A review of health economic models exploring and evaluating treatment and management of Hospital-Acquired Pneumonia (HAP) and Ventilator Associated pneumonia (VAP)

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Structured summary

Background:

Hospital-acquired pneumonia (HAP) is pneumonia occurring ≥48 hours after admission; it is the most common hospital-acquired infection contributing to death. Ventilator-associated pneumonia (VAP) arises ≥48-72 hours after intubation.

Opinions differ on whether VAP is a HAP subset; the same pathogens predominate in both. Compared with VAP-free controls, patients developing VAP are twice as likely to die, and have significantly longer ICU stays.

Guidelines recommend that microbiological cultures should guide antibiotic treatment, but these lack sensitivity and take 48-72 hours to process, meaning that initial therapy must be empiric, generally with broad-spectrum agents. Given increasing pressure to improve both antibiotic stewardship and patient outcomes, the National Institute for Health and Care Excellence, and the Infectious Diseases Society of America recommend research into rapid molecular diagnostic tests to identify causative organisms and their antibiotic resistances. Ideally, these would supersede culture, being quicker and more sensitive. The United Kingdom's National Institute for Health Research-funded INHALE research programme is exploring rapid molecular diagnostics to inform treatment of HAP/VAP and, given resource implications, incorporates a health economic component.

Aim:

Identify previous economic modelling of HAP/VAP costs to inform this component.

Methods:

Literature review of HAP/VAP studies with economic modelling identified from three databases.

Findings:

Twenty studies identified. Only one specifically evaluated strategies to improve diagnosis; others omitted this important aspect.

Conclusion:

HAP/VAP modelling would be improved by better awareness of long-term outcomes and treatment complexity. We are unaware of any similar literature reviews of economic modelling for HAP/VAP.

[244 words]

Keywords

Pneumonia; HAP; VAP; health economics; modelling

Abbreviations

ARC EoE	Applied Research Collaboration East of England
CAP	Community-acquired pneumonia
CI	Confidence interval
EED	Economic Evaluation Database
ETT	Endotracheal tube
HAP	Hospital acquired pneumonia
HE	Health economics
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
LOS	Length of stay
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
PCR	Polymerase chain reaction
PSA	Probabilistic Sensitivity Analysis
QALY	Quality adjusted life year
SA	Sensitivity analysis
UK	United Kingdom
VAP	Ventilator-associated pneumonia
WTP	Willingness to pay

1 Introduction

'Hospital-acquired pneumonia' (HAP) is pneumonia that occurs ≥48 hours after admission and was not incubating at admission [1, 2]. 'Ventilator-associated pneumonia (VAP) is 'pneumonia that arises more than 48-72 hours after endotracheal intubation' [1, p.389]. Opinions differ on whether VAP is a subset of HAP or a separate entity [1, 2]; nevertheless, both are difficult to treat, often involving pathogens with significant antibiotic resistance [3].

HAP occurs in 0.5-1.5% of inpatients [2, 4] and is the most common hospital-acquired infection contributing to death [5]. One study estimated HAP to increase mean hospitalisation duration by nine days [6]. A systematic review estimated that VAP develops in 10-20% of patients receiving ≥48 hours of mechanical ventilation [7], and that – compared to VAP-free controls – VAP patients are twice as likely to die, have significantly longer ICU stays, and create substantial additional hospital costs.

Multiple guidelines exist on prevention, diagnosis and treatment of HAP/VAP, but have poor underpinning evidence [8]. Preparing UK 2008 guidelines, Masterton et al. [4] undertook a systematic literature review of HAP prevention, diagnosis and treatment. They described the then American Thoracic Society guidelines [1] as extensive and evidence based but with shortcomings. The most recent US and European (2016 and 2017 respectively) guidelines [8, 9], continue to have many recommendations caveated as 'weak recommendation' or 'very low-quality' evidence.

These guidelines nonetheless agree on the broad HAP treatment strategy: doctors should give 'empirical' antibiotics immediately on suspecting HAP, with the choice informed by local pathogen prevalence and resistance rates, along with patient factors. Respiratory and blood samples should be taken before antibiotic initiation and the resulting culture and susceptibility results, once available, should guide 'definitive' antibiotic choice. Antibiotics may be changed based upon the patient's response, secondary infections and/or other clinical factors.

Culture results take 48-72 hours [2], and lack sensitivity: up to 70% of pneumonia patients have no pathogen identified [10]. Consequently, many patients remain on empirical treatment and, if the causative organism is drug-resistant, this may be

ineffective. More often, however, empirical antibiotic treatment is overly broad-spectrum, representing unnecessary use of valuable 'last-resort' antibiotics. Given increasing emphasis on antibiotic stewardship, and possible improved outcomes, the National Institute for Health and Care Excellence (NICE) and the Infectious Diseases Society of America (IDSA) have recommended research into rapid molecular diagnostic tests for identifying causative organisms and antibiotic resistance profiles [2, 11]. Ideally, these would augment/replace culture, as they are quicker (1-6 hours) and believed more sensitive [12, 13].

The UK's National Institute for Health Research (NIHR)-funded INHALE programme is exploring use of molecular diagnostics to inform HAP/VAP treatment in critical care [14-17]. Currently, INHALE is comparing antibiotic use and outcomes in a trial where HAP/VAP patients are randomised to standard care (i.e. empirical antibiotics, refined once culture results become available) or to treatment guided by the BioFire® FilmArray® (utilising the Pneumonia Panel – see Buchan et al. [12] and Murphy et al. [13] for further information), which identifies common pneumonia pathogens and critical antimicrobial resistance genes within 75 minutes.

Wider deployment of such diagnostics has resource implications, particularly for resource-intensive critical care, where HAP/VAP primarily occurs. It is important to look beyond test effectiveness, to consider associated resource impacts and any corresponding costs/savings. Accordingly, INHALE includes a health economic (HE) component, comparing cost and outcomes under the treatment alternatives.

