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Capturing the value of vaccination within health technology assessment and health economics: Literature review and novel conceptual framework

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ABSTRACT

Background: Vaccination provides significant health gains to individuals and society and can potentially improve health equity, healthcare systems and national economies. Policy decisions, however, are rarely informed by comprehensive economic evaluations (EE) including vaccination's wide-ranging value. The objective of this analysis was to focus on health technology assessment systems to identify relevant value concepts in order to improve current EE of non-pandemic vaccines.

Methods: Following a literature review, a novel Value of Vaccination (VoV) framework was developed with experts in vaccine EE from developed countries with established health technology assessment systems.

Results: Forty-four studies presenting value frameworks or concepts applicable to vaccination were included. Eighteen unique value concepts relevant to EE were identified and defined. These were categorised within the VoV framework using three dimensions, moving from a narrow payer perspective to a more expansive and societal perspective. The dimensions were: (I) conventional payer perspective concepts (e.g., health gains in vaccinees, direct medical costs); (II) conventional societal perspective concepts (e.g., indirect health/economic gains to caregivers/households, productivity in vaccinees); and (III) novel societal concepts (e.g., financial risk protection, peace of mind, societal health gains, healthcare systems security, political stability, social equity and macroeconomic gains). While good quality evidence and methods are available to support concepts in Dimensions I and II, further work is needed to generate the required evidence for vaccination impact on Dimension III concepts.

Conclusions: The devastating effect on nations of the COVID-19 pandemic has helped to highlight the potential far-reaching benefits that many vaccination programmes can offer. This VoV framework is particularly relevant to policy decisions considering EE, and the potential future expansion of non-pandemic vaccination value considerations. The framework helps to understand and compare current value considerations across countries and payer versus societal perspectives. It provides decision-makers with a transparent and logical path to broaden consideration of VoV in EE.

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1. Introduction

The substantial health and societal benefits of vaccination against infectious diseases are well recognised and accepted globally [1]. Vaccination is acknowledged as one of the most cost-effective means to dramatically reduce morbidity and mortality i.e., saving 2.5 million lives each year from diseases such as polio, measles and hepatitis B [2], and reducing infant mortality rates over the past 20 years from 65 to 29 per 1000 live births [3].

Vaccination provides direct protection to those vaccinated; as an example, recent real-world evidence on COVID-19 vaccination has demonstrated around 80% effectiveness against new symptomatic infections after two doses in a large community study in the United Kingdom (UK) [4]. In addition to directly protecting vaccinated populations, increasing coverage in many vaccination programmes can reduce disease transmission and protect unvaccinated populations in the wider community, through herd immunity [3]. Reduced transmission leads to disease prevention, a strategy that has successfully eradicated smallpox and eliminated polio from all but two countries worldwide [5,6].

Globally, disparities exist in health and access to healthcare due to social differences e.g., poverty, and differences in healthcare expenditure. Implementation of national immunisation programmes (NIPs) allows all socioeconomic groups access to vaccination, helping to reduce health inequity [7]. A healthier population can affect multiple sectors of the economy, producing macroeconomic benefits e.g., a positive effect on trade, investments, tourism and affordable healthcare [8,9]. Vaccination programmes can provide significant savings to healthcare systems by preventing illness, long-term disability and nosocomial infections, and thus contribute to health systems strengthening by freeing up capacity, and allowing more efficient use of resources [10,11]. In the long-term, socioeconomic benefits of vaccination, particularly observed in developing countries, include increased school/work attendance, increased lifetime productivity in patients and their caregivers [8,12], decreased chance of cognitive impairment, enabling family planning, as well as decreased infection risk with its related gain in peace of mind [8], a concept that applies globally.

As total spending on NIPs increases globally, decision-makers typically rely on economic evaluations (EE), primarily using cost-effectiveness analysis (CEA), to assess vaccination value. Despite the broad range of benefits vaccination can bring to individuals and society, these are only partly or inconsistently considered in current health technology assessment (HTA) using CEA. The benefits considered in CEA can differ by country e.g., the UK considers benefits from a healthcare payers' perspective that includes indirect health benefits (e.g., from herd immunity) but excludes indirect costs of lost productivity, while Germany, the Netherlands and United States (US) take a broader societal perspective that does include indirect productivity costs. Inconsistent consideration of the value of vaccination (VoV) in CEA and *ad hoc* deliberative processes can result in variable access to vaccination, within and across countries.

