Web appendix

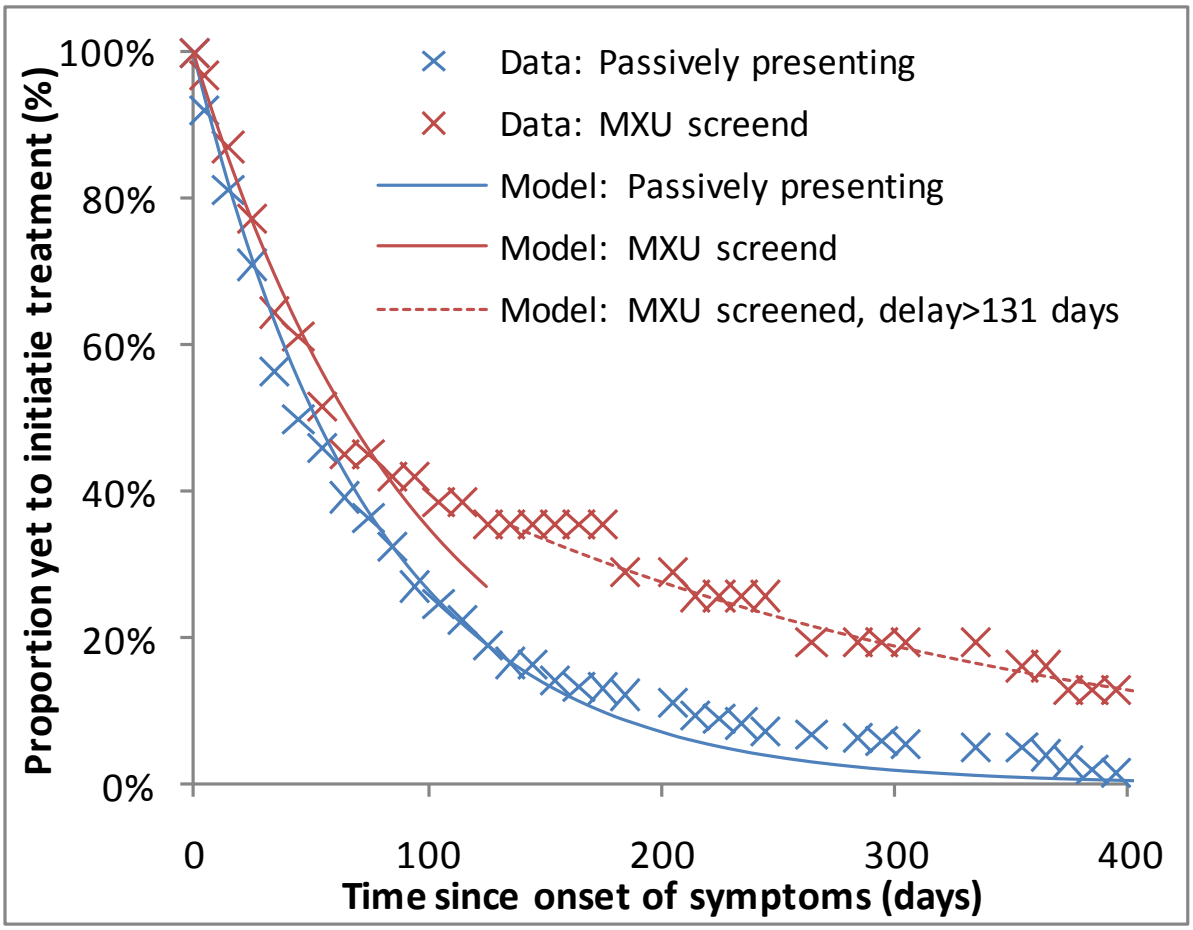
Appendix 1: Detailed justification for state transition parameters in the model

Time from onset of symptoms to treatment with and without Find and Treat

To assess the impact of the mobile screening unit, both mobile unit-screened cases and passively presenting controls from the retrospective cohort were divided into three groups: (i) asymptomatic on presentation, (ii) diagnostic delay of up to 131 days, and (iii) diagnostic delay of greater than 131 days. The cut-off of 131 days was used to separate cases that were exceedingly unlikely to present passively from those with shorter delays. The value of 131 days was based on the upper limit of the interquartile range of delays to start of treatment (median 67 days, lower limit 30 days) in a study of the effect of socio-economic deprivation on tuberculosis treatment delays in England in 2000-2005[1].

Exponential curves (representing models with a constant probability of diagnosis per patient per unit time) were fitted to the proportion of patients still untreated by time since onset of symptoms. Data were aggregated into categories of 10 days length for this purpose. A good fit was found to data from all passively presenting controls, as well as to mobile screening unit cases with delays of up to 131 days (Figure A1-1). A separate exponential curve with a shallower slope fitted the diagnostic delay for mobile screening unit cases with delays of greater than 131 days.

Figure A1-1. Time between onset of symptoms and diagnostic confirmation for mobile screening unit and passively presenting cases (shown as the proportion diagnosed within categories of size 10 days; excludes cases asymptomatic on presentation), as well as best fitting exponential curves.



The mobile screening unit population has shorter delays than those in the passively presenting population (median 29 days for mobile screening unit and 48 days for passively presenting cases). However, if cases presenting asymptomatically are excluded, the mobile screening unit population has longer delays. This is likely to represent the exceedingly hard-to-reach nature of those who present via the mobile screening unit, rather than passively. Although passive controls were chosen for having risk factors, they were by definition cases who presented for treatment, while the mobile screening unit is likely to be reaching cases who would otherwise never present.

