Calculating the Risk of Infection of *Mycobacterium tuberculosis* in Endemic Settings

by
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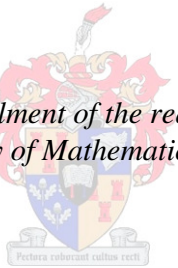

Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in the Faculty of Mathematics at Stellenbosch University

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Declaration

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Abstract

The annual risk of infection (ARI), a measure of recent transmission, has been described as the most important parameter in tuberculosis (TB) epidemics. Nevertheless, mounting evidence suggests all factors contributing to TB transmission are not yet completely understood. This research was performed to investigate the role various parameters, e.g. overcrowding, period of infectivity, ventilation, and infectivity of source cases, play in TB transmission. An established airborne transmission risk model, the Wells-Riley equation (WRE), was modified to account for scenarios where unknown numbers of infectious individuals may be present. Subsequently, the ARI for three indoor locations conducive to TB transmission were calculated. Two locations (households and minibus taxis) were identified in a social mixing survey conducted within a South African community where TB is endemic as a part of this research. The third location (prison) was identified in an earlier independent study in the same community. The impact various interventions could have in reducing the ARI associated with each location was explored. Poor ventilation, severe overcrowding, extended exposure periods, and high incidence rates contributed to high TB transmission risks in each location. The household-associated ARI was related to the number of resident adults. Current TB control programs will only reduce the ARI if household ventilation levels are improved simultaneously. Similar reductions in the ARI could be achieved by trebling current ventilation levels or by separating child and adult sleeping areas. Neighbouring households can also contribute substantially to the ARI. The minibus taxi-associated ARI for drivers and commuters was considerable but readily reduced by opening windows or keeping the fresh-air fan on. Reducing TB case prevalence through active or passive case-finding would reduce the ARI substantially. The prison-associated ARI was proportional to levels of overcrowding. No single intervention, such as improved ventilation, decreased lock-up time, or improved case-finding, would decrease the ARI substantially, but concurrent implementation of all of them to meet national or international standards would. This research shows TB is not only transmitted in epidemics by highly infectious TB cases, but that any TB case, no matter how infectious, has the potential to infect susceptible people under the right conditions.

Opsomming

Die jaarlikse infeksierisiko (ARI) – ’n maatstaf van onlangse siekteoordrag – word as die belangrikste parameter in tuberkulose- (TB-)epidemies bestempel. Nietemin dui toenemende bewyse daarop dat nie álle faktore wat tot TB-oordrag bydra, volledig verstaan word nie. Hierdie navorsing is onderneem om ondersoek in te stel na die rol van verskillende parameters – byvoorbeeld oorbevolking, tydperk van aansteeklikheid, ventilasie en die aansteeklikheid van brongevalle – in TB-verspreiding. ’n Gevestigde model vir die raming van siekteverspreiding deur die lug, die Wells-Riley-vergelyking (WRE), is aangepas vir scenario’s waar ’n onbekende aantal aansteeklike individue moontlik aanwesig is. Daarna is die ARI bereken vir drie ingeslote ruimtes wat TB-oordrag bevorder. Twee van die ruimtes (huishoudings en minibustaxi’s) is ten tyde van die navorsing uitgewys in ’n sosialevermengingsopname in ’n Suid-Afrikaanse gemeenskap waar TB endemies is. Die derde ruimte (gevangenisse) is uitgewys in ’n vroeëre onafhanklike studie in dieselfde gemeenskap. Die navorser het gevolglik bepaal watter moontlike impak verskillende intervensies op die verlaging van die ARI in elke ruimte het. Swak ventilasie, ernstige oorbevolking, verlengde blootstellingstydperke en hoë voorkomsyfers het in elke ruimte tot ’n hoë TB-oordragrisiko bygedra. Die huishoudingsverwante ARI het verband gehou met die aantal volwassenes wat in die huis woon. Huidige TB-beheerprogramme sal slegs die ARI kan verlaag indien huishoudelike ventilasievlakke terselfdertyd verbeter word. Drie keer beter ventilasievlakke of die skeiding van kinders en volwassenes se slaapareas kan soortgelyke verlagings in die ARI teweegbring. Buurhuishoudings kan ook aansienlik tot die ARI bydra. Die minibustaxi-verwante ARI vir bestuurders en pendelaars was beduidend, maar kan betreklik maklik verlaag word deur vensters oop te maak of die varslugwaaier aan te hou. Die vermindering van die voorkoms van TB-gevalle deur aktiewe óf passiewe gevalle-opsporing kan die ARI ook beduidend verlaag. Die gevangenisverwante ARI het met vlakke van oorbevolking verband gehou. Geen enkele intervensie soos beter ventilasie, korter toesluittye of beter gevalle-opsporing sal die ARI aansienlik verlaag nie, maar die gelyktydige inwerkingstelling van ál hierdie intervensies in pas met nasionale of internasionale standaarde kan wél. Hierdie navorsing toon dat TB in epidemies nie net deur hoogs aansteeklike TB-gevalle oorgedra word nie, maar dat enige TB-geval, ongeag hoe aansteeklik, die siekte in die regte omstandighede na vatbare mense kan oordra.

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Last, and certainly not least, I would like to thank my wife Heather Johnstone-Robertson and my family for all their support. You were always patient with me, often placing my needs ahead of your own, so that this thesis could be completed. I love you all and dedicate this work to you.

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Chapter 1: Introduction

1.1 The History of Tuberculosis and Its Treatment

Tuberculosis (TB) is a disease that has plagued humankind for thousands of years, with the first known records of TB including a Neolithic burial ground near Heidelberg (4000 B.C.), Hindu writings from India (2000 B.C), and a mummified Egyptian priest (1000 B.C.)[1]. The excavation of many other bodies with tuberculous-like lesions from the same region as the Egyptian priest has been proposed as reason to believe that a large TB sanatorium was situated in the area. Furthermore, a classical description of a TB case, which included symptoms such as hoarseness of voice, a bent, tender and extended neck, slim fingers with swollen joints, brilliant and glassy eyes, and most notably a body that appeared to have been consumed, with muscles wasting away and bones protruding extensively, was recorded as long ago as 200 B.C. by the Greek monk Aretæus[1].

Over the years, TB has not been limited to any particular class of society, but has affected both rich and poor, famous and not-so-famous, alike. Examples of well-known and influential people who were affected by TB include the poets, authors and musicians of John Keats, Percy Shelley, Henry David Thoreau, Robert Louis Stevenson, Ralph Waldo Emerson, Emily and Charlotte Brontë, Frédéric Chopin, and Nicolò Paganini. Royalty was not exempt from TB with several members of the Bourbon family in France also having fallen prey to the disease[1]. One of the most prominent men, in a southern African context, to be plagued with TB was that of pioneer and colonialist Cecil John Rhodes who owned many of the diamond mines in South Africa through his company De Beers, and after whom present-day Zimbabwe and Zambia were previously named Southern and Northern Rhodesia respectively. The fact that TB was also widespread amongst the common layman throughout history is clear from the proportion of deaths in England and Wales attributed to TB in 1650 and 1715, i.e. 20% and 13% respectively[1]. Also, Dubos et al argued that writers and artists in the late 19th century started associating TB with the "the miserable humanity living in the dreary tenements born of the Industrial Revolution[1]." In fact, so widespread was TB throughout Europe and America between 1700 and 1850 that it became known as 'the Great White Plague.' In more recent times it has been shown that overcrowding, shelters for the homeless, and poor living conditions continue to be associated with TB disease, and therefore TB remains common amongst the general population[2-6].

The uncertainty surrounding the exact cause of diseases in general has played a large part in governing how TB has been understood and treated over time. During the Middle Ages (5th – 15th century), diseases were largely regarded as either contagious or infectious, with contagion caused by the spread of disease between people and infection by the breathing in of noxious vapours

(miasmas)[7]. At different times, however, evidence supporting the classification of TB as either contagious or as infectious presented itself so that its cause remained a mystery. The many ways in which TB presented itself symptomatically, reflected by the multiple names assigned to the disease (lunger, poitrinaire, scrofulous, strumous glands, consumption, phthisis, asthenia, tabes, hectic fever, gastric fever, lupus, and inflammation of the lungs), would also have added to the difficulty in identifying its exact cause[1]. Furthermore, the manner in which TB was previously treated confirms the poor understanding of the cause of TB, with travel to warmer climates (especially by sea voyage), the bleeding of patients, and the use of opium all having previously been recommended[1].

It was only with the demonstration of the cellular structure of living organisms in 1861, the formation of the germ theory of disease circa 1880, and the isolation of *Mycobacterium tuberculosis* (MTB) by Robert Koch in 1882 that an accurate fundamental understanding of the cause of TB started to develop from which further investigation and research could be based[7]. For example, Flügge went on to find MTB in human spittle in 1897, and concluded that no extra cause was required to explain TB transmission, so that there was no longer any need for the miasma theory[7-9]. The next major discovery relevant to TB transmission was made by William Wells and Richard Riley, where they convincingly showed that although Flügge was correct in concluding no miasmas (noxious vapours) were required for the spread of TB, it was in fact possible for MTB to be transported on small airborne respiratory droplets, produced by coughing, sneezing, and talking, within indoor environments[7,9-11]. In hindsight, this may explain the earlier confusion with regards to whether TB was contagious or infectious since it is easy to see why TB could have been thought of as being transported on 'noxious vapours.' Last of all, the identification of MTB facilitated the finding of a cure for TB since the microbe responsible for the disease could be studied directly and not just the symptoms it produced. The result of these efforts has been the production of various drug regimens for the treatment of TB over the course of the last 60 years, the first of which was the antibiotic streptomycin, discovered by Selman Waksman and Albert Schatz. Due to the limited efficacy of streptomycin, however, owing to the development of drug resistance (which was recognized as early as 1948)[12], TB monotherapy has since been replaced by combination chemotherapy[13-19].

With multiple cures for TB now having been found, it may be tempting to believe the eradication of TB is at hand. However, due to the sheer vastness of the global TB burden and other complexities such as HIV co-infection and drug resistance, eradication remains a distant goal. For this reason, we consider the TB pandemic as it currently stands around the world and in South Africa, before discussing the main research questions to be addressed in this thesis. In particular, we first focus on

the various measures of disease morbidity, since infectious, diseased individuals are those who drive the transmission rates which subsequently determine the age-specific prevalence of infection within communities from which the next generation of infectious cases arise.

1.2 Tuberculosis in the World and South Africa Today

The World Health Organization (WHO) estimated that in 2009 there were a total of 14 million prevalent cases of TB, 9.4 million incident cases, and 1.7 million TB-associated deaths (amongst HIV-positives and negatives) across the globe[20,21]. WHO defined regions containing the greatest proportion of prevalent cases were the South-East Asia, Africa, and Western Pacific regions with 35%, 28%, and 21% attributed to each respectively[20]. It was also estimated that 12% of incident cases occurred in those who were HIV-positive, of which 92% were in Africa and 26% in South Africa[20,22]. A total of 30 000 cases of multidrug-resistant (MDR) tuberculosis were notified in 2009, but WHO estimated an additional 220 000 cases in the same year that were not reported[20]. It was not all bad news, however, as there have been a couple of positive developments in the first nine years since 2000. The first of these was the observed increase from 45% to 62% in the case detection (notification) rate of incident cases (CDR) and the second was the increase from 69% to 85% in the successful treatment of smear-positive pulmonary TB of which there were 2.6 million notified cases in 2008[20,21]. These improvements can largely be attributed to the extensive promotion of the directly observed treatment short-course (DOTS) strategy. Regrettably, despite the resultant decreasing incidence of TB cases, the overall burden of TB continues to increase due to the population growth seen in many of the most heavily affected nations[20,21]. There is therefore still a long way to go before global eradication of TB is achieved.

In South Africa, a little over 360 000 TB cases were notified in 2009, whilst WHO estimated there to be between 390 000 – 400 000 actual prevalent cases (780 – 800 per 100 000 population)[20,21,23]. The estimated number of incident cases and TB-associated (HIV-negative) deaths in that same year was 490 000 (980 per 100 000 population) and 23 000 – 26 000 (46 – 52 per 100 000 population) respectively[20,23]. These statistics place South Africa as the country with the 10th highest number of prevalent TB cases and the 3rd highest number of incident cases globally, with per capita rates that are unparalleled elsewhere in the world[20,22]. To further compound the situation, 60% of incident cases within the country are HIV-associated, as compared to 37% for the whole of Africa[20]. Despite these considerable challenges though, progress comparable to that which is being made worldwide is being achieved at the same time, with a 15% increase in the CDR to 74% over the nine years leading to 2009[21,23]. Also, the successful treatment of smear-positive pulmonary TB cases has

increased by 13% to 76% in 2008[21,23]. Nevertheless, it is clear that the burden of disease remains substantial and further progress is required for inroads to be made into the TB epidemic.

1.3 An Incomplete Understanding of Tuberculosis Transmission

A key point to be noted from Section 1.2 is that even though the CDR and the proportion of successfully treated smear-positive pulmonary TB cases have improved, a substantial amount of transmission must still be taking place in order for the number of global prevalent TB cases to increase at the same time that incidence is falling. This is supported by the fact that WHO estimates as much as a third of the world's population to be latently infected with TB by 2010[3,24], and suggests that we have not fully understood how to prevent transmission or what all the factors are that contribute towards it.

In South Africa, four recent studies have demonstrated high levels of ongoing TB transmission by illustrating the high prevalence of infection amongst children, adolescents and young adults[22,25-28]. Specifically, the prevalence of infection was found to be as high as 26.2% at school entry, 52% for those 15 years of age, and 75% in 25 year olds, so that the corresponding force of infection (FOI: the proportion of TB-uninfected individuals infected in a single year) was consistently between 3% and 5%[22,25-28]. These rates of transmission are unprecedented in modern times, with similar rates only seen 50 years ago in other comparable African countries such as Botswana and Lesotho prior to the widespread introduction of chemotherapy[22,29-32]. The current FOI in South Africa confirms that TB transmission is a component of the epidemic that has been severely neglected and in general is poorly understood.

A third indicator that we have an incomplete understanding of TB transmission is that the annual risk of infection (ARI) in England and Wales was already declining at over 4% per annum in the 50 years prior to the introduction of chemotherapy[30,32]. In fact, Vynnycky et al concluded that chemotherapy only served to speed up the decline in the ARI that was already taking place[30]. This suggests that other factors associated with TB transmission, such as overcrowding and poor living conditions[2,3,5,6], were being addressed in society at that time, and most importantly it was producing a decrease in the ARI. The importance of these factors to TB transmission, however, has largely been ignored since the start of the widespread rollout of chemotherapy, and it is appropriate now to reconsider the role these factors play in transmission considering that our current efforts are having little impact.

A final reason for the generally poor understanding of TB transmission is that the predominant means by which it takes place, i.e. on respiratory droplet nuclei (which will be discussed

comprehensively in Chapter 2), is not widely known. A consequence of this is that chemotherapy is often viewed and practiced as the only viable means of transmission prevention when in fact environmental interventions specific to the actual mode of transmission are also plausible and readily implementable.

The irony with regards to the current generally poor understanding of TB transmission as described above, together with the lack of investigation into the factors that determine whether it will take place or not, is that Vynnycky et al concluded that the FOI is the most important parameter in a TB epidemic[30,32,33]. This is because the FOI determines the age at primary infection (and consequently the life-time risk of developing disease), in addition to the risk of reinfection within a community. Thus, the general TB morbidity within a population is determined by the FOI and its decrease should remain a key priority of any future interventions.

1.4 Thesis Outline

The research reported here was performed in response to the need that the understanding of TB transmission be improved. More specifically, the goal of this study was to shed some light on the role that various parameters (such as overcrowding, average period of infectivity of a TB case, ventilation rates, and the like) play in determining whether TB transmission will occur. To accomplish this, an established airborne transmission risk model, namely the Wells-Riley equation (WRE), was modified to take into account scenarios where an unknown number of infectious individuals may be present, after which it was used to calculate the mean ARI for three locations potentially conducive to TB transmission in a South African community where TB is endemic. Two of these locations, namely households and minibus taxis, were identified in a social mixing survey conducted within the community as a part of this research. The third location, namely prison, was identified in an earlier independent study conducted in the same community. Last of all, exploration of the possible impact various interventions could have in reducing the ARI associated with each of these locations was performed by sensitivity analysis of the relevant model parameters.

For ease of reading, the reader should note that the second chapter of this thesis will be dedicated to a review of the development of the WRE, starting with the fundamental experiments performed by Wells and Riley to establish that TB is an airborne spread disease. The third chapter will subsequently focus on the derivation of the modified WRE mentioned previously. Following this, the social mixing survey, conducted to identify locations potentially conducive to TB transmission, will be outlined in Chapter 4. Chapter 5 will see application of theory to the 3 locations identified as potential TB transmission ‘hotspots’ within the community, and in Chapter 6 the findings and general conclusions one can draw from this research will be discussed.

Chapter 2: The Wells-Riley Equation

2.1 Tuberculosis and Droplet Nuclei: An Airborne Spread Disease

As mentioned in Section 1.1, sound research into TB transmission was only possible after the isolation of MTB by Robert Koch in 1882. Initially after the discovery it was thought that TB was spread by the breathing in of dust particles contaminated with dried MTB-laden sputum[9]. Flügge et al, however, found MTB in human spittle in 1897 and concluded instead that TB was spread by respiratory droplets (e.g. spittle) produced during processes such as coughing, sneezing and talking[7-9]. Droplets such as these would essentially limit transmission to the close proximity of an infectious TB case, so that transmission would not occur over distances much more than a metre or two[7,9]. Flügge's research would remain the most influential result with regards to TB transmission for the next 50 – 60 years.

The next major breakthrough in TB transmission would take place over the course of 30 years, and began in 1931 when Wells studied the seemingly unrelated process of humidification by the atomization of water[7,34,35]. The first two important findings of this work included that atomization produced droplets with a minimum diameter of 10µm and secondly that the smallest of these droplets (with large surface area-to-volume ratio) evaporated almost instantaneously whilst falling through the air to become droplet nuclei with diameters <5µm[7]. In addition, Wells found that the air resistance resulting from droplet nuclei falling through the air (and which was proportional to their surface area) would be comparable to their weight so that the droplet nuclei would remain buoyant in the air for much longer than larger respiratory droplets (>10µm)[7]. Consequently Wells recognized that droplet nuclei would disperse throughout enclosed atmospheres, extending the infectious range from a metre in front of the infectious case to the entire indoor space shared with them[9]. It also explained why Flügge had not observed the droplet nuclei during his research, since he used plates to capture the droplets emitted by an infectious individual, whereas droplet nuclei would have evaporated before landing on them[7].

Thus, when Wells was asked in 1934 to investigate the source of respiratory infections amongst textile mill workers, he was already well aware of the two potential means by which transmission may have been taking place, i.e. either by large respiratory droplets (spittle) or those droplet nuclei buoyant enough to remain airborne for extended periods of time[34,36,37]. It was this knowledge that allowed Wells to hypothesize that the bacteria causing the respiratory infections in the textile mill workers (not MTB) were the same as those found in the standing water used to humidify the atmosphere inside the mills to keep dust levels down[34,36,37]. Wells went on to confirm this by finding the bacteria in air samples he took from the mills using an air centrifuge, which in turn

showed that the bacteria were being transported on droplet nuclei produced during the humidification process until they were either breathed by the mill workers or vented out of the mills[36,37].

The textile mill findings led Wells to speculate that droplet nuclei, capable of transmitting infection (and MTB in particular), could be produced in a person's respiratory tract through processes such as talking, coughing, singing, and sneezing[7,34,37]. He first set out to confirm this by taking high speed photographs of people coughing and sneezing. The images showed the generation of droplets with diameters just slightly larger than 10µm but still small enough to evaporate and become droplet nuclei before falling to the ground[7]. At this point, however, it remained to be shown that MTB could be transmitted on droplet nuclei. This was demonstrated when Wells and Riley performed animal exposure experiments that involved the atomization of TB-containing broth culture filtrates into the air that susceptible rabbits and guinea pigs were breathing[7,10,34]. In one such experiment, twelve rabbits were exposed to the atomized culture filtrate whilst ultraviolet (UV) lights were turned on in the room. After 2 hours, 6 of the animals were removed, the UV lights switched off, and the remaining animals exposed to the atomized culture filtrate for another 3 hours. After the animals were sacrificed several weeks later, each animal in the group exposed for 5 hours had macroscopic tubercles on the surface of their lungs, which when examined contained acid-fast organisms, indicating infection with MTB. All of the animals from the group exposed for only 2 hours, on the other hand, did not present tubercles on their lungs. Wells and Riley drew two conclusions from these results, namely that MTB could be transmitted on droplet nuclei, and secondly that irradiating the room with UV light was an effective means of air sanitation[10].

The final proof that MTB-laden droplet nuclei could be produced by infectious TB cases came by way of a two-year study conducted in a 6-bed hospital TB ward by Riley et al[11,38]. In preparation for the study, the ward rooms were modified so that the air from each was vented to an animal exposure chamber housing susceptible guinea pigs on the hospital floor above (Figure 1). The guinea pigs were isolated from all possible sources of tuberculosis, and in particular from direct contact with the TB patients in the ward, so that the only means by which they could become infected was through the inhalation of buoyant infectious droplet nuclei carried on the air exhausted from the TB ward rooms below. Consequently, when 71 guinea pigs were infected during the study it provided concrete evidence that droplet nuclei, capable of transmitting MTB, could be produced in the respiratory tract of infectious TB cases[11]. As confirmation, the drug susceptibility profiles of organisms in the sputum of patients and organisms cultured from the lung tissue of infected guinea pigs were compared so that the specific patient responsible for a given guinea pig infection could be identified[11,38]. The sources of 42 of the 48 cultured guinea pig infections were determined[38]. To

remove any remaining concerns over the possibility of cross-infection having occurred as a result of the animal handlers, a second 2-year study was conducted after modification of the ventilation system to allow the installation of a second animal exposure chamber[9]. During the study, the animal handlers managed both sets of guinea pigs in the exactly the same manner, with the only difference between the two sets of animals being that one received TB ward exhaust air irradiated with UV light, whilst the other received TB ward exhaust air that was not. By the end of the study, no guinea pigs receiving irradiated air had been infected, whilst 63 guinea pigs receiving unchanged ward air had, thereby eliminating any lingering concerns about cross-contamination[9].

