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[Giuseppe Tradigo](#) , [Jayanta Kumar Das](#) , [Patrizia Vizza](#) ^{*} , Swarup Roy , [Pietro Hiram Guzzi](#) , Pierangelo Veltri

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Article

Strategies and Trends in COVID-19 Vaccination Delivery: What We Learn and What We May Use for Next Future

Giuseppe Tradigo ^{1,†} , Jayanta Kumar Das ², Patrizia Vizza ^{3,*,†}, Swarup Roy ⁴, Pietro Hiram Guzzi ^{3,†} and Pierangelo Veltri ⁵

¹ Ecampus University, Novedrate, Italy; giuseppe.tradigo@uniecampus.it

² NIH Biomedical Research Center, National Institute on Aging Bethesda, USA; dasjayantakumar89@gmail.com

³ Department of Surgical and Medical Science, Magna Graecia University, Catanzaro, Italy; vizzap@unicz.it; hguzzi@unicz.it

⁴ Sikkim University, Tadong, India; sroy01@cus.ac.in

⁵ DIMES, University of Calabria, Rende, Italy; pierangelo.veltri@unical.it

* Correspondence: vizzap@unicz.it; (P.Vi.)

† These authors contributed equally to this work.

Abstract: Vaccination has been the most effective way to control the outbreak of the Covid pandemic. The numbers and types of vaccines have reached considerable proportions, even if the question of vaccine procedures and frequency still needs to be resolved. We learn the necessity of defining a vaccination distribution strategies with regard to Covid that could be used for any future pandemics of similar gravity. In fact, vaccine monitoring implies the existence of a strategy that should be measurable in terms of input and output, based on a mathematical model, including death rates, spread of infections, symptoms, hospitalization and so on. This paper addresses the issue of vaccine diffusion and strategies for monitoring the pandemic. It provides a description of the importance and take up of vaccines and the links between procedures and the containment of Covid variants, as well as the long-term effects. Finally, the paper focuses on the global scenario in a world undergoing profound social and political change, with particular attention on current and future health provision. This contribution would represent an example of vaccination experiences which can be useful in other pandemic or epidemiological contexts.

Keywords: vaccination strategy; COVID-19; epidemiology; vaccines distributions

1. Introduction

Vaccination is the most effective method to contrast infectious diseases. World Health Organization (WHO) defined the early 1970s the Expanded Programme on Immunization (EPI) to provide large scale access to vaccines for all children. Nevertheless, approximately 20 million infants worldwide still do not have access to immunization services. WHO on March 2020 declared coronavirus become a pandemic [1]. Since the containment measures could not stop the spread. Research focused on the development of novel vaccines to prevent the spreading of the virus, while in parallel some drugs were used to treat the illness [2–5].

Many primary pharmaceutical industries, supported by an unprecedented effort by governments, focused on defining novel vaccines. With surprising speed, many candidate vaccines were approved for use by the Food and Drug Administration (FDA) and European Medicine Agency (EMA).

The Covid-19 pandemic boosted the necessity of vaccinations and accelerated the design and testing of vaccines using new procedures. With the release of the first vaccine at the end of 2021, deaths and infections started to decline. We have an increasing number of vaccinations and increasingly efficient protocols. Many Covid-19 vaccines have regulatory approval, most of which having provisional authorization, motivated by the results of trials. Table 1 reports the

list of an extracted number of vaccines; additional and updated number of vaccines with updated geographical distribution and diffusion by country can be found at the following website [6]. However, notwithstanding the rapid response to Covid-19 it became clear that it was impossible to satisfy the demand for vaccines, hence the need for prioritization strategies [7]. 70% of the world population has received at least one dose of a Covid-19 vaccine at the end of 2022. Source of vaccination trend can be found at official site [8], and in many studies monitoring real time data [9]. In lower income countries, the population is still receiving vaccines. At the same time, Covid-19 virus variants have increased, and the number of infections still affects the population. During the pandemic evolution, variants appeared to be a relevant issue to be considered both wrt vaccination response as well as disease expression. Moreover, tracking variants have become a relevant task useful to relate virus with vaccines efficacy [10]. Indeed, a new topic related to the long term effects of vaccination on virus containment as reported in [11]. This represents a valid and unique world health status that has to be considered. In China the number of positive cases started to boost, while the number of vaccinated people remained low middle 2022 (see data on <https://tradingeconomics.com/china/coronavirus-vaccination-total>). Thus lockdown containment strategies have been proven to be still the only tentative to contrast the diffusion. Vaccine strategy is a crucial challenge to fight Covid-19 and to minimise number of deaths and infections [12].

