



Challenges in Antiviral/ Vaccine Development for Respiratory Viruses During Possible Future Pandemics

WHITEPAPER

SGS

A practical guide to clinical development during a pandemic

The SARS-CoV-2 pandemic transformed life as we know it. Around the world, shops, schools, banks and borders closed en masse. Even the pharmaceutical/drug development industry – which held the key to successfully navigating through the pandemic – struggled to continue operations as usual. A significant number of clinical trials were abandoned outright for safety and logistical reasons, while those that did take place faced innumerable challenges.

This white paper examines this topic in detail. It outlines the hurdles that clinical trials had to overcome during SARS-CoV-2 and identifies key lessons we can apply if there is another pandemic in the future.

The Devastating Impact of the SARS-CoV-2 Pandemic on Global Public Health

The current SARS-CoV-2 (from here on referred to as COVID-19) pandemic further underlines the devastating impact of respiratory diseases.

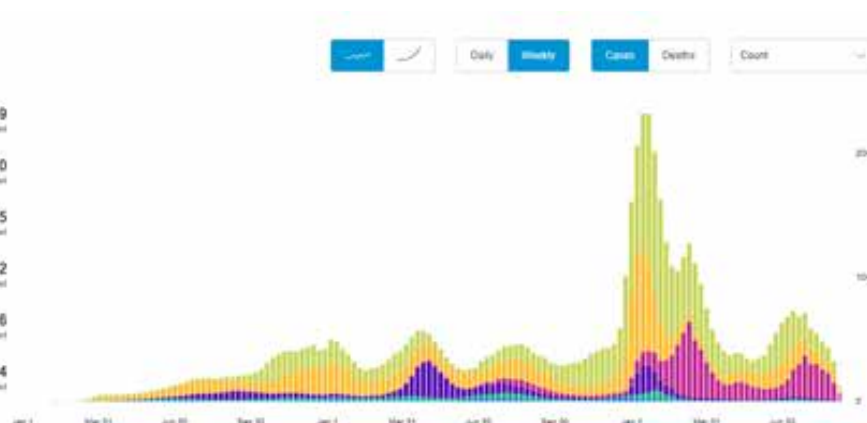
As of September 15, 2022, there have been 607,083,820 confirmed cases and 6,496,721 deaths globally. The image below demonstrates that COVID-19 has had a truly global impact:

Globally, non-essential labor was reduced or put on pause in an effort to contain the virus and reduce mortality. However, given that drug development is an essential line of work, it was allowed to continue – albeit at a slower pace than usual.

Situation by WHO Region

Europe	250,344,059	confirmed
Americas	177,023,010	confirmed
Western Pacific	87,215,385	confirmed
South-East Asia	60,153,342	confirmed
Eastern Mediterranean	23,035,306	confirmed
Africa	9,311,954	confirmed

Source: World Health Organization
Data may be incomplete for the current day or week.



Source: WHO Coronavirus COVID-19 Dashboard, <https://covid19.who.int/> (accessed Sept. 15, 2022)

Biotechs and pharma companies with relevant experience used their knowledge and facilities to try and produce vaccines or antiviral medication against COVID-19. Considering the pandemic was a pressing global medical issue, this approach makes sense – though it meant that companies were forced to deprioritize the development of other drugs.

Indeed, the pandemic led to reduced levels of drugs research and development (R&D), which influenced healthcare worldwide. And according to the Bill & Melinda Gates Foundation, global vaccine coverage was set back roughly 25 years in just 25 weeks. In addition, later diagnoses and the postponement of non-acute treatments increased morbidity in the

general population. So while these measures had a positive influence on curbing the spread of COVID-19, they had a negative influence on a myriad of other health issues. For example, they resulted in a reduced quantity of novel drugs for indications other than COVID-19.

We have to be realistic – this pandemic is unlikely to be a “once-in-a-lifetime” type of crisis. Indeed, when we examine all known respiratory pandemics of the past, we clearly see they have been increasing in frequency over time, and this increase has accelerated over the last century alone. Not all pandemics were as influential as COVID-19, but we need to keep in mind that we will encounter similar situations in the future.

