

## Short Communication

# May Vaccines Select SARS-Cov-2 Variants More Readily Escaping Immunity - An Analysis of Public Data

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### 1. SARS-CoV-2 lethality ciphers must be put in perspective with respect to those of former plagues

Vaccines are good and helpful of course. Millions of lives have been saved since Edward Jenner discovered the principle of vaccine against smallpox, a disease that killed up to 30% of the infected people and left survivors with severe sequelae. Louis Pasteur has made an unmatched breakthrough in the history of medicine with his invention of the anti-rabies vaccine, as the bite from a rabid animal meant certain death (100% lethality). Thanks to vaccines, smallpox has been eradicated and rabies rarely kills [1, 2], if the vaccine is administered early enough before symptoms onset.

Governments of Western countries have forgotten the lethality of these plagues, the meaning of the ratio benefit/risk and that these types of viruses have considerably slower mutation rates than coronaviruses. For pox viruses, the

mutation rate is  $(1.7 \text{ to } 8.8) \times 10^{-6}$  nucleotide substitutions/site/year [3], 1000 times slower compared with SARS-CoV-2, allowing for efficient vaccines. In contrast, with respect to registered symptomatic cases, SARS-CoV-2 lethality in France is only 2%, and the mortality was barely around 0.09% along 2020. The very low probability of dying, all ages confounded, has created an unprecedented situation in many respects. Despite considerable knowledge in vaccine science and industrial power, it took almost a year to produce anti-SARS-CoV-2 vaccines and, 6 months after, vaccination is far from being completed in Western countries.

## 2. Comparison of ongoing death toll curves among Western countries suggests exhaustive vaccination may not be the adequate response to Covid-19

Comparison of the death toll between UK, France, Italy and USA curves (Figure 1) allows us to distinguish three radically different situations that raise questions on the validity of exhaustively vaccinated populations : (1) the death toll in the UK has been nearly zero for the last 4 weeks with, on 21 May 2021, a level of full vaccination (2 doses) of 31.9% only ( $56.6\% \geq 1$  dose); (2) in France, with full vaccination lagging behind at a level circa 14.1% (only elderly people being massively vaccinated), the death toll has continuously dropped these last four weeks; and (3) in the USA, the country that is the most advanced in massively vaccinating its population with 38.6% of fully vaccinated people ( $48.8\% \geq 1$  dose), the death toll is plateauing.

What does that mean? Vaccination was started in late December 2020 in both the UK and the USA but, unlike the UK, the curve of the death toll in USA is not zeroed yet, and seems to hang on a slightly decaying plateau. We recall that the frontiers of UK are closed since Christmas 2020 with a drastic quarantine that may last up to 21 days if two SARS-CoV-2 PCR tests are not negative at 8 days interval during the first 10 days. In addition, any UK resident leaving the country without permission will receive a fine of 6000 pounds. France, on the contrary, since the beginning of the pandemic in January 2020, has never closed its frontiers. As a result, since the summer 2020, many variants were introduced in France generating several epidemic bounces. Since vaccination has started at a very low pace in late February and early March 2021 (on March 8, only 3% of the population was fully vaccinated with 2 doses) it is clear that the profile of the death toll indicates that the bounces are weaker and weaker independently of the vaccination status. France has been either confined or on a strict curfew continuously since the 27 October 2020. The death toll curve shows collective immunity progressively installing in the population, as the virus variants spread slowly despite the lockdown measures. At the IHU Méditerranée in Marseille, among 40 000 patients with PCR confirmed Covid-19, only 100 cases developed the disease a second time (Didier Raoult, public communication [4]). Of note, with a similar geographical situation, with open frontiers, and similar confinement status, Italy exhibits exactly the same epidemic profile as France.

Finally, the USA keeps also its frontier closed but, unlike in the UK and France, a very large proportion of its population (ca. 40%) is overweight to some degree, with as a corollary diabetes and high blood pressure. These comorbidities have certainly a negative impact on the death toll but may not explain the plateau observed, unless the vaccine has no protective effect on them.

