Tuberculosis transmission among children and adolescents in schools and other congregate settings: a systematic review

Monica Sañé Schepisi1, Ilaria Motta2, Simone Dore3, Cecilia Costa2, Giovanni Sotgiu3, Enrico Girardi1
1Clinical Epidemiology Unit - Department of Epidemiology and Preclinical Research, Istituto Nazionale Malattie Infettive “L. Spallanzani” - IRCCS, University of Turin, Infectious Diseases Unit, Department of Medical Sciences, Torino, Italy, 3Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy.

INTRODUCTION
Children, especially those aged <5 years, and adolescents are at increased risk of progression to active TB disease when infected. Management of childhood TB outbreaks is crucial for TB elimination especially in low burden countries.

We searched the electronic databases MEDLINE-CINHAL-EMBASE up to July 2017 for primary studies reporting on TB incidents which involved teacher/child-caregiver, relative or students diagnosed with TB in a school/childcare setting or in other congregate settings attended by children and adolescents. Out of 10,481 citations, 74 studies, published mostly in low TB burden countries from 1950 to 2017, describing 128 incident investigations, were included. Overall 5025 (14.2%) LTBI and 811 (2.3%) TB cases were diagnosed among 35,331 screened individuals. Incidents occurred mainly in schools (89.1%) where index cases were more frequently students (63.3%) than teachers/caregivers; almost all of the incidents exposing children aged 2-5 were attributable to a teacher/caregiver index case. In 68 individual contact investigations the pooled proportions of TB and LTBI among those exposed were 0.03 (95%CI 0.02-0.04) and 0.15 (95%CI 0.13-0.18).

The overall risk of developing TB disease in school-congregate settings seems slightly lower than in high-income country household settings. Public health interventions targeting school-congregate settings may be critical to overall TB control and towards TB elimination in low-burden countries.

SUMMARY
Children, especially those aged <5 years, and adolescents are at increased risk of progression to active TB disease when infected. Management of childhood TB outbreaks is crucial for TB elimination especially in low burden countries.

We searched the electronic databases MEDLINE-CINHAL-EMBASE up to July 2017 for primary studies reporting on TB incidents which involved teacher/child-caregiver, relative or students diagnosed with TB in a school/childcare setting or in other congregate settings attended by children and adolescents. Out of 10,481 citations, 74 studies, published mostly in low TB burden countries from 1950 to 2017, describing 128 incident investigations, were included. Overall 5025 (14.2%) LTBI and 811 (2.3%) TB cases were diagnosed among 35,331 screened individuals. Incidents occurred mainly in schools (89.1%) where index cases were more frequently students (63.3%) than teachers/caregivers; almost all of the incidents exposing children aged 2-5 were attributable to a teacher/caregiver index case. In 68 individual contact investigations the pooled proportions of TB and LTBI among those exposed were 0.03 (95%CI 0.02-0.04) and 0.15 (95%CI 0.13-0.18).

The overall risk of developing TB disease in school-congregate settings seems slightly lower than in high-income country household settings. Public health interventions targeting school-congregate settings may be critical to overall TB control and towards TB elimination in low-burden countries.

Received May 11, 2018
Accepted July 17, 2018

Key words:
Tuberculosis, Children/adolescents, Schools/congregate settings.

Corresponding author:
Monica Sañé Schepisi
E-mail: msaneschepisi@gmail.com

©2018 by EDIMES - Edizioni Internazionali Srl. All rights reserved
METHODS

We systematically reviewed the medical literature to evaluate current evidence on the risk of *Mycobacterium tuberculosis* transmission in school/childcare/congregate settings attended by children and adolescents. We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement as a reference document for reporting findings (Moher et al., 2009). The review protocol was registered in the PROSPERO open access database of systematic reviews on the 20th of April 2015 and is freely available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019581.

**Literature search**

We searched three electronic databases (i.e., PubMed-MEDLINE, EMBASE, and CINHAL) up to 31st July 2017. The key words used for the electronic search included the following words/lines: “tuberculosis”, “child/adolescent”, and “school”/“day-care centre”/“nursery”. Search strings were adapted for each database search. The complete search strategy is reported in Appendix 1, available upon request from the Authors.

The search was limited to English, French, Portuguese, and Spanish languages regardless of geographic settings and time limitations.

**Selection criteria**

Observational studies reporting the results of an investigation in which a teacher or child-carer, relative, or student was diagnosed with TB, and children or adolescents aged 2-18 years old were exposed to the potential risk of infection in a school/childcare setting (e.g., kindergarten, preschool playgroups, private day nurseries, daycare centres) were selected. Reviews, conference abstracts, editorials, letters, modelling articles, guidelines/recommendations were excluded as primary sources of information. However, their references were checked in order to retrieve original articles.

