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Original article

Comparing the cost-effectiveness of linezolid to trimethoprim/sulfamethoxazole plus rifampicin for the treatment of methicillin-resistant *Staphylococcus aureus* infection: a healthcare system perspective

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ABSTRACT

Objective: Few industry-independent studies have been conducted to compare the relative costs and benefits of drugs to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection. We performed a stochastic cost-effectiveness analysis comparing two treatment strategies—linezolid versus trimethoprim-sulfamethoxazole plus rifampicin—for the treatment of MRSA infection.
Methods: We used cost and effectiveness data from a previously conducted clinical trial, complementing with other data from published literature, to compare the two regimens from a healthcare system perspective. Effectiveness was expressed in terms of quality-adjusted life-years (QALYs). Several sensitivity analyses were performed using Monte Carlo simulation, to measure the effect of potential parameter changes on the base-case model results, including potential differences related to type of infection and drug toxicity.
Results: Treatment of MRSA infection with trimethoprim-sulfamethoxazole plus rifampicin and linezolid were found to cost on average €146 and €2536, and lead to a gain of 0.916 and 0.881 QALYs, respectively. Treatment with trimethoprim-sulfamethoxazole plus rifampicin was found to be more cost-effective than linezolid in the base case and remained dominant over linezolid in most alternative scenarios, including different types of MRSA infection and potential disadvantages in terms of toxicity. With a willingness-to-pay threshold of €0, €50 000 and €200 000 per QALY gained, trimethoprim-sulfamethoxazole plus rifampicin was dominant in 100%, 96% and 85% of model iterations. A 95% discount on the current purchasing price of linezolid would be needed when it goes off-patent for it to represent better value for money compared with trimethoprim-sulfamethoxazole plus rifampicin.
Conclusions: Combined treatment of trimethoprim-sulfamethoxazole plus rifampicin is more cost-effective than linezolid in the treatment of MRSA infection. **E. von Dach, Clin Microbiol Infect 2017;23:659**

Introduction

Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) represent a therapeutic challenge. The treatment most frequently recommended is a prolonged course of

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parenteral vancomycin or daptomycin [1]. Alternative treatment regimens with oral antibiotics (e.g. linezolid) have been proposed [2,3]. The use of older drugs such as trimethoprim-sulfamethoxazole, combined with rifampicin may represent a particularly interesting treatment alternative [1,4,5].

We previously performed a randomized, non-inferiority trial to compare the efficacy and safety of therapy with trimethoprim-sulfamethoxazole plus rifampicin versus linezolid to treat MRSA infection [6]. The principal findings of the study were: (a) compared with linezolid, the combination of trimethoprim-sulfamethoxazole plus rifampicin was not inferior for the treatment of MRSA infection; (b) there was no difference between the studied drugs in terms of total adverse events, serious adverse events or adverse drug reactions (ADR) [6]. Moreover, as trimethoprim-sulfamethoxazole and rifampicin are available as generic agents, this regimen may offer a substantial cost advantage over other agents such as linezolid and daptomycin [7]. As the launch of generic linezolid has recently been postponed in several countries and novel oxazolidinone agents (e.g. tedizolid) will be patent-protected against generic erosion for many years, the off-patent combination of trimethoprim-sulfamethoxazole plus rifampicin seems to be an attractive alternative oral treatment option for MRSA infection, though still underused because of safety concerns. Possibly, this combination therapy may generate substantial indirect costs due to rare, but costly severe ADRs. For all these reasons, we performed a cost-effectiveness analysis using data from our randomized controlled trial (RCT) and other sources to examine the economic impact of these treatment regimens from the perspective of the healthcare system.

Materials and methods

We constructed a stochastic decision tree model from a Swiss healthcare system perspective, using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA, USA). The model was developed using data from the previously published RCT comparing trimethoprim-sulfamethoxazole plus rifampicin to linezolid for the treatment of any type of MRSA infection (Fig. 1). This trial was an investigator-initiated, open-label, single-centre RCT to evaluate the efficacy of a combination of trimethoprim-sulfamethoxazole (160/800 mg thrice daily) plus rifampicin (600 mg once daily) versus linezolid (600 mg twice daily) in 150 patients (allocation ratio 1 : 1) requiring antibiotic therapy for MRSA infection at the Geneva University Hospitals. Patients who were treated for ≥72 h before study inclusion with antimicrobials active against MRSA (mostly vancomycin) were excluded. We included all types of MRSA infection except chronic MRSA osteomyelitis without surgical debridement, a super-infected indwelling foreign body kept in place, severe sepsis or septic shock due to MRSA bacteraemia, and left-sided endocarditis. Patients were followed throughout the duration of antibiotic therapy until 6 weeks after the end of treatment. A full description of the RCT is available elsewhere [6].