Based on these fits, patients were modelled in the following way:

(i) *Symptomatic cases with diagnostic delays of up to 131 days.* The proportion of cases diagnosed within a year in this group was extremely high for both passively presenting and mobile screening unit cases (one year rate of diagnosis of 99% in passively presenting cases and 98% in mobile screening unit cases). Hence the difference between passively presenting and mobile screening unit cases in this category was assumed to be negligible.

(ii) *Mobile screening unit cases with diagnostic delay greater than 131 days.* 22.9% of mobile screening unit cases had a delay of more than 131 days. These were assumed to otherwise not present for treatment without the activities of the Find and Treat service. The time between symptom onset and mobile screening unit screening was not considered, since the health state of the cases (untreated active tuberculosis) is exactly the same during that time period, whether or not the mobile screening unit exists.

(iii) *Asymptomatic cases with active tuberculosis.* 35.4% of mobile screening unit cases were asymptomatic on detection, but none of the passively presenting cases. Data from repeated radiological examination of populations suggest that individuals with positive chest radiograph changes progress rapidly to active symptomatic tuberculosis[2]. Hence it was assumed that all these cases would eventually progress to symptomatic disease, and that the time for this to occur was negligible for the purposes of discounting. Upon onset of symptoms, it was assumed that this group would behave in the same way as symptomatic cases in the absence of Find and Treat, i.e. that the majority would present for treatment almost immediately while 35.4% [= 22.9% out of (100 – 35.4%)] would not present without Find and Treat involvement.

Clinical outcomes of cases with active tuberculosis detected by the mobile screening unit

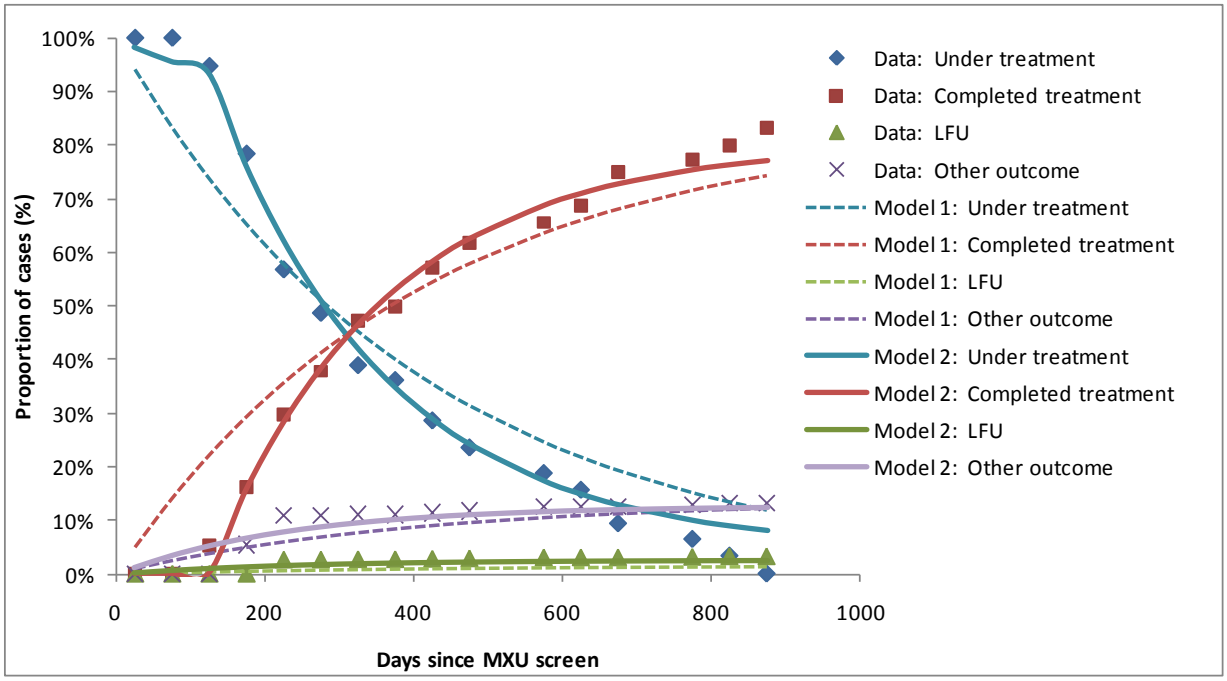
Mobile screening unit cases were divided into four groups based on their status on 30 September 2010: (i) still on treatment, (ii) completed treatment, (iii) lost to follow up (including patients who stopped treatment due to poor adherence) and (iv) any other final outcome (patients who were transferred out of London, stopped treatment for clinical reasons or died of non-tuberculosis causes). Outcomes were based on London tuberculosis surveillance case records (Enhanced TB Surveillance), or from Find and Treat records instead, where these were missing. Three cases had missing dates of outcome in the London

tuberculosis surveillance database (two who were recorded as having completed treatment, one who died of non-tuberculosis-related causes); their times to the outcomes were estimated using simple mean imputation from other cases in the same category. One patient whose date of treatment completion preceded the date of mobile screening unit screening was dropped from the dataset, so the 47 remaining patients were included in the analysis.

An exponential model was fitted to the proportion of cases who were still on treatment, had completed treatment, were lost to follow up and had any other final outcome, by time since their initial mobile screening unit screen (aggregated into 50-day categories). Cases who were still on treatment at the end of their follow up time were distributed proportionately among the four remaining categories, since their actual time to treatment completion was unknown. The model fitted data well (see Figure 7) apart from data on the first few months after the initial screen. Hence a second model was fitted to the same data but with the assumption that cases would have a 125 day interval before they could complete treatment. The 125 day interval was based on actual treatment length in the identified cases and produced a good fit to data. A delay was not incorporated into the transition to being lost to follow up or other outcomes, since there did not appear to be any *a priori* reason for such a delay.

