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Cost-effectiveness of linezolid versus vancomycin for hospitalised patients with complicated skin and soft-tissue infections in Germany

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Abstract This study used a decision analytic model approach to evaluate the cost-effectiveness of linezolid versus vancomycin in the empirical treatment of complicated skin and soft-tissue infection (cSSTI) due to suspected methicillin-resistant *Staphylococcus aureus* (MRSA) from the German hospital and health care system perspective. Clinical probabilities were obtained from trial data, resource utilisation and MRSA prevalence rates were obtained through German physician interviews, and costs from published sources were applied to resource units. Outcomes included total cost/patient and cure. The estimated first-line cure rate for linezolid-treated patients was 90.1% versus 85.5% for vancomycin; total cure rates after two lines of treatment were 98.4% and 98.1%, respectively. Average total cost/episode was 8,232 € for linezolid versus

9,206 € for vancomycin. The model outcomes were sensitive to changes in length of stay (LOS), isolation days, rate of confirmed MRSA and price of linezolid. Linezolid was expected to result in a shorter intravenous treatment duration and shorter LOS that offset its higher acquisition cost versus vancomycin in cSSTI in Germany.

Keywords Complicated skin and soft-tissue infections · Cost-effectiveness · MRSA · Linezolid · Vancomycin

JEL Classification I19

Introduction

Skin and soft-tissue infections (SSTI) are a common cause of morbidity in community settings and hospitals worldwide [1–3]. Complicated SSTI (cSSTI) include severe cellulitis and surgical-site infections. Complications of improperly treated SSTI may result in endocarditis, osteomyelitis, meningitis and pneumonia [4]. For treatment of cSSTI, hospitalisation, surgical intervention and treatment with intravenous (IV) antibiotics are often required, resulting in high treatment costs [5].

The causative agents of a majority of SSTI are *Staphylococcus aureus* or β-haemolytic streptococci, which are susceptible to methicillin/oxacillin treatment [6]. However, the increasing prevalence of methicillin-resistant *S. aureus* (MRSA) poses a serious concern [7, 8]. There has been a significant increase in the prevalence of MRSA in Germany from 15.2% in 1998 to 22.6% in 2004 [9].

Costs, morbidity and mortality associated with MRSA infection compared with those for methicillin-susceptible *S. aureus* (MSSA) infection are substantial [10–12]. The worldwide emergence of MRSA with decreased

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susceptibility to available therapies has generated renewed interest in the development of novel antibiotics to treat serious infections involving these organisms [13–17]. The glycopeptide vancomycin has been the drug of choice for empirical treatment of MRSA-suspected infections. However, the emergence of clinically significant glycopeptide resistance among enterococci [18] and glycopeptide insensitivity in staphylococci [19] has highlighted the need for new agents to treat these infections.

Linezolid is an oxazolidinone antimicrobial agent with activity against a broad spectrum of gram-positive bacteria, including MSSA and MRSA [20, 21]. With its unique mechanism of action, it is not expected to develop cross-resistance with other antibiotics. In addition to an IV formulation, linezolid is available in a 100% orally bio-equivalent form that can allow patients to be discharged from the hospital while continuing therapy rather than remaining in hospital for IV treatment only [22]. Previous studies based on clinical trial data on patients with cSSTI caused by suspected or confirmed MRSA [23] have shown that linezolid appears to reduce hospital length of stay (LOS) by 5–8 days relative to vancomycin [24, 25]. A cost-effectiveness analysis based on data from a multinational clinical trial by Weigelt et al. in patients with cSSTI due to suspected or proven MRSA [26] indicated that treatment with linezolid resulted in lower costs compared with vancomycin, which the authors attributed to a switch from IV to oral treatment and earlier hospital discharge [27]. In the multinational clinical trial [26], the clinical cure rate was higher for linezolid than for vancomycin (92.2% vs. 88.5%; $P = 0.057$), and hospital LOS was shorter in linezolid-treated patients compared with vancomycin-treated patients (7.4 vs. 9.8 days; $P < 0.0001$) [28].

Although the results of the multinational trial [26] provide evidence of the benefits of linezolid compared with vancomycin (including clinical cure and microbiological eradication rate), there were no clinical sites in Germany, making a subanalysis specific to the German health care system difficult. Additionally, the structure of clinical trials may yield resource use data that are driven more by the mandates of the study protocol than by "real-world" practice patterns. This study sought to utilise data from multiple sources, including clinical trial-based efficacy data and effectiveness data for resource use inputs obtained from practicing physicians in Germany.

Moreover, the recent implementation of a diagnosis-related-group (DRG) reimbursement system as the main funding source for German hospitals has put increased pressure on hospital physicians to select the most cost-effective treatment among the available alternatives. Drugs are generally included within the DRG reimbursement, and replacing an existing drug (e.g. vancomycin) with a new and more expensive drug (i.e. linezolid) could decrease the

hospital margin; however, any cost benefits associated with the new drug (e.g. a reduction in LOS) should be taken into account because they increase the hospital margin. Although physicians have become more cost conscious, it is important that they consider all available information on the benefits and costs (overall treatment costs). Within the context of DRG reimbursement, it is important to compare the variable cost side with the fixed revenue side and to explore any potential discrepancies in both (i.e. the hospital making either a loss or a profit).

Therefore, the objective of this study was to estimate the cost of empirically treating cSSTI with linezolid versus vancomycin in hospitalised patients in Germany from a hospital and health care system perspective. A secondary objective was to compare hospital costs estimated from the economic model with the likely DRG reimbursement to the hospital for common cSSTI treatment scenarios.

Materials and methods

Model design

A decision analytical model was developed to simulate the clinical outcomes and costs associated with empirical linezolid or vancomycin for hospitalised patients with cSSTI. The model follows an average patient until the successful conclusion of first- or second-line therapy or failure of second-line therapy. The analysis considers: (1) the perspective of the German hospital system, including direct medical costs associated with hospital treatment only, and (2) the perspective of the German health care system, which also includes posthospital discharge costs for antibiotics, visits and tests. Indirect costs such as productivity losses were not considered.

The model simulates patients initially hospitalised with cSSTI as defined in the study by Weigelt et al. [26] (also referred to as the 128 trial). The trial population included patients admitted to the hospital with proven or suspected MRSA cSSTI, including wound infection, cellulitis, abscesses, acutely infected ulcers and infected burns covering <20% of body surface, or other soft-tissue infections requiring inpatient treatment. The heterogeneous disease subentities of cSSTI were assigned to one of three groups: group 1, cellulitis and major skin abscesses; group 2, surgical site infections, infected traumatic wounds and burns; and group 3, infected ulcers. Assignments were made based on expert opinion, because resource use was expected to vary considerably across the whole cSSTI group. Separating cases into three groups enabled a more homogeneous estimation of clinical parameters and resource use.

At the start of treatment, patients are tested to determine the pathogen causing their infection. When test results

become available, patients either continue their treatment (in the case of known MRSA or unknown infection) or are switched to a drug that targets MSSA infections. This change in treatment is referred to as "therapeutic switch" and does not indicate that the patient has failed first-line treatment. The model considers the following treatment outcomes: (1) cure (clinical cure defined as resolution of symptoms or clinical improvement), (2) failure due to adverse events, (3) failure due to lack of efficacy, or (4) death. This basic structure was used in prior research [23] and was followed in this analysis because of its applicability to cSSTIs. Figure 1 presents a diagram of the decision-tree structure.

