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SAFETY OF AIRCREW AND AIRLINE PASSENGERS DURING THE COVID-19 PANDEMIC: A NARRATIVE REVIEW

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ABSTRACT

During 2020, severe acute respiratory syndrome (SARS)-coronavirus-2 (SARS-CoV-2) rapidly spread worldwide and caused over 59,000,000 confirmed cases of Coronavirus Disease 2019 (COVID-19), a mild-to-severe respiratory disease that generated a globally unexpected increase in hospitalizations and intensive care unit admissions. COVID-19 – declared a pandemic on March 11, 2020, by the World Health Organization – is substantially affecting the aviation transportation system worldwide.

In an effort to mitigate the pandemic, nearly all countries adopted preventive and containment measures – including lockdown or restriction to movements – to decrease human-to-human transmission. As a consequence of travel restrictions, a considerable drop in air passenger demand occurred, although in-flight transmission SARS-CoV-2 cases have been limited to date. In addition, the COVID-19 pandemic generated occupational health issues on aviation personnel. Given the magnitude of the disruptions, the role of governmental authorities and legislators is crucial to mitigate the impact of the COVID-19 pandemic.

Particularly, attention should be given to protect both aircrew members' and passengers' health and safety, while minimizing the risk of SARS-CoV-2 transmission. The aim of this review is to provide an overview on the impact of the COVID-19 pandemic on the aviation industry and to highlight the need of critically improving pre-flight diagnostic tests execution to protect the health of aircrew members and ensure airline passengers' safety. Optimizing communications, before and during the flight, to keep aircrew members and passengers properly informed on all travel requirements will be also crucial.

ABBREVIATIONS

2019-nCoV, 2019-Novel Coronavirus; **AAM**, Office of Aerospace Medicine; **AARP**, American Association of Retired Persons; **ACI**, Airports Council International; **ARC**, Airport Research Center GmbH; **CAAC**, Civil Aviation Administration of China; **CART**, Council Aviation Recovery Task Force; **CAT-V**, COVID-19 Air Traffic Visualization; **CoV**, coronavirus; **COVID-19**, Coronavirus Disease 2019; **EASA**, European Union Aviation Safety Agency; **ECDC**, European Centre for Disease Prevention and Control; **EUA**, Emergency Use Authorization; **EU-OSHA**, European Union information Agency for Occupational Safety and Health; **FAA**, Federal Aviation Administration; **FDA**, U.S. Food & Drug Administration; **FIND**, Foundation for Innovative New Diagnostics; **HEPA**, high-efficiency particulate air filters; **IATA**, International Air Transport Association; **ICAO**, International Civil Aviation Organization; **ICTV**, International Committee on Taxonomy of Viruses; **ICU**, intensive care unit; **MERS-CoV**, Middle East respiratory syndrome coronavirus; **MCMs**, medical countermeasures; **NATs**, Nucleic acid amplification tests; **NCAs**, national competent authorities; **NP**, nasopharyngeal swab; **NSRD**, National Security Research Division; **OP**, oropharyngeal swab; POC, point-of-care; **rAd5**, recombinant adenovirus type 5; **rAd26**, recombinant adenovirus type 26; **RAeS**, Royal Aeronautical Society; **RDT**, rapid diagnostic test; **RT-PCR**, reverse transcription polymerase chain reaction; **SAGE**, Strategic Advisory Group of Experts; **SARS**, severe acute respiratory syndrome; **SARS-CoV-2**, severe acute respiratory syndrome-coronavirus-2; **U.S.-CDC**, U.S. Centers for Disease Control and Prevention; **WHO**, World Health Organization; **WRS**, work-related stress.

1. INTRODUCTION

In December 2019, China authorities identified an epidemic initiated by a novel virus strain, belonging to the coronaviruses (CoV) family (Coronaviridae), that was initially named "2019-Novel Coronavirus" (2019-nCoV) and, then, termed severe acute respiratory syndrome (SARS)-coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). Such virus – inducing a mild-to-severe respiratory disease defined Coronavirus Disease 2019 (COVID-19) – was responsible for a globally unanticipated and substantial increase in hospitalizations, especially in intensive care unit (ICU) admissions, due to atypical forms of pneumonia associated in many cases with respiratory distress (Wiersinga et al. 2020).

SARS-CoV-2, as the previous SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), is a beta-coronavirus. Beta-coronaviruses are responsible for infections in several species of mammals, including humans (Karpiński et al. 2020). Bats are considered the probable natural hosts for SARS-CoV-2; pangolin is assumed to be a major intermediate host for the transfer of SARS-CoV-2 to humans (Machhi et al. 2020). SARS-CoV-2 is primarily transmitted from person to person via respiratory droplets during face-to-face contacts (Wiersinga et al. 2020). The transmission can also occur indirectly, by touching contaminated items/hard surfaces and, then, touching the face, eyes, or mouth (Karpiński et al. 2020).

Both asymptomatic and symptomatic carriers are able to spread the infection (Wiersinga et al. 2020). From a genetic standpoint, there is a link between this virus and another airborne coronavirus, namely the SARS-CoV. This started its propagation in late 2002 and, then, throughout 2003, thus generating a significant outbreak of SARS (Petersen et al. 2020). After appearing first in China (specifically in Wuhan, the capital city of Hubei Province), SARS-CoV-2 was characterized by a swift diffusion all over the world. As a result of both such fast viral dissemination and the clinical severity of COVID-19 in certain critical patients, the World Health Organization (WHO) declared the disease a pandemic on March 11, 2020 (Cucinotta and Vanelli, 2020; Jin et al. 2020).