Figure A1-2 shows the best fitting models to data. For the best fitting model without a 125 day interval, the annual rate of completing treatment, being lost to follow up and having a different outcome are 50%, 1% and 8% respectively. For the best fitting model with a 125 day interval, the corresponding rates are 54.6%, 67.1%, 2.1% and 10.1% for the annual rate of completing treatment in the first year, completing treatment in subsequent years, being lost to follow up and having other outcomes.

Figure A1-2. Outcomes of 48 mobile screening unit-screened tuberculosis cases by days of follow up since the initial screen, and best fitting models to the data. Model 2 incorporates a 125 day interval before cases move from being on treatment to another category, while Model 1 does not.



Probability of being lost to follow up and re-engagement in the absence of Find and Treat

The risk of being lost to follow up on treatment in the absence of Find and Treat were estimated from a cohort study of tuberculosis cases in Greater London in 2003/4, which found 321 prisoners, homeless and problem drug users out of the cohort of 1941 cases[3]. In this subgroup of cases most similar to the target group for Find and Treat, 9% were lost to follow up within 6 months of starting treatment. Assuming a constant risk of loss to follow up, this translates to a 17.2% risk in the absence of Find and Treat. It was assumed such cases have proportionately lower annual rates of completing treatment and 'miscellaneous' outcomes, but the same rates of tuberculosis-related death.

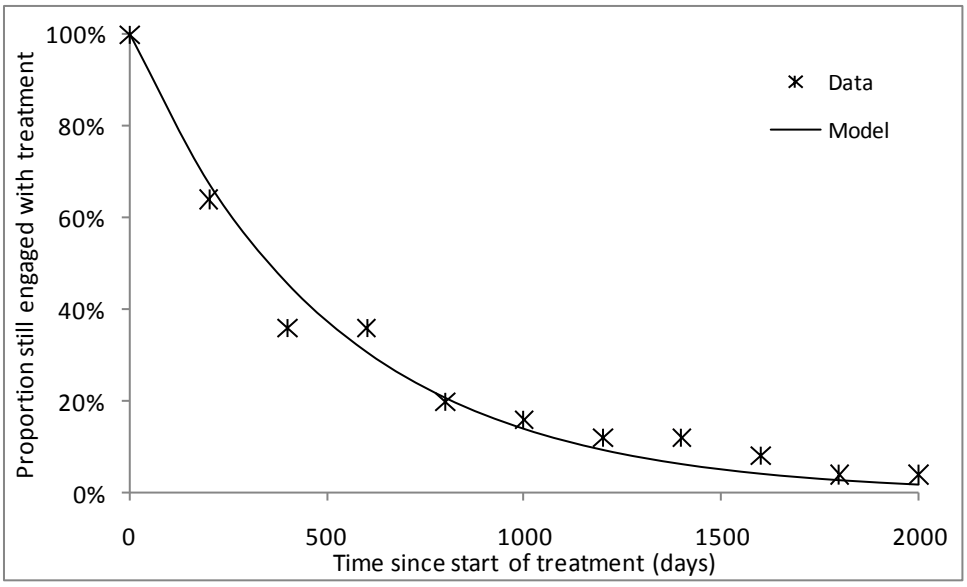
The rate at which cases lost to follow up re-engage with health services without Find and Treat involvement was estimated based on the outcomes of cases in London tuberculosis surveillance records from January 2004 to December 2005, a time period which pre-dates Find and Treat by more than a year. For those cases who were lost to follow up at one year, we looked for further episodes or notifications as indications that the cases were returned to

service. If a patient had an episode date after the Find and Treat service had started, the Find and Treat database was checked for service involvement and cases were removed from the analysis appropriately.

6810 cases were extracted, of which 219 (3.2%) were lost to follow up at one year. Of these, 27 (12%) had a new episode of care in a London tuberculosis clinic. However, 2 of the new episodes were much later and had Find and Treat involvement. The 25 remaining cases had an average of 519 (range 29-2037) days between being lost to follow up to the new episode or notification. Of the 22 cases where a further outcome is known, 7 (30%) were lost to follow up within a year of their subsequent episode.

An exponential model fitted the data well when the time to being lost to follow up was aggregated into time categories of 200 days (Figure A1-3). The best fitting model predicted that cases lost to follow up in the absence of Find and Treat re-engaged with treatment at a rate of 51.0% a year.

Figure A1-3. Proportion of cases still engaged with treatment by time since treatment and best fitting exponential model to the data.



Clinical outcomes of untreated cases

The prognosis of untreated tuberculosis cases was determined by the fate of cases detected in a 1975 survey in South India, in a region which, at the time, had no organised tuberculosis

treatment[4]. Only results from the first survey were used (duration 1½ years), since in subsequent surveys cases were given isoniazid and advised to attend rural health institutions. The study found that 27.8% of cases identified during the survey were subsequently cured, 30.2% died and 42.0% were still excreting bacilli. Mortality and recovery were assumed to be exponential processes to convert these into one year probabilities.

Probability that cases referred to Find and Treat for loss to follow up return to service following Find and Treat involvement

Between October 2007 and September 2010, 263 cases were referred to Find and Treat due to loss to follow up, of whom 180 had active pulmonary tuberculosis. Of these, 64 (36%) had completed treatment by 30 September 2010, 29 (16%) were still on treatment, 65 (36%) were still lost to follow up, 4 (2%) had died of tuberculosis-related causes and 18 (10%) had other final outcomes (transferred out of London, stopped treatment for clinical reasons or died of non-tuberculosis causes). Hence about 52% of cases could be regarded as having been returned to treatment by 30 September 2010 (final status returned to treatment or completed treatment).

