Appendix 1: Updated protocol

Factors influencing global equitable access to a COVID-19 vaccine for Low- and Middle- Income Countries (LMICs)

Proposal for scoping review

24 September 2020

Elizabeth Peacocke, Lumbwe Chola, Katrine Frønsdal and Marita Fønhus, Norwegian Institute Public Health.

Updated 24 July 2021

Elizabeth Peacocke, Lieke Fleur Heupink, Katrine Frønsdal, Elin Hoffmann Dahl and Lumbwe Chola.

1 Summary

Summary

Vaccines are important medical countermeasures to prevent the spead of infectious diseases. The World Bank forecasts a 5.2% contraction in global GDP in 2020, and long-term negative impacts are expected in terms of lower investment, an erosion of human capital through lost work and schooling, and fragmentation of global trade and supply linkages (1) Without effective vaccines, diagnostics, and therapeutics, COVID-19 will continue to spread and have severe health and socio-economic consequences. The UN's Framework for the Immediate Socio-Economic Response to the COVID 19 Crisis warns "The COVID-19 pandemic is far more than a health crisis: it is affecting societies and econ-omies at their core. While the impact of the pandemic will vary from country to country, it will most likely increase poverty and inequalities at a global scale, making achievement of SDGs even more urgent." (2)

This project includes a scoping review that identifies and characterizes the factors influencing global equitable access to COVID-19 vaccines among countries, and contextualizes these factors with global mechanisms or guidelines that address global equitable access to pandemic vaccines. The documentation of these factors will offer decision makers lessons from previous experiences and information to support the understanding of principles related to equitable access to a COVID-19 vaccine.

This scoping review was conducted during August-November 2020, with a draft report for Norad, who commissioned and partly financed the report. This draft report was then submitted as a manuscript for publication. During the review process, in May 2021, the authors updated the search. This protocol has been updated to reflect the methods used in this Scoping Review.

To our knowledge, such a scoping review has not been systematically investigated.

Title:
Factors influencing global equitable access to a COVID-19 vaccine for Low- and Middle- Income Countries (LMICs)

Proposal for scoping review

Commissioned by:
Commissioned by the Norad Evaluation Department

Start date:
24.07.2020.

End date:
19.07.2021

Project Team:
Elizabeth Peacocke, Senior Advisor, NIPH
Lieke Fleur Heupink, Advisor, NIPH
Elin Hoffmann Dahl, MD, Haukeland Universitetssjukehus, Norway
Katrine Frønsdal, Senior Researcher, NIPH
Lumbwe Chola, Senior Advisor, NIPH

Internal peer review:
Maria Fønhus, Senior researcher, NIPH

Approved by:
Ingvil Sæterdal, Department Director, NIPH, Global Health

Background

New Corona Virus: SARS-CoV-2 (COVID-19) Pandemic

The world is currently facing a global public health emergency with the emergence of the Severe acute respiratory syndrome coronavirus 2 discovered in 2019 (COVID-19), an infectious acute respiratory disease caused by a novel coronavirus. A race to increase access to existing health technologies – including diagnostics - and find new and effective treatments and vaccine is underway, and with this the international community is faced with the challenge of how to ensure equitable access of essential medicines[1] to all populations. In this scoping review, we will systematically review the literature and summarize factors pertaining to the equitable access of a COVID-19 vaccine relevant for low- and middle- income countries (LMICs). For the purpose of this study, we are using the WHO definition of equity,[2] and we take the principle that the COVID-19 vaccine is an essential medicine[3], and that access to essential medicines is part of the right to health which is well founded in international law (4).

The challenge with global equitable availability and access to pandemic vaccines

COVID-19 has seen a large effort and investment in vaccines, and diagnostics, with 22 manufacturers that have applied for and Emergency Use Listing under the WHO Pre-Qualification, 10 of which have been approved (5). Shortly following these rapid advances and regulatory approvals, questions began to be raised about the availability and access of vaccines in LMIC, and as global public goods (6, 7).

