EQUITABLE ACCESS TO VACCINES: EXPLORING THE ROLE OF THE ACCEPTABILITY, ACCESSIBILITY, AFFORDABILITY, AND AVAILABILITY WITH A FOCUS ON COVID-19

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Declaration

I, Nina Schwalbe, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

23rd day of May 2024

Dedication

This thesis is dedicated to my mother, whose pancreatic cancer was misdiagnosed as hepatitis because of her gender; to my father, who died of COVID-19 in April 2020; and to the 45,000 other residents of New York City who also lost their lives to COVID-19.

List of original papers, the role of the student and agreement from co-authors

This thesis is based on the following published papers. The publishers have given permission for reprinting.

1. Aars, O.K., Clark, M. and Schwalbe, N. (2021). Increasing efficiency in vaccine production: A primer for change, *Vaccine: X*, 8(100104), 1-7.

Role played by student: NS and OA are joint first authors. NS is the corresponding author. NS conceptualised the manuscript. OA and NS wrote the manuscript.

This article was published before the student had finalised her registration as a PhD student at the University of the Witwatersrand. The supervisors approved the inclusion of this article in the thesis and the post-graduate office also granted its permission.

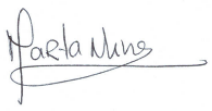
2. Schwalbe, N., Hanbali, L., Nunes, MC., et al. (2022). Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts, *Vaccine: X*, 12(100225), 1-7.

Role played by student: NS conceptualised the paper, developed the methodology, curated and validated the data, conducted the analysis, drafted, reviewed, and edited the manuscript. NS is the first author and corresponding author.

3. Schwalbe, N., Nunes, MC., Cutland, C., et al. (2023). Assessing New York City's COVID-19 vaccine rollout strategy, *Journal of Urban Health* (under review - minor revision requested).

Role played by student: NS conceived the study, designed the research plan, conducted the literature, analysed data, and drafted the manuscript. NS is the first author and corresponding author.

All of the co-authors have been informed that the papers are to be used in a PhD thesis and have agreed to the use within this thesis (see Appendix 3)



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Abstract

The coronavirus disease (COVID-19) crisis brought to light many challenges, including "vaccine equity". In other words, it raised the question: was the distribution of vaccines "fair"? While, on the one hand, there have been unprecedented advances in the science and technologies associated with vaccines, including extraordinary speed and scale-up of manufacturing, there were also significant barriers related to rollout and reaching those most at risk of severe COVID-19. These challenges have disproportionately affected low- and middle-income countries and low-income populations in high-income countries.

Building on evidence from other vaccine-preventable diseases, this thesis describes the challenges and opportunities concerning vaccine access with a focus on production and distribution (the "supply side"). It explores access using a "4A's" framework to conceptualise the components of access to medicines: affordability, availability, acceptability, and accessibility. The research identifies a range of access policy levers across the end-to-end process of vaccine research, development, and rollout (affordability, acceptability, accessibility, acceptability); reviews these levers as they apply to vaccine manufacturing (affordability, availability); explores the lever of financial incentives to increase coverage (acceptability); and explores the potential of using precision public health to improve vaccine impact by targeting vaccine distribution to groups most risk (accessibility).

This thesis identifies several policy and program interventions ranging from regulatory harmonisation and intellectual property sharing, to using precision public health to target the delivery of vaccines to those most at risk. It also shows that while financial incentives may help, governments cannot "buy" coverage. It proposes that in future, vaccine development and deployment should start and end with a "4A's" strategy and provides practical recommendations on how that can be achieved.

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List of Abbreviations

ACT(-A): Access to COVID-19 Tools Accelerator

ADIP: Accelerated Development and Introduction Plan

AIDS: Acquired immunodeficiency syndrome

AMC: Advance Market Commitment

API: Active Pharmaceutical Ingredient

AVAREF: African Vaccine Regulatory Forum

BARDA: Biomedical Advanced Research and Development Authority

Biotech: Biotechnology company

BMGF: Bill & Melinda Gates Foundation

BSL: Biosafety level

CDC: U.S. Centers for Disease Control and Prevention

CEPI: Coalition for Epidemic Preparedness Innovations

CIPIH: Commission on Intellectual Property Rights, Innovation and Public Health

CMC: Chemistry, Manufacturing and Controls

CMOs: Contract manufacturing organisations

COVAX: COVID-19 Vaccines Global Access

COVID-19: Coronavirus disease 2019

CVI: Children's Vaccine Initiative

DCVMN: Developing Countries Vaccine Manufacturers Network

DPT: Diphtheria, tetanus, pertussis

EC: European Commission

EMA: European Medicines Agency

EPI: Expanded Programme on Immunization

EU: European Union

EUA: Emergency Use Authorisation

EUL: Emergency Use Listing Procedure

FDA: U.S. Food and Drug Administration

Gavi: Gavi, the Vaccine Alliance

Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria

GMP: Good Manufacturing Practices

GMRI: Gates Medical Research Initiative

GNI: Gross national income

GSK: GlaxoSmithKline

HIV: Human immunodeficiency virus

HPV: Human papillomavirus

IFPMA: International Federation of Pharmaceutical Manufacturers & Associations

IP: Intellectual property

IPR: Intellectual property rights

LMICs: Low-and-middle income countries

MDGs: Millennium Development Goals

MNCs: Multinational corporations

MODZCTA: Modified zip code tabulation areas

MPP: Medicines Patent Pool

MSF: Médecins Sans Frontières

NCDs: Non-communicable diseases

NGO: Non-governmental organisation

NIH: U.S. National Institutes of Health

NRA: National Regulatory Authority

NYCDOH: New York City Department of Health and Mental Hygiene

NYSDOH: New York State Department of Health

OPHI: Oxford Poverty and Human Development Initiative

PAHO: Pan American Health Organization

PCV: Pneumococcal conjugate vaccines

PDPs: Product development partnerships

PHCPI: Primary Health Care Performance Initiative

PQ: Prequalification

QA/QC: Quality assurance/quality control

RITAGs: Regional Immunization Technical Advisory Groups

RSV: Respiratory Syncytial Virus

R&D: Research and development

SAGE: Strategic Advisory Group of Experts on Immunization

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SDGs: Sustainable Development Goals

TB: Tuberculosis

TPPs: Target product profiles

TRIPS: Agreement on Trade-Related Aspects of Intellectual Property Rights

UHC: Universal Health Coverage

UN: United Nations

UNDP: United Nations Development Programme

UNICEF-SD: UNICEF's Supply Division

WHO: World Health Organization

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Chapter 1: Introduction

The adoption of the Millennium Development Goals (MDGs) in 2000 drove a focus on accelerating access to therapeutics, diagnostics, and vaccines (medicines) for people living in low-income countries. Philanthropic, public, and private investments have yielded important results for new vaccine-preventable diseases, including over 100 million children vaccinated with the rotavirus vaccine (Gavi, the Vaccine Alliance, 2023f) and over 50% of the world's children now vaccinated against pneumococcal pneumonia (World Health Organization, 2022a). Despite these successes, challenges persist on the issues of medicines' affordability, availability, acceptability, and accessibility.

The coronavirus disease (COVID-19) crisis has brought to light many of these challenges, particularly concerning vaccines and vaccination. While, on the one hand, there were unprecedented advances in the science and technologies associated with vaccine development, including extraordinary speed and scale-up of manufacturing, there were also significant barriers, including those resulting from the profile of the vaccines themselves (Golob et al., 2021). There have also been policy challenges associated with the production at scale, affordable pricing, global allocation, and deployment (Flanagan et al., 2021; Wouters et al., 2021) as well as with the rollout strategies, in particular relating to reaching those most at risk of severe COVID-19 (Jean-Jacques and Bauchner, 2021). These challenges have disproportionately affected low-income populations (Khan Burki, 2021).

The initial recommendation by the World Health Organization (WHO), in the context of a limited supply of vaccines, was to first focus on those with an elevated risk of exposure (i.e. frontline health workers), populations with an elevated risk of severe disease or death, and then social or employment groups at elevated risk of acquiring and transmitting infection (World Health Organization, 2020d). However, wealthy countries "cannibalised" supply, thus delaying access for low- and middle-income countries (LMICs).

Once vaccines were available in late 2020, many countries did not prioritise high-risk groups (Amnesty International, 2021; Freed et al., 2021). Across the United States, for example, vaccines were distributed geographically according to the percentage of the population over 18 rather than considering age or other known risk factors for COVID-19 (Schmidt et al., 2021).

This was also the case in New York, where the majority of the adult population was granted access to vaccination within weeks of the initial introduction of vaccines. All adults over age

16 were eligible for vaccination within just over three months of when vaccines first reached the city, despite ongoing low coverage among low-income elderly populations, who experienced barriers to access at this time (New York State, 2021b). Except for health workers and long-term care residents, the COVID-19 vaccine rollout plan in New York did not consider individual or population risk factors or geographical context (Karmakar, Kabtz and Tuourbebu, 2021). This was despite existing evidence about the social determinants of COVID-19 mortality (Karmakar, Kabtz and Tuourbebu, 2021; Thakur et al., 2021), the importance of geographical context (Wrigley-Field et al., 2021) and the role the social determinants of health play in vaccine access, including for adults (Nagata et al., 2013).

Building on the evidence from other vaccine-preventable diseases (Pagliusi et al., 2017), this thesis describes the challenges and opportunities concerning vaccine access, focusing on the "supply-side". The vaccine supply-side refers to vaccine production, distribution, and availability. It explores the concept of access using a "4A's" framework, adapted from Penchansky and Thomas (Penchansky and Thomas, 1981; Thomson, Robinson and Vallée-Tourangeau, 2016) to conceptualise the various components of access to medicines: affordability, availability, acceptability, and accessibility. While this concept is not new, it has previously been more widely applied only to the "demand-side" of vaccine uptake (Penchansky and Thomas, 1981; Thomson, Robinson and Vallée-Tourangeau, 2016).

1.1 Objectives

- The first chapter provides an overall introduction.
- The second chapter reviews the history of the access to medicine discussion, identifies and categorises a range of access policy levers across the end-to-end vaccine research, development, and rollout process, describes how these tools are used to address challenges to affordability, acceptability, accessibility, and availability, and frames the rational for "why now" for this research.
- The third chapter reviews these levers as they apply to the vaccine development ecosystem. This section unpacks each actor's process and role in order to identify opportunities for change related to affordability and availability**.**
- The fourth chapter looks at the specific lever of financial incentives governments offer to increase acceptability (and ultimately, coverage). The research assesses the effects of incentive programs and explores their potential externalities.

- The fifth chapter explores vaccine accessibility, using a case study approach with data from New York City. Specifically, it explores the extent to which the distribution strategy deployed led to the optimal allocation of vaccines in short supply.
- The sixth and final chapter provides a general discussion and conclusion.

This thesis builds on previous definitions (Penchansky and Thomas, 1981; Thomson, Robinson and Vallée-Tourangeau, 2016) to define "access" and the "4A's" as follows:

- Access: the ability of individuals to be reached by, or to reach, vaccines.
- Availability: Sufficient, sustainable, and timely supply.
- Affordability: The ability of individuals and payers[1] to afford vaccination, both in terms of financial and non-financial costs (e.g., time, cost-benefit).
- Acceptability: Meets the needs and requirements of end users, policymakers, and health systems[2].
- Accessibility: Equitable delivery aimed at all who could benefit.

The study-specific objectives are:

1. Review the range of tools and policy interventions associated with access to medicines overall and vaccines in specific.

   1.1 Review of tools and policy interventions (across the "4A's");
   1.2 Review vaccine manufacturing (affordability/availability); and
   1.3 Review the use of incentives to increase uptake (acceptability).

2. Derive a *proof-of-concept* model to explore the extent to which counterfactual vaccine rollouts based on empirical risk could maximise the benefit of vaccination.

This thesis represents a novel approach by focusing on the practical application of the "4A's" framework and exploring associated successes (and failures) of supply-side policy interventions for each. The research combines a range of methods, including narrative review, expert knowledge, website and document review, and data and statistical analysis. Specific methods are described within each chapter.

[1] In the case of most vaccines for low- and middle-income countries, the payer is primary the public sector including government and international donors.
[2] Thompson *et al.* describe this as the "the degree to which individuals accept, question or refuse vaccination".

Chapter 2: History, Definitions, and Context

2.1 Introduction

Based on a review of literature and websites of organisations engaged in providing access to medicines for low- and middle-income countries (LMICs), this chapter begins with an overview of the history of the access to medicines debate and frames the rationale on "why now" for this research. As part of the review of this history, it describes publicly funded efforts to enhance access and develop a taxonomy and catalogue of tools created to address access-related challenges.

The chapter is not limited to vaccines because many access tools applied to drugs and diagnostics are also relevant to vaccines. That said, as has been documented elsewhere, the production of vaccines, including second-generation vaccines production, differs greatly from the production of medicines and generic medicines, in particular that in the case of vaccines, there are no generics per se as regulatory approval for second-generation vaccines follows a similar path as first-generation vaccines (Nguyen and Schwalbe, 2019). Further, vaccine manufacturing is more complex than most medicines as vaccines may contain living organisms; and finally, the cost of physical infrastructure to develop vaccines is typically much higher than for medicines (Nguyen and Schwalbe, 2019; Plotkin et al., 2017). Because of these factors, among others, there are also typically fewer manufacturers than for most medicines as vaccines have high fixed costs, deep reliance on "know-how," and ongoing quality assurance requirements (Nguyen and Schwalbe, 2019; Plotkin et al., 2017).

This chapter aims to focus on historical context and to be broad in scope rather than concentrating on any particular disease area or initiative. While COVID-19 is mentioned, COVID-19 and related initiatives like the COVID-19 Vaccines Global Access (COVAX) or the Access to COVID-19 Tools Accelerator (ACT-A) are not discussed in detail because they are being studied elsewhere and are subjects worthy of a thesis in their own right (Cooper et al., 2023; Schäferhoff et al., 2022).

2.2 Methods

2.2.1 Data collection

The research for this chapter was undertaken using three distinct approaches. The first involved an integrative literature review to understand the history of access to medicines discussions. The second involved a review of operational definitions of access, used by product development partnerships (PDPs) and other organisations working on access to medicines, and the third was a case study which drew on a previously identified list of interventions deployed by the Bill & Melinda Gates Foundation (BMGF) to increase access to medicines (Kettler, Lehtimaki and Schwalbe, 2020) to develop and apply a taxonomy based on the "4A's" and the timing of the intervention in the product development cycle. These methods are described in further detail below.

2.2.2 Literature review

To better understand the definition and operationalisation of access to medicines and how the concept has evolved over time, a systematic review of the literature was attempted. After applying three different search strategies, a narrative review approach was selected instead. The process is described below.

For the initial search, the Scopus database [https://www.scopus.com/home.uri] was selected due to its comprehensive archives of global health literature. An initial title-abstract-keyword search of "access to medicine" with a temporal parameter of the past twenty years (1993-2023) was conducted on April 17th, 2023, and returned 1,878 results. Additional filters were applied to remove surveys, erratum, and non-English articles due to linguistic limitations; this left 1,719 results for manual title and abstract scan. Inclusion criteria included a focus on access to medicines or vaccines, LMICs, and exploration of the concept or definition of access to medicines. The following exclusion criteria were applied: article focuses on non-human health; article focuses on the provision of specific medicine or treatment; article is limited case study; or access to medicine was not the main focus of article. With the exceptions of 1993-1999 and 2020-2023, results were grouped by five-year intervals to facilitate understanding of the evolution of the concept and definitions (see Table 2.1).

Table 2.1 Number of articles identified through Scopus search, grouped by five-year intervals

Year group	Number of articles (pre-title/abstract scan)
1993-1999	10
2000-2004	51
2005-2009	188
2010-2014	368
2015-2019	600
2020-2023	502

The first three groupings (1993-1999, 2000-2004, and 2005-2009) were subjected to manual title and abstract review to assess the strength of the search strategy. This revealed that the articles did not align with the search goal of documenting the definition, operationalisation, and evolution of access to medicine. The articles, mostly focused on HIV/AIDS, intellectual property (IP), and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), did not meet the inclusion criteria.

A second search using Scopus was conducted on April 22nd, 2023, with the aim being to narrow down and refine the results. The search strings used are shown in Table 2.2. A manual title and abstract review was once again undertaken to identify articles for full-text review; a total of 21 articles proceeded to the full-text review stage. None met the inclusion criteria.

Table 2.2 Search strings for the second Scopus search and number of articles identified

Search strings	Number of articles
Access to medicines AND theor* (to capture theory and theoretical) OR concept* (to capture concepts, conceptual, and conceptualising/conceptualizing)	Overall: 212 Full-text review: 10
Access to medicines AND vaccine OR vaccination OR immune* (to capture immunisation/immunization and immunization/immunizing)	Overall: 102 Full-text review: 11

A third and final search strategy aimed to produce more relevant results by focusing on articles citing Penchansky and Thomas (1981), the foundational text for this thesis. This involved the use of PubMed's "cited in" function, with no time limit applied, which returned 728 results on April 26th, 2023. References to the text (Penchansky and Thomas, 1981) nearly

doubled in 2020, after COVID-19 was declared by WHO as a Public Health Emergency of International Concern. A manual review of titles and abstracts focusing on the 145 articles published between 2011 and 2015 was undertaken to assess the effectiveness of this search strategy in producing relevant results; these years were selected as they comprised the most recent five-year interval prior to the COVID-19 spike. All 145 results were subjected to a three-step title-abstract scan. In step one, article titles were screened for the word "access" and/or variants thereof, and 69 articles which met this criterion proceeded to step two, which involved a second round of title scanning to identify articles specifically focused on access to medicines or vaccinations. Of the 69 articles, six met the step two criterion and proceeded to step three, which was an abstract scan; none of the remaining articles were found to be relevant to the search goal.

Having piloted three search strategies for a systematic review, the final decision was to use, instead, a narrative review. A narrative review or "knowledge synthesis" is distinct from a systematic review and adopts a more informal approach (Kunisch et al., 2023). It is inquiry-based, draws on the author's knowledge of the subject as an entry point to the literature, relies heavily on the snowballing of references, and allows for the use of multiple sources to offer a bigger picture that goes beyond what is documented within academia (Cronin and George, 2020; Grant and Booth, 2009; Jahan et al., 2016). Narrative reviews do not mandate the inclusion of the stringent elements typical of systematic reviews, such as the detailed presentation of methodology, specified search terms, utilised databases, and criteria for inclusion and exclusion (Green, Johnson and Adams, 2006; Jahan et al., 2016; Noble and Smith 2018).

2.2.3 Operational definitions

To understand operational definitions or how "access" was being defined in practice involved the analysis of websites of a selection of non-governmental organisations (NGOs), PDPs, multilaterals, global funds and foundations, and related processes (see Table 2.3). Those that were referenced more than once in the literature reviewed (see section 2.2.2) were selected for further analysis and "screened in" if access was mentioned as part of their name, mission, mandate, or a key outcome of their efforts. Key processes (e.g., WHO initiatives and Lancet Commissions) frequently referenced in the review were also included in this assessment.

Of note, this analysis was intended as illustrative, rather than exhaustive, to show a range of definitions.

Table 2.3 List of global health organisations (20) and processes (4) reviewed working on product development or distribution

Non-governmental organisations (NGOs)	Product development partnerships (PDPs)	Multilaterals, global funds, or foundations	Processes
• Access to Medicine Foundation • Coalition for Access to Non-Communicable Disease Medicines & Products • Clinton Health Access Initiative • Médecins Sans Frontières (MSF) • PATH • Access Accelerated • Medicines Patent Pool (MPP)	• Coalition for Epidemic Preparedness Innovations (CEPI) • Drugs for Neglected Diseases Initiative • Foundation for Innovative New Diagnostics • Global Alliance for Tuberculosis Drug Development • Gates Medical Research Institute (GMRI)	• The Bill & Melinda Gates Foundation • Gavi, the Vaccine Alliance (Gavi) • The Global Fund to Fight Aids, TB and Malaria (Global Fund) • The Joint United Nations Programme on HIV/AIDS (UNAIDS) • United Nations Development Programme (UNDP) • Access and Delivery Partnership • Unitaid • The Wellcome Trust (Wellcome)	• Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) • United Nations Secretary-General High-Level Panel on Access to Medicines • Lancet Commission on Essential Medicines • WHO Roadmap for Access 2019-2023

2.2.4 Taxonomy development

To develop a taxonomy, this thesis took as a starting point previous research conducted by the student that identified over 40 supply- and demand-side tools used by the BMGF, the largest private funder in the field of global health (Breen and Kumar, 2023), to improve access (Kettler, Lehtimaki and Schwalbe, 2020).

The data from Kettler, Lehtimaki and Schwalbe (2020) were re-analysed and categorised below (see Table 2.5) with the aim to develop a taxonomy of access interventions ("tools") according to their role (e.g., "push" or "pull"; "4A's"); whether they address global diseases or diseases of poverty (see Figure 2.1); and their role by product development phase (see Figure 2.2). Table 2.5 also offers a short description of each tool.

2.3 Findings

2.3.1 A short history

Access to medicines is frequently portrayed in the media as a highly polarised, single-issue debate between those who think IP protection is one of many tools that help *enable* access by motivating investment in innovation and those who think IP is *the central barrier* to access by

delaying competition and distorting research and development (R&D) investments in favour of profit and not considering patient's needs (United Nations Secretary-General's High-Level Panel on Access to Medicines, 2016). While advocacy groups like Médecins Sans Frontières' (MSF) Access Campaign are focused primarily on the IP and pricing systems, most stakeholders agree that access is a complex set of interdependent local and global issues that also requires a strengthened health system (Frost and Reich, 2008).

Discussions about how best to increase access are not new. For nearly fifty years, access to medicines and innovations has been a heated topic within the global health and development community. It began in the mid-1970s, when WHO created the first list of essential medicines formalising the concept of "appropriate" medicines selection and defining which products should be accessible to all (World Health Organization, 2023d). Over the next two decades, the discussion expanded to issues including sustainable supply chains, appropriate use, product quality, and affordable pricing (Bigdeli, Peters and Wagner, 2014).

Over time, there have been many attempts to address the question of access to medicines through multi-stakeholder processes (see Appendix 5 for timeline). In 2004, as a response to the discussions on TRIPS, the WHO set up the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) (World Health Organization, 2006), which focused largely on price and patents as the main barriers to access to medicines. In 2008, the first biennial Access to Medicine Index was launched, ranking 20 leading pharmaceutical companies according to access governance, market influence and compliance, R&D, pricing, manufacturing and distribution, patents and licensing, capacity building, and product donations (Access to Medicine Foundation, n.d.).

More recently, in 2015, the United Nations (UN) Secretary-General established a High-Level Panel to review access from multiple perspectives, including international human rights law, trade rules, the rights of inventors, and public health. The panel's recommendations focus on IP laws, access to knowledge, incentives for R&D, governance accountability, and transparency (United Nations Secretary-General's High Level Panel on Access to Medicines, 2016).

The shifts in the global health and development landscape over the past decade have enforced a trend to look at access as broader than price and IP. In 2016, the UN General Assembly launched the Sustainable Development Goals (SDGs), which for health shifted the focus from vertical health and disease programs implemented under the MDGs to a broader emphasis on

health systems strengthening, equity, and social determinants (World Health Organization, 2006). Access to medicines has been linked to SDG target 3.8 (World Health Organization, n.d.e.), which explicitly calls for "access to safe, effective, quality and affordable essential medicines and vaccines for all" as part of a call for universal health coverage. Another key milestone was the adoption by the World Health Assembly of the WHO Roadmap for Access 2019-2023 (World Health Organization, 2019b). In this Roadmap, WHO's role now spans the value chain ranging from R&D investment incentives to prescribing.

Within this timeframe, there have also been a number of efforts specific to vaccines. The Children's Vaccine Initiative (CVI) was launched in 1990 following the World's Summit for Children in New York in support of the Expanded Program on Immunization (EPI), established by the WHO in 1974, which had stalled in terms of coverage progress (Institute of Medicine, 1993; World Health Organization, 2024). The initiative, which itself had been a product of nearly a decade of discussion (Muraskin, 1996), focused on six features of future vaccines: single doses; administered near or at birth; combined in novel ways; heat stable, effective against diseases for which vaccines are unavailable; and affordable (Institute of Medicine, 1993). Headquartered at WHO, it was co-sponsored by UNICEF, UNDP, the Rockefeller Foundation, the World Bank, and the WHO. The Children's Vaccine Initiative sought to support initiatives that reduced the number of contacts and made vaccines easier to administer.

A key problem, however, was incorporating newer and more costly vaccines into the EPI of low- and middle-income countries (Institute of Medicine, 1995), primarily because there were no mechanisms by which to purchase these vaccines from proprietary manufacturers at a low price. This problem resulted in the creation of the Global Alliance for Vaccine and Immunization, later called "The GAVI Alliance" and "Gavi, the Vaccine Alliance". The history of this transition from CVI to the Global Alliance is well described by Muraskin (2005). Gavi's current mission is to "save lives and protect people's health by increasing equitable and sustainable use of vaccines" (Gavi, the Vaccine Alliance, 2023e). While this thesis is not a study of Gavi, it has played a significant role to date in terms of increasing access to vaccines primarily by providing predictable financing for bulk procurement of new vaccines (Gavi, the Vaccine Alliance, 2023d).

In 2020, the WHO also launched the "Immunization Agenda 2030 (IA 2030)" (World Health Organization, 2020c), also specific to vaccines. IA2030 covers a broad range of activities from communications and advocacy to coordinated national planning across disease areas. Its

associated Framework for Action has as one of its three goals a pledge to “Leave no one behind, by increasing equitable access and use of new and existing vaccines,” including through developing new vaccines and technologies and improving existing products and services for immunisation programmes (World Health Organization, 2021b). The Framework’s operational definition of access is “Introduction of new or under-utilized vaccines in low- and middle-income countries,” with a goal of “500 vaccine introductions within the decade” (World Health Organization, 2021b).

2.3.2 Defining access

While all organisations reviewed (20) describe “access” as part of their name, mission, mandate, key component, or intended outcome of their efforts, considerably fewer (11) explain exactly what they mean by the term or how they will achieve it or measure its success. Those that do describe what they mean by access, mostly reference some or all of the “4A’s” and some also include quality or sustainability. The results are summarised in Table 2.4.

Table 2.4 Summary of access definitions by global health organisation reviewed

Organisation (reference) and Web Site	Access Defined	Definition of access	Formal access or eligibility policy
Non-Governmental Organisation (NGO)			
Access to Medicine Foundation (Access to Medicine Foundation, 2021) https://accesstomedicinefoundation.org/	Yes	Access defined as available, accessible, and affordable.	No
Coalition for Access to Non-Communicable Disease Medicines & Products (Coalition for Access to NCD Medicines & Products, n.d.) https://coalition4ncds.org/	Through target setting	Members commit to contributing to "80 percent availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities".	No
Clinton Health Access Initiative (Clinton Global Health Initiative, 2023) https://clintonhealthaccess.org/	No	Access not defined. Referenced in marking shaping activities including: "accelerating market introduction, ensuring affordability, and enhancing supply security to increase equitable access".	No
Médecins Sans Frontières Access Campaign (Médecins Sans Frontières, 2017; 2018; n.d.) https://msfaccess.org/	Yes	Access defined as available, affordable, suited and adapted to low resource settings.	No
PATH (PATH, n.d.) https://www.path.org/	Yes	Access defined as affordable, available, acceptable, and sustainable.	No
Access Accelerated (Access Accelerated, n.d.) https://accessaccelerated.org/	No	Access not defined. Vision is that "all people have access to quality prevention, diagnosis, treatment, and care for NCDs".	No
Medicines Patent Pool (Medicines Patent Pool, n.d.b.)	Partially	Access defined as effective and affordable medical treatments and health technologies. Focus is on voluntary licencing and tech transfer.	No

https://medicinespatentpool.org/			
Product Development Partnerships			
Coalition for Epidemic Preparedness Innovations (Coalition for Epidemic Preparedness Innovations, 2019; 2023) https://cepi.net/	Yes	Access defined as: "Equitable access to epidemic or pandemic vaccines in the context of an outbreak means that appropriate vaccines are first available to populations when and where they are needed to end an outbreak or curtail an epidemic or pandemic, regardless of ability to pay".	Yes Equitable Access Policy and Framework
Drugs for Neglected Diseases Initiative (Drugs for Neglected Diseases Initiative, 2020) https://dndi.org/	Yes	Access defined as affordable and sustainable production and supply, introduction and adoption of registered products, and improved market dynamics.	Yes Access Policy
Foundation for Innovative New Diagnostics (Foundation for Innovative New Diagnostics, 2018) https://finddx.org/	Yes	Access defined as available, affordable, appropriate, and adopted.	Yes Global Access Policy
Global Alliance for Tuberculosis Drug Development (Global Alliance for Tuberculosis Drug Development, n.d.) https://tballiance.org/	Yes	Access defined as adopted, available, and affordable.	No
Gates Medical Research Institute (Gates Medical Research Institute, 2022; n.d.a.) https://gatesmri.org/	Yes	Access defined as "affordable price to people most in need".	Yes Commits to BMGF global access policy (see below)
Multilaterals, Global Funds and Foundations			
Bill & Melinda Gates Foundation (Bill & Melinda Gates Foundation, n.d.c.)	Yes	Access defined as "available and accessible at an affordable price to our intended beneficiaries".	Yes

https://gatesfoundation.org/			Global Access Statement and Associated Requirements related to investments
Gavi, the Vaccine Alliance (Gavi, the Vaccine Alliance, 2023a; 2023b; 2024a; 2024b) https://gavi.org/	Through target setting	Access defined through various targets (e.g., reduction in zero-dose children). Market shaping roadmaps and health market frameworks aim to foster "sustainable competitive future supplier base," "health demand," and "an enabling environment for innovation" where products "meet country preference". Eligibility based on disease burden.	Yes Health Market Framework and Market Shaping Roadmaps Eligibility Policy
The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund, 2015; 2022; n.d.b.; n.d.c.) https://globalfund.org/	Yes	Access defined through availability, affordability, consistent quality, accelerated adoption, and long-term viability. Market shaping policy aims to ensure availability and affordability, consistent quality standards, stimulate innovation, and accelerate adoption of new or cost-effective products, Eligibility defined combination of GNI and disease burden.	Yes Market Shaping Policy Eligibility Policy
The Joint United Nations Programme on HIV/AIDS (UNAIDS) (UNAIDS, n.d.) https://unaids.org/	Through target setting	Access defined through targets (e.g., 95% of HIV exposed children are tested).	No
United Nations Development Programme (UNDP) (UNDP, n.d.) https://undphealthimplementation.org/	Partially	Access defined as affordable and good quality.	No
Access and Delivery Partnership (ADP) (Access and Delivery Partnership, 2019) https://adphealth.org/	Partially	Access defined as available.	No

Unitaid (Unitaid, 2022) https://unitaid.org/	Partially	Access defined as "expanded reach of the best health products for those who need them most".	No
The Wellcome Trust (Wellcome, 2019; 2020; 2021) https://wellcome.org/	Yes	Access defined as available, appropriate, safe, effective, and affordable.	Yes Approach to equitable access (overall); Equitable Access to Vaccines, Tests and Treatments for COVID-19; Plan of Action
Processes			
Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) (United Nations Economic and Social Council, 2000; WHO, 2006)	Yes	Factors determining access include the price of medicines as well as poverty and the lack of infrastructure for delivering health care to poor people. Puts access in the human rights context and uses the framework from the General Comment number 14 on the Right to the Highest Attainable Standard of Health: 1) availability in sufficient quantities; 2) acceptable, both in terms of their usability and their appropriateness, given cultural and other factors; 3) effective and of good quality; 4) the lowest possible cost to facilitate access (i.e. financing of research, product pricing etc).	N/A
UNSG's High-Level Panel on Access to Medicines (United Nations Secretary-General's High-Level Panel on Access to Medicines, 2016)	Partially	Access not explicitly defined but discusses access broadly in the economic and political context. Recognises policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health. Notes that inequities exist in access to health technologies, despite the progress. Defines a broad set of barriers to access, including under-resourced health systems, a lack of sufficiently qualified and skilled healthcare workers, inequalities between and within countries, regulatory barriers, poor health education, unavailability of health insurance, exclusion, stigma, discrimination and exclusive marketing rights.	N/A
Lancet Commission on Essential Medicines (*Lancet* Commission on Essential Medicines, 2016)	Partially	Looks at access to medicines from a comprehensive health system perspective, covering all aspects of financing, affordability, quality, use, and essential innovation. Refers to access as a universal problem; broadens the discussion from LMICs to a global concern. Five key areas are: 1) Paying for a basket of essential medicines 2) Making medicines	N/A

		affordable 3) Ensuring quality of medicines 4) Promoting quality medicines 5) Developing new and missing medicines. Notes that essential medicines are crucial to satisfy the priority health-care needs of the population, promote health, and achieve sustainable development.	
WHO Roadmap for Access 2019-2023 (World Health Organization, 2019b) https://who.int/	Yes	Access defined as “availability, accessibility, acceptability, and affordability of medicines and vaccines of assured quality”.	N/A
Other definitions			
Frost and Reich (2008)	Yes	"Access refers to people’s ability to obtain and appropriately use good quality health technologies when they are needed. Access also involves social values, economic interests, and political processes. Access requires a product as well as services and is linked to how health systems perform in practice." (p8) Access can also mean that a patient receives too many drugs. Also, “access to a drug, vaccine, diagnostic, or other health product does not automatically translate into improved health, especially in poor countries. Too often, access means merely that patients are obtaining poor quality drugs that may cost money but have no impact on their health status. Patients and consumers of health technologies often receive little information from the dispenser about how to use a product appropriately, therefore quality included in the definition”. (p.9) Puts access into the economic, social, cultural and political context. In addition to cost, main barriers include limited capacity of public health systems, a lack of political commitment to health improvement, persistent corruption in public and private health facilities, international trade and patent disputes, cultural attitudes toward both disease and treatment, and difficulties in distributing, prescribing, delivering, and using products.	N/A

Despite the prominence of access in their respective mission statements, only a few of the organisations reviewed that fund product development or supply products have formal access policies (Coalition for Epidemic Preparedness Innovations, Wellcome Trust, Drugs for Neglected Diseases Initiative, Foundation for Innovative New Diagnostics, Gates Medical Research Institute, and the Bill & Melinda Gates Foundation). Gavi, the Global Fund, UNAIDS, and Coalition for Access to Non-Communicable Disease Medicines & Products define access through setting coverage targets; and Gavi and the Global Fund also have "eligibility criteria" which define types of standards or requirements that must be met to receive assistance. Gavi's eligibility criteria are based on gross national income (GNI) per capita, and the Global Funds criteria is based on a combination of GNI per capita and disease burden. Some organisations include some reference to "equity" or qualify access as "equitable access" (Coalition for Epidemic Preparedness Innovations, 2019; Coalition for Epidemic Preparedness Innovations, 2023; Clinton Health Access Initiative, 2023; Gavi, the Vaccine Alliance 2023a; Gavi, 2023b; Medicines Patent Pool, n.d.b.; Unitaid, 2022; Wellcome, 2019; Wellcome, 2020; Wellcome, 2021).

