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## PRACTICE GUIDELINES

# COVID-19 epidemic phases: Criteria, challenges and issues for the future<sup>☆</sup>

## *Les phases de l'épidémie du COVID-19 : critères, défis et enjeux pour le futur*

A. Migus\*, P. Netter, C. Boitard, B. Clement, J.-F. Allilaire, R. Ardaillou, P. Berche, B. Charpentier, P. Debre, F. Galibert, B. Nordlinger

Académie nationale de médecine, 16, rue Bonaparte, 75006 Paris, France

Available online 9 July 2020

### Synthesis

The specific milestones and benchmarks included in this note for optimal transition out of the epidemic are estimates based on our current knowledge. However, the epidemic is evolving rapidly, and our understanding of the best responses is also likely to evolve. The set of tasks described here will need to be updated and refined as facts, new context and additional information about the epidemic become available.

The single focus on combating COVID-19 should no longer ignore other health implications of the current situation, such as mental health problems, domestic violence and lack of access to preventive care and/or treatment for chronic diseases, as well as economic or ethical considerations. The aim of this document is to propose to decision-makers the

minimum criteria for moving away from our dependence on general confinement and distancing as the main current tool for controlling the spread of the epidemic. For this, we need:

- better data to identify the areas of spread and the rate of exposure and immunity in the population;
- improved capacity of health care systems for early identification of epidemics, containment of cases and availability of adequate medical supplies;
- therapeutic, prophylactic and preventive approaches and better organized medical actions that provide the necessary tools to protect and treat the most vulnerable (elderly, overweight, obesity, diabetes, immune deficiency, etc.) and/or those most affected by the disease.

### Objective of phase I: to slow the spread of the disease

This is the phase implemented in March of 2020 to respond to an epidemic that has grown in magnitude. To slow the spread during this period, schools are closed, workers are invited to work at home when possible, and gathering places are closed. This was the only strategy applicable once the epi-

DOI of original article:

<https://doi.org/10.1016/j.banm.2020.07.003>.

<sup>☆</sup> Pre-Report of the French National Academy of Medicine written in April 2020 by a working group.

\* Corresponding author.

E-mail address: [arnold.migus@polytechnique.org](mailto:arnold.migus@polytechnique.org) (A. Migus).

<https://doi.org/10.1016/j.banm.2020.07.004>

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demic had reached a level that was not compatible with stopping it by simply confining the patients detected as being affected (cf. South Korea).

Four simultaneous criteria were introduced for the transition to the next phase II of partial deconfinement (Fig. 1).<sup>1</sup>

### Objectives of phase II: partial deconfinement

- to lift strict distancing measures in a concerted and prudent manner;
- to enable the vast majority of businesses and schools to open;
- to continue monitoring the transmission of COVID-19 so as not to return to phase I.

Moving to phase II requires that each region be able to safely diagnose, treat and isolate cases of COVID-19 and their contacts.<sup>2</sup> Part of this step is a return to the situation that preceded the viral expansion that required containment. However, some distancing and containment measures will still be required to prevent the resumption of transmission. For those at increased risk of infection, it will be important to strictly limit the time spent away from home. As a first step, the public will be asked to limit gatherings and to wear masks outside to reduce the risk of asymptomatic spread. Sick people will be encouraged to isolate themselves and be tested. Testing should become more widespread and common as diagnoses themselves become more common, while recognizing the difficulties of doing so.

In this phase II, the development of therapeutics will have to be accelerated, the scientific community mobilized in a coordinated way for priority actions in biology and health research and digital tools used on a large scale, in particular from the large existing health databases (CNAM...).

A return to the previous phase I of slowing down the epidemic, locally or globally, could be indispensable in the event of uncontrolled difficulties. Its application criteria are summarized below (Fig. 2).

While, if phase II is successful, the criteria for moving on to the next phase of immunity or, at least, good population protection, are summarized below (Fig. 3).

Unless the epidemic is expected to end on its own without a significant new wave, the phases III.A and III.B would, if successful, allow phase II, which is currently of indefinite duration, to be terminated.

### Objectives of phase III: to establish immunity protections (vaccinations, etc.) or therapies to relieve constraints

The distancing requirement and other phase II measures may be lifted when safe and effective tools to mitigate the risk of COVID-19 are available, such as extensive surveillance, and/or treatments that can save patients or prevent serious

disease in those most at risk, and when there is also a safe and effective vaccine (phase III.A) or immunity acquired in a large part of the population (phase III.B).

### Objectives of phase IV: to deal with the aftermath of the current outbreak and to prepare for a new pandemic

In order to no longer be caught unprepared in the face of a new infectious disease threat, it will be necessary to invest in research, develop infrastructures, train the necessary public health and health care workforce, ensure the research and industrial fabric to develop prevention strategies, and put in place a rapid and clear alert process that will allow the public decision-makers to better be informed and give credit to the threats.

## Phase 1: slowing the spread

### Objectives

This is the so-called containment phase in response to the COVID-19<sup>3</sup> epidemic, which aims to save lives by:

- slowing the transmission of the virus by reducing the number of new infections;
- increasing screening capacity to test all symptomatic individuals and their families;
- ensuring that the health care system has the capacity to best treat COVID-19 patients while maintaining continuity of care for other conditions, without risk of transmission of the virus.

A successful phase I will allow a significant relaxation of distancing measures<sup>4</sup> and progression to phase II to be implemented, when more targeted interventions for individual cases are possible.

### Thresholds for action

Triggering of the "propagation slowing" phase. The trigger for the implementation of measures to "slow the spread" during phase I was the existence, in several locations in France, of confirmed cases that could not be linked to other known cases.

