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Assessing the value of new antibiotics in acute bacterial skin and skin structure infections with a focus on surgical site infections: a review of the evidence base

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Objectives

With the development and rise of antimicrobial resistance there is a strong public health need for new antibiotics. However, new antibiotics face significant scientific, regulatory, clinical and economic challenges. As discussed in a recent ISPOR panel, it is difficult to quantify their value[1] with, for example, a lack of return on investment being problematic.

Acute bacterial skin and skin structure infections (ABSSSI) was recently described by the US Food and Drug Administration (FDA) as a bacterial infection of the skin with a lesion size area of ≥75 cm^2 (based on the area of redness, oedema or induration) including the following three types of infection: cellulitis/erysipelas, wound infection and major cutaneous abscess.[2] In this context, surgical site infections (SSI) is reportedly the most common healthcare-associated infection with approximately 543,149 cases annually in the European Union and the European Economic Area (EU/EEA)[3] and are associated with longer post-operative hospital stays and therefore costs.[3]

This study aimed to understand the current and additional evidence required to help quantify the potential value of new antibiotics for ABSSSI and SSI. More specifically, it examined the epidemiology, economic and humanistic burden of ABSSSI and SSI with a focus on the European region.

Methods

Targeted literature reviews

Four targeted literature reviews (TLRs) were conducted in September 2017 in the Embase® and MEDLINE® databases to gather evidence in ABSSSI and SSI: Epidemiology (**TLR1**), utility and health-related quality of life (HRQL) (**TLR2**), economic modelling (**TLR3**) and cost and resource use (**TLR4**).

Table 1 summarises the methods used, the search date limits and the review eligibility criteria.[4] In addition, bibliographical searches and manual searching of grey and published literature were performed to identify relevant literature of interest.

Abstracts of citations were screened methodically by a reviewer, and eligible studies were included. Following abstract review, full-text articles of the potentially relevant studies were reviewed by a single reviewer. Data extraction of the included studies was carried out by an independent reviewer.

Table 1: Method summary (PICOS)

Category	Epidemiology (TLR1)	Utility/HRQL (TLR2)	Economic modelling (TLR3)	Cost and resource use (TLR4)
Population	Adult patients with ABSSSI (including SSI) or suspected MRSA-associated ABSSSI, SSSI, SSTI, uSSSI or cSSSI			
Intervention	No restriction		ABSSSI antibiotics	No restriction
Comparators	No restriction			
Outcomes	Incidence, prevalence, death rates	Utility data	ICERs, ICURs, incremental costs, QALYs/LY, or any other measure of effectiveness reported with costs	RU and costs, treatment-related AE costs, BOI costs
Study type	Observational/clinical studies, economic evaluations		Full EE, CMA, BIA	Observational/clinical studies, economic evaluations
Date limits	Last 5 years	No restriction	Studies published in last 10 years	
Language	English only			
Countries	No restriction**		No restriction**	EU5

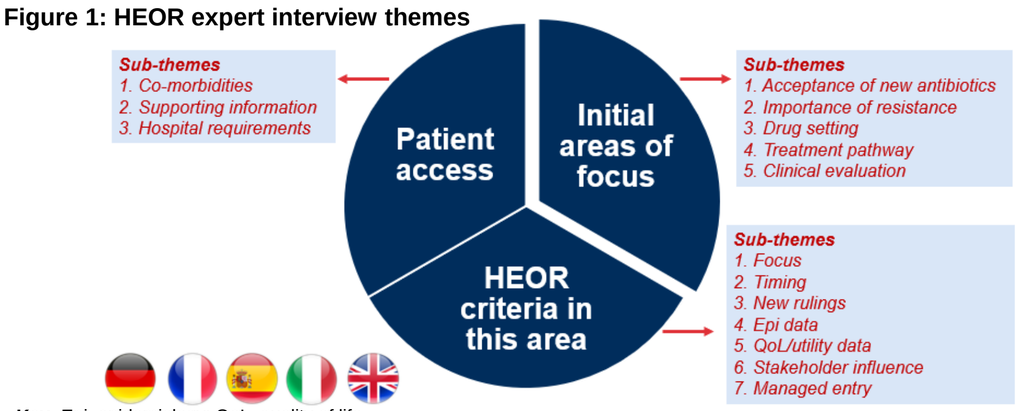
Key: ABSSSI, acute bacterial skin and skin structure infections; AE, adverse event; BOI, burden of illness; BIA, budget impact assessment; CMA, cost-minimisation analysis; cSSSI, complicated skin and skin structure infections; EE, economic evaluation; EU5, European Union Five; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratios; LY, life-year; MRSA, methicillin-resistant *Staphylococcus aureus*; QALY, quality-adjusted life year; RU, resource use; SSI, surgical site infections; SSSI, skin and skin structure infections; SSTI, skin and soft tissue infections; uSSSI, uncomplicated skin and skin structure infections.
Note: **We report EU results in this poster only.

