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Identification of multidrug resistance in previously treated tuberculosis patients: a mixed methods study in Cambodia

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SUMMARY

Setting—Previously treated tuberculosis (TB) patients are a priority for drug susceptibility testing (DST) to identify cases with multidrug resistance (MDR). In Cambodia, a recent study found that only one-third of smear-positive previously treated patients had DST results.

Objective—To quantify the gaps in detecting MDR in previously treated TB patients in Cambodia, and describe health workers' perspectives on barriers, facilitators and potential interventions.

Design—We analyzed case notifications in Cambodia (2004–2012) and conducted semi-structured interviews with key stakeholders

Results—The proportion of previously treated notifications varied significantly across provinces 2010–12, in the context of longer term trends of decreasing relapse and increasing "other" retreatment notifications. Correct classification of patients' TB treatment history and ensuring specimens from previously-treated patients are collected and reach the laboratory could nearly double the number of detected MDR-TB cases. Identified barriers include patients' reluctance to disclose and staff difficulty eliciting treatment history, partly due to availability of streptomycin only in hospitals. Facilitators include trained health workers, collection of sputum for DST even if previously treated patients are not taking streptomycin, streamlining sputum transportation and promptly reporting results.

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Conclusion—Improved monitoring, supportive supervision, and correctly classifying previously treated patients are essential for improving detection of MDR-TB.

Keywords

MDR-TB case finding; diagnostic pathway; testing coverage; qualitative methods; stakeholder engagement; implementation science

Less than one in five of the world's multidrug-resistant tuberculosis (MDR-TB) cases was estimated to have been diagnosed and reported to health authorities in 2012.{{600 World Health Organization 2012;}} Incomplete coverage of drug susceptibility testing (DST) is a major contributor to this gap, and strategies to expand testing are a global priority.{{436 World Health Organization 2011;}} When drug resistance is not detected, MDR-TB patients cannot access life-saving treatment; this puts their communities at risk of ongoing MDR-TB transmission.

In Cambodia, only one-third (74/218) of previously-treated patients – a priority group for MDR-TB case finding – notified in the second half of 2011 had DST results.{{622 Khann, S. 2013;}} Cambodia's guidelines recommend that previously-treated patients have sputum specimens tested by Xpert MTB/RIF (available in four provincial laboratories), followed by culture and species identification using liquid and solid media (available in three regional laboratories) and conventional DST at the national reference laboratory. If patients cannot travel to the laboratory, specimens may be collected in patients' homes or health centres by trained TB staff. Previously treated patients were defined as those who received one month or more of anti-TB drugs in the past.{{623 World Health Organization 2009;}} In Cambodia, patients classified as relapse or returning after treatment failure or loss to follow up are smear-positive, while "other" refers to retreatment patients who have smear-negative pulmonary or extrapulmonary disease.

The present study builds upon prior studies {{616 Chadha, S.S. 2011;615 Yagui, M. 2006;625 Noeske, J. 2012;626 Kilale, AM. 2013;}} to explore the perceptions of frontline health workers and program staff in order to better understand modifiable factors contributing to gaps in MDR-TB case finding among previously-treated patients. However, this is the first study of this kind conducted in Cambodia, and as such, it should be considered a pilot study. The objectives were to quantify the gaps in MDR-TB case finding, and elicit health workers' perspectives on barriers, facilitators, and potential interventions.

METHODS

We used a sequential explanatory mixed methods design.{{632 Pluye, P. 2014;}} The quantitative research estimates the magnitude of the gaps, which provides the context for which the project was initiated, since this gap was known but not quantified. The qualitative research then explores potential reasons why this gap exists, from stakeholder perspectives across the range of steps presented, and ideas on how to close the gaps.

For the quantitative research, we characterized the epidemiology of previously-treated patients in Cambodia in order to estimate the number of MDR-TB cases that could

potentially be found if there were no attrition along the steps to MDR diagnosis. We analyzed case notification data to determine the proportion of previously-treated patients and the reported reason for retreatment from 2004 (the first year previously treated patients were consistently categorized by all reasons for retreatment) through 2012.{{621 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2007–2013;}} http://www.who.int/tb/country/data/download/en/index.html accessed on 3/14/2013 Using the Z-test, we compared the difference between the national proportion and that of 14 provinces reporting >1000 TB cases annually from 2010–12. For the qualitative research, we conducted in-depth interviews to elicit health workers' views of barriers along each step of the path to MDR-TB diagnosis among previously-treated patients (Figure 1). We also identified and reviewed Ministry of Health guidelines, reports, reporting forms and registers.

