2019

Transmissibility and Potential for Disease Progression of Drug Resistant Mycobacterium Tuberculosis: Prospective Cohort Study

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Transmissibility and potential for disease progression of drug resistant *Mycobacterium tuberculosis*: prospective cohort study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;367:l5894 http://dx.doi.org/10.1136/bmj.l5894

Accepted: 16 September 2019

ABSTRACT

OBJECTIVE

To measure the association between phenotypic drug resistance and the risk of tuberculosis infection and disease among household contacts of patients with pulmonary tuberculosis.

SETTING

106 district health centers in Lima, Peru between September 2009 and September 2012.

DESIGN

Prospective cohort study.

PARTICIPANTS

10 160 household contacts of 3339 index patients with tuberculosis were classified on the basis of the drug resistance profile of the patient: 6189 were exposed to drug susceptible strains of *Mycobacterium tuberculosis*, 1659 to strains resistant to isoniazid or rifampicin, and 1541 to strains that were multidrug resistant (resistant to isoniazid and rifampicin).

MAIN OUTCOME MEASURES

Tuberculosis infection (positive tuberculin skin test) and the incidence of active disease (diagnosed by positive sputum smear or chest radiograph) after 12 months of follow-up.

RESULTS

Household contacts exposed to patients with multidrug resistant tuberculosis had an 8% (95% confidence interval 4% to 13%) higher risk of infection by the end of follow-up compared with household contacts of patients with drug sensitive tuberculosis. The relative hazard of incident tuberculosis disease did not differ among household contacts exposed to multidrug resistant tuberculosis and those exposed to drug sensitive tuberculosis (adjusted hazard ratio 1.28, 95% confidence interval 0.9 to 1.83).

CONCLUSION

Household contacts of patients with multidrug resistant tuberculosis were at higher risk of tuberculosis infection than contacts exposed to drug sensitive tuberculosis. The risk of developing tuberculosis disease did not differ among contacts in both groups. The evidence invites guideline producers to take action by targeting drug resistant and drug sensitive tuberculosis, such as early detection and effective treatment of infection and disease.

TRIAL REGISTRATION

ClinicalTrials.gov NCT00676754.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous molecular epidemiological studies have shown that drug resistant tuberculosis strains can be transmitted and that clusters of resistant strains can persist over long periods

Some studies have found that the risk of tuberculosis infection does not differ in household contacts exposed to drug resistant tuberculosis and drug sensitive disease

A recent study reported that household contacts exposed to multidrug resistant tuberculosis were half as likely to develop tuberculosis disease as those exposed to drug sensitive disease

WHAT THIS STUDY ADDS

Household contacts of patients with multidrug resistant tuberculosis were at higher risk of tuberculosis infection than contacts exposed to drug sensitive tuberculosis; the risk of developing tuberculosis disease did not differ among contacts in both groups

The evidence invites guideline producers to take action by targeting drug resistant and drug sensitive tuberculosis, such as early detection and effective treatment of infection and disease

Introduction

Antimicrobial resistance is a global crisis with vast clinical implications. A 2019 United Nations report to the secretary general predicted that by 2050 drug resistant infections could kill 10 million people annually.[1 2] In the next decades, resistance will become an increasing concern for the practitioner. Decisions on what strategies to prioritize in renewed efforts to contain resistance will depend on whether the drug resistant mutants are thought to be compromised or less fit in their capacity to produce new infections.

Resistance to tuberculosis drugs is a case in point.[3] For decades, the primary strategy deployed against multidrug resistant tuberculosis (tuberculosis resistant to isoniazid and rifampicin) was to try to prevent the emergence of new resistance. The focus was on the empirical treatment of tuberculosis presumed to be drug sensitive to reduce the acquisition of drug resistance in patients during suboptimal treatment.[3-5] This approach does nothing to interrupt the transmission of existing drug resistant tuberculosis strains[6]; it is largely based on the received wisdom that the price of resistance is reduced bacterial fitness, which manifests itself in a lower risk of transmission of resistant organisms.

Today the prevalence of multidrug resistance among people not previously treated for tuberculosis is as high as 38% in some countries. It is becoming increasingly clear that most people with multidrug resistant tuberculosis were infected with resistant strains, rather than acquiring resistance during suboptimal treatment.[3] Measures such as limiting antibiotic use could prevent further emergence of

resistance, however they might not lead to a reversion to a more pan susceptible pool of strains. The course of the tuberculosis epidemic will depend on how quickly patients with drug resistant tuberculosis are identified and rendered non-infectious, and on the relative transmissibility of drug resistant tuberculosis strains.[7-9] The widespread dissemination of new tools that enable rapid diagnosis of drug resistant tuberculosis will probably reduce the duration of infectiousness of patients with drug resistant disease in the future.[10] However, if drug resistant mutations in *Mycobacterium tuberculosis* do not alter its ability to spread, the incidence of drug resistant tuberculosis would be expected to decline more slowly than if resistance incurred a fitness cost.[9 11 12] The projections of mathematical models that forecast future tuberculosis incidence strongly depend on these assumptions.[9]

There is a lack of human studies that have examined whether a fitness cost is incurred when *M tuberculosis*, or any other infectious pathogen, acquires drug resistance. We conducted a study to estimate the fitness cost of drug resistance by comparing the rates of tuberculosis infection and disease among participants exposed to drug resistant tuberculosis and drug sensitive tuberculosis.

