Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Impact of COVID-19 on ongoing & ensuing dental research

Divesh Sardana\textsuperscript{a}, Cynthia K.Y. Yiu\textsuperscript{a,*,} Colman P. McGrath\textsuperscript{b}

\textsuperscript{a} Discipline of Paediatric Dentistry, Faculty of Dentistry, The University of Hong Kong, Hong Kong Special Administrative Region
\textsuperscript{b} Discipline of Dental Public Health, Faculty of Dentistry, The University of Hong Kong, Hong Kong Special Administrative Region

ARTICLE INFO

Keywords:
Clinical laboratory techniques
Clinical trial
Coronavirus
Dental research
Dentistry
Pandemics

ABSTRACT

The current global COVID-19 pandemic has almost marked its one year of existence and influenced everyone either at an individual or community level. There are plenty of clinical recommendations and guidelines for the practitioners, and beyond doubt, the treating clinicians and other healthcare providers who have been in the frontline of this battle might have been significantly affected as a direct consequence of this pandemic. However, most of the clinical recommendations and guidelines are pivoted on intense research, and thus it is entirely reasonable to foretell that if dental research is impacted, the care-providers and consequently the patients will inevitably be affected.

The present paper attempts to narratively summarize the potential disruptions on dental research due to the pandemic and endeavours to forewarn the dental researchers and scientific communities about the impact of COVID-19 on ongoing and ensuing dental research in the coming years.

The ongoing COVID-19 pandemic has significantly affected laboratory and clinical research globally and will probably change the course of individuals and organizations engaged in dental research for some time. Tailor-made contingency plans by the individuals and organizations and sustaining the momentum of dental research by maintaining the flexibility in administration and utilization of research grants, extensions of grants and funding deadlines, adaption of study designs and procedures, pause or delay enrolment of participants, innovation in research collaborations and scholarly communications across different fields are some of the suggested measures that can be utilized to minimize the disruption during this pandemic.

1. Introduction

While the efforts to restrain the ongoing Coronavirus pandemic are subsisting, even more than one year after the first reported case in Wuhan, China, the pandemic does not seem to end soon, with many countries grappling with the third or fourth wave of this pandemic \cite{1}. Globally, the health-care delivery systems have been strained to an immense extent, and the signs of fatigue in the governments and people are discernible along with a dilemma to maintain an intricate balance between the country’s economy and the healthcare system. Although the tremendous loss of lives, the sequelae of COVID-19 in its survivors, and the declining GDPs of the nations can be represented in numbers, the inconspicuous aftermath of the pandemic will probably torment us for many more years or even decades and apparently, dental research will be no exception. The following discourse attempts to underscore some of the concerns faced in dental research and its related disciplines as well as future tenable impacts (Fig. 1).

2. Laboratory research

Before the current pandemic, research in the field of virology constituted only around 2\% of all biomedical research. However, the number of researchers and laboratories that have focused on addressing the COVID-19 related research is astounding to almost 10–20 \% of the current biomedical investigations \cite{2}. According to an extensive survey conducted among medical researchers in the UK, nearly 60 \% reported switching to COVID-19 research to some extent \cite{3}. With the nationwide lockdowns in many countries and efforts to mitigate crowd gatherings as a result of state executive orders, many laboratories were shut down or are working with reduced capacity to maintain social distancing, consequently overwhelming the workforce. There is also some indication that COVID-19 has widened the disparity of research output among different research fields, nations, genders, age groups, and career stages, with every individual being impacted to a different extent \cite{4}. For instance, female researchers or researchers with dependent children or...
adults are adversely affected because of the pandemic, as are the early-career researchers or researchers with high COVID-19 load in their countries. It is very likely that the researchers might not be able to pursue research positions outside their home countries either voluntarily or due to restrictions by the governments for foreign nationals. Even if the pandemic ceases, it should not be a surprise that many researchers, laboratories, or nations will perpetuate social distancing norms for some time as a pre-emptive measure for the resurgence of COVID-19.

