

The emergence, dynamics and significance of SARS-CoV-2 variants

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Text

Part of the difficulty in scientific understanding of the SARS-CoV-2 epidemic is the lack of knowledge about viral evolution. Thus, this goes back to the definition of viruses that opposed those who saw only bioactive molecules (Stanley, Nobel Prize for Chemistry in 1946) and those who saw them as small living organisms, such as Burnet (Nobel Prize for Physiology or Medicine in 1969). In reality, apart from controversies regarding their definition, viruses are variable adaptive elements having mutations adapted to the setting, specializing in a given host and capable of being selected under the selection pressure of environmental parameters [1,2]. In practice, viruses are part of our ecosystem and evolve accordingly. Simplifications regarding epidemiology, therapy or vaccination are likely to be dangerous. The most known example has been that of influenza virus, for which new variants appear regularly [3]. The fight against viruses does not consist in fighting against a fixed object but against a moving target.

RNA viruses are the major entities involved in emerging diseases because of their gigantic zoonotic reservoir [4] and their variability, each replication generating a hundred times more mutations than for a DNA virus or any living entity with a DNA genome [2]. Under these conditions, RNA viruses constantly accumulate mutations [1,2]. For SARS-CoV-2, this was neglected for several months and we first reported the existence of variants in early September 2020 [5], three months before the term variant was adopted in December 2020 for the Alpha variant [6]. Since 2021, the WHO has defined variants of interest and of concern [7]. We defined the variants as clades

whose emergence is caused by the appearance of an original combination of at least five mutations including at least 30 members [8]. The variant that we called Marseille-4, for example, a subclade of which presents one of the hallmarks of epidemic viruses that is the knock-out of the ORF8 gene as found in the Alpha variant [9], has been detected in more than 10,000 patients in our laboratory with more than 7000 genomes obtained [8,10]. This illustrates its considerable spread. Overall, the molecular surveillance carried out in our laboratory led to genotype the virus from more than 44,000 patients and to obtain the viral genome for more than 25,000 of them, and this made it possible to show that what had been commonly called new “waves” were in fact new epidemics linked to new variants that succeeded or overlapped. Mutations occurred approximately every 14 days. Each new micro- or macro-epidemic was likely to be associated with the accumulation of approximately 8 mutations and vanished over a duration of about 4 months [8,10], and it was replaced by epidemics with new lineages. Interestingly, the incidence of almost all the variants exhibits a Gaussian-like distribution [8,11].

SARS-CoV-2 variants have been detected worldwide with differences regarding their distribution and incidence according to the country (Fig. 1). The number of variants observed in a country is related to international human circulation [8,12]. Thus in Marseille we notably identified [13] a first variant that was native from Africa [14], then an autochthonous variant from a French mink farm [15], a variant that we named Marseille-2 [5] originating from Spain [16], the Alpha variant originating from England [8], two variants (Marseille-501, or Pangolin lineage A.27, and Beta) imported from the Comoros [8,17], the Delta variant originating from India [18], the Mu variant imported from Colombia [8], then the Omicron variant originating from South Africa [19]. Recently, a variant we named IHU possibly originating from Cameroon was involved in a small epidemic in a city near Marseille [20]. Interestingly, several variants neutralized coding sequences by stop codons [9,10]. Many