The articles were assessed by four reviewers (CC, IM, MSS, SD) working independently and following a two-stage procedure:

1) titles and abstracts;
2) a full-text review of the abstracts fitting inclusion criteria.

Discrepancies were resolved by consensus. When multiple publications from the same population were selected, only those including the most complete report were included.

**Data extraction**

A predefined spreadsheet for data collection was created and the following information was gathered from each included publication: country and setting, year of publication and incident period, index case characteristics, number of children or adolescents exposed to the index case, number of screened individuals, screening strategy, screening method, BCG vaccination status of exposed individuals, number of individuals diagnosed with LTBI (outcome 1) or with active TB (outcome 2), number of children/adolescents BCG vaccinated among those diagnosed with LTBI, number of children started on LTBI therapy, confirmation of *Mycobacterium tuberculosis* transmission by molecular techniques, and follow-up of exposed individuals. When possible, results of screening of exposed individuals were extracted separately for children (2 to 5 and 6 to 15 years old) and adolescents (up to 18 years old).

The following operational definitions were adopted:

- **TB incident**: the exposure to an infectious TB case with the likely occurrence of *Mycobacterium tuberculosis* transmission, including outbreaks.
- **Index case**: a patient (parent/teacher/child-carer/student) diagnosed with active TB, regardless of diagnostic criteria, considered responsible for *Mycobacterium tuberculosis* transmission and who prompted the contact investigation.
- **Diagnostic interval**: the period from the onset of the first symptoms possibly related to TB to the date when TB was diagnosed in the index case.
- **High risk screening strategy**: the decision to screen only high risk contacts (for instance students if the index case was a teacher or a student or bus rider if the index case was a bus driver); **wide screening strategy**: the decision to screen all possibly exposed contacts (for instance all the pupils of the school).

**LTBI**: a positivity, at baseline or during the follow-up, of at least one of the following diagnostic tests: Tuberculin Skin Test - TST (including Mantoux test, Tine test, and Heaf test), Interferon Gamma Release Assays - IGRAs (including QuantiFERON-TB Gold In Tube (QFT-IT) or T-SPOT.TB). Positivity to TST was defined using the cut-off reported in the original paper.

- **Secondary case**: any person diagnosed with active TB, regardless of the diagnostic criteria, during the contact investigation. If the first diagnosed case was the index case, the second one was considered a screened person and, so, a secondary case.

The quality of the selected studies was assessed through the Newcastle-Ottawa quality assessment scale (NOS) (Wells et al., 2017). The scale consists of nine items covering three dimensions:

1) patient selection (4 items);
2) comparability of cohorts on the basis of the design or analysis (2 items);
3) assessment of outcome (3 items).

Total score can range from zero to nine, with higher scores associated with higher quality. For each study, two checklists were completed for the outcomes LTBI and TB.

**Statistical analysis**

The meta-analysis included only those studies reporting results of contact investigation separately for children (2 to 5 and 6 to 15 years old) and for adolescents (16 to 18 years old) in a single TB incident occurring in a school/congregate setting. Combined estimates of the number of individuals diagnosed with LTBI (outcome 1) or with active TB (outcome 2), together with their 95% confidence intervals (CIs), were computed. A random-effects meta-analysis was performed in order to account for the expected between-study variability; subgroup analyses were performed according to: 1. screened class age; 2. characteristics of the index case: age (*i.e.*, ≤12, ≤14, ≤16 or >16), nationality, role (*i.e.*, teacher or student), and infectiousness (*i.e.*, sputum smear and culture results, cavitary lesions at chest X-rays); and 3. diagnostic delay (*i.e.*, ≤5 or >30 days). Statistical computations were performed with the software STATA version 14 and StatsDirect 3.
RESULTS

The databases search yielded 10,481 records. A total of 74 original articles resulting from the selection process described in Figure 1 were selected. The complete list of articles along with the reasons for exclusion is available upon request from the Authors.

The above-mentioned 74 articles reported the findings of 128 incident investigations, of which 91 were single TB incidents occurring in school/congregate settings, stemming from one index case - so referred to as individual reports - the remaining 37 originated from more than one index case in one or more school/congregate settings - so referred to as cumulative reports (de March Ayuela P., 1988; Piccin et al., 2017; Rothman et al., 1993; Shannon et al., 2000; Stronge and Balmer, 1961; Stronge and Davison, 1995; Ustero et al., 2017; Shibulam et al., 2015). Articles were published from 1950 (Smith et al., 1950) to 1991; Ustero et al., 2017).