Triggering for moving to phase II (see below)

<sup>1</sup> After several weeks of containment, since it appears that the first two criteria for moving to phase II have been met and that the last two are in the process of being met, it was decided, barring any incident in recent days, to begin phase II on May 11.

<sup>2</sup> A contact is defined as a face to face beyond a few minutes.

<sup>3</sup> Also known as SARS-CoV-2, or Severe Acute Respiratory Syndrome CoronaVirus-2.

<sup>4</sup> The expression "social distancing" should be avoided as it has negative connotations. The term "physical distancing" is preferable and often used abroad. In the following, no qualifier will generally be added to the term "distancing".

<sup>5</sup> Widely implemented by France

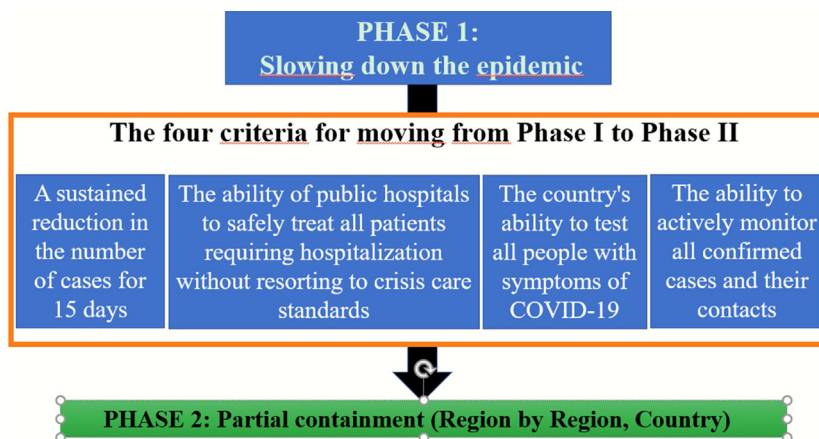


Figure 1 Triggers for the transition from phase I to phase II.

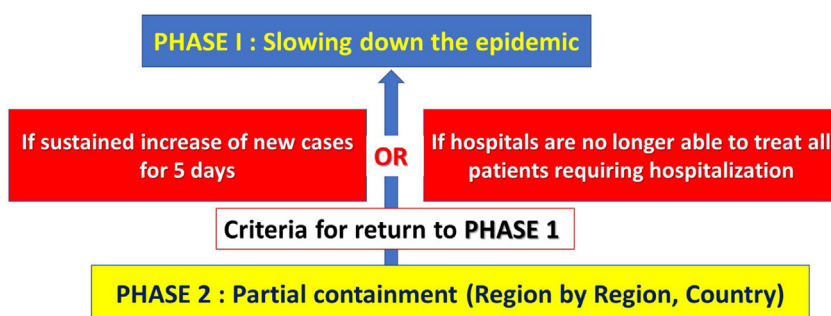


Figure 2 Triggers for moving back from phase II to phase I.

**Reminders of phase I mandatory measures<sup>5</sup>**

**To maintain physical distancing**

To maintain physical distancing<sup>6, 7</sup> until the threshold to move to phase II is reached.

<sup>6</sup> A notice of home confinement in a region is stipulated in case of doubling of affected subjects every three to five days and following the recommendations of representatives of the State and local authorities. The trigger for the recommendation to move from home confinement to a “slowing the spread” board is a steady decrease in the number of new cases reported, nationally or regionally, for 14 days (i.e., an incubation period) and the opportunity to test for symptoms of COVID-19 on all individuals in need of care.

<sup>7</sup> These phase I measures include, among others: closure everywhere of public gathering places (schools, restaurants, museums, etc.); closing of dining halls, but leaving them open for delivery and take-away services; teleworking for employees whose presence on company premises is not essential; limiting national or international travel; cancellation or postponement of meetings and mass gatherings; recommend or require home containment in hot spots where transmission is intense; wearing of masks (to be made mandatory away from home); verification of public adherence to physical distance notices, compliance incentives.

**To increase the availability of diagnostic tests**

To increase the availability of diagnostic tests and creating a data infrastructure for rapid sharing of results. The capacity for specific and sensitive diagnostic tests with same-day results, which should be widely available on an outpatient basis, is crucial for case identification, including those with asymptomatic or mild infections. Moving from interventions on large populations to interventions on individual cases to isolate infected persons requires sufficient capacity to test for:

- inpatients (with rapid diagnoses);
- health care personnel and those with essential roles (who are in contact with the public in terms of health and safety);
- people in close contact with confirmed cases;
- and ambulatory patients with symptoms.<sup>8</sup>

**To ensure the functioning of the health care system**

Ensure sufficient intensive care capacity covering all pathologies in hospitals so that the capacity of intensive care beds for patients with COVID-19<sup>9</sup> can be increased imme-

<sup>8</sup> The best way to achieve this is through diagnosis in the doctor’s office, with guidelines that encourage widespread screening and mandatory coverage for testing.

<sup>9</sup> 11 For the US, the recommendation is to increase the current capacity from 2.8 intensive care beds per 10,000 adults to 5–7 beds

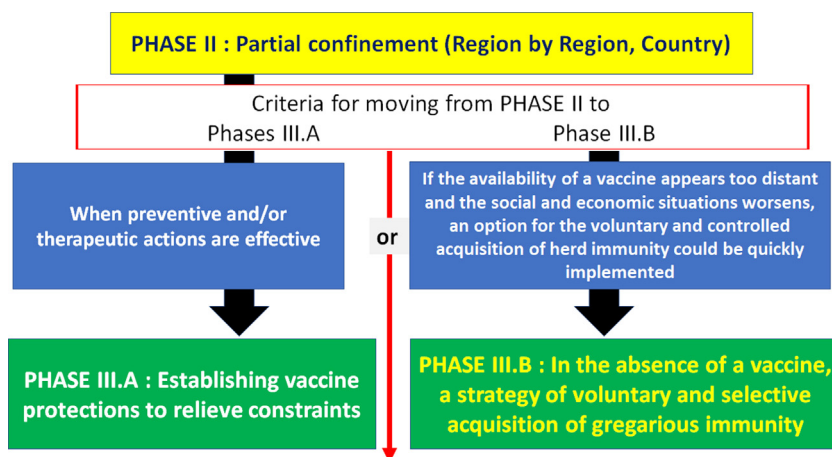


Figure 3 Triggers for the transition from Phase II to Phase III.A or Phase III.B.

diately. Increase access to ventilators in hospitals<sup>10</sup> with sufficient staff and maintain access to intensive care hospital beds<sup>11</sup> for emergencies other than those related to this epidemic.