The Impact of COVID-19 on Clinical Development Programs

The global rush to develop a COVID-19 vaccination had a huge knock-on impact, delaying clinical development programs across all therapeutic areas. Social distancing and quarantine measures resulted in many study participants (and trial personnel) being inaccessible for large portions of trials. These measures also prevented normal interactions between participants and trial personnel during study visits and scheduled follow-ups. Trial enrollments plummeted during this period, further impeding clinical development programs, while many research staff were furloughed or co-opted to assist hospitals in treating their COVID-19-positive patients.

Trials that did continue faced another major obstacle: data integrity/quality. The inevitable spread of COVID-19 among trial participants and staff called the clinical trials' integrity into question, with trial dropouts significantly influencing trial outcomes.

It's worth highlighting that trials operating during the pandemic were certainly not taking place under normal, easily reproducible conditions. For example, consider that seasonal respiratory viruses/pathogens

were far less prevalent than usual due to mass social-distancing measures.

As a result, many companies decided to prioritize COVID-19-related trials while postponing (or even canceling) other less important projects. They believed these non-COVID-related trials would be more difficult to perform and that their quality would be adversely impacted – and that the safest option was to continue them after the pandemic was over.

Therefore, lots of companies are currently trying to recover lost time and are conducting more early-phase trials than they were before the pandemic. This has resulted in a saturation of trials and significant recruitment issues, as a very large number of subjects are required for the countless global trials that are running simultaneously. In this paper, we argue that when another pandemic occurs, continuing trials will be more advantageous for both companies and general global healthcare.

How to Conduct Trials During a Pandemic

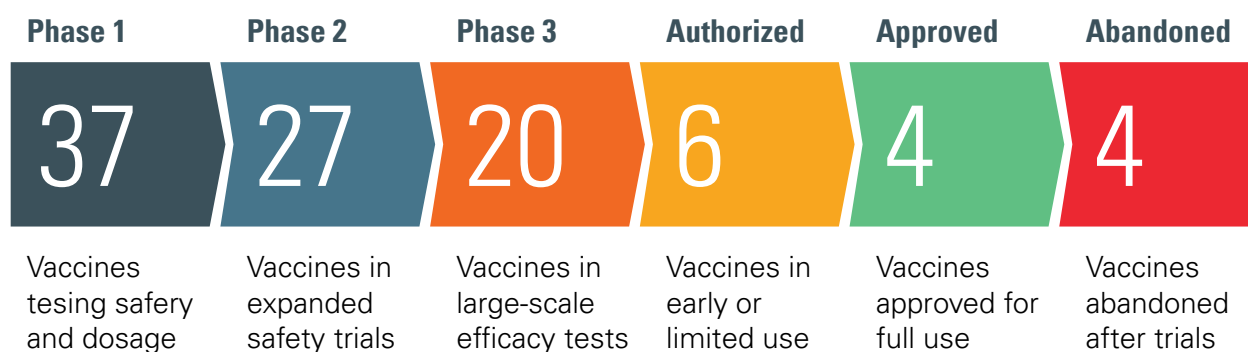
Phase 1 Unit Experiences During the COVID-19 Pandemic

Here at SGS, we continued to run a diverse range of clinical trials during the COVID-19 pandemic – though with plenty of difficulties. Below are the key lessons that we learned:

START EARLY OR CONSIDER ADAPTING OBJECTIVES

When you decide to develop treatments related to ending a particular pandemic, you need to know you're not the only one. But while competition increases the chance of developing a qualitative treatment as soon as possible, from a commercial perspective it mandates that you move quickly.

The New York Times created a tracker (shown below) demonstrating the various phases that newly developed vaccines had to pass through. When the first vaccines were (conditionally) approved and the general population had begun to be vaccinated, many potential vaccines were still in their late, early or even preclinical phases. When we compare their status then to one year later, only a fraction of them were ever fully approved. There are a few potential reasons that explain why.



For starters, the first vaccines that were approved set the bar incredibly high. The goal was for the vaccines to generate a 50% reduction in morbidity and mortality – however, the first vaccines led to reductions of approximately 90%.

