Duration of immunity following SARS-CoV2 infection: A narrative review.

COVID-19 Aviation Scientific Assessment Group (CASAG).

Introduction:
As international aviation implements travel pathways that are influenced by vaccination and recovery from previous COVID-19 infection, aviation organizations need to understand the duration of effective immunity following SARS-CoV-2 infection. In particular, within the multi-layered risk mitigation strategy, where previous infection is known to greatly reduce the risk of contracting or transmitting SARS-CoV-2, this could inform guidance on the suitable maximum duration of certificates of recovery.

Naturally acquired active immunity occurs when an individual is exposed to SARS-CoV-2 virus, becomes infected, and develops protective immunity as a result of the primary immune response. The adaptive immune response generated against the virus takes days or weeks to develop but may be long-lasting. This narrative review aims to inform how long naturally acquired immunity against SARS-CoV-2 lasts, as reported in the best scientific evidence available to date.

Methods:
CAPSCA formed a sub-committee, the COVID-19 Aviation Scientific Assessment Group (CASAG) in May 2021. In June 2021 CASAG performed a literature search of scientific literature and technical reports regarding the duration of "natural" (post-infection) immunity. The literature included Google Scholar, PubMed, and Cochrane Library databases. Numerous studies and relevant papers referenced in other documents from WHO, IATA, CDC, and EU-CDC were also included. The group performed further filtering aiming to include papers that were specific to COVID-19, that assessed one or more elements of humoral or cellular immunity, and that analyzed duration of immunity as a primary or secondary study outcome. (Fig.1)

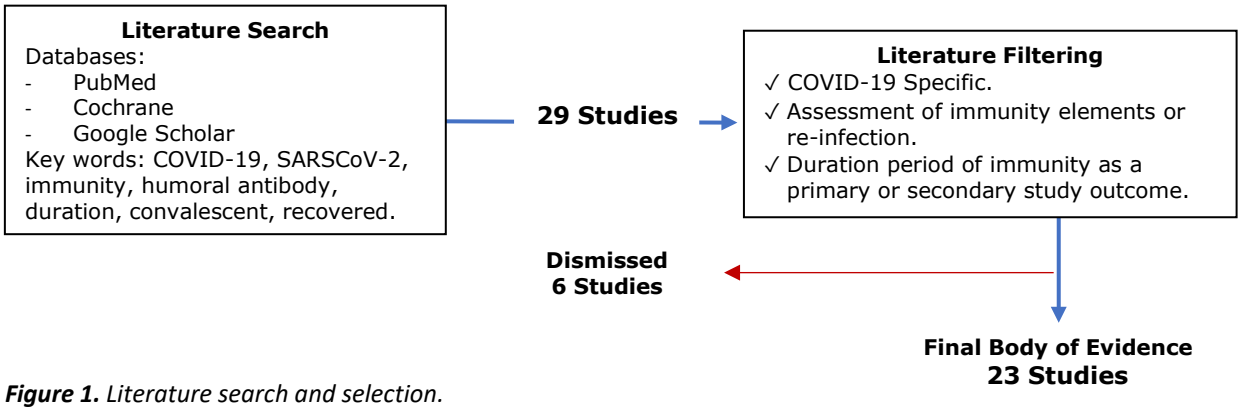

Figure 1. *Literature search and selection.*

Once the list of relevant studies was established, CASAG proceeded to assess each paper using the GRADE (The Grading of Recommendations Assessment, Development, and Evaluation) methodology. This approach is a systematic and analytical tool, used and endorsed by WHO, BMJ, NHS, CDC, IDSA, European Commission, American Red Cross, among others, to produce evidence summaries and graded recommendations. The GRADE structured process analyzes different metrics of each scientific paper such as size effect, main outcomes, secondary outcomes, study methods, discussion, and conclusions in order to establish quality and strength of certainty of the selected evidence body. GRADE process output provides the basis for panel consensus and informed support for guideline panels in developing public health policies.

