



# Heterogeneous infectiousness in mathematical models of tuberculosis: A systematic review

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## ABSTRACT

TB mathematical models employ various assumptions and approaches in dealing with the heterogeneous infectiousness of persons with active TB. We reviewed existing approaches and considered the relationship between them and existing epidemiological evidence.

We searched the following electronic bibliographic databases from inception to 9 October 2018: MEDLINE, EMBASE, Biosis, Global Health and Scopus. Two investigators extracted data using a standardised data extraction tool. We included in the review any transmission dynamic model of *M. tuberculosis* transmission explicitly simulating heterogeneous infectiousness of person with active TB. We extracted information including: study objective, model structure, number of active TB compartments, factors used to stratify the active TB compartment, relative infectiousness of each active TB compartment and any intervention evaluated in the model.

Our search returned 1899 unique references, of which the full text of 454 records were assessed for eligibility, and 99 studies met the inclusion criteria. Of these, 89 used compartmental models implemented with ordinary differential equations, while the most common approach to stratification of the active TB compartment was to incorporate two levels of infectiousness. However, various clinical characteristics were used to stratify the active TB compartments, and models differed as to whether they permitted transition between these states. Thirty-four models stratified the infectious compartment according to sputum smear status or pulmonary involvement, while 18 models stratified based on health care-related factors. Variation in infectiousness associated with drug-resistant *M. tuberculosis* was the rationale for stratifying active TB in 33 models, with these models consistently assuming that drug-resistant active TB cases were less infectious.

Given the evidence of extensive heterogeneity in infectiousness of individuals with active TB, an argument exists for incorporating heterogeneous infectiousness, although this should be considered in light of the objectives of the study and the research question.

PROSPERO Registration: CRD42019111936.

## 1. Introduction

Tuberculosis (TB) is one of the top ten causes of death and the leading cause from a single infectious agent (WHO, 2018). Although the disease burden caused by TB is falling globally, we are unlikely to see the first milestones of the *End TB Strategy* achieved in 2020 (WHO, 2014). The current global burden of TB is not homogeneously

distributed across populations, but rather is an aggregate of localised micro-epidemics, with this heterogeneous distribution likely to become more prominent as disease burden decreases (Pai et al., 2016). One of several factors that contributes to the heterogeneity of *Mycobacterium tuberculosis* (*Mtb*) transmission in a given population is the intrinsic variation in the infectiousness of individuals with active TB (Trauer et al., 2018). The heterogeneous infectiousness of such individuals has

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been established from both epidemiologic contact investigations and genotypic data (Ypma et al., 2013; Melsew et al., 2019). These studies have demonstrated that a very few highly infectious individuals with active TB are responsible for a large proportion of onward transmission, while a much larger proportion of individuals have very low or negligible infectiousness. As this heterogeneity has effects on the basic reproduction number,  $R_0$ , and the impact of interventions, incorporating heterogeneous infectiousness assumptions in TB transmission dynamic models may be critical depending on the modelling objectives (Trauer et al., 2018).

Transmission dynamic models typically have one of two broad purposes: either to improve understanding of the behaviour of the epidemic, or to make predictions of disease burden, including under counterfactual intervention strategy scenarios. Any such models should represent reality as accurately as possible, while also considering the need for model parsimony, although the optimal balance of these factors is dependent on judgement and epidemiological understanding (McLean, 2013; Cohen and White, 2016). Though the first TB model was published more than half a century ago (Waalder et al., 1962), TB models continue to differ in their assumptions due to imperfect understanding of the complex natural history of TB and lack of available data on the clinical progression of individuals through their stages of disease.

By systematically reviewing previous TB transmission modelling studies, we describe existing methods used to capture heterogeneity in infectiousness of individuals with active TB. Specifically, we aimed to identify all TB transmission models that explicitly stratified the active TB compartment by levels of infectiousness, and to understand their modelling assumptions and parameter choices.

## 2. Methods

We reviewed all published TB mathematical modelling studies that considered heterogeneity in infectiousness, with infectiousness conceptually defined as the number of secondary infections resulting from an individual with active disease per unit time. The review protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews, registration number: CRD42019111936) and can be accessed at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=111,936](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=111,936). We adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines throughout (Liberati et al., 2009) and the PRISMA checklist is provided in Appendix A in Supplementary material.

### 2.1. Search strategy

Before starting the review, we searched for systematic reviews that assessed methods used to capture heterogeneity in infectiousness of individuals with active TB in transmission dynamic models, with no such reviews found.

We searched the following electronic bibliographic databases from inception to 9 October 2018: MEDLINE, EMBASE, Biosis, Global Health and Scopus for studies in human subjects published in English. All search terms were “exploded” to capture all resources and consisted of “TB”, “Tuberculosis”, “Mycobacterium tuberculosis”, “Dynamic model”, “Transmission dynamics”, “Simulation”. Full search strategy is provided in Appendix B in Supplementary material.

### 2.2. Study selection

Search results were exported to EndNoteX8.2 (Clarivate Analytics, NY, USA) and duplicates were removed. Titles and abstracts were screened to identify potentially relevant articles. After initial screening for any TB modelling studies, the full texts of eligible articles were collected and assessed for eligibility. Included studies consisted of any

transmission dynamic TB modelling study explicitly incorporating the assumption of heterogeneous infectiousness of individuals with active TB. Studies were excluded if they were systematic reviews, did not employ mathematical models, did not model *Mtb*, were intra-host models or assumed homogeneous infectiousness.

### 2.3. Assessment of quality

As we aimed to assess the diverse methods used to capture heterogeneous infectiousness of individuals with active TB and there was no epidemiological pooling, risk of bias assessment was not performed.

### 2.4. Data extraction and analysis

Data were extracted using a standardised data extraction tool developed, tested and approved by four investigators (YAM, AIA, RR and JMT). Full manuscripts and supplementary material accompanying the main texts of each article were reviewed. YAM and AIA extracted data and any controversies in interpretation were resolved by consensus.

