Cost–benefit analysis of Xpert MTB/RIF for tuberculosis suspects in German hospitals

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ABSTRACT Our objective was to assess the cost–benefit of enhancing or replacing the conventional sputum smear with the real-time PCR Xpert MTB/RIF method in the inpatient diagnostic schema for tuberculosis (TB).

Recent data from published per-case cost studies for TB/multidrug-resistant (MDR)-TB and from comparative analyses of sputum microscopy, mycobacterial culture, Xpert MTB/RIF and drug susceptibility testing, performed at the German National Reference Center for Mycobacteria, were used. Potential cost savings of Xpert MTB/RIF, based on test accuracy and multiple cost drivers, were calculated for diagnosing TB/MDR-TB suspects from the hospital perspective.

Implementing Xpert MTB/RIF as an add-on in smear-positive and smear-negative TB suspects saves on average €48.72 and €503, respectively, per admitted patient as compared with the conventional approach. In smear-positive and smear-negative MDR-TB suspects, cost savings amount to €189.56 and €515.25 per person, respectively. Full replacement of microscopy by Xpert MTB/RIF saves €449.98. In probabilistic Monte-Carlo simulation, adding Xpert MTB/RIF is less costly in 46.4% and 76.2% of smear-positive TB and MDR-TB suspects, respectively, but 100% less expensive in all smear-negative suspects. Full replacement by Xpert MTB/RIF is also consistently cost-saving.

Using Xpert MTB/RIF as an add-on to and even as a replacement for sputum smear examination may significantly reduce expenditures in TB suspects.

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Introduction

Although tuberculosis (TB) incidence rates are steadily and globally in decline, multidrug-resistant (MDR)-TB, defined as simultaneous resistance to at least isoniazid and rifampicin (RIF), remains a major public health challenge in the World Health Organization (WHO) European region, where, in 2012, the prevalence of MDR-TB among 90 127 new TB cases was 15% [1]. This trend of increasing MDR-TB prevalence has important health economics implications: 1) it strengthens the long-established requirement of national guidelines that all patients admitted to healthcare facilities with suspected TB be maintained in costly respiratory isolation until it can be assumed that they are no longer contagious [2], and 2) it increases the need for emphasis to be placed on defining and speedily implementing case-appropriate treatment [3, 4].

Thus, the rapid diagnosis of TB disease and determination of drug resistance profiles is essential not only for early treatment and the associated prevention of TB transmission, but also highly relevant to the management of scarce economic resources, Since January 1, 2004, hospital costs in Germany have been based on the German Diagnosis Related Group (G-DRG) system, which assigns each TB case to one of two categories (E76B or E76C), depending on the severity of comorbidities. This imposes a fixed "base rate" of payment for 13 days treatment; if hospital treatment of >13 days is required (category E76A), the statutory health insurances pay locally negotiated daily rates. In most cases, these fall below the average daily reimbursement for the first 14 days. Accordingly, for TB patients under statutory health insurance, hospitals do well to keep the total number of patients treated high, but to keep the duration of their hospital stays as short as possible [5, 6].

The Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA) is a real-time PCR assay for simultaneous detection of *Mycobacterium tuberculosis* complex and of mutations in the *rpoB* gene that are associated with resistance to RIF as a proxy for MDR-TB from clinical samples. Results are obtained in 2 h [7]. After having recommended the use of Xpert MTB/RIF in December 2010, the WHO updated its guidance in October 2013, suggesting that the use of Xpert MTB/RIF to diagnose pulmonary TB, paediatric TB, extrapulmonary TB and RIF resistance [8] should be considered. Most recently, the US Food and Drug Administration suggested removing patients with suspected pulmonary TB from airborne infection isolation units after one or two negative Xpert MTB/RIF results. This guidance was based on an in-house clinical validation study that demonstrated negative predictive values (NPVs) of 99.7% for a single negative acid-fast bacilli (AFB) smear and 100% for two consecutive negative Xpert MTB/RIF results [9].

As data on the economic impact of implementing Xpert MTB/RIF in low-incidence countries are sparse, we undertook to assess the consequences of routine use of Xpert MTB/RIF with respect to confirmation or exclusion of TB disease and the timing of TB treatment in German TB wards. It is to this setting that the overwhelming majority (78.6%) of subsequently diagnosed TB cases are primarily admitted [10]. Our aim was to clarify the possible advantages of Xpert MTB/RIF, either performed at the hospital itself or in easy-to-reach local laboratories, as an add-on to conventional smear examinations or alternatively by replacing serial sputum smear microscopy with single-sample Xpert MTB/RIF examination. For our calculations, we used previously unpublished data of the German National Reference Center (NRC) for Mycobacteria in Borstel. Our model was parameterised to receive data on sensitivity, specificity, positive predictive value (PPV) and NPV of Xpert MTB/RIF testing, and to use sputum culture as the reference method. The data used were from untreated TB suspects whose sputa were sent to the NRC between January 1, 2012 and December 31, 2013.

At the NRC, Ziehl–Neelsen microscopy and Xpert MTB/RIF had been performed and one liquid culture (BACTEC MGIT 960; BD, Franklin Lakes, NJ, USA) as well as two solid cultures (Löwenstein–Jensen and Stonebrink TB Medium from NRC production) had been started on the same day. Stratified by smear status, the time (in days) until the first of the cultures became positive and until drug susceptibility testing (DST) results were available was assessed and compared with Xpert MTB/RIF results of the respective patients; negative cultures were uniformly read after 56 days. Culture results were considered as the "gold standard" to which Xpert MTB/RIF results were compared.

Material and methods

Ethical considerations

Ethical approval was not necessary as only fully anonymised secondary data were used.

Model approach

The economic analysis included the incremental costs of operating expenditures in diagnosing and treating pulmonary TB suspects for three different strategies. The perspective taken was that of the hospitals themselves, *i.e.* from admission through to patient discharge. Two Xpert MTB/RIF add-on algorithms and one Xpert MTB/RIF-only algorithm were studied. In the first Xpert MTB/RIF add-on algorithm, all sputum smear-positive individuals were tested with Xpert MTB/RIF on a single sputum specimen and in

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the Xpert MTB/RIF add-on algorithm only smear-negative TB suspects were tested with Xpert MTB/RIF. In the Xpert MTB/RIF-only algorithm, a single sputum specimen was collected for performing Xpert MTB/RIF, followed by a culture; microscopy was not performed.

