

Appendix

Table A1. Papers included in the review

Author	Country	Date study started	Incidence at beginning of study (cases per 100,000 pop)	Recurrence definition	Follow up	Ref
Kim	USA	1993	9.7	Verified disease who report previous TB and were discharged or lost to supervision >12 months [‡]	Passive	(1)
Schirolli	Italy	1995	9.5	Recurrence was defined as a culture-based diagnosis of TB in a patient with a previously cured episode of TB (this was confirmed by review of records).	Passive	(2)
Sudre	Switzerland	1988	1.5	2 cultures of Mtb positive at least 6 months apart (relapse if same, reinfection if different)	Active	(3)
Bandera	Italy	1995	9.5	Culture positive for Mtb with compatible clinical signs after patient finished ATT, culture neg and cured.	Passive	(4)
Wang	Taiwan	1999	68.2	Bacteriologically confirmed recurrence after bacteriologically confirmed cure or treatment complete	Passive	(5)
Bang	Denmark	1992-2006	6.9-10.5	A serial case with the original strain after treatment success or a case with a new strain irrespective of treatment outcome	Passive	(6)
Golub	Brazil	2004	54	Subsequent diagnosis of TB at least 9 months after the initial diagnosis (Brazilian Government definition)	Passive	(7)
Jasmer	USA / Canada	1995	8.5; 6.7	Relapse: culture conversion and treatment completion of 1 st episode with 2 nd episode with compatible clinical symptoms and culture positive with genotypes matching for both episodes. Reinfection: non-matching genotypes of original and subsequent isolates in patient with clinical course of relapse / failure.	Active	(8)
Unis	Brazil	2004	54	2 nd episode of TB occurring after 1 st had been considered cured; exclude <3-month interval as treatment failure & >60-month interval as possible new case	Passive	(9)
Nahid	USA	1990	10.3	Evidence of a 2 nd episode of TB after 1 st episode deemed treatment complete and cured. Relapse if 2 isolates same genotype. If no genotyping, considered relapse if same drug susceptibility or acquired resistance to 1 drug.	Active	(10)
Crofts	England and Wales	1998	10.9	Renotification >=12 months apart	Passive	(11)
Pascopella	USA	1993	9.7	12 months apart between completion of ATT 1 st episode and ATT reinitiated for 2 nd episode	Passive	(12)

Millett	Barcelona Spain	2003	27	New clinical / microbiological TB diagnosis in patient who finished ATT for 1st episode and disease free >1year	Passive	(13)
Pettit	USA	2000	5.8	Restarted ATT for 2 nd diagnosis of TB after adequate response to completed ATT course for 1 st episode	Passive	(14)
El-Sahly	USA	1995	8.5	2 groups 1.CDC definition [‡] ; 2. Completed adequate ATT course & 2 nd verified diagnosis regardless of time elapsed.	Passive	(15)
Hung	Taiwan	1998	66	Retreated >60 days more than 6 months after previous episode	Passive	(16)
Lee	Taiwan	2006	67	Renotification to national TB registry with bacteriological / pathological findings of TB after completion previous ATT	Passive	(17)
Interrante	USA	1993	9.7	1 st episode of TB treatment completed. Then 2 nd episode of TB: relapse: isolates for both episodes match on genotyping; reinfection >1 locus /band difference.	Passive	(18)
Avery	UK	1991	11.2	More than one episode of TB (after defaulters were excluded)	Passive	(19)
Chen	Taiwan	2007	63	A positive sputum culture at least 3 months 'after end of successful treatment'	Passive	(20)
Burman	USA/ Canada	1995	8.5 (USA); 6.7 (Canada)	Positive culture in the 2 years after treatment completion (end point review committee decided if relapse / reinfection / cross contamination)	Active	(21)
Sterling	USA	1993	9.7	Previously cured and culture converted; new episode of TB bacteriological / pathological evidence & clinical signs	Passive	(22)
Jo	Korea	2000	50	Culture negative or conversion on ATT and then after treatment became culture positive / histopathological evidence and clinical features of TB with ATT response	Passive	(23)
Nettles	USA	1993	9.7	Adequate treatment response 1 st episode (culture conversion if PTB) and positive culture result during follow up (false positive excluded)	Passive	(24)
Anaam	Yemen	2007	66	Completed treatment & declared cured diagnosed with 2 nd culture / smear positive TB episode	Active	(25)
Faustini	Italy	1999	7.7	Bacteriologically confirmed TB >3 months after successful cure, no treatment prior to the 1st notification & alive 12 months after 2nd ATT classified as recurrence	Passive	(26)
Millett	Spain	1995	21	New clinical / microbiological TB diagnosis in a patient who finished ATT for 1st episode and was disease free >1year	Passive	(27)
Selassie	USA	1970	18.1	Patients with TB who again developed verified TB after being discharged from supervision >12 months [‡]	Passive	(28)
Kim	USA	1993	9.7	Completed treatment of the initial TB episode, and whose TB did not relapse within a year of treatment completion.	Passive	(29)
Ormerod	UK	1991	10.5	Relapse was taken as a clinical, radiological or bacteriological recurrence of disease within 36 months of cessation of drug treatment.	Passive	(30)
Choi	Korea	2005	96	Restart ATT after cure of previous episode	Active	(31)

