

# COVID-19 and digestive health: Implications for prevention, care and the use of COVID-19 vaccines in vulnerable patients

## INTRODUCTION

COVID-19, a respiratory disease at origins, has emerged as a systemic disease associated with a number of extrapulmonary<sup>1</sup> complications.<sup>2</sup> Digestive healthcare is one of the medical disciplines that has been strongly affected by the SARS-CoV-2 outbreak and the implemented restrictions.<sup>3</sup>

Gastroenterologists and hepatologists have seen their clinical routines disrupted and a variety of activities suspended or limited to emergencies. Endoscopy has been one of the most affected procedures, leading to a dramatic decrease of screening and surveillance procedures.<sup>4</sup> On the other hand, lockdowns and social distancing have been associated with unhealthy eating habits, decreased physical exercise, decreased patient interactions with medical services and alcohol consumption (or relapse in abstinent patients).<sup>5</sup>

The COVID-19 vaccination process is currently of great importance. With Gastrointestinal (GI) patients being vulnerable to increased morbidity and worse outcomes from the SARS-CoV-2 infection, strategies to better protect the health of patients with impaired immunity must be a priority.

This position paper serves to inform policy makers, patients, healthcare professionals and the general public of the latest evidence on the impacts of the SARS-CoV-2 pandemic on digestive health. In the same vein, it aims to improve understanding of the clinical considerations on the use of COVID-19 vaccines in patients with chronic digestive conditions and to present UEG's latest recommendations to support evidence-informed decision making.

## IMPLICATIONS OF THE COVID-19 PANDEMIC FOR DIGESTIVE HEALTH AND CARE

The COVID-19 crisis and social lockdown measures to limit virus transmission are likely to have had considerable social consequences beyond the direct death toll attributable to COVID-19.<sup>6</sup>

## Colorectal cancer screening delays

Since the rollout of screening programmes, which now cover over 110 million EU citizens, Europe has observed a steady decline in colorectal cancer (CRC) mortality rates. With endoscopy being largely used for screening, early diagnosis, and treatment of digestive tract cancers, there is a growing concern about a possible mid or long-term increase in the GI cancer burden because of the many elective GI endoscopy procedures that were canceled.<sup>7,8</sup>

Recent data highlighted the detrimental effects on mortality of delaying diagnosis in symptomatic patients with CRC in the United Kingdom because of SARS-Cov-2 pandemic.<sup>9</sup> However, screening delays might have even more dramatic effects on the long-term with increasing incidence and delayed diagnosis once the down-staging effect is reversed by the delays.

According to a recent study,<sup>10</sup> delays up to 4–6 months do not significantly reduce the performance of screening, whereas a lockdown sustained for longer time frames would negatively affect mortality rates. It has been indicated that a backlog sustained beyond 6 months would unequivocally ensue in a significant excess of advanced stages detected through screening and thus in up-staging rather than down-staging, thus increasing disease burden and human and economic costs. Furthermore, for delays beyond 12 months, the increase of advanced stages would lead to a 12% increase in mortality rate at 5 years.

## Increased obesity rates and increased adoption of unhealthy diet and sedentary lifestyle

The impact that the COVID-19 crisis has had on weight-related behaviors, including healthy eating and physical activity is yet unclear, but estimated to be substantial.<sup>11</sup> The lockdowns have led to weight gain, due to lower exercise, boredom/anxiety/depression enhanced eating, characterized by consumption of snacks, unhealthy foods and sweets.<sup>12</sup>

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. United European Gastroenterology Journal published by Wiley Periodicals LLC. on behalf of United European Gastroenterology.

A survey<sup>13</sup> amongst residents of five European countries: Poland, Italy, Spain, Portugal and Great Britain (England and Scotland) showed an increase in the consumption of products with lower nutritional values, and a decrease in the level of physical activity. In addition, a cohort of subjects living in 21 EU countries explored that during the lockdown, body weight increased in 55% of subjects.<sup>14</sup> This worsening of lifestyle habits may increase the risk of both chronic and communicable diseases since nutritional status influences immunity. In the UK Biobank, the risk of COVID-19 positivity was lower when consuming vegetables and higher when consuming processed meats.<sup>15</sup>

There are a multitude of digestive and liver diseases that are associated with overweight and obesity. For example, almost 75% of obese individuals have a fatty liver, thus the COVID-19 pandemic may have potentially increased the prevalence of non-alcoholic fatty liver disease (NAFLD).<sup>16</sup> Non-alcoholic fatty liver disease is a potential risk factor for SARS-CoV-2 infection and severe COVID-19, independent of metabolic syndrome.<sup>17</sup>

## VACCINATION OF GI PATIENTS

As Europe is racing to get its citizens vaccinated against COVID-19, the conditions in which patients with inflammatory bowel diseases (IBD), liver disease, digestive cancer and liver transplant recipients shall be managed must be clarified. To that effect, digestive healthcare practitioners are among the main sources of information on SARS-CoV-2 vaccination for vulnerable GI patient groups.