Methods

We recruited patients from 106 district health centers in Lima (fig S1). These centers provide routine healthcare and are responsible for diagnosing and treating patients with tuberculosis. Health center clinicians use Peru national tuberculosis programme guidelines to diagnose patients with pulmonary tuberculosis. The guidelines state that at least one of two sputum smears should be positive for acid fast bacilli by Ziehl-Neelsen staining, or a chest radiograph should be consistent with tuberculosis in the absence of positive sputum smear results.

Enrollment of index patients

We invited patients with pulmonary tuberculosis to participate in the study if they were aged 16 years or older and could provide informed consent. After recruiting index patients, we visited their households and enrolled consenting household contacts into the prospective cohort study.

Baseline assessment of index patients

We recorded baseline characteristics of index patients, including age, sex, occupation, symptoms of tuberculosis, duration of symptoms, previous tuberculosis disease, alcohol consumption, intravenous drug use, smoking history, and comorbidities including HIV and diabetes mellitus. Patients who did not know their HIV status had blood tests for HIV and CD4 count. We also recorded signs associated with tuberculosis disease, and height and weight.

Ascertainment of tuberculosis disease

Bacteriological cultures

Health center staff performed routine diagnostic microbiology and recorded the results of sputum smear microscopy and culture, and drug susceptibility testing. Additionally, staff took sputum samples and sent them to the study research laboratory for repeat smears and culture, and drug sensitivity testing. Chest radiographs were performed at the health centers or at local imaging facilities. Two radiologists read each radiograph and completed a standardized form.

Ascertainment of HIV infection

In accordance with Peru's national policy, index patients received counseling from trained study staff or Ministry of Health personnel before the collection of blood samples for HIV testing. Patients were also offered counseling after testing. Trained staff gave patients their test results.

Index patient follow-up

Index patients received directly observed treatment as specified in the Peru national tuberculosis programme guidelines. Patients with drug sensitive tuberculosis had a standard six month course, including a two month "intensive phase" of isoniazid, rifampicin, pyrazinamide, and ethambutol, and a four month "consolidation phase" of isoniazid and rifampicin alone. Patients with multidrug resistant tuberculosis also received treatment according to the national guidelines. Because results of routine drug resistance testing were often not available for two to three months after the initial tuberculosis diagnosis, patients who were not previously suspected of having multidrug resistant tuberculosis were started on a first line drug regimen until the diagnosis was confirmed. Thus, many patients with drug resistant tuberculosis did not start "effective therapy" until several months into their treatment course.

Study staff collected follow-up data for all patients at two, six, 12, and 24 months; for patients with drug resistant tuberculosis, follow-up data were gathered again at 36 or 48 months. At two and six months, patients underwent repeat sputum smear microscopy and culture. Culture positive sputum samples underwent repeat drug susceptibility testing and mycobacterial interspersed repetitive unit (MIRU) genotyping. We measured the time from onset of symptoms to treatment as the number of days the patient reported coughing before diagnosis. Time to effective therapy was defined as the time from diagnosis until the patient received an "effective drug regimen."

Enrollment of household contacts

We recorded information about household contacts at enrollment, including age, sex, relationship to index case, housing information such as number of rooms, building material, and type of flooring, income, education, history of incarceration, occupation, alcohol consumption, illicit drug use, and smoking history. We also recorded general health information, including previous tuberculosis, BCG vaccination, comorbidities including HIV and diabetes mellitus, and drugs taken. Household contacts were asked

doi: 10.1136/bmj.l5894 | *BMJ* 2019;367:l5894 | the bmj

about symptoms of tuberculosis disease, including cough, night sweats, weight loss, and fever. We referred contacts who reported these symptoms to their local health center for chest radiography and clinical evaluation for tuberculosis disease. We also asked contacts if they had been offered isoniazid preventive treatment and whether they had started treatment.

All household contacts received a tuberculin skin test, with the exception of those with active tuberculosis disease or a history of tuberculosis disease, and those with positive tuberculin skin tests in the past. The test was performed by injecting the tuberculin into the skin on the forearm. The results were measured using the caliper method within 48-72 hours after intradermal injection. The diameter of induration was measured transversely to the long axis of the forearm and recorded in millimeters. We also offered household members counseling and testing for HIV.

Household contact follow-up

We asked household contacts to notify study staff if they were diagnosed as having active tuberculosis disease before the next scheduled follow-up visit. We revisited contacts at two, six, and 12 months. We also obtained information about any tuberculosis diagnoses and symptoms of tuberculosis disease that had occurred between visits. Contacts with symptoms were referred to health centers for further clinical evaluation. Contacts who had a negative tuberculin skin test at the initial study visit and who had not developed tuberculosis disease at the time of the follow-up visit underwent repeat tuberculin skin tests at six and 12 months.

