World Health Organization

Same-day diagnosis of tuberculosis by microscopy

Policy statement

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Abbreviations

CI	confidence interval
GRADE	grades of recommendation assessment, development and evaluation
LED	light-emitting diode
STAG-TB	Strategic and Technical Advisory Group for Tuberculosis
TB	tuberculosis
WHO	World Health Organization

Executive summary

Direct sputum smear microscopy is the most widely used means for the diagnosis of pulmonary tuberculosis (TB) and is available in most primary health-care laboratories at health-centre level. Smear microscopy may, however, be costly and inconvenient for patients, who have to make multiple visits to health facilities to submit multiple sputum specimens over several days. A number of TB control programmes have found high rates of initial patient default as a result, with high mortality recorded in several resource-limited settings.

It has been shown conclusively that good quality microscopy of two consecutive sputum specimens identifies the vast majority (95–98%) of smear-positive TB patients. Conventional case-finding approaches usually involve microscopic examination of 'spot-morning' sputum specimens (in countries with a two-specimen system) or examination of 'spot-morning-spot' sputa (in those with a three-specimen approach). The majority of sputum results are therefore available only on the second or third day after the patient presents to a health service.

In 2009, the strength of the evidence for a 'same-day diagnosis' approach (microscopy of two consecutive sputum specimens on the same day) was assessed by the World Health Organization (WHO), following standards appropriate for evaluating both the accuracy and the effect of new interventions on patients and public health. It was found that there was sufficient generalizable evidence that a same-day diagnosis approach is equivalent, in terms of diagnostic accuracy, to conventional microscopy case-finding strategies. Neveretheless, significant organizational and programme changes would be required to optimize the advantages of same-day diagnosis, to ensure that laboratory results are received back at the health facility and that patients start treatment on the same day. In addition, there is currently no evidence that early diagnosis of TB results in better uptake of treatment or improved treatment outcomes, so that programmes must closely monitor the effect of revised case-finding strategies.

On the basis of these findings, WHO recommends that countries that have successfully implemented current WHO policy for a two-specimen case-finding strategy consider switching to same-day diagnosis, especially in settings where patients are likely to default from the diagnostic process. Countries that are still using the three-specimen case-finding strategy should consider a gradual change to same-day diagnosis, once WHO-recommended external microscopy quality assurance systems are in place and good-quality microscopy results have been documented. It is essential that programmatic, logistic and operational implications at country level be taken into account in implementation of same-day diagnosis.

Policy statement

Same-day diagnosis of tuberculosis by microscopy

1. Background

Direct sputum smear microscopy is the most widely used means for diagnosing pulmonary TB and is available in most primary health-care laboratories at health-centre level. Smear microscopy may, however, be costly and inconvenient for patients, who have to make multiple visits to health facilities to submit multiple sputum specimens over several days. A number of TB control programmes have found high rates of initial patient default as a result, with high mortality recorded in several resource-limited settings.

It has been shown conclusively that good-quality microscopy of two consecutive sputum specimens identifies the vast majority (95–98%) of smear-positive TB patients. WHO policy on case detection by microscopy was therefore revised in 2007 (*1*) to recommend a reduction in the number of specimens examined, from three to two in settings with appropriate external quality assurance and documented good-quality microscopy. The case definition was also revised for these settings (*1*), to one positive smear, defined as one or more acid-fast bacillus in at least 100 microscopic fields. This approach greatly reduces the workload of laboratories, a considerable advantage in countries with a high proportion of smear-negative TB patients due to HIV and/or extrapulmonary disease.

Conventional case-finding approaches usually involve microscopic examination of 'spot-morning' sputum specimens (in countries with a two-specimen system) or examination of 'spot-morning-spot' sputa (in those with a three-specimen approach). Most sputum results are therefore available only on the second or third day after a patient presents to a health service.

Recent research has addressed the diagnostic accuracy of conventional case-finding strategies in comparison with an approach in which two consecutive sputum specimens ('spot-spot') are examined on the same day (so-called 'front-loaded' or 'same-day') and whether patient drop-out from the diagnostic pathway can be reduced as a result.

2. Evidence for policy formulation

2.1 Synthesis of evidence

In September 2009, WHO assessed the evidence for a 'same-day' diagnostic approach in a systematic, structured way. The first step was a systematic review and meta-analysis of published and unpublished data with standard methods appropriate for studies of diagnostic accuracy. The second step was the convening of an expert group to evaluate the strength of the evidence, recommend operational and logistical considerations for use of same-day diagnosis in national TB control programmes and identify gaps to be addressed by future research. The third step was presentation of draft recommendations to the WHO Strategic and Technical Advisory group for Tuberculosis (STAG-TB) for endorsement.

In accordance with current WHO standards for evidence assessment in the formulation of policy recommendations, the grades of recommendation assessment, development and evaluation (GRADE) system (*2*) was used by the Expert Group to assess the findings of the systematic reviews. This approach provides a systematic, structured framework for evaluating both the accuracy of new interventions and their impact on patients and public health.

