HTA's Critical Role in the (Early) Assessment of (potential) Vaccines to prevent the spread of COVID-19 globally

Negotiations between vaccine developers and countries' authorities, often represented by supranational bodies like the European Commission and the World Health Organization, to secure procurement and distribute vaccines for COVID-19 have been ongoing throughout the pandemic. This illustrates how both private and public entities are working collaboratively in earnest to prepare for the situation when one or more safe and efficacious vaccines become available. In the autumn of 2020, more than 100 different vaccines for COVID-19 are under development. A limited number of them have reached the stage of clinical trials (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), with involvement of various pharmaceutical companies and public parties in the Americas, Europe and Asia-Oceania. Globally, to ensure evidence-based decision making is at the forefront in ensuring public health and safety, HTA needs to adapt to this newly emerging situation. The HTA community needs to secure capacities and expertise to adequately manage and overcome the COVID-19 pandemic emergency state as well as be prepared for new potentially (dis)similar emergencies. In order to ensure affordable, equitable and sustainable distribution globally, all aspects of a vaccines development, registration and regulation - inclusive HTA issues such as legal, environmental and socio-economic impact evaluations - should be paid attention to, proactively. On the short term, in crises situations like the current one, the right balance between urgency and acceptable evidence from investigations into safety and efficacy has to be found. On the longer term, next issues can be addressed, inclusive cost-effectiveness and real-world data on effectiveness and safety.

Vaccines' market access processes are characterized first by the development of recommendations, performed by National Immunization Technical Advisory Groups (NITAGs), i.e. committees like Joint Committee Vaccination & Immunization (JCVI), Advisory Committee on Immunization Practices (ACIP) and Japan Committee Vaccines (JCV), often as part of the country's HTA process, and are followed by the executive policy-decision, which includes reimbursement, funding and implementation, sometimes supported by other national HTA bodies and performed by respective Ministries of Health. However, mandates of NITAGs related to the role of HTA bodies as well as factors influencing final decisions on vaccination are not always straightforward. Decision-making around prevention and vaccines in particular is not only guided by technical aspects (e.g. effective, save, economic), but also relies on political and societal considerations (e.g. impact, demand, attitudes, ethical considerations) often introducing added complexity to inform decisions and successful implementation.

The urgent need for a swift and effective *holistic* HTA of potential new COVID-19 vaccines is unprecedented. This implies that HTA-institutions have to be prepared for very early HTAs and to support potential emergency use of vaccines. This would require expediting the whole chain in development, registration, financing, production, assessments, upscaling and logistics. As parts of early HTA and emergency use provision of vaccines, which differ by country yet are consistent in involving high-priority investigational products, a process can be installed of continuously developing evidence on safety, efficacy and cost-effectiveness until final licensure in circumstances of an evolving and partly managed pandemic.

This position statement aims to list the current position for embarking on HTA of COVID-19 vaccines, allowing NITAGs/HTA-authorities to start early HTAs as soon as possible. The statement has been designed by the management of the Interest Group (IG) on Public Health of HTAi on behalf of the IG as well as the broader Society as a whole. Below, we will address the relevant issues systematically, structured as follows: a brief overview of the vaccines, the further role of HTA, inclusive roles on the short- and long-term, cost-effectiveness, affordability and sustainability.

COVID-19 Vaccines Development

NITAGs' estimates are to have the first vaccines ready for market entry as early as the end of 2020 and the more pessimistic scenario considering availability during the year 2021. Notably, typical vaccine development and testing takes 10-20 years, or more (an HIV-vaccine is not available), and in that respect also the pessimistic view can still be considered highly optimistic. Already in early stages, we may expect that more than one vaccine will be available. In later stages, this might be even more the case, as applies for many other vaccines, but likely even more for COVID-19.

Specific characteristics may differ in terms of technology, indication, relative efficacy, effectiveness and safety:

- Various platforms for vaccine design are applied
- Age for indication: elderly, adults, children and infants
- Dosage: the number of doses required (1, 2, boosters)
- Protection against (serious) disease and/or transmission
- Duration of protection
- Concomitant use with other vaccines such as influenza and pneumococcal vaccines
- The potential and the need to vaccinate seropositive individuals pose specific aspect of interest for COVID-19 vaccines, and
- Other factors, currently undetermined, may play their role