As hospital costs of the add-on algorithms were calculated separately for each of the two patient groups, *i.e.* those thought to have fully susceptible TB and those suspected of having MDR-TB, five scenarios were considered (figures 1–5; refer also to online supplementary material).

Full descriptions of the various diagnostic and treatment assumptions of the model are provided in the online supplementary material.

Model structure

A deterministic, patient-based decision-analytic model was developed simulating the costs of the three approaches as described above for adult German TB and MDR-TB suspects based on German country-specific modalities. We used TreeAge software (TreeAge, Williamstown MA, USA) for model building and analysis. Univariate sensitivity analysis was performed using all variables (with some noted exceptions) to examine the extent to which our calculations were affected by varying selected assumptions. It also revealed the relative importance of the individual variables in each of the five different scenarios. Variation was done at random using either 1) the lower and upper bounds of a parameter's standard deviation or 2) those of its confidence interval. Where these were not applicable, our model simply caused parameter values to vary by ±20% according to international practice, unless otherwise stated. Furthermore, in order to capture the interactions between multiple inputs we provided a probabilistic sensitivity analysis (PSA) by assigning an appropriate statistical (probability) distribution for all parameters which were randomly drawn in a second-order Monte-Carlo simulation (n=1000). All costs are reported in 2013 Euros (€).

As a result of a lack of valid data, we have not included in our model the effects of transmission by TB or MDR-TB patients to co-patients or healthcare workers.

Input parameters are shown together with their probabilistic distributions in table 3.

Model input

Laboratory parameters

Laboratory results for Xpert MTB/RIF compared with sputum smears (NRC)

A total of 707 sputa from untreated TB suspects were investigated in the NRC in 2012/2013 with the Xpert MTB/RIF test. Prevalence of TB in that collective proved to be 19.66% (95% CI 16.91–22.94).

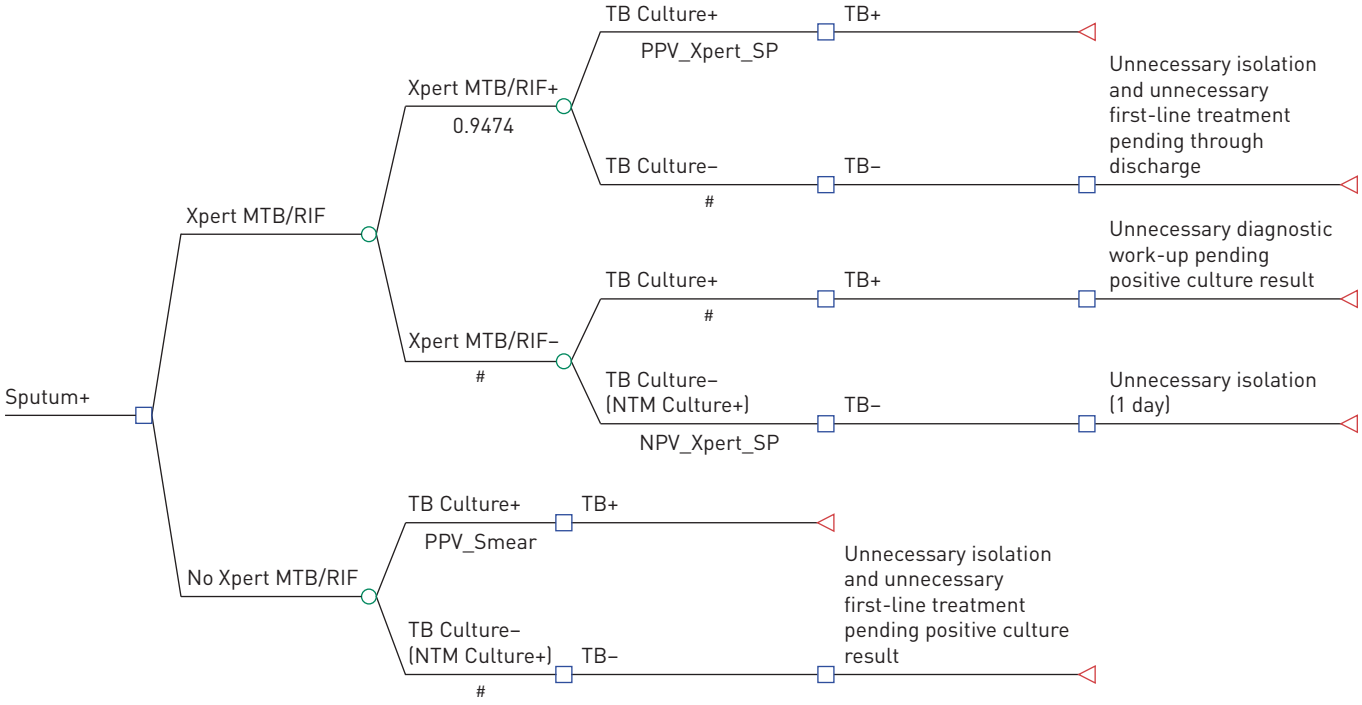

FIGURE 1 Xpert MTB/RIF replacing the sputum-based approach in tuberculosis (TB) suspects. NTM: nontuberculous mycobacteria.

