



## COVID-19:

# A summary of current medical evidence relevant to air travel. Version 13 – 28 April 2022

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## Introduction

This is a brief summary of key scientific findings on COVID-19 relevant to air travel. Given that both the state of knowledge and the virus itself continue to evolve, this summary should be read with attention to the date of the latest revision. The areas of greatest relevance have proved to be flight-associated transmission, the protective benefit of vaccination, and testing in association with travel.

## Flight-associated transmission

- Documented instances of flight-associated transmission are relatively few [Bae, Chen J, Choi EM, Eichler, Eldin, Freedman, Hoehl, Khanh, Murphy, Nir-Paz, Pavli, Schwartz, Speake, Swadi, Thompson HA]. 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]. Some studies were supported by whole genome sequencing [Choi EM, Eichler, Speake, Swadi]. Some considered the effect of masks [Gurbaxani, Riley]. There were few instances of suspected transmissions when masks were worn by passengers [Nir-Paz, Swadi, Thompson MG, Eichler]. Universal face coverings appear effective against spread via aerosols generally [Abaluck, Cheng]. One with partial mask wear suggested significant protection in those who wore them throughout [Toyokawa].
- Of all the presumed secondary cases in these published studies, a large proportion were from just three flights [Bhuvan, Khanh, Speake, Toyokawa], when mask-wearing by passengers was not yet routine. Community studies similarly show the majority of spread originates from a small minority of cases [Chen PZ2, Yang Q]. Mechanism is likely to be airborne carriage of fine aerosols [Chen, Davis, Fennelly, Klompas].
- 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 - 273 primaries and 64 possible secondaries, attack rate between zero and 8.2% in studies. Travel encompasses not only aircraft but also surface transport (road/rail etc) and airports; in many of the studies above, it is not clear at what part of the journey transmission may have occurred.
- In terms of risk the airline cabin compares favourably with other indoor environments [Hadei, Rivera-Rios] including restaurants [LuJ], buses [Shen, Tsuchihashi], churches [James, Kateralis], gymnasiums [Jang], and high-speed trains [Hu]. The mechanism presumed in such indoor environments is aerosol transmission [Allen, Kateralis]. There are even well-documented transmissions in a quarantine facilities 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, Liu J3], 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]. One study found good concordance between some reported in-flight transmission events and the predictions from computational fluid dynamics [Wang W]. 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]. Later studies have pointed to dissipation within minutes of aerosol capable of transmitting infection, and even more rapidly in low humidity environments [Oswin].

- 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]. Other factors may be relevant e.g. loud speech may be an underestimated determinant of aerosol transmission [Andersson, Coleman], which could be relevant to the apparent low risk of on-board spread. One recent analysis looked at mobility on board [Namilae].
- Most of the studies referred to above were undertaken prior to the appearance of more transmissible variants; it must be assumed that the chance of flight-related transmission of variants could be increased proportionately with Delta, and now Omicron – although data are sparse [Dhanasekaran].
- 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 major systematic review found little evidence of surface transmission [Onakpoya].

## Protective impact of vaccination

- It was demonstrated early that vaccination prevented severe disease, hospitalisation, and death [Corchado-Garcia, Dagan, Juthani, Pawlowski, Tenforde, Vahidy, Vasilieou]. Prior to the Delta variant, it appeared that vaccination also could prevent mild or asymptomatic infection [Amit, Bernal, Chodick, Dagan, Daniel, Menni, Angel, Haas, Jones, Lillie, Lumley, Milman, Pritchard, Regev-Yochay, Sadoff, Shah, Tande2, Weekes] which is an important contributor to transmission [Glenet, Johansson, Letizia, Ma, Oran, Rasmussen, Ren, Sah, Wilmes, Yonker, ZhangXS]. Some studies specifically demonstrated reduction in onward transmission, within families [Clifford2, deGier, Harris, Nordström, Salo, Shah], within residential care communities [Cavanaugh, De Salazar, Monge, Muhsen], amongst regularly screened employees [Keehner, Swift, Tang], or in modelling [Lipsitch, Marc, Marks].
- There is now an enormous body of literature relating to the efficacy of various vaccine regimens against the various variants of SARS-CoV-2, over time, using various measures. It will not be reviewed in detail here, but some key points summarised. Immunity is well-established within a few weeks after vaccination [Glatman-Freedman, Gupta K] and retained beyond 6 months following vaccination [Barouch, Doria-Rose, Hall, Pegu, Polinski, Thomas, VIKKURTHI]. 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, Guerrero, Tarke1].
- The more the SARS-CoV-2 virus continues to proliferate, the more likely it is that more transmissible variants will appear and predominate. In 2021 the Alpha, Beta, Gamma and Mu variants demonstrated increased transmission but only achieved regional dominance; subsequently, Delta became

predominant globally in mid 2021, followed by Omicron from late 2021 to early 2022. No variants will be discussed in detail here other than Delta and Omicron.

