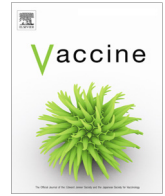




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Acceptance and application of a broad population health perspective when evaluating vaccine



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ABSTRACT

The traditional health economic analysis is limited to estimating the impact on the treated patient. As vaccines are usually aimed at preventing infectious diseases, they may be associated with additional values for the non-treated wider population. Although there are valid reasons for treating vaccines differently, and a wide support for a broader perspective in the literature (i.e., beyond the net costs and health gain related to the outcome for the vaccinated individual), it remains unclear to what extent the Health Technology Assessment (HTA) agencies accept and apply a broader perspective.

The purpose of this study is to examine and discuss what type of consequences are relevant for a health economic analysis of vaccines and which consequences are considered by HTA agencies. The study includes a strategic review of literature and HTA decisions in Sweden and other countries, online round-table discussions with stakeholders in Sweden, and a basic estimation of the value of a COVID-19 vaccination in Sweden.

The study shows that, other than herd effect, broader economic consequences for the population are generally not included in the economic evaluation of vaccines. Also, all economic consequences for the treated patient (production loss) and caregiver (health loss) are not always considered. The perspective chosen can have a major impact on the outcome of the analysis. A vaccine for COVID-19 is estimated to provide a value of €744–€956 per dose when using a societal perspective including broader consequences for the population.

Providing a complete and appropriate picture of the value of vaccination is of importance to allocate resources efficiently, to provide incentives for vaccine development, and to show the cost of delaying decisions to implement a new vaccine.

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1. Introduction

In the beginning of the 20th century, infectious diseases such as tuberculosis, cholera, and polio were a major threat to the population health in Sweden as well as in the rest of Europe and the US. Over time, these diseases have been reduced or eradicated in these parts of the world. Non-communicable diseases (NCDs) such as cancer, heart disease and diabetes have over time been viewed as a larger threat to the health of people in the Western world. However, the outbreak of the COVID-19 pandemic in 2020 shows that infectious diseases continue to pose a significant threat to public health globally.

The development of several successful vaccines during the 20th century was one of the main reasons for the reduction and eradica-

tion of infectious diseases such as measles, polio and smallpox. Today, all children in Sweden are offered vaccines against 12 infectious diseases (diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b (Hib), hepatitis B, pneumococcal disease, measles, mumps, rubella, human papillomavirus (HPV) and rotavirus [1]) which prevents pain and suffering, reduces health care resource use, and increases productivity.

Some of the first health economic studies were performed with the purpose of comparing the benefits and cost of vaccines. Even when limiting the estimation of benefits to health care cost savings and production gains, these analyses showed that many of the first vaccines generated a positive net benefit (i.e., a larger benefit than cost) [2]. The standard health economic evaluation now also considers the impact on morbidity and mortality by estimating the number of quality-adjusted life-years (QALYs) gained, a measure combining the time in life-years and health-related quality of life in a specific health state [3].

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Since treatment for NCDs has been the primary focus for health economic evaluations during the last decades, the standard health economic analysis is limited to estimating the impact on the treated patient [3]. As vaccines usually are aimed at preventing infectious diseases, they may be associated with additional health economic consequences for the non-treated wider population that are not relevant for traditional treatments aimed at NCDs (for example diabetes treatment) and therefore outside the scope of the standard health economic evaluation [4–6].

First, vaccines may, in contrast to most treatments for NCDs, impact the health of individuals in the non-vaccinated population due to less transmission and development of herd effects. These externalities are not part of the standard health economic analysis, which is usually limited to the net cost and health gain related to the outcome for the vaccinated individuals [3]. One of the main purposes of a health economic analysis is to inform decisions on what pharmaceuticals to reimburse or what medical treatments to recommend. In some countries, vaccines are assessed by special vaccines committees who may take a broader perspective than the standard one applied to pharmaceuticals for NCDs [7,8]. However, the general view is that the perspective applied by these committees are still not considering many relevant attributes [4,5,9,10].