Availability is mentioned by most organisations (see Table 2.4) with relatively holistic definitions (e.g. developed, brought to market and supply secured) (Foundation for Innovative New Diagnostics, 2021).

While "acceptability" is only explicitly mentioned by WHO (2019b), others call for products "suited", "adapted" or "tailored" to low resource settings or local needs (Médecins Sans Frontières, 2017; Foundation for Innovative New Diagnostics, 2018).

"Affordability," "cost," or "pricing" are mentioned by the majority of organisations with approaches on how to address it, ranging from "challenging patents" (Médecins Sans Frontières, 2017) to "market shaping" (Clinton Health Access Initiative, 2023; Gavi, the Vaccine Alliance 2024b) to maintaining "sustainable manufacturing" (Coalition for Epidemic Preparedness Innovations, 2023).

Outcomes of key processes, in particular, the UN, tend to frame access as a human right and thus imply universality to access (World Health Organization, 2006; United Nations Secretary-General's High-Level Panel on Access to Medicines, 2016; World Health Organization, 2019b). The WHO (2019b), the Lancet Commission on Essential Medicines (2016), and the Wellcome Trust (2019; 2020; 2021) also link access with achieving the SDGs in general and Universal Health Coverage (UHC), specifically. United Nations-led initiatives

(United Nations Secretary-General's High-Level Panel on Access to Medicines, 2016; World Health Organization, 2019b) also reference the economic, social, cultural, and political contexts that determine access and call for multisector and multidisciplinary approaches.

New leadership at WHO in 2017, with strong support from Germany and Japan, positioned UHC, including access to medicines, as key to achieving the SDGs (World Health Organization, 2019d; World Health Organization, 2023c). Embedding access to medicines as part of UHC was also used to make the case for strengthening related health systems functions (e.g., regulation, quality control, and data systems) and for producing sufficient supply to achieve effective coverage.

Of note, access has been front and centre in the COVID-19 discussions including with regard to vaccines, technology transfer, and the role of local production. New initiatives, including the ACT-A which included the COVAX initiative as its vaccine pillar, aimed at fostering equitable distribution through an advance market commitment (AMC) and pooled procurement, two of the tools described further below (World Health Organization, n.d.g.).

2.3.3. Taxonomy

A range of access tools supported by the BMGF were identified in Kettler, Lehtimaki and Schwalbe (2020). In this thesis, we described them in detail in Table 2.5, by primary function *vis a vis* access and any additional contribution or cross-influence. Here we have also further categorised them according to the "4A's" by whether they address global diseases or diseases of poverty (Figure 2.1) and by product development phase (Figure 2.2).

Table 2.5 Catalogue of supply- and demand-side tools supported by the Bill & Melinda Gates Foundation to improve access

Tool (and example)	Access Cross Reference	Value Chain	Push/ Pull	Description
Affordability				
Global Access Plans (Bill & Melinda Gates Foundation, n.d.c.)	Availability	Multiple	Pull	Global Access Plans put in place by funders require that (a) the knowledge and information gained from an investment must be promptly and broadly disseminated and (b) the funded developments be made available and accessible at an affordable price to intended beneficiaries. Beneficiaries are considered people most in need living in developing countries. Intentional intellectual property (IP) management is part of a global access plan as are retention of humanitarian licencing.
Product Development Partnerships (PDP) (Pratt and Loff, 2013; Tideline, 2017)	Availability, Acceptability	Development	Push	PDP refers to a group of non-profit organisations dedicated to funding and managing a portfolio of global health products through development; often partner with pharmaceutical companies and academics to do the work; also oversee directly with support from contract research organisations.
Vaccine Innovation - Lower Cost Manufacturing Platforms (Batavia Biosciences, 2019; Philanthropy News Digest, 2016)	N/A	Manufacturing	Both	An intentional effort to reducing vaccine manufacturing costs - fixed and/or marginal via, for example, modular facilities, process intensification, and process integration.
Vaccine Innovation - Fewer, lower doses (Bill & Melinda Gates Foundation, n.d.d.)	Acceptability	Development	Push	A dedicated effort to identify opportunities to improve the cost-effectiveness or reduce the absolute cost of vaccines through research to test efficacy with fewer or lower doses; the addition of an adjuvant etc.
Lower Active Pharmaceutical Ingredient (API) costs for essential medicines (Virginia Commonwealth University, 2023)	N/A	Manufacturing	Push	Intentional efforts to diagnose and reduce drivers of cost in the process of developing and manufacturing drugs for global health.
Voluntary License Patent Pool (Juneja et al., 2017; Medicines Patent Pool, n.d.a.)	Availability	Multiple	Push	Efforts to reduce price and increase the supply of on-patented drugs in low- and middle-income countries (LMICs), creating competition by issuing voluntary licenses. Companies donate patents

				to a “patent pool” that in terns negotiates voluntary licenses to pre-qualified generic companies to manufacture and market in LMICs.
Market Shaping (USAID, 2014)	Availability	Multiple	Both	Refers to a portfolio of tools to build "well-functioning" markets for products serving the poor - sustainable supply of quality, affordable products.
Tiered Pricing (Balasegaram, 2014; Berkley, 2014; Gavi, the Vaccine Alliance, n.d.a.)	Availability	Delivery	Pull	For products with global markets, a mechanism to secure the "lowest" price for LMICs while other groups of countries pay higher tiers reflective of a share of "costs of research, development and manufacturing" back to the manufacturer; a way to sustain supply at low prices. Multiple tools in this catalogue, e.g. volume guarantees, are used to create an environment where companies can provide a lower "lowest tier".
Advance Market Commitment (AMC) (Gavi, the Vaccine Alliance 2019c; Gavi, the Vaccine Alliance 2021a)	Availability; Acceptability	Multiple	Pull	With the goal to motivate industry investment into the development, manufacture and delivery of vaccine in relatively less attractive global health markets, advance market commitment commits a fixed mark up on the per dose price (tail price) over a set number of doses in exchange for a multi-year commitment from the company to continue to supply a negotiated amount at a specific tail price. For example, with pneumonia vaccines, companies meeting the target product profile (TPP) earned $7 per dose up to a certain number and then continued to supply at the tail price of $3.50 for the remaining time period.
Demand Pooling (Anderson et al., 2017; Dubois, Lefouili, and Straub, 2019; Global Fund, n.d.a.; Immunization Economics, n.d.)	Availability	Delivery	Pull	Order volumes are aggregated on behalf of participating recipients, e.g. GAVI countries, to negotiate prices and delivery conditions with manufacturers.
Price Subsidy (ACTwatchGroup et al., 2017; Tougher et al., 2012)	Availability	Delivery	Pull	Refers to subsidies to offset the price paid by the consumer. For example, the Affordable Medicines Facility for Malaria sought to affect people's purchasing behaviour for anti-malarial drugs and encourage them to switch from mono-therapy, affordable and available via private sector distribution channels where many buy their drugs, to artemisinin combination by subsidising the price down closer to the price of the monotherapy.
Volume Guarantee (Bill & Melinda Gates Foundation – Strategic Investment Fund, 2022; Children’s Investment Fund Foundation, n.d.)	Availability	Multiple	Pull	Drive prices down towards marginal costs quicker, provides backstop to a share of predicted demand to cover company risk of investing in new capacity and/or dedicating more of their supply to developing world markets - designed to address demand uncertainty.

Buy Down (ill & Melinda Gates Foundation – Strategic Investment Fund, 2022)	Availability	Use	Pull	For a specific period of time, the price is subsidised to an agreed upon target level; subsidy goes down as their volume goes up.
Availability				
Humanitarian license (Bill & Melinda Gates Foundation, 2018)	Affordability	Multiple	Push	Securing a non-exclusive license on results of research and of product development funded to help ensure impact to intended beneficiaries.
Direct product investment and technical assistance (ET Bureau, 2011)	Affordability; Acceptability	Development	Push	Use grants to support specific companies to develop and manufacture products; often used to bring in new local manufacturers, e.g., vaccines.
Research & Development (R&D) Policy Incentives (Center for Global Development, n.d.b.; Ridley, Grabowski and Moe, 2006)	Appropriateness	Development	Both	Beyond cost and risk mitigation provided by the PDPs and direct grant funding, support to develop and inform government policy incentives. Often designed to motivate private sector companies to invest in the R&D and commercialisation of global health priority products.
Clinical Trials Network (African Vaccine Regulatory Forum - AVAREF Steering Committee, 2017; World Health Organization-AFRO, n.d.)	Acceptability	Development	Push	Capacity-building platforms aimed at improving the regulatory oversight of interventional clinical trials being conducted in LMICs. Focus on strengthening regulatory and ethics reviews, promoting harmonised standards and approaches and accelerating the review of vaccines of high public health value.
Innovative Translational Research Design (Gates Medical Research Institute, n.d.b.)	Affordability; Acceptability	Development	Push	Specific investments into translational research with the goal to streamline and shorten translational research using platforms such as quotative science and adaptive clinical trial design.
Regulatory Strengthening (Ahonkhai et al., 2016)	Accessibility	Multiple	Push	A portfolio of activities to designed to streamline, and increase the transparency and the function of the pathways of moving products through from discovery to initial regulatory approval to country approval and uptake; while usually group with other push incentive, also serves as a pull as the added transparency and confidence in the processes motivates companies/partners to make investments in those regions.
World Health Organization Prequalification (PQ) System Strengthening (World Health	Acceptability; Accessibility	Multiple	Push	Goal to streamline and accelerate WHO's pre-qualification process, which countries look to it as an indicator of quality.

Organization, 2019a; World Health Organization, 2023e)				
Transparency of Policy Guidance Process (James et al., 2018)	Acceptability	Use	Push	Process whereby WHO agrees to recommend a product for use. Many countries base their decisions about approving and using on WHO guidelines; considered a prerequisite for uptake.
Pharmacovigilance Capacity (Global Health Network, n.d.; World Health Organization, n.d.g.)	Accessibility	Use	Push	Investment in the development of practical and scalable strategies for supporting post-market drug and vaccine safety surveillance in LMICs.
Regional Regulatory Harmonisation (African Union Development Agency, n.d.; Brennan, 2018)	Accessibility	Use	Push	To reduce the time and transaction cost of securing regulatory approval in each country, investments to harmonise processes at least by region so companies would only need to submit regional level dossier.
Individual Country Regulatory Capacity Support (Bill & Melinda Gates Foundation, n.d.a.)	Accessibility	Use	Push	Improve country capacity to review and approve global health priority products.
Supply Chain Support (Africa Resource Center, n.d.; Global Grand Challenges, 2017; Yadav and Mor, 2018)	Accessibility	Delivery	Both	Invest in the optimisation of supply chains from first to last mile.
Demand Forecasts (Center for Global Development, n.d.a.; Gavi, the Vaccine Alliance, 2022b)	Affordability	Delivery	Pull	As a key piece of the overall market shaping strategy, support market assessments, demand forecasting, and modelling studies to guide policymakers and vaccine manufacturers.
Market Manager (AVAC, 2017; AVAC, n.d.; Gavi, the Vaccine Alliance, 2019a; Gavi, the Vaccine Alliance, 2023c)	Accessibility	Use	Pull	Portfolio of activities to accelerate the introduction of a new product, ranging from country specific trials to disease experts in countries, marketing support etc. – demand and supply activities (e.g., Accelerated Development and Introduction Plans – ADIPs).
Acceptability				

Target Product Profile (TPP) (World Health Organization, n.d.f.)	Affordability	Multiple	N/A	A TPP outlines the desired "profile" or characteristics of a target product that is aimed at a particular disease or diseases. TPPs state intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics.
R&D Prioritisation (Terry et al., 2018; World Health Organization, 2022b; Young et al., 2018)	Available	Discovery	Pull	Accelerate the availability of medical technologies focusing on a list of prioritised diseases for which medical countermeasures are insufficient or do not exist.
Surveillance, Disease Burden Studies (Child Health and Mortality Prevention Surveillance, n.d.)	Accessible	Use	Pull	Fill data gaps regarding source of mortality and morbidity, access to care and other factors. that help inform R&D priorities as well as the design of delivery programs.
Health Technology Assessment (Bill & Melinda Gates Foundation, 2023b; Center for Global Development, 2014; International Decision Support Initiative, n.d.)	Availability	Use	Pull	Invest in country capacity to inform health resource allocation decisions based on health technology assessments and cost effectiveness.
Accelerators (Global Health Progress, n.d.)	Availability	Discovery	Push	Contract based coalitions of public, academic, non-profit and for-profit partners working together, leveraging respective assets and resources, to discover new drug candidates for a specific disease.
Vaccine Innovation - Fewer Injections, Packaging, Thermostability, Lower dosing; Reduce overage to reduce cost (Giersing et al., 2021)	Affordability; Acceptability	Use	Push	Investments to targeting needs of specific vaccines to improve impact by making them easier or cheaper to deliver, or improve or/retain impact at lower cost.
User Centered Design (Bill & Melinda Gates Foundation, 2023a)	Affordability; Availability; Accessibility	Use	Pull	Broad portfolio of effort to shape interventions, programs and systems to better fit target user needs and reduce activation energy for desired behaviour change.
Adherence Investments (Global Grand Challenges, n.d.)	Acceptability	Use	Push	Investments to improve product adherence through changes in the product - be that the products delivery system (e.g., long-acting oral dose forms) or through user centred design to determine better ways to deliver the product to improve appropriate use.

Precision Public Health for campaigns (Cisneros, 2016; Khoury, 2018)	Availability	Use	Push	Better surveillance data and analysis to enable more precise targeting of health interventions to populations that will most benefit. Can include investment in surveillance data including at micro planning level to facilitate the introduction of products targeted at specific sub-population.
Accessibility				
Cold Chain Innovation (Gavi, the Vaccine Alliance 2019b; Global Grand Challenges, 2020; Lee, 2016; Lee, 2017; Lee, Schreiber and Rao, 2017; Robertson, Franzel and Maire, 2017)	Acceptability	Delivery	Pull	Investments in cold and supply chain infrastructure and management to improve delivery requirements. Examples include the introduction of temperature monitoring technologies, reduce vaccine stock-outs and enhanced information systems for more accurate monitoring, as well as use of new technology - solar power, mobile technology and biometrics.
Logistics & Preparations linked to Supply Chains (Africa Resource Center, n.d.)	Availability	Delivery	Pull	Support to agencies to improve logistics and delivery systems (e.g., bar coding, drones).
Strategic Purchasing (health financing) (Results for Development, 2023)	Availability	Use	Push	Strategic purchasing strategies are part of a broader effort to improve the efficiency of the use of public health funds to deliver affordable, high-quality health services to more people in an equitable way.
Technology Enabled Delivery Systems (Kohen, 2018; Lauerman and Kahn, 2018)	Availability	Delivery	Pull	Investment in new technology-based approaches to overcome barriers in health care delivery systems to enable access.
Behavioural Economics (Children's Investment Fund Foundation, 2019; Global Grand Challenges, 2014)	Availability	Use	Pull	Understand barriers people face when confronted with different interventions or products and how these barriers can be overcome.
Country Program Alignment (Bill & Melinda Gates Foundation, n.d.b.)	Availability	Use	Pull	Pool donor resources to align with partners and government in a few key system wide areas that cross diseases (e.g., supply chain, data systems and health extension programs).
Primary Health Care Performance Initiative (PHCPI)	Availability	Use	Pull	The PHCPI aims to bring together health policymakers, practitioners, advocates and development partners to: monitor primary health care vital signs; improve the quality of primary health care data; promote country collaboration and improvement; expand the availability of existing data to

(Primary Health Care Performance Initiative, n.d.)				more countries; and provide a platform to share lessons and co-develop tools for improving health care.
Data Systems (Stewart, 2018)	Acceptability	Delivery	Pull	Efforts to both generate new data and create data management systems to support better Ministries of Health and Finance's health care expenditure decisions.

2.3.3.1 Tools by disease of poverty or global diseases

These tools can also be categorised by whether they address "diseases of poverty" or "global diseases". Global disease products are important in all countries, including high-income ones. Diseases of poverty disproportionately impact the poor in low-income countries; the absence of profit incentives to invest in these diseases means there have been relatively few innovative products for these diseases (Figure 2.1). In the case of a "global disease" like rotavirus, vaccine access tools have focused on stimulating demand, vaccine pricing, and ensuring supply. For pneumococcal disease, another "global disease," a pilot AMC resulted in the production of affordable vaccines adopted to meet low-income country product suitability requirements. (Kettler, Lehtimaki and Schwalbe, 2020). COVAX is an example of an AMC for a global disease, which also relied on the buying power of pooled procurement to reduce price (Gavi, the Vaccine Alliance 2021b). The success of this initiative is currently under evaluation and as such not addressed in this thesis.

In the case of "diseases of poverty," tools include expedited regulatory pathways, push funding, public-private research initiatives, and the development of target product profiles (TPP) (Kettler, Lehtimaki and Schwalbe, 2020).

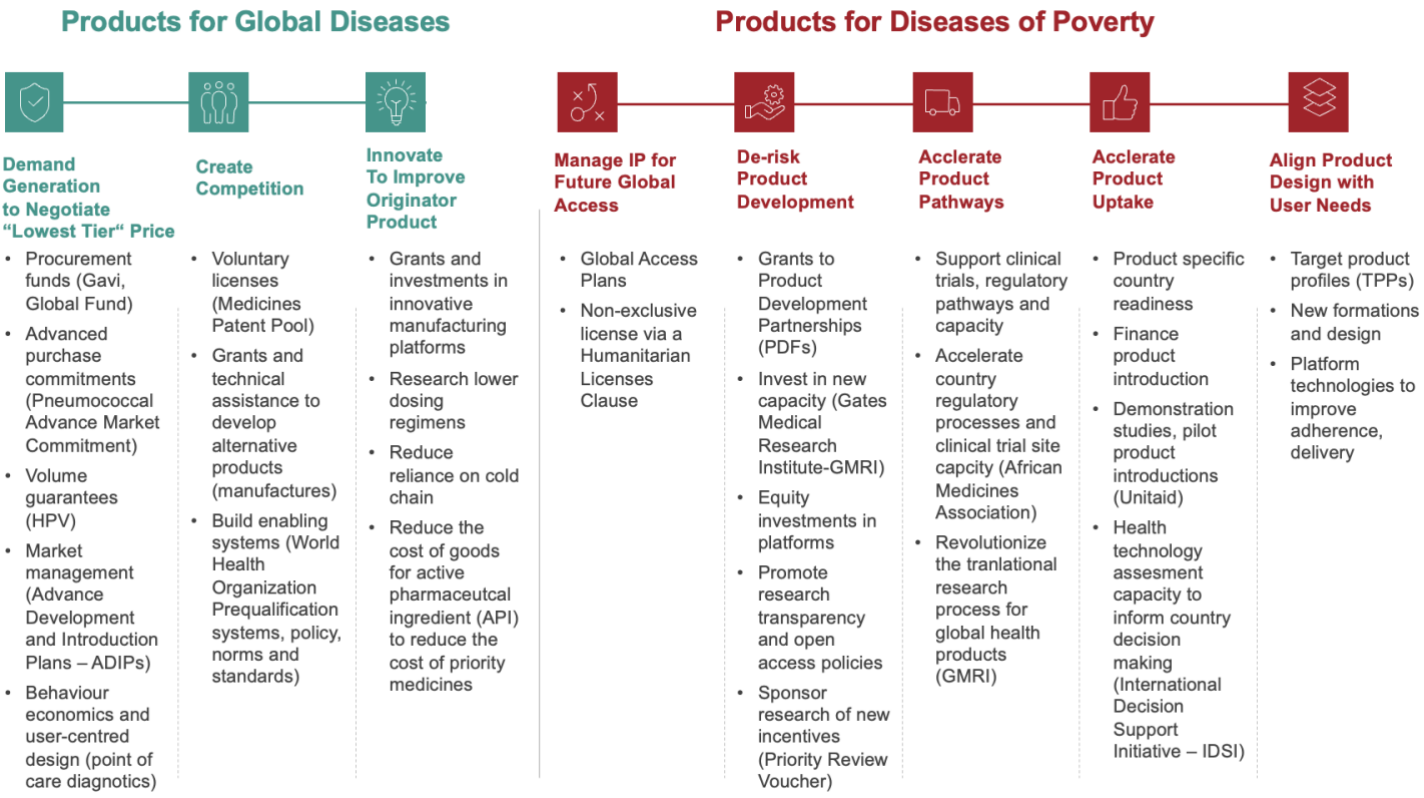

Figure 2.1 Illustrative approaches to access to medicines used by Bill & Melinda Gates Foundation, by disease type

2.3.3.2 Tools by role in the R&D value chain

In addition to looking at access tools in terms of whether they can be applied to "global diseases" or "diseases of poverty," this thesis also categorises tools by where they fit in the R&D value chain (see Figure 2.2). This exercise aimed to demonstrate that a range of interventions to improve access can be applied at any given time and that there are a range of potential access interventions that can be applied across the product development lifecycle.

Further, different tools or "levers" may be employed independently, simultaneously (e.g., volume guarantees and investments in "market managers" to generate demand), or irrespective of development phase and across the development continuum (e.g., regulatory strengthening, AMCs).

Figure 2.2 Access tools identified that are used by the Bill & Melinda Gates Foundation to improve access by stage along value chain. The list at the bottom of the graphic is relevant at multiple phases of the product development cycle.

2.4 Discussion

The research in this chapter shows that access to medicines for LMICs has been a focus of discussion since the mid-70s, and interest and activity intensified with the influx of funding in the early 21st century, the MDGs, and the SDGs. While definitions vary, the term most

frequently includes in some form or other all four "As", defined, broadly speaking as: available, in sufficient quantities and timely manner; acceptable, in terms of quality, usability, and appropriateness for LMICs; accessible, to populations where and when they are needed; and affordable, regardless of ability to pay. There is also a range of access tools across the end-to-end process of vaccine research, development, and rollout that can be categorised within the "4A's" framework and that contribute to improving access to medicines along the development process.

Optimising access to quality medicines, particularly for underserved populations and countries facing economic challenges, requires establishing a strong connection between the tools and using them purposefully and in unison (Kettler, Lehtimaki and Schwalbe, 2020). It also requires that product developers and donors take into account from the beginning of the process the needs of end users, including communities, health workers, and policymakers (Frost and Reich, 2008).

If the tools are to be truly effective and result in "end-to-end action" across the product development lifecycle, collaboration and coordination among stakeholders, including international organisations, national and local governments, civil society, communities, and the private sector, is key (Cameron et al., 2023).

The changing context and persistence of poverty across settings mean that medicines may also require some type of concessionary pricing across a range of settings (World Health Organization and World Trade Organization, 2001). Access strategies also need to account for uncertain demand, the dual disease burden faced by LMICs, the need for pooled and innovative procurement, including for non-communicable diseases (NCDs), value-for-money assessments, and an understanding of the potential trade-offs governments, health workers, and patients will face in allocating scare resource (Glassman et al., 2012).

Lessons learned from the rollout of the COVID-19 vaccine will provide an important case study on the limitations of current policies to provide access to new vaccines. With this global disease, low- and middle-income countries were squarely left out when demand exceeded supply (Duroseau, Kipshidze and Limaye, 2022). While the COVAX partnership between Gavi, UNICEF, and WHO aimed to address both upstream (R&D) and downstream (implementation) barriers and bottlenecks, this effort has been deemed largely unsuccessful and will provide ample material for future studies, many of which, including COVAX itself,

are already underway (Gavi, the Vaccine Alliance, 2022a; Goldhill, Furneaux and Davies, 2021; Shao, 2024).

While numerous access tools have been utilised over time, there has been an overall lack of end-to-end analysis and formal evaluation or assessment of impact, effectiveness, or suitability in relation to disease type. Often, multiple tools are implemented simultaneously, but their combined effectiveness and optimal application in specific circumstances are not thoroughly understood (see Figure 2.3 as an example of different tools to address vaccine affordability).

Figure 2.3 Different tools to address the same goal of affordability

Improving access to medicines requires a deliberate and evidence-based approach to applying the multiple tools available (Bigdeli et al., 2013). Conducting comprehensive evaluations of access tools, fostering patient engagement, and strengthening the linkages between the demand- and supply-sides are crucial steps toward achieving equitable and effective access, including affordability, acceptability, accessibility, and availability (Bigdeli et al., 2013; Cameron et al., 2023).

2.5 Conclusion

Many of the access tools identified (e.g., global access plans, global procurement funds, volume-based tiered pricing, geography-based voluntary licenses) were developed for a world when the majority of "core beneficiaries" were concentrated in development aid-eligible low-income countries and development aid was growing. Companies were ready to offer concessionary pricing (Chalkidou et al., 2020). However, nearly two-thirds of poor people now reside in countries classified as middle-income (Mahler, Yonzan and Lakner, 2023), making them ineligible for concessionary pricing and official development assistance. Even when concessionary pricing is available, as was shown in the case of COVAX, other barriers prevent these countries from accessing vaccines, including the incentive for manufacturers to sell to the highest bidder (Pilkington, Keestra and Hill, 2022).

With the changing context, the current system may no longer be equipped to address the access challenges of today and tomorrow (Kettler, Lehtimaki and Schwalbe, 2020; Oxford Poverty and Human Development Initiative and UNDP, 2023). For this reason, re-evaluating the structure of access and its constituent components is critically important.

In light of this, the next chapters have a use-case approach to assess the "4A's" framework with a focus: on vaccines to shed light on whether this framework continues to serve as a relevant tool for analysing and addressing access-related concerns; and on "supply-side" interventions including policy levers related to vaccine production overall (Chapter 3), incentives for COVID-19 vaccines and more broadly (Chapter 4), and distribution strategies for COVID-19 vaccines in New York City (Chapter 5).

Chapter 3: Vaccine Production

3.1 Introduction

The COVID-19 pandemic shed light on the critical role of vaccines in public health and pandemic preparedness and response. It also highlighted the challenges surrounding equitable distribution and affordable vaccine access. While these issues have been ongoing, the urgency of the pandemic magnified their significance. This chapter explores how a range of aspects related to vaccine development affect availability and affordability.

One of the key challenges in vaccine rollout in low- and middle-income countries (LMICs) is a significant time lag between the introduction of vaccines in high-income countries and their availability at scale in low-income countries. This delay can often span several years, and it is influenced by a range of factors. For example, there was an 11-year delay between when the vaccine that protects against *Haemophilus influenzae* type b (Hib) infection was introduced in high- versus low-income countries. The delay was primarily because of uncertainty about disease burden, vaccine cost, and limited global supply (Gavi, the Vaccine Alliance n.d.b..; Luthra et al., 2021).

Another challenge is the complex nature of intellectual property (IP) protection and patents. Vaccine development involves substantial investments in research and development (R&D), and intellectual property rights (IPR) play a role in incentivising innovation and recouping costs. However, stringent IP protection can create barriers to affordable access, particularly for low-income countries that may struggle to negotiate favourable licensing agreements or produce generic versions of vaccines. Rigorous regulatory oversight associated with vaccine development and approval is vital; however, it hampers timely access to vaccines in LMICs. While stringent regulations ensure safety and efficacy, they can also result in delays in the introduction of vaccines, especially in resource-constrained settings where regulatory capacities may be limited. Streamlining regulatory processes without compromising safety standards could help expedite the introduction of vaccines (Scheppler et al., 2021).