#### To increase the provision of personal protective equipment

To increase the provision of personal protective equipment, as a minimum, FFP2 (N95) masks for hospital staff in direct contact with COVID-19 patients, and single-use or disposable surgical masks for all other staff in health care facilities.

#### To implement comprehensive monitoring systems for COVID-19

Moving towards less restrictive distancing could lead to a new period of accelerated caseload. Careful monitoring will be required to track these incidental trends. Patient surveillance needs to be drastically improved by making sure:

- widespread and rapid screening at the point of care using less restrictive diagnostic tools;
- serological tests to assess exposure and overall immunity levels so as to inform decision-makers, allowing them to prevent the spread of the epidemic. Measurements of the prevalence of contamination will be carried out on a sample basis using innovative methods of cluster sampling [1], or otherwise, for example, through the analysis of waste water [2];
- a comprehensive national sentinel surveillance system to monitor the average rate of infection in the different regions and to identify the spread to the public while the epidemic is still low and at a stage where interventions based on monitoring individual cases can prevent its spread.

#### To prescribe large-scale contact tracing, isolation and quarantine

When a new case is diagnosed, the patient should be isolated, either at home or in a hospital, depending on the level of care needed.<sup>12</sup> Home isolation can be controlled using technology such as GPS tracking through mobile phone applications. In addition, close contacts of confirmed cases should be quarantined and monitored daily for 14 days.<sup>13</sup> It is also recommended to monitor international travellers and possibly impose a 2-week quarantine for arrivals.

To adapt these interventions to thousands of daily cases and tens of thousands of daily contacts<sup>14</sup> requires considerable logistics, especially human logistics, and is probably difficult to do without digital monitoring. Public health infrastructure will need to be significantly strengthened throughout the country, in coordination with improving the capacity of health care providers to prevent, diagnose and treat cases.

Action will also need to be developed and overseen:

- to enable rapid reporting to health authorities through public health staff, general practitioners whose role it is and electronic data sharing from health providers and laboratories;
- to develop and implement a technological approach to enable rapid data entry, notification and support for isolation, quarantine and appropriate community treatment of affected persons.

#### To provide accommodation for voluntary isolation and quarantine

Comfortable and free facilities should be made available to individuals and their contacts who prefer local isolation,

per 10,000 adults in the event of an outbreak or other emergency, taking into account regional variations.

<sup>10</sup> For the US, the recommendation is to increase them from 3 per 10,000 adults to a target of 5 to 7 ventilators per 10,000.

<sup>11</sup> Estimated for the US to be at least 30 per 10,000 adults.

<sup>12</sup> In the US, current CDC guidelines recommend a seven-day isolation period.

<sup>13</sup> As defined by the CDC in the United States

<sup>14</sup> Defined as a face-to-face of a few minutes without a mask and at less than one metre away.

quarantine and treatment away from home.<sup>15</sup> Field hospitals, dormitories, hotels and military barracks may be set up for this purpose.<sup>16</sup>

### To make the wearing of masks mandatory in public spaces

There is growing evidence that asymptomatic and pre-symptomatic transmission of COVID-19 is possible, complicating efforts to continue case-based interventions. To reduce this risk during phase I, it is mandatory for everyone, including those who are symptom-free, to wear a non-medical, cloth face mask away from home<sup>17</sup> [3].

### To distinguish regional responsibilities and centralized decisions

The great regional and local disparity of infectious situations and their evolution calls for policies that can be differentiated according to regions, departments and municipalities. The State should produce guidelines for prefects, regional health agencies (ARS) and those in charge of local authorities (regions, departments and communes) and leave it to the latter to assess situations, manage resources and, ultimately, propose decisions to move on to the next phase. The most important decisions at the local level could be validated at the national level when dependent on the state of the hospital system in other regions. An adapted procedure with neighbouring countries should be put in place for border departments.

### Trigger for transition to phase II

To avoid the risk of major outbreaks or epidemic spread occurring again once the initial efforts to “slow the spread” have been lifted, France or a region could safely move to phase II when all of the following criteria are met (Fig. 1):

- a sustained reduction in the number of cases<sup>18</sup> for at least 14 days<sup>19</sup>;

<sup>15</sup> For example, a member of a large family may wish to recover in a hotel room that has been refurbished rather than to risk infecting family members.

<sup>16</sup> The “hospital hotels” whose experimentation in 2017 was not finally supported by the CNAM could have been of great service from the start of the pandemic.

<sup>17</sup> Facial masks will be all the more effective in slowing the spread of COVID-19 if they are widely used, as is the case in some countries that have successfully managed their epidemics, such as South Korea and Hong Kong. WHO has recommended that the public use facemasks in the event of a severe influenza pandemic. However, personal protective equipment should be reserved for health professionals in case supplies are insufficient. For this reason, in public spaces, in the event of a shortage of so-called surgical masks, the public should wear non-medical, cloth facemasks, whose design guidelines are published and which consumers may be able to make themselves [3].