Since March 08th, 2021, the WHO documented over 116,500,000 confirmed cases of COVID-19, with over 2,550,000 deaths, worldwide (available at https://covid19.who.int/). Both preventive and containment procedures – including lockdown measurements and/or limitations to movements – have been implemented by almost all countries to diminish the human-to-human transmission pathway and limit the pandemic (Acuti Martellucci et al. 2020). The application of such restrictive measures raised crucial queries concerning the existing security of travelling and the protection of travelers. For this reason, recommendations were issued to inhibit travels, apart from those strictly necessary (The Lancet Infectious Diseases, 2020).

In this scenario, the COVID-19 pandemic is drastically affecting and changing the rationale of travelling, in general, and air transportation, in particular. The general aim of this narrative review is to: I) outline the impact of the COVID-19 pandemic on the aviation industry and II) highlight the need of critically improving pre-flight diagnostic tests execution to protect the health of aircrew members and ensure airline passengers' safety.

Particularly, the manuscript was structured across four different relevant conceptual domains: I) effect of COVID-19 pandemic on the international air transport (also including the impact on well-being of pilots and passengers); II) safety of both aircrew members and passengers; III) pre-flight SARS-CoV-2 molecular tests for both aircrew members and passengers; IV) effective vaccines against SARS-CoV-2 for aviation workers.

A rigorous systematic search strategy of the literature was conducted from PubMed and MEDLINE databases in the English language. Specifically, keywords such as "SARS-CoV-2", "COVID-19 pandemic", "infection", "in-flight transmission", "aviation industry", "air transport", "aircraft", "airport", "aircrew members", "passengers", "travelers", "safety protocols/guidelines/ guidance", "rapid antigen test", "molecular test" "screening", "RT-PCR", "vaccine", and "vaccination" were used. The search terms were combined using the Boolean operators "OR" and "AND". We also explored the official websites of European, U.S., and global air transport / aircraft / aviation associations, organizations, foundations, administrations, societies, agencies, and task forces as well as key healthcare organizations and initiatives.

2. IMPACT OF COVID-19 PANDEMIC ON AIR TRANSPORTATION

With the rise of the pandemic, several governments around the world decreed the closure of their national borders to prevent the entrance of infected travelers coming from countries exhibiting SARS-CoV-2 transmission. In this context, performing a constant global monitoring and surveillance of COVID-19 pandemic dynamics has been crucial to inform governments about border shutdown. After introducing travel restrictions, a considerable drop in air passenger demand was documented (around 70%-80% in April 2020 compared to same month in 2019), followed by a sudden temporary halt of the activity of numerous important airlines, according to the International Air Transport Association (IATA).

Next, the IATA called on the governments to provide help to the airlines and support their activities (Serrano and Kazda, 2020). The International Civil Aviation Organization (ICAO) – a United Nations-based agency committed to develop standards and policies for the worldwide progress of the civil aviation system (available at https://www.icao.int/) – estimated a loss of 28.4% in the passenger traffic capacity (in the airports) within the January 01st – March 31st period of 2020, corresponding to a decrease of over 610 million passengers.

Such estimations have been calculated in terms of both national and transnational traffic. The ICAO also stated that, overall, the COVID-19 pandemic influence on the international passenger traffic led to drop the number of travelers to over 1.5 billion and the seat capacity to over 70%, at the conclusion of 2020. In addition, there is the necessity for both airports and airlines to address the issue of loss of profits for the year 2020, around USD 100 billion and USD 314 billion, respectively. To cope with such a dramatic situation, the ICAO created the Council's Aviation Recovery Task Force (CART), acting on a globally coordinated level to help resurrect the international air transport sector.

In this regard, the ICAO reorganized its CART "Take-off" guidance, a structured framework aiming at facing the impact of the COVID-19 pandemic on the whole aviation transportation system (available at https://www.icao.int/covid/cart/Pages/CART-Take-off.aspx). The guidelines proposed by the CART, periodically revised, are expected to complement the government recommendations, adopted at regional/national level, to recover from the COVID-19 pandemic.

Because of the global nature of the issue, the role of governments and public authorities at local/regional/ national level – mainly on the category and time length of measures concerning transport activities – will be significant to support the progress of the aviation industry (Abate et al. 2020). Thus, it is necessary to develop and implement a framework that mitigates the impact of the current COVID-19 pandemic on the global aviation transportation system.

2.1. IN-FLIGHT TRANSMISSION OF SARS-COV-2

In general, the risk estimation of being infected by the SARS-CoV-2 during air travel is inferior to that estimated in other environments, including public transportation means (commuter rails and buses), offices, schoolrooms/teaching spaces, superstores/ hypermarkets (Pombal et al. 2020). While the amount of supposed and confirmed cases of in-flight COVID-19 diffusion among passengers worldwide seems to be limited, a study of COVID-19 transmission in Chinese high-speed trains among contacts of over 2,300 acknowledged cases reported a global rate of 0.3% among all commuters (Pombal et al. 2020). Technically, in the aircrafts, the entrance of the air into the cabin is allowed through the overhead inlets; then, the airflow is directed to floor-level outlets.

Both air entrance and exit occur at the level of the same seat row or adjacent rows. Since a moderately reduced airflow is present among seat rows, the diffusion of respiratory particles among rows is unusual. Compared to internal environments, the airflow circulating in the aircrafts is significantly more rapid: part of it comes from outside, the remaining is reused via the high-efficiency particulate air (HEPA) filters.

