Expected effects of adopting a 9 month regimen for multidrug-resistant tuberculosis: a population modelling analysis

Emily A Kendall, Anthony T Fojo, David W Dowdy

Summary
Background In May, 2016, WHO endorsed a 9 month regimen for multidrug-resistant tuberculosis that is cheaper and potentially more effective than the conventional, longer (20–24 month) therapy. We aimed to investigate the population-level implications of scaling up this new regimen.

Methods In this population modelling analysis, we developed a dynamic transmission model to simulate the introduction of this short-course regimen as an instantaneous switch in 2016. We projected the corresponding percentage reduction in the incidence of multidrug-resistant tuberculosis by 2024 compared with continued use of longer therapy. In the primary analysis in a representative southeast Asian setting, we assumed that the short-course regimen would double treatment access (through savings in resources or capacity) and achieve long-term efficacy at levels seen in preliminary cohort studies. We then did extensive sensitivity analyses to explore a range of alternative scenarios.

Findings Under the optimistic assumptions in the primary analysis, the incidence of multidrug-resistant tuberculosis in 2024 would be 3.3 (95% uncertainty range 2.2–5.6) per 100 000 population with the short-course regimen and 4.3 (2.9–7.6) per 100 000 population with continued use of longer therapy—ie, the short-course regimen could reduce incidence by 23% (10–38). Incidence would be reduced by 14% (4–28) if the new regimen affected only treatment effectiveness and by 11% (3–24) if it affected only treatment availability. Under more pessimistic assumptions, the short-course regimen would have minimal effect and even potential for harm—eg, when 30% of patients are ineligible for the new regimen because of second-line drug resistance, we projected a change in incidence of −2% (−20 to +28). The new regimen’s effect was greater in settings with more ongoing transmission of multidrug-resistant tuberculosis, but results were otherwise similar across settings with different levels of tuberculosis incidence and prevalence of multidrug resistance.

Interpretation The short-course regimen has potential to substantially lessen the multidrug-resistant tuberculosis epidemic, but this effect depends on its long-term efficacy, its ability to expand treatment access, and the role of second-line drug resistance.

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Introduction
Multidrug-resistant tuberculosis—present in 3–4% of new tuberculosis cases and 20% of previously treated cases worldwide (with much higher prevalence in some countries)—causes 190 000 deaths each year and is a major challenge to clinicians and policy makers.1 Fewer than half of all notified cases with underlying multidrug resistance are identified as such, and with the scale-up of Xpert MTB/RIF, many patients diagnosed with rifampin resistance have no access to appropriate treatment. In individuals appropriately treated for multidrug-resistant tuberculosis, conventional, 20–24 month regimens (subsequently referred to as longer therapy) have a success rate of only 50% worldwide2 because of factors such as low drug effectiveness,3 4 lengthy and toxic regimens that are difficult to complete,5 and high rates of prevalent6 and acquired resistance7 to second-line drugs.

Treatment of multidrug-resistant tuberculosis is also resource intensive, costing thousands of US dollars per patient8 and consuming up to half of tuberculosis control budgets in high-burden countries.9 A potential solution to these challenges is the use of a shorter, cheaper, more effective, and more tolerable new regimen to expand treatment capacity and improve treatment success. In May, 2016, WHO made a conditional recommendation for a new short-course regimen that can treat most patients with multidrug-resistant tuberculosis in 9–12 months.10 This regimen consists of an initial 4–6 month phase of seven drugs including a second-line injectable, followed by a 5 month continuation of four of the oral drugs including pyrazinamide and a fluoroquinolone. It costs less than US$1000 per patient and has shown promising effectiveness, with more than 80% of patients cured in
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**Evidence before this study**
Multidrug-resistant tuberculosis has a tremendous toll on patients who have to endure nearly 2 years of treatment, while exerting pressure on the budgets of tuberculosis control programmes and posing a major barrier to tuberculosis elimination worldwide. In May, 2016, WHO recommended a short-course regimen on the basis of promising individual-level effectiveness in several observational studies; however, to the best of our knowledge, the population-level implications of this recommendation have not been assessed.