Table 1. An extracted of Available Vaccines.

Brand	Country	Clinical trail status	Age group	#Shots (apart)	When fully vaccinated?
Pfizer-BioNTech	USA	Completed	12 >	2 shots (21 days)	4 weeks after 2nd shot
Moderna	USA	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Johnson & Johnson's	USA	Completed	18 >	1 shot (NA)	2 weeks after 2nd shot
AstraZeneca	USA	Phase 3	NA	NA	NA
Novavax	USA	Phase 3	NA	NA	NA
COVAXIN	India	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Sputnik V	Russia	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Sputnik Light	Russia	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
EpiVacCorona	Russia	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
CoviVac	Russia	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Sinopharm-BBIBP	China	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
CoronaVac	China	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Convidecia	China	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Sinopharm-WIBP	China	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
RBD-Dimer	China	Completed	18 >	2 shots (28 days)	2 weeks after 2nd shot
Minhai	China	Completed	NA	NA	NA
QazCovid-in	Kazakhstan	Completed	NA	NA	NA

Here we consider the main processes related to Covid-19 vaccine diffusion to pandemic and different variants of the Covid-19 virus. Also, we focus on monitoring different strategies implemented by governments, global associations, and pharmaceutical industries. In particular, we focus on vaccination strategies and their effects on the population, even in terms of life quality. We discuss about vaccination strategies across countries, stimulating a discussion about their consequences on life quality. The target is to highlight strategies and behaviours regarding vaccination distribution and effects on population that can be considered a relevant track that can be followed in possible future

similar emergency pandemic phenomena. Moreover, the onset of variants and their correlation with vaccination effects can be considered as relevant task for future decision making.

Existing surveys cover different aspects of the question. Some reviews focus on the experimental aspects of vaccine development and test [13,14]. For instance, [15] focuses on the experimental workflow for the production of vaccines. Similarly, [16] presents a critical review of the bioinformatics methods and tools used to support vaccine development. Information about vaccinations can be found in several papers such as [17–27]. Aspects of the vaccine uptake have been treated in [28], while in [29] the authors analyze the problem of vaccine delivery. We here treat issues related to long-term strategies and their effects on the worldwide vaccination process. The latter has been the best contrast against Covid-19, but it has also changed many life-related strategies. For this study we followed the PRISMA 2020 methodology [30]. The chosen databases for searching the reference papers are: PubMed, MDPI, Springer, ACM Digital Library and Science Direct, from which we considered the papers resulting from the search keywords: “covid”, “vaccination strategy”, “vaccines”, and “Sars-Cov-2”, selecting the most relevant among recent ones.

In the following we enumerate some of the relevant aspects treated in this paper.

- *Vaccination strategies*: We consider the applied methodologies used in different countries and we focus on the problem of having heterogeneous strategies;
- *Vaccines distribution*: we focus on the problem of doses delivering among different countries also related to economic disparity among countries; in latter case we focus on strategies of cooperation among different areas;
- *Variants and vaccines*: We focus on post emergency, on variants and on different strategies for virus containment applied in different geographic areas.

Finally, this paper highlights the effects of vaccination strategies on a dynamically changing social and sanitary worldwide scenario. Such strategies affect the pandemic evolution both in the emergency and in the post-pandemic phases effects, also impacting in a long term scenario.

2. Methods

Vaccines can be seen as a prevention therapy in pandemics [31]. Even if the vaccination process reached high percentage values, the Covid-19 global immunization still needed to be reached. This is because citizens with three vaccine doses have still been affected by the Covid-19 virus variant. [32] report for instance the situation for vaccine allocation priority in different countries, whereas [33] shows the condition in Italy at the end of third vaccines. Older citizens, for instance, in Italy, received the fourth vaccine dose in 2022. Vaccination strategies have to be monitored with respect to pandemia evolution even with decreasing values of mortality. Moreover, there are other social and political issues which must be considered [34,35]. For instance, regarding Covid-19 testing procedures for citizens moving abroad increasing positive cases oblige governments to define new strategies for border management.