Of note, the infection might also be due to the physical contact among passengers. In order to diminish this risk, seat backs are designed to offer a physical barrier in such a way that travelers can be partly stationary and face-to-face contacts are restricted (Pombal et al. 2020). Past investigations of potential SARS-CoV-2 in-flight transmissions did not report any molecular evidence (Eldin et al. 2020; Qian et al. 2020). For instance, contact monitoring of two passengers who moved from China to Canada (15-hour flight Wuhan-Guangzhou-Toronto) did not yield any indication of secondary infections from this flight, i.e. following protracted exposure to air travel (Schwartz et al. 2020).

The latest guidance from the IATA classifies the in-flight transmission risk as very low (see https://www.iata.org/en/pressroom/pr/2020-05-05-01/). It recommends the compulsory use of face masks without supplementary measures to increase physical distance on board, such as limiting or blocking the middle seats. However, these recommendations have been recently challenged (Choi et al. 2020; Khanh et al. 2020). For this reason, increasingly attention is given to precautions, not only including the need of wearing a mask, but also avoiding travelling if the healthy status is not optimal, and restricting carry-on luggage.

Physical distance should be kept from the other passengers (wherever practicable). The presence of visibly unwell passengers should be reported to staff. In case of overhead air nozzle, this needs to be controlled in order to point it to the head and kept on full. Passengers should stay at their own seats and hands should be repeatedly disinfected (Pombal et al. 2020).

2.2. ESTIMATING COVID-19 OUTBREAK RISK THROUGH AIR TRAVEL

Two substantial events affected, without precedent, the air transportation system worldwide: I) the rapid rise in the overall amount of SARS-CoV-2 cases in a constantly growing number of countries and II) the COVID-19 outbreak. The aviation industry has been suffering the pandemic outbreak effects more than any other industry (Sun et al. 2020). Beyond governmental political and economic evaluations related to the future of the aviation industry, the single individuals necessitate to critically assess both benefits and risks when undertaking the decision to travel by flight.

Actually, being next to foreigner travelers with unidentified infection status for a certain number of hours, especially during long-distance travels, might represent a big concern and generate anxiety, apprehension, and nervousness, although in-flight transmission SARS-CoV-2 cases have been very restricted, to date. Analyses have been conducted to estimate the risk of different sites and environments as sources of potential future COVID-19 outbreaks through air travels. Alterations in flight capacities and destination population densities can induce an inhomogeneous distribution of such a risk.

According to a model developed by Daon and colleagues (2020), airports situated in East Asia show the most elevated risk of being causes of upcoming outbreaks. Potential outbreaks in large regions susceptible to pandemics, such as Brazil and India, are expected to be generated by travelers moving from within those areas. This has been also reported for Europe, U.S., and China, normally considered less susceptible and exposed areas) (Daon et al. 2020). A precise and exact quantification of the spatial diffusion of the outbreak risk will facilitate the efficient and successful allocation of resources and activities to optimally target public health interventions.

The study of SARS-CoV-2 importation/exportation relative risk, conducted from each airport in cities across the world, reported that Asia (northeast regions), Australia, Latin America countries, and U.S. might be at risk, besides Europe, Middle East, China, and East Asia. Hence, governments that have airports in their jurisdiction and under their authority, need to develop and apply rigorous protocols to halt the COVID-19 pandemic (Nakamura and Managi, 2020). Recently, the National Security Research Division (NSRD) of the non-profit RAND® Corporation, in charge of performing studies for the U.S. government and its allies (https://www.rand.org/nsrd.html), settled the COVID-19 Air Traffic Visualization (CAT-V) tool.

This device is able to integrate records from the Johns Hopkins University (particularly, the Coronavirus Resource Center, gathering specialists in infectious diseases and public health issues) with accurate air travel files provided by the IATA's Nationality Traffic Report (see https://www.rand.org/nsrd/projects/cat-v.html). Thus, such a tool makes it doable to monitor the interaction between SARS-CoV-2-related infections and commercial air travels in order to globally track the infection risk.

As a result, this device provides a "heat map" illustrating the risk associated with distinct air travel itineraries. This will allow governmental authorities, legislators, and analysts to appraise the real effect of travel-related policy interventions; for instance, the restrictions of air travel from various countries and areas.

2.3. COVID-19 PANDEMIC AND PILOT WELL-BEING

By exerting a deep impact on the individuals, from both economic and psychophysical standpoint, the COVID-19 pandemic is increasingly disrupting the sense of community, thus damaging society. By touching, on a global level, the aviation transportation system, the outbreak caused a substantially increased stress on pilots, aircrew members, hence affecting the flight performance. Airline pilot stress is a phenomenon frequently occurring in the aviation industry and consists of at least three types of stressors: I) physical stressors, including extremely high humidity and temperature, oxygen deficiency, vibration/noise, etc.); II) physiological stressors, including tiredness, sensation of hunger, suboptimal physical condition, presence of an illness, etc.), and III) psychological stressors, including business/financial uncertainties, emotional factors, awful and unhealthy interpersonal relationships with boss/colleagues or with family members, etc.) (Harris, 2011; Moriarty, 2015).

Studies concerning the correlation between stress and workload highlighted that stress is at its highest levels during the most critical phases of a flight – i.e. take-off and landing – both inducing increased workload (Roscoe, 1978). In this regard, heart rate (mean values) and incremental (delta) heart rate are relevant parameters of physiological workload. Peak heart rate occurs in both take-off and landing; delta heart rate results significantly increased during these two phases, as well (Lee and Liu, 2003). Thus, there is the urgent need to develop tools to support and improve pilot stress coping and resilience. Stress coping strategies encompass cognitive, behavioral, and psychological approaches that help diminish and/or overcome internal and external stressors.

