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Decision making on vaccination in an uncertain and rapidly changing context

Strategia vaccinale in un contesto incerto e in costante evoluzione

Silvia Forni,[1] Chiara Doccioli,[2] Annibale Biggeri,[2] Mario Braga[3]
[1] Agenzia Regionale di Sanità della Toscana, Florence (Italy)
[2] Dipartimento di Statistica, Informatica, Applicazioni "G. Parenti" (DiSIA), Università di Firenze, Florence (Italy)
[3] AUSL Ferrara (Italy)
Corresponding author: Silvia forni; silvia.forni@ars.toscana.it

ABSTRACT

Politics is facing the need to make important decisions about anti-COVID-19 vaccination campaign in uncertain and changing contexts. With reference to the time frame between the administration of the first and second dose, the scientific evidence is still weak and comes from different contexts. New ways to collect and synthesize expert knowledge and opinions are needed with the direct involvement of the citizens in order to explain the uncertainties and maintain trust in institutions and their decisions.

Keywords: vaccination policy, uncertainty, efficacy

RIASSUNTO

La politica ha dovuto prendere decisioni rilevanti e tempestive sulla gestione della campagna vaccinale contro COVID-19 in contesti incerti e mutevoli. Con riferimento al tempo tra la somministrazione delle due dosi di vaccino, le conoscenze disponibili sono risultate spesso deboli e provenienti da contesti differenti, non facilmente assimilabili al nostro. Nuove modalità per raccogliere e sintetizzare le conoscenze e opinioni degli esperti sono necessarie, e devono necessariamente coinvolgere i cittadini al fine di spiegare le incertezze in campo e mantenere un buon livello di fiducia nelle istituzioni e nelle loro decisioni.

Parole chiave: strategia vaccinale, incertezza, efficacia

INTRODUCTION

The COVID-19 pandemic is facing our communities with the need of making decisions in a rapidly changing epidemiologic context. Furthermore, the bulk of knowledge on the virus and the pharmacological and non-pharmacological tools at our disposal to fight this infectious disease is growing at an incredibly fast pace with frequent, and sometime radical, changes in behavioural and therapeutic indications. This is now being reflected on the planning and management of the vaccination campaign, which requires very quick choices to solve complex situations. This complexity is attributable to contingent factors such as delays in vaccine delivery, difficulties in organizing their administration, and in-progress modifications of the anti-COVID-19 vaccine indications.

All this is happening in a context in which scientific knowledge availability is limited and in continuous change. Currently, the results of few large sized randomized controlled clinical trials have been considered to authorize the vaccine use under an exceptional procedure.[1-5]

Studies published on vaccine efficacy are frequently prospective observational cohort studies[6] related to specific subpopulations in individual nations and they measure vaccination short-term effects. Based on the evidence produced by these studies, the scientific community must make recommendations that have been used for the planning of the anti-COVID-19 vaccination campaign, with a great impact on citizens' life.

Without considering possible biases in study designs, some concerns relate to replicability in different contexts. In particular, the first published studies concern the vaccination campaign conducted in the UK, Israel, and USA. The COVID-19 vaccination campaign has been handled in different ways between countries and, if compared to Italy, these nations differ in speed, incidence at the beginning of the campaign, control measures during the campaign (i.e., lockdown) and incidence of cases at the moment of re-opening (Table 1).[7] Moreover, vaccine supply differs between countries.

Therefore, the need to adapt the vaccination strategy to constantly evolving knowledge has led to frequent changes of strategies based on recommendations with limited evidence.[8] People in general – and even the experts – fail to understand the logic behind the different decisions taken by different countries, apparently based on the same scientific data, and the reasons for changes within the same country.

Indeed, we are in the situation in which facts are uncertain, values in dispute, stakes high, and decisions urgent.[9] The scientific evidence was far from being considered as 'facts', because of rapidly changes in the available information, the large number of pre-prints – i.e., not peer-reviewed articles – and observational studies compared to randomized trials. Some countries privileged local observational studies in lack of consolidated evidence from pooled meta-analysis or large trials, a behaviour that may enhance the heterogeneity with regard to public health actions.