TB incidents occurred mainly in school settings (114, 89.1%), and less frequently in school buses (7, 5.5%) (Mahady, 1961, Rogers, 1962; Yusuf et al., 1997). The infectiousness of the index case was described by the majority of manuscripts: 106/128 (82.8%) were pulmonary and 4 (3.1%) by extra-pulmonary or extrapolumony TB cases (3, 2.3%), of which 54 (81.8% were those reporting data on CXR results) with a cavitary pattern, 81 (76.4%) and 54 (50.1%) sputum smear and culture positive, respectively.

Overall, the quality was low (median score 4). The most frequent reasons for the low quality were the absence of a non-exposed cohort, the lack of demonstration that the outcome of interest was not present at the start of the study, and a missing, or short follow-up for the assessment of the outcome “active TB”. Results of quality assessment are available upon request from the authors.

Description of included studies

All studies were designed as retrospective cohort studies with TB case investigation and LTBI screening. TB incidents occurred mainly in school settings (114, 89.1%), and less frequently in school buses (7, 5.5%) (Mahady, 1961, Rogers, 1962; Yusuf et al., 1997; Neira-Munoz et al., 2008), day-care/play group settings (4, 3.4%) (Smith, 2000; Millership et al., 1998; Müller et al., 2008) and orphanages or other residential settings (3, 2.3%) (Bates, 1965; Guigou and Charpin, 1961). Index cases were students (80, 62.5%) and, less frequently, teachers/caregivers (33, 25.8%) or bus drivers (8, 6.3%). The median age of index cases was 17. No index cases younger than 5 years of age were described. Index cases aged 6 to 10 were reported in 5/85 incidents where the age was reported (Rothman and Dubeski, 1993; Curtis et al., 1999; Howard, 2007; Paranjothy et al., 2008; Cardona, 1999).

The infectiousness of the index case was described by the majority of manuscripts: 106/128 (82.8%) were pulmonary only (103, 80.5%) or pulmonary and extrapolumony TB cases (3, 2.3%), of which 54 (81.8%) were those reporting data on CXR results) with a cavity pattern, 81 (76.4%) and 54 (50.1%) sputum smear and culture positive, respectively. Among 128 index cases 10 (7.8%) showed infection caused by drug-resistant mycobacterial strains, and 4 (3.1%) by multi-drug resistant mycobacterial strains. 27 (21.1%) index cases were foreign born; in 22 cases the country of origin was a medium or high TB burden country (Table 1).

Methods and results of contact investigations

35,331 exposed children or adolescents were screened. When the number of exposed students was available, the
Tuberculosis transmission among children and adolescents in schools and other congregate settings: a systematic review

2017; Higuichi et al., 2007; Higuichi et al., 2009; Döllner et al., 2002; QFT (Alvarez-Alvarez et al., 2013), T-SPOT.TB (Caley et al., 2010; Ewer et al., 2003; Howard et al., 2007; Paranjothy et al., 2008; Müller et al., 2008). In five investigations IGRAs were used as the only test (Gillini et al., 2015; Neira-Munoz et al., 2008; Williams et al., 2016; Trollfors et al., 2010; Tuuminen et al., 2012) (Appendix 2).

Overall, 5,836 out of 35,331 (16.5%) screened students were infected, of whom 14.2% (5,025) were LTBI and 2.3% (811) TB cases. Both LTBI and TB transmission rates were lower in more recent studies.

In 91 individual investigations, a total of 780/31,333 (2.5%) TB cases were diagnosed. According to the age category of exposed children, TB was diagnosed in 2.8% of the children aged 2 to 5, 2.8% of the children aged 6 to 15, and 1.4% of the adolescents aged 16 to 18. 37 cumulative investigations identified active TB in 31,398 (0.8%) screened students, of which 0.9% children aged 2 to 5, 0.8% children aged 6 to 15 years, and 1.0% adolescent students. (Appendix 3) In 4 reports (Prieto Lozano et al., 1996; Steppacher et al., 2003) it was not possible to detail age groups of exposed individuals. 31/128 (24.2%) of the reports provided data on a total of 6,356 exposed children and adolescents who did not develop TB disease (de March Ayuela et al., 1988; Piccini et al., 2017; Ustero v. 2107; Miravet Sorribes et al., 2016; Bates et al., 1965; Curtis et al., 1999; Smith, 2000; Wang et al., 2010; Yusuf et al., 1997; Herrick and Davison, 1995; Rivest, 1993; Millership et al., 1998; Trollfors et al., 2013; Steppacher et al., 2014; Higuichi et al., 2007; Higuichi et al., 2009; Hadjichristodoulou et al., 2005; Banner et al., 2013; Cardona et al., 1999; Tuuminen et al., 2012; Döllner et al., 2012), whereas the highest number of secondary cases was described by Ewer et al. (Ewer et al., 2003) in a UK school in 2001, where 69 (6.1%) of the secondary cases were detected among 1,128 students exposed for 9 months to a sputum smear-positive, cavitary TB. The highest TB transmission rate (27.3%, 9/33) was reported in 1950 in Canada by Smith et al. in a school outbreak strongly related to a community outbreak (Smith et al., 1950).