<sup>18</sup> “Cases”, as measured regionally, are defined as symptomatic patients, hospitalized or outpatient.

<sup>19</sup> That is, the incubation period

- the ability of public hospitals to safely treat all patients requiring hospitalization without resorting to crisis care standards;
- the ability to test all persons with symptoms of COVID-19. The ability of public hospitals to safely treat all patients requiring hospitalization without the use of crisis care standards;
- the ability to actively monitor all confirmed cases and their contacts.

After several weeks of containment, it appears, at the time of finalization of this document, that the first two criteria for moving to phase II have been met and that the last two are in the process of being met, it has been decided to begin phase II on May 11, 2020.

### Phase II: partial deconfinement (region by region, country)

In this phase II, the majority of schools, universities and businesses can reopen. Teleworking should continue where possible; meetings should still be limited, initially to fewer than 20 people. Other local restrictions should be considered, such as those, which prevent people from meeting in close proximity.

Institutions with a high level of contact, such as schools, should continue to implement distancing measures with increased hygiene measures and cleaning of common surfaces.

For people who have underlying health problems and are at an increased risk of COVID-19 (age, addiction, overweight, obesity, cancer, immune deficiency, etc.), it should still be recommended to limit the amount of time spent in public during phase II. This recommendation may change if effective therapy becomes available.

### Objectives

The objectives of phase II are as follows:

- to lift the strict distancing measures in a concerted and prudent manner;
- to allow the vast majority of businesses and schools to open;
- to continue to control the transmission of COVID-19 so as not to return to phase I.

The adoption of these phase II measures will require a careful balance constantly reassessing their implementation based on available surveillance data, and the ability to take a differentiated approach over time based on the epidemiology of local, national and global spread.

### Thresholds for action

To trigger the lifting of containment measures while maintaining distancing, once the criteria for transition from phase I to phase II have been met. This should be done progressively, region by region, department by department, and combined with increased monitoring of new cases. The

restrictions will be relaxed gradually, with sufficient time between each adjustment to carefully monitor the resurgence of transmission.

To trigger returning to phase I.<sup>20</sup> As distance is gradually reduced, monitoring will be essential to quickly identify an increase in cases. A district (region or other) should return to phase I and continue to “slow the spread” if a significant number of cases cannot be linked to known cases, if there is a sustained increase in new cases for at least five days, or if hospitals are no longer able to safely treat all patients requiring hospitalization.

To trigger to move to phase III. It may be triggered once a vaccine has been developed, tested for safety and efficacy, and has received a Transitional Use Exemption (TUE), or once there are other therapeutic options that can be used for preventive or therapeutic indications and that have a measurable impact on disease activity and can help to treat patients with a severe disease. A natural evolution of the pandemic cannot be excluded, in the sense of either mitigation or aggravation.

## Steps required for phase II

### To control the virus circulation by virological tests on samples from populations in the region, or, if not, in the department

In addition to virological tests carried out on medical staff, patients and in EPHADs, virological tests on representative samples of the population should be carried out during phase II. These tests carried out on samples of a thousand volunteers should correspond to the densest possible coverage of the territory, at least one per region and ideally one per department. These tests must also be repeated at least once a week according to the same geographical distribution. Increasing or decreasing the percentage of positive or negative responses will make it possible to adapt the rhythm of the surveys to the constraints of confinement as close as possible to the territory.

### To implement interventions based on individual cases

Using the public health capacity developed in phase I by general practitioners, each confirmed case must be isolated, either at home, in a hospital or (voluntarily) in a local isolation centre for at least fourteen days according to the latest guidelines of the health authorities. Persons awaiting the results of at least two tests four days apart will be quarantined until the results are returned.

To trace persons who have had close contact with these confirmed cases and to place them in quarantine at home or in a quarantine centre, with active daily surveillance for at least 14 days according to the latest guidelines of the authorities. Diagnostic tests must be carried out immediately in all those who show symptoms.

### To begin to adjust distancing measures while maintaining barrier gestures

General distancing precautions should always be the norm during phase II, including teleworking (as much as possible), maintaining hand hygiene, wearing a mask when away from home, regular disinfection of frequently contacted surfaces, and initially limiting social gatherings to fewer than 50 people (or 20 or another number to be delimited). These recommendations should be complemented by technological solutions to assess distancing behaviour and adapt risk messages as appropriate. This could be done through partnerships with the private sector, taking care to preserve individual lives and avoiding coercive means to encourage compliance.

To reopen cautiously the country which is about to create the most freedom through a modest opening of society. For example, it might be a good idea to start by letting the smallest children go to school so that their parents can return to work. It may also be a matter of deciding where the public sectors that are considered the most important can be opened up as a matter of priority. As children return to school or daycare (i.e., in places with high attendance) and people return to densely populated workplaces, those in charge of these institutions must continue to implement physical distancing measures for schools, which for the smallest children will require an organizational effort, and for businesses.

The French authorities could also follow the example of the Danish Prime Minister, who is considering that his countrymen have to work, educate and go to school at different times of the day, outside of regular business hours. This would, among other things, help avoid peak hours in the public transport but would imply significant changes in the usual organization of the work.

### To maintain a special care for vulnerable populations

Although distancing is diminishing, highly vulnerable populations should continue to use it as much as possible until an effective vaccine or treatment is available, or until community transmission ceases. Special attention should be paid to long-term care facilities and nursing homes, which will need to maintain high levels of infection prevention and control efforts and limit the number of visitors to prevent outbreaks.

To give priority to high-risk and vulnerable populations, if a prophylactic or therapeutic drug, such as a monoclonal antibody becomes available, both to protect these individuals and to reduce the likelihood of an increase in serious illness and a further increase in the number of patients in hospital intensive care units.