A patient who fails first-line linezolid or vancomycin treatment as a result of adverse events or lack of efficacy is treated with a second-line therapy as determined by the physician panel. Second-line treatment in this model has the same potential outcomes as first-line treatment: cure, failure due to adverse events or lack of efficacy or death. The model results include the percentage of patients cured (on first- and second-line treatment) and the average treatment cost per patient (total and by cost category).

Model assumptions

In constructing a decision analytical model, it is necessary to make simplifying assumptions to generalise the paths of patients and allow the application of data from various sources to a single-patient population. The main model assumptions are listed below:

- Patients entering the model were assumed to have gram-positive infections with suspicion of MRSA.
- Patients may have received gram-negative coverage empirically as part of the clinical trial, but it is assumed that the impact of such treatment will be equivalent in the two arms of the model. Because gram-negative infections are beyond the scope of this study, their costs were not considered in this analysis.
- Efficacy of drugs used after first-line failure is not adjusted to reflect that patients may respond differently to subsequent lines of treatment, even in the case of combination therapy.
- The efficacy of the MSSA-targeting drugs, clindamycin and second-line cephalosporin (e.g. cefuroxime) was assumed to be the same as for oxacillin due to the lack of published evidence for a similar population.
- If cultures to determine the organism are inconclusive (i.e. unknown infection), empirical therapy would be continued. For unknown MSSA infection being successfully treated with empirical linezolid or vancomycin, we assume the same treatment duration and hospital LOS as for successfully treating MRSA infection.
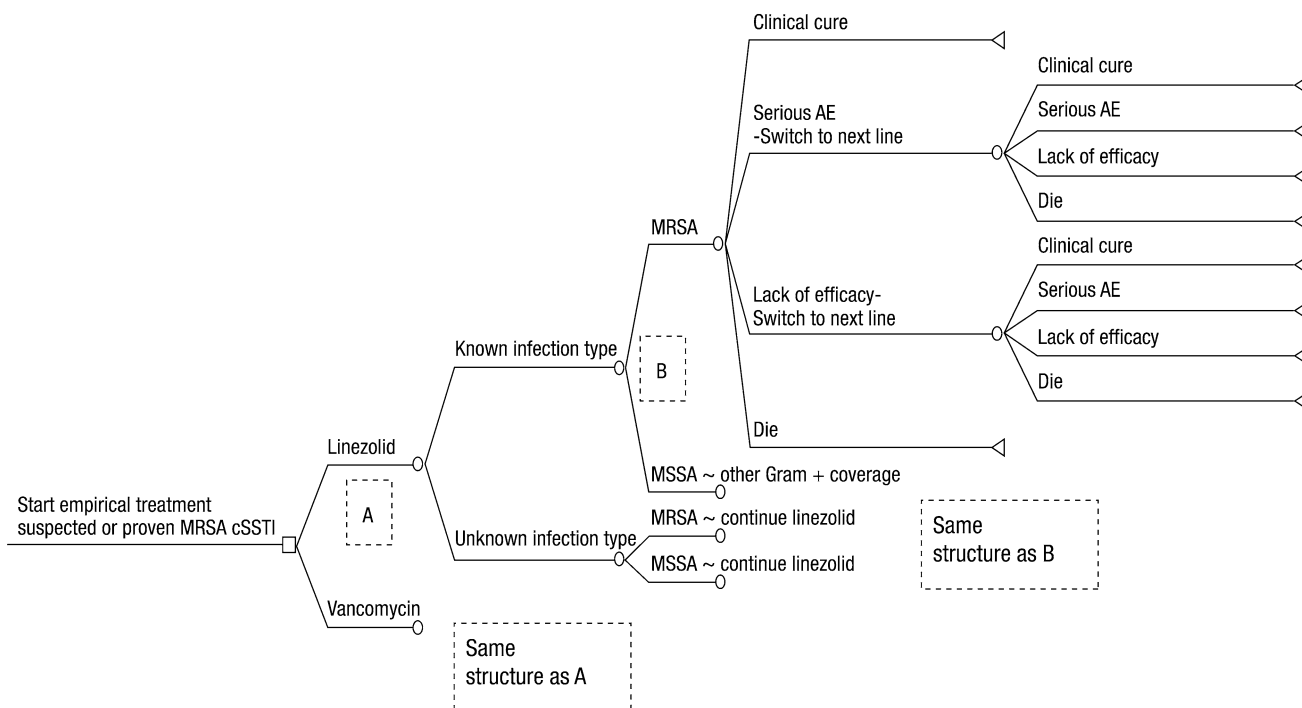

Fig. 1 Decision-tree structure for the empirical treatment of complicated skin and soft-tissue infections due to suspected or proven MRSA. *MRSA* methicillin-resistant *Staphylococcus aureus*, *cSSTI* complicated skin and soft-tissue infection, *MSSA* methicillin-susceptible *S. aureus*, *AE* adverse event

Data sources

Clinical model inputs

Clinical parameters used in the model are shown in Table 1. Intent-to-treat (ITT) cure rates stratified by confirmed MRSA and non-MRSA status were obtained from additional analyses of the same ITT population as the published 128 clinical trial. Rates of adverse events and death rates were obtained from Weigelt et al. [26] and other published literature [4, 23, 29]. The prevalence of MRSA among patients strongly suspected of having an infection caused by this pathogen and the known pathogen rate (rate of test returned with conclusive results) were obtained from the physician panel. Drug choice for patients with known infection and choice of second-line treatment were also obtained from the physician panel (Table 2). The impact of these parameters was assessed in one-way and probabilistic sensitivity analyses.

Resource use inputs

Given that the 128 trial was not German, and to reflect German clinical practice, we conducted structured interviews using the modified Delphi approach with a panel of five practicing physicians experienced in treating cSSTI. This approach consists of reaching consensus among panel members through two separate rounds of consultation. A guiding clinical consultant reviewed the model structure and assumptions and assisted in the development of the survey instrument. Participating physicians were asked to estimate resource use for patients meeting the inclusion criteria from the trial. Data were collected for the three cSSTI groups as specified above and included hospital stay by ward type [i.e. intensive care unit (ICU) vs. general ward], duration in isolation, length and route of treatment,

management of adverse events, selection of second-line treatment, use of concomitant medications, overall length of treatment, frequency of monitoring tests and use of testing and follow-up visits after discharge. Data resulting from these interviews were summarised as mean and standard deviation (SD) or frequency where relevant. During a second round of consultation, any discrepancy between mean values and each physician's individual response was discussed. Subsequently, a new summary with means/SD or frequencies was generated. Individual responses were not disclosed to other panel members. Parameters used in the model are shown in Table 3.

As a scenario analysis, resource use data (first-line IV treatment and oral treatment duration by MRSA status, and LOS in the ICU and other wards by MRSA status) and clinical parameters (distribution by subtype of infection, cure rates) collected in the 128 trial for the ITT population were tested as an alternative to panel data (Pfizer; data on file).