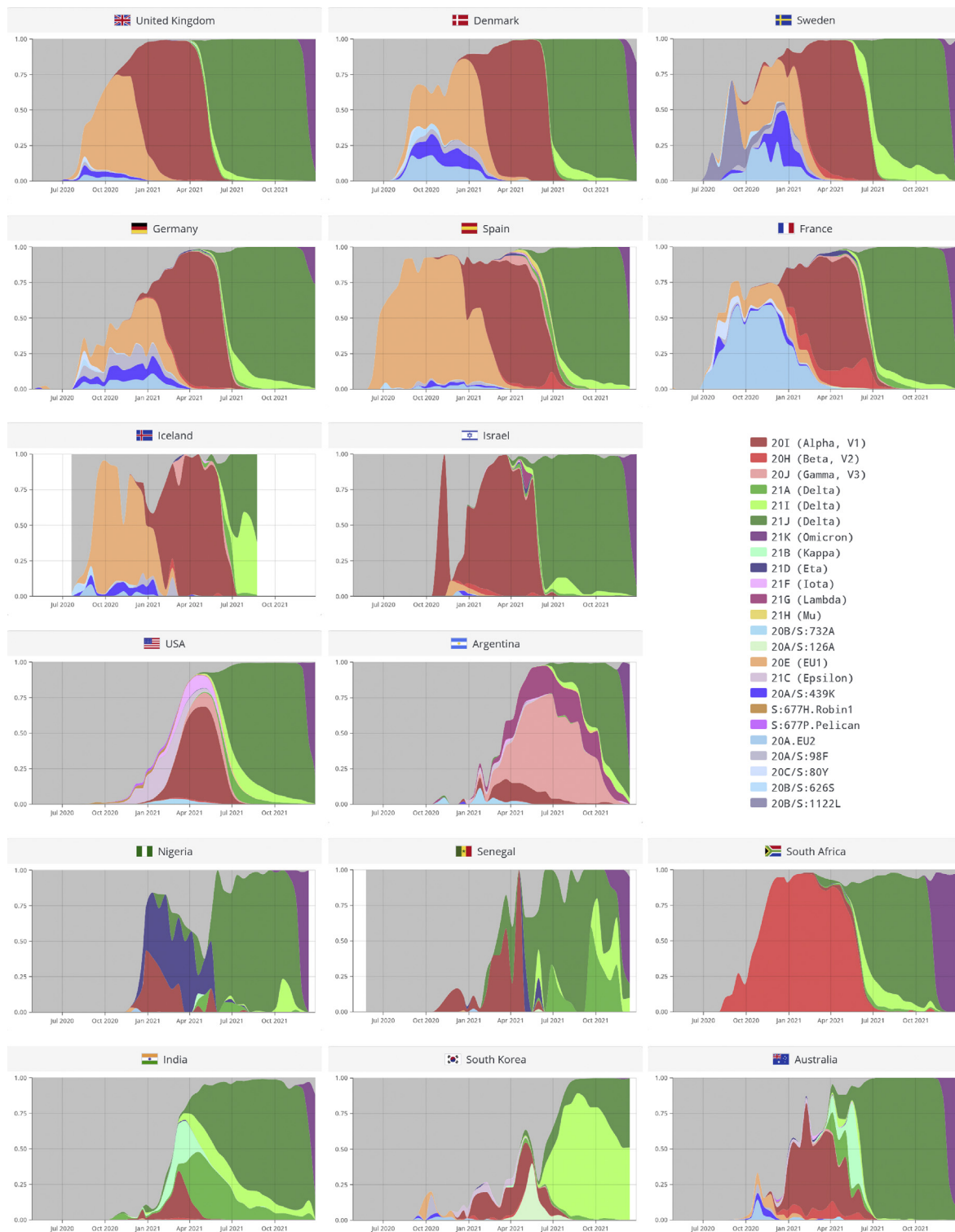


FIG. 1. Distribution and incidence of major SARS-CoV-2 variants in several countries on the five continents. The figure is comprised by screenshots from the CoVariants website (<https://covariants.org/>) [11,29]. Graphs show the proportion of total number of sequences over time that fall into defined variants. Sequence counts are binned into 2-week intervals.

mutations of these variants occur in regions of the spike protein described as targeted by neutralizing or facilitating antibodies and may decrease the efficiency of monoclonal antibodies or vaccines [7,21–23]. The Omicron [24] and also the Delta variant [25] are good examples of this. Finally, variations of the spike protein can change the entry route of SARS-CoV-2 [26] and therefore are likely to change the susceptibility of the virus to several anti-infectious agents, in particular those that act on the phagolysosome such as Hydroxychloroquine [27]; this could explain a decreased susceptibility of a variant to this drug [28]. However, since the Omicron variant was reported to enter via endosomes [26], it is expected to be extremely susceptible to agents that manipulate the phagolysosomal vesicle.

Author contributions

Study conception and design: D.R., P.P., P.C. Writing of the first draft of the manuscript: D.R., P.P., P.C. All authors approved the final manuscript.

Transparency declaration

D.R. is a scientific board member of Eurofins company, a founder of a microbial culture company (Culture Top), and was a consultant for Hitachi High-Technologies Corporation, Tokyo, Japan from 2018 to 2020. P.C. does not have any competing interest to declare. P.C. does not have any competing interest to declare. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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