To estimate the impact of attrition along the MDR-TB diagnosis pathway, we applied the results of two prior studies to the country's smear-positive, previously-treated patients notified in 2012.{{622 Khann, S. 2013; 620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011;}} Based on these studies, we assumed that 1) 11% of patients missed at each step had MDR-TB (prevalence of MDR-TB among previously-treated TB cases in 2006–2007 drug resistance survey, DRS);{{600 World Health Organization 2012;}} (not including 13% of smear positive, previously treated patient specimens received in the culture laboratory who would have nontuberculous mycobacteria){{622 Khann, S. 2013;}} 2) 80% of patients not correctly classified as previously treated or who did not undergo culture would have had culture recovery permitting DST,{{620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011;}} 3) 36% of smear positive patients registered as previously treated had specimens that were either not collected or did not reach the culture laboratory,{{622 Khann, S. 2013;}} 4) of the patients whose specimens were received in the culture laboratory, 45% were either culture negative or nontuberculous mycobacteria,{{622 Khann, S. 2013;}} and 5) correct classification could double the number of previously-treated patients registered among notified smear-positive cases. The last assumption is based on the finding that 8.7% of the smear positive cases in the country's 2006–7 DRS were previously treated (personal communication, Dr. Norio Yamada, Japan Anti-TB Association), compared to 4.4% among all reported smear positive cases in 2007 in the same districts as the DRS (Z-test, $p < 0.05$).{{620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011; 621 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2007–2013;}} The ratio of 8.7% ("expected" when WHO-recommended research methods are used) divided by 4.4% ("observed" in routine practice) is approximately 2 to 1.{{430 World Health Organization 2009;}}

While Cambodia guidelines and WHO recommend DST of all previously-treated patients regardless of smear status,{{623 World Health Organization 2009;}} this analysis is limited to smear-positive patients since the two available studies used this subset of previously treated patients.{{620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011; 622 Khann, S. 2013;}}

In April 2013, we held focus group discussions with members of the National MDR-TB Technical Working Group to: (1) identify and prioritize barriers and facilitators along the

pathway to MDR-TB diagnosis, (2) determine how to best conduct sites visits and interviews among diverse stakeholders in Cambodia and (3) determine target areas for further investigation and intervention. Based on the group's recommendations, we then conducted semi-structured interviews of national TB programme staff and partner organizations, as well as with provincial and local TB staff. It was not feasible to conduct field observations, due to resource limitations. Among the ten provinces with the largest number of reported cases, we selected one province that tested a high proportion of previously-treated patients, and another province that tested a low proportion, along with the capital province.{{622 Khann, S. 2013;}} Based on recommendations by the working group and on accessibility during the field visit, we interviewed staff at a high-performing district within the high-testing province, and a low-performing district within the low-testing province.

We interviewed 26 individuals (28% women), including doctors or clinical officers (9), nurses (8), laboratory staff (6), and TB officers (3) working at the following levels/settings: national (5, Ministry of Health and 6, partner organizations), provincial (3), district (2), referral hospital (6), and health centres (4). Participants had a mean age of 44 years (range 30–55), and an average of 13 years of TB program experience (range 3–27). All invited staff provided written informed consent. The thirty- to ninety-minute interviews used open-ended questions[1] to focus on factors that could facilitate or hamper efforts at each step in the path to detecting MDR in previously-treated patients (Figure 1). The interview guide also elicited individual, clinic and system factors, such as knowledge, attitudes, and other predisposing factors, as well as individual staff perspectives on the priorities for intervention.{{617 Green, LW. 2005;}} The questions were pilot tested and revised. Interviews were conducted and audio-recorded in English or Khmer in a private setting in the participant's worksite by one of the investigators, none of whom was a supervisor of any interviewee. Participants received a gift worth approximately 5 USD. A bilingual translator transcribed the audiotapes and translated the Khmer interviews to English. Participants did not review the transcripts of their interviews. One investigator (SR) redacted personally-identifying information. The study was approved by the Cambodian National Ethics Committee for Health Research and the University of California, San Francisco Committee on Human Research.

