COVID-19: Air Travel, Public Health Measures and Risk

A Brief Summary of Current Medical Evidence

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Introduction / Purpose of the document

This summary is intended to provide the scientific foundation to assessing risk related to air travel during COVID-19. As the pandemic continues, and as vaccination programmes are under way in most countries, the considerations behind decisions regarding travel will continue to change. This document aims to provide an up to date evaluation of those considerations, based on available scientific evidence. It should be read with attention to the date of the latest revision, as the state of knowledge will continue to evolve rapidly.

Part 1: Risk

Risk Assessment Frameworks

- An assessment of risk needs to consider both likelihood and consequence. Risk cannot be avoided but the risk of a process can be balanced against the benefits, and against the risks of the counterfactual, to assist those who are tasked with making decisions. In particular the risks of international travel must be balanced against the risks of maintaining restrictions which include economic, employment, social and health risks, and which may not be effective in the long term [Grout, Lai Yang]. Part of the risk assessment process for a country will be determining how much risk, related to importing cases of COVID-19, can be accepted; this in turn may depend on the state of the public health system to detect (contract tracing, testing facilities) and manage (isolation and health care system) those cases. It may also be influenced by political considerations in each state.
Flight-associated transmission

- Information on in-flight transmission is incomplete, but several published papers have examined instances of probable and possible flight-associated transmission. Documented instances are very few [Bae, Chen J, Choi EM, Eichler, Eldin, Freedman, Hoehl, Khanh, Murphy, Nir-Paz, Pavli, Schwartz, Speake, Swadi, Thompson HA] compared with the total numbers of travellers, and while it must be assumed that these reports greatly underestimate the actual incidence, there appears sufficient evidence to conclude that this risk is low, particularly when supplemented with the added protection from masks [Gurbaxani], and particularly when compared with other indoor environments. The papers referred to describe instances of probable/suspected transmission associated with flight: some had little or no evidence of flight-related transmission compared with other origins [Eldin, Murphy, Schwartz] and most described flights with 1 or 2 presumed secondary cases in close proximity to the index case [Bae, Chen, Hoehl, Pavli]. In the more recent studies the transmission was supported by whole genome sequencing [Choi EM, Eichler, Speake, Swadi].

- Since the start of the pandemic many protections have been added to commercial air travel aimed at preventing transmission [Khatib], and collectively have been referred to as the "Public Health Corridor" [ICAO]. One of the most obvious changes on-board is the implementation of mask wearing by passengers. There were few instances of suspected transmissions on flights when masks were worn by passengers [Nir-Paz, Swadi, Thompson MG, Eichler]. Universal wearing of face coverings appears to be an effective protection against spread via aerosols [Cheng]. Of all the presumed secondary cases in these published studies, half were from just three flights [Bhuwan, Khanh, Speake, Toyokawa], at a time when mask-wearing by passengers was not yet normal practice. This finding is in keeping with other studies showing that the majority of spread in the population originates from a small minority of cases [Chen PZ2, Yang Q]. The mechanism in those unusual cases with multiple secondaries is likely to be related to airborne carriage of fine aerosols [Chen, Davis, Fennelly, Klompas]. One of the flights had partial mask wear, and analysis suggested significant protection in those who wore them throughout [Toyokawa].

- An analysis of 18 UK-bound flights (in early 2020 before masking) with 55 primaries [Blomquist] found five possible secondaries, all on four of the flights, with a rate of 3.8% amongst those contact traced. Other investigations confirm the flights having been undertaken by highly infectious passengers without evidence of transmission to nearby passengers [Böhmer, Draper]. A review of 18 studies of flight-associated transmission [Rosca] concluded that data do not permit any conclusive assessment of likelihood and extent. The review enumerated 273 primaries and 64 possible secondaries, with an attack rate varying between zero and 8.2% in studies with a good follow-up rate.

- In terms of risk the airline cabin compares favourably with other indoor environments [Hadei, Rivera-Rios] including restaurants [Lu], buses [Shen, Tsujihashi], churches [James, Kateralis], gymnasiums [Jang], and high-speed trains [Hu]. The mechanism presumed in such indoor environments is aerosol transmission [Allen, Kateralis]. There is even a well-documented transmission in a quarantine facility where the only contact between primary and secondary (linked by genome sequencing) was non-simultaneous opening of their room doors to the same corridor [Eichler], once again pointing to suspended aerosols. It has been suggested [Allen] that the characteristics of airline cabin air supply (rapid air flow, increased air changes, and HEPA filtration) should be applied to these other indoor environments, and separately that carbon dioxide monitoring could be used as a measure of adequacy of air circulation [Burridge]. Prior to COVID, reports of flight-associated transmission of respiratory viruses were relatively unusual [Baker, Kenyon, O’Connor, Olsen] and some related to events with failure of air circulation [Moser].

