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Cost of illness of tuberculosis in Germany

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Abstract

Background: 4,444 new cases of tuberculosis (TB) were reported in Germany in 2009; of those, the proportion of multidrug-resistant TB (MDR-TB) cases increased to 2.1% (63 cases).

Methods: On the basis of the therapy guidelines of the German Central Committee against Tuberculosis and the new WHO guidelines, this study estimates the mean direct outpatient and combined in- and outpatient costs of TB, together with other attributable costs of the disease on the basis of the most recent German official health statistics and scientific literature.

Results: According to this, the mean outpatient costs (rounded) per case were €1,197 (adults) and €1,006 (children) for standard therapy, but €36,543 for treatment of MDR-TB. The mean combined inpatient/outpatient costs were €7,364 (adults) and €7,300 (children), respectively; the combined costs for treatment of MDR-TB amounted to €52,259. Including MDR-TB cases the mean costs of treatment per TB case were €7,931.

These are joined by the mean costs due to loss of productivity (€2,313), costs per case for rehabilitation (€74) and contact tracing (€922), summing up to €11,240.

Conclusion: With respect to the probably increasing number of MDR-TB cases in the next future, TBs is still a disease of significant economic impact in Germany.

Introduction

It has become almost a strict convention that original papers on TB disease begin with the statement that tuberculosis (TB) is still the world´s most frequent contagious disease, causing about 1.7 million deaths in 2010, with more than 8 million people contracting the disease every year according to the World Health Organization (WHO) [*1*]. Globally, in 2010 just over 46,000 patients of MDR-TB were enrolled on treatment [*2*]. Thus, from a health economics point of view, the prevalence of the disease, estimated to be 12 million cases in 2010 [*1*], is associated with considerable socioeconomic problems.

Since a first cost calculation arising for a “typical” pulmonary TB patient in 2001 in Germany was made [*3*], the official number of new cases of TB in Germany has decreased from 7,539 to a total number of 4,444 reported cases in 2009 [*4*]. That relatively modest number fails, however, to indicate the economic burden tuberculosis places on the health system. Seven years having lapsed since the publication of our work, and today an up to date, more comprehensive cost-of-illness study, now also addressing the costs of MDR-TB, is overdue.

In its aim to provide a realistic report of the current morbidity costs for TB in Germany, the present update on this subject extends the scope to a societal point of view and includes all types of tuberculosis, not only that affecting the lungs.

Methods

This analysis considers only costs the charging of which is legally mandated to or that are due to procedures representing "state of the art" of therapy. Because they cannot be adequately modelled, some costs that may arise from cases of tuberculosis are not taken into consideration. For example, the cost of chemoprevention in persons exposed to TB patients is dependent on individual decisions and unclear adherence patterns, making meaningful modelling impossible.

In taking a societal point of view, the following cost categories are defined and calculated if possible based on the most recent available data in each case:

1. Costs for diagnosis and therapy of tuberculosis bourn by the state health insurance system (GKV).
2. Costs incurred by Public Health units for execution of contact investigations as required by the Federal Law on Infectious Diseases.
3. Costs incurred of rehabilitation borne by the German pension insurance.
4. Indirect costs dues to loss of productivity on the part of the general economy.
5. Costs for productivity losses caused by deaths.
6. Intangible Costs.

Our calculations of the direct costs are based on the rates established by the uniform appraisal scale (EBM) [*5*] and the InEK (Institute for the Hospital Remuneration System) data [*6,7*] for the German DRG system; these constitute the costs effectively incurred by the GKV. Specifically, we used data provided by the Barmer-GEK Krankenkasse (Barmer-GEK health insurance institute) as the basis for a special evaluation of daily reimbursement costs to the GKV for patients hospitalised more than 14 days.

Given that no representative random sampling study of the number of workdays lost due to TB in Germany (ICD-10 A15-A19) exists, calculation of the indirect costs is simplified by taking the latest available sick leave period (in 2009) for gainfully employed compulsory members of the AOK, which is the statutory health insurance fund with the largest number of members in Germany [*8*]. It is not possible to say how representative the AOK patient

contingent is for all people insured in the GKV. Given, however, the AOK's large share of coverage throughout Germany, the probable deviations are likely to be negligible.

Loss of productivity from the point of view of the general economy is then calculated on the basis of the gainfully employed rate (share of the 15 to 65 year olds in the country's population that are gainfully employed).

The basic presumptions for the cost calculations stated below are based strictly on the new joint guidelines (in press) of the German Central Committee against tuberculosis (DZK) and the German Respiratory Society for TB therapy [*9*], which adopted the new WHO guidelines on therapy for multi-drug resistant tuberculosis (MDR-TB) [*10*].

Epidemiological background

Since the last German cost of burden analysis for tuberculosis [*3*] was published, epidemiological data as well as cost figures have changed remarkably.

In Germany for 2009, the Robert Koch Institute in Berlin was notified of a total of 4,444 TB cases, generating a TB incidence rate of 5.4 cases per 100,000 population [*4*]. Only 146 new cases were reported in children, so the large majority of cases (96.7%) is in adults (defined as 15 years or older [*11*]). Treatment in hospital wards or special lung hospitals occurred in 71.2% of the 4,444 TB cases, followed up by physicians in private practice.

In adults 80.2% of the cases were pulmonary tuberculosis, and 3,150, 80.5%, of 3,913 TB cases for whom a culture was performed (independent of the specimen investigated) were culture-positive. In 231, 5.5% of the 4,201 adults patients, for whom organ manifestations were reported, TB cases were by definition extrapulmonary, but intrathoracic.

The proportion of MDR-TB increased from 1.6 % (49 cases) in 2008 to 2.1 % (63 cases) in 2009 of the 2,989 cases for whom information on strain resistance was reported, or 1.4% of all reported 4,444 TB cases. Of the 63 MDR- patients, 46 were treated in hospital (73.0%) for a mean duration of 86.36 days ([*12*]; of whom all but one (with 9 days hospital treatment) were hospitalized longer than 14 days.