Economic evaluations alongside trials have limitations [18]: short time horizons (meaning that ultimate costs and benefits are not fully captured); inability to consider all relevant options and limited generalisability. Therefore, an economic model will be constructed to extrapolate beyond the trial and to allow exploration of various scenarios.

Considerable information is required in constructing HE models, including the following. First, the research question that the model is designed to address; this can vary from narrow (e.g. comparison of a new intervention against existing care) to wider questions (e.g. whole disease-based models that evaluate multiple interventions). Second, the model structure, defining the different health states or events occurring within the model and how they interact. Third, model perspective

(e.g. secondary care only), determining the required range of information. Fourth, the model's timeframe: what period should it capture to include important costs and benefits? These factors influence required data.

Prior to INHALE's trial, we conducted a literature review to identify studies that constructed a health economic model relating to HAP or VAP. We had two broad objectives. First, to identify the context in which the health economic modelling had been undertaken (i.e. the research question(s) the modelling was addressing). Second, and more importantly, to summarise model structures, modelling perspectives and timeframes.

2 Methods

2.1 Literature search

Embase Ovid and MEDLINE Ovid databases, along with the National Health Service Economic Evaluation database (NHS EED), were searched on 5/4/17 to identify articles that:

- Contained economic modelling;
- Focused on pneumonia acquired in hospital.

When searching Embase and MEDLINE, terms from both components were used (Supplementary materials, Appendix 1); searching the NHS EED database, which only includes health economic studies, did not require economic modelling terms. The single term 'pneumonia' was used to search the latter database. Searches were restricted to English language articles.

The Embase/Medline search was updated on the 4/6/2020 to identify any recently published work. The NHS EED search was not repeated since that database has not been updated since the initial search – see [19].

2.2 Eligibility criteria and selection of studies

Studies were considered for inclusion if they:

- Related to the treatment or management of HAP or VAP;
- Included an economic model;
- Were undertaken in, and pertinent to, a hospital setting.

Studies were excluded if they:

- Were not in the English language;
- Were just abstracts;
- Only considered community-acquired pneumonia (CAP);
- Focused on prevention rather treatment of HAP/VAP;
- Considered HAP/VAP as management outcomes, without specific treatments.

For the first and the subsequent searches, records from the Ovid (Embase/MEDLINE) search were considered first. Duplicates were removed; titles and abstracts of the remaining records were then independently screened for

eligibility by two reviewers, using a pre-piloted checklist. This was repeated with the NHS EED search results. Duplicates already identified in the Ovid (MEDLINE/Embase) search were then removed

Reference lists of included studies were screened for additional eligible studies.

2.3 Data extraction

Data extracted were: study characteristics, models and economic evaluations. Study characteristics included: authorship; journal; country of study; population; costing year; comparators/study groups; and any industry funding links. Characteristics of the model and economic evaluation included: costing perspective; outcome measure; model type; time horizon; cost discount rate; Quality Adjusted Life Year (QALY) discount rate; sensitivity analyses and study results.

2.4 Health economic concepts

The costing perspective relates to the breadth of costs considered: this can be narrow (e.g. secondary care costs), or broad, including wider perspectives (e.g. at the broadest, 'costs to society'). A narrow perspective can be problematic when important costs arise because of an intervention but are not captured (e.g. adopting a narrow secondary care perspective in respect of a hospital intervention will miss possibly large impacts on primary care). 'Discount rate' refers to how costs and benefits were adjusted to allow for differences in *when* they occur, with events occurring further into the future valued less. 'Sensitivity analysis' (SA) covers different ways in which uncertainty is accommodated in models, and explores the impact on results of varying key parameters [20]. Simple 'one-' or 'two- way SA' varies one or two parameters within a set value range and notes resulting impacts on results and model conclusions. SA can include threshold analysis, in which parameters are varied to determine the value where a "'threshold' is reached, for example a change of model conclusions" [21, p.56]. SA can also include scenario analysis, where a number of model parameters are set to reflect particular scenarios; for example, best/worst cases. More sophisticated forms of SA includes 'Probabilistic Sensitivity Analysis' (PSA), which uses probability distributions to model the uncertainty around point estimates of multiple model parameters simultaneously [22].

Incremental cost-effectiveness ratios (ICERs) are reported for some studies: these are “a summary measure representing the economic value of an intervention, compared with an alternative,” and are “calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of ‘extra cost per extra unit of health effect’” [23].

3 Results

3.1 Study selection process

The flow chart (Supplementary materials, Figure S1) depicts the number of records retrieved, screened for eligibility, and the numbers of exclusions/inclusions. Overall, 698 records were identified from databases and two more were found [24, 25] through screening reference lists. Following removal of 80 duplicates, 592 records deemed ineligible at initial screening, and six [26-31] deemed ineligible during full text review, 20 valid studies were identified.

3.2 General characteristics of included studies

Key details of the 20 selected publications are in Table I. Only one was published before 2000 [32]; seven [24, 33-38] were published between 2001 and 2006, and twelve [25, 39-49] between 2009 and 2019. The USA was the most-represented country (n=13) [24, 25, 32, 35-39, 42, 44, 47-49], with two studies in Germany [40, 45], and one in each of: Brazil [34]; China [46]; Spain [33]; Taiwan [43] and the UK [41].

Studies differed in patient populations considered. Six studies considered HAP/VAP broadly [24, 33, 36, 39, 42, 44], whereas the remaining studies focused on HAP and/or VAP caused by specific pathogens, especially Methicillin-resistant *Staphylococcus aureus* (MRSA). Six only considered VAP [24, 35, 36, 43, 45, 47].