Stress coping methods facilitate flight mission efficiency and contribute to flight safety, therefore they are associated with flying performance (Joseph, 2016). A recent analysis exploring work-related stress (WRS) and pilot stress coping practices emphasized that fatigue/sleep self-management, diet control, and performing physical activity, are the most effective solutions that result in lowered depression severity.

In this regard, the Royal Aeronautical Society (RAeS) organized a webinar on mental wellbeing, stress coping methods, and ways to promote resilience and wellness management (available at https://youtu.be/pT8uB7fVV44). As a result of the COVID-19 pandemic, several pilots could not keep their job, others are on extended leave, or have to deal with a reduced work schedule (Sobieralski, 2020); furthermore, others were able to keep their job but they had to work in totally dissimilar environments, thus cumulating additional stressors.

This negative picture had a deleterious impact on the sense of purpose and economic safety of the pilots (Cahill et al. 2020a). Moreover, the existing restrictions on social distancing, coupled with the present work vicissitudes, are affecting the main key points – biological, psychological, and social (based on the WHO "BioPsychoSocial model of Health and Wellbeing") – of pilots' health (Cahill et al. 2020a).

Notably, the Flight Safety Foundation (available at https://flightsafety.org/) developed a guide, based on the above-mentioned "BioPsychoSocial model of Health and Wellbeing", to promote and optimize wellbeing management and resilience for the specialists of the aviation industry during the COVID-19 pandemic and also after (Cahill et al. 2020a). Particularly, self-management practices are advocated that cover six "core" (primary) behaviors, namely: activities, physical exercise, diet, sleep, stress management, and social relationships (Cahill et al. 2020b).

2.4. COVID-19 PANDEMIC AND PASSENGER WELL-BEING

The majority of individuals are trying to address the delicate issue of deciding to: I) travel after months spent under restrictions or II) remain at home to avoid hours of "confinement" in an aircraft with other unknown individuals. Reflections include, among other, questions on the exact risk of travelling, the areas where it is really safe to go, and the specific protocols currently in place to diminish the risk of COVID-19 exposure, for the individuals who need to travel (The Lancet Infectious Diseases, 2020).

A relevant support to the travelers that airports can provide is: I) delivering effective guidelines to deal with travelers' apprehension and II) boosting initiatives in the field of public health. In order to set homogeneous rules that efficiently coordinate air travel, as advocated by airlines and airports, the previously mentioned ICAO's CART "Take-off" framework has been introduced to face the threats associated with COVID-19 pandemic.

A crucial urgency is strengthening public education to guarantee simple and effective communication of strategies and procedures as well as consistent information (Brugger, 2020). In this regard, an articulated "Public Health Risk Mitigation Measures" plan has been established under the CART "Take-off" guidance (available at https://www.icao.int/covid/cart/Pages/Public-Health-Risk-Mitigation-Measures.aspx).

In general, after the terrorist assaults of September 11, 2001, travelers became more flexible and compliant to novel improved security rules in airports. Likewise, the COVID-19 pandemic is assumed to redefine what is normal for travelers, with the theoretically positive consequence of decreasing the risk of transmission of several other categories of infections, in addition to SARS-CoV-2 (The Lancet Infectious Diseases, 2020).

3. PROTECTING HEALTH AND SAFETY OF AIRCREW MEMBERS AND PASSENGERS

The currently globally acknowledged situation about the COVID-19 pandemic (including the implemented containment measures), the possible risk of being exposed to infected individuals, and the necessity to deal with atypical and unique situations in the workplace, are assumed to adversely impact the mental health and wellbeing of both aviation personnel and passengers. The progressive reopening of international flights will entail several discussions and meetings about the measures for risk management related to the COVID-19 pandemic.

In general, once the limitations from the governments on the aviation industry will start being less severe, the practices established by the appropriate authorities and specialists will need to be accurately obeyed to regularly monitor the COVID-19 pandemic. Operatively, thinking to a passenger trip, a reliable and efficient risk management must be warranted along the path "departures airport-flight-arrivals airport".

3.1. SAFETY GUIDANCE FOR AIR CARRIERS, AIRCREW MEMBERS, AND PASSENGERS

Delegates from ICAO, IATA, and the Airports Council International (ACI) produced, in cooperation with the WHO, guidance on how to deal with suspected cases onboard the aircraft (WHO, 2020). Then, other protocols have been released, including a publication resulting from the collaborative effort between IATA and ACI. This provides strategies to promote the secure resume of the aviation operations and states that novel potential measures, introduced along the whole trip, should reduce SARS-CoV-2 transmission risk in both airports and aircrafts (ACI and IATA Joint Approach, 2021).

The employees of the aviation might also refer to the guidance elaborated by the European Union information Agency for Occupational Safety and Health (EU-OSHA; https://osha.europa.eu/en/themes/covid-19-resources-workplace). Besides these operational guidelines, the "COVID-19 Pandemic – Operational recommendations", integrated in the amendment of the European Union Aviation Safety Agency (EASA) Safety Information Bulletin, could be useful to both airport and aircraft workers.

Such bulletin – based on the documentations circulated by the WHO, ICAO, and the European Centre for Disease Prevention and Control (ECDC) – delivers recommendations to airport/aircraft operators and national competent authorities (NCAs) on how to abate the risk of SARS-CoV-2 diffusion. The European Commission's Communication authorized the EASA and the ECDC to cooperatively produce highly comprehensive and accurate operational protocols for the aviation area, finally arranged under the Aviation Health Safety Protocol.