However, taking the proportion of cases who had been returned to treatment by 30 September 2010 is misleading for two reasons. First, each case had been followed up for a different length of time (and cases who had been followed up by Find and Treat for longer presumably had a greater chance of being eventually returned to treatment). Secondly, there were 9 cases who had a treatment start date in London tuberculosis surveillance records after the date of Find and Treat referral, but a final outcome which was not that of having completed treatment or still being on treatment. These were presumably returned to treatment by Find and Treat but subsequently became lost to follow up again.

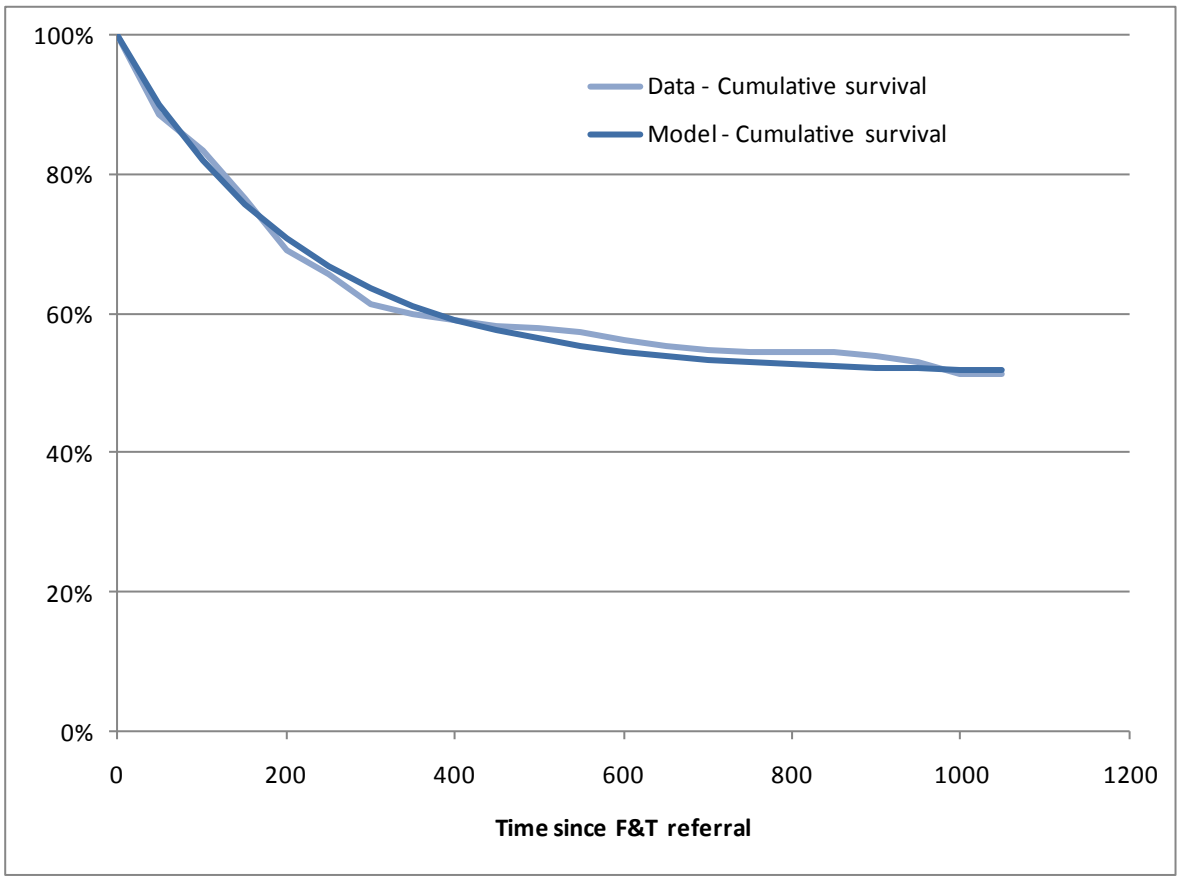
To incorporate these considerations, Kaplan-Meier survival analysis was used to investigate the probability of remaining lost to follow up by follow-up time (i.e. the number of days since a case was first referred to Find and Treat). A "failure to survive" for the purpose of the analysis was being returned to treatment, defined as having a treatment start date in London tuberculosis surveillance records which came after the date of Find and Treat referral, or as having a final outcome of completing treatment or still being on treatment. Hence cases returned to treatment are included even if their final outcome was not being on or having

completed treatment; the possibility that they may subsequently have been lost to follow up again (or had another adverse outcome) is considered separately below.

The date of failure was defined as the first treatment start date in London tuberculosis surveillance records which came after the date of Find and Treat referral, or where the date was missing, the date at which treatment was completed. If both dates were missing, then the date of end of follow up (30 September 2010) was used as the date of failure. Hence the most conservative assumption was used where information was missing. Time to failure was then defined as the time between Find and Treat referral and failure date. Cases were censored at the end of their follow-up period if they were still lost to follow up at that time, and at their time of event if they were reported if they had other outcomes (death, transfer out or stopping treatment for clinical reasons).

Figure A1-4 shows the cumulative survival probability (i.e. probability that a case will not have been returned to treatment yet) of the cohort of cases by time since their time of referral to Find and Treat. Even after 1000 days, the survival model suggests that about 51.0% of cases were still lost to follow up. Hence we assumed that this proportion of cases referred to Find and Treat due to loss to follow up would never be returned to treatment. For the remaining cases, the best fitting exponential model suggests they will be returned to treatment at the rate of about 81.7% a year.

