Profiles of tuberculosis disease activation among contacts of patients with tuberculosis

To the Editor:

The risk of a person progressing to tuberculosis (TB) disease after infection with *Mycobacterium tuberculosis* remains poorly understood, with some contacts developing TB in the early period following exposure, while others take many years to progress or never do so [1, 2]. We described profiles and patterns of contacts' progression to TB disease following exposure by linking a large, prospectively collected contact investigation dataset from Victoria, Australia to data on subsequent cases of active TB disease, after obtaining ethical approval from the Monash University, Human Research Ethics Committee. Unlike many past studies, this approach offers the opportunity to disaggregate by various characteristics of both index patient and exposed contact.

The main outcomes of interest were early progression (development of active TB within 6 months of exposure) and late reactivation (development of TB thereafter). Our definition for early progression is supported by previous findings that the risk of TB is highest in the first 3–9 months after infection [3, 4]. We used a survival analysis approach to describe patterns of TB disease reactivation and used logistic and Cox regression to quantify risks associated with early and late reactivation respectively, incorporating variables pertaining to both contact and index patients.

17 740 contacts of pulmonary TB patients were included in the analysis, of which 82.0% were aged 15 years and above. Over more than 7 years of median follow-up, 224 (1.3%) contacts were diagnosed with TB disease, resulting in an overall incidence rate of 189 cases per 100 000 person-years. Most cases (62.5%) accrued during the first 6 months following exposure and so were defined as early progression episodes. We found that male contacts had a slightly greater rate of TB than their female counterparts (log-rank p=0.03), while children aged <5 years at exposure had the greatest rate of active TB development, followed by children aged 5–14 years (log-rank p<0.001). Tuberculin skin test (TST) positivity (⩾10 mm) was associated with a greater rate of TB (4.6%, 148/3213) than for TST-negative contacts (0.2%, 29/12 233), despite TST positives being more likely to receive preventive therapy. Younger age of contact, close contact, high-burden country of birth, absence of BCG vaccination and recurrent TB in the index patient were associated with early progression, while close contact, high-burden country of birth, BCG vaccination history and BCG status not stated were associated with contacts' higher hazard of late reactivation (table 1).

Every TB case observed among children aged <5 years occurred in the first 18 months of follow-up, of which 44/51 (86.3%) were early progressions. Although a similar proportion (49/60, 81.6%) of early progressions was found among child TB contacts aged 5–14 years, there were seven TB activation episodes that occurred after more than 2 years of follow-up in this age group. These episodes predominantly occurred as these children aged into adolescence and reached approximately 15 years of age. This pattern has also been observed in historical works, which have reported that when a first exposure occurred in children (aged 1–14 years), TB typically did not develop until after the age of 15 years [3]. A prospective study from Hong Kong provided similar evidence that infected children were at greater risk of TB beyond the age of 15 years after an initial low-risk window period [4]. The predilection of TB to affect young

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The risk of TB reactivation among infected children increases as they reach the age of adolescence. BCG vaccination history seems to increase the risk of TB disease reactivation among adults exposed to *Mycobacterium tuberculosis*. http://bit.ly/2YReXej

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TABLE 1 Regression analyses for early progression and late reactivation of tuberculosis (TB) among contacts of TB patients in Victoria, Australia 2005–2015