Diagnosis and therapy

The diagnostic algorithm for TB is largely defined by the catalogue of procedures for which the GKV will pay. Currently, these begin with a tuberculin skin test according to Mendel Mantoux to verify infection (payment by the GKV for the use of the more specific IGRAs paid by the GKV is still restricted to persons screened for latent TB prior to administration of

TNF-alpha or in HIV-positives). In patients with suspected pulmonary TB this is generally followed by a chest X-ray (affected organ) and bacteriological confirmation – usually from sputum or bronchoalveolar lavage following referral to a pneumologist, with microscopic verification of acid-fast bacillus (indicator of contagiousness) and/or culture (pathogen verification) together with a sensitivity test of the first isolate for anti-TB chemotherapy drugs. In any case of suspected TB, including suspected extrapulmonary TB involving other (non-lung) specialists, NAAT assays should in addition be performed routinely for rapid identification of the *M. tuberculosis* complex or for MDR, e.g. by GeneXpert® (Cepheid), detecting R-resistance in sputum samples and other body fluids, especially in patients from MDR high-burden countries and in patients with known previous contact to a MDR TB cases.
According to the guidelines of the DZK [9], the therapy for lung TB and also for all extra-pulmonary varieties of TB disease (apart from TB of the CNS) lasts at least six months, a regimen that keeps recurrence rates at a minimum (3%). In view of the fact that in Germany 11.4% of all culturally verified cases of TB are resistant to at least one of the first-line drugs, the quadruple combination with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) is recommended. After a so-called initial phase of two months that preceeds the arrival of the resistance results, in the subsequent continuity phase, patients with fully sensitive strains are then treated with H and R for a further four months. In children only, an initial phase with three drugs (H, R, Z) is necessary if there are no risk factors for resistance (prior treatment, etc.). This combination can be used because in children colonization is relatively limited and consequently the probability of spontaneous resistance mutations is very low. Drug resistant TB in children is a rare exception in Germany.

Basically, although therapy of MDR-TB (at least resistance against H and R simultaneously) is complex and in an exceptional cases highly individual, the WHO has proposed a fixed regimen schedule combination that should include at least pyrazinamide added to a minimum of four second-line anti-TB drugs that are likely to be effective: a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid (PAS) if cycloserine cannot be used.
For the German situation the combination of Z (if there is no known resistance), moxifloxacin (the most effective fluroquinolone), amikazin (routinely available in the German pharmacies), prothionamide and terizidon (a pharmacological improvement of cycloserine; cycloserine is not available in Germany) will be considered for the cost estimation of MDR therapy in our study [9].

Derogating from the previous WHO guidelines [*13*] proposing a treatment duration for MDR-TB patients based on the use of a parenteral agent for a minimum of 6 months and a minimum total length of treatment of 18 months after culture conversion, in the current update [*10*] an intensive phase of 8 months' duration (including the parenteral agent) is conditionally recommended instead of the previous minimum of 6 months and a total duration of treatment of at least 20 months.

Basic presumptions for calculating costs

1.) The responsibility for diagnosis and therapy for primary outpatient treatment or outpatient treatment following initial hospitalisation lies throughout the disease with the private lung specialist or general practitioner (adults) or pediatrician (children). If there were fee schedule positions for different age groups, the respective cheapest position was chosen. According to the number of 231 TB cases among adults that were extrapulmonal but intrathoracic, the proportion of patients basically to be monitored by pneumologists increased from 80.2% to 85.8% (3,373+231/4,201).

2.) The drug costs are calculated on the basis of the recommended maximum dose for the drugs being administered on a daily basis. The cheapest drugs with the corresponding effective substance are taken according to the 2011 issue of the Rote Liste (German drugs directory). The quadruple therapy including E is also used in adults for culturally unconfirmed TB. Where drug sensitivity cannot be determined, an unknown H resistance may exist and Z will be ineffective in non-acid milieu. When using H, Z and R without E in such cases, a de facto R monotherapy would be in effect, which may result in a selection of R-resistant mutations in large populations of bacteria.

3.) Although numerous side effects can occur throughout therapy, costs for adjuvant medication do not apply: gastrointestinal side effects from R occur in approximately 2% of the cases and can usually be eliminated by having the drug taken after a meal, without antiemetic secondary medication. For short-term chemotherapy with Z over 2 months, any reduction in uric acid clearance caused by metabolites usually runs without arthralgia or only in the per-mille range, so that accompanying application of uricosuric agents is not indicated [*14*]. In the therapeutic dose, H causes peripheral neuropathy induced by pyridoxine deficiency in approximately 2% of cases. The low-priced isoniazid preparation calculated here already contains pyridoxine as a prophylactic measure so that no additional costs are incurred [*15*]. Malfunctions of the liver occur in up to 20% of the cases with combination therapy (particularly following prior alcohol-toxic damage of the

liver) and regularly either recede again spontaneously or after interrupting the therapy. This is not accessible to medication.

Extremely rare, neuritis of the optic nerve under E with distortion to the sense of colour depends on the dose and is normally reversible after stopping the medication; this cannot be influenced by therapy. A nephrotoxic effect of amikacin is possible, but reversible; an extremely rare ototoxic effect (disturbed sense of balance or reduced hearing) is often irreversible and cannot be treated. Gastrointestinal side effects also occur when taking moxifloxacin and prothionamide, as do headache and sleeplessness. The costs of antiemetic or analgetic concurrent medication are, however, negligible. Psychotic disorders may be a side effect of terizidone, but these are rare, in contrast to those caused by cycloserine.

4.) As the rate of hospitalisation (71.2%) reported for German TB patients in [4] did not differentiate between any sites of TB this figure was assumed for patients with extrathoracic as well as with intrathoracic TB.