- In the aircraft environment, although some earlier studies (pre-COVID) pointed to the possibility of spread particularly across rows [Chen, Olsen, Wang&Galea, Wilder-Smith], supporting evidence for low transmission risk in flights comes from modelling with computational fluid dynamics [Davis, Davis, Pang] and a large experimental study using actual aircraft cabins [Kinahan], subsequently largely
confirmed [Netherlands]. A modelling study reinforces the gradient of risk with distance from source, suggesting lower relative risk with the "empty middle seat" [Dietrich] but does not account for mask wear, and conflicts with the more complex analysis above [Davis]. Finally, note that other factors may be relevant, and of particular note is that speech, particularly loud speech, may be an underestimated determinant of aerosol transmission [Andersson, Coleman], and one which could be relevant to the apparent low risk of on-board spread.

- Travel encompasses an entire journey including not only aircraft but also surface transport (road/rail etc) and airports. Any discussion of air travel, or of its risk, needs to have all of those elements considered. In some of the studies above, it is not clear at what part of the journey transmission may have occurred.

- Most of the studies referred to above were undertaken prior to the appearance of more transmissible variants, which are discussed in part 3 of this report. In the absence of evidence to the contrary, it must be assumed that the chance of flight-related transmission of variants could be increased proportionately. This of particular interest with respect to the Delta/B.1.617.2 variant for which there is evidence of much greater viral load in those infected. A study of a flight into Hong Kong including mostly Kappa/B.1.617.1 and just two Delta/B.1.617.2 cases has been published as a pre-print but information in support of possible flight-related transmission is sparse [Dhanasekaran].

- Even if transmission during travel was completely eliminated, the much more challenging problem to solve is the risk of importation of cases which are incubating at the time of travel [Pana]. The main focus of this document is on factors relevant to importation risk. This is the risk to be weighed by countries in seeking to allow increased international travel, one which in many countries is managed with mandatory quarantine after arrival [Kiang].

- The surface route of transmission has been assessed as very low when compared with droplet and aerosol routes – and dealt with by standard cleaning and disinfection practices. A US CDC report [CDC] suggested that “the risk of fomite transmission can be reduced by wearing masks consistently and correctly, practicing hand hygiene, cleaning, and taking other measures to maintain healthy facilities” and a major systematic review found little evidence of surface transmission [Onakpoya].

- Measures to reduce aerosol transmission during travel have been widely discussed and documented in the “Take-off Guidance” produced by ICAO CART (Council Aviation Recovery Taskforce). Other potential developments include advances such as UV treatment of air [Eadie].

Part 2: Vaccinations and immunity – effect on risk

Impact of vaccines on severe disease/mortality, and transmission

- There is abundant evidence from clinical trials and real-world data that vaccination reliably prevents severe disease, hospitalisation, and death [Corchado-Garcia, Dagan, Juthani, Pawlowski, Tenforde, Vahidy, Vasilieou] – even in the minority who become infected after vaccination [Bernal, Uschner]. What is less clear is the degree to which vaccination can prevent mild or asymptomatic infection – the likely pathway being that viral colonisation of the upper respiratory tract could result in shedding of virus before the immune response has fully been triggered and effected. Even in the scenario of a strong vaccine-mediated immune response [Lustig], a proportion of mild or asymptomatic cases may not be prevented [Bleier]. Therefore, since asymptomatic transmission is an important contributor to transmission [Johansson, Letizia, Oran, Rasmussen, Ren, Sah, Yonker], it is necessary to determine the extent to which vaccination will reduce transmission.
A number of studies have provided results suggesting that vaccination also reduces infections of all severity, including asymptomatic [Amit, Bernal, Chodick, Dagan, Daniel, Menni]. Some specifically demonstrate reduction in asymptomatic infection [Angel, Haas, Jones, Lillie, Lumley, Milman, Pritchard, Regev-Yochay, Sadoff, Shah, Tande2, Weekes], in most cases by a large percentage. Others demonstrate that onward transmission is significantly reduced, looking at data on transmission within families [deGier, Harris, Nordström, Salo, Shah], within residential care communities [Cavanaugh, De Salazar, Monge, Muhsen] or amongst regularly screened employees [Keigher, Swift, Tang]. Modelling also suggests that vaccination of adolescents and children reduces mortality and morbidity across all age groups [Li H, Shiri, Walter], safely.

Efficacy has been studied more extensively with some vaccines (particularly the mRNA vaccines from Pfizer and Moderna, and also the Astra-Zeneca vaccine), than others. There are apparent differences in the efficacy of different vaccines [Abi-Raddad2, Collier AY2, Li X, Montoya, Richards, Sharma, Steensels, Tehrani, Wei] in some trials but not others [Hulme]. There are also differences due to the interval between initial doses [Payne], and evidence of the efficacy of heterologous (mixed) vaccines [Huat, Pozzetto, Sablerolles]. Studies of the Sinopharm [Al Kaabi] and Coronavac [Jara] vaccines also show good efficacy after two doses at preventing death and hospitalisation, with lesser effectiveness at preventing total cases. The first large real-world study of the Gamaleya (Sputnik V) vaccine, in Argentina, showed high effectiveness after the first dose [Gonzalez].