With it having been established that infectious TB cases produce droplet nuclei capable of infecting susceptible *animals*, the question remained as to whether infectious TB cases could infect other *people* in the same way. The answer would come by way of a TB epidemic that broke out aboard a United States Navy vessel, namely the Richard E. Byrd[39]. Here, the initial TB case managed to infect 78.8% of his fellow crew members who shared sleeping quarters with him during the seven months he was onboard. In addition, 54.3% of the crew members in a second sleeping compartment were also infected by the same TB case. The crew members in each of the compartments had little to no interaction with one another whilst working or during social hours, so that the only way in which transmission could have taken place on such a large scale was by infectious droplet nuclei transported through the ventilation system shared by the two compartments. Other suggestive evidence in support of this conclusion was that the relative infection rate of crew members sleeping in the second compartment (54.3%/78.8% = 0.69) was similar to the proportion of air the compartment received from the one in which the initial TB case slept (9 out of 12 vents = 0.75; assuming the volume air flow in each of the twelve inlet vents of the second compartment was the same). Thus human-to-human transmission by droplet nuclei had been demonstrated, the biggest breakthrough in terms of the understanding of TB transmission achieved, and once and for all TB had been irrevocably shown to be an airborne spread disease.

2.2 Deriving the Wells-Riley Equation

Whilst conducting the multiple animal exposure experiments described above, Wells and Riley determined that each infectious droplet nucleus inhaled by an animal would induce a single tubercle on the surface of the animal's lungs[7,9,11,34]. Thus the total number of TB-infected droplet nuclei inhaled by an animal was equal to the number of tubercles that subsequently presented[7,10,34]. From these findings, Wells and Riley calculated the concentration of infectious droplet nuclei in the hospital TB ward to be roughly 1 per 300 - 350 cubic metres of air[9,11,34]. This they noted was approximately the same amount of air breathed in a year by a student nurse working on a TB ward

(during the pre-chemotherapy era) prior to converting tuberculin skin test (TST) positive, and they therefore concluded that the inhalation of just a single infectious droplet nucleus was all that was required for TB infection in humans, just as they had shown for guinea pigs and rabbits[11,34]. Wells and Riley also recognized that because tubercles were an indication of infection with TB[7,9,11], and because there was a one-to-one relationship between the number of droplet nuclei inhaled and the number of tubercles that subsequently developed, if the concentration of infectious droplet nuclei in the air of an enclosed (indoor) space was known then the probability that a susceptible person or animal would become infected could be calculated using the Poisson distribution[7,34]. They derived the risk of infection by defining the parameters below as follows,

I = the number of infectious cases present,

p = the respiration rate of the susceptible people or animals (m^3hr^{-1}),

q = the rate at which infectious cases produce TB-infected droplet nuclei (hr^{-1}),

t = the length of time the susceptibles are exposed to the infectious cases (hr),

Q = the fresh-air ventilation rate in the enclosed environment (m^3hr^{-1}),

so that

Iq/Q = equilibrium concentration of infectious droplet nuclei and

pt = the volume of air breathed by each susceptible during the exposure time.

Under equilibrium conditions, therefore, the expected number of infectious droplet nuclei inhaled by a susceptible is given by $\lambda = Ipqt/Q$[34,40]. Assuming that the infectious droplet nuclei are discrete, randomly distributed, and in very low concentration (all of which were demonstrated in the multiple experiments conducted by Wells and Riley[9-11]) the risk of infection is given by

$$P_{WRE} = 1 - e^{\frac{-Ipqt}{Q}}. \quad (1)$$

If V is defined as the volume of the indoor space (m^3) and F the number of times the volume of air is replaced with fresh air every hour (hr^{-1}), then $Q = V \times F$, and Equation 1 can be rewritten as follows

$$P_{WRE} = 1 - e^{\frac{-Ipqt}{VF}}. \quad (2)$$

Wells went on to recognize that when one TB-infected droplet nucleus on average had been inhaled by rabbits ($\lambda = 1$), the risk of infection was equal to

$$P_{WRE} = 1 - e^{-1} = 0.632, \quad (3)$$

so that only 63.2% of the rabbits would be infected[7,34]. In generalizing the theory, to make it applicable to other diseases where the number of infectious droplet nuclei required for infection was not known, Wells defined a 'quantum' of infection as the number of infectious droplet nuclei required to infect 63.2% of the susceptibles, which could be one or more infectious droplet nuclei depending on the disease[7,34,40]. He therefore redefined q to be the rate at which infectious cases produce quanta (hr^{-1}), which was consistent with its previous definition since a quantum of infection for TB was just a single infectious droplet nuclei. Therefore, to remain consistent with Wells' definition and the terminology used in the papers included in this thesis, a quantum of infection shall be referred to from this point onwards.

2.3 Subsequent Developments of the Model

For the last 30 years, the standard method to determine whether the airborne transmission of an infectious disease will take place in an indoor or enclosed environment has therefore been to make use of the WRE (Equation 2). The equation has several limitations however, the first of which is that it is only applicable in steady state conditions. Other limitations discussed in the literature include that the equation incorrectly assumes all people not yet infected are equally susceptible, that it does not allow its parameters to vary with time, that it does not take into account proximity of a susceptible person to the infectious case(s), and that it ignores immune system response to different pathogen dosage.

Work has already been done to take into account some of these weaknesses though. For example, Gammaitoni and Nucci accounted for situations where the steady state condition does not hold by incorporating the transient effects of ventilation on the concentration of pathogens in an ordinary differential equation model[41]. A method to account for diseases with short incubation periods has been discussed by Beggs[3], whilst Noakes demonstrated how the equation could be included in a traditional SEIR model to allow the number of infectious cases to vary with time[42]. Noakes has also presented a stochastic model based on the WRE, for those scenarios, such as hospitals, where the number of susceptibles is low and the stochastic variability in risk should be taken into account[43]. This stochastic model was linked together with a zonal model to investigate the dependence of the risk of infection with proximity to an infectious case at the same time. Zonal models have also been used to assess how the risk of infection in different airplane compartments depends on where the

infectious case sits during extended national and international flights[44]. Computational fluid dynamic models have also been applied to better understand the effect of proximity on infection risk as well[45]. Efforts to incorporate immune system dose-response and pathogen-host biological interaction have been reported[43,46,47]; however this is not applicable to TB, since it is generally agreed that a single inhaled infectious bacterium renders a susceptible person infected[43], as was established in Sections 2.1 and 2.2. In addition to the above model developments, the difficulty in measuring ventilation rates, especially when multiple connected spaces are considered, has resulted in other methods to determine the concentration of infectious airborne particles to be explored. One such method has been to measure the concentration of carbon dioxide inside a building to determine the proportion of air that has been re-breathed, which then allows the volume of fresh air flowing into the building to be calculated[48].

Despite these model developments, there remain several gaps in the applicability of the WRE to situations where the number of infectious cases may not be known. The modification of the WRE required to take these situations into account is discussed next in Chapter 3, after those scenarios to which the WRE has already been applied have been reviewed.

Chapter 3: A Generalized Epidemic (Endemic Tuberculosis)

3.1 Retrospective Applications of the Wells-Riley Equation

Since the WRE was first derived, it has been applied to several epidemics, the first of which was a measles outbreak in a suburban elementary school near Rochester, New York, USA in 1974[40]. This particular epidemic attracted a lot of attention because of the fact that it took place in a school where 97% of its attendees had already been vaccinated for measles. The initial case was a girl in second grade who managed to infect at least 28 of her fellow scholars, who were either in the same class as herself or in other classes sharing the same ventilation system, within 3 days. The outbreak lent itself to mathematical analysis because the daily movement of children between classes at school, and on buses to and from school, was documented, and the exposure time for each susceptible child could therefore be determined. Also, the ventilation rates in each classroom of the school could be approximated since the percentage of fresh and recycled air could be estimated relatively easily. Using the WRE, the infectiousness of the initial and second generation cases was estimated, with the initial case calculated to have emitted 5,580 quanta per hour (qph) and those in the second generation an average of 480 qph.

The second application of the WRE involved a TB epidemic in 1981 that resulted after a bronchoscopy and intubation procedure was performed on a 64 year old, smear-negative, culture-positive gentleman resident at a university hospital in San Diego, California, USA[49]. The epidemic was recognized after one of the patient's physicians converted TST positive and started to show symptoms of TB including malaise, increased fatigue, and a slight persistent cough a couple of months later. After comprehensive contact tracing, it was determined that during the bronchoscopy and intubation procedure, 10 of the 13 susceptible doctors, nurses, nurse aids, and respiratory specialists had converted TST positive. The time it took for the bronchoscopy and intubation procedure to be performed was known, as well as the amount of fresh-air ventilation flowing into the intensive care unit (ICU), which allowed the rate at which infectious quanta were produced by the TB case to be calculated. An estimated 249 quanta per hour were produced by the patient. In addition the concentration of infectious droplet nuclei in the air of the ICU was estimated at 1 quantum in every 1.95 cubic metres.

The WRE was next used to determine the impact improved ventilation would have had in reducing the risk of infection during a TB epidemic that took place in an office block in 1985[50]. The index case was a 30 year old woman with smear positive TB, who had been symptomatic from the time she returned to work after a holiday until she went to seek medical attention 4 weeks later. After diagnosis, contact tracing was performed amongst her work colleagues to determine who the index

case may have infected during the 4 week period – 27 (40%) of 67 susceptible office colleagues had been infected, 1 of whom subsequently developed active TB. The office block's fresh air ventilation rate was measured only a couple of weeks after the TB epidemic and found to be below the minimum standard recommended by authorities for offices at that time. The authors went on to calculate the infectivity of the initial TB case to be 12.7 qph using the WRE, and after performing sensitivity analysis showed that doubling ventilation would only prevent 12 of the 27 infections. They also noted that because of the logarithmic relationship between ventilation and the risk of infection, ventilation only had a limited efficacy in preventing transmission.

Another application of the WRE was devoted to calculating the infectivity of a TB case travelling aboard an airplane from Chicago to Honolulu in 1994[51]. The number of passengers infected during the 8.5 hour flight was obtained from a previous contact tracing study conducted by Kenyon et al[52], and the ventilation rates in each of the plane's cabins were obtained from a commercial aircraft constructor. The infectivity of the infectious case was calculated to be 108 qph. The risk of infection for susceptible passengers in each cabin was then modelled, together with how that risk depended on the infectivity of the TB case and the amount of ventilation available in each of the cabins. In the cabin in which the index case sat, it was also shown that the risk of infection decreased exponentially with distance from the infectious case.

The WRE has more recently been used by Furuya et al to determine the risk of TB infection for those who spend time in internet cafés in Japan[53]. The proportion of employees and patrons of an internet café who converted TST positive after a TB epidemic broke out in 2004 had previously been reported in a separate contact tracing study. Furuya et al approximated the quanta production rate of the symptomatic index case responsible for the outbreak (who went undetected for 6 months) at 17.58 qph using previously published TB infection risks for a similar untreated TB case[50,51,53]. Using this measure of infectivity, together with transmission parameters describing the conditions typically found in a internet café from that area, the risk of infection was estimated using the WRE and found to be comparable to the TST conversion rates of the employees and patrons.

The common theme in each of the above mentioned applications of the WRE is that the model was always applied *retrospectively* to well-documented epidemics. A question to be asked, though, is whether it is possible to apply the WRE *prospectively* to determine the risk of infection in a community where TB is endemic and where parameter values may not be known or are hard to estimate? More specifically, is it possible to use the WRE to determine the ARI associated with a particular indoor setting (enclosed space) in the community when the number of infectious cases present is not known but the proportion of the community's population who become infectious

during the course of the year is? In Section 3.2 it will be shown that it is in fact possible and the relevant theory will be developed accordingly.

3.2 Prospective Application of the Wells-Riley Equation in a Generalized Epidemic

When using the WRE (Equation 2) to determine the risk of infection in an indoor setting (enclosed space) it is necessary to know the number of infectious individuals (I) present. When the number of infectious cases is not known, though, it needs to be estimated. To do this, it is necessary to first identify who the infectious cases are for the disease being considered, which in the case of TB, is more often than not adults who are smear-positive. Thus a requirement for TB transmission to take place is that at least one adult is present, and that at least one of the adults present is infectious (smear-positive). Now, if it is assumed that there are A adults present in an indoor setting and that every adult is equally likely to be infectious during the period of exposure with probability R, then the probability there will be I infectious adults present is given by the Poisson distribution

$$P(I|A) = \frac{\lambda^I}{I!}e^{-\lambda}, \tag{4}$$

where $\lambda = R$ x A is the expected number of infectious adults present in the indoor setting. The mean ARI (P_{ARI}) can then be determined by summing over all possible values for I as follows,

$$P_{ARI} = \sum_{I=1}^{A} P(I|A)P_{WRE} \tag{5}$$

$$P_{ARI} = \sum_{I=1}^{A} \frac{\lambda^I}{I!}e^{-\lambda}\left(1 - e^{\frac{-Ipqt}{VF}}\right). \tag{6}$$

In the case where the number of adults (A) in an indoor setting is not known or varies between similar indoor settings, the mean ARI can be determined by summing over all possible values for A as well, so that

$$P_{ARI} = \sum_{A=1}^{N}\sum_{I=1}^{A} P(A)P(I|A)P_{WRE} \tag{7}$$

$$P_{ARI} = \sum_{A=1}^{N}\sum_{I=1}^{A} P(A)\frac{\lambda^I}{I!}e^{-\lambda}\left(1 - e^{\frac{-Ipqt}{VF}}\right) \tag{8}$$

where $P(A)$ is the probability that A adults are present, and N is the maximum number adults present in such a setting.

Chapter 4: Social Mixing Survey – Identifying Indoor Locations Conducive to Tuberculosis Transmission

From Equation 8 it is clear that the number of infectious cases (I) and the time of exposure (t) are two key parameters in determining whether TB transmission will take place or not. To identify indoor settings where social contact takes place regularly, and the presence of at least one infectious case is therefore likely, as well as those settings where people spend a large proportion of their time, a social mixing survey was conducted in a township community where TB is endemic on the outskirts of Cape Town, South Africa in 2010. The paper describing this survey in full forms the central component of this chapter (see Addendum for full publication details). Nevertheless, it is still worth mentioning here that survey participants were requested to record all locations visited within a 24 hour period in diary format, together with the demographics of all contacts met and the time spent at each location. A graph (not included in the published paper, but relevant to the current discussion) of the total number of contacts met by participants at various indoor locations (enclosed spaces) versus the total amount of time they spent at each is shown in Figure 2. Four types of enclosed spaces can be seen to meet the criteria that either a large number of social contacts were met there or that a lot of time was spent there, namely households (own and other), crèche/school, work, and transport (predominantly minibus taxis). Figure 2 therefore offers suggestive evidence of locations where transmission is likely to occur. On a precautionary note, though, it is important to emphasize that Figure 2 should not be over-interpreted. Just because there were few social contacts met and a small amount of time spent at health clinics this does not mean that TB transmission will not take place there (since people frequenting a clinic are more likely to be infectious cases than the general public). All that Figure 2 does indicate therefore are those *potential* transmission 'hotspots' where there is a good chance of finding an infectious adult or where the exposure time may be extensive, both of which are required for TB transmission to occur. Of the four locations identified, households and travel by minibus taxi were selected for further analysis with Equation 8, the reasons for which are explained in Chapter 5.

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Social Mixing Patterns Within a South African Township Community: Implications for Respiratory Disease Transmission and Control

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A prospective survey of social mixing patterns relevant to respiratory disease transmission by large droplets (e.g., influenza) or small droplet nuclei (e.g., tuberculosis) was performed in a South African township in 2010. A total of 571 randomly selected participants recorded the numbers, times, and locations of close contacts (physical/nonphysical) and indoor casual contacts met daily. The median number of physical contacts was 12 (interquartile range (IQR), 7–18), the median number of close contacts was 20 (IQR, 13–29), and the total number of indoor contacts was 30 (IQR, 12–54). Physical and close contacts were most frequent and age-associative in youths aged 5–19 years. Numbers of close contacts were 40% higher than in corresponding populations in industrialized countries ($P < 0.001$). This may put township communities at higher risk for epidemics of acute respiratory illnesses. Simulations of an acute influenza epidemic predominantly involved adolescents and young adults, indicating that control strategies should be directed toward these age groups. Of all contacts, 86.2% occurred indoors with potential exposure to respiratory droplet nuclei, of which 27.2%, 20.1%, 20.0%, and 8.0% were in transport, own household, crèche/school, and work locations, respectively. Indoor contact time was long in households and short during transport. High numbers of indoor contacts and intergenerational mixing in households and transport may contribute to exceptionally high rates of tuberculosis transmission reported in the community.

disease transmission, infectious; models, theoretical; particulate matter; respiratory tract infections; social behavior; tuberculosis, pulmonary

Abbreviation: HIV, human immunodeficiency virus.

Respiratory diseases are major causes of morbidity and mortality in Africa (1–3). Africa's population reached 1 billion in 2009, with 40% living in cities (4). While urbanization can be associated with improved human development, social mixing increases the potential for person-to-person disease spread. Urban economies are lagging behind population growth, resulting in large numbers of people living in slum conditions (4). Person-to-person contact within these poor communities, with high rates of human immunodeficiency virus (HIV) disease and low access to basic amenities, further puts these populations at increased risk of epidemic and endemic infectious diseases, including respiratory diseases (1–3, 5, 6). In South Africa, which has high rates of urban migration, residents of townships have one of the highest tuberculosis notification rates in the world, with over 1% of the population developing active tuberculosis annually (7–9).

Transmission of communicable diseases results from exposure of susceptible hosts to infectious organisms under propitious conditions. Infectious respiratory pathogens spread by means of either large respiratory droplets or small droplet nuclei. Viral infections (e.g., influenza) are thought to be spread predominantly by large respiratory droplets which become trapped in the nasal passages of a new host (10–13). A single sneeze can produce 2 million infectious particles, which not only remain airborne but can also contaminate and survive in the environment (11, 14, 15). Hands may become

contaminated, with subsequent transfer of virus to the oral or nasal mucosa of a new host. Although the quantitative contribution of direct physical contact to influenza spread is unknown, hand-washing is widely promoted as a control strategy (16–19).

In contrast, tuberculosis is predominantly transmitted by small infectious droplet nuclei which remain airborne longer than larger particles and are able to be inhaled and reach the lung alveoli (20). One cough and 5 minutes of loud talking produce similar numbers of infectious droplet nuclei, which can remain airborne for up to 30 minutes (21). Transmission therefore results from time-dependent exposure to infected air (22, 23). Ventilation dramatically dilutes the concentration of infectious droplet nuclei, so that transmission occurs predominantly within poorly ventilated indoor settings (22–26).

We explored the role of different person-to-person social interactions in the potential for respiratory disease spread within a crowded South African township. Social mixing patterns were quantified by means of a randomly selected population sample using a diary record of all social contacts made during a 24-hour period. The numbers of physical and nonphysical close contacts recorded by participants were used to model the potential for spread of influenza-like illnesses. We analyzed indoor contacts by location to identify settings conducive to tuberculosis transmission by small infectious droplet nuclei.

MATERIALS AND METHODS

Population size and age distribution

The study population comprised residents of a poor township 40 km south of Cape Town, South Africa, that is highly affected by HIV and endemic tuberculosis (8, 9, 24, 27–29). A 2008 household census conducted by the Desmond Tutu HIV Centre (unpublished data) estimated the resident population at 14,592, with 18.0%, 47.3%, and 34.7% of residents aged <15 years, 15–29 years, and >29 years, respectively (median age, 28 years).

Social mixing survey participant selection

Participants were randomly selected by age group (0–5, 6–11, 12–17, 18–23, 24–29, 30–40, or ≥41 years) from the census data by assigning each resident a randomly generated number in Excel (Microsoft Corporation, Seattle, Washington) and selecting residents in ascending order. The 738 selected township residents were visited at home over a period of 4 months in 2010 and invited to participate by community educators. The dwellings of unavailable residents were revisited on another day at a different time, to ensure maximum opportunity to engage with them. The maximum number of recruitment visits was 4. If a resident had emigrated since the census, a replacement was randomly selected from the same age group. Residents who chose not to participate or could not be contacted were not replaced. The census, conducted 2 years prior to the random selection, could not generate a list of participants under 3 years of age; therefore, the age group 0–5 years was selected from the children of randomly selected women of childbearing age (ages 15–45 years). Participants were given shopping vouchers valued at 75 South African rand as an incentive, and community educators were rewarded by the number of participants they enrolled who completed diaries.

Consent

The study was approved by the Human Research Ethics Committee of the University of Cape Town, and written informed consent was obtained from all participants. Parental/guardian consent was obtained for participants under 18 years of age, and signed assent forms were obtained from adolescents aged 12–17 years.

Diary survey

A paper diary (see Web Appendix 1, which appears on the *Journal*'s Web site (http://aje.oxfordjournals.org/)) in vernacular language was adapted from an earlier European study (30) to allow stratification of contacts by location. Participants completed the diary over a 24-hour period (5 AM–5 AM), after having received face-to-face coaching instruction. For participants under 11 years of age, parents/guardians completed the diary survey together with the child. All participants completed a face-to-face follow-up interview within 48 hours of diary completion to fill in missing data and clarify inconsistencies.

Participants recorded the types and names of locations visited within the assigned period, including whether the location was inside or outside the community and indoors or outdoors, as well as the duration of the visit, the time of day, and the number of social contacts met. Information was recorded for 2 classes of contacts, namely close contacts and casual contacts. Close contacts were defined as those involving physical touch (type I) or those involving a 2-way conversation with 3 or more words in the physical presence of another person without physical touch (type II). Casual contacts (type III) were defined as those occurring in an indoor location but not satisfying the criteria for a close contact. Participants recorded demographic data on close contacts met, whether physical touch was involved, whether it was the first time each close contact had been met within the 24-hour period, and the number of casual contacts present when indoors.

Data analysis

Data were entered into an Access database (Microsoft Corporation) and analyzed using STATISTICA 10.0 (StatSoft, Inc., Tulsa, Oklahoma). The numbers and ages of participants' contacts were nonnormally distributed; therefore, Kruskal-Wallis analysis of variance by ranks, followed by multiple comparisons of mean ranks for all groups, was used for comparison of both median numbers and ages of contacts across baseline characteristics of study participants and day of diary completion. A Mann-Whitney *U* test was performed to compare median numbers of close contacts (types I + II) met per participant in this study and in the European study (30). All statistical tests were 2-sided at $\alpha = 0.05$.

Midpoints between time-category limits were used to calculate the average contact time spent at a location. That is,

"1–2 hours" was taken to be 1.5 hours (the upper limit of the "more than 12 hours" category was 24 hours).

