Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Two waves and a high tide: the COVID-19 epidemic in France

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Sixteen months have passed since the first cases of Coronavirus disease (COVID-19) were identified in Wuhan, China [1]. By the end of April 2021, the pandemic has already caused the death of at least three million people worldwide, and despite the spatially heterogeneous deployment of 10–20 vaccines, the global incidence is reaching new heights, often driven by the evolution of variant strains exhibiting increased contagiousness or immune evasion [2].

Analyses of incidence [3] and genomic sequence [4] data indicate that the first epidemic wave started in France in the second half of January 2020. In this country, COVID-19 has already claimed more than 100,000 lives, which is unfortunately in line with models that estimated the potential mortality in the absence of sanitary measures in hundreds of thousands of deaths using fatality ratios from the early stage of the epidemic [5]. This health burden is further increased by the critical care aftermath and post-acute COVID-19 syndromes [6].

The COVID-19 epidemiological history progressively diverged between European countries after Spring 2020. With estimates of 4000 daily new cases after 8 weeks of firm lockdown [3], France experienced an epidemiological "honeymoon" during the summer. Instead of seizing this opportunity to durably control the epidemic, many non-pharmaceutical interventions were lifted and the incidence resumed upwards at the end of July, foreshadowing – in a textbook deterministic way – a second wave whose containment was mainly addressed in October 2020 with belated nationwide measures, even though the benefits of an early and territorialised response were already documented [3,7] and applied in other countries. Besides, the underestimation of the within-school transmission risk and the alleviations related to the Christmas holiday season caused the second lockdown to be neither strong nor long enough to reduce the incidence below 5000 daily positive tests, as planned initially. From then on, France stood out in the management of its epidemic by maintaining a substantial level of circulation and hospital occupancy, described as a ‘‘high plateau’’, through nevertheless socially restrictive measures such as 6 p.m. curfews. This intermediate level of control (insufficient to strongly reduce epidemic burden, but still requiring important sacrifices from the population) led to a high mortality and was maintained in 2021, despite the documented risks originated from the B.1.1.7 variant of concern’s increased contagiousness [8]. With less than 20% of relative cumulative incidence, only 5% of first vaccine injections but more than 3500 COVID patients in intensive care units (ICUs) as of the 1st of March 2021, France was forced to implement a third lockdown on the 3rd of April, which included three weeks of school closure (of which two were regular holidays) and relative mobility freedom during the day compared to the first lockdown. The epidemiological timeline, from the ICU capacity strain viewpoint, is depicted in Fig. 1.

The effective reproduction number R (*i.e.*, the number of secondary cases per infected individual averaged over a cohort of infectors contaminated a given day) estimated from hospital time series after three weeks of lockdown was 0.95 ([0.93–0.96] 95% confidence interval, after averaging estimates from the 23rd to the 29th of April 2021), while the first and second lockdowns managed to bring its value below 0.8 [9]. That ten cases contaminate on average nine others in early April 2021 instead of eight in early November 2020 might appear marginal but the exponential nature of the respiratory disease propagation amplifies these numbers: instead of halving daily incidence, conventional medicine hospitalisations, and ICU admissions in two weeks, it is necessary, as of late April 2021 and all other things being equal, to wait four times longer. Furthermore, the median age of the 6000 COVID-19 patients in ICU in April 2021 has dropped by three years compared to 2020 [10], which means they are experiencing longer stays [11]. Therefore, the resumptions of interventions that were deprogrammed several weeks ago to accommodate the rebound (particularly in the Ile-de-France and Hauts-de-France regions) will likely be spread out over a longer transition period.

Based on this current situation, we explore several scenarios for the near future using our COVIDSIM model [3]. Without any non-pharmaceutical interventions relaxation (not even school reopening), we would have to wait for mid-June 2021 to bring the ICU COVID-19 occupancy back below 3000 patients, a threshold that was targeted and reached to lift the second lockdown (Fig. 2A). Note that these trends account for an increase in vaccination coverage following official projections of vaccine shipments. Furthermore, the model makes several favourable assumptions, such as an 80% decrease in transmission and risk of critical illnesses from the day of the first injection, as well as perfect post-primary infection immunity.

