



THE BRAVE INITIATIVE

The BRAVE Narrative for Broad Assessment of Value in Vaccines Engagement

RESEARCH | REPORT
SEPTEMBER 2020

Eleanor Bell, Margherita Neri, Lotte Steuten

[ohe.org](https://www.ohe.org)

Funding and Acknowledgements

This report was initiated and funded by Pfizer, the contributors received an honorarium from Pfizer.

The Office of Health Economics A Company Limited by Guarantee of Registered No. 09848965
OHE Consulting Ltd Registered Company No. 09853113
OHE is a Charity Registration No. 1170829
Registration Office Southside, 105 Victoria Street, London SW1E 6QT

SEPTEMBER 2020

THE BRAVE INITIATIVE

The BRAVE Narrative for Broad Recognition of Value in Vaccines Engagement

Eleanor Bell

Office of Health Economics, London

Margherita Neri

Office of Health Economics, London

Lotte Steuten

Office of Health Economics, London

Please cite this report as:

Bell, E., Neri, M. and Steuten, L., 2020. THE BRAVE INITIATIVE. The BRAVE Narrative for Broad Recognition of Value in Vaccines Engagement. OHE Research Paper, London: Office of Health Economics. Available at: <https://www.ohe.org/publications/brave-initiative-brave-narrative-broad-recognition-value-vaccines-engagement>

Corresponding Author:

Lotte Steuten

lsteuten@ohe.org

For further information please contact:

Professor Lotte Steuten, PhD

Vice-President and Head of Consulting, OHE

Honorary Visiting Professor at City, University of London

Tel +44 (0)207 747 1441

Email lsteuten@ohe.org

About OHE Research Papers

OHE Research Papers are intended to provide information on and encourage discussion about a topic in advance of formal publication. They are subject to internal quality assurance and undergo at least one external peer review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views or approval of the OHE's Editorial Panel or Research and Policy Committee, or its sponsors.

Once a version of the Research Paper's content is published in a peer review journal, that supersedes the Research Paper and readers are invited to cite the published version in preference to the original version.

Table of Contents

Executive Summary	iv
Why do we need a broader assessment of the value of vaccines?.....	iv
State-of-Play	v
Gaps in the recognising the value of vaccines.....	vii
The BRAVE roadmap to change	vii
Conclusion	x
<hr/>	
1 Introducing the BRAVE Initiative	1
1.1 Background	1
1.2 The BRAVE initiative	1
1.3 Methods.....	2
<hr/>	
2 Why is a broader assessment of the value of vaccines needed?	2
2.1 The economic and policy rationale for broader assessment	2
2.2 Frameworks for understanding the broader value of vaccines	3
2.3 Recommendations for recognising the broader value of vaccines	8
<hr/>	
3 State-of-Play	10
3.1 What value elements are considered around the world?	10
3.2 What type of evidence is available and accepted for each value element?.....	13
<hr/>	
4 Gaps in the recognition of vaccines' value	16
4.1 Gap analysis.....	16
4.2 Assessment of countries' willingness and ability	17
4.3 Prioritisation of gaps	18
<hr/>	
5 The BRAVE roadmap to change	20
5.1 Roundtable discussions: the process of developing the roadmap	20
5.2 The BRAVE roadmap	20
5.2.1 Overall recommendations towards full recognition	22
<hr/>	
6 Conclusion	23
7 References	24
Appendix 1: Summaries of the current state of play in sample countries	29
Appendix 2: Roadmaps and specific recommendations by priority-gap	34

Executive Summary

Vaccines are widely regarded as one of the most important public health achievements of the last century (Centers for Disease Control and Prevention (CDC), 2011; Levine et al., 2011). Recent literature, however, highlights gaps between what policymakers typically count as vaccine benefits and the full benefits that vaccines confer (Jit et al., 2015; Bloom et al., 2017; Gessner et al., 2017; Mauskopf et al., 2018). Failure to consider substantial portions of vaccines' full benefits, referred to as 'broader' benefits, can lead to undervaluing vaccines. This, in turn, may lead to suboptimal vaccine development, recommendation, and reimbursement decisions (Bloom et al., 2018).

OHE is undertaking a research programme called the *Broad Assessment of Value in Vaccines Engagement (BRAVE)*. The overarching aim of the BRAVE initiative is to increase recognition of the broader value elements of vaccines and consistency of their assessment within HTA and wider decision-making processes in nine target markets. These markets are Belgium, Canada, France, Germany, Italy, Japan, Sweden, the UK and the US.

The activities of the BRAVE initiative to date are incorporated into this paper, the 'BRAVE narrative'. The BRAVE narrative first describes the current 'state-of-play' of vaccine assessments in a range of higher-income countries. Based on insights from a Roundtable with academic and HTA experts in each country, the narrative then goes on to recommend on how (pragmatic) use of the newest and most advanced evidence and analytics might facilitate consideration of the broader value of new vaccines. Future work will involve engaging with other stakeholders in vaccines assessment in these target markets to investigate the feasibility and desirability of implementing these recommendations for broader value assessment of vaccines. The final 'BRAVE narrative' will ultimately be disseminated as a science and policy paper.

Why do we need a broader assessment of the value of vaccines?

Traditionally, HTA considers "only benefits in terms of improved health, reduced health care costs and resource use (and improved quality of care) and short-term productivity increases to patients and their caregivers" (WHO, 2019). However, vaccines can also generate substantial externalities (indirect effects on third parties) that are not necessarily observed with other types of medical interventions (Mauskopf et al., 2018). In the context of health care, these are benefits and costs to the health system beyond those attributable to the treated patient. Beyond the health system perspective, vaccines might also have social and economic externalities which are important to society. Consideration of these broader benefits should be applied to *all* interventions funded by the same budget, where they are relevant, in order for consistent decision-making (Jit and Hutubessy, 2016; WHO, 2019). However, some of the broader benefits are unique, or unusually large, in the case of vaccines (Mauskopf et al., 2018). As a result, the estimated cost-effectiveness of vaccines in comparison to other interventions is systematically disadvantaged compared to the true cost-effectiveness (Beutels et al., 2008), leading to sub-optimal prioritisation of health care budgets.

In recent years, a number of frameworks have been proposed to conceptualise the full value generated by vaccinations (Bärnighausen et al., 2011, 2014; Bloom et al., 2017; Deogaonkar et al., 2012; Jit and Hutubessy, 2016). Recognising the many overlaps between these frameworks, OHE has developed a synthesising framework designed to provide a comprehensive overview of the categories of effects which might result from vaccination (see Figure 1).

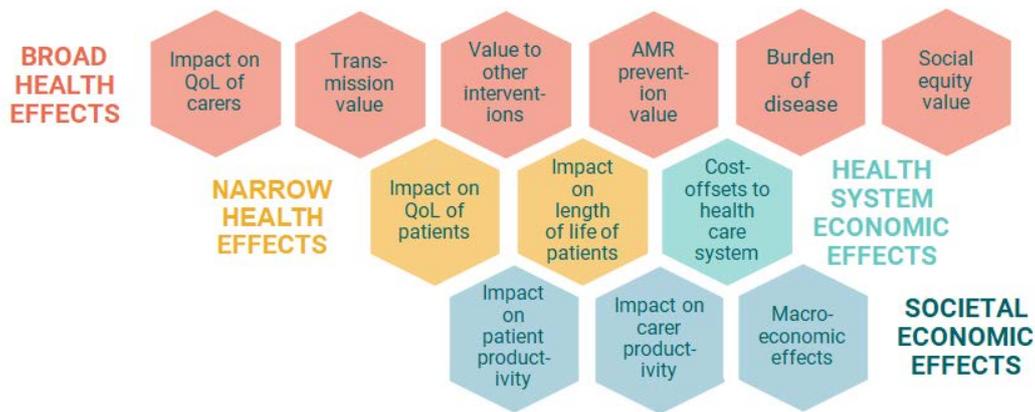


Figure 1: OHE Value Framework
 Notes: QoL = Quality of Life; AMR = antimicrobial resistance.

Recognising the increasing academic consensus that vaccines generate value which is not typically covered within HTA and the wider decision-making processes they support, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the WHO have recently published guidelines on the HTA of vaccines which explicitly advise on how these could, and should, incorporate broader value¹ (Mauskopf et al., 2018; WHO, 2019). In 2016, a convening of experts from the European vaccines economics community organised by the Robert Koch Institute developed a similar consensus framework intended to support the development of national guidelines in Europe (Ultsch et al., 2016). Section 2.3 summarises the recommendations covered in these three publications.

These three publications argue for comprehensive consideration of the narrow and broad effects of vaccines on both health and economic outcomes – although they recognise that the choice of whether to incorporate burden of disease, social equity, productivity costs and macroeconomic effects is ultimately dependent on the objective function of the decision-maker.

State-of-Play

The below table illustrates how HTA and broader decision-making processes in the countries in our sample consider the value elements identified in our framework. This is based on a review of the published HTA methodologies in each country, to establish which value elements are explicitly recognised as potential components of a formal HTA. In cases where there is no formal reference to a value element, we supplement this with the findings from a rapid literature review and written feedback from recognised vaccines experts within each of the countries in our sample, to determine whether it might be informally considered within HTA and the wider decision-making process, and the frequency with which this takes place. If a value element is informally considered in the assessments of the majority of vaccines to which it is relevant, this is defined as ‘commonly and informally considered’.

¹ These guidelines focus on economic evaluations, which are the predominant method of HTA assessment in the countries in our sample, and globally. HTA may also be carried out through evaluations of clinical effectiveness only (as opposed to in tandem with economic effectiveness), although this is increasingly rare. Within our sample, only France and Germany (sometimes) carry out evaluations of clinical effectiveness.

Table 2: – matrix of value elements considered by country

* Note that although productivity of patients and carers should be considered according to the Japanese guidelines, to date there is no evidence that this has happened except in recent discussions of vaccinations for rotavirus (productivity of carers) – source: Pfizer Japan.
 QoL = Quality of Life; AMR = Antimicrobial Resistance

	Belgium	Canada	France	Germany	Italy	Japan	Sweden	UK	US
Disease impact on length of life	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Disease impact on QoL of patients	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Disease impact on QoL of carers	Uncommonly and informally considered	Commonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Not considered	Uncommonly and informally considered	Formally considered	Not considered
Burden of disease	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Value to other interventions	Not considered	Not considered	Formally considered	Not considered	Not considered	Not considered	Not considered	Uncommonly and informally considered	Uncommonly and informally considered
Transmission value	Commonly and informally considered	Formally considered	Formally considered	Formally considered	Commonly and informally considered	Commonly and informally considered	Formally considered	Formally considered	Formally considered
Prevent the development of AMR	Uncommonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Not considered	Uncommonly and informally considered	Uncommonly and informally considered
Social equity	Formally considered	Formally considered	Commonly and informally considered	Formally considered	Commonly and informally considered	Commonly and informally considered	Formally considered	Uncommonly and informally considered	Not considered
Productivity of patients	Not considered	Formally considered	Uncommonly and informally considered	Uncommonly and informally considered	Commonly and informally considered	Uncommonly and informally considered *	Formally considered	Not considered	Formally considered
Productivity of carers	Not considered	Commonly and informally considered	Uncommonly and informally considered	Uncommonly and informally considered	Commonly and informally considered	Uncommonly and informally considered	Formally considered	Not considered	Formally considered
Costs-offset to health care system	Formally considered	Formally considered	Commonly and informally considered	Commonly and informally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Macroeconomic effects	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Uncommonly and informally considered

Key: Formally considered Commonly and informally considered Uncommonly and informally considered Not considered

Gaps in the recognising the value of vaccines

Comparing the current 'state of play' in our sample countries with international recommendations allows us to identify gaps between the two. Closing these gaps would achieve more consistent recognition of the full value generated by vaccines.

For HTA policymakers and practitioners to fully recognise any aspect of value created by vaccines, they must have:

- *Evidence*: empirical high-quality data demonstrating the value accrued for each relevant value element
- *Willingness*: motivation to incorporate this evidence into HTA and broader decision-making processes
- *Ability*: technical/analytic tools and approaches to incorporate this evidence into HTA and broader decision-making processes:

As such, gaps between the current 'state of play' and full recognition can be conceptualised in terms of constraints, or 'hurdles', which can present in the form of limited/no evidence, willingness, and/or ability. Identifying these gaps and hurdles is a key step in developing a roadmap towards full recognition of the broader value of vaccines.

In order to identify gaps and hurdles, we developed an initial longlist based on our comparison of the current 'state of play' and international recommendations. This longlist was then reviewed and added to by experts on value assessment of vaccines from each of our nine target markets, who have backgrounds working within HTA decision-making bodies and/or academia. Two rounds of shortlisting were done to select five priority gaps for discussion at the roundtable.

The BRAVE roadmap to change

The primary foci of the roundtable discussions were, for each of the five prioritised value elements:

1. to understand which hurdles are between full recognition and the current state of play in the respective countries
2. to develop recommendations as to how these hurdles in evidence, ability and willingness could be overcome and full recognition achieved.

At the roundtable, each of the gaps was discussed in turn. Firstly, participants were asked to position their country on a stylised roadmap representing to show whether they had already surpassed, or had yet to overcome, hurdles in evidence, ability and willingness. This was a qualitative exercise intended to generate discussion and provide a simplified visual of a country's position with respect to each gap. Secondly, participants were asked to discuss how the existing hurdles (in any of the target markets) could be overcome.

A stylised representation of the BRAVE roadmap is provided in Figure 2. The roadmap should be read from left to right. The roadmap is populated by hurdles (in red) of three types: willingness (W), ability (A) and evidence (E). The five priority gaps (P symbols in green) were positioned on the roadmap to show where they are on the road towards full recognition (indicated by full recognition award symbol). As such the hurdles that are considered overcome, i.e. on the left hand side (or behind) the priority-gap symbol and those that remain to be crossed, i.e. on the right hand side (or ahead) of the priority-gap symbol. (It should be noted that the order of the hurdles does not imply that future progress would rely on addressing them sequentially; further discussion of this is

included in the priority-gap specific roadmaps). The position of each priority gap reflects the average of the positions occupied by each target country with respect to that priority gap.

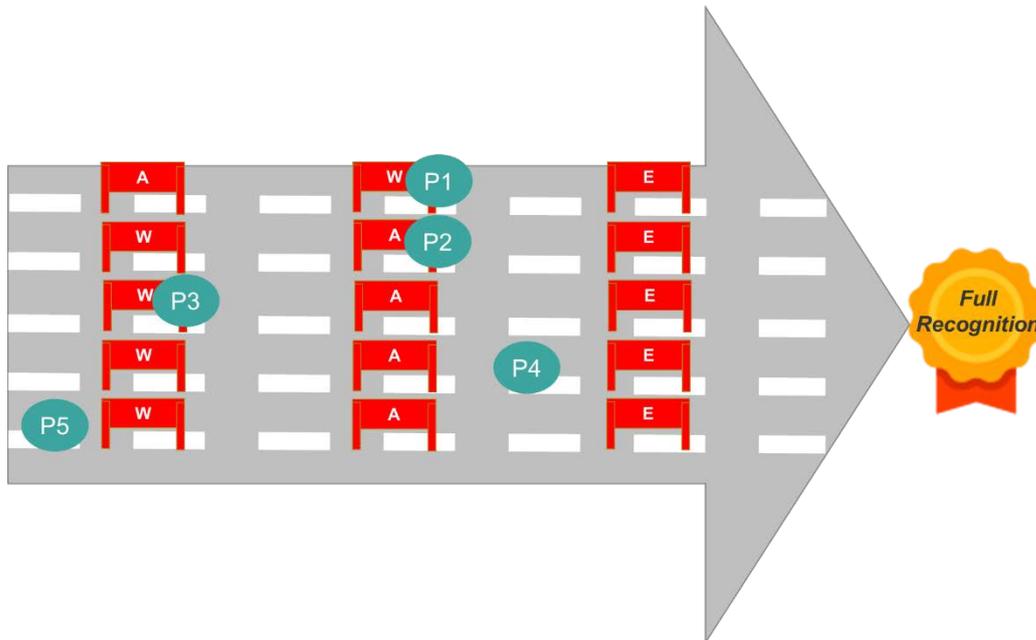


Figure 2: The BRAVE Roadmap

Notes: W = willingness; A = Ability; E = Evidence; P1 = 'Broad' cost offsets at the community-level; P2 = Effects on carer's health; P3 = Transmission value; P4 = Effects on AMR; P5 = Macroeconomic effects.

