New Microbiologica, 41, 4, 282-290, 2018, ISN 1121-7138

FULL PAPER

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

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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

INTRODUCTION

Children, especially those under the age of five, and adolescents are a high-risk group vulnerable to developing tuberculosis (TB) disease when infected by *Mycobacterium tuberculosis*. Children are less likely to achieve immunological control, resulting in a high risk of pulmonary and extrapulmonary disease (Newton *et al.,* 2008; Perez-Velez *et al.,* 2012) and of a rapid clinical progression, inversely correlated with increasing age (Marais *et al.,* 2004). Childhood TB is an indicator of ongoing transmission within a community. To rapidly identify and stop the transmission of TB involving children, it is crucial to achieve TB elimination in low burden countries, since children with latent *Mycobacterium tuberculosis* infection (LTBI) could generate a pool of infection and become future TB cases. Children under the age of 15 accounted for 10% - over 1 million - of the 10.4 million incident cases estimated globally in 2016 (WHO, 2017). A situational analysis on childhood TB in 2000-2009 in EU/EEA countries found a poor correlation between childhood TB and overall rates in low TB endemic countries, possibly as figures on childhood TB might be particularly sensitive to TB outbreaks against a background of low incidence and stable trends. In addition, it was hypothesized that paediatric TB increases due to outbreaks among children might occur against a background of low incidence and stable trends (Sandgren *et al.,* 2011).
The risk of *Mycobacterium tuberculosis* transmission in schools was previously reviewed by Roberts et al. The transmission rate in outbreaks involving children aged 3 to 11 was found higher if the index case was a child rather than an adult (weighted average 69.8% vs 39.3%) (Roberts *et al.,* 2012). A more recent systematic literature review on published descriptions of TB incidents and verified outbreaks affecting children in congregate settings in the EU/EEA during the period 2004-2011 (ECDC, 2014) reported a detection rate of active TB varying from 0.08% to 38% and of LTBI from 6.2% to 34.5%.
To better assess the risk of *M. tuberculosis* transmission among children and adolescents in school/childcare (e.g., kindergartens, pre-school playgroups, private day nurseries, day-care centres) and other congregate settings we systematically reviewed TB incidents in which a teacher or child-carer, relative, or student was diagnosed with TB, and children or adolescents aged 2 to 18 were exposed to a *Mycobacterium tuberculosis* source in these settings.

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

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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, day-care 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 spread sheet 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); *concentric circles/ring approach:* contact categorization according to the likelihood of transmission (skin testing begins in high risk contacts and is continued until the rate of positivity equals the background prevalence of LTBI in the community).
- *LTBI*: a positive result, 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.*, ≤ 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; Piccini *et al.,* 2017; Rothman *et al.,* 1993; Shannon *et al.,* 1991; Ustero *et al.,* 2017).