The most common interventions evaluated (n=15) were simple comparisons between pairs of antibiotics. In seven studies, antibiotics were used from the empiric treatment phase [34, 39, 40, 43, 44, 46, 47]; three after the empiric phase [25, 41, 45]; for five it was unclear [33, 35, 38, 42, 48]. The systematic review by Zhang et al. [49] compares vancomycin against five other antibiotics (linezolid; teicoplanin, telavancin; quinupristin/dalfopristin; trimethoprim/sulfamethoxazole/rifampicin) for treating HAP due to MRSA. Three of the remaining four studies focused on single antibiotics. Shah et al. [37] estimated the cost of treating HAP caused by MRSA with the antibiotic vancomycin. Paladino et al. [32] compared ‘dual individualization’ (where ‘Antibiotic [cefmenoxime] regimens are manipulated to optimize the area under the plasma concentration time curve above the minimum inhibitory concentration [MIC] of [*sic*.] the infecting bacteria’ [32, p.384]) – however, it is

important to note that cefmenoxine is no longer used and that time above MIC is the driver of β-lactam efficacy rather than area under the concentration time curve. McNabb et al. [24] compared continuous versus intermittent infusion of ceftazidime. Ost et al. [36] is the only study that compared different diagnostic and treatment strategies, focusing on VAP with 16 combinations arising from four diagnostic options [nothing; bronchoscopy; quantitative culture of unprotected ETT aspirate; quantitative cultures of protected specimen blind mini-bronchoalveolar lavage (mini-BAL)] and four initial antibiotic treatment options (none, one, two, or three agents). The model did not consider specific named antibiotics, but rather used expected coverage rates when guidelines [50] were applied to sample late-onset VAP cases [51]. See Ost et al. [36] supplementary materials for further detail.

3.3 Modelling approaches and scope

Details and results of models are in Table II. A range of outcomes were considered across studies, and some studies used multiple outcomes. The most commonly used outcomes included: survival [34-36, 38, 40, 42, 47]; clinical cure rate [24, 25, 40, 43, 45, 46, 48]; QALYs [33, 38, 39, 41, 47]; and life years gained [33, 38, 40, 47, 49]. Two studies [37, 44] only considered costs, with no consideration of outcomes: Shah et al. [37] only considered the costs of treating with vancomycin, with no comparator, precluding cost-effectiveness conclusions; McGarry et al. [44] justify their analysis as cost-minimisation since 'the two comparators [doripenem and imipenem] were found to be equally safe and efficacious' [44, p.143]. Other outcomes included: duration of antibiotic therapy while in hospital [32]; length of stay [42]; proportion of admission spent in an intensive care unit (ICU) [42]; and proportion (denominator unclear) of time on a ventilator [42]. There is an approximate even split between studies in the choice of costing perspective: nine adopted a healthcare payer perspective [25, 35, 38, 39, 42-46] and ten adopted a healthcare system perspective [24, 32-34, 36, 37, 40, 41, 48, 49]. Zilberberg et al. [47] adopted a healthcare system and a societal perspective; this was the only study to consider a societal perspective.

Most (n=18) studies used a decision tree model. One used discrete event micro-simulation [42] (`a computer-modelling technique … in which individual patient experience is simulated over time, and events occurring to the patient and the

consequences of such events are tracked and summarised' [52]). Another study used a Markov cohort model (where specific health states are defined and movement between these is modelled) [41]. It was difficult to categorise time horizon: some studies were not explicit (e.g. 'until cure' [40]). However, several gave a specific duration in days [25, 33, 38, 39, 41-43, 45, 46]. Only six ran the model for the lifetime of participants [33, 38, 39, 41, 47, 49]. Except for Machado et al. [34], SA was conducted in all studies. Sixteen studies used one- or two- way sensitivity analyses. Ten studies used PSA [25, 36-39, 41, 44, 45, 47, 49].

3.4 Modelling results reported by studies

Nine studies [25, 33, 34, 38-40, 43, 45, 46] solely compared linezolid to vancomycin. At the time of the analyses linezolid was proprietary. Of these, only two did not have exclusive focuses on particular pathogen subsets: Collins and Schwemm [39] found linezolid to be cost-effective for HAP treatment with a life-time horizon; Grau et al. [33] found linezolid to be cost-effective for VAP.

All but two [38, 39] of the nine studies considered MRSA HAP/VAP: four found linezolid to be cost-effective [33, 40, 43, 46]; and three found linezolid to be less costly and more effective [25, 34, 45]. These conclusions for treating MRSA HAP accord with those reached by Zhang et al. [49], who include vancomycin and linezolid amongst a number of comparators. These authors conducted a meta-analysis of clinical studies (incorporating those that provide data for the seven MRSA HAP/VAP studies noted above), and incorporated them in an economic model: linezolid was found to have an ICER of $2,185 per additional life year saved compared with vancomycin – a gain that was very likely to be considered cost-effective. Of the other treatments considered by Zhang et al. [49], teicoplanin was found to dominate (cost saving and more effective) vancomycin, but the limited clinical evidence was judged weak. The other antibiotics evaluated by Zhang et al. [49] were not considered cost-effective compared to vancomycin (ICERs per life year saved were >$50,000).

Two studies considered other subsets of HAP pathogens: Shorr et al. [38] considered VAP attributed to *Staphylococcus aureus* in general, and found linezolid to be cost-effective; Grau et al. [33] found linezolid to be cost effective for treating VAP caused by Gram-positive bacteria.

Linezolid and vancomycin are only active against Gram-positive infections and five studies focused solely on cases where these organisms were confirmed [25, 34, 43, 45, 46]; four studies drew on clinical trials where patients received aztreonam for Gram-negative coverage, but either did not consider its costs in their model [38-40] or excluded patients with Gram-negative infections [33].

In considering linezolid and vancomycin comparisons, undertaken a decade or longer ago, it is important to note the substantial context change: linezolid is now out of patent and substantially less costly to purchase.