Second, the effect of the vaccine is also highly dependent on the vaccination strategy, for example, who is vaccinated (children, adults, older adults) and when. Consequently, the effectiveness of vaccines can usually not be estimated or extrapolated based solely on clinical trial data but needs to be modelled using epidemiological data that consider different levels of transmission and types of vaccination strategies. Similarly, pharmaceuticals are used quite differently in the real world than they are in randomised controlled trials (RCTs) (e.g., RCTs seldom include people with comorbidities) so similar issues apply for medicines as well [11]. However, there are additional considerations that may be specifically relevant to vaccines as they are aimed at preventing transmission, including difficulties in determining human behaviour in advance that will impact the effectiveness, such as adherence and risk compensation (starting to involve in riskier behaviour after feeling safer after vaccination) [5].

Third, while NCDs typically have a relatively stable incidence, infectious diseases may peak with a large number of cases at the same point in time giving rise to crowding out of other health care interventions and the need for non-pharmaceutical interventions (NPIs) such as restrictions on social gatherings and lock-down. Consequently, vaccines may contribute to broader health economic consequences that are not considered in the standard health economic analysis, including improved health care capacity and macroeconomic performance.

Forth, most treatments for NCDs aim to improve the health of a currently ill individual while most vaccines aim to prevent health loss for a currently healthy individual. Consequently, the value to the vaccinated individual may not be entirely captured through the expected value (in terms of cost offsets and health gains) but may also need to include the value of risk reduction per se (“peace of mind”) [6,12,13]. Moreover, preferences for vaccination could also be highly impacted by the risk of adverse events. When evaluating vaccines, it may therefore be relevant to consider individual risk preferences (“insurance value”), which are not included in the standard health economic analysis [13].

To summarize, there are reasons for considering additional aspects of health economics consequences and ways to collect information to understand the consequences when considering vaccines. Both methods for valuation as well as scope of perspective may differ between vaccines and general pharmaceutical interventions. The need for a broader perspective when evaluating vaccines has been recognised in a European consensus guideline [14], an ISPOR Special Task Force Panel Report [5], and WHO guide-

lines [15]. The support for a broader perspective has also been argued for in several publications during recent years [4,6,16,17]. This is also in line with a general trend in support for a wider perspective in health economic evaluations. Several additional “value elements” of health-care interventions not included in the standard health economic evaluation have been proposed, including the “insurance value” of specific relevance for the vaccine context [13,18].

There are valid reasons for treating vaccines differently and a wide support for a broader perspective in the literature. Methods used for valuation and economic evidence requested by HTA organisations are important signals to inform internal project-level go/no-go decisions and the value creation process in pharmaceutical companies. If signals to firms about commercial viability of the projects they have in development do not correspond to the medical need and demand of society, there is a risk for insufficient development of new vaccines.

The purpose of this study is to examine and discuss what types of consequences are relevant for a health economic analysis of vaccines, which consequences are considered by HTA agencies and some insight into the estimated sizes of non-traditional broader population consequences by using COVID-19 vaccination as an illustrative example.

2. Methods

2.1. Literature review

A literature review was performed to identify studies of the health economic consequences of relevance for vaccine. The search was primarily performed on PubMed and Google Scholar using search terms that was iteratively defined based on the terms used in articles of relevance. Reference lists of relevant articles were checked to identify cross-references of importance (“snowballing” [19]). The search was limited to articles published in the year 2000 or later and written in English or Swedish. Peer-reviewed articles were of primary interest (including original articles, commentaries, reviews) but grey literature of relevance was also included. The health economic consequences extracted were limited to those of relevance for high-income countries. Health economic consequences were structured into a framework based on a health care perspective and a societal perspective.

A review was also performed to study the health economic consequences considered by HTA agencies in Europe and the US. The review was limited to assessments of vaccine strategies for pneumococcal vaccine in the adult population and rotavirus vaccine for children. HTA assessments for the pneumococcal strategy have been performed recently in several countries and include broader population impacts such as herd effects. HTA assessments for rotavirus vaccination can be assumed to include wider societal consequences such as health gain for caregiver and production loss. The review was also limited to HTA assessments in Sweden (Folkhälsomyndigheten, FoHM, Public Health Agency of Sweden and the Dental and Pharmaceutical Benefits Agency, TLV), UK (Joint Committee on Vaccination and Immunisation, JCVI), Germany (Standing Committee on Vaccination, STIKO), and the US (Advisory Committee on Immunization Practices, ACIP). Data was extracted from the documents on recommendations with respect to the review of health economic evidence.

