World Health Organization

SAME-DAY-DIAGNOSIS OF TUBERCULOSIS BY MICROSCOPY

- POLICY STATEMENT -

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EXECUTIVE SUMMARY

Direct sputum smear microscopy is the most widely used test for the diagnosis of pulmonary tuberculosis (TB), available in most primary health care laboratories at health centre level. However, smear microscopy may have considerable patient costs and inconvenience associated with the need for multiple visits to health facilities to submit multiple sputum specimens over several days. A number of TB control programmes have reported high rates of initial patient default as a result, with high mortality in such patients 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 microscopy 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 only available on the second or third day that the patient presents to the health service.

In 2009, the strength of the evidence base for a 'same-day-diagnosis' approach (microscopy of two consecutive sputum specimens done on the same day) was assessed by the World Health Organization (WHO) following standards appropriate for evaluating both the accuracy and patient/public health impact of new interventions. The evidence showed that there was sufficient generalisable evidence that a same-day-diagnosis approach is equivalent, in terms of diagnostic accuracy, to conventional case-finding strategies by microscopy. However, significant organizational and programmatic changes would be required to optimize the advantages of a same-day diagnosis, ensuring 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 increased uptake of treatment or improved treatment outcomes, requiring that programmes closely monitor the impact of revised case-finding strategies.

Based on these findings, WHO recommends that countries that have successfully implemented current WHO policy for a two-specimen case-finding strategy consider a switch to the same-day-diagnosis approach, 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 the same-day-diagnosis approach, once WHO-recommended external microscopy quality assurance systems are in place and good quality microscopy results have been documented. It is essential that implementation of a same-day-diagnosis approach consider the programmatic, logistic and operational implications at country level.

POLICY STATEMENT

SAME-DAY-DIAGNOSIS OF TUBERCULOSIS BY MICROSCOPY

1. Background

Direct sputum smear microscopy is the most widely used test for the diagnosis of pulmonary tuberculosis (TB), available in most primary health care laboratories at health centre level. Smear microscopy may have considerable patient costs and inconvenience associated with the need to submit multiple sputum specimens over several days. A number of TB control programmes have reported high rates of initial patient default as a result, with high mortality in such patients 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 (http://www.who.int/tb/dots/laboratory/policy/eng), recommending a reduction in the number of specimens examined from three to two, in settings with appropriate external quality assurance and documented good quality of microscopy. The case definition was also revised for these settings (http://www.who.int/tb/dots/laboratory/policy/eng), to one positive smear, defined as one or more acid-fast bacillus in at least 100 microscopic fields. This approach greatly reduces the workload in laboratories, a considerable advantage in countries with a high proportion of smear-negative TB patients due to HIV and/or extra-pulmonary disease.

Conventional case-finding approaches usually involve microscopy 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 only available on the second or third day that the patient presents to the health service.

Recent research has investigated the diagnostic accuracy of conventional case-finding strategies compared to an approach where two consecutive sputum specimens ('spot-spot') are examined on the same day (so-called 'front-loaded' or 'same-day-diagnosis'), and also assessed whether patient drop-out from the diagnostic pathway can be reduced as a result.

2. Evidence base for policy formulation

2.1 Process

In September 2009, WHO assessed the evidence base for a 'same-day-diagnosis' approach through a systematic, structured process: The first step consisted of a systematic review and meta-analysis of available data (published and unpublished) using standard

methods appropriate for diagnostic accuracy studies. The second step involved the convening of an Expert Group to a) evaluate the strength of the evidence base; b) recommend operational and logistical considerations for implementing a same-day-diagnosis approach within national TB control programmes; and c) identify gaps to be addressed in future research.

In accordance with current WHO standards for evidence assessment in the formulation of policy recommendations, the GRADE system (http://www.gradeworkinggroup.org) was used to assess the findings of the Expert Group. The GRADE approach provides a systematic, structured framework for evaluating both the accuracy and the patient/public health impact of new interventions.

The Expert Group findings and the final GRADE evaluation are available at http://www.who.int/tb/dots/laboratory/policy and were presented to the WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) in November 2009. STAG-TB acknowledged existing evidence showing that examining two specimens in one day was equivalent, in terms of diagnostic accuracy, to existing case-finding strategies, but also acknowledged that significant organizational and programmatic changes would be required to optimize the advantages of a same-day diagnosis approach (http://www.who.int/tb/advisory_bodies/stag/en/index.html). STAG-TB subsequently advised WHO to proceed with policy guidance.

2.2 Summary of results

The results from seven studies involving 7,308 patients were reviewed.

2.2.1 Same-day-diagnosis ('spot-spot') vs the conventional strategy ('spot-morning'), using two specimens and direct ZN microscopy

Same-day-diagnosis was on average 2.8% less sensitive than the conventional approach (95CI -5.2% - +0.3%), also indicating that this strategy would be no more than 5% worse than the conventional approach. Specificity for the two approaches (using culture as reference standard) was identical (98%; 95CI 97% - 99%;).

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

One large randomised controlled trial (6,068 patients in four different geographical sites) reported data on patient loss to follow-up: Patients assigned to the same-day-diagnosis scheme were more likely to submit both specimens (drop-out 2%) than patients screened with the conventional scheme (drop-out 5.8%).