COUNTRY	BEGINNING OF THE CAMPAIGN			INCIDENCE AT RE-OPENING^	VACCINATION SPEED**
	DATE	INCIDENCE^	STRINGENCY INDEX*		
Italy	27 December 2020	223.31	84.3	217.6 (26 April 2021)	0.74 (5 May 2021)
Israel	19 December 2020	282.23	71.3	425.29 (7 March 2021)	2.6 (25 January 2021)
UK	8 December 2020	226.6	67.6	24.5 (12 April 2021)	0.65 (13 April 2021)
USA	14 December 2020	655.4	71.7	153.3 (30 April 2021)	0.89 (21 March 2021)

Source: https://ourworldindata.org/coronavirus (last accessed: 10.05.2021)
^ Cases per 100,000 people (rolling 7-day average at the day of beginning of vaccination campaign) / *Casi su 100.000 persone*
* Stringency index: this is a composite measure based on 9 response indicators, including school closures, workplace closures, and travel bans, rescaled to a value from 0 to 100 (100: strictest) / *Indice della severità di risposta dei Governi: è una misura composta, basata su nove indicatori di risposta, che includono la chiusura di scuole e posti di lavoro e i divieti di spostamento, in una scala da 1 a 100 (100: il più severo).*
** Maximum daily number of vaccination doses administered per 100 people (rolling 7-day average) / *Numero massimo giornaliero di vaccinazioni COVID-19 somministrate su 100 persone*

Table 1. Comparison between incidence and control measure during the vaccination campaign and vaccination speed.
Tabella 1. Confronto di incidenza e misure di controllo durante la campagna vaccinale e velocità della vaccinazione.

Different values were adopted. For example, the UK mathematical modelling approach vs the Swedish public health-oriented approach in the beginning of the COVID-19 pandemic reflects the adoption of different styles which are more related to moral premises than to hard science.
In the early period of the pandemic, health appeared as the main stake, while on the subsequent waves economy and other side effects of the containment strategies received more concern.
Decisions were always urgent in face of uncertainty and disputed values.[10] What happened is not surprising.
The amplitude of the public debate on scientific issues was never so large in the past: experts were in disagreement and lay people participated in the debate. An example is the decision on time between first and second dose. In this paper, we are going to describe the landscape of the anti-COVID-19 vaccination campaign in Italy. We will then focus on the recommended time frame between the administration of the first and second dose, pointing out the debate and the implications of the decisions taken in Italy in June 2021.

THE VACCINATION OVERVIEW

The mass vaccination plan has started with different speed and vaccine products in many countries all over the World.
The differences depend on several factors, such as the vaccine characteristics, the number of doses needed for reaching immunity, the health system organization and resources, the political commitment, the population size and response, and media pressure.
The first vaccine which was authorized by the Western competent national and supranational agencies was the one developed by Pfizer, followed by AstraZeneca, Moderna, and Johnson & Johnson's vaccines.
The source of technical scientific information on vaccines in Italy is the Italian National Medicine Authority (AIFA) and the Italian National Health Institute (ISS) and media are contributing to the dissemination to the population.[11]
For Pfizer[1] vaccine, efficacy at the beginning of the vaccination campaign was 95% (95%CI 90.3%-97.6%) and two doses were administered with an interval of 21 days between the first and the second inoculation. For Moderna[2] vaccine, efficacy is 94% (95%CI 89.3%-96.8%) with an interval of 28 days between the first and the second dose. Instead, the information about AstraZeneca[3] reported an efficacy of 63% (95%CI 51.8%-71.7%) with two doses given with an interval of 12 weeks. For the Johnson & Johnson[4] vaccine, efficacy was 66.1% (95%CI 55.0-74.8) administered in one single dose.
In January, the Italian Government decided to launch a national strategy to speed up the vaccination process, initially enacting the National Strategic Plan for the anti-SARS-CoV-2 vaccination[12] and, on March the 13th, releasing a new Plan for the execution of the national vaccination campaign.[13] The way for Governments to increase the number of vaccinated people has been to boost the personnel involved in the campaign and to widen the time dedicated to the vaccination, while covering regional gaps through the Civil Protection and the Italian armed forces.
The impressive scientific results obtained by the research community in developing an effective vaccine in less than one year is, in the same way, hampered by the difficulty of producing enough doses to vaccinate the World population. Production, in fact, has represented the main hurdle until July: shortfalls in vaccine deliveries have caused several countries in Europe to delay their vaccination programme or to modify it (for example, by changing the vaccination priority criteria for the reference population).[14]

Since the start of the vaccination campaign, AIFA has changed multiple times the recommendations for the use in the public health programme of the AstraZeneca vaccine. It was initially limited to people under the age of 55 in good health; the age range was later extended to people under the age of 65 and, after that, to people all ages, with at most one chronic condition. However, it has then changed again: initially by being only recommended to people over the age of 60, while on 11th June it has been strictly restricted to the over-60s.[15]

Initially, in Italy the vaccination campaign aimed to reduce the damage caused by the disease by protecting health professionals and the most vulnerable people: in the first stage, the vaccination campaign was targeted to the health workers and the care homes residents; the second stage was directed at the people of 70 years or more, clinically extremely vulnerable individuals, and at-risk categories of workers (such as teachers, police, and judicial staff). The following stage has been targeting people over the age of 60, then the vaccination has been extended to all ages. At the end of July, the Italian Government established that only those who are immunized or have a negative swab are allowed to enter the most crowded places, making the green pass mandatory from the 6th of August.[16] At that day, in Italy more than 39.5 million people were partially or fully vaccinated.[17]

Under these conditions, the vaccination campaign has been in some circumstances chaotic and faced some difficulties in communicating to the population.