5.) In 2009, 36.4% of the TB patients treated solely as outpatients were diagnosed by microscopy or NAT, with samples taken by bronchial lavage [*12*]. Accordingly, that proportion was used for weighting costs in adults with intrathoracic TB. Costs of bronchoscopy were not included for patients with extrathoracic TB or children. Estimates of the frequency with which computer tomography is used as a diagnostic supplement in unclear radiologic cases were not available and thus cost data were not included.

6.) This calculation adds all attributable costs of “state of the art” diagnostics and therapy in children and adults as recommended by relevant guidelines/recommendations utilizing proportions from routine surveillance data and fixed or already weighted costs. It takes into consideration neither outcomes from clinical trials nor different size samples. Confidence intervals are not provided, as their application to this non-probabilistic model would have been inappropriate.

Direct outpatient costs

In spite of the mandatory diagnosis encryption introduced by law on 1 January 2000 according to ICD-10-SGB V (according to the publication in the Federal Gazette by the Federal Ministry for Health on 8.7.1999) and the subsequently theoretically possible allocation of outpatient costs, there are still no statistical data available for treatment costs by panel doctors in Germany. However, the costs involved in outpatient therapy for TB can still be delimited by a model calculation, as follows:

Monitoring during therapy

The monitoring of anti-TB therapy described below is closely meshed:

1.) Microbiology: sputum test for primarily microscopically positive TB in the initial phase (three samples for the larger yield) weekly and then every four weeks until negative results are obtained [*16*], i.e. at least five times for a presumed conversion within eight weeks. Cultures are bred in the initial phase (positive culture results followed by resistance test), then after four and eight weeks (conversion should have occurred by that time) and then once more towards the end of the therapy (verification of successful therapy according to WHO criteria). According to the latest WHO recommendations, MDR-TB patients should be monitored with monthly sputum smear microscopy and culture examination throughout therapy [*10*]. For patients with extrathoracic TB it was assumed that only one culture would be performed at baseline.

2.) Material costs of the TST

The TST licensed for Germany is PPD RT 23, 2 TU 0.1 mL from the Danish Statens Serum Institute, and distributed by Pharmore Ltd. The delivered price for 10 glass vials, each containing 1.5 mL RT 23 is €83.26. Since droplets always remain in the cannula and the vial, only 10 test doses of 2 TU are withdrawn from the 1.5 mL vials. According to the manufacturer's specifications, opened vials can be used only up to a maximum of 24 h after the withdrawal of the first dose. Whether only one or the maximum of 10 test doses per vial are used depends on the number of persons tested per day. Consequently, the material costs per TST range from €1.83 to €18.37. The mean dose amount of five test doses, with costs of €9.15 per contact individual, is assumed as the base-case value in the present analysis [*17*].

3.) Laboratory tests: in accordance with the DZK guidelines, a broad blood profile is necessary before therapy starts, together with definition of the kidney retention values (creatinine, urea), the liver values (GOT, GPT, bilirubin, GGT [which is required as alcohol abuse parameter and also allows for differentiation between H-induced hepatitis and R-induced cholangitis in case this value increases as a result of the medication]); it is also advisable to determine uric acid level in adults (as compliance parameter because an increase under Z is almost certain), together with hepatitis serology (HBs-Ag, Anti-HBc), as well as HIV serology. The liver values are controlled 2–4 weeks after starting the therapy, and every 4 weeks thereafter (bilirubin is not checked if there are no anomalies in the liver parameters in the first test and subsequent checks). The uric acid values are checked only every 4 weeks until the Z is stopped, i.e. altogether only twice in standard

therapy if a prior hyperuricemia was not reported. Blood tests and the renal retention parameters are checked every month through to the end of the therapy, together with checks of the liver values.

The serum level of amikacin in MDR drug resistance patients should be controlled at the end of the first week, furthermore 2 weeks and 6 weeks after starting the therapy (given normal kidney function).

4.) Ophthalmic examination: under E, before therapy starts and usually every 4 weeks, i.e. for a 2-month treatment with E, altogether three times (in the initial phase, and then after 4 and 8 weeks); and audiometry in the initial phase and then every 4 weeks during amikacin therapy in MDR patients, altogether 10 times in total.

5.) X-rays (given pulmonary TB): in the initial phase, after 4 weeks (to control if the TB is reacting to the therapy), and after 8 weeks (end of the initial therapy: success assessment). After 8 weeks x-ray checkups in the 4th and 6th month are sufficient. For patients with extrathoracic TB, only one X-ray examination at baseline is necessary for the exclusion of intrathoracic TB. Further follow-up of patients by chest X- ray after the end of treatment was not a matter for this analysis.

Calculations

The resulting costs are charged to the GKV according to EBM ("Einheitlicher Bewertungs-Maßstab") [5] and multiplied by the average number of points for all service types and providers as far as no fixed prices are given. The GKV point value for Germany ("bundeseinheitliche Orientierungspunktwert") in 2011 is €0.035048. The calculation tables show, separately for primary outpatients and outpatients following primary hospitalisation, the outpatient costs for diagnostics and monitoring (Table 1) and treatment (Tables 2, 3, and 4), and result in mean case costs for purely outpatient therapy amounting to altogether €1,197.41 for adults and €1,006.48 for children (see Table 5).

The outpatient costs after initial hospitalisation were €749.21 for adults and €672.66 for children. The costs for treating MDR-TB amounted to €36,543.22 for primary outpatients.and €27,271.95 for post-hospitalization outpatients (for detailed information see Online Supplement)

Inpatients costs (Direct hospital costs)

As far as inpatients are concerned, since 1 January 2004 hospital costs are based on the uniform German G-DRG system, which allocates each case to a diagnosis-related group.

Under that system, reimbursement of hospital services is no longer based on fixed daily rates for the period of stay, but focuses on the kind and severity of the diseases. A calculated base rate for the hospitals in the corresponding federal state is then multiplied by the specific cost weight of a disease, resulting in the proceeds for the hospital providing the treatment. For tuberculosis, there are three categories: Whilst the costs for E76B cases (with severe complications, hospital stay less than 14 days) and E76C cases (without severe complications, hospital stay less than 14 days) are fixed by multiplying the national base rate ("Bundesbasisfallwert") for 2010 of €2,935.78 with different cost weights depending on their different degree of disease severity (1.022 for E76 B and 0.912 for E76C), the costs per day for patients being diagnosed and treated in hospital for longer than 14 days (E76A, introduced since 2007) have to be negotiated separately between third party payers and the respective hospital and may vary accordingly.

