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COVID-19/CLINICAL PHARMACOLOGY

Efficacy of COVID-19 vaccines: From clinical trials to real life

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Summary Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread around the globe leading to the COVID-19 pandemic. To mitigate the effects of the virus on public health and the global economy, vaccines were rapidly developed. In less than one year, with respect to usual clinical development rules, several vaccines have been put on the market and mass vaccination campaigns have been deployed. During the phase I to phase III clinical trials, most of these vaccines have demonstrated both their safety and efficacy. Despite questions remain about the impact of virus variants and the duration of the immune response, messenger RNA (mRNA)-based and adenoviral vectored vaccines have demonstrated an overall efficacy from 70 to 95% in both phase III trials and real life. In addition, all these vaccines also reduce the severe forms of the disease and might strongly impact the mortality which could change the course of the pandemic.

Abbreviations

COVID-19 Coronavirus Disease 2019
EMA European Medicines Agency
FDA Food and Drug Administration
Ig Immunoglobulin
MERS-CoV Middle East Respiratory Syndrome Coronavirus
mRN messenger RNA
R&D Research and Development
RBD Receptor binding domain
NK (cells) Natural killer
SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
WHO World Health Organization

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Introduction

Since December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has rapidly spread around the globe leading to the Coronavirus Disease 2019 (COVID-19) pandemic. From January 2020 to the beginning of second quarter of 2021, the intensity and rapidity of SARS-CoV-2 transmission have led to about 150,000,000 cases and more than 3,000,000 deaths in the world putting considerable pressure on public health systems and the global economy. In the context of extraordinary scientific and technical mobilization, the genetic sequence of SARS-CoV-2 was published on January 11th 2020, triggering intense global Research and Development (R&D) activity to develop a vaccine against this disease. To date, World Health Organization (WHO) lists about 200 vaccine candidates in preclinical development, 100 in clinical evaluation and 13 received authorization [1].

In Europe, 4 vaccines have already been authorized by the European Medicines Agency (EMA) and several mass vaccination campaigns are also underway worldwide. These rapid developments have been made possible by the important contribution of both public and private funding, high level of volunteers' participation in clinical trials as well as by changes in the review process of regulatory agencies [2]. On the other hand, the success of messenger RNA (mRNA) vaccine platform is probably the consequence of previous researches for more than 15 years and their previous identification as vaccine platform of choice for emerging infectious diseases [3]. Since the mechanisms of action and undesirable effects of these vaccines are addressed in other articles of this special issue, we will focus on the efficacy of coronavirus disease 2019 (COVID-19) vaccines, more particularly on the four vaccines already available in Europe.

COVID-19 vaccine development: an unprecedented timeframe

In the last decade, there was a marked evolution of vaccine platforms including the development of nucleic acid-based vaccine candidates and vectored vaccines, a number of approaches that have been used to accelerate COVID-19 vaccines elaboration. Moreover, previous preclinical data from vaccine candidates for SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) enabled the initial step of exploratory vaccine design to be largely overlooked, saving a considerable amount of time. In most cases, production processes were also adapted from those of existing vaccines [2].

As a result, a first phase I clinical trial of a vaccine candidate for SARS-CoV-2 began in March 2020 testing the mRNA 1273 (Moderna) [4]. In April 2020, another phase I trial testing different sequences of the mRNA BNT 162 (BioNTech/Pfizer) has also begun [5] then followed by adenovirus vectored vaccines, in June and July 2020, respectively ChAdOx1nCov-19 (AstraZeneca/Oxford) and Ad26COVS1 (Janssen) [6,7]. One important particularity of this period was that clinical phases were overlapping and trial starts were staggered, with initial phase I/II trials followed by fast progression to phase III trials mainly considering interim analysis of the phase I/II data. Most of the manufacturers had also rapidly started the large-scale commercial production of vaccines despite the absence of any result from phase III trials [2].

Finally, both Food and Drug Administration (FDA) and EMA implemented a rolling review process, which means that a drug company can submit completed sections of its new drug application for review, rather than waiting until every section of the application is completed before the entire application can be reviewed. Beyond these exceptional adaptations, one of the key factors of the accelerated development of COVID-19 vaccines was financial risk-taking that was greatly sustained by public funds, namely in Germany, UK and USA. Nonetheless, it should be underlined that despite these financial considerations but also the pandemic-associated emergency, no concession was made on safety.