We study vaccination distribution process and reaction to its effects as well as social and strategies modification wherever virus vary. There exist six types of vaccines:

1. *inactivated microorganisms*: consisting of viruses or bacteria killed by physical or chemical means (used for typhus, cholera, whooping cough, polio Salk);
2. *live and attenuated microorganisms*: made up of live viruses or bacteria capable of reproducing in the individual and guarantee lasting immunity (used for polio Sabin, TB, Measles, Rubella, Mumps, Chickenpox);
3. *fractions of microorganisms*: “split” vaccines consist of fragmented viruses but without purification of protective antigens so that they do not cause adverse reactions;
4. *purified microbial antigens*: bacterial or viral components are purified and, in some cases, conjugated to carrier molecules (used for Meningococcus, Hib, Pneumococcus);

5. *anatoxins (or toxoids)*: they are toxins treated with formol to obtain an antigenically intact product without toxicity;
6. *vaccines from genetic manipulation*: produced with part of the virus.

Another widely adopted classification for Covid-19 vaccines is as follows:

- *mRNA vaccine*, which is a type of vaccine containing cells instructions for the production of S protein, a molecule found on the surface of the virus, which helps in creating antibodies. These will be a defence layer in case of future infection by the Covid-19 virus. This type of virus does not interfere with DNA information in the cell nucleus. Examples in such category are Pfizer-BioNTech and Moderna Covid-19 vaccines;
- *Vector vaccine*, a type of vaccine using a modified virus (the viral vector) in which parts form the Covid-19 virus are inserted. The viral vector is acquired by the cells and causes them to produce Covid-19 S protein copies, who induce the immune system to respond. Examples in such category are Janssen/Johnson & Johnson Covid-19 and AstraZeneca vaccines;
- *Protein subunit vaccine*, which include parts of the virus that stimulate the immune system by using an harmless S proteins.

The SARS-CoV-2 is a single strand of RNA made up of 30,000 building blocks wrapped in a protein envelope. mRNA vaccines instruct the immune system to recognize the pathogen. Synthetic mRNA molecules can induce the formation of a spike protein, which is sufficient to create an immune response and stimulate the production of antibodies. In other cases, vaccines are built from an adenovirus whose genetic information is changed to convey parts of the new coronavirus suitable for stimulating an immune response.

The current landscape of existing vaccines is reported in Table 1 (data taken from [36]). Nevertheless, since the scenario is changing, updated vaccine trackers are available such as the one provided by the London School of Hygiene and Tropical Medicine at [37].

The design of an effective vaccination strategy requires the availability of a computational model for designing and implementing interventions at all levels and ensuring the targeting of the desired goals. There exist some mathematical models to simulate the course of the disease and the effect of different strategies (e.g. containment, vaccination) [25]:

- forecasting based on time-series data;
- compartmental models;
- graph-based models.

Compartmental models are commonly used to track the spread of infectious diseases. In such models, the whole population is assigned to compartments identified by labels (e.g. Susceptible Infected -SIS-, Susceptible, Infectious, or Recovered - SIR- Susceptible, Infectious, Recovered and Vaccinated - SIRV -). Such models study the evolution of the population belonging to each compartment through a system of ordinary differential equations. In contact based models, the population is modeled as a temporal graph $\mathcal{G}$. Nodes of $\mathcal{G}$ represent the patients. Node labels represent the status of the individual (e.g. Susceptible, Recovered, Vaccinated). Temporal edges represent contacts among them. Thus, the spread is easily represented by a markovian model [26].

The vaccination campaign covers every population throughout the world involving all the population [38] [39]. The production rates of vaccines remained insufficient for several months to cope with the growing transmission rates of the emerging variants [12,40]. Consequently, there is the need to define and implement a prioritisation strategy [41].

Vaccination strategies started in December 2020. [42] reports that by January 2021, 30 European countries started the vaccination process and vaccination tracking can be found at [43]. By September 2021 every country had begun vaccinating the populations.

