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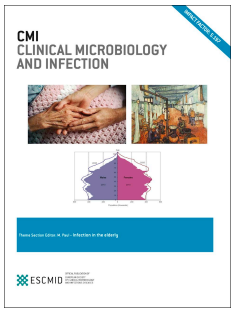

Comparing The Cost-Effectiveness Of Linezolid To Trimethoprim/Sulfamethoxazole Plus Rifampicin For The Treatment Of MRSA Infection: A Health-Care System Perspective

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COMPARING THE COST-EFFECTIVENESS OF LINEZOLID TO TRIMETHOPRIM/SULFAMETHOXAZOLE PLUS RIFAMPICIN FOR THE TREATMENT OF MRSA INFECTION: A HEALTH-CARE SYSTEM PERSPECTIVE

E. von Dach[1], C.M. Morel[1, 2], A. Murthy[3], L. Pagani[4, 5], M. Macedo-Vinas[6], F. Olearo[7], S. Harbarth[1, 7]

Affiliations

[1] Infection Control Program, Geneva University Hospitals and Medical School, Geneva, Switzerland

[2] London School of Economics, London, UK

[3] Incyte Corporation, Epalinges, Switzerland

[4] Infectious Diseases Unit, Bolzano Central Hospital, Bolzano, Italy

[5] Antimicrobial Stewardship Program, Annecy-Genevois Hospital Center, Annecy, France

[6] Dpto. de Laboratorio de Patología Clínica, Facultad de Medicina, Udelar, Uruguay.

[7] Division of Infectious Diseases, Geneva University Hospitals and Medical School, Geneva, Switzerland

Address for correspondence:

Prof Stephan Harbarth

Geneva University Hospitals

Infection Control Program

Rue Gabrielle-Perret-Gentil 4

1211 Geneva 14, Switzerland

stephan.harbarth@hcuge.ch

Tel number: +41 (0)22 372 33 57

Fax number: +41 (0)22 372 39 87

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ABSTRACT (250 words)

Objective:

To date few industry-independent studies were conducted to compare the relative costs and benefits of drugs to treat 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 data from published literature, to compare the two regimens from a health-care 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:

MRSA treatment with trimethoprim-sulfamethoxazole plus rifampicin and linezolid were found to cost on average 160€ and 2877€ per QALY gained, 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 98%, 94% and 74% 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 to trimethoprim-sulfamethoxazole plus rifampicin.

Conclusions:

Combined treatment of trimethoprim-sulfamethoxazole plus rifampicin is more cost-effective than linezolid in the treatment of MRSA infection.

INTRODUCTION

Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) represent a therapeutic challenge. The treatment most frequently recommended is a prolonged course of parenteral vancomycin or daptomycin [1]. Alternative treatment regimens with oral antibiotics (e.g. linezolid [LZD]) have been proposed [2, 3]. The use of older drugs such as trimethoprim-sulfamethoxazole (TMP-SMX), combined with rifampicin (RMP) 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 TMP-SMX plus RMP versus LZD to treat MRSA infection [6]. The principal findings of the study were: (i) compared with LZD, the combination of TMP-SMX plus RMP was non-inferior for the treatment of MRSA infection; (ii) there was no difference between the studied drugs in terms of total adverse events (AE), serious adverse events (SAE) or adverse drug reactions (ADR) [6]. Moreover, as TMP-SMX and RMP are available as generic agents, this regimen may offer a substantial cost advantage over other agents such as LZD and daptomycin [7]. As the launch of generic LZD 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 TMP-SMX plus RMP seems to be an attractive alternative oral treatment option for MRSA infection, though still underused because of safety concerns. However, 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.

METHODS

We constructed a stochastic decision tree model from a Swiss health-care system perspective, using TreeAge Pro 2015 (TreeAge Software, Williamstown, Massachusetts, USA). The model was developed using data of the previously published RCT comparing TMP-SMX plus RMP to LZD for the treatment of any type of MRSA infection (Figure 1). This trial was an investigator-initiated, open-label, single-centre RCT to evaluate the efficacy of a combination of TMP-SMX (160/800 mg thrice daily) plus RMP (600 mg once daily) versus LZD (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 prior to 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 superinfected 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 adverse drug reactions (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 vs IV). 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 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 lab 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 exams 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 (HQORL) score using the EuroQol 5D Health Domains (with United Kingdom 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 LZD and TMP-SMX + RMP, 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 utilizing a decision tree. The base case scenario was defined by the following:

Incremental cost (€) = TMP-SMX plus RMP cost - LZD cost

Incremental effectiveness (QALYs) = TMP-SMX plus RMP effectiveness - LZD effectiveness

The incremental cost-effectiveness ratio (ICER) is the ratio of these two values. A strategy is considered as 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 LZD efficacy (stratified also by type of MRSA infection), ADR cost and LZD 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 utilizing 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 ICERs over 10'000 iterations. The 95% confidence ellipse was obtained to create an incremental cost-effectiveness plane in order to facilitate interpretation of the results. Cost-effectiveness acceptability curves (CEAC) were also calculated to summarize information and support decision-making under differing perceptions of potential risk and benefits.

Generic linezolid cost

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

Linezolid efficacy

Several RCTs on LZD efficacy to treat MRSA infection have already been published. A literature review was therefore performed utilizing each of these studies in order to extract the various efficacy levels of LZD in treating MRSA infection (Appendix 2). Twenty different trials were identified, with a LZD 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 was 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 TMP-SMX plus RMP treatment did not occur during our study and were thus 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 per patient, 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 (TEN) and acute renal failure necessitating dialysis (both deriving from TMP-SMX consumption) and acute liver failure requiring liver transplant (deriving from RMP consumption), among others (Appendix 3). QALYs were constructed for these serious ADR using data from the published literature.

