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Original article

Reprint of: Development of vaccines and vaccinal strategies against COVID-19: The information contributing to shared decision-making

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\textbf{ABSTRACT}

The public has many questions about COVID-19 vaccines. The informing of general practitioners and other vaccinators provides healthcare users with clear and reliable information conducive to shared decision-making. While they constitute a bulwark against widespread vaccine hesitancy, informative supports can be tainted by doubt if they are not backed up by solid arguments convincingly addressing the manifold questions and concerns of healthcare users.

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\textbf{Introduction}

In December 2019, an epidemic caused by an emerging virus known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2, due to its similarities with SARS-CoV, which appeared in 2003) broke out in the city of Wuhan, China. On 11 March 2020 the World Health Organization (WHO) characterized the phenomenon as a pandemic [1]. By 4 December 2020 the number of COVID-19 cases (coronavirus disease 2019) throughout the world was estimated at 65 million, while the number of deaths ascribed to COVID-19 had exceeded 1.5 million [2]. In France, by 9 December 2020 the number of confirmed cases was 2,324,216, and the number of deaths ascribed to COVID-19 was 56,648 [3].

In the face of this pandemic, different nations have drawn up non-pharmaceutical strategies to limit transmission of the virus [4]. In the modeling developed by Li, the closing of schools and workplaces, the prohibition of public events and of gatherings of more than ten persons, the imposition of home confinement and restrictions on mobility seemed associated with reduced transmission of SARS-CoV-2 [4]. That said, these different strategies have major social costs; in France, the first lockdown (17 March to 11 May 2020) led to a decrease in economic activity of 25% [5].

Multiple active principles have been the subject of highly numerous randomized clinical trials in different parts of the world, the common objective being to reduce the transmission and/or severity of COVID-19 [6]. As the majority of the world population is not immunized against this emerging infection, vaccination against COVID-19 is shaping up as the long-term solution.

For one century, vaccination in general has been considered as the procedure saving a maximum number of lives, and little by little, it has come to represent the optimal solution against infectious diseases [7]. With this in mind, the WHO considers vaccinal hesitation as one of the ten most menacing threats to health. Vaccinal hesitation has been defined as “the reluctance or refusal to vaccinate despite the availability of vaccines [...] Several factors come into play, including misinformation, complacency, inconvenience and lack of trust” [8]. Feelings regarding vaccine safety vary according to country. In 2016, France seemed to be the most vaccine-hesitant nation, with 41% of vaccine skeptics as opposed to 13% worldwide [9]. In March 2020, 10 days after the outset of the initial lockdown, nearly 25% of the 5108 French persons interrogated, a representative sample of the overall population, stated that if a COVID-19 vaccine were to exist, they would probably or certainly refuse to have it administered to them [10].

The initial results of phase I and phase II trials were published in August and November 2020 [11,12]. In December, the United States Food and Drug Administration (FDA) rendered public its reports including effectiveness and safety data on the Pfizer-BioNTech\textsuperscript{a} and Moderna\textsuperscript{a} vaccines, and The Lancet published intermediate data derived from the randomized clinical trial for the ChAdOx1 nCoV-19 vaccine [13,14]. At the request of the French ministries of health and social solidarity and of
higher education, research and innovation, and in coordination with different hospitals and the Collège national des généralistes enseignants (CNGE), the French national institute of health and medical research (INSERM) has been commissioned to put into place an infrastructure for the organization of clinical trials on COVID-19 vaccines: COVIREIVAC [15].

The structure has as objectives (i) to set up a nationwide platform for volunteer recruitment, (ii) to establish coordination between investigation centers in the pursuit of industrial and academic trials, (iii) to conduct work on vaccine acceptability (iv) and to assess vaccine tolerance in close conjunction with pharmacovigilance activities. On 30 November 2020, the French health authority (HAS) proposed a five-phase vaccination strategy prioritizing the most fragile individuals in France [16], and the first vaccinations against COVID-19 are slated to take place in January 2021.

The French prime minister has emphasized the central role of general practitioners (GPs) with regard to this vaccination. According to a BVA poll, during the first lockdown 93% of his fellow countrymen maintained confidence in their GPs; for 74%, he or she represents their entranceway to the health care system [17]. GPs and, more broadly speaking, the caregivers tasked with administering anti-COVID-19 vaccination, will be called upon to answer the questions put forward by healthcare users. In Australia, a letter to GPs aimed at “building vaccine confidence” and “optimizing uptake” [18] has been published.

The primary objective of this article is to address and answer questions on vaccine development, vaccination strategy and vaccine acceptability. The second objective is to facilitate shared decision-making involving the caregiver and the health care user [19].