The 2005 experience with the sharing of avian influenza A (H5N1) and the 2009 influenza A (H1N1) pandemic made apparent the need for equity considerations and ensuring that global coordination and distribution mechanisms are in place and adhered to, supporting equitable access to scarce vaccines. During H5N1, concerns raised by LMICs about the lack of mechanisms for ensuring global equitable access to vaccines prompted Indonesia to refuse to share H5N1 virus samples with the World Health Organization (WHO) (8). With Asia being the epicenter of the outbreak, fears were raised by the international community that Indonesia's refusal to share virus samples would impede the research and development, surveillance and response efforts, and made the re-

[1]**Essential medicines** are those that satisfy the priority health care needs of the population 3.World Health Organization. Essential medicines and health products. Essential medicines definition 2020 [cited 2020 August 13]. Available from: https://www.who.int/medicines/services/essmedicines_def/en/.
[2] **Equity** is the absence of avoidable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically or geographically or by other means of stratification. "Health equity" or "equity in health" implies that ideally everyone should have a fair opportunity to attain their full health potential and that no one should be disadvantaged from achieving this potential (World Health Organization. Health Topics: Health Equity. 2020 [cited 2020 August 12]; Available from: https://www.who.int/topics/health_equity/en/).
[3] WHO (2020)

sponse to the global health emergency more difficult. Ensuing negotiations with the WHO and its member states to create a new system of influenza virus sharing and vaccine availability did not immediately yield consensus.

During the 2009 pandemic, high income countries (HIC) bought virtually all vaccine supplies, leaving limited supplies for LMICs. One prominent example for this asymmetry was Mexico. Despite it being one of the first nations affected by H1N1 (concurrently with Canada and the United States), Mexico gained access to vaccines much later than the two other countries (9). The WHO intervened to mediate this potential challenge, engaging in talks with manufacturers and LMIC governments to secure equitable access to the vaccine for LMIC (10). Consequently, donation pledges to LMIC were made by manufacturers and HICs, with the exception of Canada (10, 11). These pledges from manufacturers were made without a fixed delivery date and were perceived to leave HICs with more than enough vaccines for full coverage in their own countries, leaving LMICs with limited access to timely supplies (11).

Lessons from previous collective responses to support global equitable access to vaccines

In response to the H5N1 and H1N1 experiences, WHO and member states developed and adopted the Pandemic Influenza Preparedness (PIP) framework in 2011, a global approach to pandemic influenza preparedness and response (12). The intention of PIP was to improve and strengthen the sharing of influenza viruses with human pandemic potential; and to share the benefit of, which is to increase the access of LMICs to vaccines and other pandemic related supplies. There are, however, several gaps in the framework, not least, that it is not legally binding (13).

There are other relevant frameworks and mechanisms, such as establishing the Advanced Market Commitment for AMC for Pneumonia Vaccine, and the Pan Americal Health Organisation's Revolving Fund for Vaccines. Much can be learnt from these initiatives that is relevant to the current COVID-19 pandemic. Recent events related to COVID-19 have shown some countries and technology holders' tendencies to control the global supply of personal protective equipment, ventilators, diagnostics and therapeutic medicines and reserve supply to HIC, as well as the challenges with limited manufacturing capacity and access to know-how, intellectual property and data; indicating that it is highly likely that similar controls will be placed on a vaccine that meets the necessary safety, efficacy and regulatory standards, to be used for mass vaccination (14).

To manage anticipated issues with the distribution of COVID-19 vaccine, the WHO is convening the Access to COVID-19 Tools (ACT) Accelerator, which brings together governments, scientists, businesses, civil society, and philanthropists and global health organizations (the Bill & Melinda Gates Foundation, CEPI, FIND, Gavi, The Global Fund, Unitaid, Wellcome, the World Bank and Global Financing Facility), in efforts to support the development and equitable distribution of the tests, treatments and vaccines. The ACT-Accelerator is organized into four pillars of work: diagnostics, treatment, vaccines and health system strengthening (15). Gavi and CEPI are leading implementation of the vaccines pillar, "the COVID-19 vaccine global access (COVAX) facility", which is committed to supporting the acute phase of the pandemic through the appropriate allocation of safe and effective doses of a vaccine (16, 17).

The barriers in access to medicines to COVID-19 vaccines relate the demand and the supply of the vaccine, and there continues to be unprecedented demand for a safe and

effective vaccine (18, 19). The supply of this vaccine is hampered by complex vaccine innovation and manufacturing processes. Depending on the candidates that prove to be the most effective, the approach used will determine the necessary manufacturing capacity and length of time for development, (19). In terms of the quantity of the vaccine needed to be produced, this is also influenced by whether one or two does are necessary, in addition other challenges including e.g. with lack or insufficient global vaccine manufacturing capacity & access to know-how and implementation in LMIC countries are also essential for access to vaccines for many. All of these factors will limit the supply of vaccines.