Articles were published from 1950 (Smith *et al.,* 1950) to 2017 (Piccin *et al.,* 2017; Ustero *et al.,* 2017) and reported data on incidents which occurred in Spain (25, 19.5%) (de March Ayuela *et al.,* 1988; Álvarez-Álvarez *et al.,* 2013; Alvarez-Castillo *et al.,* 2007; Marcos Rodríguez *et al.,* 2007; Miravet Sorribes *et al.,* 2016; Prieto Lozano *et al.,* 1996; Penín Antón *et al.,* 2007; Sánchez Marenco *et al.,* 2003; Tagarro *et al.,* 2011), USA (22, 17.2%) (Adler-Shohet *et al.,* 2014, Bates *et al.,* 1965; Curtis *et al.,* 1999; Darney *et al.,* 1971; Fulton *et al.,* 2008; Hoge *et al.,* 1994; Mahady, 1961; Phillips *et al.,* 2004; Reves *et al.,* 1981; Ridzon *et al.,* 1997; Rogers *et al.,* 1962; Sacks *et al.,* 1985; Smith *et al.,* 2000; Wang *et al.,* 2010; Washko *et al.,* 1998; Yusuf *et al.,* 1997), Italy (20, 15.6%) (Ariano *et al.,* 1994; Binkin *et al.,* 1994; Biscione *et al.,* 1969; Faccini *et al.,* 2013; Filia *et al.,* 2011; Gillini *et al.,* 2015), Canada (14, 10.9%) (Rothman and Dubeski, 1993; Smith *et al.,* 1950; Arneil *et al.,* 1973; Herrick and Davison, 1995; Rideout and Hiltz, 1969; Rivest, 1993), UK (13, 10.2%) (Aspin *et al.,* 1965; Beresford, 1962; Caley *et al.,* 2010; Ewer *et al.,* 2003; Howard *et al.,* 2007; Milburn *et al.,* 2000; Millership *et al.,* 1998; Neira-Munoz *et al.,* 2008; Paranjothy *et al.,* 2008; Rona *et al.,* 1983; Twisselmann and Watson, 2001; Wales *et al.,* 1985; Williams *et al.,* 2016), Ireland (7, 5.5%) (Shannon *et al.,* 1991; Bredin *et al.,* 1991; Connolly and Murphy, 1987; O'Meara *et al.,* 2005; Stronge and Balmer, 1961), Swaziland (7, 5.5%) (Ustero *et al.,* 2017), Sweden (3, 2.3%) (Gillman *et al.,* 2008; Müller *et al.,* 2008; Trollfors *et al.,* 2013), Switzerland (3, 2.3%) (Steppacher *et al.,* 2014), Japan (3, 2.3%) (Higuchi *et al.,* 2007; Higuchi *et al.,* 2009; Toivgoogiin *et al.,* 2005), Greece (2, 1.6%) (Hadjichristodoulou *et al.,* 2005), Australia (2, 1.6%) (Banner, 2013; Cardona *et al.,* 1999), France (2, 1.6%) (Guigou and Charpin, 1961; Mande and Aubriet, 1955), Iran (Baghaie *et al.,* 2012), Finland (Tuuminen et al., 2012), Norway (Døllner *et al.,* 2012), Macao (Chou *et al.,* 2015) and Brazil (Brólio, 1974) (1 each, 0.8%). Very few investigations were conducted in low or middle income countries or in high TB or MDR TB burden countries (Ustero *et al.,* 2017; Chou *et al.,* 2015; Brólio, 1974).