One way to consider the effect on transmission is to model the predicted spread on the basis general efficacy trials [Lipsitch], also suggesting transmission is low in those vaccinated. Another is to look at viral load, which correlates with infectiousness [Marc, Marks]. There is animal evidence that vaccination leads to reduced viral load in the unvaccinated population, and human evidence that those who become infected post-vaccination have reduced viral load [Levine-Tiefenbrun, McEllistrem, Mostafa, Muhsen, Regev-Yochay]. Study of viral culture from the nasal cavity suggests significantly less amongst the vaccinated who become infected, compared with unvaccinated [Brown, Chia, Ke]. However data from outbreaks with the Delta variant have sometimes showed no difference in viral load between those infected who were vaccinated and those unvaccinated, albeit with a faster fall in viral load in the vaccinated [Chia, Kang, Pouwels, Riemersma]. Note that immune response and change may vary with age [Bates, Israel, Moustsen-Helms, Müller, Yang HS]. Antibodies detected in the upper respiratory tracts of vaccinated people, both IgA and IgG [Becker, Mades, Sterlin] suggest a mechanism for reduced transmission. Infection which occurs despite prior vaccination is likely to be associated with a reduction in neutralising antibodies [Bergwerk].

Taken together, these findings point to significant reduction in transmission by those who have been fully vaccinated [Mostaghimi, Richterman]. The question of duration of immunity and the effect of variants are important caveats and are discussed below. Some vaccines perform better than others [Robles-Fontán, van Gils], and this is likely to be a factor considered by countries in permitting international travel.

One group that shows reduced immune response from vaccination is the immunosuppressed [Embi], particularly solid organ transplant recipients [Benotmane, Boyarsky], for whom an additional dose is suggested, along with those treated for haematological cancers and those given any treatment diminishing B cell response.

It is known that asymptomatic transmission is an important contributor to spread [Glenton, Wilmes, Yonker, ZhangXS]. Most of these studies show that the vaccines prevent asymptomatic transmission somewhat less efficiently than symptomatic, therefore it is likely that a high proportion of those “breakthrough” cases occur in a vaccinated community will be asymptomatic [Bergwerk, Gruskay, White]. This observation may prompt consideration of some surveillance testing of vaccinated travellers in communities with a low tolerance for introduced cases – even though they will have reduced chance of onward transmission.
Immunity following vaccination or infection

- Studies point to immunity being established within a few weeks after vaccination [Glatman-Freedman, Gupta] and retained beyond 6 months following vaccination [Barouch, Doria-Rose, Hall, Pegu, Polinski, Thomas]. Immunity is complex, and laboratory studies looking only at antibody production do not tell the full story of immunity which involves cellular and local responses as well [Milne]. Cell-mediated immunity may be maintained even with declining antibody levels [Dolgin, Geers, Goel RR, Tarke]. Immunity following vaccination has been demonstrated in pregnant and lactating women [Dagan2, Collier AY], with reduced infection in those vaccinated and pregnant [Dagan2, Goldshtein] (although a study suggests dose response may be reduced in pregnancy [Atyeo]). Memory B cell response in lymph nodes and peripheral blood show a robust germinal centre response after mRNA vaccination which suggests very long lasting immunity [Mortari, Sokal2, Turner2]. However, many studies have suggested some waning of immunity after some months [Chemaiteelly, Gilbert, Goldberg, Keegan, Levin, Naaber, Public Health England, Suthar, Tang], with seroconversion sometimes demonstrated [Sembajwe]. As well as neutralising antibody response [Khoury], cellular immunity is also important [Gangaev, Lucas] – but there is also evidence of decline in T-cell response [Suthar]. Abundant real-world evidence describes the frequency of “breakthrough” infections in the fully vaccinated [Uschner]. Total infections have also been seen to increase beyond 5-6 months [Cohn, Israel, Keenher2] which has occurred in the context of the Delta variant, and is a combined effect of Delta and waning vaccine effectiveness [Harder, Rosenberg2]. Booster vaccine doses were investigated [Wu], including heterologous [Atmar, Iketani], and introduced, even as others struggled to provide first doses to their most vulnerable. On the basis of initial evidence this was difficult to justify [Krause] but evidence pointed to high efficacy and safety [Atmar, Barad2, Bar-On2, Saig, Sacluk] of boosters.

- Studies have also evaluated delayed second dose [Abu-Raddad, Flaxman], and reduced doses [Mateus]. Using a different vaccine for the second dose from the first, known as “heterologous prime-boost,” has shown strong or enhanced antibody response particularly when the second dose is an mRNA vaccine [Borobia, Barros-Martins, Frias, Groß, Normark, Sablerolles, Schmidt]. This has been studied most with a combination of AstraZeneca and Pfizer [Hillus, Hammerschmidt, Liu X, Nordström2, Pozzetto] but more recently combinations with Sinovac and CanSino [Li2, Saure, Yorsaeng] and various other combinations. Data more recently provide evidence of rapid enhancement of immunity following a third booster dose [Atmar, Bar-On, Eliakim-Raz, Flaxman, Patalon, Yorsaeng2]. There is limited evidence on the boost to immunity in those who contract infection after being vaccinated [Glatman-Freedman].