This delivers the best practices on how airport/aircraft operators and NCAs can safeguard the health and safety of travelers, as well as of the aviation staffs while, at the same time, lowering the risk of SARS-CoV-2 circulation (EASA ECDC COVID-19 Aviation Health Safety Protocol, 2020). Interestingly, some authorities, such as the Civil Aviation Administration of China (CAAC), released guidelines where risk scoring mechanism were used to separate responses requested for international versus national flights. Different prevention and control methods are suggested based on the risk score (CAAC, 2020).

4. APPROPRIATENESS OF TESTING BEFORE TRAVEL

Performing an early and timely recognition of SARS-CoV-2 is unquestionably essential for estimating COVID-19 incidence and mortality rates. Developing a fast, accurate, manageable, and economical detection method of SARS-CoV-2 – at the early stage of the viral infection – can assist in the containment of the COVID-19 pandemic.

Hence, the steps of design / development / substantiation / validation / implementation of diagnostic tests during the early phase of the pandemic have been actively addressed by a large number of diagnostic test manufacturers under the Emergency Use Authorization (EUA) of the U.S. Food & Drug Administration (FDA) (Dhamad and Abdal Rhida, 2020; Vandenberg et al. 2020). The EUA aims at reinforcing the defense of the public health and expediting the prompt accessibility to medical countermeasures (MCMs) – namely, medical devices, diagnostic tools, vaccines, and drugs – throughout public health crises (Mitchell et al. 2020).

4.1. DIRECTIONS BY THE INTERNATIONAL AIR TRANSPORT ASSOCIATION AND THE INTERNATIONAL CIVIL AVIATION ORGANIZATION

The IATA advocated the planning of systematic COVID-19 testing for all travelers prior to departure: this represents an alternative to quarantine procedures in order to effectively restore air connectivity worldwide. IATA is expected to act in cooperation with the ICAO and health authorities to execute this practice. According to the IATA, a test has to be scalable, i.e. it needs to meet the standards of rapidity, precision, user-friendliness, and cost-efficiency; additionally, it has to be distributed systematically under the government authorities, based on approved international criteria.

Once a test is requested, it shall be carried out within 24h prior to traveling and implemented off-airport (Bwire et al. 2020; Wang et al. 2020). At present, there is no a screening test for SARS-CoV-2 that has been definitively validated for the use in the aviation industry. However, innovative screening methods are constantly under elaboration; these are expected to be increasingly faster, more consistent, and less expensive.

Moreover, various health check situations are frequently reproduced in the airport, on both departure and arrival areas (Dhamad and Abdal Rhida, 2020; Kilic et al. 2020; Vandenberg et al. 2020). In general, the implementation of a COVID-19 testing prior to departure seems to be preferred to other options, as it paves the way for a "clean" environment throughout the travel process. In contrast, examinations done on arrival spots would discourage passengers with the prospective of undergoing quarantine and isolation at destination in case of a positive outcome.

4.2. FEASIBILITY OF FAST AND NON-INVASIVE MOLECULAR TESTS FOR COVID-19 DETECTION OR ANTIGEN (IMMUNOLOGICAL) TESTS IN AIRPORTS

Generally, molecular screenings are significant for COVID-19 diagnosis, as its clinical symptoms (fever, fatigue, dry cough, breathing complications) can have similarities with those of common cold and influenza, or even further respiratory diseases. As other viral detection methods, numerous molecular targets exist (Kilic et al. 2020). The choice of highly definite targets is decisive to select the most appropriate assay formats and effective diagnostic approaches. Amended information on FDA-cleared commercial tests is documented in the "COVID-19 Diagnostics In Context" file (available at https://csb.mgh.harvard.edu/covid) (Weissleder et al. 2020).

The instructions settled by the U.S. Centers for Disease Control and Prevention (U.S.-CDC) state that upper and lower respiratory tract specimens – including nasopharyngeal (NP) or oropharyngeal (OP) swabs, aspirates from lower respiratory tract, sputum, and bronchoalveolar lavage – are the right varieties of samples that need to be examined. For the purpose of initial diagnoses, collecting an upper respiratory specimen, i.e. selecting the NP swab first (although OP swabs might denote a satisfactory specimen type) is advocated (Center for Disease Control and Prevention, 2020).

Nucleic acid amplification tests (NATs) used for COVID-19 diagnostics are anticipated to identify distinctive viral RNA sequences in the N (nucleocapsid), E (envelope), S (spike), or RNA-dependent RNA polymerase genes. Notably, NATs are able to provide elevated accuracy; moreover, results are normally acquired in few hours (Kilic et al. 2020). Thus, NATs are performed to identify viral infection within its early period. Consequently, NATs are suggested to disclose the acute disease even when the individuals show minor or undefined clinical signs (Kilic et al. 2020).

Particularly, reverse transcription polymerase chain reaction (RT-PCR) was the first diagnostic approach used for COVID-19 detection and is the present gold standard for COVID-19 identification (Corman et al. 2020). Indeed, RT-PCR has been designated as the most consistent methodology to implement, by both the WHO and the ECDC (ECDC, 2020). RT-PCR-based screenings are typically carried out in centralized laboratories since they need a specific equipment, qualified personnel, and a strict monitoring of contamination (Kilic et al. 2020). Immunoassays help identify viral proteins (i.e. antigens) or antibodies produced by the host against the virus.