Analyses

Categorization of drug resistance profiles of index cases

We classified drug resistance profiles of index cases into six categories: (a) sensitive to all drugs (pan susceptible); (b) resistant only to isoniazid (mono isoniazid); (c) resistant only to streptomycin (mono streptomycin); (d) resistant only to isoniazid and streptomycin (isoniazid+streptomycin); (e) resistant to isoniazid and rifampin (multidrug resistant); and (f) other resistant patterns that were not included in a-e (other).

Outcomes

Our analyses included the following infection outcomes: infection among contacts at baseline; infection during 12 months of follow-up among contacts who were uninfected at baseline; and infection by 12 months of follow-up. We considered contacts to be infected at baseline if they had a history of tuberculosis disease, if they had a previous positive tuberculin skin test, or if they had a positive tuberculin skin test at baseline. We considered contacts to have become infected with tuberculosis during follow-up if they had a negative tuberculin skin test at baseline and a positive tuberculin skin test during follow-up.

We identified incident tuberculosis disease during household visits and from medical records at the health centers. We defined household contacts as having coprevalent tuberculosis if they had a diagnosis within two weeks of the diagnosis of the index case. Contacts were defined as "secondary" cases if they received a diagnosis between day 15 and day 455 of follow-up (allowing a three month buffer for the 12 month follow-up time). Diagnosis of secondary tuberculosis among contacts aged 18 years and over followed the same criteria as outlined above for index cases. Diagnosis of tuberculosis disease in contacts less than 18 years of age was based on consensus guidelines for classifying tuberculosis disease in children.[13]

Data analysis

Infection at baseline and by end of follow-up

We estimated prevalence ratios for infection at baseline and by the end of follow-up by using a modified Poisson generalized estimating equation to account for correlation among participants within a household; an exchangeable working correlation structure was specified for observations within the same household. For inference, we obtained empirical standard error estimates that were used to construct Wald type 95% confidence intervals. Firstly, we performed age adjusted univariable analyses for potential predictors of tuberculosis infection based on a priori knowledge. Subsequently, all covariates were entered into a backwards stepwise algorithm, with the exception of sputum smear status, length of symptomatic period, presence of cavitary disease, and time to effective treatment of index case. We hypothesized that these risk factors could mediate the effects of the index patient's drug susceptibility status on the risk of tuberculosis infection among household contacts. We retained variables with a P value less than 0.1 and variables deemed likely to modify tuberculosis infection in the multivariable model. The direct effect of potential mediators was evaluated by adding them to the regression model. We assumed that after adjusting for the observed covariates, no unobserved confounding prevailed for the joint effects of the degree of the index patient's immunosuppression and the four mediators on the contacts' risk of tuberculosis infection. We conducted a sensitivity analysis by restricting the analysis to children who were assumed to be less likely to be infected outside the household than adults.

Time to infection

We measured time from enrollment to infection among household contacts who were uninfected at baseline; the date of infection was defined as the midpoint between the date of enrollment and the date of a positive tuberculin skin test result. We censored contacts who remained tuberculin skin test negative at the date of the last result. We used a Cox frailty proportional hazards model to evaluate risk factors for incident tuberculosis infection; clustering within households was taken into account. We verified the proportional

hazards assumptions for each covariate by introducing an interaction term between the covariate and time, and then we stratified the results by variables for which the proportional hazards assumption did not hold.

Incidence of tuberculosis disease

We measured the time from enrollment to disease occurrence among household contacts without coprevalent tuberculosis. We used a Kaplan-Meier curve to examine the disease-free survival time and Cox frailty proportional hazards models to evaluate risk factors for incident tuberculosis disease; clustering within households was taken into account. The multivariable model included variables identified a priori as potential confounders (HIV status of index case, smoking and drinking status of index case, socioeconomic status of household, and isoniazid preventive treatment); additionally we included any other variables associated with the outcome which had a P value less than 0.1 using a backwards stepwise algorithm. We performed a sensitivity analysis that considered only contacts with secondary disease who shared a genotype with the index case; contacts with secondary disease who did not share an index case were excluded. We conducted this sensitivity analysis in two different ways. Firstly, we considered contacts with secondary disease whose 24 locus MIRU patterns were an exact match with the index case; secondly, we considered those with secondary disease whose MIRU patterns matched on 22 of 24 loci.

Patient and public involvement

Our community advisory board reviewed the protocol for this study and provided ongoing input into its implementation. This group includes patients with tuberculosis, patient advocates, and care providers, but did not include participants in the study. Patients were not involved in setting the research question, choosing the outcome measures, or in the interpretation or writing up of results. Participants and their care providers were notified of study results that pertained to the care they received for tuberculosis (tuberculin skin test, drug susceptibility testing). We are currently sharing the general results of the research with participants and the general community through written and video public service announcements disseminated at the health clinics involved in the study.

Results

Between September 2009 and September 2012, we enrolled 4500 index patients, of whom 4044 had microbiologically confirmed tuberculosis disease (table S1). Of the 3339 for whom drug susceptibility tests were available, 1274 (38%) had isolates resistant to at least one drug: 538 (16%) to only one drug, 478 (14%) to isoniazid and rifampicin (multidrug resistant tuberculosis), and 258 (7%) to more than one drug but not multidrug resistant.

We enrolled 10 160 household contacts of 2563 index patients who had microbiologically confirmed tuberculosis disease, drug susceptibility tests available, and at least one household contact (table 1). Index patients for whom we had a drug resistance profile differed from those without a profile on a number of clinical variables associated with the severity of disease (table S2).