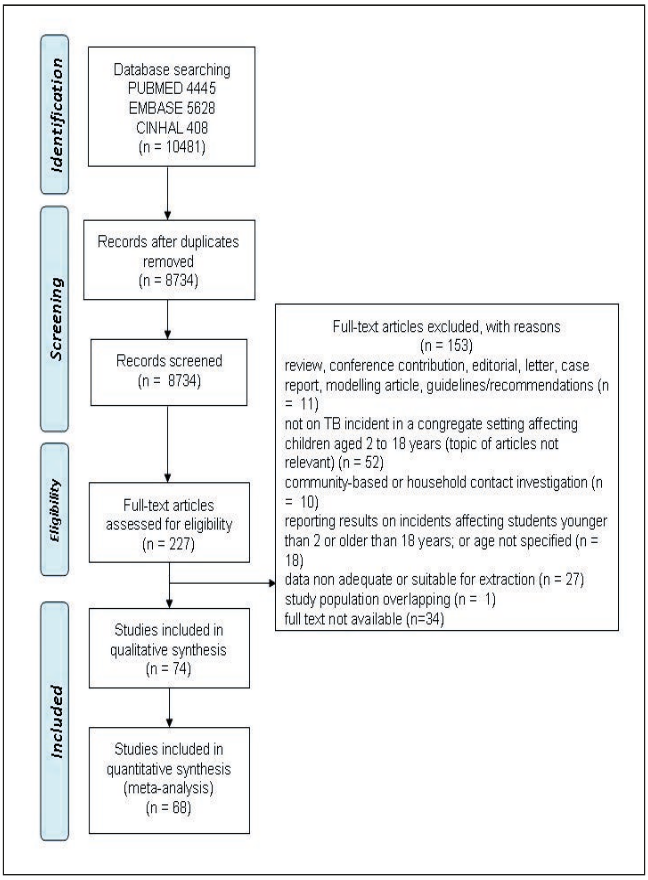

Figure 1 - *Selection process – Prisma Diagram.*

Study quality

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; Gillman *et al.,* 2008; Müller *et al.,* 2008)· and orphanages or other residential settings (3, 3.1%) (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 extrapulmonary 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. 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 proportion of those screened ranged between 71% and 100%. In half of the incident investigations (52: 51.0% of those -102- reporting this information), all individuals who were in the school/congregate setting during the period of infectivity of the index case were considered candidates for screening and no criteria for prioritisation were reported. The "only high-risk contacts" and the classic concentric circle approach for contact screening principles were applied in 34 (33.3%) and 16 (15.7%) investigations, respectively. In one incident the exposed children or adolescents were not screened for LTBI, as only TB exclusion and surveillance of TB occurrence were performed (Ustero *et al.,* 2017).

TST was used to detect LTBI in all but five studies (69/74, 93.2%), as a single test or combined with other assays (*i.e.*, IGRA not otherwise specified (Piccini *et al.,* 2017; Higuchi *et al.,* 2007; Higuchi *et al.,* 2009; Døllner *et al.,* 20012), QFT (Álvarez-Álvarez *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.,* 20 Tuuminen *et al.,* 2012) (*Appendix 2*).

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

Characteristics	*n.*	*(%)*
Role (128)		
student	81	63.3
teacher	27	21.1
bus driver	8	6.3
care-giver	6	4.7
other	4	3.1
parent	1	0.8
not reported	1	0.8
Nationality (128)		
autochthonous	15	11.7
foreign-born	27	21.1
data not reported	86	67.2
Diagnostic interval (days) (128)		
<30 d	6	4.7
≥30 d	52	40.6
data not reported	70	54.7
Tuberculosis location (128)		
pulmonary (P)	103	80.5
extrapulmonary (EP)	5	3.9
pulmonary and extrapulmonary (P-EP)	3	2.3
data not reported	17	13.3
Sputum smear (106 P or P-EP)		
negative	17	16.1
positive	81	76.4
data not reported	8	7.5
Sputum/gastric aspirate culture (106 P or P-EP)		
negative	12	11.3
positive	54	50.1
data not reported	40	37.6
Chest X Ray (106 P or P-EP)		
cavitary lesions absent	12	11.3
cavitary lesions present	54	50.1
data not reported	40	37.6

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 31/3,998 (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.,* 2014) it was not possible to detail age groups of exposed individuals. 31/128 (24.2%) of the reports provided data on a total of 6,336 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; Higuchi *et al.,* 2007; Higuchi *et al.,* 2009; Hadjichristodoulou *et al.,* 2005; Banner *et al.,* 2013; Cardona *et al.,* 1999; Tuuminen *et al.,* 2012; Døllner *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.*: this 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= 88.50%) -age 2 to 5 years- to 0.13 (95% CI: 0.09 to 0.17; I^2= 90.30%) - age 6 to 10 years - and to 0.09 (95% CI: 0.06 to 0.13; I^2= 85.00%) - >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 (TB: 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= 85.9%); 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*).