Vaccine development during a pandemic

From the outset of the COVID-19 pandemic, a race against the clock clicked into gear, the objective being to achieve safe and effective vaccines, mostly via public-private partnerships [20]. By 2 December 2020, 214 vaccines had been identified by the WHO and were being developed, and 51 of them had entered into a phase of clinical development, that is to say phase I (Fig. 1) [21]. Usually, as depicted in Fig. 1a, the development of a vaccine takes 10 to 15 years [18] and consists in (a) the preclinical phase (cellular and animal models), (b) Phase I (safety tests involving dozens of volunteers), (c) Phase II (safety and immunogenicity involving hundreds of volunteers), (d) Phase III (effectiveness and safety involving thousands of volunteers), and (e) commercialization after having been granted market authorization (MA) by national medicines regulatory authorities (Agence nationale de sécurité du médicament et des produits de santé/ national agency of drug and health product safety - ANSM in France) and post-commercialization monitoring of possible side effects (phase IV). As concerns COVID-19, scarcely 12 months have elapsed since the first reported cases of COVID-19 and the first emergency authorizations of vaccine use (Pfizer/BioNTech vaccine in the United Kingdom and the United States) [22].

How is it possible to accelerate so many things, practically all at once?

First of all, the 2003 SARS epidemic determined the role of the Spike protein and made it the target of vaccination [23]. What is more, in the midst of an epidemic the vaccine development phases tend to overlap (Fig. 1b). That said, safety and effectiveness assessment during clinical trials remains in compliance with the usual rules governing clinical vaccine research. Authorization processes have been accelerated and vaccine production anticipated [18].

Concerning production, it can be accelerated in accordance with the vaccine platform procedure, as is the case with RNA messenger (RNAm) platforms. That is why the two vaccines that were the first to have completed Phase III and to have communicated their effectiveness results are RNAm vaccines (Pfizer/BioNTech and Moderna®).

Developed for more than 20 years in the framework of anticancer and anti-infective vaccine approaches, the platforms do not necessitate a step-by-step procedure utilizing cell lines and embryonated eggs, which means that and vaccine production can be exceedingly (sidebar 1) [24]. Different clinical trials utilizing other vaccine platforms are concomitantly ongoing. Two platforms that currently stand out are (i) non-replicating viral vector (for example, phase III Adenovirus vector: AstraZeneca®/University of Oxford or Janssen; (ii) whole inactivated or subunit vaccine type (for example, phase II Sanofi/GSK).

Most vaccines necessitate two injections [21]. RNAm vaccines require conservation at -80 °C (Pfizer/BioNTech) and at -20 °C (Moderna), and the latter can be conserved for 30 days at 2 to 8 °C, and for 12 h at room temperature.

Information on the effectiveness of the Pfizer/BioNTech®, Moderna® and AstraZeneca®/Oxford vaccines was initially communicated in the press. Data on phases II/III of the Pfizer/BioNTech® vaccine were subsequently disseminated by the FDA and published in the New England Journal of Medicine [13,25], while AstraZeneca®/Oxford recently published its aggregated data on phase I/II, II/III and III trials (United Kingdom, Brazil, and South Africa) [14]. As regards the Moderna® vaccine, the FDA has made available data from the phase III trial and immunogenicity data on elderly patients (a small population) [12,26–28]. At this time, the reported effectiveness of the Pfizer/BioNTech® vaccine is 95% for the entire population (93.7% in persons over 55 years of age) [13]. As for the AstraZeneca®/Oxford vaccine, overall effectiveness neighbors 70%, and is greater in volunteers having received first a 1/2 dose followed by a full dose than in those having received two full doses; that said, the difference has yet to be wholly elucidated [14]. As concerns Moderna®, the data transmitted to the FDA show 94.5% effectiveness (95% CI = 86.5–97.8). In addition to immunity engendering neutralizing antibodies, cellular immunity is apparently triggered by these 3 vaccines [20].

Concerning safety, the reported adverse effects of these vaccines are essentially benign side effects and seem more or less pronounced according to age. With the Pfizer/BioNTech® vaccine, local “reactogenicity” has appeared after the 2nd injection among over 60% of volunteers, and general signs (fever, myalgias, asthma) have been found in 5 to 10% [13]. As regards the AstraZeneca/Oxford® vaccine, frequent “reactogenicity” (> 60%) has likewise been reported (pain at the injection site, feverish sensation, muscle pain) [14]. Available safety data are being communicated and monitored, after as well as prior to commercialization [13,14].