**Added value of this study**
In this study, we estimated the epidemiological benefit of adopting the newly endorsed short-course regimen for multidrug-resistant tuberculosis. We also explored the extent to which the anticipated effect depends on characteristics of the regimen that remain to be determined, such as treatment success under programmatic conditions, durability of effectiveness, exclusions on the basis of additional drug resistance, treatment outcomes after such exclusions, and the extent to which cost savings from the new regimen can be used to expand treatment access. We provided a numerical estimate of the potential population-level effect of the short-course regimen in a representative setting—a 23% reduction in incidence after 8 years—and explored factors that modify this projection under different conditions. Under some reasonable sets of assumptions (eg, lower effectiveness of the short-course regimen than that suggested in initial observational studies or a higher prevalence of resistance to second-line drugs), the new regimen was projected to result in minimal, or even negative, effects on the incidence of multidrug-resistant tuberculosis.

**Implications of all the available evidence**
The new short-course regimen can potentially have an important role in the control of multidrug-resistant tuberculosis. However, this effect needs to be balanced against uncertainties related to long-term effectiveness and the importance of additional drug resistance. To optimise the effect of this new regimen, early-adopter countries should simultaneously expand diagnosis and treatment of multidrug-resistant tuberculosis and closely monitor treatment outcomes in both patients receiving the regimen and those ineligible because of additional drug resistance. An important, positive population-level effect of introducing this regimen is realistic but cannot be assumed without further evidence on the role of resistance to second-line drugs and long-term efficacy data from ongoing clinical trials.

Initial observational cohorts in previous tuberculosis models, with explicit representation of diagnosis and treatment of multidrug resistance (figure 1; see appendix for description of the full model). In brief, both drug-susceptible and multidrug-resistant strains circulate in a population, with multidrug resistance emerging during treatment of drug-susceptible disease and subsequently also spreading through person-to-person transmission. Active tuberculosis, once symptomatic, is identified and treated at a given rate, but only a proportion of patients are tested for multidrug resistance and treated accordingly. Treatment is either apparently effective (ie, symptoms and infectiousness resolve, followed by lasting cure or by temporary resolution with subsequent relapse to active disease) or ineffective (ie, associated with ongoing tuberculosis mortality risk and infectiousness). Longer therapy was modelled as lasting a median of 20 months and representing a full attempt at treatment, including any changes made to the initial regimen based on clinical response or drug susceptibility testing results; outcomes under different assumptions regarding regimen effectiveness, treatment access, treatment outcomes in patients with additional drug resistance, and underlying epidemiology of multidrug-resistant tuberculosis.

**Methods**

**Model overview**
In this population modelling analysis, we developed a compartmental transmission model of a multidrug-resistant tuberculosis epidemic, similar to previous tuberculosis models, with explicit representation of drug-susceptible and multidrug-resistant tuberculosis. We also explored the extent to which cost savings from the new regimen can be used to expand treatment access. We provided a numerical estimate of the potential population-level effect of the short-course regimen in a representative setting—a 23% reduction in incidence after 8 years—and explored factors that modify this projection under different conditions. Under some reasonable sets of assumptions (eg, lower effectiveness of the short-course regimen than that suggested in initial observational studies or a higher prevalence of resistance to second-line drugs), the new regimen was projected to result in minimal, or even negative, effects on the incidence of multidrug-resistant tuberculosis.
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were based on results in observational cohorts. We assumed that those who do not respond to a full treatment attempt for multidrug-resistant tuberculosis remain infectious until either death or spontaneous resolution.

Calibration

To explore a large and representative number of scenarios consistent with these data, we considered 2 million sets of model parameters drawn from distributions based on the literature (table 1; appendix pp 7–8). We used log-normal distributions for continuous measures bounded from 0 to infinity, logit-normal distributions for continuous measures bounded from 0 to 1, and uniform distributions when data to suggest a most likely value were missing or sparse. In the primary analysis, we calibrated the model to a setting characterised by WHO estimates of incidence, prevalence, and mortality of tuberculosis, as well as prevalence of multidrug resistance in new and retreatment tuberculosis notifications, in people aged 15 years and older for the WHO southeast Asian region—ie, Bangladesh, Bhutan, North Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste—in 2014 (table 2; appendix pp 10–11).1

To model the expansion of diagnosis and treatment of multidrug-resistant tuberculosis in the past decade, we linearly increased the proportions of patients who are identified as having drug resistance (eg, by Xpert MTB/RIF) and considered for treatment over time, from zero in 2004 to reported levels (3·8% of new tuberculosis cases and 67% of retreatment cases) in 2014. For the primary analysis, we assumed that, in absence of a short-course regimen, the probability of receiving multidrug-resistant tuberculosis treatment would subsequently remain constant (reflecting a relatively fixed treatment budget), whereas the short-course regimen allows...
the proportion of the southeast Asian population aged 15 years and older. 