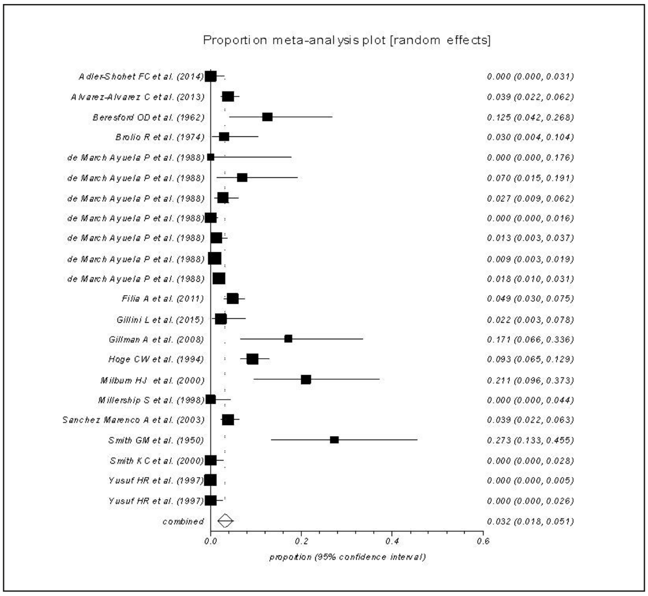

Figure 2 - *Combined proportions of active TB cases among screened children aged 2 to 5 years.*

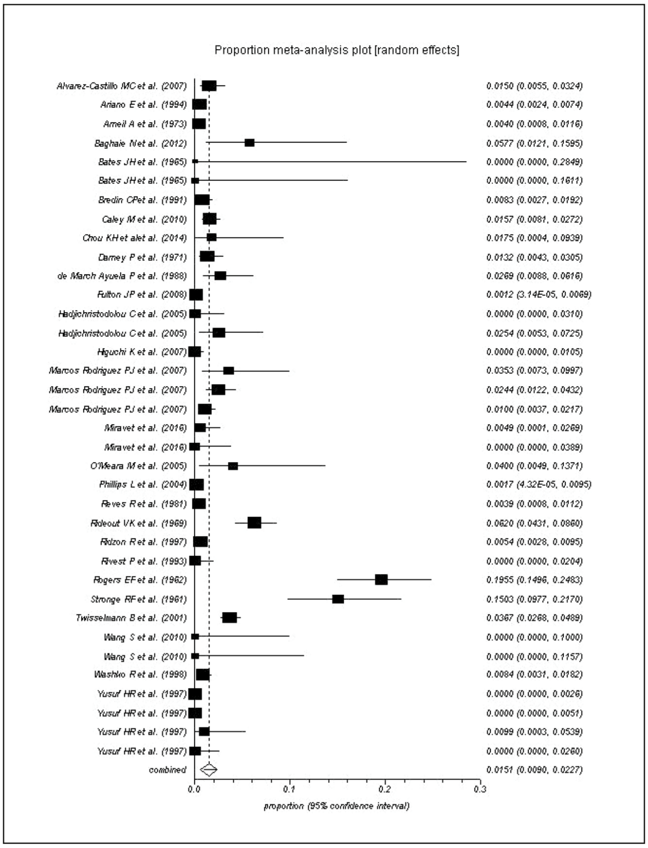

Figure 3 - *Combined proportions of active TB cases among screened adolescents aged 16 to 18 years.*

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 trend in the general population.

Child household exposure has been estimated to result in a proportion of active TB of 4.7% and 2.9%, and in a proportion of LTBI of 16.3% and 18.4% among children up to five years of age and among children six to fourteen years old in high-income countries, respectively (Fox *et al.*, 2013). A review of published literature and national UK data on nosocomial TB in infants showed that only 0.14% of exposed individuals were found to be infected (Millership *et al.*, 2009), with the highest yield among contacts of mothers with TB and the lowest among contacts of infants with TB. 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 Schepisi *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.*

