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A structured methodology for essential medicines lists and health emergency stockpiles: Experience with the Emergency Medicines Buffer Stock in the United Kingdom

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ABSTRACT

Introduction: Formularies of essential medicines, such as Essential Medicines Lists (EMLs) and health emergency stockpiles, are intended to be always available, including in emergency situations, acting as important tools for access to medicines. The Emergency Medicines Buffer Stock (EMBS) in the United Kingdom (UK) was a stockpile of critical medicines managed by the UK Department of Health and Social Care (DHSC). We propose a new methodology for selecting and including medicines in EMLs and health emergency stockpiles and empirically apply it for selecting medicines in the case of the UK EMBS.

Methods: We used Multi-Attribute Value Theory and Portfolio Decision Analysis to develop a three-phase methodological framework for medicines selection, involving: (i) the decision context definition and selection of evaluation criteria, (ii) the therapeutic area prioritisation, and (iii) the medicines value-for-money evaluation and product selection. The EMBS application took place in 2018–2019 and focused on therapeutic area prioritisation, involving primary data collection through expert interviews (n = 4), a workshop with DHSC decision-makers (n = 13), and an online survey with National Clinical Directors and relevant experts (n = 24). A Monte Carlo simulation supported therapeutic area prioritisation using the British National Formulary (BNF) classification.

Findings: Two criteria sets were selected for i) therapeutic area prioritisation, reflecting the value concerns of population need and shortage severity, and ii) medicines evaluation, reflecting magnitude of clinical benefit and supply vulnerability, among others.

Primary evidence was collected for "national need" and "shortage severity", based on which a "population health loss" index was developed. A total of 51 therapeutic areas were ranked using their index value while assessing the robustness of the ranking. The top ranked therapeutic area was antisecretory drugs and mucosal protectants, closely followed by diabetes drugs.

Conclusions: The methodological application generated a ranking of therapeutic areas based on expected "population health loss" index, while addressing evidence uncertainty. The methodology can be adapted for other EMLs and emergency stockpile contexts to inform medicines selection.

1. Introduction

A common strategy for effective use of resources for access to medicines are drug formularies of essential medicines. An Essential Medicines List (EML) is a basket of pharmaceutical products aiming to "satisfy the priority health care needs of the population", selected based on the "public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness", intended to be available at all times and in sufficient quantities (WHO, 2023).

Besides such EMLs, supplementary arrangements for health emergency stockpiles might also exist, guaranteeing the supply of certain medicines in case of shortages or emergencies, acting as a special case of

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EMLs. Shortages of medicines are complex and can be caused by a number of reasons relating to supply or demand factors, with important clinical and economic consequences (Ferner et al., 2019). They often involve disruption in medicines' infrastructure or supply chains, ranging from the availability of raw ingredients and manufacturing problems, to distribution and logistical problems, or even an unexpected surge in demand (Ferner et al., 2019), for example, due to a change in clinical practice or the epidemiological landscape. Typically, they include medicines which, or whose active ingredients, are imported from other markets, with packaging taking place in the country of intended use.

In recent years, drug shortages resonated in the United Kingdom (UK), where supply chain problems emerged for a range of medicines across drug classes (Ferner et al., 2019; Wise, 2022), but also because few medicines are exported and a large majority are imported, an issue which was highlighted in the context of a possible no-deal Brexit after the 2016 referendum (Pisani, 2019; Rimmer et al., 2019; Willett and Geddes, 2019). Another timely example is how a combination of increased demand for penicillin due to a spike in streptococcal infections and a change in national clinical guidance, together with supply issues, led to an antibiotic shortage (Iacobucci, 2022). This seems to be a global concern, with the recent surge in bacterial infections leading to a shortage of antibiotics worldwide and 80% of 35 countries reported by WHO having some type of shortage for amoxicillin-related antibiotics (Mancini and Kuchle, 2023). As a result, the European Commission is planning to stockpile basic drugs and propose legislation obliging manufacturers to secure access to medicines for all patients in need (Bounds and Varvitsioti, 2023). Such global supply vulnerability issues, together with unforeseen surges in demand as witnessed in the COVID-19 pandemic, pushed the establishment of the European Union (EU) Health Emergency Preparedness and Response Authority (HERA), responsible for stockpiling essential medicines for rapid response in health emergencies (Anderson et al., 2021).

In the UK, the Essential Medicines Buffer Stock (EMBS) served to stockpile essential or critical medicines that can maintain population health care needs in case of supply chain disruption (NHSBSA. Support services for the, 2023). The EMBS was originally set up in 2010 as part of a £260 million deal (with further £80 million budget over 5 years for additional stock) (Moberly, 2010), stockpiling medicines that were prone to supply disruptions, or whose shortage might have devastating effects on public health resulting in loss of life or increased hospitalisations, including medicines for treating flu symptoms (NHSBSA. Support services for the, 2023; Emergency, 2017). The policy objectives for the EMBS were to sustain regular supply levels of essential medicines to meet national demand in specific emergency situations (such as, but not limited to, a pandemic), including protecting against supply disruptions of vulnerable products that are critical. The Department of Health and Social Care (DHSC) procures, manages and owns stockpiles of medicines to cope with a range of scenarios and as part of robust contingency planning; for EMBS, suppliers were required to store the medicines for at least one year and rotate the stock through their normal supply chain to prevent it from expiring (NHSBSA. Support services for the, 2023; Emergency, 2017). During the COVID-19 pandemic, the DHSC put together a new stockpile with critical supportive medicines as part of which relevant medicines in the EMBS were included (Hammond, 2019). The EMBS formally ended in 2019/2020, with a small number of products retained in stock until 2022, as part of the COVID-19 Supportive Medicines stockpile (Quince, 2022).