RESULTS

The base case suggested that, on average, the combination treatment of TMP-SMX plus RMP (146€ and 0.916 QALY) was less costly and slightly more effective than LZD for treatment of MRSA infection (2536€, 0.881 QALY). TMP-SMX plus RMP dominated LZD in the treatment of MRSA infection, with an average cost by one QALY gain of 160€ compared to 2877€ (Table 2). Stratified by type of MRSA infection (respectively, non-severe, severe or deep-seated infection), the average cost-effectiveness ratios were 44, 115 and 477€/QALY for TMP-SMX plus RMP versus 1348, 2595 and 6105 €/QALY for LZD. Results of the simulation suggest that with a willingness-to-pay threshold of 0€, 50'000€ and 200'000€, TMP-SMX plus RMP was dominant in 100%, 82% and 73% of the time (Figure 2). Appendix 4 shows the results of the MC simulation by type of infection.

One- and two-way sensitivity analyses showed that TMP-SMX plus RMP dominated LZD even when we used extreme scenarios such as a LZD efficacy fixed at 1.0, a maximum assumed ADR cost attributed to TMP-SMX plus RMP (320€ per patient), or the highest possible discount offered on the LZD price of 60% (Figure 3). Results of the one-way sensitivity analysis suggested that a 95% discount on the price of LZD would need to be applied for it to become more cost-effective than TMP-SMX plus RMP.

These results were confirmed by the three-way sensitivity analysis. The treatment of TMP-SMX plus RMP stayed dominant in each case (Appendix 4). When we performed probabilistic sensitivity analyses (MC simulations) to reproduce CEACs, with maximum assumed ADR costs attributed to TMP-SMX plus RMP, varied LZD efficacy and varied LZD prices, results suggested TMP-SMX plus RMP to be dominant over LZD (Table 4.B.). Even when utilizing an extreme willingness-to-pay of 200'000€ per QALY gained, the TMP-SMX & RMP regimen remained dominant in over 77% of cases, with a 50% discount on LZD prices.

DISCUSSION

We previously showed in a RCT that anti-MRSA therapy with a combination of older antibiotics (TMP-SMX plus RMP) is non-inferior to LZD 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 TMP-SMX plus RMP versus LZD for the treatment of MRSA infection, we conducted a CEA whose principal findings were: (i) in the base case scenario the combined treatment of TMP-SMX plus RMP is dominant and more cost-effective compared to LZD, also considering different types of MRSA infection; (ii) 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; (iii) even in extreme scenarios with substantial discount rates applied to LZD prices and assumed high costs of ADRs for TMP-SMX plus RMP treatment, the combined treatment using the older antibiotics remains dominant.

With the emergence of intermediate resistance against vancomycin or LZD [13], the use of older antibiotics such as TMP-SMX plus RMP 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 [14, 15], the use of TMP-SMX 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 LZD. Most of them showed that, compared to vancomycin, LZD is the more cost-effective strategy in the treatment of MRSA infection due to earlier discharge from hospital [16-23]. In contrast, our

analysis shows that with a willingness-to-pay of 50’000€ per QALY gained - a commonly used threshold for determining value-for-money of new healthcare interventions [24] - a strategy of using a combination of older drugs such as TMP-SMX & RMP is more cost-effective than LZD. 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 [25, 26].

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 analyses, especially with regard to relative effectiveness. 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 are applicable to many different clinical and health-economic settings. Finally, with a sensitivity analysis performed on potential discounts to simulate alternative LZD prices, this study suggests that generic LZD is still not cost-effective in Switzerland or Germany, and allows for future comparisons between the older treatment combination and the generic equivalent of LZD 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 [27], 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 TMP-SMX plus RMP is more cost-effective than LZD for the treatment of MRSA infection from the perspective of the health-care system.

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Conflicts of interest

S. H. reports having received peer-reviewed research grants funded by Pfizer and B. Braun and he is a member of advisory boards of GSK, Janssen, Novartis; Bayer and DaVolterra.

Figure Legends

Figure 1. Decision tree model.

LZD, linezolid; TMP-SMX, trimethoprim-sulfamethoxazole; RMP, rifampicin; ADR, adverse drug reaction; MRSA, methicillin-resistant Staphylococcus aureus.

Figure 2. Incremental cost-effectiveness plane and table, with cost-effectiveness acceptability curves (CEAC)

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

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

Figure 3. One-Way and Two-Way sensitivity analysis on assumed inputs

ADR: adverse drug reaction; LZD: linezolid; QALYs: quality-adjusted life years; RMP: rifampicin; TMP-SMX: trimethoprim-sulfamethoxazole

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 colors (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.