Characteristics	*Screened positive/ Screened*		*Active TB/ Screened*		*Active TB/ Screened positive*	
	(95%CI)	I2	(95%CI)	I2	(95%CI)	I2
Total	*0.15 (0.13-0.18)*	*97.60%*	*0.03 (0.02-0.04)*	*93.50%*	*0.13 (0.10-0.17)*	*88.50%*
Exposed students						
aged 2-5 years	0.12 (0.07-0.17)	*96.70%*	0.03 (0.02-0.05)	*90.00%*	0.26 (0.16-0.38)	*88.50%*
aged 6-15 years	0.16 (0.13-0.20)	*97.70%*	0.03 (0.02-0.04)	*94.30%*	0.13 (0.09-0.17)	*90.30%*
aged 16-18 years	0.15 (0.11-0.19)	*98.20%*	0.02 (0.01-0.02)	*91.90%*	0.09 (0.06-0.13)	*85.00%*
Index case						
age (years)						
5-10 y	0.34 (0.21-0.46)	*92.20%*	0.06 (0.01-0.15)	*94.40%*	0.16 (0.03-0.34)	*92.40%*
> 10 y	0.17 (0.13-0.21)	*97.80%*	0.02 (0.01-003)	*90.90%*	0.09 (0.06-0.13)	*89.60%*
≤ 12 y	0.30 (0.19-0.41)	*94.40%*	0.04 (0.00-0.11)	*95.90%*	0.11 (0.01-0.30)	*94.70%*
> 12 y	0.17 (0.13-0.22)	*97.80%*	0.02 (0.01-0.03)	*90.70%*	0.10 (0.06-0.13)	*89.00%*
≤ 14 y	0.25 (0.16-0.36)	*97.90%*	0.04 (0.02-0.08)	*95.50%*	0.14 (0.04-0.28)	*95.80%*
> 14 y	0.17 (0.13-0.21)	*97.50%*	0.01 (0.01-0.02)	*84.90%*	0.08 (0.06-0.12)	*81.20%*
≤ 16 y	0.19 (0.14-0.26)	*97.10%*	0.04 (0.02-0.06)	*93.80%*	0.15 (0.08-0.24)	*93.50%*
> 16 y	0.14 (0.11-0.18)	*98.00%*	0.01 (0.01-0.02)	*85.90%*	0.10 (0.07-0.12)	*76.10%*
country of birth						
foreign-born	0.13 (0.09-0.17)	*90.70%*	0.01 (0.00-0.02)	*75.80%*	0.06 (0.02-0.12)	*77.20%*
non foreign-born	0.16 (0.08-0.26)	*99.10%*	0.03 (0.01-0.05)	*95.30%*	0.14 (0.08-0.23)	*88.30%*
role						
teacher	0.16 (0.11-0.21)	*96.00%*	0.04 (0.02-0.06)	*92.00%*	0.19 (0.11-0.27)	*89.60%*
student	0.19 (0.15-0.23)	*97.80%*	0.02 (0.01-0.03)	*92.60%*	0.10 (0.07-0.14)	*90.40%*
microbiological/clinical characteristics						
sputum negative/culture positive	0.14 (0.03-0.30)	*98.40%*	0.03 (0.01-0.07)	*93.60%*	0.25 (0.16-0.34)	*49.90%*
sputum positive/culture positive	0.17 (0.13-0.22)	*98.10%*	0.02 (0.01-0.03)	*92.20%*	0.06 (0.04-0.09)	*76.20%*
cavitary lesions absent	0.13 (0.05-0.24)	*97.70%*	0.02 (0.00-0.05)	*91.70%*	0.11 (0.05-0.20)	*70.10%*
cavitary lesions present	0.16 (0.13-0.19)	*97.90%*	0.02 (0.01-0.03)	*92.10%*	0.12 (0.08-0.15)	*89.10%*
diagnostic delay ≤30 days	0.06 (0.02-0.12)	*97.20%*	0.01 (0.00-0.01)	*73.60%*	0.09 (0.06-0.12)	*0.00%*
diagnostic delay >30 days	0.16 (0.12-0.20)	*98.00%*	0.03 (0.02-0.04)	*94.90%*	0.16 (0.11-0.22)	*93.30%*

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 (Herrick 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 rates of tuberculosis to children and infants during nosocomial versus school outbreaks: a systematic literature review" Monica Sañé Schepisi, Enrico Girardi Available at: http://ecdc.europa.eu/en/ESCAIDE/past-ESCAIDE/Documents/ESCAIDE-2013-abstract-book.pdf

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