2.2. Round-table discussions

Two on-line round-table discussions were performed with Swedish stakeholders to gain more insight on their views on what type of health economic consequences and evidence could be

accepted in health economic analyses of vaccine. The first round-table discussion included representatives from national stakeholders, including the FoHM, TLV, the Research-Based Pharmaceutical Industry (LIF), and a patient organization. The second round-table discussion included two representatives from the regions which are the health care providers in Sweden. Each round-table discussion started with a presentation of the health economic consequences related to vaccines as identified and structured in the literature review. Next, stakeholders were asked to provide their views on whether they considered the consequence to be of relevance for health economic analysis of vaccines or not.

Finally, a basic analysis was performed to estimate the value of COVID-19 vaccination in Sweden from a broad perspective to gain some understanding of the possible size of these wider consequences. The analysis was limited to the consequences that have been estimated in previous studies, including the value of health gain due to a reduction in COVID-19 related mortality estimated by some of the authors using widely accepted methods [20], health gain in the population due to less restrictions (non-pharmaceutical interventions, NPIs) estimated by the authors using a unique comparison of health-related quality-of-life before and after the outbreak of the pandemic in Sweden [21,22], and value of avoiding further macroeconomic losses in terms of GDP estimated by Sweden's central bank (The Riksbank) using scenario analysis [23]. Details of the methods applied (e.g., estimations of QALYs) can be found in the references included.

3. Results

3.1. Framework for perspectives and consequences related to health economic evaluation of vaccines

The review of literature on health economic consequences for vaccine resulted in 14 articles of some relevance [4–6,10,12,14,17,24–30], whereof 5 included a more structured framework for health economic consequences [4–6,17,30]. Table 1 summarizes the health economic consequences that were included in most frameworks and/or considered to be of relevance for economic evaluations of vaccine in high-income countries.

Within the health-care perspective, most articles included cost offsets in health care and health-gain for the vaccinated individual. There was also a wide consensus to include health-gains for the caregiver. Other relevant health economic consequences suggested by individual articles included secondary outcomes or complications (for example less risk of heart attack after influenza), risk compensation (more risk taking after being vaccinated), and future unrelated health-care costs (incremental costs during additional life years).

With respect to the broader, population-focused consequences within the healthcare perspective, most articles included herd effect (reduction in risk among non-vaccinated population), serotype replacement (increase of non-vaccinated serotypes), reduction in antimicrobial resistance due to less use of antimicrobials and improvement in health care capacity due to less crowding out during peak of infections.

Within the societal perspective, most articles included production gains for the patient (due to morbidity and mortality) and caregiver. Other relevant health economic consequences suggested by individual articles included presenteeism (reduced productivity while at work), formal and informal (provided by relative or friend) care, leisure, household work and transportation.

There was also a broad consensus on including preferences for risk reduction per see. Many articles also included macroeconomic impacts. An additional consequence that was not mentioned in any of the articles but has become apparent during the COVID-19 pan-

demic, includes the impact on the quality of life of the population due to the use of NPIs such as limiting social gatherings and lockdown.

3.2. The perspective used when estimating the value of vaccines against pneumococcal disease in the elderly and rotavirus in children

All HTAs reviewed included the standard core components of a health economic analysis, including cost offsets in health care and health gain for the vaccinated individual [31–38]. JCVI (UK) considered health gain for the caregiver in their analysis of CEA for rotavirus vaccination, which was found to be of similar size to the health gain for the vaccinated individual [35]. The Incremental Cost Effectiveness Ratio (ICER) was also found to be lower in the UK (£61,000–£79,900 per QALY) [35], compared to in Germany (€117,000–€143,000 per QALY) [37], where a health care perspective is also applied but excluding health gain for caregivers. Future unrelated health care cost, enablement and risk compensation were not considered in any of the analyses. Both herd immunity and serotype replacement were either discussed or formally included in the HTA analyses. Dynamic modelling was applied by the FoHM (Sweden) for rotavirus vaccination [34] and by STIKO (Germany) for pneumococcal vaccination [32]. No country included considerations of antimicrobial resistance or health care capacity even though observational studies have later found evidence to support these consequences [39–43].