This made them incredibly difficult to beat.

Furthermore, recruitment suffers greatly when vaccines are made commercially available. When the objective is to create a primary vaccine, you need seronegative subjects to prove an antibody response to the vaccine in the early phase. Therefore, as the general population had already been offered vaccinations, the number of possible trial participants reduced. Also, asking people to refuse an approved vaccine so that they can participate in an experimental vaccine trial is unethical. At SGS, we refused five early-phase COVID-19 vaccine trial requests on healthy volunteers since the general population could already be vaccinated against the disease.

Lastly, performing field trials is very expensive. And when there are existing alternatives on the market, it's less likely that you will receive funding unless you can prove that your vaccine has an added value.

If you have already performed extensive research but are not yet on the front line, don't be afraid to adapt your goals if possible.

The approved COVID-19 vaccines proved that boosters (with or without adaptations to new variations) are necessary. Your product can play a role in facilitating these types of demands. Adjust your objectives – aim to become a provider of a booster vaccine, perform clinical trials on vaccinated subjects and investigate further immunological improvement. You will need a larger population due to the added variable of different priming vaccinations, but we found that finding subjects willing to join COVID-19 vaccination trials was a relatively easy process.

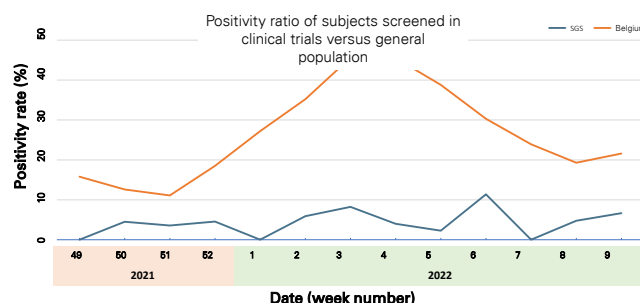
If you notice that your product is falling behind in terms of timing, efficacy or tolerability, don't be afraid to cancel the project early. Refocus on your regular development projects so that you don't lose too much time on these.

TRIALS CAN CONTINUE DURING PANDEMICS WITH THE CORRECT RISK MITIGATION

Trials can continue during pandemics provided clinical study teams implement rigorous risk mitigation measures. During the COVID-19 pandemic, SGS ensured that study volunteers and staff followed basic measures like social distancing, wearing a mask and regularly washing their hands.

Subjects that were at high risk or had symptoms possibly related to a COVID-19 infection weren't allowed to visit the CPU.

As an additional measure, PCR testing was performed before every admission and on indication (for instance, subjects developing possible COVID-19-related symptoms during admission). The combination of these measures resulted in a PCR positivity rate that was consistently lower than the Belgian national average – mostly below or around 5%.



SGS's extensive risk mitigation measures and testing protocols kept positivity rates among study volunteers far lower compared to the general population. Of course, however, there were still plenty of missed visits – this was unavoidable. Some subjects couldn't attend trial activities or be dosed as they were currently infected with COVID-19, others were in quarantine as close contacts had been infected, and on occasion subjects were unable to attend after having their holidays revoked due to coworkers falling ill. However, this had a limited overall impact on trial timelines, or the quality/integrity of the data that the trials generated.

Postponing your trial will limit the effect the pandemic has on your data and trial-specific timelines. However, this data shows that with the correct risk mitigation, you can still collect data in a safe and correct manner without majorly impacting your overall drug development timelines.

