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

Variants, vaccines and vaccination passports: Challenges and chances for travel medicine in 2021

Since its onset, the pandemic of SARS-CoV-2/COVID-19 has radically changed the travel medicine landscape resulting in significant air travel restrictions. In this editorial we broach the complexities of variants, vaccines and vaccination passports and their complex interplay with travel medicine and how these elements will change travel medicine practice.

The threat of variants: During December 2020, an unexpected increase in the number of COVID-19 cases in the United Kingdom and South Africa was found to be associated with the emergence of the new SARS-CoV-2 variants of concern (VOC) 501Y.V1 (B.1.1.7) and 501Y.V2 (B.1.351), respectively. Such variants had mutations (N501Y) at the receptor-binding domain of the spike protein associated with an apparent increase in transmission of the virus of 40%–70%, and possibly also with an increased clinical severity. In January 2021, other VOC began to be reported, including from Brazil [P.1 (501Y.V3)], USA, France, Italy, Denmark and others [1–3]. This increase in VOC resulted in new restrictions on air travel to and from these countries.

SARS-CoV-2 variants add extra complexity to the pre-travel risk assessment and advice. Consideration needs to be given to the clinical implications and country-related responses to emerging variants but is compounded by the lack of genomic sequencing capacity and real-time detection of VOC globally.

Clinically, the primary considerations are the transmissibility of the variant, the severity of the disease it causes, its ability to be detected by diagnostic tests, its susceptibility to therapeutic agents, and its ability to evade natural or vaccine-induced immunity. The 501Y.V2 (B.1.351) and the P.1 (501Y.V3) have the E484K mutation with additional concerns that this affects the ability of the virus to be recognized by antibodies [4].

For the traveller, VOC adds a material but unquantifiable risk. Traveller choices depend on many factors, including their risk tolerance, but the additional uncertainties posed by VOC may make the traveller reconsider their travel plans. For example, travellers need to be aware of the increased likelihood of infection and the implications this may have particularly concerning public health measures associated with illness abroad. For a vaccinated traveller, the concern that the predominant circulating virus strain at their destination may be less responsive to vaccine will need to be discussed.

Equally, the destination's approach to variants needs to be considered; since early 2020, short notice travel restrictions and strict quarantine measures have been commonplace. The recent identification of VOC in Denmark, UK, South Africa, and Brazil has similarly resulted in many countries introducing travel bans, enhanced surveillance, mandatory hotel quarantine, or a combination of measures to prevent importation of VOC [5]. COVID-19 has resulted in continually evolving challenges for those advising travellers, and mutation of SARS-CoV-2 is yet another consideration that adds to the complex and evolving situation.

Where is travel medicine with regard to COVID vaccination? Several vaccines against COVID-19 are currently available worldwide which vary in efficacy and quantity available. Prioritisation of population targets also varies from country to country. Should travellers to or from areas with high incidence of COVID-19 also be prioritised for vaccinatination? For most currently available COVID-19 vaccines, a minimum of three weeks is recommended between two doses and the same vaccine should be used for the booster dose. In addition, it is recommended to avoid other vaccine injections in the weeks prior to vaccination against SARS-CoV-2, which expands the period during which theoretically no other vaccine should be given to around six to seven weeks. All of these constraints make it challenging to integrate the COVID vaccination into the traditional 'travel vaccination schedule', especially if the destination is in a tropical area or if mandatory vaccinations are indicated. Moreover, the duration of protection of COVID vaccines is currently unknown. Mutations of the spike protein as the principal virus target complicate the situation further, and vaccine evolution will have to keep pace with virus evolution.