- There are still questions about the strength and duration of immunity of those who have had documented infections with COVID-19 (but not vaccination), but although immune markers decline [Beaudoin-Bussières, Seow, Wheatley], they may then plateau [Crawford, Marcotte], and evidence is available to suggest good immunity for several months [Ahluwalia, Bilich, Cromer, Dan, Krutikov, Sokal1, Turner1, Wajnberg, Zuo] and even beyond a year [Abbasi2, Eyran, Gaebler, Gallais, Lau, LuZ, Marcotte, Radbruch, Wang&Muecksch]. Additionally, serology studies have shown, in survivors of SARS in 2003, [Anderson DE] persistence of neutralising antibodies to the virus for 9-17 years afterwards, which is of interest because of the viral similarity. Likewise, T-cell cross-immunity from seasonal coronaviruses seems to suggest the possibility of long-lasting protective immunity [Sokal1]. However, looking across all human coronaviruses, decline in immunity with time is common [Townsend]. Immune protection appears to be less in older people [Brockman, Collier DA, Hansen, Weij], and is less following milder [Caniels, Legros] or asymptomatic [Long] initial infections. Some studies [Assis, Cavanaugh2] have shown naturally acquired immunity to produce inferior antibody response to that from vaccination, while others suggest naturally acquired immunity is more robust [Gazit]. Seroprevalence studies show antibodies in significant numbers of those without a history of diagnosed COVID-19 [Vázquez Rivas]; mild [Ogega] or even asymptomatic [Nielsen] infections are capable of generating adequate antibody response, and there has been some evidence of T-cell response in the absence of documented infection [Swadling, Wang&Yang]. Some have suggested that those who have a history of proven infection have reduced priority/requirement for vaccination [Kojima, Ontanon, Weij], or that for them one
dose is sufficient [Anderson M, Angyal, Havervall, Keeton, Pape, Zollner], and it appears that this "hybrid immunity" is superior to vaccination alone [Andreano, Appelman, Ke, Lucas, Shenai], or optimal [Agrawal, Crotty, Eyran, Pape, Reynolds, Shuford, Stamatatos, Zhong, Zollner]. Serial seroprevalence surveys of highly infected communities have shown retention past six months [Dorigatti]. A large review of over 50 studies [Chivese] concluded that around 90% of recovered cases had immunological memory at 6-8 months and low reinfecion risk, although there is potential for important decline later [Townsend]. The effect of variants on post-infection immunity is discussed below.

- There are cases of individuals with proven second infections (with genetically different virus) including some with more severe cases in the second infection, but they remain rare [Piri, Tillett, Qureshi, Vitale] with a tendency to less severe infections the second time. They are more common in older [Wall] and immunosuppressed [Agha, Borobia] people, particularly solid organ transplant recipients and those treated for blood cancers. Second infection is more common with some of the variants, most notably Delta [Mizrahi, Musser]. A CDC study showed better protection from full vaccination than from previous infection [Bozio]. Recovery from infection followed by a booster vaccination has been shown to produce strong antibody response [Anichini, Gallais, Ibarondo, Saiag, Wei] as mentioned above. The reverse situation of breakthrough infection after vaccination has been more recently shown to produce robust immune response [Collier AY3], and this is of importance as it will be a likely pathway for many of the population in the long term.

Vaccine safety

- A high degree of safety has been established for all the approved vaccines, with greatest research available for mRNA vaccines [Agrawal, Klein]. Safety [Kharbanda, Magnus] and efficacy [Collier AY, Dagan2, Goldshleifen] has also been demonstrated with pregnancy and lactation, and vaccination not lead to adverse birth outcomes, or even impaired reproductive performance during in-vitro fertilisation. By contrast, infection with COVID-19 during pregnancy is associated with greater risk of hospitalisation and severe disease amongst the non-pregnant (with further increase in the case of the Delta variant [Vousden]).

- Early in 2021, cases were observed of a rare type of blood clotting disorder, sometimes severe/fatal, in the days after receiving the AstraZeneca vaccine [Greinacher, Schultz]. This has been given various names including vaccine induced thrombotic thrombocytopenia (VITT) and thrombosis and thrombocytopenia syndrome (TTS). Initially these cases were considered not elevated above population rates, but subsequently they were classified as rare side effects of vaccination for the AstraZeneca vaccine [See, Schultz]. The benefit was assessed as outweighing risk in the older age groups, but many countries suspended use of some vaccines in younger age groups (using a variety of age cut-offs) and some suspended use altogether [Karron]. Investigations continue into mechanisms of how this may be triggered by vaccination, such as by induction of antibodies to clotting pathway mediators [Cines]. It is also reported in association with the Johnson & Johnson vaccine, perhaps at lower rates [Klok, Sadoff]. A meta-analysis [Chan] of data from 10 countries points out the low incidence in the elderly, with a clear overall benefit of vaccine, with a higher risk in the younger adults where the risk-benefit ratio may depend on local COVID prevalence; a South African study [Takuva] showed low rates of these complications and others show it is exceedingly rare after the second dose [Klok, Pavord]. The counter-factual risk, of cerebral and portal vein thrombosis following COVID-19 infection is significantly elevated [Taquet2].