Mycobacterium tuberculosis transmission was assessed by molecular techniques in 21 outbreaks occurring from 1997 onwards; secondary cases were confirmed as linked to the index case in all but one study (Williams et al., 2016), where 3 unrelated strains were identified and only 1/3 secondary cases shared an identical strain with the index case. Long-term follow-up, described by 21 studies and ranging from 6 months to 5 years, did not detect additional active TB cases.

In 91 individual studies LTBI was diagnosed in a total of 4,517/31,333 (14.4%) individuals, and specifically 11.6% among children aged 2 to 5, 14.6% among children aged 6 to 15, and 12.5% among adolescents aged 16 to 18. A wide range of infected individuals (7% to 100%) received LTBI treatment. In studies where it was not possible to identify the age groups of the exposed individuals, 71/475 (14.9%) infected students were reported. In cumulative studies LTBI was diagnosed in 508/3,998 (12.7%) screened students, of which 18.2% among children aged 2 to 5, 14.1% among children aged 6 to 15, and 7.2% among adolescents aged 16 to 18 (Appendix 3).

Considering only individual studies on incidents occurring in schools, no studies on students aged 2 to 5 exposed to a student index case were found except in one school outbreak reported in 1950 in Canada by Smith et al.:

---

**Table 1 - Characteristics of 128 Index cases of tuberculosis in 74 included investigations.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n. (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role (128)</td>
<td></td>
</tr>
<tr>
<td>student</td>
<td>81 (63.3)</td>
</tr>
<tr>
<td>teacher</td>
<td>27 (21.1)</td>
</tr>
<tr>
<td>bus driver</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>care-giver</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>other</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>parent</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>not reported</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Nationality (128)</td>
<td></td>
</tr>
<tr>
<td>autochthonomous</td>
<td>15 (11.7)</td>
</tr>
<tr>
<td>foreign-born</td>
<td>27 (21.1)</td>
</tr>
<tr>
<td>data not reported</td>
<td>86 (67.2)</td>
</tr>
<tr>
<td>Diagnostic interval (days) (128)</td>
<td></td>
</tr>
<tr>
<td>&lt;30 d</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>≥30 d</td>
<td>52 (40.6)</td>
</tr>
<tr>
<td>data not reported</td>
<td>70 (54.7)</td>
</tr>
<tr>
<td>Tuberculosis location (128)</td>
<td></td>
</tr>
<tr>
<td>pulmonary (P)</td>
<td>103 (80.5)</td>
</tr>
<tr>
<td>extrapulmonary (EP)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>pulmonary and extrapulmonary (P-EP)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>data not reported</td>
<td>17 (13.3)</td>
</tr>
<tr>
<td>Sputum smear (106 P or P-EP)</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>17 (16.1)</td>
</tr>
<tr>
<td>positive</td>
<td>81 (76.4)</td>
</tr>
<tr>
<td>data not reported</td>
<td>8 (7.5)</td>
</tr>
<tr>
<td>Sputum/gastric aspirate culture (106 P or P-EP)</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>12 (11.3)</td>
</tr>
<tr>
<td>positive</td>
<td>54 (50.1)</td>
</tr>
<tr>
<td>data not reported</td>
<td>40 (37.6)</td>
</tr>
<tr>
<td>Chest X Ray (106 P or P-EP)</td>
<td></td>
</tr>
<tr>
<td>cavitary lesions absent</td>
<td>12 (11.3)</td>
</tr>
<tr>
<td>cavitary lesions present</td>
<td>54 (50.1)</td>
</tr>
<tr>
<td>data not reported</td>
<td>40 (37.6)</td>
</tr>
</tbody>
</table>
outbreak was nevertheless strongly suspected to be related to a community outbreak (Smith et al., 1950). Older student index cases were more efficient *Mycobacterium tuberculosis* transmitters and when students aged 16-18 were exposed, index cases were more frequently school or class-mate students than teachers.

**Meta-analysis**

The quantitative analysis included 68 individual studies for which the proportion of TB cases or of LTBI individuals could be computed separately for the age categories. Overall, pooled proportions of TB disease and LTBI among exposed individuals were 0.03 (95% CI: 0.02 to 0.04; $I^2 = 94.2\%$) and 0.15 (95% CI: 0.13 to 0.18; $I^2 = 97.8\%$), respectively.