Some rays of hope - the West African Ebola virus disease (EVD) outbreak (2013–2016) and the ongoing COVID-19 pandemic provide proof-of-concept that accelerated vaccine development is possible under exceptional circumstances, markedly shortening the time lapse between outbreak onset, preclinical testing, clinical trials and vaccine registration [6,7]. The path to SARS-CoV-2 vaccine development is, to date, breathtakingly brief, with two mRNA vaccines (and a third one half-way through a pre-registration phase 2b/3 trial) being the first representatives of a novel platform originally envisaged for onco-vaccine development but now the front runner in the COVID-19 vaccine race in terms of efficacy. This technology could also be harnessed for travel medicine. Over the past couple of years, a range of mRNA vaccines successfully underwent preclinical (amongst others - malaria, Ebola) [8] and even early phases of clinical testing (amongst others - rabies, Zika, chikungunya) [8], thus encompassing a wide range of vaccines of potential interest for tropical medicine and travel medicine. It is to be expected that the safety profile and efficacy of the SARS-CoV-2 mRNA vaccines will act as a strong booster, to further mRNA vaccine development.

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1. Can we adapt antigen sparing approaches to the SARS-CoV-2 vaccinations?

Paucity of antigen amount available to protect large populations in resource-limited settings is a challenge, and techniques to reduce the necessary amount of antigen required to achieve long-lasting protection are for obvious reasons also of interest in the field of travel medicine [9]. There has been a considerable research into fractional dose antigen administration via the intradermal (ID) route as compared to the routine intramuscular or subcutaneous routes. A recent systematic review and meta-analysis demonstrated non-inferiority of ID administered vaccines at a statistically significant level for influenza, rabies and hepatitis B; with some other antigens administered via the ID route (e.g. Yellow Fever) yielding results trending towards non-inferiority but without reaching statistical significance due to a paucity of adequately powered clinical trials [10]. Another approach to antigen saving attracting research over the recent past years and ongoing are dose-sparing vaccination regimens, for example, against rabies (pre-exposure prophylaxis, PrEP [11] or post-exposure prophylaxis (PEP) [12] as well as the skipping of a booster immunisation dose (as with yellow fever [13]). These are all scenarios that could be investigated for SARS-CoV-2 vaccines in a travel medicine setting.

2. Human challenge models as potential accelerators in travel medicine vaccine development

SARS-CoV-2 vaccines could also be evaluated using human challenge models. In the field of (chemoprophylaxis and) vaccine development relevant for travel medicine, a limitation in trial design is very often that large numbers of travellers would be required to determine prophylactic efficacy, further complicated by difficult-to-determine individual exposure to the target organism given lack of highly sensitive biomarkers correlating with exposure. Human challenge studies have been vital in pushing research on a number of infections including typhoid and malaria [14]. Media reports now describe that a new UK study will use the "human challenge" approach to assess second generation COVID vaccinations and to evaluate whether current vaccines protect against variants [15].

3. The Holy Grail of vaccination passports

The introduction of 'vaccination passports' is now a topic of hot debate. Such passports could mean that those carrying proof of immunisation might be able to travel freely. This would facilitate the re-opening of air travel and assist in reviving national economies. The concept has obvious appeal. Vaccination passports differ from 'immunity passports' which involve providing evidence of past infection. 'Immunity passports' are currently not recommended by either ECDC or the WHO as the parameters and duration of immunity post infection are undefined, antibody testing is costly, they may incentivise exposure to infection and there are issues regarding re-infection and susceptibility to new strains. 'Vaccination passports' are different in that they incentivise vaccination, and COVID-19 vaccines and vaccination schedules have documented correlates of protection. Some governments in Europe have already announced that international travellers who have proof of vaccination are exempt from official border restrictions and quarantine - Romania has become the first European country to abolish testing and quarantine requirements for incoming foreign visitors, provided they have been adequately vaccinated against SARS-CoV-2. Denmark is developing a digital vaccine passport that will facilitate travel, allow privileges and ease restrictions. Estonia has pledged to drop quarantine requirements for travellers with proof of vaccination. This situation has fuelled intense debate in the European Union.