We used qualitative data analysis methods{{631 Sandelowski, M. 2012; 628 Strauss, A. 1998; 630 Voils, C. 2008;}} in which general topic area prompts orient the qualitative data descriptively.{{634 Handley 2013;}} Within the broad topic areas, participants were queried on how the identified barriers could potentially be overcome. A thematic survey approach was used to describe the data without transforming it significantly.{{631 Sandelowski 2012;}}. Two of the authors (Royce and Handley) independently reviewed the data by using inductive reasoning, reading transcripts, and detecting patterns and regularities, such as the consistency of barriers and themes across the job titles and roles. These themes were then discussed in analysis meetings to reach agreement on the primary themes. Because the queries were specific to the barriers at each step, data saturation on the barriers was reached with a smaller number of interviews, than if the questions had been broader across the entire

[1]Interview guide available upon request to corresponding author.

range of TB diagnosis and care delivery. Lastly, themes that had tangible implications for systems improvements were selected.

RESULTS

Quantitative findings

Epidemiology of previously treated patients—While Cambodia's new TB case notifications rose from 30,193 in 2004 to 38,367 in 2012, the proportion of previously treated patients among all notifications has remained approximately 4%. However, the main reasons for retreatment have changed. From 2004 to 2012, the number of "other" retreatment case notifications increased more than five fold from 197 to 1102 (or 68% of the 1621 total previously treated notifications in 2012). During the same time period, the number of relapse notifications decreased from 645 to 446 (or 28% of all previously treated notifications in 2012). In 2012, the 51 patients returning after treatment failure and the 22 returning after being lost to follow-up represented little change from 2004. In the most recent three years, retreatment notifications have fluctuated between 1036 to 1102 "other" retreatment cases, 367 to 466 relapses, 49 to 59 patients whose treatment had failed, and 19 to 30 patients returning after being lost to follow up.

We explored variation across provinces in notifying previously treated cases in 2010–2012 (Figure 2). Among the 14 Cambodian provinces reporting over 1000 total TB cases during 2010–2012,{{621 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2007–2013;}} reported previously treated patients as a proportion of all notifications varied significantly from the national average of 3.9% for 12 provinces (range 1–11%, Z-test < 0.05), as did smear-positive retreatment patients as a proportion of all notifications in 7 provinces (range 0.4–3.3%, Z test < 0.05). The 14 provinces had markedly different reasons for retreatment. Relapses as a proportion of all retreatment patients ranged from 9.0–71.7%, treatment failure from 0–9.4%, return after loss to follow up from 0–4.8%, and "other" from 28.3–91.0%.

Estimates of missed MDR-TB cases—We estimated that 75 additional MDR-TB cases could have been identified if there were no attrition along the path to detecting multidrug resistance among smear positive TB cases notified in 2012 (Figure 1). Forty-six of the 75 were lost at Step 1 due to misclassification of previously treated patients as "new." As described in the Methods section, this assumes that correct classification would double the number of previously treated notifications, that 80% of the cases misclassified as "new" would have had culture recovery permitting DST, and that 11% of *M. tuberculosis* isolates would be multidrug resistant. Ensuring specimens of notified previously treated patients are collected and transported to the culture laboratory (Steps 2,3) could lead to identification of approximately 16 more MDR-TB cases. Closing the gaps in Steps 1–3 would nearly double the number of MDR-TB cases that were reported in 2012; {{600 World Health Organization 2012;}} closing gaps in identifying and reporting *M. tuberculosis* (Step 4) would yield 12 MDR-TB cases, and detecting and reporting drug resistance (Step 5) could identify one additional MDR-TB case.

Qualitative findings

For each step in the pathway to detecting multidrug resistance in previously-treated TB patients, we present selected quotes that characterize the common themes expressed by various cadre of participants regarding barriers, facilitators, and proposed interventions.

Step 1. Identify and register as previously treated

Participants placed high priority on correct registration of TB patients' treatment history: *"The most important [step] is identifying the patient [as suspected to have MDR]. If the patient cannot be identified, we cannot do anything."* They cited many barriers to correct classification. For patients who live far from the hospital, the label of "retreatment" requires travel to the hospital to stay one night to provide sputum, then two months for daily streptomycin injections that are not available in the health centres. *"If we refer him to hospital again, he won't go…That old patient…doesn't even have a bike to ride…Because he didn't have the ability to go; not because …he didn't want to go. That is why health workers at some sites decided to put those patients in category 1 treatment [for new patients] …Mostly [health centre staff] know…about the importance of treatment by category. The formula of category 1 [for new patients] and category 2 [for retreatment patients] is hanging on the wall in every health centre."* Some participants noted that *"many patients hide their previous treatments…they are ashamed [of revealing that they interrupted treatment previously]." "If treated at [the national hospital] then [when they] return to village…[they] are afraid to tell others."*