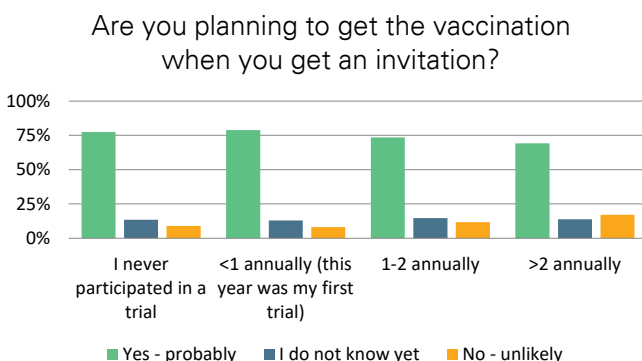


REMEMBER: STUDY PARTICIPANTS CONSIDER VACCINATION AND VACCINE TRIALS A HURDLE

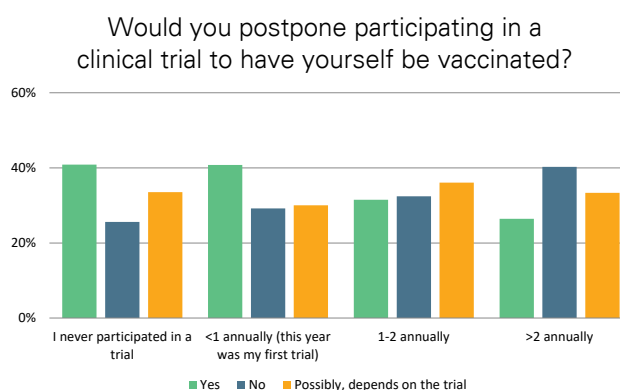
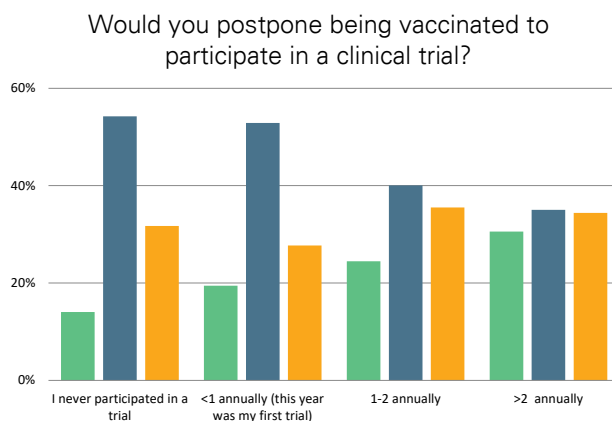
During the pandemic, it was clear that a portion of the general public appeared hesitant to receive a vaccination. Many of those that refused to be vaccinated argued that the vaccinations hadn't been tested thoroughly enough and that nobody knew all the potential side effects. Conversely, we expected that clinical trial participants would be less hesitant than the general population, as they were used to being dosed with medication that hadn't yet been thoroughly tested.

We performed a survey of 2,370 people from our database, but to our surprise the results contradicted what we'd expected.

They showed that volunteers who regularly participated in clinical trials were less likely to get vaccinated for COVID-19 when they were invited to do so.



When we looked at the reasons, many stated they didn't feel adequately informed, they didn't have access to enough data to make a decision or that the side effects were largely unknown. We then asked if clinical trial participants would postpone their vaccine if they could be part of a clinical trial, or if they would postpone their clinical trial when a vaccine was made available. Both questions showed that subjects who participate in several clinical trials per year prioritize these clinical trials over being vaccinated.



Consider this data when planning your clinical trial. On the positive side, it seems that frequent participants will still join your trial if possible, and will even prioritize it over being vaccinated – or will plan their vaccination around the clinical trial agenda. However, doing so increases the risk of them developing symptomatic COVID-19 during the trial and impacting your data.

When you're in the running to create a vaccine against the pandemic virus, bear in mind that first-in-human (FIH) vaccine trials are the least popular trials for subjects to join – according to a survey performed by Chen et al. Only 65.2% of those surveyed said they would probably join a FIH vaccine trial, which is significantly lower than the figure for FIH trials in general.



STUDY TYPE	PROBABLY WILLING TO PARTICIPATE
Marketed drugs	99.5%
Lifestyle interventions	97.2%
First-in-human trials	73.1%
Lifestyle interventions	97.2%
First-in-human trials	73.1%