Figure A1-4. Cumulative survival probability (i.e. probability that a case will not have been returned to treatment yet) of cases referred to Find and Treat due to loss to follow up.



Probability that cases referred to Find and Treat for loss to follow up, who are returned to service, then become lost to follow up again

To estimate the probability that cases returned to treatment by Find and Treat after being referred for loss to follow up were again lost, we identified 28 cases with a recorded date of starting treatment that occurred after the date of Find and Treat referral. Of these 28 cases, 13 completed treatment, 9 were recorded as lost to follow up at the end of the follow-up period and 6 were still on treatment at the end of this period.

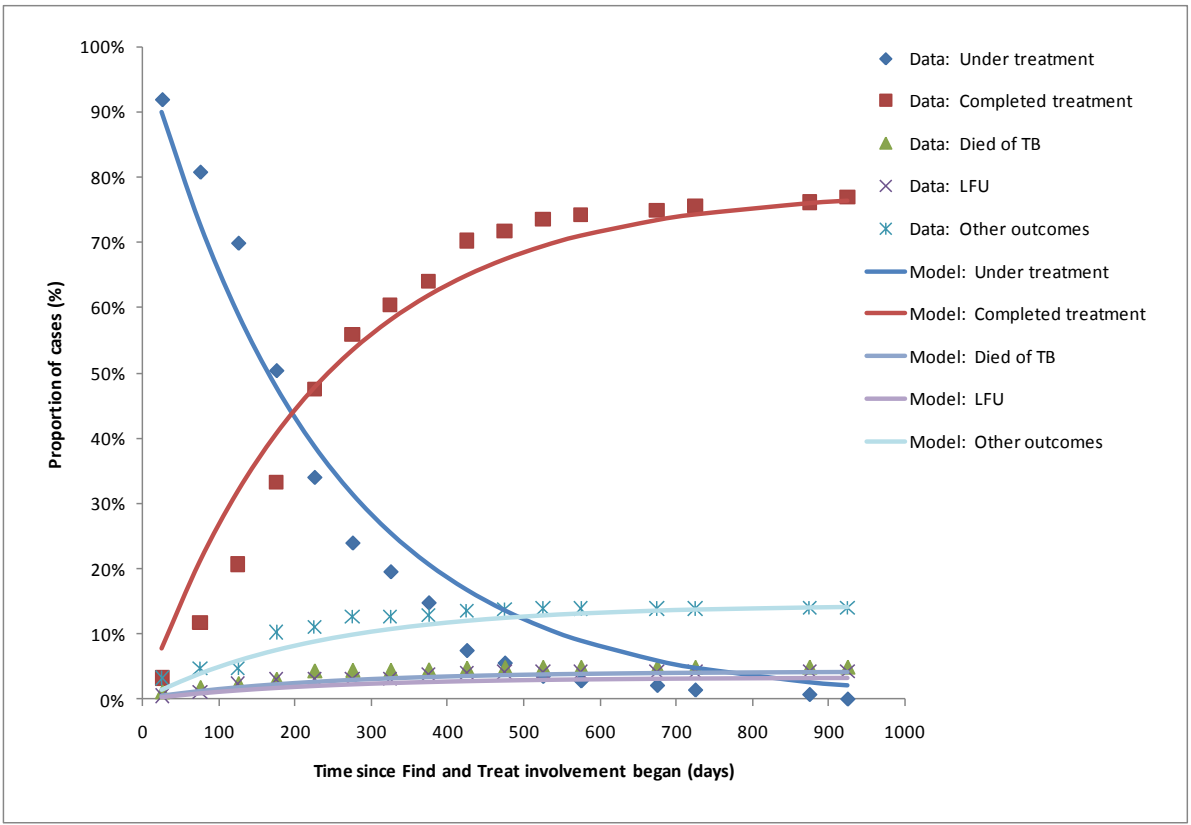
Because of the small sample size and lack of information about the date at which cases became lost to follow up, it was not possible to fit a model to the time to loss to follow up in this group. Hence a simpler approach was taken. Assuming that each loss to follow up event occurred halfway between the time a case was placed on treatment and the end of the follow

up period, the total number of days at which the 28 cases were at risk of being lost to follow up was 9475. Since 9 loss to follow up events occurred during this time, the probability that a case would be lost to follow up in a year was estimated to be 34.7%. It was assumed that these cases still had the opportunity to be returned to treatment at the rate that they did before (81.7% a year).

Cases with active tuberculosis referred to Find and Treat for enhanced case management

To analyse the outcomes of the 188 tuberculosis cases referred to Find and Treat for case management support, an exponential model was fitted to the proportion of cases who were still on treatment, had completed treatment, were lost to follow up and had a different outcome, by time since their referral to Find and Treat (aggregated into 50-day categories). Time was not allocated for the period during which no case can complete treatment as this was not necessary to achieve a good fit, presumably because most of these cases had already been on treatment when they were first engaged by the Find and Treat service. The annual rate of completing treatment, dying of tuberculosis, being lost to follow up and having a different outcome in the best fitting model are 61.2%, 3.3%, 2.6% and 11.3% respectively (Figure A1-5). If the cases are not managed by Find and Treat, they are assumed to have a one-year probability of loss to follow up of 34.7%, the same as the risk of being lost again in the group of cases referred to Find and Treat for loss to follow up who subsequently re-engage with treatment.