For the HTA of COVID-19 vaccines, the pandemic stage has to be differentiated from the later stage. Below, we will detail both stages, for example, concerning the pricing, real-world evidence, role of cost-effectiveness and knowledge on transmission impacts. Pandemic emergency use of vaccines is likely already in the pre-registration phase, requiring continuous collection of safety and efficacy data throughout the development phases and beyond licensure too. Given the unprecedented strain on the timeline of development during the pandemic stage, safety might be a concern for the broader public, potentially endangering high coverage to achieve adequate protective levels and endangering general trust in vaccination programs (reflecting a general worry around introducing new vaccines). On the other hand, with the knowledge on the devastating impact of the epidemic, willingness of the general population to get vaccinated may be expected to increase, which may also apply to this year's uptake of the influenza vaccine. Additionally, it can be expected that minimum levels of protective efficacy will be required for registration and use, as vaccines with too low efficacies may have detrimental effects as other preventive measures may be relaxed at individual levels in vaccinees. In addition to the general assessment of the comparison of (heterogenous) intervention strategies, HTA could also play a role here in both communication of the value propositions for the general public.

Affordability, Sustainability & Distributional Effects

Pricing of drugs and vaccines is based on various criteria: value-based pricing, cost-based pricing as well as sheer negotiation with authorities. Lack of transparency in financing of pharmaceutical R&D often hampers insights allowing cost-based pricing as the prominent principle. During the pandemic stage, pricing seems to follow from negotiations between companies and authorities, with tendencies to allow prices potentially below value-based levels from the industries' side and willingness to cover universal mass vaccination from the governments' side. Potential value-based pricing seems potentially an issue for later stages with possible post-pandemic seasonal vaccination and provision of booster doses.

With potential affordability issues for economies with low incomes as well as those with high incomes, value-based pricing does not seem an option during the pandemic period. The most likely pricing for the coming periods seems negotiation/co-operation between public and private parties, and competitive pressure from the availability of multiple vaccines with different qualifications. For example, in the US, Operation Warp Speed is initiated as a public–private partnership, initiated by the Federal Government of the United States, to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. In Europe, EU health ministers have given the go-ahead for the European Commission to negotiate COVID-19 vaccines contracts on behalf of all 27 member states, approving the use of a €2.3 billion (US$2.6 billion) emergency fund for down payments. Tiered pricing between HICs, MICs and LICs can be expected to enhance equity, with an important role for the Bill & Melinda Gates Foundation, WHO (for example, COVAX initiative) and GAVI (for example, the AMC92 initiative), enhancing a – what may be considered – fair distribution of available stocks of vaccines over the globe.

If through tiered and affordable pricing, support, upscaled production, many countries can access the COVID-19 vaccines, they have to embark on integrating the vaccine into already stocked National Immunization Programs or by putting more stress on the currently overwhelmed health system and -personnel. One strategy could be to consider alignment with influenza and pneumococcal vaccination for older adults. In addition, an alternative route of administration, such as a respiratory mucosal vaccine strategy, could aid in the provision of an early and effective response to SARS-CoV-2, possibly essential in the high-risk and elderly population. In general, a silver lining emerges the potential of COVID-19 to enhance the overall position of prevention in health-care systems and increasing such investments can strengthen health-care systems' sustainability overall. In particular, broader access to vaccines can be enhanced through reduced vaccine hesitancy due to generally conceived relevance of the COVID-19 vaccine. For example, in the slipstream of COVID-19 vaccines likely coverage of influenza and pneumococcal vaccines may increase.

Finally, in various countries societal and legal issues may emerge, concerning, for example, voluntary versus obligatory vaccination. For example, health-care workers will likely be prioritized as soon as limited stocks of vaccines become available, and pressure to be vaccinated might occur, inclusive the need for a positive vaccination status required for employment. Also, with initially limited numbers of COVID-19 vaccines being available, equity issues may arise, with equal access for all as a reasonable principle but prioritization of specific groups (elderly, health-care workers…) likely unavoidable. Last but not least displacement effects should be considered; i.e. while the attention to COVID-19 vaccines is great, stakeholders also should be aware that under a constrained health care budget, cost increases in preventive/vaccines' budgets may displace funds from existing and other -potentially curative - new healthcare technologies. Yet, in this respect, prevention/vaccines should be seen as investment rather than cost.