Cacho	Spain	1992	40	Culture positive 2 nd TB episode after completing full ATT course for 1 st episode.	Passive	(32)
Chiang	Taiwan	1992	41	Those considered cured 18 months into treatment and then represent bacteriologically positive TB episode	Passive	(33)
Pulido	Spain	1997	38.5	New positive Mtb culture after clinical resolution and microbiological sample negativity after 6 months of ATT (each case validated by 2 blinded authors)	Passive	(34)
Avendaño	Canada	1986	8.2	Positive culture for Mtb two years after persistently neg cultures (culture conversion)	Passive	(35)
El-Sadr	USA	1993	9.7	1. Culture positive after sputum culture converted and completed treatment or 2. Culture positive after clinical resolution and ATT finished.	Active	(36)
Lee	Korea	2002	80	After cure / treatment completion of 1 st episode: either 1. Culture positive during follow up or 2. Aggravation of respiratory symptoms / radiographic lesion improving after initiation of MDR ATT 3. Pathological findings of TB after biopsy of new lung lesion	Passive	(37)
De Boer	Netherlands	1981	12.2	Recurrence: disease reported prior to 1981 with a 2 nd new infection 1993-1997. Definition of reinfection: isolate 1993-97 that clustered with another isolate but was not first of that cluster; reactivation (relapse) unique typing signature 1993-97	Passive	(38)
Driver	USA	1993	9.7	'Recurrence' - a positive culture within 30 days after the last treatment date. 'Relapse' - positive culture >30 days after the last treatment date.	Passive	(39)
Li	China	2007	86	The retreatment TB patients (sputum smear positive and/or culture positive) who were not drug-resistance and had declared to be cured after 8-month retreatment for more than 2 years by Jan 2011	Passive	(40)
Khan	USA	1995	8.5	Patients with positive sputum post treatment and whose isolates were genotypically identical termed 'relapse'	Active	(41)
Blondal	Estonia	2001	58	Disease recurrence was confirmed by culture, without performing genotyping of isolates to differentiate between recurrence caused by the former strain and re-infection	Passive	(42)
Vernon	USA	1995	8.5	Patients 'could be assessed for relapse who had completed 16 weeks of study drug within 22 weeks of enrolment'; bacteriological relapse=culture positive from any site after successful completion of ATT	Active	(43)
Dobler	Australia	1994	5.91	Any new clinical and/or microbiological TB diagnosis in a patient who had completed anti-TB treatment and had been TB disease-free for at least one year since treatment completion	Passive	(44)

‡ CDC definition: Verified TB in the past, were discharged from or lost to supervision for more than 12 months and had a new verified TB diagnosis. (Verification of a TB case - the process whereby a TB case, after the diagnostic evaluation is complete, is reviewed at the local level (e.g., state or county) by a TB control official who is familiar with TB surveillance definitions; if all the criteria for a TB case are met, the TB case is then verified and eligible for counting). Abbreviations: ATT – anti-tuberculous therapy; MDR – Multidrug resistant; Mtb – *Mycobacterium tuberculosis*; PTB- pulmonary tuberculosis; TB - tuberculosis

