Title: Border control and SARS-CoV-2: an opportunity for generating highly policy-relevant, real-world evidence

Running title: Border control and SARS-CoV-2: generating policy-relevant evidence

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Highlight

We propose a study type that would contribute to the evidence base related to border control measures. Over a study period during which arriving travellers are quarantined, repeated testing and/or screening at regular intervals would provide real-world data on the relative and combined effects of various screening and testing measures.

Since the beginning of the SARS-CoV-2 pandemic, international travel has changed drastically as governments have used a range of travel-related measures aiming to slow and contain the growth of the pandemic. Given the unique nature of the risk as well as the policy landscape associated with international travel, it is important that research specific to the travel setting be conducted and made available to decision makers.[1] We recently completed the first update of a Cochrane systematic review on international travel-related control measures. [2](Burns, forthcoming) We applied systematic and rigorous methods to search for, identify, appraise and synthesize evidence on, among other measures, border control measures comprising screening (e.g. presence of cough, fever, and/or risk factors), testing (e.g. RT-PCR) and quarantining of international travellers (e.g. 14-day government mandated quarantine); altogether, we identified thirty-three studies assessing such measures. The conduct of this review provides us a unique perspective regarding the current state of the evidence, including where filling research gaps could support more informed decisions. In this comment, we highlight one such gap related to the evidence on border control measures.

Many studies conducted to date to evaluate these measures largely fall into one of two broad types: observational studies and mathematical modelling studies.

The observational studies generally involve the reporting of observational data on border control measures, including, for example, measures implemented in conjunction with evacuation flights from one country to another[3, 4] or as part of an overall strategy at international ports of entry.[5, 6] One such study assessed control measures implemented at Bahrain International Airport, comprising the RT-PCR testing upon arrival and subsequent fourteen-day quarantine of all passengers.[5] By providing data on how many travellers tested positive on arrival, as well as how many tested positive by the end of the quarantine period, such a study provides valuable empirical data on the effectiveness of testing upon

arrival – i.e. it describes how many cases testing upon arrival was able to detect, as well as, importantly, how many cases testing upon arrival missed.

The mathematical modelling studies generally aim to simulate the effect of border control measures, some assessing a single measure, but most assessing a range of related measures combined.[7, 8] This generally involves predicting or assuming how much travel occurs between two countries, the probability of a traveller from the departure country to be infected with SARS-CoV-2 and the sensitivity of the assessed measures; from this, the study can estimate the number and proportion of infected individuals the relevant measure(s) would detect. One such study modelled the probability of releasing an infectious case from the EU or the US into the UK with a quarantine period of three, seven and fourteen days, both with and without one or two PCR tests.[7] Such a study models the relative effectiveness, not only of one specific measure, but of a range of more and less stringent border control measures.

Although informative, each of these two types of studies represented by these examples is also limited. The observational study provides information on the effectiveness of testing upon arrival; what proportion of cases would have been detected if travellers had been tested on day three or seven, or if testing had occurred only in symptomatic individuals, we cannot know. The modelling study, like all modelling studies, is built on multiple assumptions; where assumptions about the travel patterns between two countries, the prevalence of infection among travellers or the performance of border control measures are not based on real-world data, results may poorly reflect the reality of implementation.

We contend that a third type of study, which based on the evidence base identified through our systematic review has yet to be conducted, would utilize the strength of the two described above to

provide empirical, real-world data on a range of border control measures. Two important requirements include that i.) the study be conducted in a real-world port of entry and ii.) all individuals be quarantined long enough, and tested often enough that most cases will be detected. Regarding the latter, a 14-day quarantine period should be long enough and testing directly before or upon arrival and at days 7 and 14 should be often enough to detect most cases; some travellers may still become infectious after day 14, however this number is likely to be small.[9] With many countries already conducting testing and requiring long-term quarantine periods for travellers, meeting these requirements is not infeasible. Thus, for a given cohort of travellers, this isolation and repeated testing while in quarantine allows for determining how many travellers become infected with SARS-CoV-2. This study period also, however, provides an opportunity to evaluate the relative and combined effects of various screening and testing measures – i.e. to assess how many cases the respective measure(s) would have detected and missed, if each had been the primary measure in place. A schematic for such a study, which would allow for the assessment of symptom screening and/or PCR testing upon arrival and/or at day three, seven and eleven, is shown in Figure 1. This is just one example, and in principle numerous measures, timelines and combinations could be assessed commensurate with the local contexts; e.g. requiring a negative pre-flight test, followed by testing on days two, five and ten could be assessed in the same manner.