We extracted general information that included: year of publication, study setting, study objective, model structure, and information about our main objective, including: the number of infectious compartments, factors used to stratify the infectious compartment and the relative infectiousness of each active compartment.

## 3. Results

Our search strategy returned 1899 unique references, of which the full text of 454 records were assessed for eligibility, and 99 studies met the inclusion criteria of explicitly capturing heterogeneous infectiousness (Fig. 1). Of the 99 included TB models, 89 were compartmental models implemented using ordinary differential equations, one study used both ordinary and partial differential equations and the remaining nine were individual-based models (IBM). Included studies spanned many different epidemiological settings: 25 studies were from Asia or the Asia-Pacific, 21 were from sub-Saharan Africa, 12 studies were from Europe or North America. Nineteen studies represented hypothetical settings based on TB burden, economic development or HIV prevalence. Eight of these models were from high TB-burden settings (or “low/middle income”), two were from low TB burden settings (or “the developed world”), two were from high HIV prevalence settings and one aimed to represent global TB epidemiology.

### 3.1. Aims of models

The broad objectives of most included TB models were to evaluate the impact of various intervention strategies and make predictions of future disease burden based on various settings and scenarios. Forty-four of the 99 models were designed to estimate the likely impact of currently available interventions (Tuite et al., 2017; Vynnycky et al., 2015; Trauer et al., 2016a; Okuonghae and Aihie, 2008; Okuonghae and Ikhimwin, 2016; Okuonghae and Korobeinikov, 2007; Okuonghae and Omosigho, 2011; Rayhan and Bakhtiar, 2017; Sachdeva et al., 2015; Salje et al., 2014; Salomon et al., 2006; Sharomi et al., 2008; Suen et al., 2014; Thomas et al., 2010; Hickson et al., 2011; Hickson et al., 2012; Hill et al., 2012; Hughes et al., 2006; Huynh et al., 2015; Jung et al., 2002; Kendall et al., 2015; Knight et al., 2015; Liao and Lin, 2012; Mellor et al., 2011; Menzies et al., 2012; Moualeu et al., 2015; Bowong and Alaoui, 2013; Dowdy et al., 2014; Dowdy et al., 2013a; Dowdy and Chaisson, 2009; Dowdy et al., 2008; Dowdy et al., 2006; Dowdy et al., 2013b; Dowdy et al., 2013c; Dye and Williams, 2008; Espindola et al., 2012; Fofana et al., 2017; Garcia et al., 1997; Gomes et al., 2007; Guzzetta et al., 2011; Bacaer et al., 2008; Basu et al., 2007; Basu et al., 2009; Bhunu and Garira, 2009), while five models evaluated the potential impact of interventions that were new, under development or hypothetical (Abu-Raddad et al., 2009; Knight et al., 2014; Lin

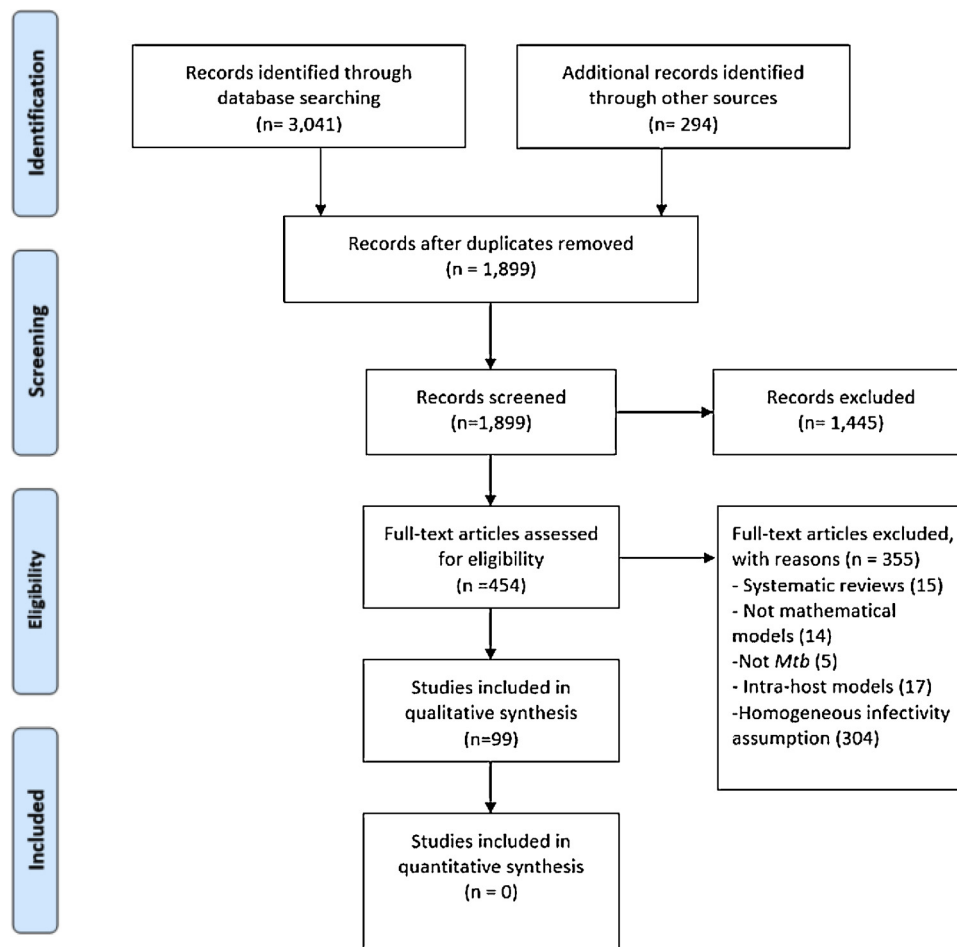


Fig. 1. Flow diagram of study selection process.