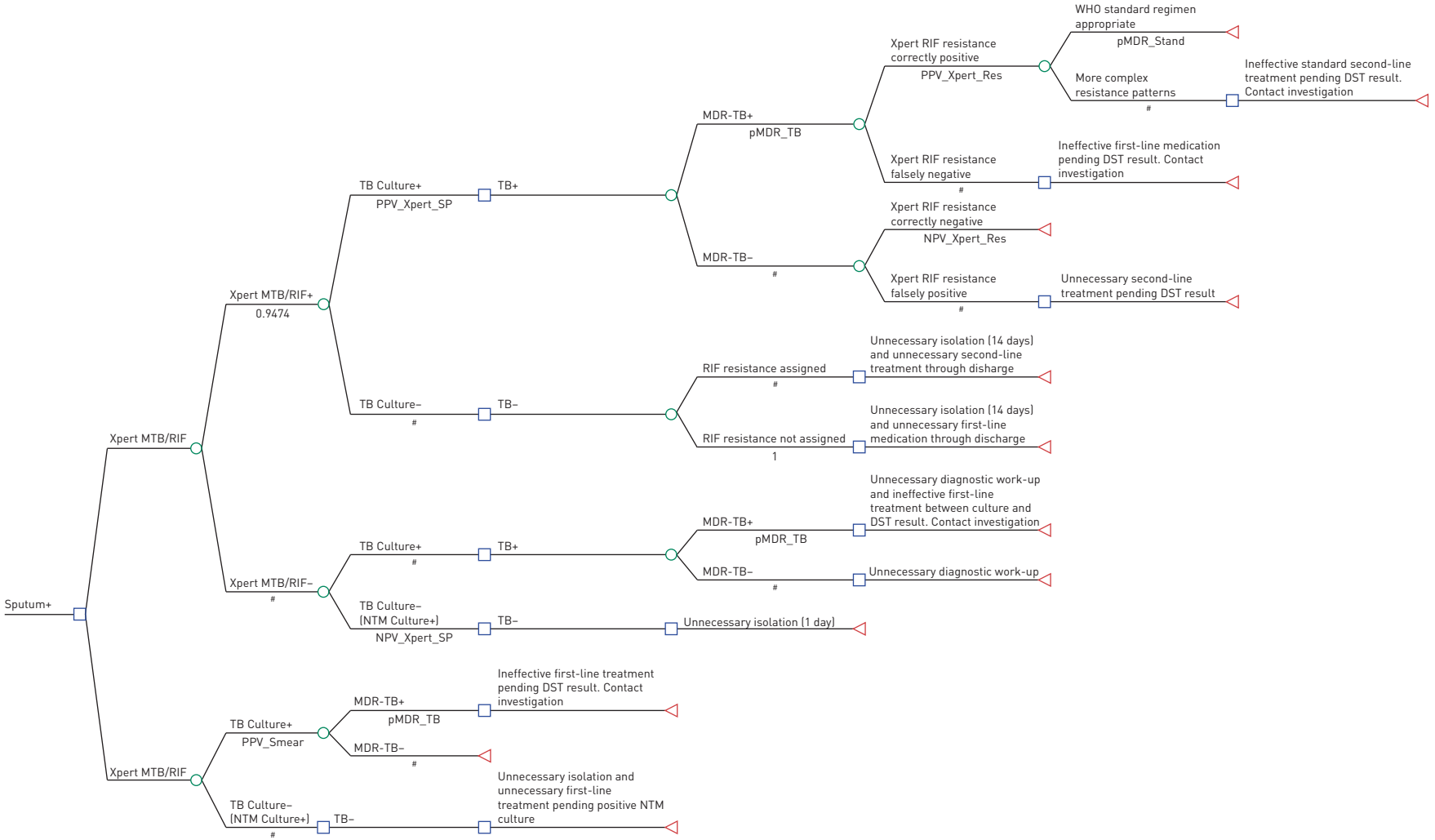

FIGURE 2 Xpert MTB/RIF *versus* the conventional approach in smear-positive multidrug-resistant tuberculosis (MDR-TB). NTM: nontuberculous mycobacteria; DST: drug susceptibility testing; RIF: rifampicin; WHO: World Health Organization.

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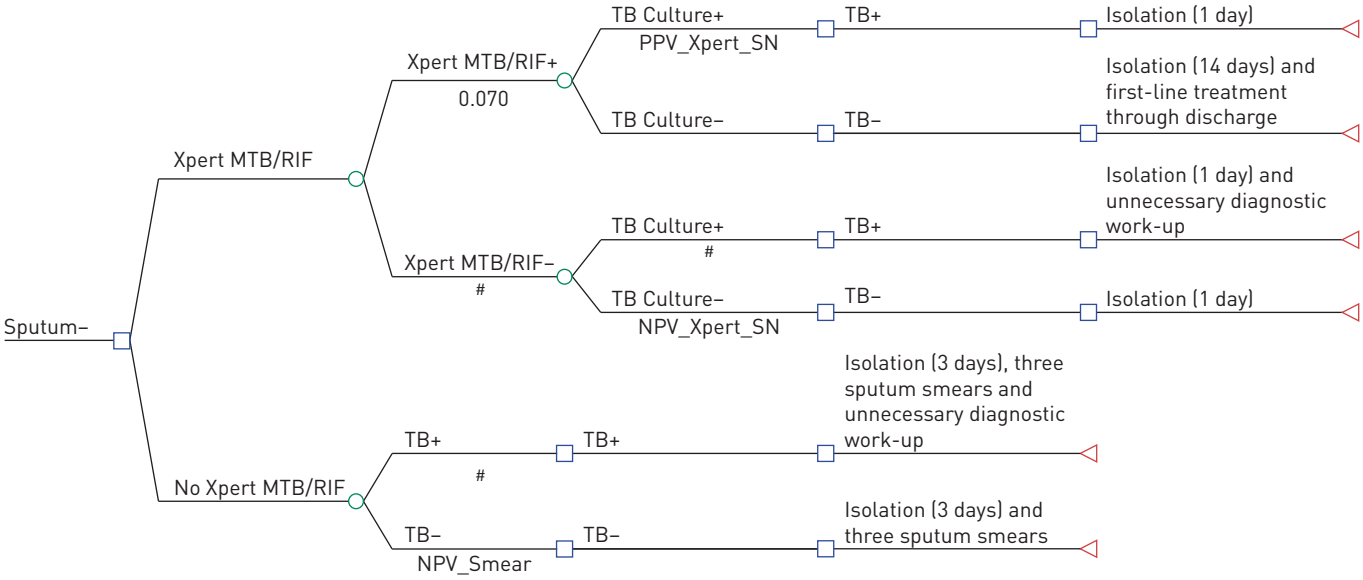

FIGURE 3 Xpert MTB/RIF *versus* the conventional approach in sputum-negative tuberculosis (TB) suspects.