A more recent study [48] compares first line telavancin to vancomycin for treating HAP caused by Staphylococcus aureus. The model considers both MRSA and Methicillin-sensitive Staphylococcus aureus (MSSA), with different treatment approaches for each. Telavancin was found to have a higher cure rate, but at an increased cost, with an ICER of $4,156 per additional cure.

Four studies [35, 42, 44, 47] compared doripenem and imipenem. They concluded doripenem was preferable, given similar efficacy, and being cost-saving in two studies [42, 44] and having a relatively low ICER for additional benefits in the others [35, 47]. However, these results are no longer relevant as doripenem was subsequently found to have higher mortality in HAP/VAP [53] and its European license was withdrawn. Edwards et al. [41] found meropenem to be more effective and cost-saving compared with piperacillin/tazobactam in HAP patients not responding to first-line antibiotics.

Ost et al. [36], compare diagnostic and treatment options across three dimensions: cost; antibiotic use; and survival. Initial treatment with three antibiotics was optimal for cost and survival. Mini-BAL testing did not improve survival, but decreased costs and antibiotic use. Across all three domains, mini-BAL with three antibiotics was optimal.

4. Discussion

Our review identified 20 studies that applied economic modelling to the treatment of HAP and/or VAP. Only one model [36] specifically evaluated strategies to improve HAP/VAP diagnosis, meaning that most models reported had little direct relevance to the evaluation of a rapid molecular diagnostic test for microbiological investigation of HAP/VAP. We are unaware of any similar literature reviews of economic modelling for HAP/VAP.

4.1 Conclusions of studies and generalisability

Most studies compared two antibiotics and of these, most were undertaken in connection with the launch of then-new products, linezolid and doripenem. Such comparisons do not necessarily require complex models: e.g. Machado et al. [34] has one decision node to choose antibiotic, and a chance node for therapy success. Many studies focused on MRSA and other Gram-positive pathogens, limiting relevance, as approximately two-thirds of HAP/VAP cases involve Gram-negative pathogens [4]. Studies relating to single pathogens (e.g. MRSA) have limited scope to represent the typical situation faced by clinicians treating HAP where the causative pathogen is unknown.

Most models considered a short-time frame, typically until resolution, with only six models considering a longer, life-time, time horizon. Most captured the patient 'journey' until case resolution – generally being cure or death – meaning 60 days or less. This likely undervalues benefits from more successful treatments (e.g. if measuring in QALYs, the value of saving a life will be much greater if considering a life-time horizon rather than only until case resolution). Moreover, those models that do capture longer time-frames and QALYs typically do so in a simplistic way, using strong assumptions rather than long-term follow-up. Thus, five of the six studies [33, 38, 39, 47, 49] adopting a life-time horizon have broadly adopted the same strong assumptions, in particular that survival post VAP is similar to that observed in sepsis survivors. Another assumption used to estimate QALYs draws on evidence that survivors of acute respiratory failure requiring ventilation have their quality of life reduced by 8% [46]: accordingly, post-discharge QALYs are reduced from 1 to 0.92 [37]. Some authors have further reduced this to 0.83 [33, 38, 47]. An alternative approach assumes that, once discharged, patients 'accrued their normal age- and

sex-adjusted HRQL [health-related quality of life]' [41, p.185-186]. The importance of long-term data for decision making is illustrated by estimates of the cost-effectiveness of linezolid compared to vancomycin, which has a cost per additional QALY estimated at $19.6million [resulting from dividing an incremental cost ($892) by a very small incremental QALY gain (<0.001)] over 60 days, decreasing to $6,089 with a life-time horizon [39].

4.2 Model sophistication and implications for economic modelling of rapid diagnostics

We found variation in model sophistication, though most models tended towards simple structures. Only two models did not use decisions trees, with one using a Markov model [41] and one using a discrete event micro-simulation model [42]. Additionally, the model by Edwards et al. [41] was the only one to incorporate different hospital settings such as ICU and wards, potentially supporting more precise costings.

Among decision trees, the simplest was that of McNabb et al. [24] and Machado et al. [34] consisting of a decision node choosing between treatment alternatives (vancomycin or linezolid) and a chance node representing treatment outcome (cure or death). The model in Mullins et al. [35] is more complex, with four outcomes: survival with bacteraemia; survival without bacteraemia; death with bacteraemia; and death without bacteraemia. The model of Zhang et al. [49] deals with three outcomes: cure, death and treatment switch following initial treatment failure. Its simplicity is likely a result of synthesising a literature review and comparing a relatively large (five) number of alternatives to vancomycin: more sophistication would require very strong assumptions. A subset of more sophisticated models have an additional level of chance nodes: the first chance node captures treatment success, followed by another node modelling either survival [33] or adverse event occurrence [32, 43]. Among the two most sophisticated decision trees were found in the later studies by De Cock et al. [40], Patel et al. [45], Patel et al. [25] and Tan et al. [46] ([45], [25] and [46] use the same model structure). Both models capture a wide range of outcomes: cure, adverse event, lack of efficacy and death. Additionally, both models more closely follow clinical practice by capturing switching antibiotics when the 'first line' agents prove ineffective. The model used in the papers by Patel et al. [45], Patel et al. [25] and Tan et al. [46] is less generalizable given they focus on confirmed MRSA HAP, while the model in De Cock et al. [40]

incorporates nodes relating to determining infection cause. Another more sophisticated tree is used in McKinnell et al. [48]: focusing on HAP due to Staphylococcus aureus, it explicitly models cure and adverse event (nephrotoxicity) occurrence, along with causative subset of Staphylococcus aureus (MRSA or not; mono- or poly-microbial), but does not explicitly address death or treatment switching (patients not achieving cure with the first-line treatment were assumed cured following switching to linezolid for seven days).

