(A\) adults. Prevalence was defined as \(M/(365\Delta)\).

Modeled inputs. Germ-free ventilation (\(Q\)) was calculated as air changes per hour (ACH) for a standard shack dwelling with a volume of 30 m\(^3\). Three values of ACH were modeled: 2 ACH (poor ventilation), 6 ACH (moderate ventilation), and 12 ACH, which is recommended by the World Health Organization for an airborne precaution room [21]. Shacks with closed windows and doors would have an ACH of ≈2. Shacks with an open window (size, 0.25 m\(^2\)) facing the prevailing wind and an open door on the leeward side would achieve 6 ACH with low prevailing wind speeds of 4–5 km/h and 12 ACH with winds of 8–10 km/h [22].

The rate of production of infectious tuberculosis quanta (\(q\)) was modeled at a value of 1 infectious quantum per hour, which is the mean measured value of smear-positive inpatients in a tuberculosis ward [15]. Sensitivity analyses were performed for values of \(q\) between 0.1 and 10 infectious quanta/h. The mean respiratory rate of preschool children aged 0–5 years was estimated to be 225 L/h, which approximates a respiratory volume of 150–200 mL/kg/min [23].

The period of diagnostic delay during which an adult may be infective has been estimated in a systematic review to be very variable but is frequently reported to be 60–90 days [24]. Since \(\Delta\) may exceed the period of diagnostic delay and is the primary modeled parameter influenced by the functioning of the tuberculosis control program, it was allowed to take values of 30, 60, 90, and 120 days in the model.

For modeling purposes, child time allocation within a 24-h period was 12 h within the home, to allow interaction with resident adults during the evening and night, including 8 h for sleeping and 4 h for other family activities. Similar exposure to nonresident adults can result from adults visiting the primary home or from the child visiting other households. For modeling purposes, 12 h of daytime was allocated to 3 h outdoors, during
which tuberculosis transmission was assumed to be negligible, and 9 h allocated equally between 1–3 additional households with similar numbers of residents as in the primary residence.

RESULTS

Household Survey 2008

The total population of the study community in December 2008 was 14,788, of whom 12,097 were adolescents and adults aged >15 years and 2691 were children aged <15 years, including 1051 children aged <5 years. The total number of households was 6654, of which 1708 contained children aged <15 years and 918 contained children aged <5 years. The age distribution of residents of households with adults only and with both adults and children is shown in Table 1. Crowding in child-containing households was twice as high as that in adult-only households. Of the 918 households with children aged <5 years, 800 contained a single child, 109 contained 2 children, and 9 contained 3 children aged <5 years. The median number of adults in these households was 2.27 per household, and only 28% of these households had ≥3 resident adults (Figure 1).

Tuberculosis Notifications

From 2004 through 2008, 1289 cases of tuberculosis were notified to the national tuberculosis control program, of which 90% occurred in adults and 10% occurred in children aged ≤15 years. Of the childhood tuberculosis cases, 66% occurred in children aged <5 years (Table 2). The population increased from 12,803 in 2004 to 14,788 in 2008, resulting in a total of 67,747 person-years of residence. The population growth was restricted to adults, because the population of children aged <5 years remained relatively constant, with 1057 children in 2004 and 1051 children in 2008. A mean of 1.35% of the adult population were identified as having sputum smear–positive tuberculosis each year (Table 2).

Transmission from Resident Adults

Ventilation. The modeled impact of increasing the shack ventilation on the probability of a child becoming infected with tuberculosis is shown for 4 periods of adult infectivity (Δ = 30, 60, 90, and 120 days) in Figure 2A. The maximal risk of tuberculosis transmission even under poor environmental ventilation and a prolonged period of adult infectiousness reached only 3%. This maximal condition was primarily determined by the mean number of adults resident in the household and their tuberculosis incidence rate. Transmission could be reduced by a combination of high ventilation and a reduction of the infectivity period. For example, a reduction of the risk of transmission to 1.5% would require either 4, 8, or 12 ACH for Δ values (period of infectiousness) of 30, 60, and 90 days, respectively. Sensitivity analyses with low values of infectious quanta (q = 0.1) were unable to reach significant transmission probabilities, and high values of infectious quanta (q = 10) reached probabilities >2.75% at all achievable values of Δ and ACH.