- A rare side effect of myocarditis was identified following second doses of the Pfizer vaccine, particularly in younger males [O'Leary]. Several studies show that this is a rare event (estimates ranging around 10-100 cases per million second shots) and usually self-limiting [Diaz, Mevorach, Perez, Shay, Simone, Witberg], and evidence appears to indicate it occurs with the Moderna mRNA vaccine also [CDC3, Gargano, Montgomery, Pepe], but is much more common after infection than after vaccination [Barda, Rosenblum, Singer]. A separate concern has been raised relating to Guillain-Barre syndrome, with early data suggesting this is a rare side effect of the Johnson&Johnson vaccine [Woo], and
subsequently a possible association with the AstraZeneca [Oo] but more common after infection than after vaccination [Patone]. There may be a small increase in incidence of Bell’s palsy after the first dose of Pfizer vaccine but this is yet to be established [Shibli]. With any vaccine, there is a small risk of anaphylactic reaction, and with the Pfizer vaccine this is estimated at around 11 cases per million first doses [Shimabukuro], or around 5 per million for mRNA vaccines in a larger study [Klein]. Vaccination has been shown to be effective in adolescents [Olson, ReisB] and myocarditis risk in this group will be monitored. Consistent with the observed vaccine safety, overall mortality from non-COVID causes was found to have been lower amongst the vaccinated in the USA [Xu].

Part 3: Virus variants – effect on risk

Impact on transmission

- The appearance and proliferation of more transmissible variants of the SARS-CoV2 virus since late 2020 have changed the risk equations somewhat. Currently the variants of concern according to the WHO classification are Alpha/B1.1.7 (first identified in UK), Beta/B1.351 (South Africa) Gamma/P1 (Brazil) and Delta/B.1.617.2 (India), and there is well-established evidence of greater transmissibility in all [Dagpunar, Faria, Faria, Horby, Mascola, Munitz, Tegally, Wall]. In Israel the Alpha/B.1.1.7 variant became the dominant strain in under a month, being significantly more transmissible [Munitz]. The Alpha variant appears to lead to a longer period of infectiousness [Kissler], which may contribute to its increased transmissibility.

- Subsequently the Delta variant proved even more transmissible, and rapidly became established as the dominant variant in almost all of the world. It has been suggested the replication rate is 1000 times higher than that of the original wild-type strain [Li] with a reproduction number (R0) considerably greater, probably in the range 5-6 with greater household transmission [Allen]. Additionally it has been observed that the viral load, in those who are infected with Delta strain despite vaccination, is in fact as great as in the unvaccinated [Acharya, Riemersma] although it appears to decline more rapidly [Chia], and is associated with less viable virus [Shamier]. The more the SARS-CoV-2 virus continues to proliferate, the more likely it is that more transmissible variants will appear and predominate. Reasons for the greater transmissibility of Alpha remain to be determined, one possibility being the characteristics of the spike protein on fusion of the cell membrane, affecting cell entry [Zhang J].

- The Delta variant is not only more transmissible, with a R0 value (reproduction number) estimated at up to 6.4, but also leads to higher viral loads [Chau, Li], with a shorter but more variable incubation period [Li, Wang Y], therefore a shorter serial interval (between a primary case and the secondaries), and additionally a greater likelihood of transmission prior to symptoms commencing [Kang]. Others [Pung] report an unchanged serial interval but increased numbers of secondary cases from each primary. Doubling time is reported as 25 days [Elliott].

Impact on severity

- There was early evidence that variants have slightly greater propensity to cause severe illness than the original “wild type” virus – in particular, in the case of the Beta/B.1.351 and possibly the Gamma/P1. Although there were preliminary indications of greater mortality for the Alpha/B.1.1.7 variant [Davies], other studies did not bear this out [Frampton, Graham]. In the case of the Delta/B.1.617.2 variant studies indicate significantly greater risk of hospitalisation [Bager, Fisman, Ong, Sheikh] especially in those with multiple co-morbidities (and worse pregnancy outcomes [Vousden]. Other studies variously found greater chance of severity, progression, hospitalisation or of emergency room attendance [Ong, Taylor, Twohig, Wang Y].
Impact on testing effectiveness

- Studies to date seem to agree that PCR tests remain sensitive to the currently circulating variants of concern, but some antigen tests which target single spike protein sites could be of reduced efficacy against some or all of those variants with spike protein differences. Some caution should be applied before implementing any antigen tests at scale, to verify their effectiveness with variants of concern in circulation.

Impact on natural immunity

- Although recovery from COVID-19 infection is associated with good immunity against variants [Dupont, Hall, Milne, Redd], immunity post-infection may be reduced or shortened with respect to the Delta variant [Eyre, Marcotte, Planas, Suthar].