Phase I/II clinical trials: safety and immunogenicity analysis

While phase I trials are usually designed to determine the safety profile at several dosages of a drug candidate, in the field of vaccines, the immunogenicity as a marker of drug-response is also evaluated. Indeed, this evaluation constitutes an essential step in the construction of future trials. In this context, phase II trials are intended to more precisely evaluate immunogenicity in relation to dose regimen in the way to determine the final dose to use in phase III trials. Here, most of the published studies were combined phase I/II trials aiming to determine safety and immunogenicity including the effect of a second vaccine dose according to different dosages and intervals [4—8].

Phase I studies usually recruited a low number of subjects but during the early development of COVID-19 vaccines at least one study reported here included about 200 volunteers [5] and according to a phase II design, another study included more than 500 subjects [6]. Such an important recruitment clearly helped to provide stronger results and has probably facilitated the design of phase III studies. This large number of subjects also allowed to strengthen the excellent results about safety profile of these vaccine candidates whatever the platform used namely mRNA or adenoviral vector [4—8].

As summarized in Table 1, all the vaccine candidates reported here were able to induce an immune response against the spike protein of the SARS-CoV-2. Thus, there was a clear dose- or time-dependent increased in both specific Ig-G and neutralizing antibody titers (Table 1) which are enhanced by the second dose of vaccine [4—8]. Some differences regarding Ig-G and neutralizing antibody titers may be discussed between these vaccines but it is important to point out that the assays used to perform these measures vary greatly and then comparisons must be made with caution. Nevertheless, an increase in specific Ig-G and neutralizing antibody titers has been shown in 90 to 100% of subjects while cellular responses were also observed. The phase I study on Ad26COVS1 vaccine also brings more details about immune response by analyzing the binding and functional profiles of vaccine-elicited antibodies by systems serology analyses. It was then showed the induction of S- and RBD-specific IgA1,

Table 1 Main data from phases I/II clinical trials of the 4 vaccines available in Europe.

	mRNA 1273 Moderna [4]	mRNA 1273 Moderna [8]	BNT 162 b2 BioNTech/Pfizer [5]	ChAdOx1nCov-19 AstraZeneca/Oxford [6]	Ad26COVS1 Janssen [7]
Platform	mRNA	mRNA	mRNA	Adenoviral vector Chimpanzee Ad26	Adenoviral vector Human Ad26
Study design	Phase I Non-randomized	Phase I Non-randomized	Phase I Randomized	Phase II Randomized	Phase I Non-randomized
Participants	45	40	195	560	25
Age range	18—55 y	56—70 y and ≥71 y	18—55 y and 65—85 y	18—55 y; 56—69 y; ≥70 y	18—55 y
Number of doses	2 (days 1/29)	2 (days 1/29)	2 (days 1/22)	1 or 2 (1/29)	1 or 2 (days 1/57)
Vaccine groups	25, 100, 250 μg	25, 100 μg	10, 20, 30 μg 18-55 y 10, 20, 30 μg 65-85 y Placebo	10 subgroups with low ($2.2.10^{10}$ vp) or full dose ($3.5—6.5\ 10^{10}$ vp) Placebo (MenACWY)	5 subgroups with 5.10^{10} or 1.10^{11} vp or placebo
Specific Ig-G titers[a]	782 719 GMT *Elisa anti S*	1 183 066 GMT *Elisa anti S*	8147 GMT *Luminex anti S1*	639 GMT *Elisa anti S*	478 GMT *Elisa anti S*
Neutralizing antibody titers[a]	654 GMT $PRNT_{80}$	878 GMT $PRNT_{80}$	163 GMT $wtVNA_{50}$	136 MT MNA_{80}	224 GMT *pseudoVNA*
Cellular responses	CD4+ and CD8+	Strong CD4+ (low CD8+)	ND	413 SFCs *IFN-ã ELISpot*	> 400 SFCs *IFN-ã ELISpot*

Ad26: adenovirus type-26; GMT: geometric mean titer; MNA: microneutralization assay; MT: microneutralization titer; ND: not determined; PRNT: plaque reduction neutralization testing; SFCs: spot-forming cells; VNA: virus neutralizing antibody; VP: viral particles; Y: years.

[a] Results of titration at 14 to 28 days after the boost in youngest group with dosage used for phase III trial (comparisons should not be made as assays are not standardized).