Simulating the initial spread of an influenza epidemic

The age-specific number of new infections was modeled for an influenza strain introduced into a completely susceptible population similar to the study community and spread by either physical touch or large respiratory droplets (i.e., physical or close contacts). Tuberculosis transmission by droplet nuclei (i.e., all indoor contacts) was not modeled, since the ages of casual contacts were not recorded by participants and consequently an age-structured model for this mode of transmission could not be constructed.

The "social contact hypothesis" states that the number of age-specific newly infected cases is proportional to the number of age-specific social contacts, with a proportionality constant, q, indicating the disease-specific infectivity (probability of infection per social contact) (31). This is reasonable because spatial proximity of social contacts acts as a proxy to that required for exposure to infection. Wallinga et al. (31) estimated $q = 0.036$ for an Asian influenza outbreak using age-specific numbers of weekly conversational contacts, and this is therefore applicable to close-contact transmission as defined here (types I + II). Correcting for the fact that weekly, not daily, contacts were used (see Web Appendix 2), we estimated $q = 0.252$. Corresponding values for physical contact (type I) transmission have not been reported. Consequently, we performed sensitivity analysis for physical touch, varying q from 0.252 to 0.756 (relative risk = 1–3), since physical touch is more likely to result in transmission than close contact. Two other assumptions of this model include that individuals are contacted randomly within age groups and that the aging of hosts can be ignored because the duration of influenza virus infection is much shorter than the life span of human hosts.

The age-structured model was constructed by partitioning the population under 45 years of age into nine 5-year age groups, with a tenth group for those aged 45 years or older. The number of newly infected individuals per infectious case was characterized by the "next generation matrix" $\mathbf{N} = (n_{jk}) = (qm_{jk})$, where m_{jk} corresponded to the mean number of individuals from age group j a participant in age group k interacted with (through physical or close contact) in a single day (see Web Table 1). The number of individuals a participant met each day was determined from those diary contacts recorded as having been met for the "first time today." This prevented individuals from being infected multiple times in a single generation of infection, so that the number of newly infected cases was not overestimated.

The number of infections i generations after disease introduction, $\mathbf{x}_i$, was iteratively calculated from $\mathbf{x}_i = \mathbf{N}\mathbf{x}_{i-1} = \mathbf{N}^i\mathbf{x}_0$, where $\mathbf{x}_0$ is the 0th generation of infectious cases. The initial infectious case was assumed to be a person 25–29 years of age, such that $\mathbf{x}_0 = [0,0,0,0,0,1,0,0,0,0]^T$, since people in this age group made use of transport (predominantly minibus taxis) most frequently and were therefore most likely to bring infection into the community.

Matrix theory governs that for large values of i (in practice, from the fifth generation onwards), the age distribution of newly infected cases is independent of the initial case and proportional to the leading eigenvector of $\mathbf{N}$. Furthermore, the leading eigenvalue is equivalent to the basic reproductive number, R_0, which describes the average number of secondary cases produced by an infectious case when introduced into a completely susceptible population. Consequently, we determined the characteristic age distribution of newly infected cases in the fifth generation of infection, along with the basic reproductive number, for influenza transmitted by physical and close contact.

RESULTS

Sampled population characteristics

Of 738 randomly selected residents, 86 were replaced (census address no longer existed, resident corresponding to census demographics was not known at address, resident had moved out of community since census, or woman had no child under 5 years of age) and 39 were not replaced (chose not to participate or could not be contacted or replaced within the study period). Of the 699 residents who consented to participate, the diaries of 106 were excluded from analysis because of concerns that 1 educator had completed the diaries instead of the participants. Of the 593 remaining participants, 10 subsequently withdrew, 4 were lost to follow-up, and 8 did not return completed diaries.

Baseline characteristics of the 571 study participants who completed diaries, along with the day of diary completion, are shown in Table 1. Of these participants, 34.0%, 38.0%, and 28.0% were aged <15 years, 15–29 years, and >29 years, respectively.

Number of reported contacts

The number and duration of 571 participants' contacts were categorized into close (types I + II) or casual (type III), within or outside of the study community, and indoors or outdoors (Figure 1). Participants reported 29,125 contacts, of which 12,946 (44.4%) were close and 16,179 (55.6%) were casual. Of close contacts, 10,633 (82.1%) occurred within the community and 7,903 (61.0%) involved physical touch (type I). A total of 6,455 (81.7%) physical contacts took place within the community. Casual contacts (type III) accounted for 16,179 (64.5%) of all indoor contacts, with 7,465 (46.1%) occurring within the community.

Close and physical contacts

The median number of close contacts (types I + II) per participant was associated with participant age, gender, employment status, and level of schooling, but not day of diary completion (Table 1). Participants aged 10–14 years were the most socially active, recording 27 close contacts and 14 physical (type I) contacts per day. Mean numbers of close (types I + II) and physical (type I) contacts per participant by 5-year age stratum (Web Figure 1) demonstrated strong age-associative behavior (meeting people of similar age as oneself) among adolescent and young adult participants. Participants aged 5–9, 10–14, and 15–19 years recorded the highest proportions of age-associative close

Table 1. Median Number of Close Contacts per Participant, Median Age of Close Contacts, and Median Number of Indoor Contacts per Participant, According to Baseline Demographic Data on 571 Randomly Selected Residents of a South African Township Community, 2010

Category	Total No. in Sample	Close Contacts					Median No. (IQR) of Indoor Contacts			
		Total No. of Individuals Contacted[a]	Median No. (IQR) of Close Contacts			Median Age (IQR) of All Close Contacts, years				
			Type I (Physical)	Type II (Nonphysical)	Types I + II (All)		Type I (Physical)	Type II (Nonphysical)	Type III (Casual)	Types I + II + III (All)
Total sample	571	9,049	12 (7–18)	9 (5–15)	20 (13–29)	21 (13–30)	8 (5–13)	6 (3–11)	14 (0–32)	30 (12–54)
Age group, years										
0–4	66	760	13 (9–17)	5 (3–8)	14 (10–22)	23 (10–31)	9 (7–14)	3 (2–7)	3 (0–24)	16 (9–40)
5–9	63	1,040	14 (9–20)	10 (4–12.5)	23 (16–32)	10 (7–22)	9 (5–13)	6 (3–10)	15 (1–29)	32 (13–52)
10–14	65	1,211	14 (10–22)	13 (7–19)	27 (18–39)	14 (11–19)	10 (6–13)	8 (6–12)	23 (4–40)	43 (19–57)
15–19	74	1,449	13 (8-21)	14 (7-22)	25.5 (18-38)	18 (15-25)	8 (6-13)	8 (5-15)	22 (4-35)	40 (18-60)
20–24	81	1,284	10 (6–16)	10 (7–15.5)	19 (12–29)	24 (19–30)	7 (4–13)	8 (4–11)	17 (0–35)	33 (10–66)
25–29	62	1,002	11 (7–17)	9.5 (5.5–15.5)	20.5 (13–27)	27 (19–32)	8 (4–13)	6 (3–11)	16.5 (0–47)	32 (10–70)
30–34	48	792	10.5 (8–18)	8 (5–12)	18.5 (12.5–27)	28 (20–34)	8 (6–12)	5 (3–8)	18.5 (0–37.5)	31.5 (10.5–58)
35–39	26	383	11.5 (9–18)	6 (3–11.5)	19 (12–26)	29 (20–37)	8 (5–12)	4 (2–10)	8 (0–29)	20.5 (10–49)
40–44	47	680	9 (5–18)	9 (4–13)	18 (12–27)	30 (19–39)	6.5 (4–14)	5 (3–9)	13 (0–29)	25 (11–50)
≥45	39	448	9 (4–13)	9 (4–13)	15 (10–21)	29 (19–40)	7.5 (4–11)	7 (4–10)	6 (0–25)	18 (10–41)
P value[b]			<0.001	<0.001	<0.001	<0.001	0.11	<0.001	0.01	<0.001
Gender										
Female	293	4,847	12 (8–19)	10 (5–16)	21 (14–32)	19 (12–30)	9 (6–13)	7 (4–11)	16 (0–33)	32 (13–55)
Male	278	4,202	11 (7–17)	9 (5–13)	19 (13–27)	22 (14–32)	7 (4–12)	6 (3–9)	13 (0–30)	29 (10–53)
P value			0.10	0.05	0.02	<0.001	0.001	0.01	0.61	0.05
Employment status										
Unemployed[c]	152	2,031	9 (5–14)	9 (5–12)	17 (11.5–22.5)	26 (18–33)	6 (4–10)	6 (3–9)	3 (0–20)	16 (9–36.5)
Employed	154	2,563	11 (7–18)	9 (5–14)	19.5 (13–29)	28 (20–35)	9 (5–14)	6 (3–10)	25 (3–45)	39.5 (16–66)
P value			0.002	0.38	0.001	<0.001	0.001	0.77	<0.001	<0.001
Level of schooling										
Nonattending[d]	64	699	12 (8–15)	4.5 (3–8)	14 (10–19.5)	24 (12–32)	8 (6–10.5)	3 (2–7)	1.5 (0–7)	12.5 (8–20)
Crèche	16	223	16 (13–26)	5 (4–7)	22.5 (14.5–28.5)	6 (3–28)	12.5 (9.5–18)	5 (4–7)	25 (20–26.5)	39.5 (34.5–47.5)
Primary school	105	1,912	14 (10–20)	11 (7–18)	27 (17–37)	12 (9–18)	9 (5–13)	8 (5–11)	21 (2–35)	37 (17–54)
Secondary school	75	1,537	16.5 (10–24)	12 (6–22)	29 (20–38)	17 (15–23)	9 (6–16)	8 (3.5–14)	24 (5–40)	46 (31–70)
Tertiary education	5	84	12 (11–27)	8 (6–12.5)	26 (20–33)	27 (20–35)	11 (11–14)	7.5 (6–12)	59 (29–81)	78 (55–92)
P value			0.02	<0.001	<0.001	<0.001	0.01	0.004	<0.001	<0.001

Day of survey												
Sunday	66	1,038	12 (8–18)	9 (5–14)	22 (13–27)	23 (15–32)	8 (4.5–12)	6 (4–10)	5 (0–32)	22.5 (9–56)		
Monday	56	961	13 (7–20)	9.5 (3.5–20)	23 (13–37)	17 (12–28)	9 (5–14)	6 (2–13.5)	23 (4.5–34)	40 (22–66.5)		
Tuesday	75	1,189	12 (7–16)	8 (5–14)	19 (14–28)	25 (15–32)	8 (5–13)	6 (3–11)	14 (1–35)	35 (12–56)		
Wednesday	135	2,182	13 (8–19)	10 (5–16)	21 (14–30)	19 (11–30)	9 (6–13)	7 (4–11)	15 (1–32)	34 (13–53)		
Thursday	73	1,084	14 (9–19)	10.5 (3–13)	19 (12–29)	21 (10–30)	8 (6–13)	6 (2–10)	18 (0–30)	30 (9–51)		
Friday	65	1,057	10 (7–18)	11 (7–20)	20 (13–33)	20 (13–31)	8 (6–14)	8 (4–14.5)	25 (6–39)	42 (19–60)		
Saturday	101	1,538	11 (6–15)	8 (4–12)	18 (13–25)	23 (14–32)	7 (4–11)	6 (3–9)	4 (0–21)	16 (9–45)		
P value			0.27	0.26	0.51	<0.001	0.13	0.26	0.001	0.004		

Abbreviation: IQR, interquartile range.

[a] Close contacts met for the "first time today."

[b] *P* values (Kruskal-Wallis analysis of variance by rank(s)) indicate whether a significant difference between median numbers or ages of contacts exists across a given category (age group, gender, employment status, level of schooling, or day of survey).

[c] Participants were regarded as unemployed if they were older than age 18 years and not employed.

[d] Participants were regarded as school nonattendees if they were aged 18 years or younger and were not attending crèche, primary school, secondary school, or a tertiary educational institution.

contacts, at 41.6%, 43.2%, and 43.2%, respectively. Similarly, the proportion of age-associative physical contacts peaked in the same respective participant age strata at 41.8%, 42.5%, and 39.9%. Among other age groups, age-associative mixing was greatly reduced.

The median age of close contacts (types I + II) was significantly associated with participant age, gender, employment status, level of schooling, and day of diary completion (Table 1). In particular, the median age of close contacts was significantly lower on Mondays than on every other day, except Thursdays ($P = 0.07$).

Indoor contacts

The median number of indoor contacts (types I + II + III) per participant was associated with participant age, gender, employment status, level of schooling, and day of diary completion, with participants aged 10–14 years recording the most indoor contacts at 43 per day (Table 1). Numbers of indoor casual contacts (type III) were significantly lower on Saturdays than on Mondays and Fridays ($P = 0.04$ and $P = 0.003$, respectively), possibly because 59.3% of casual contacts were met during travel and when children were at crèche/school midweek (Table 2).

Location of close, physical, and indoor contacts

Most close (types I + II) and physical (type I) contacts occurred at 6 locations: contacts occurring within the participant's own household, in the participant's neighborhood (outside household environs and streets), at crèche/school, during transport, in other households, and at work accounted for 33.6%, 23.5%, 12.8%, 8.9%, 7.1%, and 6.2% of close contacts and 36.3%, 22.0%, 11.6%, 10.2%, 6.3%, and 6.0% of physical contacts, respectively (Table 2). Similarly, 95.3% of indoor contacts (types I + II + III) were recorded at 7 locations: during transport (27.2%), in one's own household (20.1%), at crèche/school (20.0%), in shops (8.9%), at work (8.0%), in community buildings (6.0%), and in other households (5.0%).

Duration of indoor contacts

Indoor contact time was predominantly spent in 5 congregate settings, with 80.0%, 5.0%, 4.9%, 4.9%, and 2.3% of the time spent in participants' own households, at crèche/school, at work, in other households, and in transport, for average durations of 15.2 hours, 4.1 hours, 6.4 hours, 2.3 hours, and 1.4 hours, respectively. Prolonged contacts over 4 hours in length were reported in 73.9%, 47.3%, and 38.3% of visits to work, own household, and crèche/school, respectively, but in only 7.9% of visits to other households. The contact period was shortest for transport, with 98.1% of contacts lasting under 4 hours. Figure 2 shows the mean numbers of indoor contacts met daily per participant within these congregate settings, stratified by 5-year participant age group and contact type.

Influenza epidemic simulation

The number of new infections in the fifth generation of an influenza epidemic was simulated (Figure 3). Most infections

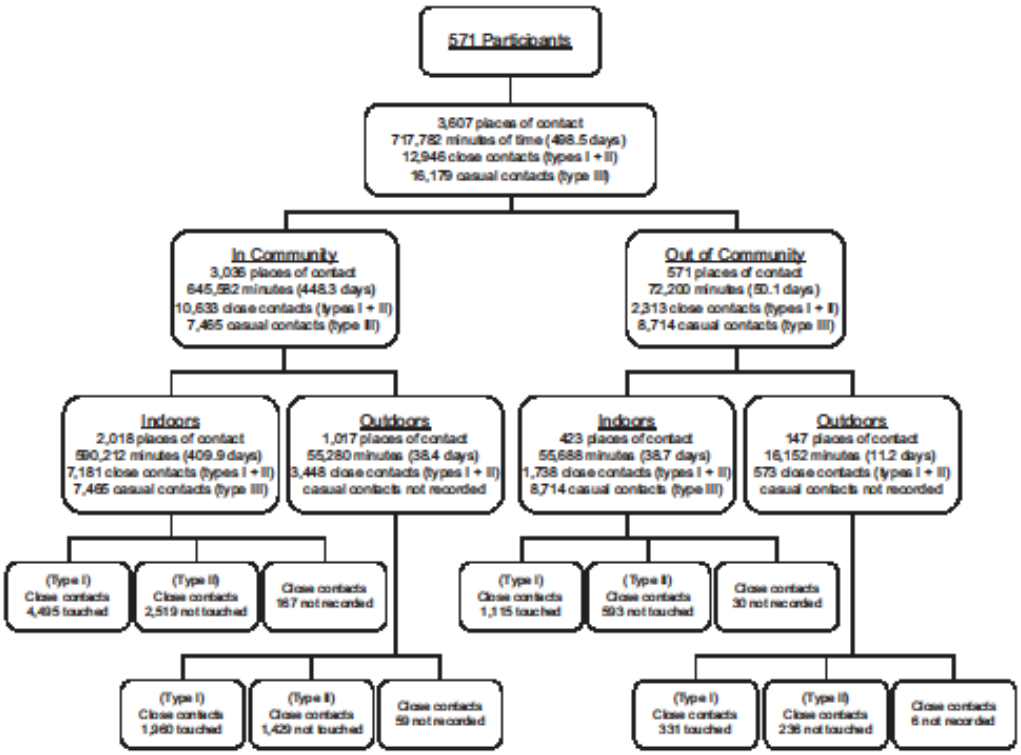

Figure 1. Number and duration of 571 participants' contacts, categorized as close (types I + II) or casual (type III) within or outside of the study community (a South African township) and indoors or outdoors, 2010. Close contacts were further stratified into those involving physical contact (type I) or 2-way conversation of 3 or more words without physical contact (type II). Casual contacts (type III) were defined as those people sharing an indoor space but not satisfying the criteria for a close contact. For 2 locations, indoors or outdoors was not specified; the first was within the community, lasting 90 minutes, with 4 close contacts (2 touched (type I), 2 not touched (type II)) and 0 casual contacts (type III), and the second was outside the community, lasting 360 minutes, with 2 close contacts (0 touched (type I), 2 not touched (type II)) and 0 casual contacts (type III).

will occur among persons aged 15–19 years and 25–29 years for both physical and close-contact transmission (Figure 3, parts A and B), highlighting the increased social interaction in these age groups and the consequential increased exposure to infectious diseases they face. The proportion of infections occurring in young children (under 9 years of age) and in adults 30–44 years of age is greater for physical transmission than for close contact, and consequently epidemics spread by physical touch will be more widespread across age groups. Sensitivity analysis showed that the number of new infections by physical touch was highly dependent on the transmission probability per social contact, with 14 and 3,533 newly infected individuals aged 15–19 years when $q = 0.252$ and $q = 0.756$, respectively. It also revealed that the basic reproductive number was directly proportional to q, with $R_0 = 2.48$, $R_0 = 4.96$, and $R_0 = 7.44$ when $q = 0.252$, $q = 0.504$, and $q = 0.756$, respectively. R_0 was estimated at 4.15 for transmission by close contact.

DISCUSSION

We have described the social mixing patterns of a South African township population. The analyses focused on social contacts (physical, close, and indoor) relevant to 3 major pathways (physical touch, large droplets, and droplet nuclei) for respiratory disease transmission (10, 17, 20). The number and age distribution of contacts and the transmission probability per contact affected the number and age distribution of new infections simulated for an influenza epidemic in the township community.

Physical contacts (type I) accounted for 27.1% of all contacts. The mean number and proportion of age-associative physical contacts peaked among youths aged 5–19 years, steadily decreasing as participant age increased. Younger age groups would therefore be most heavily affected in epidemics spread by physical touch. Simulations confirmed this, with the rate of the new infections highest among adolescents

Table 2. Numbers of Close and Indoor Contacts Recorded During a 24-Hour Period by 571 Randomly Selected Participants From a South African Township Community, According to Location and Type of Contact, 2010

Location	Close Contacts			Indoor Contacts			
	Type I (Physical)	Type II (Nonphysical)	Type Not Recorded	Type I (Physical)	Type II (Nonphysical)	Type Not Recorded	Type III (Casual)
Community building	206	73	2	191	61	2	1,258
Crèche/school	920	651	91	610	422	79	3,916
Health clinic	15	12	0	14	12	0	102
Neighborhood[a]	1,737	1,260	47				
Own household	2,868	1,420	56	2,868	1,420	56	703
Other households	498	404	23	498	404	23	340
Local "shebeen" bar	78	83	1	77	75	1	574
Shop	181	106	4	172	102	4	1,944
Sports venue	69	52	1	1	4	0	10
Transport	803	326	27	803	326	27	5,677
Work	474	320	4	345	243	4	1,411
Other miscellaneous sites	54	74	6	31	43	1	244
Total	7,903	4,781	262	5,610	3,112	197	16,179

[a] Outside household environs and streets.

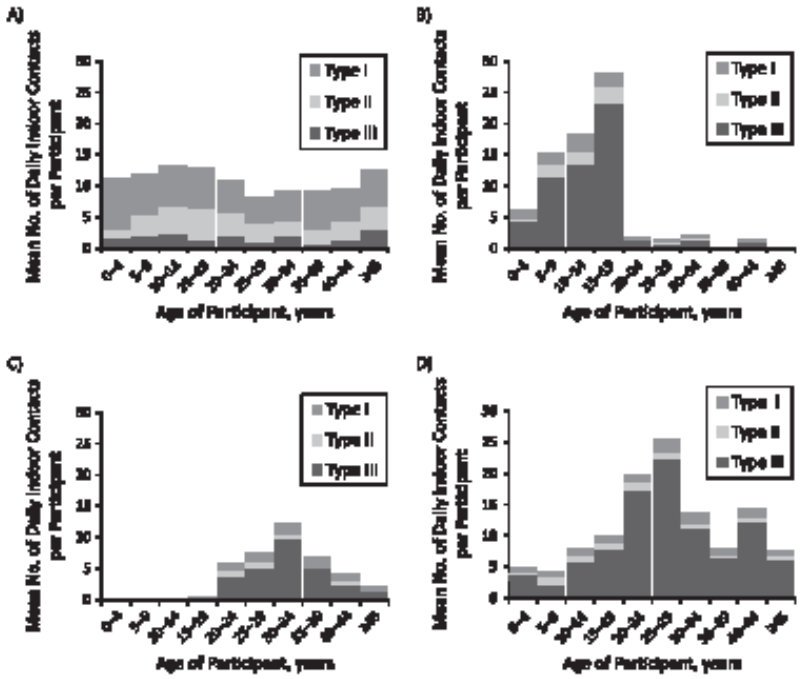

Figure 2. Mean number of indoor contacts (types I + II + III) per participant recorded during a 24-hour period A) in all households (participants' own households and other households), B) at crèche/school, C) at work, and D) during transport (predominantly minibus taxis), by 5-year participant age group and contact type, in a South African township community, 2010. Average durations of indoor contact in participants' own households, in other households, at crèche/school, at work, and during travel were 15.2 hours, 2.3 hours, 4.1 hours, 6.4 hours, and 1.4 hours, respectively, with prolonged contacts lasting over 4 hours reported for 47.3%, 7.9%, 38.3%, 73.9%, and 1.9% of visits to each location.