Although the EMBS listed around 500 medicines for stockpiling (either off-patent or on-patent products), in the most recent procurement exercise undertaken within the principles of the initial EMBS, the DHSC procured less than half of the medicines on the list (Office, 2018). According to the DHSC Annual Report and Accounts for the period 2019–2020, the value of stockpiled products was around £65 million, corresponding to strategic goods held for use in national emergencies, the majority of which related to pharmaceuticals and related consumables (DHSC, 2021).

Previous lists of medicines in the EMBS were based on the customisation of the WHO's Model List of Essential Drugs with the help of National Clinical Directors (NCDs) and other experts to reflect NHS usage and identify key medicines required to keep the population well and avoid hospitalisations or deaths during a (n influenza) pandemic. Originally developed in 1977 (WHO Expert Committee on the Selection of Essential Drugs & World Health Organization, 1977), the WHO Model List of Essential Drugs is being updated periodically in light of new scientific evidence by the WHO Expert Committee, having become a global standard for national and institutional medicine lists. Following an update of the procedure for the WHO's Model List of Essential Drugs in 2001, essential medicines were: i) defined as those satisfying the priority needs of the population, ii) selected based on criteria relating to disease burden, efficacy, safety and cost-effectiveness, and iii) specified a purpose, e.g. intended to be available at all times in adequate quantities, therefore at a price the community can afford (Marks et al., 2017; WHO, 2001). The WHO EML has also been adapted for other contexts, including the design of an EML for emergency care in Africa (Broccoli et al., 2018).

Therefore, the EMBS and WHO lists had similar but not identical objectives; the former aimed to serve as a stockpile of critical medicines that are prone to supply disruptions or whose shortage might have devastating effects for public health, to avoid hospitalisations and treat people in the community, while the latter acts as a global standard for national and institutional medicine lists. As a result, about 530 products were on the EMBS list, the majority of which corresponded to older, off-patent medicines, whereas the latest WHO Model List has 479 medicines, including, more recently, a number of patented medicines (WHO, 2021).

The EMBS list needed to be updated using a more systematic and transparent methodology, to inform an evidence-based prioritisation for medicines procurement. The goal was to spend the budget on a medicines portfolio delivering the best value-for-money, while considering a number of value concerns and objectives (including national need, shortage severity, medicines' health benefits and their supply vulnerability). To our knowledge, no such prioritisation and resource allocation attempts have been documented in the literature in the context of the EMBS specifically and, more broadly, for EMLs and health emergency stockpiles. There is a lack of decision support tools with sound axiomatic basis that could help policy makers to identify therapeutic areas with the highest needs and medicines with the highest value-for-money. This forms the basis of the intended research objective. The paper proposes a new methodology for EMLs and health emergency stockpiles, being especially relevant in light of the recent global supply chain vulnerabilities.

First, the methods section outlines the conceptual framework of the methodology, which is composed by a three-phase process involving the definition of the decision context (Phase 0), the prioritisation of therapeutic areas based on specific evaluation criteria (Phase 1), and the selection of medicines for each therapeutic area (Phase 2). The section then describes an empirical application of the methodology for the EMBS, capturing the decision context definition (Phase 0) and the prioritisation of therapeutic areas (Phase 1). Subsequently, the main findings of the application are presented, followed by a discussion on the potential usefulness of the methodology to guide policy makers involved in the design of EMLs and health emergency stockpiles, and conclusions indicating future research.

2. Methods

2.1. Conceptual framework

A health decision analysis (Long et al., 2022) approach is adopted based on Multi-Attribute Value Theory (Keeney and Raiffa, 1993) and Portfolio Decision Analysis (Salo et al., 2011), involving (i) primary research through expert consultation via interviews, (ii) qualitative

preference elicitation via a decision conference (Phillips et al., 2007), and (iii) quantitative preference elicitation via an online survey. The overall methodological process consists of three main components outlined below and shown in Fig. 1.

2.1.1. Decision context definition and evaluation criteria selection (Phase 0)

In the first step of the methodology, the decision context is defined, involving a preliminary scoping of the decision problem and objectives of the essential medicines under consideration, followed by the selection of evaluation criteria reflecting the value concerns of decision makers (Fig. 1, Phase 0). Such tasks can be informed by expert consultation and facilitated meetings, for example via decision conferencing corresponding to facilitated workshops engaging relevant stakeholders and key experts (Phillips et al., 2007). This is defined as a "gathering of key players who wish to resolve important issues facing their organisation, assisted by an impartial facilitator who is expert in decision analysis, using a model of relevant data and judgements created on-the-spot to assist the group in thinking" (Phillips and Bana e Costa, 2007) (p.54). Following the identification of objectives, which are operationalised as evaluation criteria, the evaluation is structured into different components, focused on the prioritisation of therapeutic areas ("Phase 1"), followed by the evaluation of individual medicines within each therapeutic area and final product selection ("Phase 2"), which are described next in this order.

2.1.2. Therapeutic area prioritisation (Phase 1)

In this phase of the methodology, therapeutic areas are ranked and prioritised. Research tasks involve evidence collection, evidence synthesis and evidence analysis (Fig. 1, Phase 1), using a combination of primary and secondary evidence sources.

One type of evidence collection required is the national utilisation of medicines at therapeutic area level (i.e., drug classes), representing the national population need; for example, this could take the form of total volume dispensed, using historical prescribing data. For this purpose, a classification system for therapeutic areas or drug classes is needed, together with a metric for medicines' utilisation, which could be informed based on drug prescribing database(s) and resources available in the setting of interest.