et al., 2012; Sun et al., 2013; Trauer et al., 2016b). Twenty-one models were built to capture TB epidemiology in a specific setting and make predictions by using local data (Arregui et al., 2018; Blower et al., 1995; Herrera et al., 2013; Houben et al., 2016; Legrand et al., 2008; Liao et al., 2012; Liao et al., 2013; Liu et al., 2011; Melnichenko and Romanyukha, 2009; Menzies et al., 2018; Moualeu et al., 2014; Moualeu-Ngangue et al., 2015; Mushayabasa and Bhunu, 2013; Nishiura et al., 2004; Oxlade et al., 2011; Pandey et al., 2017; Perelman et al., 2004; Sun et al., 2011; Wu et al., 2010; Zhang et al., 2015). Eight models were more theoretically focused, aiming to draw general conclusions about transmission dynamics, such as determining equilibrium points or reproductive numbers, and in some cases undertaking stability or sensitivity analyses around these quantities (Houben et al., 2016; Apriliani et al., 2016; Blower and Gerberding, 1998; Cohen and Murray, 2004; Liu et al., 2008; Liu and Sun, 2010; McBryde et al., 2017; Trauer et al., 2014). Four models assessed the impact of risk factors, such as smoking, age and diabetes mellitus (Garcia et al., 1997; Bhunu et al., 2011; Moualeu et al., 2012; Rodrigues et al., 2015), three evaluated the impact of immigration (Korthals Altes et al., 2018; Moualeu et al., 2018; Okuonghae and Aihie, 2010), and two evaluated the impact of *Mtb* re-infection (Moualeu et al., 2016; Sharomi et al., 2017). Six models additionally assessed aspects of the MDR-TB epidemic and its control (Kendall et al., 2015; Agosto et al., 2015; Ahmadin and Fatmawati, 2014; Bishai et al., 2010; Raimundo et al., 2014; Shrestha et al., 2014).

Models stratified the active TB compartment according to the level of infectiousness for a range of reasons, the commonest being to capture the impact of interventions directed at specific sub-groups of individuals with active TB or that had differential effectiveness depending

on the level of infectiousness. Within this group, forty-three models stratified the active TB compartment in order to capture the impact of detection and treatment interventions (Tuite et al., 2017; Vynnycky et al., 2015; Okuonghae and Korobeinikov, 2007; Rayhan and Bakhtiar, 2017; Sachdeva et al., 2015; Salje et al., 2014; Salomon et al., 2006; Sharomi et al., 2008; Suen et al., 2014; Thomas et al., 2010; Huynh et al., 2015; Jung et al., 2002; Knight et al., 2015; Mellor et al., 2011; Bowong and Alaoui, 2013; Dowdy et al., 2014; Dowdy et al., 2013a; Dowdy and Chaisson, 2009; Dowdy et al., 2008; Dowdy et al., 2006; Dowdy et al., 2013b; Dowdy et al., 2013c; Fofana et al., 2017; Garcia et al., 1997; Basu et al., 2007; Basu et al., 2009; Bhunu and Garira, 2009; Abu-Raddad et al., 2009; Lin et al., 2012; Sun et al., 2013; Trauer et al., 2016b; Legrand et al., 2008; Nishiura et al., 2004; Perelman et al., 2004; Blower and Gerberding, 1998; Liu et al., 2008; Liu and Sun, 2010; Korthals Altes et al., 2018; Okuonghae and Aihie, 2010; Agosto et al., 2015; Huo and Zou, 2016; Kendall et al., 2017; Osgood et al., 2011). By contrast, forty-four models incorporated stratification in the process of estimating key parameters in TB epidemiology, such as the number of secondary infections per infectious individual and  $R_0$  (Trauer et al., 2016a; Okuonghae and Aihie, 2008; Okuonghae and Ikhimwin, 2016; Okuonghae and Omosigbo, 2011; Hickson et al., 2011; Hickson et al., 2012; Hughes et al., 2006; Liao and Lin, 2012; Menzies et al., 2012; Moualeu et al., 2015; Gomes et al., 2007; Guzzetta et al., 2011; Bacaer et al., 2008; Blower et al., 1995; Herrera et al., 2013; Liao et al., 2012; Liao et al., 2013; Melnichenko and Romanyukha, 2009; Menzies et al., 2018; Moualeu et al., 2014; Moualeu-Ngangue et al., 2015; Mushayabasa and Bhunu, 2013; Oxlade et al., 2011; Pandey et al., 2017; Zhang et al., 2015; Apriliani et al., 2016; Cohen and Murray, 2004; McBryde et al., 2017; Trauer et al., 2014; Bhunu et al.,

2011; Moualeu et al., 2012; Moualeu et al., 2018; Moualeu et al., 2016; Sharomi et al., 2017; Ahmadin and Fatmawati, 2014; Raimundo et al., 2014; Aparicio and Castillo-Chavez, 2009; Kasaie and Dowdy, 2013; Li et al., 2011; Nyabadza and Kgosimore, 2012; Okuonghae, 2013). Eight models also stratified the active TB compartment to predict the future proportion of each type of TB simulated (Kendall et al., 2015; Espindola et al., 2012; Arregui et al., 2018; Sun et al., 2011; Wu et al., 2010; Rodrigues et al., 2015; Bishai et al., 2010; Shrestha et al., 2014). In a further six models, the rationale for stratifying the active TB compartment was not explained (Hill et al., 2012; Dye and Williams, 2008; Knight et al., 2014; Trauer et al., 2016b; Houben et al., 2016; Ackley et al., 2015).

### 3.2. Model structures

Models most commonly presented the natural history of TB using Susceptible, Exposed, Infectious, Recovered (SEIR) compartmental structures, although SEI, SEIS and SEIE structures were also used. (Some of these models employed more than one latency compartment; thus, “E” may represent multiple latency compartments.) In our review, the majority (64) of the models adopted a SEIR compartmental structure, while 12 used SEI structures and 11 employed SEIS.

