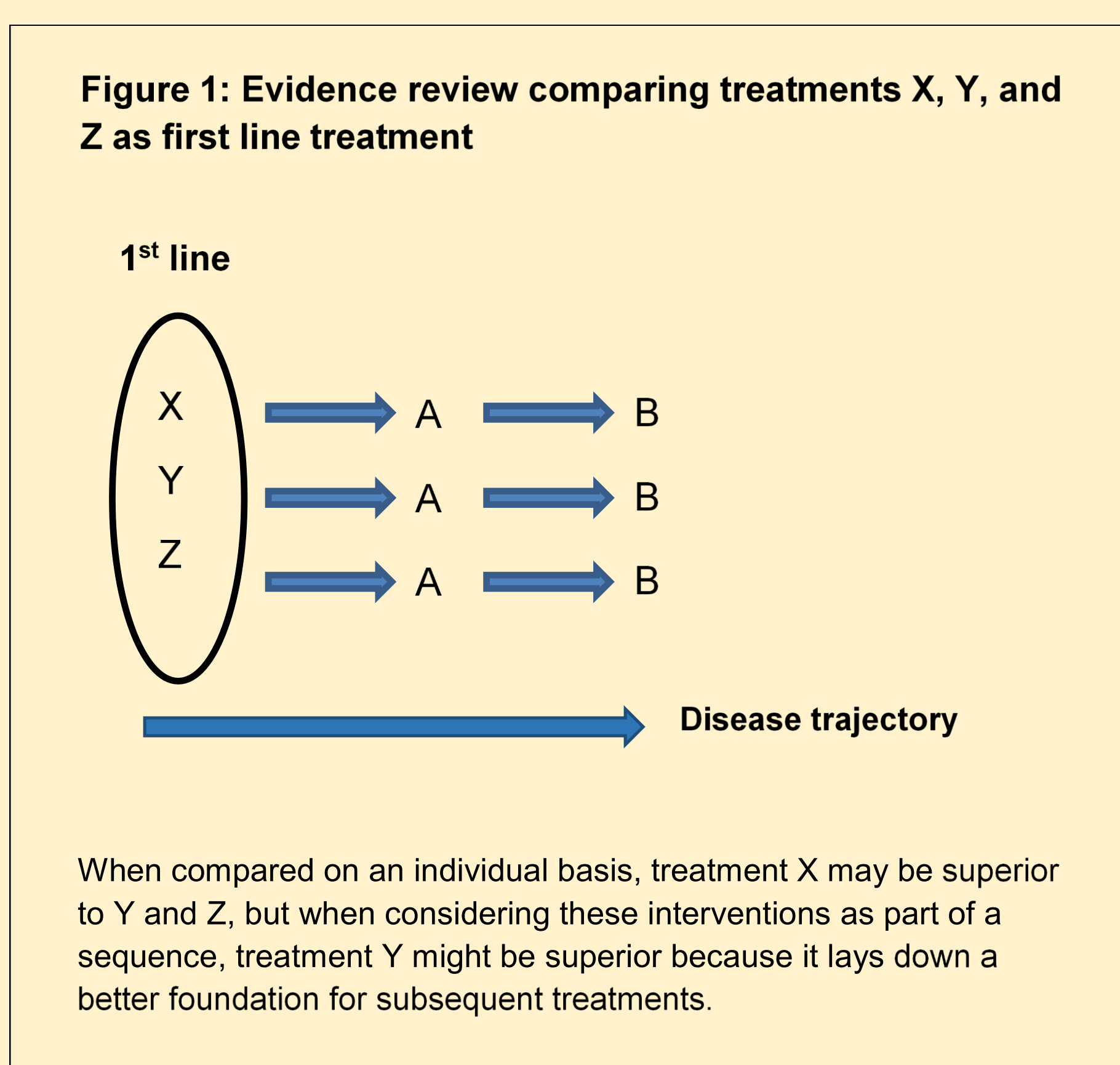# Methods for the assessment of the effectiveness of treatment sequences for clinical and economic decision making in the NHS