Unit costs

To estimate hospital costs incurred by an average German hospital (i.e. bottom-up costing approach), a variety of nationally relevant unit cost sources was used, and all costs were inflated to 2003 levels [30–34] (Table 4). Unit costs for IV and oral medications were obtained from Rote Liste [35] (Table 5). German hospitals are now funded through the DRG system and no longer by means of per diem rates. Hence, the cost per day of hospitalisation was calculated using the DRG episode costs for infection/inflammation of the skin or subskin with or without very severe complications (DRG J64A-B). Costs of diagnoses and laboratory tests were excluded to avoid double counting of resources. The estimated per diem cost of treating a patient with a cSSTI was 217 €, which represents an average of hotel

Table 1 Clinical parameters used as input in the model

Parameter	Linezolid (%)	Vancomycin (%)	Source
MRSA cure rate, ITT population	94.0	83.6	128 trial additional analyses[a]
MSSA cure rate, ITT population	91.5	90.6	128 trial additional analyses[a]
Discontinuation due to intolerable adverse events	2.1	3.2	Weigelt et al. [26]
Death rate	0.4	0.9	Weigelt et al. [26]
Oxacillin cure rate (CE and ME)	86	86	Stevens et al. [4]
Oxacillin rate of intolerable adverse events	4.8	4.8	Stevens et al. [4]
Oxacillin death rate	0	0	Stevens et al. [4]
Rate of resistant infection, mean (SD)	43 (16)	43 (16)	Physician panel
Rate of unknown infection, mean (SD)	20 (12)	20 (12)	Physician panel

ITT intent to treat, *CE* clinically evaluable, *ME* microbiologically evaluable, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *S. aureus*, *SD* standard deviation

[a] Pfizer; data on file

Table 2 Switch options after treatment failure as determined by physician panel

First-line treatment	Situation	Second-line treatment
Linezolid	Known MRSA	Vancomycin
Vancomycin	Known MRSA	Linezolid
Oxacillin	Known MSSA	Clindamycin
Linezolid or vancomycin (unknown pathogen)	Known MSSA (after further testing)	Cephalosporin second generation (cefuroxime)
Linezolid or vancomycin (unknown pathogen)	Unknown pathogen (remains unknown after further testing)	Linezolid plus carbapenem

MRSA methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *S. aureus*

costs in the general/surgery wards as well as the ICU, as costs by type of ward could not be separated out [33].

The cost of isolation represents the increased resource use associated with this level of care. This covers protective clothing, time spent preparing and changing clothing, washing clothing after use, gloves, masks, and extra nursing and physician care. The estimated cost of 323 € per day was calculated from the bottom up using resource-use data from the physician panel and unit costs from one hospital and a publication by Popp et al. [34] on staff costs associated with isolation measures. This cost was added onto the standard per diem cost by type of ward.

Sensitivity and scenario analyses

We conducted a series of one-way sensitivity analyses to evaluate the sensitivity of model results to changes in the value of individual model parameters that were expected to have some impact on overall results. We evaluated the relative impact of a 25% change above and below the base case value of each selected parameter with all other parameters held constant. Results are presented as a tornado chart.

We conducted a probabilistic sensitivity analysis in which efficacy parameters from the trial and resource use parameters were varied simultaneously by taking a random value for each from their respective probability distributions. Beta distributions were used to describe probabilities, as this distribution is confined to the 0–1 range, and gamma distributions were used to describe resource use and costs, as this distribution is bound by 0 and has a right skew. One thousand simulations were undertaken, whereby for each of the selected parameters the point estimate was replaced by a value drawn from the distribution. Results are presented as scatter plots of 1,000 trials conducted, with each point showing the incremental cost and incremental effect of empirical treatment with linezolid versus vancomycin. For different willingness-to-pay values of a patient cured (0–100,000 €), the probability of the results being cost effective was calculated.

Identification of the pathogen causing the infection is difficult and may have an important impact on treatment cost, given that in this model isolation is applied as long as susceptibility is not confirmed. With increasing resistance (but same level of knowledge of the pathogen), more patients will be kept in isolation. However, with increasing susceptibility to methicillin (but same level of knowledge of the pathogen), more patients having inconclusive test results will be put into isolation when it is unnecessary. Also, local prevalence of resistance varies depending upon the location. To address these concerns, we performed a two-way sensitivity analysis to explore the impact on the incremental cost and cure of both model arms when simultaneously changing the prevalence of antibiotic resistance and the rate of inconclusive test results.

Given the uncertainty of length of treatment and length of hospitalisation for linezolid compared with vancomycin, a scenario analysis was conducted utilising resource use and clinical values collected in the multinational 128 trial (this trial did not include Germany and therefore was not used in the base case). According to this trial analysis, the most common infection type was cellulitis and major abscess (72%). In confirmed MRSA patients, total treatment duration with linezolid was 12.1 days (of which 10.2 days were on oral therapy) compared with 11.5 days (of which 0.2 days were oral) for vancomycin. In unconfirmed MRSA patients, treatment duration was 11.7 days (of which 9.8 days were oral) for linezolid versus 10.7 (of which 2.7 days were oral) with vancomycin. In MRSA patients, LOS was 7.2 days for linezolid patients versus 9.9 days for vancomycin patients. In unconfirmed MRSA patients, LOS was 6.6 days for linezolid patients versus 9.2 days for vancomycin patients. Other parameters unavailable from the trial were assumed to be the same as the base case.

DRG analysis and reimbursement

DRG reimbursement for an individual patient is determined by the combination of all relevant diagnosis and