Combined proportions of active TB cases among screened individuals were 0.03 (95% CI: 0.02 to 0.05; $I^2 = 90.0\%$) for children aged 2 to 5 (Figure 2), 0.03 (95% CI: 0.02 to 0.04; $I^2 = 94.3\%$) for children aged 6 to 15 (Figure available upon request from the Authors), and 0.02 (95% CI: 0.01 to 0.02; $I^2 = 91.9\%$) for adolescents aged 16 to 18 years old (Figure 3).

Combined proportions of individuals with LTBI were: 0.12 (95% CI: 0.07 to 0.17; $I^2 = 96.7\%$) for children aged 2 to 5 (Supplementary Figure 1 available upon request from the Authors), 0.16 (95% CI: 0.13 to 0.20; $I^2 = 97.7\%$) for children aged 6 to 15 (Supplementary Figure 2 available upon request from the Authors), and 0.15 (95% CI: 0.11 to 0.19; $I^2 = 98.2\%$) for adolescents aged 16 to 18 years old (Supplementary Figure 3 available upon request from the Authors).

The ratio of those diagnosed with TB on those screening positive was highest if those exposed were younger -aged 2 to 5-, and decreased with increasing age: from 0.26 (95% CI: 0.16 to 0.38; $I^2 = 88.5\%$) - age 2 to 5 years - to 0.13 (95% CI: 0.09 to 0.17; $I^2 = 90.3\%$) - age 6 to 10 years - and to 0.09 (95% CI: 0.06 to 0.13; $I^2 = 85.0\%$) - >15 years -. Nevertheless, as in other subgroup analysis, a very high heterogeneity was found (Table 2).

The youngest index case was 7 years old. Younger children aged 7 to 10 were more efficient in *Mycobacterium tuberculosis* transmission, and then the pooled proportion of TB and of LTBI decreased progressively with increasing age: from 0.06 (95% CI: 0.01 to 0.15; $I^2 = 94.4\%$) to 0.01 (95% CI: 0.01 to 0.02; $I^2 = 89.5\%$); LTBI: 0.34 (95% CI: 0.21 to 0.46; $I^2 = 92.2\%$) to 0.14 (95% CI: 0.11 to 0.18; $I^2 = 98.0\%$). The probability of screened individuals being diagnosed with TB or with LTBI according to country of birth and according to role (teacher or student) could not be interpreted due to almost total overlapping of confidence of pooled estimates and to very high heterogeneity. Pooled estimates were higher when the index case was native in comparison with a foreigner and if the role was teacher in comparison with the role of student. Confidence intervals did not overlap for the higher probability of progressing from infection to disease or when the diagnostic delay was over 30 days. Furthermore, pooled estimates of the probability of LTBI were higher when the index case was sputum smear and culture positive and when cavitary lesions were found but partial confidence intervals overlapping and high heterogeneity were present (Table 2).

**DISCUSSION**

TB outbreaks have been described in different settings, such as hospitals (Sane Schepisi et al., 2015), bars (Ishibatake and Onizuka, 1997; Kline et al., 1995; Nakamura et al., 2004), churches (Dutt et al., 1995), and even among travellers on a bus (Edelson and Phypers, 2011). Schools are settings where shared living space and close proximity facilitate outbreaks.
We performed a systematic review of primary studies reporting TB incidents where a teacher/child-caregiver, relative, or student in a school/childcare setting, and other congregate settings were diagnosed with TB, to which children and adolescents were exposed. Overall, 14.2% LTBI and 2.3% active TB cases were diagnosed among 35,331 screened children. Considering all investigations, both rates showed a decreasing trend over time, from 1948 to 2014, possibly related to the decreasing TB incidence rate. The risks of LTBI and TB in infants, children and adolescents estimated in this review were slightly lower - for TB among exposed children aged 2 to 5 - or in the range - for LTBI in children aged 2 to 5 years old and for TB and LTBI among exposed children and adolescents aged 6 to 15 - than those previously reported in household settings and higher than those reported in nosocomial settings (Sane Sánchez et al., 2015; Millership et al., 2009). If compared with the previous reviews on school outbreaks (Roberts et al., 2012, ECDC, 2013) the overall transmission rate was lower than that reported by Roberts et al. (Roberts et al., 2012, ECDC, 2013); TB and LTBI detection rates were closer to the lower limit of the range identified by the ECDC (ECDC, 2013), which could be likely explained by the increased number of studies in our review and by both the geographical and temporal limitations of the ECDC review.