Another critical aspect is technical support and know-how transfer from vaccine innovators to manufacturers in low-income countries. Vaccine manufacturing requires specialised knowledge and infrastructure. Facilitating technology transfer and providing technical assistance to manufacturers in low-income countries can enable local production and contribute to the availability of affordable vaccines (Price, Rai and Minssen, 2020).

Market dynamics also play a role in impeding vaccine access. High-income countries with greater purchasing power often secure large volumes of vaccines through advance purchase agreements, leaving fewer doses available for low-income countries. This imbalance in purchasing power and competition for limited supplies hinders equitable distribution.

This chapter explores the potential for increasing LMICs' access to new vaccines. It provides an overview of vaccine R&D, key actors in the ecosystem, costs and timelines, barriers to accelerating time to market for vaccines in LMICs, and potential policy levers to explore moving forward, taking into account some early lessons learned during the COVID-19 pandemic.

3.2 Methods

In order to provide a comprehensive overview of vaccine production, we conducted an integrative literature review to allow for inclusion of both primary research studies, along with other documents (including opinions, discussion papers, and policy documents) (Cronin and George, 2020; Lubbe, Ham-Baloyi and Smit, 2020; Snyder, 2019). This review drew on existing published and grey literature to answer the following questions: "What is the process of developing a vaccine?"; "what does the market look like?"; "what are the main challenges/opportunities for scaling up and ensuring access in LMICs?"; and "where can efficiencies be made?"

The initial step included a search through PubMed [https://pubmed.ncbi.nlm.nih.gov/] using the search terms "vaccine," "manufacturing," and "access." The terms "low income," "low- and middle-income country," or "LMIC" were then added with an aim to identify relevant articles. The search was limited to publications between 2000 (the founding of Gavi) and the end of 2020.

This search identified 268 results. A title-abstract review was then conducted, excluding non-English language publications, publications that were antigen-specific (e.g., influenza or tuberculosis [TB]) or initiative-specific (e.g., pneumococcal advance market commitment), publications focused on high-income countries, and working group or conference proceedings. This resulted in 26 articles for full-text review and reference scanning ("snowballing"). When adding the term "low-income," "low- and middle-income," or "LMIC," an additional 10 articles were identified with two advancing to full-text review.

To complement the literature search, we searched grey literature by relevant organisations in the field (e.g., Gavi, WHO, CEPI) with an aim to capture key insights, emerging trends, and foundational works not captured through the formal literature searches. Through this combined approach, we aimed to provide a thorough and nuanced analysis of vaccine manufacturing, drawing on established and grey literature and author insights.

To address potential author bias in the selection of sources and synthesis of information, an early draft of the published version of this chapter was circulated to independent vaccine research and development experts, including: Esteban Burrone, Elena Villanueva (MPP), Marie-Paule Kieny (formerly WHO), Aurelia Nguyen (Gavi, the Vaccine Alliance), Pat Fast (International AIDS Vaccine Initiative), Judit Ruis Sanjuan (UNDP), and Neil Cherian (CEPI).

3.3 Findings

The results are described in two sections below: the vaccine development process and key actors and their roles.

Of note, in the findings below, the developing country vaccine manufacturing network (DCVMN) is referenced as a group. It is important to note the diversity of membership and that some represent private companies while others are state-owned entities. While this chapter identifies some of the problems faced by developing countries vaccine manufacturers, it does not aim to provide an in-depth analysis of these issues. Key aspects that would require further exploration include: the proportion of DCVMN members that are state-owned and the extent of this ownership; the diversity of their product portfolios; the actual impact of technology transfer issues on their operations; their capacity for innovation and adaptation around existing technologies; and the real extent to which IP is a barrier for their vaccine manufacturing.

3.3.1 Vaccine development process

Vaccines are specialised biological products created through the manipulation of genetic material and living organisms, such as animal cells, yeast, bacteria, insect cells, or fertilised eggs (Aars, Clark and Schwalbe, 2021). Unlike small molecule medicines, vaccines have distinct characteristics in terms of their development, production, regulatory requirements, target population, and patent structure. While generic medicines are chemically identical to their originators, vaccines that contain the same active components are essentially considered

as a "new" entity. Therefore, even the so-called second-generation vaccines need to undergo human studies to ensure their safety and effectiveness (Nguyen and Schwalbe, 2019). Additionally, any new entrant in the vaccine market must replicate the development and manufacturing processes undertaken by the original innovator to establish equivalence or non-inferiority.

Vaccine development involves several key steps, beginning with R&D. The initial stage of R&D involves pre-clinical development in the laboratory, often accompanied by patent filings. If a candidate vaccine shows promise in animal models, it progresses to clinical trials. Phase I trials test dosing and safety in humans, followed by phase II trials that assess immunogenicity and efficacy. Phase III trials involve larger sample sizes to further establish efficacy and safety. The company applies for licensure and registration after the vaccines have proven safe and effective. After market approval, ongoing monitoring of adverse events, known as pharmacovigilance, occurs in phase IV (Plotkin et al., 2017).

Developers plan for large-scale production to meet future demand as soon as a vaccine begins phase I trials. Initially, production quantities are limited to what is required for laboratory testing. Refinements to the manufacturing process are made during clinical and commercial scale-up. Scaling up biological processes can be challenging, requiring robust quality assurance and quality control measures. Even after licensure, manufacturers continue efforts to try to improve production (World Health Organization, n.d.d.).

Guidelines for conducting clinical trials are established by regulatory authorities, who also grant developers authorisation to proceed based on successful preclinical results. New trial designs, such as pragmatic trials, are starting to be used to complement data generated from randomised controlled trials and, for industry, it can be incredibly valuable as it decreases the costs of post-licensure evaluations. Safety and efficacy data are submitted to the relevant regulatory body for licensing following pre-clinical and clinical testing. Regulators conduct inspections of manufacturing sites and oversee lot release to ensure ongoing adherence to quality standards even after market authorisation. Regulatory scrutiny also applies to post-licensing product improvements and post-marketing requirements (World Health Organization, n.d.d.).

Developers file for patents as they gain insights about their products. Patents can provide a time-limited exclusivity period for manufacturing, sales, and related activities, including follow-on innovation. In practice, the period of exclusivity may be shorter than the actual

patent duration because patent filings may occur during product development (e.g., before market authorisation) (Höpfner, 2014). Market development considerations, such as market potential, likely purchasers, production capacity, pricing structures, and logistics influence decisions on where to market the vaccine and whether new manufacturers would want to compete.

3.3.2 Key actors and their roles

The vaccine research and development ecosystem involves many actors whose roles have evolved over time. These actors, and their main focus of work, are described below.

3.3.2.1 Research and Development

Government entities primarily focus on early-stage R&D within their domestic mandates. For instance, the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH) in the United States and the European Commission (EC) are all significant research funders, alongside governments including France, Japan, and Germany, who support research either by grants to privately owned entities or their dedicated agencies.

Vaccine manufacturers can be broadly categorised into multinational corporations (MNCs) and developing country manufacturers. Multinational corporations are mostly organised under the trade group International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), representing companies involved in the production of drugs and vaccines. Most developing country manufacturers are part of the DCVMN. The DCVMN is a public health-driven, international alliance of over 40 vaccine manufacturers from 15 countries and territories engaged in vaccine research, development, manufacturing, and supply for local and global use (DCVMN, n.d.).

A significant portion of innovation is now also driven by private biotechnology companies (biotechs) and academic institutions. Multinational corporations focus more on development, registration, and manufacturing - areas that align with their strengths and require substantial capital. As a result, MNCs increasingly replenish their development pipelines through in-licensing and occasional mergers and acquisitions (Schuhmacher et al., 2013). Additionally, DCVMNs have made notable progress in rapidly developing complex second-generation vaccines, such as hexavalent vaccines, human papillomavirus vaccines (HPV), and pneumococcal conjugate vaccines (PCV), without formal technology transfer. Structural biology, protein engineering, immunology, manufacturing platforms, and other vaccine

science advances have further contributed to changing the vaccine landscape (Lurie et al., 2020).

While biotech firms, academia, and public research entities play a vital role in early-stage research, they may face challenges in generating sufficient data and navigating the clinical development and licensure processes due to financial constraints and a lack of in-house technical capabilities. Nevertheless, the number of vaccine development programs among small biotechs has more than doubled in recent years, and there has been a substantial increase in emerging-market players (Azimi et al., 2019). A focus on second-generation vaccines and increased competition is also reshaping the vaccine manufacturing landscape, as has the COVID-19 pandemic, with many more players now engaged (World Health Organization, 2023b).

Despite limited financing and technical capabilities, DCVMN manufacturers are increasingly involved in R&D, often by collaborating with organisations possessing specialised capabilities for different stages of the development process. Notable examples include the development of the meningococcal A conjugate vaccine (MenAfriVac) by the Serum Institute of India with investment and technical assistance from the BMGF and PATH (Gavi, the Vaccine Alliance 2015).

Product development partnerships, established around two decades ago by organisations like the BMGF and Rockefeller Foundation, have contributed significantly to the development of vaccines for neglected diseases or diseases of poverty, such as TB, HIV/AIDS and malaria (Morrison, 2015). These partnerships have generated awareness and galvanised efforts in their respective fields, even though the complex scientific challenges associated with these diseases have resulted in a limited number of licensed products over the years (Moran et al., 2010).

Some organisations also now focus on "enabling sciences" to accelerate development timelines and facilitate comparisons across similar biological entities. This includes investing in the development of harmonised biological standards and assays to compare products and improving animal models to enhance the validation of proof of concept (Coalition for Epidemic Preparedness Innovations, 2022).

With regard to COVID-19, WHO championed a new mRNA vaccine “hub” in South Africa. The hub, based in South Africa, provides financial assistance and training support to build capacity among LMIC vaccine producers (World Health Organization, 2021c).

3.3.2.2 Manufacturing

Government-backed industries and larger MNCs have traditionally carried out manufacturing because it is particularly resource-intensive. However, there has been a shift towards outsourcing manufacturing, including contract manufacturing organisations (CMOs), valued at $1.8 billion in 2016 (Grand View Research, 2018). The main drivers for this outsourcing trend include the ability of CMOs to provide quality, reliability, and regulatory expertise (Pharma's Almanac, n.d.). Outsourcing manufacturing functions can lower financial risks and facilities costs, particularly in pre-clinical and phase I/II trials. As projects progress to phase III and commercialisation, there is often a transition to in-house manufacturing to gain greater control over the product when the level of financial risk is lower.

From a volume perspective, the Serum Institute of India is the largest vaccine manufacturer, producing almost as much as its three closest competitors combined. However, although they produce lower volumes, MNCs such as Pfizer, Sanofi, Merck, and GlaxoSmithKline (GSK) rank higher in value due to their substantial presence in high-income markets. Several governments, including China, Russia, Indonesia, and Brazil, also have significant manufacturing capabilities focused on domestic and regional demand (World Health Organization, n.d.b.).

Because of the intrinsic biological variability of the materials and their interactions, vaccine manufacturing poses higher risks of batch failure than other pharmaceuticals (Nguyen and Schwalbe, 2019). Batch release processes, which involve *in-vivo* testing, can further prolong the manufacturing timeline.

Because they are producing biologics, developers must demonstrate quality control, consistency, and quality assurance throughout the manufacturing process, including scale-up. These processes, collectively known as "Chemistry, Manufacturing and Controls" (CMC) (Peterson and Altan, 2016), often require investments exceeding $50 million and significant labour resources, amounting to more than 80 person-years (Plotkin et al., 2017). Such a high fixed investment can be a challenge for second-generation developers. Additionally, all manufacturers are required to have lot-testing procedures to analyse purity, potency, and safety. This may involve *in-vitro* and *in-vivo* tests that take months to complete.

One way in which MNC manufacturers have supported DCVMN manufacturers is through fill finish agreements, whereby the product is made by an MNC and shipped in bulk, with syringes or vials filled locally, as are the labelling, packaging, and quality inspection. This

DCVMN fill finish has been utilised with a range of antigens including, most recently, COVID-19 vaccines (Pagliusi et al., 2020).

3.3.2.3 Regulatory engagement and approval

A Regulatory Body appointed by a government establishes and maintains the rules, laws, and policies required to ensure that medicines (including pharmaceutical products, vaccines, and other biologicals) are safe and effective and fulfil the quality specifications offered by the producer (Pan American Health Organization, n.d.). National regulatory agencies (NRAs) are responsible for the review of licensing applications, lot release, and monitoring the performance of the product in their country (World Health Organization, n.d.c.). Regulatory agencies also review technological innovations, including injection devices, platform technologies, and adjuvants. Each innovation requires a bespoke new regulatory pathway (Elmgren et al., 2013).

Vaccine manufacturers typically seek approval from the NRA in the country where they operate. To ensure compliance with Good Manufacturing Practice (GMP) and Quality Assurance/Quality Control (QA/QC) standards, regulators conduct inspections of manufacturing facilities. Regulators are also responsible for market authorisation applications. Market authorisation can be granted by the NRAs in the country of operation, through the centralised procedure in the European Union (EU), or by a regulatory authority of choice by the manufacturer. European countries have mutual recognition of assessments conducted by member states under the oversight of the European Medicines Agency (EMA) (Charloner-Larsson, 2003). National regulatory agencies approval is also required for batch-release of vaccines, and manufacturing facilities must undergo periodic inspections for QA/QC and GMP.

Through a process known as “prequalification,” WHO also plays a significant role. This process involves an assessment of a vaccine's compliance with safety and efficacy requirements for use in immunisation programs, as well as the functionality of the NRA responsible for its release (World Health Organization, n.d.a.). The WHO prequalification is required for vaccine purchases by UN agencies such as UNICEF and PAHO. Manufacturers pay product-by-product fees for the prequalification process (for both innovator and second-generation vaccines). WHO prequalification, which can take as long as 12 months, is required for LMICs procuring through a UN agency (Plotkin et al., 2017).

Across different geographies, from clinical trials to registration, efforts are underway to harmonise regulatory processes to reduce the burden on companies for filing and data requirements, including the recent creation of the Africa Medicines Authority (AMA) (Health Policy Watch, n.d.). Other examples of enhancing alignment include the African Vaccine Regulatory Forum (AVAREF) for clinical trials and the WHO Prequalification system for lot release (World Health Organization, 2020a). Both aim to streamline regulatory processes and ensure consistent standards. Harmonisation can help accelerate time to market while still addressing critical steps such as biosafety requirements.

3.3.2.4 Market development

Before the 1990s, large pharmaceutical companies did not consider vaccines a lucrative market, and smaller players lacked the financial capital or technology to engage. More recently there has been, however, significant growth in both value and volume, attributed, in part, to "blockbuster" vaccines, including multivalent diphtheria, pertussis and tetanus (DPT), pneumococcal, HPV, zoster, and hepatitis B vaccines.

Another driver was the establishment of Gavi. Gavi is a funding and procurement partnership that aims to improve LMICs' access to vaccines. Currently, Gavi purchasing covers over 20 diseases (versus six diseases when it was established in 2000). Gavi negotiates tiered pricing for low-income countries to increase access to vaccines. Under tiered pricing arrangements, eligible lower-income countries can purchase vaccines at significantly lower prices compared to middle-income and higher-income countries (Moon et al., 2011). This tiered pricing approach helps ensure affordability and accessibility for countries in need. For instance, Gavi-eligible countries in the WHO Africa region paid, on average, USD 37 million for HPV vaccines from GSK in 2018, while non-Gavi countries paid USD 114 million (World Health Organization, n.d.b.). As described in the previous chapter, eligibility for access to lower prices through Gavi is based on a country's gross national income (GNI). When a country transitions to a higher-income bracket, Gavi continues to give concessional pricing for a limited number of years so that countries can gradually assume the cost of payment (rather than face a price cliff) (Gavi, the Vaccine Alliance 2018).

As a result of logistical complexities (e.g., need for cold chain infrastructure), economies of scale (e.g., large shipping volumes), and requirements for stockpiling, many LMICs rely on procuring their vaccine supplies through UNICEF's Supply Division (UNICEF-SD) and PAHO's Vaccine Revolving Fund, which are also Gavi procurement partners. In contrast, upper-middle and higher-income countries primarily self-procure and finance vaccine

purchases through their national budgets and agencies (World Health Organization, n.d.b.). However, these different pathways can lead to access gaps, leaving certain countries with challenges in obtaining vaccines.

3.3.2.5 Normative guidance and WHO processes

Vaccine adoption decisions and immunisation policies are ultimately the responsibility of individual countries. Still, the WHO plays a significant role through its Regional Immunization Technical Advisory Groups (RITAGs) and Strategic Advisory Group of Experts on Immunization (SAGE). These expert groups review the efficacy and effectiveness of vaccines and provide recommendations on immunisation policy. Their recommendations may take into account factors such as cost-effectiveness, cost, and vaccine presentation suitability for specific settings. The recommendations can apply to a disease area or be directed towards a manufacturer (World Health Organization, 2016a; World Health Organization, 2016b). It is worth noting that all vaccines, whether they are innovator or second-generation, are assessed by these advisory groups.

The WHO's R&D Blueprint also contributes to vaccine-related decision-making (World Health Organization, n.d.i.). The document (and the process of developing it) aims to improve coordination and accelerate R&D for diseases of epidemic potential that pose a public health risk (World Health Organization, n.d.h.). It serves as a foundation for organisations like CEPI in determining their focus areas for disease prevention and response.

Special procedures are in place for the use of new or unlicensed products during emergencies. The U.S. Food and Drug Administration (FDA) Emergency Use Authorisation (EUA) (Food and Drug Administration, 2020a) allows, for example, expedited regulatory assessment and use of products during pandemics, epidemics, or outbreaks. Similarly, the WHO has the Emergency Use Listing Procedure (EUL) (World Health Organization, 2020c) in place, which serves a similar purpose of accelerating regulatory evaluation and facilitating the use of critical products during public health emergencies. These procedures help streamline the regulatory process and enable the rapid deployment of necessary interventions.

3.4 Discussion

3.4.1 Time to market barriers

Vaccine development involves multiple stakeholders and poses a range of complex challenges. While funding is a crucial factor in accelerating development, structural challenges can also impact the speed and efficiency of the vaccine development process.

First, the availability of well-equipped research facilities and infrastructure is essential for conducting vaccine research. Access to specialised laboratories, equipment, and skilled researchers can contribute to the efficient development of vaccines. Adequate investment in research infrastructure can help accelerate the discovery and development process.

Second, regulatory requirements must be in place to guarantee vaccine safety, efficacy, and quality. However, lengthy and complex regulatory processes can delay the approval and introduction of new vaccines. Streamlining regulatory pathways, harmonising standards, and facilitating faster review processes can help expedite vaccine development without compromising safety and efficacy.

The third area is manufacturing capacity. Vaccine production requires specialised manufacturing facilities and expertise. Limited manufacturing capacity can hinder the rapid scaling up of production to meet global demand, especially during public health emergencies. Enhancing manufacturing capabilities, investing in advanced technologies, and fostering collaborations between manufacturers can contribute to increased vaccine production capacity.

Collaboration and knowledge sharing are key. Collaboration between different stakeholders, including researchers, manufacturers, governments, and international organisations, is crucial for advancing vaccine development. Sharing knowledge, data, and resources can help avoid duplication of efforts, promote innovation, and accelerate the development of new vaccines.

Despite being dismissed by Gavi and others (Forrest, 2022), IPR and lack of know-how or technology transfer can create barriers to the timely development and availability of vaccines, particularly in low-income countries. Encouraging technology transfer, licensing agreements, and knowledge-sharing initiatives can enable faster and more equitable dissemination of vaccine technologies, contributing to improved accessibility and affordability.

Finally, adequate and sustained funding is essential for vaccine R&D. Funding mechanisms that prioritise and incentivise vaccine development, particularly for diseases that disproportionately affect low-income countries, help address financial barriers and accelerate vaccine development efforts.

3.4.2 Opportunities for efficiencies

Addressing these structural challenges requires a collaborative and coordinated effort among governments, research institutions, manufacturers, regulatory agencies, and international organisations. By working together to overcome these hurdles, the vaccine development process can be accelerated, leading to faster access to safe and effective vaccines for global health challenges. Examples in each area of the product development value chain are described below.

3.4.2.1 Research & Development

Identifying indirect biomarkers or correlates of protection can help streamline vaccine efficacy studies. By using these biomarkers, it may be possible to avoid large-scale efficacy trials, reducing the time and cost required to demonstrate vaccine effectiveness. However, not all vaccines can rely solely on correlates of protection, and further research is needed to establish their validity (Plotkin, 2010).

Utilising innovative trial designs, such as adaptive or platform trial approaches, can expedite the development timeline. These designs allow for more efficient and parallel testing of multiple vaccine candidates, as seen during the Ebola crisis (Henao-Restrepo et al., 2016). Applying such innovative trial designs more broadly, particularly for diseases of poverty, could help accelerate vaccine development.

New technologies and enabling sciences offer opportunities to accelerate vaccine development and reduce costs. The development of new biological standards, assays, adjuvant technologies, and vaccine antigens, for example, can enhance the immune response, potentially reducing vaccination frequency or enabling dose sparing (Pashine, Valiante and Ulmer, 2005). Viral vector technology and mRNA vaccines, as demonstrated in the fight against COVID-19, have shown promise in terms of rapid development and scalability (World Health Organization, 2021a).

DNA and mRNA vaccines represent novel approaches with the potential to revolutionise vaccine development (Sandbrink and Shattock, 2020). These vaccines deliver genetic material that codes for specific antigens, stimulating the recipient's cells to produce the corresponding

proteins and provoke an immune response (Park et al., 2021). These technologies offer simplified research steps, standardised production methods, scalability, and potential flexibility in adjusting vaccines to pathogen mutations or changes. mRNA vaccine success for COVID-19 has marked an important milestone in this field (Rohner et al., 2022).

Given the involvement of public funders and the potential of emerging technologies, it is important to address access issues upfront in the R&D process. This includes IP, technology transfer, and pricing considerations. Fragmented IP landscapes can hinder access (Martin and Lowery, 2020), but initiatives like the COVID-19 patent pool established by the WHO aim to promote access to these technologies (Bioworld, 2020).

In summary, leveraging innovative trial designs, embracing new technologies, and addressing access and IP concerns can help overcome structural challenges and accelerate vaccine development.

3.4.2.2 Manufacturing

The manufacturing of vaccines presents both general challenges that apply to all vaccines and specific challenges that are unique to different vaccine classes (Plotkin et al., 2017).

The optimisation of each step in the production process, along with associated scale-up, takes years of development and is typically done concurrently with preclinical and clinical development. This expertise and knowledge, often referred to as "know-how," can be a significant barrier to the rapid development of second-generation vaccines. New players in the field may lack access to this know-how, making it challenging to reproduce and scale up the manufacturing processes (Price, Rai and Minssen, 2020).

Further, vaccine manufacturing facilities must be dedicated or reconfigured for the specific biological entities being produced. This adds complexity and time to the manufacturing process, as facilities must meet stringent regulatory requirements and ensure appropriate infrastructure and equipment. Also, manufacturers must establish and implement lot-testing procedures to assess the stability, purity, and potency of vaccine products. These testing procedures are essential for ensuring product quality but can also introduce delays in the manufacturing timeline.

With upfront investment, many of these challenges can be overcome. Technology transfer plays a crucial role in overcoming manufacturing challenges. It involves transferring the knowledge, processes, and expertise required for vaccine production from one entity to

another. Efforts to address this challenge include establishing IP and "know-how" pools, technology transfer hubs, and making requirements for technology transfer a condition of public funding support. It also requires investing in R&D capacity and human resource capacity, particularly in low-income countries, which are largely underfunded (Franzen, Chandler and Lang, 2017).

Investing in capacity building and supporting knowledge transfer can help address manufacturing challenges and increase access to vaccines in low-income countries. Philanthropic organisations and donor support, along with partnerships and collaborations, can play a vital role in facilitating this capacity building (Médecins Sans Frontières, 2017).

Brokering partnerships and facilitating discussions and agreements related to IPR and technology transfer can also help overcome barriers and promote collaboration between targeted DCVMN manufacturers and potential players in other regions. For example, the MPP and WHO have moved forward on such an effort in COVID-19 therapeutics, diagnostics, and vaccines and could do more to advise on agreement structures and facilitating partnerships (World Health Organization, 2020b).

In summary, addressing these manufacturing challenges, promoting technology transfer, investing in capacity building, and facilitating collaborations are important areas for future reform and improvement. By reducing costs, diversifying manufacturing (with a focus on regional production in LMICs), increasing volumes, and enhancing overall access, these efforts can contribute to vaccine development and availability of vaccines.

3.4.2.3 Regulatory

The complex nature of vaccine production and the need for biosafety add additional layers of scrutiny and approval. Compliance with biosafety level (BSL) standards is important for vaccines that involve the manipulation of dangerous pathogens during production. Requirements involve certification for biological hazard and biosafety level, prevention of contamination, proper cell line management, sourcing specific-pathogen-free raw materials (such as eggs), freeze-drying capacity, conjugation technology, and access to non-standard adjuvants, among other conditions.

Regulatory agencies need to have sufficient competencies and resources for product assessment, including the capability to evaluate complex vaccine development processes. Building and maintaining expertise within regulatory agencies and adequately resourcing them is essential for efficient and effective regulatory oversight.

Improving regulatory processes, harmonising standards, and ensuring that regulatory agencies have the necessary competencies and resources are key areas of focus to accelerate access to safe and effective vaccines without compromising safety and efficacy.

3.4.2.4 Intellectual Property

Intellectual property protection, including patents, is crucial in incentivising companies to invest in vaccine R&D and manufacturing. However, the IP landscape for vaccines can also present challenges and barriers, particularly for new entrants (Médecins Sans Frontières, 2017).

Vaccine manufacturers rely on patents of vaccine technologies to protect various aspects of vaccine development and production, including manufacturing technologies, production processes (filtration, purification, conjugation, freeze-drying), and active ingredients (antigens, adjuvants), among others. Numerous patent families have been filed for vaccine-related technologies (World Intellectual Property Organization, 2012). While IP protection encourages innovation, there can be instances where patenting does not reflect substantial technological advancements, leading to potentially lengthy and unjustified exclusivity periods that limit price competition and follow-up innovation (Médecins Sans Frontières, 2017).

Some patents may be subject to complex licensing agreements and royalty payments, involving multiple holders of IPR (Cunningham et al., 2016). Negotiations and disputes over licensing terms can create financial stakes and further complicate the IP landscape (Plotkin et al., 2017).

Developers normally file patents in multiple jurisdictions, as patents are generally not transferrable across countries. This adds to the complexity and costs associated with protecting vaccine-related IP. The IP landscape, coupled with complex licensing agreements and the need for expertise in navigating IP rights, can create substantial obstacles for new entrants in the vaccine market (Nguyen and Schwalbe, 2019). Understanding and accessing relevant patents require resources and expertise, which may be a challenge for smaller vaccine manufacturers.

A dedicated clearinghouse or resource centre focusing on reducing IP-related barriers for vaccine manufacturers could help facilitate access to patent licenses and provide support in navigating the IP landscape. This could include initiatives such as creating a vaccine patents database, offering financial resources or other tools, for example, analysis on freedom-to-operate.

In summary, addressing IP-related challenges and promoting access to affordable vaccines require a balance between protecting innovation and ensuring the wider availability of life-saving products. Measures to streamline patenting processes, promote licensing agreements that facilitate access, and support capacity-building efforts can help improve the IP landscape for vaccines.

3.4.2.5 Costs

The economics and market dynamics of vaccines differ from those of small-molecule medicines. The absence of "generic vaccines" means that even after the expiration of patents, new entrants face significant upfront investments and fixed costs, creating a barrier to competition. The original vaccine manufacturer may have already recouped its investments during the patent monopoly period, which could enable them to reduce prices over time in the presence of competition (Nguyen and Schwalbe, 2019).

To address this challenge and promote competition, various initiatives have been implemented. To help offset fixed and development costs, the BMGF and governments have provided "push funding" and incentives to DCVMN's companies developing second-generation vaccines for low-income countries. DCVMN with partial government ownership may have lower profit margin requirements than private- or shareholder-based structures. This allows them to prioritise affordability and accessibility, potentially enabling them to offer vaccines at lower prices.

By providing upfront funding, incentives, and alternative business models, efforts are being made to overcome the barriers to competition in the vaccine market and ensure access to affordable vaccines, especially for low-income countries. These strategies aim to balance the need for sustainable vaccine development with the goal of improving global health outcomes.

3.5 Conclusion

While during COVID-19 there was a critical need for expediting vaccine development and deployment, it highlighted multiple opportunities to overcome challenges and expedite access for LMICs. Lessons learned from this experience informed actions for each vaccine development and distribution stage to improve the affordability and availability of new and second-generation vaccines. Three areas stand out in particular where action could lead to expedited availability: regulatory acceleration, adequate manufacturing capacity, and sharing of IP.

Strengthening international cooperation to harmonise regulatory processes, standards, and requirements across different agencies (while ensuring safety and efficacy) can enhance efficiency, lessen resource requirements, and expedite approvals and introduction, including and in particular new technologies (like mRNA and DNA vaccines) (Lurie et al., 2020). Also important is the use of special procedures to expedite approvals, such as Emergency Use Authorisation, which allowed early market entrance for all COVID-19 vaccines (Food and Drug Administration, 2020a).

To ensure rapid and large-scale deployment of vaccines, manufacturing capacity must be in place to meet high demand. Simply having access to manufacturing facilities is not enough; there is a need for sufficient know-how about manufacturing processes, particularly in low-income countries and regions (Price, Rai and Minssen, 2020). As COVID-19 has demonstrated, enhancing global vaccine production capacity requires investment in technology transfer, freedom to operate around patents, and collaborative agreements between originators and manufacturing companies in different regions. Promoting technology transfer and providing technical support to manufacturers in low-income countries can enable local production and reduce dependence on external suppliers.

Biopharmaceutical manufacturers and governments have utilised various strategies to accelerate access to new technologies. These include governmental compulsory licensing, voluntary licensing agreements, patent oppositions, patent pooling, and technology transfer. While the application of these approaches to vaccines has been limited, in future, improving transparency and streamlining IP arrangements can contribute to increased diversity of suppliers and, ultimately, alleviation of supply constraints (Contreras et al., 2020).

Whichever of these levers is prioritised, financial support is required for vaccine development, procurement, and distribution in low-income countries, as is an investment in regulatory, manufacturing, and distribution capacities.

The advancements achieved through the R&D of COVID-19 vaccines showed that many of the challenges related to vaccine access could be overcome with political will and sufficient financing. Continued investment, collaboration, and commitment are essential to building on these advancements and ensuring affordability and availability of future life-saving vaccines.

Chapter 4: Financial Incentives for Adult Vaccination

4.1 Introduction

In December 2020, the United States (US) introduced the first COVID-19 vaccine under emergency use authorisation (EUA) (Food and Drug Administration, 2022). Within a span of 18 months, WHO authorised 11 COVID-19 vaccines for use globally (COVID-19 Vaccine Tracker, 2022), and over two-thirds of the world's population received at least one vaccine dose (Our World in Data, 2022).