The COVID-19 pandemic has highlighted the broad impact of infectious disease, and raises many questions about the future evaluation of non-pandemic vaccines. As countries review their approaches to evaluating vaccines, in light of the COVID-19 pandemic, this is a timely moment to propose an objective and structured approach on how to capture the full VoV in HTA focussed on CEA, so that changes can readily be adopted in the near to midterm future to support vaccine NIP decisions. Previous vaccination value frameworks were disease-specific or focussed on methodologies beyond the HTA setting. There is, therefore, a need for a comprehensive and critical appraisal of the global VoV literature and frameworks that can be applied to current HTA/CEA perspectives.

The ultimate objective was to understand how the VoV can be captured more broadly in HTA focussed on CEA. This paper presents (1) a targeted literature review and critical appraisal of the evidence on vaccination value frameworks and the concepts they include, and (2) the development, with experts from countries with well-established HTA systems, of a framework with unique defined concepts. A further analysis of how the new framework concepts are currently captured in these countries, and an objective and transparent methodology to prioritise key concepts, is presented in a parallel publication in this journal, by Postma et al. [13]. An overview of how these key concepts can be concretely considered in the CEA of vaccines will be published later this year.

2. Methodology

Fig. 1 summarises the key phases for the development of a VoV framework with unique value concepts for HTA/CEA.

In phase 1, the aim was to develop a draft VoV framework focussed on CEA with unique value concepts identified from the literature with a global scope. A targeted literature review was conducted in Medline (on 13 October 2020) for English-language vaccine studies presenting a VoV framework or discussing individual value concepts (see Tables S1 for search strategy and S2 for inclusion/exclusion selection criteria). Vaccine CEA is used globally as a tool for vaccine NIP efficiency assessments, and is used routinely in countries with well-developed HTA systems. For this reason, no country-specific restrictions were applied, as well as no restrictions on population, comparator, timeframe or study design. In addition, the grey literature was searched from Google Scholar and key international and national health/vaccination websites [14–21].

The types of frameworks presented in the literature were assessed. Frameworks were typically divided into broad categories or 'dimensions', which included a range of subcategories or 'concepts' which could include specific examples of vaccine benefits or 'elements' of value. For example, the framework by Bloom et al. [22] included two dimensions; "narrow" and "broad" benefits

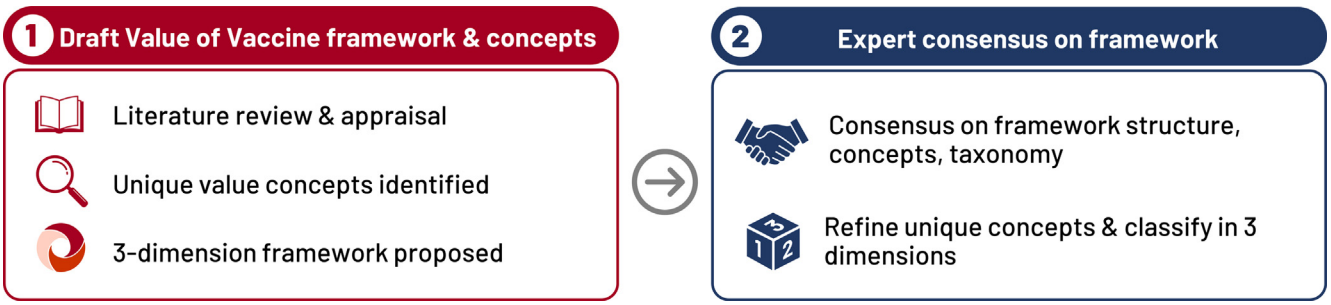

Fig. 1. Overview of framework development phases with key objectives.

of vaccination. Within the narrow benefits dimension, concepts included 'health gains' and 'medical costs avoided' whereas the broad benefit concepts included 'productivity gains'. Further subcategorization within the concept of health gains led to examples of vaccine benefit or elements e.g., 'reduction in mortality' and 'gains in Disability-adjusted life-years (DALYs)'.

For each VoV framework identified, dimensions, concepts and elements were extracted. VoV frameworks with the same or similar dimensions were then grouped together. The number of final groups was not pre-specified. Extraction and grouping was performed by some study members and was critically appraised by other study members including two external experts.

Based on the review of the full list of extracted concepts, a list of unique concepts was derived and clearly defined, and a suitable VoV framework for HTA focussed on CEA with three broad dimensions was developed.