There are two other decision tree models. Zilberberg et al. [47] present a model that seems to be ill-formed: chance nodes have perhaps been confused with decision nodes. The decision tree of Ost et al. [36] is the most relevant for informing a model to evaluate rapid diagnostics: there are two decision nodes for choosing between diagnostic tests and number of initial antibiotics. They also capture antibiotic switching if needed and consider a range of outcomes, but do not explicitly address adverse events. Ost et al. [36] is also the only model that explicitly captures the empiric treatment phase.

4.3 Limitations

For this literature review we searched three databases, selected for their comprehensive, international biomedical (Embase Ovid and MEDLINE Ovid) and speciality health economic coverage (NHS EED) [19]. Additional eligible studies might have been identified had we broadened the search to additional databases such as: EconLit [54]; HEED [55]; and HTA [56]. However, our aim was to identify studies to inform economic modelling in this area. This contrasts with systematic reviews of effectiveness studies, where the intention is to derive a pooled estimate of effect, within which the aim is to identify as many eligible studies as possible to help reduce bias. We have not assessed studies for risk of bias or quality.

5 Conclusions

We found 20 studies using economic modelling in HAP/VAP treatment. Only one – Ost et al. [36] – compares different diagnostic approaches, making it the most relevant for informing our model evaluating rapid diagnostics for treating HAP. Most models used simple decision trees, short time horizons, and assumed a known pathogen. The clinical utility of future work would be improved by considering long-term outcomes and increased awareness of the complex reality of HAP/VAP

treatment, in particular, explicitly addressing the commonly occurring situation where the causative organism is initially unknown.

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Conflicts of interest

APW, JVC and DT have no conflicts of interest relevant to the study. DML: Advisory Boards or ad-hoc consultancy Accelerate, Allecra, Antabio, Centauri, Entasis, Integra-Holdings, Meiji, Melinta, Menarini, Mutabilis, Nordic, ParaPharm, Pfizer, QPEX, Roche, Shionogi, T.A.Z., Tetraphase, VenatoRx, Wockhardt, Zambon, Paid lectures – Astellas, bioMerieux, Beckman Coulter, Cardiome, Cepheid, Merck/MSD, Menarini, Nordic, Pfizer and Shionogi. Relevant shareholdings or options – Dechra, GSK, Merck, Perkin Elmer, Pfizer, T.A.Z, amounting to <10% of portfolio value. VIE has received speaking honoraria, consultancy-fees and in-kind contributions from several diagnostics companies including bioMerieux, Curetis GmbH and Oxford Nanopore Technologies.

Authors' contribution

APW: Study rationale and design, literature search, interpretation and reflection, manuscript writing and redrafting.

DT: Study rationale and design, literature search, interpretation and reflection, manuscript writing, guarantor of the study, reviewing manuscript.

All authors contributed to manuscript writing and approved the final draft.

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Tables

Table I: Characteristics of HAP or VAP studies involving economic modelling.

Key: VAP= ventilator associated pneumonia. HAP= hospital acquired pneumonia. NA= not applicable. NR= not reported. MRSA= methicillin resistant *Staphylococcus aureus*.|

Reference	Journal	Country	Population	Costing year	Comparators	Industry funding/links
Collins and Schwemm [39], 2015	Value in Health	US	HAP (radiographic documented, signs & symptoms)	2014	Antibiotics: linezolid vs vancomycin (empiric)	No
De Cock et al. [40], 2009	Infection	Germany	HAP (suspected/ proven MRSA)	2006	Antibiotics: linezolid vs vancomycin (empiric)	Pfizer Deutschland
Edwards et al. [41], 2012	European Journal of Health Economics	UK	HAP (severe, ICU treated, post failed 1st-line antibiotics (pre/post ICU admission))	2008	Antibiotics: meropenem vs piperacillin/tazobactam (post empiric)	AstraZeneca
Grau et al. [33], 2013	Journal of Chemotherapy	Spain	VAP (all, Gram +ve, *S. aureus*, MRSA)	2003	Antibiotics: linezolid vs vancomycin (unclear if empiric)	Pfizer
Kongnakorn et al. [42], 2010	Current Medical Research & Opinion	US	HAP	2007	Antibiotics: doripenem vs imipenem (unclear if empiric)	Johnson & Johnson
Lin et al. [43], 2016	Journal of Microbiology, Immunology and Infection	Taiwan	HAP (confirmed MRSA)	NR	Antibiotics: linezolid vs vancomycin (empiric)	Pfizer
Machado et al. [34], 2005	Brazilian Journal of Infectious Disease	Brazil	VAP (MRS*A*)	2004	Antibiotics: linezolid vs vancomycin (empiric)	NR
McGarry et al. [44], 2010	Journal of Medical Economics	US	VAP (diagnosis)	2006	Antibiotics: doripenem vs imipenem (empiric)	Johnson & Johnson
McKinnell et al. [48], 2018	Clinical Therapeutics	US	HAP (*Staphylococcus aureus*)	2016	Antibiotics: telavancin vs vancomycin (post empiric?)	Theravance Biopharma Antibiotics
McNabb et al. [24], 2001	Pharmaco-therapy	US	HAP	1999	Treatment: continuous v intermittent Ceftazidime dosing	NR