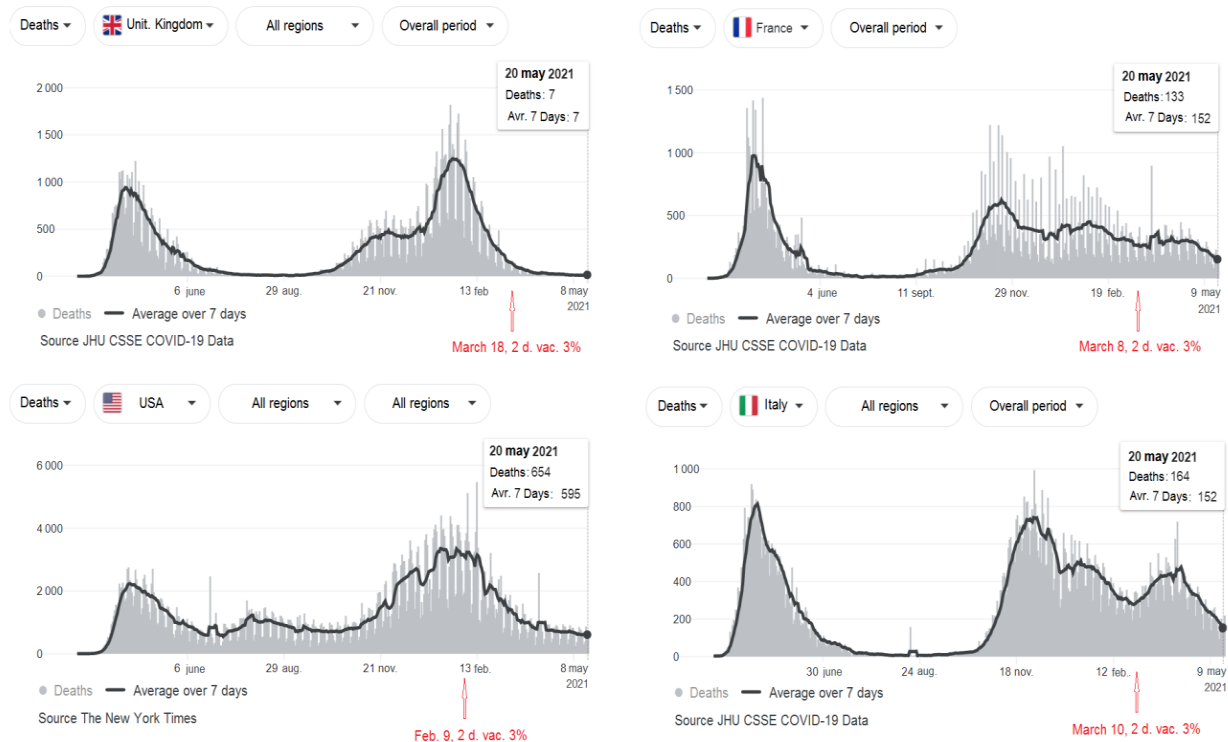


Figure 1

### 3. Could have SARS-CoV-2 vaccine trial generated new variants more readily able to escape vaccine immunity?

When exhaustive vaccination is not needed or when it does not fully protect a population, can it participate in the selection of new variants? This question has been vigorously swept away and deemed irrelevant by the French Health authorities. Nevertheless, variants selection is a very well known immune escape mechanism, especially for viruses with relatively high mutation rates such as influenza viruses and corona viruses [5]. Vaccines against these viruses may favor the apparition of new mutants that can spread more easily since they do not compete with the strains decreased by the vaccine. Then, large sections of the whole population have not yet been exposed to the original virus, which creates immunity voids readily available for the new variants to become dominant.