Impact on vaccine effectiveness

- Some evidence has indicated decline in effectiveness of some vaccines against circulating variants of concern [Emary, Ho, Ikegame, Kustin, Mascola, Wang&Nair], with early studies pointing to limited effectiveness against the Beta/B.1.351 variant of the AstraZeneca [Madhi, Wang&Nair] and Novavax [Shinde]. Most approved vaccines appeared effective in preventing severe disease, hospitalisation and death [Hall, Redd, Rubin]. Furthermore, available evidence suggests that the mRNA vaccines in wide distribution (Pfizer-BioNTech and Moderna) appear to retain reasonably strong effectiveness overall against most variants [Abu-Raddad, Benenson, Keenner, Kustin, Liu Y, Tarke, Thompson MG, Wu], particularly in terms of preventing severe cases. Neutralizing antibodies appear have been shown to be produced against a range of variants [Caniels, Edara] but at reduced levels [Caniels, Wall] but with evidence of preserved T-cell response [Geers]. Another study showed efficacy in pregnant and lactating women [Collier AY]. The Pfizer vaccine demonstrated in vitro activity against the Beta and Alpha variants as well as the variants identified in New York [Iota/B.1.526] and California (Epsilon/B.1.429) classified in USA as variants of concern [Liu Y], and activity of the vaccine was confirmed beyond 6 months [Pegu]. Some studies indicated reduced efficacy of Coronavac against Gamma [Ranzini, Souza]. There is evidence of effectiveness of mRNA vaccines against the Lambda variant [Tada2]. New vaccine formulations continue to be tested to improve efficacy against variants. A study [Uriu] of the Mu variant indicated resistance to neutralisation by both convalescent serum and vaccine (Pfizer) serum.

- Reduced efficacy with Delta (B.1.617.2) is clearer in terms of preventing all (including mild/asymptomatic) cases. There were early indications of likely activity of vaccine-induced antibodies against the B.1.617 subgroups and B.1.618 [Tada], but studies pointing to more “breakthrough” infection by Delta in those vaccinated [Cohn, Micchova]. A study from Public Health England showed effectiveness (at preventing total cases) after two doses of either AstraZeneca (67%) or Pfizer (68%) [Bernal2], against Delta/B.1.617.2, slightly lower than Alpha and much reduced compared with the wild-type virus; similar results were found in Scotland [Davis] and India [Thiruvengadam]. Subsequent studies show reduced activity of the Pfizer vaccine against the B.1.617 variants [Hoffman, Vaidyanathan], and of reduced activity specifically against Delta [Wall] particularly after only one dose, but in general with response retained after two doses (especially if there is previous history of infection [Urbanowicz]). Moderna was similarly shown to have good, but reduced, efficacy against Delta [Choi A], and Johnson&Johnson associated with reduced neutralising antibodies against Delta [Jongeneelen] as well as real world efficacy [Corchado-Garcia2]. Some studies [Micchova, Sheikh] indicated less efficacy of AstraZeneca than Pfizer against the Delta variant. However, many studies show, in spite of a reduced overall efficacy [Fowlkes, Gomes, Kislaya, Nanduri, Tartof, WangB] against preventing infection, high effectiveness at preventing hospitalisation and death [Gomes, Havers, Hirotsu, Nasreen, Pouwels, Rosenberg, Sheikh2, Stowe, Tartof, Tenforde2, Thiruvengadam, Thompson MG3] or at
preventing infection in the vulnerable [Hyams, Shrotri]. A series of CDC studies [Bajema, Grannis, Scobie, Self] confirmed high effectiveness of mRNA vaccines against hospitalisation and death notwithstanding the rising dominance of Delta, but with some differences between vaccines [Bruxvoort, Eyre, Pouwels, Self] and between age groups [Cerquiera-Silva, Israel, Robles-Fontán, Scobie], and some evidence of maintenance of immunity up to and beyond 6 months [Goel RR, Puranik].

- Those who become infected with the Delta variant despite vaccination do retain the potential of transmission [Ng, Singanayagam]. However, there is evidence of reduction of onward transmission, including within families [de Gier, Nordstrom].

Part 4: Reducing importation risk with international travel

Quarantine of travellers

- Quarantine is applied differently in different locations. It ranges from total confinement in a locked guarded hotel room through to instruction to remain home but relying on an “honesty system” – the latter having been shown to have non-compliance rates up to 80% in studies. At the stringent end of the spectrum it is substantially (but not completely) effective at preventing importation of cases, whereas at the lax end of the spectrum it may provide only modest reduction of risk [Oxera]. As discussed above, testing programmes can enhance quarantine and may be able to allow reduction of the duration or stringency of quarantine measures, without significantly increasing importation risk [Johansson, Russell]. IATA has determined from repeated customer surveys, and observed travel patterns that quarantine requirements are a major disincentive to travel [IATA internal].

Testing technologies and strategies

- While PCR has remained the primary diagnostic test throughout the pandemic, there has been increasing development of rapid antigen tests (RAT). Initially these were of much lower cost and higher speed than PCR testing, but of reduced sensitivity and specificity. Progressively through the pandemic these differences have reduced, with the cost and time of PCR testing reducing, and the sensitivity (and specificity) of RAT improving. Now there are some extremely rapid PCR tests and some studies show RAT tests with very good sensitivity and specificity [Pickering, Pilarowski, Pekosz] although this is not a consistent finding [Dinnes] and all tests are not equal [Jones]. In some situations, RAT testing may have an advantage over PCR in detecting only those cases most likely to be infectious [Norizuki, Pekosz, Schuit], with high viral load, whereas PCR also detects virus well beyond the infectious period [Mina]. However, the sensitivity of RAT testing is less when used in asymptomatic people [Dinnes, Fernandez-Montero, Nkemakonam, Pollock, Wagenhauser], or when viral load is low [Muhi, Oh]. This is important in the context of testing travellers, since asymptomatic cases are a large contributor to transmission [Johansson, Letizia, Oran, Ren]. This area continues to evolve rapidly [Humphries] and a further Cochrane review of RAT performance is awaited [Dinnes].