Another relevant type of evidence required relates to the health loss impact resulting from medicines' lack of access, representing the value concern of drug shortage severity; for example, this could take the form of expected Quality Adjusted Life Years (QALYs) lost due to the treatment not being available, using input from patient or clinical expert surveys.

The collection of evidence is then followed by its synthesis, combining the respective medicines utilisation data and health loss impact data to generate an aggregate index that reflects both concerns; for example, this could take the aggregated form of an index representing "population health loss" for each therapeutic area or drug class, in essence combining the two variables together.

Finally, the index is analysed, involving at least a simple deterministic ranking of the therapeutic areas considering the most likely estimates of inputs employed in the index (e.g., for medicine utilisation and health loss from the lack of access to the medicine), possibly followed by a more advanced probabilistic ranking that incorporates parameter uncertainty for the index inputs considering a particular distribution, for example via a Monte Carlo simulation (Briggs, 2006; Montibeller, 2022). Subsequently, the ranking of medicines should undergo a sensitivity analysis, ideally a probabilistic sensitivity analysis that can identify the probability of each therapeutic area being placed in their respective ranked position.

2.1.3. Medicines value-for-money evaluation and product selection (Phase 2)

A similar evidence collection and synthesis process is then followed, relating to the evaluation and selection of individual medicines in the next phase of the methodology (Fig. 1, Phase 2). These steps are required to generate a product performance matrix detailing the performance of each medicine across the respective evaluation criteria of interest, which, in turn, is needed for the elicitation of preferences at product level. The evidence collection can be on medicines' expected degree of health gain, reflecting a value concern of magnitude of clinical benefit (e.g., in terms of number of QALYs gained), which could be informed via surveys with clinical experts.

Other relevant evidence can relate to the number of manufacturers supplying each medicine, therefore reflecting a value concern of supply vulnerability, which could be informed using existing databases. Further evidence collection can relate to other medicines' aspects judged to be relevant for each decision context, such as, for example, the knock-on consequences on the health care system resulting from the provision of an alternative treatment and ease of switching. Ultimately, following the incorporation and synthesis of any additional evidence needed (e.g., the unit costs/prices of medicines), the synthesised evidence is used to elicit the value preferences of decision-makers, including trade-offs between the various medicines' aspects, and analyse the results to support the final product selection.

A second facilitated meeting can engage again the relevant decision-makers, having a three-fold aim: first, to construct their value preferences in relation to the performance of the products across the criteria of interest, possibly through the elicitation of value functions for each criterion (e.g., normalising and valuing product performance to a value scale); second, to elicit their value trade-offs, which are represented as criteria weights (e.g., reflecting the relative importance of these criteria in the overall value of the medicine), and enable the construction of multi-dimensional benefit metrics for assessing the overall value of individual products; and, third, to explore the solution space in which the products are ranked based on their overall value against their

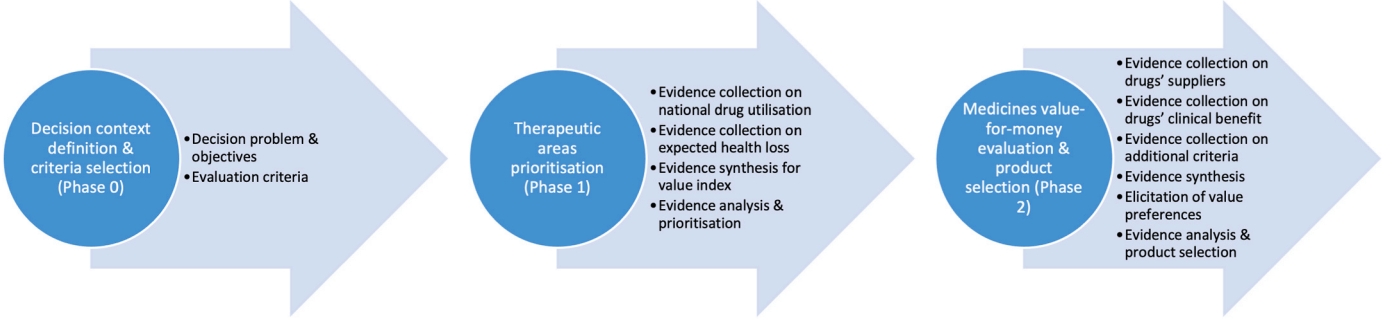

Fig. 1. Conceptual framework of the methodological process for the design of Essential Medicines Lists
Caption: A three-phase process involving the definition of the decision context, the prioritisation of therapeutic areas based on specific evaluation criteria, and the selection of medicines for each therapeutic area.

purchasing costs, as part of a portfolio decision analysis (e.g., prioritising the medicines based on their value-for-money).

An empirical application for Phases 0 and 1 of the methodology is described next, providing an illustration for prioritising therapeutic areas in the context of UK EMBS.

2.2. The EMBS application

The empirical application of the methodological process described above is illustrated in Fig. 2 for supporting the design of the EMBS, including its various stages, data sources and outcomes. Secondary data collection took place using proprietary national medicines utilisation databases (Epact2, Rx-Info Define).

2.2.1. Decision context definition and evaluation criteria selection (Phase 0)

2.2.1.1. Scoping of EMBS context. A consultation with relevant experts guided the design of the methodological application, providing expert judgement on the requirements for the EMBS, including the basis for medicines selection and the associated challenges intiated the application. Four clinical experts were consulted having a current or past affiliation with NHS England; two public health experts with an NHS advisory capacity focusing on medicines safety and infectious diseases and specialised health services and two clinical pharmacists with expertise in hospital pharmacy and procurement specialist pharmacy respectively. Experts' insights were received following a series of semi-structured interviews and were used for the preparation of a decision conference, targeting the preliminary selection of potential evaluation criteria.