In Figure 2, the five priority gaps (Ps) are ordered from the closest to the farthest to full recognition:

- P1: 'Broad' cost offsets at the community level are not comprehensively considered.** Overall, all countries are willing and able to consider cost offsets. However, evidence of 'broad' cost offsets should be improved to ensure that value is consistently recognised.
- P2: Effects on carers' health are not considered, or not consistently considered.** The ability to include effects on carers' health is overall available, but the willingness to do so has not been established in all countries, and the evidentiary standards could be improved.
- P3: Transmission value is not consistently considered in all countries.** Willingness to model transmission value is overall available. While ability may improve through an effort to standardise methods to advanced modelling approaches, the availability of good quality evidence is currently the main hurdle.
- P4: Effects on AMR are rarely considered.** Many countries have explicitly expressed their willingness to consider AMR effects given the related public health risks. Research on methods and evidence to quantify AMR effects is ongoing.
- P5: Macroeconomic effects are rarely considered.** Consideration of macroeconomic effects requires rethinking many aspects of the value assessment approach of vaccines, as well as researching suitable evidence. So far, i.e. prior to the COVID-19 pandemic, and in the higher-income countries under study, these efforts have been limited by the lack of recent experience with infectious diseases with significant macroeconomic effects.

In light of the challenges described above, we identified areas for change and improvement in the way that vaccines are assessed. Below, we list *recommendations* for starting to address the willingness, ability and evidence hurdles for each prioritised value element.

Willingness

- Stimulate decision makers and the public awareness of the significant impact on carers' health (P2) and macroeconomic effects (P5) that vaccines could help prevent by leveraging the global experience with COVID-19, and further develop metrics and models to quantify this.
- As a complementary activity to the above, and showing that macroeconomic impact is not unique to COVID-19 vaccine-preventable disease, develop 'case studies' demonstrating the impact of other vaccine-preventable diseases on carers' health and macroeconomic effects.
- Effects on AMR are not unique to vaccines and can accrue from various health technologies such as antibiotics. In the countries where willingness is currently missing, the issue should be addressed by promoting a broader discussion around the role of HTA in rewarding the incremental impact of preventing or mitigating AMR (P3) in all technologies expected to do so.

Ability

- Short- and long-term adaptations of the approaches for assessing vaccines should be considered, when willingness to consider AMR (P4) and macroeconomic effects (P5) exists. In the short-term, where the available evidence may not be perceived sufficient to quantify the impact of vaccines on AMR and macroeconomic effects, decision makers may consider aiding resource allocation decisions with qualitative methods/judgements (e.g. multi-criteria decision marking, MCDA). In the long-term, consideration of non-health effects (e.g. macroeconomic effects) may require a permanent change of the approaches to assess vaccines, either through an adaptation of traditional methods (e.g. differential cost-effectiveness thresholds) or adoption of new ones (e.g. macroeconomic models).

Evidence

- Target the collection of evidence of 'broad' cost offsets (P1) and carers' health (P2) based on the disease characteristics (e.g. high infectiousness) and the vaccine target population.
- More effort is needed to generate and maintain high-quality evidence of transmission value and effects on AMR. This requires i) continuation of research that aims to generate evidence on infection dynamics, to estimate the impact of vaccines on the development of herd immunity (P3) and of AMR (P4); ii) strengthening national surveillance systems of infection transmissions (P3) and of resistant infections spread (P4).
- Overall, efforts to improve the available evidence base around the impact of vaccines may also generate willingness on the decision makers' side. However, if both evidence and willingness hurdles exist, they may be most effectively tackled simultaneously, rather than sequentially. For example, an explicit statement of willingness and commitment by the decision maker to consider such evidence and an open dialogue with manufacturers of what the evidence should look like may incentivise the development of further technical/analytic expertise where needed and the evidence collection itself.

Conclusion

The BRAVE narrative outlines the rationale for consideration of the broader value of vaccines; describes the gaps which currently exist between full recognition of this broader value and recognition in the HTA processes of nine target markets; and provides concrete recommendations for addressing five of these priority gaps. For these recommendations to translate into policy change requires constructive conversation and a shared understanding of key issues. Beyond that, it requires alignment among key stakeholders and – ultimately – shared willingness, ability and data to then make the change. Further work of the BRAVE initiative will address the willingness and ability of a broader range of stakeholders including payers, policymakers and HTA-bodies.

1 Introducing the BRAVE Initiative

1.1 Background

Vaccines are widely regarded as one of the most important public health achievements of the last century (Centers for Disease Control and Prevention (CDC), Levine et al., 2011). They save the lives of an estimated 2.5 million children a year (Maurice and Davey, 2009), and with current and anticipated technological advances have the potential to prevent a far greater number of deaths and illnesses amongst children and adults (Levine et al., 2011). However, there is increasing consensus amongst authoritative academic groups and the World Health Organisation (WHO) that vaccines have valuable health and economic effects which are not captured within traditional health technology assessments (HTAs), and the wider decision-making processes they support. These effects have been termed the 'broader' benefits of vaccinations, to underline that such benefits fall outside the scope of traditional health technology assessments (WHO, 2019). In the context of increasing pressure on health care budgets, the failure to recognise these broader benefits means that decision-makers risk sub-optimal allocation of funding towards new vaccines and other technologies with similar value profiles.

1.2 The BRAVE initiative

OHE is undertaking a research programme called the *Broad Assessment of Value in Vaccines Engagement (BRAVE)*. The overarching aim of the BRAVE initiative is to increase recognition of the broader value elements of vaccines and consistency of their assessment within HTA and wider decision-making processes in nine target markets.

The activities of the BRAVE initiative to date are incorporated into this paper, the 'BRAVE narrative'. The BRAVE narrative first describes the current 'state of play' of vaccine assessments in a range of higher-income countries. Based on insights from a Roundtable with academic and HTA experts in each country, the narrative then goes on to recommend how (pragmatic) use of the newest and most advanced evidence and analytics might facilitate consideration of the broader value of new vaccines. The recommendations included in the BRAVE narrative were developed considering the 'broader' value dimensions of vaccines, which typically fall outside traditional HTA approaches. In this sense, vaccines are an exemplary case study to argue for recognising the 'broader' value of *all* technologies showing these effects.

We restrict our focus of study to a sample of higher-income markets that have relatively advanced HTA and evidence-based decision-making processes, yet within which there is still significant variability. These markets are Belgium, Canada, France, Germany, Italy, Japan, Sweden, the UK and the US.

Future work will involve engaging with other stakeholders in vaccines and health technologies assessment in these target markets to investigate the feasibility and desirability of implementing these recommendations for broader value assessment. The final 'BRAVE narrative' will ultimately be disseminated as a science and policy paper.

1.3 Methods

The first phase of developing the 'BRAVE narrative' (section 2) involved a literature review to synthesise current evidence for the broader value generated by vaccines and recommendations for considering this value into HTA and related decision-making processes. Based on the findings of the literature review, we developed a framework depicting the various value elements to be considered in vaccines assessment.

We also reviewed published HTA guidelines (section 3), in addition to relevant grey literature, in order to understand the current 'state of play' for assessments of the value of vaccines in each of our target markets². This allowed us to identify a long list of gaps between value elements currently considered in vaccines assessments and value elements that have been recommended, and evidence provided for, in the (health economic) literature.

The second phase of developing the 'BRAVE narrative' involved convening a group of expert representatives in the value assessments of vaccines from each of our nine target markets, who have backgrounds working within HTA decision-making bodies and/or academia. The experts were invited to take part in a 2-day roundtable meeting and related engagement activities (sections 4 and 5) in order to:

- a) validate the conceptual appropriateness of the vaccines value framework (section 2), and provide insights on how the value assessment of vaccines in their country of expertise is conducted in practice, compared to the description in the published guidelines (section 3).
- b) from the long list of gaps in vaccines value assessment (identified in our literature review), prioritise the value elements for inclusion in HTA and discuss current barriers to their full recognition.
- c) develop suggestions for overcoming these barriers.

It is the feasibility and desirability of implementing these suggestions in practice which will be tested and refined in the future stages of the BRAVE initiative.

2 Why is a broader assessment of the value of vaccines needed?

2.1 The economic and policy rationale for broader assessment

From an economic perspective, optimising the allocation of scarce resources is the fundamental aim of decision makers responsible for health care budgets, and for tax revenue more widely. In many health systems, decisions about which health technologies to fund – and the level at which they are reimbursed – are informed by HTA. HTA evaluates the clinical- and/or cost-effectiveness of a health technology (York Health Economics Consortium, 2016). Traditionally, HTA considers “only benefits in terms of improved health, reduced health care costs and resource use (and improved quality of care) and short-term productivity increases to patients and their caregivers” (WHO, 2019). This decision-making approach is consistent with the 'health-maximisation' objective of health systems that is advocated by the 'extra-welfarist' school of thought. However, health

² HTA submission documents were not included in this scope, although a number of illustrative examples subsequently identified by expert representatives are discussed.

technologies like vaccines can also generate substantial ‘externalities’ (indirect effects on third parties) (Mauskopf et al., 2018). Externalities are defined as spillover benefits and/or costs of a product’s activity, beyond the effects on the immediate consumer, to other consumers, which are not accounted for in market transactions (Donaldson and Gerard, 2004). In the context of health care, these are benefits and costs to the health system, beyond those attributable to the treated patient, and to the broader society. In the value of vaccines literature, these effects have been termed ‘broader’ benefits of vaccinations, to underline that such effects fall outside the scope of traditional health technology assessments (WHO, 2019). While some of the ‘broader’ benefits have been shown to be particularly large in the case of vaccines (Mauskopf et al., 2018), consideration of ‘broader’ benefits should be applied to *all* interventions funded by the same budget, where they are relevant, in order for consistent decision making (Jit and Hutubessy, 2016; WHO, 2019). If major ‘broader’ effects of vaccines and other health technologies are neglected in HTA, their true cost-effectiveness may be underestimated. As a result, the allocation of health care resources will be sub-optimal, and the objective of allocative efficiency undermined³.

2.2 Frameworks for understanding the broader value of vaccines

In recent years, a number of frameworks have been proposed to conceptualise the full value generated by vaccinations (Bärnighausen et al., 2011, 2014; Bloom et al., 2017; Deogaonkar et al., 2012; Jit and Hutubessy, 2016). Recognising the many overlaps between these frameworks, OHE has developed a synthesising framework designed to provide a comprehensive overview of the categories of effects which might result from vaccines based on economic theory. As such, it is flexible to incorporate new dimensions as research evolves, whilst trying to minimise the risk of ‘double-counting’⁴.

We distinguish four categories of effects: (1) ‘narrow’ health effects, concerning the impact of vaccines on the health of vaccinated individuals; (2) ‘broad’ health effects, concerning the impact of vaccines on the health of the unvaccinated population; (3) health system economic effects, concerning the costs of vaccination and its cost offsets to the health care budget; and (4) societal economic effects, concerning the economic impact of vaccines outside of the health system, for example on productivity or macroeconomic growth. Within these are multiple distinct effects, or value elements that vaccines may generate. This structure aligns with the perspectives commonly adopted by HTAs, which typically consider narrow health effects and economic effects within the health system, but not necessarily effects external to these⁵. Below, we discuss the relevance and the evidence supporting the appropriateness of these effects in the case of vaccines. These effects may not necessarily be exclusive to vaccines. However, an extension of this discussion to other health technologies is considered beyond the scope of this paper.

This framework was first developed with reference to the value elements that are currently or may plausibly in the future be considered in assessments of vaccines in the UK (Brassel et al., 2020). An updated version, which includes the additional value elements of social equity and

³ This conclusion stems from the assumption that society values additional outcomes of health care in addition to health improvements. This view is more typical of ‘welfarist’ approaches and shows the tension with ‘extra welfarist’ approaches that determine the optimality of budget allocation decisions according to the achievement of specific objectives (e.g. health maximisation).

⁴ A potential problem in cost-utility analysis when some value elements, in principle, can be included both in the costs (i.e. numerator) and in the quality adjustment weight (i.e. part of the denominator) of the incremental cost-effectiveness ratio, which can lead to double-counting.

⁵ The WHO guide for standardisation of economic evaluations of immunisation programmes (WHO, 2019) notes that there is also precedent for considering health effects on caregivers, and productivity effects on patients and caregivers, in traditional HTA. We define these effects as broad for two reasons: firstly, in order to maintain a conceptual distinction between costs and effects of treating patients and externalities to this treatment; secondly, to reflect the majority approach in the markets in our sample.

macroeconomic effects, was developed for the BRAVE initiative following a review of the literature and discussed and validated at the BRAVE expert roundtable convened in May 2020. A range of opinions were offered by roundtable participants relating to the relative importance and feasibility of considering these value elements in the value assessment of vaccines. These are discussed in more detail in section 4.3 where we explore participants' reasons for prioritising certain gaps in current value assessments of vaccines. It was also noted that the relevance of value elements might vary by vaccine and pathogen. However, the majority opinion was that every value element was conceptually appropriate to consider in assessments of the value of vaccines. Where full consensus did not emerge amongst the roundtable participants, this is discussed below in reference to the relevant value element.

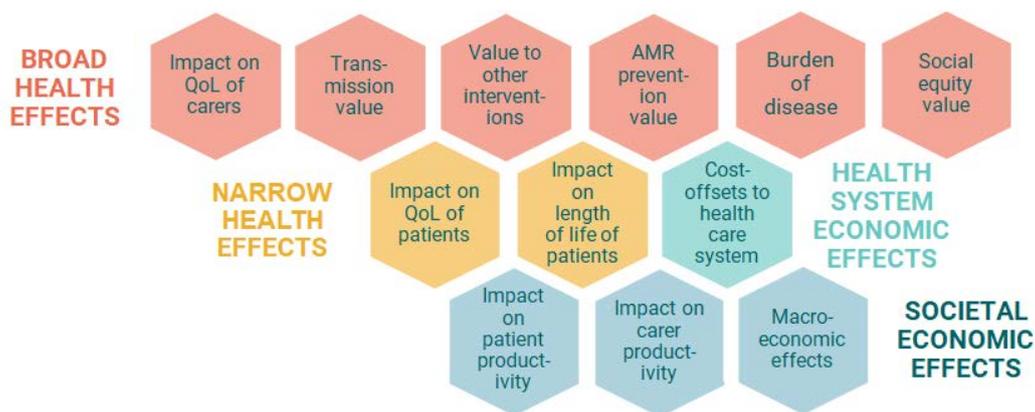


Figure 3: OHE Value Framework

Notes: QoL = Quality of Life; AMR = antimicrobial resistance.