To deal with the new vulnerabilities that have emerged as an indirect consequence of COVID-19: chronic patients whose follow-up has been interrupted, de-scheduled surgical patients, serious medical or surgical emergencies being significantly reduced, and new patients diagnosed. This is a massive effect that affects a large number of people, probably in the millions, and is the source of a disorganized logistical flow in the health system that must be absorbed.

### To relaunch, mobilize and coordinate research

The way in which the strategies and disordered implementation of research have unfolded during this epidemic

<sup>20</sup> Case of Singapore which, on 11 April 2020, had to initiate phase I after successfully containing the spread (Phase II) for almost two months.

emergence, and the weight of research in the fight against COVID-19 (cf. decision-making in public policy) reinforce the previous recommendations of the National Academy of Medicine on the merits of coordination combining programming, evaluation, implementation, monitoring, European and international policy, innovation and communication and education [4]. The lack of coordination and the multiplication of small trials make it difficult to recruit and delay recruitment in larger trials and thus diminishes the prospect of usable results.

### Immediate actions to be taken in biology and health research

The first steps are:

- to establish coordination of the research response on COVID-19 under the aegis of the Life Sciences and Health Alliance (AVIESAN) in association with National research agency (ANR), AIDS and viral hepatitis national research agency (ANRS) and Hospital clinical research programs (PHRCs);
- to quickly restore the functioning of laboratories, animal houses and technological platforms to working order, as a prolonged shutdown would be fatal to the restarting of research projects;
- to support the launch of the cohorts associated with the pandemic, including: survivors, asymptomatic infected subjects, healthcare personnel, etc., in order to coordinate epidemiological, phenotypic, genetic, and human and social science studies;
- to create a network between biological resource centres (biobanks) to coordinate and optimize access to biological sample collections, including autopsy specimens;

### To accelerate the development of therapeutics<sup>21</sup>

Accelerating the research, development, production and distribution of safe and effective therapeutics is a top priority. At a minimum, the expected profile of a treatment that will influence the risk of future spread is to significantly reduce the risk of death or serious illness and possibly prevent the onset of symptoms or progression to serious illness in exposed individuals. Through effective development strategies and early investments in commercial scale manufacturing, an effective therapy could quickly receive a Transitional Use Exemption (TUE) or a Marketing Authorization (MA) as early as the summer or fall, if tests show that it meets either of the standards set out in the legislation for these two provisions, and even more quickly if it is a repositioned drug.

Treatments can have two different purposes, be directed against the virus or against the pathophysiological consequences of its contamination:

- against the virus, several attempts are underway to limit its replication by action on its membrane receptor, the

capsid proteins reacting with this receptor, its replication enzymes as polymerases and protease, or against virions by specific monoclonal or polyclonal neutralising antibodies or by interferon;

- against the physiopathological consequences of the viral infection, the therapeutics are of two orders: some fight the cytokine storm, as antibodies against interleukin-1, other cytokines, or against their receptors (in particular IL6, IL1, TNF, and complement factor inhibitors), others facilitate oxygen transport or limit the risk of thrombosis (anticoagulants);

At a minimum, the optimal treatment profile that will influence the risk of future spread is one that significantly reduces the risk of death or serious illness and possibly prevents the onset or worsening of symptoms in exposed individuals. Oral administration to an outpatient basis would be ideal, but other methods of administration (e.g., infusions and injections) could also be adopted, with sufficient planning;

In immunoprophylaxis, different approaches can be used: non-specific immunotherapy (BCG), passive immunization by monoclonal or polyclonal immunotherapy (serotherapy) or vaccine (in progress). In this case, indications are different depending on whether the aim is to prevent infection in those most at risk, such as front-line health workers or frail people with pre-existing health problems, or whether the aim is to prevent a serious form or its progression in those who are immunocompromised or those at risk after exposure.

Information sharing between the public and private sectors is essential to rapidly advance promising therapies and prophylaxis and to ensure that the best possible resources are devoted to them.

### To make an extensive use of digital tools

These tools are essential for understanding the development of the epidemic. However, by making it possible, at least temporarily, to substitute machines for human beings tasks, they have also made it possible to maintain part of the activities through teleworking while helping to maintain physical distance. In addition to telework, which must be maintained if not amplified and secured in this phase II in order to maintain the country's activity in security, the current context offers opportunities to develop new applications or to amplify those already existing in the medical field:

- telemedicine and telediagnosis, which do not replace a human presence but avoid the risks of virus transmission;
- 3D printers, which are used to manufacture protective screens, masks, respirator mouthpieces;
- automatic analysis of virological and serological tests as well as automatic thoracic CT scans for the diagnosis of pneumonia at COVID-19;
- e-pharmacy to enable the prescription of drugs via the web and their dispensing by robot, for example in establishments for accommodation of elderly (EHPADs);

<sup>21</sup> OPECST published on March 30 a note on possible treatments and ongoing clinical trials, including the European trial, DisCoV-eRy, under the guidance of the REACTing network: "Coronavirus epidemic — Update on treatments, vaccines..."



- operating public health data thanks to artificial intelligence<sup>22</sup> algorithms to better understand the disease, its risk factors, etc. To do this, it is imperative to shorten the information systems medicalization program (PMSI) uptake time, currently several months;
- robots to reduce the risks of pathogen transmission: surface disinfection, waste management, nasopharyngeal swabs, laboratory robots, virus ARN research in wastewater, etc.;
- mathematical models to calculate prevalence on population samples.

### To identify immunized individuals

In this return-to-work phase, it is important to know the prevalence of the disease in the deconfined population using the serological tests already or soon to be available. These tests are all based on the detection of antibodies directed against viral capsid proteins.