The structures used by TB models to stratify the active TB compartment according to infectiousness level varied between models, with most models employing two active TB compartments. Fig. 2 presents a summary of the compartmental structures used and Table 1 maps the specific models to the compartmental structure employed. Henceforth, we refer to the specific model structures by the alphabetical structure names introduced in Fig. 2. It is important to note that several of these classifications include models that use the same compartmental

structure, but use these structures to represent different factors (and so employ different parameter values). Stratifying the active TB compartment into two unconnected infectiousness levels (*Structure A*) was the commonest structure used, followed by a structure employing two infectious levels and with an additional transition process linking these two states (*Structure B*).

### 3.3. Factors for stratification

TB models stratified the active TB compartment by infectiousness in order to capture a range of clinical characteristics. These factors included: factors related to characteristics of the host, such as disease manifestation, co-morbidities and age; factors related to the organism, i.e. impaired fitness of *Mtb* due to drug resistance mutations; and factors related to the health care system. The factors used for stratification of the active TB compartment were sometimes combined in the included studies and are not mutually exclusive.

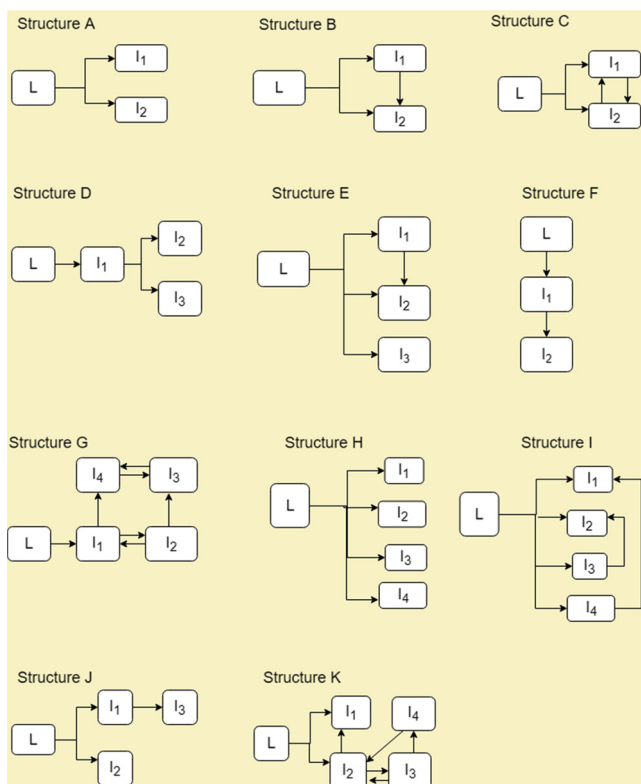
#### 3.3.1. Factors related to disease characteristics

**3.3.1.1. Pulmonary involvement.** Six TB models explicitly classified the active TB compartment based on the clinical site of TB disease, as either representing cases with lung involvement (pulmonary TB), or with disease limited only to body organs other than the lungs (extrapulmonary TB) (Thomas et al., 2010; Hickson et al., 2012; Dye and Williams, 2008; Korthals Altes et al., 2018; Aparicio and Castillo-Chavez, 2009). These models universally assumed that only pulmonary TB cases were infectious without further stratification by smear-status. Five of these models employed *Structure A* (Thomas et al., 2010; Hickson et al., 2012; Mellor et al., 2011; Dye and Williams, 2008; Korthals Altes et al., 2018; Aparicio and Castillo-Chavez, 2009), while one model also incorporated conversion from non-infectious to infectious TB (*Structure B*) (Mellor et al., 2011).

**3.3.1.2. Sputum smear-status.** Sputum smear-status was a commonly used factor for stratifying active TB cases into varying levels of infectiousness. Twenty-two TB models stratified the active TB compartment by sputum smear-status (Tuite et al., 2017; Vynnycky et al., 2015; Menzies et al., 2012; Dowdy et al., 2014; Dowdy and Chaisson, 2009; Dowdy et al., 2008; Dowdy et al., 2006; Dowdy et al., 2013b; Dowdy et al., 2013c; Garcia et al., 1997; Gomes et al., 2007; Guzzetta et al., 2011; Abu-Raddad et al., 2009; Knight et al., 2014; Lin et al., 2012; Sun et al., 2013; Arregui et al., 2018; Houben et al., 2016; Menzies et al., 2018; Oxlade et al., 2011; Pandey et al., 2017; Ackley et al., 2015), of which eleven characterised active TB as either smear-positive or smear-negative TB (with smear-negative TB always considered less infectious). Among these models, seven employed *Structure A* (Dowdy et al., 2013b; Gomes et al., 2007; Knight et al., 2014; Lin et al., 2012; Oxlade et al., 2011; Pandey et al., 2017; Ackley et al., 2015), while the remaining used *Structure B* to incorporate a transition from smear-negative to smear-positive (Tuite et al., 2017; Menzies et al., 2012; Garcia et al., 1997; Houben et al., 2016; Menzies et al., 2018), thereby assuming that some smear-positive individuals must have initially been smear-negative at disease onset.

Employing *Structure E*, TB models used a three-tier stratification incorporating pulmonary involvement and smear-status to divide the active TB compartment into smear-positive TB, smear-negative TB and extrapulmonary TB (non-infectious) (Dowdy et al., 2014; Dowdy et al., 2013c; Abu-Raddad et al., 2009; Arregui et al., 2018). Five models included four active TB compartments, four of which used detection status to further cross-stratify smear-positive and TB smear-negative, while one model cross-stratified HIV status and smear-status (Vynnycky et al., 2015; Dowdy and Chaisson, 2009; Dowdy et al., 2008; Dowdy et al., 2006; Sun et al., 2013). Under each of these approaches, infectiousness was influenced by smear status, such that smear-positive individuals were considered more infectious than those smear-negative.