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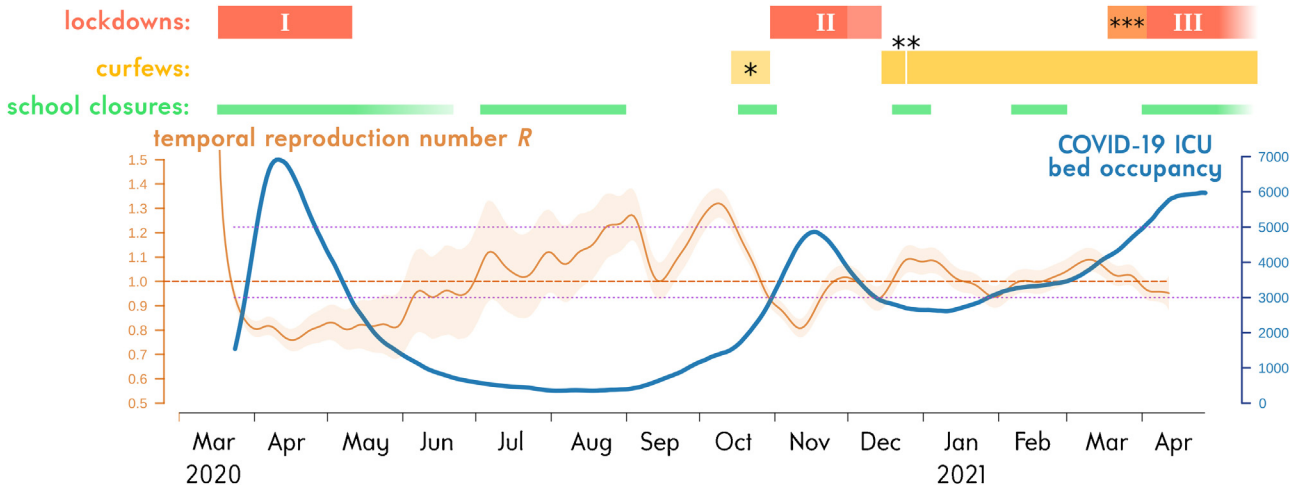

Fig. 1. Timeline of the French COVID-19 epidemic (March 2020–April 2021). The thick blue curve represents the nationwide 7-day rolling average number of COVID-19 patients in ICU. The thin orange curve corresponds to the smoothed 14-day ([3]) shifted mean temporal reproduction *R* estimated ([9,19]) on daily nationwide COVID-19 hospitalisations, along with its 95% confidence interval (orange shaded area). The purple dotted horizontal lines shows a key ICU capacity threshold highlighted by health authorities (3000 COVID-19 patients) and the pre-pandemic French ICU capacity, ca. 5000 beds. The dashed orange line represents the $R = 1$ threshold under which the epidemic is under control. The upper bars indicate epidemiologically relevant periods such as school closures (in green), major curfews (in yellow; *: localised; **: Christmas eve easing) and lockdowns (in orange; ***: localised and partial). Hospital data are from *Santé Publique France*.

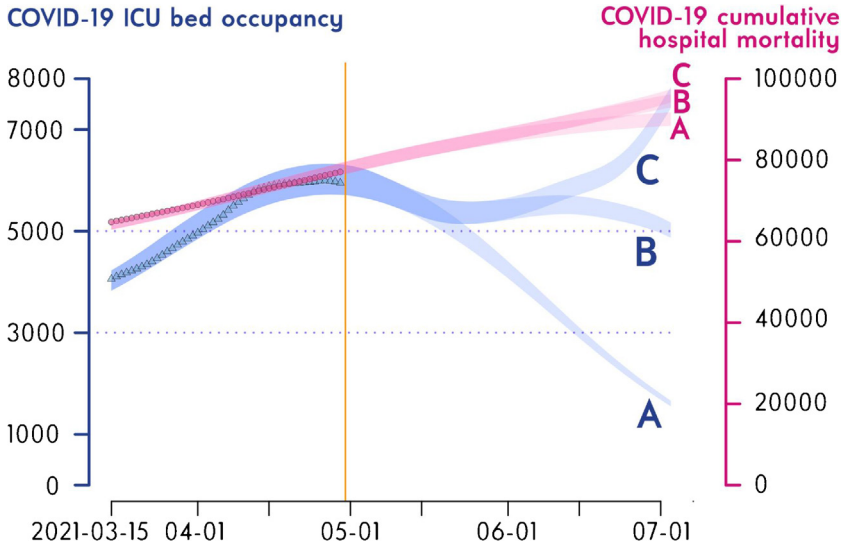

Fig. 2. COVIDSIM projections of the French COVID-19 epidemic following the third lockdown lifting. (A) No lockdown lifting (*statu quo*, assuming the same contact rate as infered from the 5th to the 29th of April 2021). (B) Transmission increase following the easing of restrictions such that $R = 1.04$ on average between the 4th of May and the 10th of June, with a contact rate on the 10th of June equal to that of October 2020. (C) Transmission increase following the easing of restrictions such that $R = 1.08$ on average between the 4th of May and the 10th of June, with a contact rate on the 10th of June greater than that of October 2020 by 10%. Simulated scenarios are based on data available up to the end of April 2021 and included vaccine rollout. The blue and pink shaded areas correspond to the range spanned by 95% of the simulations for respectively COVID-19 ICU patients nationwide and cumulative hospital mortality (nursing homes are excluded from the model for they exhibit distinct spreading patterns). The turquoise triangles and red circles are the rolling 7-day averaged data counterparts. The purple dotted horizontal lines show a key ICU capacity threshold highlighted by health authorities (3000 COVID-19 patients) and the pre-pandemic French ICU capacity, ca. 5000 beds. The orange vertical line represents the day the simulation was performed.