- A further relevant consideration is acceptability. Importantly saliva-based testing which has been validated extensively for PCR but not for RAT, can be applied frequently with high effectiveness [Babady, Grijalva, Norizuki, Tan, Wyllie] and much less drop-out than nasopharyngeal or oronasal swabbing [Ehrenberg]. Although reported results have been varied, the effectiveness depends on having clarity of the method used; salivary PCR was suggested to have potential to become the gold standard [Tan] but more recently caution was raised around its use in asymptomatic patients [Congrave-Wilson]. A further development is the use of anterior nasal self-sampling, shown to be sensitive to medium to high viral loads [Osmanodja], but perhaps less sensitive in asymptomatic cases
such a method was adopted by US CDC if done with an approved test, in conjunction with a telehealth provider affiliated with the test manufacturer, and with identity verified and documented.

- Effectiveness needs to be considered in the real world, which means consideration of implementation, delivery, reliability (across different users), acceptability and scalability. Turnaround time is also important – if a more accurate test takes 1-2 days to get a result, this may be less effective than a less sensitive test with an immediate result (to allow earlier intervention such as isolation) [Pickering]. It is more appropriate to consider not just a test, but the effectiveness of a test strategy, such as RAT testing of a group of workers every day or every second day [Abbasi, Holmdahl, Larremore, Mina, Mina] compared with less frequent PCR testing. Conversely, routine one-off testing of low prevalence populations does have a risk of missed cases (due to reduced sensitivity in asymptomatic people) as well as false positives (due to the Bayesian effect of amplifying their likelihood in a low prevalence group). Routine RAT testing may need to have a means of conducting confirmatory (possibly PCR) testing as rapidly as possible. Such a system was examined in Japanese travellers, using salivary antigen tests as the primary with PCR confirmation when required [Yokota] but limited sensitivity may still be a concern and further analysis is awaited. More recently a study in USA [Tande] with an airline in a different setting, a randomised controlled trial of attending an indoor event included demonstration of the possible utility of an antigen test pre-entry [Revollo].

- There are other molecular tests as alternatives to PCR, including isothermal PCR or “LAMP” which use alternative amplification methods, usually achieving greater speed of testing. There are also quantitative antigen tests which may have improved acceptability in certain domains. This is a rapidly changing field. Other novel technologies such as breath spectroscopy [Rusciewicz] and detector dogs [Angeletti, Grandjean, Guest, Hag-Ali] show potential. These should be considered, although both efficacy and scalability are yet to be established.

Reduction in importation risk from testing

- The first requirement may be for the country of destination to set the level of risk of importation that it can accept, taking into account the epidemiological situation, the capacity of the health system to manage cases, and the capacity and reliability of the contract tracing system locally [Steyn].

- A number of studies have modelled the possible reduction in importation risk from testing in association with international travel [Clifford, Dickens, Goel V, Johansson, Kiang, Russell, Smith, Steyn, Wells]. A Cochrane review of 62 studies [Burns] noted that most of the studies were from modelling only, with few real-word examples, but it only covered publications up to November 2020 and a further review is awaited. WHO [personal communication] also undertook a detailed analysis but only of papers up to November 2020. Several further papers have subsequently been published [Dickens2, Johansson, Quilty].

- In situations where travel is from low prevalence to high prevalence, the importation risk is low with a negligible incremental case likelihood. Modelling has indicated that destinations already with a high circulating prevalence receive minimal impact from imported cases [Russell].

- With travel between countries of similar new case rates at the time of travel (provided that the rate data is reliable, with adequate testing programmes in place) then testing around the time of travel will reduce importation by a significant proportion [Clifford, Johansson, Oxera]. This should ensure that the travellers entering are of lower risk than the community at the destination and protect significantly against introducing a variant not already present.

- Efficacy of testing to reduce importation is better if closer to the time of travel; testing on arrival is still more effective. However in-airport testing creates logistical challenges at large scale.
• Travel from high prevalence to low prevalence locations presents more challenges, and in most cases, such travel currently requires some form of quarantine. There is consensus from modelling studies that a programme of testing in association of travel can be applied which will reduce the required quarantine, if not eliminating it entirely [Goel V, Johansson, Kiang, Quilty, Russell, Smith, Wells]. Many seem to converge on a short period of quarantine (3-7 days) with testing at the start and end [Humphries, Johansson, Quilty]. Many indicate that a quarantine period of around 5-7 days, with 2 or 3 occasions of PCR/RAT testing (or daily serial RAT testing after arrival) can be as effective as a 14 day quarantine period, at reducing importation risk [Dickens, Johansson, Quilty3].