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BACKGROUND: Treatment sequencing is the order in which interventions are administered within a treatment pathway. The effectiveness of treatments may differ according to their pharmacology and positioning in the pathway. Policy and clinical decisions based on the optimum sequence rather than the effectiveness or cost-effectiveness of individual treatments are becoming increasingly important, but it is both impractical and prohibitively costly to evaluate all conceivable treatment sequences in randomised controlled trials (RCTs). RCTs of individual treatments used at single points in the treatment pathway provide poor evidence on sequencing effects (FIG 1-3), and generally fail to consider the long term impact of multiple treatments. Alternative data sources are longitudinal studies based on patient registries, but these are subject to selection bias and confounding. Sequencing questions are frequently addressed using decision analytic modelling, which makes full use of the best available data, supplemented by judgements and assumptions where the evidence is absent. These are tested in sensitivity analyses.

OBJECTIVES: To assess existing methods of modelling treatment sequences and identify assumptions made in relation to treatment sequencing effects.
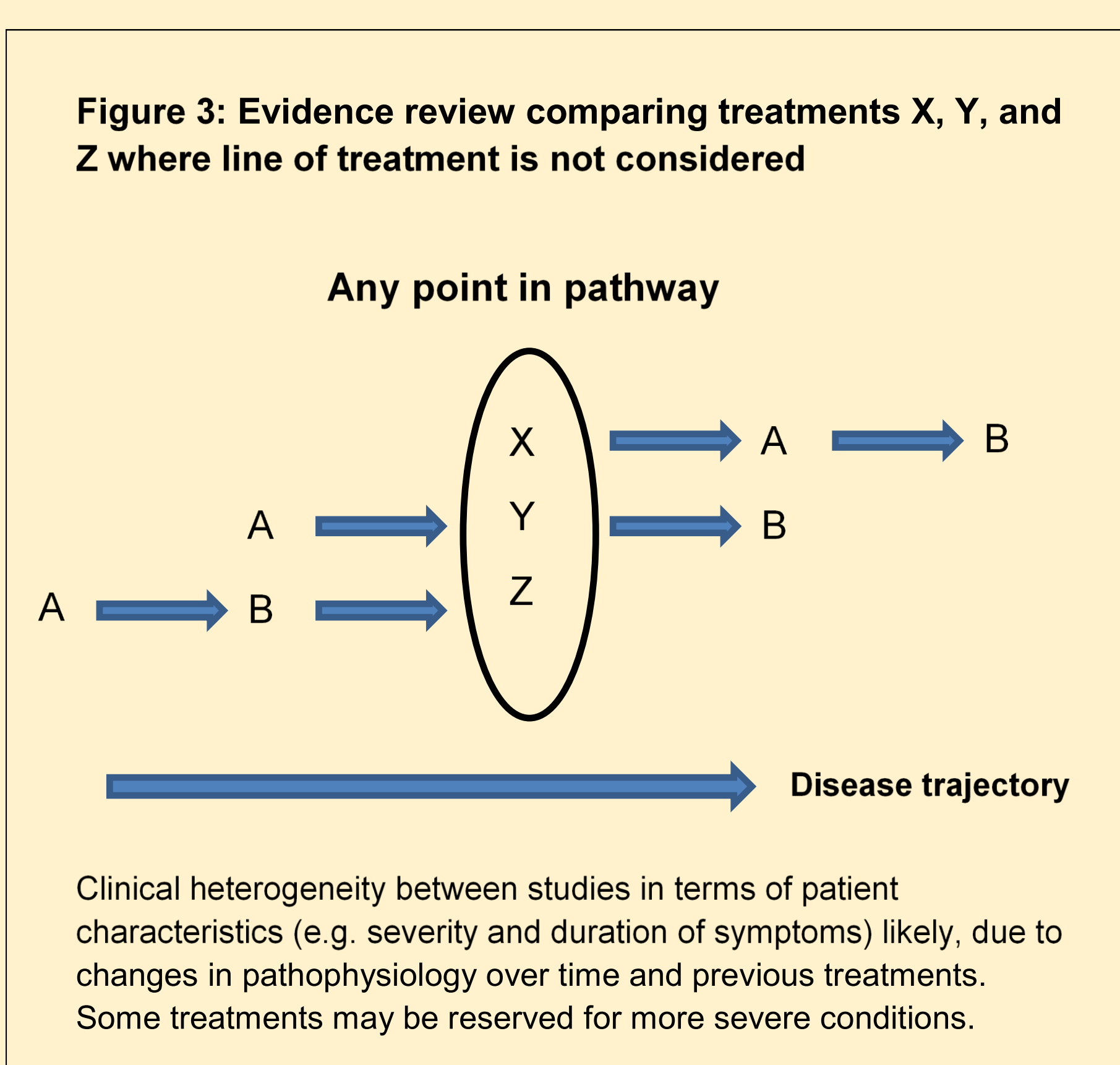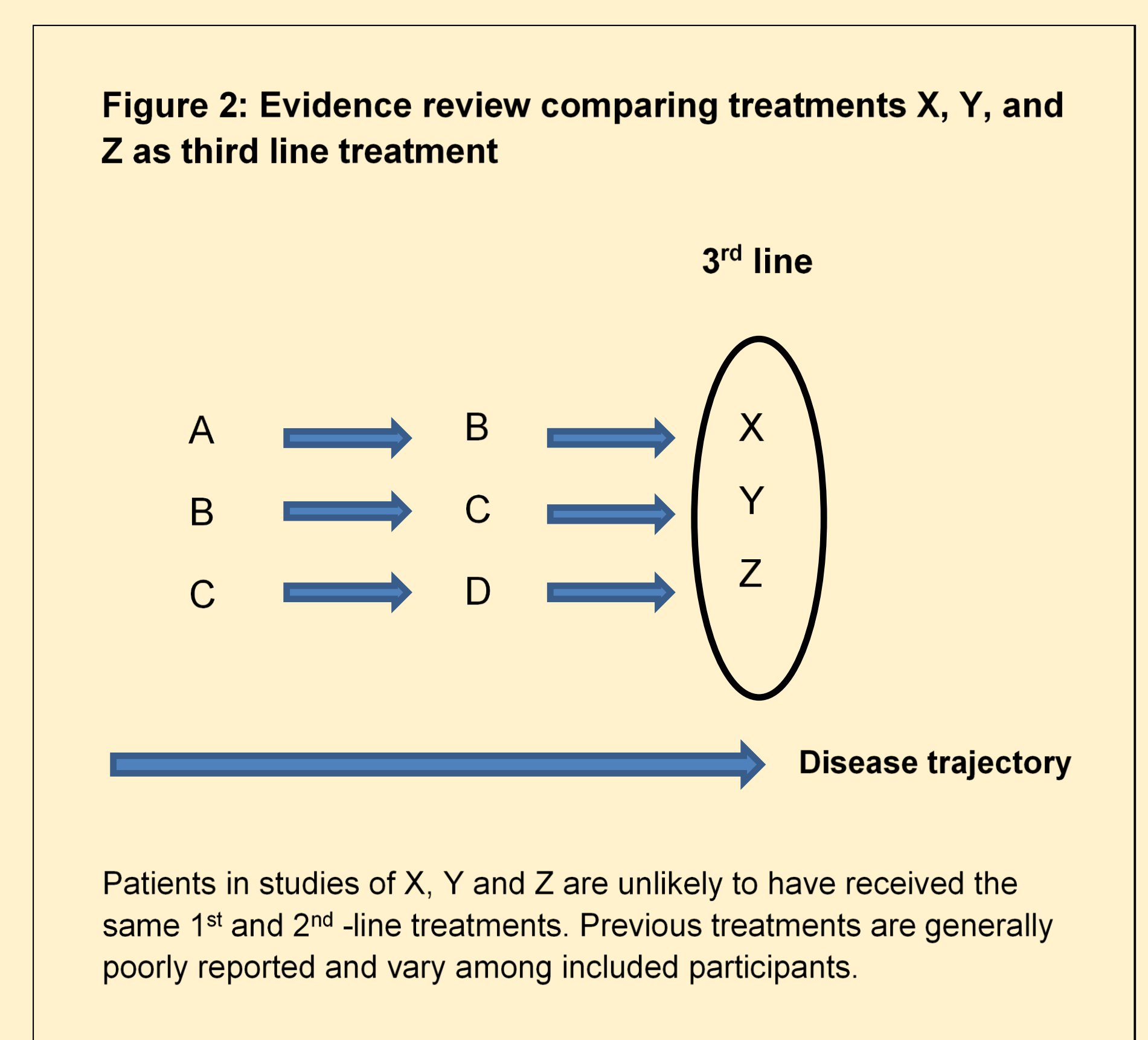
METHODS: A comprehensive literature review of MEDLINE, Embase and the Cochrane library, supplemented by Internet and hand searches. Due to scarce relevant indexing terms and no clear methodological taxonomies, a conventional systematic search was combined with a pragmatic and iterative process. Only studies that investigated the use of an active treatment after treatment failure were considered. Studies were categorised according to their overall modelling approach, decision problem, and assumptions used.