2.2.1.2. The decision conference. The aim of the decision conference was to understand the concerns of a panel of clinical experts and decision-makers, relating to the objectives and use of the EMBS. A facilitated decision analysis modelling approach for expert panels was adopted (Franco and Montibeller, 2010; Montibeller, 2022). Participants were affiliated with the DHSC and other public health institutions and included 13 experts with knowledge of, and past experience with, the national UK procurement process of EMBS or other medicines stockpiles held by the DHSC, but also the epidemiological needs of the UK population. The outcome of the decision conference was a set of evaluation criteria to inform the prioritisation of products for the EMBS, and also the agreement on a number of other features in the methodological process. The evidence collection and evidence synthesis tasks for the selected evaluation aspects were divided between "across diseases" (i.e. therapeutic areas) and "within disease" (i.e. medicines) related value concerns as shown in Table 1 and illustrated in Fig. 3, described below.

2.2.2. Therapeutic areas prioritisation (Phase 1)

2.2.2.1. Evidence collection on national utilisation from prescribing databases. The ePACT2 is the most comprehensive primary care prescribing database at general practitioner (GP) level in the UK (NHS Business Services Authority), whereas the Rx-Info Define database covers secondary care prescribing data at hospital level whose data is sourced from the National Trusts in England (Rx-Info). These two databases were used to provide evidence on the national utilisation of medicines at therapeutic area level (i.e., drug classes).

In terms of the therapeutic areas/drug classes classification system, the British National Formulary (BNF) was used because ePACT2 data are analysed using the BNF. This was also the reason why other systems, such as the Anatomical Therapeutic Chemical (ATC) classification, adopted at international level by the WHO, were not used. Specifically, the BNF was used at the second BNF Section level (e.g., Section 3.1. Bronchodilators); although the third BNF Subsection level would more precisely reflect different drug classes in more detail (e.g., Subsection 3.1.1. Adrenoreceptor Agonists), this was not chosen due to the impracticalities arising from the large number of Subsections that would

Application component	**Decision context definition & criteria selection (Phase 0)**		**Therapeutic area prioritisation (Phase 1)**			
EMBS stage	Scoping of study's context	Decision conference	Evidence collection		Evidence synthesis and analysis	
Source/ model	*Clinical experts*	*DHSC decision makers*	*Prescription databases*	*Survey with clinical experts*	*Evidence synthesis on national utilisation and health loss*	*Aggregation models for deterministic and probabilistic ranking*
Outcomes	Decision context and objectives specification	EMBS value concerns and criteria selection	National utilisation estimation	Expected health loss estimation	Population Health Loss Index estimation	Therapeutic areas ranking

Fig. 2. The empirical application of the methodological process for the prioritisation of therapeutic areas in the EMBS
Caption: The various stages, data sources and outcomes in the empirical application of the methodological process for the design of the EMBS, spanning Phase 0 stages (scoping of the study's context, decision conference) and Phase 1 stages (evidence collection, evidence synthesis and analysis).

Table 1
Evaluation aspects and their performance measures for the EMBS application, divided into value concerns across-diseases and within-disease.

Across-Diseases Value Concerns (therapeutic areas' level)		Within-Disease Value Concerns (medicines' level)	
Evaluation aspect	*Performance measure*	*Evaluation aspect*	*Performance measure*
National Population Need*	Medicines' utilisation at national level by using ePACT2 "items" (primary care) and Rx-Info Define "transactions" (secondary care) as measuring units	Magnitude of Clinical Benefit	Expected degree of health gain from the medicine, which could be measured using the number of QALYs gained
Severity of Shortage*	Expected health loss following medicines' hypothetical shortage by using the number of "QALYs lost" as a measuring unit	Maximum Proportion of Relevant Patient Population Treated	Size of patient population that can use the medicine for the relevant indication, which could be measured using a constructed value scale for the proportion of patients covered by the medicine e.g., high >95%, 95% ≤ moderate >50%, 50% ≤ low
Population Health Loss Index	Combination of medicines' utilisation at national level and expected health loss following shortage, using 3 different aggregation models	Maximum Interchangeability	Number of additional indications for which the medicine can be used, which could be measured using a constructed value scale for the number of indications covered e.g. high >5, 5 ≤ moderate >2, 2 ≤ low
		Minimum Supply Vulnerability	Number of manufacturers supplying the medicine in combination with its patent status, which could be measured using a constructed value scale for the number of manufacturers in combination with the patent status, for example (in decreasing order of preference): on-patent medicine with single manufacturer, off-patent medicine with multiple manufacturers, off-patent medicine with single manufacturer

Caption: * The two evaluation aspects of National Population Need and Severity of Shortage were combined and evaluated together as part of the Population Health Loss Index.
QALY: Quality Adjusted Life Year.