Narrow health effects

- **Impact on length of life of patients.** Impact on life expectancy.
- **Impact on quality of life (QoL) of patients.** Impact on patients' physical, mental, emotional, and social functioning. This includes impacts related to vaccine-preventable diseases, and the complications and long-term sequelae which may arise from them. It may also include non-specific benefits relating to heterologous immune stimulation (Annemans et al., 2021).

All roundtable participants agreed that impact on QoL of patients should be incorporated into assessments of vaccines' value. There was some debate about whether measures of QoL should aim to capture 'peace of mind' or 'utility in anticipation' effects that are hypothesised to occur when quality of life of vaccinated individuals improves due to a reduction in anxiety about illness and disruptions to normal life (Beutels, Scuffham and MacIntyre, 2008; Ultsch et al., 2016). However, this debate centred around the practicability of capturing these effects, and corresponding 'disutility in anticipation' effects, as opposed to the conceptual appropriateness of measuring QoL effects comprehensively. It is therefore outlined in section 4.3.

Broad health effects

- **Impact on QoL of caregivers.** Impact on caregivers' physical, mental, emotional, and social functioning. 'Peace of mind' and 'utility in anticipation' effects are also relevant to caregivers of children (Beutels, Scuffham and MacIntyre, 2008; Drummond, Chevat and Lothgren, 2007).

However, capturing these effects involves the same practical challenges as when they apply to patients.

- **Transmission value.** Impact on disease transmission patterns and associated morbidity and mortality. Vaccines for infectious diseases can have an impact on population-wide epidemiological outcomes by providing herd immunity to unvaccinated individuals (Bärnighausen et al., 2011; Jit and Hutubessy, 2016). They may also cause changes in the average age of those infected, serotype replacement, or outbreak periodicity, with implications for morbidity and mortality (Mauskopf et al., 2018).
- **Prevention of antimicrobial resistance (AMR).** Impact on the rate of development and transmission of resistant bacterial infections, and associated morbidity and mortality. Vaccines targeting resistant bacterial infections can reduce the transmission and growth of AMR. Other vaccines can reduce the (appropriate and inappropriate) use of antibiotics for treating infections, thus slowing the development of AMR (Bärnighausen et al., 2011; Jit and Hutubessy, 2016; Sevilla et al., 2018).
- **Value to other interventions.** Impact on the cost-effectiveness of other non-vaccine interventions. It has been argued that vaccines should not be evaluated in isolation because they are complementary with – i.e. enhance the cost-effectiveness of, and have their cost-effectiveness enhanced by – related non-vaccine interventions. For example, malaria vaccines have been suggested to synergise with bed nets to produce larger health gains than the sum total of benefits from each intervention on its own (Jit and Hutubessy, 2016).

Roundtable participants expressed some reservations about the evidence that vaccines do generate value to other interventions, although it was also noted that this is endogenous to the types of evaluations used to assess vaccines effectiveness. Participants agreed that, if there is empirical evidence that vaccines generate value to other interventions, this would be conceptually appropriate to include in assessments of their value. They also noted that the definition of this value element could be broadened to include value to non-medical interventions if the objective function of the decision maker is to maximise welfare.

- **Burden of disease.** Impact on overall burden of disease to society, in terms of prevalence and severity, estimated through the total amount of associated morbidity and mortality. Society, and decision makers acting to reflect societal preferences, might value an intervention not only for its cost-effectiveness, but for its ability to treat conditions which are more common or severe (Gessner et al., 2017). In this case, an efficiency-equity trade-off may improve the allocation of resources (Nord, 1999).
- **Social equity.** Although consideration of the burden of disease captures equity concerns related to how many people suffer from a disease, and how seriously, interventions may also have different impacts across demographics which are relevant to society's preferences for equity. For example, vaccines may be particularly beneficial to disadvantaged socio-economic groups (Bloom, Fan and Sevilla, 2018).

Roundtable participants again noted that, whilst a full conceptualisation of the value of vaccines should incorporate social equity, the decision to incorporate this into HTA assessments depends on whether the objective function of the decision-maker is to maximise health, or welfare more broadly.

Health system economic effects (narrow and broad)

- **Cost offsets to health system.** While there are costs associated with any health care intervention, vaccines may also create value in the form of cost offsets. These can be narrow, in that they relate to a reduction in health care consumption amongst a vaccinated individual due to the prevention of morbidity. The long term 'peace of mind' following vaccination may also lower the rates of unnecessary clinical visits (Christensen et al., 2019). Alternatively, they may be broad, in that they relate to a reduction in health care consumption at the community level, for example through lower spending on health care for individuals protected by herd immunity or outbreak prevention savings (Bloom et al., 2017). Care should be taken to avoid double counting of cost savings achieved through the value of vaccines to other related interventions, ideally by evaluating them together.

Societal economic effects (broad)

- **Impact on patient productivity.** Impact on lost days of work and on the level of productivity at work, both for getting vaccinated and for disease or mortality avoided.

Roundtable participants noted that, whilst a full conceptualisation of the value of vaccines should incorporate productivity effects, the decision to incorporate this into HTA assessments depends on whether the objective function of the decision maker is to maximise health, or welfare more broadly. The role of the decision makers perspective in determining what is included in assessments of the value of vaccines is discussed in section 2.3.

- **Impact on caregivers' productivity.** Impact on caregivers' time spent and level of productivity at work due to caring for a patient or taking them to be vaccinated.
- **Macroeconomic effects.** Vaccinations can have macroeconomic effects in the short-run, for example by preventing pandemics and outbreaks of emerging diseases (Jit et al., 2015; Bloom, Kuhn and Prettnner, 2020). They might also have long-run macroeconomic effects. Changes to health and survival patterns, particularly amongst children, can improve lifetime productivity – for example, because of their ability to reach full cognitive potential and access more education (Bärnighausen et al., 2011; Deogaonkar et al., 2012). A reduction in infectious diseases can also stimulate foreign direct investment (Deogaonkar et al., 2012), whilst pandemics can have long-term consequences on trade patterns (Bloom, Kuhn and Prettnner, 2020).

Participants expressed some caution about assuming that all vaccines have macroeconomic effects, and the uncertainty involved in measuring these, which is discussed in section 4.3. However, consensus was reached that it was conceptually appropriate to measure macroeconomic effects, even if they were only relevant to some vaccines and pathogens. That said, it is important to be aware of the potential for double counting with effects on productivity of patients and caregivers.

Below, we present a mapping of existing frameworks onto the OHE framework, to clarify the overlaps and our exclusions.

Table 1: Matrix of the frameworks for valuing vaccinations

OHE Category	OHE Value elements	Deogaonkar et al. (2012) value elements	Barninghausen et al. (2014) value elements	Jit et al. (2015) value elements	Bloom et al. (2017) value elements
Narrow health effects	Impact on QoL of patients	Health gains	Health gains; risk reduction gains	Health gains	Health gains; risk reduction gains; co-morbidities; nosocomial infections
	Impact on length of life				
Broad health effects	Impact on QoL of carers	Health gains	Health gains	Health gains	Health gains
	Burden of disease to health system	Ecological effects	Community health externalities	Ecological effects	Health based community externalities
	Transmission value				
	AMR prevention value				
	Value to other interventions	Equity	Equity	Equity	Social equity
Social equity					
Health system economic effects	Costs-offset to health care system	Health care savings; financial sustainability	Health care cost savings	Health care cost savings; financial and programmatic synergies and sustainability	Health care cost savings
Societal economic effects	Productivity of patients	Productivity gains related to short-term outcomes; productivity gains related to long-term outcomes	Outcome-related productivity gains	Productivity gains related to health effects; productivity gains related to non-utility capabilities	Outcome related productivity gains
	Productivity of carers	Productivity gains related to care	Care-related productivity gains	Productivity gains related to care	Care-related productivity gains
	Macroeconomic effects	Productivity gains related to household behaviour	Community economic externalities Behaviour-related productivity gains	Changes to household behaviour; Public sector budget impact; Short-term macroeconomic impact; Long-term macroeconomic impact	Behaviour related output gains
N/A	N/A			Household security	

2.3 Recommendations for recognising the broader value of vaccines

Recognising the increasing academic consensus that vaccines generate value which is not typically covered within HTA and wider decision-making processes, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the WHO have recently published guidelines on the HTA of vaccines which explicitly advise how these could, and should, incorporate broader value⁶ (Mauskopf et al., 2018; WHO, 2019). In 2016, a convening of experts from the European vaccines economics community organised by the Robert Koch Institute developed a similar consensus framework intended to support the development of national guidelines in Europe (Ultsch et al., 2016). This section summarises the recommendations covered in these three publications. We note that some of these recommendations may also be valuable to improve the evaluation of other health technologies that, like vaccines, generate value outside the traditional HTA dimensions.

All three publications state that assessments of the clinical- and/or cost-effectiveness of vaccines should involve comprehensive consideration of their health effects. They also recognise that some of these effects may be challenging to incorporate into these assessments but may alternatively be considered through alternative methodologies as part of the broader decision-making process.

Narrow health effects on patients' quality and length of life are traditionally considered in HTA, but some aspects, for example effects due to adverse events, may be more challenging to consider (WHO, 2019). Nonetheless, the guidelines advise a comprehensive consideration of these effects where possible. The ISPOR guidelines, for example, recommend extending the time horizon of cost-effectiveness models to ensure that any reductions in a disease's long-term effects, such as chronic sequelae, are captured (Mauskopf et al., 2018).

Within the category of broad health effects, recommendations for the consideration of effects on carers' quality of life are more flexible. However, the WHO notes that health effects on carers' quality of life can be "substantial", and the framework developed by the European vaccines economics community advises that they should "routinely be considered in uncertainty analysis, even if input data is scarce" (WHO, 2019; Ultsch et al., 2016).

All three publications provide extensive guidance to support the consideration of transmission value within existing HTAs. The effects of vaccines on disease transmission patterns, and associated morbidity and mortality, must be estimated using modelling. Static models, which are simpler and less resource-intensive to develop, are considered an adequate means to conservatively estimate transmission value, but only when this does not risk a) underestimation of dynamics such as serotype replacement which may have negative effects on morbidity and mortality b) underestimation of the positive herd immunity to the extent that results become unfavourable or borderline favourable for vaccination (Ultsch et al., 2016; WHO, 2019). Otherwise, dynamic models are advised. When input data is a challenge, surrogate endpoints (Ultsch et al., 2016) and expert opinion (Mauskopf et al., 2018) are recommended.

The three publications also recommend that the effect of vaccines on antimicrobial resistance (AMR) should be considered when possible, although recognise that this might be challenging because it is difficult to quantify and requires stronger assumptions than modelling of transmission effects. The WHO and ISPOR guidelines state that AMR should be considered if appropriate data

⁶ These guidelines focus on economic evaluations, which are the predominant method of HTA assessment in the countries in our sample, and globally. HTA may also be carried out through evaluations clinical effectiveness only (as opposed to in tandem with economic effectiveness), although this is increasingly rare. Within our sample, only France and Germany (sometimes) carry out evaluations of clinical effectiveness.

is available, although this might be rare in practice. The European vaccines economics community advises that it should be part of uncertainty analyses wherever relevant.

For consideration of the value to other interventions, all publications state that vaccines should be assessed in combination with other interventions which could be delivered through the same platform (Ultsch et al., 2016) or could be used to provide related treatments, in order to determine their cost-effectiveness (Mauskopf et al., 2018). However, the contribution of vaccines to easing pressure on health systems, and thus facilitating more cost-effective delivery of other interventions, is not addressed.

Burden of disease and social equity are distinct from the other types of health effects generated by vaccines, in that they relate not to the efficacy with which a vaccine produces health (reduces mortality and morbidity), but the distribution of this health. The WHO guidelines recognise that such effects may be important to society and the decision makers who represent them, and describe how mortality and morbidity may be weighted in terms of the social equity they provide through extended or distributional cost-effectiveness analysis if this is an explicit goal of the decision maker. Alternatively, the guidelines encourage qualitative assessment of equity and disease burden considerations through methods such as multi-criteria decision analysis (MCDA). The ISPOR guidelines and European vaccines economics community framework similarly note that qualitative approaches, including MCDA and less formal methods, may be necessary in order to reflect the full effect of vaccines on social welfare, as well as incorporate understandings of operational feasibility, all of which should be considered as part of a broader appraisal (Ultsch et al., 2016). The ISPOR guidelines state that a qualitative approach may also be used to aid in the consideration of other health effects which are difficult to incorporate into clinical- and/or cost-effectiveness models not because of the types of outcomes they generate but due to lack of data (Mauskopf et al., 2018).

Turning to health system economic effects, all publications state that cost offsets should be considered. This includes both those 'narrow' offsets resulting from reductions in health care resource usage by patients through, for example, prevented disease sequelae (Mauskopf et al., 2018), and 'broad' offsets resulting from changes in community-level resource use such as lower spending on preventing disease outbreaks (WHO, 2019).

Within the category of economic effects, all three publications recognise that the decision of whether or not to incorporate productivity effects depends on the normative judgement of decision makers and the social preferences they represent. The majority of decision makers in our sample take the perspective of the health care payer when conducting HTA and aim to maximise the health that can be achieved for a given health care budget (which might be a budget designated solely for vaccinations, or a broader set of health care interventions). Others take a societal perspective, which incorporates productivity effects in order to maximise health relative to broader economic impact – and therefore welfare. A consequence of taking a societal perspective is that health care interventions that are less efficient at improving health may be favoured because productivity gains, for example, are higher – which might disadvantage interventions predominantly consumed by the population outside of the workforce. In the current public sector decision-making settings, this is an issue because budgets tend to be siloed, and chances are low that the savings that productivity gains accrue to other sectors will be redirected to the health care budget. On the other hand, the societal perspective arguably leads to more efficient allocation of resources in the short- and long-term (Jönsson, 2009). Whilst decision-makers are free to determine which perspective is most appropriate for their goals, all three publications advise that a societal perspective is the preferable 'base case' for HTA in general (Ultsch et al., 2016). This should include productivity effects both for patients, and their carers; effects on carers' productivity often have major effects on the results of HTAs (Ultsch et al., 2016).

The literature also stipulates that the decision as to whether to include macroeconomic effects is similarly dependent on the objectives of decision makers. However, and unlike any of the other value elements discussed above, measuring these effects is likely to require the use of different

methodologies as alternatives or complements to the clinical- or cost-effective analysis used in traditional HTA. The WHO argues that, “where an infectious disease and interventions against it can have economy-wide impacts that exceed the impacts on infected individuals, their contacts, their employers and the health care sector, a macroeconomic evaluation using a computable general equilibrium (CGE) model would be more appropriate than the traditional microeconomic approach in health care”. They also note that these situations are ‘exceptional’, for example in the case of (prevention of) pandemics (WHO, 2019). The ISPOR guidelines also recognise additional types of macroeconomic effects, which might be captured using different methods. For example, fiscal health modelling can be used to estimate “the changes over a lifetime in tax revenues and transfer costs attributable to changes in the birth cohort’s morbidity and mortality rates because of the new intervention”(Mauskopf et al., 2018). A summary of these approaches is beyond the scope of this report, but the publication notes that a broad macroeconomic perspective might be useful and that there are multiple alternative approaches which might facilitate this (Ultsch et al., 2016).

In conclusion, the two internationally recognised published guidelines on vaccines HTA, in addition to a consensus framework intended to support the development of European guidelines, argue for comprehensive consideration of the narrow and broad effect of vaccines on both health and economic outcomes – although they recognise that the choice of whether to incorporate burden of disease, social equity, productivity costs and macroeconomic effects is to be determined by the decision maker. This is consistent with the views expressed by roundtable participants, who noted that whilst a full conceptualisation of vaccines’ value includes these value elements, the decision as to whether to include them in HTA assessment of vaccines – and whether to do so through incorporation into the ICER or through qualitative methods – depends on whether the decision makers’ objective function is to maximise health or welfare.