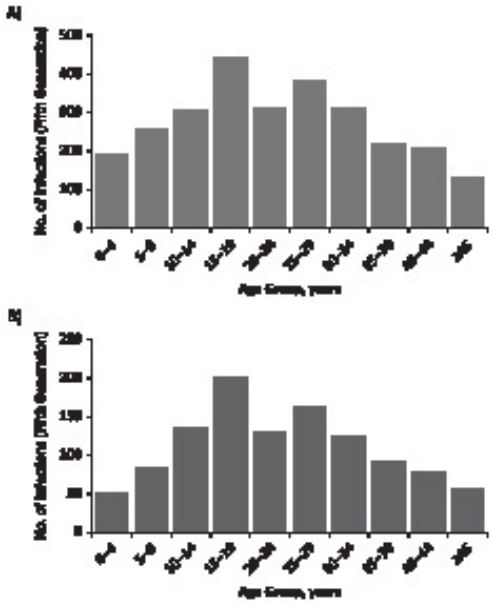

Figure 3. Simulated numbers of new infections in the fifth generation of an influenza epidemic spread by A) physical contact (type I) and B) close contact (types I + II) in a population comparable to that of a South African township community, by 5-year age group.

aged 15–19 years. Sensitivity analysis showed that the contribution of physical contact to influenza epidemics could be substantial but was highly dependent on the transmission probability per contact. Accurate predictions of the relative contribution will require precise values for the transmission probability. Nevertheless, the chain of infection would be readily affected by promotion of hand-washing (17, 18).

The frequency of close contact (types I + II) is thought to be a major determinant of the spread of diseases transmitted by large respiratory droplets (10, 11). Close contacts contributed 44.4% of all contacts and were most frequent and age-associative among youths aged 10–19 years. Simulations confirmed that the greatest number of infections would occur within these age strata. Of particular significance was the fact that the number of individuals met (i.e., "first time today" close contacts) was 40% higher in this township than that reported for European populations (median of 14 vs. 10; $P < 0.001$) (30). This suggests that influenza epidemics, transmitted by close contact, may affect this community more than European populations. We also note that the locations where close contacts were recorded were similar to those of the European study, but the proportion of contacts met at each location was significantly different (χ^2 test: $P < 0.001$). Social distancing strategies such as individual quarantine, school closure, and banning of public gatherings, previously applied with some success, may need to be tailored to the community (32). However, social distancing strategies and vaccination should particularly target adolescents (33).

Where tuberculosis is endemic, such as in the study community (27–29), transmission is determined by the number of exposures to infectious cases, time of exposure, and the volume and ventilation characteristics of the shared enclosed space (22–24). Indoor contacts (types I + II + III) were the most common type of social mixing, accounting for 86.2% of all contacts and occurring both within (58.4%) and outside (41.6%) the township. The high numbers of these contacts may therefore be contributing to the high tuberculosis rates seen in this community (8, 27–29, 34). Indoor contacts were also noted as being predominantly limited to a few key locations. Intergenerational mixing was most frequent in households and during transport, with long exposure times in households but short exposure times during travel. Contact times at crèche/school and at work were long, but contacts made there were markedly age-associative. Therefore, prolonged social interactions between adults and young children occurred predominantly within households. This is consistent with reports of high household transmission from smear-positive adults to young children within this community (24, 29). Numbers of nonhousehold indoor contacts increased rapidly during adolescence, increasing their potential for exposure to infectious adults, which in turn may be contributing to the increasing rates of tuberculosis infection observed in these age groups (9, 35).

Another significant finding for endemic tuberculosis transmission was that high numbers of contacts take place during transport. In a study conducted in Peru, use of public transportation was associated with increased incidence of tuberculosis (36, 37). However, because exposure time during travel was short (mean travel time of 1.4 hours), tuberculosis transmission would be sensitive to ventilation during transport (24). High use of public transportation and high potential for respiratory disease transmission warrant further studies of tuberculosis transmission within public transportation systems in South Africa.

To our knowledge, this study was the first to explore social interactions relevant to the spread of respiratory disease in an African population and one of the few using social mixing data to model the spread of a respiratory disease (30, 31, 38). Participants were randomly selected from a South African township; therefore, the findings may be generalized to similar newly urbanized communities. Two important features of the study were the modification of the European diary to include casual contacts, relevant to the indoor spread of respiratory diseases by droplet nuclei, and the face-to-face interviews with participants after diary completion to ensure data integrity and entirety. Study limitations included the fact that the mode of influenza transmission can vary between strains. Our analysis assumed that influenza is spread predominantly by physical or close contact (12). Therefore, values used for q may only be applicable to the Asian influenza strain considered by Wallinga et al. (31). Another aspect of the study to be reconsidered in future research was participants' not recording the ages of casual contacts. Large numbers of casual contacts were expected in certain locations (e.g., shops), so the recording of casual-contact demographic data would be difficult in a diary format. Novel approaches should address

this to allow age-structured models for droplet nuclei transmission to be constructed and used to resolve the debate around which mode of transmission is predominant for various respiratory diseases.

In summary, we investigated the role various person-to-person social interactions play in the spread of infectious respiratory disease within a South African township population. Simulations revealed that physical contact could contribute substantially to the spread of influenza-like illnesses. Casual contacts were defined to identify indoor locations conducive to respiratory disease transmission by droplet nuclei, with households and transport recognized as two such potential transmission "hot spots." Long-term tuberculosis control in communities with high endemic burdens will require further research on reducing tuberculosis transmission risks in these locations (34). Social mixing patterns within a South African township were found to differ from those reported in an earlier European study (30). These differences may have a marked influence on the spread of acute infectious respiratory disease within township communities and should be used to identify social distancing strategies and interventions required for epidemic control.

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Web Appendix 1

The social mixing survey diary each participant used to record all the contacts that they met during a 24-hour period.

Participant ID || | Assigned Date | | / |/| ||

Place 1	☐ In Masi ☐ Out of Masi	☐ Indoors ☐ Outdoors	☐ Your household ☐ Other household on your plot ☐ Outside on your plot ☐ Other household off your plot ☐ Street(s) ☐ Taxi ☐ Bus ☐ Train ☐ Spaza shop ☐ Community hall ☐ Soccer field ☐ Your work: _____ ☐ Your school: _____ ☐ Crèche: _____ ☐ Church: _____ ☐ Clinic/hospital: _____ ☐ Library: _____ ☐ Gym: _____ ☐ Shebeen: _____ ☐ Other: _____	Time spent: ☐ 0 - 15min ☐ 15min – 1hr ☐ 1 – 2hrs ☐ 2 – 4hrs ☐ 4 - 8hrs ☐ 8 – 12hrs ☐ More than 12hrs	Time of day: ☐ Morning ☐ Afternoon ☐ Evening	People touched or talked to:

Age	Gender	Touched	First time today
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
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☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N
☐☐	☐M ☐F	☐Y ☐N	☐Y ☐N

If indoors
People not touched or talked to:
Number:

NOTE: 'Masi' is short for Masiphumelele, the name of the study community near Cape Town. Diaries included 20 pages to allow participants to record contacts met at up to 20 locations visited. If required, extra pages were available at the face-to-face follow up interview.

Web Appendix 2

The method and assumptions used to derive a value for the probability of infection per social contact, q, for a social contact matrix describing the daily number of social contacts.

The Probability of Infection per Social Contact

Wallinga et al estimated the probability of infection per social contact q to be 0.036 by making use of the number of weekly conversational contacts participants self-reported in a study conducted in the Netherlands (31). We show here that this value depends on the construct of the next generation matrix (whether its elements represent the number of daily contacts, weekly contacts, etc), and subsequently derive an estimate for q that corresponds to the daily number of conversational contacts our study participants recorded. First, we define the following matrices:

$\mathbf{M}^*$ = the social contact matrix, used by Wallinga et al (31), with elements m^*_{jk} corresponding to the mean number of weekly contacts a person in age group k meets from age group j.

$\mathbf{M}$ = the social contact matrix with elements m_{jk} corresponding to the mean number of daily number of contacts a person in age group k meets from age group j.

q^* = the value obtained by Wallinga et al (31) using the number of weekly contacts
= 0.036

q = the value to be determined, corresponding to the number of daily contacts

$\mathbf{N}^*$ = the next generation matrix used by Wallinga et al (31)
$= q^*\mathbf{M}^*$

$\mathbf{N}$ = the next generation matrix corresponding to the number of daily contacts
$= q\mathbf{M}$

The i^{th} generation of infections, as calculated by Wallinga et al (31), is described by

$$\begin{aligned} \mathbf{x}_i^* &= \mathbf{N}^*\mathbf{x}_{i-1} \\ &= q^*\mathbf{M}^*\mathbf{x}_{i-1} \\ &= (q^*\mathbf{M}^*)^i\mathbf{x}_0 \\ &= (q^*)^i(\mathbf{M}^*)^i\mathbf{x}_0. \end{aligned} \tag{1}$$

At this point, we need to assume some kind of relationship between $\mathbf{M}^*$ and $\mathbf{M}$. The simplest such relationship would be to assume that the number of conversational contacts a person has grows linearly with the number of days, so that $\mathbf{M}^* = 7\mathbf{M}$, i.e. the mean number of weekly contacts m^*_{jk} is 7 times greater than the mean number of daily contacts m_{jk}. Substituting this back into Equation (1) above we find that

$$\begin{aligned} \mathbf{x}_i^* &= (q^*)^i(7\mathbf{M})^i\mathbf{x}_0 \\ &= (7q^*)^i(\mathbf{M})^i\mathbf{x}_0 \\ &= (q)^i(\mathbf{M})^i\mathbf{x}_0 \\ &= (q\mathbf{M})^i\mathbf{x}_0 \\ &= (\mathbf{N})^i\mathbf{x}_0 \\ &= \mathbf{N}\mathbf{x}_{i-1}, \end{aligned}$$

so that $q = 7q^* = 7(0.036) = 0.252$, i.e. the probability of infection per social contact (for a social contact matrix corresponding to the number of daily contacts met) would have been 7 times greater than the value calculated with a social contact matrix corresponding to the number of weekly contacts met. Thus we have a rough estimate for the transmission probability per social contact to be used in our age-structured model.

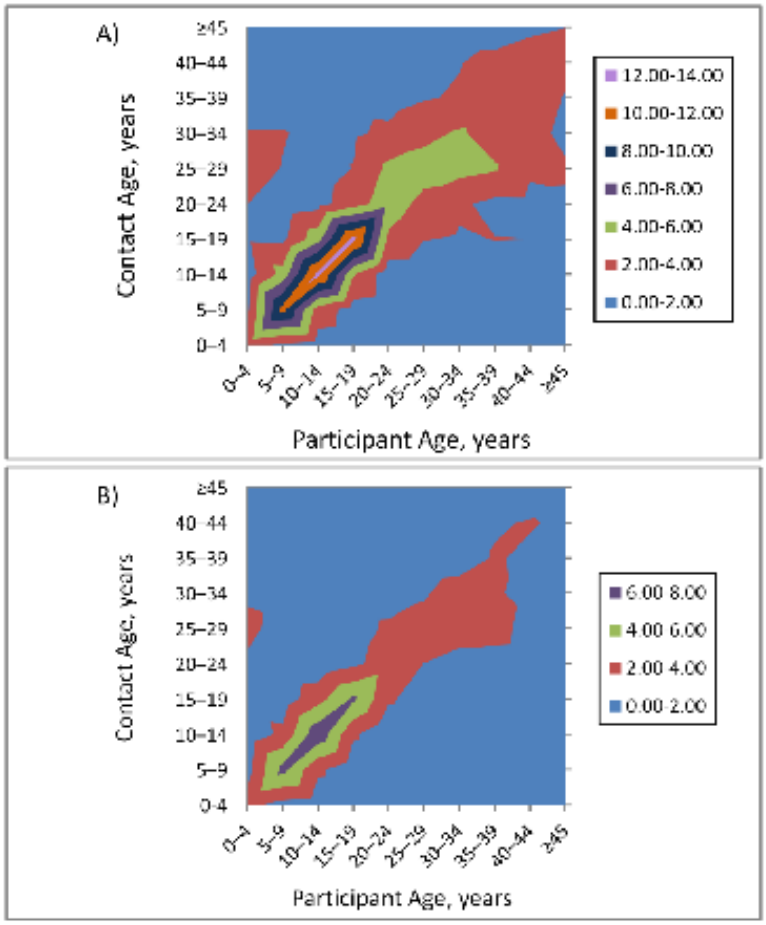
Web Table 1. The 'social contact matrices' **M**, constructed from the mean numbers of age-specific physical and close contacts recorded by participants, and used to simulate the initial spread of an influenza epidemic by physical contact and large respiratory droplets (Figures 4A and 4B) within a population similar to that of the study community.

The data used to construct the social contact matrix below, corresponding to Figure 4A, were all those contacts involving physical touch and indicated as being met for the '1st time today.'

	Participant Age Group									
Contact Age Group	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45+
0-4	1.73	0.84	0.55	0.47	0.37	0.73	0.81	0.50	0.89	0.21
5-9	0.97	4.37	1.42	0.39	0.37	0.45	0.44	0.35	0.53	0.33
10-14	0.56	1.52	4.68	1.55	0.25	0.29	0.27	0.35	0.36	0.49
15-19	0.79	0.56	2.35	3.97	1.64	0.92	1.00	1.00	0.68	0.49
20-24	1.05	0.24	0.35	1.18	2.42	1.52	1.17	0.65	0.81	0.77
25-29	1.48	0.68	0.43	0.97	1.74	1.89	2.23	2.04	0.89	0.90
30-34	1.11	0.70	0.57	0.72	0.80	1.45	2.04	1.58	1.26	0.67
35-39	0.59	0.43	0.37	0.49	0.48	0.94	1.08	1.65	1.26	0.85
40-44	0.62	0.32	0.31	0.42	0.48	0.76	1.02	1.31	1.62	1.18
45+	0.39	0.21	0.25	0.35	0.44	0.61	0.46	0.58	0.68	0.97

The data used to construct the social contact matrix below, corresponding to Figure 4B, were all those close contacts indicated as being met for the '1st time today.'

	Participant Age Group									
Contact Age Group	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45+
0-4	1.97	1.03	0.65	0.53	0.42	0.85	0.88	0.50	1.00	0.23
5-9	1.12	7.21	1.97	0.62	0.47	0.63	0.56	0.54	0.64	0.49
10-14	0.71	3.30	8.02	2.77	0.54	0.58	0.46	0.46	0.53	0.59
15-19	1.17	0.97	3.60	7.92	2.46	1.69	1.58	1.73	1.36	1.05
20-24	1.29	0.49	0.77	2.24	3.95	2.60	1.85	1.15	1.38	1.18
25-29	1.67	1.06	0.88	1.73	3.33	3.53	3.67	3.04	1.81	1.90
30-34	1.41	1.02	1.02	1.31	1.79	2.50	3.06	2.23	2.19	1.28
35-39	0.76	0.62	0.65	1.08	1.01	1.60	1.90	2.27	1.98	1.46
40-44	0.91	0.51	0.54	0.68	0.95	1.19	1.63	1.96	2.43	1.74
45+	0.52	0.30	0.55	0.70	0.90	0.98	0.90	0.85	1.15	1.56



Web Figure 1

Mean numbers of (A) close (Type I + II) and (B) physical (Type I) contacts during a 24 hour period, stratified by 5-year participant and contact age strata. Peaks along the central diagonal indicate high levels of age-associative mixing, so that both close and physical contacts were most age-associative between the ages of 5 and 19 years. In particular, the proportion of age-associative close contacts peaked at 41.6%, 43.2%, and 43.2% amongst participants 5-9, 10-14, and 15-19 years old respectively, with the proportion of age-associative physical contacts peaking at 41.8%, 42.5%, and 39.9% in the same age strata.

Chapter 5: Application of Theory

In the previous chapter it was described how the social mixing survey identified four locations as potential transmission 'hotspots,' namely households (own and other), crèche/school, work, and transport (predominantly minibus taxis). Of these locations, crèche/school was not considered for mathematical analysis since very few adults visited them (Figure 3B) and it was therefore regarded as unlikely for an infectious adult to be present. Similarly, the ARI associated with work environments was not modelled, because despite the fact that many contacts were made by participants whilst at work (Figure 3C), the variability between different working environments meant that accurate estimation of parameter values would be difficult, if not impossible. Households, on the other hand, lent themselves to being evaluated for several reasons, the first of which was that people of all ages were recorded as residing in households within the community (Figure 3A), so that infectious adults are likely to expose susceptible people to infection whilst at home or whilst visiting other households. In addition, the availability of population census data, describing the number of residents per child-containing household, as well as TB notification rates from the community TB register, meant that the probable number of infectious adults resident in each household could be determined. Last of all, and perhaps most importantly, by defining the susceptibles to be children, and therefore specifically considering the risk of TB transmission from adults to children, the modelled ARI could be compared with directly-measured ARI data for children from the same community. The published paper describing the analysis of household transmission can be found in Section 5.1. Likewise, minibus taxis, the predominant means by which community residents travelled, were also analyzed using Equation 8 because of their relatively constant volumes and high occupancy levels. In addition, it is also clear from Figure 3D that the vast majority of minibus taxi transport users are between 20 and 44 years of age, so that infectious adults are likely to expose susceptible adults to TB infection during this form of transport. The ease with which parameters such as ventilation could be measured also contributed to the analysis of minibus taxi transport as well. The paper describing TB transmission within minibus taxis can be found in Section 5.2.

The third indoor location to which Equation 8 was applied was a hypothetical prison cell, corresponding to the standard incarceration conditions an awaiting trial prisoner would find themselves in at present in South Africa. A prison cell was considered for mathematical analysis for two reasons: (1) because previous incarceration was identified as a significant risk factor for prevalent TB in an earlier independent study conducted in the *same* community as that of the social mixing survey[54], and (2) because the availability of data from court evidence and judicial reports, describing typical South African awaiting trial prison cells, meant that parameters could be readily

estimated. The published paper describing the methods and assumptions used to calculate the probability of TB transmission within a South African prison cell can be found in Section 5.3.

5.1 Households

Please refer to the paper below entitled “Tuberculosis transmission to young children in a South African community: modeling household and community infection risks” for the full description of all data sources and methods used to calculate the mean ARI for children exposed to potentially infectious adults within households in a South African township. This paper was published in *Clinical Infectious Diseases* on 15 August 2010 (see Addendum for full publication details).

MAJOR ARTICLE

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

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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

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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

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

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.

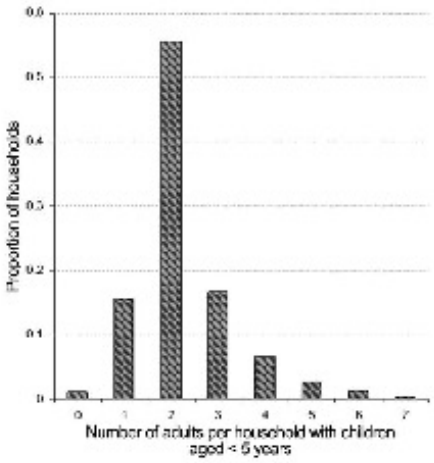

Figure 1. The proportions of households with preschool children (aged <5 years) in which different numbers of adults are resident. A total of 2083 adults and 1051 preschool children were resident in 918 households. Data were derived from a 2008 household survey performed at the study site.

Table 2. Tuberculosis Notifications at the Study Site Reported in 2004–2008, Stratified by Age

Measure	Total population	Adults aged >15 years	Children aged 5–15 years	Children aged <5 years	Adults with smear-positive tuberculosis
No. of tuberculosis notifications	1289	1158	45	86	670
Population years of exposure	67,747	53,056	9181	5510	53,056
Tuberculosis rate per 100,000 population (95% CI)	1909 (1799–2018)	2137 (1984–2339)	546 (346–546)	1522 (1419–1533)	1347 (1108–1437)

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: $C = S(1 - e^{-Ipqt/Q})$. The number of infectious adults at any time is given by the smear-positive incidence rate *(M)* and the period of infectivity (Δ). The risk of contact with an infectious adult is given by the Poisson distribution $(\lambda^I/I!)e^{-\lambda}$, where $\lambda = M * A$ 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 Δ 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 2*A*. 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 2*B*. 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 3*A*. 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

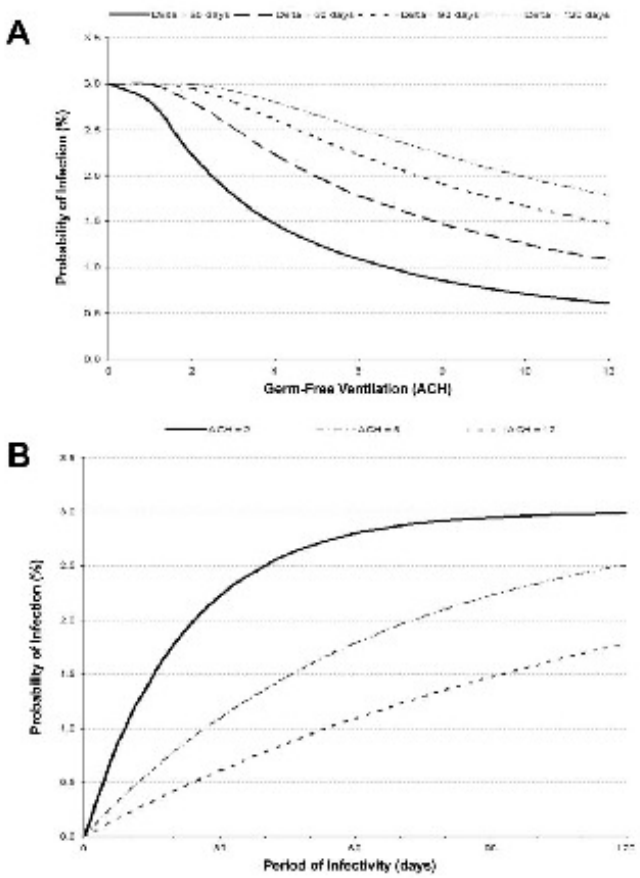

Figure 2. *A*, Effect of ventilation (air changes per hour [ACH]) and mean period of infectivity (delta) on the mean annual risk of tuberculosis infection resulting from a child sleeping in a shack shared with adults. Values are plotted for mean periods of adult infectivity of 30, 60, 90, and 120 days. *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 Δ.