Health economics and outcomes research expert interviews

To complement the targeted literature reviews, interviews with health economics and outcomes research (HEOR) experts from the European Union Five (EU5) were conducted. The aim was to gain further insights into the best approaches to fill data gaps and to understand what they considered important for patient management, patient access and combating resistance.

The themes included in **Figure 1** were discussed during the interviews and the interviewees provided information that they considered key to their country.

Figure 1: HEOR expert interview themes



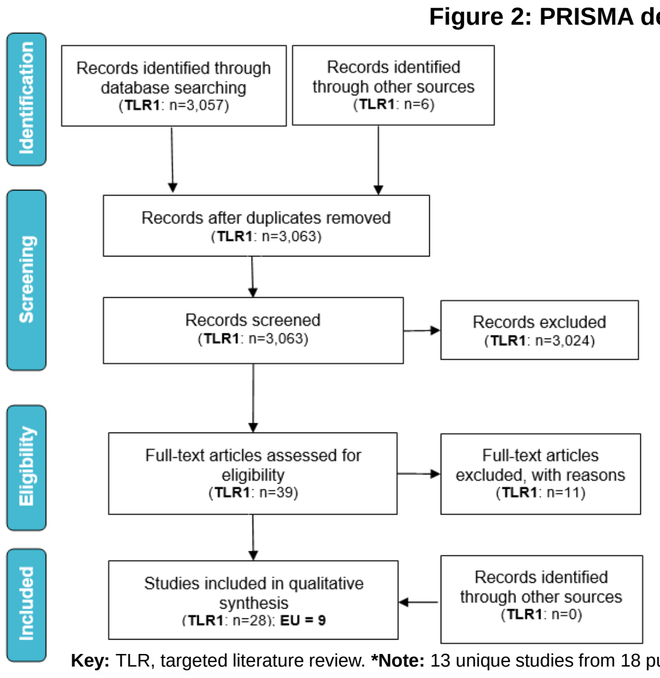
Key: Epi, epidemiology; QoL, quality of life.

Results

Targeted literature reviews

Figure 2 shows the number of studies included. A total of 38 EU studies were included for qualitative synthesis. **Figure 3** shows the distribution of studies by location. Limited European studies were retrieved.

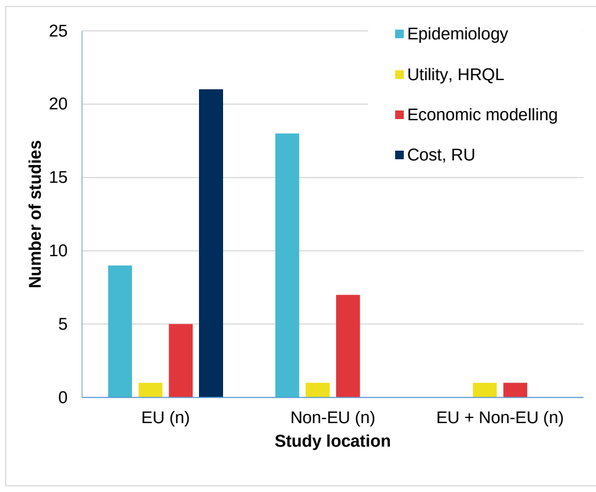
Figure 2: PRISMA details[4]