Probabilities and duration of study treatment

All effectiveness probabilities used in the model were based on the previous RCT (Table 1), including the efficacy of the study drugs stratified by type of MRSA infection, the cumulative incidence of death and the rate of ADR observed in each study arm. Data surrounding duration of treatment (days) were obtained from the RCT and then stratified by mode of administration (oral versus intravenous). Of note, the overall length of hospital stay was similar between the two treatment groups [6].

Costs

In this analysis, we used only direct costs in 2016 Swiss francs (CHF) and Euro (€) (1CHF = €0.92, December 2016) for the study drugs and ADR costs (Appendix 1). Drug costs were obtained from the Swiss medicines agency (Table 1). In the base case the highest unit price was used where there was variation due to packaging or

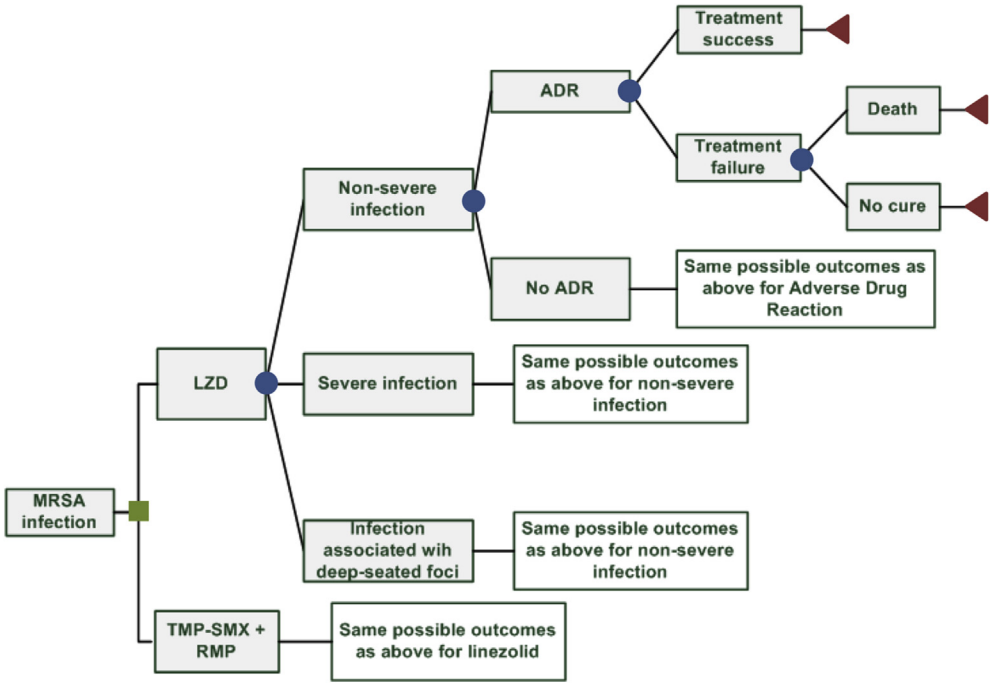


Fig. 1. Decision tree model. Abbreviations: LZD, linezolid; TMP-SMX, trimethoprim-sulfamethoxazole; RMP, rifampicin; ADR, adverse drug reaction; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 1
Model input data for the base-case scenario