Unfortunately, it is reasonable to doubt the realisation of such an optimistic scenario because, according to the official schedule of measure lifting, several transmission situations (schools, workplaces, or restaurants) will be allowed again by the end of May. Lockdowns, which have psycho-socio-economic, educational, and cultural negative effects that everyone acknowledges, have two objectives: to limit ICU capacity strain (short-term) and regain epidemic control (medium-term). If the former has been achieved, it is highly likely that second-line levers (test-trace-isolate) and vaccination alone will not be sufficient to lower the high incidence in the weeks following the lifting of the measures. Summer weather is often invoked as a factor unfavourable to transmission, but in metropolitan France, since the period preceding the first lockdown, the reproduction number *R* reached a peak in August 2020 that was only equaled once later (two months later) (Fig. 1). Furthermore, the potential collective enthusiasm resulting from the reopening of conviviality places after 7 months of closure calls for vigilance concerning the epidemic trajectory in the coming weeks.

Given the uncertainties inherent to some degrees of freedom presiding over the dynamics (*e.g.*, population mixing following the gradual return to school, curfew alleviation, vaccination of the youngest, prevalence and virus phenotypic evolution) and the time window considered (more than a month), it is impossible to make

reliable predictions. However, valuable insights can be gained by comparing two remarkable scenarios that differ from the transmission increases on the 19th of May and the 9th of June, the key dates of the easing of restrictions (reopenings of shops, cultural places, restaurants, bars, gyms). In the first case (Fig. 2B), assuming a return to the average contact rate inferred in mid-October 2020 (when bars were closed, however), the incidence would increase slightly before beginning a slow descent mainly thanks to the increase in vaccine coverage. However, this would not allow the prevalence of COVID-19 patients in critical care to drop below 4000 until July. In the last case (Fig. 2C), if the contact rate is only 10% higher than in October, the epidemic could experience a rebound that would again expose ICUs to high-capacity strain levels as early as mid-June, after a nadir at the end of May around 5000 COVID-19 patients.

These projections show how fragile the situation in metropolitan France is. The latest (third) national lockdown was insufficient and belated, but the current situation also results from a series of health policy decisions made since last summer that appear to be driven by two main goals: (*i*) minimise the number of lockdown periods, rather than the number of days under lockdown (therefore resulting in a sub-optimal stop-and-go approach with high socio-economic cost and low public health benefit), and (*ii*) delay the onset of strict non-pharmaceutical interventions by betting on a weather effect or an unrealistic vaccine rollout. By not strongly reducing the incidence before relying on vaccination coverage to control the epidemic (as sought by the United Kingdom, Portugal, or Denmark), France exposed itself at the end of this spring to a tide whose consequences might go beyond the sole sanitary outcome of the COVID-19 spread [20]. In addition, the population has been heavily burdened by the decisions taken since January (or even before) and the resulting attrition will make the control of the epidemic in the coming months even more costly.

Over the medium term, the vaccination coverage corresponding to the theoretical collective immunity threshold, corrected for the increased transmissibility of the variant of concern's (but leaving aside the possible immune escape of B.1.351 (V2) and P.1 (V3)) and the relative cumulative incidence, is of the order of 70%,*i.e.*, more than 90% of the French adult population. While this could be achieved by the end of August based on the planned doses shipments, the increase of vaccination coverage in the youngest age groups may be slower, given their lower risk of complications and the gradually improving sanitary situation. Without extending the vaccination to the population under eighteen, the nationwide control of the epidemic would require keeping some level of non-pharmaceutical interventions [12]. Furthermore, epidemiological modeling at high spatial resolution suggests that this vaccine coverage issue is likely to be particularly acute in large urban areas because their group immunity thresholds are higher than that of small cities and rural territories where population density and connectivity to the rest of the habitat are lower [13]. The risk of local circulation in areas with low vaccination coverage (younger or more reluctant population) should also not be neglected, as illustrated by the measles outbreaks in The Netherlands [14].

In the long-term, epidemiological modelling shows that, based on the SARS-CoV-2 age-dependent infection fatality ratio and on realistic hypotheses regarding immunity to coronaviruses (in particular a lasting protection against severe disease but not against potential reinfection), this virus could cause epidemics resembling that of mild seasonal respiratory viruses in a matter of years [15]. However, each new infection constitutes an additional opportunity for SARS-CoV-2 to mutate [16], now from a genetic background that has already been proven to be more contagious [8]. Above all, this picture could be complicated by the shift in selective pressure on the virus population associated with the increase in natural, but also potentially vaccinal immunisation. The emergence of immune escape variants that need not be less virulent [17] and could circulate in auxiliary hosts [18] further underlines the importance of monitoring and controlling the epidemic at a global scale using non-pharmaceutical interventions and vaccination.

Conflict of interest

The authors have no competing interest to declare.

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