Tuberculosis infection

At enrollment, 4488 (44%) household contacts were infected with *M tuberculosis*. Contacts of index patients with isoniazid monoresistant tuberculosis had a 16% (95% confidence interval 8% to 24%) higher risk of infection by 12 months compared with contacts exposed to drug sensitive tuberculosis; contacts exposed to multidrug resistant tuberculosis had an 8% (4% to 13%) higher risk (table 2).

In sensitivity analyses, the positive association between exposure to isoniazid monoresistant tuberculosis and multidrug resistant tuberculosis and the risk of infection remained similar when we assessed the prevalence ratio of infection at baseline (table S3) and the hazard of tuberculin skin test conversion during follow-up (table S4); when we restricted all of the above analyses to children; and when we estimated the direct effect of the drug resistance pattern on infection by controlling for smear status, cavitary disease, treatment delay, and time to effective treatment (tables S5-S7). The results also remained consistent when we used 5 mm and 15 mm as cut-off points for tuberculin skin test positivity (tables S8 and S9), and when we restricted the analyses to household contacts with fewer than two BCG scars (see supplement and table S10).

Tuberculosis disease

Relative hazard of incident tuberculosis disease did not differ among household contacts exposed to drug resistant tuberculosis compared with drug sensitive tuberculosis (isoniazid monoresistant tuberculosis: adjusted hazard ratio 0.17, 95% confidence interval 0.02 to 1.26; multidrug resistant tuberculosis: 1.28, 0.9 to 1.83; table 3 and fig S1). For multidrug resistant tuberculosis, this result persisted when we only considered participants with secondary disease if the molecular fingerprint matched that of the corresponding index patient and when matches were based on either more or less stringent criteria (table S11). We obtained similar results in sensitivity analyses in which we considered only household contacts who did not receive isoniazid preventive treatment (table S12); only household contacts who were infected at baseline (table S13); only contacts with secondary disease that occurred 30 days or more after the diagnosis of the index patient (table S14); and only contacts with secondary disease who had MIRU and drug susceptibility testing profiles that matched the index patient (table S15). We also conducted a sensitivity analysis using a parsimony algorithm for the multivariable model and again found no difference in our results (table S16).

Table 1 | Characteristics of household contacts of index patients with pulmonary tuberculosis. Values are No (%)

Variable	Drug resistance profile of index patient*				P value
	Pan susceptible	Monoresistant	Polyresistant	Multidrug resistant	
Age (years; n=10 160):					
0-15	2193 (62)	592 (17)	242 (7)	526 (15)	<0.001
16-30	1667 (60)	425 (15)	225 (8)	443 (16)	
31-45	1063 (59)	316 (17)	130 (7)	302 (17)	
≥45	1266 (62)	326 (16)	174 (9)	270 (13)	
Sex (n=10 160):					
Female	3375 (61)	948 (17)	427 (8)	823 (15)	0.16
Male	2814 (61)	711 (16)	344 (8)	718 (16)	
HIV status (n=10 040):					
Negative	6098 (61)	1639 (16)	753 (8)	1515 (15)	0.45
Positive	21 (60)	4 (11)	5 (14)	5 (14)	
Diabetes (n=10 085):					
No	6034 (61)	1620 (16)	748 (8)	1500 (15)	0.95
Yes	110 (60)	30 (16)	16 (9)	27(15)	
BCG scars (n=10 159):					
0	866 (61)	211 (15)	121 (9)	217 (15)	0.17
≥1	5323 (61)	1447 (17)	650 (7)	1324 (15)	
Smoking status (n=10 057):					
Non-smoker	5745 (61)	1528 (16)	724 (8)	1443 (15)	0.61
Smoker	379 (61)	113 (19)	38 (7)	87 (14)	
Nutrition (n=10 067):					
Normal weight	3561 (61)	935 (16)	422 (7)	881 (15)	0.61
Underweight	103 (61)	22 (13)	16 (10)	27 (16)	
Overweight	2470 (60)	683 (17)	327 (8)	620 (15)	
Socioeconomic status (n=9943):					
Low	2125 (60)	602 (17)	261 (7)	528 (15)	0.03
Middle	2670 (61)	682 (16)	325 (7)	728 (17)	
High	1261 (62)	347 (17)	138 (7)	276 (14)	
Preventive treatment (n=10 154):					
No	4688 (60)	1238 (16)	596 (8)	1258 (16)	<0.001
Yes	1498 (63)	419(18)	175 (7)	282 (12)	

*Pan susceptible: sensitive to all drugs; monoresistant: resistant to only one drug; polyresistant: resistant to more than one drug, but not multidrug resistant; multidrug resistant: resistant to isoniazid and rifampicin.

Discussion

Principal findings

This study found that household contacts exposed to patients with multidrug resistant tuberculosis are at higher risk of becoming infected with tuberculosis compared with those exposed to drug sensitive tuberculosis. However, these contacts are at similar risk of developing tuberculosis after the index patient has been diagnosed as having the disease. These data suggest that the transmissibility and potential for disease progression do not differ between multidrug resistant *M tuberculosis* and drug sensitive disease. This hypothesis is also consistent with our observation that the proportion of patients with multidrug resistant tuberculosis was highest among the younger groups; that is, those most likely to have been recently infected.