Variables	Non-severe infections ($n = 62$)		Severe infections ($n = 53$)		Infection associated with deep-seated foci ($n = 35$)			Ref.
	Mean	SD	Mean	SD	Mean	SD	Distrib.[b]	
Probabilities								
LZD treatment ($n = 75$)	0.36	0.06	0.41	0.06	0.23	0.05	*Beta*	[6]
Presence of ADR	0.04	0.04	0.13	0.06	0.00	0.00	*Beta*	[6]
Treatment failure	0.19	0.07	0.29	0.08	0.29	0.11	*Beta*	[6]
Death among treatment failure	0.00	0.00	0.67	0.16	0.40	0.22	*Beta*	[6]
TMP-SMX + RMP treatment ($n = 75$)	0.47	0.06	0.29	0.05	0.24	0.05	*Beta*	[6]
Presence of ADR	0.14	0.06	0.06	0.04	0.06	0.05	*Beta*	[6]
Treatment failure	0.14	0.06	0.23	0.09	0.33	0.11	*Beta*	[6]
Death among treatment failure	0.00	0.00	0.60	0.22	0.33	0.19	*Beta*	[6]
Durations of treatment (days)								
LZD treatment ($n = 75$)								
IV administration	0.63	1.84	0.97	2.95	1.65	3.46	*Gamma*	[6]
PO administration	7.11	3.37	10.98	4.56	28.71	10.74	*Gamma*	[6]
TMP-SMX + RMP treatment ($n = 75$)								
IV administration	0.03	0.17	0.73	2.98	4.83	9.86	*Gamma*	[6]
PO administration	7.89	2.18	12.00	4.27	32.28	28.64	*Gamma*	[6]
Costs, price, by drug unit,[a] CHF/€								
LZD IV treatment (600 mg)	92.23 / 84.77		92.23 / 84.77		92.23 / 84.77			[c]
LZD PO treatment (600 mg)	94.14 / 86.53		94.14 / 86.53		94.14 / 86.53			[c]
TMP-SMX IV treatment (800/160 mg)	5.08 / 4.67		5.08 / 4.67		5.08 / 4.67			[c]
TMP-SMX PO treatment (800/160 mg)	0.67 / 0.62		0.67 / 0.62		0.67 / 0.62			[c]
RMP PO treatment (600 mg)	3.48 / 3.20		3.48 / 3.20		3.48 / 3.20			[c]
RMP IV treatment (600 mg)	37.60 / 34.56		37.60 / 34.56		37.60 / 34.56			[c]
ADR due to LZD treatment (mean)	0.00 / 0.00		10.09 / 9.27		0.00 / 0.00			[c]
ADR due to TMP-SMX + RMP treatment (mean)	20.24 / 18.60		0.00 / 0.00		42.77 / 39.31			[c]
IV material by days of treatment	1.44 / 1.32		1.44 / 1.32		1.44 / 1.32			[d]
QALYs								
Death	0.00		0.00		0.00			[8–10]
Cure	1.00		1.00		1.00			[8–10]
No cure								
LZD	0.96		0.90		0.86			[8–10]
TMP-SMX + RMP	0.95		0.89		0.82			[8–10]

Abbreviations: ADR, adverse drug reaction; Distrib., Distribution; LZD, linezolid; PO, per os; QALYs, quality-adjusted life-years; Ref., References; RMP, rifampicin; TMP-SMX, trimethoprim-sulfamethoxazole; IV, intravenous.

[a] Costs are adjusted to December 2016.

[b] We used a beta distribution, a continuous probability distribution defined on the interval [0, 1], for the following variables: efficacy of the study drugs, cumulative incidence of death and ADR. All variables surrounding duration of treatment were assumed to follow a gamma distribution, due to their continuous nature.

[c] http://www.listedesspecialites.ch/ Federal Department of Home Affairs—Federal Office of Public Health—List of specialties [cited 2016 December].

[d] The price of this kit is 5.75 CHF, provided by the pharmacy of the Geneva University Hospitals. According to the local recommendations, the peripheral venous catheter has to be changed every 4 days, representing a daily price of this supply for intravenous administration of 1.44 CHF.

volume. For the studied antibiotic drug, no discount was offered to our institution, so none were considered in the base case scenario. Equipment costs were added for therapeutic intravenous administration and those needed for ADR treatment. ADR-related costs also included those pertaining to the laboratory testing required for investigation as well the additional therapeutic treatment. The costs of the laboratory tests were attributed according to the price charged to Geneva University Hospitals (adjusted to December 2016). In the base case, no ADR-related supplementary medical examinations or hospital stay extensions were costed in, as per the findings of the RCT.