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

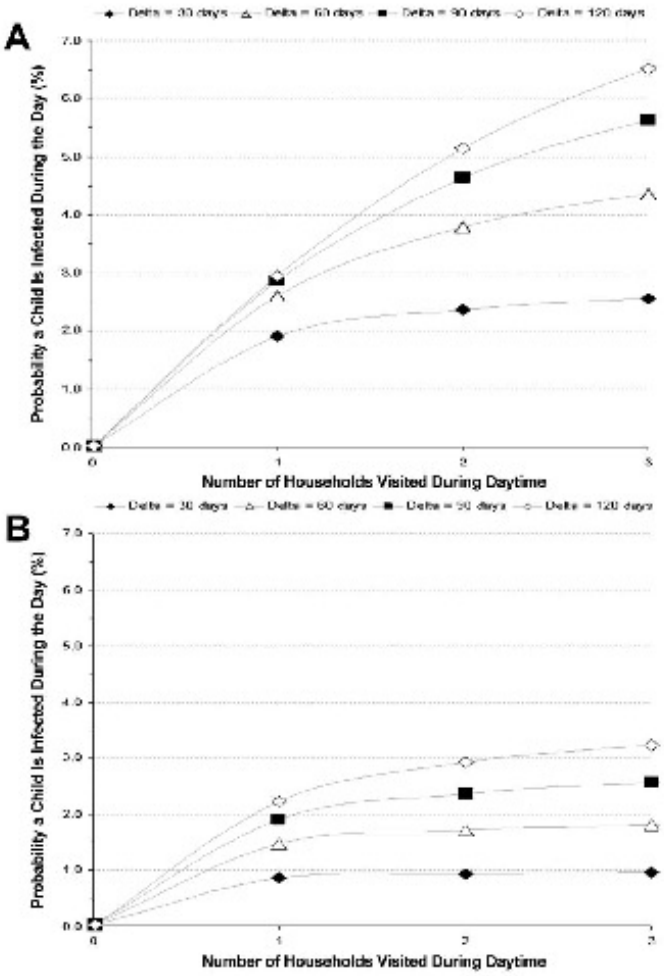

Figure 3. Mean annual risk of tuberculosis infection for a child visiting 1–3 households other than his or her own residential household during the day with ventilation of 2 air changes per hour *(A)* and 6 air changes per hour *(B)*. Values are plotted for mean periods of adult tuberculosis infectivity (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.

real-life situations [15–19]. This study used a novel approach of incorporating population data from a specific South African township to populate the Well-Riley equation, to explore household and nonhousehold tuberculosis transmission to preschool children.

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 Δ (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 Δ, 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 Δ 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 Δ 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, Δ 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 crèche 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.

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5.2 Taxis

The modelled risk of TB transmission between adults (commuters-to-drivers and commuters-to-commuters) whilst travelling in minibus taxis is described in full in the paper below entitled "Exposure to *Mycobacterium tuberculosis* during minibus taxi journeys in South Africa: modelling tuberculosis transmission risks." This paper is in draft form and is not currently under review for publication in any journal (see Addendum for contribution of SP Johnstone-Robertson to this paper).

Exposure to *Mycobacterium tuberculosis* During Minibus Taxi Journeys in South Africa: Modelling Tuberculosis Transmission Risks

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Abstract

Background

Minibus taxis are frequently used as public transport in sub-Saharan Africa. We hypothesized that conditions within minibus taxis might pose significant risks for tuberculosis (TB) transmission.

Methods

Taxi ventilation was assessed by carbon dioxide levels and tracer gas concentration-decay technique. The probability of passengers having infectious TB was estimated from the national smear-positive TB incidence rate and the mean period of TB infectiousness (Δ). The Wells-Riley equation was used to estimate the TB transmission probabilities.

Results

During observed taxi journeys, windows were typically closed or only partially open and high ambient levels of carbon dioxide were recorded (maximum, 5,866 parts per million). Ventilation in a popular minibus taxi model was 0.51 air changes per hour (ACH) with windows closed and increased to 9.17 ACH with mechanical fresh-air ventilation. Modeling of TB transmission probabilities were estimated using base case scenario of 14 passengers, ACH=0.51, infectivity (q)=1 and Δ=60 days. Transmission risk for a single 10 hour journey reached 0.5%, annual cumulative TB risk of passengers commuting 2-hours per working day reached 29%. The annual risk for a driver spending 8-hours per day in an unventilated taxi was as high as 75% but reduced 10-fold with fresh-air ventilation. All transmission probabilities were reduced by shortening Δ.

Conclusions

In South Africa where TB is endemic, minibus transport could add significantly to the national TB burden. Transmission probabilities were related to crowding and journey time. However, transmission could be reduced by efforts to increase ventilation and decrease the mean period of infectiousness of TB cases.

Key Words: Minibus taxi**,** tuberculosis, transmission, ventilation, period of infectiousness, Wells-Riley equation.

Introduction

The TB epidemic in South Africa is extraordinary. South Africa is a country with the 3rd highest TB burden in the world, with approximately 1% of the population developing TB each year [1, 2]. Multi-drug resistant (MDR) and extensively drug resistant (XDR) TB are now being increasingly reported [3, 4]. In Cape Town one of the largest cities in South Africa, the calculated life time risk of an HIV-uninfected individual developing primary and retreatment TB is approximately 30% [5] and the TB risk for HIV-infected individuals is in excess of 5% per annum [6, 7]. The rate of acquisition of TB infection among adolescents (7% per annum) is as high as reported in the pre-chemotherapy era in industrialized countries. In a random selection of adults in an African Township population, laboratory confirmed pulmonary TB was detected in 1.6% of those investigated [8]. Therefore, there is a risk for TB transmission whenever numbers of adults congregate, particularly in poorly ventilated spaces.

The World Health Organization (WHO) and Stop TB Partnership have recognized the importance of TB transmission within congregate health care settings [9, 10]. However, extremely high annual rates of TB infection have been reported South African populations [6, 7] emphasizing the further importance of TB transmission within community settings. TB transmission is predominantly airborne from smear positive cases [11, 12]. In the USA outbreaks of TB have been reported in those using public buses and trains [13-15]. Increased rates of TB disease have been reported in regular users of public transport in Lima, Peru [16] where employment in the public transport sector has also been associated with a 2.7 to 4.5-fold increased risk of TB [17]. In a high burdened country such as South Africa there is a particularly high risk of being exposed to an infectious TB case while sharing crowded public transport.

There are 126,000 minibus taxis in South Africa which are frequently overcrowded and comprise the dominant mode of public transport for the black population [18]. Taxis are used by all age groups including 87-92% of school going children [18]. Approximately 2.5 million of the 3.9 million public transport commuters use taxis for travel to and from work or school and a further 325,000 use taxis as a feeder to other forms of public transport [18]. In metropolitan areas commuters spend approximately 1 hour each trip to and from work [18]. There are in excess of 4.5 million hours of person time spent in minibus taxis in South Africa daily.

We hypothesized that conditions within minibus taxis might pose significant risks for tuberculosis (TB) transmission. A preliminary survey demonstrated markedly elevated carbon dioxide levels indicative of poor ventilation during routine minibus taxis journeys. We therefore measured ventilation characteristics of a popular type of minibus taxi commonly used in South Africa and modeled the risk of TB infection for susceptible individuals during taxi commuter journeys of varying lengths and under varying ventilation conditions. The model was used to further explore the ability of the national TB control program to decrease TB transmission in these settings by reduction of the period between the onsets of infectivity and starting effective chemotherapy by intensified and active case finding.

Methods

Study Design

The study aim was to explore TB transmission probabilities between adults travelling in minibus taxis (Figure 1). In preliminary surveys of minibus taxi journeys in Cape Town, South Africa, carbon dioxide levels (CO_2) were recorded longitudinally throughout the duration of 22 urban commuting journeys using an EA80: EasyView™ Indoor Air Quality Meter/Datalogger (Extech Instruments Corporation, Waltham MA, USA.). The probability of an infectious TB case being among a standard passenger and driver complement of 15 individuals was determined from the South African adult national smear-positive notification rate and the time period of infectiousness (Δ) prior to initiation of effective chemotherapy. The ventilation characteristics of a typical minibus taxi were explored under a variety of conditions using carbon dioxide dilution. The Wells-Riley equation has been used to describe airborne transmission probabilities within a single enclosed space with defined ventilation [19] and has been applied to a wide range of transmission scenarios [20-25].

Mathematical Transmission Model

The number of TB infections (C) occurring in a taxi with susceptible commuters (S) was assumed to be a function of the number of infectious adults (I), their infectivity (q=number of infectious quanta produced per hour), time of journey (t=time of exposure in minutes), respiration rate (p=liters per hour), and germ-free ventilation (Q=liters per hour) as given by Wells-Riley equation $C=S(1-e^{-Iptq/Q})$. The prevalence (P) of infectious adults at any time is given by the annual smear

positive incidence rate (M) and the period of infectivity (Δ days) as P = M/[365/Δ]. The risk of contact with an infectious adult is given by the Poisson distribution $(\lambda^I/I!)e^{-\lambda}$, where $\lambda = P^*(A-1)$ is the expected number of infectious adults in a taxi with A = I + S adults. The probability that a susceptible person was infected per taxi journey (P_{journey}) was therefore calculated as

$$P_{\text{journey}} = \sum_{I=1}^{A-1} \frac{\lambda^I}{I!} e^{-\lambda} \left(1 - e^{-\frac{Ipqt}{Q}}\right),$$

and the annual probability of infection (P_{annual}) was subsequently calculated using

$$P_{\text{annual}} = 1 - (1 - P_{\text{journey}})^N,$$

where N is the number of journeys travelled per year.

Model Inputs and Analyses

The South African government requires minibus certification by the South African national standards bureau. Twenty four models of minibus from 12 manufacturers have been certified for public transport, each with seating capacities between 13 and 16 passengers [26]. The germ-free ventilation (Q) was measured for a popular recently certified model of minibus (Quantum Ses'fikile 2007, Toyota South Africa Motors (Pty) Ltd) as air changes per hour (ACH) for a variety of ventilation options.

Taxi volume and ACH were measured using a tracer gas concentration-decay technique [27]. Carbon dioxide (12 grams) was released and distributed by fan throughout the stationary vehicle, whereupon the fan was switched off. Five repeated experiments were performed for each of the 4 ventilation configurations. CO2 concentrations were measured at 5-10 second intervals using an infrared gas analyzer (Model LCA2, Analytical Development Corporation, Hoddesdon, UK). ACH

was calculated as the gradient of the straight line through the natural logarithm of CO2 change plotted against time.

Single journeys were modeled up to 10 hours and annual cumulative commuting was estimated for 2 taxi trips per day of 60 minutes for 250 days per year. The daily period of exposure of the taxi driver was assumed to be an 8-hour working day. The South African national adult smear positive notification rate in 2007 was 396/100,000 population.[1] The period of TB diagnostic delay has been reported in a meta-analysis of 58 studies to be a mean of 72 days with most studies reporting total diagnostic delay of 60-90 days [26]. Since the period of infectiousness (Δ) may exceed the period of diagnostic delay and is the primary modeled parameter influenced by case finding within the TB control program, it was allowed to take values of 30, 60, 90, and 120 days to populate the model.

The respiratory volume for adults lies within a range of between 5 and 8 liters per minute. For modeling purposes we assumed a resting respiratory rate of 12 breaths per minute and a tidal volume of 500 milliliters resulting in a respiratory rate (p) of 360 liters per hour.

A wide range of estimated values for the rate of production of infectious TB quanta (q) have been reported. Laryngeal TB is highly infectious with q estimated at 60 infectious quanta per hour [25]. In a work place outbreak due of an untreated smear-positive pulmonary case, q was estimated at 12.7 infectious quanta per hour [23]. Over a 2 year period in a TB ward, q was directly measured at 1.25 infectious quanta per hour [25]. In order to be conservative, (q) was modeled at a value of 1 infectious quantum per hour and sensitivity analyses were performed to values of q as low as 0.2 infectious quanta per hour.

Results

Preliminary Survey

During 22 observed typical commuter minibus taxi journeys, the average number of passengers was 16. Windows were fully closed or only partially open during 62% of journeys made during October 2010 (South African spring). The maximum CO_2 concentration recorded was 5,866 parts per

million (ppm) which was more than 10-fold greater than ambient levels. Carbon dioxide concentrations were above 1000 (ppm) for 87% of the journey-time, even with windows partially open. These data indicated that ventilation was frequently suboptimal during routine minibus journeys.

Ventilation Measurements of Minibus Taxi

The results of the tracer gas experiments for the minibus taxi are shown in table 1. The taxi volume was measured at 9.31 m^3 and the mean ventilation with windows closed without mechanical ventilation was 0.51 ACH. ACH increased sequentially with fresh air fan activation, driver window open and combination of driver and passenger windows open. The ventilation with 2 windows open was much more variable and may be more dependent on external factors such as cross-winds.

Risk of Tuberculosis Transmission During a Single Taxi Journey

The probability of TB infection for a single journey is shown in figure 2A, and is strongly related to the length of potential exposure during the journey and the prevailing ventilation of the taxi. The modeled risk for a commuter in a taxi with a complement of 14 passengers with ventilation of 0.51 air exchanges per hour (ACH) and a Δ of 60 days is 0.49% for a single long-distance journey lasting 10 hours. The transmission probabilities are shown for scenarios of improved taxi ventilation with 4.29 ACH and 9.17 ACH, resulting in transmission probabilities of 0.08% and 0.04%, respectively.

The impact of changing values of Δ on transmission probability is shown in figure 2B for a ventilation of 0.51 ACH. A TB control program in which patients have a mean period of infectiousness of 60 days before diagnosis and treatment initiation would result in a transmission risk in a single 10 hour trip of 0.49%. Greater values of Δ of 90 days and 120 days would result in increased transmission probabilities of 0.73% and 0.97%, respectively. In contrast shortening Δ to 30 days by means of improved TB case finding would decrease transmission risk to 0.25%. Therefore the transmission probability during a 10 hour journey varies over a 4-fold range between the upper and lower modeled values of Δ.

Cumulative Risk of Tuberculosis Infection During a Year of Commuting

The effect of ventilation on the cumulative TB infection risk for a commuter undertaking 2 journeys of 1 hour each per day is shown in figure 3A for a period of infectivity of 60 days. The cumulative risk for an individual commuting for 250 days per working year approaches 28.7% at a ventilation of 0.51 ACH. The cumulative TB risk is very dependent on the ventilation during the journey time. Ventilation of 4.29 ACH and 9.17 ACH reduces transmission to 4.0% and 1.9%, respectively.

The effect of changes in Δ on cumulative TB transmission risk is shown in figure 3B for a ventilation of 0.51 ACH. Transmission risk with a Δ of 60 days is 28.7% per annum. Increases of Δ to values of 90 days and 120 days would result in estimated transmission risks of 39.7% and 49.1%, respectively. Reduction of Δ to 30 days through enhanced TB case finding could reduce transmission risk to 15.5%.

Annual Risks of Tuberculosis Transmission to Drivers

We next explored the exposure risk that taxi drivers themselves are subject to during a working year. The effect of different values of ventilation on the cumulative TB transmission risk for a taxi driver who spends 8 hours a day in a taxi for 250 days of the year is shown in figure 4A for a period of infectivity of 60 days. The cumulative TB risks are considerable reaching 73.9% for a driver who drives without ventilation. Even when ventilation levels are increased to 4.29 ACH and 9.17 ACH, however, accumulated annual TB transmission risks remain at very high values of 15.2% and 7.5%, respectively. The risk is not appreciably sensitive to the number of trips driven during a standard 8 hour working day, so that increased TB transmission risk associated with additional passengers was compensated by the shorter period of contact per passenger.

The impact of differing levels of infectiousness of the TB source individuals (q) on the cumulative annual TB transmission probability for a driver was explored. TB transmission risk for a driver undertaking 8 trips during an 8-hour working day for 250 days a year is shown in figure 4B. For the lowest explored value of q that was equal to 0.2 infectious quanta per hour, the cumulative transmission risk at 250 days in a closed taxi (ACH=0.51) remained substantial at 12.9%, 24.2%, 34.0% and 42.5% for values of Δ of 30, 60, 90 and 120 days respectively.

Discussion

We have used mathematical modeling to explore the risks of TB infection in minibus taxis which are used as the predominant public transport modality in South Africa. Our preliminary observations of taxi journeys found that windows typically remained closed and ventilation was poor even during mild spring weather. Our mathematical modeling suggests that the risk for TB transmission in minibus taxis is considerable and identified that the transmission risk was related to fixed parameters such as commuting frequency and carrying capacity of the vehicles. These parameters determine the length of potential exposure and the numbers of individuals at risk of airborne transmission. However, our model also highlighted the importance of two other critical parameters: the ventilation characteristics of vehicles and the period of infectiousness of TB cases prior to treatment initiation, both of which are amenable to interventions.

The period of infectiousness (Δ) is a composite parameter resulting from individual health-seeking behavior, programmatic health system delays and time required for establishing a laboratory diagnosis. The combination of TB incidence rate and Δ determine the prevalence of untreated TB in a population which in turn provides the source for ongoing TB infection. Intensified and active TB case finding in communities and streamlining of diagnosis and referral within the health system can decrease the period of infectiousness [28-30]. While these measures can rapidly impact TB prevalence, TB incidence will remain for many years to come due to a very large latent pool of infection already in the population [6, 7]. However, the benefits of a decrease in Δ may be even larger than presented in the model as the more infectious cases are likely to be most easily identified [31, 32].

Our model addresses risk of TB infection during travel and did not quantify the numbers of TB cases which subsequently result from such exposures. The Wells-Riley equation describes the numbers of infections resulting from exposure of susceptible individuals to infectious cases under specific environmental conditions but not the rate of progression to TB disease. However, the large proportion of children, HIV-infected individuals and previously treated TB cases regularly using minibus taxis are at increased risk for progression from TB infection to TB disease [33-35].

The novel mathematical model used in this study combined a probabilistic analysis of the likelihood of an infectious individual to be amongst the complement of passengers, together with the well established Wells-Riley model of airborne TB transmission in confined spaces. The probability analysis is dependent on the assumption of a generalized TB epidemic with equal mixing of infectious cases throughout the population. Currently there are two modeling approaches for quantification of respiratory disease infection risk: the Wells-Riley model and dose-response models [36]. The Wells-Riley model provides a simple assessment of transmission risk utilizing the quantum of infection (q) as the hypothetical infectious dose unit, and is predicated on stable equilibrium conditions. Stochastic transmission events due to proximity of an infectious case however, are not captured by this model [37].

While it is preferable to populate any model only with primary measured inputs this is often not possible. There is currently no method to estimate the infectious source strength of TB cases except by back calculation from outbreaks assuming a well mixed approach. Back-calculation of the number of infective quanta of source patients has been reported values between 1.25-60 infective quanta/hour [23-25]. For these analyses we used a conservative value of q=1 infective quanta/hour and performed sensitivity analyses down to 0.2 quanta/hour.

Our ventilation studies were performed on a recent model of minibus and did not take into account illegal overcrowding. However, the South African minibus fleet consists predominantly of old and poorly maintained vehicles in which mechanical ventilation would be less efficient and overcrowding is very common [38].

An important strength of this study is that it highlights a largely ignored but important mode of potential TB transmission. While absolute TB transmission risks will vary widely with the diversity of prevailing conditions during minibus taxi journeys, the model has enabled identification and exploration of the interactions between major risk factors. In particular we have identified an urgent need for improved ventilation which will require education of passengers and drivers of the importance of ventilation during travel. Furthermore, the national TB control programs of very heavily burdened countries such as South Africa should also prioritize strategies to decrease the prevalence of infectious TB disease.

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Conflict of Interest Statement

No conflicts of interest to declare

Role of the Authors

RW and SR designed the analyses and wrote the paper with input from SDL, LGB, PU, JH, CM. CM and LGB collected the data. All authors contributed to and approved the final version of the paper.

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Table 1 Ventilation characteristics of a minibus taxi

	Air changes per hour	**Ventilation litres per hour***
Closed windows and no fan	0.51 (SD±0.1)	4,722
Driver window open and no fan	4.29 (SD±0.6)	39,948
Closed windows with "fresh-air" fan	9.17 (SD±0.5)	85,360
Driver and passenger windows open	9.7 (SD±2.9)	89,853

* Ventilation [liters/hour] = Air changes per hour x volume of taxi (9.31 m^3) x 1000

Figure Legends

Figure 1

A popular model of minibus taxi with occupants in Cape Town, South Africa. These older minibus taxis have less ventilation than modern replacement models but still constitute the major form of public transport throughout sub-Saharan Africa.

Figure 2A

The TB transmission probability for a susceptible individual traveling on a single journey of up to 10 hours duration calculated for a period of infectiousness of 60 days. Transmission probabilities as percentage are shown for 3 levels of ventilation 0.51, 4.29 and 9.17 air changes per hour and reach up to 0.49%, 0.08% and 0.04% respectively after a journey length of 10 hours.

Figure 2B

The TB transmission probability for a susceptible individual traveling on a single journey of up to 10 hours duration for a ventilation of 0.51 air changes per hour (ACH). Transmission probabilities as percentage for different values of period of infectiousness (Δ) are shown. For values of Δ of 30 days, 60 days, 90 days and 120 days the corresponding transmission probabilities after a 10 hour journey are 0.25%, 0.49%, 0.73% and 0.98% respectively.

Figure 3A

The annual cumulative TB transmission probability for a TB susceptible commuter traveling twice daily for a mean time of 1 hour per trip up to 250 days per year is shown for 3 levels of taxi ventilation. The period of infectiousness is modeled at 60 days. At ventilation levels of 0.51, 4.29 and 9.17 air exchanges per hour (ACH) the accumulated TB risk of infection after 250 days of commuting is 28.7%, 4.0% and 1.9% respectively.

Figure 3B

The annual cumulative TB transmission probability for a commuter susceptible for TB infection traveling twice daily for a mean time of 1 hour per trip for up to 250 days is shown for 4 values of the period of infectiousness (Δ).The ventilation is modeled for 0.51 air changes per hour. For values of Δ of 30 days, 60 days, 90 days and 120 days the corresponding transmission probabilities after 250 days of commuting is 15.5%, 28.7%, 39.7% and 49.1% respectively.

Figure 4A

The cumulative annual TB transmission probability of a taxi driver exposed during 1-8 trips per 8-hour working day over 250 days of a year. TB transmission risks are relatively independent of the number of trips driven per day. TB transmission probabilities for 0.51, 4.29 and 9.17 air changes per hour (ACH) are 73.9%, 15.2% and 7.5% respectively for 8 trips per day. Analysis performed for input values of q = 1 quantum per hour and Δ = 60 days.