	TB disease		Crude OR/HR (95% CI)	Adjusted OR/HR (95% CI)	p-value
	No	Yes			
Factors associated with early progression#					
Contact characteristics					
Sex					
Female	9132	62	Ref	Ref	
Male	8349	78	1.38 (0.98–1.93)	1.23 (0.88–1.73)	0.227
Not stated	119	0	NA	NA	
Age					
0–4 years	1153	44	11.78 (7.75–17.84)	7.79 (4.80–12.62)	<0.001*
5–14 years	1951	49	7.75 (5.17–11.61)	5.23 (3.39–8.07)	<0.001*
15 years and above	14496	47	Ref	Ref	
Type of contact					
Close contacts	7871	123	8.94 (5.54–15.40)	5.73 (3.39–9.69)	<0.001*
Other contacts	9729	17	Ref	Ref	
Country of birth					
Low burden	11824	100	Ref	Ref	
High burden	5090	40	0.73 (0.52–1.02)	1.76 (1.11–2.81)	0.017*
Not stated	686	0	NA	NA	
Tuberculin skin test					
Negative	12222	11	Ref	Not included	
Positive	3112	101	36.06 (20.24–71.31)*		
Not performed	2266	28	13.73 (7.02–28.83)*		
BCG					
No	4995	69	Ref		
Yes	7505	37	0.36 (0.24–0.53)	0.47 (0.29–0.77)	0.002*
Not stated/unknown	5100	34	0.48 (0.32–0.73)	0.79 (0.50–1.23)	0.288
Index characteristics					
Sex					
Male	9439	75	Ref		
Female	8161	65	1.00 (0.72–1.40)	1.14 (0.80–1.62)	0.485
Age					
1–14 years	521	10	3.76 (1.76–7.31)	0.20 (0.03–1.45)	0.110
15–24 years	7249	37	Ref		
25–44 years	5181	73	2.76 (1.87–4.15)	1.04 (0.69–1.55)	0.860
45–64 years	1713	17	1.94 (1.06–3.40)	1.57 (0.91–2.71)	0.101
65 years and above	2936	3	0.20 (0.05–0.55)	0.60 (0.32–1.13)	0.111
Country of birth					
High burden	8897	77	Ref	Ref	
Low burden	8703	77	0.84 (0.60–1.17)	1.15 (0.81–1.63)	0.446
Method of case finding					
Clinical presentation	16628	132	Ref	Ref	
Other methods	972	8	1.04 (0.46–1.99)	1.71 (0.91–3.21)	0.096
Site of TB					
Pulmonary	14655	122	Ref	Ref	
Pulmonary plus other site	2945	18	0.73 (0.43–1.17)	1.20 (0.76–1.90)	0.435
Type of TB					
New	16584	130	Ref	Ref	
Recurrent	774	10	1.65 (0.81–2.99)	2.68 (1.42–5.06)	0.002*
Unknown	242	0	NA	NA	
Chest radiography finding					
Abnormal, no cavity	10172	79	Ref	Ref	
Abnormal, cavity	5959	55	1.19 (0.84–1.68)	1.20 (0.82–1.75)	0.347
Abnormal, no details	265	1	0.49 (0.07–3.51)	0.30 (0.04–2.21)	0.236
Normal	339	2	0.76 (0.19–3.10)	0.72 (0.17–3.04)	0.655
Not stated/done	865	3	0.45 (0.14–1.42)	0.42 (0.13–1.36)	0.146
Sputum smear					
Yes	2212	15	Ref	Ref	
No	3609	31	0.85 (0.49–1.47)	0.88 (0.47–1.62)	0.677
Not done/recorded	11779	94	1.08 (0.72–1.62)	1.29 (0.83–2.01)	0.264

Continued

TABLE 1 Continued

	TB disease		Crude OR/HR (95% CI)	Adjusted OR/HR (95% CI)	p-value
	No	Yes			
Factors associated with late reactivation[¶]					
Contact characteristics					
Sex					
Female	7585	31	Ref	Ref	
Male	6733	35	1.26 (0.77–2.06)	1.20 (0.74–1.96)	0.460
Not stated	112	0	NA	NA	
Type of contact					
Close contacts	5785	50	4.43 (2.49–7.86)	3.25 (1.81–5.82)	<0.001*
Other contacts	8645	16	Ref		
Country of birth					
Low burden	9246	23	Ref	Ref	
High burden	4602	43	3.73 (2.23–6.24)	2.17 (1.26–3.75)	0.005*
Not stated	582	0	NA	NA	
Tuberculin skin test					
Negative	9629	16	Ref	Not included	
Positive	2729	35	6.94 (3.78–2.74)*		
Not performed	2072	15	5.06 (2.45–0.43)*		
BCG					
No	3374	3	Ref	Ref	
Yes	6794	46	7.89 (2.43–25.65)	4.54 (1.35–15.28)	0.014*
Not stated	4262	17	4.48 (1.30–15.42)	3.52 (1.01–12.26)	0.048*
Index characteristics					
Sex					
Male	7632	24	Ref	Ref	
Female	6798	42	2.08 (1.14–3.82)	0.55 (0.29–1.03)	0.06
Country of birth					
High burden	7672	36	Ref	Ref	
Low burden	6758	30	1.39 (0.76–2.54)	1.43 (0.78–2.60)	0.24
Method of case finding					
Clinical presentation	13533	64	Ref	Ref	
Other methods	897	2	0.50 (0.11–2.27)	0.42 (0.09–1.89)	0.26
Type of TB					
New case	13553	64	Ref	Ref	
Recurrent	704	2	0.72 (0.14–3.69)	0.82 (0.16–4.11)	0.81
Unknown	173	0	NA	NA	
Chest radiography finding					
Abnormal, no cavity	8025	40	Ref	Ref	
Abnormal, cavity	5285	25	0.92 (0.56–1.52)	0.62 (0.16–4.11)	0.17
Abnormal, no details	185	0	NA	NA	
Normal	291	0	NA	NA	
Not done/stated	644	1	0.27 (0.04–1.99)	0.40 (0.04–3.89)	0.43