Quality-adjusted life-year

The effectiveness outcome from our model was quality-adjusted life years (QALY; Table 1). This is a generic measure of disease burden (including quality and quantity of life lived), which is commonly used in health economics. QALYs are estimated by applying utility weights that typically range from 0 (death) to 1 (perfect health). In this study we attributed a utility weight of 1 if the patient fully recovered and 0 if the patient died. In the case of treatment failure without death, we attributed a utility weight according to the severity of MRSA infection [8]. The categories of MRSA infection (severe, associated with deep-seated foci, or non-severe) were determined by site of infection and duration of therapy, as defined in the RCT [6]. The utility weights attributed to each type of infection were derived from the Health-Related Quality-of-Life score using the EuroQol 5D Health domains (with UK scoring) [9,10]. The QALY was calculated by multiplying weights by average duration of MRSA infection in the RCT (7/8 days for non-severe-infections, 13/13 days for severe infections and 30/38 days for infections associated with deep-seated foci, for linezolid and trimethoprim-sulfamethoxazole plus rifampicin, respectively [6]). The same procedure was performed to attribute QALYs to patients who developed an ADR.

Cost-effectiveness analysis

We conducted a cost-effectiveness analysis (CEA)—more specifically a cost–utility analysis—to compare the two interventions using a decision tree. The base case scenario was defined by the following:

Incremental cost (€) = trimethoprim-sulfamethoxazole plus rifampicin cost – linezolid cost

Incremental effectiveness (QALYs) = trimethoprim-sulfamethoxazole plus rifampicin effectiveness – linezolid effectiveness

The incremental cost-effectiveness ratio is the ratio of these two values. A strategy is considered dominant if it is both less expensive and more effective.

One-, two- and three-way sensitivity analyses

Sensitivity analyses were conducted to test how variation in one, two or three variables could affect model results. Several key parameters, including linezolid efficacy (stratified also by type of MRSA infection), ADR cost and linezolid drug price were altered to capture potential differences in a real-world setting (see below for full list).

Probabilistic sensitivity analysis

We also conducted a probabilistic sensitivity analysis using Monte Carlo (MC) simulation in order to allow for simultaneous variation of all variables [11], each assigned an appropriate type of probability distribution according to the type of uncertainty the variable represents. We performed a MC simulation to sample randomly from those distributions, comparing possible incremental cost-effectiveness ratios over 10 000 iterations. The 95% confidence ellipse was obtained to create an incremental cost-effectiveness plane to facilitate interpretation of the results. Cost-effectiveness acceptability curves were also calculated to summarize information and support decision-making under differing perceptions of potential risk and benefits.

Generic linezolid cost

As generic linezolid was made available in several European countries in 2016, we modelled the cost-effectiveness using several potential wholesale prices of generic linezolid. According to the Swiss regulatory authorities, the generic linezolid price is permitted to be 10%–60% less expensive than the originator linezolid price, depending on sales volume [12]. Recently, the price of linezolid was fixed in Switzerland with a 10% discount compared with the originator. However, the reduction can be as much as 50%, as proposed in Italy and Germany. We performed a sensitivity analysis altering the linezolid generic price in line with the different possible price levels.

Linezolid efficacy

Several RCTs on linezolid efficacy to treat MRSA infection have already been published. A literature review was therefore performed using each of these studies to extract the various efficacy levels of linezolid in treating MRSA infection (Appendix 2). Twenty different trials were identified, with a linezolid efficacy against MRSA infection ranging from 37% to 100%, with a median of 75% and a weighted average of 69% (weighted by the number of patients included in the study). The range of values and the weighted average retrieved from the literature were incorporated within a triangular distribution in the sensitivity analysis to allow for variation.

Serious adverse drug reactions

Due to the relatively small patient sample size in our RCT, rare and serious ADR due to trimethoprim-sulfamethoxazole plus rifampicin treatment did not occur during our study and so were not accounted for in the base case. However, as some types of serious ADR can be extremely expensive and could increase the cost of treatment considerably, the risk of such occurrences could not be ignored. After a thorough literature review, including the official prescribing manuals and the pharmaco-vigilance reference standards, a number of previously described serious ADRs appeared relevant and were added to the CEA, including toxic epidermal necrolysis and acute renal failure necessitating dialysis (both deriving from trimethoprim-sulfamethoxazole consumption) and acute liver failure requiring liver transplant (deriving from rifampicin consumption), among others (Appendix 3). QALYs were constructed for these serious ADR using data from the published literature [13–15].