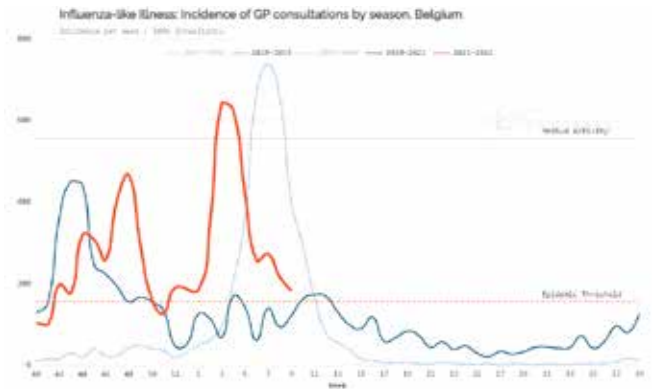
Source: Chen et al. "Phase 1 healthy volunteer willingness to participate and enrollment preferences." Clin Trials. 2017; 14(5): 537-46

PERFORMING CHALLENGE TRIALS DURING PANDEMICS IS POSSIBLE AND IN SOME CASES EVEN ADVANTAGEOUS

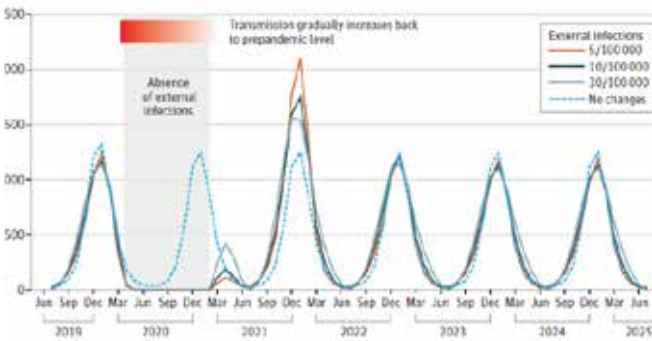
Performing challenge trials, where subjects are inoculated with a specific microbe, may seem to be an ethical issue during a pandemic. There was a great reduction in challenge trials performed during the COVID-19 pandemic. However, despite the difficulties, there are certain advantages to performing challenge trials during pandemics.

Subjects participating in a challenge trial are confined in at least a biosafety level 2 (BSL-2) facility. This means there’s only very limited personal contact, and this only occurs with the appropriate protection measures. Therefore, participants have less chance of being infected with the pandemic virus compared to the general population. They’re inoculated with a microbe which has been validated for this use, and so is better known than the pandemic virus.

Being infected with the pandemic virus or other respiratory viruses is one of the major exclusion criteria. PCR testing upon admission to the quarantined ward confirms whether or not subjects have existing viral infections. However, the COVID-19 pandemic led to a reduction of other respiratory viruses. Annual epidemics were reduced or even absent due to global risk mitigation measures, such as social distancing and mask-wearing. In 2020-2021, the epidemic threshold for influenza in Belgium was only marginally reached, while incidences of RSVs in the US were greatly reduced in the same period. This lower incidence has a positive influence on the number of participants being excluded based on concomitant infections.



Source: Sciensano, "Incidences of influenza in Belgium"



Source: Zheng Z, e.a. "Estimation of the Timing and Intensity of Reemergence of Respiratory Syncytial Virus Following the COVID-19 Pandemic in the US." JAMA Network Open. 2014;4(12)e2141779"

The presence of antibodies to the challenge agent is the other major exclusion criteria. When this reaches a significant level, it reduces the agent’s attack rate. Subjects inoculated with the challenge agent or who have recently obtained a natural infection have already formed antibodies, which can be confirmed via microneutralization tests (MNT). Low test values indicate the subject has no (or limited) antibodies, meaning the subject can be included. The table below demonstrates just how significant an impact this had on SGS’s influenza clinical trials in 2021/2022. For comparison, in the last trials that SGS performed, subjects had to have an MNT under 20. Reduced levels of influenza seem to have resulted in more participants having a low enough MNT value.



TRIAL	NUMBER SCREENED	MNT<10	MNT≤10	MNT≤20
2016	182	52%	61%	71%
2017	409	40%	44%	54%
2018	372	30%	38%	51%
2019	796	26%	32%	44%
2021-22	193	27%	36%	55%

That said, the decreased incidence of respiratory infections/viral pathogens due to social restrictions did result in considerable recruitment issues for respiratory infective field trials. When fewer people have a natural infection, it's more difficult to find enough subjects for your Phase 2 trials. This further increases the benefits of running a controlled challenge trial versus a field Phase 2a trial.