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Appendix 1. Adverse Drug Reaction costs during the RCT

Case	Group of treatment	Type	Treatment administered				Laboratory test		Costs
			Name	Administration	Dosage	Number	Type	Number	
1	TMP-SMX + RMP	**Neurological**		Ø			Ø		0€
2	LZD	**Tongue discoloration**		Ø			Ø		0€
3	TMP-SMX + RMP	**Dermatological**	clemastine fumarate	IV	2mg	2	Ø		7.11€
			prednisone	PO	20mg	2			
4	TMP-SMX + RMP	**Gastrointestinal**	metoclopramid	PO	10mg	1	Ø		39.31€
			ondansetron	PO	8mg	4			
			domperidone	PO	10mg	2			
5	LZD	**Nephrological**	NaCl	IV	0.9% - 1.5l	1	creatinine	3	31.19€
							urea	3	

6	TMP-SMX + RMP	**Nephrological**		ø			Ø		0€
7	LZD	**Haematological**		ø			Ø		0€
8	TMP-SMX + RMP	**Gastrointestinal**	domperidone	PO	10mg	1	Ø		0.44€
9	TMP-SMX + RMP	**Dermatological**	clemastine fumarate	IV	2mg	4	Ø		12.47€
10	LZD	**Gastrointestinal**	domperidone	PO	10mg	1	Ø		5.91€
			ondansetron	PO	4mg	1			
11	TMP-SMX + RMP	**Gastrointestinal**	domperidone	PO	10mg	2	pregnancy test	1	22.43€
			ondansetron	PO	4mg	1			
12	TMP-SMX + RMP	**Nephrological**		ø			Ø		0€
13	TMP-SMX + RMP	**Gastrointestinal**	ondansetron	PO	8mg	3	Ø		50.56€
			ondansetron	PO	4mg	4			

LZD: linezolid; PO: per os; RMP: rifampicin; TMP-SMX: trimethoprim-sulfamethoxazole; IV: intraveinous

Appendix 2. Literature Review on the Efficacy of LZD to treat MRSA infection, generated by RCTs

Author	Year	Title	n (success)	Total N	Linezolid efficacy (%)
Rubinstein [1]	2001	Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study.	15	23	0.65
Stevens [2]	2002	Linezolid versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus infections.	59	98	0.60
Wible [3]	2003	Linezolid versus cefadroxil in the treatment of skin and skin structure infections in children.	13	14	0.93
Kaplan [4]	2003	Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children.	15	18	0.83
Yogev [5]	2003	Linezolid for the treatment of complicated skin and skin structure infections in children.	9	10	0.90
Wunderink [6]	2003	Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia.	36	75	0.48
Lipsky [7]	2004	Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of	13	18	0.72

		linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate.			
Weigelt [8]	2004	Linezolid eradicates MRSA better than vancomycin from surgical-site infections.	26	30	0.87
Sharpe [9]	2005	Clinical and economic outcomes of oral linezolid versus intravenous vancomycin in the treatment of MRSA-complicated, lower-extremity skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus.	15	30	0.50
Weigelt [10]	2005	Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections.	125	176	0.71
Kohno [11]	2007	Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant Staphylococcus aureus in Japan.	22	60	0.37
Wunderink [12]	2008	Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant Staphylococcus aureus.	13	23	0.57
Wilcox [13]	2009	Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.	42	48	0.88
Itani [14]	2010	Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus.	223	276	0.81

Craft [15]	2011	A randomized, double-blind phase 2 study comparing the efficacy and safety of an oral fusidic acid loading-dose regimen to oral linezolid for the treatment of acute bacterial skin and skin structure infections.	37	37	1.0
Covington [16]	2011	Randomized, double-blind, phase II, multicenter study evaluating the safety/tolerability and efficacy of JNJ-Q2, a novel fluoroquinolone, compared with linezolid for treatment of acute bacterial skin and skin structure infection.	25	29	0.86
Wunderink [17]	2012	Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study.	102	186	0.55
Noel [18]	2012	A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections.	30	32	0.94
Prokocimer [19]	2013	Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial.	77	90	0.86
Chavanet [20]	2013	The ZEPHyR study: a randomized comparison of linezolid and vancomycin for MRSA pneumonia.	95	165	0.58

Harbarth [21]	2015	Randomized non-inferiority trial to compare trimethoprim/sulfamethoxazole plus rifampicin versus linezolid for the treatment of MRSA infection.	56	75	0.75

Appendix 3. Serious Adverse Drug Reaction simulation

Treatment	Type of ADR	Incidence maximum	Cost by ADR	Average cost by patient treated by the study drug	QALYs
RMP	Liver failure requiring liver transplant	Rare 1/1000[b]	190'000CHF/174'632€[a]	190CHF/178€	0.69 [22]
TMP-SMX	Lyell, Stevens-Johnson syndrome	Very rare 1/10'000[b]	32'000CHF/29411€[a]	3CHF/3€	0.66 [23]
TMP-SMX	Renal failure with dialysis	Very rare 1/10'000[b]	70'000CHF/64338€/year[a] (Average duration, 21 years)	140CHF/135€	0.70 [24]