Importance of the project

The access to, and distribution of a scarce vaccine is one of the pegged solutions to enable the world to return some semblance of life pre-COVID 19. With COVID-19 affecting the world, the equitable distribution of this vaccine is important because the virus will cause unnecessary disability and loss of life unless the benefit of a vaccine is distributed fairly among and within countries. To our knowledge, a scoping review of the the factors for the equitable access of a COVID-19 vaccine relevant for LMIC has not been systematically investigated. The project is considered highly relevant to the current situation as it aims at identifying and describing of these factors which can inform decision makers in terms of lessons from previous experiences and supporting the understanding of principles related to equitable access to a COVID-19 vaccine, and further potentially guide implementation of future initiatives to ensure equitable access.

Objective

This objective of this scoping review is to identify and summarize the factors for the equitable access of a COVID-19 vaccine relevant for LMICs. We will address the following question: *What are the factors influencing global equitable access to a COVID-19 vaccine among countries?*

Methods

Scoping searches

We will perform systematic scoping searches for publications according to PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) (20).

Inclusion criteria

We aim to identify and describe factors influencing global equitable access to a COVID-19 vaccine among countries as identified in our search (see the manuscript supplementary material), following the inclusion criteria shown in Table 1.

Table 1. Inclusion criteria

Topic	Pandemic vaccines incl. influenza or COVID-19 vaccine
Outcomes	The factors influencing equitable access to a pandemic vaccine incl. COVID-19 vaccine
Type of publication	Primary studies, systematic reviews
Language	English
Publication date	2002-2021

Restriction to publications from 2002 are made as a pragmatic choice from the date of the 2003-04 SARS pandemic. Furthermore, the limitation to English language journal articles in scientific databases was balancing completeness with the resources available.

Search strategy and Information sources:

An information specialist at NIPH will develop the search strategies together with the project leader, and another information specialist will review the search strategy. The literature search will be conducted in the following databases: Medline (PubMed and Ovid), EMBASE (Ovid), Global Index Medicus, WHO https://www.globalindexmedicus.net/ and Web of Science Core Collection Clarivate Analytics (see supplementary information for updated search strategies and databases).

Additional relevant information will be searched from websites of multilateral agencies and international philanthropic agencies identified in the literature through the database search (e.g. WHO Pandemic Influenza Preparedness Framework) as a means to understand the particular framework or initiative.

Selection of literature

First screening

We will first review articles that are determined to be relevant (according to predefined inclusion criteria described above). Three project team members (EP, LF and LC) will independently go through all identified titles and abstracts and determine if articles should be included for full-text review.

Where there are divergent views, inclusion will be determined through discussion and consensus between the reviewers or by consulting a fourth team member (KF). Records not fulfilling the inclusion criteria will be excluded.

Full text review

Given time constraints, the review group will divide the studies by two and each study will be read in full and assessed for inclusion by one reviewer. This is verified by a second reviewer. Disagreement over exclusion or inclusion will be handled in the same way as for the first screening.

Extraction and presentation of data

Data to be extracted are mainly qualitative data on the predefined outcomes. Standard data extraction templates were designed, and piloted specifically for this scoping review (see the manuscript supplementary material for a copy of the data extraction form).

The predefined outcomes for extracting data include: the setting (LMIC or globally focused or normative guidance that affects LMIC), and argument/ discussion on equity, access, allocation or prioritization of pandemic vaccines, other aspects that article tells us about the knowledge in this topic area, challenges in implementing equitable access to vaccination between countries, and recommendations for strengthening the equitable access to vaccination. In addition, we collected names of relevant global initiatives and mechanisms as identified in our search. Data is to be extracted by one team member and a second reviewer will review the data extraction.

Analysis of data

The analysis of the data collected will provide information on the body of research and evaluations related to the factors influencing global equitable access to a COVID-19 vaccine among countries. Our analysis will include how factors influencing global equitable access to a COVID-19 vaccine among countries pertain to global frameworks and mechanisms identified in our searches.

We will consider using the following framework for analysis, adapted from Liu et al (21), which includes three main areas related to:

- A country's ability to develop or to purchase pandemic vaccines
- Reciprocity
- A country's ability to implement or vaccinate.

Reporting, submission of manuscript and updating of search

A draft report based on the findings from the scoping review was prepared and presented to Norad and two external peer reviewers. A manuscript was then prepared and submitted to BMJ Open in January 2021. Based on feedback from peer review, the search was updated in May 2021.

Risk of bias and limitations

Due to time constraints we are extracting data directly related to our topic of interest. This will mean that some papers are excluded due to their lack of direct relevance to our question, and will not be included in the analysis.