Results

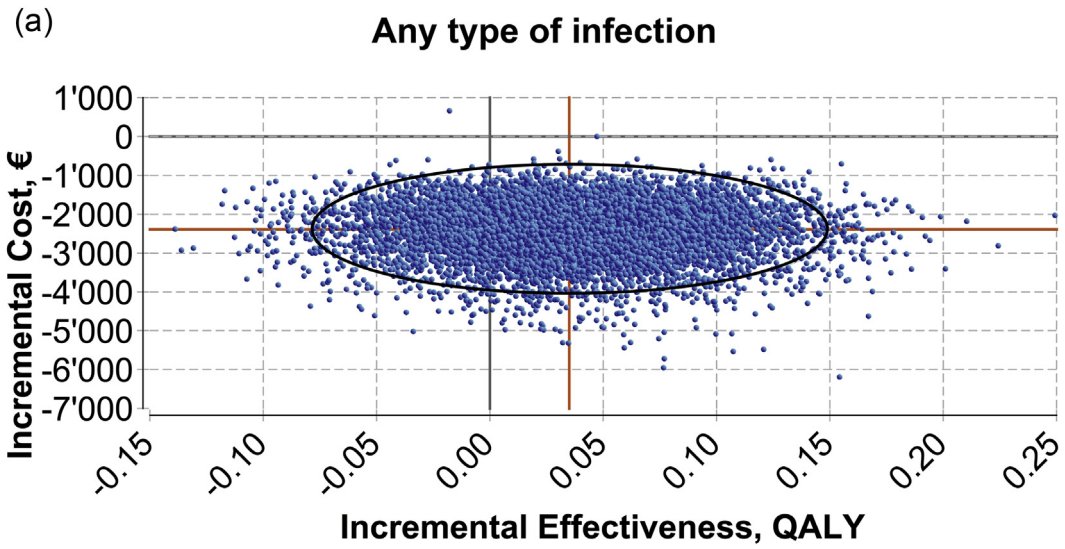
The base case suggested that, on average, the combination treatment of trimethoprim-sulfamethoxazole plus rifampicin (€146 and 0.916 QALY) was less costly and slightly more effective than linezolid for treatment of MRSA infection (€2536, 0.881 QALY), thus suggesting dominance (Table 2). Stratified by type of MRSA infection, ICER results suggest that trimethoprim-sulfamethoxazole is dominant in cases of non-severe and severe infection. In the case of deep-seated infection, trimethoprim-sulfamethoxazole is much less costly and slightly less effective (Table 2). Results of the simulation suggest that with a willingness-to-pay threshold of €0, €50 000 and €200 000, trimethoprim-sulfamethoxazole plus rifampicin was dominant in 100%, 96% and 85% of the time (Fig. 2). Appendix 4 shows the results of the MC simulation by type of infection.

One- and two-way sensitivity analyses showed that trimethoprim-sulfamethoxazole plus rifampicin dominated linezolid even when we used extreme scenarios such as a linezolid

Table 2
Base case scenario by type of methicillin-resistant *Staphylococcus aureus* infection

	Any type of infection	Non-severe infections	Severe infections	Infections associated with deep-seated foci
TMP-SMX + RMP treatment				
Cost	146.23€	43.91€	96.96€	406.16€
Effectiveness (QALY)	0.916	0.993	0.846	0.851
ACER (€/QALY)	159.59	44.22	114.63	477.10
LZD treatment				
Cost	2535.75€	1337.70€	2066.16€	5248.04€
Effectiveness, (QALY)	0.881	0.992	0.796	0.860
ACER (€/QALY)	2876.97	1347.94	2595.26	6104.93
Incremental cost	−2389.51€	−1293.79€	−1969.20€	−4841.88€
Incremental effectiveness (QALY)	0.035	0.001	0.050	−0.008
ICER (€/QALY)	Dominant	Dominant	Dominant	631 883

Abbreviations: ACER, average cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LZD, linezolid; RMP, rifampicin; TMP-SMX, trimethoprim-sulfamethoxazole.