In some places, within weeks to months following introduction, acceptability became a challenge. Vaccine hesitancy, indecision, and uncertainty, observed in relation to other vaccine-preventable diseases, were also manifest in the context of COVID-19 (Centers for Disease Control and Prevention, 2021; Larson et al., 2014; Lazarus et al., 2022; Shen and Dubey, 2019).

In response to COVID-19, many governments and local authorities implemented incentive programs to encourage vaccination among individuals to foster acceptability (Roy and LeBlanc, 2021). Incentives range from direct cash transfers and lottery tickets to non-financial rewards, including doughnuts, blenders, herring, and even cows (Bremner, 2021; Henley, 2021; Sullivan, 2021). Residents of New York City, for example, were offered incentives such as a $100 pre-paid debit card, free amusement park tickets, and a trip to the Statue of Liberty (City of New York, 2022; New York State, 2021a).

This narrative review examines the use and effectiveness of incentives as a policy lever to increase coverage through improving acceptability, defined in this case as “the degree to which individuals accept, question or refuse vaccination” (Thomson, Robinson and Vallée-Tourangeau, 2016).

4.2 Methods

This chapter is based on a narrative review. It follows a narrative review approach to allow for the inclusion of various types of interventions, outcomes, and populations and thematic analysis (Green, Johnson and Adams, 2006). While some methods from the practice of a systematic review were borrowed (e.g., PRISMA statement), because of the limited number of studies available and the breadth of scope of the research question, we were unable to

conduct any grading of evidence or combined statistical data analysis that could help reduce bias in the data and conclusion (Collins and Fauser, 2005).

4.2.1 Search strategy

The search was conducted by utilising MEDLINE, PubMed, and Cochrane databases to identify peer-reviewed articles published in English and Arabic between January 1, 2012, and February 9, 2022. Relevant articles were identified by conducting an abstract and title search using any of the following keywords: (Incentiv*; cash transfer) AND (COVID-19; SARS-CoV-2; Coronavirus; influenza; flu; maternal/pregnan*/wom*n tetanus) AND (Vaccin* or immunis* or immuniz*). Additionally, reference lists of the included articles were searched manually to identify any additional relevant publications. Preprint studies on MedRxiv were also reviewed.

4.2.2 Selection criteria

The review focused on adult vaccines, in particular COVID-19, influenza, HPV, hepatitis B, and maternal tetanus vaccines. Childhood immunisation studies were excluded since these incentives typically target caregivers rather than patients.

Identified articles were screened by two independent reviewers using inclusion criteria as follows: 1) immunisation targeting the adult population, and 2) provision of material or financial incentives. More specifically:

- Population: human population;
- Intervention: any positive (financial, material, reputational) incentives;
- Comparison: any but ideally no incentive or placebo – this was kept broad because this was a narrative review;
- Outcome: uptake of public health measure (vaccination) – again broad for narrative review;
- Study design: interventional or observational – because interested in practical rather than theoretical evidence;
- Time period: February 2020 onwards for COVID-19, <10 years old for non-COVID-19 to maintain relevance and applicability; and
- Language: English or Arabic – languages spoken by the team.

Articles were excluded that focused on: 1) negative or punitive incentives (such as penalties or restriction of movement), 2) routine childhood immunisation where incentives were

directed at caregivers (rather than patients), and 3) incentivising behaviour at the facility level (e.g., clinic). More specifically:

- Population: animal studies, children – because incentives are usually targeted at caregivers;
- Intervention: negative incentives, including vaccine mandates – these have different mechanisms and theories compared to positive incentives. Combined interventions were excluded because it would not be possible to isolate effects;
- Comparison: an ideal is a comparator group, but the bare minimum was baseline measurement to ensure the ability to measure an effect;
- Outcome: studies which did not measure uptake of desired intervention; and
- Study design: modelling studies, commentary/letters that do not include reference to practical data to maintain practical applicability of findings.

Opinion papers, study protocols, and modelling studies were also excluded. The evidence from the selected articles was then synthesised following the approach described in the results section below.

4.2.3 Data extraction and analysis

The reviewers extracted relevant information from these articles, building a matrix using an Excel spreadsheet and including the study's objective, key findings, incentive type, vaccine, target group, and geography. The studies were categorised based on whether the incentives offered were material or financial in nature. Most studies (13) were conducted in the US. Additional ones were identified in Nigeria (2), Germany (2), and one each from Sweden, Singapore, Mexico, India, Australia, and the United Kingdom (UK). There were no studies identified for LMICs on incentives related to COVID-19. Two relevant studies on MedRxiv were not included in the review as they had not yet undergone peer review.

4.3 Results

The initial search yielded a total of 617 articles. Following the screening of titles and abstracts, the reviewers conducted a full-text assessment of 110 articles (80 identified through databases and 30 from reference lists), excluding duplicates (13) and three articles that could not be retrieved. In total 93 articles were reviewed, of which 26 met the inclusion criteria (see

Table 4.1). The PRISMA flow diagram in Figure 4.1 provides a comprehensive overview of the reasons for exclusion. Among the included articles, three were systematic reviews.

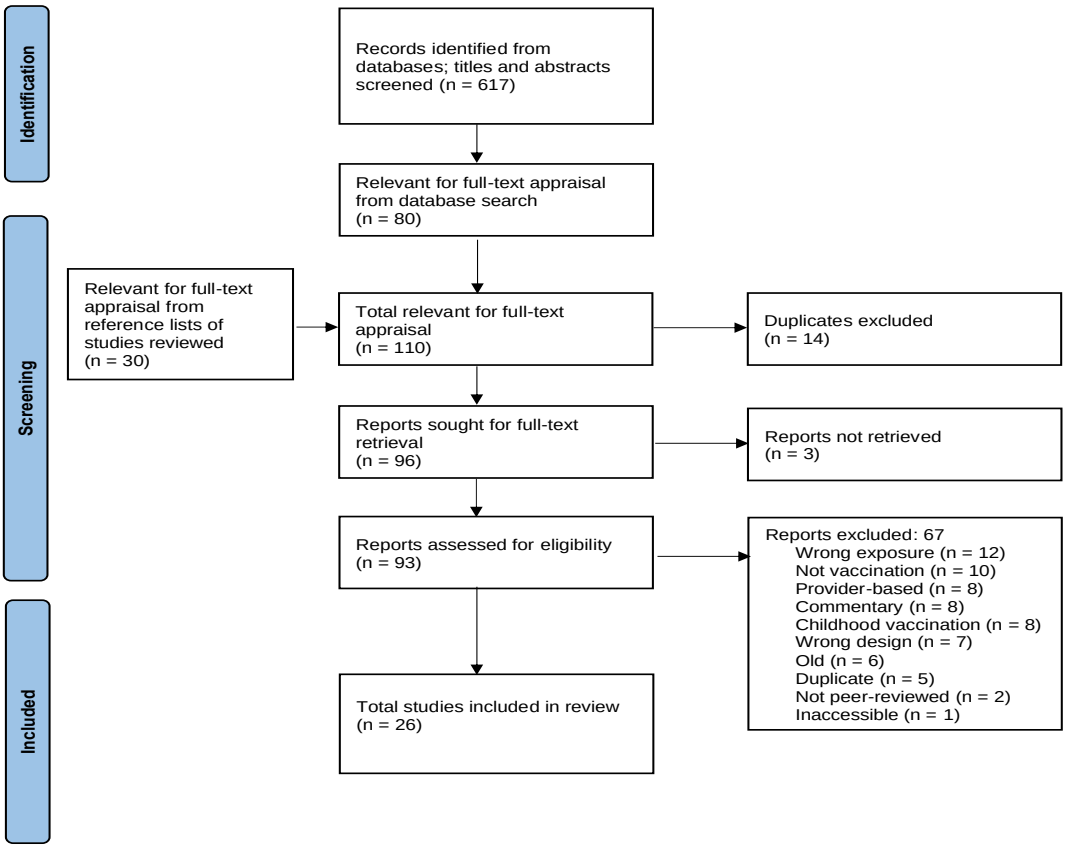

Figure 4.1 PRISMA flow diagram detailing article selection

The review identified 26 articles that discussed the use of incentives in relation to vaccination. These studies covered a range of vaccines, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis B, HPV, influenza, maternal tetanus, and a mix of different vaccinations. Among the identified articles, 12 focused on SARS-CoV-2 vaccines (Acharya and Dhakal, 2021; Barber and West, 2022), two on hepatitis B (Day et al., 2016; Tressler and Bhandari, 2019), two on HPV (Caskey et al., 2017; Mantzari, Vogt and Marteau, 2015), three on maternal tetanus (Chakrabati, Pan, and Singh, 2021; Okoli et al., 2014; Sato and Fintan, 2020), five on influenza (Bronchetti, Huffman and Magenheim, 2015; Cheema et al., 2013; Clark, Corrigan and Rousu, 2021; Lytras et al., 2016; Yue et al., 2020), one on a combination of tetanus, pneumococcus, and influenza (Salinas-Rodriguez and Manrique-Espinoza, 2013), and one on a mix of different vaccines (Herrmann et al., 2017). The target groups varied and included adolescents, students, older people, health care and social workers, and people who inject drugs.

4.3.1 Incentives

Of the 26 articles, the majority discussed financial incentives (18), lotteries, or the opportunity to win cash prizes (5). One article examined time off as an incentive, and two investigated a combination of different incentives.

For hepatitis B, HPV, influenza, and maternal tetanus vaccines, conditional cash transfers were explored as incentives. In Singapore, a study by Yue et al. (2020) involved offering a partial subsidy in the form of shopping vouchers to individuals aged 65 and older who received a seasonal influenza vaccine. The study found that increasing the incentive amount from 10 SGD to 20 SGD improved vaccine uptake, particularly among non-working individuals. Another study by Clark, Corrigan and Rousu (2021) assessed the willingness of college students in Pennsylvania, US, to receive the influenza vaccine at various price points. The results showed that for a certain price, the majority of participants would accept the vaccine, with most requiring less than 100 USD. Bronchetti, Huffman and Magenheim (2015) investigated the impact of financial incentives on influenza vaccine uptake among college students and found a significant difference when comparing the study to the control group.

The use of financial incentives to increase hepatitis B vaccine uptake among people who inject drugs was the focus of two systematic reviews. Herrmann et al. (2017) reported that incentives were associated with an absolute increase in vaccine uptake compared to control groups. Tressler and Bhandari (2019) also found higher odds of completing a 3-dose vaccine course than the pooled incentive group compared to a control group.

Mantzari, Vogt and Marteau (2015) examined the effect of financial incentives among girls aged 16-18 in the UK on HPV vaccine uptake. The study found an association between increased uptake of the first dose and completion of the vaccination course. Another study by Caskey et al. (2017) showed that adolescents receiving financial incentives had higher completion rates for the full HPV vaccination course compared to the control group.

Salinas-Rodríguez and Manrique-Espinoza (2013) assessed the effect of cash transfers among older adults in rural communities on pneumococcal, tetanus, and influenza vaccine uptake in a study in Mexico. Results indicated that those incentivised were more likely to have received each of the three vaccines.

Regarding maternal tetanus vaccines, three studies explored the use of conditional cash transfers. A pilot program in Nigeria demonstrated a significant increase in vaccination rates when incentives were part of a broader range of interventions (Okoli et al., 2014). Another

study from Nigeria found that financial incentives had a positive effect on vaccine uptake when the incentive amount was sufficient to cover travel costs (Sato and Fintan, 2020). Similarly, a program in India offering incentives for maternal health interventions, including tetanus, demonstrated a small positive effect (Chakrabati, Pan and Singh, 2021).

4.3.2 Non-cash transfers

Limited evidence was found regarding the use of non-cash incentives for any of the vaccines included (hepatitis B, HPV, or maternal tetanus vaccinations). For seasonal influenza, one systematic review and one cross-sectional study focused on healthcare worker vaccination. The systematic review by Lytras et al. (2016) included 11 studies and found that non-cash incentives such as gifts, perks, raffles, or group-level rewards did not significantly impact influenza vaccine uptake among healthcare workers. Similarly, the cross-sectional study by Cheema et al. (2013) surveyed healthcare workers and found no association between a one-hour time off incentive and influenza vaccination uptake.

4.3.3 COVID-19

Conditional cash transfers were also explored in the context of COVID-19 vaccination. Four of the six studies identified focused on the intent to vaccinate. Two assessed actual cash transfer programs.

A randomised survey conducted in the US by Robertson et al. (2021) in December 2020 found that financial incentives would lead to an 8% increase in COVID-19 vaccine uptake among American adults. While the middle-income group was the most responsive, the incentive size was not significantly associated with the outcome. The highest incentive was counterproductive for Black and Latino participants.

A German study from November 2020 did not identify any effect of offering a future financial incentive on intent to vaccinate, even controlling for participants' financial status (Sprengholz et al., 2021). However, a March 2021 nationally representative survey demonstrated that financial incentives would have an impact. Doubling the incentive corresponded to a doubling effect on vaccine uptake, primarily among undecided people (Kluver et al., 2021).

Two studies evaluated cash transfer programs implemented after the introduction of COVID-19 vaccines. In Sweden, a randomised control trial by Campos-Mercado et al. (2021) offered a cash incentive for COVID-19 vaccination within 30 days of vaccine availability of 200 Swedish kroner (approximately USD 24), resulting in a 4.2% increase compared to the

baseline. The effect was observed across all socioeconomic groups (Campos-Mercado et al., 2021).

Wong et al. (2022) conducted a non-randomised trial in North Carolina, US, using a difference-in-differences approach. The trial offered a cash card to adults (USD 25) receiving their first dose of the COVID-19 vaccine or driving someone to receive the vaccine. The incentives were associated with a higher vaccine uptake rate with 41% of participants stating that the cash card was an important reason for vaccination and 9% reporting that they would not have been vaccinated without it.

These studies demonstrate that cash transfers can positively impact COVID-19 vaccine uptake, particularly among undecided individuals and certain population groups. However, assessing the long-term sustainability and cost-effectiveness of cash transfer programs as incentives for vaccination requires further research.

Six studies were identified on the effects of lottery entry on vaccine coverage. The overall impact was limited. The Vax-A-Million campaign in Ohio, US, offered a chance to win a million-dollar prize to residents who received at least one dose of a COVID-19 vaccine. The result was a modest increase (from approximately 42% to 47%) in vaccination coverage (Sehgal, 2021). Other studies assessing lottery programs in the US found mixed results, with some states showing a positive association between lottery incentives and vaccination coverage while others did not.

Table 4.1 List and summary of included articles (from Schwalbe et al., 2022)

Reference	Incentive	Vaccine	Target group	Sample size	Country	Findings
Campos-Mercado et al., 2021	Financial incentive	COVID-19	General	8826	Sweden	200 Swedish kroner associated with 4.2% increase in vaccination rates (baseline 71.6%)
Kim and Rao, 2021	Financial incentive	COVID-19	General	~7.5 million (Ecological)	US	Incentive associated with 44% increase in first dose, no effect on second dose

Klüver et al., 2021	Financial incentive	COVID-19	General	20 500	Germany	Increased willingness to be vaccinated associated with financial incentive
Robertson et al., 2021	Financial incentive	COVID-19	General	1000	US	Incentive expected to yield 8% increase in uptake; most changes in incentive size inconsequential, very large incentive counterproducti ve
Sprengholz et al., 2021	Financial incentive	COVID-19	General	1349	Germany	Incentives were not associated with a change in participants' willingness to receive vaccine
Wong et al., 2022	Financial incentive	COVID-19	General	394	US	Centres participating in incentive associated with higher vaccine uptake
Bronchetti et al., 2015	Financial incentive	Influenza	Students	9358	US	Incentive associated with an 11% absolute increase in vaccination uptake (~doubling of baseline rate)
Clark et al., 2021	Financial incentive	Influenza	Students	66	US	70% willing to receive vaccine for $5 or less, half for £1 or less
Yue et al., 2020	Financial incentive	Influenza	Elderly	4000	Singapore	Incentive associated with increased vaccination uptake

Caskey et al., 2017	Financial incentive	HPV	Adolescents	188	US	Incentive associated with increase in 1st/2nd dose (75% vs. 47%) and completed course (36% vs. 13%)
Mantzari et al., 2015	Financial incentive	HPV	Adolescents	1000	UK	Incentive associated with higher uptake of 1st/2nd dose and course completion for previous non-attendees and first-time invitations
Chakrabarti et al., 2021	Financial incentive	Tetanus	Pregnant women	~200 000 (Cluster RCT)	India	Increase in maternal tetanus vaccine uptake (79.1% to 82.8% in 2006, 84.6% to 88.9% in 2016) in conditional cash transfer program
Okoli et al., 2014	Financial incentive	Tetanus	Pregnant women	20 133	Nigeria	Conditional cash transfer for preventive care associated with 21.66 per 100 000 increase in maternal tetanus vaccine uptake
Sato and Fintan, 2020	Financial incentive	Tetanus	Women aged 15 to 35	2482	Nigeria	Financial incentive associated with large increase in vaccination uptake (85.5% for 800 naira, 75.7% for 300 naira, 54.8% for 5 naira)
Day et al., 2016	Financial incentive	Hepatitis B	People who inject drugs	139	Australia	Incentive associated with higher vaccination

						completion rate (87% vs. 66%)
Tressler and Bhandari, 2019	Financial incentive	Hepatitis B	People who inject drugs	Not provided	N/A (Review)	Financial incentives effective at increasing compliance with 3-dose schedule (Odds Ratio 7)
Herrmann et al., 2017	Financial incentive	Multiple	People with substance use	5052 (pooled)	N/A (Review)	Incentives effective at increasing completion of 3-dose vaccination course
Salinas-Rodríguez and Manrique-Espinoza, 2013	Financial incentive	Tetanus, pneumococcus, influenza	Elderly	12 146	Mexico	Incentive recipients more likely to receive each vaccination (41-71% to 46-79%)
Acharya et al., 2021	Statewide lottery	COVID-19	General	403 714	US	Positive association between lottery programs and uptake, variable extent of increase
Barber and West, 2022	Statewide lottery	COVID-19	General	~8 million (Ecological)	US	Lottery associated with 1.5% increase in vaccination rates
Dave et al., 2021	Statewide lottery	COVID-19	General	~258 million (Ecological)	US	Lottery incentives not associated with statistically significant effect on state vaccination rates
Law et al., 2022	Statewide lottery	COVID-19	General	~258 million (Ecological)	US	No significant difference associated with use of lotteries
Sehgal, 2021	Statewide lottery	COVID-19	General	~8 million (Ecological)	US	Modest increase (0.98%) in vaccination

						rates associated with lottery state
Walkey, Law and Bosch, 2021	Statewide lottery	COVID-19	General	~258 million (Ecological)	US	No significant difference in vaccination uptake associated with introduction of lottery incentive
Cheema et al., 2013	Time off	Influenza	Health and social care workers	154	US	Quarter of respondents reported one-hour time-off incentive influenced vaccination decision
Lytras et al., 2016	Mix of incentives	Influenza	Health and social care workers	Not provided	N/A (Systematic Review)	No significant difference associated with individual and group incentives (gifts, raffle, free drinks, bonus for meeting target)

4.4 Discussion

Incentives have been deployed as part of a strategy to address vaccine hesitancy, classified by the WHO in 2019 as one of the top ten global health threats (World Health Organization, 2019c). Hesitancy can arise due to factors ranging from trust in expertise and authority, religious or political beliefs, concerns related to specific types of vaccines, potential side effects, and even fear of needles. Concerns can also be influenced by geography, social networks, community dynamics, and ethnic and socioeconomic backgrounds (Larson et al., 2014; Ranganathan and Lagarde, 2012). In recent years, the spread of misinformation through social media, referred to as an "infodemic," has contributed to vaccine hesitancy. A 23-country survey found an association between COVID-19 vaccine hesitancy and trust in vaccine safety, scientific validity, and scepticism about effectiveness (Lazarus et al., 2022).

This chapter highlighted that cash incentives, including lotteries, had only modest effects on vaccination coverage, typically resulting in small percentage point increases. There was

limited evidence on the effectiveness of non-cash incentives in the context of COVID-19 vaccines. As such, there is no clear evidence that incentives materially impact vaccine confidence, which appears to be a main driver of non-compliance (Dubé et al., 2013).

It was noted that incentives were generally more effective for the first dose of a vaccine than for subsequent doses. However, none of the studies explored the rationale for this difference nor were studies identified that investigated the impact of incentives on booster shots or other annual vaccinations. Furthermore, the studies did not assess the long-term effects of incentivisation on health-seeking behaviour or the potential impact on hesitant populations.

There was limited evidence in the studies reviewed on the effect of social norms, perceived risks, or other contextual factors on the effect of incentives. Three studies broadly discussed the role of perceived risk (e.g., perceptions of safety) on vaccination acceptance overall (Cheema et al., 2013; Clark, Corrigan and Rousu, 2021; Sprengholz et al., 2021). One study related to HPV found no relationship between attitude about the participant risk of HPV disease and the effect of incentives (Mantzari, Vogt and Marteau, 2015). However, none specifically assessed the influence of social norms or perceived risks of vaccines on the effect (or lack thereof) of incentives.

There was also limited evidence related to other contextual factors. Lotteries were usually targeted at the general population (Acharya and Dhakal, 2021; Barber and West, 2022; Dave et al., 2021; Kim and Rao, 2021; Law et al., 2022; Sehgal, 2021; Walkey, Law and Bosch, 2021), as were other incentives related to COVID-19 (Campos-Mercado et al., 2021; Kim and Rao, 2021; Kluver et al., 2021; Robertson et al., 2021; Sprengholz et al., 2021; Wong et al., 2022). For other diseases, vaccine incentives were targeted at specific risk groups, e.g., elderly (Salinas-Rodriguez and Manrique-Espinoza, 2013; Yue et al., 2020); health and social care workers for influenza vaccine (Cheema et al., 2013; Lytras et al., 2016); people who inject drugs for Hepatitis B (Day et al., 2016; Tressler and Bhandari, 2019); people with substance abuse issues (Herrmann et al., 2017); women for tetanus (Chakrabarti, Pan and Singh, 2021; Okoli et al., 2014; Sato and Fintan, 2020); adolescents for HPV vaccine (Caskey et al., 2017; Mantzari, Vogt and Marteau. 2015); and university students for influenza (Bronchetti, Huffman and Magenheim, 2015; Clark, Corrigan and Rousu, 2021). However, there was no discussion on particular characteristics of these groups, per se, that might have impacted the effect of the incentives.

While not a focus of the study per se, the lack of attention to the potential effects of social norms, perceived risks, and other contextual factors is notable. Future research on incentives would benefit from deeper understanding of these factors as well as incentive programs' cost-effectiveness and long-term sustainability.

While conditional cash transfer programs have shown promising results in low-income populations, the cost-effectiveness of incentives for COVID-19 vaccines specifically has not been extensively analysed. Ethical concerns were also raised regarding the potentially coercive nature of financial incentives and the possible backlash from hesitant populations. Additionally, there is a concern that incentivisation may create an expectation of rewards for vaccination, which could affect future vaccination programs (Pennings and Symons, 2021; Wertheimer and Miller, 2008; Wong et al., 2022). Also, in politically divided contexts, government-promoted incentives might generate a backlash among those who are already hesitant, heightening suspicion of vaccine programs (Pennings and Symons, 2021; Volpp and Cannuscio, 2021).

While not specific to vaccine hesitancy per se, a substantial body of literature demonstrates that for various healthcare interventions, "pay for performance" programs aimed at providers and conditional cash transfers aimed at individuals can increase coverage in both high- and low-income countries (Ranganathan and Lagarde, 2012).

Our review acknowledged some limitations, including the focus on the adult population and the limited number of studies available. The search was also limited to peer-reviewed literature and may have missed unpublished studies on incentive schemes implemented in LMICs. While incentives can have a modest impact on vaccination coverage, more research is needed to fully understand their effectiveness, cost-effectiveness, and potential long-term consequences.

4.5 Conclusion

This review highlights the lack of evidence and understanding regarding the effectiveness, mechanisms, and unintended consequences of incentive programs for increasing vaccination coverage, particularly in the context of COVID-19 vaccines. Despite the limited evidence, many governments and organisations implemented incentive programs without conducting implementation research to evaluate their effectiveness or the extent to which they did function to increase vaccine acceptability and drive up coverage.

What is known is that trust between primary care providers and patients, providing clear information about vaccine safety and efficacy, being transparent about side effects, and explaining the role of vaccination in both individual and community protection have demonstrated the potential to change the attitudes and behaviours of vaccine-hesitant individuals (Piltch-Loeb and DiClemente, 2020). Primary care has played a critical role in addressing parental vaccine hesitancy and enhancing vaccine confidence for childhood immunisations (Bogart et al., 2021).

Moving forward, it will be important to understand the concrete factors that lead to hesitancy when designing a policy to overcome and monitor the long-term impacts of incentive programs at both individual and population levels. Additional research is required to understand these programs' underlying mechanisms of action (e.g., how do they affect acceptability?) and determine whether incentives are more effective for hesitant individuals or undecided individuals. Additionally, the cost-effectiveness of incentive programs will need to be assessed in comparison to other strategies to increase vaccine uptake, such as increasing accessibility, building trust with healthcare providers (Solís Arce et al., 2021), reducing out-of-pocket costs for individuals (Lau et al., 2012; Omer et al., 2021), and providing recipients with clear information and reminders (Thomas and Lorenzetti, 2018). Future research is also required to understand what, if any, negative impact such programs may have on future vaccine uptake.

Our review also suggests exploring provider-based incentives, such as "pay for performance" programs, which have demonstrated effectiveness in increasing the uptake for other adult vaccinations (Benabbas et al., 2019; Dexter et al., 2012). Further investigation is needed to understand their potential role in promoting COVID-19 vaccine uptake.

Overall, there is a need for rigorous contextual research and evaluation of incentive programs to inform the extent to which they increase acceptability and improve vaccination coverage while minimising unintended consequences and optimising resource allocation.

Chapter 5: COVID-19 vaccine rollout in New York City – A case study

5.1 Introduction

On December 11, 2020, the United States (US) granted emergency authorisation for newly developed COVID-19 vaccines to prevent severe morbidity and mortality (Food and Drug Administration, 2020b). Three days later, on December 14, New York administered its first vaccines to high-risk hospital workers. By order of the State of New York, this was followed by nursing home workers and residents (December 21, 2020), all hospital workers (January 4, 2021), essential workers and all adults 75 years and over (January 11, 2021), all adults with underlying health conditions, including obesity (February 15 2021), all adults aged 60 years and over (March 10 2021), public-facing government and non-profit workers (March 17 2021), all adults aged 50 years and over (March 23 2021), all adults aged 30 years and over (March 30 2021), and all adults aged 16 years and over (April 6 2021) (New York State, 2021b).

During this same period, the New York State Department of Health (NYSDOH), in collaboration with the New York City Department of Health and Mental Hygiene (NYCDOH), delivered vaccines through mass, fixed-point sites. Vaccination appointments were arranged through an English-language internet-based appointment system (New York State, 2021c). Vaccination appointments were subject to self-verification that the applicant met the criteria.

The rapid pace with which vaccine eligibility was widened during the early months of 2021 may have been a rational choice if there had been adequate stocks of vaccines. However, stocks were in limited supply, which meant that groups at lower risk were added to the pool of eligible recipients before those at higher risk had been cleared from the pool. There were many reports in the press about difficulties faced by people aged 65 years and older getting appointments to receive even their first dose of vaccine (Fung, 2021; Kim, 2021; Mogul, 2021; Otterman, 2021).

In New York, as elsewhere, the probability of dying from COVID-19 was not equally distributed across the population. The single greatest risk factor for COVID-19-related mortality was older age. By December 31, 2021, about 77% of all COVID-19 deaths in New York State were in the 65+ age group (New York State, 2023). While in New York City, the 65+ age group only accounted for about 13% of the total population (Greer et al., 2019), the risk of dying from COVID-19 in that age group was 5.1 times greater than it was for the 0-64

age group (Tejada-Vera and Kramarow, 2022). Low-income households were particularly vulnerable to severe morbidity and mortality from COVID-19 (McGowan and Bambra, 2022).

In light of these two equity-related vulnerabilities, this analysis explores the extent to which their evidence shows that New York widened vaccination eligibility too quickly in the face of shortages of vaccines and whether focusing on those at higher risk might have been more prudent. Higher risk is defined in this case as age equal to 65 years or older and lower income quintile (Sepulveda and Brooker, 2021; Yanez et al., 2020).

To assess this question, we first focused on the differences in coverage of people aged 65 years and older between the highest and lowest wealth quantiles when eligibility was opened to those over 16 years and still supply-constrained. We then look at the extent to which those differences (or lack thereof) persisted when vaccines were no longer supply-constrained. We then focused on the relationship between risk factors, vaccination coverage, and COVID-19 mortality rates by geography. Specifically, using an ecological analysis, we explored the extent to which there was an association between income level, vaccine coverage, and COVID-19 mortality rates for New York City residents aged 65 years and older.

5.2 Methods

A retrospective analysis of linked Census Bureau data and New York City Health administrative data aggregated at the level of modified zip code tabulation areas (MODZCTA) was conducted to answer the two questions. The first question was examined by looking descriptively at vaccination rates stratified by age and area level wealth. To answer the second question, we modelled the total mortality rate within MODZCTA using measures of area-level wealth, the proportion aged 65+, and the vaccination rate among those aged 65+ as predictors.

All analyses, creation of maps, and figures were done with R software (version 4.1.3). Access to research data was granted by special request from the New York City Department of Health through the Open Data initiative (City of New York, n.d.).

5.3 Data sources

Data on vaccination rates, stratified by age and MODZCTA, were obtained by special request from the New York City Department of Health (NYC Health, n.d.). Data on race, income, and age were obtained from the US Census Bureau (Minnesota Geospatial Commons, n.d.).

New York City (NYC) is divided into 177 MODZCTAs. The shapefile for NYC with polygons for the MODZCTA is available on the geography resources of the NYC Health GitHub site devoted to coronavirus-data (New York City, 2023). There is a many-to-one mapping between Zip Code Tabulation Areas (ZCTA) and MODZCTAs. MODZCTA comprises either (i) a single ZCTA or a combination of contiguous ZCTAs, and (ii) no ZCTA contributes to more than one MODZCTA.

One hundred fifty-seven (88.7%) of the MODZCTA map have one-to-one correspondence with a ZCTA, 14 MODZCTAs map to two ZCTAs (7.9%), three MODZCTAs map to three ZCTAs (1.7%). Only 2 MODZCTAs map to 4 and 5 ZCTA (0.6% each). One MODZCTA outlier maps to 11 ZCTAs. MODZCTAs range in size from 3260 to 108,661 residents, with a median size of 43,173 (see Table 5.1).

5.3.1 Demographic data

Data on the population, disaggregated by age and sex, were obtained for each ZCTA from the US Census Bureau using their application programming interface (API). The data were drawn from the 2020 ACS 5-Year Estimates Detailed Tables (group B01001) (United States Census Bureau, 2023). The data available for each ZCTA were aggregated up to MODZCTAs using the mapping described above.