The shipping of research samples and procurements of equipment have been significantly delayed [5]. There were also time-dependent steps of the laboratory experiments that could not be maintained due to shutdowns and thus might cause a compromise in the quality of such studies, despite well-designed study setups and focused research groups. Acquiring human tissue samples, especially healthy extracted teeth for dental research, is getting more difficult over time. The processing and analysis of these teeth to avert the spread of infection added extra human resources, time, and cost to the original research methodology. Many researchers, especially PhDs, postdocs, and other early-career researchers, are not able to complete their laboratory studies in a time-bound manner and require additional funding from the limited funds for dental research. In a survey from Australia, nearly 90% of the researchers identified delays in achieving project milestones, and 65% indicated delays in acquiring new funding [6]. Thus, the lack of research progress and decreased research output might jeopardize future grant applications and funding possibilities for the research groups [7]. Moreover, the time between submitting a paper to its final acceptance has probably increased as publication workflows were impacted, causing a delay in the publications and dissemination of results findings [3]. Funders and the institutions might be stricter with research grant applications that are vulnerable to the pandemic and more flexible towards proposals that can be easily kicked-off and terminated in uncertain scenarios like the current one.

Dental research, like many other fields, utilizes animal models to simulate clinical research, which might have been unethical if conducted in humans. However, there have been concerns of COVID-19 infection in rabbits, cats, ferrets, fruit bats, hamsters, minks, and macaques, but fortunately, laboratory mice, pigs, chickens are not known to be infected with COVID-19 [8,9]. Most of the institutions have taken measures to ensure the laboratories’ safety by limiting the number of animals for only rare genetic lines of the animals. Adequate sanitation and disinfection of the animal cages and chambers, a social distancing between the staff and animals, proper maintenance of food and commodities supplies for the animals, as well as effective communication between the laboratory care-takers and researchers are the keys to sustain dental research involving laboratory animals. Despite the relatively unexplored and minimal risk of animal-to-human transmission, an apprehension of the spread of infection remains in the mind of researchers, and the committees for the regulation of research on live animals will be looking at the research protocols more stringently in the coming years.

3. Clinical studies

The impact of COVID-19 on ongoing clinical studies and community trials has been shattering, with many trials being abruptly halted either as a ramification of the closure of dental facilities for elective dental treatment or due to the closure of kindergartens, schools, and community organizations (like residential organizations for geriatric or people with special health-care needs). Even when they are allowed to resume activities, many kindergartens and community organizations are reluctant and possibly finding it challenging to enable dentists to conduct check-ups in their premises, thereby affecting the follow-up of cohort

Fig. 1. COVID-19 and its ramifications on dental research with suggested approaches for dental researchers.
studies. Furthermore, many recruited participants for these trials have been affected by lockdowns, travel disruptions, or even infected with COVID-19 and received its treatment, thereby were excluded from the ongoing trial. Most patients are unwilling to return to the dental clinic for treatment or follow-up because of the high COVID-19 risk, unless for some emergency dental needs. Therefore, in due course, it should not be a surprise to see higher attrition rates or lower participation rates in future published clinical trials [10].

The bulk materials procured for the trial participants to maintain standardization of both arms of the study (like the same concentration of fluoride dentifrices or mouth rinses) remain underutilized and at the risk of expiry due to the difficulties in arranging follow-up of recruited participants and recruitment of new participants during the pandemic. Data collection is severely hampered due to delayed treatment and follow-up, resulting in unrecoverable data gaps, which may affect data integrity and outcomes of the clinical trial. The methods of data collection are also evolving with a remarkable shift towards the use of online platforms for collecting qualitative data or questionnaire data. However, these technologies might not accurately simulate the data collected in disturbance-free interviewee rooms. Some participants might be concerned about the lack of privacy and confidentiality, while the researchers might have doubts about the validity of the results as the participants could potentially be mentally and emotionally impacted by COVID-19 [11]. All these factors should logically affect the statistical power and validity of the results for “non-pandemic times.”