Table 3 Health resource use parameters used as input in the model

Parameter	Linezolid	Vancomycin	Source
Total length of treatment for patients who die, days (IV/oral)	12.0 (3.0/9.0)	7.7 (7.7/0.0)	Derived from 128 trial data [26]
Total length of hospitalisation for patients who die, days (ICU/GW)	16 (8.3/7.7)	16 (8.3/7.7)	Physician panel
Days in isolation for patients who die (MSSA vs. MRSA)	2.8 versus 16.0	2.8 versus 16.0	Derived from 128 trial data [26]
Days on treatment before therapeutic switch, mean (SD)	2.7 (0.27)	2.7 (0.27)	Physician panel
Days on treatment before failure is determined (LoE) for known MSSA, mean (SD)	3.3 (0.76)	3.3 (0.76)	Physician panel
Days on treatment before failure is determined (LoE) for known MRSA, mean (SD)	3.9 (0.65)	3.9 (0.65)	Physician panel
Days on treatment before discontinue due to adverse events, mean (SD)	5 (2.25)	5 (2.25)	Physician panel
Total length of successful first-line treatment, days (IV/oral)	15.8 (6.4/9.4)	17.3 (14.2/3.1)	Physician panel
Total length of hospitalisation for successful first-line treatment, days (ICU/GW)	10.5 (0.4/10.1)	15.9 (0.4/15.5)	Physician panel
Days in isolation—successful first-line treatment	9.7	15.1	Physician panel
Total length of successful second-line treatment, days (IV/oral)	16.6 (6.6/10.0)	18.4 (15.3/3.1)	Physician panel
Total length of hospitalisation for successful second-line treatment, days (ICU/GW)	9.9 (0.4/9.5)	16.6 (0.4/16.2)	Physician panel
Days in isolation—successful second-line treatment	9.5	16.2	Physician panel
Monitoring tests (per day), mean (SD)			
Biochemistry	0.37 (0.39)	0.43 (0.36)	Physician panel
Haemogram	0.46 (0.31)	0.46 (0.31)	Physician panel
C-reactive protein	0.31 (0.06)	0.31 (0.06)	Physician panel
Drug blood level test	0.00 (0.00)	0.34 (0.41)	Physician panel
Visits after discharge (per week), mean (SD)			
Duration of follow-up	7 weeks	7 weeks	Physician panel
Dermatologist (office)	0.20 (0.45)	0.20 (0.45)	Physician panel
GP visit (home)	0.31 (0.52)	0.31 (0.52)	Physician panel
GP visit (office)	1.11 (1.38)	1.11 (1.38)	Physician panel
Specialist visit (hospital)	0.37 (0.52)	0.37 (0.52)	Physician panel
Nurse visit (home)	1.07 (1.41)	1.07 (1.41)	Physician panel
Tests after discharge (per week), mean (SD)			
Biochemistry	0.76 (0.61)	0.76 (0.61)	Physician panel
Haemogram	0.93 (0.48)	0.93 (0.48)	Physician panel
C-reactive protein	0.80 (0.59)	0.80 (0.59)	Physician panel
Drug blood level test	0.20 (0.45)	0.20 (0.45)	Physician panel

IV intravenous, *ICU* intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *S. aureus*, *LoE* lack of efficacy, *SD* standard deviation, *GP* general practitioner, *GW* general ward

procedure codes accumulated by the patient during hospital stay. In Germany, diagnosis codes follow the *International Statistical Classification of Diseases, 10th revision, German Modification* (ICD-10-GM) [36], and procedure codes are derived from the Operationen-und Prozedurenschlüssel (OPS)-301 classification. At patient discharge, all relevant codes are entered in a DRG grouper software programme.

The software "groups" all codes and other information such as LOS, determines which code (either a diagnosis or procedure) drives DRG calculation, assigns a DRG cost weight and calculates the reimbursement amount for the episode of care. We used the DRG grouper (2007) from the University of Münster [37] to estimate expected DRG reimbursement amounts. We maintained the standard price

Table 4 Unit costs (euro, 2003) used as input in the model

	Value (€)	Source
Hospital costs per diem		
Hospital ward	217/day	DRG [33]
Additional cost of isolation ward	323/day	Physician panel[a] [34]
Intravenous infusion	15.67	DKG-NT [30]
Monitoring test costs		
Biochemistry (klinische Chemie)	33.59	DKG-NT [30]
Haemogram (grosses Blutbild)	5.60	DKG-NT [30]
C-reactive protein	13.99	DKG-NT [30]
Drug blood level test	31.49	DKG-NT [30]
Postdischarge costs		
GP (per home visit)	17.13	EBM [31]
Specialist (per consultation)	39.88	KVWL[b] [32]
GP (per office visit)	38.52	KVWL[b] [32]
Adverse-event management costs (per episode)		
Thrombocytopaenia	787	Resource use from physician panel
Renal insufficiency	2,483	
Fever	2,183	
Diarrhoea	451	

DRG diagnosis-related group, *DKG-NT* Tarif der Deutschen Krankenhausgesellschaft, *EBM* Einheitlicher Bewertungsmaßstab, *GP* general practitioner, *KVWL* Kassenärztliche Vereinigung Westfalen-Lippe

[a] Cost per day of protective clothing, gloves, masks, putting on and taking off protective clothing, preparing clothing and washing after use and extra nursing and physician care

[b] Ratio of remuneration (HVM) of the Regional Association of SHI-Accredited Physicians Westfalen-Lippe

(Basisfallpreis) for the DRG cost weight of 1.0 of 2,900 €. This rate is the cost attached to the DRG weight and is variable across regions (Bundesländer). According to the panel experts, the standard rate is a valid average for Germany.

In collaboration with a clinical expert, we determined relevant diagnosis and procedure codes for five common treatment settings of cSSTI in patients for whom infection is the reason for hospitalisation. The codes that comprise these scenarios and the expected DRG reimbursement amount are described in more detail below:

1. Phlegmon/cellulitis with or without abscess (due to IV drug abuse): abscess forearm (*ICD-10-GM*: *L02.4*); phlegmon arm (*ICD-10-GM*: L03.10); abscess split with drainage (OPS-301: 5–892.18): reimbursement = 1,775 € (G-DRG code J64C)
2. Surgical wound infection (due to infected nail bed after ambulatory toenail excision): infection after surgical procedure (*ICD-10-GM*: T81.4); phlegmon lower extremity (L03.11); acute lymphadenitis lower extremity (*ICD-10-GM*: L04.3); debridement and wound toilet (OPS-301: 5–893.1 g): reimbursement = 4,307 € (G-DRG code T01C)
3. Surgical wound infection (due to pain relief injections subcutis/muscles/backbone because of back pain: phlegmon back (L.03.3); abscess back (L02.2); retroperitoneal abscess, hypostatic migrating abscess (*ICD-10-GM*: K 65.0); retroperitoneal abscess split and drainage (OPS-301: 5–892.1b); debridement and wound toilet (OPS-301: 5–893.0a): reimbursement = 3,573 € (G-DRG code J21Z)
4. Traumatic wounds (due to ambulatory occupational nail/splinter hand injury): posttraumatic wound infection (*ICD-10-GM*: T79.3); phlegmon hand (*ICD-10-GM*: L03.10); phlegmon finger (*ICD-10-GM*: L03.01); debridement and wound toilet (OPS-301: 5–893.09): reimbursement = 4,307 € (G-DRG code T01C)

Table 5 Drug costs (euro) used as input in the model

	Dosing per day	Costs (€)	
		IV	Oral
Linezolid	IV/oral: 600 mg × 2	182.12	176.40
Vancomycin	IV: 1,000 mg × 2	79.44	–
Rifampicin (in combination with vancomycin)	IV: 600 mg × 2	39.42	–
Rifampicin + cotrimoxazole (oral switch from IV vancomycin)	Oral: 600 mg × 2 and 800 mg × 2	–	6.10 + 1.13
Oxacillin	IV: 1,000 mg × 3	32.31	12.92
	Oral: 500 mg × 6		
Clindamycin	IV: 600 mg × 4	62.64	7.38
	Oral: 600 mg × 4		
Cephalosporin second generation (cefuroxime)	IV: 1500 mg × 3	31.10	10.81
	Oral: 500 mg × 3		
Imipenem with linezolid	IV: 1000 mg × 3	72.08	–
Amoxicillin/clavulanic acid (oral switch from IV carbapenem)	Oral: 875 mg × 3	–	11.07

Source: Rote Liste [35]

5. Infected decubitus ulcer (due to being bedridden in the setting of primary ambulatory care): decubitus ulcer grade 3 sacral bone region (*ICD-10-GM*: L89.34); debridement and wound toilet (OPS-301: 5–893.1d): reimbursement = 4,321 € (G-DRG code J20Z)

DRG code U80.1, which is specifically for infection due to MRSA, was added for all scenarios. We applied an estimated LOS of 13.2 days to each scenario, which is the average LOS for vancomycin and linezolid obtained from the physician panel. Ventilation time, which has an important impact on DRG reimbursement, was not expected for cSSTI and therefore was not included.