Twenty-one of the 22 models that stratified the active TB



**Fig. 2.** Structures for the infectious compartments used by TB models that incorporate multiple levels of infectiousness. L: latent infection, I: active TB, with subscripts to indicate the multiple infectious compartments. Some of these models used more than one compartment for latency, thus “L” may represent multiple latency compartments here. The subscript numbers to the “I” compartments are arbitrary.

**Table 1**  
Infectious compartment structures used by compartmental TB single strain models.

Structure	Number of studies	Citation
A	27	(Okuonghae and Aihie, 2008; Okuonghae and Ikhimwin, 2016; Okuonghae and Korobeinikov, 2007; Okuonghae and Omosigho, 2011; Sharomi et al., 2008; Hill et al., 2012; Bowong and Alaoui, 2013; Dowdy et al., 2006; Dowdy et al., 2013b; Dowdy et al., 2013c; Dye and Williams, 2008; Gomes et al., 2007; Lin et al., 2012; Blower et al., 1995; Herrera et al., 2013; Liao et al., 2012; Liao et al., 2013; Oxlade et al., 2011; Pandey et al., 2017; Zhang et al., 2015; Apriliani et al., 2016; Korthals Altes et al., 2018; Okuonghae and Aihie, 2010; Sharomi et al., 2017; Aparicio and Castillo-Chavez, 2009; Okuonghae, 2013; Ackley et al., 2015)
B	11	(Hughes et al., 2006; Menzies et al., 2012; Garcia et al., 1997; Bacaer et al., 2008; Knight et al., 2014; Houben et al., 2016; Menzies et al., 2018; Moualeu et al., 2014; Bhunu et al., 2011; Moualeu et al., 2012; Moualeu et al., 2018)
C	1	(Huo and Zou, 2016)
D	2	(Dowdy et al., 2014; Dowdy and Chaisson, 2009)
E	2	(Abu-Raddad et al., 2009; Arregui et al., 2018)
F	2	(Dowdy et al., 2013a; Mushayabasa and Bhunu, 2013)
G	3	(Vynnycky et al., 2015; Melnichenko and Romanyukha, 2009; Perelman et al., 2004)
H	1	(Wu et al., 2010)
I	1	(Legrand et al., 2008)
J	6	(Hickson et al., 2011; Hickson et al., 2012; Moualeu et al., 2015; Moualeu-Ngangue et al., 2015; Liu et al., 2008; Moualeu et al., 2016)
K	1	(Osgood et al., 2011)
Others	5	(Salomon et al., 2006; Thomas et al., 2010; Dowdy et al., 2008; Sun et al., 2013; Moualeu et al., 2012)

**Table 2**  
Proportions and relative infectiousness of active TB compartments among models that use two levels of infectiousness based on lungs involvement or smear status. Reference group.

Citation	Active TB compartment		Proportion progressing to high	Relative infectious of low	Conversion rate (low to high), per year
	High infectiousness	Low infectiousness			
(Ackley et al., 2015)	Infectious	Non-infectious	0.85	0	NA
(Aparicio and Castillo-Chavez, 2009)	Pulmonary	Extrapulmonary	0.7	0	NA
(Blower et al., 1995)	Infectious	Non-infectious	0.5-0.85	0	NA
(Dye and Williams, 2008)	Infectious	Non-infectious	0.6	0	NA
(Gomes et al., 2007)	Infectious	Non-infectious	0.66-0.87	0	NA
(Herrera et al., 2013)	Infectious	Non-infectious	0.7-0.85	0	NA
(Liao et al., 2012)	Infectious	Non-infectious	Normal distribution (0.78, 0.11)	0	NA
(Liao et al., 2013)	Infectious	Non-infectious	Normal distribution (0.78, 0.11)	0	NA
(Thomas et al., 2010)	Infectious	Non-infectious	HIV+ = 0.87 HIV- = 0.57	0	NA
(Hughes et al., 2006)	Infectious	Non-infectious	0.64	0	0.015
(Knight et al., 2014)	Infectious	Non-infectious	age < 15 = 0.1 age ≥ 15 = 0.5	0	0.015
(Dowdy et al., 2006) <sup>a</sup>	Smear-positive	Smear-negative	HIV- = 0.45 HIV+ = 0.35	0.22	NA
(Dowdy et al., 2013b) <sup>#</sup>	Smear-positive	Smear-negative	HIV- = 0.65 HIV+ = 0.5	0.15	NA
(Lin et al., 2012) <sup>#</sup>	Smear-positive	Smear-negative	HIV- adult = 0.7, HIV+ adult = 0.48 HIV- children = 0.17 HIV+ children = 0.1	0.22	NA
(Oxlade et al., 2011)	Smear-positive	Smear-negative	0.5	0.2	NA
(Pandey et al., 2017)	Smear-positive	Smear-negative	China, Korea, Philippines = 0.45 India = 0.63	0.2	NA
(Garcia et al., 1997)	Open cases	Non-open cases	0.5	0	to non-open <sup>b</sup>
(Houben et al., 2016)	Smear-positive	Smear-negative	0.85	0.22	0.015
(Menzies et al., 2012)	Smear-positive	Smear-negative	0.62	0.17-0.3	0.012-0.019

<sup>a</sup> Although these models include multiple stratifications which influenced progression proportions, infectiousness was only dependent on smear status.

<sup>b</sup> Infectious cases convert to non-infectious cases at rate of diagnosis and treatment.

compartment by smear-status considered both smear-positives and smear-negatives to be infectious, with smear-negatives having a lower level of infectiousness. The parameterisation for the relative infectiousness of smear-negative individuals compared to smear-positive was highly consistent across multiple modelling studies and almost universally fell in the range of 15–25%. Only one model that assessed the impact of changes in TB programs in low prevalence setting was an exception and assumed smear-negatives to be non-infectious (Garcia et al., 1997). Table 2 presents proportions and relative infectiousness of active TB compartments among models that incorporated two levels of infectiousness based on pulmonary involvement or smear status.