In phase 2, individual feedback was obtained using questionnaires and surveys, and Advisory Board meetings with the experts were held, to review the literature findings, proposed framework and concepts identified. Experts involved in HTA and decision-making for vaccines participated from Australia, France, Germany, the Netherlands, Spain, the UK and US i.e., countries with well-established HTA processes applying CEA for vaccines. The objective was to reach consensus on the VoV framework structure and concepts included within each dimension of the framework.

3. Results

Of the 6661 abstracts identified and screened, 278 full-text articles were reviewed, and 24 relevant studies included. An additional 20 studies were included from website searching. Of the 44 studies included in the review, 26 described frameworks and their value concepts and elements [1,2,8,9,12,22–41], while 18 described individual value concepts or elements, five in the context of COVID-19 [37,42–45]. The majority of framework studies were not country-specific, although around half of concept studies focussed on high-income countries. Around 80% of framework and concept studies did not focus on specific child or adult populations while 14% only included children.

3.1. Overview of VoV framework studies

In 2005, Bloom et al. [22] proposed a framework with two dimensions defined as 'narrow' benefits and 'broad' benefits. Over time, frameworks have evolved to include more types of vaccination benefits. Four groups of conceptual VoV frameworks were identified, based on the types of dimensions they included (Fig. 2).

In Group 1, 16 studies proposed frameworks based on two dimensions: 'narrow' perspective (e.g., individual health gains, disease avoided, productivity gains in patients and caregivers, vaccine costs and healthcare cost savings); and 'broad' perspective (e.g., outcome- and behaviour-related productivity gain, community health externalities such as herd immunity and antimicrobial resistance (AMR), reductions in comorbidities and nosocomial infections, outbreak prevention, risk reduction gains, macroeconomic gains and equity). The concepts rarely included, however, willingness to pay, political stability, retention of tourism, demographic dividend, and cognitive gains [1,2,9,22–34].

In Group 2, five studies [8,12,35–37] proposed new frameworks, expanding on concepts included in Group 1, and using four dimensions: health gains, productivity gains, community/social externalities, and broad economic benefits beyond direct healthcare cost-savings and out-of-pocket spending e.g., gross domestic product growth and improved financial sustainability of healthcare

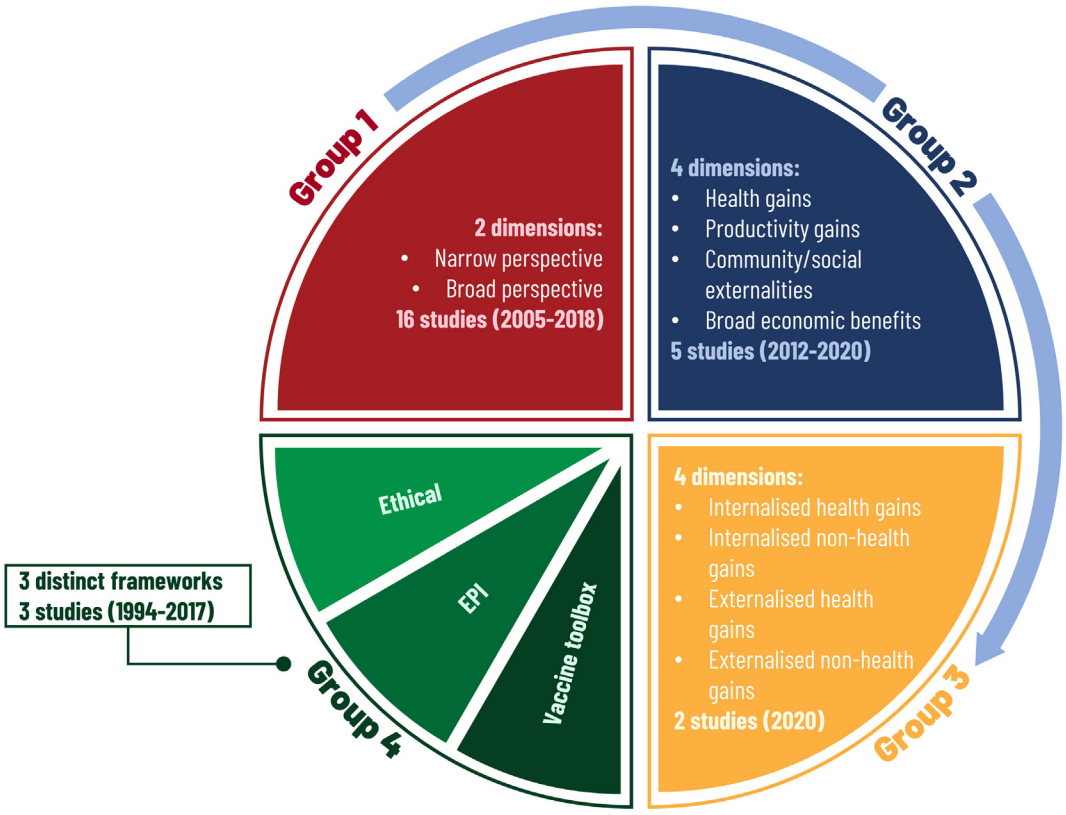

Fig. 2. Four groups of VoV frameworks based on dimensions EPI: Expanded Programme of Immunization; **VoV**: value of vaccination.