Infective period. The modeled impact of increasing periods of adult infectiousness (Δ) on the probability of a child aged <5 years becoming tuberculosis infected is shown for 3 levels of ventilation (2, 6, and 12 ACH) in Figure 2B. The benefits of increased ventilation are greatest when Δ is low. Increasing ventilation from 2 to 6 ACH reduces transmission to 2.5% (−16%), to 2.2% (−25%), 1.8% (−36%), and 1.1% (−51%) for Δ values of 120, 90, 60, and 30 days, respectively. Identical reductions in transmission could be alternatively obtained by reducing the child exposure time by 8 h per day. A reduction in exposure time could be achieved by separation of child sleeping areas from those of adults for an 8-h sleeping period. When the modeled infective number of infectious quanta were low (q = 0.1), the transmission probabilities of transmission did not reach 1%, and when the number of quanta were high (q = 10), the tuberculosis transmission probabilities rapidly became maximal at 3% with minimal sensitivity to either increased ventilation or shortened period of infectivity. The modeled proportions of annual risk of tuberculosis infection due to transmission from resident adults were 70% and 74% for periods of infectivity of 60 and 90 days, respectively. Therefore, we went on to explore additional transmission (26%–30%) that might occur as a result of contact with other potentially infective adults in addition to those residents in the home.

Transmission from Nonresident Adults

The probability of tuberculosis infection as a result of spending 75% of daytime indoors and visiting 1–3 households other than the child's home is shown for visited households with poor ventilation (2 ACH) in Figure 3A. Increasing the number of visited households increased the exposure to an additional 2.2 potentially infective adults per household, which resulted in greatly increased probabilities of infection when Δ exceeded 30 days. When multiple poorly ventilated households were visited, annual risks of tuberculosis infection exceeding 4%, 5.5%, and 6% could be achieved when Δ was 60, 90, and 120 days, respectively. Sensitivity analyses of low infectious quanta (q = 0.1) resulted in transmission risks <1%, and high infectious quanta (q = 10) resulted in rates of transmission that were directly related to the number of households visited for all modeled values of Δ.

In contrast, the corresponding risks of infection when visiting households with 6 ACH showed minimal increase in transmission risk with increasing number of households visited. Under these moderate ventilation conditions, Δ became the major...
Figure 2. A, Effect of ventilation (air changes per hour [ACH]) and mean period of infectivity (delta) on the mean annual risk of tuberculosis infection resulting from a child sleeping in a shack shared with adults. Values are plotted for mean periods of adult infectivity of 30, 60, 90, and 120 days. B, Effect of period of infectivity (delta) and ventilation (ACH) on the mean annual risk of tuberculosis infection resulting from a child sleeping in a shack shared with adults. Values are plotted for 2, 6, and 12 ACH. Note that the period of infectivity (delta) is the mean time from onset of infective tuberculosis until initiation of effective antituberculosis chemotherapy. Modeled estimations are based on a potential nighttime exposure of 12 h, a median of 2.2 adult residents per shack, a 1.35% annual risk for smear-positive tuberculosis, and a mean production of 1 infectious airborne quantum of tuberculosis per hour during untreated smear-positive disease.

determinant of tuberculosis transmission risk. Sensitivity analyses of low infectious quanta (q = 0.1) resulted in transmission risks of <0.4%, and high infectious quanta (q = 10) resulted in rates of transmission of 6%–9% that were directly related to number of households visited for all values of D.

DISCUSSION

These modeling analyses demonstrate that the high reported rates of community tuberculosis transmission to children in southern Africa [9–13] can be explained by the interplay between the prevalence of adult infectious tuberculosis, social mixing between adults and children, and the prevailing domestic ventilation characteristics.

The model in this study was based on the Wells-Riley equation, which has been used to examine airborne tuberculosis disease transmission since the 1970s [14] in a wide variety of medical and nonmedical settings and thus has been useful for examining the relative importance of transmission factors in
Figure 3. Mean annual risk of tuberculosis infection for a child visiting 1–3 households other than his or her own residential household during the day with ventilation of 2 air changes per hour (A) and 6 air changes per hour (B). Values are plotted for mean periods of adult tuberculosis infectivity (delta) of 30, 60, 90, and 120 days. Note that the period of infectivity (delta) is the time from onset of infective tuberculosis until initiation of effective antituberculosis chemotherapy. Modeled estimations are for a preschool child spending 75% of daytime indoors, a median of 2.2 resident adults per visited shack, a 1.35% annual risk for smear-positive tuberculosis, and a mean production of 1 infectious airborne quantum of tuberculosis per hour during untreated smear-positive disease.