As described by other authors (Millership et al., 2009), the infectiousness of the index case, (i.e., proportion of screened positive among those screened) was associated with sputum culture positive results and with cavitary lesions of the index case. Diagnostic delay (detection fail-

---

### Table 2 - Subgroup analysis of 68 individual investigations: pooled estimates of 1. Screened positive/ Screened; 2. Active TB/ Screened and 3. Active TB/ Screened positive.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Screened positive/ Screened</th>
<th>Active TB/ Screened</th>
<th>Active TB/ Screened positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95%CI)</td>
<td>(95%CI)</td>
<td>(95%CI)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.15 (0.13-0.18)</td>
<td>97.60%</td>
<td>0.03 (0.02-0.04)</td>
</tr>
<tr>
<td><strong>Exposed students</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aged 2-5 years</td>
<td>0.12 (0.07-0.17)</td>
<td>97.60%</td>
<td>0.03 (0.02-0.05)</td>
</tr>
<tr>
<td>aged 6-15 years</td>
<td>0.16 (0.13-0.20)</td>
<td>97.70%</td>
<td>0.03 (0.02-0.04)</td>
</tr>
<tr>
<td>aged 16-18 years</td>
<td>0.15 (0.11-0.19)</td>
<td>98.20%</td>
<td>0.02 (0.01-0.02)</td>
</tr>
<tr>
<td><strong>Index case</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 y</td>
<td>0.34 (0.21-0.46)</td>
<td>92.20%</td>
<td>0.06 (0.01-0.15)</td>
</tr>
<tr>
<td>&gt; 10 y</td>
<td>0.17 (0.13-0.21)</td>
<td>97.80%</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td>≤ 12 y</td>
<td>0.30 (0.19-0.41)</td>
<td>94.40%</td>
<td>0.04 (0.00-0.11)</td>
</tr>
<tr>
<td>&gt; 12 y</td>
<td>0.17 (0.13-0.22)</td>
<td>97.80%</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td>≤ 14 y</td>
<td>0.25 (0.16-0.36)</td>
<td>97.90%</td>
<td>0.04 (0.02-0.08)</td>
</tr>
<tr>
<td>&gt; 14 y</td>
<td>0.17 (0.13-0.21)</td>
<td>97.50%</td>
<td>0.01 (0.01-0.02)</td>
</tr>
<tr>
<td>≤ 16 y</td>
<td>0.19 (0.14-0.26)</td>
<td>97.10%</td>
<td>0.04 (0.02-0.06)</td>
</tr>
<tr>
<td>&gt; 16 y</td>
<td>0.14 (0.11-0.18)</td>
<td>98.00%</td>
<td>0.01 (0.01-0.02)</td>
</tr>
<tr>
<td><strong>country of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>foreign-born</td>
<td>0.13 (0.09-0.17)</td>
<td>90.70%</td>
<td>0.01 (0.00-0.02)</td>
</tr>
<tr>
<td>non foreign-born</td>
<td>0.16 (0.08-0.26)</td>
<td>99.10%</td>
<td>0.03 (0.01-0.05)</td>
</tr>
<tr>
<td><strong>role</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teacher</td>
<td>0.16 (0.11-0.21)</td>
<td>96.00%</td>
<td>0.04 (0.02-0.06)</td>
</tr>
<tr>
<td>student</td>
<td>0.19 (0.15-0.23)</td>
<td>97.80%</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td><strong>microbiological/clinical factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sputum negative/culture positive</td>
<td>0.14 (0.03-0.30)</td>
<td>98.40%</td>
<td>0.03 (0.01-0.07)</td>
</tr>
<tr>
<td>sputum positive/culture positive</td>
<td>0.17 (0.13-0.22)</td>
<td>98.10%</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td>cavitary lesions absent</td>
<td>0.13 (0.05-0.24)</td>
<td>97.70%</td>
<td>0.02 (0.00-0.05)</td>
</tr>
<tr>
<td>cavitary lesions present</td>
<td>0.16 (0.13-0.19)</td>
<td>97.90%</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td>diagnostic delay ≤30 days</td>
<td>0.06 (0.02-0.12)</td>
<td>97.20%</td>
<td>0.01 (0.00-0.01)</td>
</tr>
<tr>
<td>diagnostic delay &gt;30 days</td>
<td>0.16 (0.12-0.20)</td>
<td>98.00%</td>
<td>0.03 (0.02-0.04)</td>
</tr>
</tbody>
</table>
ure of TB-related symptoms or diagnostic errors (Ridzon et al., 1997; Faccini et al., 2013) of index cases might have also caused prolonged infectiousness and a higher risk of presenting TB disease once infected (i.e. screened positive).