Comparison with other studies

This large human study assessed whether an infectious pathogen incurs a fitness cost when acquiring resistance, and it also examined the relative transmissibility and risk of disease progression of drug resistant tuberculosis. The study adds to a diverse body of work on the fitness cost of *M tuberculosis* drug resistance. Laboratory studies that compared bacterial growth rates of drug sensitive and drug resistant strains in media or bacillary loads and survival in infected animal models[14-16] indicate that, while some resistance causing mutations reduce growth rates or virulence,[17-19] others have little or variable impact.[20-22] Even when mutations do confer fitness costs, subsequent "compensatory" mutations can reverse these growth defects and preserve resistance phenotypes.[23 24] As would be expected, such low cost or compensatory mutations are observed more frequently than other resistance mutations.[25 26]

Studies of the relative fitness of drug resistant tuberculosis in human populations have approached the question in two ways. Firstly, by assessing the effect of drug resistance pattern on the relative frequency of clustered cases; secondly, by directly measuring the risk of infection and disease among contacts of patients with drug sensitive tuberculosis or drug resistant tuberculosis.[7] Multiple molecular epidemiological studies show that drug resistant tuberculosis strains can be transmitted and that clusters of resistant strains can persist over long periods.[27-30] However, previous molecular epidemiological studies have reached different conclusions; some have found that drug resistant strains are more likely to be clustered than drug sensitive strains, while others have shown the reverse.[31-33] Some studies have suggested that the association with clustering depends on the specific drug resistance phenotype or mutation.[34 35] Many of these previous studies have been small and subject to biases owing to convenience sampling of isolates.[36 37]

Table 2 | Risk of *Mycobacterium tuberculosis* infection after 12 months among household contacts of index patients with tuberculosis by drug resistance profile. Values are prevalence ratio (95% confidence interval) unless stated otherwise

Drug resistance profile	Prevalence of infection* (No (%))	Univariable analysis (n=8630)	Multivariate analysis		
			Model 1 (n=7463)†	Model 2 (n=7463)‡	Model 3 (n=7190)§
Pan susceptible	3597 (69.3)	Reference	Reference	Reference	Reference
Mono isoniazid	185 (80.8)	1.17 (1.09 to 1.25)¶	1.16 (1.08 to 1.24)¶	1.14 (1.07 to 1.23)¶	1.15 (1.06 to 1.24)¶
Mono streptomycin	716 (72.2)	1.04 (0.99 to 1.09)	1.03 (0.98 to 1.08)	1.03 (0.98 to 1.08)	1.02 (0.98 to 1.08)
Isoniazid+streptomycin	256 (74.4)	1.08 (1.01 to 1.16)¶	1.06 (0.99 to 1.14)	1.06 (0.99 to 1.14)	1.04 (0.95 to 1.12)
Multidrug resistant	1041 (75.7)	1.08 (1.04 to 1.13)¶	1.08 (1.04 to 1.13)¶	1.08 (1.04 to 1.13)¶	1.11 (1.04 to 1.17)¶
Other	353 (70.3)	1.02 (0.95 to 1.09)	1.04 (0.97 to 1.11)	1.04 (0.97 to 1.11)	1.05 (0.97 to 1.13)

*Prevalence of the univariable model.
†Model 1 adjusted for index patient characteristics (age category, HIV status, smoking status, alcohol consumption) and household contact characteristics (age category, self reported diabetes mellitus, number of BCG scars, alcohol consumption, nutritional status, socioeconomic status, use of isoniazid preventive treatment, and previous tuberculosis disease).
‡Model 2 adjusted for the factors included in model 1 plus characteristics of the index case (presence of cavities on chest radiograph, sputum smear grade, and diagnostic delay).
§Model 3 adjusted for the factors included in model 2 plus the time until initiation of effective treatment.
¶Effects that are statistically significant.

Our study, which aimed to prospectively capture all notified cases in a geographically contiguous area, closely followed a cohort of household contacts for infection and incident tuberculosis disease. Additionally, our study systematically examined drug resistance as a risk factor for transmission and disease.

The few studies to date that have directly measured the capacity of drug resistant and drug sensitive *M tuberculosis* strains to cause infection or disease have also yielded conflicting results. Snider and colleagues reported no difference in the risk of tuberculosis infection in child household contacts exposed to either isoniazid or streptomycin resistant *M tuberculosis* compared with drug sensitive *M tuberculosis*.[38] Although the authors also reported no differences in disease incidence in these groups, the study was not powered to detect this outcome and confidence intervals were wide. Similarly, in a small study conducted in Brazil, Teixeira and colleagues found that household contacts of patients with multidrug resistant tuberculosis were slightly more likely to be infected at baseline than contacts of patients with drug sensitive tuberculosis, and equally likely to develop disease.[39] In 2011, the Tuberculosis Research Centre in India reported on 5562 household contacts exposed to drug sensitive tuberculosis and 779 exposed to isoniazid resistant tuberculosis. This cohort was followed for up to 15 years; the prevalence of tuberculosis infection was higher in the contacts of patients with isoniazid resistant tuberculosis, while the hazard of disease was similar in the two groups.[40] In contrast to these results, in a study also conducted in Peru, Grandjean and colleagues found that household contacts of patients with multidrug resistant tuberculosis were half as likely to develop tuberculosis disease compared with contacts exposed to drug sensitive tuberculosis.[41] Compared with our study, the study by Grandjean and colleagues was smaller, matched index patients with multidrug resistant disease and drug sensitive disease, and involved a single household visit at the end of the study to identify secondary disease but did not measure tuberculosis infection. Finally, in a small Vietnamese study, Fox and colleagues found greater incidence of tuberculosis infection and disease among contacts of patients with known multidrug resistant tuberculosis than in contacts of patients with recently diagnosed tuberculosis presumed to be drug sensitive tuberculosis (drug susceptibility testing was not available for the second group).[42] Thus, our results are consistent with most previous studies on risk among household contacts.