Confinement for trial participants, reduced concomitant natural infections, lower MNT values towards the challenge agent and the increased difficulty to recruit subjects for field Phase 2a trials show that challenge trials can be advantageous to perform in a pandemic period.

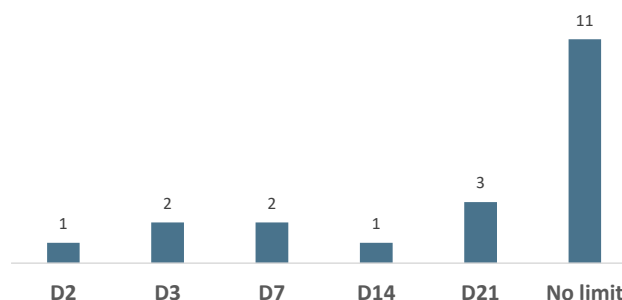
BUILD FLEXIBILITY INTO YOUR PROTOCOLS

Last but not least, study teams must build enough flexibility into their protocols to account for the ever-changing landscape. For instance, out of 56 trials SGS ran during the pandemic, 25 didn't mention a vaccine in the protocol, while 36 strictly forbade participants from receiving any concomitant medication, including vaccinations, during the trial. The protocols approved after the lockdown (but before any commercial vaccinations became available) didn't mention the possibility that subjects might be vaccinated during the trial. When the vaccinations became available, protocols therefore needed to be amended, or this would have had an incredibly negative impact on recruitment. Additionally, new approved protocols that allowed participants to have their first round of vaccinations needed to be further amended when boosters were administered. These continuous changes had a significant impact on protocols that were very strict in their permitted concomitant medications and had little flexibility.

N = 56	YES	NO
Vaccine described in the protocol	31	25
Vaccine allowed during the trial	20	36

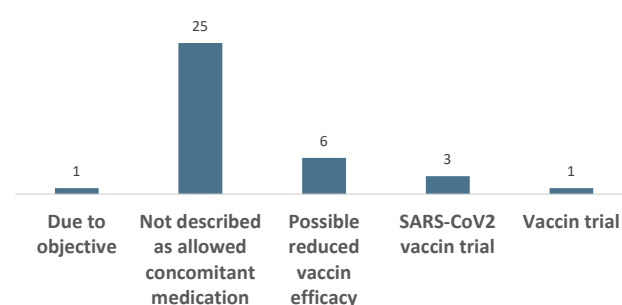
When reviewing protocols that allowed vaccinations to be performed, we can see that most of these protocols provided investigators with a large degree of flexibility. Some forbade participants from receiving vaccinations until specific days after dosing, for instance day 2, day 14 or even day 21. This was potentially due to possible interactions, or to bias regarding how the vaccination's adverse effects could impact the trials.

When is vaccination allowed



The majority of trials where vaccinations weren't allowed didn't describe the possibility of being vaccinated in their protocol. These trials would have benefited from writing a more flexible protocol. Of course, not all trials can allow vaccinations due to their objectives, or because possible interactions between the compound and the vaccination may result in reduced vaccine efficacy.

Why is vaccination not allowed



The landscape will continuously change during a pandemic. Writing flexible protocols will allow you and the investigator to adapt quickly when needed, without losing time in writing an amendment or having subjects withdraw their consent.

Summary

Conducting antiviral/vaccine development for respiratory viruses during pandemics is certainly a challenge – but it's far from impossible. In fact, in some cases it's even advantageous. To ensure challenge trials are a success during possible future pandemics, clinical study teams must bear the following in mind at all times:

1. Start early or consider adapting objectives.
2. Know that trials can continue during pandemics with the correct risk mitigation.

3. Remember that study participants consider vaccination and vaccine trials a hurdle.
4. Understand that performing challenge trials during pandemics offers certain advantages.
5. Build flexibility into your protocols.

Doing so will give your clinical trials the greatest possible chance of succeeding, no matter the challenges that pandemics present.

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WHEN YOU NEED TO BE SURE