Results

Physician panel results

In cases of known MSSA, patients were switched to oxacillin after an average 2.7 days of empirical treatment when microbiological test results were available (Table 3). When the pathogen remained unknown, empirical linezolid or vancomycin is continued. A patient was considered a failure after an average 3.3 days of unsuccessful treatment for MSSA and 3.9 days for MRSA. The most frequently mentioned second-line treatment options after failed first-line treatment are shown in Table 2.

The observed frequency of monitoring tests (including biochemistry, haemogram and C-reactive protein levels) was the same across drugs, with minor increases in some tests for patients treated with vancomycin (e.g. drug blood-level tests). Postdischarge resource consumption, including specialist and GP office and nurse home visits, were expected to be the same for both drugs.

According to the panel, an estimated 50% of patients on empirical vancomycin receive treatment in combination with IV rifampicin for the whole treatment duration. No comedications with linezolid were reported. Table 3 shows that the estimated total average length of successful first-line treatment for linezolid was 1.5 days shorter than for vancomycin (15.8 vs. 17.3 days). Patients receiving linezolid were switched to its oral formulation after an average 6.4 days of IV treatment and complete oral treatment outside the hospital. Patients on vancomycin were switched to oral linezolid or oral rifampicin plus oral co-trimoxazole after an average 14.2 days of IV treatment to allow for earlier discharge. The estimated total average length of hospitalisation for successful first-line treatment (Table 3) covers the complete IV therapy phase and part of the oral treatment phase. The total estimated length of hospital stay for successful first-line treatment for linezolid is 10.5 days compared with 15.9 days for vancomycin, or a

difference of 4.5 days. Less than 10% of the duration of hospitalisation was reported to be in the ICU, and more than 90% of the hospitalisations for MRSA were in isolation. Patients with proven MSSA did not remain isolated.

Clinical results

Table 6 presents the overall cure rate generated by the model for patients beginning empirical treatment on linezolid or vancomycin. Overall, 98.4% of patients who started on linezolid were cured versus 98.1% of patients starting on vancomycin. When only cure due to first-line therapy was considered, 90.1% of patients beginning treatment with linezolid were cured compared with 85.5% of patients who began treatment with vancomycin, a difference of 4.6%. Of the patients who failed first-line treatment with linezolid, 84% were cured on second-line therapy (the equivalent of 8.4% of all patients starting treatment on linezolid) compared with 87% of patients who failed treatment on vancomycin being cured on second-line treatment (the equivalent of 12.6% of all patients starting treatment on vancomycin).

Base-case economic results

From the hospital perspective, empirical treatment with linezolid was estimated to be 1,326 € less costly than empirical treatment with vancomycin (6,714 € for linezolid vs. 8,040 € for vancomycin) and 973 € less costly from the health care system perspective, which includes post-discharge costs (8,232 € for linezolid and 9,206 € for vancomycin, respectively) (Table 6). The main cost components for patients receiving empirical linezolid were hospitalisation (4,666 €; 57%), inpatient antibiotics (1,751 €; 21%) and postdischarge (1,518 €; 18%). These were also the main cost categories in the vancomycin arm: hospitalisation (5,902 €; 64%), inpatient antibiotics (1,689 €; 18%) and postdischarge (1,165 €; 13%). For patients beginning treatment with linezolid compared with vancomycin, savings were projected for hospitalisation and in-hospital tests, whereas additional expenditures were seen in antibiotics and postdischarge costs (due to oral linezolid usage).

Probabilistic sensitivity analysis

Figure 2a shows that in 94% of trial simulations, a treatment beginning with linezolid was more effective than a treatment beginning with vancomycin and that in 87.2% of trials, a treatment beginning with linezolid was less costly. A total of 81.7% of trials resulted in linezolid dominating vancomycin (less costly and more effective). The

Table 6 Comparison of cure rates and costs by treatment arm

	Linezolid	Vancomycin	Difference[a]
Clinical outcome cure rates (%)			
Overall	98.4	98.1	0.3
First-line treatment	90.1	85.5	4.6
First-line MRSA	94.0	83.6	10.4
Costs (€)			
Hospitalisation	4,666	5,902	−1,236
Antibiotic drug (inpatient)	1,751	1,689	62
Other inpatient (tests and AEs)	298	450	−152
Total costs (hospital)	6,714	8,040	−1,326
Postdischarge (outpatient antibiotic drug, tests, visits)	1,518	1,165	353
Total costs (health care system)	8,232	9,206	−973

MRSA methicillin-resistant *Staphylococcus aureus*, *AEs* adverse events

[a] Difference is calculated by subtracting the value for vancomycin from the corresponding value for linezolid

remaining scatter plots (Fig. 2b, c, d) present a simulation of 1,000 trial results for each of the three subgroups in the model. In these analyses, trial efficacy estimates as well as resource use estimates by subgroup obtained from the physician panel were used. The results for each of the subgroups indicate that for a majority of trials, a treatment beginning with linezolid was more effective than a treatment beginning with vancomycin and that for a slimmer majority of trials, linezolid was less costly than vancomycin. If a payer is willing to pay 10,000 € or more per additional patient cured in a starting cohort of 1,000 patients, the simulation predicted that linezolid is the cost-effective treatment strategy in at least 88% of trials.

One-way sensitivity analyses

Figure 3 shows that the values of incremental cost of linezolid versus vancomycin remain negative, which implies that in all scenarios, linezolid remained cost saving. Of the parameters tested, incremental cost of treatment was most sensitive to the days in the isolation ward, the local MRSA rate and duration of treatment. If we apply overall trial ITT cure rates for linezolid and vancomycin (92.2% vs. 88.5%) instead of stratifying cure rates by pathogen (data from 128 trial analysis), model results differed only marginally: 913 € cost saving and similar modeled cure rate after two lines of treatment.

