Evaluating the cost of antimicrobial resistance and errors in estimates: a systematic review and meta-analysis

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In response to greater levels of antibiotic resistance worldwide, several organizations including the World Health Organization and Centers for Disease Control have named antibiotic resistance one of the greatest threats of the modern age[1,2]. As antibiotic resistance becomes an ever-greater global concern, it is important for policymakers, healthcare professionals, and patients to know the cost of resistance as expressed in standardized currencies. Several systematic reviews and meta-analyses have also attempted to amalgamate these data into overall cost estimates, both in high resource and low resource settings. There are currently five large meta-analyses that attempt to capture overall costs of antibiotic-resistant infection as compared to non-resistant infections, ranging in meta analysis size from 22 papers to 50 papers and in time from 2002 to 2018[3,4,5,6,7]. These papers focus on different organism classes ranging from focusing mainly on Staph aureus (Naylor et. al) to gram negatives (Smith et. al). However, none of them take into account important types of confounding such as patients with greater complexity necessitating greater costs or time-dependent biases. These basic errors in statistical analysis affecting accuracy in estimating of the true cost of an antibiotic resistant infection.

This systematic review and meta-analysis seeks to address these errors, providing a more accurate cost estimate across diverse organism/antibiotic classes.

Aims and objectives

Aim: Draw from diverse AMR costing studies to more accurately determine the cost of AMR resistance, and to examine the impact of study design and methodological quality upon estimates of costs of antibiotic-resistant infections.

Objectives:

1. Provide an estimate of the cost of AMR infections globally using the current evidence base
2. Assess the evidence base for the prevalence of various design errors
3. Explore the relationship of various design errors to one another
4. Assess the impact of design errors on costing estimates

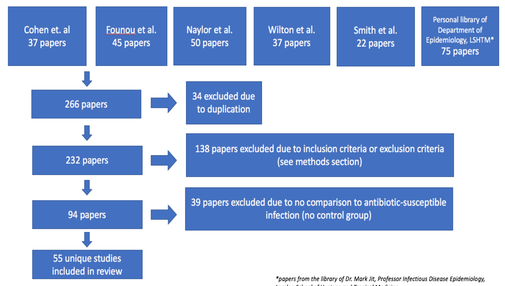
Materials and methods

Search strategy:

Pubmed, Embase, Cochrane, and Web of Science were searched for systematic reviews of AMR costing studies using the search terms “cost” “length” “antibiotic” “antimicrobial” and “infection” using meta-analysis filters. Inclusion criteria: cohort studies, case control studies, modeling studies, ecological studies; studies collected on humans after birth published since 1990; studies with hospital or patient-level costing.

Exclusion criteria: Papers reporting in QUALYs, DALYs, and other metrics that could not be converted to USD; papers with no control group.

Fig. 1: Paper inclusion flow diagram



Data collection:

The 52 relevant studies were then screened for study type, geographic location, organism(s), antibiotics to which resistance was evaluated, and population type. The mean difference in cost and length of stay were noted, and currencies were converted to June 2019 USA using the United States Bureau of Statistics currency converter.

Fig. 2: Studies by geographical region

Evaluation of study design errors:

Design errors in the analysis of each paper were noted using specified criteria. Design errors considered included: unmeasured baseline confounding, time-dependent confounding, time-dependent bias, model misspecification, and lack of conflict of interest.

Data analysis:

Univariate analyses, t-tests/ANOVA, and 95% confidence intervals of difference in cost were generated to explore data using STATA15. A meta-analysis was generated using a random effects model to explore difference in cost, stratifying by gram positivity and study setting. A meta-regression was used to explore relationships between bias types.

Results

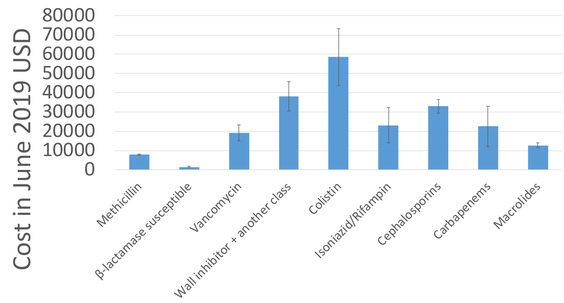
Descriptive analyses

Most studies (67.3%) were retrospective cohort studies, came from high income countries (84.2%), involved adults (96.4%), and were from the United States (56%). The studies represented a variety of different organisms/organism classes, with most studies (36.4%) on Staphylococcus aureus resistance.

Cost by categories of interest

Within countries defined as high income by the 2018 World Bank Census, the median incremental cost of an antibiotic resistant infection was 210,136.50 USD (95% CI, 184,920.12, 235,352.88). In contrast, the median AMR infection cost in studies performed in middle income countries was 3,976.00 USD (95% CI 3,419.36, 4,532.64).

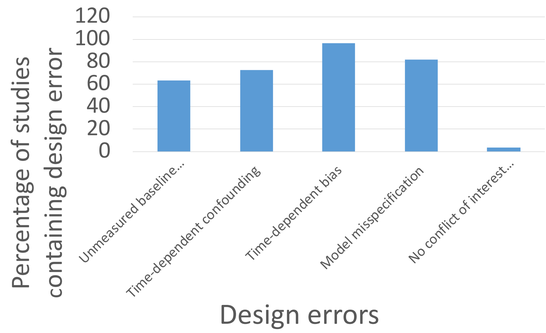
Fig. 3: Median cost of AMR infection with respect to non-AMR infection by antibiotic



Design errors

Most studies contained a design error (figure 5: 53, 96.4%). The most common type of design error was time-dependent bias, affecting 96.4% of studies.

Fig. 4: Percentage of studies containing design errors



Meta-analysis

The pooled incremental cost of an AMR infection was found to be 130.23 USD overall (95% CI, 111.58, 148.89), 1149.53 USD (fig 6: 95% CI, 996.57, 1302.50) in high income countries and 114.98 USD (96.18, 113.77) in LMICs.

Relationship between study design error types

Fig. 5: Correlation coefficients of association between errors

	Unmeasured baseline confounding	Time-dependent confounding	Time-dependent bias	Model misspecification
Unmeasured baseline confouding				
Time-dependent confounding	0.25			
Time-dependent bias	0.65	0.37		
Model misspecification	0.74	0.40	0.49	

Conclusions and limitations

- Country income, organism type, antibiotic type, and gram stain all have a profound impact on the cost of an AMR infection as compared to a non-AMR infection, suggesting that it is difficult to procure one overall number representing the cost of an AMR infection.
- The marked differences between high and low income country AMR infection cost represents the impact of a much greater reliance on specialists, laboratory technology, and less reliance on primary care interventions in high income countries.
- The clear majority of studies contained some type of design error, demonstrating the importance of standardization and study design in costing estimates.
- Factors which limit the generalizability of this study include the heavy weighting of these studies towards countries with high income/adults, selection bias towards academic medical centers, and heterogeneity in studies themselves which limit application of results to one specific population.

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