IgA2, IgG1, IgG2, IgG3, IgG4, and IgM subclasses; FcγR2a, FcγR2b, FcγR3a, and FcγR3b binding; antibody-dependent complement deposition, antibody-dependent neutrophil phagocytosis, antibody-dependent cellular phagocytosis, and antibody-dependent NK cell activation functional antiviral responses [7].

Another important information provided by these phase I/II studies was related to the effect of age. Among studies shown in Table 1, only studies on BNT 162 b2 and ChAdOx1nCov-19 vaccines included subjects over 65 years of age [5,6,8]. These studies demonstrated both antigen-binding Ig-G and virus-neutralizing responses in older adults but also a possible decrease in such responses with increasing age [5,6]. Nevertheless, an elderly-dedicated phase I study showed that mRNA 1273 vaccine induces a good Ig-G response against the spike-protein as well as significative neutralizing antibody titers in adults older than 70 years of age [8]. Taken as a whole, these results suggested the possibility to demonstrate COVID-19 vaccines' efficacy in phase III trials.

Phase III studies: evidence about a high level of efficacy

One of the main issues of phase III trials, particularly in the case of a new pathology, is to define the primary criterion to be used as efficacy markers as well as to define the level of efficacy that will be considered as pertinent. Undeniably, the definition of the primary criterion strongly impacts both the conduct of the trial and the future modalities of prescription of the vaccine. On June 2020, the FDA has released a guidance document for the development and licensure of COVID-19 vaccines [9]. This document stated that symptomatic laboratory-confirmed COVID-19 might be an acceptable primary endpoint for a COVID-19 vaccine efficacy trial with an efficacy level of at least 50% required. Moreover, other secondary criteria might be used to determine the possible efficacy on asymptomatic or severe infections. As a consequence, study sample sizes and timing of interim analyses had to be based on the statistical success criteria for primary and secondary efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 for the populations and locales in which the trials are conducted [9].

According to these conditions, phase III studies have been conducted in countries where the virus spread was extremely high and have included in a few months several tens of thousands of subjects [10—13]. According to these studies and except unwanted effects related to usual reactogenicity, these vaccines appear safe. As summarized in Table 2, among the four vaccines already authorized in Europe the overall efficacy defined as reduction of symptomatic COVID-19 varies from 67% to 95% [10—13]. These results are largely greater than the minimum efficacy level of 50% required by the FDA [9]. Furthermore, these levels of

Table 2 Clinical efficacy observed in phase III studies of the 4 vaccines available in Europe.

	BNT 162 b2 BioNTech/Pfizer [10]	mRNA 1273 Moderna [11]	ChAdOx1nCov-19 AstraZeneca/Oxford [12]	Ad26COVS1 Janssen [13]
Number included in the analysis	37,706	30,351	17,178	43,783
Age	≥16 y	≥18 y	≥18 y	≥18 y
Elderly (%)	> 55 y (42.2%)	> 65 y (24.8%)	56—69 y (10.4%) ≥70 y (5.7%)	≥60 y (33.5%)
Doses	30 μg (days 1/22)	100 μg (days 1/29)	Several combinations of low and full doses at different times	5.10^{10} vp (single dose)
Primary end-point	Symptomatic COVID-19[a]	Symptomatic COVID-19[b]	Symptomatic COVID-19[b]	Symptomatic COVID-19[b]
Overall efficacy (95% CI)	95% (90.3—97.6)	94.1% (89.3—96.8)	66.7% [63.1 or 80.7%[c]] (57.4—74.0)	66.9% (59.1—73.4)
Clinical efficacy on variants	ND	ND	B.1.1.7: 70.4% [21] B.1.351: 10.4% [22]	B.1.351: 52%
Neutralization activity on variants	B.1.1.7 preserved B.1.351 reduced	B.1.1.7 preserved B.1.351 reduced	B.1.1.7 preserved B.1.351 reduced	B.1.1.7 preserved B.1.351 preserved
Protection against severe infection	100%	100%	100%	76.7[b] to 85.4[c]%

ND: not determined; VP: viral particles; Y: years.
[a] Seven days after the last dose.
[b] Fourteen days after the last dose.
[c] According to administration scheme (full dose/full dose versus low dose/full dose).