Scenario analyses

Figure 4 presents results of the two-way sensitivity analysis. The convergence of the different solid lines indicates
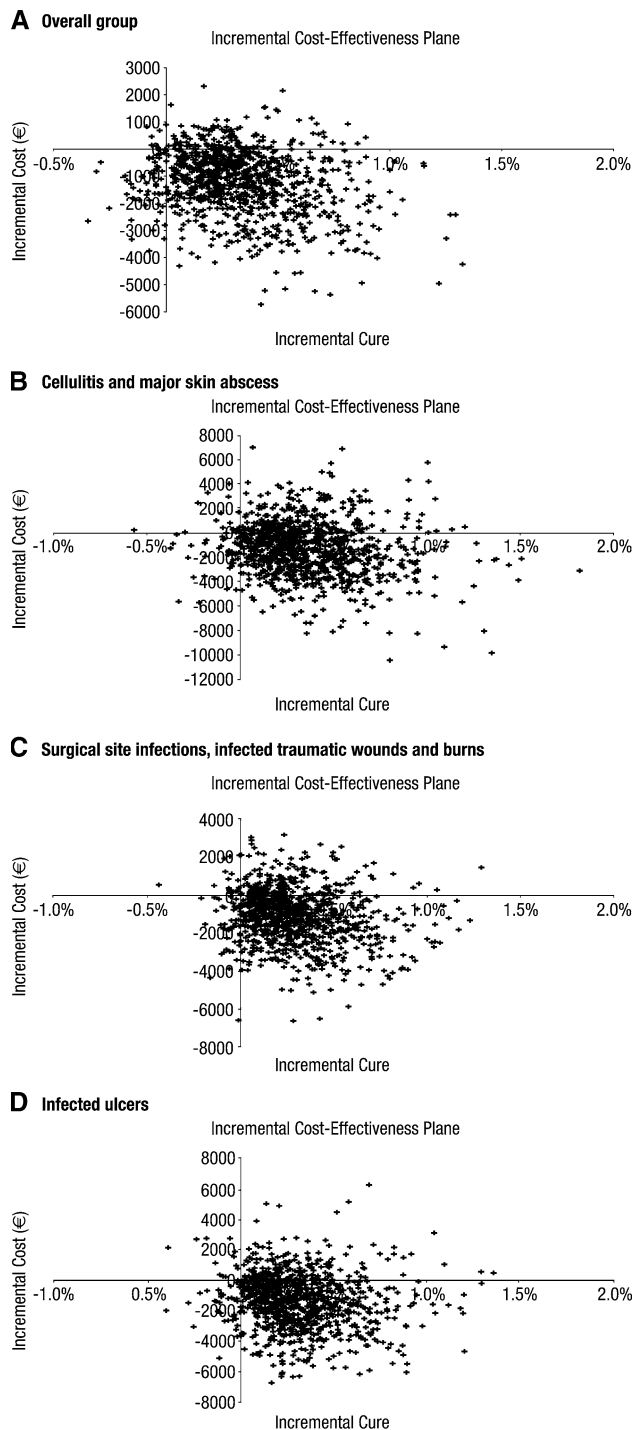

Fig. 2 Incremental cost-effectiveness of linezolid versus vancomycin for treating complicated skin and soft-tissue infection (cSSTI). Scatter plot of 1,000 individual trials in the probabilistic sensitivity analysis: **a** overall group; **b** group 1: cellulitis and major skin abscesses; **c** group 2: surgical site infections, infected traumatic wounds and burns; **d** group 3: infected ulcers

the diminishing effect of the rate of inconclusive test results on the cost of treatment along the rate of resistance (*x*-axis). The ascending dashed lines indicate the trend in

incremental cure. As the resistance rate increases, the incremental percentage of patients cured increases (the gap between linezolid and vancomycin widens in favour of linezolid). The slight convergence of the four lines again indicates the diminishing impact of a potential inconclusiveness of the microbiology resistance testing on the results of the model. Overall, as the rate of resistance increases, it becomes less important to know whether the infection is resistant or not.

In a scenario using resource-use data and clinical parameters from the 128 trial, the linezolid arm remained less costly compared with vancomycin from the health care system perspective (−203 €) and also the hospital perspective (−425 €), despite a smaller difference in LOS between the two arms. In this scenario, an additional 10.3% of MRSA-infected patients were cured with first-line linezolid compared with first-line vancomycin (92.7% vs. 82.2%). After two lines of treatment, 97.7% of patients receiving empirical linezolid were cured versus 97.8% of patients who started on vancomycin.

DRG analysis

For four of five scenarios, the DRG code and reimbursement were driven by the procedure, with DRG reimbursement ranging between 1,760 € for scenario 1 and 4,512 € for scenario 5. The estimated 13.2-day LOS was always within the range of LOS associated with each resulting DRG code (upper LOS limit of 14 days in scenario 1 and 30 days in scenario 5).

We observed a large discrepancy between likely revenue (DRG reimbursement) and likely cost (as generated by the model) for some common cSSTI scenarios. Assuming that scenarios were comparable with the average patient profile in the model calculations, estimated hospital cost in excess of likely revenue means a loss for the hospital. Given that estimated hospital costs with linezolid were smaller than with vancomycin, this loss may be somewhat reduced if linezolid were used.

Discussion

In this study, a decision analytical model was developed based on clinical data from a phase 3 trial of linezolid in patients with proven or suspected MRSA cSSTI. To better capture German treatment practices, interviews using the modified Delphi approach with a panel of practicing physicians were used to determine resource use and treatment pattern parameters. The results of the model indicate that empirical treatment with linezolid was associated with a higher estimated percentage of patients cured (both over two lines of treatment and at the conclusion of first-line

treatment) and a lower average cost when compared with empirical treatment beginning with vancomycin; however, no statistical tests of significance could be performed. The results of the model did not vary by subgroup. The robustness of the model results was evaluated using probabilistic sensitivity analysis. The majority of simulated trials (81.7%) found that linezolid was more effective and less costly than vancomycin. One reason for the disparity among results of the probabilistic trial runs is the relatively small sample size for resource-use estimates from the physician panel, which consequently led to a large variance in those parameters. The clinical parameters on the other hand were drawn from a fairly large sample of patients enrolled in the clinical trial. A scenario analysis based on the 128 trial, which used LOS and treatment duration, estimates that were more conservative than those estimated by the physician panel, showed that linezolid remained less costly than vancomycin due to a shorter average LOS. Robustness was also checked using one-way sensitivity analyses. The model cost results were sensitive to days spent in the isolation ward, MRSA rate and treatment duration but did not change the overall conclusions.

Reducing costs in MRSA infection is particularly important given the substantial additional treatment costs compared with MSSA infection [11, 12]. In an economic study of patients with MRSA and non-MRSA cSSTIs, those with confirmed MRSA infections were more expensive to treat than those with non-MRSA infections. Even when controlling for other factors, MRSA was a significant predictor of increased costs ($P = 0.004$) [27]. In our analysis within the German health care system, linezolid for treating a suspected case of MRSA was approximately 1,326 € less expensive than vancomycin from the hospital perspective and 973 € less expensive from the health care system perspective. Our findings were similar to those of other published studies. McKinnon et al. [27] examined total treatment costs and determinants of costs for the subset of US patients in the 128 trial ($n = 717$). Findings indicate that duration of IV therapy was shorter for linezolid-treated patients versus vancomycin-treated patients [on average 7–11 days shorter ($P < 0.001$)], although overall duration of treatment was similar. LOS was 5.5 ± 6.4 days in linezolid-treated patients versus 7.7 ± 7.7 days in vancomycin-treated patients ($P < 0.001$). The LOS differences were greater in the MRSA subset (3.5 days shorter; $P < 0.001$). The mean $\pm$ SD cost for ITT patients treated with linezolid versus vancomycin was $\$4,865 \pm \$4,367$ versus $\$5,738 \pm \$5,190$, respectively ($P = 0.017$), and $\$4,881 \pm \$3,987$ versus $\$6,006 \pm \$5,039$, respectively ($P = 0.041$) in the MRSA population. After adjusting for all other factors (e.g. age, comorbidities, type of infection, MRSA status) treatment with linezolid was associated with significantly lower treatment costs compared with vancomycin (and more so in