Table A2. Papers excluded from the review

Author	Reason excluded	Reference
Slutkin	TB recurrence was not defined	(45)
Garcia	Recurrence defined as 2 TB cultures separated by ≥ 100 days	(46)
Das	TB recurrence was not defined	(47)
He	TB recurrence was not defined	(48)
Chaves	TB recurrence was not defined	(49)
Li	TB recurrence was not defined	(50)
Leung	TB recurrence was not defined	(51)
Small	TB recurrence was not defined	(52)
He	TB recurrence was not defined	(53)
Chang	TB recurrence was not defined	(54)
Various	TB recurrence was not defined	(55)
Lourenco	TB recurrence was not defined	(56)
Geerligs	TB recurrence was not defined	(57)
Farnia	Clustering used to determine reinfection vs. relapse; no genotyping of paired isolates	(58)
Sahebi	TB recurrence was not defined	(59)
Roh	TB recurrence defined as retreatment after cure; basic science research paper	(60)
Caminero	Recurrence case definition includes retreatment after cure, retreatment after default and retreatment after failure.	(61)
Chang	Incidence rate at start of study (1998) was 117 cases per 100,000 population	(62)
Leung	Incidence rate at start of study (2001) was 108 cases per 100,000 population	(63)
Sun	Incidence rate at start of study (2001) was 105 cases per 100,000 population	(64)
Ahmad	Incidence rate at start of study (2000) was 128 cases per 100,000 population	(65)
Lee Kim	TB recurrence was not defined	(66)
Leung	TB recurrence was not defined	(67)
TB trials consortium	Risk factors calculated for relapse & failure combined	(68)
Vieira	Compares 'early' and 'late' recurrences rather than recurrence vs. no recurrence	(69)
Varghese	TB recurrence was not defined	(70)
Kim	TB recurrence defined as retreatment after cure; basic science research paper.	(71)

Table A3: Newcastle-Ottawa scores of case-control studies

Author	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of design or analysis (max 2)	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score (max 9)
Petit	0	1	1	1	2	1	1	0	7
El-Sahly	1	1	1	1	2	1	1	0	8
Hung	0	1	1	1	2	1	1	0	7
Lee	1	1	1	1	2	1	1	0	8
Anaam	1	1	1	1	2	1	1	0	8
Faustini	1	1	1	1	2	1	1	0	8
Selassie	1	1	1	1	2	1	1	0	8

Please note: a study can be awarded a maximum of one point (star) for each category asides from comparability for which a maximum of two points (stars) are awardable.

Table A4: Newcastle-Ottawa Scores of cohort studies

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	Comparability of cohorts on the basis of the design or analysis (max 2)	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up	Total score (max 9)
Kim 2013	1	1	1	0	0	1	1	1	6
Schiroli	1	1	1	0	2	1	1	0	7
Sudre	0	1	1	0	0	1	1	0	4
Bandera	1	1	1	0	1	1	1	0	6
Wang	1	1	1	0	0	1	1	0	5
Bang	1	1	1	0	2	1	1	0	7
Golub	0	1	1	1	2	1	1	0	7
Jasmer	1	1	1	0	0	1	1	0	5
Unis	1	1	1	0	1	1	1	0	6
Nahid	0	1	1	0	2	1	1	0	6
Crofts	1	1	1	0	2	1	1	0	7
Pascopella	1	1	1	0	2	1	1	0	7
Millett 2013	1	1	1	0	2	1	1	1	8
Interrante	1	1	1	0	2	1	1	0	7
Avery	0	1	1	0	0	1	1	0	4
Chen	1	1	1	0	2	1	1	0	7
Burman	0	1	1	0	2	1	1	0	6
Sterling	0	1	1	0	1	1	1	0	5
Jo	0	1	1	0	2	1	1	0	6
Nettles	0	1	1	0	0	1	1	0	4
Millett 2009	1	1	1	0	2	1	1	0	7
Kim 2016	1	1	1	0	2	1	1	0	7

Ormerod	1	1	0	0	0	0	1	0	3
Choi	0	1	0	0	2	1	1	0	5
Cacho	1	1	1	0	1	1	1	0	6
Chiang	0	1	1	0	0	1	1	0	4
Pulido	0	1	1	0	2	1	1	0	6
Avendaño	0	1	1	0	0	1	1	0	4
El-Sadr	0	1	0	0	0	1	1	0	3
Lee	0	1	1	0	0	1	1	0	4
De Boer	1	1	1	0	0	1	1	0	5
Driver	1	1	1	0	2	1	1	0	7
Li	1	1	0	0	2	0	1	0	5
Khan	0	1	1	0	2	1	1	1	7
Blondal	1	1	1	0	2	1	1	0	7
Vernon	0	1	1	0	1	1	1	0	5
Dobler	1	1	1	0	0	1	1	0	5

Please note: a study can be awarded a maximum of one point (star) for each category asides from comparability for which a maximum of two points (stars) are awardable.

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