[Figure 1 here]

While Figure 1 illustrates the basic study design, specific design aspects could be added or adapted to provide a more informative evaluation. Repeated testing of those who have already tested positive, along with the monitoring of the cycle threshold (Ct) as an indicator for viral load,[10] would facilitate an estimation of the remaining days of infectiousness for each individual with regard to different release days, e.g. if an infected traveller were released on day three or on day six, how many days of infectiousness would this traveller carry into the community? Genome sequencing of all cases would allow the investigation of whether they are truly imported, or whether infection occurs while in transit or

due to the quarantine itself. Genome sequencing, additionally, could help establish the risk of importing genetic mutant forms of the virus from abroad, as well as the contribution of border control measures to mitigating this risk. As the options and requirements for measures to be implemented evolve, the frame of this study type can readily be adapted; the comparative effect of rapid antigen tests, for example, which have been less studied, could also be assessed. Similarly, an evolving policy context can be reflected; as vaccines become increasingly available, such a study could help assess how this moderates the impact of border control measures. Finally, monitoring of implementation would enable a better assessment of and explanation for what does and does not work, as well as opportunities for improvement.

Of course there are other important considerations in the planning and conduct of such a study. It would require significant resources and logistical planning, and close collaboration between researchers and decision-makers, as well as those implementing and enforcing the intervention. Importantly, the well-being of the traveller would be of utmost importance – it would be critical to ensure that all participants clearly understand any risks, and that they are not overburdened. Some countries, such as Australia and New Zealand, in the aim to suppress the SARS-CoV-2 virus, have kept stringent border control measures in place for almost the entire pandemic. Such countries may continue to sharply restrict travel, and may be uninterested in adapting their strategy. Many other countries, however, such as those in Europe and North America, will likely aim to balance the risk of case importation with the required resources, economic and societal consequences of border controls, as well as the benefits of at least partially reestablishing international travel. The type of study we propose, would provide nuanced real-world data on border control measures, and could help decision-makers to balance these aspects in deciding upon an 'optimal' strategy. If similar studies were conducted in various settings globally, the lessons learned and knowledge gained would be invaluable for navigating international travel during the SARS-CoV-2 pandemic.

Authors' contributions

Jacob Burns conceptualized and wrote the first draft of this comment. Ani Movsisyan, Eva Rehfuess and Jan Stratil provided input, and Jacob Burns subsequently finalized the manuscript. All authors were substantially involved in the conduct and writing of the systematic review upon which this comment draws.

Conflict of interest statements

Mr. Burns reports grants from the German Federal Ministry of Education and Research, and grants as well as other engagement with the World Health Organization, outside the submitted work.

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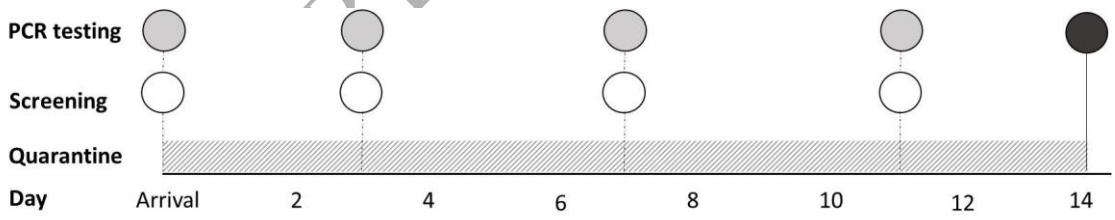

Figure 1: Schematic illustrating the various measures and combinations of measures that could be evaluated over the 14-days after arrival. Gray circles indicate PCR-testing, white circles symptom screening, the black circle indicates the final test before release, and the gray striped area represents the quarantine