Fig. 3 Tornado graph. One-way sensitivity analyses presenting incremental costs (euro) of linezolid versus vancomycin for treating complicated skin and soft-tissue infection (cSSTIs) in hospitalised patients. Parameters varied 25% from base case (*black* +25%; *white* −25%). *IV* intravenous, *MRSA* methicillin-resistant *Staphylococcus aureus*
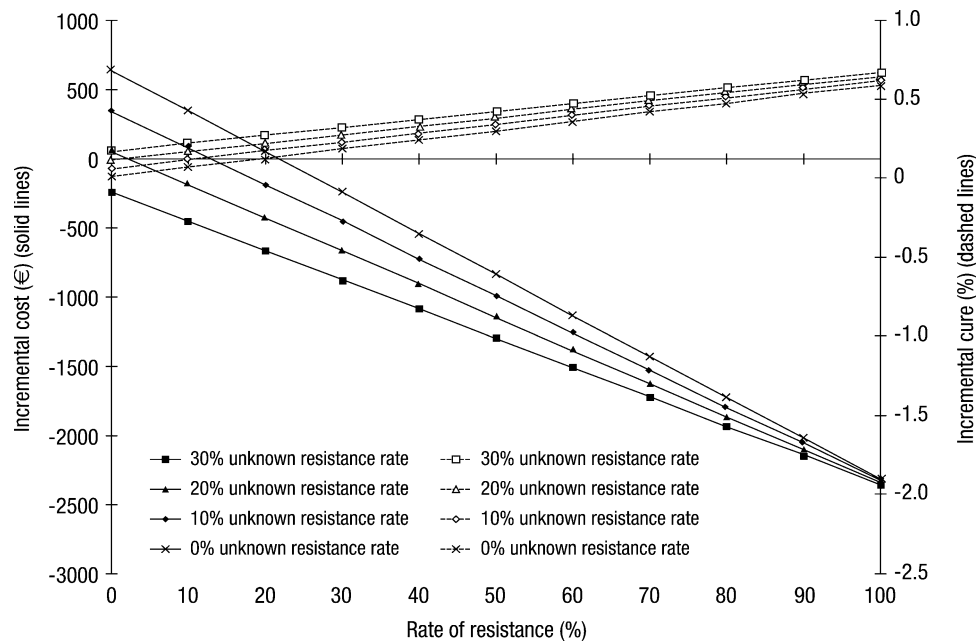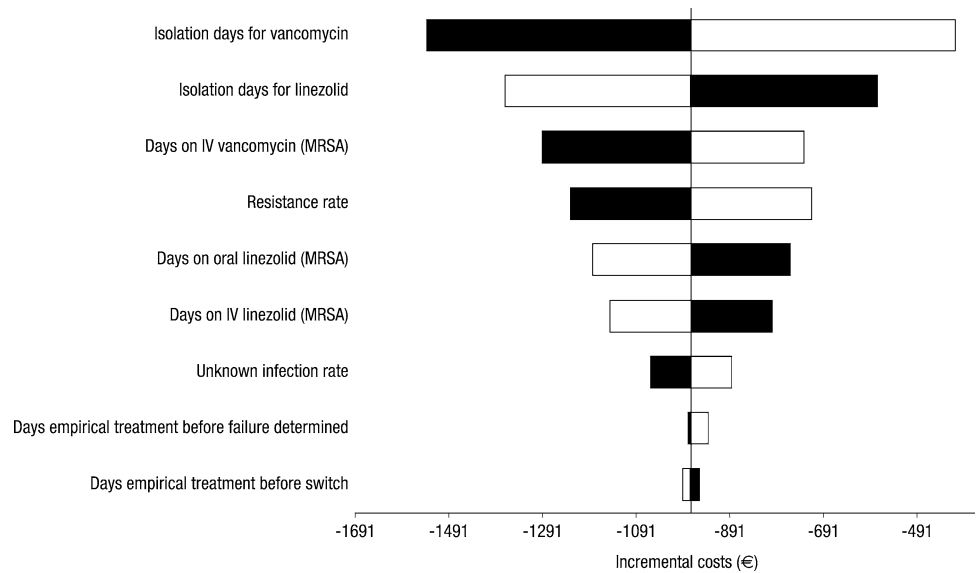

Fig. 4 Incremental costs and incremental cure rates of linezolid versus vancomycin with varying methicillin-resistant *Staphylococcus aureus* rate (at 0%, 10%, 20%, and 30% unknown pathogen rates). The *descending solid lines* indicate the trend in incremental cost: as the resistance rate increases, the savings associated with the use of linezolid compared with vancomycin increases (incremental cost becomes increasingly negative). The *upsloping dashed lines* indicate the trend in incremental cure: the incremental cure of linezolid versus vancomycin increases with the resistance rate. The graph further shows the effect of inconclusive laboratory testing (known infection rate). The narrower this difference, the less important it becomes to know the resistance status of the infection

patients with documented MRSA cSSTI) [27]. Using a decision analysis framework, Vinken et al. conducted two similar economic evaluations comparing linezolid, vancomycin and flucloxacillin in the UK [24] or oxacillin in the USA [38] as empirical treatment for hospitalised patients. The models used efficacy data from two clinical trials [4, 23] and LOS data from one of the trials [23] and that were reported by Li et al. [39]. Results of both analyses found that empirical linezolid resulted in lower total costs than vancomycin for the entire spectrum (0–100%) of the risk of being infected with methicillin-resistant gram-positive pathogens. In the USA, when the risk of methicillin-resistant infection was 100%, total average cost per patient treated with linezolid was $11,267 compared with $11,627 per patient treated with oxacillin and $11,645 per patient treated with vancomycin [38]. Vinken et al. concluded that

the economic benefit of linezolid versus vancomycin is likely due to its oral formulation, which may reduce LOS, and its improved clinical response to MRSA, which may reduce costs associated with treatment failures.

The potential reduction in LOS as a result of a reduction in the duration of IV therapy with linezolid is surrounded by uncertainty. Li et al. [39] evaluated resource use as part of a phase 3 multinational trial in patients with known or suspected MRSA infection receiving either linezolid ($n = 240$) or vancomycin ($n = 220$). Median LOS in the ITT group of 460 patients was 14 days in the linezolid treatment arm compared with 15 days in the vancomycin treatment arm, and the difference was not statistically significant; however, in the ITT subgroup of patients with cSSTI ($n = 230$), median LOS for linezolid patients was 9 days compared with 14 days for vancomycin patients, which was close to being statistically significant. Results in the subgroup of clinically evaluable patients ($n = 144$) were statistically significant (8 days for linezolid vs. 16 days for vancomycin; $P < 0.01$). These results suggest that in the cSSTI population, there is a trend toward a reduction in LOS as a result of the switch from IV to oral linezolid. However, Plosker and Figgitt [25] highlighted that these results should be interpreted with caution because the groups were not identified prospectively in the protocol and patients were not stratified prior to randomisation (i.e. the study protocols for the clinical trials that were used as the basis of health care resource use and economic analyses may not have adequately assessed the use of the study drugs in a real-world setting). Also, the multinational trials, as reported by Weigelt et al. [26], may not be representative of a German setting. These were the two main arguments for relying upon German physician opinion instead.