The proportion of cases that are pulmonary, the proportion estimated to occur in those aged 15 years and older, and the burden of pulmonary tuberculosis in the adult population (ie, those aged 15 years and older), on the basis of the 

Calibration targets and model fit

*We derived these estimates from WHO-reported point estimates (uncertainty intervals),1 adjusted to reflect the

values of treatment-related parameters translate to observed treatment outcomes. *2 2.5th to 97.5th percentiles of 

Select model parameters

Table 1:

| Parameter                                                                 | Median estimate | Distribution | Sampling range |
|--------------------------------------------------------------------------|-----------------|--------------|---------------|
| Probability of rapid progression after initial tuberculosis infection†   | 0.14            | Logit-normal | 0.08–0.25     |
| Protection against rapid progression after reinfection, if latently infected† | 0.5             | Logit-normal | 0.1–0.9       |
| Reactivation rate from latent to early (asymptomatic) active tuberculosis, † / year | 0.001           | Log-normal   | 0.0005–0.002  |
| Rate of tuberculosis diagnosis and treatment initiation, † / year         | 1               | Log-normal   | 0.7–1.5       |
| Proportion failing to initiate treatment for multidrug-resistant tuberculosis after diagnosis (in excess of loss to follow-up of patients with drug-susceptible tuberculosis)† | 0.05            | Logit-normal | 0.03–0.10     |
| Proportion of treated patients who have an apparent treatment response†  |                 |              |               |
| Newly diagnosed patients with drug-susceptible tuberculosis, first-line therapy† | 0.98            | Logit-normal | 0.96–0.99     |
| Patients with multidrug-resistant tuberculosis, longer therapy†          | 0.77            | Logit-normal | 0.66–0.85     |
| Proportion who relapse, among those with apparent treatment response      |                 |              |               |
| Newly diagnosed patients with drug-susceptible tuberculosis, first-line therapy† | 0.040           | Logit-normal | 0.026–0.060   |
| Patients with multidrug-resistant tuberculosis, longer therapy†          | 0.040           | Logit-normal | 0.015–0.100   |
| Probability of loss to follow-up during therapy                          |                 |              |               |
| First-line therapy†                                                      | 0.06            | Logit-normal | 0.03–0.1      |
| Longer therapy for multidrug-resistant tuberculosis†                      | 0.19            | Logit-normal | 0.14–0.25     |
| Relative transmissibility of multidrug-resistant strain‡                 | 0.60            | Log-normal   | 0.38–0.94     |
| Risk of acquiring multidrug resistance during first-line therapy‡        | 0.005           | Logit-normal | 0.0025–0.001  |
| Proportion of patients with multidrug resistance disqualified from the short-course regimen‡ | 0.1             | Logit-normal | 0.07–0.15     |

See the appendix pp 7–8 for a complete list of parameters and additional references, and p 9 for an illustration of how the values of treatment-related parameters translate to observed treatment outcomes. *2.5th to 97.5th percentiles of unbounded distributions. Including those who might later be lost to follow-up or relapse, or both.

Table 2: Select model parameters

| Parameter                                                                 | Reported values for southeast Asia† | Median model values (95% uncertainty range) |
|--------------------------------------------------------------------------|------------------------------------|---------------------------------------------|
| Tuberculosis incidence per 100 000 adult population per year             | 203 (192–232)                     | 203 (191–207)                               |
| Annual change in incidence                                              | -2%                                | -2.2% (1.8–2.8)                             |
| Tuberculosis prevalence per 100 000 adult population                     | 275 (224–330)                     | 271 (228–323)                               |
| Tuberculosis mortality per 100 000 adult population per year             | 26.2 (20.9–32.6)                  | 26.7 (21.2–32.3)                            |
| Proportion of new notifications with multidrug resistance                | 2.2% (1.9–2.6)                    | 2.1% (1.9–2.5)                              |
| Proportion of retreatment notifications with multidrug resistance        | 16.4% (14.8–17.9)                 | 16.7% (14.4–17.9)                           |

*We derived these estimates from WHO-reported point estimates (uncertainty intervals),1 adjusted to reflect the burden of pulmonary tuberculosis in the adult population (ie, those aged 15 years and older), on the basis of the proportion of cases that are pulmonary, the proportion estimated to occur in those aged 15 years and older, and the proportion of the southeast Asian population aged 15 years and older.