Vaccination certificates are not new. In travel medicine, we are familiar with the need for proof of yellow fever vaccination for specified destinations and proof of meningococcal immunisation for those travelling to the Hajj or proof of polio vaccination in certain circumstances. The revised International Health Regulations (IHR) in 2005 expanded the scope of internationally important diseases from three (cholera, plague and yellow fever) to include all "*events which may constitute public health emergencies of international concern*" [16]. The former 'International Certificate of Vaccination or Revaccination Against Yellow Fever' was revised to the 'International Certificate of Vaccination or Prophylaxis' and includes documentation not just on yellow fever but on any vaccination or prophylaxis. So, is a framework already in place for COVID vaccination documentation? No, this is a quagmire:

There are the issues of the wide palette of COVID vaccines and the correct documentation of vaccination. Yellow fever vaccination is a single shot, using WHO pre-approved vaccine, and is administered in regulated centres with defined conditions for vaccine administration and documentation. Currently the mass COVID vaccine roll-out, the need in many cases for two doses, the variety of vaccines, and the absence of guidelines for homogenous documentation constitute a very different landscape. Then there is the question of the efficacy. It is not known if any of the currently available vaccines will prevent those who have been vaccinated from transmitting the virus. This may differ according to the specific vaccine administered as well as according to circulating strains in each country. Are all vaccines equal? Would documentation of a receipt of a vaccine not licensed in the country being visited be adequate? If not, equity issues could be compounded. The duration of immunity provided by vaccines and the appropriate validity of a passport following vaccination is another unanswered question – the idea of 6 months is being touted, but this may encourage 'richer' nations to offer boosters before poorer more vulnerable populations have had the chance to receive even a first round of vaccines. There is also a side issue of fake COVID vaccine currently receiving media attention.

Vaccination passports are associated with equity issues given current restrictions to vaccine access, resulting in potential exacerbation of discrimination. Since there is not yet universal access to the vaccine, limiting individual freedom on the basis of vaccine access would disadvantage poorer nations and minority groups where vaccine rollout is likely to be slower.

If these passports are introduced, it could also be interpreted as making the vaccine compulsory, since those who will not be vaccinated will be deprived of their freedom to travel.

The ethical counter-argument [17] relates to the restriction of free movement for individuals, potentially including those vaccinated who may be at low risk of transmitting COVID-19 and therefore pose little or no public health risk. The 1950 Convention for the Protection of Human Rights and Fundamental Freedoms is a legal tool that defends individual rights and freedoms in all signatory countries, stating that everyone has a right to freedom of movement that cannot be restricted but 'for the prevention of the spreading of infectious diseases'.

Another key question: should the vaccination passport be digital or paper-based? Should it be an updated version of the International Certificate of Vaccination or Prophylaxis, potentially as a digital record? Issues of concern are falsified or counterfeit vaccine certificates. Privacy plagues the digital approach, and digital solutions combining health data and identification could exclude those who do not own a smartphone or access to stable internet connections. Personal health data in newly devised digital systems may also become gatekeepers to workplaces, schools, and other spaces and this opens vast bioethical debate.

What does seem clear is that a country-by-country approach will not work as a global solution. The World Health Organization (WHO), currently does not endorse proof of vaccination or immunity for international travel as a condition of entry. WHO is however working on Smart Vaccination Certificate technical specifications and standards to support harmonised processes for inclusion of the COVID-19 vaccine into in an updated version of the International Health Regulations. This will include language that should an IHR requirement of proof of COVID-19 vaccination for international travellers be introduced in the

future, such vaccines must be approved, or prequalified, by the WHO [18]. Regardless of any possible future digital technology, COVID-19 vaccination status should be recorded in parallel on the existing paper International Certificate for Vaccination and Prophylaxis. The yellow book or card is still key for international travellers for some time to come. Any future digital vaccination certificate will additionally have to support the needs of national immunization programmes; while ensuring that digital technologies do not engender or perpetuate inequities.

Furthermore, vaccination passports will not allow the lifting of recommendations for mask wearing and social distancing on flights. And while it seems inevitable that vaccination passports, in some form, will evolve, the road to this outcome needs careful navigation. What is certain is that travel medicine has changed utterly and that practitioners will need to stay updated on the challenges and chances of this evolving situation.

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