efficacy are also similar or even higher than that the mean 60% observed with the influenza vaccines [14]. It should be underlined that mRNA vaccines [10,11] appear to have a higher efficacy than that of adenoviral vectored vaccines [12,13]. Nevertheless, a definitive conclusion about any comparisons should be done with caution. The complexity of the design of ChAdOx1nCov-19 vaccine phase III study does not facilitate neither the interpretation nor any comparisons of data. On the other hand, regarding interim analyses of trials reported in the Table 2, the protection against severe infection appears to be close to 100% for all vaccines but not for Ad26COVS1 vaccine where data recently published show protection against severe infection with one dose of vaccine of only 77% [13]. It remains to determine how this result is only representative of this vaccine rather than may be finally observed with all other COVID-19 vaccines when long-term follow-up data will be available.

Some other elements remain to be clarified in real life conditions, namely the effect on mortality, the level of efficacy in the elderly and the clinical efficacy of vaccines according to emerging variants and the duration of protection. Concerning mortality, the studies have not been designed to answer this question, it may then be difficult to bring clear and conclusive result. Moreover, according to the drastic reduction of severe infections observed in vaccinated-people, these studies are probably underpowered to clearly demonstrate the effect of vaccines on mortality.

Regarding elderly, not all published phase III studies had included many elderly people but in studies with a significant number of elderly participants (Table 2), the efficacy level remains relatively close to the one observed in younger subjects (86.4% and 94.7% in people of 65 or over, for mRNA 1273 and BNT 162 b2 respectively) [10,11]. Clinical efficacy of vaccines on emerging variants remains also to be more precisely evaluated. Due to the relatively recent emergence of different virus variants', only few clinical data are available but they show the preservation of ChAdOx1nCov-19 vaccine efficacy on B.1.1.7 variant [15] and a possible decrease in efficacy of both Ad26COVS1 and ChAdOx1nCov-19 vaccines on B.1.351 variant (Table 2) [13,16].

COVID-19 vaccines effectiveness in real life

When a new drug comes on the market, it takes usually several years before it could be demonstrated the reproducibility of the phase III clinical trial results' in real life. Here, according the pandemic situation and the rapid devel-

Table 3 Effectiveness of SARS-CoV-2 vaccination in real life.

Settings	Vaccinated population	Vaccine	Symptomatic and asymptomatic infections (95% CI)	Severe infections (95% CI)	Mortality (95% CI)
Clalit Health Services Israel [17]	596,618	BNT 162 b2	92% (88—95)[a]	92% (75—100)[a]	84% (44—100)[b]
Mayo Clinic Health System USA [18]	31,069	BNT 162 b2 or mRNA 1273	89% (68—97)[a]	60% (14—79)[a]	None
Mass vaccination Scotland [19]	1,331,993	BNT 162 b2 or ChAdOx1nCov-19	ND	91% (95% CI 85—94)[c] 88% (95% CI 75—94)[c]	ND
Health Care Workers England [20]	20,641	BNT 162 b2 or ChAdOx1nCov-19	85% (74—96)[a]	None	None

CI: confidence interval; ND: not determined; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
[a] Seven to 14 days after the last dose.
[b] 21 to 27 days after the first dose.
[c] Reduction in hospitalization 28—34 days after the first dose.

opment of mass vaccination campaigns in Israel, USA and UK, we already have many data demonstrating this achievement and also providing supplementary informations. Indeed, as summarized in Table 3, at least 4 studies that had included 20,000 to more than 1,300,000 vaccinated people provide us impressive results on symptomatic or asymptomatic infections, severe infections as well as on mortality [17—20].

Israel was probably the country which developed the most rapid and extensive mass vaccination campaign in the world by using the BNT 162 b2 vaccine. All people recorded on the Clalit Health Services (53% of Israeli population) who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls according to demographic and clinical characteristics leading to 2 study groups of 596,618 persons each [17]. Looking on results 7 days or more after the second dose of vaccine, symptomatic and asymptomatic as well as severe COVID-19 infections are reduced by 92%. Mortality was also reduced by 84% when regarding 21 to 27 days after the first dose [17]. Even if such results have to be strengthened by a longer-term follow-up, the present study also provides informations about a similar vaccine effectiveness across different age groups and a slightly lower effectiveness among patients with multiple coexisting pathological conditions [17].