Besides, the use of special COVID-19 protection kits by the dental care providers following the new safety protocol has added expenditure to the already dwindling dental research funding. The mandatory COVID-19 testing of the patients and the dental care-providers in many areas before dental treatment add further complexity to this unrivalled time. The concerns related to aerosol generation in dentistry and a rapid shift towards less-aerosol producing dental interventions are some of the other possible sources, leading to turmoil in the methodology of clinical trials and possible protocol deviations [12]. Another issue to be considered for the dental fraternity is the COVID-19 risk among dentists and other oral health specialists. A recent report by ADA [13] has found that the COVID-19 transmission rate among dentists to be approximately 1%, which might look encouraging at a cursory glance and the risk of dying with the COVID-19 infection among dentists to be 0.008 % (1:13,000) [14]. Still, another ADA report mentions that nearly 200,419 dentists are practising in the USA [15]. If we are to believe the statistics from both studies, almost 2000 dentists will be affected in the USA, impacting the already fatigued system and clinical dental research. However, the extent of this impact on dental research in the upcoming years depends on the exact figure of dentists being affected by COVID-19. Additionally, the data and opinions regarding the effect of the pandemic on dental research might continue to differ across countries due to different national laws, dissimilar disease burden, varied healthcare and research human capital factors, as well as the possible resurgence of mutations of COVID-19.

Furthermore, it would be interesting to see how the development and institution of coronavirus vaccine [16] to a large population will affect the research on caries vaccine as there is a possibility that many of the individuals recruited for the clinical trials on either of the vaccine will simultaneously receive both types of vaccines. The optimistic outcome of COVID-19 vaccine research should, however, motivate dental researchers involved in caries vaccine research to collaborate with COVID-19 vaccine laboratories in the refinement of the processes for caries vaccine development.

Finally, while it is true that we have made considerable progress in the understanding of COVID-19 prevention and treatment with the vaccine commercially available anytime soon, the effectiveness and the challenges of vaccine delivery at the doorstep will need to be gauged. Currently, all the efforts of the governments, researchers, and organizations are directed at ceasing the pandemic spread and controlling the losses; the dental researchers should be prepared for the impediments in dental research in the coming years and be able to modify their research studies considering some of the factors discussed. The National Institutes of Health and Food & Drug Administration have provided some guidance and recommendations regarding the ongoing and ensuing research affected by COVID-19 and can serve as a useful resource for dental researchers [17,18].

4. Conclusion

Considering the fluidity of the current pandemic, which is unlikely to dissipate any time soon, the need to continue dental research cannot be overstated. Dental researchers should develop tailor-made contingency plans for their ongoing research at all possible means. Some practical measures to be implemented so that dental research could be sustained through the pandemic times include improved access to laboratory facilities balanced with COVID-19 preventive regulations, flexibility in administration and utilization of research grants, extensions of grants and funding deadlines, adaption of study designs and procedures, pause or delay enrolment of participants, innovation in research collaborations and scholarly communications across different fields. Furthermore, the COVID-19 pandemic calls for concerted efforts from government, funding bodies, university, industry, and the scientific community to overcome the critical challenges in these unprecedented times and preserve research momentum to maximize patient health benefits.

CRediT statement

Sardana D contributed to the conception and design, the interpretation of the manuscript and drafted the manuscript. Yiu CKY and McGrath CP contributed to the conception and the critical revision of the manuscript draft. All the authors gave final approval of the manuscript before submission and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