Participants offered a number of solutions to misclassification. "*Health centre[s] should have formula 2 treatment…Because we…know which patients have been previously treated…If we ask them to stay at hospital, they would not go. Until they…[were so ill that] could not stand."* Other participants suggested providing adequate social protection using existing mechanisms like health equity funds[2] to enable TB patients to access care, since "*some patients are not only poor in money but poor in words too; they could not find help from other people*." In addition, patients could be allowed to be registered as previously-treated and have sputum collected for DST even if they are not taking streptomycin or have no documentation available (such as after treatment in the private sector). If a history of TB treatment is elicited after registration as a new case, they could be re-registered as previously treated and have sputum collected for DST. Now, *"even if we find the correct information… the staff does not want to change the classification. What will the [supervisor] think if he looks at my register and it is changed?"*

Participants also proposed training to improve skills and motivation of staff to help patients understand *"that hiding their medical history could make them not cure…and cause difficulty to their children."* Participants suggested that the training should focus on staff of health centres with smear microscopy (where patients start the diagnostic process), as well as community volunteers since these volunteers *"…know all stories. Where patients A and B have taken drugs; how many times those patients have been treated."*

[2]financing by the government and/or others such as development partners used to purchase health care and cover associated costs of illness

Step 2. Collection of quality sputum from all previously treated patients

Participants described the need for real-time, individual patient-level monitoring systems to ensure sputum is collected for MDR testing on every registered previously-treated patient. The current approaches of matching paper registries with culture centre log books each quarter were described as labour-intensive and too late to make a difference in patient care; the newly instituted MDR-TB suspect registers are time-consuming to complete and not kept up-to-date. Some health workers record on the TB Registry row for each previously-treated patient whether sputum was obtained or not, thus enabling them to track individual results. Other respondents described the need for electronic patient data management and laboratory information systems.

Even if specimens reach the laboratory, one interviewee estimated that half the specimens received in the laboratory are not of adequate quality: *"Sometimes, our lab cannot identify whether it [was] originally a good sample or not because when it comes, we saw that the quality is watery…"* Factors described as contributing to poor quality sputum specimens included insufficient instructions for patients and collecting sputum many days after retreatment initiation, by which time cough may be resolved (making it harder to collect a specimen and recover *M. tuberculosis*). Proposed interventions included improved supervision of sputum collection by trained health workers or laboratory technicians. If a checklist recorded quality of sputum at time of collection, supervisors could compare differences in specimen quality when collected by health centres versus hospitals and across different districts, and then focus attention on those collection sites needing improvement.

Step 3. Rapid transportation of specimens under appropriate conditions

Participants cited long delays due to many "handoffs" of specimens through different levels of health system and unintended consequences of health worker incentive payments: *"All is about money, if [health workers] receive incentive, then it's working…. the trouble is that… if one place does not get the money, it gets stuck. They are links in the chain. If one place does not motivate them to do, the others they just wait, wait, wait because the first or the second one does not pass the job to the next link."*

Health workers have to pay in advance from their own pockets to reimburse patient travel or to arrange for specimen transportation. Reimbursement is delayed until the provincial TB officer visits the capital city, provides original documents, and obtains the required signatures. *"People in the field… said 'Oh, never mind,' and just stop [collecting sputum for DST]."* Health workers introduce additional delays if they batch specimens (to lower transportation costs).

Proposed solutions include: *"simplify the supporting documents to make sure that the field people spend less time to do paper work and spend more time on doing technical work."* Participants also pointed to the need to increase adequate health worker salaries to decrease their reliance on incentive payments. The country's health equity fund could channel funds to health workers in a timely and secure manner to cover transportation costs.

It is difficult to arrange reliable transport; specimens carried by taxi may arrive liquefied or splashed after long delays and heat exposure. When health workers transport or pick up

specimens, they are pulled away from their technical work: *"the…taxi driver… said [on phone]: 'Hello, we have something from province… Now could you come and get this?' I mean…lab staff they have to go to the taxi station."*

Interventions suggested to optimize specimen referral systems included establishing a unified health courier service for all programs, use of community volunteers, and using transport systems of other programs. Participants also proposed that the Ministry of Health collaborate with partners to spell out district-specific plans for how specimens will be transported or patients referred for sputum collection and how performance will be monitored and improved.