Figure 4B

The cumulative annual TB transmission probability of a taxi driver exposed during 8 trips during an 8-hour working day for 250 days of a year. Transmission risks are high although very sensitive to values of Δ (30, 60, 90 and 120 days) and q (0.2, 0.4, 0.6, 0.8 and 1 quanta per hour). With a value of q=1 cumulative risks were 48.9%, 73.9%, 86.7% and 93.2% for values of Δ of 30, 60, 90 and 120 days respectively. With a value of q=0.2 accumulated risks were 12.9%, 24.2%, 34.0%, and 42.5% for values of Δ of 30, 60, 90 and 120 days respectively. Analysis performed for input value of ACH = 0.51.

Figure 1

Figure 2A

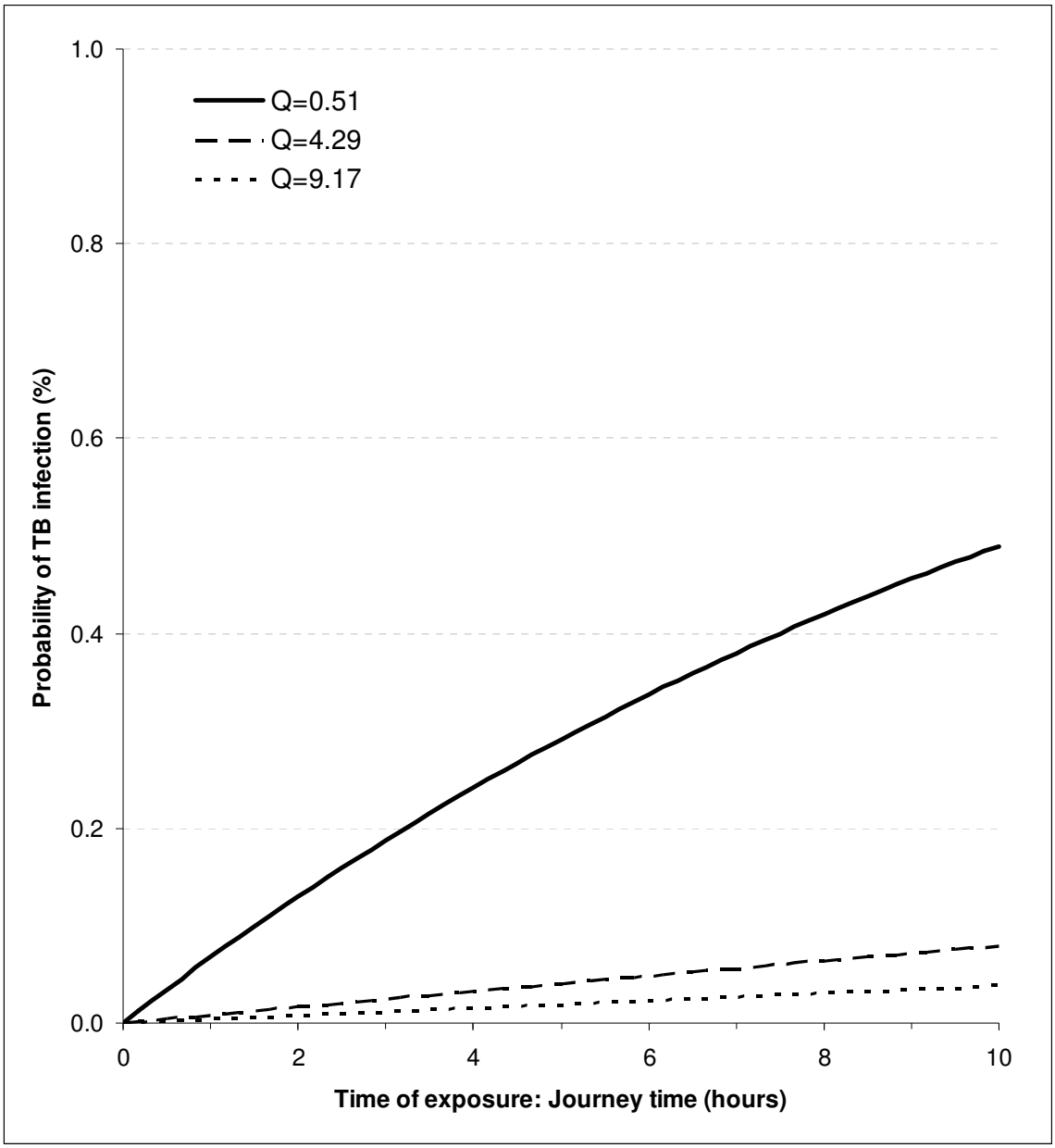


Figure 2B

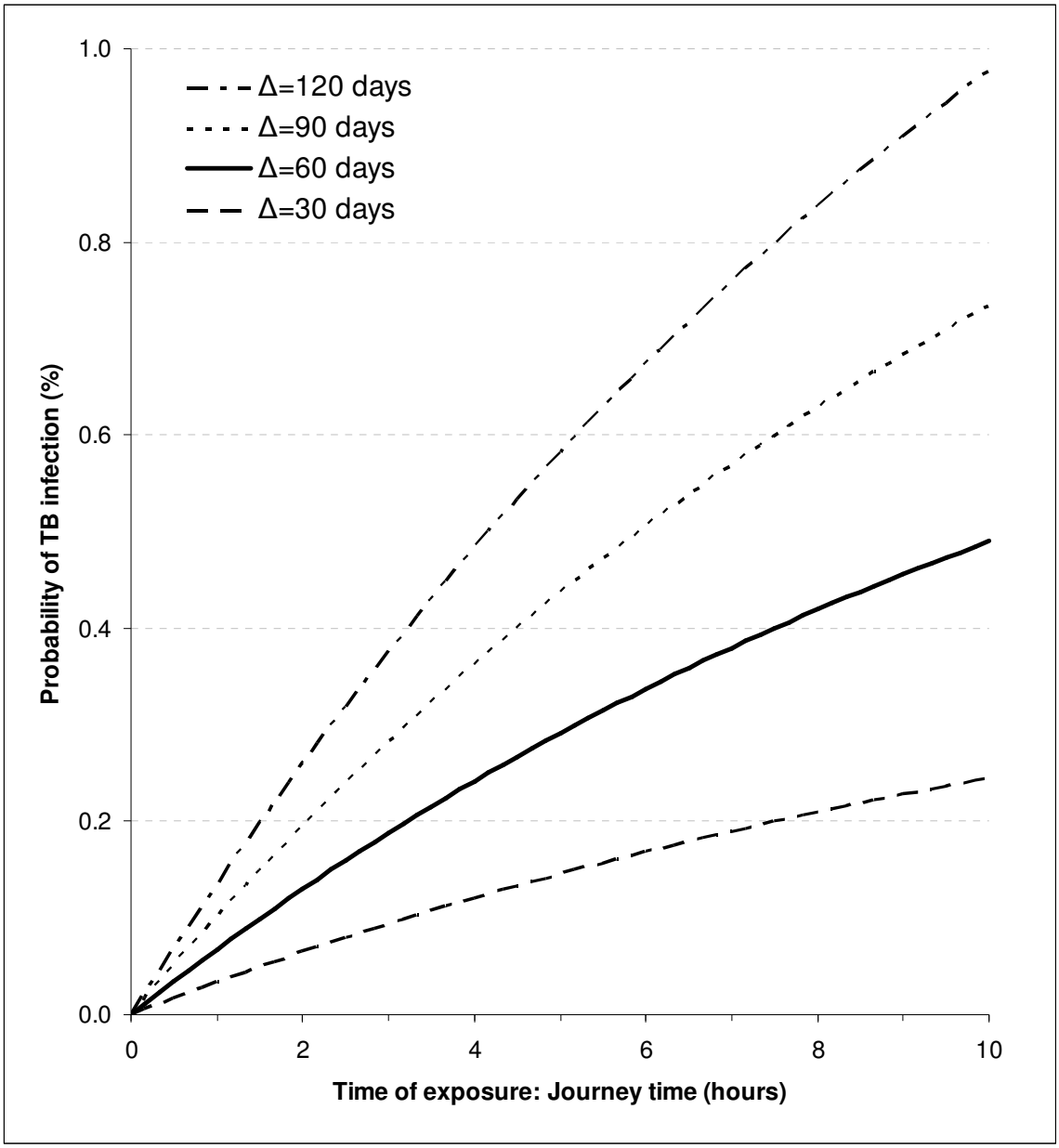


Figure 3A

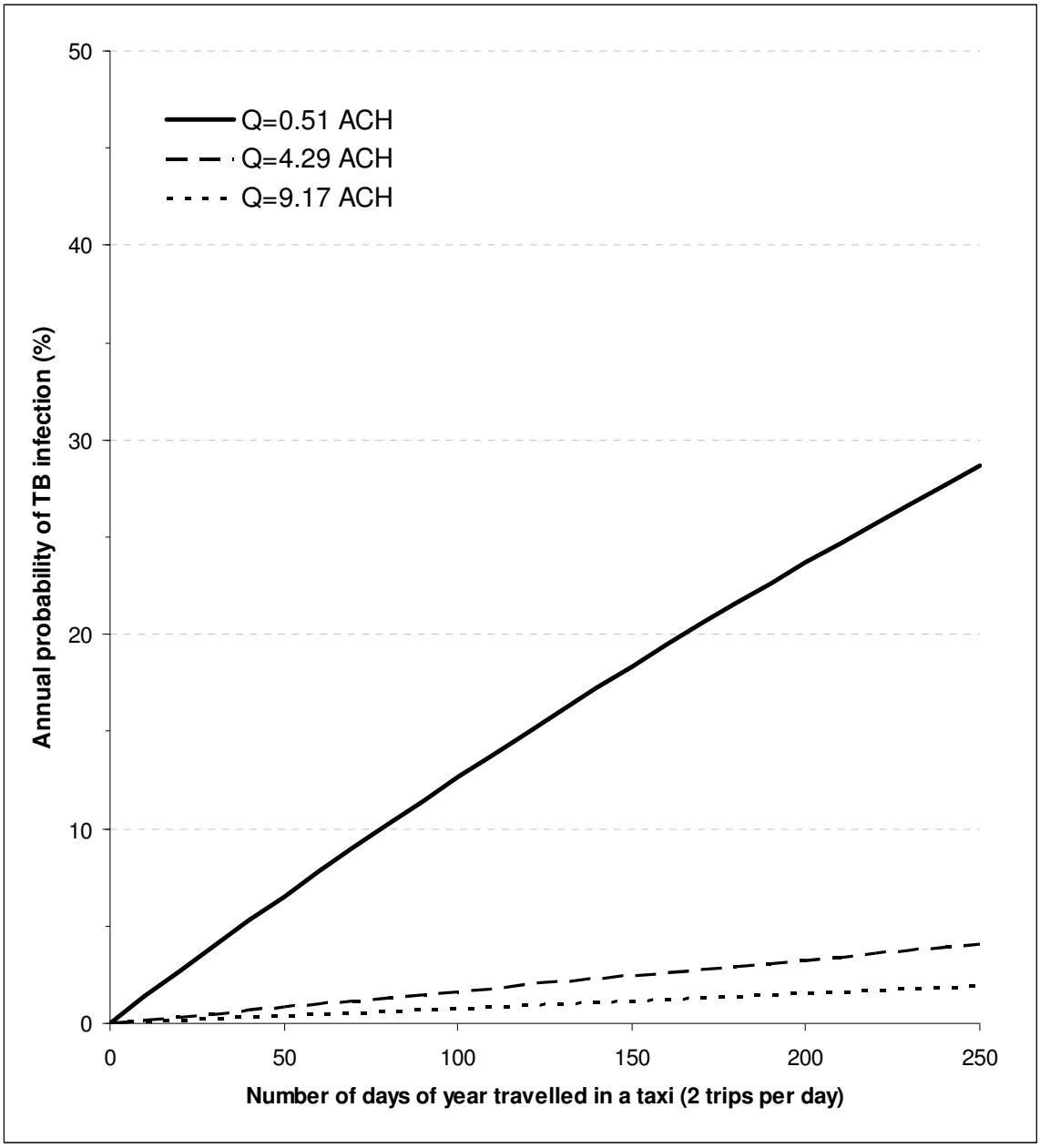


Figure 3B

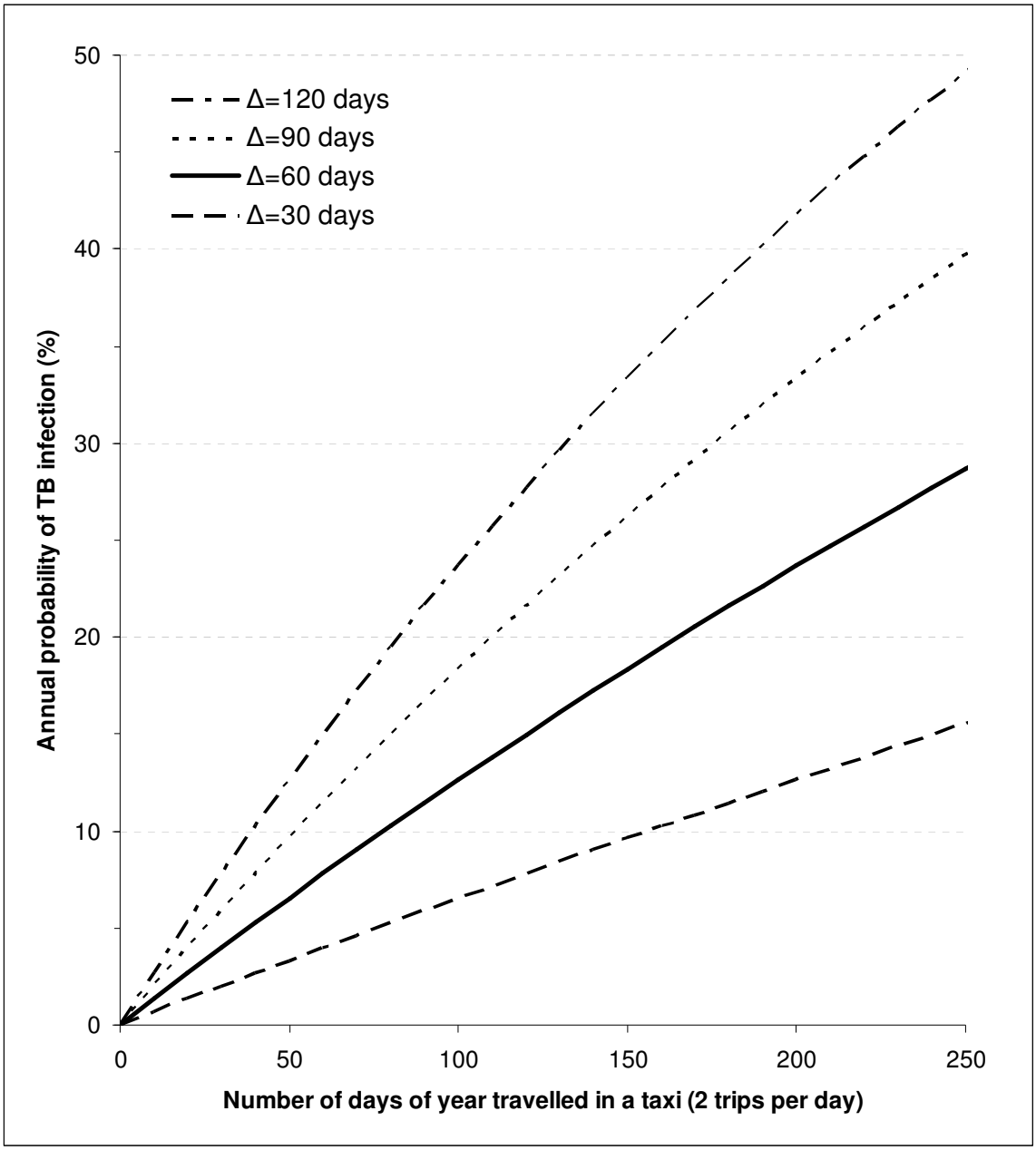


Figure 4A

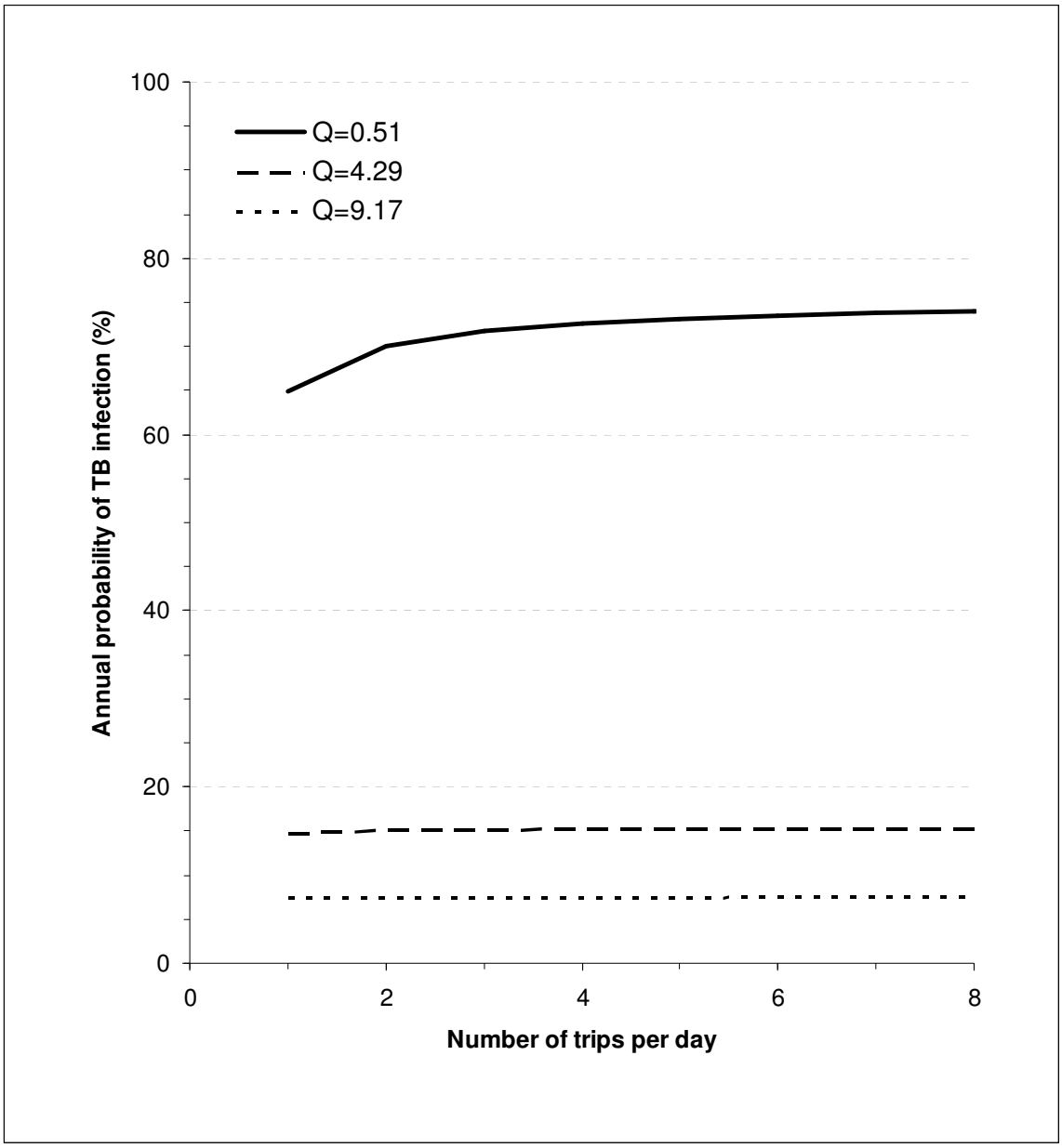
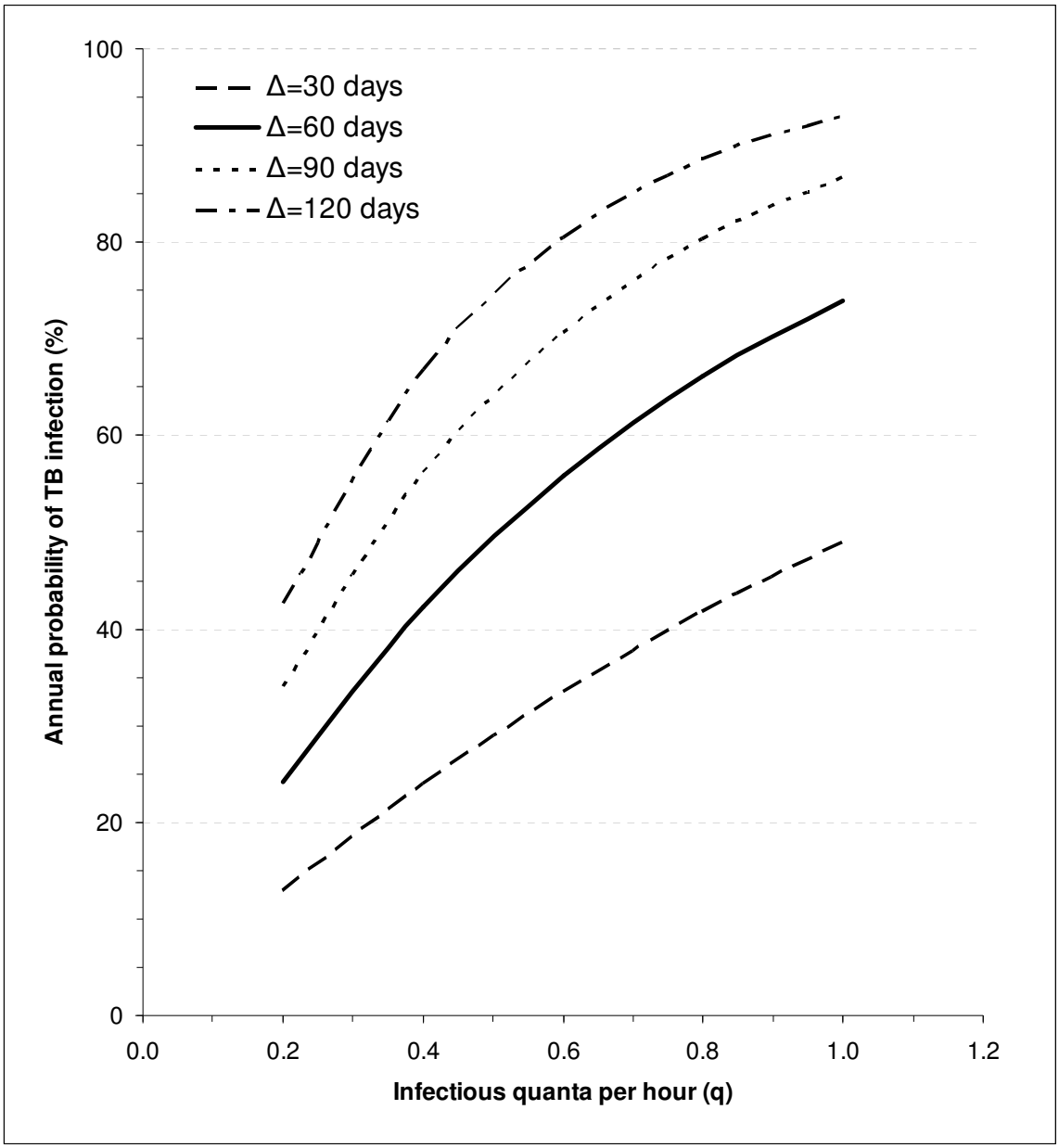


Figure 4B



5.3 Prisons

Please refer to the paper below entitled “Tuberculosis in a South African prison: a transmission modelling analysis” which describes the tuberculosis ARI an awaiting trial prisoner would face whilst incarcerated in a South African prison. The aim of this paper was to investigate the effect increased ventilation, reduced overcrowding, shorter lock-up times, and active case-finding would have on the ARI if current recommended South African and international standards were implemented. The paper was published in the *South African Medical Journal* in November 2011 (see Addendum for full publication details).