Production loss was included in the CEA by ACIP (USA) [31,38], FoHM (Sweden) [33,34] that applies a societal perspective as the base case, and by STIKO (Germany) [32,37] as an alternative scenario in sensitivity analysis. JCVI (UK) [35,36] applies a health care perspective and does not include production loss. The inclusion of production loss can have a significant impact on the outcome of the analysis. For example, the ICER for rotavirus vaccination in Sweden was SEK600,000 when applying a health care perspective and dominant (cost-saving) when including the production loss [33]. The cost of leisure and transportation for extra visits to pharmacies was considered in a decision by the TLV in Sweden [44].

No country considered the value of risk reduction. However, the JCVI has stated a request for more research about the “peace of mind” effect and how that can be incorporated into the CEA [45]. Other broader population-focused consequences within the societal perspective (macroeconomic impact, quality of life in the population) were not relevant to the included analyses.

Except for the UK, all HTA agencies recommended rotavirus vaccination for children. Vaccination against pneumococcal disease is also recommended in all countries for certain adults and elderly. However, in contrast to the relatively standardized recommendations for pneumococcal conjugate vaccines (PCVs) in paediatric National Immunization Programs (NIPs), pneumococcal vaccine recommendations for adults and elderly are more diverse and differences exists in terms of age groups eligible for vaccination, medical conditions included in classification of risk groups and also for which type of pneumococcal vaccine to be used (PCV or pneumococcal polysaccharide vaccine (PPV) or combination of both).

3.3. The perspective accepted by Swedish stakeholders based on round-table discussions

The overall view expressed by all participants in the round table discussions was that it is more important to collect appropriate and valid data for the most important consequences than to aim for inclusion of all kinds of consequences. Another shared view was that the type of vaccine and illness has an important impact on what consequences should be considered relevant.

Table 1

Framework for perspectives in health economic evaluations of vaccines and the views of stakeholders in Sweden and other countries about relevant health economic consequences for health economic analysis of vaccine (white = include, black = exclude, grey = divergent opinions/ unknown).

Perspective	Health economic consequence	Stakeholders in Sweden (TLV, FoHM, regions)	Stakeholders in Germany (STIKO), the UK (JCVI) and the US (ACIP)
Healthcare	Cost-offsets in health care		
	Future unrelated health care cost		
	Health gain vaccinated individual		
	Health gain caregiver		
	Secondary outcomes/Complications	a	
	Enablement	a	
	Risk compensation (Moral hazard)	a	
	Herd immunity		
	Serotype replacement	a	
	Antimicrobial resistance	a	
	Health care capacity	a	
Societal	Production loss morbidity	b	c
	Production loss mortality	b	c
	Production loss caregiver	b	c
	Presenteeism		
	Formal caregiving		
	Informal caregiving		
	Leisure		
	Household work		
	Transportation		
	Value of risk reduction	d	
	Macroeconomic impact	d	
	Quality of life in the population	d	

TLV = Tandvårds- och läkemedelsförmånsverket (The Swedish Dental and Pharmaceutical Benefits Agency), FoHM = Folkhälsomyndigheten (Public Health Agency of Sweden), STIKO = Standing Committee on Vaccination, JCVI = Joint Committee on Vaccination and Immunisation, ACIP = Advisory Committee on Immunization Practices.

^aInclude if it is possible to collect evidence.

^bRegions: Include, TLV: Exclude, FoHM: Include production loss morbidity and production loss caregiver. Exclude production loss mortality.

^cACIP: Include, STIKO: Include in sensitivity analysis, JCVI: Exclude (health-care perspective).

^dNot necessarily a part of the economic analysis but could be part of decision-making.

With respect to the health-economic perspective, there was a consensus to include cost-offsets and health-gains for the vaccinated individual. All stakeholders considered future unrelated health care cost to be potentially relevant but did not advocate for inclusion due to ethical concerns, such as age-specific and gender issues in the human value principle. There was also a consensus to include secondary outcomes and enablement when relevant. There were divergent opinions with respect to the inclusion of health-gains for caregivers and risk compensation.

As for the broader population-focused consequences within the health-economic perspective, there was consensus to include herd effect. The other, broader consequences were considered relevant in principle, but questions were raised regarding the feasibility of deriving evidence for these consequences.