2.2.2 Same-day diagnosis ('spot-spot'morning' vs the conventional strategy ('spot-morning-spot') using three specimens and direct ZN microscopy

The 'spot-spot-morning' strategy showed 3% higher sensitivity (71%; 95CI 65% - 77%) than the 'spot-morning-spot' approach (68%; 95CI 83% - 73%), although this difference was not statistically significant. Specificity (using culture as reference standard) was also similar at 98% (95CI 96% - 99%) and 99% (95CI 97% - 99%) respectively.

In the same randomized controlled trial mentioned 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%).

2.2.3 Same-day diagnosis vs conventional strategies in HIV-infected patients

The abovementioned randomised controlled trial reported data on the performance of the two strategies in a subset of HIV-infected patients (n=586). The study was underpowered for this sub-analysis and results should therefore be interpreted with caution.

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

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

2.2.4 Same-day-diagnosis vs conventional strategies using LED fluorescent microscopy

The randomized controlled trial mentioned above compared LED microcopy to conventional fluorescent microscopy in a subset of patients (n=2,303). The study was underpowered for this sub-analysis and results should therefore be interpreted with caution.

Overall, LED microscopy performed equally well than conventional fluorescent microscopy irrespective of the case-finding approach: Using the two specimen strategy, sensitivity of LED microscopy (68%; 95CI 62% - 74%) did not differ significantly from that of conventional fluorescent microscopy (72%; 95CI 66% -77%). Specificity of LED microscopy (95%; 95CI 93% -96%) was also not statistically different when compared to conventional fluorescent microscopy (94%; 95CI 92% - 95%).

Using the three-specimen strategy, sensitivity of LED microscopy (75%; 95CI 69% - 80%) did not differ significantly from that of conventional fluorescent microscopy (74%;

95CI 6%8 - 79%). Specificity also did not differ, at 92% (95CI 91% - 94%) for LEB and 93% (95CI 91% - 94%) for conventional fluorescent microscopy.

2.2.5 Same-day-diagnosis using two smears from a single sputum specimen

Two studies carried out secondary analyses on the yield from two smears prepared from the same sputum specimen (n=1,849). Overall, the quality of evidence for both studies was rated as low and data were therefore excluded.

3. Policy recommendations

The GRADE process confirmed that there was sufficient generalisable evidence that a same-day-diagnosis approach (microscopy of two consecutive spot-spot sputum specimens) is equivalent, in terms of diagnostic accuracy, to conventional case-finding strategies by microscopy.

As stated in previous WHO policy guidance, the majority of patients with smear-positive TB is identified by examination of the first two sputum specimens. The proposed same-day-diagnosis approach provides the potential for initiation of anti-tuberculosis treatment on the same day, which would contribute to lowering of patient-related costs and conceivably reduce patient loss in the diagnostic pathway.

However, significant organizational and programmatic changes would be required to optimize the advantages of a same-day diagnosis, ensuring 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 increased uptake of treatment or improved treatment outcomes, requiring that programmes closely monitor the impact of revised case-finding strategies.

As with any new diagnostic approach/tool, current evidence arose from carefully conducted studies and replication of findings under routine, programmatic conditions will be heavily dependent on key health service and operational considerations.

WHO therefore recommends that:

- Countries that have successfully implemented the current WHO policy for a two-specimen case-finding strategy consider a switch to the same-day-diagnosis approach, especially in settings where patients are likely to default from the diagnostic process;

- Countries that are still using the three-specimen case-finding strategy consider a gradual change to the same-day-diagnosis approach, once WHO-recommended external microscopy quality assurance systems are in place and good quality microscopy results have been documented;

- Changes to a same-day-diagnosis strategy be preceded by a detailed situation assessment of the programmatic, logistic and operational implications at country level, and supported by a carefully phased implementation plan that considers the following programmatic issues:

  - Service providers should be able to initiate or refer patients for treatment on the same day of consultation. This will require training of health staff responsible for requesting sputum smear microscopy, instructing patients on sputum collection, and those responsible for registering patients and initiating treatment;

  - Laboratory operations and procedures should be realigned with sputum collection and reporting of results on the same day, within existing human resource and laboratory workload constraints. Particular attention must be given to internal quality control and external quality assurance of microscopy procedures;

  - Contact time between infectious patients and other vulnerable groups attending the same facility should be minimized, especially in settings with high HIV prevalence and/or drug-resistant TB burden. Separation and rapid triage of coughing patients is especially important to reduce the risk of TB transmission in health care settings;

  - Monitoring of patient drop-out between laboratory- and patient registers, and of trends in case detection and treatment outcomes are therefore essential.

WHO will assist countries with implementation of same-day-diagnosis by facilitating, with partners and technical agencies, a coordinated approach to revised case finding strategies at country level.

4. Target audience

This policy statement should be used to guide implementation of a same-day-diagnosis approach to TB case finding by microscopy within national TB control programmes, and is intended to be used by National TB Control Programme Managers and Laboratory Directors, in coordination with external programme consultants, donor agencies, technical advisors, health care and laboratory staff, other service providers, other relevant government officials, and individuals responsible for TB training activities.

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