ORIGINAL ARTICLES

Tuberculosis in a South African prison – a transmission modelling analysis

Simon Johnstone-Robertson, Stephen D Lawn, Alex Welte, Linda-Gail Bekker, Robin Wood

Background. Prisons are recognised internationally as institutions with very high tuberculosis (TB) burdens where transmission is predominantly determined by contact between infectious and susceptible prisoners. A recent South African court case described the conditions under which prisoners awaiting trial were kept. With the use of these data, a mathematical model was developed to explore the interactions between incarceration conditions and TB control measures.

Methods. Cell dimensions, cell occupancy, lock-up time, TB incidence and treatment delays were derived from court evidence and judicial reports. Using the Wells-Riley equation and probability analyses of contact between prisoners, we estimated the current TB transmission probability within prison cells, and estimated transmission probabilities of improved levels of case finding in combination with implementation of national and international minimum standards for incarceration.

Results. Levels of overcrowding (230%) in communal cells and poor TB case finding result in annual TB transmission risks of 90% per annum. Implementing current national or international cell occupancy recommendations would reduce TB transmission probabilities by 30% and 50%, respectively. Improved passive case finding, modest ventilation increase or decreased lock-up time would minimally impact on transmission if introduced individually. However, active case finding together with implementation of minimum national and international standards of incarceration could reduce transmission by 50% and 94%, respectively.

Conclusions. Current conditions of detention for awaiting-trial prisoners are highly conducive for spread of drug-sensitive and drug-resistant TB. Combinations of simple well-established scientific control measures should be implemented urgently.

S Afr Med J 2011;101:809-813.

Prisons have high burdens of tuberculosis (TB) where overcrowding, lack of ventilation and poor prevention practices dramatically increase transmission risks of TB.[1-5] The TB burden is exacerbated in sub-Saharan Africa by a high prevalence of HIV infection among inmates, as TB is the most common opportunistic infection among people living with HIV in Africa.[6] A high TB prevalence and poor control policies within prisons also create potential breeding grounds for multidrug-resistant TB (MDR-TB).[4] TB transmission within prisons can also significantly impact on the wider community.[5]

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South Africa has the fourth highest global incarceration rate, with more than 165 000 prisoners in 237 operational prisons.[7] There is a rapid turnover of awaiting-trial prisoners with 79% being incarcerated for periods of less than 12 months.[8] The number of individuals passing through the prison system annually therefore exceeds 368 000.[8] Detainees either awaiting sentencing or awaiting trial comprise approximately a third of prisoners; they suffer the worst prison conditions, frequently being kept in large crowded communal cells housing 40 - 60 inmates for 23 hours per day.[7-10] International agencies recommend a minimum allocation of 5.4 m^2 of floor space per prison inmate,[11] while South African prison regulations stipulate a minimum allocation of 3.34 m^2 floor area in communal cells.[7] However, awaiting-trial prisoners are frequently housed in overcrowded communal cells for prolonged periods of time with floor space allocations as low as 1.4 m^2 per inmate.[7-10]

South African prisons' TB notifications have not been reported in the public domain or included in the annual judicial prison inspectorate reports.[7-10] The consequences of overcrowding on TB transmission in prisons have therefore not previously been quantified. However, previous incarceration was found to be a significant risk factor for prevalent TB in a population survey in Cape Town.[12] Prison inmates elsewhere have been identified as at high risk for TB, including MDR-TB and extensively drug-resistant TB (XDR-TB).[4-6]

A judgment was published in the case of Dudley Lee and the Minister of Correctional Services in which the plaintiff developed TB while an awaiting-trial prisoner in Pollsmoor prison, Cape Town.[13] Evidence during the trial described an understaffed and poorly functioning prison TB control programme, and data were presented on TB incidence, delays in accessing TB diagnosis and care, hours of lock-up, crowding and poor ventilation.

We aimed to explore probabilities of TB transmission of awaiting-trial prisoners incarcerated in communal cells in Pollsmoor correctional facility, Cape Town. We used the court case evidence[13] as parameters in a deterministic model[14,15] of the risks of TB transmission during imprisonment.

Methods

Study design

TB transmission probabilities were estimated using the Wells-Riley equation, a well-known transmission model that has been applied to a wide range of transmission scenarios,[14-20] including describing airborne transmission probabilities within a single enclosed room or space with defined ventilation characteristics.[15] We used this equation in combination with the distribution of inmates per cell and their probability of having TB that had been infectious for different periods of time, in order to explore prisoner-to-prisoner TB transmission probabilities. The modelled transmission probabilities were adjusted for daily lock-up periods and variable cell ventilation characteristics.

We then explored the effects of decreased crowding, shorter lock-up times, improved ventilation and improved case finding on TB transmission probabilities. Finally we explored combinations of changes to the TB control programme and prison conditions necessary to achieve significant reductions in TB transmission. Table I shows the values and ranges of key parameters used to populate the model.

Prison population

Pollsmoor maximum-security prison is the third-largest facility housing unsentenced prisoners in South Africa, with approximately 3 200 awaiting-trial and unsentenced prisoners at any time. They are predominantly incarcerated in communal cells of 40 - 60 prisoners and confined for 23 hours each day.[13] Overcrowding is persistently high with reported average occupancy rates of 235% in 2003[13] and 239% in 2008.[7] Cell ventilation is poor with a single slatted window on an exterior wall with openings of 6 088 cm^2 and a small ventilator grille with area of 126 cm^2 on the solid metal door, which is closed at night.

The TB control programme

South African prisons' TB control programme is similar to the national TB programme, which focuses on passive case finding of sputum smear-positive cases and directly observed short-course therapy.[25] However, because of chronic nursing shortages the strategy was poorly implemented, with no active case finding, and inmates with symptomatic TB could wait up to 4 months before referral to the prison hospital.[13] Medical staff did not systematically screen newly arriving prisoners for symptoms or signs of TB.[13] Notification registers between 1998 and 2009 were inconsistently completed, resulting in significant under-reporting of TB cases; 177 prisoners commenced TB therapy in 2001 – a notification rate of 5.5 TB cases per 100-person prison years.[13] However, a prison medical officer gave evidence that during the year, 264 prisoners had laboratory confirmation of acid-fast bacilli on direct sputum smear, indicating marked under-reporting of a TB incidence rate of 8.25 cases per 100-person prison years, that MDR-TB was prevalent among inmates, and that a staff member had died from this form of the disease.[13]

Mathematical transmission model

The number of TB infections (C) occurring in a prison cell with susceptible prisoners (S) was assumed to be a function of the number of infectious cases (I), their infectivity (q = quanta of infectious particles produced per hour), time of exposure (t = time of exposure in minutes), respiration rate (p = litres per hour), and germ-free ventilation (Q = litres per hour) as given by Wells-Riley equation $C = S(1-e^{-(pqt/Q)})$. The prevalence (P) of infectious adults at any time is given by the annual smear-positive incidence rate (M = per cent) and the period of infectivity (Δ = days) as $P = M/[365/\Delta]$. The risk of contact with an infectious adult is given by the Poisson distribution $(\lambda^1/1!)e^{-\lambda}$, where $\lambda = P^*(A-1)$ is the expected number of infectious cases in a cell with 'A = I + S' adults.

Modelled input parameters

Germ-free ventilation (Q) was calculated as air changes per hour (ACH) for a standard cell of 9.1 m long × 6.4 m wide × 3.35 m high with a volume of 195 m^3. Current cell ventilation would provide less than 1 ACH with all windows and the door ventilator grille open with

Table I. Parameter definitions and ranges used in model

Parameter	Description	Values	Data sources
M	TB incidence rate	5.5 cases/100-person prison years*	Lee v Minister of Correctional Services[13]
Δ	Period of infectiousness	1 - 180 days	Lee v Minister of Correctional Services,[13] Storla *et al.*[21]
q	Infectious quanta	1 per hour	Riley *et al.*,[15] Cantazaro,[16] Noakes & Sleigh,[17] Nardell *et al.*,[18] Furuya *et al.*,[19] Wood *et al.*[20]
Q	Ventilation	1, 3, 8, 12 ACH†	Lee v Minister of Correctional Services,[13] Dara *et al.*,[22] WHO[23]
p	Respiratory volume	360 litres/hour	Pinna *et al.*[24]
S	Prisoners/cell	58.24 m^2/3.34 m^2‡	
	Cell dimensions	9.1 m × 6.4 m × 3.35 m	Lee v Minister of Correctional Services[13]
	Floor area per prisoner	1.42 m^2, 3.34 m^2, 5.4 m^2	Lee v Minister of Correctional Services[13], Dara *et al.*,[22] WHO [23]

NB *TB incidence rate based on 177 cases in prison population of 3 200.[13]

†ACH = air changes per hour for cell of 195 m^3 volume.

‡Cell floor area is 9.1 m × 6.4 m = 58.24 m^2. Prisoners per cell = the floor area divided by the space allocated per prisoner, a minimum of 3.34 m^2 according to South African regulations. If the cell was 200% full then there would be twice as many prisoners present.

totally free flow of air through the cell and a 10 km/h wind directed towards the window.[26] International recommendations for prison ventilation[22] based on the floor area of this cell would recommend 1.8 - 3.58 ACH, and the World Health Organization (WHO) recommends 12 ACH for health settings and congregate settings where TB is prevalent.[23] Four values of ACH were therefore modelled: the *status quo* of 1 ACH (poor ventilation); 3 ACH (minimum international recommended ventilation); 8 ACH (intermediate ventilation); and 12 ACH (optimal ventilation).

A wide range of estimated values for the rate of production of infectious TB quanta (q) have been reported. Laryngeal TB is highly infectious with 'q' estimated at 60 infectious quanta per hour.[16] In a workplace outbreak due to an untreated smear-positive pulmonary case, 'q' was estimated at 12.7 infectious quanta per hour.[18] Over a 2-year period in a TB ward, 'q' was directly measured at 1.25 infectious quanta per hour.[15] A study applying molecular strain characterisation to track airborne TB transmission from HIV/TB-infected inpatients to guinea pigs demonstrated markedly variable infectiousness.[27] Values of 'q' for infectious cases varied between 3 and 12 and 2.5 and 226 quanta per hour for individuals with drug-sensitive and MDR-TB respectively. In order to be conservative, 'q' was modelled at a mean value of 1 infectious quantum per hour.

The mean respiratory rate of adults (p) was estimated to be 360 litres per hour corresponding to a normal adult respiratory minute volume of 6 litres per minute.[24]

A key parameter of the model, the period of infectiousness (Δ), has a strong inverse association with the TB control programme effectiveness of case finding. Δ is a composite of delays, including time to access medical care, diagnostic delay and time to commence chemotherapy. The diagnostic delay period during which an adult may be infective is variable, but is frequently reported to be 60 - 90 days.[21] However, delays in accessing treatment within this prison were reported to be very prolonged; therefore analyses were performed with values of Δ from 1 day up to 180 days.

Passive case finding depends on individuals with symptoms of TB self-presenting for investigation. It was modelled that with increased TB awareness health messaging, minimal delay in accessing TB services, expeditious diagnosis and rapid initiation of chemotherapy, the period of infectiousness (Δ) could be reduced to 60 days. Active case finding (regular seeking out symptomatic prisoners) and rapid diagnostic testing[28] was modelled with values of Δ of less than 60 days.

Results

We explored the impact of cell occupancy on TB transmission probabilities. Transmission probabilities at existing levels of overcrowding, the recommended minimum South African and international recommended occupancy are shown across a spectrum of time periods of infectiousness of source cases (Δ) from 1 to 180 days in Fig. 1. Transmission probabilities under prevailing conditions of incarceration were estimated at 90% per annum for all values of Δ (>60 days) currently implementable by the prison TB control programme. The benefits of decreasing cell crowding were proportionate at all values of Δ. Implementing current South African recommended cell minimum levels of occupancy would reduce transmission by 30% and implementing international recommendations would reduce transmission by over 50%, even with current levels of TB case finding.

The effect of decreasing lock-up time (period restricted to cells each day) is shown for the existing conditions of 23 hours per day and for reductions to 12 and 8 hours per day respectively in Fig. 2. The benefits of decreasing lock-up time are modest at current values of Δ

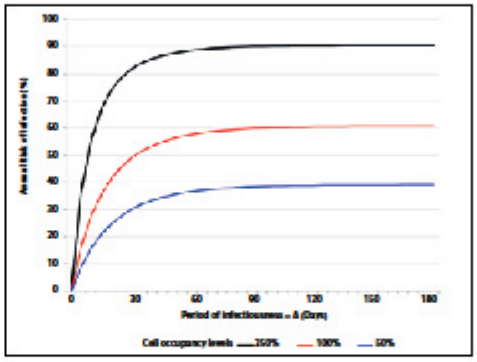

Fig. 1. The effect of prison cell overcrowding on TB transmission probabilities is plotted against time periods of infectiousness up to 180 days. They are shown for 3 levels of overcrowding; 250% approximates the current level cell occupancy;[13] 100% represents implementation of current South African statutory minimum occupancy of 3.44 m² of floor space per inmate,[7-10] and 50% corresponds to international space recommendations.[22]

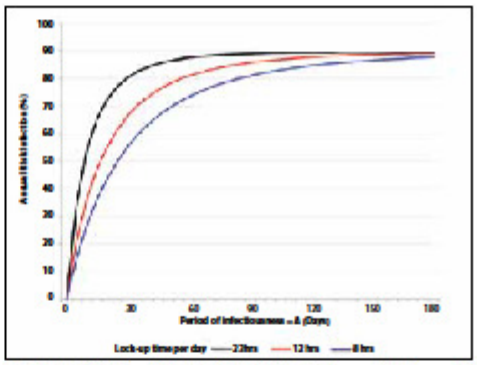

Fig. 2. The effect of length of period of restriction in prison cell per day on TB transmission probabilities is plotted against time periods of infectiousness up to 180 days, shown for 3 time periods of cell occupancy during a 24-hour period;[23] hours per day, 12 hours per day and 8 hours per day. NB: 23 hours per day is the current period of restriction to cells in Pollsmoor prison.[13]

(approximately 180 days). However, the benefits of decreased lock-up times are amplified by improving case finding with consequent reductions in Δ. When Δ is reduced to 60 days, reduction of lock-up time to 12 and 8 hours would reduce TB transmission by 10% and 20%, respectively.

The effect of cell ventilation on TB transmission probability is shown in Fig. 3. Three levels of ventilation were modelled in addition to the current reported estimate of 1 ACH: 3 ACH; 8 ACH; and 12 ACH. Improved ventilation markedly decreases TB transmission probabilities at all values for Δ. However, improvements in ventilation are amplified when accompanied by reductions in the value of Δ which could be achieved by improved case finding.

Finally, we explored effects of improved case finding in three different scenarios (Fig. 4): scenario 1 – *status quo*; scenario 2 – current South African regulations for imprisonment with modest increase of ventilation to 3 ACH fully implemented; and scenario 3 – international standards for imprisonment together with ventilation

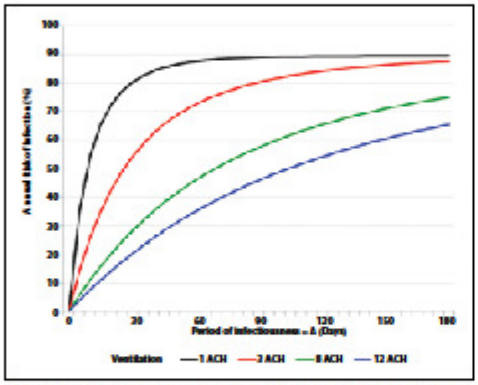

Fig. 3. The effect of increasing levels of cell ventilation on TB transmission probabilities is plotted against time periods of infectiousness up to 180 days. They are shown for 4 values of ventilation air change per hour (ACH): 1 ACH (current estimated cell ventilation), 3 ACH (minimal international recommendation),[22] 8 ACH (moderately increased ventilation) and 12 ACH (the optimal level of ventilation recommended by WHO for health care settings).[23]

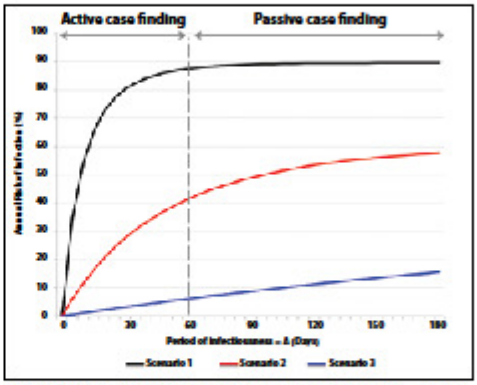

Fig. 4. TB transmission probabilities for 3 scenarios: scenario 1 – approximates the status quo using parameters of 250% overcrowding, 1 air change per hour (ACH) and cell occupied for 23 hours per day; scenario 2 – immediately achievable parameters of 100% occupancy, 3 ACH and cell occupied for 23 hours per day; scenario 3 – optimised implementation of international recommendation of 5.4 m² floor space, 14 hours of cell occupancy per day and 12 ACH.

at 12 ACH fully implemented. Improving passive case finding to achieve a Δ of 60 days would have minimal effect on TB transmission in scenario 1 and 20% and 50% reductions in scenarios 2 and 3, respectively. Active case finding to achieve a Δ of 30 days would decrease transmission by 10% with current scenario 1, 50% with implementation of scenario 2, and 90% with implementation of scenario 3.

Discussion

This study shows that conditions prevailing in a South African prison are extremely conducive for ongoing transmission of TB. Crowding, substandard living conditions and a poorly functioning prison TB control programme combine to contribute to high TB transmission risks. Overcrowding of cells directly and proportionately increases the probability of contact with infectious sources. Delays of 3 - 4 months in accessing medical care,[13] together with time required for diagnosis and implementing therapy,[21] markedly increase the prevalence of infectious cases, and act as the primary source for ongoing transmission.

We show that the very high prevalence of infectious cases within the prison population potentially negates the benefits of improved ventilation and shortened exposure time within cells. The interdependence of all the transmission risk factor parameters is further highlighted by the observation that improved passive case finding sufficient to reduce the period of infectiousness from 6 to 2 months would have a minimal effect under current conditions of crowding and poor ventilation. However, the multiplicative benefits of concurrent improvements in case finding, crowding and environmental conditions are demonstrated. Active case finding and implementing current national minimum standards of cell occupancy[7] can reduce transmission by 50%. Introducing international environmental standards[22,23] could reduce transmission from the *status quo* by as much as 94%.

Our study strength was available accurate information specific to this prison: number of TB cases, cell dimensions, number of prisoners per cell and likely delays in accessing TB treatment. A limitation of the model is that precise enumeration of the number of infective quanta produced by a prisoner with TB is difficult. A very conservative estimate was therefore derived from published data.[15-20,25,26] The modelled analysis was also restricted to transmission events within an illustrative typical communal prison cell within a single operational prison. However, similar and even more severely crowded conditions are endemic in South African prisons.[7-10] The model was based on the epidemiological assumption that the TB epidemic was generalised, with equal mixing of infectivity and contact risks. Therefore the analysis was restricted to transmission events occurring within the cell, and stochastic transmission events such as close contact with highly infectious individuals outside the cell are not captured. Despite these limitations, the model outputs are compatible with the very high TB incidence rate relative to the rest of Cape Town's population,[15,20] and robustly demonstrated the proportional impact of different control strategies on transmission probabilities.

The analysis was restricted to acquisition of infection and not development of disease. The relationship between newly acquired infection and disease development is complex.[30,31] Prior TB infection in immune-competent individuals, which is common in Cape Town,[32] gives some protection against disease related to subsequent infection.[33] However, those not previously infected,[34] those with previously treated TB[31] and those with HIV infection[35] would be particularly vulnerable to progress to active TB disease following recent exposure to infection. We did not specifically address transmission of MDR- and XDR-TB, but transmission risks with these may be heightened as a result of the prolonged period of infectiousness that often results from failure of diagnosis and subsequent receipt of inappropriate therapy. However, accurate MDR- and XDR-TB prevalence data are not available to permit modelling.

'A society should be judged not by how it treats its outstanding citizens but by how it treats its criminals.'[36] We show that the conditions in which awaiting-trial prisoners are confined fall far below our own national[7-10,13] and international standards for incarceration[22,23] and constitute a health emergency. The medical and environmental health professions and the judiciary must urgently work with the Department of Correctional Services to institute

simple scientifically based disease control measures that need to be tailored to circumstances and resources. Many strategies are available to address the problem. The Judicial Inspectorate has repeatedly proposed the measures required to decrease the awaiting-trial prison population.[7-10] Cell ventilator grills should not be closed at night; cross-ventilation of communal cells could be encouraged by using barred rather than solid doors and incorporating corridor ventilator extraction systems. Since 1847, carbon dioxide levels have been used as a measure of adequate ventilation[37] and carbon dioxide monitoring could readily establish if effective improvements in cell ventilation are being achieved. Prison TB control programmes should introduce active case finding[21] and use recent technological advances in rapid TB diagnosis and drug resistance.[38] TB notification data for South African prisons should not be considered secret or restricted information, but accurate data should be made available to the Judicial Inspectorate of Prisons to include in the annual report on the state of our prisons.[7-10]

TB transmission risks within our prison system are unacceptably high, posing a direct hazard to prisoners and contributing to the general population TB burden. Overlooking TB prevention and control in prisons carries serious health consequences for both prisoners and the general community.[1-2,38]

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Chapter 6: Discussion

The research presented in this thesis was performed with the aim of improving the current, generally poor understanding of TB transmission. In addition, the role several key parameters, such as overcrowding, fresh-air ventilation, and period of infectivity, play in determining whether transmission will take place or not was explored, together with the potential impact various interventions could have in reducing the TB transmission risk associated with several indoor settings. An established airborne transmission risk model, namely the WRE, was first modified to take into account scenarios where the number of infectious cases may not be known, such as settings where TB is endemic or where prospective TB transmission risk assessment is to be performed. Subsequently, indoor locations (enclosed spaces) conducive to TB transmission were identified in a social mixing survey performed in a South African community where TB is endemic. Of the four indoor locations identified in the survey, the TB transmission risk in households and during travel in minibus taxis was determined using the modified WRE. Likewise, the risk of TB transmission in a hypothetical prison cell, similar to that which awaiting trial prisoners would typically be incarcerated in within South Africa, was also calculated.