Quadrant	Incr. Cost (€)	Incr. Effect. (QALY)	Incr. Cost-Effect.	Freq.	Prop.
North-East	IC>0.0	IE>0.0	ICER>0.0	1	0%
North-West	IC>0.0	IE<0.0	Dominated	1	0%
South-West	IC<0.0	IE<0.0	ICER>0.0	2227	22%
South-East	IC<0.0	IE>0.0	Dominant	7771	78%

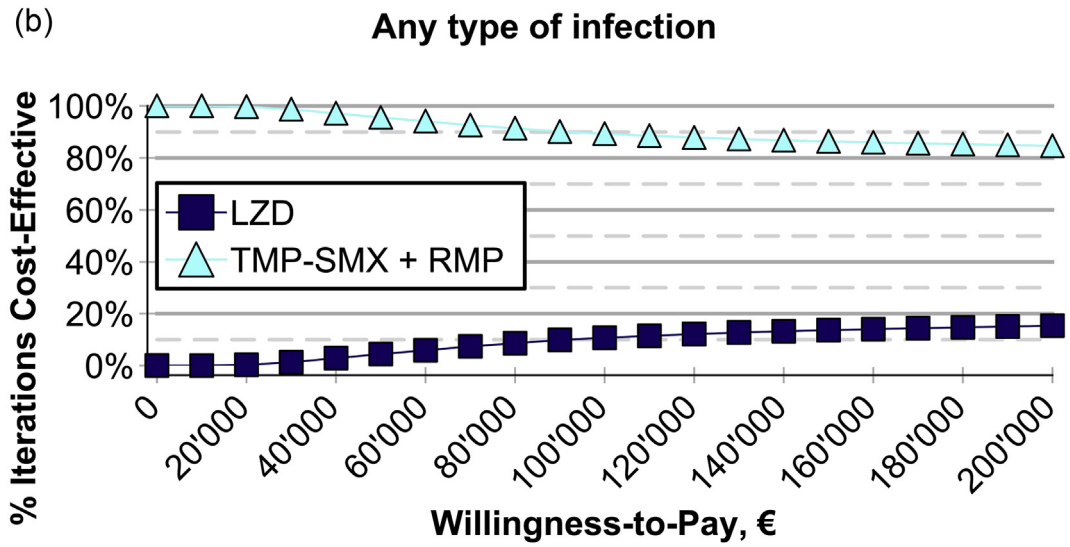


Fig. 2. Incremental cost-effectiveness plane and table, with cost-effectiveness acceptability curves (CEAC). (a) Monte Carlo simulation. Each blue spot represents one of the 10 000 iterations. The two orange lines represent the base-case scenario. (b) Cost-effectiveness acceptability curves. Abbreviations: LZD, linezolid; Incr. Cost, incremental cost; Incr. Eff, incremental effectiveness; Incr. Cost-Effect., Incremental cost-effectiveness; QALYs, quality-adjusted life years; RMP, rifampicin; TMP-SMX, trimethoprim-sulfamethoxazole.

efficacy fixed at 1.0, a maximum assumed ADR cost attributed to trimethoprim-sulfamethoxazole plus rifampicin (€320 per patient), or the highest possible discount offered on the linezolid price of 60% (Fig. 3). Results of the one-way sensitivity analysis suggested that a 95% discount on the price of linezolid would need to be applied for it to become more cost-effective than trimethoprim-sulfamethoxazole plus rifampicin.

These results were confirmed by the three-way sensitivity analysis. The treatment of trimethoprim-sulfamethoxazole plus rifampicin stayed dominant in each case (Appendix 5). When we