In response to the insurgence of variants B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) -listed as variant of concern (VOC), some countries changed the timing between vaccine doses in order to provide first dose to a major fraction of people.

Vaccine allocation strategy requires the use of a model of transmission and the epidemiological characteristics of the disease among social groups [44–46], where a framework for prioritisation of vaccines has been proposed.

In [47] Jentsch et al., discusses the optimisation of vaccination strategy, demonstrating the necessity of a contact-based strategy. They develop a mathematical model fitted on Ontario data and simulate the impact of different vaccination strategies. The contact strategy is based on the allocation of vaccines according to different age groups. Vaccine distribution and administration is crucial for the healthcare community since they drive the healing phase of any pandemics. We can learn valuable lessons and be prepared for the next global pandemic by analyzing what worked and what went wrong in the disease evolution in relation with the vaccine distribution strategies.

[48] authors treat the problem of promoting vaccines and vaccination strategies. The analysis of these approaches suggests, to the best of our knowledge, three considerations: (i) the optimisation strategy is dependent on the desired goals, (ii) the integration of the characteristics of the modelling improves the performances, (iii) a dynamic strategy may outperform a static one. Despite this, we believe that the spreading using only a classical SEIR modelling (i.e. Susceptible, Exposed, Infected, Recovered model) may not be the best choice since some parameters are considered at a global scale, while the spread involves single contacts. In parallel, some previous works such as [49–53] have demonstrated that the use of a model coming from graph theory may be helpful to describe the spread. In this way, comprehensive graphs may be derived using nodes, people and edges of their contacts.

Finally, there have been different proposals of optimal vaccination in different countries, such as South Korea [54], or WHO's proposed framework for distributing Covid-19 vaccines among countries [55]. Similarly, strategies depending on different ages (e.g., A Differential Evolution Algorithm Approach [56]) or temporal variation with seasons (e.g., seasonal influenza vaccine under temporal constraints [57]).

3. Results

In [58,59] the authors analyze several allocation and distribution strategies for Covid-19 vaccines, as well as the design of a robust and resilient vaccine distribution network has been defined in [60]. Geostatistical modelling has been used to take into account classical logistic constraints (i.e. from the Operations Research domain) and global/local geographical peculiarities which can greatly vary across different areas (inter-area variability) and within the same area (intra-area variability) [61,62].

Typical constraints and features of this problem which have to be taken into consideration during the conceptualization and modelling phases are [63]:

1. The vaccine distribution network should meet geographical constraints both for populations and vaccination centres (i.e., clinic centres);
2. The locations of the clinics and the distribution centres are fixed, but some distribution centres can be designated as hubs;
3. Each clinic is assigned to a hub and supplied by the national centre or by another hub;
4. The national centre is the root node of the network;
5. A hub is replenished either quarterly or monthly (as per WHO guidelines);
6. Every open facility has an appropriately sized storage device.

Vaccines are distributed through a medical supply chain. In [64] the authors propose a redesign of the vaccine distribution chain with intermediate distribution centres for a number of sub-Saharan countries in Africa.

As reported in ¹ policies for vaccine delivery can be divided in for different groups: (i) Availability for ONE of following: key workers/ clinically vulnerable groups / elderly groups; (ii) Availability for

¹ <https://ourworldindata.org/grapher/covid-vaccination-policy>

TWO of following: key workers/ clinically vulnerable groups / elderly groups; (iii) Availability for ALL of following: key workers/ clinically vulnerable groups / elderly groups; (iv) Availability for all three plus partial additional availability (select broad groups/ages); (v) Universal availability.