The publications also recognise that there may be some limitations to the consideration of broad health and societal economic effects within existing HTA and broader decision-making processes, although do not provide analysis of the specific barriers which countries may face in recognising these effects, nor make recommendations to overcome these.

3 State-of-Play

3.1 What value elements are considered around the world?

In this section, we describe how HTA and broader decision-making processes in the countries in our sample consider the value elements identified in our framework, in order to understand to what extent the recommendations outlined above are being applied. This is a summary of the individual country descriptions presented in Appendix 1. This is based on a review of the published HTA methodologies in each country, in order to establish which value elements are explicitly recognised as potential components of a formal HTA. In cases where there is no formal reference to a value element, we supplement this with the findings from a rapid literature review and written feedback from recognised vaccines experts within each of the countries in our sample, to determine whether it might be informally considered within HTA and the wider decision-making process, and the frequency with which this takes place. Each country summary was reviewed and approved by at least one recognised vaccines expert. If a value element is informally considered in the assessments of the majority of vaccines to which it is relevant, this is defined as ‘commonly and informally considered’.

We consider formal recognition to be a helpful categorisation in this section because it provides the clearest indication available of the intentions of decision makers in our target markets to consider

each value element. We note however that formal recognition of a value element does not necessarily require this value element to be included in every individual HTA. Like any other value element, if it is not relevant to the vaccine under assessment it can justifiably be left out.

Effects on the length and quality of life of patients are formally considered in all countries under study. Effects on the quality of life of carers are only formally considered in the UK, and in practice are rarely considered there. In Canada effects on the quality of life of carers are commonly but informally considered. The rest of the sample is split equally between effects being uncommonly and informally considered, and not considered.

Turning to broader health effects, burden of disease is considered formally in all countries except Japan, where it is considered informally but commonly. Transmission value is also considered formally in the majority of countries, and informally but commonly in Belgium and Italy. In contrast, value to other interventions is only considered formally in France and Japan; in the majority of other countries it is not considered, although it may be considered uncommonly and informally in the UK and the US. Effects on AMR are not formally considered in any country; in half of the sample they are considered informally and uncommonly, and in half, they are not considered at all. Effects on social equity present a more mixed picture, although the majority of countries do have precedent in considering them. They are considered formally in Belgium, Canada, Germany and Sweden; informally but commonly in France, Italy and Japan; informally and uncommonly in the UK; and not considered in the US.

All countries consider costs offset to the health care system formally, except Germany which does not mandate that costs are considered but where they are considered informally but commonly. There is a mixed picture with respect to productivity effects. Consistent with a societal perspective, effects on the productivity of patients and carers are formally considered in France (although as complementary information, rather than directly incorporated in the ICER), Sweden and the US. In Canada, effects on the productivity of patients are formally considered, and effects on carers informally but commonly considered. Productivity effects of both patients and carers are also informally but commonly considered in Italy. Reflecting the occasional use of a societal perspective, productivity effects on patients and carers are informally and uncommonly considered in Germany and Japan. They are not considered in Belgium or the UK.

Table 2: Matrix of value elements considered by country

* Note that although productivity of patients and carers should be considered according to the Japanese guidelines, to date there is no evidence that this has happened except in recent discussions of vaccinations for rotavirus (productivity of carers) – source: Pfizer Japan. QoL = Quality of Life; AMR – Antimicrobial resistance.

	Belgium	Canada	France	Germany	Italy	Japan	Sweden	UK	US
Disease impact on length of life	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Disease impact on QoL of patients	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Disease impact on QoL of carers	Uncommonly and informally considered	Commonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Not considered	Uncommonly and informally considered	Formally considered	Not considered
Burden of disease	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered	Commonly and informally considered	Formally considered	Formally considered	Formally considered
Value to other interventions	Not considered	Not considered	Formally considered	Not considered	Not considered	Formally considered	Not considered	Uncommonly and informally considered	Uncommonly and informally considered
Transmission value	Commonly and informally considered	Formally considered	Formally considered	Formally considered	Commonly and informally considered	Commonly and informally considered	Formally considered	Formally considered	Formally considered
AMR prevention value	Uncommonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Uncommonly and informally considered	Not considered	Not considered	Uncommonly and informally considered	Uncommonly and informally considered
Social equity	Formally considered	Formally considered	Commonly and informally considered	Formally considered	Commonly and informally considered	Not considered	Formally considered	Uncommonly and informally considered	Not considered
Productivity of patients	Not considered	Formally considered	Formally considered	Uncommonly and informally considered	Commonly and informally considered	*	Formally considered	Not considered	Formally considered
Productivity of carers	Not considered	Commonly and informally considered	Formally considered	Uncommonly and informally considered	Commonly and informally considered	Uncommonly and informally considered	Formally considered	Not considered	Formally considered
Costs-offset to health care system	Formally considered	Formally considered	Formally considered	Commonly and informally considered	Formally considered	Formally considered	Formally considered	Formally considered	Formally considered
Macroeconomic effects	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Uncommonly and informally considered

Key:	Formally considered	Commonly and informally considered	Uncommonly and informally considered	Not considered	Unknown
------	---------------------	------------------------------------	--------------------------------------	----------------	---------

3.2 What type of evidence is available and accepted for each value element?

Impact on patients' length of life

All countries in our sample also formally consider the effect of vaccines on patients' length of life as a fundamental component of any HTA. These effects can generally be evidenced through real-world data. However, vaccines may also lead to reductions in all-cause mortality which are not typically captured, for example through immune stimulation (Annemans et al., 2020; Mina, 2017), although these effects are more relevant in low-income settings and are challenging to evidence (Donzelli, Schivalocchi and Giudicatti, 2018).

Impact on patients' quality of life

All countries in our sample formally consider the effect of vaccines on patients' quality of life as a fundamental component of any HTA. The short-term health effects of vaccinations, either therapeutic or preventative, are typically well-evidenced in clinical trials, and accepted by all countries.

Long-term disease sequelae may be more difficult to evidence, due to the time constraints of clinical trials, but can often be quantified through use of real-world evidence and modelling. Their inclusion can be important to the results of HTAs. For example, in the UK the JCVI revised its initial conclusion that a new meningococcal vaccine was not cost-effective, and instead recommended it for reimbursement, partly on the basis of inclusion of data about minor and major disease sequelae (JCVI, 2014). Evidence for the effects of sequelae is incorporated into HTA in all countries in our sample, with the exception of Japan. However, there are concerns that in some cases a lack of sensitivity in the existing tools for converting evidence on the clinical outcomes associated with sequelae into measures of quality of life may lead to underestimates (Hernandez-Villafuerte et al., 2020). In addition, some late-onset or mild sequelae, or sequelae associated with the exacerbation of underlying conditions, may be challenging to evidence (Annemans et al., 2021; Christensen et al., 2019). Recognising these deficiencies, JCVI has applied an adjustment factor of x3 to the quality of life effects of long-term sequelae in its assessments of meningococcal vaccines (Christensen et al., 2019).

Although there is increasing recognition in the academic sphere that vaccines can have important effects on patients' (and carers') quality of life by providing peace of mind, this is routinely excluded from HTA in all countries in our sample due to a lack of measurement tools and evidence (WHO, 2019; Christensen et al., 2019).

Impact on carers' quality of life

Despite the fact that inclusion of carers' quality of life can have a large impact on the results of HTA (Annemans et al., 2021), at present, the effect of vaccines on carers' quality of life is only considered formally in the UK. It may be considered informally and uncommonly in Germany, Italy and Sweden. Even in these countries, consideration of this effect is relatively recent, in general, at present evidence may be relatively scarce (Ultsch et al., 2016). However, evidence of the short-term effects on carers' quality of life could be straightforwardly integrated into clinical trials. The effects of caring for individuals with long-term sequelae may also be significant, a case study of meningitis demonstrates how these effects can be evidenced through surveys (Al-Janabi et al., 2016).

Burden of disease

The burden of disease is formally considered in all countries in our sample, although typically as an additional factor in decision making rather than integrated into estimates of clinical- or cost-effectiveness. In general, the weights given to burden of disease and processes by which it is incorporated into decision making are not systematic or transparent. The criteria by which burden of disease is defined also vary, which affects the ranking of its relative importance. In Germany, for example, vaccinations may be prioritised by disease incidence, as well as the number of severe incidents associated with a disease (mortality, number of hospitalisations, number of long-term sequelae) (STIKO, 2018). In Belgium, disease severity may be considered in reimbursement decisions (Cleemput et al., 2012). However, in general, these criteria are relatively straightforward to estimate. For example, evidence about current prevalence can be found in epidemiological surveys such as the Global Burden of Disease Study (IHME, 2019).

Value to other interventions

In our sample, only Germany formally considers the effect of vaccines' value to other interventions in the health care pathway (STIKO 2016); there is also consideration of various comparators (STIKO 2016) to understand how a vaccines' cost-effectiveness may change if it is delivered in combination with other vaccines or related interventions such as screening, e.g. cytology-based cervical cancer screening in addition to HPV vaccination (Takla et al., 2018). France, the UK and US may uncommonly and informally recognise value to other related interventions. JCVI, for example, has considered implications for cervical cancer screening related to the effect of an HPV vaccination programme (JCVI, 2018). Estimating the combined effect of multiple interventions requires more complex – and time-consuming – modelling, which may explain why it is relatively uncommon even in countries with advanced modelling capabilities.

Estimating the value of vaccinations to unrelated interventions, for example by reducing seasonal pressure, is more challenging, and there is little evidence of this type of value to other interventions being considered in practice (with the exception of AMR).

Transmission value

The effect of vaccines on transmission dynamics is the second most commonly considered externality in our sample; it is formally considered in Canada, France, Germany, Japan, Sweden, the UK and the US, and informally and commonly considered in Belgium and Italy. In Belgium, Germany and Sweden, there is precedent for estimating these effects using data from other countries, when country-specific evidence is lacking, as per ISPOR guidelines (Cleemput et al., 2012; STIKO, 2016; Personal Communication Swedish HTA experts, 2020). However, past OHE research indicates that counter to ISPOR and WHO recommendations, these effects are often estimated through static rather than dynamic models – and therefore underestimated – even in countries with high capacity for dynamic modelling (Hernandez-Villafuerte et al., May 2020). It should be recognised that there are trade-offs between the use of dynamic and static models, given that the former may be more accurate, but also more complex and time consuming.

AMR prevention value

None of the countries in our sample formally evaluate the effect of vaccines on AMR, although it is formally and uncommonly considered in Belgium, Italy, the UK and the US. Although the theoretical link between vaccines and AMR is undoubted, it is very difficult to estimate (WHO, 2019). Better quantifying this relationship is a current priority of the JCVI, which formed a working group on antibiotic resistant hospital acquired infections in 2019. There is also a significant amount of academic research ongoing in this area. Recent work by Sevilla et al. (2018) provides an outline of the methodological challenges in quantifying the effects of vaccinations on AMR, but also a roadmap for future work to overcome these challenges (UK Parliament, 2019). Atkins et al. (2018) have also published a review of current modelling approaches which have been used in economic

evaluations to understand the effect of vaccinations on AMR, as well as suggestions for overcoming their limitations.

Social equity

The effect of vaccines on social equity is formally considered in Belgium, Germany and Sweden. It is informally and commonly considered in Canada and Italy, and informally and uncommonly considered in the UK. As in the case of burden of disease, social equity is typically considered as an additional factor in decision making. In general, the weight given to social equity and processes by which it is incorporated into decision making are not systematic or transparent.

The differential effects of vaccinations across society – for example by socio-demographic group or age – cannot be determined from clinical trials but can be estimated through static models. Key inputs into these models include estimates of vaccination uptake by group; such evidence is frequently already available for vaccinations because it is needed to inform governments' uptake strategies (see for example the NICE Guidelines on vaccines uptake in the general population, National Institute for Health and Care Excellence (2019)).

Impact on patients' productivity

Effects on the productivity of patients are formally considered within HTA in Sweden and the US; informally and uncommonly considered in Italy and Japan, and informally and uncommonly considered in France and Germany. Evidence on short-term productivity losses to patients can be collected through clinical trials, although in practice is often not (Hernandez-Villafuerte et al., 2020). Evidencing long-term productivity effects on patients, for example through the prevention of sequelae, is more complex, and less evidence is available. However, it has been shown to be possible – for example using real-world evidence from a sample of sequelae sufferers which is then weighted to match the demographics of the vaccinated population, as in a meningitis case study by Scholz et al. (2019). Sevilla et al. (2020) also show how productivity effects of multiple sequelae resulting from adult pneumococcal disease can be estimated for patients (and carers).

Impact on carers' productivity

Effects of vaccines which prevent childhood diseases on the productivity of carers are, as in the case of effects on patients' productivity, formally considered within HTA in Sweden and the US; informally and uncommonly considered in Italy and Japan, and informally and uncommonly considered in France and Germany. As above, longer-term productivity costs for carers are more difficult to evidence, although are often incorporated in the case of more serious sequelae (OHE 2019).

Cost offsets to health care system

The effect of vaccines on cost offsets to the health care system is formally considered in the majority of countries in our sample: Belgium, Canada, Italy, Japan, Sweden, the UK and the US. They are informally and commonly considered in Germany, and informally and uncommonly considered in France.

Narrow cost offsets, as a result of averted disease in patients, are relatively easy to evidence, and usually considered comprehensively. Cost offsets occurring due to a vaccine's transmission value are also generally captured. However, other broad health effects – specifically on AMR and the value to other interventions – also generate cost offsets which are challenging to evidence, and therefore rarely considered (Sevilla et al., 2018; WHO, 2019).

Macroeconomic effects

At present macroeconomic effects are not formally recognised within HTA in any of the countries in our sample but may be rarely and informally considered in the US. This is in part due to the lack of evidence available about the macroeconomic effects of vaccines. Although the links between

vaccines and economic growth are strong in theory, they are complex to demonstrate empirically (Jit et al., 2015). Isolating the specific contribution of a vaccine to macroeconomic outcomes in an individual country setting is harder still, although a systematic literature review of studies evaluating the broader economic impact of vaccination in low and middle-income countries demonstrates that it is possible to capture at least some macroeconomic outcomes such as financial sustainability and lifetime productivity (Deogaonkar et al., 2012). However, work is ongoing to develop new analytical approaches which can estimate these effects more accurately, complemented by observational and experimental field studies which can build the evidence base itself.

4 Gaps in the recognition of vaccines' value

4.1 Gap analysis

Comparing the current 'state of play' in our sample countries with the international recommendations summarised in section 2.3 allows us to identify gaps between the two. Closing these gaps would achieve more consistent recognition of the full value (both 'broad' and 'narrow') generated by vaccines.

For HTA policymakers and practitioners to fully recognise any aspect of value created by vaccines, they must have

- *Evidence*: empirical high-quality data demonstrating the value accrued for each relevant value element
- *Willingness*: motivation to incorporate this evidence into HTA and broader decision-making processes
- *Ability*: technical/analytic tools and approaches to incorporate this evidence into HTA and broader decision-making processes:

As such, gaps between the current 'state of play' and full recognition can be conceptualised in terms of constraints, or 'hurdles', which can present in the form of limited/no evidence, willingness, and/or ability. Identifying these gaps and hurdles is a key step in developing a roadmap towards full recognition of the broader value of vaccines.