Fostering HTA Collaborations

Generally, HTA-evaluation, procuring, prioritization and acquisition are only started around the time drugs/vaccines are registered. Also, only too often governments and industry confront each other with separate individual goals, potentially arguing on various aspects such as prices, tender criteria and price/volume/quality agreements. Additionally, often the type of evidence on vaccines is immunologically driven - rather than based on hard clinical endpoints – which differs from what HTA-authorities are used to in assessing curative drugs. Coordinated and cooperative early HTA is needed as illustrated by current public-private initiatives trying to overcome such differences and challenges in a much earlier stage than usually. Such public-private co-operation allows to anticipate already in an early stage on upscaling and securing production to levels required to serve (relevant parts) of the global population.

Despite potential early upscaling, not enough doses will immediately be available to vaccinate all and prioritization of at-risk populations or local areas will be important in the initial stages. An important, ethically-challenging choice in this respect that NITAGs are immediately faced with is whether to target COVID-19 health impact (comparable to older adults and chronic-diseased patients corresponding with influenza vaccination) or to target impact on transmission (comparable to paediatric influenza vaccination) to also target the indirect effect of vaccination, i.e., herd immunity. As currently not enough is understood concerning transmission and acquired immunity, presently the only realistic priority seems targeting groups at highest risk for infection (e.g., healthcare workers), and individuals at high-risk for severe diseases (e.g., older adults). Under constraints of supply, further prioritization of local areas of highest transmission may be needed to optimize protection of the population in areas with elevated activity. Obviously, this may change if more information on transmission becomes available and vaccines' characteristics become clear.

Cooperation between vaccine-specific NITAGs between each other as well as with other HTA-bodies, such as those involving drug reimbursements, has to be started already in early stages of vaccine development to be well prepared. Such cooperation between NITAGs and other HTA-bodies will be essential to ensure that: (i) shifting responsibilities causing delays are prevented due to shared involved in the assessment of vaccines of both organisations, (ii) both curative/preventive drugs as well as vaccines (as assessed versus alternative strategies such as social distancing, and COVID-19 (rapid) tests will be given priority to control the COVID-19 pandemic, (iii) all relevant information is identified, registered, and shared in a situation of lacking information infrastructures, scarce availability, high uncertainty and potentially relevant (yet) unpublished information, and (iv) the HTA activities will be (partially) centralized by international organizations to establish a rapid and effective country specific, locally conducted HTA process, especially in countries lacking those HTA resources. In Europe, obviously, we can build on existing initiatives as EUNetHTA and BeNeLuxAI.

Need for Early, Adaptive and Living HTA

Likely, HTA's role will transition from the early stages of vaccines' availability to later stages. Notably, on the short term, it is expected that regulators and payers will mainly focus on the clinical profile of the vaccine candidates, as well as on the supply capacities, rather than on the economic profile. Obviously, safety poses a core area and fast control of the pandemic in addition to keeping up the trust in immunizations programs in general. HTA bodies usually have additional requirements in term of clinical data when looking at the reimbursement submission, both concerning safety as well as efficacy. This type of clinical data might go beyond that required for market authorization. In the case of COVID-19, some stakeholder plea for more flexibility in terms of efficacy requirements. Real-world

data will further evidence efficacy and effectiveness, safety, budget impact and vaccine specifics. Concerning the latter, in particular vaccines will come on the market with evidence on efficacy on (serious) disease rather than on transmission. There is a need for a living and adaptive HTA with strong post-marketing surveillance on all mentioned aspects, inclusive transmission studies related to the introduced vaccines. In the first year of use, focus may be intensified on the safety aspect given the relatively short prior-use development period as compared to other vaccines. Yet, underlying mechanisms for safety can be extrapolated from experiences with previous vaccines for various platforms applied.

It is unlikely that a cost-effectiveness analysis in the assessment of a potential vaccine would be a priority in the early assessments. The main priority will be to protect those groups at high risk of transmission (health-care workers) and at high risk of disease (older adults, comorbid individuals etcetera), without question on economic efficiency. In a living HTA-environment, on the longer term, cost-effectiveness could play a role in future vaccine decision making. Notably, similarities may emerge with other vaccines for respiratory conditions, such as influenza, pertussis and pneumococcal infections. For these conditions, typically vaccinations of broad groups of, for example, children (influenza and pneumococcal infections) and adolescents (pertussis) to control transmissions come with major cost-effectiveness considerations. On the long term, cost-effectiveness will play a role in further future vaccine decision making for COVID-19 (also see below).