Reference	Journal	Country	Population	Costing year	Comparators	Industry funding/links
Mullins et al. [35], 2006	Clinical Therapeutics	US	HAP (MRSA)	NR	Antibiotic: doripenem vs imipenem (unclear if empiric)	Pfizer
Ost et al. [36], 2003	American Journal of Respiratory and critical care medicine	US	VAP (CDC criteria)	2002	Management strategies - 16 options: 4 diagnostics (nothing; bronchoscopy; quantitative culture of unprotected ETT aspirate; quantitative cultures of protected specimen blind mini-bronchoalveolar lavage (mini-BAL)) with 4 treatments (0-3 empiric antibiotics)	One author: Merck & Roche
Paladino et al. [32], 1994	Pharmaco-economics	US	HAP (Gram -ve)	1992	Treatment: individual tailoring vs standard dosing of cefmenoxime (empiric)	NR
Patel et al. [25], 2014	Critical Care	US	HAP (MR*SA* confirmed)	2012	Antibiotics: linezolid vs vancomycin (post culture)	Pfizer
Patel et al. [45], 2014	Infection and Drug Resistance	Germany	HAP (MR*SA* confirmed)	2012	Antibiotics: linezolid vs vancomycin (post culture)	Pfizer
Shah et al. [37], 2004	Current Medical Research & Opinion	US	HAP (MR*SA*)*	2003	NA	Cubist Pharma
Shorr et al. [38], 2004	Critical care medicine	US	VAP (*Staphylococcus aureus*)	2001	Antibiotics: linezolid vs vancomycin (unclear if empiric)	NR
Tan et al. [46], 2014	Value in Health Regional Issues	China	HAP (MRSA confirmed)	NR	Antibiotics: linezolid vs vancomycin (empiric)	Pfizer
Zhang et al. [49], 2019	Antimicrobial Resistance & Infection Control	US	HAP (MRSA)	2017	Antibiotics: vancomycin vs. each of: linezolid; teicoplanin, telavancin; quinupristin/dalfopristin; trimethoprim/sulfamethoxazole/ rifampin (post empiric)	No
Zilberberg et al. [47], 2010	Surgical Infections	US	VAP (non-*Pseudomonas aeruginosa* ignored)	2008	Antibiotics: doripenem vs imipenem (empiric)	Johnson & Johnson

* Shah et al. [37] also considers: skin and soft tissue Infections; bacteraemia; infective endocarditis. We only consider HAP here.

Table II: Modelling details and results of identified economic models in the area of HAP and VAP.
Key: VAP= ventilator associated pneumonia. PSA= probabilistic sensitivity analysis. ICER= incremental cost effectiveness ratio. QALY= quality adjusted life year. HAP= hospital acquired pneumonia. LOS= length of stay. MR*SA*= methicillin resistant *Staphylococcus aureus*. ICU= intensive care unit. NA= not applicable. NR= not reported. WTP= willingness to pay. CI= confidence interval.

Reference	Perspective	Outcome measure	Model type	Time horizon	Cost discount rate	QALY discount rate	Sensitivity analyses	Results
Collins and Schwemm [39], 2015	Healthcare payer	QALY	Decision tree cohort model	Primary - lifetime (assume survive 15 years more); secondary - 60-day	0.03	0.03	1-way; PSA	Lifetime horizon ICER per: QALY= $6,089; life saved= $68,615. Vancomycin dominated in documented cases of MRSA. 60-day horizon ICER per: QALY= $19,608,688; life saved= $443,662. Model sensitive to changes in: mortality; population; and time horizon.
De Cock et al. [40], 2009	Healthcare system	Life years gained; survival; clinical cure rate	Decision tree cohort model	Cure on either 1st- or 2nd-line treatment, or failure on 2nd-line	NR: not expected given horizon	NA: QALYs not used	1-way; 2-way; scenarios	ICERs: per life gained= €180; per death avoided= €3,171; per additional cure= €4,813. In scenarios, linezolid dominates. Consistent under sensitivity analyses.
Edwards et al. [41], 2012	Healthcare system	QALY	Markov cohort model	Lifetime	Explicit: no discounting as no costs past a year	0.035	PSA	Meropenem dominated (PSA: meropenem dominated in 94% of simulations). Consistent under sensitivity analyses.
Grau et al. [33], 2005	Healthcare system	Life years gained; QALY	Decision tree cohort model	Lifetime	Explicit: no discounting	Explicit: no discounting	1-way; scenario	ICER per life year saved: all VAP= €1,501; Gram +ve VAP= €827; *S. aureus* VAP= €955; MRSA VAP= €289. ICERS per life year saved: all VAP= €1,804; Gram +ve VAP= €997; *S. aureus* VAP= €1,149; MRSA VAP= €349. Base case consistent under sensitivity analyses.
Kongnakorn et al. [42], 2010	Healthcare payer	Survival; LOS; % time in ICU; % time on ventilator	Discrete event micro(?)-simulation	Until death or 35-49 days	Explicit: no discounting as no costs past a year	NA: QALYs not used	1-way	Similar relapse and death rates. LOS (days): doripenem= 16.0; imipenem= 18.9. Doripenem gave $7,000 in savings per patient (driven by reduction in LOS). Consistent under sensitivity analyses.

Reference	Perspective	Outcome measure	Model type	Time horizon	Cost discount rate	QALY discount rate	Sensitivity analyses	Results
Lin et al. [43], 2016	Healthcare payer	Clinical cure rate	Decision tree cohort model	7-30 days after treatment	NR: not expected given horizon	NA: QALYs not used	1-way (±20%)	ICER per cured person $3,421 (PSA 95% CI= $1,714 to $5,127).
Machado et al. [34], 2005	Healthcare system	Survival (cure versus death)	Decision tree cohort model	Not explicit: time to cure/death	NR: not expected given horizon	NA: QALYs not used	None	Cure rate: linezolid= 62.2%; brand-name vancomycin= 21.2%; generic vancomycin= 21.2%. Invested amount per cured patient: linezolid= R$7,765; brand-name vancomycin= R$13,232; generic vancomycin= R$11,278.
McGarry et al. [44], 2010	Healthcare payer	Cost	Decision tree cohort model	Unclear: inpatient stay	NR: not expected given horizon	NA: QALYs not used	PSA	Average doripenem costs were $10,630 lower (PSA 95% CI= $5,100 to $16,500).
McKinnell et al. [48], 2018	Healthcare system (hospital)	Clinical cure rate	Decision tree cohort model	Inpatient stay	NR: not expected given horizon	NA: QALYs not used	1-way; scenario	ICERs: per additional cure= €4,156. In scenario (monomicrobial infections only) telavancin dominates. ICER sensitive to probabilities of cure, length of treatment in cures, ICU cost, telavancin cost, and additional length of stay due to failure.
McNabb et al. [24], 2001	Healthcare payer (treatment excluding hotel)	Clinical cure rate	Decision tree cohort model	Not explicit: time until resolution (cure/death)	Explicit: no discounting as no costs past a year	NA: QALYs not used	1-way; 2-way; threshold	Cure rate: continuous infusion= 94%; intermittent= 83%. Costs (significantly different): continuous infusion= $627±388; intermittent= $1,007±430.
Mullins et al. [35], 2006	Healthcare payer	Survival	Decision tree cohort model	Time to cure/death	NR: not expected given horizon	NA: QALYs not used	1-way; 2-way	ICER per life year saved= $3,600. Consistent under sensitivity analyses.
Ost et al. [36], 2003	Healthcare system	Survival	Decision tree cohort model	Time to: death due to VAP; death in ICU; surviving ICU	NR: not expected given horizon	NA: QALYs not used	1-way; 2-way; PSA; scenario	Use of 3 antibiotics was better than 0-2 antibiotics, giving improved survival (54% vs. 66%) and decreased cost ($55,447 vs. $41,483 per survivor). Mini-BAL testing did not improve survival but decreased costs ($41,483 vs. $39,967) and antibiotic use (63 vs. 39 antibiotic days per survivor). 3 antibiotics with mini-BAL