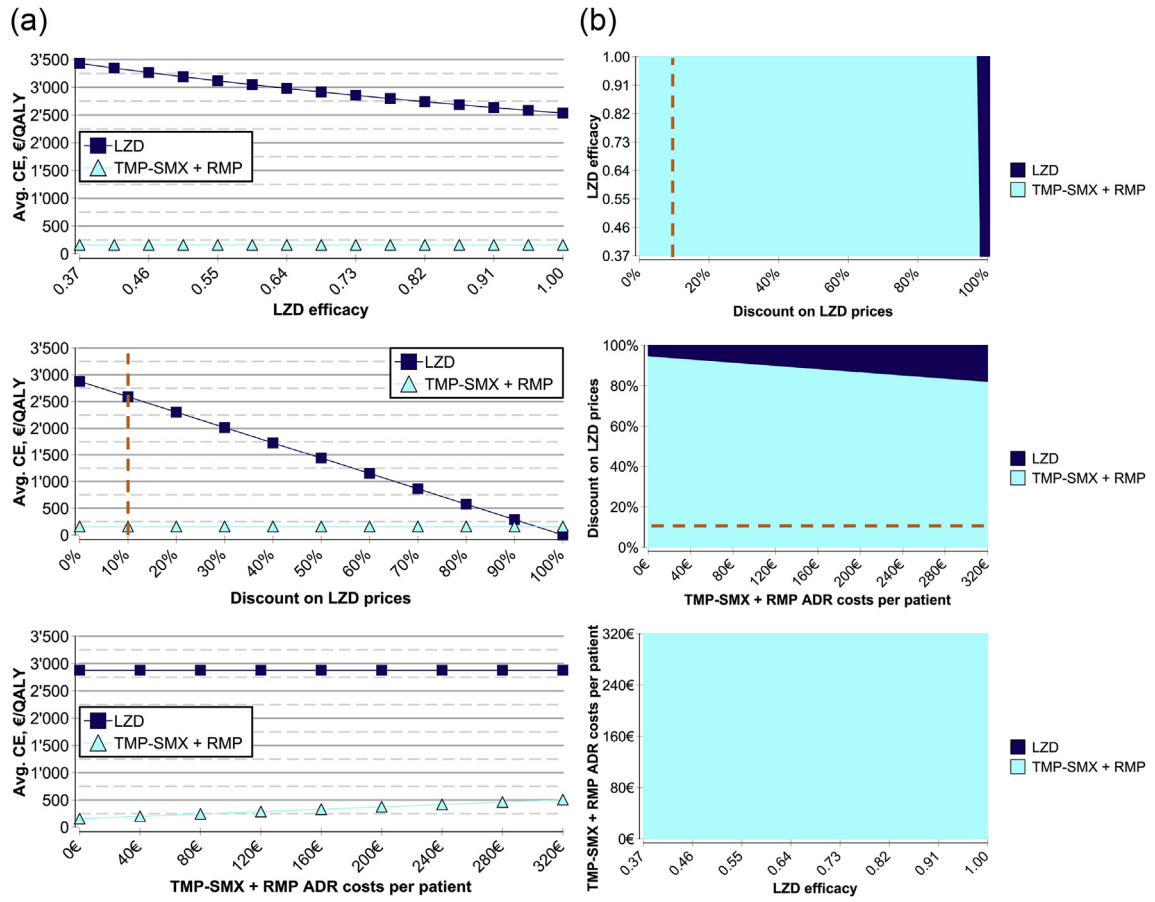


Fig. 3. One-way and two-way sensitivity analysis on assumed inputs. (a) One-way sensitivity graph: the cost by QALY gained is represented for each treatment according to the value for the variable tested. (b) Two-way sensitivity analysis is an analysis in which two variables of interest are simultaneously varied over a range of plausible values while holding all other variables constant (according to the base case scenario). In these types of graphs the most cost-effective interventions according to the value for the variables tested are represented according to their colours (TMP-SMX + RMP: light blue, LZD: dark blue). The orange line represents the 10% discount on generic LZD price applied in Switzerland since late 2016. Abbreviations: ADR, adverse drug reaction; LZD, linezolid; QALYs, quality-adjusted life years; RMP, rifampicin; TMP-SMX, trimethoprim-sulfamethoxazole.

performed probabilistic sensitivity analyses (MC simulations) to reproduce cost-effectiveness acceptability curves, with maximum assumed ADR costs attributed to trimethoprim-sulfamethoxazole plus rifampicin, varied linezolid efficacy and varied linezolid prices, results suggested that trimethoprim-sulfamethoxazole plus rifampicin was dominant over linezolid (Appendix 5). Even when using an extreme willingness-to-pay of €200 000 per QALY gained, the trimethoprim-sulfamethoxazole & rifampicin regimen remained dominant in over 77% of cases, with a 50% discount on linezolid prices.