DELAYING THE SECOND DOSE?

POLITICAL CONTEXT

At first, the vaccination campaign in Italy provided the administration of the two doses of vaccine in the recommended time ranges. Only in April 2021 this choice has been questioned, considering the slowdowns in the supply of vaccines, and even for the mRNA vaccines the interval between the two doses was extended up to 42 days.[18] In addition, a single dose was provided to people infected in the previous 3-6 months.[19]

Since the beginning of the vaccination campaign, UK has made a different and pragmatic choice to increase the number of people who received the vaccine, using all the available doses and postponing the second jab up to 12 weeks (AstraZeneca).[20] This choice was based on a clear public health perspective in absence of scientific evidence from randomized trial on the different vaccination strategies. It has been preferred to favour enlargement of the vaccinated population instead of sticking to a greater vaccine efficacy limited to a smaller number of fully vaccinated individuals.

In the first semester of 2021, the EU governments were under pressure to plan an effective and timely vaccination campaign, having to face possible delays in the vaccination supplies. The decisions they made on the vaccine programmes had a major impact over the course of the epidemic in terms of lives saved and of a likely return to normality. Moreover, there was not much evidence on many aspects concerning efficacy of different vaccine strategies.

EFFICACY CONCERNS

One of the main concerns about the decision of postponing the second dose of vaccine regarded the efficacy in reducing hospitalizations and death of SARS-CoV-2. World Health Organization[6] published an overview of observational study designs on the effectiveness of COVID-19 vaccination: since 25th June, 144 studies have

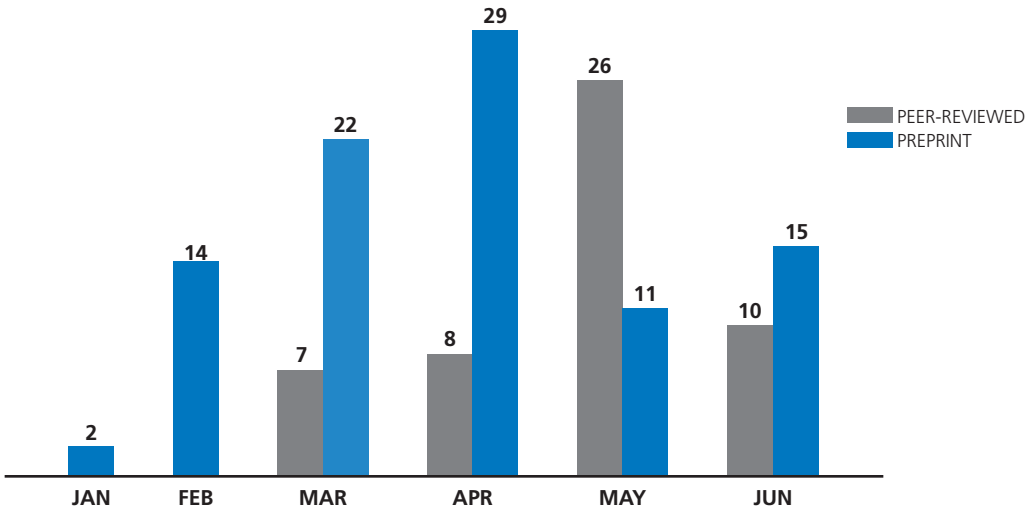

Figure 1. Overview of published observational studies (peer-reviewed and pre-prints) on effectiveness of COVID-19 vaccination available at 25th June 2021.[6]
Figura 1. Panoramica degli studi osservazioni pubblicati (peer-reviewed e pre-print) sull'efficacia dei vaccini disponibili al 25 giugno 2021.[6]

been published about vaccine efficacy, 51 peer-reviewed (figure 1). More than 20 studies regard the efficacy of the first dose strategy and they are almost all available as non-peer-reviewed pre-prints. Delaying the administration of the expected second dose of the vaccine was a matter of discussion in Spring 2020, especially with the emergence and spread of new variants in UK.[21,22]