In another paper under review, similar results are provided with the Mayo Clinic Health Database showing a 90% decrease in the development of a symptomatic or asymptomatic COVID-19 infection after BNT 162 b2 or mRNA 1273 vaccination in 31 609 persons [18]. Same kind of results are also provided by both Scotland and England data where both BNT 162 b2 and ChAdOx1nCov-19 vaccines were largely used with evidence of 85% decrease in symptomatic and asymptomatic infections and about 90% decrease in severe infections (Table 3) [19,20]. Interestingly, in the Scottish study, such results were observed while the vaccines were administered at only one dose to extend the number of subjects receiving at least one dose of vaccine. Besides the fact that all these data confirm the results of phase III clinical trials, they also help to discuss the question of the effect of vaccine on virus transmission. Because asymptomatic infections are also reduced, it may be that virus transmission is decreased. Moreover, a recently published paper brings supplemental arguments about an effect of vaccines on transmission. Indeed, people who develop a COVID-19 despite vaccination with the BNT 162 b2 vaccine have a clear reduction of viral load that might help to break the spread of the virus [21]. Complementary strategies, such as vaccines able to develop mucosal immunity are also under development [22].

Several questions remain on hold

One of the first questions on hold is the duration of the protection afforded by the vaccination. According to studies follow-up duration, it might be supposed that this protection is as at least 6 to 12 months. This duration will determine the need of a new vaccine boost and possibly the need of annual boost. Some large population-based studies using test-negative designs might help to evaluate these different issues particularly the situations of vaccine failure [23].

The question of using different vaccines than the one use initially is also crucial. New studies should be designed including studies for the evaluation of the impact of immunogenicity against adenoviral vector if such a vaccine is used for a third injection. Because phase III clinical studies provide no or only few data about immunogenicity, it remains important to also designed studies able to determine more precisely the immune response according to real life administration scheme namely regarding the role of both cellular and innate immunity. Actually, in France, 2 studies are in course to answer such questions by using BNT 162 b2 or mRNA 1273 vaccines in adults including a sub-population of elderly people over 75 years of age.

Besides older people, the question of the efficacy of vaccines in particular populations is also crucial. Several recently published studies bring some answers. To date, there is only few data about the efficacy of vaccine in young people under 18 years of age [10]. Studies evaluating COVID-19 mRNA vaccines in young people aged 12 to 16 years are actually in course but both FDA and EMA have already beenquestioned to provide an authorization of use. On the other hand, COVID-19 mRNA vaccines seem to generate robust humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in non-pregnant women [24]. In this study, vaccine-induced immune responses were also significantly greater than the response to natural infection and immune transfer to neonates occurred via placenta and breastmilk [24]. Other data also suggest that a single dose of mRNA vaccine elicits rapid immune responses in SARS-CoV-2 seropositive participants, with post-vaccination antibody titers similar to or exceeding titers found in seronegative participants who received two vaccinations [25]. On the other hand, the immunization rate among kidney transplant recipients who received 2 doses of an mRNA vaccine can be as low as 48% [26]. Very low immune response is evidenced also in others immunocompromised populations. The issue of a third vaccine dose in these non-responsive patients is an intriguing one that will be usefully explored in further research. In this context, a large cohort has been opened in France (COV-POPART) to evaluate the immune response in a number of particular populations including patients with cancer, transplant recipients as well as patients with autoimmune disease receiving immune-modulator treatments.

Last, an important challenge also concerns the efficacy of vaccines regarding the emergence of viral variants [27]. We have previously described some data from clinical trials regarding the decrease or the absence of efficacy of the ChAdOx1nCov-19 namely on B.1.351 variant (Table 2) [12]. Some similar concerns are discussed with the other vaccines but most of the data come from *in vitro* studies that are not able to consider the possible role of cellular immune response [27,28]. Besides to evaluate the effect of a boost particularly with new mRNA sequences, future trials should also explore more precisely the whole immune response against viral variants.

Conclusion

In less than one year, face to a worldwide pandemic due to an unknown virus, several vaccines have been put on the market and have been already used in several tens of millions of people. These vaccines are importantly effective and relatively safe according to the severity of the disease they prevent. Beyond this impressive efficacy of COVID-19 vaccines, notably those based on mRNA, such a technology may first contribute to modify the course of the pandemic but also could bring the world in a new era of specific treatments for numerous pathologies [3].

Disclosure of interest

The authors declare that they have no competing interest.

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