Table 3 | Risk of incident tuberculosis disease among household contacts of index patients with tuberculosis by drug resistance profile. Values are hazard ratio (95% confidence interval) unless stated otherwise

Drug resistance profile	Incident tuberculosis disease* (No (%))	Univariable analysis (n=10 396)	Multivariable analyses		
			Model 1 (n=8788)†	Model 2 (n=8788)‡	Model 3 (n=8459)§
Pan susceptible	181 (2.9)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Mono isoniazid	3 (1.2)	0.39 (0.12 to 1.32)	0.17 (0.02 to 1.26)	0.16 (0.02 to 1.12)	0 (0 to infinity)
Mono streptomycin	44 (3.7)	1.18 (0.81 to 1.72)	1.18 (0.78 to 1.77)	1.17 (0.77 to 1.76)	1.23 (0.81 to 1.86)
Isoniazid+streptomycin	6 (1.5)	0.52 (0.22 to 1.23)	0.49 (0.19 to 1.26)	0.48 (0.19 to 1.24)	0.55 (0.21 to 1.42)
Multidrug resistant	57 (3.6)	1.22 (0.87 to 1.72)	1.28 (0.9 to 1.83)	1.28 (0.89 to 1.82)	1.36 (0.77 to 2.38)
Other	27 (4.6)	1.57 (0.99 to 2.48)	1.79 (1.09 to 2.93)¶	1.8 (1.09 to 2.96)¶	1.73 (1.00 to 3.00)¶

*Proportion of incident cases of the univariable model.
†Model 1 adjusted for index patient characteristics (age category, HIV status, smoking status, alcohol consumption) and household contact characteristics (age category, self reported diabetes mellitus, number of BCG scars, alcohol consumption, nutritional status, socioeconomic status, use of isoniazid preventive treatment, and previous tuberculosis disease).
‡Model 2 adjusted for the factors included in model 1 plus characteristics of the index case (presence of cavities on chest radiograph, sputum smear grade, and diagnostic delay).
§Model 3 adjusted for the factors included in model 2 plus the time until initiation of effective treatment.
¶Effects that are statistically significant.

Limitations

Our study has several important limitations. Firstly, because tuberculin skin tests only measure previous infection and not the time of its occurrence, there is no ideal way to measure the incidence of tuberculosis infection caused by a specific, time dependent exposure. Baseline tuberculin skin test positivity might reflect a remote infection that occurred before a contact was exposed to the index patient, while tuberculin skin test conversion among contacts who tested negative at baseline is subject to survival bias (see supplement). We examined these issues by conducting multiple sensitivity analyses; all were consistent with our main results.

Secondly, our study was designed to use molecular fingerprinting to determine whether transmission had taken place between an index patient and a contact with secondary disease; however, most secondary cases occurred among child contacts, many of whom did not have microbiological confirmation of tuberculosis disease. Although it is expected that a child with tuberculosis was most likely infected by someone in the home, it is possible that the infection resulted from community exposure. Within the subset of 133 contacts with secondary disease for whom a genotype was available, only 56 (43.6%) matched the genotype of the index patient. Our finding that the hazard of disease did not differ after exposure to a patient with drug resistant tuberculosis or drug sensitive disease in this subset could reflect the small numbers rather than the absence of an effect. Interestingly, our finding that less than half of the index patients and their household contacts shared a genotype is consistent with the results reported from household contact studies in other high burden settings, where this proportion ranged from 25% to 50%.[40 42] It is unclear whether the incidence of unmatched secondary cases signals background rates of community transmission or particularly high levels of vulnerability to tuberculosis as a result of shared genetic or environmental risk factors.

Conclusion and policy implications

The results of our study have major implications for public health policy and for measuring the burden of drug resistant tuberculosis. Mathematical models suggest that the expected trajectories of drug sensitive tuberculosis and drug resistant tuberculosis strongly depend on the fitness cost of clinically relevant resistance mutations. If *M tuberculosis* drug resistance exacts no fitness cost, the incidence of drug resistant and multidrug resistant tuberculosis will be expected to fall more slowly than would be expected; this prediction would apply even in populations where the acquisition of new drug resistance is minimized through measures such as supervised treatment to ensure adherence to standardized empirical regimens.[43] Our findings provide evidence that invites guideline producers to take action by targeting drug resistant tuberculosis and multidrug resistant tuberculosis, such as the early detection and effective treatment of infection and disease. These guidelines should include the wider deployment of existing tools and the development of diagnostic and therapeutic strategies designed specifically for people already infected with drug resistant tuberculosis.