Any caregiver or citizen can make a declaration of an adverse event following vaccination on https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil.

Analysis of the different reports is carried out by a French network composed of 31 regional pharmacovigilance centers, each of which is commissioned to provide expert appraisal of a precise type of adverse event. Ongoing monitoring enables open and transparent communication on the safety of COVID-19 vaccines.

Sidebar 1. RNAm vaccines (based on Pardi et al. [24])

RNAm vaccines consist in messenger RNA coding for the Spike protein of SARS-CoV-2. These synthetic RNAs are encapsulated in lipid nanoparticles protecting them from enzymatic degradation (fragile material) and enabling them to enter into our cells. These RNA messengers are not infectious, and cannot be incorporated into the human genome (DNA); men and women do not possess reverse transcriptase. The RNA messengers consequently remain in the cell cytoplasm and code for the spike protein, which will serve as an antigen stimulating cellular and humoral immunity. Their half-life in cells lasts for several days. Prior to the COVID-19 pandemic, RNA vaccines against the Zika and Ebola viruses, Chikungunya and the Cytomegalovirus were in a phase of clinical evaluation.
Prioritizing strategy for populations

The launching of a vaccination campaign in the midst of an epidemic, at a time when the clinical development of vaccines is ongoing, imposes a number of possibly unprecedented organizational constraints, which are partially associated with dose availability (initial critical period, followed by supply ramp-up and deployment of vaccination systems), the conditioning of single dose or multi-dose vials, and the ensuring of conservation (refrigeration chain).

Public policy makers are tasked with defining a prioritization strategy for populations to be vaccinated [16]. In public health as well as clinical practice, it is initially of paramount importance to identify the populations at risk of hospitalization or death in the overall context of SARS-CoV-2 infection. Age is the factor most closely associated with this risk; while less pronounced, other factors are cumulative (sidebar 2).

Sidebar 2. Comorbidities entailing confirmed risk of hospitalization and death (according to HAS [16])
- obesity (BMI > 30), particularly in young children,
- COPD and respiratory insufficiency,
- complicated arterial hypertension,
- cardiac insufficiency,
- diabetes (type 1 and type 2),
- chronic renal insufficiency,
- cancers and malignant hematological pathologies, active or fewer than 3 years previous,
- solid organ transplantation or hematopoietic stem cells,
- Down’s syndrome.
Following which, the overriding priority is to identify populations at risk of exposure to the disease. The categories are stratified: on the one hand, health professionals (medical practitioners and auxiliaries, pharmacists, stretcher-bearers, firefighters, etc.) and human services professionals; on the other hand, persons in community residence or housing projects for dependent elderly individuals (EHPAD), prisoners, persons with disabilities inhabiting a group home, persons dwelling in temporary or insecure accommodations.

Taking into account these different objectives and constraints, as well as models from other countries, the HAS (French health authority) has proposed a 5-phase schedule (Table 1) with two categories of targets: system users, and their caregivers [16,18].

During phase 1, which is deemed critical, vaccination priority is given to: residents in establishments accommodating the elderly, long-term residents in medicalized facilities; and professional caregivers at heightened risk of severe form/death (over 65 years old and/or with comorbidities), This phase is placed under the responsibility of the coordinating doctors. La phase 2 is stratified into 3 stages: all persons more than 75 years old, prioritizing those with comorbidities; persons from 65 to 74 years old presenting with comorbidities; caregivers over 50 years old presenting with comorbidities. Stratification entails the attentive participation of general practitioners in the detection and identification of comorbidities.

Starting with phase 3, vaccination policy is addressed to the rest of the at-risk population (over 50 years old and/or with comorbidities). The different caregivers are called upon to undergo vaccination, as are non-caregiving professionals in the essential sectors of the economy (security, education, food supply, banking, transportation). Determination of who belongs to the last two categories remains open to debate; during this phase, occupational physicians are likely to have a major role to assume.

As for phase 4, which targets marginalized, precarious and homeless populations, it entails the mobilization not only of general medicine, but also of associational and institutional networks in contact with a problematically accessible public that does not necessarily receive regular medical care. During this phase, the professionals assisting these persons are likewise targeted. Occupational physicians shall be called upon to orient vaccination of workers in enclosed areas (construction, slaughterhouses). General practitioners shall help to identify persons at risk due to confined living quarters. This period may exacerbate existing health care inequalities.

Phase 5 extends the vaccination campaign to the entire adult population that has yet to be vaccinated.