Only one reviewer will complete the full-text review and data extraction, to limit the risk of bias, one reviewer will peer review the full-text categorisation and data extraction.

Peer –review

External and internal peer review is being used to strengthen the methods and improve the rigor of this scoping review.

Internal:
The project plan (this document) has been reviewed by all authors and peer reviewed internally at NIPH. Internal reviewers at NIPH will also review any publication of results presented to Norad.

External:
Two external peer reviewers will be used in addition before publication of results.

Acronyms

CEPI	Coalition for Epidemic Preparedness Innovations
COVAX	the COVID-19 vaccine global access (COVAX) facility
COVID-19	2019 Pandemic corona virus strain
CIS	Critical Interpretive Synthesis
DNA	Deoxyribonucleic acid
Gavi	Gavi, the Vaccine Alliance
FIND	the Foundation for Innovative New Diagnostics
HIC	High income countries
H1N1	2009 influenza A
H5N1	2006 avian influenza A
LMIC	Low- and Middle- income countries

References

1. Bank TW. The Global Economic Outlook During the COVID-19 Pandemic: A Changed World: The World Bank; 2020 [updated June 8 2020; cited 2020 September 23]. Available from: https://www.worldbank.org/en/news/feature/2020/06/08/the-global-economic-outlook-during-the-covid-19-pandemic-a-changed-world.
2. United Nations. A UN framework for the immediate socio-economic response to COVID-19. New York: United Nations; 2020.
3. World Health Organization. Essential medicines and health products. Essential medicines definition 2020 [cited 2020 August 13]. Available from: https://www.who.int/medicines/services/essmedicines_def/en/.
4. World Health Organization. Access to essential medicines as part of the right to health 2020 [cited 2020 August 13]. Available from: https://www.who.int/medicines/areas/human_rights/en/.
5. World Health Organization. Status of COVID-19 Vaccines within WHO Emergency Use Listing / Pre-Qualification 2021 [updated 15 July 2021; cited 2021 24 July]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
6. Bollyky TJ, Gostin LO, Hamburg MA. The equitable distribution of COVID-19 therapeutics and vaccines. Jama. 2020.
7. Gopinathan U, Peacocke E, Gouglas D, Ottersen T, Røttingen J-A. R&D for Emerging Infectious Diseases of Epidemic Potential: Sharing Risks and Benefits Through a New Coalition. Infectious Diseases in the New Millennium: Springer; 2020. p. 137-65.
8. Fidler DP. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. PLoS Med. 2010;7(5):e1000247.
9. Jefferies N. Levelling the playing field? Sharing of influenza viruses and access to vaccines and other benefits. Journal of Law and Medicine. 2012;20(1):59-72.
10. Organization WH. Report of the WHO pandemic influenza A (H1N1) vaccine deployment initiative. 2012.
11. Fidler DP. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. Negotiating and Navigating Global Health: Case Studies in Global Health Diplomacy: World Scientific; 2012. p. 161-72.
12. World Health Organization. Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. 2011.
13. Fidler DP, Gostin LO. The WHO pandemic influenza preparedness framework: A milestone in global governance for health. JAMA - Journal of the American Medical Association. 2011;306(2):200-1.
14. Jakes L. U.S. Limits Virus Aid for Masks, Gloves and Other Medical Gear Abroad New York2020 [updated June 9 2020. Available from: https://www.nytimes.com/2020/06/09/us/politics/coronavirus-international-aid-masks.html.
15. WHO. The Access to COVID-19 Tools (ACT) Accelerator: WHO; 2020 [cited 2020 August 3]. Available from: https://www.who.int/initiatives/act-accelerator.
16. Gavi the Vaccine Alliance. COVAX, the act-accelerator vaccines pillar- Insuring accelerated vaccine development and manufacture: Gavi; 2020 [cited 2020 August 3]. Available from: https://www.gavi.org/sites/default/files/covid/COVAX-Pillar-background.pdf.
17. World Heaøth Organization. A global framework to ensure equitable and fair allocation of Covid-19 products. In: WHO, editor. Geneva: WHO; 2020.

18. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B, et al. Access to medicines from a health system perspective. Health policy and planning. 2013;28(7):692-704.
19. Khamsi R. If a coronavirus vaccine arrives, can the world make enough. Nature. 2020 April 9 2020.
20. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-73.
21. Liu Y, Salwi S, Drolet BC. Multivalue ethical framework for fair global allocation of a COVID-19 vaccine. J Med Ethics. 2020;46(8):499-501.