CASAG gathered via online meetings to agree on methods of analysis, assign reviewers, and measure progress against due dates. During virtual work sessions, group members discussed literature relevance, quality, strengths, caveats, and limitations as the evidence assessment process advanced. Discussions led to panel consensus and formulation of conclusions.

Results:

An initial search of the databases using relevant keywords retrieved a total of 25 peer-reviewed articles and 4 pre-print articles as of July 13, 2021. After filtering out articles that were not relevant or specific to the main research question, 19 peer-reviewed articles and all 4 pre-prints were selected for analysis, where duration of naturally acquired immunity was a primary or secondary study outcome (Tab. 1). Afterindependent reviewing, discussion, and analysis of the final body of evidence by CASAG members, the GRADE evidence grading process retrieved 9 moderate level of quality of evidence, and 10 low level of quality evidence studies (Tab. 1). All articles were observational studies, 19 were observational cohorts (17 prospective, 2 retrospective), and 4 were case-control studies (Fig. 1).

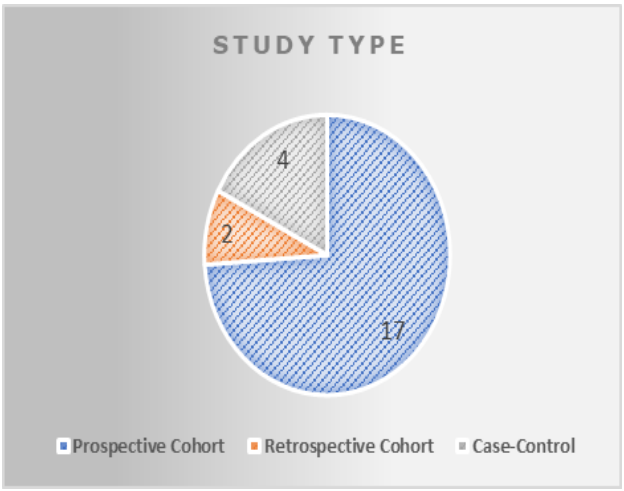

***Figure 1**. Study types.*

On reporting naturally acquired immunity, the body of evidence presented remarkable heterogeneity. All papers being observational in nature, the timeframes referenced in their outcomes are limited to the follow-up intervals for each study. Those observation periods started at 48 days for one study (Zhongfang Wang et al) and extended to over 13 months for another study (Gallais et al) (Tab. 1). The recurring endpoint for 12 out of 23 studies was in between 6 and 7 months, with 3 studies reporting the presence of at least one element of neutralizing immunity a year after infection. (Fig. 4)

Study Author	Level of Evidence Quality	n	Duration of Immunity	Assessment of Immunity
Peer-Reviewed				
Dan et al	Moderate	188	5-8 months	Spike IgG, Nucleocapsid IgG, B cells, CD4+ T Cells, CD8+ T
Wajnberg et al	Moderate	30082	5 months	Spike IgG
Krutikov et al	Moderate	2111	6-10 months	Spike IgG, Nucleocapsid IgG
Lumley el al	Moderate	12541	>6 months	Spike IgG, Nucleocapsid IgG
Hansen et al	Low	525339	>7 months	PCR confirmed reinfections
Hall el al	Moderate	25661	7 months	Spike IgG
Rodda et al	Low	15	>3 months	Spike IgG, CD4+ T Cells, CD8+ T Cells
Gubjartsson et al	Low	30576	4 months	Spike IgG, Spike IgM, Nucleocapsid IgG, Nucleocapsid IgM
Ripperger et al	Low	5882	5-7 months	Spike IgG, Nucleocapsid IgG
Harvey et al	Moderate	3257478	>3 months	Spike IgG, Nucleocapsid IgG
Figueiredo-Campos et al	Low	307	6 months	Spike IgG, Spike IgM, Spike IgA
Isho et al	Moderate	54	>3 months	Spike IgG, Spike IgM, Spike IgA
Zuo et al	Low	100	6 months	CD4+ T Cells
Gaebler et al	Low	87	6 months	Memory B cells
Turner et al	Low	77	7-11 months	Spike IgG
Wang Zh et al	Moderate	90	>2 months	CD4+ T Cells, CD8+ T Cells
Wang Zi et al	Low	63	6-12 months	Spike IgM, Nucleocapsid IgM, Memory B cells
Iyer et al	Low	343	>3 months	Spike IgG, Spike IgM, Spike IgA
Sokal et al	Moderate	39	6 months	Memory B cells
Pre-Prints				
Lumley et al	Low	12219	>6 months	Spike IgG
Gallais et al	Moderate	1309	13 months	Spike IgG, Nucleocapsid IgG
Abu-Raddad et al	Low	314	>7 months	Nucleocapsid IgG
Ward et al	Low	17576	>6 months	Spike IgG