Acceptability of the COVID-19 vaccine

The herd immunity threshold corresponds to the proportion of individuals who, on account of acquired immunity, can no longer participate in the transmission chain of a pathogenic agent. It depends directly on the reproduction number of the infectious disease (starting with an “index case”, the number of infected persons: RO). Given that in SARS-CoV-2 infections, the number ranges from 2 to 3, the herd immunity threshold would be set between 50 and 67% [29]. For comparison’s sake, with a RO between 12 and 18, the herd immunity threshold for measles exceeds 90%. Given present-day uncertainty as to post-infection natural immunity by SARS-CoV-2, it remains difficult to determine a target rate for vaccination coverage. That said and most importantly, in order for herd immunity to be acquired it behooves the population to accept vaccination, and in France, vaccine hesitancy is highly pronounced [9].

As regards intentions among the French to be vaccinated against COVID-19, during the first epidemic wave they were estimated at approximately 75% [10,30], and then, in June 2020, at 60% [31]. Today, as vaccines are beginning to become available, the intentions collected in the latest public opinion polls range from 40 to 60% [17,32,33]. While an overwhelming majority (>85%) of health professionals, particularly physicians and pharmacists, have declared the intention to be vaccinated, among nurses and health assistants only 60 to 65% have concurred [34]. In a context of emerging pathology, the main barriers to vaccination (in order of frequency) are fears concerning vaccine safety, doubts as to vaccine effectiveness, fear of developing COVID-19 due to vaccination, and limited perception of the risks associated with COVID-19 [35].

In France, women and youth (under 30 years of age) seem less inclined to be vaccinated than men over 30 years of age [30]. Motivating factors for being vaccinated against COVID-19 have been identified as: strong perception of the potential severity of the infection, and high risk of being infected [30]. The wish to recover a normal life (without restrictive measures) has likewise appeared as a reason for acceptance of vaccination against COVID-19 [32].

In a past epidemic situation involving emergence (the 2009 H1N1 flu), the attitudes (vaccine advocacy or hesitancy) of professionals, particularly GPs, were of genuine importance in individual decision-making [36]. In today’s context of a vaccine developed at “pandemic” speed, it seems legitimate, if only as a basis for discussion with health care users, for caregivers to require reliable, up-to-date information on the safety and effectiveness of a given vaccine. Tools specifically designed for use in COVID-19 vaccination decision-making should be rolled out, a key example being the VAC-SI information system, which will facilitate identification of patients for whom vaccination is recommended, ensure tracing of pre-vaccinal consultation and subsequent vaccinations, and report adverse effects. At this stage, however, several issues remain pending, and some of them may render the decision-making process conflictual (sidebar 3).

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**Table 1**

Chronological phases of the vaccination campaign and target populations (according to HAS [16]).

| Phases | Key actors | Targets (users) | Targets (professionals) |
|--------|------------|----------------|------------------------|
| Phase 1 | Coordinating doctors | Long-term residents in medicalized facilities. Professionals who care for residents, and themselves present heightened risk of severe form/death (over 65 years old and/or with comorbidities). |
| Phase 2 (in 3 stages) | GP | S1: All persons over 75 years old, prioritizing those with comorbidities, S2: persons from 65 to 74, and presenting with comorbidities, S3: caregivers over 50, and presenting with comorbidities. |
| Phase 3 | GP, OP | At-risk populations (50 years and/or comorbidities) All caregivers and non-caregiving professionals in essential sectors of the economy (security, education, food supply, banking, transportation) |
| Phase 4 | Associations, GP, OP | Marginalized, precarious populations; homeless persons, Professionals assisting precarious populations, workers in enclosed areas (construction, slaughterhouses), persons residing in confined living quarters |
| Phase 5 | GP | The entire adult population not yet vaccinated |

Legend: GP general practitioners, OP occupational physicians
Conclusion

Informing patients on the benefit-risk ratio of COVID-19 vaccinations corresponds to both the evidence-based medicine (EBM) model for therapeutic decision and, more generally, to the shared decision-making model [38]. The two models are closely correlated with the 4 core principles of medical ethics, particularly the non-maleficence (primum non nocere) ensured by vaccine safety, and the beneficence associated with vaccine effectiveness. Clinically relevant and applicable scientific data are delivered to a patient who consults his or her physician in the form of suitable information enabling the person to make an enlightened choice in accordance with the principle of respect for autonomy. Last but not least, the COVID-19 strategy put into place by the French health authority (HAS) highlights observance of the equity principle.

Declaration of Competing Interest

The authors have no conflict of interest to declare concerning the data published in this article. The possible ties of interest of each author may be consulted at: https://www.transparence.sante.gouv.fr/

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