Table 2: Calibration targets and model fit

expansion of case detection and treatment, reflecting the lower cost and resource requirement of the new regimen.

Modelling of short-course regimen

We modelled the introduction of a short-course regimen as an instantaneous switch from the conventional, longer therapy in 2016 for patients who are diagnosed with multidrug-resistant tuberculosis and not found to have additional drug resistance that makes them ineligible. This scenario reflects a simulated policy change with rapid restructuring of the treatment programme for multidrug-resistant tuberculosis.

To estimate the number of additional patients who could be treated in a budget-neutral introduction of the new regimen, we compared the costs of drugs and clinical care for each regimen. Drug costs for the short-course regimen are less than half of those of longer therapy, and the shortened durations of the intensive phase and the overall treatment course also reduce other associated health-care costs,4 whereas added costs of second-line drug susceptibility testing are small relative to the total cost of treatment.5 For simplicity, we assumed in the primary analysis that introduction of the short-course regimen would allow twice as many patients to be treated on the same multidrug-resistant tuberculosis treatment budget. We implemented this doubling by expanding the number of patients with multidrug-resistant tuberculosis offered treatment, first to previously treated patients and then to new patients.

In the primary analysis, we modelled a scenario in which roughly 10% of patients with multidrug-resistant tuberculosis have additional drug resistance (or suspected resistance) that disqualifies them from the short-course regimen, leading to very poor outcomes. We used a median duration of 10 months for the short-course regimen and 20 months for longer therapy,7 and assumed that loss to follow-up is reduced by half with the short-course regimen. Treatment success for people remaining in treatment was set at 92.5% for the short-course regimen8 and 66–85% for longer therapy;9 these percentages include only those who are not lost to follow-up and are therefore higher than reported figures that do not distinguish between loss to follow-up and other adverse outcomes. Relapse risk after successful treatment was set at 1% for the short-course regimen and 1–10% for longer therapy. The estimated outcomes of the short-course regimen were based on results from an observational cohort study in Bangladesh;10 similar results were obtained elsewhere.11,12 The estimated 10% ineligibility for the short-course regimen is based on the assumptions that patients would be screened for second-line drug resistance with a line probe assay (of imperfect sensitivity),13 moxifloxacin resistance would be similar to levels observed in Pakistan and Bangladesh,14 and mono- and dual resistance to second-line injectables would be rare.8,15 We also assumed, conservatively, that patients
found to have such disqualifying additional drug resistance would have very poor outcomes, comparable to those reported for extensively drug-resistant tuberculosis and to tuberculosis outcomes in the pre-antibiotic era (ie, that half of these patients will ultimately die of tuberculosis, although such deaths might occur well after treatment is completed).

We explored several alternative scenarios to the above assumptions (table 3). Alternatives involving inter-related aspects of prevalence, diagnosis, and associated treatment outcomes of second-line drug resistance were explored combinatorially (table 4).

The primary outcome for each scenario was the percentage reduction in multidrug-resistant tuberculosis incidence in 2024, compared with projections under continued use of longer therapy. Results are reported as the median simulated value and corresponding 95% uncertainty range (UR), reflecting the 2·5th to 97·5th percentile of data-consistent simulations.

Sensitivity analyses
We assessed the sensitivity of the primary results to the value of all underlying model parameters. We also assessed the sensitivity of our results to assumptions about ongoing scale-up of drug susceptibility testing even in the absence of the short-course regimen, to underlying dynamics of acquisition, transmission, and reactivation of multidrug-resistant tuberculosis, and to alternative epidemiological scenarios reflecting a range of tuberculosis incidence and multidrug-resistant tuberculosis prevalence (appendix).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Our model generated 11 289 data-consistent simulations, which fitted well with our epidemiological calibration targets (table 2). Posterior distributions of model parameters favoured lower rates of acquisition and transmission of multidrug-resistant tuberculosis (reflecting that multidrug resistance is present in only 2% of new tuberculosis notifications, despite decades of treatment with isoniazid and rifampin) but otherwise suggested no strong support for specific parameter values within the ranges of the specified prior distributions (appendix p 13).