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Contributors: MCB, MM, PF, TC, and CDM contributed to the conception and design of the study. LL, CC, RY, and JG led the study implementation and data collection in Lima, Peru. RC oversaw the clinical laboratory input. ZZ and SA oversaw data management and data quality assurance. CCH, MM, and MCB did the analysis. MM and MCB prepared the first draft. All authors reviewed the whole draft and approved the final manuscript. MM and MCB are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by the US National Institutes of Health (NIH/NIAID U01AI076217 and U19AI111224). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all study data and had final responsibility for the decision to submit for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the US National Institutes of Health for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the Harvard University Institutional Review Board (Ref. No 19332) and by the Research Ethics Committee of the National Institute of Health of Peru.

Data sharing: Additional data are available on reasonable request to MCB and MM. All requests for data access will need to specify the planned use of data and will require approval from MCB and MM before release.

The lead author (MM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 World Health Organization. UN Interagency Coordination Group (IACG) on Antimicrobial Resistance. 2019 [cited 23 May 2019]. https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/

2 The World Bank. Drug-resistant infections: a threat to our economic future. 2019 [cited 23 May 2019]. https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

3 World Health Organization. WHO Tuberculosis Report. 2018 [cited 23 May 2019]. https://www.who.int/tb/publications/global_report/en/

4 Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med* 1994;330:1179-84. doi:10.1056/NEJM199404283301702

5 Loddenkemper R, Sagebiel D, Brendel A. Strategies against multidrug-resistant tuberculosis. *Eur Respir J Suppl* 2002;36:66s-77s. doi:10.1183/09031936.02.00401302

6 Horsburgh CRJr. The global problem of multidrug-resistant tuberculosis: the genie is out of the bottle. *JAMA* 2000;283:2575-6. doi:10.1001/jama.283.19.2575