95 specimens were smear-positive and 612 smear-negative compared with 133 specimens tested Xpert MTB/RIF-positive and 574 Xpert MTB/RIF-negative (table 1). Accuracy of microscopy and Xpert MTB/RIF compared with culture results were calculated as well as PPV and NPV, and directly transferred as probabilities into the model. Of note, in our study the overall sensitivity (90.65%; 95% CI 84.54–94.93) and specificity (98.77; 95% CI 97.48–99.50) of the Xpert MTB/RIF assay for the diagnosis of pulmonary TB was slightly higher than the pooled sensitivity of 88% (95% CI 83–92) and pooled specificity of 98% (95% CI 97–99) reported in a recent Cochrane meta-analysis [13].

Based on the NRC data, the time (mean±SD) to report positive cultures of *M. tuberculosis* among Xpert MTB/RIF-positives was 10.32±4.7 days (median 9 days, interquartile range (IQR) 7–11.75 days) for smear-positives and 13.17±5.15 days (median 13 days, IQR 9–17 days) for smear-negatives (table 2). The time required from sample acquisition to DST results was registered; the waiting period was 23.9±8.9 days (median 21 days, IQR 18–27 days) for smear-positives and 29.6±7.26 days (median 29 days, IQR 24.75–35 days) for smear-negatives.

In concurrence with the findings of Steingart *et al.* [13], Xpert MTB/RIF was able to correctly distinguish between TB and nontuberculous mycobacteria (NTM) in smear-positive samples.

Calculation of the PPV and NPV of the Xpert MTB/RIF RIF resistance test follows the following definitions: PPV=sen×pre/(sen×pre+(1−spe)×(1−pre)) and NPV=spe×(1−pre)/((1−sen)×pre+spe×(1−pre)), where sen=sensitivity, spe=specificity and pre=prevalence. According to a review by Weyer *et al.* [14], sensitivity and specificity of Xpert MTB/RIF for RIF resistance is 95% and 98%, respectively, using culture as the reference method.

Although we assume the same prevalence for MDR-TB in our collective of MDR-TB suspects as for fully susceptible TB in the base case, that estimate is varied between 0% and 30% in our sensitivity analysis.

Susceptibility of MDR-TB strains

The determination of RIF resistance alone is not sufficient information for the establishment of case-appropriate therapy. The WHO standard concept for MDR-TB is effective in many RIF-resistant cases and it may be credibly started based on RIF resistance determination. However, DST must be performed in parallel and the therapy reconsidered once the full resistance pattern is known. If a change in therapy proves necessary, expensive but inappropriate treatment produces extraordinary costs as do the days spent with ineffective second-line treatment. In a recently published German cost analysis including the resistance patterns of MDR-TB strains [11], most strains (51/55, 92.72%) were *in vitro* susceptible to at least four drugs of the WHO standard scheme. We use that estimate as the base case value (pMDR_Stand).

Economic parameters

The analysis includes the drug and laboratory costs as well as the opportunity costs arising from revenue losses for the hospital (table 3): according to US and German guidelines [2, 15], sputum smear-positive