[1] W.H.O. (World Health Organisation), Timeline of WHO’s Response to COVID-19, 2020. https://www.who.int/news/item/29-06-2020-covidtimeline.
[2] N.I.H. (National Institutes of Health), Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), 2020. https://report.nih.gov/funding/categorical-spending/.
[3] VITAE, The Impact of the Covid-19 Pandemic on Researchers in Universities and Research Institutes, 2020. https://www.vitae.ac.uk/impact-and-evaluation/the-impact-of-the-covid-19-pandemic%20on-researchers-in-universities-and-research-institutes.
[4] K.R. Myers, W.Y. Tham, Y. Yin, N. Cohodes, J.G. Thurby, M.C. Thurby, P. Schiffer, J.T. Walsh, K.R. Lakhani, D. Wang, Unequal effects of the COVID-19 pandemic on the sciences, Nat. Hum. Behav. 4 (9) (2020) 880–883. https://doi.org/10.1038/s41591-020-00010-4.
[5] P. Webster, How is biomedical research funding faring during the COVID-19 pandemic? Nat. Med. (2020) https://doi.org/10.1038/s41591-020-00010-4.
[6] A. Peeters, G. Mullins, D. Becker, L. Orellana, P. Livingston, COVID-19’s impact on Australia’s health research workforce, Lancet 396 (10249) (2020) 461, https://doi.org/10.1016/S0140-6736(20)31533-6.
[7] J. Bromberg, C. Baan, J. Chapman, I. Anegon, D.C. Brennan, A. Chakera, A. Chong, E.K. Geissler, C. Guillonneau, N. Heaton, D.A. Hesselink, W. Jassem, C. Jones, R. Josien, B. Kaplan, C.L. Kaufman, W. Lim, Y. Ma, E. Massey, D.B. Ostrander, M.S. Slaughter, S. Tullius, P. Witkowski, G. Wong, The Impact of COVID-19 on the State of Clinical and Laboratory Research Globally in Transplantation in May 2020, Transplantation 104 (11) (2020) 2252–2257. https://doi.org/10.1097/TP.00000000000035362.
[8] C.D.C. (Centers for Disease Control and Prevention), COVID-19 and Animals, 2020. https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html.
[9] A.Z. Mykytyn, M.M. Lamers, N.M.A. Okba, T.I. Breugem, D. Schipper, P.B. van den Doel, P. van Run, G. van Amerongen, L. de Waal, M.P.G. Koopmans, K. Stittelaar, J. M.A. van den Brand, B. Haagmans, Susceptibility of rabbits to SARS-CoV-2, Emerg. Microbes Infect. 23 (2020) 1–17, https://doi.org/10.1080/22221751.2020.1868951.

[10] S. Upadhaya, J.X. Yu, C. Oliva, M. Hooson, J. Hodge, V.M. Hubbard-Lacey, Impact of COVID-19 on oncology clinical trials, Nat. Rev. Drug Discov. 19 (6) (2020) 376–377, https://doi.org/10.1038/d41573-020-00093-1.

[11] J. Bradt, Impact of COVID-19 on clinical research, Nord. J. Music Ther. 29 (4) (2020) 297–299, https://doi.org/10.1080/08098131.2020.1777785.

[12] Z.Y. Ge, L.M. Yang, J.J. Xia, X.H. Fu, Y.Z. Zhang, Possible aerosol transmission of COVID-19 and special precautions in dentistry, J. Zhejiang Univ. Sci. B 21 (5) (2020) 361–368, https://doi.org/10.1631/jzus.B2010010.

[13] A.D.A. (American Dental Association), Report Finds COVID-19 Rate Among Dentists is Less Than One Percent, 2020. https://www.ada.org/en/press-room/news-releases/2020-archives/october/report-finds-covid-19-rate-among-dentists-is-less-than-one-percent.

[14] Y. Ren, C. Feng, L. Baishabala, H. Malmstrom, E. Eliav, Risk for dental healthcare professionals during the COVID-19 global pandemic: an evidence-based assessment, J. Dent. 101 (2020) 103434, https://doi.org/10.1016/j.jdent.2020.103434.

[15] A.D.A. (American Dental Association), Workforce, 2020 https://www.ada.org/en/science-research/health-policy-institute/dental-statistics/workforce#:~:text=How%20many%20dentists%20are%20there,percent%20in%20the%20U.S.

[16] W.H.O. (World Health Organisation), Coronavirus Disease (COVID-19): Vaccines, 2020 https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines?topicsurvey=v8kj13x&gclid=CjwKCAiAnvj9BRA4EiwAuUMDF5ja8hiLQR79pkTRkPou6LeDuytp5FOFx1HWMbfUyGuaOlMr2FpaCoJ3xQAvD_BwE

[17] N.I.H. (National Institutes of Health), Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected by COVID-19, 2020. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-067.html.

[18] F.D.A. (Food and Drug Administration), FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.