With respect to the societal perspective, there was a consensus to include formal care and transportation if expected to be of importance for the specific case. There were divergent opinions on production loss and presenteeism. Representatives of the regions argued for inclusion of all production loss while representatives of the governmental agencies argued for exclusion of all of the production loss for ethical considerations (the TLV) or parts of the production loss (due to premature mortality) for methodological reasons (friction cost approach, the FoHM). Finally, there was consensus to exclude informal care, leisure and household work.

As for other non-traditional consequences of the societal perspective (value of risk reduction, macroeconomic impact, quality

of life in population), all stakeholders agreed that these consequences were relevant to include when expected to be of importance for the specific case. However, there was no consensus on how to include them in the economic analysis and some argued for inclusion of these consequences as part of the decision-making process and not as part of the economic analysis.

3.4. Value of vaccination against COVID-19 in Sweden

By vaccinating the Swedish population against COVID-19, the society will avoid health losses due to morbidity and mortality as less individuals will be infected by COVID-19. However, the society will also avoid health and economic losses in the population as the society opens up and NPIs are lifted.

By achieving sufficient vaccination coverage, our conservative assumption is that this means we avoid around 3 months with NPIs due to the avoidance of another wave of the pandemic.

During the first wave of the pandemic (March-June 2020), there was an excess mortality of around 5,300 individuals. Assuming that the individuals who died would have had the same expected remaining lifetime and QoL as the general population, this would correspond to around 32,000 QALYs [20]. This means that around 8,000 QALYs are lost due to mortality each month (32,000/4) during a wave of the pandemic. Avoiding a new wave of three months would therefore result in a gain of around 24,000 QALYs. This may be an overestimate of the health gain due to a reduction in COVID-

19 related mortality as many of those who die have comorbidity and a lower expected remaining lifetime compared to the general population. However, in the absence of data for estimating the possible health gain due to a reduction in COVID-19 related morbidity, this overestimation is assumed to cover at least some of that gain.

The loss in QoL in the Swedish general population during the pandemic would translate to a total loss of between 21,000 (based on EQ-5D index) and 44,000 (based on VAS) QALYs per month [21]. Avoiding three months with another wave of the pandemic would consequently save 63,000–132,000 QALYs.

There is no specific point estimate for the value of a QALY. Governmental agencies in Sweden do not apply an explicit threshold value but decide what should be considered cost-effective based on disease severity and parameter uncertainty. A review of decisions by the Dental and Pharmaceutical Benefits Agency (TLV) shows that the willingness to pay (WTP) for a QALY is between €70,000 and €120,000 [46]. The WTP is higher for more severe diseases, for example cancer. A review of studies of the WTP among the general population found a mean WTP of around €74,000 [47]. However, there was a wide variation depending on the study design. We apply a WTP of €50,000 per QALY as this is often referred to as an acceptable threshold for most diseases.

Based on a WTP of \$50,000 per QALY, the value to the society of avoiding COVID-19 related mortality and morbidity would amount to around €1.2 billion (24,000 QALYs × €50,000). The value to the society of avoiding NPI-related health losses in the general population would amount to around €3.2–6.6 billion (63,000–132,000 QALYs × €50,000).

In addition to this, society will avoid economic losses. Sweden’s central bank (Riksbanken) has estimated that the loss in GDP amounts to around €2.5 billion per month during the pandemic [23]. This means that avoiding three additional months of another wave of the pandemic would result in a total gain of €7.5 billion (3 × €2.5 billion).

To summarize, vaccinating the Swedish population against COVID-19 is expected to result in a total value of €11.9–15.3 billion (see Table 2). Assuming that all adults in Sweden (8 million) are vaccinated with two doses, means that the value per dose is around €744–€956 (€11.9–15.3/16 million doses).

4. Discussion and conclusion

Health economic analyses of vaccine differs from the traditional health economic analysis in that vaccines may have an impact on non-vaccinated individuals. Herd effects, serotype replacement, and antimicrobial resistance are examples of consequences of vaccines that have an impact on non-vaccinated individuals. Macroeconomic effects and quality of life impacts for the general population following non-pharmaceutical interventions (NPIs), as well as crowding out of health care are additional examples of consequences for non-vaccinated individuals. All these consequences motivate a broader societal perspective for the assessments of vaccines that are usually not required for the assessment of traditional pharmaceutical interventions.