3.3.1.3. Type of infection. A model employing Structure A stratified

active TB based on history of previous infection, as symptomatic primary infection or symptomatic re-infection, with the assumption that re-infected individuals were twice as infectious as primarily infected counterparts (Sharomi et al., 2017). An IBM further subdivided smear-positive and smear-negative TB into three groups based on the timing of disease onset from infection; namely primary TB, endogenous reactivation, and exogenous re-infection. However, under this approach the level of infectiousness was dependent only on smear-status, with smear-positive individuals four-times as infectious as smear-negatives (Guzzetta et al., 2011).

3.3.1.4. Stage of disease. A theoretical model of heterogeneous progression sub-divided the active TB compartment according to

progression time from infection to active TB, with fast progressors more infectious than their slowly progressing counterparts (Okuonghae, 2013). A model evaluating case finding strategies employed modified form of *Structure F* to stratify active TB into subclinical, pre-diagnostic and clinical phases (Dowdy et al., 2013a), with infectiousness increasing with progression between each of these three sequential stages. Similarly, an IBM simulated infectiousness using a linear function of time, with infectiousness increasing from zero to maximum infectiousness over the first nine months of the disease episode, and remaining unchanged thereafter (Kasaie and Dowdy, 2013).

### 3.3.2. Co-morbidities

Some models considered HIV co-infection and comorbid diabetes mellitus to affect the level of infectiousness of individuals with active TB. One model employed *Structure B* to stratify active TB based on HIV status, assuming that individuals co-infected with HIV were less infectious than HIV-negative (Bacuer et al., 2008). Using the same structure, another model sub-divided the active TB compartment based on diabetes status, assuming that individuals co-morbid with diabetic were more infectious than their non-diabetic counterparts (Moualeu et al., 2012). Smoking status was used in one model that assessed the impact of smoking on TB transmission dynamics, with smokers assumed to be more infectious (Bhunu et al., 2011).

### 3.3.3. Age

Twenty-three models incorporated age-specific infectiousness (Tuite et al., 2017; Vynnycky et al., 2015; Suen et al., 2014; Hughes et al., 2006; Huynh et al., 2015; Knight et al., 2015; Mellor et al., 2011; Menzies et al., 2012; Dye and Williams, 2008; Garcia et al., 1997; Guzzetta et al., 2011; Abu-Raddad et al., 2009; Knight et al., 2014; Arregui et al., 2018; Houben et al., 2016; Liao et al., 2012; Liao et al., 2013; Menzies et al., 2018; Wu et al., 2010; Rodrigues et al., 2015; Osgood et al., 2011; Aparicio and Castillo-Chavez, 2009; Nyabadza and Kgosimore, 2012). The great majority of these models assumed children to be markedly less infectious than adults, although there were considerable differences between models in the age categories chosen and parameterisation.

Twenty-one of these models incorporated other factors in addition to age, while the remaining two considered age as the only factor for infectious heterogeneity. Of the models that considered age as the only factor determining heterogeneous infectiousness, one stratified the active TB compartment into adults and children, assuming that only adults were infectious (Nyabadza and Kgosimore, 2012). The other model of TB epidemics in a Chinese city employed *Structure H* taking active TB cases of age 24 years as the reference group and assuming that children were 81% less infectious relative to this group, while younger adults were seven-times more infectious (Wu et al. (2010)).

### 3.3.4. Unspecified factors

Of all included models, eight classified the active TB compartment as either infectious or non-infectious, but the rationale for this classification was often not explained (Hill et al., 2012; Hughes et al., 2006; Knight et al., 2014; Blower et al., 1995; Herrera et al., 2013; Liao et al., 2012; Liao et al., 2013; Apriliani et al., 2016). Among these models, two (Hughes et al., 2006; Knight et al., 2014) employed *Structure B*, while six (Hill et al., 2012; Blower et al., 1995; Herrera et al., 2013; Liao et al., 2012; Liao et al., 2013; Apriliani et al., 2016) did not allow for progression between the active TB compartments (*Structure A*).

### 3.3.5. Drug resistance

Variation in infectiousness associated with drug-resistant *Mtb* strains was used to stratify active TB in 32 models (Trauer et al., 2016a; Rayhan and Bakhtiar, 2017; Sachdeva et al., 2015; Salje et al., 2014; Suen et al., 2014; Jung et al., 2002; Kendall et al., 2015; Liao and Lin, 2012; Espindola et al., 2012; Fofana et al., 2017; Basu et al., 2007; Basu

et al., 2009; Bhunu and Garira, 2009; Trauer et al., 2016b; Liu et al., 2011; Nishiura et al., 2004; Sun et al., 2011; Blower and Gerberding, 1998; Cohen and Murray, 2004; Liu and Sun, 2010; McBryde et al., 2017; Trauer et al., 2014; Rodrigues et al., 2015; Agosto et al., 2015; Ahmadin and Fatmawati, 2014; Bishai et al., 2010; Raimundo et al., 2014; Shrestha et al., 2014; Kendall et al., 2017; Li et al., 2011; De Espindola et al., 2011). In 31 of these models, cases with multidrug-resistant TB (MDR-TB) were assumed less infectious than cases with drug-susceptible TB (DS-TB), due to a fitness cost associated with the resistance-conferring mutation. Most of these models considered infectiousness of individuals with MDR-TB relative to individuals with DS-TB to be around 0.8.