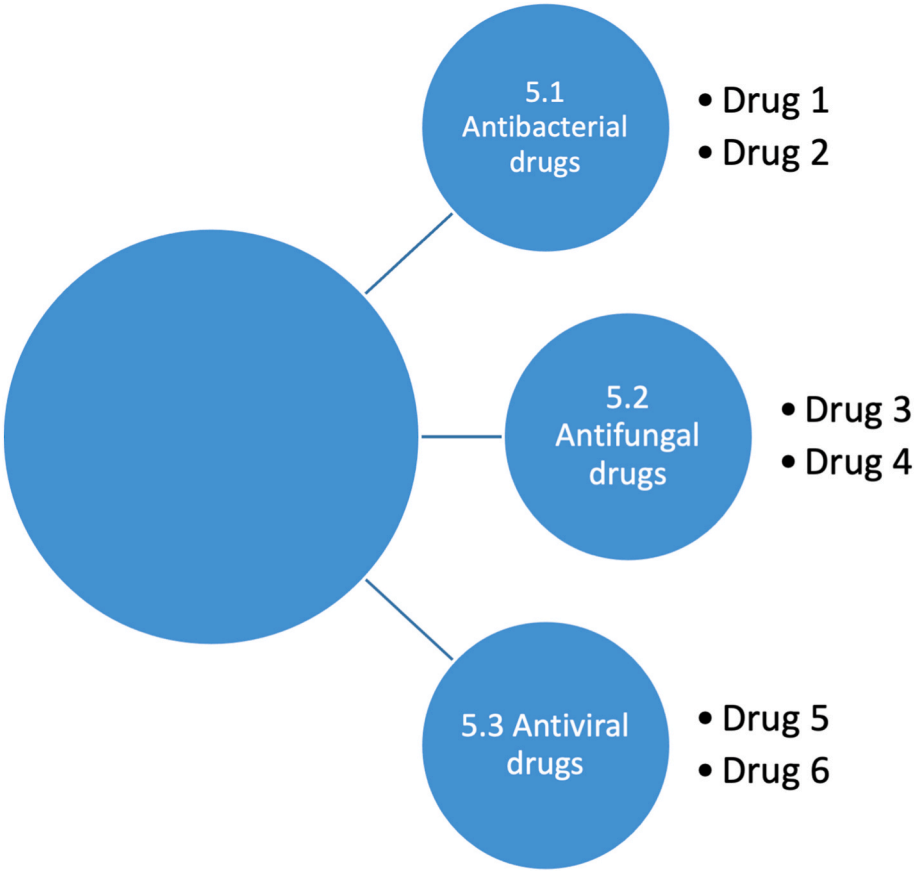

Fig. 3. Illustration of "across diseases" vs "within disease" phases in the methodological process Caption: Phase 1 corresponds to the prioritisation of therapeutic areas, i.e., "across diseases" (e.g., Antivirals vs Antifungals); Phase 2 corresponds to the evaluation and selection of drugs, i.e., "within disease" (e.g., Antibacterial drug 1 vs drug 2).

have to be considered as separate online questionnaires during evidence collection (see next section). The different BNF Sections are listed in the Appendix (Table A1).

In terms of the medicines' utilisation metric, at primary care level the "items" variable from ePACT2 was used, defined as the "number of times a product appears on a prescription form" (both in terms of paper prescriptions and electronic messages). At secondary care level, the "transaction" variable from Rx-Info Define was used, defined as an "issue of drug from one location of a hospital, normally pharmacy, to a consumer site" (e.g., ward, patient or sale). Although these two are not

identical definitions, both variables represent a comparable utilisation measure, in combination accounting for both primary and secondary care while capturing utilisation differences between BNF Sections. Data for two years (2016 and 2017) were analysed.

For more information on the medicines' utilisation metric used, including the alternative options that were considered, see the Appendix.

2.2.2.2. Evidence collection on expected health loss from online survey. The QALY is known to be one of the most comprehensive health outcome metrics used in economic evaluation, capturing the dimensions of mortality and morbidity (Loomes and McKenzie, 1989). The EQ-5D is a non-disease specific instrument, widely used as a preference-based measure for HRQoL needed for QALYs estimation (Devlin and Brooks, 2017), spanning the domains of Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression (EuroQol. EQ-5D-5L About). We used an amended version of the EQ-5D-5L as a measure of health loss impact. More precisely, each BNF Section formed the topic of different web-surveys adopting the amended EQ-5D-5L instrument for collecting primary data looking at the "expected health loss" for a "typical serious patient" resulting from a hypothetical scenario of "3 months lack of treatment". In collaboration with the DHSC, from the total list of BNF Sections for which utilisation data was collected, about half were excluded because they were irrelevant for the EMBS objectives. For each of the remaining BNF Sections a survey was sent to a pool of 24 national clinical experts affiliated with the NHS, including National Clinical Directors, aiming to collect responses from at least 2 relevant experts per (BNF Section) survey. Each survey asked the EQ-5D-5L questionnaire for different points in time, from baseline (while a patient is assumed to be still on treatment), up to 12 months, assuming a 3-month treatment interruption between months 1–3. Where treatment interruption could cause long-term effects, an additional EQ-5D-5L response could be given which was capped to 24 months. Additionally, a question about the "probability of dying" due to treatment interruption was also included. More information about the structure of the survey is provided in the Appendix.

The EQ-5D-5L scores obtained from the surveys were converted into utilities ranging from 0 to 1 using the crosswalk index value calculator, essentially by mapping the EQ-5D-3L value sets into the EQ-5D-5L index (EuroQol, 2021). The amount of "lost QALYs over 2 years" was then calculated by first measuring the area under the curve (AUC) on the utility scale over time for the baseline scenario of no treatment interruption, and then estimating the difference with the AUC emerging from the treatment interruption scenario. Using the "probability of dying" information input, "mortality adjusted lost QALYs in 2 years" was calculated. An example of such a calculation from a hypothetical participant's EQ-5D-5L score response is shown in Table 2. In some instances where "illogical responses" were discovered in which the experts' responses seemed to contradict a deterioration in patients' health states following the lack of medications, individual follow-up calls with the respective responders acted as a quality assurance step to validate their answers and clarify any possible misinterpretations.