Value of risk reduction (peace of mind) is an example of extension of value attributes, that might be of relevance for the assessment of vaccines. Value of risk reduction (willingness to pay, WTP, for risk aversion) is currently accepted for the assessment of preventive measures in the transport sector in many countries. Valuation of traffic safety measures is in this aspect similar to valuation of vaccines. However, inclusion of additional value attributes may require additional methodological efforts and challenges in the assessment process. There is also an increasing consensus that the traditional health economic analysis may be insufficient to provide a correct picture of the value of vaccines. Many suggest to instead use WTP [12,17,29,48] as it can include the value from a population perspectives, including insurance value and fear of contagion [13].

This study is similar in scope to the project “Broad Assessment of Value of Vaccines Engagement (BRAVE)” performed by The Office of Health Economics (OHE) in the UK [9,30]. The aim of BRAVE was to investigate the willingness, ability and evidence requirements to include value elements in economic evaluation of vaccine in Belgium, Canada, France, Germany, Italy, Japan, Sweden, the UK and the US. The study reported here presents a similar value framework as BRAVE but differ in the structuring of the framework. In contrast to the BRAVE framework, this study does not include burden of disease and social equity value as these are factors considered outside of the economic evaluation as such in Sweden. Moreover, while the BRAVE framework includes “peace of mind” as a component of “impact on qol of patients”, this study includes it separately as “value of risk reduction”. There are benefits to treating this component separately. Firstly, it allows for the utility of others than the vaccinated to be included. This may be important as non-vaccinated individuals can also benefit from vaccination by a reduction in the risk of contagion and less pressure on health-care capacity. Secondly, it emphasizes the specific nature of risk reduction and the fact that it cannot be measured using standard approaches to measure quality of life. This value was highlighted in the currently debated ISPOR “value flower” as an important value (“fear of contagion”/“insurance value”) that is not included in the QALY measure, but which may be of significant value and therefore raise the question of the need for allowing for new approaches [13,49]. This study also differs from the BRAVE project by focusing on one country (Sweden), revealing that there may be divergent opinions across stakeholders within one country. Also, this study investigates the application procedures of HTA when evaluating two vaccines and exemplifies the size of broad population-based consequences that are not included in current evaluations, but which have potential to become very large as revealed by the current COVID-19 pandemic.

Among the Swedish stakeholders, the main objections to include a specific consequence included (i) lack of feasibility, e.g., no data available or not compatible with current methods for health economic evaluation, (ii) small, expected impact, or (iii) ethical reasons, e.g., future unrelated health care costs, productivity loss.

An additional opinion that was emphasized during the roundtable discussions was that the analysis should focus on giving a cor-

Table 2
Estimated value of vaccinating the Swedish population against COVID-19 assuming avoidance of 3 months with a new wave of the pandemic.

Health economic consequence	QALY gain	Monetary gain*	Based on ref.
Health gain vaccinated individual	24,000 QALYs	€1.2 billion	[20]
Macroeconomic impact		€7.5 billion	[23]
Quality of life in the population	63,000–132,000 QALYs	€3.2–6.6 billion	[21,22]
TOTAL		€11.9–15.3 billion	

* €50,000 per QALY.

rect estimate of the most important consequences instead of capturing all possible consequences. The consequences that are important vary greatly depending on the type of vaccine in question and the part of the population that is vaccinated. Vaccines against viruses that are not transmitted between humans (for example, TBE, tick-borne encephalitis) can largely be evaluated using the same methods as for pharmaceuticals because they cannot give rise to broader effects in the population in the form of, for example, herd immunity. Several vaccines against viruses that are transmitted between humans (for example, HPV vaccines) can be captured relatively well with the current health economic models for vaccines in the form of epidemiological modelling and cost-effectiveness analysis. Nevertheless, a vaccine against a virus that can cause an epidemic or pandemic (e.g., COVID-19) may require a completely different type of analysis that allows for the inclusion of risk aversion, crowding out effects, macroeconomic consequences and quality of life in the population. In general, the issue with the current health economic model is greater for vaccines against diseases that have a potential to lead to rapid and widespread spread in society.