The data were grouped into five age groups: 0-17, 18-24, 25-44, 45-64, and 65+. These groups were predetermined by age-grouped vaccination data available from NYC Health.

5.3.2 Wealth data

The median household wealth data for each NYC ZCTA was also obtained from the US Census Bureau using API. The data were drawn from the 2020 ACS 5-Year Estimates Detailed Tables (group B19013). The data for each ZCTA of NYC was also aggregated up to MODZCTAs.

There were 26 ZCTAs with missing median income (coded as -666666666). In most cases (n=23 ZCTAs), the population was 0; i.e., there was no median income to calculate. The remaining three ZCTAs with missing median household data had small populations (n = 44,

96, and 220). Because the populations were so small, they were treated as having zero median income. Median income was aggregated up to MODZCTA as a population-weighted sum of the median income of each contributing ZCTA. Thus, in the case of the three ZCTAs with small populations, the population weight of the bigger ZCTA with which they are combined overwhelms the “zero” median income value.

5.3.3 Vaccination data

NYC Health provided data on the percentage of the population in each MODZCTA who had received at least one dose of a COVID-19 vaccine, stratified by age group (0-17, 18-24, 25-44, 45-64, and 65+ years) and date. We focused on the vaccination coverage for the week of March 27, 2021, because, before that date, people under 50 years were not generally eligible for vaccination.

For a series of descriptive analyses of the data, we first divided the MODZCTA into wealth quintiles based on the median household wealth of each MODZCTA. We visualised the percentage of the population in each age group that had been vaccinated by the week of March 27, 2021, within quintiles of MODZCTA wealth.

5.3.4 Mortality data

NYC Health Department provided a count of the total number of deaths with a registered cause of COVID-19 in each MODZCTA over the 13 months from December 1, 2020, up until December 31, 2021. These data were not stratified by age. A zero (0) was recorded for any MODZCTA with no deaths, and an "*" was recorded for any MODZCTA with less than ten deaths. NYC Health did this to preserve privacy. As disaggregation by any factor (age, sex, or gender) would have increased the number of cells with mortality counts less than ten and thus the number of cells with missing count data, we opted for total mortality, unstratified.

Eleven MODZCTAs were recording less than ten deaths, i.e., 6.2% of all 177 MODZCTAs. The minimum number of deaths in a MODZCTA was 0; the maximum was 302. For data analytic purposes, we replaced the missing deaths with a mid-point value of five. Sensitivity analyses suggested that this choice had little effect on the final analysis.

Combining the mortality data and the population data, we calculated the COVID-19 mortality rate per 100,000 in each MODZCTA.

5.4 Data Analysis

The description of the analyses is divided by the outcome focus: vaccination or mortality.

5.4.1 Vaccination

We conducted a series of descriptive analyses of the data; we first divided the MODZCTA into wealth quintiles based on the median household wealth of each MODZCTA. We visualised the percentage of the population in each age group (18-24, 25-44, 45-64, 65+) within each quintile that had been vaccinated by the week of March 27, 2021, after which eligibility was expanded to younger age groups.

Using the population size of each age group in each quintile and the vaccination coverage, we calculated the minimum number of doses that had been distributed. Using that information, we estimated the "misallocation" of doses based on the vaccination entitlement based on age.

5.4.2 Mortality

We conducted an ecological analysis looking at the relationship between the MODZCTA mortality rate and the percentage of the population aged 65+, the coverage rate in the 65+, and the median household wealth. The percentage of the population aged 65+, the coverage rate in the 65+, and the median household wealth were centred to overcome instability in the models.

Initially, we estimated the relationship using ordinary least squares regression. We used Moran's I to estimate spatial dependency in the residuals, which was significant. We then used a spatial error model to estimate the relationship. Spatial error models help to avoid inflating the significance of results by accounting for spatial dependence and to improve predictive model fit (Anselin, 1988).

We started with a "full factorial" model, including all the individual predictors and their interactions. We then looked at the effect of removing higher-order interactions, using an ANOVA test and found that removing any interaction effect resulted in a model with a significantly poorer fit. Based on an analysis of the residuals in the first step, we tested the inclusion of a dummy for MODZCTA 11235, which was an outlier.

5.5 Results

Table 5.1 shows the variation across the NYC MODZCTAs of the total population, the proportion aged 65+, the median household income, and the COVID-19 mortality rate.

Table 5.1 Summary statistics to illustrate the substantial variation across NYC MODZCTAs

	Minimum	**Median**	**Mean**	**Maximum**
Total population	3260	43173	47693	108661
Proportion population 65+	<1	14.5	15.1	31
Median household income	$23,337	$74,042	$81,381	$250,001
Covid-19 Mortality Rate per 100,000 (for year 2022)	94	126.8	127.6	397

The difference in the total population between the smallest and largest MODZCTAs was substantial. The size of MODZCTA ranges from 3260 to over 108,000 people. Similarly, there is a 30-fold range in proportion over the age of 65 (less than 1% to 31 %) and a 10-fold range in median household income ($23,337 to $250,001). COVID-19 mortality in 2022 had a 400% difference in highest compared to lowest mortality area (94/100,000 vs 397/100,000).

5.5.1 Vaccine Coverage

We explored the relationship between age, wealth, and vaccination coverage across the MODZCTAs. We focused on vaccination coverage by the last week of March. It was only mid-way through this week that all people over 30 years also became eligible for vaccination.

The mean vaccination rate for those aged 65+ ranged from 52.8% in the poorest quintile to 74.6% in the wealthiest quintile—a difference of over 20 percentage points. The difference in maximum coverage is also striking. It was 99.0% among those aged 65+ in the wealthiest quintile (lower Manhattan) versus 67.9% in the poorest quintile—a difference of 31 percentage points. For those aged 45 to 64 years, the difference was equally stark, with mean coverage in the wealthiest quintile of 60% versus 34.6% in the poorest quintile—more than a 25-percentage point disparity.

The following choropleths show the proportion of people 65 years and older vaccinated three months after the vaccine was introduced and the overall death rates by geographical area for 2021. They are close to mirror images with opposite polarity. In other words, areas with higher values in Figure 5.1 tend to have lower values in Figure 5.2, suggesting an inverse spatial relationship between the proportion vaccinated and the death rate.

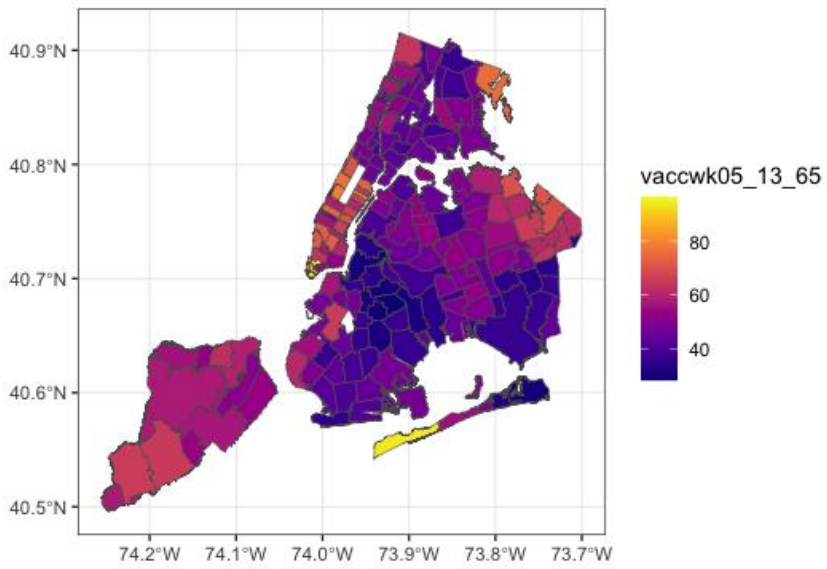

Figure 5.1 Proportion vaccinated with at least one dose by MODZCTA 65+ (March 27, 2021)

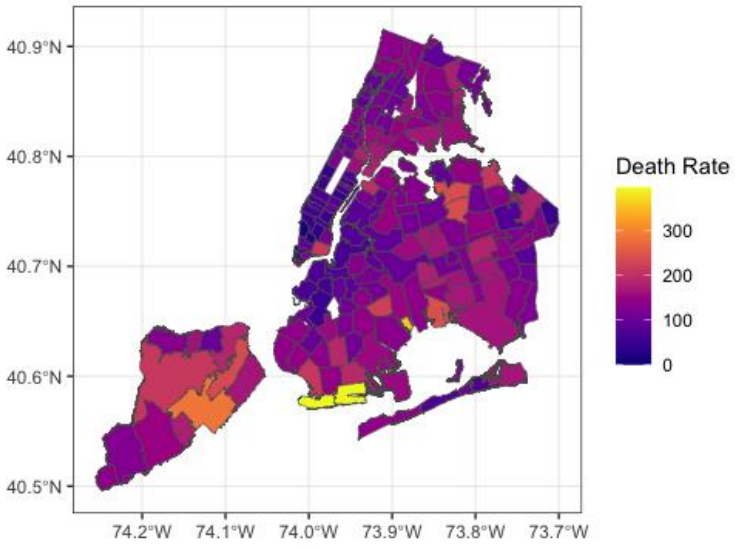

Figure 5.2 Overall date rates by MODZCTA 2021

Figure 5.3 shows a boxplot of vaccination coverage, by age group, for each income quintile by the week of March 27, 2021. The plot shows a consistent pattern whereby, for any age group, there is a monotonic and increasing relationship between wealth and vaccination coverage. As expected, given the New York vaccination policy, older groups consistently

received higher coverage than younger age groups. However, recalling that up to the week of March 27, 2021, vaccines were not generally available to those aged 18 to 44 years, it is striking that (i) so many younger people were being vaccinated, and (ii) the wealth gradient favoured the wealthier. Poorer people tend to live in poorer areas, and poorer people also make up the largest numbers of essential workers, i.e., those who would also be eligible for the vaccine. While it is impossible to know from these data, it is reasonable to assume that the vaccination rates in younger adults should have been higher in poorer areas providing a larger pool of essential workers.

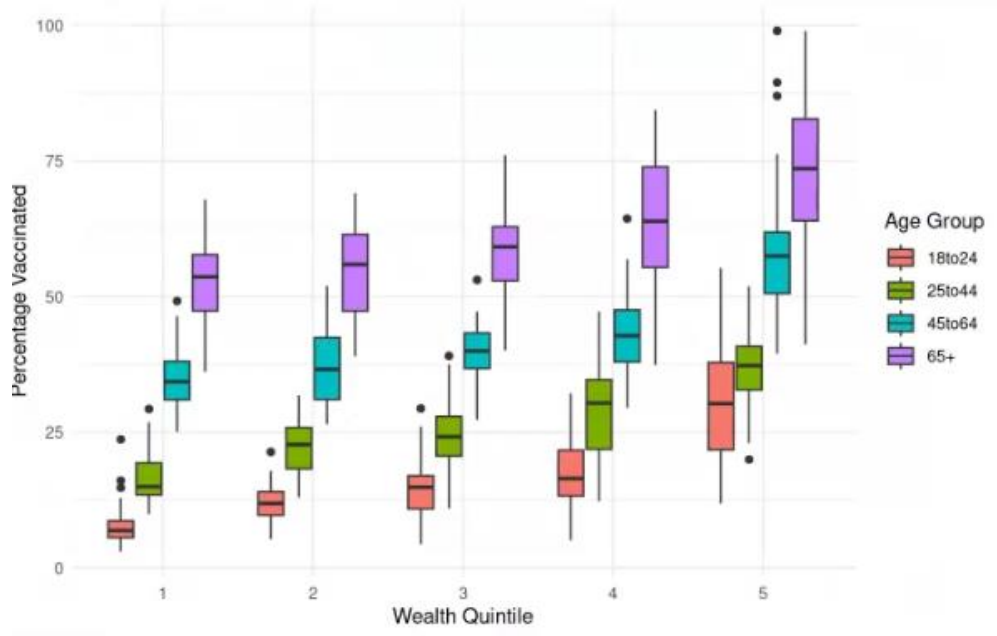

Figure 5.3 Percentage vaccinated by wealth quintile and age group

As a comparison, a year later, for those residents 65 years or older, while minimum and maximum values indicate a wide range within each respective wealth quintile, median and mean demonstrate that on average, vaccination coverage exceeded 86% in both wealth quintiles (see Table 5.2).

Table 5.2 Vaccination coverage by March 19, 2022 (by MODZCTA)

Vaccine coverage at week March 2022	Minimum	Median	Mean	Maximum
Lowest wealth quintile >=65	65.6	87.4	86.8	99
Highest wealth quintile >=65	52.1	94.6	90.2	99

The table and graphic (Figure 5.4) both demonstrate that the values are concentrated, and a year later, there is little difference in coverage by wealth quintile.

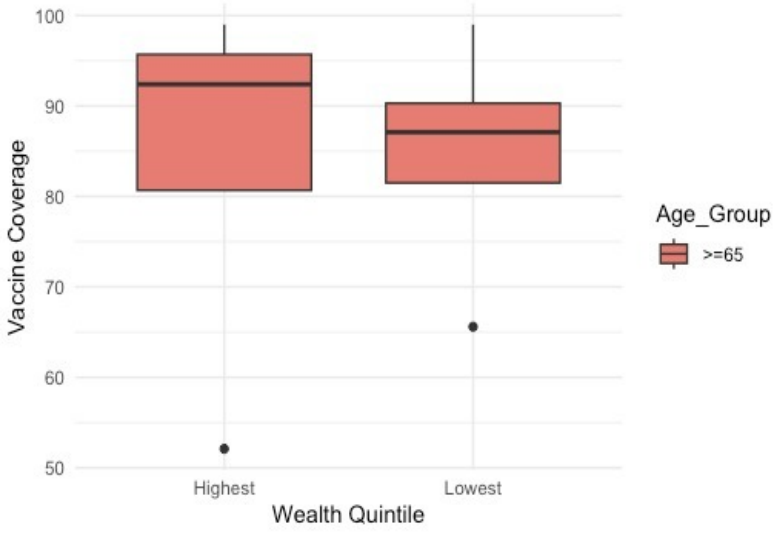

Figure 5.4 Vaccine coverage by wealth quintile and age group

We reanalysed vaccination coverage using absolute numbers of doses to account for the potential misallocation of vaccines to younger age groups. We converted coverage rates to doses delivered by age group by multiplying coverage rates by the population, per MODZCTA.

From this analysis, we identified that by the week of March 27, 2021, the MODZCTAs in the wealthiest quintiles had received enough vaccine doses to cover 41.6% of their total population. This coverage dropped monotonically by wealth quintile: 31.6% coverage for the second wealthiest quintile, 27.3% coverage for the middle quintile, 24.9% for the second poorest quintile, and 20.7% coverage for the poorest quintile.

We then estimated the "misallocated doses" as all doses received by a person under 45 years. On the analysis date of March 27, 2021, only people over 50 years were eligible for vaccination unless they were younger and in high-risk health or employment categories, so some younger people were given access, thus slightly overestimating the misallocation. However, it is worth noting that nurses, healthcare attendants, and teachers would tend not to live in the wealthier quintiles, and younger people living in poorer quintiles would be more

likely to have pre-existing health conditions than younger people living in wealthier quintiles (Sepulveda and Brooker, 2021). Thus, we would expect to observe a larger proportion of younger people living in the poorest quintile vaccinated, which was not the case.

The greatest estimated overallocation of doses occurred in the wealthiest quintiles. In the wealthiest quintile, 38.6% of doses were "misallocated" from older (65+) to younger (0-17, 18-24, 25-44) age groups. The "misallocation rate" dropped monotonically by wealth quintile. Not only were poorer quintiles more efficient in allocating their doses to higher risk age-groups, their "misallocation rates" were, in all likelihood, lower than estimated.

We then asked the counterfactual question: What could the coverage of the highest-risk age category have been if the “misallocated doses” had been given to the 65+ age group?

Based on overall vaccination coverage in NYC, there were enough doses in those given to the 65+ age group combined with "misallocated doses" to have vaccinated the 65+ age group 1.19 times over, i.e., there was almost a 20% excess. There was a 69% excess in the wealthiest quintile. The excess dropped monotonically but remained in the second poorest quintile, with a 9% excess. In the poorest quintile, there was a 3.6% deficit, i.e., there were only enough doses to vaccinate 96.4% of the 65+ age group, even with "misallocated doses".

The two choropleths below show the inverse correlation between wealth (weighted median income) and vaccination coverage for those 65 years or older (vax56) (see Figure 5.5) and between wealth (weighted median income) and mortality (see Figure 5.6).

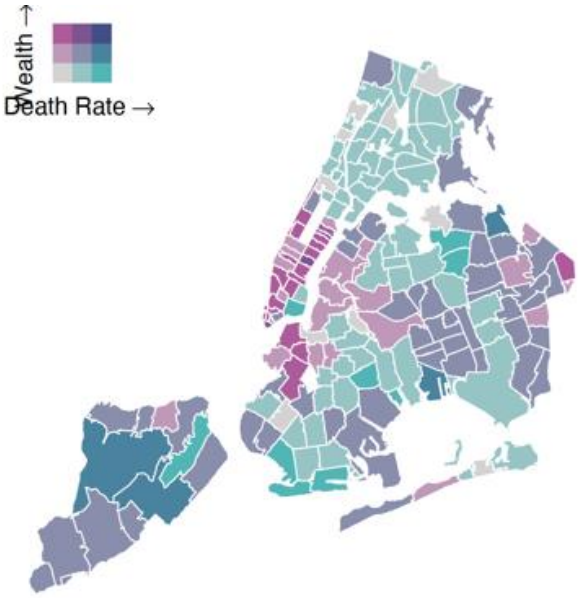

Figure 5.5 Wealth and 65+ vaccination rate

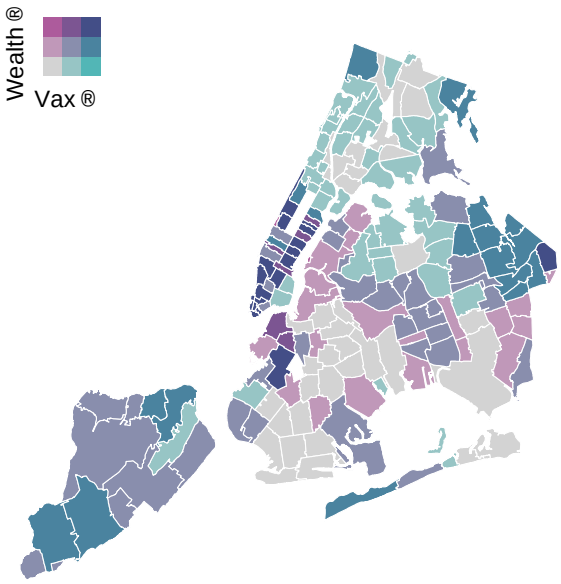

Figure 5.6 Wealth and overall COVID-19 mortality rate

5.5.2 Mortality

In this section, we explore the statistical relationship between MODZCTA mortality rates and three predictor variables: 1) the percentage of the population aged 65+ in each MODZCTA, 2) the COVID-19 vaccination coverage among residents aged 65+, and 3) the median household income.

We first centred these three predictor variables by subtracting the median before analysis. Centring makes the variables easier to work with for computations, visualisations, and interpretation. It adjusts each variable so its average value becomes zero. This makes the regression model intercept more interpretable as the value when all predictors are at their mean. Centring also reduces multicollinearity between predictors.

We then fitted an Ordinary Least Squares (OLS) regression model with all main effects and interactions (a full factorial model). We then conducted a Moran's I test on the OLS model residuals. The test revealed strong evidence of positive spatial autocorrelation (Moran's I = 0.299, $p<0.0001$). This result means observations situated close together geographically exhibited more similar outcome values than would be expected by chance alone.

The spatial clustering in the OLS residuals motivated the use of a spatial regression model to properly account for this autocorrelation. Specifically, we used a spatial error model, which includes a spatially correlated error term to adjust for spatial dependence.

After fitting the spatial error model, we tested the new residuals using a Monte Carlo version of Moran's I test. This detected no remaining significant spatial autocorrelation (I = -0.053, p = 0.799), indicating the spatial error model had effectively accounted for the spatial autocorrelation.

The full results of the spatial error model are presented in Table 5.3.

Table 5.3 Spatial error regression with centred predictors

Variable	Estimate	Standard Error	*z* value	*p* value
(Intercept)	125.23	4.56	27.4573	<.0001
% Age 65+	5.8227	0.6996	8.3224	<.0001
Median Income	-1.0944	0.1144	-9.5647	<.0001
% Vaccinated (65+)	-0.3056	0.3241	-0.9428	0.3458
Sheepshead Bay	146.38	30.618	4.7809	<.0001
%65 X Median Income	-0.0971	0.0157	-6.1686	<.0001
%65 X %Vaccinated	-0.0239	0.0506	-0.4725	0.6366
Income X %Vaccinated	0.0233	0.0060	3.8723	0.0001
%65 X Income X %Vaccinated	0.0025	0.0008	3.0352	0.0024

Except for one MODZCTA (Sheepshead Bay with an exceptionally higher than average proportion of older adults), mortality was higher in lower-income areas and areas with a greater proportion of people aged 65 years or older (NYU Furman Center, 2022). Those areas were also less vaccinated.

The fitted spatial error model provides insights into the factors affecting the COVID-related mortality rate in the MODZCTAs. First, all other things being equal, and assuming a MODZCTA with centred values for income ($74K), percentage aged 65 years or older (14.5%), and vaccination rate in the 65 years or older age group (14.5%), the expected mortality rate was 125.2 per 100,000 people.

The coefficient for the percentage of the population aged 65+ was positive and statistically significant ($b=5.82$, $p<0.001$), indicating that a higher percentage of 65+ in the population was associated with increased COVID-19 mortality rates, holding all other variables constant. Median household income had a negative and significant effect ($b=-1.09$, $p<0.001$), suggesting that higher-income areas experienced lower mortality rates on average.

The vaccination coverage among those aged 65+ had a negative but non-significant coefficient (b=-0.31, p=0.35), aligned with the protective effect of vaccination against mortality risk. Residence in Sheepshead Bay (MODZCTA=11235) was a positive and significant predictor of higher mortality compared to other areas (b=146.38, p<0.001).

There were also significant interactions between the percentage of 65+, median income, and vaccination coverage. The negative interaction between the percentage of 65+ and income (b=-0.10, p<0.001) indicated that the mortality effect of a larger elderly population diminished in higher-income areas. The positive income by vaccination coverage interaction (b=0.02, p=0.001) suggested that vaccination played a greater role in lowering mortality in higher-income regions. Finally, the three-way interaction between the percentage of 65+, income, and vaccine coverage was positive and significant (b=0.003, p=0.002), implying a complex relationship between age, income, vaccination, and mortality.

While coefficient estimates were robust, accounting for spatial autocorrelation in the error term improved model fit and controlled for potential bias. Formal interpretation of the spatial structure is necessarily limited.

All other things being equal, a 1% increase in the percentage of a MODZCTA's population aged 65+ is associated with a 5.8% increase in the mortality rate (p<.0001). Similarly, every $1,000 increase in median household income of a MODZCTA is associated with a 1.1% decrease in the mortality rate (p<.0001). These findings are consistent with the literature on the effects of age and wealth on COVID-19 mortality.

Assuming centring, every 1% decrease in the vaccination coverage in the 65+ age group was associated with a small (-0.3056) decrease in the mortality rate. Despite this decrease being non-significant, the effect was in the expected direction. We discuss this further below.

To investigate the effect of the higher interaction terms, we modelled the predicted mortality rate based on relatively narrow variations around the centred values. The results conform to what one might *a priori* anticipate concerning age, vaccination coverage, and wealth. The models are more complex and harder to explain, with values further away from the centred values. This finding may reflect a mis-specified (spatial) model or data issues discussed in the limitations section of the paper.

5.6 Discussion

As has been demonstrated in other studies, age and wealth are associated with COVID-19 deaths (Sepulveda and Brooker, 2021). Our analysis supports these conclusions.

By the time vaccines were available, it was clear that the primary risk for COVID-19 mortality was 65 years or older, with over 81% of deaths in the US occurring in this age group. Deaths among people over age 65 were 97 times higher than the number of deaths among people ages 18-29 years (Centers for Disease Control, 2023).

Social determinants, particularly income, are also a clear predictor of overall morbidity and mortality (Khullar and Chokshi, 2018) specifically for COVID-19 (Schwalbe, Lehtimaki and Gutiérrez, 2020; Sepulveda and Brooker, 2021). Delaying vaccination in high-risk groups for COVID-19 resulted in avoidable deaths (Albani et al., 2021).

Given that the rate of vaccination uptake for all income groups over 65 years of age was over 80% when vaccines were no longer in short supply, our findings suggest that in the early months of the vaccine rollout, it was access rather than hesitancy that was the main barrier to uptake for residents in low-income areas of NYC.

While New York State was aware that new vaccines were coming, very little thought was given to distribution before their arrival (Schwalbe, Lehtimaki and Gutiérrez, 2020). The initial vaccination sites were "mass distribution" located in just a few areas of the city and requiring people to travel to them to receive the shots, and appointments had to be made through an English-language internet portal. From the earliest days of putting this system in place, there were multiple media reports that it was difficult to make an appointment, in particular for older people and non-English speakers, and nearly impossible for those without access to the internet (Michaels, Pirani, and Carrascal, 2021; Press, Huisingh-Scheetz and Arora, 2021). In New York, as elsewhere in the US, access to the internet is associated with income (Jean-Jacques and Bauchner, 2021).

Our analysis shows that many people outside of the eligibility brackets for COVID-19 vaccines were accessing them ahead of schedule, particularly in high-income areas. While there is some plausibility that access was granted because these people worked as health care, hospital, elderly care, or education workers or had an underlying risk condition, it is unlikely that would account for the magnitude of difference between low and high-income MODZCTAs.

We note that our analysis used data up through the week of 27 March. However, as vaccines were still in short supply at this time, and there was no forewarning by the government that eligibility would be expanded on this date, we concluded that four days of official inclusion of younger group, in particular as vaccination was by appointment and appointments needed booked weeks in advance, would not adversely affect our conclusions.

There were widespread reports of younger individuals getting a note from their doctor saying they had an underlying condition when this was not the case (Walker, 2021). There were also stories about just people happening upon so-called "unused doses." (Fetters, 2021). The significantly high coverage number for younger age groups in high-income areas is a systematic and widespread abuse of privilege (Oreskes, 2021).

While the case was made to State and City governments by public health professionals on the need to target low-income zip codes most severely affected by COVID-19 and collaborate with communities to deliver vaccines (including through mobile vans or establishing sites near public transport (Jean-Jacques and Bauchner, 2021)), this message went unheeded in the early stages of vaccine distribution.

Community-based distribution through pharmacies only started at the end of March and was initially also subject to an internet-based appointment system (Eyewitness News, 2021). At-home vaccine programs were only initiated six months into the initial availability of vaccines (NYC Health+Hospitals, 2021).

5.7 Limitations

This study had several limitations. First and foremost, the mortality model is ecological and does not permit inferences about the association at the individual level. This was further complicated by the fact that the mortality rate was based on the cumulative COVID-19 mortality for all ages in 2022, even though the group of interest was those 65 years or older.

We also used area-level measures of vaccination coverage for the 65 years or older age group for March 2021 and the percentage of 65 years or older in the MODZCTA populations. These data choices were not ideal and were driven by availability. The challenge of interpreting the higher interaction terms of the mortality model may be attributable to this and could be overcome with the availability of better mortality data.

5.8 Conclusion

In the initial days of the vaccine rollout in New York, low COVID-19 vaccine coverage rates in low-income areas were frequently attributed by media, pundits, and even New York State's governor to so-called vaccine hesitancy (CBS News, 2021; Sanchez and Wilkinson, 2022). However, the fact that all areas of NYC had coverage of over 80% once there was sufficient supply and community-based distribution suggests it was access, not hesitancy, that prevented high coverage (Herman, 2021).

Next time policymakers can do better to focus on the most vulnerable by deploying a "precision public health" approach (Khoury, Iademarco and Riley, 2016). All over the US, income data are available by zip code, and Medicare and Medicaid have detailed records of household age and related medical conditions. Information on household age and composition is also available from voter registration data, thus making it possible to target at-risk populations.

In the future, if there is a limited initial vaccine supply, vaccine distribution can be prioritised to reach the most affected communities "where they are" to ensure equitable access. For COVID-19, while this approach did happen, it happened later than it could have happened. While income and age breakdown in a particular geographical area may be static variables in access equality, targeting vaccines to those most at risk, which has a direct impact on mortality, can and should be influenced by public policy.

Chapter 6: General Discussion and Conclusion

6.1 Summary of findings

The individual papers presented in this thesis offered the opportunity to review the supply-side of vaccine access through the "4A's" framework. Together they provide perspectives on multiple evidence-based interventions that governments can drive to enable access.

The "Review of History, Context, and Definitions" chapter shows that challenges to access have existed for decades and that many of the tools developed to address them may no longer be relevant given the shift in demographics where the majority of poor populations are no longer located in low-income countries. We also identified a range of evidence-based tools to improve all "4A's" that could be more effectively and holistically deployed. The chapter on "Vaccine Production" provides distinct policies to improve and speed up the availability of new vaccines in low- and middle-income countries (LMICs) – notably by investing in manufacturing, incentives for IP sharing, and streamlining regulatory processes. The chapter on "Financial Incentives" demonstrates that acceptability cannot be an afterthought and that coverage cannot be "bought". It requires advanced engagement and community trust. Moreover, in the last chapter we conducted a data-driven approach to accessibility, focused on social determinants, which is vital for an equitable response.

6.2 The way forward

While COVID-19 laid bare for many the access divide within and between countries, the problem is one the public health community has been trying to tackle for decades (see Appendix 5 for timeline).

This thesis demonstrates that there are ways to change the paradigm by applying a "4A's" framework to vaccine supply policy, including and in particular when supply shortages are anticipated, as has been the case with each new vaccine introduced over the past decade. From pneumococcal to human papillomavirus, malaria to monkeypox, demand exceeded supply from day one. There is no reason to think this will be different for Respiratory Syncytial Virus (RSV) vaccines which have recently been approved for older adults in the United States (Pfizer, 2023), and new tuberculosis (TB) vaccines, which are expected to be available in the next five years (Tozer, 2023).

Vaccine access is not a last-minute thought or just about delivering a finished product. The "4A's" need to be considered and applied at the start of the research and development (R&D) process, from the very conceptualisation of the product to manufacturing and delivery. Each "A" needs formal consideration as they are separate pillars but one comprehensive approach.

While there is much discussion about vaccine confidence as the main barrier to uptake, the COVID-19 pandemic demonstrated that supply was as much, if not more, of an issue. Confidence increases when vaccines are available at the right time, in the right place, and in the right quantity. The greater the confidence in the process, the greater the trust, and the greater the uptake (de Figueiredo et al., 2020).