2.2.2.3. Evidence synthesis and analysis for deterministic ranking of therapeutic areas. Following the collection of evidence on medicines' national utilisation and expected health loss as described above, a "population health loss" index was synthesised for each BNF Section by multiplying the average values of the two components together and deriving weighted averages which were then ranked (a deterministic ranking). Given that utilisation data came from two years and that health loss data typically came from two or more participants, minimum, average and maximum figures were also calculated using the lowest, mean and highest numbers of the two variables respectively. An example of such a calculation for one BNF Section is shown in the Appendix (Table A2).

Table 2
Calculation example of "mortality adjusted lost QALYs in 2 years" from a set of EQ-5D-5L scores (4 time points).

Time points	Survey participant EQ-5D-5L scores	Calculated utilities (crosswalk index)	Calculated QALYs
Baseline	1, 1, 1, 2, 2	0.768	N/A
At 3 months	1, 1, 2, 3, 3	0.696	0.183
At 6 months	1, 1, 1, 2, 2	0.768	0.183
At 12 months	1, 1, 1, 2, 2	0.768	0.384
At 24 months			0.768
Over 2 years baseline scenario			1.536
Over 2 years shortage scenario			1.518
Lost QALYs in 2 years			0.018 (1.536 - 1.518)
Mortality adjusted (0.1 death probability) 2 years shortage scenario			1.3662 (1.518 *(1–0.1))
Mortality adjusted lost QALYs in 2 years			0.1698 (1.536 - 1.3662)

Caption: An example of the calculation of "mortality adjusted lost QALYs in 2 years" by using a hypothetical participant's EQ-5D-5L scores from the survey, converting them into utilities using the crosswalk index, calculating the QALYs for the baseline scenario vs treatment interruption scenario to estimate the difference of "lost QALYs over 2 years", and, finally, using the "probability of dying" to derive "mortality adjusted lost QALYs in 2 years".
QALY: Quality Adjusted Life Year; EQ-5D-5L: EuroQoL 5-dimensions, 5-levels.

2.2.2.4. Evidence synthesis and analysis for probabilistic ranking of therapeutic areas. Following the evidence synthesis of the "population health loss" index and the deterministic ranking described above, a Monte Carlo simulation with a 1000 iterations triangular distribution was constructed in order to incorporate uncertainty of the two variables making up the index (Montibeller, 2022), i.e. national utilisation data and health loss data. These Monte-Carlo simulated values corresponded to expected values that could be viewed as more reliable estimators than the deterministic mean values, as they incorporate the uncertainties in the two variables that were collected for two years or elicited from expert judgements.

3. Findings

Following the application of the methodology in practice with DHSC decision-makers and UK clinical experts, in this section we describe preliminary empirical findings relating to the selection of evaluation criteria for EMBS (Phase 0 of the methodology) and the respective prioritisation of therapeutic areas (Phase 1 of the methodology).

3.1. Decision context definition and evaluation criteria selection (Phase 0)

In terms of the EMBS policy objectives and the decision context definition, following the decision conference with the DHSC decision-makers it became clear that its primary objective was to "maximise the amount of benefit per total population given a budget constraint", without aiming to explicitly address and resolve any equity issues. Additional objectives included to "sustain normal UK population needs" (e.g., without aiming to protect against exceptional events such as a bioterrorism attack), "treat flu and secondary complications of flu" (i.e., conditions exacerbated by flu), "protect against supply disruptions of vulnerable products that are critical", and "aim to cover national needs for essential medicines over a minimum period of 3 months".

In terms of the evaluation criteria for the EMBS, two sets of criteria were agreed, one corresponding to "across-diseases concerns" at therapeutic area level and one to "within-disease concerns" at medicines

level. The former concerned the original prioritisation of different disease/therapeutic areas reflecting the value concerns of population need and shortage severity; the latter concerned the prioritisation of different medicines within particular disease/therapeutic areas reflecting value concerns relating to magnitude of clinical benefit and supply vulnerability, among others, to decide on the final selection of EMBS products. Fig. 3 shows a simple example illustrating the level of "across-disease concerns" taking place between three different BNF sections at therapeutic area/drug class level (antibacterial drugs vs antifungal drugs vs antiviral drugs), and the level of "within-disease concerns" taking place within a specific BNF section at product level (e.g., antibacterial drug 1 vs drug 2, antifungal drug 3 vs drug 4, antiviral drug 5 vs drug 6).

In terms of "across-diseases concerns", two main evaluation aspects were selected to prioritise different disease/therapeutic areas relating to: i) "national population need" operationalised through evidence of medicines utilisation at national level, by collecting prescribing data on the medicines' numbers of "items" and "transactions" in primary care and secondary care, respectively; and, ii) "severity of shortage" operationalised through evidence of expected health loss following a medicine's hypothetical shortage, by measuring the number of QALYs lost, obtained via an online survey with clinical experts. The two evaluation aspects were then combined into a common evaluation criterion to produce a composite index of expected "population health loss" at national level, which was used for the prioritisation of the therapeutic areas.

In terms of the "within-disease concerns", four evaluation aspects were identified to prioritise different medicines relating to i) "magnitude of clinical benefit", ii) "maximum proportion of relevant patient population treated", iii) "maximum interchangeability" and iv) "minimum supply vulnerability". We discuss next how each aspect could be operationalised in this evaluation.

The concern about "magnitude of clinical benefit" corresponded to the expected degree of health gain from the medicine, i.e., size of treatment effect. This aspect could be measured using the number of QALYs gained.