Figure A1-5. Outcomes of the 188 active tuberculosis cases referred to Find and Treat



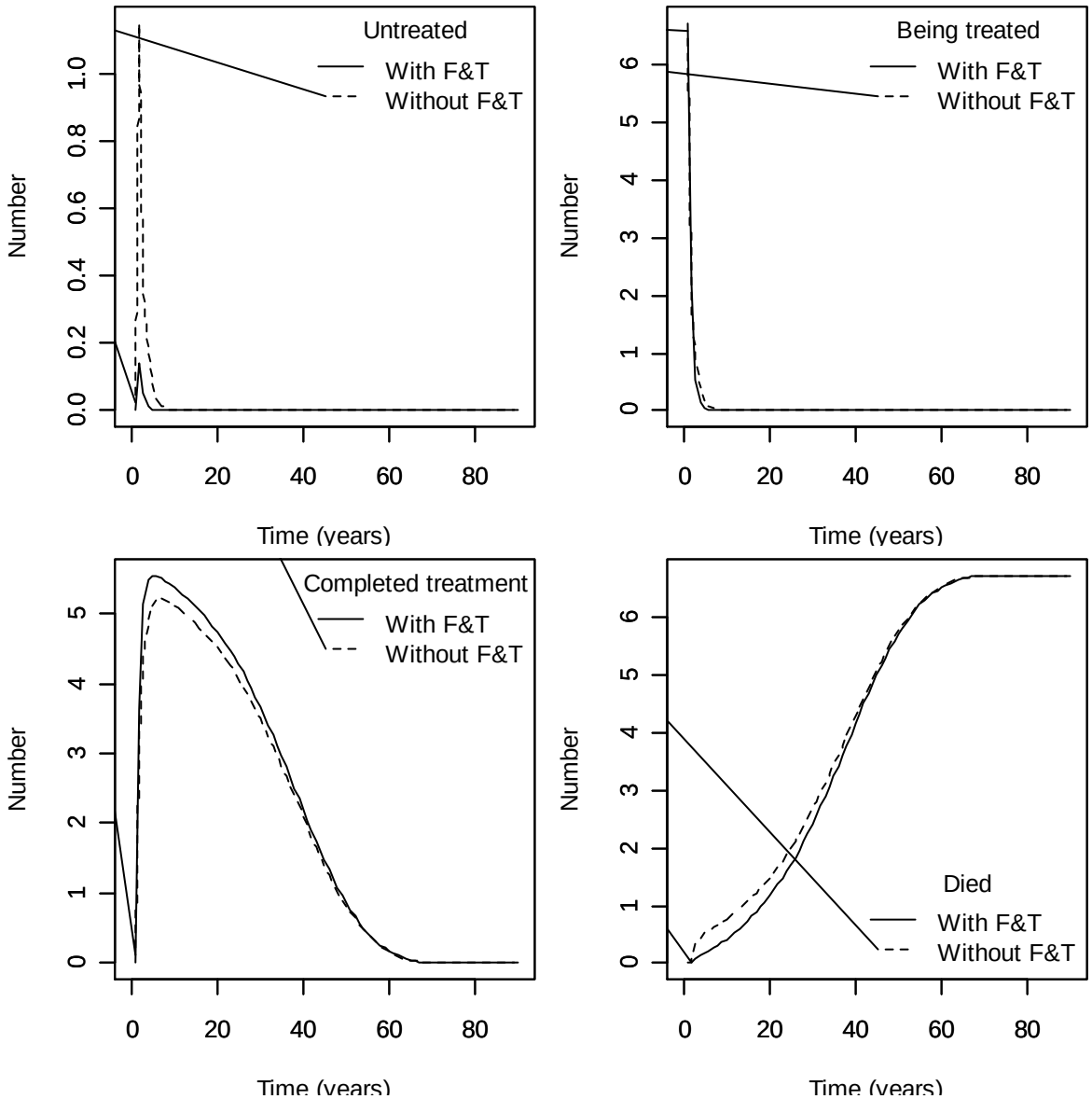
because of complex management issues, by days of follow up since the initial screen and best fitting models to the data.