Steps 4 and 5. Identify and report *M. tuberculosis*, detect and report drug resistance

As reasons for non-growth in culture of smear-positive specimens, participants cited the impact of poor quality specimens or collection after treatment initiation (from Step 2), long transport times without temperature control (from Step 3), as well as not applying criteria for rejection of inadequate sputum specimens and problems with internal laboratory processes.

Participants described serious problems with reporting results. "*[The laboratory] is only calling back for MDR-TB cases… not the culture negative or the culture positive [cases] without drug resistance…So no news might mean not done, or culture negative, or culture positive but not MDR. [Health workers] don't know… that feedback is missing*." Besides impeding patient care and the ability to assess MDR testing coverage, lack of feedback leads to staff losing trust and giving up on collecting sputum for DST.

Interviewees also described long delays in receiving results, since reporting relies on district staff to pick up hard copy results when they are dropping off specimens and then hand-carrying them to health centres. *"I am asked to go and get [paper copy], but I don't have time to get it."* The sender may wait months for results, only to find the specimen never arrived and a new one must be collected. Underutilization of newly implemented Xpert MTB/RIF testing also contributes to delays.

Suggested interventions to improve laboratory performance included: technical assistance from the supranational reference laboratory, training in sputum collection, packaging and transport procedures; and developing a specimen rejection policy to reduce laboratory testing of suboptimal quality specimens. Participants also suggested that Xpert, culture, and DST laboratories use mobile phones and email to report receipt of each specimen as well as results of culture, identification, and drug resistance.

Monitoring and supervision

Information was not routinely available to assess and prioritize MDR-TB case finding efforts, including frequency of MDR in each group of patients with suspected MDR (such as failure of treatment, relapse, return after loss-to-follow-up, or "other" retreatment).{{623 World Health Organization 2009;}} *"Identify which places do well, otherwise it's a blur. If [we can identify which area or facility has] bad performance, [we] can improve it. If [we] don't start with this, it's bad always."*

Incomplete monitoring of new patients during treatment (and poor quality follow-up smear microscopy) may miss patients whose sputum smear does not convert to negative, who are not clinically improving, or whose treatment is failing. *"They do not want to report the case as a failure…so they just report cure…[When] your boss learns that you fail to treat the patients, the first they do is scolding…"* There is also incomplete monitoring of previously treated patients. Cambodia reported to the WHO that 10% of the 2011 cohort of retreatment patients had no outcome evaluated, and that the retreatment cohort comprised only 28% of all previously treated notifications.{{600 World Health Organization 2012;}} National TB publications{{621 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2007–2013;}} do not report on treatment outcomes for previously treated patients.

Improved monitoring data would allow better targeting of MDR-TB case finding efforts: "*[We] have to classify areas around the country into the spot that we need to focus first… After we clean these [hot spots of many undetected MDR-TB cases]…then probably we can divide our team into the not very hot spots."* Other proposed interventions were to use simple indicators for MDR-TB case finding, providing sufficient funding for supervisory visits, ensuring supervision is supportive and documented in supervisory reports, and including MDR-TB case finding performance in the country's internal program reviews conducted by peers.

DISCUSSION

This pilot study estimates that the largest gap in MDR-TB case finding among previously-treated patients in Cambodia is correct identification and recording of treatment history (Step 1 in Figure 1). The significant variation in the proportion of previously treated patients (and reasons for retreatment) across provinces supports the possibility of clinic staff not consistently using the case definition of previously treated when evaluating patients, and thereby misclassifying some patients as "new."

The use of streptomycin (requiring injections) and its availability only in hospitals were cited as key barriers to correct classification of patients' treatment history by interviewees. This barrier is especially problematic given lack of proven benefit of this regimen,{{624 Menzies, D. 2009;}} the 5% prevalence of streptomycin resistance in non-MDR retreatment patients in Cambodia,{{620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011;}} and the promise of rapid molecular tests detecting rifampicin and isoniazid resistance to obviate the need for an empiric retreatment regimen. {{623 World Health Organization 2009;}} Correct classification of patients' TB treatment history along with ensuring specimens from previously-treated patients are both collected and reach the laboratory could nearly double the number of detected MDR-TB cases.{{600 World Health Organization 2012;}}