Assuming that current practices continue, we projected that the incidence of multidrug-resistant tuberculosis would decrease by a median of 14% (95% UR –36 to 39) from 4·9 [95% UR 4·2–5·9] per 100 000 population in
(A) Continued use of longer therapy. (B) Implementation of the short-course regimen in 2016.

Projected incidence of multidrug-resistant tuberculosis in the primary scenario

Figure 2: Projected incidence of multidrug-resistant tuberculosis in the primary scenario
(A) Continued use of longer therapy. (B) Implementation of the short-course regimen in 2016.
Discussion
This epidemic model suggests that implementation of the short-course regimen could have an important effect on the multidrug-resistant tuberculosis epidemic, with an estimated 23% reduction in incidence over 8 years relative to continued use of longer therapy. This effect depends on key assumptions, including improved long-term effectiveness, the ability to use resource savings to expand access, and minimised poor outcomes resulting from additional drug resistance. If these assumptions prove incorrect, then the short-course regimen could have minimal or even detrimental effect—eg, possibly having no effect on the incidence of multidrug-resistant tuberculosis even if the number of people treated could be doubled. These findings emphasise the need for additional data collection as the short-course regimen is rolled out and highlight that implementation of this regimen could have important population-level effects, but also that this result is far from certain.

More effective regimens for multidrug-resistant tuberculosis are sorely needed, and a substantial proportion of the projected impact of a shorter regimen derives from the assumption of superior efficacy in those treated. The high treatment success rates (>80%) and low relapse risks (<1%) of the short-course regimen observed in initial cohorts are promising compared with longer therapy (50% success rate worldwide and 62% in those who would have met inclusion criteria for the short-course regimen). Whether efficacy of this new regimen is truly superior (and durable) awaits the results of an ongoing clinical trial. Our results suggest that if the short-course regimen is not more efficacious than longer therapy in eligible patients, then its impact will largely depend on whether it can facilitate expansion of treatment access and whether patients with disqualifying resistance can be appropriately triaged and successfully treated. In hotspots of more extensive drug resistance, the conditions under which the short-course regimen offers benefit will be more limited and will depend even more on the achievable gains in efficacy and resource use.

Because of the high cost of traditional care, the potential to diagnose and treat more patients within constrained budgets contributes strongly to the short-course regimen’s potential effects. Our projections are similar to an estimate of the effect of universal Xpert use in India, accompanied by gradual improvement in treatment outcomes (ie, 25% reduction in incidence of multidrug-resistant tuberculosis over a decade). However, unlike that analysis, we explored a mechanism (short-course regimen) by which such increased treatment access and improved treatment outcomes could potentially be achieved in a budget-neutral manner, if per-patient savings were used to identify and treat more patients. If resources were reallocated elsewhere, the effect of the short-course regimen on incidence would shrink, but the overall impact on burdened tuberculosis control programmes and health systems, as well as on patients for whom multidrug-resistant tuberculosis can be economically devastating, could remain substantial. Future analyses to explicitly assess the economic effects of the short-course regimen are warranted. We also assumed that availability of clofazimine will meet demands, that second-line drug susceptibility can be tested before patients are lost to follow-up, and that the short-course regimen will be scaled up rapidly. To the extent that scale-up is slow, incomplete, or associated with increased pretreatment losses to follow-up, the effect will be diminished. Moreover, although children and extrapulmonary tuberculosis contribute little to tuberculosis transmission, the still-uncertain usefulness of the short-course regimen in such populations will affect its ability to reduce morbidity and mortality of multidrug-resistant tuberculosis.