In general, poor ventilation conditions, severe levels of overcrowding, extended periods of exposure, and high incidence rates all contributed to the high TB transmission risks calculated for each of the three indoor locations. Specifically in households, the ARI for children was determined by the number of adults living in their household, and was shown to be comparable to previous estimates determined independently for the same community[26]. Also, the excessively high levels of overcrowding meant that the household-associated TB transmission risk would not be substantially impacted by the passive case-finding efforts of the existing TB control program unless ventilation rates within households were improved at the same time. Similar reductions in the ARI could be achieved by either the trebling of current ventilation levels or by the separation of child and adult sleeping areas. Neighbours' households were also shown to be potential sources for further infection, with the difference being that the risk of infection in these households was more dependent on fresh-air ventilation and the average period of infectivity of infectious cases within the community. The analyses also indicated that as children become more socially active, neighbours' households could potentially become the largest contributors to a child's overall TB transmission risk. During travel in minibus taxis, windows were for the most part kept fully closed or only partially open during the journey so that ventilation was generally very poor. Consequently, the ARI for both commuters and drivers was found to be exceptionally high. By opening windows or keeping the vehicles fan on to circulate fresh-air, the risk of transmission would be reduced substantially. Also, the risk of transmission was found to depend on the average period of

infectivity since this would determine the prevalence of infectious cases travelling on such transport. Any reduction in the period of infectivity, whether through active or passive case-finding, would therefore serve to decrease the risk of infection as well. It is important to note that the modelled ARI calculated for minibus taxi transport did not take into account transmission by non-buoyant large infectious respiratory droplets (i.e. Flügge droplets) or contaminated surfaces (fomites). Transmission by either of these two modes, however, is probable during such transport since the level of crowding is greater than even that seen in households in the social mixing study (as well as in the census data used to calculate the household infection risk in Section 5.1). Thus the risk may be even greater than that which was modelled. In the analysis of the South African prison cell, it was found that the current levels of overcrowding contributed considerably to the high ARI, with the risk of TB transmission proportional to the level of overcrowding. The poorly functioning prison TB control programme also only served to further exacerbate the situation by extending the average length of time that any susceptible person would be exposed to infectious cases. In addition, it was noted that with such poor living conditions any one single intervention on its own, such as increased ventilation, decreased lock-up time, or increased case-finding, would not make a significant difference to the ARI, however the concurrent implementation of each of these interventions to meet current recommended national or international standards would.

Importantly, when it comes to understanding TB transmission, this research has shown that TB is not only transmitted in epidemic outbreaks where TB cases are usually highly infectious (sometimes referred to as "super-spreaders" or "dangerous disseminators")[55], but rather that any TB case, no matter how infectious they may be, has the potential to infect susceptible people in the general population. This is a direct consequence of the mathematical analysis of the three TB transmission 'hotspots' which revealed that the risk of infection in settings where TB is endemic may be considerable. In addition, although the purpose of this research was not to determine the predominant means by which TB is spread, it did reveal that airborne transmission by droplet nuclei has the potential to account for all the ongoing transmission still seen in communities where TB is endemic[22,25-28]. Thus any lingering doubt there may have been (after Wells' and Riley's TB ward experiments) with regards to the predominant mode of TB transmission has been quashed.

At this point it is relevant to mention that both the WRE (Equation 2) and its modified form (Equation 8) describe the number of susceptible people that will be infected after exposure to infectious cases and not the number of TB cases that will develop subsequent to infection. However, in populations such as the one in which the social mixing survey was conducted, where young children, HIV-infected individuals, and those previously treated for TB comprise a

substantial proportion of the community, one can expect to see a significant proportion of those who are infected to progress to disease.

One of the strengths of the modified WRE (Equation 8) worth mentioning here is that, without losing any information contained in the original WRE (Equation 2), it managed to capture any uncertainty there may be with regards to the number of infectious cases when being used in prospective risk assessment or applied to scenarios where TB is endemic. The most important consequence of this modification is that the effects of overcrowding, previously associated with TB transmission but never before quantified[2-6], can now be estimated.

The modified WRE does not do away with any of the original equation's assumptions either, but instead adds an extra condition to those already assumed. The first of the assumptions was that the susceptibles are exposed to the infectious TB case(s) under *equilibrium conditions* (when the quanta production rate equals the rate at which quanta are removed from the indoor environment by fresh-air ventilation). The risk of infection in situations where equilibrium has not yet been reached may therefore differ slightly from that predicted by the model. However, due to the typically extended length of time residents spend in households (as determined by the social mixing survey) and prisoners are locked up in their cells, the time it would take for equilibrium conditions to be reached would be short compared to the overall exposure time, and therefore the modelled infection risks in households and prisons can be taken as approximately equal to the actual transmission risks. Although this same argument is not always necessarily true for travel in minibus taxis, the fact that sustained poor ventilation conditions were frequently recorded during this means of transport supports the high TB transmission risk that was modelled with the modified WRE. For more accurate estimates in this and other settings where the equilibrium assumption is not strictly valid, though, the model developed by Gammaitoni and Nucci, which allows the concentration of quanta to vary with time, would be more appropriate[41]. In the second assumption it was held that quanta are discrete, randomly distributed, and in low concentration, all of which were confirmed by Wells and Riley in their TB ward experiments[9-11]. On occasion however, it is likely that the quanta will be non-randomly distributed but related to the proximity from the infectious source case(s). Such scenarios have been dealt with previously by treating individual rooms (spaces) separately in zonal and computational fluid dynamic models[43-45]. This added complexity was not deemed necessary to fulfil the primary purpose of this research though, and consequently it was not incorporated into the model. The third and extra assumption of the modified WRE was that every adult present in an indoor location (enclosed space) was equally likely to be an infectious case. Although simplistic, this 'first principles' approach at estimating the number of infectious cases became one of the strengths of the model, allowing the quantification of the effects of overcrowding on the TB

transmission risk as already discussed above. With this being said, the homogenous distribution of infectious cases throughout a community is unlikely, though, with it being more probable that infectious cases are grouped together within the same households for example. Other methods to take this fundamental assumption closer to that of reality is therefore required to better understand the relationship between overcrowding and TB transmission risk.

One potential weakness of the modelling was that of the quanta production rate q chosen to represent the infectiousness of the *average* TB case. Other than the fundamental TB ward experiments performed by Wells and Riley[9,11,38], all previous estimates of q were back-calculated from well documented TB epidemics resulting from *highly infectious* cases[49-51,53], and were therefore not directly applicable. Consequently, q was made equal to the *average* infectivity of the patients residing on the TB ward. This was despite Wells and Riley recommending the use of caution when doing so, due to the large variation they observed between individual TB cases residing on the ward[9]. A variable such as the quanta production rate is likely to be complicated by other factors which were not considered here, some of which may include the cough and sneeze frequency of the infectious individual, the pathogen concentration in their respiratory fluid, and the aerosol volume per expiratory event[55]. A first step to improve estimates of the risk of TB transmission would therefore be to improve the current understanding of the variability in infectiousness of TB cases. One way this could be done would be to determine the proportion of TB cases in a population with a given measure of infectivity and to then use a probabilistic approach for the level of infectivity q similar to that used in Equation 8 for the number of infectious individuals. A further caveat with regards to the modelling was that the effect of HIV on the parameter values was completely ignored. HIV co-infection may alter the infectiousness of a TB case or the period of infectivity (due to differing presentation of those infected with HIV compared to those who are not), so that communities where HIV prevalence is high (such as the one in which the social mixing survey was performed) should have its effects taken into account. A final potential weakness of the modelling was that the proportion of TB cases on treatment was not taken into account when using the annual smear positive incidence to determine the number of infectious cases present in an indoor setting. Sultan et al showed that upon initiation of chemotherapy the infectiousness of TB cases decreases dramatically within a short space of time, so that these cases can essentially be regarded as non-infectious[38]. The number of infectious cases may therefore have been overestimated in this analysis and should be adjusted for in future estimations of the ARI.

Despite the above mentioned limitations, the modified WRE holds potential for application to other ‘hotspot’ settings within similar communities and in particular to those settings where there is uncertainty in the number of infectious cases. Also, it can be easily extended to account for any

uncertainty that may exist with regards to other parameters as well, so that ultimately more accurate estimates of the ARI can be determined.

In conclusion, the extension of a well-established airborne transmission model has enabled the ARI associated with several TB transmission 'hotspots' in a South African community where TB is endemic to be calculated. The relationships between parameters such as ventilation, source case infectivity, time of exposure and risk of infection, as established by Wells and Riley, were revisited at the same time, whilst the effect of overcrowding on the ARI was quantified for the very first time. In general, it was found that the current efforts of the TB control program need to be intensified and the general population needs to be better educated about the role ventilation and overcrowding can play in determining the risk of TB infection.

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Addendum – Evidence of Publication of Peer-Reviewed Papers and Permission to Include Them as Chapters

Chapter 4: Social Mixing Survey – Identifying Indoor Locations Conducive to Tuberculosis Transmission

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The contribution of SP Johnstone-Robertson included designing and directing the study, randomly selecting participants, simulating disease spread, and writing the manuscript. The journal's permission to reproduce this paper as a chapter in this thesis is provided below.

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Simon Johnstone-Robertson <spjohnstonerobertson@gmail.com> **Fri, Jun 24, 2011 at 12:14 AM**
To: "Barbre, Cynthia" <cbarbre@jhsph.edu>, "Telljohann, Harriett" <htelljoh@jhsph.edu>

Dear Harriet/Cynthia,

I have two things that I need to find out but am not exactly sure who I should be asking and so have emailed both of you. The first thing is that I have followed the instructions in the technical review emailed to me by Dr. Lipsitch with regards to submitting figures designed in Word, Excel, Powerpoint. The instructions requested that 'figures created in Word, Excel, Powerpoint, ... be submitted in that format.' Whilst submitting these files I selected that they were 'high-resolution figures' as I was not sure what else to select, but consequently when viewing the pdf output at the end of the submission process, they looked blurry and low resolution. What I would like to know is whether this matters, or will the fact I have submitted the Word, Excel, Powerpoint files allow AJE to ensure the figures are high quality when being published?

The second thing that I would like to find out is the following... As I am currently completing my MSc by research (registered at Stellenbosch University with the South African Centre for Epidemiological Modelling and Analysis) I am required to include papers that I have published as individual chapters in my thesis. The social mixing paper accepted by AJE would form an integral part of my results, and consequently I request that AJE give me permission to use the paper as a chapter. The paper will be introduced by a brief 1 or 2 page outline of what the aim of the research was, and I will make sure to reference that the paper was published by AJE. Would you be so kind as to grant me permission to use the paper as a chapter in my thesis?

Regards,

Simon Johnstone-Robertson
[Quoted text hidden]

Telljohann, Harriett <htelljoh@jhsph.edu> **Fri, Jun 24, 2011 at 12:31 AM**
To: Simon Johnstone-Robertson <spjohnstonerobertson@gmail.com>, "Barbre, Cynthia" <cbarbre@jhsph.edu>

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"There is only one satisfying way to boot a computer!"

Harriett Telljohann

Administrator, American Journal of Epidemiology

Chapter 5: Application of Theory

5.1 Households

Publication details:

Wood R, Johnstone-Robertson S, Uys P, et al. Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. *Clin Infect Dis.* Aug 15 2010; 51(4):401–408 (DOI: 10.1086/655129, http://cid.oxfordjournals.org/content/51/4/401.full) by permission of Oxford University Press.

The contribution of SP Johnstone-Robertson included designing the study, modelling the infection risk, interpreting the results, and writing the manuscript. The journal's permission to reproduce this paper as a chapter in this thesis is provided below.

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5.2 Taxis

This paper is in draft form and is not currently under review for publication with any journal. The contribution of SP Johnstone-Robertson included designing the study, modelling the infection risk, interpreting the results, and writing the manuscript.

5.3 Prisons

Publication details:

Johnstone-Robertson S, Lawn S, Welte A, Bekker L-G, Wood R. Tuberculosis in a South African prison – a transmission modelling analysis. *S Afr Med J.* Nov 2011; 101(11):809–813

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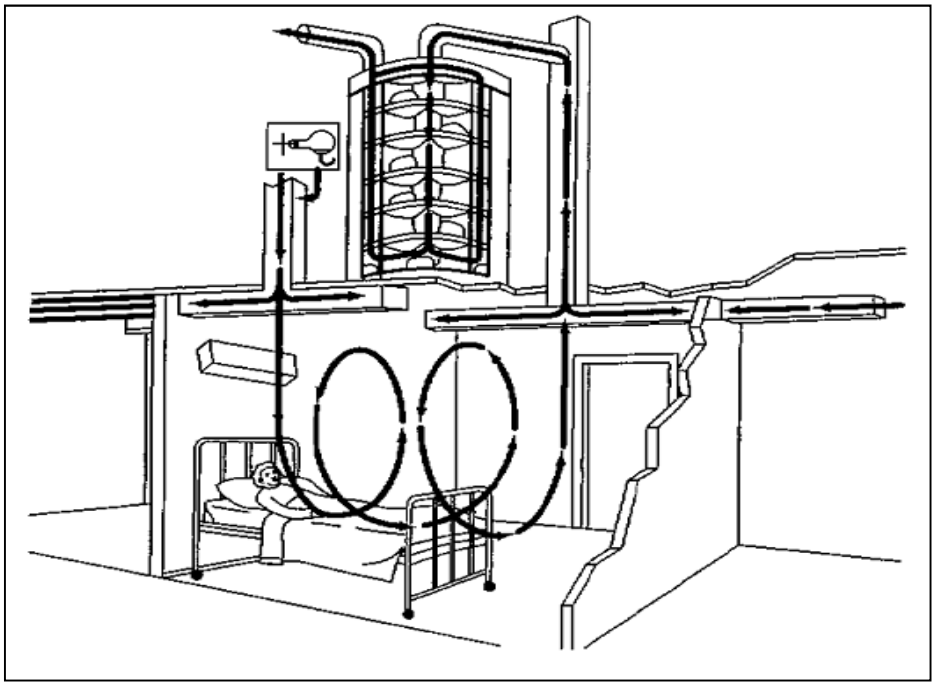

Figure 1

A schematic diagram of the 6-bed hospital TB ward and animal exposure chamber used by Riley et al to confirm that droplet nuclei, capable of transmitting MTB, could be produced in an infectious TB case's respiratory tract during processes such as talking, coughing, and sneezing.[10]

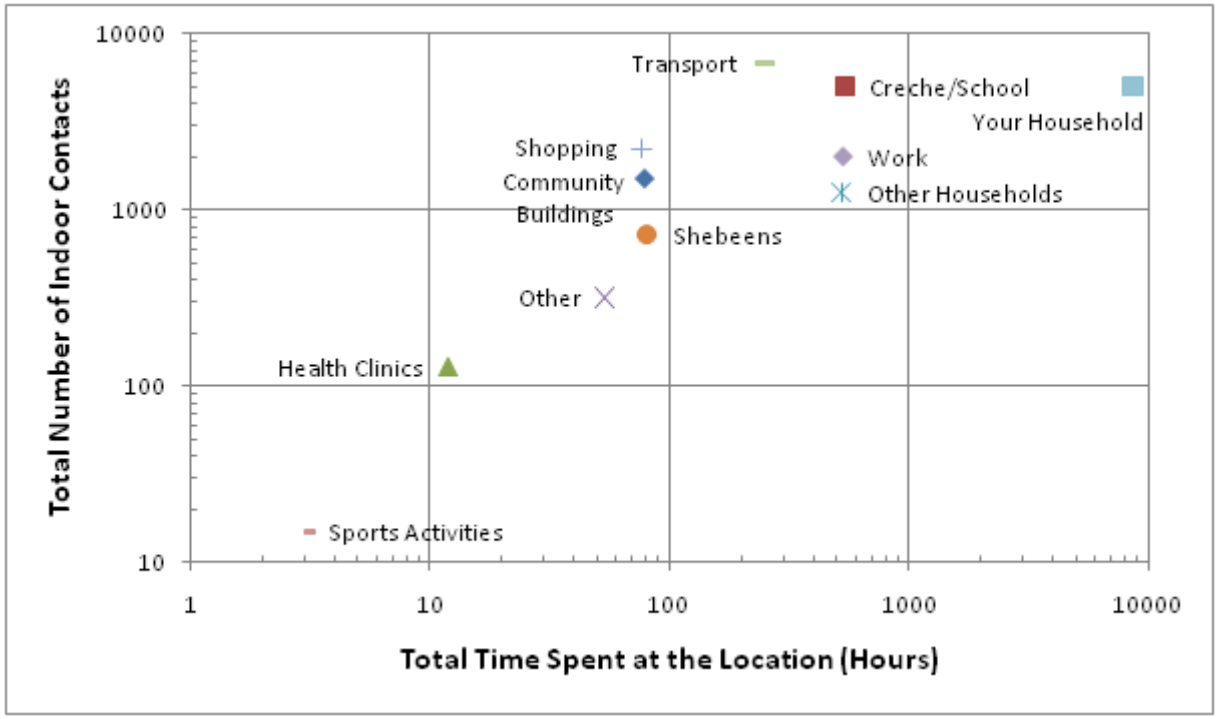

Figure 2

The total number of contacts met at various indoor locations (enclosed spaces) versus the total amount of time spent at each location, as recorded over a 24 hour period by residents of a township community where TB is endemic just outside Cape Town, South Africa in 2010.

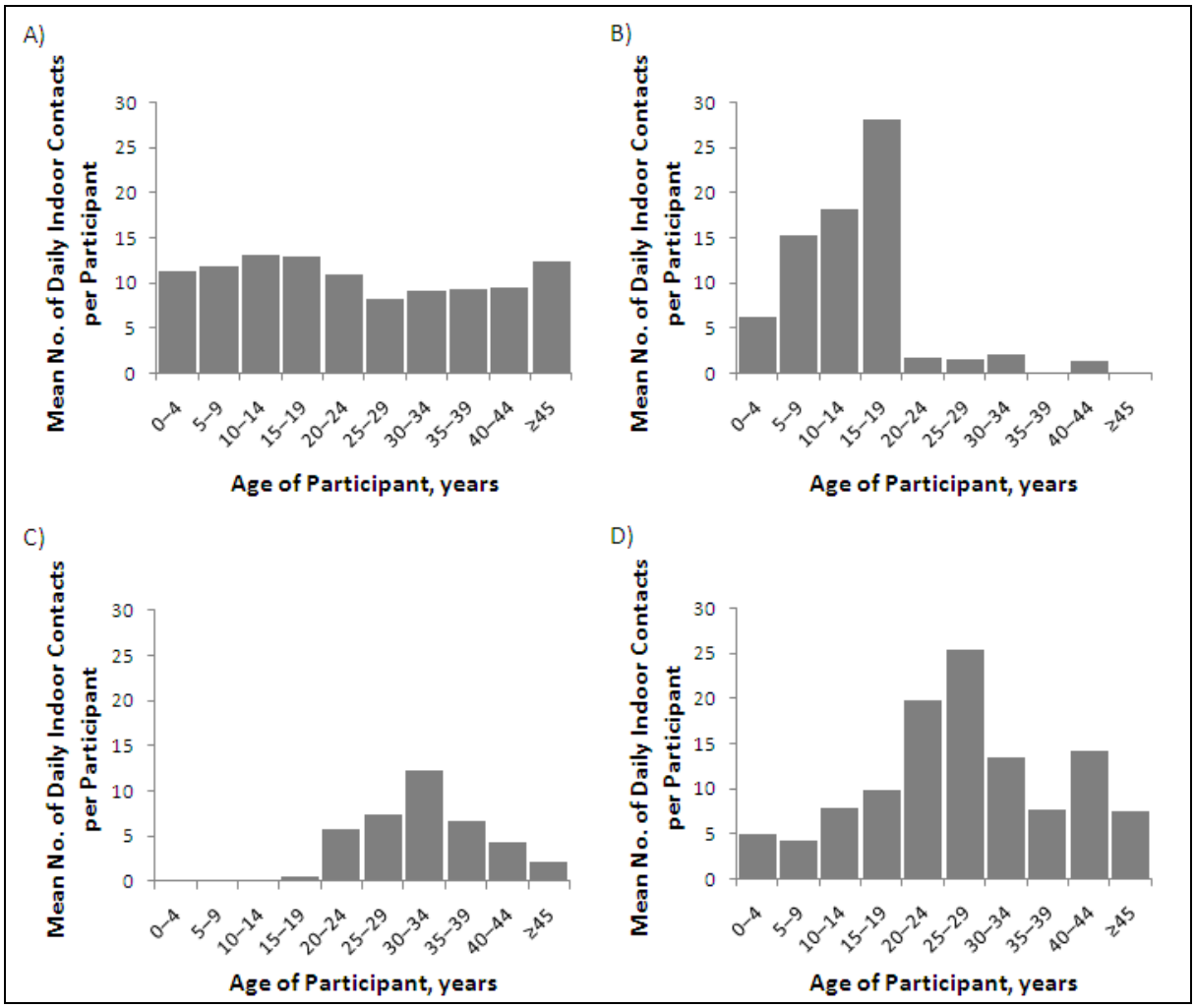

Figure 3

The mean number of daily indoor contacts per participant recorded during a 24 hour period (**A**) in all households (own households and other households), (**B**) at crèche/school, (**C**) at work, and (**D**) during transport (predominantly minibus taxis), stratified by 5-year participant age group. The average indoor contact times lasted 15.2 hours, 2.3 hours, 4.1 hours, 6.4 hours, and 1.4 hours in own households, in other households, at crèche/school, at work, and during travel respectively, with prolonged contacts lasting over 4 hours reported for 47.3%, 7.9%, 38.3%, 73.9%, and 1.9% of visits to each location (see Figure 2 in the published paper entitled "Social mixing patterns within a South African township community: implications for respiratory disease transmission and control" included in Chapter 4).