programmes. The framework by Jit et al. [36] introduced value elements for improvement in the net present value of investment, change to potential lifetime earnings and female labour participation. The framework by Deogaonkar et al. [8] discussed value elements such as changes in household investment per child and changes in the national economy. In this group, concepts of equity and macroeconomic impact of vaccination were commonly included, however, only one framework each included changes to household behaviour and public sector budget impact [36], risk reduction gains and intergenerational effects [35] and empowerment of women [37].

In Group 3, two recent studies [38,39] introduced societal VoV frameworks with four dimensions: internalised health gains (e.g., direct health gains, household health externalities, reduced comorbidities and nosocomial infections); internalised non-health gains (e.g., education, labour market productivity, non-market productivity and leisure, caregiver productivity and leisure, and risk reduction); externalised health gains (e.g., full public health benefits of vaccine); and externalised non-health gains (e.g., healthcare cost-savings, social preference fulfilment, outbreak control, macroeconomic gains, equity, and health system efficiency). Bloom et al. [38] also included political implications, while Stawasz et al. [39] also included litigation mitigation and institutional disruptions.

Some parallels may be drawn between the dimensions described in Groups 2 and 3 (e.g., health and productivity gains relate to internalised health and non-health gains, and there is overlap between community externalities and externalised health gains, and between broad economic benefits and externalised non-health gains). Overall, Group 2 dimensions appear to differentiate between concepts traditionally included in CEA in dimensions 1 and 2 with broader concepts not generally included in dimensions 3 and 4. Group 3 dimensions appear to include a more holistic welfarist perspective which could be better suited to cost–benefit analysis (CBA).

Group 4 included three differently structured frameworks: an ethical framework [41], a framework for the evaluation of a vaccine for use in the Expanded Programme of Immunization (EPI) [40] and a vaccine value toolbox [28]. Some concepts reported across all three were disease control, health gains, safety and efficacy, and ecological effects. Other concepts included in at least one framework were immunogenicity, scientific spillovers, productivity gains, macroeconomic gains, household financial security, healthcare costs, justice, and autonomy.

3.2. Overview of VoV single concept studies

Among the studies describing individual value concepts without a framework, in addition to the common concepts presented above, concepts of utility in anticipation [46], household financial security [47] and healthcare system efficiency [48] were also introduced. Five of these studies [37,42–45] discussed vaccination value with respect to the impact the COVID-19 pandemic has had on society (Fig. 3).

In addition to the health and productivity gains, macroeconomic benefits, community and healthcare system externalities (e.g., equity, household financial security), the less common concepts included psychological gains, disease severity, family or scientific spillovers and willingness-to-pay for coverage (Fig. 3).

3.3. Development of a framework to capture the VoV for HTA/CEA

Based on the literature review findings, vaccination benefits were sometimes reported as value elements or concepts, and similar benefits could use different terminology. As the framework by Jit et al. [36] evolved from previous frameworks and was based on a robust methodology (including systematic review and expert validation), it was used as a reference and wording of concepts from this study was used.

Based on how often value concepts and elements were reported, a unique list of concepts was developed from the most to least commonly reported (Supplementary Table S3). A framework was developed with three possible dimensions relevant to