Antibody tests enable to disclose current or previous infection, hence elucidating the viral transmission dynamics (Kilic et al. 2020). Antigens and antibodies exhibit increased stability than RNA; thus, they are less subject to degradation during the steps of transport and storage. Serologic analysis is used as a large-scale screening tool. For instance, by examining antibodies among the general population via random selection of the specimens ("serosurvey"), public health agencies are able to compute the infection prevalence and fatality rate, hence excluding the requisite for prolonged molecular confirmatory investigations (Kilic et al. 2020).

At present, "rapid antigen tests" – designating a novel generation of faster, more inexpensive, transferable, and easy-to-execute assays – are increasingly accessible in the European market. By disclosing the existence of antigens, these assays can be applied to identify an enduring and persistent infection. They are appropriate for point-of-care (POC) examinations of fingerpick blood, saliva, or nasal swab fluids (Kilic et al. 2020).

In the European Commission "COVID-19 In Vitro Diagnostic Devices and Test Methods Database" file (available at https://covid-19-diagnostics.jrc.ec.europa.eu/), 72 CE-marked rapid antigen assays have been integrated.

The application of immunoassays at the POC is a practice collectively acknowledged within the post-restriction COVID19 control strategy, as documented by the WHO (please, see https://apps.who.int/iris/handle/10665/331713). A massive volume of data is obtainable on over 240 EUAlevel COVID19 diagnostic assays. The amount of commercially manufactured COVID19 molecular tests is nearly comparable to that of commercially manufactured immunoassays (Vandenberg et al. 2020).

The Foundation for Innovative New Diagnostics (FIND, see https://www.finddx.org/) is in the process of appraising over 800 diagnostic tests. Around 250 out of these assays have been designated as rapid diagnostic tests (RDT), given their limited time (< 30 minutes) to produce a result. Remarkably, all these novel assays should have clinical cutoff values that would be useful to enrich their medical value (Woloshin et al. 2020).

Currently, negative outcomes achieved in these kinds of assays do not entirely exclude present or former infections because of potential falsenegative outcomes (Kucirka et al. 2020). Whether SARS-CoV-2 screening tests necessitate to be qualitative or quantitative is still argued (D'Cruz et al. 2020). Actually, quantitative test scores are a potential requirement to select COVID19 therapy approaches, for therapy follow-up, or for supporting the development of vaccine trials.

4.3. IMPLEMENTING AND EXTENDING PRE-FLIGHT COVID-19 TESTING FOR BOTH AIRCREW MEMBERS AND PASSENGERS

Recently, due to troubles concerning the identification of SARS-CoV-2 infected asymptomatic individuals, screening tests of SARS-CoV-2 are acquiring a mounting significance. In particular, SARS-CoV-2 RT-PCR test centers have been settled in a number of airports, based on government requirements, to deliver free tests for travelers coming back from countries acknowledged as "risk areas".

Other airports took deliberately the decision to install SARS-CoV-2 RT-PCR screening centers adjacent to them and are still waiting for formal directions and assistance by the governments on the way health checks need to be implemented. For instance, United Airlines, Inc. demanded aircrew members operative in the San Francisco-Tahiti air route to get a pre-flight SARS-CoV-2 assay. The company arranged to extend this screening service to additional international destinations (Maszczynski, 2020). Another relevant example comes from Virgin Atlantic Airways Limited, that has been the first airline in UK to organize a rapid

POC pre-flight COVID-19 testing trial for aircrew members. This action was aimed to safeguard the health of its customers (Airport World, 2020).

The airlines need to be involved in disinfecting aircrafts (for instance, the U.S.-CDC, ECDC, and EASA delivered protocols for aircraft operators to properly clean and sanitize the aircrafts), supervising and correcting boarding/de-boarding processes, including effectively running health checks on customers before their embarkment, implementing practices on board to detect and deal with suspicious SARS-CoV-2 cases, optimizing communication protocols both before and during the flight to preserve a proper information with aircrew members and passengers about travel requirements.

However, the general picture is that each state still acts on a specific national level concerning travel restrictions. As a result, practices are implemented with individual approaches that are largely different. For instance, some NCAs asked for negative SARS-CoV-2 RT-PCR screening test prior to travel or on arrival; others allow waiver of self-quarantine in case of recent negative result on the SARS-CoV-2 RT-PCR assay (EUROCONTROL, 2020).

5. VACCINES

5.1. COVID-19 VACCINE DEVELOPMENT

Although an efficient vaccine protecting against the COVID-19 health emergency is expected to be available, the world is currently relying on adhering to social distancing guidelines, hygiene and cleaning protocols as well as using repurposed medicines. In general, to effectively produce safe vaccines, it is fundamental that both pre-clinical and clinical trials are carried out with the highest level of caution to prevent adverse effects (Sempowski et al. 2020).

Based on the WHO-based COVID-19 candidate vaccine landscape and tracker database, as of March 08th, 2021, over 180 candidate vaccines are in preclinical development and over 75 in clinical development (in different steps of clinical assessment) (WHO, 2021). Although the volume of production of the vaccines could not satisfy the general need of vaccines in the immediate future, it would be even highly valuable to generate a partial amount of vaccines accessible for emergency issues and the most exposed and weakest individuals within as short time frame.

Then, the final aim would be the worldwide vaccines delivery to the remaining population categories within the end of 2021 (Sharma et al. 2020).

5.2. NEED OF PRIORITIZATION OF COVID-19 VACCINE FOR AVIATION WORKERS

Because of the relevance of the air transportation system in the global delivery of vaccines, both the IATA and the ICAO advocated a significant prioritization of the aviation personnel to get access to vaccines, once the other more susceptible categories (including vulnerable individuals, older individuals, health professionals, police officers, etc.) will have received the vaccine. Such IATA's appeal to the governments is perfectly in line with the WHO "SAGE [Strategic Advisory Group of Experts] Roadmap For Prioritizing Uses Of COVID-19 Vaccines In The Context Of Limited Supply" framework.