Beyond streptomycin policies, participants identified additional underlying administrative barriers.{{617 Green, LW. 2005;}} Health workers across job titles and settings cited inadequate feedback on whether specimens are collected and received in the laboratory, and the lack of systems to rapidly report culture and DST results. This impairs clinical decision-

making, and without feedback, there is little reinforcement for collecting sputum for DST. At the individual level, incomplete monitoring misses patients whose treatment may be failing; of greatest concern are patients whose retreatment regimens are failing since they are at very high risk of MDR.{{623 World Health Organization 2009;}} At the health system level, lack of a robust monitoring system impedes the evaluation, prioritization, and improvement of MDR-TB case detection efforts. To address these challenges, participants in this study identified facilitating factors including training, supportive supervision, systematizing sputum transportation and reporting of results, and use of simple MDR-TB case finding indicators.

This study is subject to several limitations. The small number of health workers interviewed in a few provinces may not have enabled us to elicit the full range of views of all the key players in MDR-TB case finding in Cambodia. Further studies are warranted with a larger group of participants from more provinces (including field observations) to provide a more complete assessment and help determine whether this initial sample was subject to reporting biases related to the location of the study. However, we found that participant responses were not limited to socially desirable responses; instead, many spoke frankly about how the fear of supervisor reprisal impedes finding cases of MDR-TB. While health workers provided insights into patient factors, these should be explored in a subsequent study where patients and their families are asked directly about their experiences. Since Figure 1 is based only on smear positive previously treated patients, we have probably underestimated the number of missed MDR-TB cases. To further refine these estimates, further investigation is needed to characterize “other” retreatment patients, their prevalence of MDR, and why some provinces reported no patients whose treatment had failed or who were returning after being lost to follow-up. Finally, the estimates of MDR testing coverage in 2012 are based on the 2006 DRS and a 2011 study, each of which evaluated a sample of the nation’s smear-positive retreatment patients;{{620 National Center for TB and Leprosy Control (CENAT), Ministry of Health, Cambodia 2011; 622 Khann, S. 2013;}} they may not be generalizable to all previously-treated patients nationwide in 2012. However, all are based on cases that are notified to the TB program and thus are potentially reachable for DST.

Resolving the barriers to identifying priority patients, collecting quality specimens, rapidly transporting them to the laboratory, and promptly reporting results are essential for improving testing coverage of any group, and for maximizing the potential of new TB diagnostic technologies.{{615 Yagui, M. 2006;}}

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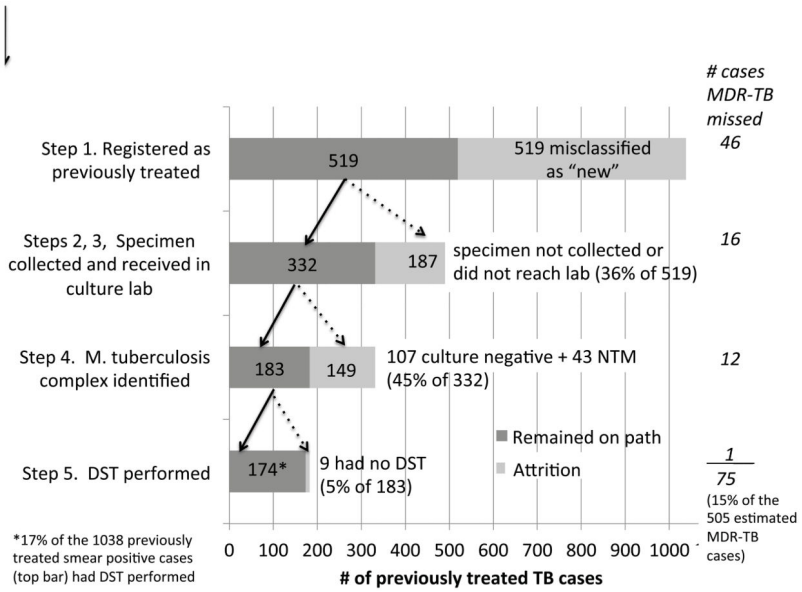

Figure 1.