As witnessed during COVID-19, access is particularly important in responding to public health emergencies. In order to meet the access challenge, national-level introduction planning must start even before a product is available. Manufacturers must invest in timely, geographically representative, and inclusive phase III trials. They must also focus on developing suitable presentations, including through a WHO-led target product profile approach. At the same time, government regulators and WHO must offer rapid and simplified regulatory and licensure pathways, ideally harmonised across countries and regions. National and global procurement agencies, including Gavi, UNICEF, and PAHO, must develop a robust understanding of demand and must also preposition financing for manufacturing scale-up to meet it.

By focusing on each "A" this thesis offers an evidence base for future policy recommendations. It gives hope that there is potential to do better in future with purposeful planning. In fact, with the support of the Author, the framework has already been adopted and adapted to inform WHO's rollout of new TB vaccines (World Health Organization, 2023a).

6.3 Recommendations, by "A"

With many new vaccines on the horizon that fall outside of the typical childhood schedule, the time is now to build in access planning from the beginning and throughout the development process to reach everyone who could benefit.

6.3.1 Acceptability

As new vaccines begin the clinical development process, developers can engage with communities on acceptability, exploring with patients, healthcare workers, and policymakers

product attributes that will make the end product both usable and desirable. From day one, aided by a range of publicly funded push and pull mechanisms, they can also design the product and its scale-up to maximise affordability both for the product itself and to decrease costs for end users and health systems (e.g., side effects, number of visits required). Focusing on global demand manufacturing from the get-go can solve availability, particularly with investment in tech transfer, open intellectual property (IP), and early engagement with regulators and the WHO to harmonise data needs and expedite introduction.

6.3.2. Accessibility

These efforts can also help accessibility, bringing the products' manufacturers closer to where they are used. However, as we demonstrate, accessibility is not just about whether a country can access vaccines. It is about micro-planning and precision public health so that those at the highest risk are first in line. Moreover, as with acceptability, community engagement is critical to engendering the design of better products, building trust, and designing programs that access those most in need.

6.3.3. Availability

Regarding availability, country stakeholders can assess demand and define a policy pathway and the data required for approval and introduction.

6.3.4. Accessibility

Regarding accessibility, implementation strategy, including priority groups and delivery systems, can be designed in parallel to the clinical development process. Furthermore, for acceptability, manufacturers can engage with patients, health workers, and policymakers early to define the value proposition and communicate proactively.

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Appendices

Appendix 1: Ethical clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Human Research Ethics Committee (Medical)

Research Office Secretariat:
Faculty of Health Sciences, Phillip Tobias Health Sciences Building, 3rd Floor, Office 301/2/4, 29 Princess of Wales Terrace, Parktown, 2193
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Ref: W-CBP-220504-04 04/05/2022

TO WHOM IT MAY CONCERN:

Waiver:	This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)
Investigator:	Miss Nina Schwalbe
Supervisor:	Associate Prof Marta Nunes
Department:	Pathology
Project title:	Equitable access to vaccines: exploring the role of the acceptability, accessibility, affordability, availability with a focus on COVID-19
Reason:	A review of information in the public domain. No human participants will be involved in the study.

Dr CB Penny

Chairperson: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Ms Zanele Ndlovu, Ms Mapula Ramaila and Mr Rhulani Mkansi

Appendix 2: Publications included in this thesis

The research presented in Chapter 3 (Aars, Clark and Schwalbe, 2021) was completed with the engagement of the supervisor prior to the protocol approval and included in this Ph.D. thesis with permission from the Department.

1. Aars, O.K., Clark, M. and Schwalbe, N. (2021). Increasing efficiency in vaccine production: A primer for change, *Vaccine: X*, 8(100104), 1-7.
2. Schwalbe, N., Hanbali, L., Nunes, MC., et al. (2022). Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts, *Vaccine: X*, 12(100225), 1-7.
3. Schwalbe, N., Nunes, M. C., Cutland, C., et al. (2023). Assessing New York City's COVID-19 vaccine rollout strategy, *International Journal of Urban Health*, 100(2), 123-145.

Appendix 2.1 Increasing efficiency in vaccine production: A primer for change

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Increasing efficiency in vaccine Production: A primer for change

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ABSTRACT

The COVID-19 pandemic has highlighted the importance of vaccines as public health and pandemic preparedness tools and amplified the importance of issues ranging from equitable distribution to reliable supply of quality, affordable vaccines. These issues however are not new. Delays in time from the first dose in a high-income country to introduction at scale in a low-income country can take years. These delays are driven by several challenges, some of which are unique to the vaccine development ecosystem. The patenting and overall intellectual property (IP) protection are complex, regulatory oversight is rigorous, manufacturing processes require technical support or know-how transfer from the innovator, and market dynamics create obstacles to delivering at scale. However, there are opportunities to accelerate the introduction of vaccines at scale in low and middle-income countries. To identify those opportunities, this paper provides an overview of the vaccine research and development process and where reform of the current system could increase access.

Contents

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1. Definitions and background information

Vaccines are biological products[2] produced through the manipulation of genetic material and living organisms such as cultures of animal cells, yeast, bacteria, insect cells, or host organisms (fertilized eggs). The fact that they are biologicals makes many aspects of development, production, regulatory constraints and patent structure distinct from small molecule medicines [2,3]. In contrast to generic medicines that are chemically identical, most vaccines produced with the same active components are in effect a "new" entity. Thus, even so-called second-generation vaccines require human studies to demonstrate safety and efficacy, and development and manufacturing steps undertaken by the innovator must be replicated by the new entrant to prove equivalence or non-inferiority to the originator.

2. The vaccine development process

The main steps required to bring a vaccine to market are research and development, manufacturing scale-up, and regulatory approval.

Research and Development (R&D) begins with preclinical development in the laboratory and is increasingly often the subject of patent filing. If a preclinical candidate is deemed to have the potential for use against a particular disease after testing in animal models, clinical trials follow to test dosing and safety in humans (phase I), before immunogenicity and efficacy are assessed (phase II) and efficacy and safety further established with increasing human sample sizes (phase III). If the product is deemed both efficacious and safe, the company applies for licensure and registration. This is followed by ongoing pharmacovigilance (phase IV), which is the process of monitoring adverse events post-marketing approval [3].

Manufacturing scale-up: As a product enters phase I trials, developers should begin to identify the necessary steps to produce at scale to meet future demand, as quantities for phase I arelimited to only what was required for testing in a laboratory. Refinements to the production process are made as part of both clinical and commercial scale-up. The biological processes are often difficult to replicate at scale and quality assurance and quality control (QA/QC) are therefore an integral part of scale-up. After licensing, production improvements continue.

Regulatory: Regulatory authorities set guidelines for how trials are conducted and give developers authorization to conduct trials in humans (in the "clinic") based on successful results in the lab ("preclinic"). After having undertaken preclinical and clinical testing, data on safety and efficacy is submitted to the relevant regulatory body for licensing. After a market authorization is granted, regulators oversee lot release and manufacturing site inspections to ensure that products and facilities continue holding the same standards. Post licensing product improvement is also subject to regulatory scrutiny and post-marketing requirements.

Market development: Throughout the R&D and production processes, a developer will file for patents as it acquires a new understanding of the behaviour of the product under development. If approved by the relevant patent office, the patent holder is granted a time-limited monopoly on sales, manufacturing and other activities, including follow on innovation. Since filings will often take place early in the development process, prior to market authorization, the effective patent time (time that the patent holder has exclusivity on sales and other activities) will be shorter than the actual patent time [4]. Considerations on where to market the product start early in the development process, taking into account market potential. The decision also depends on likely procurers of the product (i.e., national agencies, multilateral entities and or private market), production capacity, pricing structures, and logistics. These same factors inform whether a new manufacturer may want to engage in the same disease or area.

[2] "Biological" refers to either one or several components of the vaccine, or the method of production.

3. Key actors in vaccine R&D

Several different actors are engaged in vaccine R&D, although roles have shifted over time with the consolidation of multinational corporations (MNCs), a proliferation of biotech companies and the entrance of developing country manufacturers to supplying global markets.

3.1. Research and development (R&D)

Government entities play a key role in advancing product development, but primarily with a domestic mandate and often focused on early-stage development. For example, the European Commission and the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health in the US are also major funders of vaccine research, as are several other governments (i.e. Germany, Japan, France) – either through dedicated agencies or grants made to privately owned entities.

There are two major groupings of vaccine manufacturers. MNCs are for the most part organized under the "International Federation of Pharmaceutical Manufacturers & Associations" (IFPMA), a trade group that represents companies involved in both therapeutic drugs and vaccines. Vaccine manufacturers from developing countries for the most part belong to the "Developing Countries Vaccine Manufacturers Network" (DCVMN). MNCs previously controlled most parts of the vaccine research and development processes, but their dominance is diminishing.

There is a growing presence of academic and private biotechnology players in the research field driving a large part of innovation. This means that MNCs are increasingly focused on development, registration, and manufacturing. These activities require large amounts of capital and play to their strengths. As a result, MNCs' development pipelines are more and more being replenished from external sources through in-licensing and occasionally through mergers and acquisitions [5]. Another trend is the increasing success of DCVMNs to rapidly develop complex second-generation vaccines without formal technology transfer (i.e. pneumococcal conjugate vaccines (PCV), hexavalent, and human papillomavirus vaccine (HPV)). Finally, there have also been significant advances in vaccine science such as structural biology, protein engineering, immunology, and manufacturing platforms, among others [6]. These trends, together with the intensity of activity and discussion around COVID-19 vaccine research and access, may lead to considerably more manufacturers in the coming decades.

Biotech firms, academia and public research entities conduct much of the early research but may not have the financial backing,

incentives, or competence to generate sufficient data and take products through clinical development and licensure. Where the growth in the number of new vaccine development programs amongst MNCs has stagnated over the last 15 years, amongst small biotechs it has more than doubled, and emerging-market players saw a 13-fold increase [7]. While on one hand this suggests increasing competition for MNCs, most of the programs have focused on second-generation vaccines, changing the vaccine manufacturing landscape. Looking at the landscape of novel COVID vaccine candidates, we also find many that have been taken forward by smaller biotechs [8]. As such, the pandemic might be a further catalyst for changing the landscape.

Despite more limited financing and in-house technical capabilities to develop new products, DCVMN manufactures are also increasingly capable of R&D, in part because of the ability to bring in organizations with specialized capabilities for different parts of the development process. An early example was the meningococcal A conjugate vaccine (MenAfriVac). With investment from the Bill & Melinda Gates Foundation (BMGF) and technical assistance from PATH, the Serum Institute of India developed the first-ever vaccine for Africa and is now the sole global manufacturer [9].

Another important contributor to the development of vaccines for low-income markets was the "product development partnerships" (PDPs), set up nearly 20 years ago by the BMGF and Rockefeller Foundation, among others, to target neglected diseases or diseases of poverty (i.e., malaria, tuberculosis, and HIV/AIDS). The scientific challenges of developing vaccines for these diseases are formidable, which is reflected in the fact that few new products have been brought to market over the last two decades. For example, it took 30 years for GSK to develop its Mosquirix vaccine due to the complex biological nature of the malaria parasite [10]. Despite the lack of progress in licensed products, however, these partnerships are considered highly successful in terms of galvanizing their respective fields of work and bringing attention to the need to develop products for neglected diseases [11].

Beyond disease-specific R&D, some organizations are developing "enabling sciences". This refers to challenges that are not unique to one entity but may help accelerate development timelines or ease comparison across similar biologicals entities [12]. For example, investments in diagnostics are critical for case detection in clinical trials during outbreaks [13], epidemiological surveillance capabilities are crucial for needs-forecasting, the establishment of harmonized biological standards and assays is important to compare products across geographies [14] and better animal models can improve validation of proof of concept [12] and thus speed development for products for a range of diseases. CEPI, the Coalition for Epidemic Preparedness Innovation, has been especially active in this area with investments in particular with regards to the development of harmonized biological standards, assays and animal models.

3.2. Manufacturing

Manufacturing vaccines is very resource-intensive, whereby government-backed industries and larger MNCs – at least traditionally – have been the main entities with the capabilities required. Whereas previously manufacturing was an integrated part of a vaccine developer's portfolio, it is now increasingly being outsourced, including to so-called "contract manufacturing organizations" (CMOs) – a market that has been valued at $1.8bn in 2016 [15]. The ability of these organizations to help with quality, reliability and regulatory issues have been highlighted as some of the main drivers of the trend to outsource [16]. Outsourcing these functions can also lower facilities cost and financial risk in early project stages (e.g. pre-clinical and phase I/II) and then switched to in-house for phase III/ commercialization when the level of financial risk is lower and greater control over the product is required.

The largest manufacturer from a volume perspective (e.g. the number of doses) is Serum Institute of India, whose output almost exceeds that of its three closest competitors. In terms of value, however, MNCs' (Merck, Pfizer, Sanofi and GlaxoSmithKline GSK) substantial footprint in high-income markets means that they rank considerably higher despite producing a lower volume. Several government-controlled organizations also have large manufacturing capabilities that cater to domestic and sometimes regional demand. Examples include the government-backed entities of China (Chengdu Institute of Biological Products Co), Russia (Chumakov Federal Scientific Center for Research), Indonesia (Bio Farma), and Brazil (Fiocruz and Instituto Butantan) [17].

While all pharmaceuticals require batch testing, the risk of batch failure is higher for vaccines than for most other pharmaceuticals due to the intrinsic biological variability of most materials and interactions between them [2]. Batch release processes can also lengthen the time required for manufacturing as they often require in-vivo[3] testing.

Likewise, the sensitive nature of biological materials requires the developer to demonstrate consistency, quality control and quality assurance for the entire process of manufacturing, including the critical stage of scale-up. Generally known as "Chemistry, Manufacturing and Controls" (CMC) [18] these processes can require investments exceeding USD 50 m and more than 80 person-years in terms of labour [3]. This fixed investment represents a significant barrier for second-generation vaccine developers. Further, all manufacturers also need to develop lot-testing procedures that include the analysis of potency, safety, and purity. These may include in-vitro and in-vivo tests that take weeks or months to conclude.

3.3. Regulatory engagement and approval

Regulators determine whether a vaccine is sufficiently safe and effective to enter and stay in the market. They also periodically inspect the manufacturing facilities for "Good Manufacturing Practices" (GMP) and QA/QC. Regulators are also now experiencing and expanding roles as requirements towards safety and efficacy have increased, as have technological innovations, such as platform technologies[4], adjuvants, and injection devices, that also require the development and application of new regulatory pathways [19]. For example, some regulators may require additional clinical studies if the target population in their respective settings differs from those tested in trials[20]. Applications for market authorization are reviewed either by the national regulatory agencies (NRA) where the manufacturer operates, by the centralized procedure if in the European Union (EU), or by a Regulatory Authority of specific choice if the manufacturer so chooses. European countries have mutual recognition of assessments made by other member states under the auspices of the European Medicines Agency (EMA) [20]. Similarly, the African Vaccine Regulatory Forum (AVAREF) attempts to drive alignment through engagement between NRAs on the continent, but without regulations that allow for the mutual recognition process that the EMA has instated [21]. CEPI has also established a regulatory working group, aiming to drive progress in the area.

WHO also plays an important role through its prequalification process; a comprehensive assessment of whether a vaccine meets requirements for safety and efficacy in immunization programs,

[3] "In vivo" refers to inside a living organism, as opposed to "in vitro" which is outside a living organism

[4] A vaccine candidate is platform-based if "an underlying, nearly identical mechanism, device, delivery vector, or cell line [is] employed for multiple target vaccines" [54].

and the assessments of the functionality of the releasing national regulatory authority [23]. WHO prequalification is a requirement for purchase by United Nations agencies (e.g. PAHO, UNICEF). Prequalification is paid by the manufacturer through a fee system and is done on a product-by-product basis for both innovator and second-generation vaccines.

3.4. Vaccine market development

Before the 1990 s, the vaccine market was considered non-attractive by large pharmaceutical companies and smaller players did not have the technology or financial capacity to get involved. Over the past 25 years, the global vaccines market has grown in terms of value and volume in part due to the launch of several "blockbuster" vaccines such as hepatitis B, multivalent DTP, pneumococcal, HPV and zoster. Another driver behind this trend is the establishment of procurement and funding partnerships that enable access to vaccines for low and some middle-income countries.

Gavi, the Vaccine Alliance, the largest of these initiatives, now procures vaccines for nineteen diseases, up from six diseases when it was first established in 2001. Their success in increasing access to vaccines has to a large extent been enabled the Alliance's ability to negotiate "tiered pricing" arrangements. Practically, manufacturers agree to sell large volumes of vaccines to eligible lower-income countries for a price significantly lower than for middle-income and higher-income countries [24]. For example, for Gavi-eligible countries in WHO's Africa region, the price for HPV vaccines from GSK in 2018 was on average USD37m versus USD114m for non-Gavi countries [17]. While countries that have never been eligible for Gavi support do not have access to these lower tiers of pricing, countries that are transitioning from Gavi support are granted access to continued concessional pricing for a period of time to avoid sudden budgetary impacts from assuming responsibility for vaccine procurement [25]. This policy was adopted after some criticism that countries would face "price walls" as increases in the per capita income moved them out of eligibility for Gavi support. Gavi, together with UNICEF, the Gates Foundation, and others also prepares supply and procurement roadmaps [26] for each vaccine in the Gavi portfolio, which identifies actions required to sustain or increase affordability.

Market concentration in vaccine procurement is driven by logistical complexities (i.e., the need for cold chain), economies of scale (large shipping volumes), and requirements for stockpiles. This has resulted in countries primarily relying on three different pathways; i) self-procurement/regional procurement, ii) the Pan America Health Organization's (PAHO) Vaccine Revolving Fund and iii) UNICEF's Supply Division (UNICEF-SD). Low-income countries (and some lower-middle-income countries) are primarily supplied vaccines through UNICEF-SD and PAHO. UNICEF-SD and PAHO also serve as the primary procurement partners for Gavi.[5] Most upper-middle and higher-income countries conduct self-procurement and financing through national agencies [17], resulting sometimes in important access gaps.

3.5. Normative guidance and related WHO processes

While decisions around vaccine adoption and schedule are ultimately sovereign, some players influence those decisions by providing guidance on immunization policy. In particular, the WHO through its Strategic Advisory Group of Experts on Immunization (SAGE) and Regional Immunization Technical Advisory Groups (RITAGs) are important in this regard. In addition to reviewing efficacy and effectiveness, recommendations from these groups can include considerations of costs, cost-effectiveness and appropriateness of presentation for the setting or conditions in which the vaccine will be deployed . Recommendations may be directed towards a specific manufacturer or applicable for a disease area [27,29]. All vaccines are assessed regardless of whether they are an innovator or second-generation.

WHO also plays an important role through the development and publication of a vaccine R&D Blueprint. The Blueprint is aimed at improving coordination and accelerating R&D for diseases that are considered to pose the greatest public health risk due to their epidemic potential [30]. The Blueprint served as the basis for CEPI's decision making around its current disease focus.

There are also specialized procedures in place for new or unlicensed products for use in emergencies. For example, the U.S. Food & Drug Administration (FDA) and WHO have established the Emergency Use Authorization (EUA) [31] and the Emergency Use Listing Procedure (EUL) [32] respectively, helping to accelerate regulatory assessment and use of urgently needed products during a pandemic, epidemic or outbreak.

4. Key barriers to "time to market and opportunities to drive efficiencies

Vaccine development takes place in a complex ecosystem with many actors involved. The biological nature of the products and the associated regulatory requirements make it even more difficult to accelerate the process. The result is that vaccine R&D can be lengthy and costly, which can create challenges for accessibility and affordability [1]. While acceleration is of development can be related to adequacy of funding, here we focus on some of the more structural challenges that can either incentivize or create opportunities to speed development, from discovery to delivery.

4.1. Research & Development (R&D)

Both second generation as well as innovator vaccines [3] share barriers to accelerating development. By using indirect biomarkers, correlates of protection[6] is an opportunity to avoid larger efficacy studies. However, few vaccines can rely on this method alone to guarantee efficacy [33]. Together with the fact that vaccines are mostly given to healthy recipients to avoid a potential disease, this results in large, complex and costly trials to produce sufficient statistical evidence to prove protection [3]. Some of these challenges can be met through innovative trial designs, as was seen in the Ebola crisis. In this case, the development timeline was truncated substantially due to a design that allowed for parallel implementation of phase I, II and III trials [34]. Although such advancements are often made during emergencies, they could be considered more broadly or in particular for diseases of poverty.

While regulatory oversight must be maintained, there are also emerging R&D opportunities in the form of new technologies and enabling sciences that have the potential to either leapfrog typical steps or cut development timelines and costs found in standard pathways. For example, the development of new vaccine antigens and biological standards and assays can help accelerate proof of concept [44]. Moreover, new adjuvant technologies can strengthen and/or orient the immune response, reducing the frequency of vaccination and facilitating dose sparing, helping reduce the cost of vaccine doses [35,36]. As demonstrated in the fight against COVID-19, the use of viral vector technology has proven promising and 13 candidate vaccines are using this technology [37]. Potential advantages include strong immune response, "plug and play" development and easily replicable manufacturing [38].

[5] In Latin America, PAHO serves as Gavi's procurement partner.

[6] A correlate of protection is a biological marker, such as an antibody level.

With regards to the approach to vaccine development, mRNA vaccines have the potential to revolutionize the field [39]. DNA vaccines also present a novel approach, but the field has not advanced as far. The basic principle of these vaccines is to deliver DNA or mRNA that codes for selected antigens of the target pathogen; the recipient person's cells will synthesize the coded proteins and the immune system will recognize and act against them. There are three main benefits of such a system: i) research steps are considerably simplified and accelerated, ii) production methods are non-pathogen specific and therefore standardized, flexible, and potentially rapid and easy to scale up and iii) it may provide a more flexible way of adjusting the vaccine if the pathogen mutates or changes.

Among the 76 vaccines against SARS-CoV-2 in clinical development as of March 2, 2021, nine are mRNA-based and eleven are DNA-based [37]. These technologies, if confirmed successful mid-to-long-term, could represent a significant potential for new vaccines made faster at lower production costs. As such, the recent roll-out by BioNTech/Pfizer and Moderna of their mRNA vaccines against COVID-19 is a landmark. While DNA vaccines have not shown the same progress, there has been positive development (i.e. Inovio) [40]. Given the engagement of many public funders in this field, access agreements upfront in the R&D process, including around management of IP and know-how, transfer of technology and pricing considerations, will be particularly important to monitor. The IP landscape for these vaccines have already proven to be highly fragmented [41], and given the nascency of the technology, developers might take a restrictive approach to participating in technology transfer or granting IP access. The WHO initiative to establish a COVID-19 patent pool is such a promising development [42].

4.2. Manufacturing

Some of the challenges related to the manufacturing of vaccines apply to all vaccines and others are specific to a particular vaccine class [3]. The fine-tuning of each step in the production process takes years to develop and is often done in parallel with preclinical and clinical development. Associated scale-up involving experiment-based adjustments are therefore not available to or discoverable by new players in the field. Further, production facilities must be dedicated or reconfigured for other biological entities. Manufacturers also need to develop and implement lot-testing procedures that include the analysis of potency, stability and purity that can delay timelines. Together, this complex range of production steps is often referred to as "know-how". This know-how is probably the most critical barrier to the speedy development of second-generation vaccines and may, at least partly, be addressed through technology transfer.

In a report by the WHO, recipients of technology transfer highlighted that insufficient R&D capacity and human resources to support and demonstrate successful technology transfer were among the main obstacles [43]. Some efforts have been initiated to tackle this, including the establishment of know-how and other intellectual property pools and technology transfer hubs to facilitate handover, or requiring that recipients of public funding (e.g. CEPI) support technology transfer efforts. Despite these efforts, there have been few agreements for technology transfer for second-generation vaccines [2]. The potential of technology transfer to reduce costs and time to market in low-income countries as well as increase volumes and overall access remains largely untapped and this could be a key area for future reform and one where a neutral organization could consider a role in brokering partnerships and advising on deal structures. With support from donor and philanthropic organizations like PATH, DCVMN related vaccine manufacturers are increasingly developing in-house technical skills and know-how which over time may help address this issue. This is an area that could benefit from further investment, as could facilitation of discussions and agreements (e.g. IPR, technology transfer) between targeted DCVMN manufacturers that do not have access to other regional markets and potential DCVMN players in those regions.

4.3. Regulatory

Regulatory agencies play a vital part in ensuring safe and effective vaccines, but also face difficult trade-offs; on one hand by asking for additional evidence, they keep harmful or ineffective drugs from entering the market; on the other, the time advisable to perform the due diligence may lead to potentially foregoing health benefits by delaying access. Vigilance in evaluating vaccines is well-founded, but not without opportunities for improvements. Contrary to most traditional medicines, some vaccines require that producers meet biosafety level (BSL) standards because they can include the manipulation of dangerous pathogens during the production process. This may require biological hazard and biosafety level certification, prevention of contamination, cell line management, sourcing of raw materials (for example, specific-pathogen-free eggs), freeze-drying capacity/fine-tuning, conjugation technology, access to non-standard adjuvants, etc.

It also requires an in-depth understanding of the development process, which contains additional layers of approval as compared to small molecules. Approval is granted usually by the NRA where the manufacturer operates, by a centralized procedure if in the EU, or by a Regulatory Authority of specific choice if the manufacturer so chooses. If targeting low and middle-income countries, a WHO Prequalification is required. This can take up to 12 months [3]. Batch release also requires NRA approval, and NRA must periodically inspect the manufacturing facilities for "Good Manufacturing Practices" (GMP), and QA/QC. Both of these require that the NRA have adequate competencies and resources for product assessment. To address these issues, there are several global efforts underway to harmonize regulatory processes across geographies from clinical trials through to registration and beyond. The African Vaccine Regulatory Forum (AVAREF) is an example of this for clinical trials and the WHO's prequalification system for lot release [22]. While this does not obviate critical steps such as biosafety requirements related to batch release, it should speed time to market. Such efforts are especially important for vaccines with potential for high public health impact.

4.4. Market development

In theory, intellectual property incentivizes companies to make substantial investments in R&D and manufacturing. However, it also deters new entrants – both for existing products that are off-patent and for those that build on previous innovations [45].

Patents and other intellectual property protections for vaccine manufacturers are numerous and diverse and address most of the specificities of vaccine "knowledge" and "know-how" (trade secrets). For example, a study done in 2012 by the World Intellectual Property Organization [46] found that 11,800 patent families had been filed between 1921 and 2011 for active constituents of prophylactic vaccines against infectious diseases. Among these, 516 patent families related to flu vaccines, 165 patent families related to pneumococcal conjugated vaccines, and 36 patent families related to typhoid conjugated vaccines. Patents include technologies required for manufacturing (cell cultures, nucleic acid sequences, viral vector technology, virus/cell bank technologies, egg-based virus replication, etc.), active ingredients (antigens, adjuvants), production technologies, and processes (e.g., filtration, purification, conjugation, freeze-drying, etc.). The safeguarding of know-how and patenting of smaller components of the vaccine

development process can be important to vaccine manufacturers as it extends protection in time far beyond the initial patent for active ingredients. However, when such patenting does not reflect substantial technological advancements, it may lead to unreasonably long patent protection. Such an unjustified extension of the exclusivity period can impede price competition and follow-up innovation, ultimately limiting access to potentially life-saving products [45]. This is an area that could benefit, for example, from additional scrutiny of regulatory authorities granting of an extension of protections.

Since patents are, for the most part, not transferrable across jurisdictions, vaccine developers will often need to file their patents in multiple jurisdictions. Specific licenses are also required before exporting a vaccine; for example, the importing country may require the manufacturer to conduct country-specific clinical trials [3]. Such barriers add to the difficulties around logistics and production economics for vaccine manufacturers [47]. Some patents are also the subject of complex licensing cross-agreements and royalty payments between several intellectual property rights (IPR) holders as a result of negotiations to terminate disputes [44]. This may generate high financial stakes for several patent holders and make potential IPR negotiations further complex [3]. For example, Bio-Manguinhos had to pay 4–5% running royalties on the Hib vaccine to GSK [48].

Despite the growth in manufacturing in India and China in recent years [49,50], the IPR landscape for vaccines – from discovery to delivery – creates substantial obstacles for new players [2]. Understanding the landscape requires costly expertise, resources, and a capacity to undertake difficult and lengthy navigations around IPR. This could be in part addressed by a dedicated clearinghouse that focuses on reducing IPR-related barriers for DCVMN manufactures and potentially facilitates access to patent licenses. Activities to consider include: the creation of a vaccine patents database on strategically selected areas; supporting targeted freedom to operate analyses and solution-based resource tools; and, potentially, support DCMVN manufacturers with skills like legal expertise and negotiation strategy.

4.5. Costs

As discussed, there is no such thing as a "generic vaccine." This makes the economics and market dynamics of vaccines different compared to small molecule medicines. This means that even when patents expire, much of the large fixed costs cannot be avoided for new entrants, creating an added barrier to competition. The originator may, depending on the time to market, have recouped its investments during the monopoly period that the patent(s) have granted, allowing an opportunity to reduce the price over time to closer to marginal cost, if there is competition [2]. Since new entrants are forced to undergo many of the same upfront investments, the large initial fixed costs may make it difficult for them to compete on price unless tech-transfer partnerships are entered into. As a way to address this, the BMGF and governments have provided so-called up-front "push funding" and incentives for many DCVMN companies working on second-generation vaccines for low-income countries to offset fixed and development costs (e.g., pneumococcal, pentavalent, rotavirus). Also, some DCVMN business models, in particular those with partial government ownership, can allow for lower profit margins than a private or shareholder-based structure.

5. The way forward

In this paper, we have highlighted actions that can be taken at each stage from the process to accelerate access. From R&D, to manufacturing and regulatory, to the management of incentives like patents and public funding, there are ways to speed time to market and decrease costs. Examples highlighted include development of correlates of protection, innovative trial designs, enabling sciences such as adjuvant technologies, new technology approaches like mRNA vaccines, patent pools, conditions attached to public funding, materials sharing and technology transfer hubs and agreements, regulatory harmonization, and upfront push funding to offset fixed costs.

The COVID-19 outbreak and steps that have been taken to speed time to market could act as a catalyst for other vaccines, including new products and second-generation vaccines.

First, regulatory agencies are making use of specialized procedures for accelerating access. Just recently, the FDA made use of the EUA procedure to accelerate approval of COVID-19 vaccines [31]. With this has come the strong recognition of a need for harmonization of requirements by different regulatory agencies around the world, which will enable efficiencies to save both time and money. This is particularly important with regard to new technologies. For example, mRNA and DNA vaccines have the greatest potential of speeding the development processes [6] and the recent approval of mRNA vaccine against COVID-19, brings promise for fully establishing regulatory pathways for these innovations. While mRNA vaccines do pose some challenges for low-income settings, in particular their requirement for ultra-cold storages, there are ongoing efforts to try to address this issue, including the establishment of a COVID-19 mRNA vaccine technology transfer hub [51].

Second is the recognition that for vaccines to be deployed quickly and at scale, manufacturing capacity must be in place to allow for sufficient scale up when demand is high – as seen during the current pandemic. Given the substantial know-how required, access to facilities is not enough; low-income countries and regions must also have sufficient know-how about manufacturing processes [52]. This will require freedom to operate around patents and investment in technology transfer. To face the unprecedented need and opportunity for rapid and massive worldwide availability of COVID-19 vaccines, new business models have emerged with agreements between originator companies and manufacturing companies operating in different geographical and market environments. These precedents may pave the way towards a more flexible ecosystem involved in the continuum of vaccine production.