The concern "maximum proportion of relevant patient population treated" corresponded to the size of relevant patient population that can use the medicine for the relevant indication; the rationale was that potential exclusions of specific patient sub-populations due to contraindications of use could affect population size treated. Therefore, this value aspect could be measured using a constructed value scale for the proportion of patients covered by the medicine (e.g., ranging from a high level at 95% to a low level at below 50%).

The concern "maximum interchangeability" corresponded to the number of additional indications for which the medicine can be used; the rationale was that in times of supply shortage a medicine might be used for other non-typical or off-label indications. Therefore, this value aspect could be measured using a constructed value scale for the number of indications covered (e.g., ranging from a high number of indications at 5 to a low number at 2).

Finally, the concern "minimum supply vulnerability" corresponded to the number of manufacturers supplying the medicine in England (i.e., the marketing authorisation holder who holds product licence) in combination with the patent status of the medicine and the relevance to a pandemic situation. The rationale was that the lower the number of generic suppliers, the more challenging it would become to find adequate volumes (of off-patent medications), an effect which would become amplified in the context of a pandemic. However, the existence of a single branded manufacturer supplying an on-patent medication was eventually perceived as less risky because of the strong selling incentives in place due to the expected higher profit margins. Therefore, this value aspect could be measured using a constructed value scale for the number of manufacturers in combination with the patent status (e.g., in decreasing order of preference: on-patent medicine with single manufacturer, off-patent medicine with multiple manufacturers, off-patent medicine with single manufacturer).

All evaluation aspects and their respective performance measures, including their distinction between "across diseases" and "within disease", are listed in Table 1.

3.2. Therapeutic areas prioritisation (phase 1)

In collaboration with the DHSC, out of nearly 150 BNF Sections for which utilisation data were collected, about half were excluded because they deemed to be irrelevant for EMBS leaving a total of 81 BNF Sections, forming the topic of the therapeutic area ranking.

The rankings of the BNF Sections based on the expected simulated values from the Monte-Carlo simulation, proved to be virtually identical to the BNF deterministic rankings based on the average figures of each variable (with the exception of the 56th and 57th ranked BNF Sections which exchanged positions), shown in the Appendix (Table A3); more information about how this type of simulation can be employed in health decision analysis problems can be found elsewhere (Montibeller, 2022; Montibeller et al., 2019). A robustness analysis was also conducted as part of the Monte Carlo simulation, outlining the probability for each BNF Section to be placed in each position of the ranking, from 1st to 81st. This sensitivity analysis could then be used to inform the definition of boundaries for different tiers of rankings, to describe an n-level classification of varying importance for the prioritisation of the respective BNF Sections as proposed in the next section.

3.3. Transition to medicines value-for-money evaluation and product selection

A possible way forward to select the number of molecules for the next stage of the methodology (Phase 2) could be to define different BNF tiers according to their importance. A relatively simple classification could involve three tiers: BNF Sections in the top-tier would have a higher number of molecules compared to sections in the middle-tier, which, in turn, would have a higher number of molecules compared to the bottom-tier, reflecting a decreasing importance for each tier. As an illustration, 3 molecules could be selected for top-tier BNF Sections (with >10 million index value), 2 molecules could be selected for middle-tier BNF Sections (with 1–10 million index value), and 1 molecule could be selected for bottom-tier BNF Sections (with <1 million index value). The definition of the suggested different BNF tiers, their respective numbers of molecules per BNF Section and their actual figures for this example are summarised in Table 3 (with the different tiers represented by the different colours in Table A2).

Table 3
Example of a 3-level BNF tiers classification based on the Population Health Loss Value Index for selecting the number of molecules in the "within-disease value concerns" methodology stage.

	Population Health Loss Index value	Molecules per BNF Section	BNF Sections per tier	Molecules per tier
Top-tier	>10,000,000	3	19	57
Middle-tier	1,000,000–10,000,000	2	38	76
Bottom-tier	<1,000,000	1	24	24

Caption: Illustrative definition of different BNF tiers based on the values of their Population Health Loss Index, their respective numbers of molecules per BNF Section, their BNF Sections per tier and total number of molecules per tier, as a way forward to select the number of molecules in the next stage of the methodology. The different tiers are also represented by the different colours in Table A2.
BNF: British National Formulary.

4. Discussion

In this study we proposed a methodology leveraging a health decision analysis approach, grounded on Multi-Attribute Value Theory and Portfolio Decision Analysis for the design of EMLs and health emergency stockpiles and described its empirical application for the case of UK EMBS. The methodology consists of three phases, involving the definition of decision context and evaluation criteria (Phase 0), the prioritisation of therapeutic areas (Phase 1), and the evaluation of medicines value-for-money and product selection (Phase 2).

We described the application of the methodology in the context of EMBS spanning Phases 0 and 1, leading to the prioritisation of 51 therapeutic areas based on a value index reflecting the relevant value aspects of interest (National Population Need and Severity of Shortage). Although the framework can be used to inform the design of medicines portfolios in the context of EMLs and health emergencies, for which the EMBS acted as an empirical application, it can also be applied to any procurement decision problem concerning the selection of a list of medicines, including medicines selection in light of supply chain vulnerabilities.

To our knowledge, this is the first study attempting to develop a decision theoretical-based, axiomatic methodology to inform an evidence-based procurement process for medicines in the context of EMLs and health emergency stockpiles. Importantly, given the ongoing policy need for EMLs across the globe, especially in low- and middle-income countries with more restricted budgets, the proposed methodology could be used more broadly as a decision support tool to aid pharmaceutical product selection in a structured, systematic, and transparent way to facilitate access to affordable medicines.