The binding domain of the SARS-CoV-2 spike protein to the ACE2 receptor is the location where most adaptive mutations take places. It is also the part of the virus targeted by vaccines. Remdesivir, which hampers the correct functioning of the viral polymerase, has been shown to cause accelerated SARS-CoV-2 viral evolution in an immune-suppressed, recurrently ill, patient treated 4 times with it [6]. “Amino-acid changes were predominantly in the spike gene and the receptor binding domain (RBD), which make up 13% and 2% of the viral genome, respectively, but harbored 57% and 38% of the observed changes”. It is also reported that known variants can be selected artificially in laboratory [7]. “Using an *in vitro* evolution technique with a lentivirus construct bearing the SARS-CoV-2 receptor-binding domain (RBD) of the spike protein towards ACE2 has resulted in the more contagious mutations, S477N, E484K, and N501Y, to be among the first selected, explaining the convergent

evolution of the “European” (20E-EU1), “British” (501.V1), “South African” (501.V2) and “Brazilian” variants (501.V3)”. All these observations are proven scientific facts indicating that SARS-CoV-2 is subjected to adaptive evolutionary pressure upon treatment constraint or imperfectly immunizing vaccines.

Generally, avoiding variants escape in SARS-corona viruses vaccination is one of the two key issues in elaborating safe and valid vaccines [8]. The second is to prevent an aggravated course of the disease in individuals who have been immunized by the vaccine [28]. A research article in PLOS Medicine published in 2006 reported that “For an effective immune prophylaxis in humans, broad coverage of different strains of SARS-CoV and control of potential neutralization escape variants will be required. Combinations of virus-neutralizing, non-competing mAbs (monoclonal antibodies) may have these properties.” By indicating that vaccines elaborated against SARS-CoV-2 would not prevent from developing the disease or being contagious, the vaccine manufacturers have clearly admitted that they could not entirely satisfactorily tackle both issues.

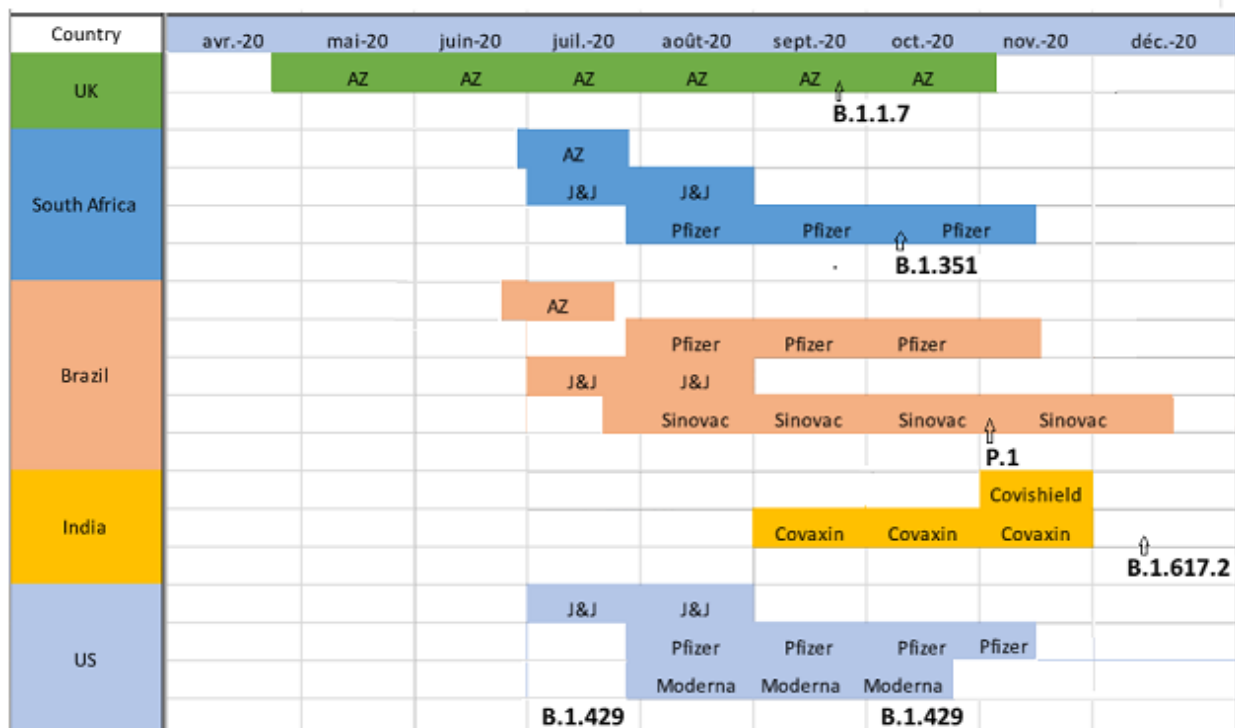
Taking all these observations into consideration, the question whether the vaccines used have generated new variants is relevant. From diverse public sources, we have reconstructed the history of the vaccine trials conducted worldwide and established their chronology with respect to the dates of first appearance of the main variants of concern (VOC) [9-14]. Result are gathered in Table 1a and 1b and Figure 2. We observe that VOCs have emerged in the countries where large trials were conducted. The emergence occurred towards the end of the vaccine trial periods, or shortly after.