In order to identify gaps and hurdles, we proposed an initial longlist based on our comparison of the current 'state of play' and international recommendations. This longlist was then reviewed and added to by expert representatives in the value assessments of vaccines from each of our nine target markets, who have backgrounds working within HTA decision-making bodies and/or academia.

Below is the longlist of gaps identified by OHE and the group of expert representatives.

Table 3: long-list of gaps between state of play and recommendations

Value element	Gap
Impact on patients' quality of life	Some sequelae are not consistently considered Peace of mind is not considered
Impact on patients' length of life	Reductions in all-cause mortality may be underestimated
Impact on carers' quality of life	Effects on carers' health are not considered, or not consistently considered Peace of mind is not considered
Transmission value	Transmission value is not consistently considered in all countries Static models may underestimate effect of vaccines on transmission-related outcomes
AMR prevention value	Effects on AMR are rarely considered
Value to other interventions	Effects on related interventions are not consistently considered Effects on unrelated interventions are rarely considered
Burden of disease	Effects on burden of disease are not considered systematically
Social equity	Effects on social equity are not considered systematically
Cost offsets to health care system	'Broad' cost offsets at the community-level are not comprehensively considered
Impact on patients' productivity	Effects of long-term sequelae on productivity may be underestimated
Impact on carers' productivity	Effects of long-term sequelae on productivity may be underestimated
Macroeconomic effects	Macroeconomic effects are rarely considered

4.2 Assessment of countries' willingness and ability

We note that there is variation within our sample in the gaps identified above. There is also variation in HTA bodies' level of existing ability and willingness to address these gaps, which have implications for which constraints to recognition of value may be plausibly addressed. Relevant dimensions of this variation are described below. These descriptions are based on inputs from at least one vaccines HTA expert from each country in the sample.

The existence of specialist technical groups for assessing vaccines

In Canada, France, Germany, Sweden, the UK and the US, HTA of vaccines is carried out separately from that of other interventions, by specialist technical groups or committees. No such provision is made in Belgium, Italy and Japan. In countries where specialist technical groups exist, there is implicit willingness to consider the broader value of vaccines beyond what is captured in other HTA processes. These groups also provide greater technical capacity than is likely to exist when HTA is carried out by non-specialists.

The use of modelling to extrapolate from evidence on the value of vaccines

HTA bodies in some countries have greater ability to use models to extrapolate from quantitative data, and greater willingness to tolerate the uncertainty which is associated with this. Particular

differences exist in the willingness to use data from other countries as inputs, and the ability and willingness to estimate effects into the future on the basis of real-world evidence.

The use of qualitative decision-making processes

HTA bodies in some countries have greater willingness and ability to consider value elements for which there exists limited quantitative evidence by incorporating them into qualitative decision-making processes (as opposed to directly into an evaluation of cost- or clinical-effectiveness).

The decision-makers' perspective

HTA in Belgium and the UK is carried out from the perspective of the health care payer, meaning that productivity effects of vaccines are not considered. This creates a 'roadblock' in willingness which cannot be overcome, at least in the near future. To a lesser extent, similar 'roadblocks' may apply to the consideration of carers' health effects.

In the roadmap laid out in section 5, we highlight where the efficacy strategies to overcome constraints in ability or willingness may vary according to these dimensions.

The existence of a separate budget for vaccines

In Belgium, vaccines are funded from earmarked vaccines budgets at the regional level, and therefore do not have to 'compete' with other health technologies. In Canada and Italy, they are funded from budgets for prevention and public health interventions. Although there is no central budget for health care technologies in the US, vaccines for vulnerable children may be funded on the advice of the Advisory Committee on Immunisation Practices without the need for Congressional approval. There is no such dedicated budget in the other countries in our sample.

4.3 Prioritisation of gaps

We conducted an iterative prioritisation process with ten experts representing each of our target countries⁷. Before attending the roundtable, each expert was asked to prioritise for discussion three gaps from the longlist, using the following criteria: i) the feasibility of addressing this gap, and ii) the potential impact of including this value element on the outcomes of an HTA. Participants were also asked to state whether they felt each prioritised gap was a short- or medium-term goal, and whether the gap currently existed in the country they were representing. At the roundtable, the results of the first round of the prioritisation exercise were presented, and participants were invited to repeat the process following clarifications and discussions. On the basis of this second round, five priority gaps (no 1-5 in Table 4) were chosen for further discussion (where gaps received the same number of votes, they were ranked by prevalence). The results are shown below.

⁷ One representative from every country, except for Sweden which was represented by two experts.

Table 4: results of prioritisation exercise

Gaps (value element)	Round 1: number of votes	Round 2: number of votes	Prevalence of gap
<i>Macroeconomic effects are rarely considered (Macroeconomic effects)</i>	40%	40%	70%
<i>Transmission value is not consistently considered in all countries (Transmission value)</i>	30%	40%	10%
<i>Effects on carers' health are not considered, or not consistently considered (Carers' QoL)</i>	40%	30%	90%
<i>Effects on AMR are rarely considered (AMR prevention value)</i>	20%	30%	60%
<i>'Broad' cost offsets at the community-level are not comprehensively considered (Cost offsets to health care)</i>	20%	30%	40%
Some sequelae are not consistently considered (Patients' QoL)	20%	30%	20%
Peace of mind is not considered (Patients' QoL)	20%	20%	60%
Effects of long-term sequelae on productivity may be underestimated (Patients' productivity)	30%	20%	50%
Static models may underestimate effect of vaccines on transmission-related outcomes (Transmission value)	20%	20%	30%
Reductions in all-cause mortality may be underestimated (Patients' length of life)	10%	20%	0%
Effects of long-term sequelae of carers' productivity may be underestimated (Carers' productivity)	10%	10%	70%
Effects on burden of disease are not considered systematically (Burden of disease)	10%	10%	20%
Effects on unrelated interventions are rarely considered (Value to other interventions)	10%	0%	90%
Peace of mind is not considered (Carers' QoL)	10%	0%	80%
Effects on social equity are not considered systematically (Social equity)	10%	0%	50%
Effects on related interventions are not consistently considered (Value to other interventions)	0%	0%	50%

5 The BRAVE roadmap to change

5.1 Roundtable discussions: the process of developing the roadmap

The primary foci of the roundtable discussions were, for each of the five prioritised value elements:

- 1) to understand which hurdles are between the full recognition and the current state of play in our target markets
- 2) to develop recommendations as to how these hurdles in evidence, ability and willingness could be overcome and full recognition achieved.

At the roundtable, each of the gaps was discussed in turn. Firstly, participants were asked to locate their country on a stylised roadmap representing to show whether they had already surpassed, or had yet to overcome, hurdles in evidence, ability and willingness. This was a qualitative exercise intended to generate discussion and provide a simplified visual of countries' positions with respect to each gap. The results of the exercise are qualified with the discussion accompanying them in section 5.2, in combination with which they should be read. We recognise that in practice constraints, or 'hurdles', may have only been partially overcome, and this is reflected in the discussion.

Secondly, participants were asked to discuss how the existing hurdles (in any of the target markets) could be overcome. Prior to the roundtable, participants were asked to share suggestions for practical tools and good practice approaches which could be useful in helping HTA policymakers and practitioners to overcome the constraints identified. Discussions were initially motivated around these suggestions, but also flexible to incorporate additional suggestions which emerged in the convening process. Trade-offs involved in utilising these tools were explicitly considered, as were variations in their applicability to countries in our sample based on their ability and willingness. A list of the questions used to motivate the discussion of each gap is included in Appendix 2.

5.2 The BRAVE roadmap

A stylised representation of the BRAVE roadmap is provided in Figure 2. The roadmap should be read from left to right. The roadmap is populated by hurdles (in red) of three types: willingness (W), ability (A) and evidence (E). The five priority gaps (P symbols in green) are numbered to reflect the order in which they were discussed at the roundtable, and are positioned along the roadmap to show where they are on the road towards full recognition (indicated by the 'full recognition' award symbol). As such the hurdles that are considered overcome are on the left hand side (or behind) of the priority-gap symbol and those that remain to be crossed are on the right hand side (or ahead) of the priority-gap symbol. (It should be noted that order of the hurdles does not imply that future progress would rely on addressing them sequentially; further discussion of this is included in the priority gap specific roadmaps in section 5.2.2). The position of each priority gap reflects the average of the positions occupied by each target country with respect to that priority gap. A breakdown of the countries' positions with respect to each priority gap is detailed in Appendix 2.

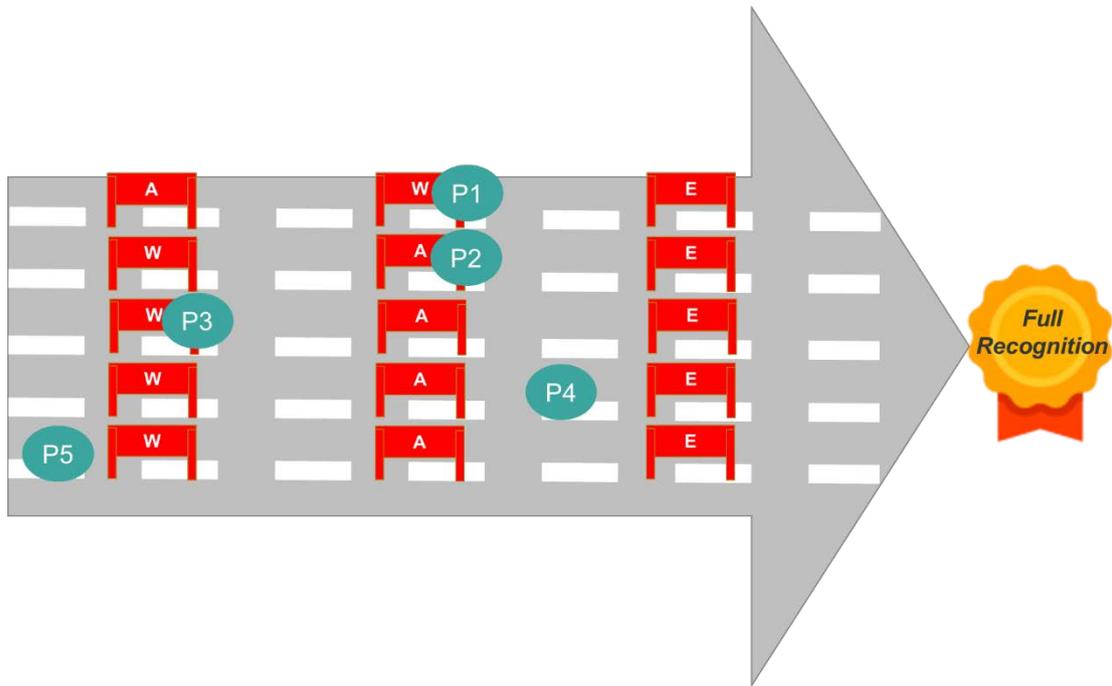


Figure 4 The BRAVE Roadmap

Notes: W = willingness; A= Ability; E = Evidence; P1 = 'Broad' cost offsets at the community level; P2 = Effects on carers' health; P3 = Transmission value; P4 = Effects on AMR; P5 = Macroeconomic effects.

- **P1: 'Broad' cost offsets at the community level are not comprehensively considered.** Overall, all countries are willing and able to consider cost offsets. However, evidence of broad cost offsets should be improved to ensure that value is consistently recognised.
- **P2: Effects on carers' health are not considered, or not consistently considered.** The ability to include effects on carers' health is overall available, but the willingness to do so has not been established in all countries, and the evidentiary standards could be improved.
- **P3: Transmission value is not consistently considered in all countries.** Willingness to model transmission value is overall available. While ability may improve through an effort to standardise methods to advanced modelling approaches, the availability of good quality evidence is currently the main hurdle.
- **P4: Effects on AMR are rarely considered.** Many countries have explicitly expressed their willingness to consider AMR effects given the related public health risks. Research on methods and evidence to quantify AMR effects is ongoing.
- **P5: Macroeconomic effects are rarely considered.** Consideration of macroeconomic effects requires rethinking many aspects of the value assessment approach of vaccines, as well as researching suitable evidence. So far, i.e. prior to the COVID-19 pandemic, and in the higher-income countries under study, these efforts have been limited by the lack of recent experience with infectious diseases having substantial macroeconomic impact.

The lack of good quality **evidence** that can be used in a specific HTA, is considered a hurdle towards the full and systematic recognition of hurdles P1 to P4. Some challenges also exist in the

ability to incorporate transmission value (P3) and effects on AMR (P4) in HTA. These are typically due to the lack of knowledge of the underlying infection dynamics and the need to improve the standards of infection surveillance. In part, an adaptation of vaccines assessment methods may also be necessary in the case of AMR, where qualitative approaches may aid decision making in the absence of quantitative evidence.

Overall, there does not appear to be a lack of **willingness** to consider P1 to P4 – although there is room for improvement for P4. While these value elements P1 to P4 relate to the broader community, rather than to the vaccinated individuals, their impact is directly relevant to the health system's perspective. Therefore, while willingness may not always be explicit in the guidelines, decision makers should be expected to recognise these value elements when robust evidence is presented. That said, more explicit willingness, or commitment, from decision makers to consider these broader value elements may provide an incentive for (further) developing the technical/analytic ability and collecting the required evidence.

The same willingness is currently not as apparent regarding inclusion of macroeconomic effects (P5). Willingness to recognise macroeconomic effects requires adopting a welfarist perspective and cost-benefit analyses to assess vaccines' value for money (Bloom, Fan and Sevilla, 2018). Therefore, differently from P1 to P4, both willingness and ability for full recognition of P5 require an overall rethinking of the HTA approach in use (likely for *all* technologies if paid for from the same budget) and alignment on what (additional) macroeconomic evidence would then be required.

5.2.1 Overall recommendations towards full recognition

In light of the challenges described above, we identified areas for change and improvement in the way that vaccines are assessed. Below, we list *recommendations* for starting to address the willingness, ability and evidence hurdles for each prioritised value element. While these recommendations were developed in consideration of the current gaps in the value assessment of vaccines, they should be tackled with the objective of improving HTA of all health technologies showing value on such broader dimensions.

For a detailed list of the individual recommendations relating to each priority gap, we refer to Appendix 2 of this report.

Willingness

- Stimulate decision makers and public awareness of the significant impact on carers' health (P2) and macroeconomic effects (P5) that vaccines could help prevent by leveraging the global experience with COVID-19, and further develop metrics and models to quantify this.
- As a complementary activity to the above, and showing that macroeconomic impact is not unique to COVID-19 vaccine-preventable disease, develop 'case studies' demonstrating the impact of other vaccine-preventable diseases on carers' health and macroeconomic effects.
- Effects on AMR are not unique to vaccines and can accrue from various health technologies such as antibiotics. In the countries where willingness is currently missing, the issue should be addressed by promoting a broader discussion around the role of HTA in rewarding the incremental impact of preventing or mitigating AMR (P3) in all technologies expected to do so.

Ability

- Short- and long-term adaptations of the approaches for assessing vaccines should be considered, when willingness to consider AMR (P4) and macroeconomic effects (P5) exists. In the short term, where the available evidence may not be perceived sufficient to quantify the

impact of vaccines on AMR and macroeconomic effects, decision makers may consider aiding resource allocation decisions with qualitative methods/judgements (e.g. multi-criteria decision marking, MCDA). In the long-term, consideration of non-health effects (e.g. macroeconomic effects) may require a permanent change of the approaches to assess vaccines, either through an adaptation of traditional methods (e.g. differential cost-effectiveness thresholds) or adoption of new ones (e.g. macroeconomic models).