## Delta variant

- The Delta variant led to reductions in the strength and duration of immunity, but there was still high effectiveness at preventing hospitalisation and death [Feiken, Gomes, Havers, Hirotsu, Nasreen, Pouwels, Rosenberg, Sheikh2, Stowe, Tartof, Tenforde2, Thiruvengadam, Thompson MG3, Wang SY] 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. Boosters have generally been effective at restoring waned protection [Andrews, Arbel, Atmar, Barda2, Bar-On2, Chemaitelly3, Mok, Munro, Niesen, Saiag, Sacluk, SchultzBM, Sharma2, WangK1] especially against severe outcomes.
- Studies of Delta showed much faster replication [Li] with reproduction number considerably greater, ( $R_0 = 5-6$ ), and shorter but more variable incubation period [Li, Wang Y]. However, despite much greater viral load with Delta [Chau, Li] there was no difference in viral load between those infected who were vaccinated and those unvaccinated [Acharya, Riemersma], just a faster fall in viral load in the vaccinated [Chia, Kang, Pouwels, Shamier]. Immune response varied with age [Bates1, Israel, Moustsen-Helms, Müller, Yang HS] and with immunosuppression [Benotmane, Boyarsky, Embi].
- Thus the effect of vaccination on transmission was reduced. Studies showed Delta to cause more severe disease with greater risk of hospitalisation [Bager, Fisman, Ong, Sheikh], greater chance of severity, progression, hospitalisation or of emergency room attendance [Ong, Taylor, Twohig, Wang Y]. Immunity post-infection may be reduced or shortened with the Delta variant [Eyre, Marcotte, Planas1, Suthar]. Similarly, vaccination was found to be of reduced effectiveness at overall prevention of infection [Fowlkes, Gomes, Kislaya, Nanduri, Tartof, WangB] but remained highly effective 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].

## Omicron variant

- The Omicron variant appeared early on to have a reduced severity of disease, even accounting for confounding by age or immune status [Ferguson, Goga, Sheikh2], with lower hospitalisation rates, lengths of hospital stay, and requirement for advanced therapies [Davies M, Lewnard, Maslo]; lower severity was confirmed with subsequent data [Abdullah, Jassat, Mahdi, Nyberg, Sheikh3, UKHSA2, Ulloa]. This however was accompanied by such high transmissibility that the overall impact on populations was greater in many locations.
- Concerning immune protection against the Omicron variant, initial indications, along with even higher transmissibility [Brandal, Gu, Yang W] were of immune escape [Planas2, Pulliam] increased reinfection [Goga, Pulliam2], and increased onward transmission [Allen, Jørgensen]. There was reduced neutralisation by serum from vaccinated and recovered individuals [Basile, Cele, Dejnirattisai, Edara2, Gardner, Gruell, Lu L, Sheward, Wilhelm, Yu X, Zhang L], and corresponding results with regard to breakthrough infection and re-infection [Accorsi, Andrews2, Collie, Pulliam2]. There is evidence of improved immunity following boosters [Andeweg, Andrews1, Basile, Cameroni, Chemaitelly3, Garcia-Beltran, Gruell, Johnson, Kislaya2, Liu Y2, Mayr, Menni2, Nemet, Schmidt F, Spitzer, Vanshylla, WangK2, Yu X, Zeng, Zhao]; this initial protection declines rapidly [Ferdinands, Levine-Tiefenbrun2, UKHSA1] but there is likely retention of T-cell immune responses [Hall2, Jergovic, Keeton2, Redd2, Tarke2]. Regarding the effect of vaccination on transmission of Omicron, there was evidence of reduction of onward transmission, including within families [de Gier, Goel RR, Hsu, Nordström] by vaccinated cases but less of a reduction than with previous variants [Eyre].