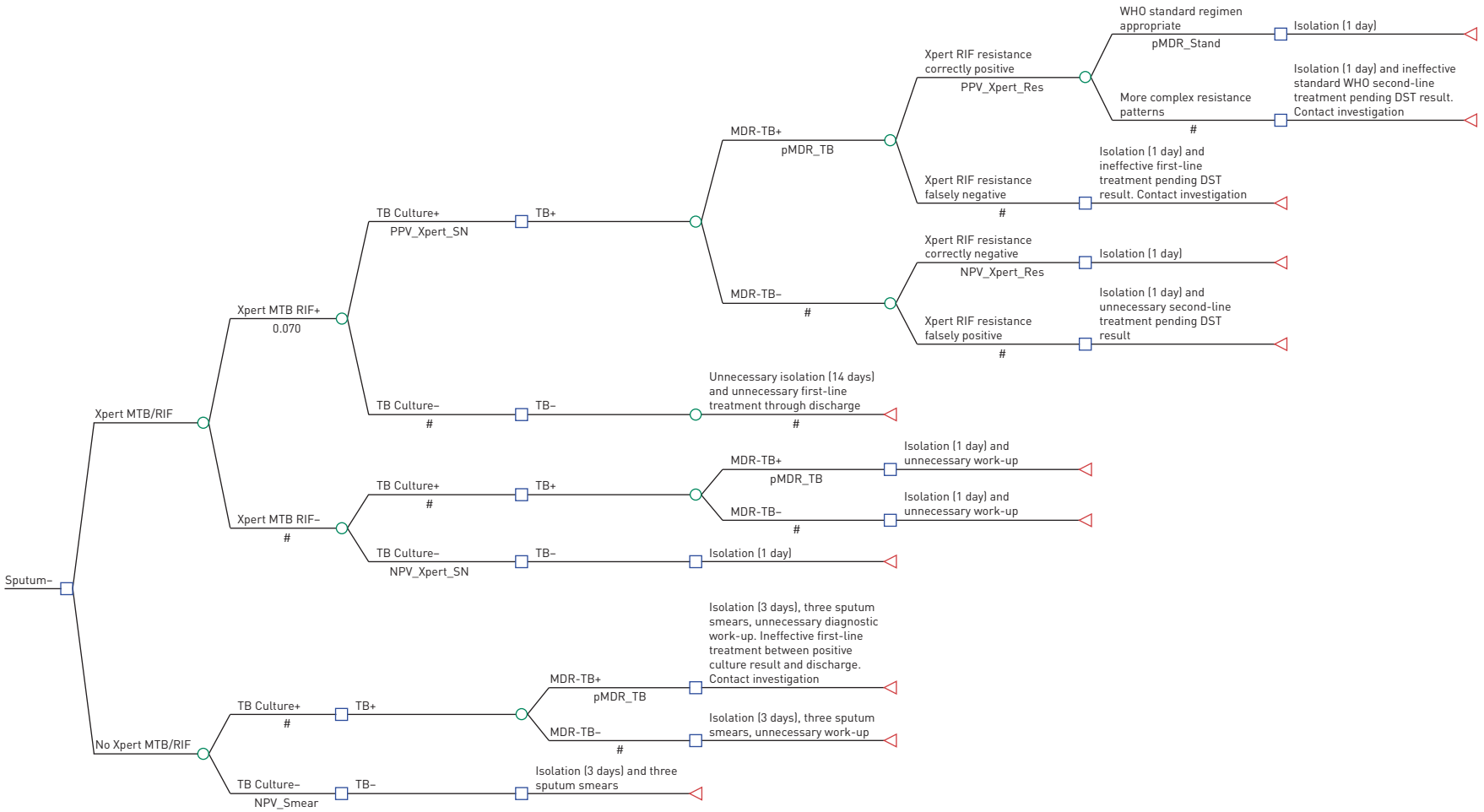

FIGURE 4 Xpert MTB/RIF *versus* the conventional approach in sputum-negative multidrug-resistant tuberculosis (MDR-TB) suspects. RIF: rifampicin; WHO: World Health Organization; DST: drug susceptibility testing.

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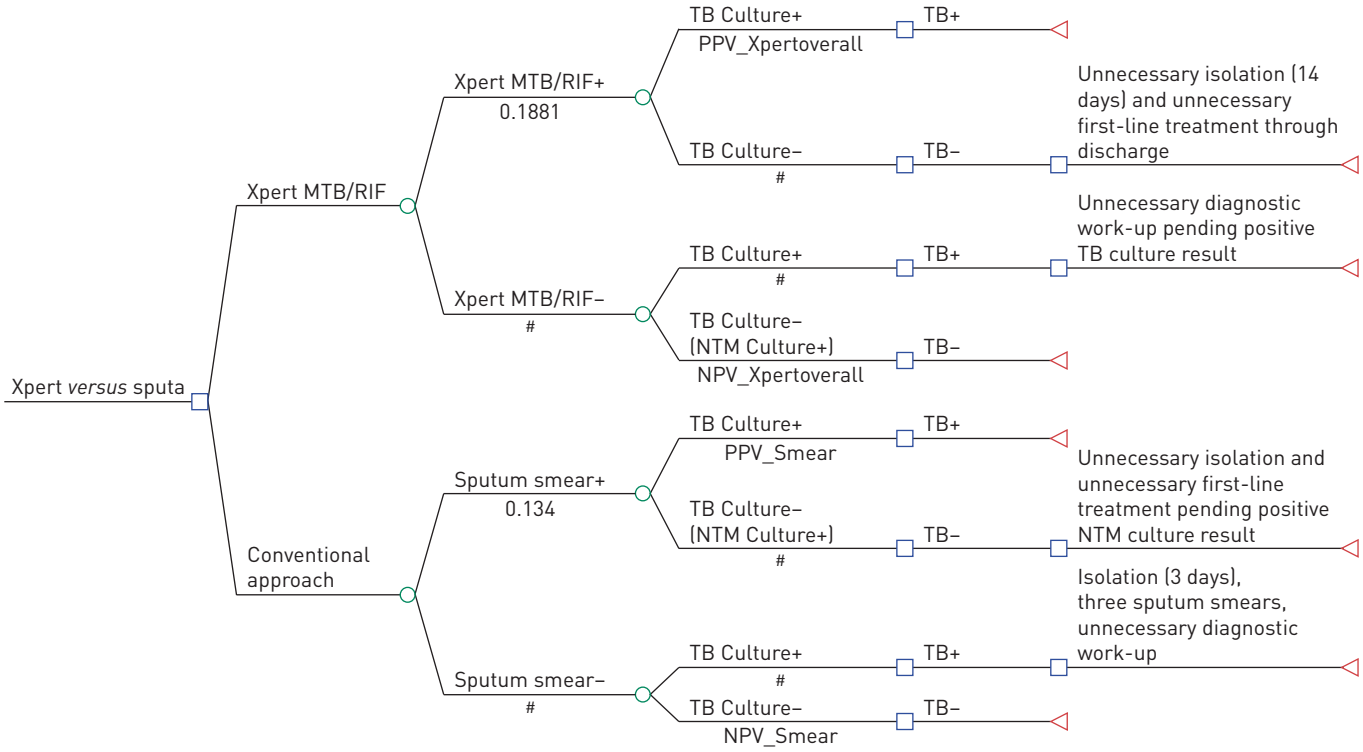

FIGURE 5 Xpert MTB/RIF *versus* the conventional approach in sputum-negative multidrug-resistant tuberculosis (MDR-TB) suspects. NTM: nontuberculous mycobacteria.

TB suspects must be isolated from the moment of admission through the first 14 days of treatment to counteract the nosocomial spread of TB, as must be smear-negative TB suspects until they have produced negative sputum samples on 3 subsequent days. Under the premise that most TB patients are accommodated in a twin-bedded room and that TB wards in Germany are working at full capacity, the loss of the use of one bed per day (cOpp) is incurred by the hospital during the isolation period.

The handling of smear-negative TB suspects or of those with a negative Xpert MTB/RIF result usually requires additional diagnostic work-up, the procedures and costs (cDcs) of which are presented in table 4.

In cases of unidentified MDR-TB, ineffective first-line treatment is administered either 1) following the conventional approach in the waiting period between positive TB culture and DST result or 2) in TB culture- and Xpert MTB/RIF-positives when no RIF resistance is assigned erroneously pending the DST result. Furthermore, ineffective second-line treatment is administered when the later DST result reveals more complex resistance patterns. Consequently, as in all of these cases when isolation is ended prematurely, intrahospital contact investigation must be performed (cContact). For full details and derivation of the cost parameters, see the online supplementary material.

Results

In base case analysis, performing Xpert MTB/RIF is cost-saving for every one of the five scenarios, when compared with the conventional procedure (sputum smear followed by culture), although to widely varying degrees (table 5).