*: statistically significant. [#]: logistic regression (all contacts, n=17740); analysis results are presented as odds ratios with 95% confidence intervals. [¶]: Cox regression (contacts age ⩾15 years, n=14496); analysis results are presented as hazard ratios with 95% confidence intervals.

adults has been recognised since Hippocrates, although there are multiple possible explanations for the considerable burden of TB in adolescents, particularly assortative mixing by age leading into the years in which active TB is most infectious [5–7]. Given our very low transmission setting and the fact that all of these children were born in low-burden settings, our findings provide considerable evidence for the explanation that infected children enter a higher risk phase as they progress towards adulthood, which has major implications for clinical care and public health responses. The absence of any cases occurring in adolescence among those aged 0–4 years at the time of exposure likely reflects insufficient follow-up duration, as only the oldest such contacts entering during the earliest period of the study would have reached adolescence, and could also reflect more consistent use of preventive therapy in this group.

Consistent with previous studies, we found that BCG vaccination was highly protective against early progression in contacts aged 0–14 years at exposure, which is a similar effect size to those reported by a previous meta-analysis [8]. However, unexpectedly, risk of late reactivation was greater among BCG vaccinated and BCG not stated adult contacts than BCG unvaccinated counterparts. Previous studies have

consistently reported that BCG is effective in preventing TB disease among children and that its effectiveness is reduced when all ages are considered [9–11]. We note similar findings from the largest ever trial estimating the efficacy of BCG, which reported nonsignificantly higher rates of TB among every age group of vaccinated adults than in the unvaccinated over 15 years of follow-up [12]. One possible interpretation of this evidence is that BCG is effective in reducing TB-related child morbidity and mortality, but may increase late reactivation rates in adults. These phenomena may lead to perverse effects on the overall epidemic because the adult forms of TB are typically most infectious, and they are critical when considering BCG revaccination programmes and interpreting recent trials of novel vaccines whose outcomes consider immunological responses to *M. tuberculosis* rather than incidence of TB disease [13]. Although we found no evidence of an association between BCG vaccination and absence of preventive therapy, this or other unmeasured factors could confound these findings. Furthermore, adults with unknown BCG status were also associated with higher rates of late reactivation, such that ensuring comprehensive collection of BCG status will be a future focus of our research.

Although the development of active TB in contacts after infection is largely dependent on contacts' endogenous factors, we also found associations with index patients' characteristics. Specifically, index patients with recurrent TB appeared more infectious, with their contacts at a considerably greater odds of early progression than for new TB cases. This may be explained by patients with recurrent TB having longer infectious periods or more frequently being smear-positive TB than those with a first episode, although this effect was not seen for late reactivation.

Important limitations of our study include that transmission was inferred based on epidemiological links due to the absence of genotyping data and we did not have universal information on the provision of preventive therapy that could have significantly influenced our findings. However, because preventive therapy is recommended universally for all contacts of patients with active TB in our setting, we would generally expect this to reduce the absolute TB risk across the cohort, but be less likely to systematically bias the trends reported in this manuscript.

In conclusion, child contacts were at highest risk of early progression, but high rates of late reactivation among infected children as they reached adolescence imply that children should be strongly considered for preventive interventions even after their initial high-risk period has elapsed. BCG seems to have an important effect on TB epidemiology in preventing early activation but increasing rates of late reactivation in adults. This effect requires further investigation with more comprehensive data on contacts' receipt of preventive therapy.

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