Eighteen of the 32 TB models used two active TB compartments to represent DS-TB and MDR-TB without any additional stratification (Rayhan and Bakhtiar, 2017; Suen et al., 2014; Jung et al., 2002; Liao and Lin, 2012; Espindola et al., 2012; Fofana et al., 2017; Bhunu and Garira, 2009; Liu et al., 2011; Nishiura et al., 2004; Blower and Gerberding, 1998; Liu and Sun, 2010; Rodrigues et al., 2015; Agosto et al., 2015; Ahmadin and Fatmawati, 2014; Bishai et al., 2010; Raimundo et al., 2014; Shrestha et al., 2014; Li et al., 2011; De Espindola et al., 2011). Out of the three models that stratified active TB into three compartments based on drug-susceptibility, with categories being DS-TB, MDR-TB and extensively drug-resistant TB (XDR-TB) and the assumption of a progressive gradient towards more resistant strains being less infectious (Agosto et al., 2015). The second such model incorporated detection status to stratify active TB compartment into three as undetected infectious TB, detected DS-TB and detected MDR-TB such that the undetected cases were the most infectious followed by detected MDR-TB. (Sun et al., 2011). The third model simulated active TB as either: on ineffective treatment (a treatment course without curative potential), on inadequate treatment (a treatment course with curative potential but taken for an insufficient duration) and not on treatment. This model assumed that individuals on ineffective or insufficient treatment were less infectious than individuals not on treatment (Fofana et al., 2017).

Six models integrated drug susceptibility with other factors, such as stage of disease, detection and treatment status, to stratify active TB into four compartments with varying levels of infectiousness (Trauer et al., 2016a; Basu et al., 2007; Basu et al., 2009; McBryde et al., 2017; Trauer et al., 2014; Kendall et al., 2017). For instance, a model of TB dynamics in South Africa stratified TB as either infectious or non-infectious and further sub-divided by drug susceptibility, assuming individuals with MDR-TB to be less infectious due to a resistance-associated fitness cost (Basu et al., 2007). A model evaluating the impact of diagnosis and treatment further stratified DS-TB and MDR-TB into early preclinical TB and symptomatic TB, to capture the variation in infectiousness associated with stage of disease in addition to a resistance-associated fitness cost (Kendall et al., 2017).

Further stratification of active TB into six compartments was undertaken in two models (Kendall et al., 2015; Cohen and Murray, 2004). A theoretical model of MDR-TB fitness characterised active TB compartment as detected or undetected, and further stratified as DS-TB, unfit MDR-TB or fit MDR-TB, assuming unfit MDR-TB to be the least infectious followed by fit MDR-TB and DS-TB (Cohen and Murray, 2004). The second model sub-divided both DS-TB and MDR-TB into early stage, active TB and TB on treatment (Kendall et al., 2015). This model assumed infectiousness variation by stage with early-stage TB the least infectious followed by TB on treatment. Further stratification of active TB into nine (Trauer et al., 2016b), 24 (Salje et al., 2014) and 28 (Sachdeva et al., 2015) compartments was used in models that integrated detection, treatment, HIV and smear-statuses with drug susceptibility status.

### 3.3.6. Health system-related factors

#### 3.3.6.1. Detection and treatment.

Nineteen TB models stratified the infectious compartment by diagnosis status (Okuonghae and Aihie,

2008; Okuonghae and Ikhimwin, 2016; Okuonghae and Korobeinikov, 2007; Okuonghae and Omosigho, 2011; Salomon et al., 2006; Sharomi et al., 2008; Hickson et al., 2011; Moualeu et al., 2015; Bowong and Alaoui, 2013; Legrand et al., 2008; Melnichenko and Romanyukha, 2009; Moualeu et al., 2014; Moualeu-Ngangue et al., 2015; Mushayabasa and Bhunu, 2013; Perelman et al., 2004; Liu et al., 2008; Moualeu et al., 2018; Okuonghae and Aihie, 2010; Moualeu et al., 2016). These models employed different assumptions regarding the greater infectiousness of undetected cases compared to those receiving treatment. Ten of these models sub-divided the active TB compartment into two compartments, detected and undetected, employing *Structure A* or *Structure B* (Okuonghae and Aihie, 2008; Okuonghae and Ikhimwin, 2016; Okuonghae and Korobeinikov, 2007; Okuonghae and Omosigho, 2011; Sharomi et al., 2008; Bowong and Alaoui, 2013; Moualeu et al., 2014; Mushayabasa and Bhunu, 2013; Moualeu et al., 2018; Okuonghae and Aihie, 2010). Further stratification into three compartments as provided by *Structure J* was employed in four models, three of which stratified active TB as diagnosed, lost to follow-up and undiagnosed infectious, with the assumption that undiagnosed individuals were most infectious followed by lost to follow-up (Moualeu et al., 2015; Moualeu-Ngangue et al., 2015; Moualeu et al., 2016). A theoretical model of global TB dynamics with the same compartmental structure stratified active TB as infectious treated, infectious untreated and non-infectious, with the assumption that untreated cases were seven times more infectious than patients under treatment (Liu et al., 2008).

A further four models implemented *Structure G* to divide active TB into four compartments based on detection status and other factors (Hickson et al., 2011; Legrand et al., 2008; Melnichenko and Romanyukha, 2009; Perelman et al., 2004). A model of HIV/TB coinfection included nine compartments based on detectability (a function of geographical location, local health services, and case-finding effort, as well as health seeking behaviour and intensity of symptoms), smear and treatment status, with the assumption that smear-positives were the most infectious and patients treated in high-quality treatment programs are non-infectious (Salomon et al., 2006).

**3.3.6.2. Place of treatment.** A model evaluating alternative TB treatment strategies in China used the place of treatment as a stratification factor and employed *Structure C* with the assumption that patients treated at home were more infectious than patients treated in hospitals (Huo and Zou, 2016). Similarly, a model employing *Structure A* assumed only hospitalised patients received treatment, thereby implying a higher level of infectiousness for non-hospitalised individuals with active TB (Zhang et al., 2015).

#### 4. Discussion

Although the infectiousness of individuals with TB is known to be profoundly heterogeneous, with the epidemic significantly contributed to by a small group of highly infectious, the great majority of published TB models did not incorporate this phenomenon in any way. The infectiousness of individuals with active TB depends on their ability to release aerosolised droplets with sufficient bacilli concentrations (Turner et al., 2017). This process is particularly heterogeneous in the case of TB, due to associated risk factors such as the anatomical site of TB disease, demographic characteristics, behavioural characteristics and other co-morbidities (Melsew et al., 2018a). Moreover, instances of very extensive transmission of *Mtb* have been reported from case studies (Curtis et al., 1999; Valway et al., 1998), genotypic data analyses (Ypma et al., 2013) and contact investigation offspring data analyses (Melsew et al., 2019).