Missed MDR-TB cases due to attrition along the path to detecting multidrug resistance in previously treated patients among smear positive notifications, Cambodia, 2012

The dark grey segment of each bar shows the number of previously treated smear positive patients the program successfully kept on the path to detecting multidrug resistance, while the light gray segments show the attrition. According to the following assumptions (see Methods section), an estimated 75 MDR-TB cases could be found if there were no attrition:

- Step 1: correct classification could double the number of previously-treated patients registered among notified smear-positive cases.
- Steps 1–3: 80% of patients would have had culture recovery permitting DST[10]
- Steps 1–5: 11% of patients missed at each step would have MDR-TB (prevalence of MDR-TB among previously-treated TB cases in 2006–2007 Drug Resistance Survey),[10] not including the 43 patients in light gray bar of Step 4 who would have NTM.[3] (Two components of attrition in Step 4 do not sum to 149 due to rounding)

Abbreviations: drug susceptibility testing (DST); *Mycobacterium (M.);* multidrug resistant-tuberculosis (MDR-TB); nontuberculous mycobacteria (NTM).

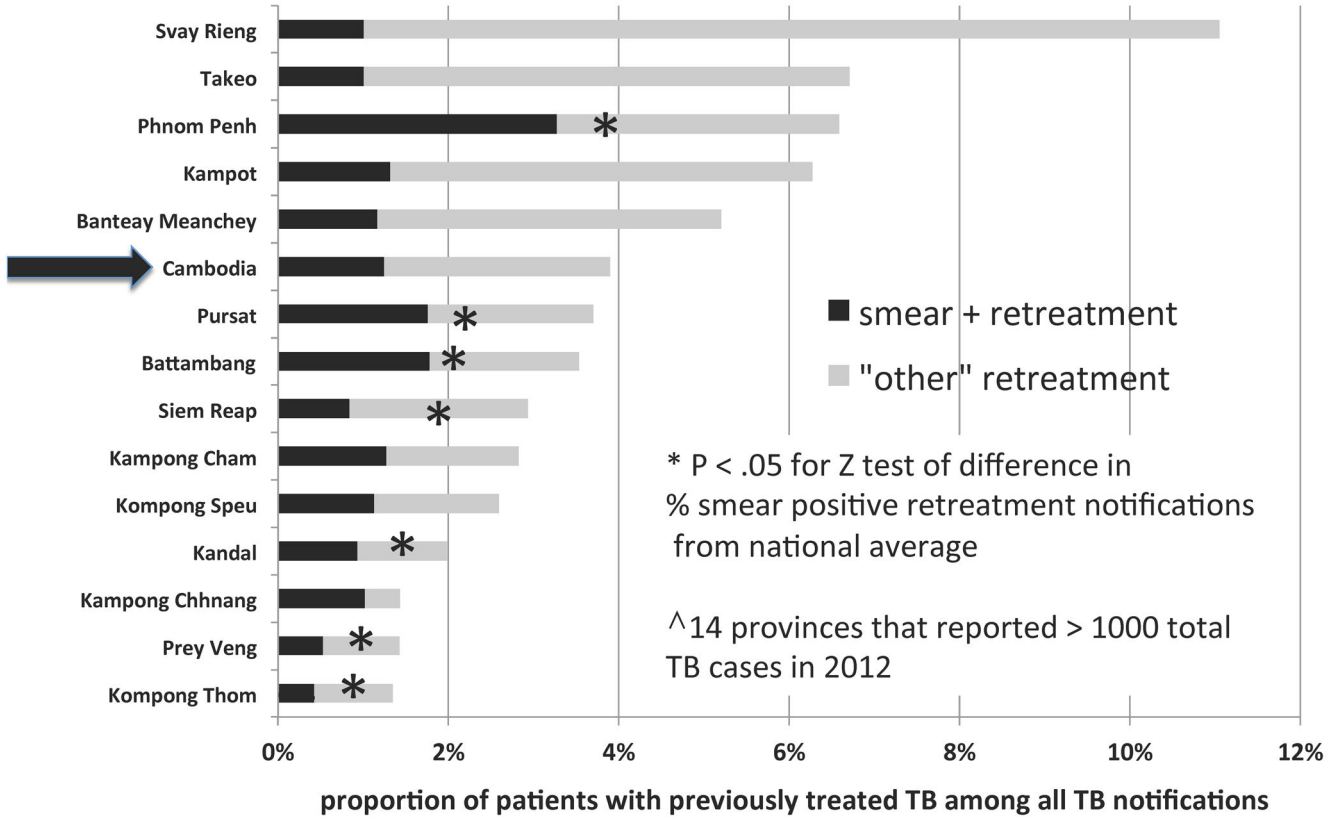

Fig 2.

Reported smear positive and "other" previously treated patients as a proportion of all TB notifications, 14 provinces, ^ Cambodia, 2010–2012