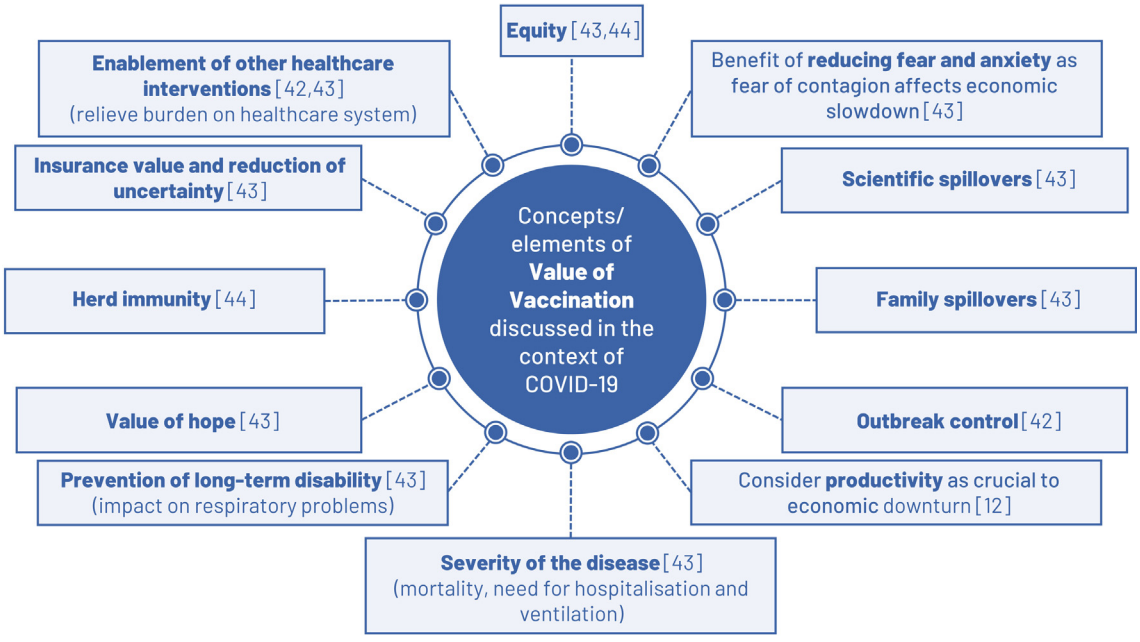

Fig. 3. The VoV in the context of COVID-19 VoV: value of vaccination.

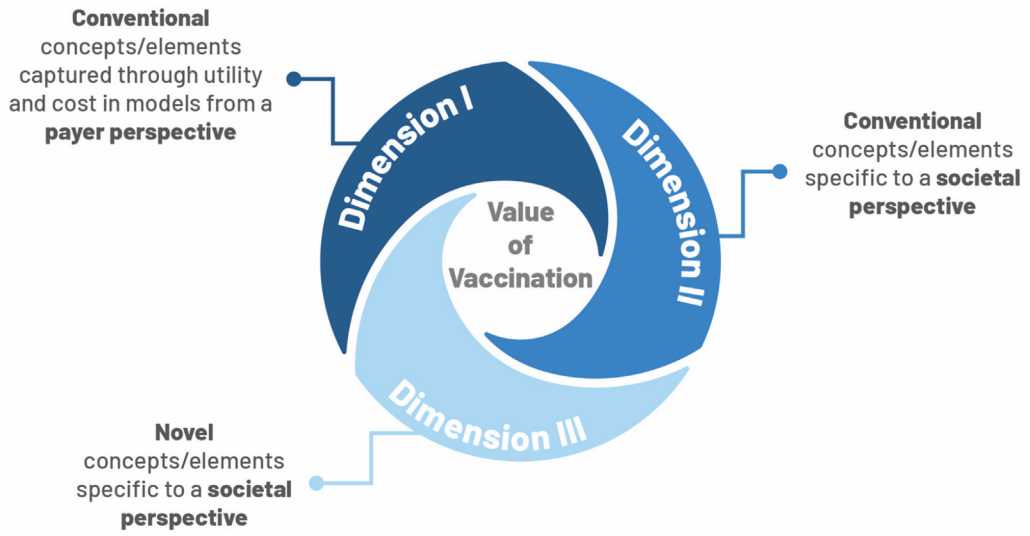

Fig. 4. Novel VoV framework relevant to HTA/CEA CEA: cost-effectiveness analysis; **HTA**: health technology assessment; **VoV**: value of vaccination.

capturing value for HTA/CEA. The unique concepts were then allocated to one of the dimensions (Fig. 4).

As this framework is the first to have a goal of achieving near-future expansion of value attributes relevant to CEA, three dimensions were determined based on moving from the current to a broader value consideration within CEA methodology.

Dimension I included conventional concepts and elements captured in current economic modelling practice, using utilities for health benefits and costs from a healthcare payer perspective. Health gains to vaccinated individuals and healthcare cost-savings were typically included in Dimension I.

Dimension II included conventional concepts and elements, captured within a societal perspective in EE. Conventional concepts were defined as well-known, with an established methodology for measurement, and/or impacting QALYs or costs. Productivity gains to patients and caregivers were typically included in Dimension II.