**Table 1a:** Dates and Countries of first occurrence of VOC

VOC	Name (Nexstrain)	First Detected	
		Country	Date
B.1.1.7	20I/501Y.V1	UK	20-Sep-20
B.1.351	20H/501.V2	South Africa	8-Oct-20
P.1	20J/501Y.V3	Brazil	3-Nov-20
B.1.617.2	20A/S:478K	India	10-Dec-20
B.1.427	20C/S:452R	US	July-2020

**Table 1b:** Covid-19 vaccines brands vs countries where trials took place

Country	Vaccines	Vaccines Trials Date	Number of Volunteers
UK	Astra Zeneca	April 23 2020-Nov 4 2020	11750
South Africa	Astra Zeneca	June 28 2020	2096
	Pfizer	July 27 2020 - Nov 14 2020	372
Brazil	Astra Zeneca	June 23 2020	10002
	Pfizer	July 27 2020 - Nov 14 2020	1145
	Sinovac	July 21 2020-Dec 16 2020	12396
India	Covishield (AZ)	October 31 2020	1600
	Covaxin	September & November 2020	26180
	Sputnik V	NA	100
US, Peru, Chile	Astra Zeneca	February 17 2021	32449
US	J&J	July - Aug 2020	805
	Pfizer	July 27 2020 - Nov 14 2020	14460
	Moderna	July 27 2020 - Oct 23 2020	30420
Argentina	Pfizer	July 27 2020 - Nov 14 2020	2883
Total			146658



**Figure 2:** Gantt diagram of trials time periods and VOC emergences

### **3 Discussion**

The Californian VOC 20C is an exception since it was first isolated in a single sample before the vaccine trials conducted in this area. But the vaccine could have helped its selection over other stains in a vaccinated cluster of individuals. Data on escape variant researches, possessed by pharmaceutical companies, could shed light on whether observation of these coincidental events reveal a causative link with the tested vaccines. Countries like UK, South Africa, Brazil, India, Russia and USA are places where most participants were enrolled in vaccines trials. With large numbers of participants, the suboptimal immunity generated by trialed vaccines will be increased. Reports posted at Forbes, in February 2021, indicate that both Novavax and Johnson & Johnson vaccines showed a substantial drop in efficacy in South Africa.

Brazil is the country where, proportionally to the population, the largest number of participants were included in trials. It is also the country where the largest number of variants have been detected (up to 72). Wang et al. 2021 reported VOC B.1.1.7 and B.1.351 have extensive mutations in the spike protein that could lead to antigenic changes detrimental to mAb therapies and vaccine protection [15][16]. It is of equal concern that another variant known as P.1 or 501Y.V3 is increasing rapidly in Brazil (population 212.5 million people) and spreading far beyond. P.1 contains three mutations (K417T, E484K, and N501Y) at the same RBD residues as B.1.351. N501Y is shared among viruses in these three lineages (VOC of UK, SA and Brazil); while this mutation may confer enhanced binding to ACE2; its antigenic impact is limited to a few mAbs with no pronounced effects on the neutralizing activity of convalescent plasma or vaccine sera.