Such a protocol defines eligibility and priority criteria for individuals to be vaccinated according to epidemiologic data and specific circumstances of vaccine delivery: notably, air transportation system workforces have been integrated by SAGE into this framework (WHO SAGE, 2020). In parallel, different airlines are intensely promoting incentives to recover the typical volume of passengers before the pandemic commenced: vaccination for both pilots and flight attendants. In particular, Etihad Airways stated to be the first airline around the globe with all aircrew members on board vaccinated.

Then, Singapore Airlines, SilkAir, and Scoot, i.e. the carriers of the Singapore Airlines Group, indicated to be the earliest air companies to carry out air travels with all pilots and aircrew members protected by the vaccine. Thus, performing vaccinations is considered the crucial practice – accompanied by rigorous screening procedures and safety protocols – for promoting borders reopening and fully recovering optimism, confidence, and enthusiasm on travels (Sampson, 2021). In a recent report, the American Association of Retired Persons (AARP) emphasized that passengers might necessitate an evidence of COVID-19 vaccination in order to regularly fly.

In this regard, some airlines started assessing digital "health passports" that should consistently attest the negative test result for each passenger and, ultimately, his/her vaccination status. However, there is a heated debate about the introduction of such "vaccine passports", i.e. digital certificates of vaccination. They should offer evidence to other countries that the travelers received vaccination against COVID-19. This should imply to passengers: I) the unrestricted access to flights and II) eluding quarantine/isolation requirements (Ianzito, 2021).

On the other side, inoculating a vaccine into millions of travelers might be a very long process, especially for two-dose vaccine regimens, that would excessively protract the attempts to recover long-distance flights. Notably, the IATA is setting the "IATA Travel Pass", a digital platform enabling passengers to collect certified screening tests and vaccination outcomes on their smart devices.

Specifically, the IATA Travel Pass will allow travelers: I) to record health requirements, II) to find testing/vaccination centers at their departure and/or arrival sites that can perform COVID-19 screening tests, III) to safely receive analysis outcomes or vaccination certificates, and IV) to check whether their test/vaccination match the regulations. Hence, the final aim is to get passengers traveling safely. Efficient pre-departure COVID-19 screening tests would act as a mean to avoid quarantine practices (IATA, 2021).

5.3. RECENT COVID-19 VACCINE UPDATES RELATED TO AVIATION WORKERS

The U.S. FDA provided EUA for vaccines developed by Pfizer/BioNTech partnership (issued on December 11, 2020) and Moderna, Inc. (issued on December 18, 2020). Furthermore, in very recent times, the U.S. FDA released an EUA for the single-shot COVID-19 vaccine, that is property by Johnson & Johnson and was manufactured by its vaccine division Janssen Pharmaceuticals (issued on February 27, 2021) (ALPA, 2021). In this regard, the acting Commissioner of the U.S. FDA, Janet Woodcock, stressed the relevance of authorizing such a single-inoculation vaccine since this action enlarges the accessibility and use of vaccines, currently assumed to be the most practical prevention strategy to halt COVID-19 pandemic (Branswell and Cohrs, 2021).

Remarkably, following a meticulous assessment of safety profiles, the Federal Aviation Administration (FAA) Office of Aerospace Medicine (AAM) decided to implement a program consisting in administrating the three Pfizer/BioNTech, Moderna, Inc., and Johnson & Johnson vaccines to the bearers of FAA-issued airman medical certificates or medical clearances.

Though, some conditions need to be observed: I) it is mandatory to take a 48-hour no-fly/no safety-related-duty interval following each dispensed dose; II) prior to restarting their duty, pilots should be free of side effects related to the vaccine. AAM will analyze the patient response to each vaccine and, if needed, may amend this policy to safeguard the protection of the aviation. In addition, novel vaccines will be singularly assessed once U.S. FDA EUAs are released (ALPA, 2021; FAA, 2021).

5.4. HETEROGENEITY OF PLATFORMS FOR COVID-19 VACCINES

The existing COVID-19 vaccine pipeline includes a large and heterogeneous range of platforms. Candidate vaccines can be categorized into: I) virus-based vaccines (inactivated viruses and live-attenuated viruses), II) protein-based vaccines (protein subunits purified from the virus, recombinant proteins, and virus-like particles), III) next-generation vaccine platforms, including: genetic vaccines (DNA and RNA), replicating or non-replicating viral vectors, and antigen-presenting cells (WHO, 2021; van Riel and de Wit, 2020).

Genetic vaccines, based on naked DNA or RNA platforms, show many benefits because they can be promptly and inexpensively made in laboratories, exhibit an adequate safety profile with no issues in terms of pathogenicity, and can generate a vigorous immune response (Conforti et al. 2020). Non-replicating viral vectors are generally safe and highly efficient and can be produced on a large scale (Sharpe et al. 2020). Thus, owing to the pressing request of a vaccine, it is reasonable to find both nucleic acid-based vaccines (although not yet licensed for use in humans) and non-replicating vector vaccines in current clinical trials (Sharma et al. 2020).

In general, the overall platforms available across different countries are significantly different, both conceptually and technologically. Thus, it is possible that different vaccines will be better appropriate for diverse strata of the human population (Forni and Mantovani, 2021). For instance, in case of passengers travelling across the long route Italy-Russia, it is well-known that these two countries make use of dissimilar vaccine platforms. For Italy, the Pfizer-BioNTech COVID-19 mRNA BNT162b2 (or “Comirnaty”) vaccine (Pfizer, Inc; Philadelphia, PA, U.S.) has been approved.