- Vaccination appears still to provide substantial protection against hospitalisation [Andrews, Collie, Keeton, Laurant, Nyberg, Tartof2, Tseng] from infections with the Omicron variant, especially if previously infected prior to initial vaccination [Shrestha2]. Average incubation time also appears to be shorter [Brandal, Hay, UKHSA2]. The subvariant BA.2 of Omicron appears more transmissible than the original BA.1, but not more severe [Wolter], and the increased transmissibility is possibly due to longer duration of infection or greater viral load [Qassim]. Reduced strength/duration of immunity following infection was observed, to a greater degree than with Delta [Altaranweh, Planas2, and see above]. As with previous variants, it appears that “hybrid immunity” from having had both infection and vaccination may be superior [Richardson].
- In summary, the Omicron variant currently dominates, being much more transmissible than Delta, exhibiting immune escape, and transmitting rapidly. Although average severity of illness with Omicron is reduced, high overall numbers of infections have resulted in a heavy load of severe cases and strain on health services. Vaccination still protects against severe disease, hospitalisation and death (particularly with booster vaccination, or if combined with previous infection), but is unreliable at protecting against milder/asymptomatic cases, and against preventing transmission. Therefore, while vaccination remains a vitally important tool for protecting individuals, it is relatively ineffective at controlling transmission.

## Testing and its use in air travel

- Since the start of the pandemic, the mainstay of diagnostic testing for COVID-19 has been molecular testing, specifically PCR (polymerase chain reaction) - which requires multiple time-consuming cycles of heating and cooling to amplify the genetic material from the sample (typically a nasopharyngeal swab or saliva) to a detectable and quantifiable level. This requires a sample to be supervised or carried out by a trained worker, getting the specimens to laboratory facilities, and time (hours to days). PCR also allows subsequent WGS (whole genome sequencing) to determine new variants. Less accurate “isothermal” PCR methods such as RT-LAMP use non-thermal methods to amplify the sample and can be completed more quickly without a full laboratory. The other mainstay of testing has been rapid antigen tests, done on the spot, usually with a “lateral flow device” from a self-sampled anterior nasal specimen, producing a less sensitive/specific result but providing it at low cost, within 15-20 minutes.
- Testing technology has developed rapidly during the pandemic. There are many studies published looking at the efficacy, limitations, advantages, drawbacks, and potential of various methods, but most by far have focused on PCR and RAT. Both have been used as pre-requisites for air travel. A number of studies modelled the possible reduction in importation risk from testing in association with international travel [Clifford, Dickens, Goel V, Johansson, Kiang, Russell, SmithB, Steyn, Wells1]. PCR was used extensively as a pre-requisite for international travel, but was logistically difficult, expensive, and of limited effectiveness because of the necessary time delay between the time of the test and the time of travel.
- RAT testing may have an advantage over PCR by virtue of being most sensitive during the period of greatest infectiousness [Norizuki, Pekosz, Schuit] thus avoiding false positives in a travel setting [Smith R], 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-Monteroa, 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]. 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. Numerous studies have now demonstrated the utility of routine testing in specific groups such as workplaces, schools, universities, conferences, sports competitions, and indeed travellers.

- Any testing requirement in association with travel needs to be examined as to its potential to reduce either flight-associated transmission, importation, or both. Omicron is now almost ubiquitous, and by definition any future variant which outcompetes Omicron will be even more transmissible. Even the strictest border controls rapidly proved ineffective at preventing the importation of Omicron. Therefore the scenario of controlling importation appears to be one which now will not be in consideration until a future pandemic. When such a consideration is undertaken, it will need to again take into account the tolerable risk of importation, and the current prevalence of infection at origin and destination [Clifford, Johansson, Oxera], against the effectiveness of testing, and any associated measures (such as quarantine, vaccination, etc) of achieving that risk.
- Other novel technologies such as breath spectroscopy [Ruszkiewicz], breath mass spectrometry [Liangou] and detector dogs [Angeletti, Grandjean, Guest, Hag-Ali] show potential. Also, little explored to date is the potential for rapid antibody tests to demonstrate immunity in travellers, if the correlates of protection can be established [Gilbert, Khoury, Yamamoto].