Evidence

- Target the collection of evidence of broad cost offsets (P1) and carers' health (P2) based on the disease characteristics (e.g. high infectiousness) and the vaccine target population.
- More effort is needed to generate and maintain high-quality evidence of transmission value and effects on AMR. This requires i) continuation of research that aims to generate evidence on infection dynamics, to estimate the impact of vaccines on the development of herd immunity (P3) and of AMR (P4); ii) strengthening national surveillance systems of infection transmissions (P3) and of resistant infections spread (P4).
- Overall, efforts to improve the available evidence base around the impact of vaccines may also generate willingness on the decision maker's side. However, if both evidence and willingness hurdles exist, they may be most effectively tackled simultaneously, rather than sequentially. For example, an explicit statement of willingness and commitment by the decision maker to consider such evidence and an open dialogue with manufacturers of what the evidence should look like, may incentivise the development of further technical/analytic expertise where needed and the evidence collection itself.

5.2.2 Limitations

As all studies, ours has its limitations. First, rather than aiming to be fully comprehensive, the study was based on a targeted literature research and a selection of ten experts to cover nine countries. A broader stakeholder consultation was beyond the scope of this research and may provide further insight into stakeholders' opinions and suggestions for achieving broader value recognition of vaccines. While our analysis of vaccine HTA practices in the nine target markets was based on an in-depth review of HTA guidelines, and their use in practice was validated by local experts, we did not review specific vaccines assessments to validate the practical implementation of these guidelines. Second, the expert roundtable happened to fall in the first wave of the COVID-19 pandemic, as a result of which this meeting was transformed from an in-person to a virtual two-day meeting and the discussion therefore in part reflects participants experiences and thinking on the broader value of vaccines amidst a pandemic. Finally, the study results are reflective of higher income countries with relatively developed HTA-processes and cannot necessarily be generalised beyond such countries.

6 Conclusion

The BRAVE narrative outlines the rationale for consideration of the broader value of vaccines; describes the gaps which currently exist between full recognition of this broader value and recognition in the HTA processes of nine target markets; and provides concrete recommendations for addressing five of these priority gaps. For these recommendations to translate into policy change requires constructive conversation and a shared understanding of key issues. Beyond that, it requires alignment among key stakeholders and – ultimately – shared willingness, ability and data

to then make the change. Further work of the BRAVE initiative will address the willingness and ability of a broader range of stakeholders including payers, policymakers and HTA bodies.

7 References

- Al-Janabi, H., Van Exel, J., Brouwer, W., Trotter, C., Glennie, L., Hannigan, L. and Coast, J., 2016. Measuring Health Spillovers for Economic Evaluation: A Case Study in Meningitis: Health Spillovers and Economic Evaluation. *Health Economics*, 25(12), pp.1529–1544. 10.1002/hec.3259.
- Andrew J. Leidner, Harrell W. Chesson, Martin I. Meltzer, Mark L. Messonnier, Grace M. Lee, and Lisa A. Prosser, 2019. *Guidance for Health Economics Studies Presented to the Advisory Committee on Immunization Practices (ACIP), 2019 Update*. Available at: <https://www.cdc.gov/vaccines/acip/committee/downloads/Economics-Guidance-for-ACIP-2019.pdf> [Accessed 30 Jan. 2020].
- Annemans, L., Beutels, P., Bloom, D.E., De Backer, W., Ethgen, O., Luyten, J., Van Wilder, P., Willem, L. and Simoens, S., 2021. Economic Evaluation of Vaccines: Belgian Reflections on the Need for a Broader Perspective. *Value in Health*, 24(1), pp.105–111. 10.1016/j.jval.2020.09.005.
- Annemans, L., Bresse, X., Gobbo, C. and Papageorgiou, M., 2010. Health economic evaluation of a vaccine for the prevention of herpes zoster (shingles) and post-herpetic neuralgia in adults in Belgium. *Journal of Medical Economics*, 13(3), pp.537–551. 10.3111/13696998.2010.502854.
- Atkins, K.E., Lafferty, E.I., Deeny, S.R., Davies, N.G., Robotham, J.V. and Jit, M., 2018. Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance. *The Lancet Infectious Diseases*, 18(6), pp.e204–e213. 10.1016/S1473-3099(17)30478-4.
- Barnighausen, T., Bloom, D.E., Cafiero-Fonseca, E.T. and O'Brien, J.C., 2014. Valuing vaccination. *Proceedings of the National Academy of Sciences*, 111(34), pp.12313–12319. 10.1073/pnas.1400475111.
- Barnighausen, T., Bloom, D.E., Canning, D., Friedman, A., Levine, O.S., O'Brien, J., Privor-Dumm, L. and Walker, D., 2011. Rethinking the benefits and costs of childhood vaccination: The example of the Haemophilus influenzae type b vaccine☆. *Vaccine*, 29(13), pp.2371–2380. 10.1016/j.vaccine.2010.11.090.
- Belgian Health Care Knowledge Centre, 2010. *Drug reimbursement systems: international comparison and policy recommendations*. Available at: https://kce.fgov.be/sites/default/files/atoms/files/KCE_147C_Drug_reimbursement_systems_4.pdf.
- Beutels, P., Scuffham, P.A. and MacIntyre, C.R., 2008. Funding of drugs: do vaccines warrant a different approach? *The Lancet Infectious Diseases*, 8(11), pp.727–733. 10.1016/S1473-3099(08)70258-5.
- Bloom, D., Kuhn, M. and Prettnner, K., 2020. *Modern Infectious Diseases: Macroeconomic Impacts and Policy Responses*. [online] Cambridge, MA: National Bureau of Economic Research, p.w27757. 10.3386/w27757.

Bloom, D.E., Brenzel, L., Cadarette, D. and Sullivan, J., 2017. Moving beyond traditional valuation of vaccination: Needs and opportunities. *Vaccine*, 35, pp.A29–A35. 10.1016/j.vaccine.2016.12.001.

Bloom, D.E., Fan, V.Y. and Sevilla, J., 2018. The broad socioeconomic benefits of vaccination. *Science translational medicine*, 10(441).

Brassel, S., Neri, M., O'Neill, P. and Steuten, L.M., 2020. *Realising the Broader Value of Vaccines in the UK*. Available at: <https://www.ohe.org/publications/realising-broader-value-vaccines-uk>.

Centres for Disease Control and Prevention, 2019. *Charter of the Advisory Committee on Immunization Practices*. Available at: <https://www.cdc.gov/vaccines/acip/committee/acip-charter.pdf>

Centers for Disease Control and Prevention (CDC), 2011. Ten great public health achievements-- worldwide, 2001-2010. *MMWR Morb Mortal Wkly Rep.*, 60(24), pp.814–818.

Christensen, H., Al-Janabi, H., Levy, P., Postma, M.J., Bloom, D.E., Landa, P., Damm, O., Salisbury, D.M., Diez-Domingo, J., Towse, A.K., Lorgelly, P.K., Shah, K.K., Hernandez-Villafuerte, K., Smith, V., Glennie, L., Wright, C., York, L. and Farkouh, R., 2019. Economic evaluation of meningococcal vaccines: considerations for the future. *The European Journal of Health Economics*. [online] 10.1007/s10198-019-01129-z.

Deogaonkar, R., Hutubessy, R., van der Putten, I., Evers, S. and Jit, M., 2012. Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries. *BMC Public Health*, 12(1), p.878. 10.1186/1471-2458-12-878.

Department of Health and Social Care, 2018. *Cost-effectiveness methodology for vaccination programmes: Consultation on the Cost-Effectiveness Methodology for Vaccination Programmes and Procurement (CEMIPP) Report*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807856/CEMIPP_Consultation_Response_1.pdf [Accessed 30 Jan. 2020].

Donaldson, C. and Gerard, K., 1993. *Economics of Health Care Financing: The Visible Hand*. [online] London: Macmillan Education UK. 10.1007/978-1-349-22512-5.

Donzelli, A., Schivalocchi, A. and Giudicatti, G., 2018. Non-specific effects of vaccinations in high-income settings: How to address the issue? *Human Vaccines & Immunotherapeutics*, 14(12), pp.2904–2910. 10.1080/21645515.2018.1502520.

Drummond, M., Chevat, C. and Lothgren, M., 2007. Do we fully understand the economic value of vaccines? *Vaccine*, 25(32), pp.5945–5957. 10.1016/j.vaccine.2007.04.070.

Floret, D. and Deutsch, P., 2010. The French Technical Vaccination Committee (CTV). *Vaccine*, 28, pp.A42–A47. 10.1016/j.vaccine.2010.02.032.

Folkhälsomyndigheten, 2018. *Arbetsmodell för ändringar av nationella vaccinationsprogram*. Available at: <https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/a/arbetsmodell-for-andringar-av-nationella-vaccinationsprogram-/?pub=56058> [Accessed 20 Feb. 2020].

Hernandez-Villafuerte, K., Shah, K., Herdman, M. and Lorgelly, P., 2020. *Meningococcal vaccines: An international comparison of decision making processes, frameworks and methodologies. Are values missing?* Available at: [file:///C:/Users/ebell/Downloads/Consulting%20Report%20-%20Meningococcal%20Vaccines%20\(K\)%20\(2\).pdf](file:///C:/Users/ebell/Downloads/Consulting%20Report%20-%20Meningococcal%20Vaccines%20(K)%20(2).pdf).

Hoefman, R.J., van Exel, J. and Brouwer, W.B., 2017. Measuring care-related quality of life of caregivers for use in economic evaluations: CarerQoL tariffs for Australia, Germany, Sweden, UK, and US. *Pharmacoeconomics*, 35(4), pp.469–478.

IHME, 2019. *Global Burden of Disease (GBD 2019)*. [online] Institute for Health Metrics and Evaluation. Available at: <http://www.healthdata.org/gbd/2019> [Accessed 4 Aug. 2021].

IMPACT HTA, 2021. *Impact HTA | Health Technology Assessment | home*. [online] impacthta. Available at: <https://www.impact-hta.eu> [Accessed 4 Aug. 2021].

Irina Cleemput, Mattias Neyt, Stefaan Van de Sande, and Nancy Thiry, 2012. *Belgian guidelines for economic evaluations and budget impact analyses: second edition*. Available at: <https://kce.fgov.be/en/belgian-guidelines-for-economic-evaluations-and-budget-impact-analyses-second-edition> [Accessed 30 Jan. 2020].

Ismail, S.J., Langley, J.M., Harris, T.M., Warshawsky, B.F., Desai, S. and Farhang Mehr, M., 2010. Canada's National Advisory Committee on Immunization (NACI): Evidence-based decision-making on vaccines and immunization. *Vaccine*, 28, pp.A58–A63. 10.1016/j.vaccine.2010.02.035.

JCVI, 2013. *Code of Practice*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/248664/JCVI_Code_of_Practice_revision_2013_-_final.pdf [Accessed 20 Feb. 2020].

JCVI, 2014. *JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf [Accessed 21 Feb. 2020].

JCVI, 2018. *Statement on HPV vaccination*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPВ_vaccination_2018.pdf [Accessed 21 Feb. 2020].

Jit, M. and Hutubessy, R., 2016. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? *Applied Health Economics and Health Policy*, 14(3), pp.245–252. 10.1007/s40258-016-0224-7.

Jit, M., Hutubessy, R., Png, M.E., Sundaram, N., Audimulam, J., Salim, S. and Yoong, J., 2015. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. *BMC Medicine*, 13(1), p.209. 10.1186/s12916-015-0446-9.

Jönsson, B., 2009. Ten arguments for a societal perspective in the economic evaluation of medical innovations. *The European Journal of Health Economics*, 10(4), pp.357–359. 10.1007/s10198-009-0173-2.

Levine, O.S., Bloom, D.E., Cherian, T., de Quadros, C., Sow, S., Wecker, J., Duclos, P. and Greenwood, B., 2011. The future of immunisation policy, implementation, and financing. *The Lancet*, 378(9789), pp.439–448. 10.1016/S0140-6736(11)60406-6.

Maurice, J.M. and Davey, S., 2009. *State of the world's vaccines and immunization*. 3rd ed ed. Geneva: World Health Organization.

Mauskopf, J., Standaert, B., Connolly, M.P., Culyer, A.J., Garrison, L.P., Hutubessy, R., Jit, M., Pitman, R., Revill, P. and Severens, J.L., 2018. Economic Analysis of Vaccination Programs: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value in Health*, 21(10), pp.1133–1149. 10.1016/j.jval.2018.08.005.

Mina, M.J., 2017. Measles, immune suppression and vaccination: direct and indirect nonspecific vaccine benefits. *Journal of Infection*, 74, pp.S10–S17. 10.1016/S0163-4453(17)30185-8.

National Advisory Committee on Immunization (NACI), 2009. Evidence-based recommendations for immunization--methods of the National Advisory Committee on Immunization. An Advisory Committee Statement (ACS). *Canada Communicable Disease Report = Relevé Des Maladies Transmissibles Au Canada*, 35(ACS-1), pp.1–10.

National Advisory Committee on Immunization (NACI), 2019. *2019-20 National Advisory Committee on Immunization (NACI) Workplan*. Available at: <https://www.canada.ca/content/dam/hc-sc/documents/services/health/drug-health-products/2019-20%20NACI%20Workplan.pdf>.

National Institute for Health and Care Excellence, 2019. *Equality Impact Assessment: Vaccines uptake in the general population*. Available at: <https://www.nice.org.uk/guidance/GID-NG10139/documents/equality-impact-assessment>.

Outterson, K., 2014. *New Business Models for Sustainable Antibiotics*. Available at: <https://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0214SustainableAntibiotics.pdf>.

Scholz, S., Koerber, F., Meszaros, K., Fassbender, R.M., Ultsch, B., Welte, R.R. and Greiner, W., 2019. The cost-of-illness for invasive meningococcal disease caused by serogroup B *Neisseria meningitidis* (MenB) in Germany. *Vaccine*, 37(12), pp.1692–1701. 10.1016/j.vaccine.2019.01.013.

Sevilla, J.P., Bloom, D.E., Cadarette, D., Jit, M. and Lipsitch, M., 2018. Toward economic evaluation of the value of vaccines and other health technologies in addressing AMR. *Proceedings of the National Academy of Sciences*, 115(51), pp.12911–12919. 10.1073/pnas.1717161115.

Sevilla, J.P., Stawasz, A., Burnes, D., Agarwal, A., Hacibedel, B., Helvacioğlu, K., Sato, R. and Bloom, D.E., 2020. Indirect costs of adult pneumococcal disease and the productivity-based rate of return to the 13-valent pneumococcal conjugate vaccine for adults in Turkey. *Human Vaccines & Immunotherapeutics*, pp.1–14. 10.1080/21645515.2019.1708668.

Smith, J.C., 2010. The structure, role, and procedures of the U.S. Advisory Committee on Immunization Practices (ACIP). *Vaccine*, 28, pp.A68–A75. 10.1016/j.vaccine.2010.02.037.

STIKO, 2016. *Modelling methods for predicting epidemiological and health economic effects of vaccinations – Guidance for analyses to be presented to the German Standing Committee on Vaccination*. Available at: https://www.rki.de/EN/Content/infections/Vaccination/methodology/Guidance_for_analyses.pdf?__blob=publicationFile.

STIKO, 2018. *Standard Operating Procedure of the German Standing Committee on Vaccinations (STIKO) for the systematic development of vaccination recommendations, Version 3.1*. Available at: https://www.rki.de/EN/Content/infections/Vaccination/methodology/SOP.pdf?__blob=publicationFile [Accessed 30 Jan. 2020].