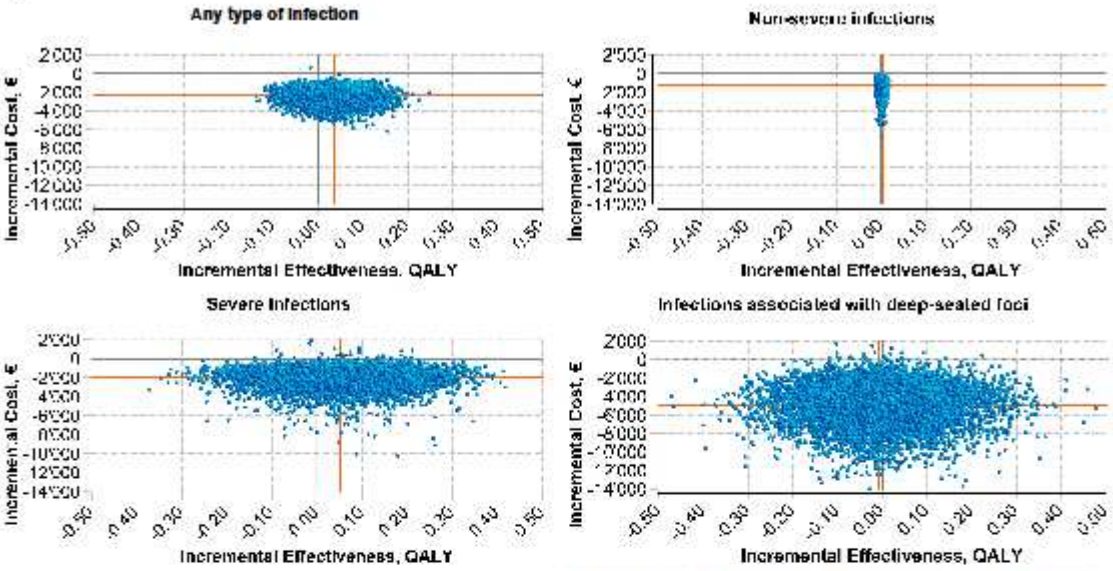
ADR: adverse drug reaction; LZD: linezolid; QALYs: quality-adjusted life years; RMP: rifampicin; TMP-SMX: trimethoprim-sulfamethoxazole

[a] Average cost charged at Geneva University Hospitals in 2015

[b] Real incidence is unknown, the maximum incidence found in the Swiss drug information has been applied

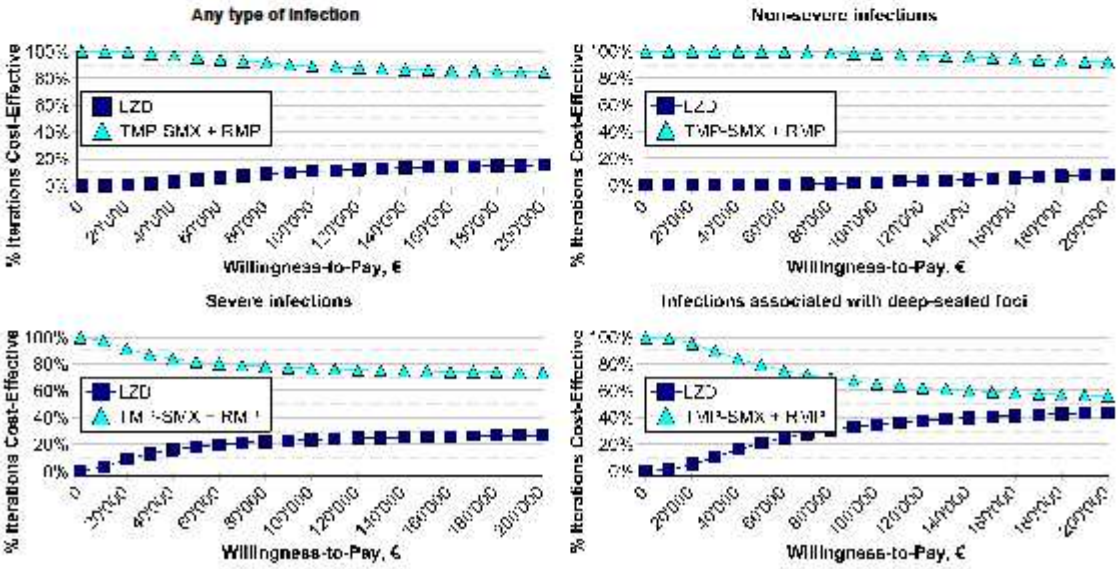
Appendix 4. *Incremental cost-effectiveness plane and table, cost-effectiveness acceptability curves (CEAC) by type of infection*

A.



				Any type of infections		Non-severe infections		Severe infections		Infections associated with deep-seated foci	
Quadrant	Incr. Cost (€)	Incr. Effect. (QALY)	Incr. Cost-Effect.	Freq.	Prop.	Freq.	Prop.	Freq.	Prop.	Freq.	Prop.
North-East	IC>0.0	IE>0.0	ICER>0.0	1	0%	0	0%	24	0%	14	0%
North-West	IC<0.0	IE>0.0	Dominated	1	0%	0	0%	6	0%	13	0%
South-West	IC<0.0	IE<0.0	ICER>0.0	2227	22%	4459	45%	2976	30%	5376	54%
South-East	IC>0.0	IE<0.0	Dominant	7771	78%	5541	55%	6994	70%	4597	46%