References

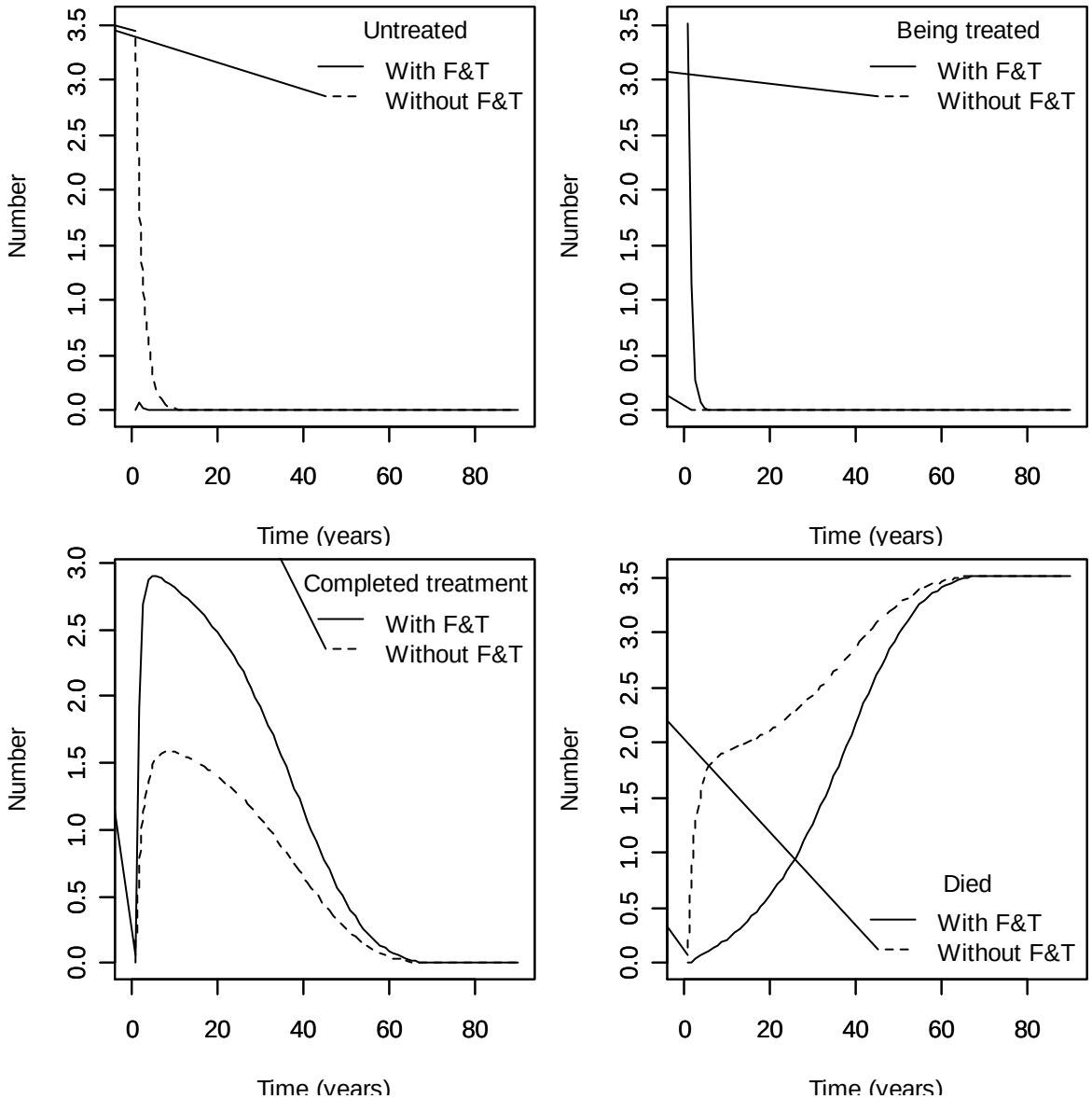
1. French CE, Kruijshaar ME, Jones JA, Abubakar I. The influence of socio-economic deprivation on tuberculosis treatment delays in England, 2000-2005. *Epidemiol.Infect.* 2009;**137**:591-6.
2. Toman K. How does pulmonary tuberculosis develop and how can it be detected at an early stage? *Toman's Tuberculosis. Case detection, treatment, and monitoring - questions and answers. Second edition.*, pp 66-71. 2004.
3. Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax* 2007;**62**:667-71.
4. Tuberculosis in a rural population of South India: a five-year epidemiological study. *Bull.World Health Organ* 1974;**51**:473-88.

Appendix 2: Health states over time for cases engaged with Find and Treat, and hypothetical equivalent cases without Find and Treat

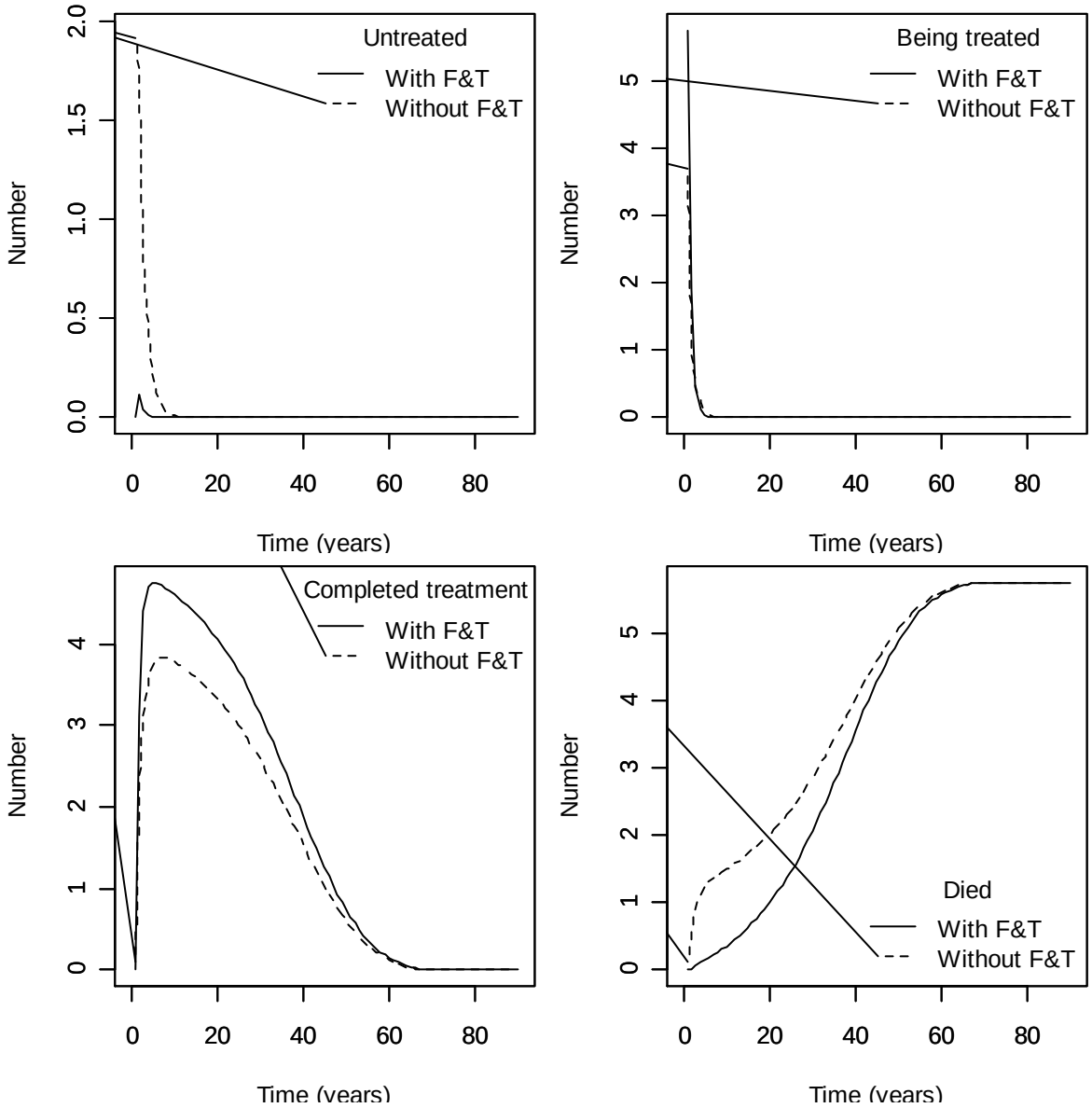
Different health states over time for the cases detected by the mobile screening unit in a single year that have had active tuberculosis symptoms for at most 131 days before being screened.