HTA agencies in several countries accept the inclusion of herd effects and serotype replacement, and these consequences (especially herd effects) are sometimes taken into consideration by modelling the population impact of the vaccination. Other broader population-based consequences are not currently included as part of the health economic analysis. The Swedish stakeholders accept inclusion of these consequences when relevant. However, non-traditional consequences that may be difficult to incorporate into the cost effectiveness analysis (value of risk reduction, macroeconomic impact) were recommended by representatives of the FoHM to only be considered as part of decision-making and not as part of the health economic evaluation as such. This is in line with how severity of disease is currently treated. The impact of severity of disease is not formally included in the economic evaluation but is considered when determining the willingness to pay (WTP) for a QALY. A weakness of this weighting approach is that it may lead to less transparent and consistent decisions if clear criteria is lacking as raised by the Swedish National Audit Office (Riksrevisionen) [50]. Including additional consequences in this manner without any formal analysis may reinforce these weaknesses. An alternative approach is to search for a way to estimate the size of these consequences by for example using stated preference surveys and macroeconomic models. Interestingly, the JCVI, that apply a healthcare perspective, has advised research into how additional consequences, such as peace of mind, could be estimated and incorporated into the health economic analysis [45].

There was also a reluctance to formally include other broader consequences that can be estimated within a traditional cost-effectiveness analysis, but which are difficult to quantify. For example, the impact of vaccination on antimicrobial resistance, health care capacity and serotype replacement. There are suggestions on how to incorporate these consequences (antimicrobial resistance [51], health care capacity [43], serotype replacement [52]) but there is a need for more research.

When the consequence is expected to be small, it may be reasonable to exclude it from the analysis. However, this cannot always be determined until the size of the consequence has been estimated. For example, the health gain for the caregiver was found to be of a significant size in the UK analysis of rotavirus vaccination [35].

There is a variation in the acceptance across HTA agencies in different countries and across HTA agencies within Sweden with respect to what consequences to include in the health economic analysis. The main difference is regarding the use of production loss. Sweden is among the countries using a societal perspective. However, the Swedish agencies have interpreted the societal per-

spective differently and do not incorporate value of production loss in the same way. FoHM demand estimates of the production loss by the friction cost method (excluding production loss due to premature mortality) and the TLV allow the applying company to include production loss, by the human capital method, but do rarely include the value in their decision-making process for ethical reasons.

The Swedish National Audit Office (Riksrevisionen) recently reviewed the procedures of the TLV and requested a clarification regarding the use of the societal perspective as it is currently inconsistent with the economic view and the Swedish law for pharmaceutical benefits since production loss is not included [50]. Adding to this inconsistency, is the fact that all stakeholders agreed to include macroeconomic performance when relevant even if they do not consider production loss to be a relevant component. The ethical objection to including production loss, i.e., that it makes interventions aimed at the population in the workforce seem more cost-effective, would also apply to macroeconomic performance.

There are also differences across countries with respect to the acceptance of production loss. While the US committee (ACIP) accepts production loss, the Germany committee (STIKO) only includes it in sensitivity analysis while the UK committee (JCVI) does not include production loss at all. One reason that could explain the different approaches of different agencies across countries as well as within countries is that the mandate differs. The committees in Europe have a mandate to inform decision-makers and although their recommendations are generally not binding, they usually form the basis for the decisions. The committee in US, however, does not have the same mandate which may explain some of the differences in approach [53].

Providing a complete and appropriate picture of the value of vaccination is also of importance to show the cost of delaying decisions to introduce a new vaccine. There are several examples of long time to implementation in Sweden. First PCV for children was authorized for use in the EU in 2001 [54], but it wasn't included until 2009 in the Swedish paediatric NIP [55]. First HPV vaccine had European approval in 2006 [56] but wasn't included in the NIP for adolescent girls until 2010, and in 2020 also for boys [55]. Vaccine against rotavirus was similarly approved in 2006 [57] but not included in the paediatric NIP until 2019 [55].

It is important that the value of vaccines is understood and evaluated from a societal perspective as it is not only the vaccinated individual that experience a reduction in the risk of being sick or having a shorter life, but the whole society that gains. This has not least been shown by the ongoing COVID-19 pandemic. Payers and HTA agencies, as agents of their plan participants or taxpayers, should aim to send clear signals to their suppliers about what they value.

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