STIKO, 2020. *Methodology of STIKO for the development of vaccination recommendation*. Available at: https://www.rki.de/EN/Content/infections/Vaccination/methodology/methoden_node.html [Accessed 8 Jul. 2020].

St-Martin, G., Lindstrand, A., Sandbu, S. and Fischer, T.K., 2018. Selection and Interpretation of Scientific Evidence in Preparation for Policy Decisions: A Case Study Regarding Introduction of Rotavirus Vaccine Into National Immunization Programs in Sweden, Norway, Finland, and Denmark. *Frontiers in Public Health*, 6, p.131. 10.3389/fpubh.2018.00131.

Takashi Fukuda, 2019. *Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council*. Available at: https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf [Accessed 30 Jan. 2020].

Takla, A., Wiese-Posselt, M., Harder, T., Meerpohl, J.J., Röbl-Mathieu, M., Terhardt, M., van der Sande, M., Wichmann, O., Zepp, F. and Klug, S.J., 2018. Background paper for the recommendation of HPV vaccination for boys in Germany. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*, 61(9), pp.1170–1186. 10.1007/s00103-018-2791-2.

UK Parliament, 2019. *Written questions and answers - Written questions, answers and statements - UK Parliament*. [online] Available at: <https://questions-statements.parliament.uk/written-questions/detail/2019-02-14/221733> [Accessed 4 Aug. 2021].

Ultsch, B., Damm, O., Beutels, P., Bilcke, J., Brüggjenjürgen, B., Gerber-Grote, A., Greiner, W., Hanquet, G., Hutubessy, R., Jit, M., Knol, M., von Kries, R., Kuhlmann, A., Levy-Bruhl, D., Perleth, M., Postma, M., Salo, H., Siebert, U., Wasem, J. and Wichmann, O., 2016. Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community. *Pharmacoeconomics*, 34(3), pp.227–244. 10.1007/s40273-015-0335-2.

World Health Organization, 2014. *Antimicrobial Resistance: Global Report on Surveillance*. Available at: <https://apps.who.int/iris/handle/10665/112642> [Accessed 5 August 2021].

World Health Organization, 2019. *WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition*. Available at: <https://apps.who.int/iris/bitstream/handle/10665/329389/WHO-IVB-19.10-eng.pdf?ua=1> [Accessed 30 Jan. 2020].

York Health Economics Consortium, 2016. *Health Technology Assessment [online]*. Available at: <http://www.yhec.co.uk/glossary/health-technology-assessment/> [Accessed 6 Mar. 2020].

Appendix 1: Summaries of the current state of play in sample countries

These summaries are based on a combination of literature review and input from at least one vaccines expert from each country. The final descriptions were reviewed and approved by the relevant representatives.

Belgium

In Belgium, HTA informs the decision to reimburse a vaccine at the level of the communities and at the federal level. The communities are responsible for preventive care and can decide to fully reimburse and include a vaccine in the routine vaccination programme. A vaccine can be granted partial reimbursement for certain sub-groups at the federal level by the National Institute for Health and Disability Insurance (INAMI/RIZIV). At the federal level, HTAs are then appraised by an expert committee, the Committee for the Reimbursement of Medicines (CTG/CRM), which makes non-binding recommendations to the minister responsible for social affairs (Belgian Health Care Knowledge Centre, 2010). Guidelines for HTA are published by the Belgian Health Care Knowledge Centre, an independent research centre. There exist no separate guidelines for the HTA of vaccines.

The most recent HTA guidelines, updated in 2012 state that the quality and length of life of patients should be considered (Cleemput et al., 2012). No specific reference is made to carers' quality of life, transmission value, prevention of AMR, or value to other interventions. However, it is recognised that social equity and disease burden (severity) might be considered as part of HTA appraisal – although the methodology for incorporating these value elements is not described. In terms of economic effects, a health care payer's perspective is recommended in the base-case analysis, but a societal perspective which also considers the impact on patient productivity can be presented in a sensitivity analysis. Cost offsets at the patient level are considered, but macroeconomic effects are not.

In practice, it appears that HTAs may commonly but informally incorporate considerations of transmission value. Carers' quality of life and AMR may also be informally considered, albeit more rarely. Macroeconomic effects are not considered.

Canada:

In Canada, non-binding recommendations about reimbursement of vaccines are made by the National Advisory Committee on Immunisation (NACI), an advisory committee of the Public Health Agency of Canada. NACI forms expert working groups to assess individual vaccines, which develop recommendations that the advisory committee votes on (Ismail et al., 2010). There are published methods by which NACI arrives at recommendations, last updated in 2009 (National Advisory Committee on Immunization (NACI), 2009), although new guidelines and frameworks for health economic evaluation of vaccines are anticipated in 2020 (National Advisory Committee on Immunization (NACI), 2019).

NACI develops recommendations based on reviews of existing literature, as opposed to by conducting its own research. NACI allows consideration of burden of disease, direct and indirect health benefits (including transmission value), and other factors such as its impact on particular populations (social equity).

While NACI does not explicitly mention carer QoL, value to other interventions, or AMR, its use of the catch-all phrase “community or population health outcomes” suggests that NACI may already be willing to accept evidence of these value elements; carer QoL is in fact already commonly considered. Although there is no reference to costing approaches in the methods. A societal perspective is consistently applied in practice; macroeconomic effects are not considered in the decision-making process.

France

In France, the Technical Vaccination Committee (CTV) is a specialised commission of the National Authority for Health (HAS). The CTV responsible for HTA of vaccines and provides non-binding recommendations on the integration of new vaccines into the national immunisation schedule to HAS (Christensen et al., 2019). To carry out HTA, the CTV forms expert working groups to develop recommendations that the committee votes on (Floret and Deutsch, 2010).

The CTV make recommendations on a case-by-case basis, rather than in adherence to methods guidelines. Typically, the elements of primary consideration are the effect on morbidity, including quality of life (personal communication French expert), length of life, and hospitalisation (which is a burden of disease aspect); transmission value is also considered where relevant (Floret and Deutsch, 2010). There is no reference in the literature relating to the operations of the CTV to the effect of vaccines on the quality of life of carers, nor to their effects on other community health externalities including value to other interventions, AMR and social equity. However, the CTV may consider guidelines developed by the WHO as part of their considerations (Floret and Deutsch, 2010) – and therefore in theory consider these effects implicitly. The CTV are not bound to incorporate economic considerations into HTAs, but do so with increasing regularity (Floret and Deutsch, 2010; Christensen et al., 2019). These considerations typically consider productivity costs associated with providing an intervention, both for patients and carers, but may uncommonly consider productivity offsets due to averted disease. ‘Narrow’ and ‘broad’ cost offsets to the health system are also occasionally considered, although these do not extend to macroeconomic effects.

Germany

In Germany the Standing Committee on Vaccination (STIKO) is responsible for appraising vaccinations and making recommendations for reimbursement. These recommendations are not legally binding but do form the basis of the directives issued by the Federal Joint Committee (GBA) on reimbursement. Each state in Germany also has a vaccines committee which makes official recommendations at the federal level.

The methodology STIKO follows is outlined in the “Standard Operating Procedure of the German Standing Committee on Vaccinations (STIKO) for the systematic development of vaccination recommendations” (STIKO, 2018).

The Standard Operating Procedure (SOP) state that the health outcomes and mortality effects of disease on patients ought to be incorporated into appraisals; no reference is made to the impacts of disease on carers’ health outcomes, although our research suggests that they may be uncommonly and informally considered. The SOP also consider “population-relevant outcomes” in their appraisals, explicitly noting the role of value elements such as the burden of disease; herd immunity; and the impact on “health inequities”; the potential for co-administration with other vaccines is noted, although there is no discussion of a wider consideration of the value of a vaccine to other interventions nor AMR (STIKO, 2018).

STIKO does not require an evaluation of cost-effectiveness in order to make an appraisal, nor undertake this internally, but can take cost-effectiveness considerations into account if these are available (STIKO, 2018). This is also true for the federal vaccines committees. The methods suggested for health economic analyses presented to STIKO recommend that ‘narrow’ and ‘broad’ cost offsets are considered and that a societal perspective in incorporating productivity concerns (but not macroeconomic effects) is taken in the reference case, for vaccinations that prevent illnesses

which mainly affect children (in order to estimate the productivity lost due to parental caregiving) (STIKO, 2016). However, in practice a health care perspective may be more common.

Italy

The Italian Ministry of Health issues the National Vaccine Prevention Plan (PNPV), which provides vaccines guidance and sets national coverage targets. HTAs to inform the Ministry of Health's guidance are undertaken by the National Immunization Technical Committee (of the Ministry of Health), which was established in 2017 after the approval of the 2017-2019 PNPV. Academic departments in Italian universities play a key role in supporting the HTA process.

The final decisions about vaccines reimbursement are made by regional health authorities, although there is an expectation that they follow the non-binding recommendations issued in the PNPV. However, regional health authorities are also able to undertake their own HTAs taking into account local considerations.

The National Vaccine Prevention Plan (PNPV) 2017-2019 introduced new guidelines for the HTA of vaccinations. Every vaccination recommendation must be supported by a review of evidence regarding the economic impacts of vaccination from a health payer perspective, in addition to their effects on patient quality of life and mortality. Whilst the formal position is that these should be performed from perspective of society and the Italian National health System (Capri et al., 2001), in practice effects on the productivity of patients and carers are not fully considered (OHE 2020). Herd immunity and social equity can be informally considered, yet macroeconomic effects are not considered (Personal communication Italian HTA expert, May 2020).

Japan

In Japan decisions about vaccine reimbursement are made by Ministry of Health, Labour and Welfare (MHLW) on the basis of non-binding recommendations from the Health Sciences Council (HSC) Vaccines Evaluation Committee. The HSC bases its recommendations primarily on consultations performed by the Pharmaceuticals and Medical Devices Agency (PMDA), as well as HTA assessments commissioned by the Central Social Insurance Medical Council (CSIMC or Chū-i-kyō) of the MHLW and carried out by external working groups.

The CSIMC's official methodological guidelines for HTA were last updated in 2019 (Takashi Fukuda, 2019). Methodological guidelines for cost-effectiveness analysis specific to vaccines are separately implemented by the HSC, alongside these guidelines. The HSC guidelines state that HTAs should consider the effects of vaccines on patients' quality and length of life in terms of QALYs, but make no reference to effects on carers' health or broader community health externalities (Fukuda, 2019). They state that 'narrow' cost offsets should be considered, although no reference is made to 'broad' cost offsets; productivity costs may be measured if relevant but are not considered in the 'base case' (Fukuda, 2019). Disease burden and herd immunity will typically be considered for vaccine evaluations yet value to other interventions and macroeconomic effects are not considered formally or informally (Personal communication Japanese HTA expert, May 2020).

Sweden

In Sweden the Folkhälsomyndigheten (Swedish Public Health Agency) is responsible for carrying out HTA and providing recommendations to the Ministry of Health and Social Affairs on which diseases should be included in the national vaccination programme and suggesting changes to the existing programme. The Tandvård och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency, or TLV) is responsible for HTA of medical technologies in Sweden and is involved in HTAs of vaccines applying for reimbursement outside of the national vaccination programme.

For each disease under consideration, a working group is formed comprising clinical and public health experts and representatives from government and professional associations. Diseases are assessed against 13 factors (Folkhälsomyndigheten, 2018); if the disease is considered to meet all

of these, the Folkhälsomyndigheten's recommendation for inclusion is binding. If not, the Folkhälsomyndigheten may issue a non-binding recommendation, and regions are able to determine whether vaccines are provided for free or paid for out-of-pocket, and to which sub-populations (Personal communication Swedish HTA experts, May 2020).

The 13 factors considered by the Folkhälsomyndigheten primarily relate to the safety and clinical- and cost-effectiveness of the vaccine. The anticipated impact of the vaccine on burden and epidemiology of disease, as well as socio-economic impacts are considered within these criteria (in addition to the likely effect of inclusion of the disease on overall public confidence in the national vaccination programme). On the cost side, 'broad' and 'narrow' cost offsets for example to the state, municipalities and counties are to be considered (Folkhälsomyndigheten, 2018).

The effects of vaccines on the quality of life of carers may be informally and uncommonly considered, not in HTA but as part of the broader decision-making process. Effects on AMR, the cost-effectiveness of other interventions, and macroeconomic outcomes are not currently considered in a formalised way (Personal communication Swedish HTA experts, May 2020).

UK

HTAs of preventative vaccines in the UK are carried out by the Joint Committee on Vaccination and Immunisation (JCVI), which is the body responsible for providing recommendations to the UK Department of Health and Social Care on the introduction of new, and changes to existing, vaccine programmes. These recommendations are binding if JCVI concludes that the vaccine is cost-effective. A JCVI Code of Practice was published in 2013 (JCVI, 2013), although in practice there may be some flexibility in how this is applied.

According to the Code of Practice, JCVI recommends that health effects on both patients and carers are considered in HTAs; burden of disease and herd immunity are also considered where relevant (JCVI, 2013). On the cost side, 'narrow' and 'broad' cost offsets are considered, but effects on productivity are not due to the preference for a health system perspective.

The Code of Practice also recognises that some important effects and costs might not be possible to explicitly capture in the cost-effectiveness model which forms the basis of the HTA, and that these should be stated and the estimates produced by the cost-effectiveness model adjusted "commensurate with a reasonable view of the relative magnitude of the additional factors".

Examples noted in the Code of Practice include value to non-related interventions (for example due to the prevention of seasonal outbreaks of disease) and peace of mind (as part of the effect on quality of life on patients are carers). In practice, however, these are rarely considered.

Macroeconomic effects are not considered. Following a review of JCVI's methodology, the Department of Health and Social Care has prioritised future research to identify how peace of mind, AMR and social equity might be incorporated into HTA (Department of Health and Social Care, 2018). This research is part of a broader agenda to review the HTA methods used by the National Institute for Health and Care Excellence, which is currently ongoing.

US

In the US, the Advisory Committee on Immunisation Practices (ACIP) is responsible for producing recommendations to the Director of the Centres for Disease Control and Prevention (CDC) on the use of new and existing vaccinations. Although these recommendations are non-binding, once approved by the Director of the CDC they are generally regarded as national policy and are respected and adopted by most insurers (Smith, 2010). To carry out HTA, ACIP typically forms working groups to develop recommendations that the full committee votes on.

The ACIP Charter states that HTA of vaccines should consider clinical- and cost-effectiveness, safety, and burden of disease. The ACIP also publishes guidance for the health economic evaluations which it uses to assess clinical- and cost-effectiveness (Leidner et al., 2019). This guidance does not make explicit which narrow or broad health effects should be considered, only

that they should be “relevant to the perspective and policy question”. Effects on quality and length of patients, along with herd immunity, do receive specific mention. On the cost side, ‘narrow’ and ‘broad’ cost offsets and effects on productivity are considered.

In practice, there is some precedent for the consideration of AMR and the value of vaccines to other interventions. Social equity is also not considered.

Appendix 2: Roadmaps and specific recommendations by priority-gap

P1: 'BROAD' COST OFFSETS AT THE COMMUNITY LEVEL ARE NOT COMPREHENSIVELY CONSIDERED

Overall, the willingness and ability to formally include cost offsets in the HTA of vaccines is available in all but one country under study. Japan represents the exception because HTA has relatively recently been introduced and it has not been applied to vaccines yet.

Evidence of cost offsets is typically available but limited to the impact of vaccines on health systems' resources concerning vaccinated individuals. However, the quality of the evidence of broad cost offset, accruing for example from herd-immunity or preventing infection outbreaks, could be improved. We note that even narrow cost offsets, relating to long-term sequelae for example, are not always comprehensively considered, despite a willingness and ability to do so, when the evidence is considered insufficient.