Third, with regards to IP arrangements, biopharmaceutical manufacturers and governments have made use of governmental compulsory licensing, patent oppositions, IP pools and voluntary IP licenses and technology transfer to advance access to new technologies. Although this has been limited in the field of vaccines, because of the issues discussed [53], improving transparency and creating more streamlined IP arrangements, could contribute to increased diversity of supplier which will also help alleviate supply constraints.

While still very much a "work in progress" the advancements demonstrated through the R&D of COVID-19 vaccines, give promise that many of the issues outlined above can be successfully addressed with adequate financing and political will.

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CRediT authorship contribution statement

NS conceptualized the manuscript. OA and NS wrote the manuscript. MC reviewed and edited the manuscript. NS and OA are joint first authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 2.2 Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts

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Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts

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ABSTRACT

To encourage COVID-19 vaccination, governments have offered a wide range of incentives to their populations ranging from cash to cows. Often these programs were rolled out at scale before assessing potential effectiveness. To inform future policy, we conducted a narrative review to understand the evidence base informing these programs and the extent to which they are effective. While we found evidence on cash transfers increasing both the coverage and intention to be vaccinated for COVID-19 and other adult vaccines, improvements in coverage were limited. With mixed evidence, lottery programs did not appear to have a consistent meaningful impact on vaccination for COVID-19, and no evidence was identified on the positive effects of other non-cash incentives for COVID-19 or other adult vaccines. We conclude that the impact of cash transfers in incentivizing adult vaccination is marginal and their effectiveness in addressing vaccine hesitancy remains inconclusive.

Introduction

Access to medicines is often characterized as influenced by four factors: accessibility, availability, affordability, and acceptability [1]. In December 2020, the first coronavirus disease 2019 (COVID-19) vaccine was introduced in the United States (US) through emergency use authorization (EUA) [2]. In 18 months, eleven COVID-19 vaccines are now authorized for use by the World Health Organization (WHO) [3], and more than 66 percent of the world's population has received at least one vaccine dose [4].

While COVID-19 vaccines are available and affordable in most countries, accessibility is an ongoing challenge in many areas of the world, leading to calls for increased investment in vaccine delivery [5]. In addition, there remain individuals and groups who are "hesitant" towards vaccinations - meaning they display indecision or uncertainty [6,7]. While this phenomenon has been observed for other vaccine-preventable diseases, it is also true for COVID-19 [7–9].

The WHO classified vaccine hesitancy as among the ten biggest global health threats in 2019 [10]. Some hesitancy is due to contextual factors, including trust in expertise and authority, or religious and political beliefs. Some is tied to individuals' concerns about specific vaccines, potential side effects, or even fear of needles. Reasons for hesitancy can also be more rooted in community, geography, or social networks and can be correlated with ethnic or socio-economic background [7,11]. More recently, hesitancy has been fueled by social media and a so-called "info-demic". For COVID-19 specifically, a survey in 23 countries found vaccine hesitancy associated with a lack of trust in COVID-19 vaccine safety and science and skepticism about its efficacy [6].

Several factors have demonstrated the potential to shift attitudes and behavior of vaccine-hesitant individuals. These include trust between patients and primary care providers, clarity about vaccine safety and efficacy, honesty around side effects, and an explanation of the role of vaccination in terms of both community

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and individual protection levels [12]. For childhood immunizations, strategies to overcome parental vaccine hesitancy and strengthen vaccine confidence canter around the key role of primary care in promoting vaccination [13].

While not specific to addressing hesitancy, there is also a wide body of literature that many health care interventions, including vaccines, provider-based "pay for performance" and conditional cash transfers (CCTs), can incentivize care-seeking behavior in both high- and low-income country settings [14].

For COVID-19, many governments and municipalities have put in place incentives aimed at individuals to encourage them to get vaccinated [15]. These included direct cash transfers, lottery tickets, and non-financial incentives, such as doughnuts, blenders, marijuana, herring, or even cows [16–18]. In New York City, residents were offered a range of items – from a $100 pre-paid debit card, to free amusement park tickets, to a trip to the Statue of Liberty [19,20].

In this narrative review, we assess the evidence on offering cash transfers and other incentives for increasing adult vaccination uptake. We focus on COVID-19, influenza, hepatitis B, maternal tetanus, and human papillomavirus (HPV). We excluded studies of routine childhood immunizations because the target of those incentives is usually the caregivers rather than the patients themselves.

Methods

We conducted a narrative review of the literature using MEDLINE, PubMed, and Cochrane databases. The narrative review approach was chosen to enable a thematic approach and inclusion of different types of interventions, outcomes, and populations [21]. The review was limited to peer-reviewed articles published in English and Arabic between 1 January 2012 and 9 February 2022. Relevant articles were identified by conducting an abstract/title search with any of the following key terms: (Incentiv*; cash transfer) AND (COVID-19; SARS-CoV-2; Coronavirus; influenza; flu; maternal/pregnan*/wom*n tetanus) AND (Vaccin* or immunis* or immuniz*). We also hand searched the reference lists of included articles to identify additional relevant publications and searched preprint studies in MedRxiv.

Identified articles were screened by two reviewers independently with the following inclusion criteria: 1) immunization targets the adult population and 2) material or financial incentives are offered. We excluded articles that focused on 1) punitive or negative incentives (e.g., sanctions, restrictions of movement); 2) routine childhood immunization where incentives, when offered, are provided to caregivers rather than patients; 3) incentivizing behavior at the facility level (e.g., a hospital). We also excluded study protocols, opinion papers, and modeling studies. We then synthesized evidence from the articles as described below.

Results

The initial search yielded 617 articles. After title and abstract screening, we conducted a full-text appraisal of 110 articles, excluded duplicates, and identified 26 articles that met our inclusion criteria (Table 1). The rationale for exclusion is detailed in the PRISMA flow diagram in Fig. 1. Three of the articles were systematic reviews. We extracted information on the purpose of the study, key findings as well as a type of incentive, vaccine, target group, and country. We grouped the findings according to whether the incentive was financial or material. The majority of studies were from the United States (US) (13). Studies were also identified from Nigeria (2), Germany (2), and one from each of the United Kingdom (UK), Singapore, Mexico, India, Sweden, and Australia. No studies on COVID-19-related incentives were identified from low- or middle-income countries. While we identified two relevant studies in MedRxiv, we did not include them as they have not yet been peer-reviewed.

Incentives

We identified a total of 26 articles that discussed incentives and vaccination, including vaccines for SARS-CoV-2 (12 studies) [22–33], hepatitis B (2 studies) [34,35], HPV (2) [36,3], maternal tetanus (3) [38–40], influenza (5) [41–43], adult tetanus, pneumococcus, and influenza (1) [46], and a mix of different vaccinations (1) [47]. Target groups, if specified, included adolescents (2), students (2), elderly (2), health and social care workers (2), people with substance misuse disorders (1), and people who inject drugs (2). Of these, 18 were about financial incentives, five about lotteries (or an opportunity to win a cash prize), and one about time off. Two were about a mix of different incentives. We found some evidence that financial incentives may increase immunization coverage in the short term, while material incentives did not have an impact on uptake.

Hepatitis B, HPV, Influenza, and maternal tetanus

Conditional cash transfers

We identified twelve studies, including two systematic reviews, on conditional cash transfers for incentivizing uptake of hepatitis B, HPV, influenza, or maternal tetanus vaccinations and found evidence that cash transfers (or the promise thereof) can increase vaccination uptake or stated intent to be vaccinated.

A study by Yue et al. in Singapore randomly sampled 4,000 people aged 65 and older to take part in an experimental design where some participants were offered a partial subsidy (shopping vouchers worth 10/20/30 SGD (approx. 7.5/15/23 USD) following receipt of a seasonal influenza vaccine which they paid for themselves) [45]. Increasing incentive from 10 to 20 SGD was associated with improved vaccine uptake, while no additional gains were found with a further increase to 30 SGD. Non-working people were more sensitive to the amount offered than those working, being over 2.3–2.8 times more likely to get vaccinated if incentivized [45].

Clark et al. assessed incentives required to promote influenza vaccine uptake among 66 college students in Pennsylvania, USA [43]. Among students that had previously been offered a vaccine but had not yet been vaccinated, 85 % of participants responded that they were willing to receive the influenza vaccine for 20 USD or less, 70 % for 5 USD or less, and half required less than 1 USD. All participants in the study were willing to accept a vaccine for a certain price, and for the overwhelming majority, this was less than 100 USD. Participants were not asked if they would take the vaccine without remuneration [43].

Bronchetti et al. also focused on influenza vaccines for college students, investigating the effect of social networks and financial incentives [41]. They found that a financial incentive (30 USD) offered within two weeks of vaccine uptake was effective at increasing vaccine uptake among college students, with an 11 % difference between the study and control group [41].

Two systematic reviews have been conducted on the use of incentives to increase uptake of hepatitis B vaccine among people who inject drugs, both of which concluded that financial incentives are effective at increasing coverage. Herrmann et al., based on 5 randomized control trials (RCTs) and 1 historical trial, reported incentives being associated with an absolute increase of between 21 % and 36 % in vaccine uptake compared to control [47]. Tressler and Bhandari, based on 3 RCTs, found that the pooled incentive

Table 1
List and summary of included articles.

Reference	Incentive	Vaccine	Target group	Sample size	Country	Findings
Campos-Mercado et al 2021 [24]	Financial incentive	COVID-19	General	8826	Sweden	200 Swedish kroner associated with 4.2 % increase in vaccination rates (baseline 71.6 %)
Kim and Rao 2021 [26]	Financial incentive	COVID-19	General	~7.5 million (Ecological)	USA	Incentive associated with 44 % increase in first dose, no effect on second dose
Klüver et al 2021 [27]	Financial incentive	COVID-19	General	20 500	Germany	Increased willingness to be vaccinated associated with financial incentive
Robertson et al 2013 [29]	Financial incentive	COVID-19	General	1000	USA	Incentive expected to yield 8 % increase in uptake; most changes in incentive size inconsequential, very large incentive counterproductive
Sprengholz et al 2021 [31]	Financial incentive	COVID-19	General	1349	Germany	Incentives were not associated with a change in participants' willingness to receive vaccine
Wong et al 2021 [33]	Financial incentive	COVID-19	General	394	USA	Centers participating in incentive associated with higher vaccine uptake
Bronchetti et al 2015 [41]	Financial incentive	Influenza	Students	9358	USA	Incentive associated with an 11 % absolute increase in vaccination uptake (~doubling of baseline rate)
Clark et al 2021 [43]	Financial incentive	Influenza	Students	66	USA	70 % willing to receive vaccine for $5 or less, half for £1 or less
Yue et al 2020 [45]	Financial incentive	Influenza	Elderly	4000	Singapore	Incentive associated with increased vaccination uptake
Caskey et al 2017 [36]	Financial incentive	HPV	Adolescents	188	USA	Incentive associated with increase in 1st/2nd dose (75 % vs 47 %) and completed course (36 % vs 13 %)
Mantzari et al 2015 [37]	Financial incentive	HPV	Adolescents	1000	UK	Incentive associated with higher uptake of 1st/2nd dose and course completion for previous non-attendees and first-time invitations
Chakrabarti et al 2021 [38]	Financial incentive	Tetanus	General	~200 000 (Cluster RCT)	India	Increase in maternal tetanus vaccine uptake (79.1 % to 82.8 % in 2006, 84.6 % to 88.9 % in 2016) in conditional cash transfer program
Okoli et al 2014 [39]	Financial incentive	Tetanus	General	20 133	Nigeria	Conditional cash transfer for preventive care associated with 21.66 per 100 000 increase in maternal tetanus vaccine uptake
Sato and Fintan 2020 [40]	Financial incentive	Tetanus	General	2482	Nigeria	Financial incentive associated with large increase in vaccination uptake (85.5 % for 800 naira, 75.7 % for 300 naira, 54.8 % for 5 naira)
Day et al 2016 [34]	Financial incentive	Hepatitis B	People who inject drugs	139	Australia	Incentive associated with higher vaccination completion rate (87 % vs 66 %)
Tressler and Bhandari 2019 [35]	Financial incentive	Hepatitis B	People who inject drugs	Not provided	N/A (Review)	Financial incentives effective at increasing compliance with 3-dose schedule (Odds Ratio 7)
Herrmann et al 2017 [47]	Financial incentive	Multiple	People with substance misuse	5052 (pooled)	N/A (Review)	Incentives effective at increasing completion of 3-dose vaccination course
Salinas-Rodríguez and Manrique-Espinoza 2013 [46]	Financial incentive	Tetanus, pneumococcus, influenza	Elderly	12 146	Mexico	Incentive recipients more likely to receive each vaccination (41–71 % to 46–79 %)
Acharya et al 2021 [22]	Statewide lottery	COVID-19	General	403 714	USA	Positive association between lottery programs and uptake, variable extent of increase
Barber and West 2022 [23]	Statewide lottery	COVID-19	General	~8 million (Ecological)	USA	Lottery associated with 1.5 % increase in vaccination rates
Dave et al 2021 [25]	Statewide lottery	COVID-19	General	~258 million (Ecological)	USA	Lottery incentives not associated with statistically significant effect on state vaccination rates
Law et al 2022 [28]	Statewide lottery	COVID-19	General	~258 million (Ecological)	USA	No significant difference associated with use of lotteries
Sehgal 2021 [30]	Statewide lottery	COVID-19	General	~8 million (Ecological)	USA	Modest increase (0.98 %) in vaccination rates associated with lottery state
Walkey et al 2021 [32]	Statewide lottery	COVID-19	General	~258 million (Ecological)	USA	No significant difference in vaccination uptake associated with introduction of lottery incentive
Cheema et al 2013 [42]	Time off	Influenza	Health and social care workers	154	USA	Quarter of respondents reported one-hour time-off incentive influenced vaccination decision
Lytras et al 2016 [44]	Mix of incentives	Influenza	Health and social care workers	Not provided	N/A (Systematic Review)	No significant difference associated with individual and group incentives (gifts, raffle, free drinks, bonus for meeting target)

group had seven times the odds of completing a 3-dose vaccine course compared to control [35].

Mantzari et al. investigated the effects of financial incentives on HPV vaccine uptake in the UK. Girls 16–18 years old were offered vaccination (control) or vaccination with a voucher upon completion of the three-dose vaccination course (treatment) [37]. Incentives were associated with increased uptake of the first dose and completion of the course among both those invited for the first time and those who had been previously invited for vaccination but not attended. (Among those invited for the first time, OR 1.63 for receiving the first dose in the treatment group compared to control, OR 2.15 for completing the course. Among those with the previous non-attendance, OR 2.65 for the first dose, OR 4.28 for completing the course.) However, the uptake in the treatment

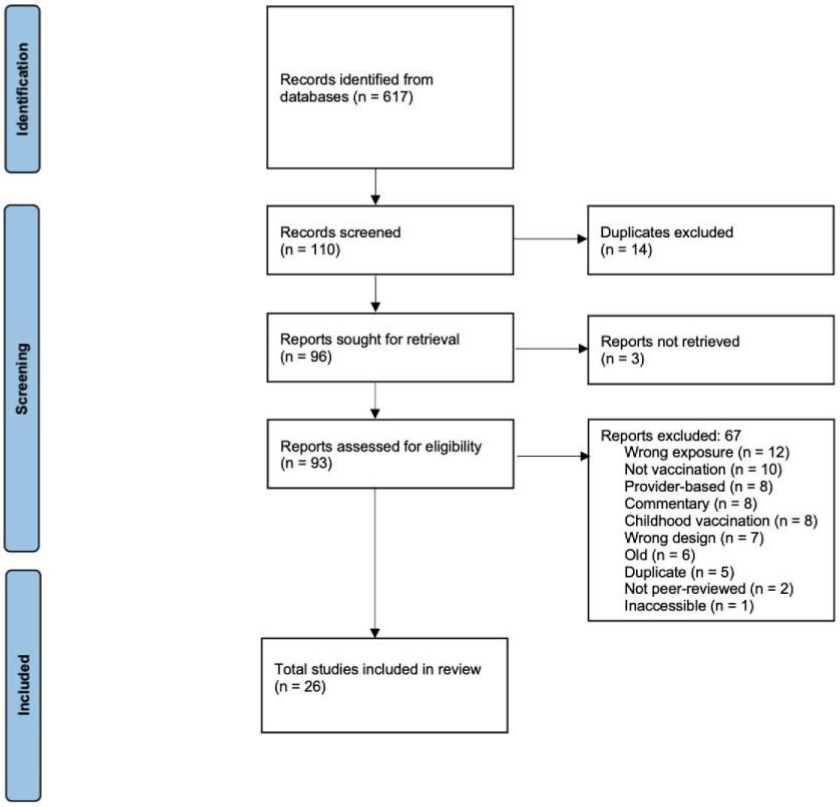

Fig. 1. PRISMA flow diagram detailing article selection.

group was still below the national target, suggesting that the incentive may have been more effective at reaching the undecided than the hesitant [36]. A randomized control trial by Caskey et al. found that 36 % of adolescents receiving incentives completed the full HPV vaccination course and 75 % received one or two doses, compared to 13 % completing the course and 47 % receiving one or two doses in the control group [36]. The offer of an incentive for HPV did not result in a difference between the experimental and control groups vis-à-vis seeking influenza vaccination at a later date [36].

In one of four studies identified from a low- or middle-income country, Salinas-Rodríguez and Manrique-Espinoza assessed the effect of cash transfer on tetanus, pneumococcal, and influenza vaccine uptake among the elderly in the 731 poorest rural communities in 13 Mexican states using a cross-sectional design matching cases to controls [46]. 44 000 households were surveyed, and vaccination status was self-reported. Those incentivized were more likely to have each of the three vaccinations (influenza 46 % vs 41 %; pneumococcal 52 % vs 45 %; tetanus 79 % vs 71 %) [46]. The amount of the cash transfer was not reported nor was there any analysis of cost-effectiveness more broadly.

Three studies looked at the use of conditional cash transfers on the uptake of maternal tetanus vaccines. A pilot program in Nigeria, where the incentive was part of a broad range of interventions from antenatal to postnatal care, demonstrated a significant increase of 21.66 vaccinations per 100 000 catchment population per month over the baseline (9.23 to 34.08) [39]. Another also from Nigeria, where a payment was made at the clinic upon receipt of the vaccine, showed a positive effect of a financial incentive when the incentive was large enough to compensate for the cost of travel to the clinic [40]. A study of a program in India, also offering an incentive for a range of maternal health interventions, including tetanus vaccine during antenatal care visits, similarly demonstrated a small positive effect on uptake [38].

Non-cash transfers

Evidence of non-cash incentives for hepatitis B, HPV, influenza, or maternal tetanus vaccinations was limited. We found only one systematic review and one cross-sectional study, both focusing on seasonal influenza vaccinations for health care workers. According to these studies, non-cash incentivization did not increase vaccine uptake. A systematic review by Lytras et al. (11 studies in total) on interventions to increase seasonal influenza vaccine uptake in health care workers found that incentives (including gifts, perks, raffles at the individual level or free drinks, bonus/rewards for meeting target at the group level) did not significantly affect influenza vaccination uptake [44]. Cheema et al. surveyed health care workers on the effect of a one-hour time off incentive for influenza vaccination and found no association with this influencing their decision to get vaccinated [42].

Covid-19

Conditional cash transfers

We identified six studies on COVID-19 vaccination, four of which focused on 'intent to vaccinate' with a hypothetical offer of a vaccine and two assessing actual cash transfer programs. The studies reported a positive effect of financial incentivization, with an increase in uptake ranging from 4.2 % to 9 %. The effect was more significant among those that identified themselves as "undecided" than those who "refused." One study found a significant increase in first-dose uptake but no difference in course completion [26].

A randomized survey conducted prior to the availability of vaccines by Robertson et al. in the USA of one thousand American adults in December 2020 on the intent to vaccinate for COVID-19 demonstrated financial incentives would yield an 8 % increase in uptake [29]. While the incentives proposed in this study were dramatically larger than in other studies (1000, 1500, or 2000 USD), the size of the incentive did not significantly affect the outcome. The middle-income group was most responsive to an incentive. For Black and Latino respondents, the largest incentive (2000 USD) was counter-productive [29].

A study in Germany in November 2020, also prior to the availability of vaccines, asked randomly selected participants (non-probabilistic sample; quota representative) about intent to vaccinate for COVID-19, and did not find any effect of a potential financial incentive, even after controlling for participant financial status [31]. A later nationally representative survey conducted in March 2021, also on intent to vaccinate, showed that financial incentives would have an impact and that doubling the incentive from 25 Euros to 50 Euros corresponded to a doubling effect on vaccine uptake [27]. However, the effect size was noted only for those who were declared as "undecided" (at 5 percentage points). Those who "refused" were less likely to respond to the incentive suggesting it may be better to focus incentives on the "undecided" [27].

Two studies on cash transfers conducted following the introduction of COVID-19 vaccines showed a positive impact. In Sweden, Campos-Mercado et al. conducted a randomized control trial between May and July 2021 with over 8000 participants, offering 200 Swedish kroner (24 USD) for vaccination within 30 days of the vaccine becoming available to them [24]. This was associated with a 4.2 % increase in COVID-19 vaccination rates from the baseline of 71.6 %. A similar increase was reported for "intention" to get vaccinated. The effect was noted as similar across all socio-economic groups [24].

A non-randomized trial by Wong et al. using a difference-in-differences approach reported findings of a two-week pilot for a COVID-19 vaccination in four counties in North Carolina, USA [33]. A 25 USD cash card was given to adults who either received or drove someone to receive their first dose of COVID-19. Incentives were associated with a higher vaccine uptake rate. 41 % reported that the cash card was an important reason for vaccination, more so if Hispanic or other non-white and if from the lower-income groups. About 9 % reported they would not have been vaccinated if the cash card had not been offered, and 15 % waited to get vaccinated until they found an event that gave a cash card or other incentive [33].

Non-cash transfers

We identified six studies on the effects of lottery entry on vaccine coverage, all assessing the impact at a population level, which showed limited to no effect. No studies were identified on the effects of other types of material incentives for increasing uptake of COVID-19 vaccines.

Studies by Barber and West and Sehgal et al. found modest improvements (approx. 1.5 % and 0.98 %, respectively) comparing vaccination rates in Ohio to a synthetic control from other states, weighted to match Ohio's population ("synthetic Ohio") [23,30]. In Ohio, the Vax-A-Million campaign offered a ticket to a weekly prize of one million USD during five weeks in May-June 2021 for the residents that had received at least one dose of a COVID-19 vaccine. In absolute terms, between the lottery announcement and the end date, the increase in vaccination coverage was modest, from approximately 42 % to 47 % [30].

A cross-sectional study by Acharya et al. using a difference-in-differences analysis estimated an aggregate 2.1 % increase in vaccination coverage associated with lottery programs in the US (11 states with a program vs 28 states without) [22]. However, when analyzed separately by state, the results were mixed, with a positive association in some states but not in others [22].

Dave et al., also using a difference-in-differences method, compared states implementing incentives against those that did not, and found that lottery-based incentives in US states were not associated with a statistically significant effect on COVID-19 vaccination rates either before or after the announcement of the drawing [25]. A study by Law et al. comparing 15 states using lotteries with 31 non-lottery states did not find a significant effect when compared with the pre-lottery trend [28]. Results from Walkey et al. similarly found no difference when comparing first-dose vaccination rates in Ohio and with states without lotteries [28].

Discussion

In this review, we explored cash and non-cash incentives offered for the adult population to improve vaccination coverage. While we found evidence of cash transfers increasing both the coverage and intention to be vaccinated, very few studies considered these effects at a population level and the ones that did found that the improvements were limited to a few percentage points in vaccination coverage. While the evidence is limited, findings on the experience with financial incentives and COVID-19 vaccines are largely consistent with findings from other adult vaccination such as hepatitis B, HPV, maternal tetanus, and influenza as well as the literature on the effectiveness of conditional cash transfers. According to evidence to date, lottery programs do not appear to have a meaningful impact on vaccination for COVID-19, with effects ranging from none to a 2.1 % increase in coverage, and no evidence was identified of positive effects of other non-cash incentives for COVID-19 or other adult vaccines. Further, most studies were conducted in the US with only four from low- and middle-income countries, none of which were on COVID-19.

Of note, for all vaccines, incentives were found to be more effective for the first dose than the second dose [26]. The reason behind this difference was not explored in any of the studies. There were also no studies identified evaluating the extent to which incentives would affect booster shots or other annual vaccination. As "point in time," studies did not assess the extent to which payments "now" may affect health-seeking behavior in the future, including for vaccines that are offered without incentives. Only one study explored the impact of incentivizing one vaccination (HPV) and found no adverse impact vis-a-vis later vaccination for seasonal influenza [36]. Perhaps most surprising, there was no evidence presented in any of the studies on the extent to which incentives serve to address the concerns of those who are hesitant or even increase uptake among this specific subset of the population.

Data from other conditional cash transfer programs do show that when targeted at low-income populations, incentives can be highly cost-effective as well as lifesaving [48–50]. For COVID-19

vaccines, only one study reported on findings related to cost or marginal cost [22]. No analysis was identified on the extent to which programs were either cost-effective or cost-saving.

Some studies raise ethical concerns that financial incentives for vaccination could be construed as coercive [51,52], and that in politically-divided contexts, government-promoted incentives might generate a backlash among those who are already hesitant, heightening suspicion of vaccination programs [51,53]. Considering existing problems with vaccine hesitancy in many populations, this is an important concern to bear in mind and plan for. There is also a question about whether the use of financial incentives as a tool to promote vaccination uptake for COVID-19 may result in a societal expectation of these in the future, affecting both COVID-19 and other vaccination programs and one study did point out a delay based on an expectation of an incentive [33].

In terms of study design, the choice of the narrative review allowed us to conduct a comprehensive overview of the published literature. While we have borrowed some methods from the practice of a systematic review (e.g. PRISMA statement), because of the limited number of studies available and the breadth of scope of the research question, we were unable to conduct any grading of evidence or combined statistical data analysis that could help reduce bias in the data and conclusion [54]. With regard to limitations, our search focused on the adult population. Expanding it to routine or other childhood immunization could have yielded more results, particularly from low-and middle-income countries. The number of databases and languages used may have also limited the findings. There are also likely to be incentive schemes implemented in low-and middle-income countries but not described or investigated in peer-reviewed literature.

Conclusion

Given the paucity of evidence, and the seriousness of the potential unintended consequences, it is remarkable how many governments, states, and cities offered incentives to increase vaccination coverage and did not embark on any type of implementation research to evaluate program effectiveness. Equally puzzling, while we may have evidence that some programs work, we do not necessarily understand why or for whom.

Moving forward, it will be important to monitor the impact of these incentive programs over time at both the individual and population levels. It will also be important to unpack the theory of change of these programs and understand whether their impact is more on those who are truly hesitant or those who are undecided. It will also be important to assess their cost-effectiveness against other known and effective ways to improve coverage, such as increasing trust with providers [55], increasing points of access and community outreach, and reducing out-of-pocket costs [56,57], and providing clear information and reminders [58].

While we did not explore the role of provider-based incentives ("pay for performance") for COVID-19 vaccines, these have shown promise to increase coverage for other types of adult vaccination and should be further explored [59–60].

CRediT authorship contribution statement

Nina Schwalbe: Conceptualization, Methodology, Data curation, Validation, Formal analysis, Wrote orignal draft, Reviewed, and Edited. **Layth Hanbali:** Data curation, Formal analysis and Contributed to the drafting, Revewing and Editing. **Marta C. Nunes:** Formal analysis, Writing, Review and Editing. **Susanna Lehtimaki:** Methodology, Formal analysis, Validation, Drafting, Reviewing and Editing.

Ethical Approval

Ethical approval for this type of study is not required by our institute.

Data availability

No primary data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 2.3 Assessing New York City's COVID-19 vaccine rollout strategy: a case for risk-informed vaccine distribution

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Assessing New York City's COVID-19 vaccine rollout strategy: a case for risk-informed vaccine distribution

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Abstract:	This study reviews the impact of eligibility policies in the early rollout of the COVID-19 vaccine on coverage and probable outcomes, with a focus on New York City. We conducted a retrospective ecological study assessing age >65, area-level income, vaccination coverage and COVID-19 mortality rates, using linked Census Bureau data and New York City Health administrative data aggregated at the level of modified zip code tabulation areas (MODZCTA). The population for this study was all individuals in 177 MODZCTA in New York City. Population data were obtained from Census Bureau and New York City Health administrative data. The total mortality rate was examined through an ordinary least squares (OLS) regression model, using area-level wealth, the proportion of the population aged 65 and above, and the vaccination rate among this age group as predictors. Low-income areas with high proportions of older people demonstrated lower coverage rates (mean vaccination rate 52.8%; maximum coverage 67.9%) than wealthier areas (mean vaccination rate 74.6%; maximum coverage 99% in the wealthiest quintile) in the first three months of vaccine rollout and higher mortality over the year. Despite vaccine shortages, many younger people accessed vaccines ahead of schedule, particularly in high-income areas (mean coverage rate 60% among those 45-64 years in the wealthiest quintile). Low-income areas with high proportions of older people demonstrated lower coverage rates than wealthier areas in the first three months of vaccine rollout, and higher mortality over the year, while younger adults accessed vaccines ahead of schedule, particularly in high-income areas. A vaccine program that prioritized those at greatest risk of COVID-19-associated

	morbidity and mortality would have prevented more deaths than the strategy that was implemented. When rolling out a new vaccine, policymakers must account for local contexts and conditions of high-risk population groups. If New York had focused limited vaccine supply on low-income areas with high proportions of residents 65 or older, overall mortality might have been lower.

Assessing New York City's COVID-19 vaccine rollout strategy: a case for risk-informed distribution

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Abstract

This study reviews the impact of eligibility policies in the early rollout of the COVID-19 vaccine on coverage and probable outcomes, with a focus on New York City. We conducted a retrospective ecological study assessing age >65, area-level income, vaccination coverage and COVID-19 mortality rates, using linked Census Bureau data and New York City Health administrative data aggregated at the level of modified zip code tabulation areas (MODZCTA). The population for this study was all individuals in 177 MODZCTA in New York City. Population data were obtained from Census Bureau and New York City Health administrative data. The total mortality rate was examined through an ordinary least squares (OLS) regression model, using area-level wealth, the proportion of the population aged 65 and above, and the vaccination rate among this age group as predictors. Low-income areas with high proportions of older people demonstrated lower coverage rates (mean vaccination rate 52.8%; maximum coverage 67.9%) than wealthier areas (mean vaccination rate 74.6%; maximum coverage 99% in the wealthiest quintile) in the first three months of vaccine rollout and higher mortality over the year.

Despite vaccine shortages, many younger people accessed vaccines ahead of schedule, particularly in high-income areas (mean coverage rate 60% among those 45-64 years in the wealthiest quintile). Low-income areas with high proportions of older people demonstrated lower coverage rates than wealthier areas in the first three months of vaccine rollout, and higher mortality over the year, while younger adults accessed vaccines ahead of schedule, particularly in high-income areas.