Implementing Xpert MTB/RIF as an add-on in smear-positive TB suspects saves on average €48.72 per admitted patient. That this saving is relatively small is due to the fact that, according to our data, a positive TB culture result can be expected in as little as 10 days time; in non-TB smear-positives a NTM-positive culture result is also usually received. Thus, unnecessary isolation and unnecessary first-line treatment are promptly terminated. Potential cost savings strongly depend on the PPV of sputum smears and that of Xpert MTB/RIF as well as on the actual delay until the sputum culture result can be received. Univariate sensitivity analysis, in which all variables in the decision trees receive assigned values within their respective ranges, reveals that due to the low proportion of NTM (5.3%) in sputum smear-positives, even a minimal increase in the PPV of sputum smears (by 1.5% from 94.7% to 96.2%) or a minimal decrease in the PPV of the Xpert MTB/RIF (by 1.1% to 98.9%) results in a reversion of cost savings by utilising Xpert MTB/RIF as an add-on (online supplementary table S6a). The same is true if the waiting period for a positive culture result falls below a threshold of 7.5 days.

TABLE 1 Comparison of results by sputum smear culture on tuberculosis (TB) and real-time PCR Xpert MTB/RIF in a total of 707 patients in 2012/2013

Test and result	TB culture-positive	TB culture-negative	Sensitivity	Specificity	PPV	NPV
Sputum smear			64.75 (56.20–72.66)	99.12 (97.96–99.71)	94.74 (88.14–98.27)	91.99 (89.55–94.02)
Positive	90	5[#]				
Negative	49	563				
Xpert MTB/RIF						
Overall			90.65 (84.54–94.93)	98.77 (97.48–99.50)	94.74 (89.46–97.86)	97.74 (96.16–98.79)
Positive	126	7				
Negative	13	561				
Smear-positive			100.0 (95.98–100.00)	100.00 (87.66–100.00)	100.00 (95.98–100.0)	100.00 (47.82–100.00)
Positive	90	0				
Negative	0	5				
Smear-negative			73.47 (58.92–85.05)	98.76 (97.46–99.50)	83.72 (69.30–93.19)	97.72 (96.12–98.78)
Positive	36	7				
Negative	13	556				

Data are presented as n or % (95% CI). NPV: negative predictive value; PPV: positive predictive value. [#]: samples from patients suffering from nontuberculous mycobacterial disease.

An increase in the cost of Xpert MTB/RIF by 20% reduces the average cost saving to a small total amount of only €26.12 and a 20% lower per-day cost of blocking a twin bed marginalises it to €17.15. Thus, in PSA with Monte-Carlo simulation of 1000 TB suspects, adding Xpert MTB/RIF in smear-positives suspected of having fully susceptible TB is less costly in only 46.4% of cases (online supplementary table S7).

In smear-positive MDR-TB cases, as compared with fully susceptible TB cases, additional cost savings may occur. These are attributable to the principal advantage of Xpert MTB/RIF of recognising RIF resistance and to the associated avoidance of ineffective first-line treatment during a wait for the result of a culture-based DST report. Furthermore, with Xpert MTB/RIF, a clearly lower number of contact individuals has to be screened for latent MDR-TB infection compared with the conventional approach, where MDR-TB may be spread to healthcare workers in the lag between termination of isolation after 14 days of ineffective treatment and the later DST report. Here, in the base case analysis, cost savings amount to €189.56 per person.

Depending on the PPV of assignment of RIF resistance by Xpert MTB/RIF, a variable percentage of cases receives ineffective, but costly second-line treatment, whilst the phenotypical DST result is initially lacking. MDR-TB prevalence strongly influences that PPV and consequently the amount of saving will be reduced to only €48.30 if MDR-TB prevalence goes to zero (online supplementary table S6b). Cost savings will also decrease in line with a decreasing number of contacts investigated and does not exceed €105.44 if only a total of five healthcare workers has to be screened, as compared with the 10 assumed in our base case (see online supplementary section 2.e).

In smear-positive MDR-TB cases, the probability that the WHO standard second-line treatment is applicable following the assignment of RIF resistance by Xpert MTB/RIF also plays a role. If the DST reveals more complex resistance strain patterns, cost savings in favour of Xpert MTB/RIF decrease remarkably to €79.08, assuming the standard regimen is effective in only 74% as a lower bound in univariate sensitivity analysis (online supplementary table S6b). PSA demonstrates that adding Xpert MTB/RIF in smear-positives suspected of having MDR-TB is less costly in 76.2% of cases (online supplementary table S7).

TABLE 2 Delays in reporting positive cultures and drug susceptibility testing results for *Mycobacterium tuberculosis* isolates separated by sputum smear status

	Sputum smear-positive	Sputum smear-negative
Time for reporting positive culture for *M. tuberculosis* days	10.32±4.7 (7–11.75)	13.17±5.15 (9–17)
Time to drug susceptibility testing report for isolates days	23.9±8.9 (8–27)	29.6±7.26 (24.75–35)

Data are presented as mean±SD (interquartile range).

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TABLE 3 Input for cost–benefit analysis