Our model highlights an important drawback of the short-course regimen: its reliance on component drugs to which resistance is prevalent in some populations. At baseline, we assumed that 10% of people without previous treatment for multidrug-resistant tuberculosis would be identified as having resistance to fluoroquinolones or second-generation aminoglycosides (ie, contraindications to the short-course regimen) and excluded on that basis. In settings where this proportion is 30% or higher, we projected a substantially diminished effect of the new regimen. Similarly, settings that implement the short-course regimen without sufficient capacity for rapid second-line drug susceptibility testing might experience reduced...
effectiveness and diminished short-term benefit, as well as long-term risk of amplified second-line drug resistance. Pyrazinamide resistance also could limit the effect of the short-course regimen. Pyrazinamide is included for the whole duration of the regimen and might be important for ensuring good treatment outcomes or preventing additional drug resistance, but 37–81% of multidrug-resistant strains might be pyrazinamide resistant.\(^1\) Therefore, assessment of pyrazinamide’s role is urgently needed; if further study determines that individuals with resistance to pyrazinamide should also be excluded from this regimen (resulting in exclusion of nearly 50% of patients with multidrug-resistant tuberculosis in southeast Asia\(^1\) and a greater proportion in some other settings), then the regimen’s population-level effect is likely to be very small.

As with all modelling studies, our analysis has some limitations. Our model projections reflect uncertainty related to trends in resistance to first-line and second-line drugs, rapidly changing diagnostic and treatment practices, and the scarcity of data on the population dynamics of multidrug-resistant tuberculosis. Importantly, our homogeneously mixed model could have overestimated the effect of this regimen in specific settings. We also simplified the dynamic representation of drug resistance to only two strains. Resistance to other drugs was implicitly factored into treatment outcomes, but transmission of multiple drug-resistant strains was not explicitly modelled. For this reason, we limited projections to a relatively short (<10 year) timeframe over which the selection of resistance to second-line drugs is expected to have relatively little epidemiological effect. Mounting second-line resistance, if it occurs, could lead to worse outcomes over time than those projected here, especially in the long term. Future modelling analyses could assess the effect of the short-course regimen on the acquisition and emergence of fluoroquinolone resistance. We were also unable to model all the complexities of tuberculosis epidemics—for example, we did not explicitly model individual heterogeneity in HIV or diabetes status or variation in tuberculosis-associated or diabetes-associated factors.

In summary, this modelling analysis illustrates the potential important effects of a newly recommended short-course regimen on the multidrug-resistant tuberculosis epidemic. However, it also highlights that this effect is dependent on certain key factors, including the regimen’s long-term efficacy, the ability to facilitate scale-up of treatment access through resource savings, and the number and outcomes of patients who are excluded on the basis of additional drug resistance. Crucial data in estimating the ultimate effect of this regimen include evidence of durable efficacy from randomised controlled trials and data for the effect of pyrazinamide resistance, which is highly prevalent in patients with multidrug resistance. Additional research to develop improved regimens in the future will be essential, in view of the key limitations of the present short-course regimen. Ultimately, in making urgent decisions about whether to implement this new regimen at the country and global levels, the potential to reduce incidence by 20% or more needs to be weighed against the substantial uncertainty still surrounding the long-term effects of this regimen on the population dynamics of multidrug-resistant tuberculosis.

**Figure 4:** Relative change in incidence of multidrug-resistant tuberculosis in 2024, under different combinations of apparent response to short-course regimen and regimen exclusions, by treatment outcome in those excluded.

| Apparent response to short-course regimen | Proportion ineligible for short-course regimen |
|-----------------------------------------|---------------------------------------------|
| **A Fair**                              |                                             |
| 98%                                     | -38% (-54 to -22)                           |
| 92.5%                                   | -31% (-48 to -19)                           |
| 85%                                     | -23% (-38 to -11)                           |
| 77%                                     | -13% (-28 to 0)                             |
| **B Poor**                              |                                             |
| 98%                                     | -38% (-54 to -22)                           |
| 92.5%                                   | -31% (-48 to -19)                           |
| 85%                                     | -23% (-38 to -11)                           |
| 77%                                     | -13% (-28 to 0)                             |
| **C Very poor**                         |                                             |
| 98%                                     | -38% (-54 to -22)                           |
| 92.5%                                   | -31% (-48 to -19)                           |
| 85%                                     | -23% (-38 to -11)                           |
| 77%                                     | -13% (-28 to 0)                             |

We declare no competing interests.

**Contributors**

DWD and EAK conceived the study. EAK developed the model, analysed the data, and wrote the first draft of the report. DWD and ATF contributed to study design, data interpretation, and critical review of the report.

**Declaration of interests**

We declare no competing interests.
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