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COMMENTARY
From mass vaccination to personalized vaccinology? The COVID-19 case

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Abstract
In recent times, especially as a result of the experience gained worldwide with the COVID19 pandemic vaccination campaigns, the personalization of vaccination strategies is becoming increasingly important. This does not yet mean bringing precision medicine and genomics approaches into immunization campaigns, but where there is more than one vaccine against the same disease, there is a need to identify criteria for personalizing vaccination.
Vaccination strategies based on prescription appropriateness – whenever is possible – can lead to more effective immune response, reduced rates of adverse events, increased public confidence in vaccination and higher vaccination coverage, contributing to a decrease of morbidity and mortality related to preventable diseases.

Key words
- personalized vaccinology
- vaccination campaigns
- national immunization plans

INTRODUCTION

Scientific progress is not an accumulation of knowledge aimed at discovering the truth, but an alternation between standard scientific discovery and scientific revolutions, starting with a group of elements that tend to be articulated and specialized in what Thomas Kuhn described as "paradigm shift" [1]. As Sir Muir Gray argued, shifts in healthcare are more likely to result from new ways of thinking rather than new technologies [2]. However, unprecedented scientific and technological innovation has revolutionized healthcare in the last 40 years. In particular, the advent of genomics and digital data science in healthcare research, with the consequent exponential growth of analytical and diagnostic capabilities in clinical practice, led to what is known as personalized medicine.

According to the National Research Council, "personalized medicine" is an older term with a similar meaning to "precision medicine" [3]. Personalized medicine is a medical model that aims to provide prevention and treatment strategies tailored to defined groups of individuals. To date, there is no universally accepted definition. The European Union Health Ministers in their Council conclusions, published in December 2015, provided the following definition on personalized medicine: "A medical model using characterization of individuals genotypes and phenotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or for determining the predisposition to disease and/or to deliver timely and targeted prevention" [4].

From the perspective of the population, precision medicine has promoted a profound reflection – in recent years – on what has been called precision public health, previously defined in the literature as an analytical resource for policymakers and a useful paradigm for directing healthcare interventions towards disadvantaged social groups through granular data [5].

In analogy to precision medicine, precision public health can be also described as an innovative domain for developing data-driven approaches to public health interventions, encompassing both pharmaceutical and non-pharmaceutical interventions, as partially experienced in their implementation during the COVID-19 pandemic [6, 7].

Although most advances in personalized medicine and public health regard the field of individualized medical treatment, several factors can undoubtedly trigger a paradigm shift in modern vaccinology also in the post-mass vaccination campaign against COVID-19.

THE COVID-19 VACCINATION CAMPAIGN EXPERIENCE

The COVID-19 global pandemic has represented a health and socio-economic challenge with few precedents in human history. Vaccination was the most effective intervention to control the spread of the virus and, consequently, to save lives and protect the health

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of the population. In general, it can take 4 to 15 years to develop an effective and safe vaccine; however, starting with the first cases of COVID-19 detected in Wuhan, China, researchers have quickly identified the genome of the SARS-CoV-2 virus and developed viable vaccine candidates using new sequencing methods. Vaccines against SARS-CoV-2 use different technologies, such as mRNA, viral vectors, protein subunits, and inactivated virus. During the COVID-19 pandemic, clinical trials started within 5 months after the first reported cases, leading to the development of effective vaccines, and to "fast-track" authorisation within less than 12 months after virus isolation. The first authorised vaccines were produced with a modified RNA technology encoding a version of the SARS-CoV-2 spike protein capable of inducing neutralising antibody responses. The quick development of vaccines with mRNA technology is considered a triumph for preventive medicine and modern vaccinology [8].

A successful worldwide mass-vaccination campaign followed the authorization of several vaccines based on different technological platforms. To summarize, during anti-COVID-19 national immunization campaigns, for the first time: i) several effective vaccines, mostly based on innovative mRNA platforms, were developed in less than 12 months; ii) the entire world population was affected simultaneously by such a large and rapid immunization program; iii) health policy decisions and immunization strategies were updated on the basis of real world data (RWD) and real world evidence (RWE).

During mass vaccination campaigns, all types of available vaccines were used, and the offer could not be differentiated on the basis of individual's characteristics. Because of limited knowledge, the choice of target groups tended to be updated over time as a result of empirical experience. For example, the use of more effective vaccines, such as mRNA vaccines, was initially prioritized to those at highest risk, while vectored vaccines were preferentially recommended to healthy younger individuals, but after the observation of rare severe adverse events, such as the so-called vaccine-induced thrombotic thrombocytopenia (VITT), following the administration of adenovirus vector vaccines, these vaccines were preferentially recommended to older people, binding their use among younger people to epidemiological driven risk benefits analysis [9].

Nowadays, the end of the acute pandemic phase forces us to reconsider the modalities of COVID-19 vaccine offer, taking in account the so-called personalized vaccinology, extensively theorized, and described by Gregory Poland and colleagues as "vaccinology 3.0, (…) able to provide the right vaccine to the right patient – for the right reason and at the right dose" [10].

FROM THE ONE-SIZE-FITS-ALL APPROACH TO PERSONALIZED VACCINOLOGY

The standard medical practice in vaccinology is to universally deliver the same set of vaccines/vaccinations to the entire population (*one-size-fits-all approach*), in the absence of a contraindication, with several generalizations supporting this approach [10]. It also assumes that everyone is at approximately the same level of risk against the disease being prevented, and that the vaccine dose amount and number of doses needed to develop immunity are the same across the population. The major weakness of this approach is that it ignores individual variability in disease risk/immunologic response, and any genetic propensity for reactogenicity, as well as differences in the dose amount needed for protection [10, 11].