The Expert Group's findings and the final GRADE evaluation (*1*) were presented to STAG-TB in November 2009. STAG-TB recognized that the evidence showed that examining two specimens in 1 day was equivalent, in terms of diagnostic accuracy, to existing case-finding strategies but acknowledged that significant organizational and programme changes would be required to optimize the advantages of same-day diagnosis (*3*). STAG-TB subsequently advised WHO to proceed with policy recommendations on same-day diagnosis and asked WHO to prepare an overarching policy framework to guide the use of new TB diagnostics, methods and approaches at country level (*3*).

This document provides a pragmatic summary of the evidence and recommendations for same-day diagnosis. It should be read in conjunction with the detailed findings of the Expert Group (which include the GRADE tables) and the WHO framework for using TB diagnostics (*1*).[1] The framework gives the context for use of one or more of the currently approved WHO diagnostic tools and methods in relation to country infrastructure, resources, TB epidemiology and TB policy reform.

The existing TB diagnostic tools are not mutually exclusive: they can be used in various combinations in country screening and diagnostic algorithms, which are highly setting- and resource-specific. Expert laboratory input is therefore needed to define the most cost-effective and efficient algorithms for individual countries, guided by WHO standards (e.g. for laboratory biosafety) and procedures and in the context of overall, integrated, laboratory strengthening.

2.2 Management of declarations of interest

Expert Group members were asked to submit completed declaration of interest forms, which were reviewed by the WHO secretariat before the Expert Group meeting. None of the members declared any conflict of interest. The declaration of interest statements were summarized by the co-chair of the Expert Group meeting at the start of the meeting. No additional declarations were made.

Selected individuals with intellectual or research involvement in same-day diagnosis were invited as observers to provide technical input and answer technical questions on the methods. These individuals did not participate in the GRADE evaluation and were asked to leave the meeting during the final discussions, when the recommendations were developed. They were also not involved in writing the final meeting report, nor in preparation of the STAG-TB documentation or the final WHO policy statements.

The process for evidence synthesis and policy development was reviewed by the WHO Guidelines Review Committee, and the policy recommendations were approved in June 2010.

The target date for review is 2015.

3. Summary of results

The results of seven studies involving 7308 patients were reviewed.

Same-day diagnosis ('spot-spot') versus the conventional strategy ('spot-morning'), with two specimens and direct Ziehl-Neelsen microscopy

Same-day diagnosis was on average 2.8% less sensitive than the conventional approach (95% confidence interval [CI], –5.2% – +0.3%), indicating that this strategy would be no more than 5% worse than the conventional approach. The specificity of the two approaches (with culture as the reference standard) was identical (98%; 95% CI, 97–99%).

As expected, spot specimens were more likely than morning specimens to give low-positivity results, indicating the need for strict internal quality control during smear preparation and meticulous examination of smears.

One large randomized controlled trial (6068 patients at four geographical sites) included data on patient loss to follow-up. Patients assigned to same-day diagnosis were more likely to submit both specimens (drop-out, 2%) than patients screened conventionally (drop-out, 5.8%).

Same-day diagnosis ('spot-spot morning') versus the conventional strategy ('spot-morning-spot') with three specimens and direct Ziehl-Neelsen microscopy

The 'spot-spot-morning' strategy was 3% more sensitive (71%; 95% CI, 65–77%) than the 'spot-morning-spot' approach (68%; 95% CI, 63–73%), although this difference was not statistically significant. The specificity (with culture as reference standard) was also similar, at 98% (95% CI, 96–99%) and 99% (95% CI, 97–99%), respectively.

In the same randomized controlled trial described above, patients assigned to the 'spot-spot-morning' approach were more likely to submit the third specimen (drop-out, 5.9%) than those assigned to the spot-morning-spot' strategy (drop-out, 6.7%).

Same-day diagnosis versus conventional strategies in HIV-infected patients

The above-mentioned randomized controlled trial included data on the performance of the two strategies in a subset of 586 HIV-infected patients. The study was underpowered for this sub-analysis, and the results should therefore be interpreted with caution.

Overall, HIV coinfection seemed to reduce the sensitivity of microscopy, independently of the approach used. In the three-specimen strategy, the sensitivity decreased from 81.3% for HIV-negative to 71.4% for HIV-positive patients screened with the 'spot-spot-morning' approach, and from 68.4% to 51.9% for those screened with the 'spot-morning-spot' strategy. These differences were not statistically significant.

In the two-specimen strategy, the sensitivity decreased from 76.7% for HIV-negative patients to 66.7% for HIV-positive patients screened with the 'spot-spot' approach, and from 68.4% to 50.0% for those screened with the 'spot-morning' approach. These differences were not statistically significant.

Same-day diagnosis versus conventional strategies with light-emitting diode fluorescence microscopy

The randomized controlled trial mentioned above compared light-emitting diode (LED) microscopy with conventional fluorescence microscopy in a subset of 2303 patients. The study was underpowered for this subanalysis, and the results should therefore be interpreted with caution.

Overall, LED microscopy performed as well as conventional fluorescence microscopy, irrespective of the case-finding approach. With the two-specimen strategy, the sensitivity of LED