The InEK (Institute for the Hospital Remuneration System) provides detailed data for tuberculosis patients treated for the first time or retreated after relapse in hospitals on its G-DRG-Browser (G-DRG V2010 Data according to §21 KHEntgG). Based on a mean per-day reimbursement for those patients of €296.31 [*18*] the mean hospitalization cost per standard TB patient was €9,109.13 and €24,986.89 per MDR-TB patient (see Online Supplement).

Combined inpatient/outpatient TB costs

The average combined inpatient/outpatient costs for non-MDR-TB in Germany in 2009 per adult patient was €7361.87, but €52,258.84 for MDR-TB patients (see Online Supplement).

Indirect costs (Loss of productivity)

From a societal point of view, losses in productivity due to disease, the so called "indirect costs", must be included in disease cost estimates. In accordance with the *human capital approach,* indirect costs represent the production loss for the economy at large caused by absence from the workplace on sick leave. According to the „Hanoverian Consensus" [*19*], the productivity losses caused by sickness should be evaluated without consideration of differences in the branches, differences in age or sex ("overall employees"), with the average gross income for the period from non-self-employed employment.

The average productivity loss to cover the self-employed as well is calculated as follows: productivity loss = sick leave days × [gross income from non-self-employed work divided by the number of employer-dependent gainfully employed times 365 days]. As more detailed

information is not available, an estimate is recommended on the basis of the data provided by the Federal Statistics Department: The mean sick leave duration in 2008 of mandatory members of the AOK (previously mentioned) throughout Germany for TB (ICD-10 A15-A19) was on average 43.368 days/1,286 cases = 33.7 days per case [*8*]. For 2010 the loss of productivity in Germany is considered to be €95.82 (2009: €93.92) per sick leave day [*20*].
The proportion of gainfully employed in the mandatory age group (15-64 years) was 71.0% in 2009 [*21*]). Accordingly, loss of productivity per person ill with tuberculosis was €95.82 x 34 days (rounded), multiplied by the proportion of employees in 2009 (x 0.71) = €2,313.09. It should be noted that this figure is a weighted mean and that in MDR-TB cases at the individual level the loss of productivity may be by far higher.

Costs of public health screening for LTBI

According to §16 and §25 of the Infection Protection Act (IfSG), the responsibility for diagnosis of LTBI before sending a screened contact to settled pneumologists lies with the public health service. The Public health departments to whom each patient suffering from active TB disease has to be reported routinely perform contact investigations according to §16 and §25 of the Contagion Protection Law (IfSG). Thus, each case of a person with infectious, i.e., culture confirmed pulmonary TB disease results in further cost for those contact investigations, the purpose of which is to minimize possible chains of infection. A further exercise is the so called “source tracing” in patients with TB that may be have been developed recently, such as tuberculous pleuritis or meningitis, and/or in children.
Mean costs of €52.05 per person for tracing a source case and of €74.30 per qualified contact person of infectious TB patients have been recently documented in a cost study [*17*], based on a dual step testing approach (TST first, if positive, followed by a highly specific Interferon-gamma release assay (IGRA) as confirmation. Both cost figures have to be added to the costs of treatment of the disease itself, irrespective of whether in infected contacts of infectious TB patients subsequent preventative chemotherapy will be performed.
Based on statistics from the Fingerprinting Study of the German Central Committee Against Tuberculosis [*22*], in which 2,562 patients were involved, the weighted total costs arising per TB case due to contact investigations from the Public Heath perspective were €921.80 (see Online Supplement).

Costs of rehabilitation measures

The costs for rehabilitation measures for TB are not negligible, because in 2009 for all forms of TB together (ICD-10 A15–19) there were 113 subsequent therapies [*23*], i.e. for 2.5% of all TB cases, with an average duration of 24 days. The daily costs per rehabilitation facility in 2009 was €123 [*24*], resulting in costs of €2,952 per patient. Thus, the costs that have to be added to the treatment costs per patient is €2,952 x 0,025 = €73.8.

Costs for productivity losses caused by deaths

The mortality rate for TB of 154 deaths in 2009 (3.5% of all 4,444 cases of the disease [*4*]) is not low. However, the share of elderly (65+) among the deceased amounted to 74.1% [*25*], for whom it appears to make little sense in calculating the loss of productivity due to the very low gainful employment in that age group. Furthermore, TB correlates closely with membership in specific risk groups which are already removed from the production process to a great extent, in other words, alcoholics, drug addicts and the homeless [*26*,*27*]. Together with hepatotoxic and/or prior immunosuppression damage to other organs regularly to be found with this group of patients, it would have been difficult to clearly attribute TB as the agent causing death also in many of the remaining cases in age groups younger than 65 years. Thus, costs for productivity losses due to death in TB patients was not considered in this study.

Intangible costs

Evaluation of the intangible costs would require a differentiated, prospective survey with a specific TB-related instrument for measuring the quality of life. It is a known fact that the general instruments for measuring the quality of life (e.g. QALYs, Nottingham Health Profile, EuroQol) are not very sensitive to short-term changes in the state of health such as occur in the various stages of the disease and therapy for lung TB with regard to the highly differing risk populations in the various countries with low TB incidence [*28*]. However, to our knowledge no such instrument has yet been published.

Total of costs per TB case

Taking all costs together the mean costs in adults per TB case is €7931.02 (treatment costs including 1.4% MDR TB cases) plus €73.8 (rehabilitation costs) plus €2,313.09 (loss of productivity) plus €921.80 (mandatory contact tracing), summing up to a total of €11,239,71.