In Manaus, Brazil a second wave of infection due to P.1 is sweeping through a population that was already 76% seropositive due to prior infection in the spring of 2020, as reported by Sabino et al. 2021 [17].

In India the virus variant combining a double mutation, corresponding to both the South African and California variants, emerged in the western state of Maharashtra between December 2020 and March of this year, and is now dominant [18]. Despite intriguing coincidence between the loci of vaccination and subsequent variant emergence [19], one explanation put forward is that “patients previously infected with SARS-CoV-2, but who did not have a severe case of COVID-19, might get even sicker if they are infected” [20] This explanation is weakly convincing in the light of the extremely low rate of measured re-infection rate in France, where numerous highly infectious variants have circulated [4]. It was estimated that India by the end of 2020 had 1/3 of immunity [21] and the pandemic was strictly under control until 20 February 2021, before massive vaccination started in the Maharashtra state. The journal Nature has put forward population mixing, moving and traveling as the explanation of this variant burst [18].

The largest absolute number of participants in Covid-19 vaccines trials was in the USA. The main mutation in the California variant (L452R) is found also in the Indian B.1.617 variant. The Californian strain, CAL.20C, was first observed in July 2020 in only one out of 1230 samples from LA county and then not detected again until October [22]. It is probable that this variant, though undetected between July and October, was still present in rare persons,

symptomatic or not, and that the large vaccine trials and campaigns favored its emergence, simply by selective pressure. There is a contradiction between, on the one hand, the claims by the authorities and manufacturers that vaccines are highly efficient [23] and, on the other hand, that new variants may abrogate their efficacy [15]. They perfectly know that the antibodies generated are not broad enough and may thus induce suboptimal immunity in vaccinated populations.

Perez, 2021, hypothesized that mRNAs of the Modern and Pfizer vaccines will result in a low functionality of the spike vaccines because they were designed by seeking a greater stability [24]. They present sequences doped with CG which, as soon as they are inserted into the human host, will, paradoxically, seek to mutate, like SARS-CoV2 variants, towards CG  $\Rightarrow$  UA forms, in order to improve their stability and lifetime in the cells. According to this principle, differences in stability and shelf life of the two mRNAs vaccines are predicted. Synonymous codons optimization, using different strategies, may lead to different quantities of antibodies generated due to difference in mRNA propensity to be processed by ribosomes and eliminated by cells [25].

In fact, the underlying question of Perez is what happens when an mRNA vaccine is administered to an asymptomatic carrier of SARS-CoV-2? Is it possible that the vaccine mRNA recombines with the natural strain of the virus? If this happens, the harmonically unbalanced artificial spike protein mRNA, integrated in a viable virus, may accelerate new variants production. His study suggests that UK, California, South Africa and India variants have the probable folding of the spike protein mRNA in the form of a "hairpin", which can strengthen the cohesion and the lifespan of this mRNA. For the Indian B.1.617 variants, Perez's work shows a greater stability and lifespan of messenger RNAs, which could lead to a greater infectious character of these variant genomes [26].

#### **4. Concluding Remarks**

It is unclear that vaccines are necessary to stop the pandemic and it cannot be ruled out that vaccine trials may have had a contribution in emerging VOC (UK, Brazil, South Africa, India) escaping vaccine immunity [27] and in emerging variants of interest VOI (Russia) [14] due to suboptimal immunity and greater pressure given to the virus. Thus, vaccines may have selected new variants in the pools of volunteers participating in trials across the world and contributed to prolong the Covid-19 pandemic. Further investigations and complete data disclosure on the conducted trials is advocated.

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