There are a number of arguments in favour of the acquisition of protective immunity through the use of neutralising antibodies:

- the disease in its mild form is easily curable (85% of cases);
- the absence of recurrence among those cured, as shown by the absence of cases published in France out of hundreds of thousands of declared cases<sup>23</sup>;
- symptomatic subjects have a good antibody response, the paucisymptomatic forms have a weaker and sometimes delayed response;
- recent experimental data in the macaque monkey show that it presents a benign disease, that it responds, like humans, by producing neutralizing antibodies, that it becomes resistant to massive superinfection and is no longer contagious.

Uncertainties remain about the antibody response of asymptomatic healthy carriers, which is expected to be lower and about the duration of immunity. The antibody response against the other four benign human coronaviruses lasts two to three years, which would lead to optimism. For this reason, serological tests could be predictive of good protection and form the basis for herd immunity.<sup>24</sup> The existence of this acquired immunity is an omen for the likely effectiveness of future vaccines.

However, more knowledge is still needed on the duration of antibody response and acquired immunity to reinfection to determine:

- the safety of return to work for those who test serologically positive;
- the durability of immunity;
- the likely effectiveness of vaccination;

<sup>22</sup> Cf. the CovidIA project (covid-ia.org).

<sup>23</sup> There have been a few reports of a few healed persons with negative PCR, in whom positive PCRs were found within 15 days, but without clinical signs, which led to erroneous conclusions (these may be false negatives).

<sup>24</sup> A recent, as yet unpublished study in New York shows that 20% of the sampled population (1000 people) is seropositive, while in New York State the rate is much lower at around 3%.

- and the possibility of achieving herd immunity to COVID-19.

The strength of the immune response in transiently infected healthy carriers, in symptomatic individuals who are cured, and the length of time individuals remain immune to re-infection also need to be better understood. A major uncertainty stems from the lack of regression from early cures, but lessons can be learned from data on the duration of antibody effectiveness against SARS-CoV and MERS-CoV, which are related viruses [5].

A campaign of serological testing to determine prevalence in the population. Determining prevalence in a given population involves examination of a representative sample as is already done by polling institutes. This sample must include a sufficient number of subjects living in a territory to be defined in which a serological test will be carried out.

Two types of tests can be used:

- self-tests by depositing a drop of blood on a strip that can be done at home or at the doctor's office, considered as rapid diagnostic orientation tests (TROD) that determine the presence of specific IgG and/or IGM;
- serological tests by the enzyme-linked immunosorbent assay (ELISA) method, the latter being feasible in a private medical analysis laboratory, hospital or veterinary school and more reliable than the former.

As the results of these tests can be used to improve our knowledge of the epidemiology of the disease, the test subject will have to fill in a questionnaire indicating essential data (sex, age, weight and height, blood pressure, occupation, place of residence, present or previous illnesses, treatments followed). The questionnaires and test results will be sent to Santé France, which will use them anonymously. Therefore, it is better that the tests are carried out on prescription in a medical analysis laboratory with the results sent to the doctor.

A second interest of this campaign of tests will be to give instructions to persons according to their positivity or negativity in order to avoid any contamination from the positive subjects and any risk of being contaminated in the negative subjects. As the COVID-19 is still not well known, the individuals tested will have to be re-tested 2 or 3 months later in order to clarify the evolution of the antibody level in the positive subjects.

### Public-private coordination

A national official has just been appointed to prepare and implement the deconfinement steps. He or she could rely on a public-private working group made up of health officials, academia and key private sector groups (e.g. serology manufacturing companies) to oversee the development, production, distribution, data collection, design of serological studies and analyse their use on a large scale.

### Mastering policy communication

Citizen confidence in research may have been affected by public controversies over the need to maintain ethical principles in biomedical research, even in times of pandemic. Indeed, the temporality of research and the difficulty

of communicating unconsolidated results, the continuous information on treatments offered to patients, the power of social networks that convey unfounded information, have induced doubts in the population about the effectiveness of research. This may have resulted in patients refusing to participate in randomized clinical trials and the rise of a form of “medical populism” [6] that relies partly on continuous information channels but mainly on social networks.

#### To trigger for a return to phase I (cf. thresholds for action)

- explain this strategy which, in the end, will limit the number of deaths and will allow a better management of the media by the political power to obtain a total collaboration of the population;
- determine population immunity and the timing of the end of the epidemic through serological studies.

Unless the epidemic is seen to end on its own without a significant new wave, the phases III.A and III.B, if successful, would bring an end to the phase II, the duration of which is currently indefinite (Fig. 3).

### Phase III A: establishing vaccine protections to remove constraints

This phase III with positive economic implications will be possible when a robust sentinel surveillance system is put in place, combined with a widespread testing and a capacity to implement tracing, isolation and quarantine — supported by the availability of therapies that can help mitigate the risk of spread or reduce the serious consequences for those with infections — or when a vaccine has been developed and tested for safety and efficacy.

#### Objectives

The objectives of transmission control are as follows:

- to prevent infection;
- to treat early so as to avoid severe complications;
- to provide prophylaxis to those exposed to infection so as to prevent them from developing the disease or reduce its severity;
- if a vaccine is available, to enhance the population’s immunity to the virus in order to reduce disease and death and to stop or significantly slow the spread of the disease;
- to allow the lifting of all distancing measures.

#### Thresholds for action

Triggering large-scale manufacturing and planning of vaccine or therapeutic priorities. As soon as a vaccine or therapy shows promise in key clinical trials (i.e., it has been proven to be safe and also appears to be effective), government should work with industry to begin planning for mass manufacturing, distribution and administration even before approvals, to ensure that there will be a sufficient supply for mass distribution and obtain a final regulatory approval by ensuring that the manufacture of other vaccines (seasonal

influenza vaccine, mandatory infant vaccines) will not be affected.

