AN EXPLORATION OF THE UNCERTAINTIES UNDERLYING THE QUANTIFICATION OF THE BROADER VALUE OF ANTIBIOTICS

Is STEDI steady?

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Background

- A framework called STEDI has been conceptualised that describes antibiotics' specific value outside of the value captured by standard Technology Appraisal (TA) methods.
- The STEDI framework is named after five broader value elements (Spectrum, Transmission, Enablement, Diversity and Insurance) and captures an antibiotic's value beyond the value accrued to the treated individual.
- In 2022, the NICE-NHS England AMR pilot was the first attempt to consider STEDI values formally during an HTA process. However, due to the complexity and uncertainty surrounding this novel evaluation process, it fell short of fully quantifying each element.

Aim

To identify, categorise, and rank the importance of the various types of uncertainties in estimating the broader value of antibiotics using the STEDI value framework

Methods

DESK RESEARCH: Mentions of uncertainty were extracted from the official NICE-NHS England AMR pilot documents by STEDI element as defined below[1].

Spectrum	The benefit associated with the use of narrow(er)-spectrum antibiotics stemming from a reduction in collateral damage on the treated individuals' microbiome and the prevention of resistance selection in untargeted bacteria.
Transmission	The indirect benefit of reduced infection rates by avoiding the onward spread of pathogens to other individuals within a population using antibiotics.
Enablement	The benefit associated with enabling or improving the outcomes of other treatments or procedures where antibiotics are also needed.
Diversity	The indirect benefit stemming from preserving the activity of existing antibiotics for longer as they will be used less if the novel antibiotic is added to the treatment options.
Insurance	The indirect value associated with having an antibiotic treatment as a last line option for a patient if all other treatments fail, and for dealing better with (or completely avoiding) major catastrophic outbreaks of AMR in the future.

ANALYSIS Classification of retrieved results as conceptual, scientific, evidentiary, or methodological uncertainty as defined below.

What/how can we measure?

METHODOLOGICAL
There is not an agreed or reliable method for estimating the value element.

EVIDENCE
There is a lack of robust, relevant and standardised evidence or data inputs require to estimate the value element.

What do we want to measure?

SCIENTIFIC
There is a lack of scientific understanding of the relevant microbiological processes, physiological phenomena or clinical contexts.

CONCEPTUAL
There is no consistent definition or concept of the value element within the field.

SURVEY&ROUNDTABLE to re-fine, validate and rank uncertainties.

A group of interdisciplinary experts (n=7) was provided with a survey to rank, face-validate and refine identified uncertainties per value element.

Results were consolidated and discussed with the same group during a 2-hour roundtable discussion.

The group consisted of
- two microbiologists,
- two health economists from industry,
- two health economists from academia/non-profit, and
- one health economist specializing in advanced modelling.

Results

Figure 1 provides a summary of the importance of each uncertainty domain for each value element.

CONCEPTUAL UNCERTAINTY is inherently linked to the definitions, concepts and operationalisation of the STEDI framework.

- Vague definitions, unclear value element boundaries and blurry separation of patient and population benefits can lead to valuation issues and risk double counting value due to overlapping element definitions.

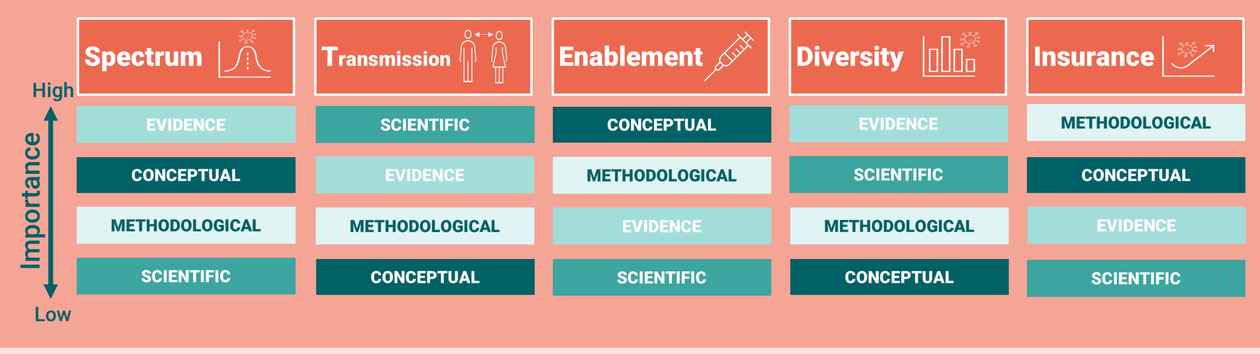
SCIENTIFIC UNCERTAINTY stems from an insufficient understanding of microbiological process.

- Understanding of the drivers, epidemiology and clinical implications of resistance build-up at both the patient- and population-levels is limited.
- Dynamics between treatment and gut colonisation leading to possible onwards infection are not well understood.
- The impact of international usage of antibiotics on local stewardship and resistance trends requires further research.

EVIDENTIARY UNCERTAINTY stems from a lack of robust, relevant, and standardized evidence or data.

- Trial populations with specific resistance mutations are generally small and resistance measurement is not standardized.
- For example, there is generally a poor understanding of how resistant mutations affect bacterial fitness or how to measure the collateral damage to the microbiome.
- A lack of a repository of registries for relevant Real-World Evidence (RWE) or a missing standardized data structure further hinder efficient STEDI value estimation.

FIGURE 1: RANKING OF UNCERTAINTIES BY STEDI VALUE ELEMENT



METHODOLOGICAL UNCERTAINTY occurs as long as robust methods and data for estimating annual patient numbers are not well established.

- No standardized methodology, separating enablement value from insurance and clinical effects already captured in a therapeutic area.
- Concerning transmission value, modelling transmission dynamics with resistance patterns is complex and has no standardised methodology.
- E.g., for enablement value it is unclear whether this should be modelled via a bottom-up approach or top-down approach.
- No agreed method on how to deal with risk when evaluating insurance value.

Discussion and Conclusion

- The STEDI framework is crucial in quantifying the broader value of antibiotics and therefore to appropriately incentivising antibiotic innovation. However, application of the STEDI framework to date has been incredibly challenging.
- STEDI needs to be conceptually refined, underpinned by better methodological guidance and based on solid evidence.
- In the short term, stakeholders will need to build clarity and consensus on the underlying concepts and definitions of each STEDI value element.
- In the medium term, science and methods associated with the quantification of individual value elements must be developed.
- In the long-term, complex integrated methods that will contribute to a full QALY-based evaluation of the STEDI value elements should be developed.

[1] Definitions based on work by Karlsberg Schaffer et al (2017), Rothery et al (2018) and Towse & Silverman (2022).

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