The case of COVID-19 has clearly shown that next to the health-care sector, broad impact on other sectors have emerged, making an intersectoral or multisectoral health economic analysis of crucial importance. Inclusion of these broader aspects require alternative economic methods (e.g. constraint optimization, fiscal modelling and inclusion of macro-economic assessments). Also, broadening the scope to potential future non-COVID-19 threats (e.g. viral and bacterial infections) may require other tools and methods in order to inform public investment decisions (e.g. real options methods). Also, JCVI recently stated that a full economic analysis of the continued lockdown should be taken into account rather than the usual more confined health economic analysis, requiring new methods including broader economic impacts and posing corresponding academic challenges.

Cost-effectiveness Considerations

As is well-known, vaccines face specific issue in cost-effectiveness, concerning, among others, discounting, indirect herd immunity effects, and quality of life-effects related to avoiding fear of infection. Discussions on broader impacts of vaccines already included potential macro-economic effects before the COVID-19 pandemic. Obviously, the economic impact of the strict COVID-19 control measures has enhanced the argumentation to include macro-economic effects into the economic analyses of vaccines, potentially bringing the traditional cost-effectiveness analysis applied to vaccines closer to cost-benefit analysis with a much broader view. For HTA-authorities, the major consideration seems which of those broader effects to include into the cost-effectiveness of a COVID-19 vaccine. Likely, the present situation illustrates and warrants that the impact of the COVID-19 vaccine has to be assessed beyond the health sector, due to spill over of COVID-19 to every sector of society (labour, financial markets, education, household etc.). Additionally, quality-of-life impacts go far beyond the COVID-19 patient population, with additional effects on partners, families, worries of the general public and potential psychological consequences of alternative non-vaccine intervention with lockdowns as the (so far) extremes. Inclusion of such broader (mostly positive) impacts of a vaccine will enhance the cost-effectiveness outcome. Already, willingness-to-pay thresholds for

COVID-19 vaccines will be relatively high because of the acute situation and seriousness of the disease.

Developing countries are facing huge challenges to control the COVID-19 pandemic and are expecting the vaccines soon. Medical trials for vaccines are carried out in some developing countries which could point towards favourable cost-effectiveness. Similarly, first model-based studies are underway, both for HICs as well as LMICs. However, caution is needed when trying to generalize the results to the whole world when using these outcomes as the basis for cost-effectiveness assessment. Traditional methods of HTA assessment for vaccine, including economical aspects, are likely to be implemented in the longer term in order to prioritize the likely heterogenous array of COVID-19 vaccines which will be available, combined with country specific demographic characteristics (e.g., age distribution, intergenerational contact) which have already made an impact on the spread and consequences of the pandemic, and strategies to enhance the uptake of the vaccine.

Key Messages

- Early HTA of COVID-19 vaccines is needed to allow timely upscaling of and access to promising vaccine candidates
- Public-private as well as NITAGs-HTA-bodies co-operation is core in all stages of HTA, e.g., evidence generation of vaccination pre- and post-market entry
- Registration of COVID-19 vaccines will likely follow abbreviated pathways, which emphasizes the need for regular updates of COVID-19 HTA as new data emerges
- Various types of COVID-19 vaccines will emerge, with differences in age-groups, number of doses, efficacy, duration of protection and the need for boosters
- Prioritization of vaccination will likely be given to the high-risk group of severe disease outcomes and people at highest occupational risks for transmission of infection, e.g. health staff
- Trust in safety of COVID-19 will be crucial for uptake and achieving potential coverage required for herd immunity
- HTA attention will shift from safety and effectiveness on the short term to cost-effectiveness issues covered in later stages
- Cost-effectiveness analysis will potentially justify high prices for COVID-19 vaccines, however distributional, equity and other aspects concerning ethics and affordability should be considered
- Real world data are core to strengthen safety profiles both in the first year and beyond, as well as monitor efficacy and effectiveness in averting disease and transmitting infection
- In the longer term, country-specific HTAs, e.g., cost-effectiveness assessments, are still needed in order to prioritize the likely heterogenous array of COVID-19 vaccines

On behalf of the HTAi Public Health Interest Group, Arnold Hagens, Cornelis Boersma, Jurjen van der Schans & Maarten Postma led the development of this position statement in consultation with the HTAi COVID-19 response team, an interdisciplinary collective of members of the HTAi Board, Secretariat staff, and others with leadership roles within the society.

OPEN FOR COMMENT. This is intended to be a living document reflective of the insight from members across the society. The HTA Response Team will be working to review and integrate member comments. Please share your thoughts directly with Sydney Ruller (sruller@htai.org).