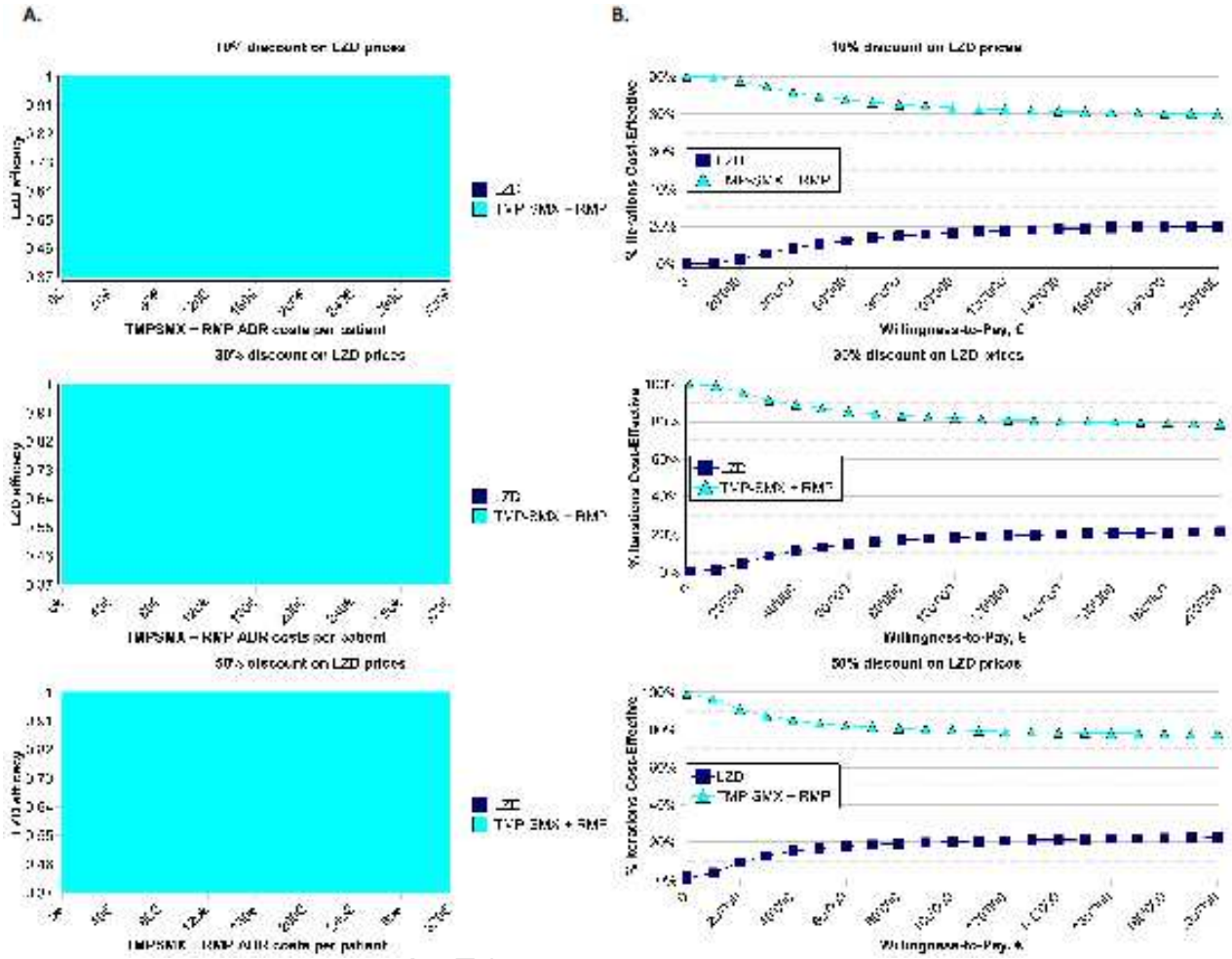
B.



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

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

Appendix 5. ***Three-way sensitivity analysis and cost-effectiveness acceptability curves (CEAC) on*** **assumed** ***inputs, considering various discounted pricing of generic linezolid***



ADR: adverse drug reaction; LZD: linezolid; RMP: rifampicin; TMP-SMX: trimethoprim-sulfamethoxazole

A. Three-way sensitivity analysis is an analysis in which two variables of interest are simultaneously varied over a range of plausible values while holding a third variable with a determinate value and all other variables constant (according to the base case scenario). In these types of graphs the most cost-effective intervention according to the value for the variables tested is represented according to their colors. B. Cost-effectiveness acceptability curves.

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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.
Probabilities	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Distrib.**[a]	
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)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Distrib.**[a]	
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,[b] CHF/€**							
LZD IV treatment (600mg)			92.23 / 84.77					[c]
LZD PO treatment (600mg)			94.14 / 86.53					[c]
TMP-SMX IV treatment (800/160mg)			5.08 / 4.67					[c]
TMP-SMX PO treatment (800/160mg)			0.67 / 0.62					[c]
RMP PO treatment (600mg)			3.48 / 3.20					[c]
RMP IV treatment (600mg)			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					[d]
QALYs								
Death	0.00		0.00		0.00			[8, 9, 10]
Cure	1.00		1.00		1.00			[8, 9, 10]
No cure								
LZD	0.96		0.90		0.86			[8, 9, 10]
TMP-SMX + RMP	0.95		0.89		0.82			[8, 9, 10]
ADR	0.00		0.00		0.00			[8, 9, 10]

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.