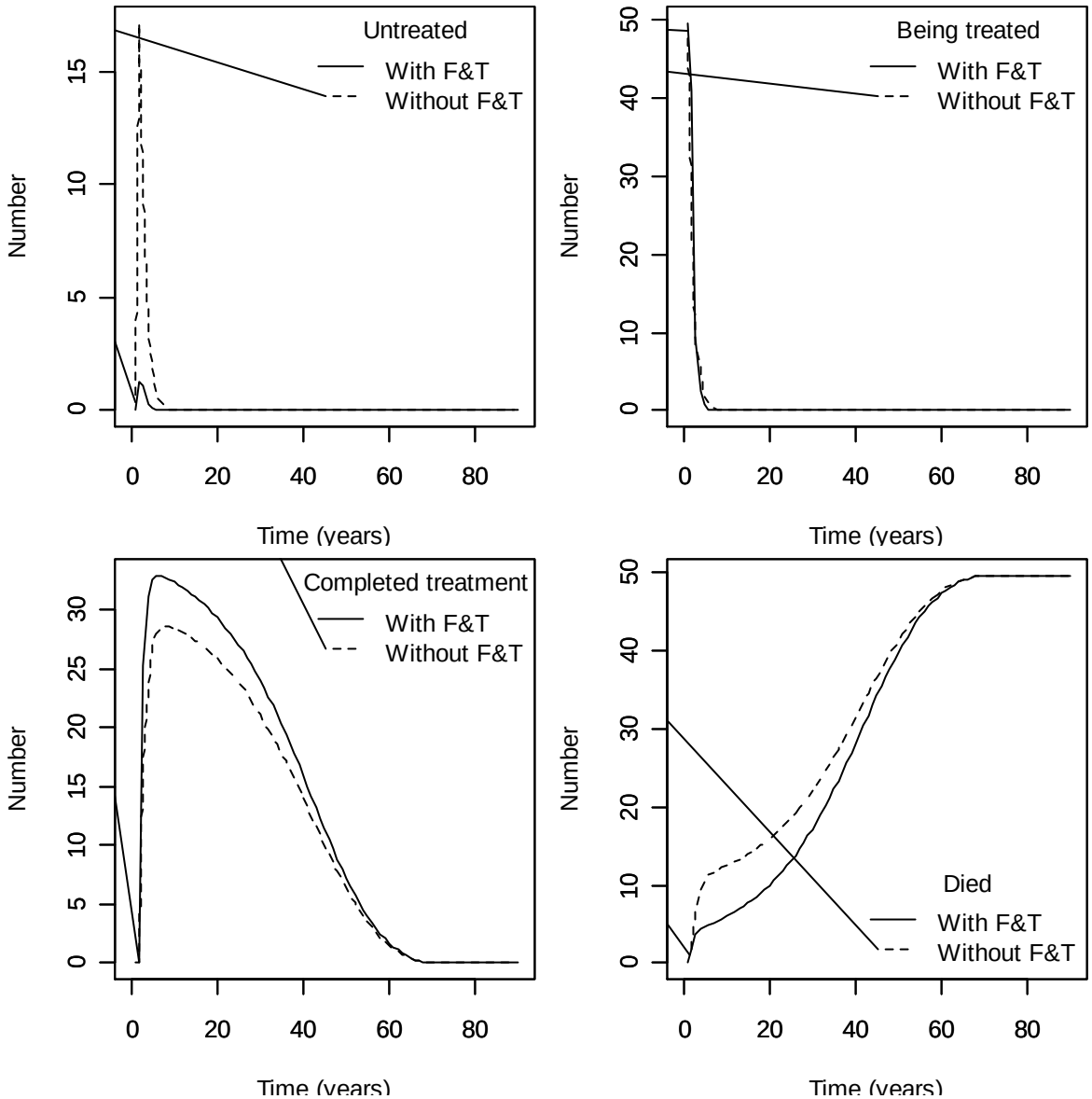
Different health states over time for the cases detected by the mobile screening unit in a single year that have had active tuberculosis symptoms for more than 131 days before being screened (and hence were assumed to be undetected by passive case finding).


Untreated
With F&T
Without F&T
Being treated
With F&T
Without F&T
Completed treatment
With F&T
Without F&T
Died
With F&T
Without F&T
Number
Time (years)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
20
40
60
80

Different health states over time for the cases detected by the mobile screening unit in a single year that did not have symptoms on detection.



Different health states over time for the cases in a single year with complex issues managed by Find and Treat.



Different health states over time for the cases in a single year who were referred for loss to follow up and subsequently found by Find and Treat.