Different variables could influence the effectiveness of a vaccine or the propensity to adverse events such as: age, gender, race/ethnicity, immune status, size (body mass index), lifestyles, medical condition, comorbidities, and genetic profile. Some of these listed factors are identifiable and therefore predictable. Among these, one of the most important factors in determining the antibody response is undoubtedly the age and state of the immune system, which is a fundamental endogenous factor in the response to natural infections and vaccinations. Immunogenetic variation might one day lead to new products designed to minimize vaccine failure. Such host variability may depend on a multiplicity of immune response genes encoding products needed to generate antibodies, T cell receptors, or Human Leukocyte Antigen, HLA loci. Furthermore, gene polymorphism may also explain inter-individual variation due to other functions involved in the response to vaccines. Up to now, vaccine immunogenetics is still under-studied, and most information derives from studies targeting immune response to the measles vaccine [12]. All this information is included in the immune response theory, as defined by Gregory Poland and the Mayo Clinic group, which is the necessary basis for vaccinomics and adversomics [10, 13, 14].

Recently, Valdés-Fernández *et al*. offered a comprehensive review of genetic variants affecting immune response constituents that can influence individual responses to SARS-CoV-2 vaccines. They also discussed the potential public health implications of differing SARS-CoV-2 vaccine effectiveness across population groups [15]. Moreover, during COVID-19 vaccination campaign in Germany in 2021, subject-specific differences in COVID-19 vaccine reactogenicity and work absenteeism after vaccination were observed in a large survey of healthcare workers [16].

The traditional public health population-level paradigm and the emerging individual-level paradigm, which acknowledges genetically encoded unique individual variability in response to biologic agents, are creating a new kind of "tension" in the field of vaccinology. Personalized screening prior to vaccination could be made possible, one day, in order to identify these variables. This would result in the delivery of the right vaccine to the right person, at the right dose, at the right time [10-12]. A system biology approach might also favour the capacity to predict immune responses and adverse reactions, favouring the development of personalized vaccines [14, 17, 18].

However, at the moment, such predictive tests are still not available nor validated and, in any case, cannot be used on a large scale; this is a strong limit to the current feasibility of a personalized approach to vaccine prophylaxis. Furthermore, other challenges still exist.

Table 1
Pros and Cons of "one-size-fits-all" vaccination approach and personalized vaccinology

	Pros	Cons
"One-size-fits-all" vaccination approach	• Ease of planning large national campaigns for macro targets (e.g., age and risk categories)	• Risk/benefit ratio only applicable on a population level, not on an individual level
Personalized vaccinology	• Improved predictability of reactogenicity, resulting in decreased adverse effects and increased vaccine effectiveness, which can also generate positive social outcomes (i.e., less work or school absenteeism)	• Increased costs and potential delays due to pre-vaccination tests, which could hinder access to vaccinations and lower uptake • Potential use of individual-level data to discriminate against certain population groups

There are problems with high costs for genetic-based assays, the complexity of data analysis and interpretation, as well as inertia on the part of current vaccine producers and health authorities, which contribute altogether to postpone the possible transition to new paradigms in the field of vaccinology [17, 19].

On the other hand, a promising field of personalized vaccinology is represented by therapeutic vaccines against cancer. In particular, the rapid mapping of somatic mutations within cancer cells genome is now possible and may lead to the identification of cancer-specific epitopes that can be recognized by autologous T cells. This may favour the selection of specific vaccine targets. Since cancer-specific neoantigens are often unique to each patient's cancer, a personalized development of immunotherapeutic products is required [20, 21].

CONCLUSIONS

The mass vaccination approach, which is absolutely needed in a pandemic phase, when morbidity and mortality rates are high, has inevitable side effects at the individual and community level, and needs to be promptly critically revised in the post-pandemic era, when the clinical impact of the disease – along with risk perception – tends to decrease. At that point in time, a new mindset (i.e., using the best vaccine only for individuals at risk for a specific event) prevails. This kind of approach has been planned by the main European Countries in their national immunization COVID-19 campaign for the 2023/2024 season, where the recommendation for vaccination has been made for specific subgroups of people characterized by specific risk factors (e.g., age, diseases, frailty) [22].

Hopefully, this strategy may also be useful in dealing with hesitation towards vaccines, which is particularly topical after a couple of years in which vaccines and immunisation have been in the spotlight like never before, and citizens have been psychologically stressed by restrictions due to efforts to manage the COVID-19 pandemic. This does not mean that a unique vaccine should be developed for each one, but just that different types of vaccine – possibly based on different platforms – should be prioritized to different population subgroups, as already happens for influenza. In fact, current scientific knowledge is still limited, and pre-vaccination tests are neither reliable nor affordable.

Thus, we may move now from the mass vaccination approach, in which whatever vaccine is available is given to as many people as possible on the basis of a simple risk-benefit analysis, to approaches based on the possibility of differentiating between individuals at higher and lower risk of adverse events and severe disease, using simple variables such as age and gender, even within a restricted range of age classes. Pros and cons of one vaccination strategy versus the other are listed in *Table 1*. Of course, this is possible only in case different types of vaccines are available. Times are not mature for a real personalized vaccinology, but vaccination strategies based on prescription appropriateness – whenever is possible – can lead to more effective immune response, reduced rates of adverse events, increased public confidence in vaccination and higher vaccination coverage, contributing to a decrease of morbidity and mortality related to preventable diseases. It is important that those called upon to support decisions on vaccination campaigns, in particular NITAGs, take these elements into account [23]. To this end, it is necessary to improve training, curricula and professional skills in the field of vaccinology at all levels and among all health professionals.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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