Dimension III included novel concepts and elements, from a societal perspective. Novel concepts were, by definition, difficult to capture or measure and may only be described qualitatively at present, as methods for their quantification are yet to be developed or validated. Other productivity gains, community and health system benefits and macroeconomic benefits were typically included in Dimension III.

The concept of societal health gains beyond vaccinated individuals has multiple value elements that span all three Dimensions e.g., in Dimension I: reduction in transmission of disease, herd immunity and outbreak control/preparedness; in Dimension II: disease eradication; and in Dimension III: reductions in nosocomial infections (secondary infections), reduction in antibiotic use, decrease in antimicrobial resistance, and health utility gains from the altruistic aspect of herd immunity.

The final concepts in the VoV framework (Table 1) were refined with the experts, for example, by merging overlapping concepts (e.g., 'value of hope' was merged into 'peace of mind'), removing concepts (e.g., 'litigation cost'), redefining some (e.g., 'political stability' was redefined focussing on 'erosion of trust in government institutions' as other aspects covered originally within this concept such as 'exacerbation of social inequalities' were included in other concepts i.e., 'social equity and ethics') and rewording some (e.g., 'financial risk protection' reworded to 'vaccine-attributable financial risk protection').

The full definition of each concept, with illustrative examples, is provided in Supplementary Table S4.

4. Discussion

The extensive value that vaccination brings to individuals, society and nations is well recognised in the literature, but so is its lack of consideration in the assessment of new vaccines. Current approaches to EE tend to consider a narrow set of benefits such as individual health gains, healthcare cost-savings and productivity gains. The recent impact of the COVID-19 pandemic has highlighted the far-reaching effects infectious diseases can have and the full potential VoV. The failure to identify, measure and value these wider benefits risks underinvestment in vaccines that are good value for money, especially when considered from a societal perspective.

Between 1994 and 2020, 26 publications described possible frameworks that would allow the comprehensive VoV to be captured. The published frameworks commonly proposed expanding the vaccination benefits currently considered to include outcome-related and behaviour-related productivity gains, herd immunity, equity, prevention of AMR and macroeconomic impact. While there is interest in considering some of these additional benefits in CEAs, a practical framework to help consistently and transparently manage this in CEA focussed on vaccines is currently lacking. A recent systematic review on how productivity was considered in vaccine CEAs published between 2010 and 2019 found inconsistencies in the types of productivity costs included (i.e., due to absenteeism, presenteeism, unemployment and premature mortality) as well as in the methodology used (friction cost or human capital approach) [49]. A systematic review of vaccine CEAs found that inclusion of herd immunity is becoming more common, with around half of studies in 2015 including herd immunity compared to less than 5% in 2001. Differences remain, however, in the methods employed (e.g., dynamic versus static modelling) and in the proportion of studies considering herd immunity by vaccine [50]. The World Health Organization (WHO) updated their guidelines for harmonisation of vaccine CEAs in 2019, recognising the need to consider so-called 'broader vaccine benefits' that are not currently included in traditional CEA, as vaccines have the potential to generate many health and non-health long-term benefits. The guidelines also specifically addressed methods to include equity e.g., through extended-CEA to assess equity and efficiency considerations in parallel, or through distributional-CEA to assess trade-offs between equity and efficiency [51]. There is increasing interest in the VoV for diseases which are currently treated with

Table 1
Concepts in each dimension of the new VoV framework for HTA/CEA.

Dimension I	A. Health gains to vaccinated individuals
	B. Savings in direct medical cost
	C*. Societal health gains beyond vaccinated individuals (e.g., herd immunity)
Dimension II	D. Indirect health and economic gains for caregivers and family/household
	E. Health-related productivity gains for vaccinated individuals
	C*. Societal health gains beyond vaccinated individuals (e.g., disease eradication)
Dimension III	F. Vaccine-attributable financial risk protection
	C*. Societal health gains beyond vaccinated individuals (e.g., decrease in antimicrobial resistance)
	G. Health systems strengthening, resilience and security
	H. Peace of mind for the individual and family/household
	I. Fulfilment of societal preferences
	J. Reduction in carbon footprint due to prevention of infection and disease
	K. Prevention of loss of leisure time
	L. Political stability
	M. Institutional disruptions
	N. Enablement value
	O. Scientific spillovers
	P. Real option value
	Q. Macroeconomic gains
	R. Social equity and ethics