• As noted above, no pre-flight testing system can fully prevent travellers from having already been infected, and incubating at the time of travel. The timing of testing in relation to travel has been studied, and many countries have introduced a requirement for testing in the 72 hours prior to travel. This strikes a compromise between the risk of becoming infected in the time between the test and the travel, and the difficulties of reliably obtaining and confirming a result prior to travel. Testing 48-72 hours prior to travel has been assessed by different studies as reducing the importation risk but to varying degrees [Clifford, Johansson, Oxera]. Antigen testing has the advantage of being able more easily to be performed close to the time of departure, reducing the opportunity for incubation prior to travel – balanced against the reduced sensitivity in asymptomatic individuals.

• If the destination is prepared to accept a higher risk of imported cases, based on its public health systems (including contact tracing), then even shorter periods, supported by testing programmes, could be acceptable. [Clifford, Goel V, Johansson, Kiang, Russell, Smith, Wells]. If the risk is further reduced by travellers being vaccinated, along with validated testing programmes, the need for quarantine may be able to be removed, if based on sound studies, perhaps supplemented with daily antigen testing [Quilty3]. Modelling of importation risk with vaccinated travellers in the context of the Delta variant, however, indicates that a destination with low risk tolerance might still require some quarantine period even with high vaccination rates, and for vaccinated arrivals [Leung].

Contact tracing

• Regardless of the state of vaccination, the systems and processes of contact tracing remain vital in blocking chains of transmission and preventing spread. As countries begin to achieve control of the epidemic, contact tracing becomes even more vital for maintaining that control [Lash]. Systems which facilitate tracking and tracing (such as applications which record places visited, with or without GPS tracking assistance or detection of other visitors in the vicinity) are part of the risk management process. For example, some countries allow exit from quarantine on condition of using a GPS tracking device for a period of days. Applications that release location data have obstacles to widespread acceptance by users although some have addressed this by ensuring users retain control over the release of information [O’Connell]. For both public health authorities and airlines, an important element of managing the risks of air travel is the use of a passenger locator form, ideally an electronic one, to assist with follow-up of any passengers later found to be a positive case, and potentially infectious during travel. The ability of a destination to carry out contact tracing on arriving travellers is an important component of assessing travel-related risk.

Part 5: Differing national approaches

• The approaches of countries have continued to be highly divergent. By mid 2021, many countries required tests for arriving travellers, and an increasing number were reducing quarantine requirements conditional on vaccination, on acceptable testing results, or both. Any of these approaches depend on being able to verify that the required testing or vaccination has been carried out, and verify the identity of the traveller as matching the person whose result is presented. IATA has developed its travel pass for exactly this purpose, and there are also other applications which fulfil similar functions; such
electronic solutions will be necessary to support scaled-up numbers of travellers and many countries are already using them on a preliminary basis.

- Since mid 2021, many countries have recommended or instituted removal of quarantine requirements for the fully vaccinated and a number of EU countries are supporting, or have introduced such a relaxation. Similarly, many countries are modifying testing requirements for the fully vaccinated travellers. Even in destinations with extremely stringent entry restrictions, modelling shows potential for relaxation within acceptable risk thresholds [Yang BY].

Part 6: Other relevant considerations

Therapeutics

- Little of the focus of this document has been on therapeutics. But if treatments become available which reliably and affordably prevent infection from progressing to becoming severe and fatal, the risk equations will be dramatically altered. Although there have not yet been any treatments which radically shift the prognosis, there continue to be incremental gains from various therapies including steroids, anti-thrombotics, antivirals, anti-inflammatories, interferon, various monoclonal antibodies [Avni], etc. One combination of monoclonal antibodies has demonstrated a 70% reduction in hospitalisation and death [Weinreich]. Convalescent plasma has been used but benefit appears questionable [Focosi, Writing Committee].

- There also needs to be consideration of the more severe and prolonged complications of COVID-19 [Groff, Huang, Nasserie, Taquet], given variously names including post-acute COVID syndrome (PACS) and “long COVID,” carrying significant health, social and economic effects [Evans, Mallapaty]. Some estimates put this at up to a third of cases [Chopra], not clearly related to the severity of the original illness, however lack of precise case definition makes it difficult to determine incidence [Groff, Whitaker, ZhangX]. Prolonged cognitive effects are frequently observed [Becker]. Vaccination has been suggested to reduce the risk of “long COVID” in those who do still get infected [Antonelli, Tran].

- There will also be other advances; for example, a sulfate polysaccharide nasal spray was shown in an initial randomised controlled trial in Argentina to prevent a high proportion of cases in health care workers [Figueroa], a nasal spray of nitric oxide being explored, and a promising trial with an old drug, probenecid [Murray]. Increasing numbers of trials suggest monoclonal antibodies can induce robust levels of neutralising antibodies [Lanini], prevent infection [O’Brien], and reduce risk of hospitalisation [Weinreich]. And even an antidepressant has shown apparent benefit in early trials [Reis G].

- Antibody testing has been considered but there is insufficient information as to the correlates of protection; while neutralising antibody levels have been proposed [Khoury] they are not consistently predictive of response [Yamamoto]. Antibody testing appears therefore not to be able to provide a sufficiently reliable indication of the adequacy of protection, from either vaccination or previous infection, to be used at scale in association with travel.

Part 7: References


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