## Additional considerations

- **NATURAL IMMUNITY.** Many questions which are inherently important are not been detailed in this paper. They include the strength and duration of immunity of those who have had documented infections with COVID-19 (but not vaccination). While evidence is available to suggest good immunity for several months [Ahluwalia, Bilich, Cromer, Dan, Jeffery-Smith, Krutikov, Sokal1, Turner1, Wajnberg, Zuo J] and even beyond a year [Abbasi2, Chemaitelly2, Eyrar, Gaebler, Gallais, Lau, LuZ, Marcotte, Radbruch, Wang&Muecksch], immune protection appears to be less in older people [Brockman, Collier DA, Hansen, Wei], and is less following milder [Caniels, Legros] or asymptomatic [Long] initial infections. Looking across all human coronaviruses, decline in immunity with time is common [Townsend]. Some studies [Assis, Cavanaugh2, Garcia-Valtanen] have shown naturally acquired immunity to produce inferior antibody response to that from vaccination, while others suggest naturally acquired immunity is more robust [Gazit]. What is clear is that the "hybrid immunity" of previous infection combined with vaccination is superior to either alone [Andreano, Appelman, Chen Y, Cho, Demonbreun1, Hall3, Hammerman, Ke, Lucas, Samanovic, Shenai, Shrestha2, Agrawal, Crotty, Eyrar, Megideshi, Pape, Reynolds, Richardson, Shuford, Stamatatos, Zhong, Zollner]. The reverse situation of breakthrough infection after vaccination has been shown to produce robust immune response [Bates2, Collier AY3, Glatman-Freedman, Shrestha2, Walls], and this is of importance as it will be a likely pathway for many of the population in the long term.
- **VACCINE SPECIFICS.** Also not detailed here are the many differences between different vaccines (including heterologous combinations), different schedules (time intervals between doses), and specifics relating to different demographic groups or underlying medical conditions.
- **VACCINE SAFETY.** This is not detailed here, but a high degree of safety has been established for all the approved vaccines [Agrawal, Klein]. Safety and efficacy [Collier AY, Dagan2, Goldshtein] has also been demonstrated with pregnancy and lactation [Kharbanda, Magnus], while COVID-19 infection during pregnancy is associated with greater risk [Metz, Vousden]. The safety remains high despite the rare type of blood clotting disorder associated with the AstraZeneca vaccine [Greinacher, Klok, Pavord, Seem Schultz JB, Schultz NH, Takuva, Taquet2], and the rare myocarditis after mRNA vaccines estimated at between 10 and 100 cases per million first doses [Ling, Llein, Oster, Patone, Shimabukuro]. Overall mortality from non-COVID causes was found to be lower amongst the vaccinated in the USA [Xu].
- **THERAPEUTICS.** Increasingly important, but not detailed here, is the developing literature regarding treatment of COVID-19 – including the many antiviral medications being developed. Convalescent plasma appears to have had mixed success [Sullivan, Tada, Zhao]; monoclonal antibodies were extremely promising until the appearance of Omicron, which evades many of them [Aggarwal A, Boschi, Cameroni, Cao, Planas2]; broad spectrum antivirals including molnupiravir and the combination



"Paxlovid" (nirmaltevir/ritonavir) continue to be promising as does the prophylactic combination "Evusheld" [Gupta A], and there are continual iterative improvements in the hospital treatment of severe COVID-19.

- **LONG COVID.** There are many studies, not detailed here, into the prolonged complications which follow COVID-19 infection in a significant proportion of cases, known as "Long COVID" or "post-acute COVID syndrome." It appears that these persistent symptoms are not reliably related to severity of illness, and they include cardiovascular complications, cognitive effects and structural brain changes [Becker, Douaud, Xie2]. While vaccination provides considerable protection [Al-Aly, Antonelli, Simon, Tran] it is not absolute.
- **CONTACT TRACING.** During the pandemic, national public health authorities employed contact tracing to varying degrees, and with varying success, to control the spread of infection. With the arrival of Omicron, it was no longer possible to keep pace with the spread of infection, and most of these efforts have been abandoned. Although contact tracing is not discussed in detail here, it remains an important consideration for the management of future outbreaks, and will require non-intrusive, efficient and presumably electronic solutions in order to be effective.
- **TRAVELLER QUARANTINE.** Many countries employed quarantine (either at home, or in government-supervised facilities) as a strategy to limit the risk of importation of disease. In many countries, this proved to be of limited benefit in slowing the spread of disease, but in some, it enabled an elimination pathway to be successfully pursued, even with the arrival of Delta. Importation of the Omicron variant proved not to be preventable with even strict quarantine requirements, and most countries have abandoned such requirements. There were many studies modelling the effectiveness of various durations of quarantine at preventing importation [Aggarwal D, Goel V, Johansson, Kiang, Quilty, Russell, Smith, Wells], in association with testing of travellers, but these are not discussed in detail here.
- **EFFECTIVENESS OF OTHER PUBLIC HEALTH MEASURES.** Many of the measures which have formed the "multi-layered protections" during the pandemic have remained in place, such as distancing, ventilation, and use of masks. In many cases, all have been applied simultaneously so the effectiveness of a single measure is difficult to analyse. There are many studies on the various interventions, but these are not considered in detail here, other than some reference above to the use of masks.

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