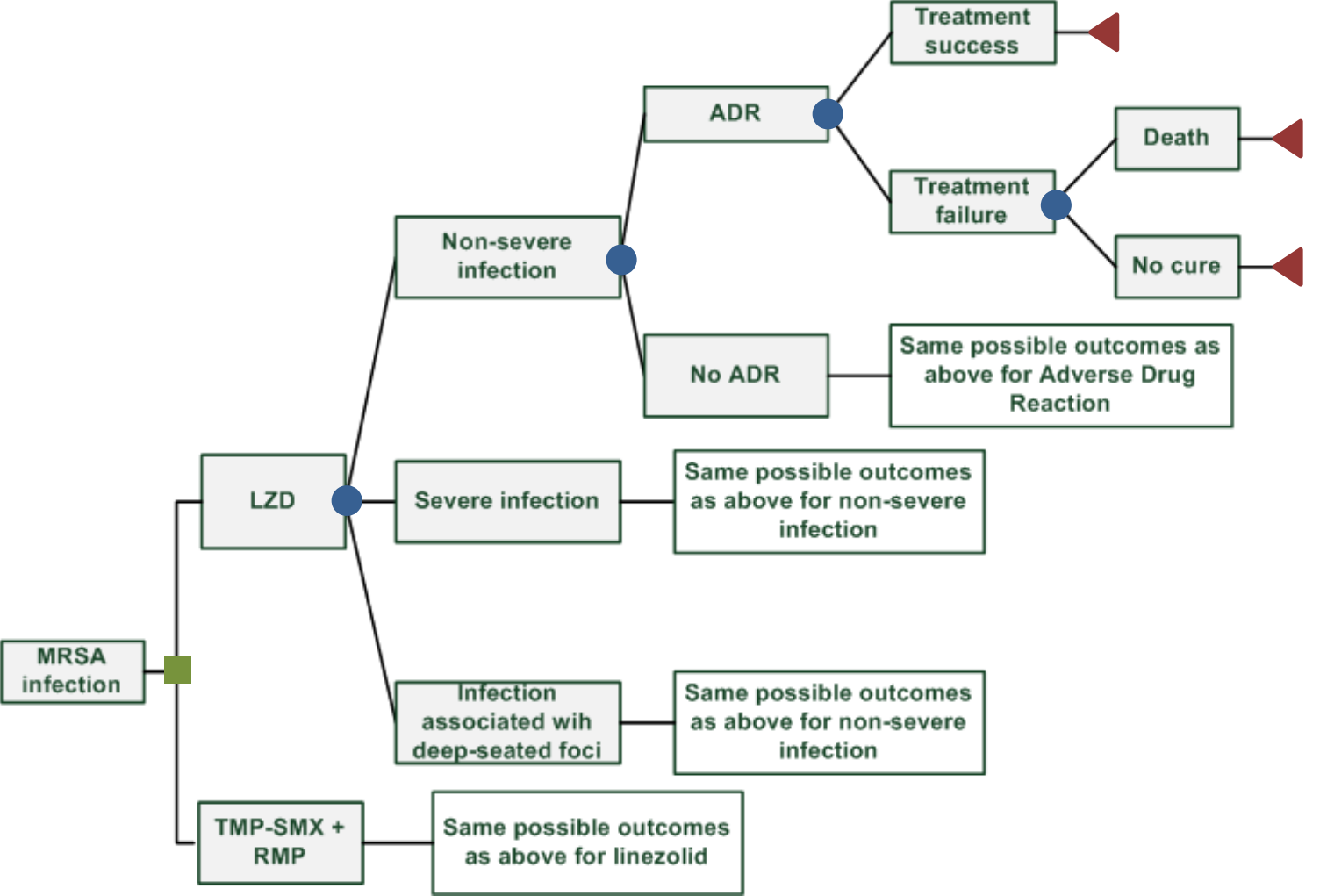
[c] http://www.listedesspecialites.ch/ Federal Department of Home Affairs - Federal Office of Public Health - List of specialties [cited 2016 December].

[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.

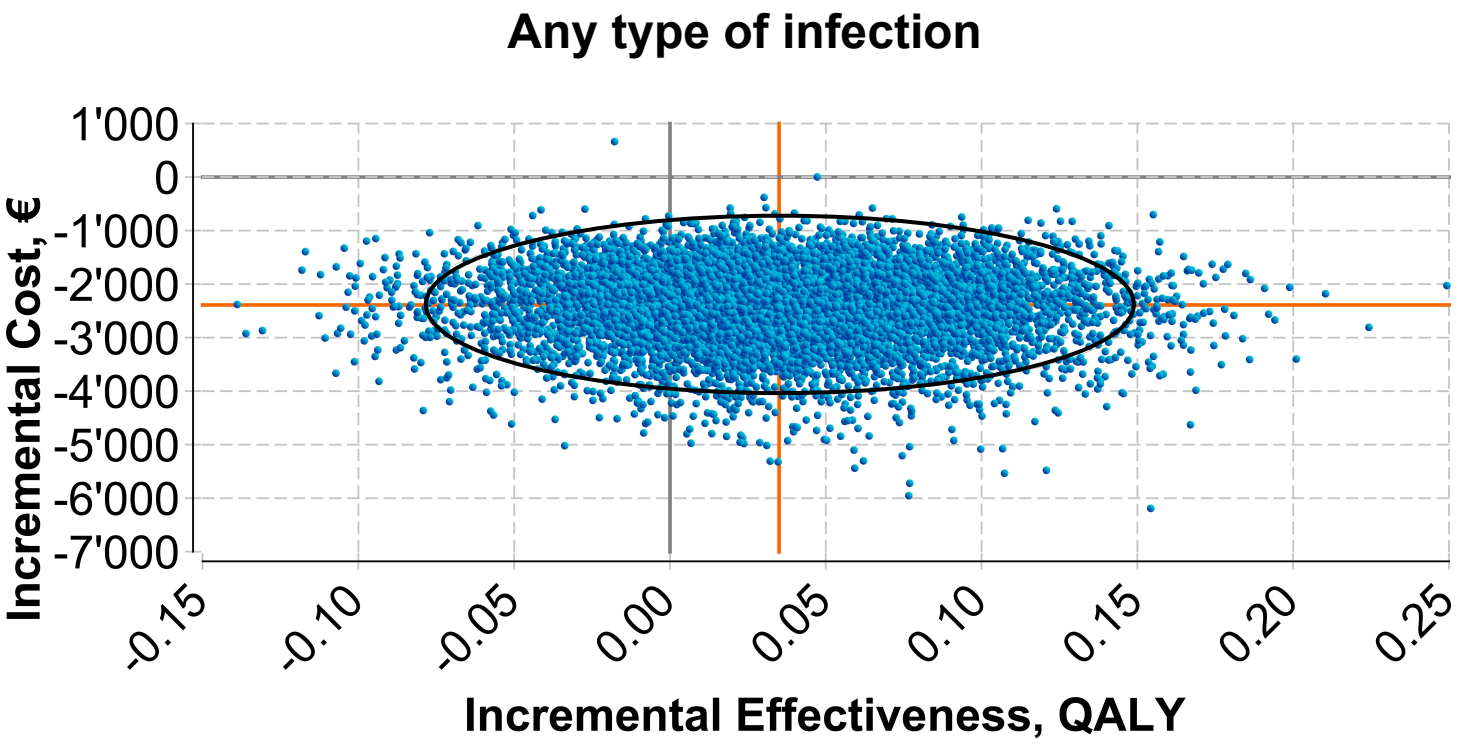
Table 2. Base case scenario by type of MRSA infection