Table 1. *Summary of the body of evidence.*

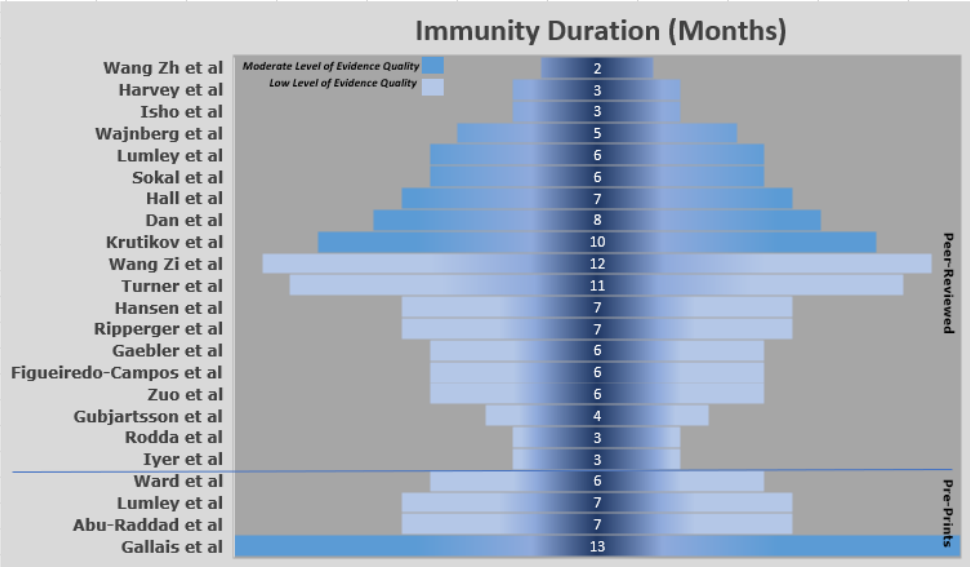

Figure 4. *Demonstrated duration of immunity.*

Conclusions:

The main conclusions from the literature review are:

Eleven peer reviewed studies and four pre-print studies showed natural acquired immunity extending to at least 6-12 months, and one pre-print study suggested immunity of 13 months. The remaining studies only followed cases for less than 6 months. No study reported significant waning of immunity. It is concluded that the current evidence indicates natural immunity is likely to be at least 6 months, and probably in between 6-12 months, but further evidence will be required to determine the upper bounds.

There are several limitations or caveats on these findings. Although most of the reports are from peer-reviewed papers, there are also some pre-print articles (not yet fully peer-reviewed) amongst them. All of the studies are, necessarily, observational in nature. Not all studies have taken into account all of the currently circulating variants of concern; more transmissible variants are likely to appear, and the possibility of altered immune responses with variants may need to be considered in applying these conclusions. Many studies examined single elements of 'immunity' such as antibody titers. More studies will be needed to determine the full spectrum of immune responses. Additionally, there may need to be consideration of those people with reduced immune response, in particular, having received renal transplant, and those under treatment for haematological cancers. Finally, the main limitation is that all studies were limited by the available duration of follow-up data; it is highly likely that data from future studies will mean the period of naturally acquired immunity could be extended. It is therefore recommended that a further review be undertaken within six months from the publication of this report.

Summary:

Currently available evidence indicates that the duration of naturally acquired immunity following SARS-CoV-2 infection is at least 6 months, and is likely longer. Further research is needed to determine the duration of naturally acquired immunity.

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