7 Cohen T, Dye C, Colijn C, Williams B, Murray M. Mathematical models of the epidemiology and control of drug-resistant TB. *Expert Rev Respir Med* 2009;3:67-79. doi:10.1586/17476348.3.1.67
8 Blower SM, Gerberding JL. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. *J Mol Med (Berl)* 1998;76:624-36. doi:10.1007/s001090050260
9 Blower SM, Chou T. Modeling the emergence of the 'hot zones': tuberculosis and the amplification dynamics of drug resistance. *Nat Med* 2004;10:1111-6. doi:10.1038/nm1102
10 Xpert Mtuberculosis/RIF - rapid tuberculosis test - WHO publishes policy and guidance for implementers. https://www.who.int/tb/features_archive/xpert_rapid_tb_test/en/. Accessed 23 May 2019.
11 Cohen T, Murray M. Modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness. *Nat Med* 2004;10:1117-21. doi:10.1038/nm1110
12 Knight GM, Colijn C, Shrestha S, et al. The distribution of fitness costs of resistance-conferring mutations is a key determinant for the future burden of drug-resistant tuberculosis: a model-based analysis. *Clin Infect Dis* 2015;61(Suppl 3):S147-54. doi:10.1093/cid/civ579
13 Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis* 2012;205(Suppl 2):S199-208. doi:10.1093/infdis/jis008
14 Cohen T, Sommers B, Murray M. The effect of drug resistance on the fitness of Mycobacterium tuberculosis. *Lancet Infect Dis* 2003;3:13-21. doi:10.1016/S1473-3099(03)00483-3
15 Andersson DI, Levin BR. The biological cost of antibiotic resistance. *Curr Opin Microbiol* 1999;2:489-93. doi:10.1016/S1369-5274(99)00005-3
16 Pope CF, McHugh TD, Gillespie SH. Methods to determine fitness in bacteria. In: Gillespie SH, McHugh TD, eds. *Antibiotic Resistance Protocols.* 2nd ed. Springer, 2010: 113-21. doi:10.1007/978-1-60327-279-7_9
17 Cohn ML, Kovitz C, Oda U, Middlebrook G. Studies on isoniazid and tubercle bacilli. II. The growth requirements, catalase activities, and pathogenic properties of isoniazid-resistant mutants. *Am Rev Tuberc* 1954;70:641-64.
18 Mariam DH, Mengistu Y, Hoffner SE, Andersson DI. Effect of rpoB mutations conferring rifampin resistance on fitness of Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2004;48:1289-94. doi:10.1128/AAC.48.4.1289-1294.2004
19 Davies AP, Billington OJ, Bannister BA, Weir WR, McHugh TD, Gillespie SH. Comparison of fitness of two isolates of Mycobacterium tuberculosis, one of which had developed multi-drug resistance during the course of treatment. *J Infect* 2000;41:184-7. doi:10.1053/jinf.2000.0711
20 Pym AS, Saint-Joanis B, Cole ST. Effect of katG mutations on the virulence of Mycobacterium tuberculosis and the implication for transmission in humans. *Infect Immun* 2002;70:4955-60. doi:10.1128/IAI.70.9.4955-4960.2002
21 Billington OJ, McHugh TD, Gillespie SH. Physiological cost of rifampin resistance induced in vitro in Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 1999;43:1866-9. doi:10.1128/AAC.43.8.1866
22 Ordway DJ, Sonnenberg MG, Donahue SA, Belisle JT, Orme IM. Drug-resistant strains of Mycobacterium tuberculosis exhibit a range of virulence for mice. *Infect Immun* 1995;63:741-3.
23 Brandis G, Pietsch F, Alemayehu R, Hughes D. Comprehensive phenotypic characterization of rifampicin resistance mutations in Salmonella provides insight into the evolution of resistance in Mycobacterium tuberculosis. *J Antimicrob Chemother* 2015;70:680-5. doi:10.1093/jac/dku434
24 Comas I, Borrell S, Roetzer A, et al. Whole-genome sequencing of rifampicin-resistant Mycobacterium tuberculosis strains identifies compensatory mutations in RNA polymerase genes. *Nat Genet* 2011;44:106-10. doi:10.1038/ng.1038
25 Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannan BJ. The competitive cost of antibiotic resistance in Mycobacterium tuberculosis. *Science* 2006;312:1944-6. doi:10.1126/science.1124410
26 Cohen T, Becerra MC, Murray MB. Isoniazid resistance and the future of drug-resistant tuberculosis. *Microb Drug Resist* 2004;10:280-5. doi:10.1089/mdr.2004.10.280
27 Shah NS, Auld SC, Brust JC, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017;376:243-53. doi:10.1056/NEJMoa1604544
28 Yang C, Luo T, Shen X, et al. Transmission of multidrug-resistant Mycobacterium tuberculosis in Shanghai, China: a retrospective observational study using whole-genome sequencing and epidemiological investigation. *Lancet Infect Dis* 2017;17:275-84. doi:10.1016/S1473-3099(16)30418-2
29 Smith CM, Trienekens SC, Anderson C, et al. Twenty years and counting: epidemiology of an outbreak of isoniazid-resistant tuberculosis in England and Wales, 1995 to 2014. *Euro Surveill* 2017;22:30467. doi:10.2807/1560-7917.ES.2017.22.8.30467
30 Marais BJ, Mlambo CK, Rastogi N, et al. Epidemic spread of multidrug-resistant tuberculosis in Johannesburg, South Africa. *J Clin Microbiol* 2013;51:1818-25. doi:10.1128/JCM.00200-13
31 García-García ML, Jiménez-Corona ME, Ponce-de-León A, et al. Mycobacterium tuberculosis drug resistance in a suburban community in southern Mexico. *Int J Tuberc Lung Dis* 2000;4(Suppl 2):S168-70.
32 van Soolingen D, Borgdorff MW, de Haas PE, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. *J Infect Dis* 1999;180:726-36. doi:10.1086/314930
33 Toungoussova OS, Sandven P, Mariandyshev AO, Nizovtseva NI, Bjune G, Caugant DA. Spread of drug-resistant Mycobacterium tuberculosis strains of the Beijing genotype in the Archangel Oblast, Russia. *J Clin Microbiol* 2002;40:1930-7. doi:10.1128/JCM.40.6.1930-1937.2002
34 Gagneux S, Burgos MV, DeRiemer K, et al. Impact of bacterial genetics on the transmission of isoniazid-resistant Mycobacterium tuberculosis. *PLoS Pathog* 2006;2:e61. doi:10.1371/journal.ppat.0020061
35 Burgos M, DeRiemer K, Small PM, Hopewell PC, Daley CL. Effect of drug resistance on the generation of secondary cases of tuberculosis. *J Infect Dis* 2003;188:1878-84. doi:10.1086/379895
36 Murray M. Sampling bias in the molecular epidemiology of tuberculosis. *Emerg Infect Dis* 2002;8:363-9. doi:10.3201/eid0804.000444
37 Glynn JR, Bauer J, de Boer AS, et al. Interpreting DNA fingerprint clusters of Mycobacterium tuberculosis. European Concerted Action on Molecular Epidemiology and Control of Tuberculosis. *Int J Tuberc Lung Dis* 1999;3:1055-60.
38 Snider DEJr, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *Am Rev Respir Dis* 1985;132:125-32.
39 Teixeira L, Perkins MD, Johnson JL, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2001;5:321-8.
40 Tuberculosis Research Centre, Indian Council of Medical Research (ICMR), Chennai, India. Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases. *Int J Tuberc Lung Dis* 2011;15:782-8. doi:10.5588/ijtld.09.0327
41 Grandjean L, Gilman RH, Martin L, et al. Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: a prospective cohort study. *PLoS Med* 2015;12:e1001843, discussion e1001843. doi:10.1371/journal.pmed.1001843
42 Fox GJ, Anh NT, Nhung NV, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *Int J Tuberc Lung Dis* 2017;21:297-302. doi:10.5588/ijtld.16.0576
43 Sharma A, Hill A, Kurbatova E, et al, Global Preserving Effective TB Treatment Study Investigators. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. *Lancet Infect Dis* 2017;17:707-15. doi:10.1016/S1473-3099(17)30247-5

Web appendix: Supplemental materials