Triggering for switching to mass vaccination.

Once the availability of a vaccine or therapy is able to meet the demand, vaccination can be expanded beyond priority groups and then to mass vaccination, which must be planned with industry and the private sector.

### Necessary steps in phase III.A

#### Production of vaccines or therapeutic products

Once a safe and effective vaccine or therapeutic product has been licensed, it must be rapidly manufactured on a large scale.

Giving priority to vaccines or therapeutics — when supply is still limited. Guidelines should be transparent and explain the rationale for priorities, with a phased approach that expands to other priority groups as vaccine availability increases.

Mass immunization or therapeutic distribution — when supply is abundant. The government should create a national plan on how mass immunization will be carried out throughout the country. This plan should determine who will administer the vaccines, where the vaccines will be offered, and how data on the number of vaccinations will be collected, as well as any adverse effects of the vaccine. Compensation to vaccine developers and manufacturers should also be considered.

Global implementation of vaccines and mass vaccination. France must continue to work with WHO and global vaccine organizations such as GloPID-R, CEPI and Gavi, coordinating their efforts and stimulating research on innovative vaccines (phase 1), as well as with national leaders and industry to (a) develop vaccines (b) test them (c) produce them, and (d) plan how higher-income states will help other countries (especially low- and middle-income countries) to procure vaccines and implement mass vaccination. This support will be critical to controlling the virus globally and saving lives around the world, as well as reducing the impact that future waves of the pandemic could have on national populations.

Serological studies to determine population immunity. One of the key elements in assessing the prevalence of the population at risk is the fraction of the population that has recovered and is protected against re-infection. If a sufficiently large fraction of the population has become immune, either by natural recovery or by vaccination, the remaining constraints can be removed.

### Phase III B: in the absence of a vaccine, a voluntary and selective acquisition strategy of herd immunity

Faced with an epidemic spreading so rapidly, with an agent so contagious but as little known as COVID-19, the only possible response by countries unprepared for this type of event, such as France, was the almost generalized containment of populations. Other countries in Europe, such as the United Kingdom, the Netherlands and Sweden, have tried with varying degrees of success and consistency to initiate herd immunity by advising only physical distancing and

voluntary confinement to the most vulnerable individuals. Thus, although Sweden [7,8] has closed neither its schools nor its businesses, its hospital system seems to respond to the influx of serious cases, and the observed death rate does not appear to be fundamentally different from that of France. The strategy for France would be to acquire group immunity through selective and controlled contamination with a lower risk.

## Objectives

Based on the analysis of the data now available on the great disparity in the dangerousness of contamination by COVID-19:

- to identify and to quantify low-risk populations, region by region, integrating the effect of population densities and let them return to a normal life on a voluntary basis;
- to identify high-risk populations for separation from previous ones and a more sustainable selective quarantine;
- to calculate the acceptable risk of the degree of contamination of the low-risk population so as not to saturate hospital services,<sup>25</sup> nationally and region by region;
- to monitor the contamination rate of the low-risk population by representative surveys and lift the containment of at-risk individuals once the rate is sufficiently high.

## Thresholds for action

Short-term unavailability of an effective and safe vaccine or too long a period of time for the population to be vaccinated.

## Necessary steps in phase III.B

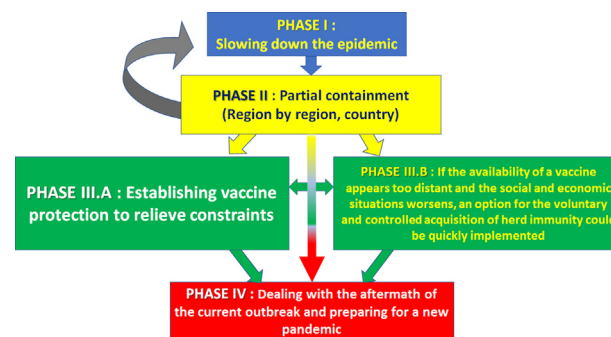
As a preliminary step, to conduct a survey by serological analysis of a representative fraction of the entire French population (children and adults) who have been in contact with the virus in order to deduce the infection and mortality rates according to the characteristics of the populations: age, sex, co-morbidity factors, genetic traits, population density, etc.

To carry out an extensive viral study (looking for mutations in the virus) in the case of isolated re-emergence of infection.

To have available therapeutic in order to mitigate the effects of the virus on infected persons.

To explain this strategy which, in the end, will limit the number of deaths and will allow a better management of the media by the political power in order to obtain a total collaboration of the population.

To determine population immunity and the timing of the end of the epidemic through serological studies.



**Figure 4** Transition to Phase IV and overall pattern of exit from COVID-19 infection.

## Phase IV: follow-up and preparedness for a new pandemic

As shown in the figure below, phase IV actually starts after phase II, but will be enriched by the potential phase III prospects in phases III A and III B. The short and medium-term consequences of phases II and III are as follows (Fig. 4).

### Treating the physical effects

The end of phase III, the return to normal life, will not be the end of the COVID-19. Indeed, in a significant number of subjects, sequelae will persist, many of which remain to be assessed in terms of severity and duration. We are beginning to know which organs will remain affected.

The main localization in the acute phase of the disease is the pulmonary alveoli and, more specifically, the pneumocytes within them. The “cytokine storm” accompanies the response to pneumocyte aggression. In addition to this, pulmonary embolisms related to coagulation disorders must be added. It is very likely that sequelae will persist in the form of pulmonary fibrosis with its usual complications of superinfection and hypoxia leading to respiratory and cardiac insufficiency.