Reference	Perspective	Outcome measure	Model type	Time horizon	Cost discount rate	QALY discount rate	Sensitivity analyses	Results
								minimised cost and antibiotic use, and maximised survival.
Paladino et al. [32], 1994	Healthcare system	Antibiotic duration in hospital	Decision tree cohort model	Not clear	NR: not expected given horizon	NA: QALYs not used	1-way	ICER antibiotic days reduced=$114. Median antibiotic duration days: 12.7 dual individualisation; 15.2 standard treatment.
Patel et al. [25], 2014	Healthcare payer	Clinical cure rate	Decision tree cohort model	28 days	NR: not expected given horizon	NA: QALYs not used	1-way; PSA; scenarios	Linezolid dominates (by $824 and 2.7% greater cure rate). Consistent under sensitivity analyses (at a WTP of €0, linezolid has a 64.4% chance of cost-effectiveness).
Patel et al. [45], 2014	Healthcare payer	Clinical cure rate	Decision tree cohort model	28 days	NR: not expected given horizon	NA: QALYs not used	1-way; PSA; scenarios	Linezolid dominates (by €123 and 2.7% greater cure rate). Consistent under sensitivity analyses (at a WTP of €0, linezolid has a 53.9% chance of cost-effectiveness).
Shah et al. [37], 2004	Healthcare system	Cost	Decision tree cohort model	Inpatient stay	NR: not expected given horizon	NA: QALYs not used	1-way; PSA	Base case cost of treating HAP=$22,493/patient (PSA gives mean and 95% CI of $22,511±3,689).
Shorr et al. [38], 2004	Healthcare payer	Survival; life years gained; QALY	Decision tree cohort model	Primary - 28 days; secondary - lifetime	3% (applied to lifetime perspective)	NR: QALYs seem not to be discounted	1-way; 2-way; PSA; scenario	ICER per: survivor= $67,202; Life years saved= $22,072; QALY= $29,945. Consistent under sensitivity analyses.
Tan et al. [46], 2014	Healthcare payer	Clinical cure rate	Decision tree cohort model	28 days	NR: not expected given horizon	NA: QALYs not used	Scenario	ICER per additional successfully treated patient: Beijing= ¥1,861; Nanjing= ¥163; Xi'an= ¥16,509. Linezolid dominates in Guangzhou. Consistent under sensitivity analyses.

Reference	Perspective	Outcome measure	Model type	Time horizon	Cost discount rate	QALY discount rate	Sensitivity analyses	Results
Zhang et al. [49]	Healthcare system (hospital)	Life years gained	Decision tree cohort model	Lifetime	NR: not expected - no costs beyond short term inpatient stay	NA: QALYs not used	1-way; PSA	Compared to vancomycin: not cost-effective (ICER per LY gained>$50,000) - telavancin, quinupristin/dalfopristin, trimethoprim/ sulfamethoxazole/rifampicin; cost-effective - linezolid (ICER per LY gained=$2,185); teicoplanin dominant but discounted (draws on one 'high risk' study). Results most sensitive to antibiotic costs and treatment duration. Telavancin unit costs <$320 would make it more cost-effective than linezolid. Other single parameter variations did not impact conclusions.
Zilberberg et al. [47], 2010	Healthcare system; societal	Survival; life years gained; QALY	Decision tree cohort model	Healthcare system - time to death or VAP resolution; societal - lifetime	Societal perspective: 3%	NR: QALYs seem not to be discounted	1-way; 2-way; PSA; scenario	ICER per: death averted= $127,178 (PSA 95% CI= -$136,534 to $568,281); LYS= $9,276 (PSA 95% CI= -$11,254 to $21,579); QALY= $5,748 (PSA 95% CI= -$6,923 to $13,904). Consistent under sensitivity analyses.