Figure 1: Evidence review comparing treatments X, Y, and Z as first line treatment

When compared on an individual basis, treatment X may be superior to Y and Z, but when considering these interventions as part of a sequence, treatment Y might be superior because it lays down a better foundation for subsequent treatments.

RESULTS: 86 relevant modelling studies were identified. Modelling approaches included decision trees, Markov cohort models, Individual-patient simulation (IPS) state transition models, and discrete event simulations (DES). Modelling approaches based on IPS, including DES, were used as they provide more flexibility than cohort based models, especially for handing patient histories, whilst cohort models were used as they benefit from being simpler and easier to implement. No study systematically tested different modelling approaches for sequences. Most studies applied simplifying assumptions to treatment effects obtained from RCTs of single treatments. These assumptions were generally not validated, or their impact assessed.

Simplifying assumptions used in modelling studies:
1. Treatment effect is independent of positioning in treatment sequence.
2. Treatment effect is dependent on the number of previous treatments used, but independent of the type of treatments used.
3. Treatment effect is the same as an alternative (substitute) treatment used at the same point in the sequence.
4. Treatment effect decreases by the same set amount at each point in the sequence (*representing diminishing effect*)
5. Treatment effect is reduced, in line with a reduction factor, when used at a later point in the sequence (*treatment effect adjusted using a reduction factor*).
6. Observational studies provide an un-biased estimate of treatment effect.

Figure 2: Evidence review comparing treatments X, Y, and Z as third line treatment

Patients in studies of X, Y and Z are unlikely to have received the same 1st and 2nd -line treatments. Previous treatments are generally poorly reported and vary among included participants.

Figure 3: Evidence review comparing treatments X, Y, and Z where line of treatment is not considered

Clinical heterogeneity between studies in terms of patient characteristics (e.g. severity and duration of symptoms) likely, due to changes in pathophysiology over time and previous treatments. Some treatments may be reserved for more severe conditions.

CONCLUSIONS: Considering the limited evidence base, it is unclear whether complex modelling is required or the more commonly used Markov cohort structure would suffice. The impact of using simplifying assumptions to represent sequencing effects is increased uncertainty around the effectiveness and cost-effectiveness of treatments, the extent of which is unknown. There needs to be greater recognition of this in decision making with further research needed to evaluate it.

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