A vaccine program that prioritized those at greatest risk of COVID-19-associated morbidity and mortality would have prevented more deaths than the strategy that was implemented. When rolling out a new vaccine, policymakers must account for local contexts and conditions of high-risk population groups. If New York had focused limited vaccine supply on low-income areas with high proportions of residents 65 or older, overall mortality might have been lower.

Introduction

On December 11, 2020, the United States granted emergency authorization for newly developed COVID-19 vaccines to prevent severe morbidity and mortality [1]. Three days later, on December 14, New York administered its first vaccines to high-risk hospital workers. This was followed in the State, in order, by nursing home workers and residents (December 21, 2020), all hospital workers (January 4, 2021), essential workers, and all adults 75 years and older (January 11, 2021), all adults (18 years and older) with underlying health conditions, including obesity (February 15 2021), all adults 60 years and older (March 10, 2021), public-facing government and non-profit workers (March 17, 2021), all adults 50 years and older (March 23, 2021), all adults 30 years and older (March 30 2021), and then all adults 16 years and older (April 6, 2021) [2].

During this period, the New York State Department of Health (NYSDOH), in collaboration with the New York City Department of Health and Mental Hygiene (NYCDOH), delivered vaccines through fixed-point mass vaccination sites. Appointments were arranged through an English-language internet-based system [3], based on self-verification that applicants met age, health or employment-related criteria.

The rapid pace with which vaccine eligibility was widened during the early months of 2021 may have been a rational choice had there been adequate availability of vaccines. However, limited stocks meant groups at lower risk were added to the pool of eligible recipients before those at higher risk were vaccinated [4,5]. There were many reports about difficulties faced by people 65 years and older getting appointments to receive even their first dose [6–9].

In New York, as elsewhere, the probability of dying from COVID-19 was not equally distributed across the population. The single greatest risk factor for COVID-19-related mortality was older age [10–12]. Low-income households were also particularly vulnerable [13].

In light of these two equity-related vulnerabilities, this analysis explores whether New York widened vaccination eligibility too quickly in the face of vaccine shortages rather than focusing first on those at

72 higher risk [14,15]. The research aimed to answer the question of whether older New Yorkers living in
73 low-income communities would have been better served in the face of COVID-19 vaccine shortages if
74 distribution had been targeted toward them.
75 We reviewed differences in coverage of people 65 years and older (65+) between the highest and lowest
76 wealth quantiles just before the State expanded eligibility to younger age groups but when vaccines
77 were still supply-constrained. We then examine whether differences persisted when vaccines were no
78 longer supply-constrained. We also analyzed the relationship between risk factors, vaccination coverage,
79 and COVID-19 mortality rates by geography.

Methods

Type of Study

We conducted a retrospective analysis of linked Census Bureau data and New York City Health administrative data aggregated at the level of modified zip code tabulation areas (MODZCTA). All analyses were done with R software (version 4.1.3). The authors complied with STROBE guidelines [16].

Data collection

Data on vaccination coverage, stratified by age and MODZCTA, were obtained by special request from the NYCDOH [17] through the Open Data initiative [18]. Race, income, and age data by MODZCTA were obtained from the US Census Bureau [19]. New York City (NYC) is divided into 177 MODZCTAs [20]. While a MODZCTA comprises either a single Zip Code Tabulation Area (ZCTA) or a combination of contiguous ZCTAs, no ZCTA contributes to more than one MODZCTA.

Demographic data

Population data, disaggregated by age and sex, were drawn from the 2020 American Community Survey (ACS) 5-Year Estimates Detailed Tables [21]. The data available for each ZCTA were aggregated up to MODZCTAs using the mapping described and grouped into five age groups: 0-17, 18-24, 25-44, 45-64, and 65+, to match age-grouped vaccination NYCDOH data. 23 ZCTAs had populations of 0 and were therefore excluded [22].

Wealth data

Median household wealth data for each NYC ZCTA were drawn from the 2020 ACS 5-Year Estimates Detailed Tables and aggregated up to MODZCTAs. The three ZCTAs with very small populations (n=44, 96, 220) for which median household income was unavailable, were treated as having zero median household income. Median income was aggregated up to MODZCTA as a population-weighted sum of the median income of each contributing ZCTA.

Vaccination coverage data

NYCDOH provided data on the percentage of the population in each MODZCTA that received at least one COVID-19 vaccine dose stratified by selected age groups and date. We focused on vaccination coverage for the week of March 27, 2021; before this, people less than 50 were not generally eligible for vaccination.

Mortality data

NYCDOH provided the total number of COVID-19 deaths in each MODZCTA from December 1, 2020 to December 31, 2021. These data were not stratified by age. To preserve patient privacy, NYCDOH did not provide the number of deaths in any MODZCTA with less than 10 deaths. As disaggregation by any factor (e.g., age, sex, gender) would increase the cells with mortality counts less than ten, and thus missing data, we opted for unstratified total mortality. 11 (6.2%) of all 177 MODZCTAs recorded less than ten deaths. The minimum number of deaths in a MODZCTA was zero; the maximum was 302. We replaced missing data with a mid-point value of five because zero was definitively zero and any number >= 10 was definitively that number. Thus, missing data were less than 10 but more than zero. While we considered estimating the number of deaths by calculating the city death rate and multiplying that by the population of the modzcta (i.e. mean replacement), that would have resulted in 6 of the 11 missing counts exceeding 10, which was not possible. An examination of the distribution of death counts in the city's modzcta's also showed wide variation suggesting that a single modzcta that was within 5-points of its true value would adequately represent the true value within the model. Choosing other values did not noticeably change the models.

Combining mortality and population data, we calculated COVID-19 mortality rates per 100,000 population in each MODZCTA from December 1, 2020 to December 31, 2021.

Data Analysis

Vaccination coverage

We first explored vaccine coverage by MODZCTA wealth quintiles. Using age-group specific population and the vaccination coverage by MODZCTA, we calculated the number of doses distributed to each age group to assess, given supply constraints, the extent of "misallocation" (i.e., the excess doses had vaccine supply been allocated exclusively to older individuals).

Mortality

We conducted an ecological analysis looking at the relationship between MODZCTA-specific mortality from December 1, 2020 to December 31, 2021, and the percentage of the population 65+, the vaccination coverage in the 65+, and the median household wealth. These three variables were centered to enhance stability of the models.

We estimated the relationship using OLS regression. We used Moran's I to estimate spatial dependency in the residuals, which was significant. We used a spatial error model to estimate the bivariate relationships between: (1) area-level proportion of individuals 65+ and COVID-19 mortality, (2) area-level median household income and COVID-19 mortality, (3) area-level vaccination coverage 65+ and COVID-19 mortality [23]. In the full model, we started with a "full factorial" approach, including all the individual predictors and their interactions. We then looked at the effect of removing higher-order interactions, using an ANOVA test and found removing any interaction effect resulted in a model with a significantly poorer fit. Based on an analysis of the residuals in the first step, we also tested the inclusion of a dummy for one outlier MODZCTA.

Ethical Considerations

This study received ethical approval from the University of the Witwatersrand's Human Research Ethics Committee (HREC), which determined that the research did not involve human subjects as defined by the university's policies and federal regulations. Therefore, informed consent was not required for

participation. The data were completely anonymized and NYCDOH did not provide the number of deaths in any MODZCTA with less than 10 deaths.

Results

Descriptive

Table 1 shows the variation across NYC MODZCTAs of the total population, proportion 65+, median household income, mortality rate, and vaccination coverage by wealth quintile at March 27 2027 and March 19, 2022.

Table 1 Summary statistics and vaccination coverage by March 19, 2022 (by MODZCTA)

Summary statistics	Minimum	Median	Mean	Maximum	IQR
Total population	3260	43173	47693	108661	27672–67989
Proportion population 65+	<1	14.5	15.1	31	11.7–18.3
Median household income	$23,337	$74,042	$81,381	$250,001	$56,908–$96,787
COVID-19 mortality rate per 100,000 (2021)	0	126.8	127.1	397	93.2–151.3
Vaccination coverage at week March 27, 2021					
Lowest wealth quintile >=65	36.1	53.7	52.8	67.9	47.4–57.8
Highest wealth quintile >=65	41.2	73.6	74.6	99.0	64.0–82.8
Vaccination coverage at week March 19, 2022					
Lowest wealth quintile >=65	65.6	87.4	86.8	99	79–100
Highest wealth quintile >=65	52.1	94.6	90.2	99	82.5–99.0

The difference in the total population between the smallest and largest MODZCTAs ranged from 3,260 to over 108,000 people. There was a 30-fold range in proportion of 65+ (less than 1% to 31 %) and a ten-fold range in median household income ($23,337 to $250,001). COVID-19 mortality in 2021 was four times higher in the highest versus lowest mortality area (397/100,000 vs 94/100,000).

Vaccination coverage

We explored the relationship between age-wealth, age-vaccination coverage, and wealth-vaccination coverage across MODZCTAs, focusing on vaccination coverage by the last week of March, just before everyone aged 30+ became eligible for vaccination.

The mean vaccination rate for 65+ ranged from 52.8% in the poorest quintile to 74.6% in the wealthiest. The maximum coverage was 99.0% among those 65+ in the wealthiest quintile versus 67.9% in the poorest. For those 45-64 years, the difference in mean coverage between the wealthiest and poorest quintiles was 25% (60% versus 34.6%). A year later, when vaccines were widely available, 65+ residents had median vaccination coverage exceeding 87%, including in the lowest wealth quintile (Table 1).

The proportion of 65+ vaccinated three months following vaccine introduction and the overall death rates by geographical area for 2021 are almost mirror images with opposite polarity. Areas with a higher proportion of 65+ vaccinated tended to have lower death rates, suggesting an inverse spatial relationship between the proportion vaccinated and the death rate (Figure 1).

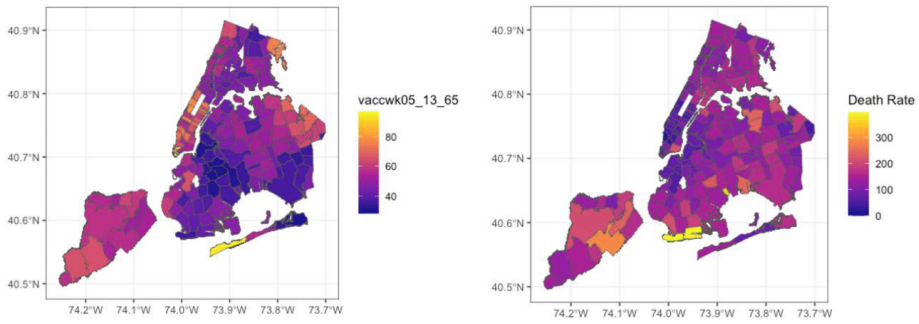

Fig. 1 Proportion vaccinated with at least one dose by MODZCTA >=65 for week of March 27, 2021 (left) and overall death rates by MODZCTA 2021 (right)

We also observed a positive correlation between weighted median income (wealth) and vaccination coverage for 65+ and an inverse correlation between wealth and mortality (Figure 2).

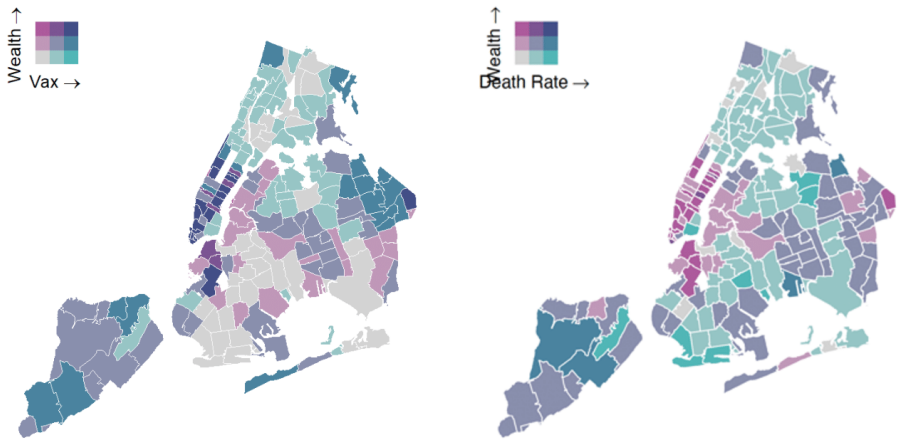

Fig. 2 Wealth and >=65 vaccination rate (left) and wealth and mortality rate (right)

Figure 3 shows a boxplot of vaccination coverage, by age group, for each income quintile by March 27, 2021. The plot shows a consistent pattern whereby, for any age group, there is a monotonic and increasing relationship between wealth and vaccination coverage. However, as up to March 27, 2021, the vaccine was not generally available to people under 50 it is striking that: (i) so many younger people were being vaccinated, and (ii) wealthier people had higher coverage across all age groups.

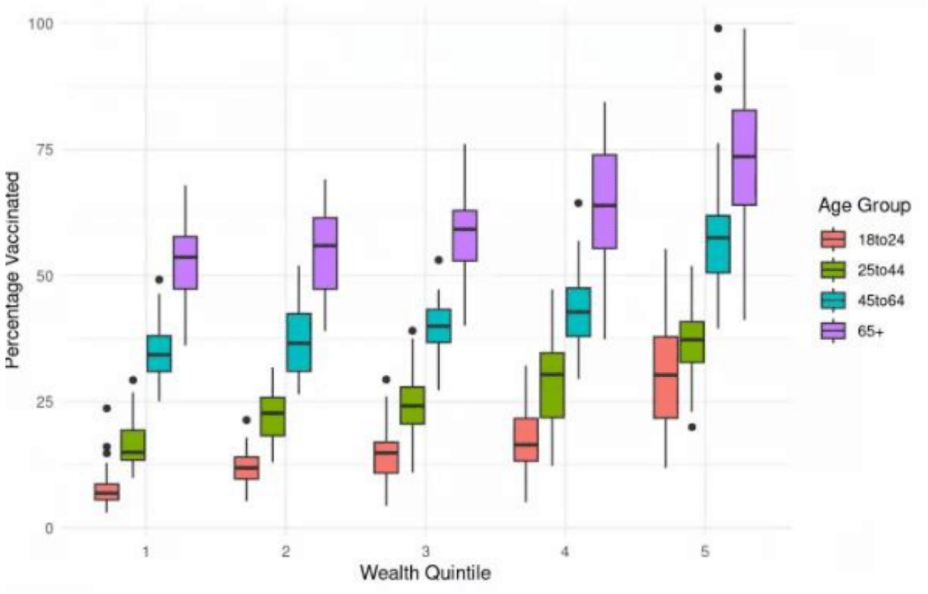

Fig. 3 Percentage vaccinated by wealth quintile and age group

We reanalyzed vaccination coverage using absolute numbers of doses to assess the potential "misallocation" of vaccines from older to younger age groups. We used coverage rates to derive doses delivered by age group by multiplying coverage rates by the population, per MODZCTA. This provided the minimum number of doses available during this period. From this, we identified that by March 27, 2021, MODZCTAs in the wealthiest quintiles had received enough vaccines to cover 41.6% of their total population. Vaccine availability dropped monotonically by wealth quintile: 31.6% coverage for the second wealthiest, 27.3% coverage for the middle, 24.9% for the second poorest, and 20.7% coverage for the poorest quintile.

We estimated the "misallocated doses" as any doses received by a person under 45 years before March 27, 2021, as by this date, only people older than 50 years were eligible for vaccination unless they were in high-risk health or employment categories. As described in the discussion section, we would expect to

observe a larger proportion of these individuals living in the poorest quintiles and commensurate "overallocation".

The greatest estimated overallocation of doses, however, occurred in the wealthiest quintiles. Among them, 38.6% of doses were "misallocated" from older (65+) to younger (0-17, 18-24, 25-44) age groups. The "misallocation rate" dropped monotonically by wealth quintile.

Moreover, if vaccination had been restricted to 65+, there would have been enough vaccines for this age group in NYC 1.19 times over. By quintile, if in the poorest all doses delivered had only been administered to older New Yorkers, there would only have been doses to vaccinate 96.4% of the 65+ age group. In contrast, in the wealthiest, if vaccinating only older adults, there would have been 69% excess doses.

Mortality

To explore the statistical relationship between mortality rates and the centred values for the percentage of the population 65+ in each MODZCTA, the vaccination coverage in the 65+, and the median household income, we fit a 'full factorial' OLS regression model. This model enables study of the effects of multiple factors simultaneously on a response variable.

The Moran's I test of the residuals, based on spatial autocorrelation, revealed strong evidence of positive spatial autocorrelation ($I=0.299$, $p<0.0001$), implying that locations close together exhibited values more similar than expected by chance alone.

To overcome the spatial correlation in the error observed in the initial model, we used a spatial error model. We tested the residuals using a Monte Carlo version of the Moran's I test, which detected no significant spatial autocorrelation ($I=-0.053$, $p=0.799$). The absence of significant spatial autocorrelation in the residuals suggests that the spatial error model successfully accounts for the spatial dependence present in the data. The model results, including coefficient estimates and statistical significance, are shown in Table 2.

Table 2 Spatial error regression with centred predictors

Predictor	Estimate	Std. Error	z value	P value
(Intercept)	125.23	4.56	27.4573	<.0001
%Age >=65	5.8227	0.6996	8.3224	<.0001
Median Income	-1.0944	0.1144	-9.5647	<.0001
% Vaccinated (>=65)	-0.3056	0.3241	-0.9428	0.3458
Interaction terms	146.38	30.618	4.7809	<.0001
%65 * Median Income	-0.0971	0.0157	-6.1686	<.0001
%65 * %Vaccinated	-0.0239	0.0506	-0.4725	0.6366
Income * %Vaccinated	0.0233	0.0060	3.8723	0.0001
%65 * Income * %Vaccinated	0.0025	0.0008	3.0352	0.0024

Except for one MODZCTA (with an exceptionally higher-than-average proportion of older adults) [24] mortality was higher in lower-income areas and areas with a greater proportion aged 65+. Those areas were also less vaccinated.

The fitted spatial error model provides insights into the factors affecting the COVID-related mortality rate in MODZCTAs. First, assuming a MODZCTA with centred values for income ($74K), percentage 65+ (14.5%), and vaccination rate in 65+ (14.5%), the expected mortality rate for the period 2021 is 125.2 per 100,000 people.

The coefficient for the percentage of the population 65+ was positive and statistically significant ($b=5.82$, $p<0.001$), indicating that, with centring, a 1% increase in the percentage of 65+ is associated with a 5.8% increase in the mortality rate ($p<.0001$), holding all other variables constant. Median household income had a negative and significant effect ($b=-1.09$, $p<0.001$); a $1,000 increase in median income is associated with a 1.1% decrease in the mortality rate ($p<0.0001$), holding all other variables constant. A 1% decrease in vaccination coverage in the 65+ age group is associated with a small (-0.3056; $p=0.3458$) decrease in the mortality rate. While not statistically significant, it is in the expected direction.

The vaccination coverage among 65+ had a negative but non-significant coefficient ($b=-0.31$, $p=0.35$), aligned with the protective effect of vaccination against mortality risk.

There were significant interactions between the percentage of 65+, median income, and vaccination coverage. The negative interaction between the percentage of 65+ and income (b=-0.10, p<0.001) indicated that the mortality effect of a larger elderly population diminished in higher-income areas. The positive income by vaccination coverage interaction (b=0.02, p=0.001) suggested that vaccination played a greater role in lowering mortality in higher-income regions. Finally, the three-way interaction between the percentage of 65+, income, and vaccination coverage was positive and significant (b=0.003, p=0.002), implying a complex relationship between age, income, vaccination, and mortality.

While coefficient estimates were robust, accounting for spatial autocorrelation in the error term improved model fit and controlled for potential bias. Formal interpretation of the spatial structure is necessarily limited.

Discussion

Income and age were clear predictors of mortality due to COVID-19 in the United States [14,25,26], where over 81% of COVID-19 deaths occurred in people aged 65+ [27]. Delaying vaccination in these groups resulted in avoidable deaths [28]. We used high-quality, public sector data to appraise the rollout of COVID-19 vaccination and COVID-19 mortality in NYC, a densely populated urban center with a widely ranging socio-economic and demographic contexts. We timed our analysis to maximize the ability to appraise vaccine uptake when vaccines were theoretically restricted to high-risk groups.

We found that low-income areas with high proportions of people 65+ demonstrated lower coverage rates (mean vaccination rate 52.8%; maximum coverage 67.9%) than wealthier areas (mean 74.6%; maximum 99%, in the wealthiest quintile) in the first three months of vaccine rollout, and higher mortality over the year following its introduction. These findings are consistent with the literature on the effects of age and wealth on COVID-19 mortality [13,14,29].

At a time when vaccine supply was still limited [30], many lower-risk, younger people accessed vaccines ahead of schedule, particularly in high-income areas (mean coverage 60% among those 45-64 years in the wealthiest quintile), suggesting “misallocation” of doses that could have been provided to older people, who had higher case fatality rates [31]. This could have been corrected by authorities through more stringent enforcement of state mandated guidelines on distribution criteria.

While there is some plausibility that access for younger people was granted to those in scheduled professions or having underlying health risks, this is unlikely to account for the magnitude of difference between low and high-income MODZCTAs. Moreover, few working in such professions would fall into the wealthiest quintile. As poorer people make up the largest numbers of essential workers and are more likely to have underlying risk conditions and thus be eligible for the vaccine, we would assume vaccination rates in younger adults should have been higher in poorer areas [14]. This, however, was not the case suggesting that many people jumped the queue, with no consequences from the state.

Of note, when vaccines were no longer in short supply, uptake for all income groups aged 65+ rose above 80%. This suggests that vaccine access drove low coverage in the early months of the vaccine rollout. Our findings demonstrate the direct results of failure to prioritize health resources according to risk in a public health emergency and underscores the importance of shepherding doses and prioritizing known high-risk groups in future. Across the US, income data are available by zip code, and Medicare and Medicaid have detailed records of household age and related medical conditions. Information on household age and composition is also available from voter registration data. These and other available data enable to target at-risk populations first and deploy a "precision public health" approach [32].

Limitations

This study had several limitations. First, the mortality model is ecological and does not permit inferences about the association at the individual level. This limitation is further complicated by the fact that the mortality rate was based on the cumulative COVID-19 mortality for all ages in 2021, though the group of interest was 65+. For data analytic purposes, we replaced the missing deaths with a mid-point value of five. Sensitivity analyses suggested that this had little effect on the final analysis.

The mortality data provided by NYCDOH was also for December 1 2020, to December 31 2021, including one month of deaths before vaccine availability. However, after an initial peak in April 2020, the number of deaths only started to increase again rapidly in January 2021, with a steady rise throughout that year. Also, while we explored the relationship between vaccination coverage in the week of March 27, 2021, and COVID-19-associated mortality rates between December 2020 and December 2021, many aspects of COVID-19 were dynamic (e.g. the emergence of variants of concern, prevalence of infection-induced immunity) and could have affected mortality.

Due to data availability, we used area-level measures of vaccination coverage for the 65+ for March 2021 and the percentage of 65+ in MODZCTA populations. The challenge of interpreting the higher interaction

296 terms of the mortality model may be attributable to this and could be overcome with the availability of
297 better mortality data. Finally, we note that sex-disaggregated vaccination coverage data by geography
298 was not available thus, gender is not considered in this analysis. This is important limitation in assessing
299 vaccine coverage and outcomes.
300 We note that lack of data and the ecological nature of the study meant that we could not explore a range
301 of potential confounders including lack of legal documentation [33], lack of primary health care provider
302 [34], languages spoken, access to transport [35]. In NYC, these are all highly correlated with income.
303 We were also unable to explore potential factors contributing to hesitancy within New York City and
304 between groups (e.g. race, ethnicity, religion). It is plausible, for example, that vaccine-hesitant people
305 could have taken a "wait and see" approach and decided to vaccinate after seeing others get the vaccine
306 [36]. While this phenomena has been analyzed by race and demonstrated among younger age groups, it
307 has not (that we know of) been analyzed by older age or income [37]. Other variables that merit further
308 exploration with regard to mortality include household crowding, which in early COVID-19 research was
309 shown to be associated with infection rates in NYC. However, this research also demonstrated that
310 neighborhood variables, including income levels, household crowding, and unemployment, were
311 moderately to highly correlated [38].

Conclusion

In the initial days of the vaccine rollout in New York, low COVID-19 vaccination coverage rates in low-income areas were frequently attributed by media, pundits and even New York State's governor to so-called vaccine hesitancy [36,39,40]. However, the fact that all wealth quintiles in NYC had a median coverage of over 87% once there was sufficient supply and community-based distribution suggests that vaccine access prevented higher coverage in low-income areas.

The study underscores the ethical implications of vaccine distribution strategies, highlighting the need for equity-focused approaches that include wealth and accessibility into risk-based formulas. Its findings can inform future strategies to prioritize high-risk groups, ensuring fair and effective public health interventions. Next time policymakers would do better to focus on the most vulnerable by deploying a "precision public health" approach.

Roles: NS conceived the study, designed the research plan, conducted the literature, analyzed data, and drafted the manuscript. DR provided R code, oversight of statistical analysis, and contributed to the development of the manuscript. MCN and CC contributed to the data analysis and reviewed the manuscript.

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459

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I, Nina Schwalbe, student number 2537099, declare that this Thesis/Dissertation/Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Dissertation.

Signature of  Student Date 23 May 2024

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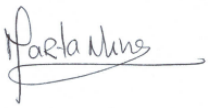
Signature of Primary Supervisor  Date 23 May 2024

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Article 1: Title: Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts

Journal name, year, volume and page numbers: Vaccine: X 12 (2022) 100225

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6th author			

Comments by primary supervisor:

Article 1: Title: Increasing efficiency in vaccine Production: A primer for change

Journal name, year, volume and page numbers: Vaccine: X 8 (2021) 100104

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Comments by primary supervisor:

4

Article 2: Title: Assessing New York City's COVID-19 vaccine roll out strategy

Journal name, year, volume and page numbers: submitted to Lancet Regional Americas

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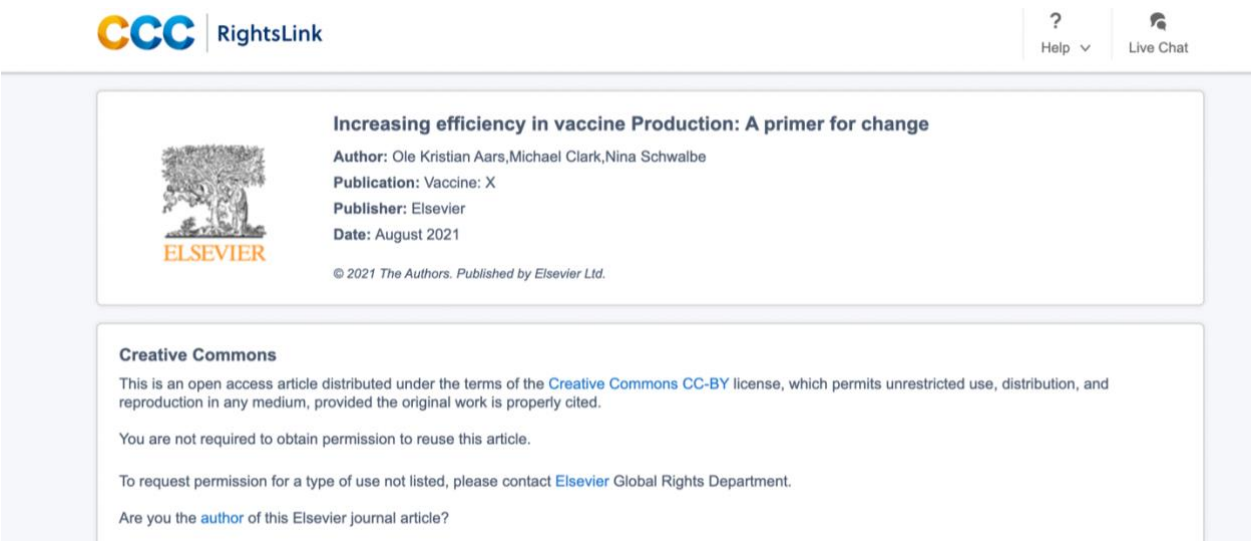

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Increasing efficiency in vaccine Production: A primer for change

Author: Ole Kristian Aars,Michael Clark,Nina Schwalbe

Publication: Vaccine: X

Publisher: Elsevier

Date: August 2021

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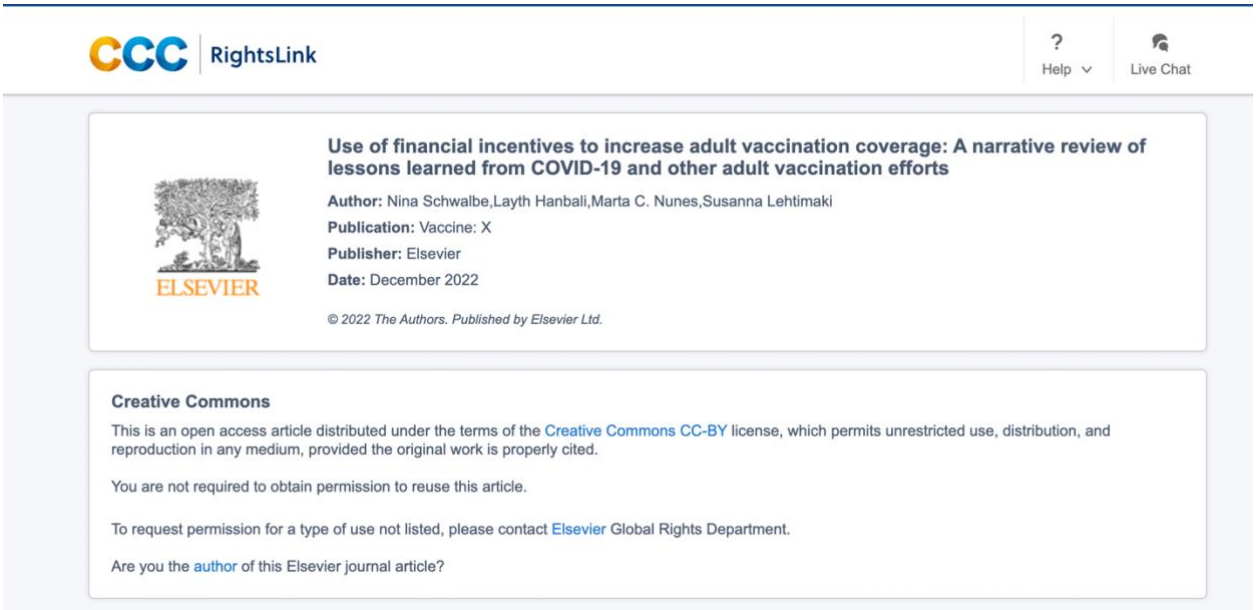

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Use of financial incentives to increase adult vaccination coverage: A narrative review of lessons learned from COVID-19 and other adult vaccination efforts

Author: Nina Schwalbe,Layth Hanbali,Marta C. Nunes,Susanna Lehtimaki

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