Discussion

Over the past decade, since 2000, published data on costs of TB disease in developed countries are sparse, usually consisting of brief summarized presentations, which vary considerably in their conclusions: Atun et al. [*29*] calculate the mean cumulative cost of treating a TB case over three years at US $886 in the Russian federation. Most data about direct and/or indirect costs of TB published still come from the USA: Mancuso et al. [*30*] assign US $17,869 as the mean costs for a hospital episode occurring in 2009 in the U.S., but do not provide a hospitalization rate for TB patients. On the basis of a questionnaire, Schwartzman et al. [*31*] estimate the indirect costs (due to two weeks lost duty time) costs for a TB patient in the USA to be US $2262 in 2003. Holland et al. [*32*] calculate the total costs per active TB case for a 6 months-treatment as high as $13,000, and $13,783 for a 9 month treatment (updated to 2011 U.S. Dollars). In a more detailed overview from Porco et al. [*33*] treatment costs amount to US $38,429, but are probably overestimated due to unweighted inclusion of costs for a hepatitis hospital stay of US $10,662 per patient. Diel et al. [*34*] ascertained weighted mean costs of €14,750 for treating pulmonary TB in Switzerland in 2006; in contrast Pooran et al. [*35*] estimate an amount of only €7,468 (€7620 GBP) for treatment in Great Britain updated to 2008. For Japan, Kowada et al. [*36*] estimate treatment costs of US $15,775.

Full transparency on the local costs of TB disease is a prerequisite to a debate on the effectiveness of preventive measures against TB to be taken by the respective health care system. Although our study provides a breakdown of costs that would be theoretically incurred in treating a typical case of TB disease in Germany, it probably underestimates the real costs of TB. First of all, it is recommended to extend the continuation period and/or to administer additional first line drugs or fluoroquinolones in cases of single drug resistance [*9*]. Furthermore, Ethambutol should be continued in the continuity phase in TB patients with relapses following prior disease and/or in those coming from foreign countries with higher INH resistance if resistance testing is not possible. This helps to avoid secondary R-resistance given unknown primary H resistance [*9*].

Such discretionary acts, however, were not taken into consideration; although 27 countries with high MDR TB-burden are known [*37*], indeed there is no available data on frequency on the respective resistances patterns or on patients suspect for unknown primary H resistance in Germany to be covered with cost estimates. As the treatment of MDR tuberculosis may be a very individual one according to resistance patterns, the cost in a given case may differ from

that of our exemplary drug schedule. Nevertheless, due to the low number of MDR cases that fact will not dramatically influence the total average costs arising per TB case. The limited relevance and/or difficulty of calculating productivity losses from TB lethality addressing primarily older patients and/ and or patients with previous medical injuries who are in many cases not available any more to the labour market has already been pointed out above.

Although other lung diseases such as chronic bronchitis (with estimated annual costs of €4 billion) or bronchial asthma (€2.1 billion) are chronic diseases which account for clearly higher aggregated disease costs of more than €24 billion [*38*], the most recently available case costs calculated here for Germany classify TB as an acute disease of economic significance.

In our comprehensive analysis for the first time also costs for MDR TB and Public Health costs for contact investigations were included. However, in comparison to the cost study of the year 2004 [*3*] in which the mean combined inpatient/outpatient costs ranged from €14,301 (adults) to €16,634 (children), the costs have clearly decreased. There are several reasons for that surprising development, firstly that the proportion of patients treated in hospitals was significantly reduced since 2004, by about 9% (from 80.0% to 71.2%). Given hospital treatment, the length of hospitalization also was reduced by far, from a mean of 50 (49.6) days to 30 (30.17) days. Thus, purely outpatient therapy has apparently increased by about one third, with much lower direct costs because of omitting the considerably long stay in hospital amounting on average to 30 days.

Referring to sickness benefit costs paid by insurances the average number of days off work due to TB disease a mean of 34 (33.7) days in our update was that low that the prerequisites of receiving that payment (days off work extending 42 days) was not fulfilled in general, whilst in 2004 sickness benefit payments of more than €2000 (€2,087.83) could be considered. This is in line with the lower indirect costs (loss of productivity), with 31 days (33.7 instead of 64.6 days) less to be considered.

With respect to cost estimates of TB disease, special attention has to be paid to on the development of the number of MDR TB cases in the future which actually contributed only to 1.4% of all cases in Germany but have already contributed to 8.5% (€672.22 of the total of €7931.022 treatment costs). According to our calculation of average costs for a TB case of €11,239.71, at present the total annual costs due to TB disease in Germany in 2009 sum up to €49,959,271.24.

Of note, only the costs of TB patients free of complications were calculated, and among MDR-TB cases minimum costs, based on relatively low-priced drugs that meet the

requirements of the drug set proposed by the WHO, were used. As in individual cases very expensive drugs, such as linezolide, may be necessary to address a more limited range of drug susceptibility, our calculation must be understood to assume the lowest plausible drug therapy costs. This figure may dramatically change when treating extensively drug-resistant (XDR) TB, for which costs of more than €170,000 may arise [*39*] although to date very few cases have occurred (in a German survey seven XDR TB cases were identified in the three-year period 2004-2006) [*40*]. Three further exercises would have been required to fully cover in our model the impact of MDR-TB costs: An analysis of the treatment needed for different patient types, based on each single resistance pattern; the determination of a representative distribution of patient types; and a Monte Carlo analysis. As answering that question was beyond the scope of our study, it remains an important task for the future.

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References

1. World Health Organization (2011) Global tuberculosis control: WHO report 2011. Geneva, Switzerland

2. World Health Organization (2011) 2011/2012 tuberculosis global facts. Geneva, Switzerland

3. Diel R, Rappenhöner B, Schaberg T. The cost structure of lung tuberculosis in Germany. Eur J Health Econ. 2004;5:243-51.