Natives might have been more efficient TB transmitters than foreign-born possibly due to the lower level of suspicion among those born in a non-endemic country, which might have caused a longer diagnostic delay (Pezzotti et al., 2015).

Age of index cases and of exposed children or adolescents are closely interrelated determinants of mycobacterial transmission. Similarly to what was reported in previous school outbreak reviews (Lincoln, 1965), index cases described by this systematic review were younger than 10 - and specifically, older than 7 years old - in less than 10% of the cases. An efficient mycobacterial transmission from children younger than 10 years old has been reported among infants in hospital settings in specific cases - requiring suctioning, or mechanical ventilation through an endotracheal tube (Rabalais et al., 1991; Lee et al., 1998; Costello et al., 1993; Cantwell et al., 1994) or in the case of a child with highly infectious cavitary TB, sputum smear and culture positive (Varteresian-Karanfil et al., 1988). According to this evidence, students aged 2 to 5 years old in the incidents included in our review were all teachers/caregivers, with the exception of one school outbreak strongly related to a community outbreak (Smith et al., 1950). The highest number of secondary LTBI and TB cases was found when the index case was a child aged 5 to 10, likely caused by an increased susceptibility of exposed same-age - classmates in comparison with older adolescents, and with increasing age students became less contagious but still more frequently index cases in comparison with teachers.

Studies differed for screening strategies, choice of tests and their combination, timing of screening, thresholds for positivity according to national guidelines (e.g., Higuchi considered positive a TST over 30 mm (Higuchi et al., 2007)), the decision to use a different threshold for BCG vaccinated individuals, and of treating for LTBI according to test results (e.g. Higuchi treated only those with positive Quantiferon (Higuchi et al., 2007)), previous BCG vaccination (e.g. in some cases those vaccinated did not receive isoniazid treatment (Millership et al., 1998; Guigou and Charpin, 1961; Mande and Aubriet, 1955), whereas some authors considered “one time reactors”, “booster” or “converters” potentially eligible for LTBI treatment (Herwick and Davison, 1995) or age of exposed individuals (Smith recommended isoniazid treatment for all exposed children (Smith, 2000); Curtis prescribed isoniazid to all young children until the TST performed 12 weeks after exposure remained negative (Curtis et al., 1999). Only one investigation, performed in Swaziland, did not screen contacts for LTBI and performed symptom screening and GenXpert testing for active TB (Ustero et al., 2017).

Strengths and limitations

Missing demonstration of LTBI before the investigation might have caused an overestimation of LBTI attributed to the exposure of interest. In low TB incidence countries, the assumption that the first screening could be evidence of LTBI acquired following exposure to the index case seems plausible in those aged less than 2 years, whereas for older children previous household and community exposures cannot be ruled out. On the other hand, an underestimation of the number of secondary TB cases could be associated with the school absence of children with TB symptoms (Ustero et al., 2017) or to the short duration of the follow-up; to overcome these limitations some authors sought additional TB cases by matching the state and county TB registries and by reviewing county TB clinic and laboratory records (Reves et al., 1981; Ridzon et al., 1997).

Incomplete data on ventilation and on exposure duration did not allow a comprehensive analysis of these important transmission determinants.

Despite the wide-ranging search, we may have missed key studies. Investigation on school incidents is a routine public health activity and therefore does not necessarily result in a scientific publication. Among published studies, positive publication bias might have over or underestimated our findings, depending on the definition of positive results (absence or presence of secondary cases).

Our extensive search had no temporal or geographical limitations, and this increased heterogeneity, since TB incidence in the general population has changed over time. Furthermore, our review was limited to children or adolescents aged 2 to 18 years old, and excluded studies without references to a lower age limit.

Conclusions

The overall risk of developing TB in schools and other congregate setting incidents seems slightly lower or in the range of the risk in household settings, suggesting that targeted prevention efforts should be implemented in these community-based structures. To define the real burden of TB incidents affecting children in these settings, surveillance data on the results of contact investigations should be collated at national levels and made available to guide and monitor current practices in outbreak management. Finally, the cost-effectiveness of different strategies of contact investigation should be evaluated. Public health interventions targeting school-congregate settings may be critical for overall TB control and towards TB elimination in low-burden countries.

Acknowledgements

We would like to acknowledge Dr Renata Mancini, librarian, and Dr Alessia Mammone, statistician, both from the INMI National Institute for Infectious Diseases, Rome (Italy) for their valuable contribution.

Conflict of interest

None of the authors has any potential financial conflict of interest related to this manuscript.