PRISMA section	TLR	Number
Records identified through database searching (records identified through other sources)	TLR1 TLR2 TLR3 TLR4	3,057 (6) 1,368 (0) 357 (0) 1,851 (0)
Records after duplicates removed	TLR1 TLR2 TLR3 TLR4	3,063 1,365 357 1,847
Records screened (records excluded)	TLR1 TLR2 TLR3 TLR4	3,063 (3,024) 1,365 (1,321) 357 (306) 1,851 (1,534)
Full text articles assessed for eligibility (excluded with reason)	TLR1 TLR2 TLR3 TLR4	39 (11) 44 (41) 51 (35) 312 (290)
Studies included in qualitative synthesis (records identified through other sources) (EU studies)	TLR1 TLR2 TLR3 TLR4	28 (0) [**EU=9**] 3 (2) [**EU=2**] 18* (2) [**EU=6**] 29** (7) [**EU=21**]

Key: TLR, targeted literature review. ***Note:** 13 unique studies from 18 publications. **21 unique studies from 29 publications.

Figure 3: Number of studies retrieved by location



Key: HRQL, health-related quality of life; RU, resources use.

Table 2: Studies retrieved (disease subtypes and sample sizes)

Category	Breakdown (number of studies)			
	Epidemiology (n=9)	Utility/ HRQL (n=2)	Economic Modelling (n=6)	Cost and resource use (n=21)
Disease subtype	SSI (2) SSTI (4) cSSSI/SSI (1) cSSTI (1) Multiple (ABSSSI+SSI) (1)	Cellulitis (1) ABSSSI (1)	cSSTI (4) Cellulitis (1) cSSSI (1)	SSTI (8) cSSTI (6) Cellulitis (3) ABSSSI (3) cSSSI (1)
Sample size	<500 (5) >100,000 (3) NR (1)	N/A		

Key: ABSSSI, acute bacterial skin and skin structure infections; cSSTI, complicated skin and skin structure infections; NR, not reported; SSI, surgical site infections; SSTI, skin and soft tissue infections; TLR, targeted literature review.

Epidemiology: Nine EU studies were retrieved for all disease subtypes (see **Table 2**). Of those, only three were considered to be large and homogeneous epidemiology studies with a sample size of >500, highlighting a need for further studies to investigate ABSSSI and SSI incidence, prevalence and mortality. In those three studies, 75.7% of patients presented with at least one comorbidity, which was in line with the results of the US studies retrieved (not part of this report). Diabetes was overall the most prevalent comorbidity (both in the EU and US studies). For the EU (n=4 studies reporting diabetes prevalence), diabetes prevalence ranged from 30.8% to 54.2%. Further epidemiology details are provided in **Table 3**.

Table 3: Summary of epidemiology results

Category	Breakdown	Number of studies
Patient demographics (n=7)	Mean age: 30.5 → 71.3	3
	Median age: 32 → 72	2
	Sex: More M than F (n=3)	4
Incidence (n=2)	cSSSI (2008–2011) average annual incidence 9 → 11 per 100,000 PYs	1
	SSTIs (2010–2013) 100 admissions per 500,000 persons/year (EU-wide)	1
Prevalence (n=3)	Cellulitis studies: 29.4% (cSSSI) to 42% (SSTI).	2
	SSTI studies: 0.3% (ABSSSI & SSI) to 36.5% (SSTI).	2
Mortality (n=2)	Range: 4.1% within 30 days (cSSSI) → 8% within 6m (SSTI), 11.8% within 12m (SSTI).	2
Antibiotic therapy (n=4)	Vancomycin followed by linezolid (both IV) most frequently used (cSSTI, confirmed MRSA) in EU5 except Italy.	1
	Cephalosporins, amoxicillin and clavulanate, beta-lactam antibacterials	3

Key: ABSSSI, acute bacterial skin and skin structure infections; cSSTI, complicated skin and skin structure infections; NR, not reported; SSI, surgical site infections; SSTI, skin and soft tissue infections; TLR, targeted literature review.

Utility and health-related quality of life: Only two studies conducted in the EU were retrieved. The disease subtypes were ABSSSI and cellulitis, both with relatively small sample sizes (n=397 and n=214, respectively). Only one reported the antibiotic therapy used. In this study, the elicitation methods included the three-level EQ-5D® (EQ-5D-3L) and Dermatology Quality of Life Index (DLQI). This study reported some improvement in utility (mean EQ-5D® score increased from baseline) and HRQL (DLQI score) for penicillin versus placebo. Further quality of life studies are needed to understand the effect of new antibiotics.