4. Robert Koch-Institut (2011) Bericht zur Epidemiologie der Tuberkulose in 2009. Berlin 2011

5. Kassenärztliche Bundesvereinigung, Einheitlicher Bewertungsmaßstab [EBM], Stand 1. Oktober 2011: http://www.kbv.de/8156.html

6. InEK –Institut für das Entgeltsystem im Krankenhaus. Definitions-Handbuch 2011. G-DRG-Version 2011

7. InEK –Institut für das Entgeltsystem im Krankenhaus. Datenveröffentlichung gem. § 21 KHEntgG: http://www.g-drg.de/cms/content/view/full/2877; last accessed 10 September 2011

8. Gesundheitsberichterstattung des Bundes. Arbeitsunfähigkeit bei AOK-Pflichtmitgliedern ohne Rentner (Arbeitsunfahigkeitsfälle und Arbeitsunfahigkeitstage), Jahr 2008.

9. Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose (2011). Empfehlungen zur Therapie, Chemoprävention und Chemoprophylaxe der Tuberkulose im Erwachsenen- und Kindesalter. Pneumologie (in press)

10. Falzon D, Jaramillo E, Schünemann HJ, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J 2011;38:516-28. Epub 2011 Aug 4

11. EuroTB (CESES/KNCV) and the national coordinators for tuberculosis surveillance in the WHO European Region (1998) Surveillance of tuberculosis in Europe Report on tuberculosis cases notified in 1996

12. Special evaluation by Dr. B. Brodhun, Robert-Koch-Institute, Berlin,Germany

13. Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008, Geneva (WHO/HTM/TB/2008.402)]

14. Zierski M (1981) Pharmakologie, Toxikologie und Anwendung von Pyrazinamid. Prax Klin Pneumol. 35:1075-1105

15. Zierski M, Rotermund C (1984) Isoniazid -Wesentliches und Neues. Prax Klin Pneumol 38:201-16

16. Schlossberg D (2001) Current therapy of infectious disease, 2nd edn. Mosby, pp 565

17. Diel R, Nienhaus A, Lange C, Schaberg T. Cost-optimization of screening for latent tuberculosis in close contacts. Eur Respir J 2006; 28:35-44

18. Special evaluation by Dr. Rutz, Barmer GEK public health insurance, reported on 7 September 2011)

19. Graf von der Schulenburg JM, Greiner W, Jost F, Klusen N, Kubin M, Leidl R,Mittendorf T, Rebscher H, Schoeffski O, Vauth C, Volmer T, Wahler S, Wasem J,Weber C; Hanover Consensus Group. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. Value Health 2008; 11:539-44. Epub 2008 Jan 11.

20. Statistisches Bundesamt. Volkswirtschaftliche Gesamtrechnungen; Fach-serie 18, Reihe 1.2 2. Vierteljahr 2011, 2.15 Arbeitnehmerengelt je Arbeitnehmer. Wiesbaden; August 2011

21. Statistisches Bundesamt: Ergebnisse des Mikrozensus: Jahresdurchschnittswerte

22. Diel R. Schwierigkeiten und Schwachpunkte der TB-Kontrolle in Deutschland. 51. Kongress der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin,

Hannover, März 2010.

23. Verband Deutscher Rentenversicherungsträger -VDR Statistik Rehabilitation. Durchschnittliche Pflegetage bei stationären Behandlungen zur medizinischen Rehabilitation und sonstigen Leistungen zur Teilhabe für Erwachsene in der Gesetzlichen Rentenversicherung (Anzahl).

24. Clade H., Rehabilitation: Steigender Bedarf, moderates Wachstum. Rheinisches Ärzteblatt 2010; 64:23-25

25. Statistisches Bundesamt, Bonn (2011). Todesursachen in Deutschland 2009. Fachserie 12 Reihe 4: 2.1 Sterbefälle 2009 nach ausgewählten Todesursachen, Altersgruppen und Geschlecht

26. Diel R, Schneider S, Meywald-Walter K, Ruf C-M, Rüsch-Gerdes S, Niemann S (2002) Epidemiology of tuberculosis in Hamburg, Germany: long-term population-based analysis in applying classical and molecular epidemiological techniques. J Clin Microbiol 40:532-9

27. Diel R, Niemann S (2003) Outcome of tuberculosis treatment in Hamburg: a survey 1997–2001. Int J Tuberc Lung Dis 7:124-31

28. Hanson K (1999) Measuring up: gender, burden of disease, and priority setting techniques in the health sector. http//www.hsph.harvard.edu/Organizations/ healthnet/HUpapers/gender/hanson.html

29. Atun RA, Samyshkin Y, Drobniewski F, Balabanova Y, Fedorin I, Lord J, Coker RJ. Costs and outcomes of tuberculosis control in the Russian Federation: retrospective cohort analysis. Health Policy Plan 2006; 21:353-64.

30. Mancuso JD, Niebuhr DW, Frick KD, Keep LW, Anderson KM. Cost-Effectiveness analysis of targeted and sequential screening strategies for latent tuberculosis. Int J Tuberc Lung Dis 2011; 15:1223-1330

31. Schwarzmann K, Oxlade O, Barr RG, et al. Domestic returns from investment in the control of tuberculosis in other countries. N Engl J Med 2005; 353;1008-20

32. Holland DP, Sanders GD, Hamilton CD, Stout JE. Potential economic viability of two proposed rifapentine-based regimens for treatment of latent tuberculosis infection. PLoS One 2011; 6:e22276. Epub 2011 Jul 18.

33. Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. BMC Public Health. 2006 Jun 19;6:157.

34. Diel R, Wrighton-Smith P, Zellweger JP. Cost-effectiveness of interferon-gamma release assay testing for the treatment of latent tuberculosis. Eur Respir J 2007; 30:321-32.

35. Pooran A, Booth H, Miller RF, Scott G, Badri M, Huggett JF, Rook G, Zumla A, Dheda K. Different screening strategies (single or dual) for the diagnosis of suspected

latent tuberculosis: a cost effectiveness analysis. BMC Pulm Med 2010 Feb 22; 10:7.