Although heterogeneous infectiousness is the reality for *Mtb* transmission, this does not necessarily imply that one must always stratify the active TB compartment irrespective of the modelling objectives. The principle of parsimony dictates the need to justify any additional

complexity added to models through stratification. In some cases, the need for stratification is obvious, for example, if the objective of the model is to predict the relative magnitude of specific types of TB, such as pulmonary, extrapulmonary, drug-susceptible or multidrug-resistant. Similarly, if the objective is to evaluate the efficacy of public health interventions such as targeting children, HIV-positive persons, or patients with drug-resistant *Mtb* strains, modellers should consider the impact of heterogeneity. Similarly, models evaluating diagnostic interventions that have differential sensitivity based on factors associated with infectiousness, such as smear-status, should usually consider stratification. It is known that even traditional smear-based case finding interventions incorporate some targeting towards highly infectious patients because of the greater sensitivity of smear-based diagnostics for such patients (Cudahy and Sheno, 2016). Active case finding interventions that employ very sensitive tools, and so may also detect less infectious TB patients, should consider the impact of heterogeneous infectiousness before claiming transmission reduction on the basis of the number of cases detected.

Most of the assumptions made by models that have incorporated heterogeneous infectiousness were broadly consistent with available epidemiological evidence. In our review, we found that TB models frequently stratified active TB based on sputum smear-status, which is consistent with our recent meta-analysis that found that contacts of smear-positive TB patients were more likely to be infected compared contacts of smear-negative patients (Melsew et al., 2018a). Positive sputum smear results are indicative of higher bacillary concentrations and disease that is in direct communication with the individuals' airway, such that these individuals are often highly infectious (Ait-Khaled et al., 2003). Several models also recognised that undetected active TB cases are typically more infectious than those receiving treatment. This is consistent with epidemiological studies that have showed that treatment rapidly reduces patients' infectiousness soon after commencement (Lohmann et al., 2012; Otero et al., 2016; Tornee et al., 2004; Xu et al., 2008). Using HIV co-infection as a factor to stratify the infectiousness of active TB cases is also broadly supported by meta-analysis results that found contacts exposed to HIV-positive TB patients had a 55% reduced risk of infection compared to those exposed to HIV-negative patients, although there were considerable differences between the individual studies (Cayla et al., 1996; Melsew et al., 2018b). There is also some evidence to support the higher infectiousness of smokers compared to non-smokers (Lohmann et al., 2012; Huang et al., 2014; Singh et al., 2005), although there is no strong epidemiological evidence that TB patients with co-morbid diabetes mellitus have increased infectiousness (Grandjean et al., 2015). Although evidence shows that drug-resistant strains are typically less transmissible than drug-susceptible strains, the overall fitness of the strain depends on both the transmission rate and duration of the infectious period. The poorer rates of MDR-TB diagnosis and so longer periods of infectiousness may offset the fitness cost, such that there is no clear consensus on the impact of drug resistance on TB transmission (Luciani et al., 2009; Cohen et al., 2003).

Models vary in regard to their assumptions concerning conversion from non-infectious states or states with limited infectiousness to more infectious forms of disease. Most heterogeneous models did not simulate this conversion, but rather assumed that individuals immediately became smear-positive or negative at the point of disease activation. Of those that did allow for this transition phenomenon, most models assumed smear-negatives could progress to smear-positivity with time. Active TB disease progression can be viewed as a dynamic continuum, with individuals progressing from a less infectious stage of disease to a more highly infectious stage as tissue damage increases (Pai et al., 2016). However, it is impossible to quantify this phenomenon as it is unethical to observe the natural history of untreated TB (Tiemersma et al., 2011). Nevertheless, models consistently assumed such small parameter values for the rates governing this transition as to be negligible, such that if this process is epidemiologically important then past

models are unlikely to be fully capturing it.

The impact of heterogeneous infectiousness in transmission dynamic models can be explored through the basic reproduction number,  $R_0$ , with marked reductions in  $R_0$  potentially achievable by targeting control measures towards a small proportion of the population that are highly infectious (Trauer et al., 2018; Matthews et al., 2006). Increases in heterogeneous infectiousness may not necessarily lead to epidemics of a greater size for a given  $R_0$  although local outbreaks may act as driving sources of sustained disease burden (Andersson and Britton, 1998; Miller, 2007a; Miller, 2007b). As global TB control targets elimination, the phenomenon of heterogeneous infectiousness is likely to become more apparent, increasingly requiring TB models to incorporate heterogeneous infectiousness assumptions.

## 5. Conclusions

Given the evidence of extensive heterogeneity in the infectiousness of individuals with TB, there exists an argument for the stratification of active TB states by infectiousness in models. The main consideration for assuming heterogeneous infectiousness and thus stratifying active TB based on infectiousness is the objective of the model; in general, when the objective of the model is to evaluate effectiveness of targeted public health interventions or evaluation of diagnostic tools, modellers should consider incorporating heterogeneous infectiousness. Consensus has not been reached as to the optimal approach to stratifying TB models to capture the considerable heterogeneity in infectiousness between individuals, and it may be that there is no a single approach that will suit all epidemiological scenarios and research questions.

## Availability of data and materials

A list of included studies has been made available. The study protocol can be accessed on PROSPERO, registration number: CRD42019111936.

## Authors' contributions

YAM and JMT conceived the study, which was refined by ESM, ACC and RR. YAM developed the data extraction checklist, which was and approved by JMT, RR and AIA. YAM and AIA extracted the data. YAM drafted the manuscript, and all authors provided input into revisions and approved the final draft for submission.

## Declaration of Competing Interests

The authors declare that they have no competing interests.

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## Appendix A. Supplementary data

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