The need for an optimal and large-scale vaccine distribution plan for third world countries has been tackled in [65]. The authors describe a clustering-based solution for selecting distribution centers and use a Constraint Satisfaction Problem framework as a support tool for the optimal distribution of vaccines. The efficiency of the proposed models has been demonstrated in India. In [63] the authors analyze the WHO-EPI (Expanded Programme on Immunization, EPI) vaccine distribution for low- and middle-income countries and propose vaccine distribution models. They formulate this as a network design problem. A machine Learning model is used in [66], to optimize the vaccine, in terms of peptides binding. The authors present a combinatorial Machine Learning method to evaluate and optimize peptide vaccine formulations for the SARS-CoV-2 virus. The paper studies the potential impact of vaccination administration on the population with respect to expected drift. In particular, it focuses on the likelihood of a diverse set of vaccine peptides conditioned on a target human-population HLA haplotype distribution and expected epitope drift. The authors suggested SARS-CoV-2 MHC class I vaccines which would provide 93.21% population coverage, with at least five vaccine peptide-HLA average hits per person (≥ 1 peptide: 99.91%). The study reports that all vaccine peptides would be perfectly conserved across 4,690 geographically sampled SARS-CoV-2 genomes. The authors also report an MHC class II vaccine providing 97.21% predicted coverage with at least five vaccine peptide-HLA average hits per person with all peptides having an observed mutation probability ≤ 0.001 .

In [67] the authors study how spatial strategies would be able to improve the vaccines distribution efficacy. They study a scenario with a problem of optimal control of Covid-19 vaccinations in a country-wide geographic and epidemiological context characterized by strong spatial heterogeneities in transmission rate and disease history. They performed experiments examining datasets containing scenarios of disease transmission across Italian provinces from January to April 2021, generated by a spatially explicit compartmental Covid-19 model, which had been adapted to the Italian geographic and epidemiological context.

4. Discussion

The European Centre for Disease Prevention and Control (ECDC) introduced various definitions about SARS-CoV-2 variants: variant of concern, variant of interest (VOI), or variant under monitoring (VUM). For each, ECDC describes the following features:

- *WHO label*, which reports the official labels for Covid-19 variants introduced by WHO in 2021 to be used as scientific nomenclature in communications with the public;
- *Lineage and additional mutations*, which is about the variant designations (one or more Pango lineages) and any additional characteristic spike protein changes;
- *Country first detected*, which is the most probable country in which the variant was first detected;
- *Spike mutations of interest*, which includes changes to spike protein receptor binding domain and the S1 part of the S1/S2 junction and a small stretch on the S2 side, and any additional unusual changes specific to the variant;
- *Year and month first detected*, updated as new evidence is found (as per the GISAID EpiCoV database);
- *Evidence*, which reports about transmissibility, immunity, infection severity;
- *Transmission in the EU/EEA*, reports properties such as: dominant, community, outbreak(s), and sporadic/travel (based on intelligence and direct communication with affected countries).

In particular for the VOC, the evidence regarding transmissibility, severity and/or immunity (see Table 2) suggests the impact on the epidemiological situation in the EU/EEA. In fact, their properties regarding genomic, epidemiological, and in-vitro evidence imply moderate confidence. Countries

should pay attention to the vaccination policies [68], and to the rules, regulations and restrictions adopted in combination with vaccines.

Table 2. SARS-CoV-2 Variants of Concern (VOC) (x: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F). Table taken from [69]

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest
Year and month first detected	Evidence for impact on transmissibility	Evidence for impact on immunity	Evidence for impact on severity
Transmission in EU/EEA			
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V
September 2020 Community	Yes	Yes	Yes
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y
December 2020 Community	Yes	Yes	Yes
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R
December 2020 Dominant	Yes	Yes	Yes
Omicron	B.1.1.529	South Africa and Botswana	(x)
November 2021 Sporadic / Travel		Yes	

The current status of Covid-19 cases in the world suggests that the virus is not completely arrested, but the worst is over thanks to the vaccine campaign. There is still lots of work to do in terms of immunisation and social and global regulation. There remain the need to prepare for the aftermath of this and for the future pandemics through cooperation at global level.

5. Conclusions

Covid-19 vaccination has been the prominent strategy to control pandemic and to save lives, yet there is evidence of lack of sufficient doses of vaccines for all the people. Consequently, there is the need for the introduction of an efficient prioritisation strategy. The first step is the analysis of different vaccination strategies and outcomes in different countries. In this paper we shed light on the current scenario regarding vaccines, optimisation strategies and long term procedures for pandemic monitoring.

In conclusion we would stress the need for studies regarding vaccination process and virus variants and diffusion by means of geographical models to track: (i) the diffusion of the virus, (ii) status and planning of vaccination supply and, finally (iii) population movements and habits.

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