Dimension definitions: (I) Concepts captured through utilities and costs in standard modelling from payer perspective; (II) Standard concepts from societal perspective; (III) Novel concepts from a societal perspective i.e., concepts not frequently considered in HTA/CEA or for which measures and methods to include them in CEA are not developed; *Concept C* may be considered in Dimensions I to III (see additional elements included, in Table S4).
CEA: cost-effectiveness analysis; **HTA**: health technology assessment; **VoV**: value of vaccination.

antibiotics, including a recent action plan from the WHO [52], due to rising AMR levels globally and the burden this places on patients and health systems [53]. The COVID-19 pandemic has highlighted the macroeconomic impact of infectious disease outbreaks beyond healthcare e.g., the negative effect on the national economy, employment, travel, and tourism [54]. Vaccination has had a positive effect on economic recovery, especially apparent in countries with high vaccination coverage, while low coverage in other regions is likely to hold back economic recovery for many years leading to greater inequity [55]. Mauskopf et al. [56] recently reviewed the use of additional methods as a means to demonstrate the broader VoV not captured in HTA/CEA for other stakeholders i.e., CEA focusses on value for money for health system decision makers, however, Ministries of Finance that provide funding for vaccination may need fiscal health models showing value through tax revenue and return on investment; and decision makers using constrained optimization methods gain a broad view of the most efficient choice from multiple possible interventions (e.g., value of combining vaccination with other interventions). And finally, a recent study has attempted to quantify the value of hope concept, independently of survival or quality of life, for future inclusion in EE [57]. Similarly, the frameworks identified have evolved over time, from the early VoV framework developed by Bloom et al. [22], which simply distinguished between 'narrow' and 'broad' benefits, to the Group 2 and 3 frameworks, which expanded the prior grouping to account for additional vaccines, evidence and methodologies developed subsequently. Group 3 frameworks even consider insights from specific diseases, such as rare and severe

meningococcal disease, and aim to introduce a new taxonomy (i.e., internalised vs. externalised benefits; health vs. non-health gains) which may be more suited to inform broader cost-benefit analysis than CEA.

The framework described in this paper focusses on near-future expansion of value attributes relevant to CEA, with a goal of informing decision-makers on (1) the broad VoV concepts and their relation to different perspectives currently applied in CEA in HTA and (2) how to potentially include key missing concepts systematically in the EE process of vaccines. While some concepts may have been previously considered in deliberative processes, this framework proposes a consistent and transparent approach. The three dimensions of the VoV framework separate conventional HTA payer-perspective value concepts, conventional societal-perspective concepts, and novel broad societal concepts. This VoV framework allows for a logical progression to expand concepts considered in HTA, by moving to a broader societal perspective that includes benefits beyond just the vaccinated individual and healthcare environment. Another vaccination value framework was recently published [58] which also aimed to address gaps in the assessment of vaccination value from an HTA perspective – 12 core value elements were captured within four dimensions in this framework i.e., broad versus narrow health effects, and health system versus societal economic effects. Six of the 12 value elements were not currently considered as standard in HTA/CEA [58].

Although there has been an evolution in the evidence and methods available, evidence supporting the broader benefits of vaccines proposed in frameworks is still limited due to a lack of high-quality observational and experimental studies. Many of the important but novel benefits of vaccines presented in Dimension III are currently difficult to measure and thus difficult to integrate into CEA. There is a need to develop more advanced measurements and evidence supporting these value elements.

While this study attempted to provide a comprehensive overview of vaccination value concepts from the literature, there are some limitations. The literature review included concepts and frameworks from any country so that the framework developed may be applied to vaccine CEAs worldwide. However, experts involved were from high-income countries with well-developed HTA processes. While CEA is used as standard in many countries, its influence on NIP decision-making varies e.g., in the UK, a new vaccine needs to be cost-effective to be recommended for inclusion in the NIP and funded. In other developed countries such as France, Germany and Spain, however, CEA is considered as part of a broader deliberative process but is not binding [59]. Another limitation was the focus on near-term achievable changes using CEA, as the most commonly applied methodology, as opposed to broader methods e.g., CBA or multi-criteria decision analysis. Although CEA limits the full capture of some VoV concepts, this practical approach was taken so that findings can be integrated into HTA/CEA in the near to midterm future. Furthermore, the framework presents the three dimensions and 18 VoV concepts as distinct from each other to allow for pragmatic insights and guidance, although acknowledging that the concepts interact and can overlap (see comments for each concept in Table S4). Thus, an appraisal of any potential overlap between VoV concepts and single elements should be considered when actually integrating these concepts into CEA. When considering, for example, the value concept of 'health systems strengthening, resilience and security' in CEA, prevention of respiratory diseases can provide marginal savings in direct medical costs from cases prevented (dimension I value element), but vaccination can also provide larger benefits, allowing reallocation of resources to treat other diseases, especially during winter-stress months in hospitals (dimension III element). These examples are described in more detail in the third paper of this series concerned with practical applications of VoV concepts in CEA e.g., in the example above, using the opportunity cost method.