Of particular interest, our model indicated that the potential of the existing clinic-based tuberculosis control program to reduce transmission to children is somewhat limited. Even reductions in Delta (the period of infectiousness) to 30 days by active case finding and rapid tuberculosis diagnosis would have significant impact on transmission to children only when ventilation rates in households exceed 6 ACH. However, such high ventilation rates for informal dwellings during the cold Cape Town winters might be difficult to achieve throughout the year.
Since similar reductions in tuberculosis transmission could be achieved by separating child and adult sleeping areas, this might be a more practicable stratagem.

Another major finding of our study was that a maximum of 75% of the total annual risk of infection could possibly be explained by the interaction between a child and the limited number of adults resident in a primary household. Preschool children are susceptible to tuberculosis infection predominantly because of exposure to infectious adults [6, 7]; therefore, the main determinant of maximal transmission risk in either setting was the number of adults to whom a child was exposed.

Our model also indicated that at least 25% of the risk of infection resulted from exposure to nonresident adults. In well-ventilated settings, transmission was related to $\Delta$, rather than to the number of households visited. In contrast to transmission risks from adult household residents, transmission from nonresident adults can be markedly influenced by the tuberculosis control program’s ability to decrease $\Delta$ by active case finding. In poorly ventilated nonresidence settings, transmission risks increased markedly with increasing numbers of households visited. These analyses indicate that as children become more socially mobile, the potential for transmission in poorly ventilated nonhousehold settings might become the largest contributor to total transmission risk. Indeed, we have reported increasing tuberculosis infection rates throughout childhood in this community, which peak at ~8% at age 15 years [11].

The strength of this study was the availability of accurate information specific to this community, including the annual risk of tuberculosis infection, the number of adults and children per household, and smear-positive tuberculosis notification rates. A caveat is that some important parameters, such as $\Delta$ and the numbers of infective quanta produced by adults with tuberculosis disease, are difficult to measure directly, and estimates were derived from published data. Indeed, $\Delta$ may not be identical to the period of diagnostic delay in published studies, and the incidence of smear-positive tuberculosis may only approximate the smear-positive notification rate. The model used the epidemiologic assumption that the tuberculosis epidemic was generalized, with equal mixing of infectivity and contact risks. However, stochastic transmission events, such as close nonhousehold contact with highly infectious individuals, are not captured in this model. Despite these limitations, the outputs from the model were robust and were compatible with the previously observed annual risk of tuberculosis infection in this and similar communities [9–11].

Our findings may give insight to why tuberculosis rates of transmission in South Africa have remained very high despite apparent improvement in case management by the tuberculosis control program [1]. The conditions within crowded African townships with high unemployment rates may have much in common with the conditions present during the industrial revolution of the 18th and 19th centuries, when tuberculosis burdens were also extremely high. Children lived and worked side-by-side with adults [25], but successive factory acts in the United Kingdom and the United States reduced the childhood exposure to adults in the workplace [26, 27]. Improvement in housing and schooling also reduced the amount of close exposures between children and adults. The creche movement further limited the frequency of contacts between young children and potentially infectious adults [28] and may have the potential to decrease nonhousehold transmission in crowded townships. Reduction in household tuberculosis transmission in poor informal housing will be difficult to achieve. However, improvement of housing stock should particularly focus on improved ventilation and separation of child from adult sleeping areas.

These modeled analyses have identified social and environmental factors that contribute to high rates of tuberculosis transmission in this community. Social mixing patterns of preschool children result in tuberculosis transmission within the extended family, rather than the nuclear family. Where tuberculosis is highly endemic, interruption of community tuberculosis transmission requires prompt treatment of source cases. Tuberculosis control will therefore necessitate an increased focus on active case finding and a reduction in diagnostic delays.

Acknowledgments

Financial support. National Institutes of Health (CIPRA grant 1U19AI53217–01 and RO1 grant A1058736–01A1 to R.W. and L.-G.B.); Wellcome Trust, London, United Kingdom (to S.D.L.).

Potential conflicts of interest. All authors: no conflicts.

References