There was concern that deferring the second dose would leave people vulnerable to infection, and potentially fuel the rise of new variants that can evade the immune response. It might be the case of the Delta Coronavirus variant first identified in India. This variant has significantly increased transmissibility and it is now the dominant variant worldwide.[23] The immune-evading variants must first arise via mutation, then there must be substantial selection pressure in their favour. People who receive one shot may be less protected from the infection: if the virus mutates and replicates in the presence of a partial immune response, mutants with the ability to evade the immune system might be at an advantage.[24]

In parallel, the second dose is necessary to gain a complete and long-lasting immunization: our immune system works with two classes of adaptive immune responses, antibody responses and cell-mediated immune responses, carried out by B cells and T cells, respectively. After first-time exposure to vaccine, B cells are activated to secrete antibodies that can bind the virus and block its ability to attack the host cells. However, B cells are short-lived and the antibody response decreases rapidly. If the organism is re-exposed to the same antigen, as with the second dose of the vaccine, the body mounts a second immune response that is led by T cells, long-lasting memory cells that can survive for many decades and give lifetime immunity. This raises the possibility that with an initial B cell response the levels of these antibodies would not be high enough to stop new infections of SARS-CoV-2, whereas early strong T cell responses may be protective.[25]

Furthermore, some experts suggested giving two doses of anti-COVID-19 vaccine separated by a longer period: with most vaccines, an extended interval between the prime and booster doses leads to a better immune response to the second dose; even the AstraZeneca trial revealed an apparent increase in efficacy when doses were spaced further apart.[26]

Vaccine efficacy, though, is not a value that applies to everyone and another concern regarded the possible efficacy differences between patients depending on the subjects' characteristics. For instance, a King's College trial reports evidence of low vaccine responses in cancer patients 3 weeks after a single dose of Pfizer anti-COVID-19 vaccine, with little protection against the virus.[27] This evidence might suggest a possible need to review the vaccine strategy for clinically vulnerable groups and to consider adapting the vaccination strategy to ensure the people who may benefit from a different approach.[28,29]

SOCIAL CONCERNS

A concern was that changing the vaccine strategy could negatively impact on willingness of being vaccinated in the general population. This could be exacerbated by cases of severe adverse events reported in different countries. In order not to reduce citizens' trust in institutions and willingness to be vaccinated, a clear communication of the risks and benefits would be necessary. Such a communication is also needed in relation to efficacy and safety of vaccines. Unfortunately, up to now, the communication of scientific aspects and their uncertainty conveyed by Italian media has been characterized by harsh tones and exacerbation of contrast among experts. Furthermore, Italian experts are often involved in discussions on several issues even if not of their strict competence. Different opinions are opposed, fuelling disputes and reducing credibility and trust in experts and science. A change in communication, both of media and of experts in the field, could lead to various benefits.

> It is essential to adopt appropriate communication strategies to explain risks and uncertainties. New ways of synthesizing available knowledge and experts' and people's opinions must be identified to produce recommendations.

One more aspect to consider regarded the social consequences of possible delays in the vaccination campaign. Although differences in the organizational capacity persist among Italian Regions, the main hitch until July in the vaccination campaign has been the supply of vaccines. The credibility of the European Community and local governments in the spring 2021 was closely linked to the ability to guarantee access to vaccinations for the population. A slowdown in anti-COVID-19 vaccination rates would exacerbated the difficulties of some population groups, social discontent, and distrust in institutions. In this context, a strategy that allowed a greater share of people to be more quickly immunized should be considered.

CONCLUSIONS

The main aspect characterizing the described situation is the vast degree of unknowns surrounding the SARS-CoV-2 infection and the real-world safety and effectiveness of the vaccines. Just few examples:

- How effective are the vaccines against the virus variants?
- How effective is a single dose to prevent the infection?
- Will a single dose favour the development of virus mutations?

- How long will immune protection last?
- Is the vaccine really safe? What is the meaning of safety in the vaccination context?
- Is it appropriate to vaccinate young people?
- Are there specific populations that are less protected by the vaccination?

Many more questions are arising as the pandemic is progressing and the vaccination campaign proceeds. We can expect that in the next few months governments will have to make more quick decisions regarding the vaccine campaign in a context of scientific uncertainty and high stakes. Scientific studies and real-life data will integrate the knowledge available today on vaccine efficacy and safety. In addition, other vaccines will be available.