Variables category	Variable name	Distribution#	Value (base case)	Relative change (range)	Reference
Costs of first-line drugs per day €	cTBD	Triangular	6.3	±20% (5.04–7.56)	[6]
Costs of WHO standard MDR-TB drugs per day €	cMDR_TB	Triangular	101.04	±20% (80.83–121.25)	[6]
Costs of Ziehl–Neelsen microscopy €	cZN	Triangular	6.41	±20% (5.12–7.69)	GOÄ no. 4513 (online supplementary section 2.b)
Costs of mycobacterial culture €	cCulture	Triangular	23.31	±20% (18.65–27.97)	GOÄ no. 4540 (online supplementary section 2.b)
Costs of Xpert MTB/RIF €	cXpert	Triangular	110.75	±20% (88.6–130.9)	GOÄ nos. 4780 and 4784 (online supplementary section 2.b)
Opportunity costs of blocking twin bed €	cOpp	Triangular	314.71	±20% (253.97–380.95)	Calculated from InEK (http://www.g-drg.de/cms/) data (online supplementary section 2.a)
Costs of diagnostic work-up €	cDcs	Triangular	306.81	±20% (245.45–368.17)	Table 4 (online supplementary section 2.d)
Latency pending sputum culture result in smear-positive day	dCulture_SP	Normal	10.32	±SD 8.9 (5.62–15.02)	Assessed (table 2)
Latency pending DST result in smear-positives day	dResistance_SP	Normal	23.9	±SD 8.9 (15.0–32.8)	Assessed (table 2)
Latency pending sputum culture result in smear-negatives day	dCulture_SN	Normal	13.17	±SD 5.15 (8.02–18.32)	Assessed (table 2)
Latency pending DST result in smear-negatives day	dResistance_SN	Normal	29.2	±SD 7.2 (18.94–36.46)	Assessed (table 2)
Probability of MDR-TB in TB patients	pMDR_TB	Linear	0.1966	0%/30% (0.0–0.3)	Calculated (table 1)
PPV of positive sputum smear	PPV_Smear	Linear	0.9474	±95% CI (0.8814–0.9827)	Calculated (table 1)
NPV of negative sputum smear	NPV_Smear	Linear	0.9199	±95% CI (0.8955–0.9402)	Calculated (table 1)
PPV of Xpert MTB/RIF in smear-positives	PPV_Xpert_SP	Linear	1.0	±95% CI (0.9598–1.0)	Calculated (table 1)
PPV of Xpert MTB/RIF in smear-negatives	PPV_Xpert_SN	Linear	0.8372	±95% CI (0.6930–0.9319)	Calculated (table 1)
NPV of Xpert MTB/RIF in smear-positives	NPV_Xpert_SP	Linear	1.0	±95% CI (0.4782–1.0)	Calculated (table 1)
NPV of Xpert MTB/RIF in smear-negatives	NPV_Xpert_SN	Linear	0.9772	±95% CI (0.9623–0.9878)	Calculated (table 1)

Continued

TABLE 3 Continued

Variables category	Variable name	Distribution[#]	Value (base case)	Relative change (range)	Reference
PPV of Xpert MTB/RIF irrespective of smear status	PPV_Xpertoverall	Linear	0.9474	±95% CI (0.8946–0.9786)	Calculated (table 1)
NPV of Xpert MTB/RIF irrespective of smear status	NPV_Xpertoverall	Linear	0.9747	±95% CI (0.9612–0.9879)	Calculated (table 1)
Probability that WHO standard regimen is effective	pMDR_Stand	Linear	0.9272	±20% (0.741–1)	[11]
Time left to discharge from hospital days	dDischarge	Triangular	26.78	±20% (21.24–32.14)	[6]
Costs of intrahospital contact investigation per TB index case €	cContact	Triangular	105.81	±20% (84.65–126.97)	Adapted from [12]
Number of contacts to be investigated	pContact	Triangular	10	5–20	Assumption (online supplementary section 2.e)

WHO: World Health Organization; MDR: multidrug-resistant; TB: tuberculosis; DST: drug susceptibility testing; PPV: positive predictive value; NPV: negative predictive value; GOÄ: Gebührenordnung für Ärzte (German medical fee schedule). [#]: in probabilistic sensitivity analysis.

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TABLE 4 Costs of diagnostic work-up in sputum smear-negative or Xpert MTB/RIF-negative tuberculosis suspects

Procedure	n	GOÄ (1.0 times rate) €
Computed tomography thorax	5371	134.06
Contrast agent, injection intravenously, high pressure	346	17.49
Bronchoscopy including lavage	678	52.46
Cytological investigation	4852	10.14
Interferon-γ release assay test peripheral blood	3694	33.80
Ziehl–Neelsen smear (lavage)	4513	9.33
PCR (lavage)	4783	29.41
Culture mycobacteria (lavage)	4540	33.31
Total		306.81

GOÄ: Gebührenordnung für Ärzte (German medical fee schedule).

In contrast, and predominantly due to a shorter isolation period (2 days fewer blockage of a twin bed by using Xpert MTB/RIF), the cost saving in fully susceptible smear-negative TB suspects is €503 and remains constantly high, even when the main cost driver, the per-day hospital opportunity cost of blocking a twin bed, is assumed to be 20% lower (in this case reducing the saving to €385.42). Increasing the cost of Xpert MTB/RIF within its given range or decreasing the higher NPV that its 9% sensitivity advantage over sputum smear brings (73.47% *versus* 64.75%) diminishes the total amount of savings at most by 8.44% and 1.24%, respectively, and has only marginal impact (online supplementary table S6c).

For smear-negative MDR-TB cases, the figure for the cost saving is slightly higher at €515.25 because, as is the case in smear-positive MDR-TB patients, it is predominantly the costs of contact investigation of healthcare workers that have to considered. Due to the high NPV (92%) of sputum smears, however, only very few MDR-TB cases will be detected in smear-negatives which induce hospital contact investigations by possible transmission in the latency between positive culture and the later DST result. Therefore, neither variations of MDR-TB prevalence nor of the number of contact individuals in sensitivity analysis have a substantial impact on cost savings (online supplementary table S6d) and in PSA cost savings remain at 100% in all scenarios involving smear-negative TB or MDR-TB suspects (online supplementary table S7).

Full replacement of the conventional approach by Xpert MTB/RIF saves €449.98. This is primarily due to the elimination of unnecessary isolation in the 87% smear-negatives of our cohort of TB suspects (612/707; table 1). Accordingly, reducing the figure of per-day opportunity cost to its lower bound (−20%) will reduce the amount of cost saving by 59% to only €184.67 (online supplementary table S6e).