Economic modelling: Only six economic modelling studies were retrieved for the EU, potentially due to limited availability of head-to-head trials. The main comparators were vancomycin, linezolid and daptomycin. The modelling studies used a healthcare systems perspective and short time horizon. For linezolid based studies (n=3), linezolid was reported as being cost-effective compared to vancomycin/daptomycin. For a daptomycin based study (n=1), daptomycin was cost effective compared to vancomycin. Despite the high cost of daptomycin, the reduction in cost was reported as being due to reduced length of hospital stay. Length of hospital stay, antibiotic therapy duration, methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and antibiotic costs (all studies) were the reported key drivers.

Cost and resource use: Twelve observational studies and nine economic evaluations were retrieved. The economic evaluations included: three budget impact assessments, two cost-minimisation analyses and one of each of the following: cost–consequence analysis, cost–utility analysis, cost-effectiveness analysis, economic analysis and cross-sectional study. Cost-minimisation analysis was used in two recent Scottish Medicine Consortium reports (dalbavancin versus vancomycin, linezolid in ABSSSI, tedizolid versus linezolid in ABSSSI). The studies identified can be used to guide resource use inputs for models and validation of model outputs.

For ABSSSI cost and resource use, evidence suggests that antibiotic therapy cost (n=5), followed by hospital-associated costs (n=4) and duration of antibiotic treatment (n=3) were key drivers for direct cost estimations. Overall, definitive conclusions cannot be drawn because of a lack of evidence specific to ABSSSI and SSI, highlighting a high unmet need.

Health economics and outcomes research expert interviews

With respect to patient management and resistance, the HEOR experts generally felt that providing alternative antibiotic options was important in light of the fact that ABSSSI is a disease area where patient management is complicated by a high prevalence of comorbidities, presence of mixed pathogens and rapidly increasing levels of resistance to many currently available antibiotic drugs. For this reason, physicians require diverse therapeutic choices to combat these infections and tailor the therapeutic approach to patient and infection characteristics, particularly in difficult-to-manage subgroups of patients such as those with SSI.

Discussion

There are several challenges associated with the introduction of new antibiotics including significant scientific, regulatory, clinical and economic challenges. For example, health technology assessment (HTA) bodies generally require demonstration of clinical superiority, whereas antibiotics are normally investigated in non-inferiority trials. In fact, clinical evidence does not address benefits beyond the individual (i.e. it does not address the public health threat).

Limited large, homogenous epidemiology studies were retrieved for the EU. However, from the studies retrieved diabetes is reported as the most prevalent co-morbidity. Few studies were retrieved for utility and health related quality of life making it impossible to draw any conclusions. It does, however, highlight a need for further studies to understand the effects of new antibiotics and, for example, recurrent infections and increased hospital stay on patients quality of life.

Limited economic modelling evidence is available and may be due to the lack of head-to-head comparison trials for different treatments for ABSSSI. Given that ABSSSI is highly heterogeneous, and comorbid conditions play an important role in its burden, future economic evaluation studies are warranted to better assess the burden of ABSSSI.

ABSSSI and SSI that require hospitalisation represent a significant clinical and cost burden to the healthcare system. As such, it is important to analyse the cost parameters associated with an episode of infection. Increased length of hospital stay, especially in difficult-to-manage patients, impacts costs, healthcare resource use, and the risk of patients being affected by other infectious pathogens. Moreover, the cost of hospitalisation represents a key driver, in addition to patient management and costs of treatment failure, whereas the contribution of antimicrobial therapy, including drug acquisition and delivery costs, could potentially become comparatively marginal. To provide broader public health benefit, programs are necessary that enable more efficient patient management and facilitate quicker patient recovery, which would lead to reductions in length of hospital stay and risk of hospital-acquired infections.

Conclusions

Alternative and innovative HTA approaches are needed to assess the value of antibiotics, including consideration of broader public health benefits. This review highlights the evidence base for ABSSSI and SSI in the areas of epidemiology, utility and HRQL, economic modelling, and cost and resource use, principally in Europe. Further data generation in this area is needed. There is awareness of the requirement for new antibiotics, however, to accurately predict their value, it is important to understand the evidence base in terms of efficacy, safety and ultimately in terms of associated healthcare costs.

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