Discussion

We previously showed in an RCT that anti-MRSA therapy with a combination of older antibiotics (trimethoprim-sulfamethoxazole plus rifampicin) is non-inferior to linezolid in terms of efficacy and safety [6]. The use of one versus two independently marketed antibiotics and new versus old antibiotics can generate cost differences. In an effort to investigate various health-economic scenarios linked to the use of trimethoprim-sulfamethoxazole plus rifampicin versus linezolid for the treatment of MRSA infection, we conducted a CEA whose principal findings were: (a) in the base case scenario the combined treatment of trimethoprim-sulfamethoxazole plus rifampicin is dominant and more cost-effective compared with linezolid, also considering different types of MRSA infection; (b) this result is confirmed by probabilistic sensitivity analyses using MC simulation, in which the combination of the older drugs is dominant in the vast majority of iterations; (c) even in extreme scenarios with substantial discount rates applied to linezolid prices and assumed high costs of ADRs for trimethoprim-sulfamethoxazole plus rifampicin treatment, the combined treatment using the older antibiotics remains dominant.

With the emergence of intermediate resistance against vancomycin or linezolid [16], the use of older antibiotics such as trimethoprim-sulfamethoxazole plus rifampicin could be an interesting and effective strategy to cure MRSA infection [1,4,5]. Moreover, with the increasing incidence of community-associated MRSA and knowing that these strains are often more susceptible than healthcare-associated MRSA, in particular to the older antibiotics [17,18], the use of trimethoprim-sulfamethoxazole could be considered a suitable alternative treatment strategy. In addition, the oral administration of these older drugs can reduce the intra-hospital costs by enabling a faster discharge.

Several industry-sponsored CEAs have been conducted for linezolid. Most of them showed that, compared with vancomycin, linezolid is the more cost-effective strategy in the treatment of MRSA infection due to earlier discharge from hospital [19–26]. In contrast, our analysis shows that with a willingness-to-pay of €50 000 per QALY gained—a commonly used threshold for determining the value-for-money of new healthcare interventions [27]—a strategy of using a combination of older drugs such as trimethoprim-sulfamethoxazole and rifampicin is more cost-

effective than linezolid. However, despite the fact that this combination therapy appears very attractive, a potential limitation could be the lower compliance among patients, which could slightly decrease efficacy. Indeed number of drugs and frequency of administration can affect compliance [28,29].

A key strength of this work lies in the fact that it is the first industry-independent study evaluating the economic impact of these two anti-MRSA regimens. The randomized-controlled design allows for high-quality analysis of differential effects. Moreover, the use of QALYs as the effectiveness measure takes into account both therapeutic efficacy as well as the potential adverse effects of the different treatments studied. We performed several sensitivity analyses, which showed stable and robust results, suggesting with high probability that our findings may be applicable elsewhere. Finally, with a sensitivity analysis performed on potential discounts to simulate alternative linezolid prices, this study suggests that generic linezolid is still not cost-effective in Switzerland or Germany, and allows for future comparisons between the older treatment combination and the generic equivalent of linezolid in other countries.

Our analysis has some limitations. First, the RCT was confined to a selected population from a single hospital in Switzerland with a specific endemic MRSA strain [30], possibly limiting the external validity of the trial results. Second, the sample size of this RCT was too small to capture all potential treatment-related ADRs that may occur. We therefore had to simulate the financial impact of missing ADRs and related health-economic adverse outcomes in the CEA. Consequently, we chose to conservatively overestimate ADR incidence, largely increasing the potential ADR costs for the old combined antibiotics. The costs were derived from an average of DRG costs charged to patients presenting similar pathologies at the Geneva University Hospitals. For a few rare pathologies (e.g. Stevens–Johnson syndrome), the averages were generated from a small number of episodes, making them potentially less representative. Finally, whereas an itemized, franc per franc cost structure was assumed in this study, in reality bundling and profit-seeking on the part of the hospital (reimbursement claims exceeding expense) may distort some costs.

In conclusion, the result of our analysis suggests that, on cost-effectiveness grounds, treatment with trimethoprim-sulfamethoxazole plus rifampicin is more cost-effective than linezolid for the treatment of MRSA infection from the perspective of the health-care system.

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Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.02.011.

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