There are no comprehensive guidelines defining which broader vaccination benefits should be taken into account. This study has shown the need for an HTA-relevant framework in order for decision-makers to make informed decisions about VoV changes in the coming years. Previous HTAs may have been adapted in response to specific needs encountered during the vaccine evaluation process (e.g., Broader benefits of vaccination have been considered in an *ad hoc* fashion for specific diseases, as was the case for meningococcal B vaccination in the UK, where the severity of illness and impact on caregivers' quality of life was taken into account [14,15], and for human papillomavirus vaccination in boys, where valuation methods such as different discounting were applied to the target population to reflect the broader vaccination value [16]). As such, generation of evidence on the broad VoV has helped inform discussions and decision making about NIP introductions in the past. There is a need for a VoV framework that enables evidence generation to serve the needs of current HTA processes, while also producing complementary evidence to demonstrate how the assessment of value for money changes when broader aspects of benefit are properly accounted for.

The comprehensive and systematic approach used to develop the VoV framework provides an opportunity to proactively anticipate future needs consistently across all vaccine evaluations. The present framework was developed with vaccines in mind, accounting for differences between vaccines and therapeutics, such as market access pathway (i.e., NIP recommendation by National Immunization Technical Advisory Groups with different decision making criteria to HTA bodies [59]), and the larger impact on broad value concepts (e.g., macroeconomics) of disease prevention versus treatment. The framework, however, shares multiple concepts in common with value frameworks developed for health technologies in general [60], and some of the 18 distinct concepts captured here may also be applicable to therapeutics. For example, both therapeutics and vaccines can have an impact on the concept of 'health systems strengthening, resilience and security'. Postma et al. [13] provides further discussion of this topic, when considering the implementation of this framework.

The established VoV framework has been used to identify which of the framework concepts are currently considered in the represented countries' HTA processes, and to obtain an objective ranking of concepts by importance. This has allowed three priority concepts to be selected for future expansion of the VoV in CEA [13]. An overview/guide to the potential practical inclusion of these three priority concepts in HTA in the coming years is also being developed as a result (to be published separately).

A supplementary file is available with further details about the literature review and value concepts.

Disclosures

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Author contributions

All authors are members of the Advisory Board and reviewed the literature, provided substantial input, contributed to writing and reviewing of this publication. Ekkehard Beck and Eliana Biundo led publication development. All authors gave their final approval and are accountable for all aspects of the work.

Declaration of Competing Interest

Eliana Biundo, Ekkehard Beck, Mark Doherty and Shazia Sheikh are employed by and hold shares in the GSK group of companies. Antonio J Garcia-Ruiz received funding from the GSK group of companies during the conduct of this study. He also received grants and/or consulting fees and/or honoraria from SanofiPasteur, UCB, CHIESTI, Official College of Physicians, Sociedade Galega de Neuroloxía, and regional government outside of this work. Terry Nolan was a member and co-chair of the advisory board related to this study and established by the GSK group of companies and was paid an honorarium for his input to it. He received consulting fees and/or honoraria from AstraZeneca, Merck, Seqirus, SanofiPasteur, the GSK group of companies. He also received personal payment for participation for other advisory boards not related to this study from Clover, Zeria and Serum Institute of India, and is expert in the Victorian State Government advisory group on COVID vaccine roll-out outside of this submitted work. His institution received grants from the GSK group of companies, SanofiPasteur, Janssen, Seqirus and Serum Institute of India outside of this work. David Salisbury was a member and co-chair of the Advisory Board for this study, established by the GSK group of companies, and was paid an honorarium for his input. He has received consulting fees and/or honoraria, unrelated to this study, from AstraZeneca, Clover, the GSK group of companies, Janssen, Pfizer, SanofiPasteur and Seqirus. Beata Smela declared her institution received funding from the GSK group of companies during the conduct of this study. Nancy Devlin, Jürgen Wasem, Mondher Toumi and Maarten Postma were all members of the Advisory Board for this study, established by the GSK group of companies, and were paid an honorarium for their input. All authors declare no other financial and non-financial relationships and activities.

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Appendix A. Supplementary material

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