This work was presented as abstract at the 47th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) LIVERPOOL - UNITED KINGDOM 26-29 OCTOBER 2016: “EP-158-28 Transmission of Mycobacterium tuberculosis among children and adolescents in schools and congregate settings: systematic literature review and meta-analysis”. Available at: http://www.abstractserver.com/union2016/abstractbook/UNION_Abstract_Book_2016-Web.pdf

An earlier and partial version of a systematic review on TB incidents in schools and hospitals in children up to 5 years old was presented as oral communication at the ESCAIDE - European Scientific Conference on Applied Infectious Disease Epidemiology- conference in 2013. “Transmission
Tuberculosis transmission among children and adolescents in schools and other congregate settings: a systematic review

Alvarez-Castillo M.C., Cano Escudero S., Taveira Jiménez J.A. (2007). Mi-

References

Adler-Shohet F.C., Low J., Carson M., Girma H., Singh J. (2014). Manage-

ment of latent tuberculosis infection in child contacts of multidrug-re-

Alvarez-Alvarez C., Díez Fernández M., Cabero-Pérez M.J., Guerra Diez L., Galán Cuesta M., Agieró Balbín J. (2013). Description of tubercu-


Alvarez-Castillo M.C., Cano Escudero S., Taveira Jiménez J.A. (2007). Mi-
croepidemics of tuberculosis in schools. How should we select con-


- and community-based outbreak of Mycobacterium tuberculosis in


the Upper Fraser Valley Health Unit. Can J Public Health. 64, 497-9.


School. Tubercre. 46, 321-44.

Baghale N., Khalilzadeh S., Bolurzars M.R., Parsanejad N. (2012). Contact trac-
ting of a 15-year-old girl with smear-negative pulmonary tuberculo-

Banner P. (2013). Tuberculosis contact tracing within a school environ-


Bates J.H., Potts W.E., Lewis M. (1965). Epidemiology of primary tubercu-


Lancet. 1, 740.


demic of tuberculosis in an elementary school, Sanremo, Italy. 1993. Rev

Epidemiol Sante Publique. 42, 138-43.


meningitis of latent tuberculosis infection in child contacts of multidrug-re-


(2004). The natural history of childhood intra-thoracic tuberculosis:

evidence of late diagnosis, management of exposures. Clin Infect Dis

38, 745-50.


massive meningitis in a seven-year-old child in a Sydney school. J Infect

Dis. 201, 283-7.

Bonu C. (2009). The risk to infants from nosocomial exposure to tuberculosis.


Prevalence of T-cell-based assay with tubulin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tubercu-

losis outbreak. Lancet. 361, 1168-73.

Bonacci M., Codecasa L.R., Ciconial G., Cammarata S., Borriello C.R., De

Giotia C., et al. (2013). Tuberculosis outbreak in a primary school, Mi-


(2011). Tuberculosis in kindergarten and primary school, Italy. 2008-


Fox G.J., Barry S.E., Britton J.M., Marks G.B. (2013). Contact investigation for

tuberculosis: a systematic review and meta-analysis. Eur Respir J.

41, 140-56.


Tuberculosis outbreak in a Rhode Island high school. Med Health R

J. 9, 290-3.


(2015). Is Europe ready to reach tuberculosis elimination? An out-

break report from Southern Italy. Eur Respir J. 46, 274-7.


Primary tuberculosis in children at a Swedish day care center. Pediatr Infect Dis J.

27, 1078-82.

Guigou G., Charpin J. (1961). An epidemic of tuberculosis in a school envi-

Hadjichristodoulou C., Vasiliogianнакopoulos A., Spala G., Mavrou I., Ko-

lonia V., Marinis E., et al. (2005). Mycobacterium tuberculosis trans-


12, 88-92.


terium tuberculosis in a primary school outbreak: lack of racial differ-

cence in susceptibility to infection. Am J Epidemiol. 139, 520-30.


Ishibatake H., Onizuka R. (1997). A report of outbreaks of pulmonary tubercu-

losis in two bars. Kekkaku. 72, 623-8.


201.

Mahady S.C. (1961). An outbreak of primary tuberculosis in school chil-


Mamun A., Devitt J., Aubriet F. (1955). Tuberculosis epidemic discovered at the occa-

Marais B.J., Gie R.P., Schaaf H.S., Hesseling A.C., Ohlhauser C.C., Starke J.J., et al. (2004). The natural history of childhood intra-thoracic tubercu-

losis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 8, 392-402.

Marcos Rodríguez P.J., Díaz-Caballero A., Ursua Díaz M.I., Fernández-Al


Milburn H.J., Gibilaro J., Atkinson H., Heathcock R. (2000). High inci-
dence of primary tuberculosis. Arch Dis Child. 82, 386-7.


Mordan G., Miller J., Williams H., Newell C., Rowe M., et al. (2005). Pre-