We previously analysed the decision of postponing the second jab taken in the UK. By doing so, England has been able to quickly flatten the epidemic curve and on 12th April it has taken its first steps out of lockdown, since infections were falling.[30] Nevertheless, we have no clue if in the medium-long term it will prove to be successful: the above-mentioned concern about possible development of new variants is still a current topic. Now, we know that people who receive one shot is less protected from the infection, giving the virus an opportunity to mutate and create new variants that might be more transmissible or deadly. The emergence of new variants, in particular the Delta variant, is making it even more important to perform both doses to ensure the maximum efficacy of the vaccine.[31]

The vaccination campaign has been adapted during the race according to new scientific evidence and to economic and organizational aspects, and it will continue to be so. New data relating to the duration of immunity, safety, and efficacy against new variants of the virus are expected. Other fundamental aspects concern the supply capacity of the various nations and the ability to organize an efficient and fair vaccination campaign.

Based on what has happened so far, some considerations are possible for better planning the management of the vaccination campaign in the near future.

First, new models must be identified to be capable of producing recommendations synthesizing experts' and people's opinions. New ways of synthesizing the available scientific knowledge need to be found, so that absence of evidence does not result in evidence of absence. Different strategies should be therefore adopted, taking into consideration experts' different points of view. A remarkable and pragmatic example of this appeared on 17th February in the *New England Journal of Medicine* as a case vignette[32] regarding the most effective use of the currently available doses. In this article, the authors ask all the readers to choose one of two approaches: delaying the second dose or following the standard regimen. To aid the decision making, each of the approaches is defended in a short essay by an expert in the field, considering the benefits and risks of the two options. It is quite surprising that, after a total of 9,775 votes, the ending result is 49% against 50% for the two approaches, showing a great deal of uncertainty about this issue. The case vignette is a method often used in medicine to discuss clinical cases: it demands active participation in the debate and fruitful exchanges of views. In addition, case vignettes can be used to meet specific learning objectives in medical teaching sessions and to measure the students' clinical reasoning and knowledge. In the above-mentioned article, case vignette has been used with a new perspective: the possibility of voting has been extended to all the readers, and not only physicians or field experts, showing a shift in involvement, from an only expert community to an 'extended peer community' and engaged citizenry. It appears to be an attempt to include people's point of view in a scientific debate, beyond specific technical knowledge. This represents an example of knowledge production in areas where scientific evidence is absent in an inclusive and timely manner.

This case vignette is a clear example of the changes at the interface between science and society. Due to the pandemic, the intrinsic uncertainties in the scientific knowledge became evident to all. The urgency and the stakes were so pervading that any decision could actually not be deferred to an expert table or even more to a scientific discipline. Even the most renewed medical journal used the clinical case vignette to communicate the magnitude of uncertainty and, moreover, the journal extended the exercise outside the restricted circle of academics or professionals to all those interested. A remarkable fact!

The case vignette is not a decision tool. It is a didactic tool used in participatory education and communication. It is instructive of how much participation is important in the COVID-19 context.

Moreover, **it will be essential to adopt appropriate communication strategies in order to explain risks and uncertainties to the community.** There will be important decisions to take under simple rules: it is therefore desirable to choose, among the different communication options, the use of simple indicators, so that the associated risks can be explained to the general population in a correct and exhaustive way.

People should, in fact, be provided with accurate and accessible data, in order to have the right perception of what the risks and benefits of a vaccine are.

Researchers, together with journalists and decision makers, should be stimulated to implement efficient and transparent representations of health statistics: even specific numerical data can be easily understood if explained in a transparent and exhaustive way.[33,34]

In addition to the differences in experts' opinions, **it must be considered that scientists and decision mak-**

ers' points of view can diverge. The latter will be led to give greater weight to immediate utility (in terms of lives saved), rather than to future risks. Furthermore, decision makers must timely make decisions considering many other factors, in addition to that of scientific evidence on vaccines efficacy and safety, such as economic and socio-political factors. They also have to consider people's trust in institutions, consensus, and cultural aspects.

The points discussed so far have been tailored to the COVID-19 vaccine campaign and the distance between its two dosed, but it must be considered in more general terms. Decision making under uncertainty and fast changing knowledge requires:

- a clear separation of roles and responsibilities among experts who have to provide indications based on the best scientific knowledge available at that moment with the corresponding level of uncertainty, and the decision makers who have to balance the consequences associated with the different choices with a clear and explicit strategic view. Mixing these two profiles weaken their credibility and deteriorate the perception that the general public has on the measures implemented;
- a deeper understanding of the behavioural components guiding the individual and collective choices;
- a wider, continuous, active participation of the citizens to the decision processes;
- a simpler, but rigorous, way to communicate statistical analyses and results (i.e., case vignette) to the general public.

Unless we are prepared to consider all these aspects, the risk of widening the distance among experts, decision makers, and the general public is concrete, with possible catastrophic consequences on the comprehension and acceptability of the healthcare policies and decisions.

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