An important limitation of our study is the reliance on expert opinion for resource-use estimates, in particular length of treatment and LOS. Whereas some investigators report that the Delphi process generates reasonably accurate estimates, reliability has been questioned in studies in which multiple panels produced substantially different estimates for the same parameters [40, 41]. Because resource use is expected to differ between countries, it was important to tailor the analysis to the German setting as much as possible. The size of the reduction in LOS with empirical linezolid, based on the physician panel, was an average 3.3 days after two lines of treatment. However, this reflects a real-world view, which could not be obtained from trial data. A more conservative scenario using use data by pathogen from a separate analysis of the 128 trial indicated fewer hospital days for linezolid compared with vancomycin (2.7 and 2.6 fewer hospital days for MSSA- and MRSA-infected patients, respectively). This may be an underestimate because IV vancomycin for MRSA patients

in Germany is provided within the hospital, and hence LOS (reported at 9.9 days) would be expected to be at least equal to IV therapy duration (11.3 days).

There are limitations to the ability to generalise the results of the model across countries, including the use of isolation wards for this patient population. The experts consulted for this study were unanimous that patients are put into isolation when there is a strong suspicion of MRSA, and hence, isolation constitutes a main cost driver. We found that 46–51% of hospitalisation costs resulted from isolation-ward costs. Our calculation of isolation costs included direct medical costs only and did not consider indirect costs (overheads, costs related to setting up isolation measures, infrastructure of separate isolation rooms, cost of empty beds in isolation room for multiple patients, etc.), which may increase costs and the differences between linezolid and vancomycin. It may be argued that isolation is not something that is widely practised in other European countries, particularly where MRSA is endemic, and there would be no such capacity for isolating such patients. If we hypothesise no isolation, savings from the perspective of the health care system would amount to 139 €. However, no isolation is likely to result in increased MRSA prevalence and associated morbidity and costs, consequences that our model did not account for.

The rate of resistance among infectious organisms is another parameter that can vary significantly between locations. We addressed this by conducting a two-way sensitivity analysis that evaluated the impact on the point estimate results of increasing or decreasing the rate of resistance in the population included in the model. The base-case analysis used a value of 43% for the rate of resistance. Figure 4 shows that given the parameters of the model, an increase in the resistance rate is associated with greater savings and an increase in the percentage of patients cured with linezolid compared with vancomycin. According to the model, if 100% of patients entering the model have proven MRSA (0% inconclusive results), cost savings with linezolid would increase to −2,306 €, with a difference in total cure of 0.55% (Fig. 4).

Another aspect that may differ across countries is the potential option of outpatient or home parenteral therapy. None of the experts we consulted considered home parenteral therapy as an alternative, as IV infusion by nurses at home is not permitted and if performed can only be done by a doctor. In our model, patients in both arms may be switched to oral therapy during hospitalisation and continue oral medication at home (Table 3). Due to a lack of evidence-based data, there are no guidelines in Germany that detail how to switch after IV vancomycin and which drugs to switch to. One physician mentioned a switch from IV vancomycin to oral linezolid or a combination of rifampicin plus cotrimoxazole. Such a switch is not

recommended in German guidelines but may be done in clinical practice.

Given the recent implementation of a DRG reimbursement system in Germany, increasing pressure is put on hospital physicians and administrators to ensure that hospital treatment costs are covered by the fixed reimbursement amounts. In theory, patients assigned a specific DRG code are expected to have similar hospital resource use. Inevitably, some hospital cases have resource use, which is more intensive than the average cases on which the DRG weight is based. In a recent study by Wernitz et al. [42], the authors estimated that only 26.6% of MRSA patients who exceeded the DRG threshold value for LOS were adequately compensated by revenues. In patients with postoperative wound infection ($n = 21$), the average additional time past the LOS threshold was 28.8 days, the average related surcharges were estimated at 6,944 €, but the average additional cost was 11,355 €.

According to our model, the estimated cost to treat a case of suspected MRSA cSSTI was 8,232 € for a patient treated with linezolid and 9,206 € for a patient treated with vancomycin. Under the 2007 DRG system in Germany, a case of MRSA cSSTI may generate revenue of 1,760–4,512 €. This represents the range for a selection of cSSTI scenarios in which the infection is the reason for hospitalisation. In those cases in which cSSTI is a complicating condition following another reason for hospitalisation, the calculation of hospital costs and reimbursement is more complicated and needs to be assessed on a case-by-case basis.

This range indicates that in reality there is likely to be a discrepancy between estimated hospital costs and estimated hospital revenue for a case of cSSTI due to suspected MRSA. Various panel physicians highlighted this as a problem and were of the opinion that the use of innovative and more expensive antibiotics for treating MRSA infections may not be adequately covered within the current DRG system.

The model cost of antibiotic therapy and isolation-related expenses combined is 3,914 € and 4,658 € for patients starting on linezolid and vancomycin, respectively, which represents most of the expected reimbursement for the highest-paid scenario. This may show that resource use for managing MRSA infection in cSSTI patients (antibiotic therapy and isolation) may not be adequately covered by the system. Although for all scenarios we added the secondary diagnosis code for MRSA (U80.0!), its impact on the final reimbursement amount remains unclear. The G-DRG system reimburses expenses incurred by long-stay outliers with an extra payment only after the maximum range of LOS has been reached, which was not the case for our cSSTI treatment scenarios. Additional per diem reimbursement for the selected DRGs ranges between 169 € and 189 €, which likely is insufficient to cover hospital costs incurred, especially if the patient remains in isolation.

This discrepancy may also be the case in other countries that use a prospective payment system based on DRGs. However, this would need to be evaluated on a country-by-country basis, because countries use different patient classification systems and reimbursement calculation rules. It has been argued that because special procedures/high-cost cases undermine the targeted-cost homogeneity within individual DRGs, additional fees have to be used as long as DRG-oriented reimbursement mechanisms are applied [43].

If linezolid and vancomycin drug costs, which constitute 21% and 18% of total model costs, respectively, were covered by additional reimbursement, as is currently the case for other innovative and expensive treatments [e.g. trastuzumab (Herceptin) in cancer care], an important part of the budgetary pressure for treating MRSA-infected patients would be relieved. Alternatively, a separate provision for isolation (such as the case for ventilator support) could be an option to relieve cost pressures that discourage the use of newer drugs.

Conclusion

Results from this economic model suggest that linezolid is a cost-effective alternative to vancomycin for empirically treating patients with cSSTI due to suspected MRSA. Despite the higher drug acquisition costs of linezolid versus vancomycin, the expected reduction in hospital days, especially in the isolation ward, resulted in more favourable economic outcomes. These economic considerations are important given the increasing pressures faced by German hospitals to ensure that hospital costs do not exceed or exceed as little as possible the fixed hospital revenues generated by the prospective DRG-based payment.

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