The relevance of broad costs may depend on the infection type and the population targeted by a vaccine. For example, broad costs may be particularly relevant in the case of infections with high levels of transmission.

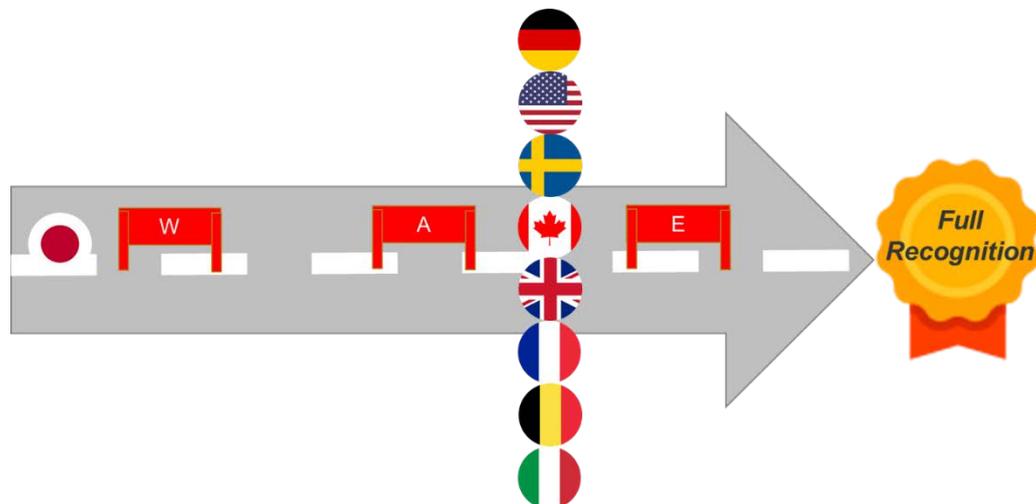


Figure 5 The roadmap towards full recognition of 'broad' cost offsets

Notes: W = willingness; A = Ability; E = Evidence

Potential strategies for overcoming the hurdles that currently prevent the recognition of 'broad' cost offsets at the community-level are listed in the table below.

Table 5: summary of recommendations for Priority Gap 1

HURDLE	WHAT	WHOM	WHEN
Willingness		<i>Assume overcome</i>	
Ability		<i>Assume overcome</i>	
Evidence	Target the collection of evidence on broad cost offsets based on disease characteristics and vaccine target population	Manufacturers	Short to medium term

P2: EFFECTS ON CARERS’ HEALTH ARE NOT CONSIDERED, OR NOT CONSISTENTLY CONSIDERED

The overall picture regarding the consistent recognition of carers’ health in vaccines assessment is mixed. Methods to measure carers’ health exist and have been used in various contexts (Hoefman, van Exel and Brouwer, 2017). Therefore, in countries with established systems for HTA, the ability hurdle may be considered overcome. Japan is currently working on defining the evidence requirements for demonstrating the effectiveness of vaccines in HTA. Hence, while at present willingness to include carers’ health may not formally exist in Japan, the international experience demonstrates that the ability to do so is available.

Willingness is currently considered a hurdle in Belgium, Italy and Germany. In these countries, the guidelines for vaccines assessment state that a perspective of analysis that focuses on the impact of vaccines on vaccinated individuals should be used. We note that in countries like the UK, willingness to consider carers’ health is stated in the guidelines but, de facto, this effect is not prioritised and rarely taken into account.

The availability of evidence represents a hurdle for all the countries included in this study. The main issue relates to the quality of the evidence that is available at the time of the HTA. This is often deemed insufficient for the formal inclusion of this effect in the vaccines’ value assessment. We note that in countries where willingness is currently lacking, improving the quality of the evidence may also increase the willingness to explicitly recognise this value element in the vaccines’ assessment guidelines. As mentioned before, initiatives to increase willingness and improve evidence may be more effective when undertaken in parallel.

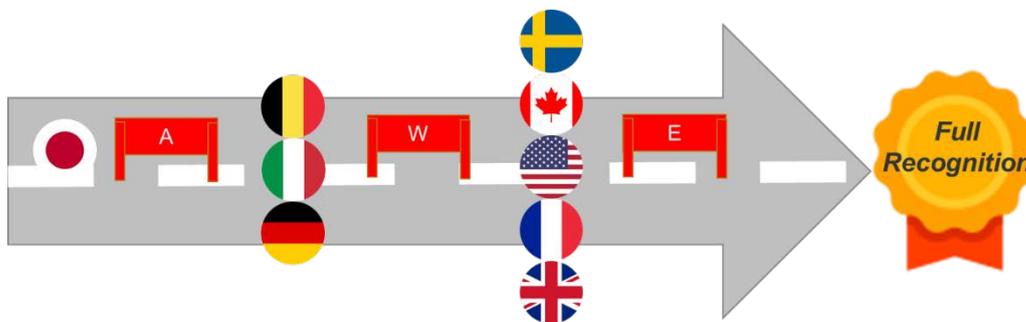


Figure 6 Roadmap towards full recognition of carers’ health

Notes: W = willingness; A = Ability; E = Evidence

Potential strategies for overcoming the hurdles that are currently preventing the recognition of effects on carers’ health are listed in the table below.

Table 6: summary of recommendations for Priority Gap 2

HURDLE	WHAT	WHOM	WHEN
<i>Assume overcome</i>			
Ability			
Willingness	Stimulate decision makers' and the public's awareness of the significant impact on carers' health that vaccines could help prevent by leveraging the global experience with COVID-19, and further develop metrics and models to quantify this	Manufacturers and decision makers	Short term
Evidence	Target the collection of evidence on carers' health based on disease characteristics and vaccine target population	Manufacturers	Medium term

P3: TRANSMISSION VALUE IS NOT CONSISTENTLY CONSIDERED IN ALL COUNTRIES

The willingness to consider transmission value is generally homogeneous among the countries of our study.

While a basic ability to model transmission value is available in all countries, the lack of consistent methods for evaluating herd effects as part of HTA represents an ability hurdle for countries like Germany and Japan. Similarly, Canada needs to consolidate its ability through an expansion of the decision makers' capacity to interpret the results of models on herd immunity. Investments in adequate ability and capacity may have been limited so far by the inconsistent quality of evidence of herd effects.

Evidence seems in fact the major hurdle towards a more consistent consideration of transmission value. In the past, evidence of health gains linked to herd immunity has been crucial for the recognition of value of meningococcal, HPV and rotavirus vaccines. However, the quality of the evidence can vary widely across diseases. For some diseases, good evidence of herd immunity may not be available at the time of the assessment. Continuous research efforts are necessary but also require time and resources to obtain. For manufacturers, the ability to recoup those in a value-based reimbursement will be critical for deciding to invest in this.

A prerequisite for obtaining good quality evidence to model herd effects are effective systems of surveillance of infection transmission. In Italy, for example, the quality of surveillance data differs widely across regions and represents a barrier.



Figure 7 Roadmap towards full recognition of transmission value
 Notes: W = willingness; A = Ability; E = Evidence

Potential strategies for overcoming the hurdles that currently prevent the recognition of transmission value are listed in the table below.

Table 7: summary of recommendations for Priority Gap 2

HURDLE	WHAT	WHOM	WHEN
Willingness	<i>Assume overcome</i>		
Ability	Develop standard frameworks for modelling transmission dynamics	Decision makers	Short term
	Improve the ability of decision makers to interpret the models on herd effects	Decision makers	Medium term
Evidence	Develop standards around the suitability of data extrapolation across countries to address the lack of evidence at the time of assessment	Decision makers and manufacturers	Short to Medium term
	Continue research on dynamics of impact of vaccines on disease transmission and immunity development	Manufacturers	Medium term
	Strengthen surveillance data collection approaches	Decision makers and surveillance bodies	Short to medium term

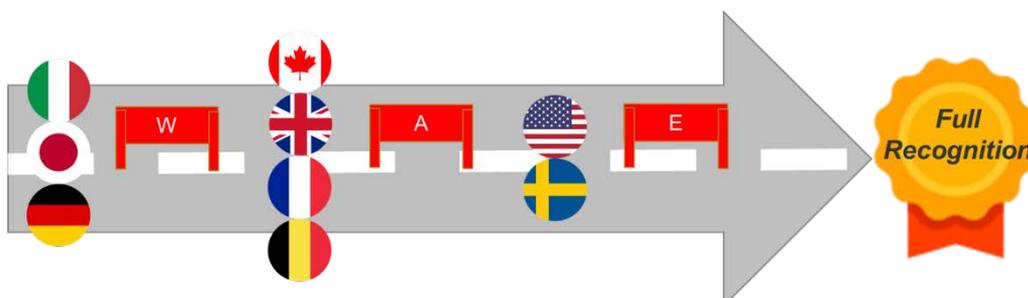
P4: EFFECTS ON AMR ARE RARELY CONSIDERED

AMR effects are not explicitly listed in vaccine assessment guidelines of Italy, Germany, Japan and Sweden. Overall, willingness may be lacking because of the currently weak evidence base and yet the need for validated and feasible approaches to modelling the effect of vaccines on AMR, which in turn may require medium to long timelines to develop.

In light of the major public health threat that AMR poses, the remaining countries under study have made their willingness to consider the effects on AMR explicit. In these countries, this willingness seems to have followed from a broader movement that emphasises the role of HTA in rewarding the value of medical technologies (e.g. antibiotics) that will help preventing and fighting AMR. However, the ability to quantify the impact of AMR and the supporting evidence to do so are currently insufficient.

Generating suitable evidence of AMR effects, requires untangling the impact of vaccines on the development of AMR from other causes. The causal impact of vaccines on AMR development is arguably better documented than that of other medical and public health interventions (Outterson, 2014; WHO, 2014). However, the existing evidence is based on many assumptions which make the true size of the impact of vaccines on AMR uncertain. An additional complication of generating suitable evidence of AMR effects for HTA purposes is that it should be country specific. In fact, AMR is a function of many country level factors including antibiotic use, type of antibiotics in use, prescription culture and demand. Research in this area and on the development of modelling approaches of AMR development and transmission is ongoing (Atkins et al., 2018).

Figure 8 Roadmap towards full recognition of effects on AMR



Notes: W = willingness; A = Ability; E = Evidence

Potential strategies for overcoming the hurdles that currently prevent the recognition of the effects on AMR are listed in the table below.

Table 8: summary of recommendations for Priority Gap 4

HURDLE	WHAT	WHOM	WHEN
Willingness	Promote broader discussion around the value of all types of medical technologies, beyond vaccines, that may prevent and/or fight AMR	Decision makers	Short term
Ability	Develop qualitative methods (e.g. MCDA) or make deliberate considerations on AMR effects until suitable evidence for modelling becomes available (high weight to QALYs generated as a result of resistance infections)	Decision makers	Short term
Evidence	Continue research on dynamics of impact of vaccines on AMR development	Manufacturers	Medium term
	Strengthen surveillance data collection approaches at country level	Decision makers and surveillance bodies	Short to medium term

P5: MACROECONOMIC EFFECTS ARE RARELY CONSIDERED

Most countries in this study need to overcome willingness, ability and evidence hurdles on the road towards recognising macroeconomic effects of vaccines. Overall, the recognition of macroeconomic effects requires a major rethinking of HTA methods that would apply to all types of medical technologies beyond vaccines.

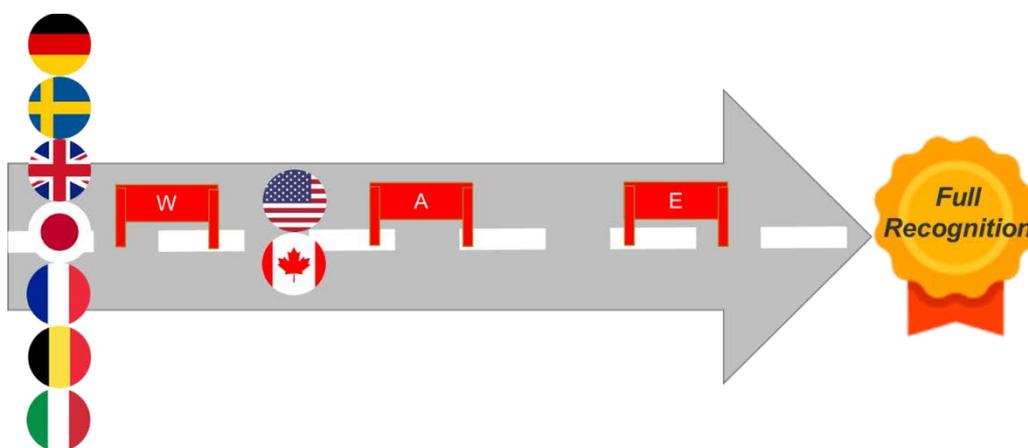
Willingness seems the primary initial hurdle to overcome when aiming to move towards the recognition of macroeconomic effects. At present, Belgium, France, Germany, Italy, Japan and the UK all use a health system perspective to carry out the HTA of medical technologies. Yet countries that take a broader societal perspective (e.g. Sweden) on HTA, and include productivity effects in the cost-effectiveness analysis (CEA), also do not currently consider macroeconomic effects.

A comprehensive consideration of macroeconomic effects may also require evolving the ability of decision makers, in terms of the type of analysis used to assess vaccines. While CEA is the most widespread analytical tool in HTA, alternative approaches (e.g. macroeconomic models) may be

more suitable to quantify macroeconomic effects. Research from an ongoing ISPOR taskforce (Mauskopf et al., 2018) and the IMPACT HTA EU project (IMPACT HTA, 2021) are examples of efforts aiming to improve the understanding of the methods for measuring macroeconomic impact. Alternative approaches that rely on adapting current CEA approaches (e.g. differential cost-effectiveness thresholds) may also be considered.

Evidence of the impact of vaccines on economic development exists but is generally focused on low-income settings. However, COVID-19 may offer an ‘opportunity’ for assessing the short- and long-term macroeconomic impact that vaccines could prevent.

Figure 9 Roadmap towards full recognition of macroeconomic effects



Notes: W = Willingness; A = Ability; E = Evidence

Potential strategies for overcoming the hurdles that currently prevent the recognition of macroeconomic effects are listed in the table below. We note that, because the recognition of macroeconomic effects is in its early stages, the strategies below will be subject to further refinement depending on future research developments, and adaptation to the setting of application:

Table 9: summary of recommendations for Priority Gap 5

HURDLE	WHAT	WHOM	WHEN
Willingness	Leverage experience with COVID-19 to show existence of significant macroeconomic effects. Macroeconomic effects from COVID-19 can also address the public opinion around vaccination scepticism. A complementary piece of work could consist in the development of ‘case studies’ showing macroeconomic effects for diseases other than COVID-19.	Decision makers and manufacturers	Medium term
	Explore opportunities for different cost-effectiveness threshold for vaccines with greater societal benefits than other medical technologies, and differential discounting for vaccines with longer-term benefits	Decision makers and manufacturers	Short to medium term

	Explore opportunities for piloting use of societal perspective, e.g. as a scenario analysis.	Decision makers and manufacturers	Short to medium term
Ability	Research in adaptation of traditional HTA methods (e.g. differential cost-effectiveness thresholds) or adoption of new ones (e.g. macroeconomic models)	Independent research	Short to medium term
Evidence	Research on short- and long-term macroeconomic impact of infectious diseases that are vaccine preventable	Independent research, public health bodies	Medium term



About us

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

OHE. For better healthcare decisions.

Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

ohe.org