Supplementary material

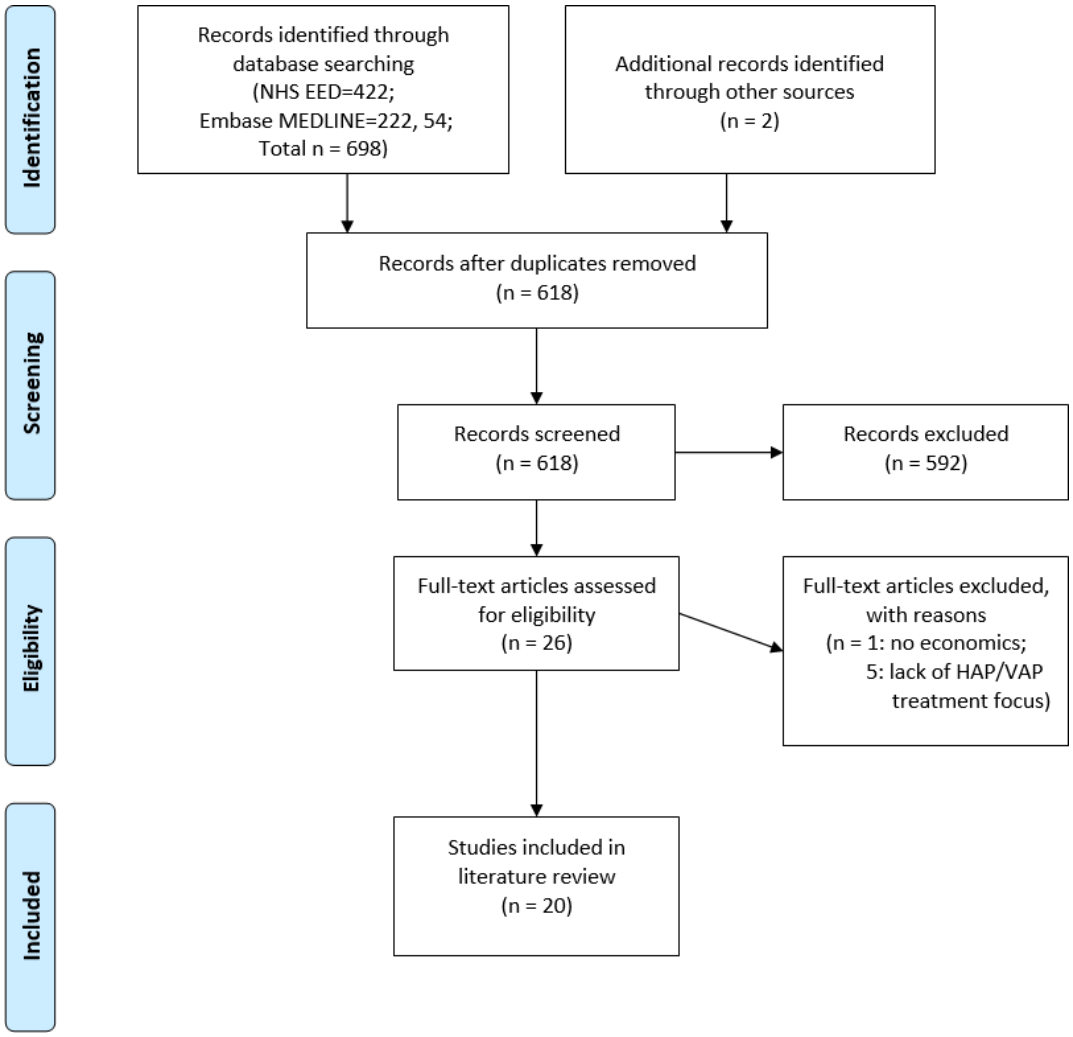

Figure S1: Process of article identification. Adapted from Moher et al. [57].
Key: NHS EED= National Health Service Economic Evaluation database.

Appendix: Ovid Medline and Embase search strategy with result hits

	OVID Medline and EMBASE search conducted:	05/04/2017	04/06/2020
1	Markov chain [Including Limited Related Terms]	5194	9177
2	Decision support techniques [Including Limited Related Terms]	3232	9013
3	(econom* adj2 model*).ti,ab.	11373	12672
4	(markov* adj5 model*).ti,ab.	30819	36072
5	(decision* adj8 model*).ti,ab.	44774	50405
6	(discrete event* adj8 model*).ti,ab.	1458	1649
7	(Discrete event* adj5 simulat*).ti,ab.	1813	2015
8	Microsimulat*.ti,ab.	2121	2948
9	or/1-8	89976	108339
10	"hospital acquired pneumonia".mp.	6420	5128
11	hospital acquired pneumonia [Including Limited Related Terms]	4528	7598
12	"hospital-acquired pneumonia".mp.	6420	5128
13	HAP [Including Limited Related Terms]	2283	3377
14	ventilator associated pneumonia [Including Limited Related Terms]	6125	11687
15	"ventilator associated pneumonia".mp.	24369	17648
16	VAP.mp.	15739	11926
17	HAP.mp.	12881	12324
18	VAP [Including Limited Related Terms]	10015	6568
19	nosocomial pneumonia [Including Limited Related Terms]	4528	7598
20	nosocomial pneumonia.mp.	10235	5777
21	hospital acquired bacterial pneumonia [Including Limited Related Terms]	4436	5990
22	"hospital acquired bacterial pneumonia".mp.	117	96
23	"ventilator acquired bacterial pneumonia".mp.	2	10
24	ventilator acquired bacterial pneumonia [Including Limited Related Terms]	4874	8935
25	healthcare associated pneumonia [Including Limited Related Terms]	938	1115
26	((healthcare adj3 associated) and pneumonia).mp.	4943	3021
27	(rapid adj3 diag*).mp.	64730	49527
28	(molecular adj3 diag*).mp.	87011	75046
29	or/27-28	147225	121622
30	or/10-26	70040	56014
31	and/29-30	1090	435
32	(bacter* and (infection$ or pneumonia$)).mp.	1278017	1114821
33	29 and 32	19907	11600
34	30 or 33	89077	67313
35	9 and 34	225	203
36	35	225	203
37	limit 36 to english language	222	200
38	limit 37 to yr=2017-2020	NA	54

Terms 1-9 terms relate to economic modelling and are taken from Edlin et al. [58]. Terms 10-26 are used to identify HAP or VAP. The rapid diagnostic device terms (terms 27 and 28) were included to find items for use elsewhere; we do not consider rapid diagnostics in this article.

Term 38 not in search conducted on 05/04/2017 search as this search was not date limited