Our key contribution of the study is towards the structured process of emergency medicines evaluation and prioritisation, which provides several benefits to these challenging decision processes. First, a systematic evaluation, starting with the prioritisation of treatment areas followed by the prioritisation of medicines within each area. Second, the ability to assess multiple evaluation criteria for each medicine. Third, the consideration of the decision problem as a portfolio evaluation under constrained budgets. Fourth, the ability to assess the impact of parameter uncertainty on the prioritisation of therapeutic areas. Fifth, the support for the selection of a medicines product portfolio that can maximise value-for-money.

Ultimately, the framework can be adapted for any medicines procurement context to accommodate resource allocation requirements and decision-maker needs. Specifically, the framekow can support the assessment of medicines towards the prioritisation of therapeutic areas based on the medical need of the required populations, followed by the selection of products that can address the value concerns of interest.

Among the limitations of the methodology are the suggested evidence collection requirements. As part of therapeutic area prioritisation (Phase 1), suggested evidence collection relates to medicines' national utilisation at therapeutic area level (i.e., drug classes) reflecting the value concern of "population need", and expected health loss impact resulting from medicines' lack of access reflecting the value concern of "shortage severity". As part of medicines value-for-money evaluation and product selection (Phase 2), suggested evidence collection relates to expected degree of health gain from the medicine reflecting the value concern of "magnitude of clinical benefit", and number of manufacturing suppliers reflecting the value concern of "supply vulnerability", among others. Ideally, these parameters should be estimated using a combination of national drug prescribing and utilisation data (which would require the respective data collection and IT infrastructure in place), primary data collected from relevant experts and stakeholders, and relevant company registration data supplying the products of interest. It could be argued that such data requirements might be more easily satisfied in high-income countries. In practice however, many of the required evaluation aspects could still be estimated based on a combination of secondary data available and expert judgements, the latter leveraging a number of qualitative preference exploration methods, either at individual-level (e.g., interviews), or group-level (e.g., Delphi methods, focus groups, nominal group technique, among others) (Soekhai et al., 2019).

Following the application of the methodology in the context of EMBS, for the purpose of evidence collection on expected health loss impact resulting from lack of access to specific drug classes (reflecting shortage severity), it became evident that a trade-off might have to be made between study comprehensiveness in analysing the impact of all possible drug classes, and the practicality of collecting this data as they might need to form the topics of different surveys. As mentioned above, for practical reasons in our study the second BNF level was used (i.e., Sections), and although the third BNF level (i.e., "Subsections") would more precisely reflect different drug classes, a much larger number of separate questionnaires would be needed. The choice of the BNF classification instead of the international ATC classification system, which was made on the grounds of alignment with the classification in the drug prescribing utilisation system used (ePACT2), may also limit the relevance of the EMBS empirical findings to other countries.

Another limitation in the EMBS application relates to the potential biases surrounding the online survey responses of the NHS affiliated clinical experts and national clinical directors. Given that the purpose of the online survey was to measure the expected health loss resulting from lack of treatment access, participant responses could be susceptible to cognitive or motivational biases (Montibeller and von Winterfeldt, 2015), the latter towards "promoting" their own clinical area, which could result in overstating the expected health loss impact. Motivational biases ranging from the existence of obvious conflicts of interest to subtle influences of professional association due to the existence of stakeholder interests could also affect study participants' judgements, such as relating to potential commercial interests with the pharmaceutical industry. Although the study did not apply any explicit conflicts of interest policy, it safeguarded against such motivational biases by avoiding to engage experts that could have a conflict of interest in the first place (decision conference participants were affiliated with the DHSC and other public health institutions whereas survey participants were affiliated with the NHS), and by using a decomposition of judgments (different participants provided judgments for different components of the model) (Montibeller and von Winterfeldt, 2015).

Finally, in terms of evaluation criteria selection, as part of the "within-disease concerns" for the evaluation of medicines, the "minimum supply vulnerability" value aspect was considered to correspond to the number of manufacturers supplying the medicine in England in combination with the medicine's patent status and the relevance to a pandemic. However, supply vulnerability could also include other aspects beyond the number of manufacturers, such as the number of active pharmaceutical ingredient (API) sites, number of packaging sites, number of testing sites, etc., which were not considered in this study.

5. Conclusions

A new evidence-based, decision-analytic methodology for EMLs and health emergency stockpiles was developed, which may be especially relevant in contexts of supply chain vulnerability. The methodology was developed under the scope of facilitating the formulation of the DHSC EMBS, through the collection, synthesis and analysis of primary and secondary data and evidence, as well as considering the priorities of the decision-makers. The application of the methodology for the prioritisation of therapeutic areas in the EMBS resulted in a clear ranking based on a value index incorporating the relevant value aspects of interest, while addressing the uncertainty of underlying data and evidence. The methodology could be adapted and applied to serve the needs of health care decision-makers in other countries, for the design and formulation of EMLs and health emergency stockpiles, involving the ranking of therapeutic areas followed by the ranking of medicines within each therapeutic area.

In terms of future research directions, given the amount of evidence required by the framework, it would be relevant to devise ways to identify early in the process which evidence is most critical for the ranking; for instance, the use of pilot data could be extrapolated or simplified protocols could be used for expert judgment. Also, the development of a potential open-access decision support system, in which different national health decision-makers could set up their priorities and share data, to obtain a recommended products list in a tailor-made way, could promote best decision-making practices, provide wider access, and increase the value-for-money in these product selection decisions.

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CRediT authorship contribution statement

A. Angelis: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **G. Montibeller:** Methodology, Software, Formal analysis, Writing – review & editing. **P. Kanavos:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Funding acquisition, Supervision.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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