TABLE 5 Results of base case analysis (five scenarios)

Base case analysis and comparator	Mean cost per patient	Incremental cost [#]
Sputum smear-positive TB suspects		
Xpert MTB/RIF as an add-on	157.2	0
Conventional approach	205.47	48.27
Sputum smear-positive MDR-TB suspects		
Xpert MTB/RIF as an add-on	240.93	0
Conventional approach	430.49	189.56
Sputum smear-negative TB suspects		
Xpert MTB/RIF as an add-on	512.17	0
Conventional approach	1015.17	503.0
Sputum smear-negative MDR-TB suspects		
Xpert MTB/RIF as an add-on	518.03	0
Conventional approach	1033.28	515.25
Xpert MTB/RIF replacing smears		
Xpert MTB/RIF	440.97	0
Conventional approach	890.95	449.98

Costs are presented as €. TB: tuberculosis; MDR: multidrug-resistant. [#]: increase in total costs resulting from using the conventional approach alone *versus* including Xpert MTB/RIF as an add-on or as a replacement.

Discussion

The present study is a differentiated cost–benefit analysis of the implementation of the real-time PCR Xpert MTB/RIF method in hospitalised patients with suspected TB, either as an adjunct to or a replacement for sputum smear microscopy. PCR, with its ability to very rapidly confirm or exclude infectious pulmonary TB, has the potential to minimise the duration of isolation and/or to avoid unnecessary isolation.

To date, only very few cost studies on the routine use of nucleic acid amplification tests have been published and their findings are unfortunately not applicable to German conditions. Adelmann *et al.* [16] found significant cost savings in a US urban public hospital (US$2003 per suspected smear-positive TB case) when using the amplified MDT (*Mycobacterium tuberculosis* Direct) test (Gen-Probe, San Diego, CA, USA) among predominantly African-American AFB smear-positive TB suspects. These subjects had a high prevalence of HIV-1 infection and for their cases the AFB smear had a very low PPV (27%) for culture-confirmed TB. Germany's HIV prevalence is low (2009: 0.1% of individuals aged 15–49 [17]) and the data we used from the German NRC give the AFB smear a PPV for culture-confirmed TB of 95%. In Adelmann *et al.* [16], one main cost driver was the cost of unnecessary contact investigations, which were begun not at the time of culture confirmation, but immediately upon recognition of the positive AFB smear. A second notable driver was the per-day cost difference between isolation and nonisolation rooms. In Germany, special airborne infection isolation rooms providing negative pressure are rare. Also in Millmann *et al.*'s cost–benefit analysis [18], the incremental cost of respiratory isolation per day in a special room and the reduction regarding the length of stay of on average from 2.7 to 1.4 days per patient saved US$2278 per admission of suspected pulmonary TB. Our hospital costs are significantly lower.

Our analysis shows that in base case analysis, performing Xpert MTB/RIF as an add-on for TB suspects admitted to a German TB ward as well as complete replacement of sputum smears by Xpert MTB/RIF is consistently cost-saving, even when the economic perspective is restricted to hospitalisation. Driving this is a reduction in the number of isolation days per case, each of which results in a blocked twin bed and corresponding revenue loss for the hospital. Smear-positive and smear-negative patients on average wait 10 and 13 days, respectively, for their positive culture results in Germany; for phenotypical DST results the average waiting periods are 24 and 30 days. There is only a marginal difference of specificity and overlapping 95% confidence interval in the PPV of fully susceptible smear-positive TB patients. This is due to a low observed proportion of 5.3% of NTM, resulting, as sensitivity analysis reveals, in a fragile economic advantage for Xpert MTB/RIF in this group of patients.

Paradoxically, and counter-intuitively, one strikingly favourable feature of Xpert MTB/RIF has its drawbacks. The immediate detection of RIF resistance in MDR-TB patients, in comparison with the much later reportable, culture-based DST, brings additional costs that occur in those patients with complex resistance patterns and for which the preliminary treatment with the recommended WHO standard second-line treatment is not effective. The treatment, ongoing for a number of weeks, must be adjusted to correspond with the pattern identified by phenotypical DST. In these cases, treatment duration is ultimately as long as it would have been under the conventional approach. However, DST cannot fully be replaced by line probe assays as the sensitivity of these for resistance to ethambutol, ofloxacin and injectable drugs is limited even in smear-positives [19]. Even in the case of a positive resistance determination, susceptibility to the other drugs must be clarified by DST in order to implement a definitely appropriate therapeutic regimen.

Another drawback of RIF detection by Xpert MTB/RIF is that unnecessary second-line treatment will be prescribed in a number of cases that corresponds to 1−PPV of the test. This rate of false resistance determinations logically increases with decreasing MDR-TB prevalence.

PSA that considers all realistic assumptions of uncertainty confirms the different degrees of potential savings between the five scenarios and underlines that Xpert MTB/RIF is most likely to be cost-saving in smear-negative TB suspects. This is of particular relevance as in 2013 in Germany 79.6% (2624/3298) of all reported pulmonary TB cases were "open" (culture-confirmed), of which 55% (1443/2624) were sputum smear-negative, and also in pulmonary MDR-TB cases only 63.5% (54/85) were sputum smear-positive (B. Brodhun, Robert Koch Institute, personal communication, 2015).

Our study also has some limitations that must be considered when interpreting our results. First, the general limitations of retrospective, single-centre studies have to be considered. Our use of extensive sensitivity analyses is an effort that addresses those limitations. To validate our estimates, more cost studies, preferably with a multicenter and prospective study design, are required.

Second, from an economic point of view, replacing smear examination by Xpert MTB/RIF rather than using it as an add-on option basically combines the advantages of implementing Xpert MTB/RIF for the

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single smear-positive or smear-negative categories. However, it must be emphasised that graduated contact tracing according to the degree of infectiousness of the index case [2, 15, 20], as is usually practiced in low-incidence countries, could no longer be done were sputum examination to lapse. In practice, then, as all index cases have to be considered potentially sputum-positives, the initial circle of contact individuals to be investigated by the public health departments would have to be drastically expanded to be on the safe side, resulting in an inestimable increase in total costs.

Conclusion

The utilisation of Xpert MTB/RIF in Germany, a high-income country, is likely to reduce overall costs in cases of suspected TB, especially in MDR-TB and smear-negative patients. As such, routine use of Xpert MTB/RIF may have a direct and positive impact on the control of TB disease. Prospective clinical studies should be undertaken to further evaluate its economic advantages in the immediate future.

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