	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**	**631883**

ACER: Average cost-effectiveness ratio; ICER: Incremental cost-effectiveness ratio; LZD: linezolid; RMP: rifampicin; TMP-SMX: trimethoprim-sulfamethoxazole

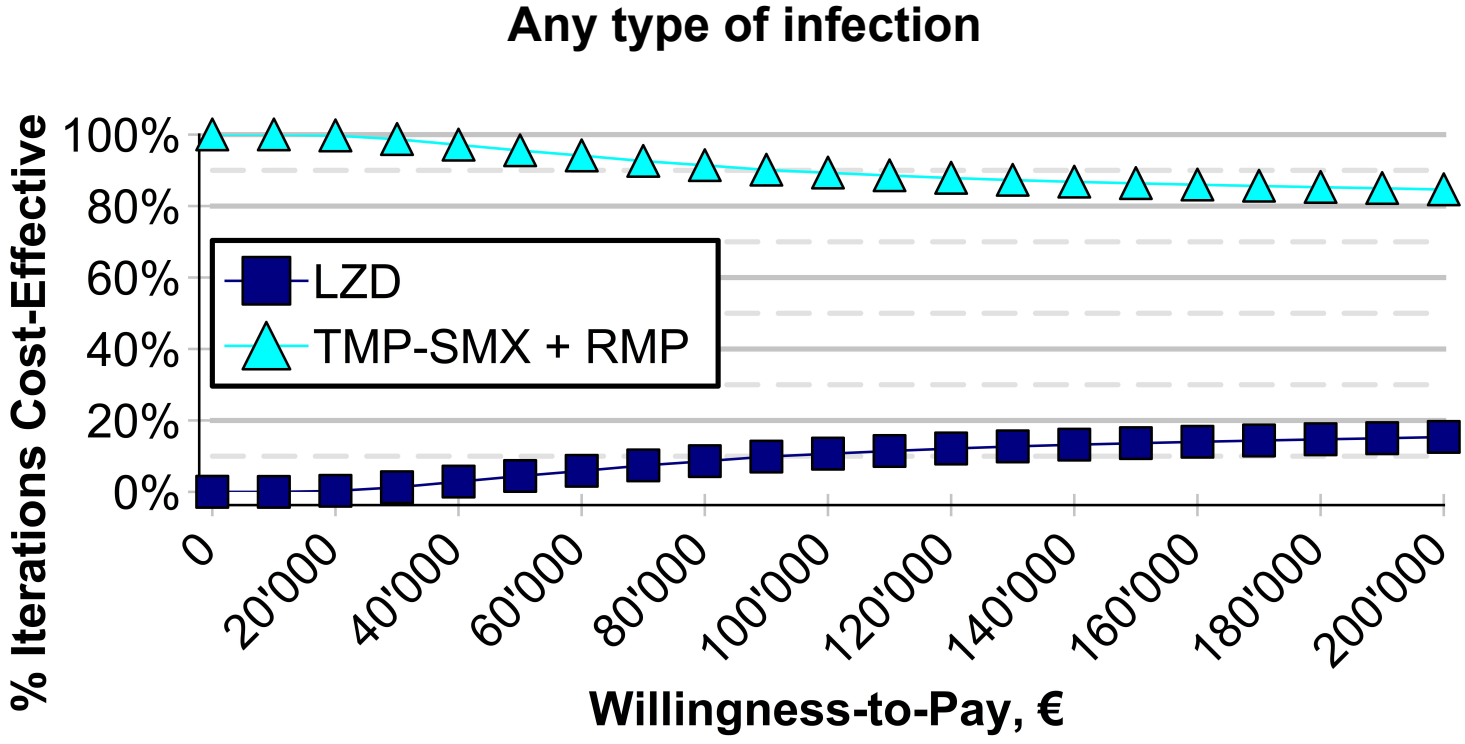

MRSA infection
LZD
TMP-SMX + RMP
Non-severe infection
Severe infection
Infection associated wih deep-seated foci
ADR
No ADR
Treatment success
Treatment failure
Death
No cure
Same possible outcomes as above for Adverse Drug Reaction
Same possible outcomes as above for non-severe infection
Same possible outcomes as above for non-severe infection
Same possible outcomes as above for linezolid

A.



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%

B.