The tubular epithelial cells of the kidneys may be, like the pulmonary pneumocytes, the target of the virus. The result is acute renal failure, which is not, as initially thought, functional in relation to hydro electrolytic disorders, but organic with necrosis of the tubular cells, often irreversible, and thus progressing to chronic renal failure. This will result in the need to resort to haemodialysis for an indefinite period of time.

Brain damage: the simplest forms are anosmia and taste loss, which fortunately mostly regress: damage to the cranial nerves, especially the olfactory with infection of the olfactory lobe; damage to the thalamus and brain stem. These lesions may also be the consequence of thromboembolic syndrome or cerebral anoxia related to acute respiratory failure. There are also cerebral lesions detected by electroencephalography, which sometimes determine a frontal syndrome with cognitive disorders and memory loss. These disorders will require a long rehabilitation. More exceptionally, acute encephalitis leading to rapid death has been described.

The cutaneous symptomatology is very diverse, ranging from acrosyndromes to drug and urticaria rashes. They are

<sup>25</sup> Cf. e.g. the mathematical analyses in references [9] and [10].

attributed to bleeding disorders and are expected to be transient. It is not yet known whether anticoagulant therapy will need to be continued.

### Treating the psychological sequelae

Psychological follow-up for health workers and EHPAD staff who have been on the front line in tense areas will be necessary.

### Anticipating the future

The current pandemic has revealed serious gaps in the pandemic preparedness of our country, in fact all western countries, in good standing with countries that had not been exposed to previous SARS-CoV and MERS-CoV type epidemics. COVID-19 will not be the last public health emergency to threaten our societies. Significant investments must be made in scientific, medical and public health infrastructures to prevent, detect and respond to the next emerging infectious disease threat. A hospital organisation based on the flexibility of its structures, as opposed to the current organisation based on sometimes compartmentalised specialities, will have to be thought through so that it can be implemented rapidly if necessary in the future. This will require a considerable relaxation of regulatory constraints and a reduction in the administrative burden of hospital management. The human and social sciences will also have to grasp this new context of a post-pandemic world where a return to normality will not be the return to the past norm, particularly in our Western societies, with political, economic and behavioural challenges. From this point of view, the systematic wearing of masks and physical distancing will become reflexes, as in Asian countries, on the eve of, for example, a new epidemic of the same nature.

Better coordination of biological-health research. In parallel with the so-called immediate actions of phase II, research in biology and health must be strengthened, particularly in terms of coordination and strategy:

- to establish a single steering structure, led by the Life Sciences and Health Alliance (AVIESAN), which is in charge of coordinating calls for research projects, particularly those of the PHRC, ANR, ANRS, their evaluation, and the allocation of resources, including those for cohort management, based on feedback from the REACTing consortium, which has demonstrated its operational efficiency. The programmes will address the major issues raised by the pandemic: epidemiology, clinical forms, prevention, pathophysiological mechanisms, phenotype/genotype relationships, risk factors including chronic diseases, treatments, vaccines, diagnosis, digital health, human and social sciences, health economics, ethical principles in times of pandemic, etc.;
- to develop a specific programme in artificial intelligence to support digital health: diagnosis, patient monitoring, telemedicine, decision support, modelling: epidemiology and therapeutic strategies;
- to pool existing infrastructures: population cohorts, biobanks, health data hubs, analytical platforms;

- to foster innovation: supporting healthcare start-ups with long-term R&D, which implies adapting regulations, funding and public-private partnerships in specific areas, including: diagnosis, patient monitoring, telemedicine, decision support, population-based sampling and clustering, modelling: epidemiology and therapeutic strategies;
- to establish a strategy and means of communication to inform citizens about research, therapeutic and diagnostic advances, ethical and regulatory aspects; insert educational elements in the curricula of primary and secondary schools to explain what research in biology and health is, particularly on the occurrence and management of epidemics;
- To put in place a genuine European strategy to respond to the health challenges, whether infectious or non-infectious, to which our societies may again be exposed in the future. European coordination of the debate on major health problems, downstream and in connection with research, will have to ensure the relevance of the European research fabric and its coordination with the industrial fabric in order to allow the development of coordinated strategies for epidemiological monitoring and, within deadlines which may be urgent, strategies for the development of biological tests, vaccines and targeted therapeutics, similar to what is being done in other fields, such as aeronautics;
- to increase the vigilance of zoonoses, develop large-scale modelling of infectious diseases and vaccines against new viruses within a few months. Zoonoses are transmissible to humans either directly (hunting and consumption of wild animals) or indirectly through previously contaminated livestock or domestic animals. Increased vigilance is necessary with the support of veterinary schools, which implies strict control of the importation of live animals and edible meat, as well as the search for viral or bacterial infection in wild animals found dead;
- to provide infectious disease modelling that plays an important role in public health decision-making. However, it proved to be deficient at the international level during this pandemic, with forecasts at excessively wide confidence intervals providing little guidance on policy. In order to better manage this crisis and try to prevent the next one, it is essential to develop on a large scale the mathematical modelling of epidemics based on information from public data,<sup>26</sup> drug consumption, numerical data from serological and virological tests and scans;
- to provide, in response to COVID-19 and in preparation for the next health threat not previously identified, an ambitious goal at national, European and international level so as to rapidly develop medical countermeasures for new or unknown threats within months, not years. A specific strategy, programmes and funding will be needed. This strategy should include support for flexible manufactur-

<sup>26</sup> A company scanning with artificial intelligence methods of official and unofficial sites in all languages was able to extract from the noise the signal of an emerging epidemic in China before official announcements and from air traffic to predict its expansion locations (<https://www.academic.oup.com/jtm/article/27/2/taaa008/5704418>).

ing capacity to increase production worldwide in case of emergency.

## Disclosure of interest

The authors declare that they have no competing interest.

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