36. Kowada A, Deshpande GA, Takahashi O, Shimbo T, Fukui T. Cost effectiveness of interferon-gamma release assay versus chest X-ray for tuberculosis screening of BCG-vaccinated elderly populations. Mol Diagn Ther 2010 14:229-36.

37. World Health Organization. Tuberculosis country profiles: www.who.int/entity/tb/country/data/profiles/en/index.html; last accessed 18 November 2011)

38. Konietzko N, Fabel H (2005) Weißbuch Lunge 2005. 3. neubearbeitete Auflage, Thieme, Stuttgart

39. Blaas SH, Muetterlein R, Weig J, Neher A, Slazberger B, Lehn N, Naumann L. Extensively drug-resistant tuberculosis in a high-income country: a report of four unrelated cases. BMC Infect Dis 2008;8:60

40. Eker B, Ortmann J, Migliori GB, Sotgiu G, Muetterlein R, Centis R, Hoffmann H, Kirsten D, Schaberg T, Ruesch-Gerdes S, Lange C, German TBNET Group. Multidrug- and extensively drug resistant tuberculosis, Germany. Emerg Infect Dis 2008; 14:1700-6

Table 1. GKV costs for out-patient therapy: medical and technical costs

Medical services	No. of points	Point value cents[a]	Individual payment	Frequency	Payment	Post-hospital payment
First doctor's visit (general practitioner or pediatrist)						
Flat rate coverage (irrespective of number of visits by patients) per quarter EBM 03111(equal to EBM 04111 for pediatrists)	880	3.5048	€30.84	2 (2[c]) [MDR patients 6 (4[c])]	€61.68 (MDR patients €185.04)	€61.68 (MDR patients €123.36)
Pneumological diagnostics (pulmonary/intrathoracic TB)						
Pneumological consultation (EBM 13641)	570	3.5048	€19.98	1 (0[c])	€19.98	-
Pneumologist, bronchoscopy to avoid (EBM 13662)	2795	3.5048	€97.96	1(0[c])	€97.96	-
Pneumologist BAL (EBM 13663, additional fee on EBM 13662)	685	3.5048	€24.01	1 (0[c])	€24.01	-
For amikacin treatment in MDR-TB						
Audiometry (EBM 09320); ENT code can also be applied	415	3.5048	€14.54	10 (5[c])]	€145.40	€72.70
Amikacin serum levels EBM32341			*€17.70*	3 (0[c])	€53.1	-
For ethambutol treatment in Non-MDR-TB						
Ophtalmologic consultation EBM 06211 (Sense of colour test can only be charged as flat per quarter)	515	3.5048	€18.05		€18.05	€18.05
Laboratory services						
Intracutaneous test as per Mendel Mantoux (EBM 02200)			*€0,88*	1(0[c])	€0.88	-
Tuberculin 2 TU RT 23 PPD (consultation requirement)			€9.15* (see price calculation above)	1	€9.15	-

Medical services	No. of points	Point value cents[a]	Individual payment	Frequency	Payment	Post-hospital payment
Transport fee per case (EBM 40100), per quarter	-	-	*€2.60*	3 (2[c]) [MDR-TB 6 (5[c])]	€7.8 (MDR-TB €15.6)	€5.2 (MDR-TB €13)
HBs-Ag (EBM 32781)	-	-	*€5.5*	1 (0[c])	*€5.5*	-
Microscopy test for mycobacteria (EBM 32176)			*€5.60*	5 (1[c])(1[b]) (1[d]) [MDR-TB 23 (18[c])]	€28.0 (MDR-TB €128.8)	€5.6 (€0[b]) (MDR-TB €100.8)
NAAT EBM 32825			*€61.40*	1(0[c])	€61,40	-
Culture test for mycobacteria (EBM 32747) per material	-	-	*€31.7*	4 (1[+)] (3[c]) [MDR-TB 22 (18[c])]	€126.8 (€31.7[+]) (MDR-TB €697.4)	€95.1 (€0[+]) (MDR-TB €570.6)
Differentiation of TB bacteria (EBM 32764) if positive **	-	-	*€18.9*	1 (0[b])	€18.9 (€0[b])	-
Resistance definition (EBM 32770) per mycobacteria type **	-	-	*€46 (€9.2* x 5 different antibiotics tested)	1 (0[b])	€46 (€0[b])	-
Creatinine [Jaffe method] (EBM 32066)	-	-	*€0.25*	7 (5[c]) [MDR-TB 22 (19[c])]	€1.75 (MDR-TB 5.5)	€1.25 (MDR-TB 4.75)
Urea (EBM 32065)	-	-	*€0.25*	7 (5[c]) [MDR-TB 22 (19[c])]	€1.75 (MDR-TB 5.5)	€1.25 (MDR-TB 4.75)
Uric acid (EBM 32 064)	-	-	*€0.25*	2 (0[c]) [MDR-TB 20 (19[c])]	€0.5 (MDR-TB 5.0)	- (MDR-TB 4.75)
Blood count (EBM 32122)	-	-	*€1.10*	7 (5[c]) [MDR-TB 22 (19[c])]	€7.7 (MDR-TB 24.2)	€5.5 (MDR-TB 20.9)
HIV serology (Immunoassay combination test) EBM 32576	-	-	*€4.50*	1(0[c])	€4.50	-
Anti-HBc (EBM 32641)	-	-	*€5.90*	1(0[c])	€5.90	-
Bilirubin total (EBM 32058)	-	-	*€0.25*	1(0[c])	€0.25	-
Gamma-GT (EBM 32071)	-	-	*€0.25*	8 (5[c]) [MDR-TB 22 (19[c])]	€2 (MDR-TB €5.5)	€1.25 (MDR-TB €4.75)