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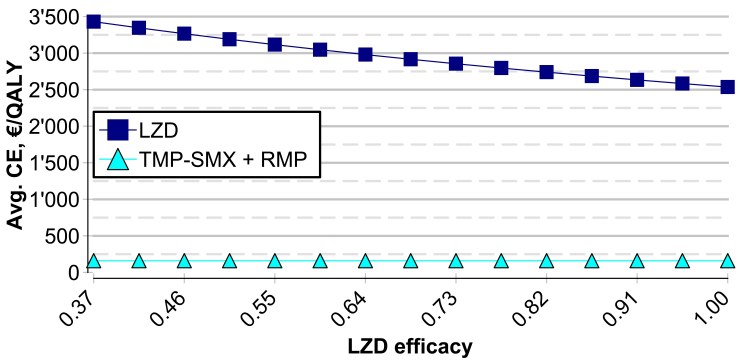
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Avg. CE, €/QALY
LZD
TMP-SMX + RMP
0.37
0.46
0.55
0.64
0.73
0.82
0.91
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LZD efficacy

B.


1.00
0.91
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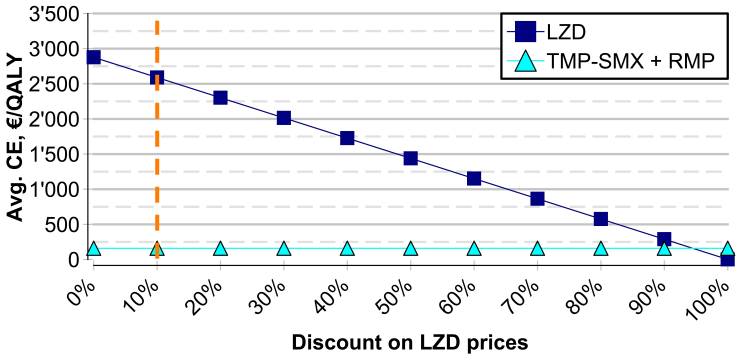
0.73
0.64
0.55
0.46
0.37
LZD efficacy
0%
20%
40%
60%
80%
100%
Discount on LZD prices
LZD
TMP-SMX + RMP


3'500
3'000
2'500
2'000
1'500
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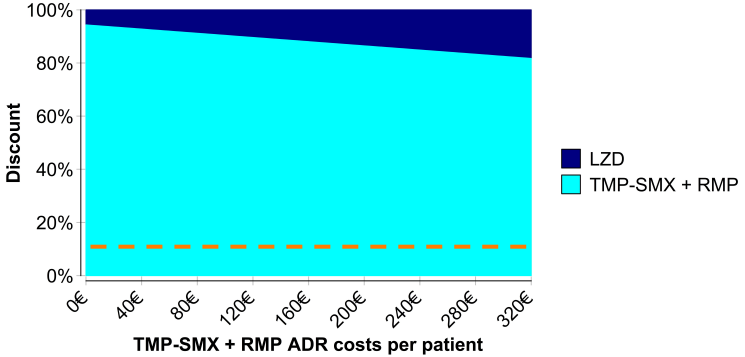
Avg. CE, €/QALY
LZD
TMP-SMX + RMP
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Discount on LZD prices


100%
80%
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Discount
0€
40€
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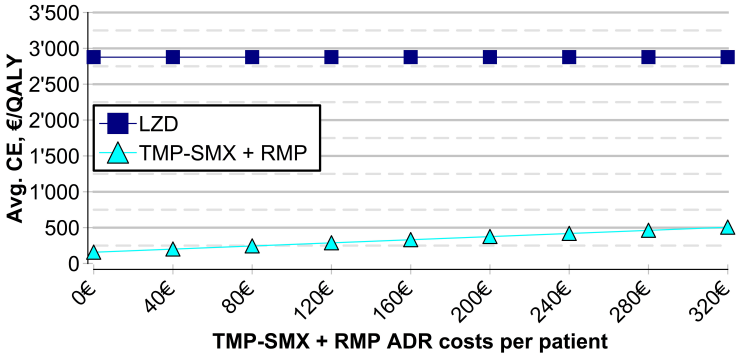
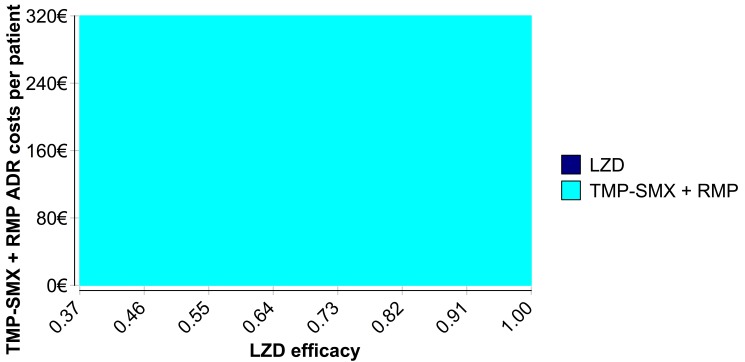
200€
240€
280€
320€
TMP-SMX + RMP ADR costs per patient
LZD
TMP-SMX + RMP


3'500
3'000
2'500
2'000
1'500
1'000
500
0
Avg. CE, €/QALY
LZD
TMP-SMX + RMP
0€
40€
80€
120€
160€
200€
240€
280€
320€
TMP-SMX + RMP ADR costs per patient


320€
240€
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TMP-SMX + RMP ADR costs per patient
0.37
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0.73
0.82
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1.00
LZD efficacy
LZD
TMP-SMX + RMP