This is a nucleoside-modified RNA vaccine encoding a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein (Polack et al. 2020). For Russia, the Sputnik V COVID-19 vaccine (Gam-COVID-Vac; Gamaleya National Centre of Epidemiology and Microbiology [Moscow, Russia]) has been approved. This vaccine is based on a heterologous recombinant adenovirus approach using two recombinant adenoviruses, type 26 (rAd26) and type 5 (rAd5), as vectors for the expression of the SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S) (Jones and Roy, 2021).

Because of this substantial diversity, there is the critical issue of assessing whether all types of vaccines are equally effective, when travelling from one country to another. Thus, there is the need, for both drug companies and regulators, to harmonize the various vaccine platforms used in the different nations to facilitate and expedite passengers entrance and circulation among countries.

Such harmonization process would result in some advantages: for instance, pharmaceutical industries would benefit from agreed recommendations about the criteria that their vaccine candidates have to satisfy. Moreover, efforts and times necessary to arrange drug applications would be significantly shortened (No authors, 2020).

6. CONCLUSIONS

COVID-19 is a worldwide pandemic that generated an unprecedented crisis that significantly touched the aviation industry like no other industrial sector, almost certainly owing to its specific business model, primarily based on aircraft load factor. By adopting the face-mask supplies, the hazard on aircrafts is substantially reduced compared to other categories of confined spaces, since modern airplanes are equipped with cabin air filtration systems that include HEPA filters, with an overall flow rate corresponding to approximately 20-30 air changes per hour (constituted by 50% outside air and 50% recirculated air).

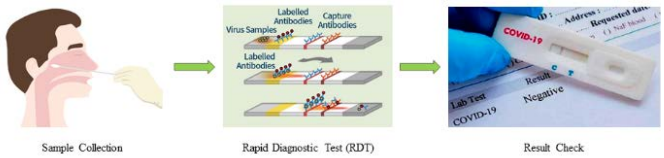
However, since passengers need to transit via airports for traveling, it is necessary to safeguard these environments to diminish the risk of SARS-CoV-2 propagation and preserve confidence into the transport means constantly considered as the safest one (EUROCONTROL, 2020). EASA/ECDC, ICAO, ACI, and IATA supplied standards and procedures to facilitate an efficient and protected recovery from COVID-19 lockdown. Providing an adequate protection to both aircrew members and passengers from the spread of the SARS-CoV-2 infection and the applying these protocols involve a substantial transformation in the way airports manage their terminal facilities.

Notably, EUROCONTROL – a pan-European civil & military association committed to support the European aviation – assigned a study to appraise the influence of the practices addressing COVID-19 pandemic on airports performance and, consequently, on the whole European air traffic network, in relation to the pre-COVID-19 scenario (https://www.eurocontrol.int/covid19). Such study was executed by the Airport Research Center GmbH (ARC), a specialized and independent provider of aviation and airport consulting at international level.

ARC was sustained by six partners, i.e. ACI EUROPE, IATA, and the airports of London Heathrow, Paris Charles-de-Gaulle, Stuttgart, and Swedavia. This report described a still unclear and very dynamic scenario; particularly, it was highlighted the need for a substantial harmonization of the anti-COVID-19 measures and precautions; furthermore, discrepancies in the application of the procedures emerged. It is firmly assumed that the harmonization process within the European framework will significantly enhance the effectiveness of the management of the COVID-19 emergency (EUROCONTROL, 2020).

Current guidelines and recommendations delivered by aviation organizations seem not to be adequate to identify all sick individuals – both aircrew members and travelers – and prevent them from flying. As a result, there is no an unanimously validated and authorized approach by specialists and local authorities and it is highly challenging for them to act in a predictive mode. Once a new regulation is developed and proposed by a local authority, airports and/or airlines need to align with this on a short notice. This adds uncertainties in a smooth operation and increases the risk to have troubles. Currently, the SARS-CoV-2 RT-PCR molecular assay appears to be the most extensively trusted; nevertheless, it is costly and time-consuming. Several practical challenges are anticipated to integrate more efficient and innovative screening methods into the travel process and to determine protocols to safely manage large-scale testing.

Airports, airlines, and governments will then need to cooperate in total alignment to effectively address these issues. The current scenario concerning health checks remains extremely dynamic. Unquestionably, joint efforts undertaken by aviation authorities and governments worldwide, in terms of both standardization and coordination, would allow comprehensive enhancement and progress in diagnostic test preparedness and vigilance that are essential for the swift and successful detection of individuals and, consequently, for increasing the safety for both aircrew members and airline passengers.



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67. FIGURES CAPTIONS

68. Figure 1. COVID-19 rapid antigen test. This RDT is a fast chromatographic immunoassay for the qualitative detection of SARS-CoV-2 antigens in NP swab samples from individuals with suspected SARS-CoV-2 infection. Positive results indicate the presence of viral antigens; however, other diagnostic parameters and the clinical correlation with patient history are essential to define infection status. Positive results do not rule out the infection or co-infection with other viruses. Negative results do not exclude SARS-CoV-2 infection and should not be used as the only basis for treatment or patient management decisions. Negative results should be considered in the context of a patient's recent exposures, clinical history, and presence of clinical symptoms consistent with COVID-19. Abbreviations: COVID-19, Coronavirus Disease 2019; NP, nasopharyngeal swab; RDT, rapid diagnostic test; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.