Medical services	No. of points	Point value cents[a]	Individual payment	Frequency	Payment	Post-hospital payment
GOT (EBM 32069)	-	-	*€0.25*	8 (5[c]) [MDR-TB 22 (19[c])]	€2 (MDR-TB €5.5)	€1.25 (MDR-TB €4.75)
GPT (EBM 32070)	-	-	*€0.25*	8 (5[c]) [MDR-TB 22 (19[c])]	€2 (MDR-TB €5.5)	€1.25 (MDR-TB €4.75)
X-ray (EBM 34241; a consultation cannot be charged)	430	3.5048 cents	*€15.07*	5 (3[c]) (1[d]) [MDR-TB 12 (9[c])]	€75.35 (15.07[d]) (MDR-TB €180.84)	€45.21 (0[d]) (MDR-TB €135.63)

[a] If no fixed price is stated (italics), average German GKV point value 2011 for all costs types
[b] If there is closed TB
[c] Following primary hospitalisation
[d] For extrathoracic patients only one chest-X-ray at start of diagnostics will we performed
[+] Controls omitted for closed TB

Table 2. GKV costs for out-patient therapy in adults: medication

Adults			
Medication[1]	Costs/day (rounded	Costs[2]	Costs post-hospital stay
Rifampicin[3]	€2.70	€486.0	€405.0 (150 days)
Isoniazid[4]	€0.28	€50.4	€42.0 (150 days)
Ethambutol[5]	€1.63	€97.8	€48.9 (30 days)
Pyrazinamide[6]	€1.61	€96.6	€48.3 (30 days)
-	-	**€730.8**	**€544.2**

[1] Based always on the smallest pack available for the necessary minimum period of treatment. The daily therapy costs are calculated from the quotient between the intake quantity stated in the dosing instructions and the pack quantity and multiplied by the number of treatment days.
[2] Based on an average treatment period of 180 days for isoniazid and rifampicin; 60 days are taken for pyrazinamide, ethambutol and streptomycin using the recommended maximum dose in each case.
[3] Eremfat 600 Tbl., one tablet taken once a day as instructed (maximum dose 600mg)
[4] Isoniazid 300 Tbl., one tablet taken once a day as instructed (maximum dose 300mg)
[5] EMB Hefa 400 Tbl. four tablets taken once a day as instructed (maximum dose 1600mg)
[6] Pyrazinamid 500 Tbl., five tablets taken once a day as instructed (maximum dose 2500mg)

Table 3. GKV costs for out-patient therapy in children: medication

Children			
Medication	Costs/day (rounded up)	Costs[1]	Costs post-hospital stay
Rifampicin[2]	€2.70	€486.0	€405.0 (150 days)
Isoniazid[3]	€0.28	€50.4	€42.0 (150 days)
Pyrazinamide[4]	€1.29	€77.4	€38.70 (30 days)
-	-	**€613.8**	**€485.7**

[1] Based on an average treatment period of 180 days for isoniazid and rifampicin, and 60 days for pyrazinamide using the recommended maximum dose in each case
[2] Eremfat 600 Tbl., one tablet taken once a day as instructed (maximal dose 600mg)
[3] Isoniazid 300 Tbl, one tablet taken once a day as instructed (maximal dose 300 mg)
[4] Pyrazinamid 500 Tbl, four tablets taken once a day as instructed (maximal dose 2g)

Table 4. GKV costs for out-patient therapy in adults with MDR tuberculosis: medication

Adults (MDR-TB)			
Medication	Costs/day (rounded up)	Costs[1]	Costs post -hospital stay (minus 86 days)
Amikacin[2]	€71.22	€17,092.8	€10,967.88
Prothionamide[3]	€3.94	€2,363.04	€2,025.16
Moxifloxacin[4]	€7.04	€4,224	€3,618.56
Pyrazinamide[5]	€1.61	€966	€827.54
Terizidone[6]	€17.28	€10,368	€8,881.92
-	-	**€35,013.84**	**€26,321.06**

[1] Based on an average treatment period of 600 days for pyrazinamide, terizidone, moxifloxacin and prothionamide; 240 days are taken for amikazin using the recommended maximum dose in each case
[2] Amikacin Fresenius infusion bottle 500mg/100ml, two infusions administered once a day as instructed (maximal dose 1000mg)
[3] Ektebin Riemser 100 Tbl. 100 (N3), four tablets taken once a day as instructed (maximal dose 1000mg)
[4] Avalox 400mg Tbl, one tablet taken once a day as instructed (maximal dose 400 mg)
[5] Pyrazinamid 500 mg Tbl., five tablets taken once a day as instructed (maximal dose 2.5g)
[6] Terizidon 250 mg Cps., 2x2 capsules taken as recommended (maximal dose 2x500mg)

Table 5: Age dependent direct treatment costs for tuberculosis

Age group	0<15 years	≥15 years
Hospital treatment		
Mean hospitalisation rate	71.2%	71.2%
Mean reimbursement per case	€9,109.13	€9,109.13
Culture confirmation	80.5%	80.5%
Mean hospital stay	30.17 days	30.17 days
Pneumological monitoring in adults		85.8%
Primary outpatient therapy (adults)		
Intrathoracic TB	-	€1,223.32
Extrathoracic TB	-	€1,040.88
Weigthed average		€1,197.41
Post-hospital outpatient therapy (adults)		
Intrathoracic TB	-	€767.15
Extrathoracic TB	-	€640.88
Weighted average		€749.21
Primary outpatient triple therapy (children)		
Intrathoracic TB	€1,036.51	-
Extrathoracic TB	€825.03	-
Weighted average	€1,006.48	
Post-hospital outpatient triple therapy (children)		
Intrathoracic TB	€690.60	-
Extrathoracic TB	€564.33	-
Weighted average	€672.66	
Primary outpatient MDR-TB patients (adults)		
Intrathoracic TB	-	€36,688.08
Extrathoracic TB	-	€35,667.97
Weighted average	-	€36,543.22
Post-hospital outpatient MDR-TB patients (adults)		
Intrathoracic TB	-	€27,386.55
Extrathoracic TB	-	€26,579.52
Weighted average	-	€27,271.95
Combined inpatients/outpatient costs		
Standard TB adults	-	€7,363.99
Standard TB children	€7,299.73	-
MDR-TB (adults only)		€52,258.84