### Oncological patients

#### Safety of COVID-19 vaccines *in oncological patients*

Patients with cancer, especially those undergoing treatment with chemotherapy, immunotherapy, and combination therapies have been shown to be at higher risk of severe COVID-19. Although evidence regarding vaccination in patients with cancer is limited, there is enough evidence to support anti-infective vaccination in general.<sup>18</sup> On that account, several oncology professional societies do strongly recommend the vaccination of patients with cancer.<sup>19</sup>

#### Efficacy of COVID-19 vaccines *in oncological patients*

The effect of the vaccination should be further evaluated as currently the evidence is scarce on how active treatment with chemo- and immunotherapy affects the amount of protective immunity against COVID-19 after vaccination. The early results of a Dutch multicentre

study on the potential impact of chemotherapy and immunotherapy on the protection afforded by COVID-19 vaccines show that at 28 days after administration of the second dose, adequate levels of antibodies to the virus in the blood were found in 84% of patients with cancer receiving chemotherapy, 89% of patients receiving chemo-immunotherapy in combination and 93% of patients on immunotherapy alone. It remains yet to be seen whether there is a difference in the duration of immune response between the patients and the controls.<sup>20,21</sup>

### Patients with IBD

The clinical management of IBD during the SARS-CoV-2 pandemic has been a matter of great concern to patients and physicians.<sup>22</sup> Inflammatory bowel diseases patients have altered underlying immune responses that may induce increased vulnerability to infections especially in patients that are treated with immunosuppressive medications.

#### Safety of COVID-19 vaccine *in patients with IBD*

To date, all approved COVID-19 vaccines are considered to be safe in immunocompromised patients. Whether mRNA vaccines might pose any additional risk of immunopathology in immunosuppressed IBD patients is still a matter of discussion. The risk of acute immune reactions following vaccination, beyond the known risk of anaphylaxis in patients with a prior history in whom the mRNA vaccines are contraindicated seems to be very low and might only become apparent after millions of doses have been administered.

#### Efficacy of COVID-19 vaccines *in patients with IBD*

Although IBD patients were mostly excluded from COVID-19 vaccine clinical trials, it can be expected from expertise with other vaccines that the immunological response to vaccination may be suboptimal in such patients. Therefore, vaccine effectiveness is indeed a greater concern in IBD patients than safety. Post-marketing studies and ongoing trials will clarify the questions on safety, effectiveness, longevity of protection and optimal vaccination schedules in IBD.

Whilst there are many unknowns in vaccination efficacy in those on immunosuppressive therapy, the risk of contracting COVID-19 in this population is known to be significant. As a consequence and although there are still many unanswered questions, recent expert reviews encourage vaccination in all IBD patients as early as possible, and preferably with mRNA-vaccines as the efficacy to protect against mild and severe disease was shown to be higher for mRNA vaccines.<sup>23,24</sup>

## Patients with liver disease

### Safety of COVID-19 vaccines *in patients with liver disease*

The registration vaccine trials have not included patients with liver diseases or very few patients with mild-moderate liver disease. In the BioNTec/Pfizer and Moderna study, only 0.6% had a mild-moderate liver disease, whereas the Astra Zeneca and Janssen vaccine trials explicitly excluded the patients with pre-existing liver disease.<sup>25</sup> The studies on other vaccines did not report any association of the vaccination with significant side effects or safety signals in patients with cirrhosis.<sup>26</sup> In the real life, in a multicenter study in 381 patients NAFLD (in China) mild adverse events were observed in 25% of the participants such as mild such as in 70 cases (18%) injection site pain, 21 (5%) muscle pain and 20 (5%) cases headache. No specific safety issues were reported in patients with NAFLD.<sup>27</sup>

### Safety of COVID-19 vaccines *in patients with liver transplantation*

In 80 liver transplant recipients who received the BioNTec/Pfizer vaccine, no cases of graft rejection or other safety issues were reported.<sup>28</sup>

### Efficacy of COVID-19 vaccines *in patients with chronic liver disease*

There are very few studies evaluating the efficacy of COVID-19 vaccine in these patients. In the study in patients with NAFLD, neutralizing antibodies against SARS-CoV-2 were detected in 364 (95%) out of 381 cases. Currently, there is an ongoing study, the COBALT study looking at COVID-19 vaccination response and biomarkers in patients with cirrhosis, autoimmune liver diseases and post-liver transplantation.

### Efficacy of COVID-19 vaccines *in patients with liver diseases awaiting liver transplantation and in liver transplant recipients*

Clinical guidelines recommend both pre-transplant and post-transplant vaccination against a variety of pathogens. The rates of immunity against vaccine-preventable viruses in patients undergoing liver transplantation have not been studied extensively.<sup>29</sup> Nevertheless, the optimal time for post-transplantation vaccine administration seems to be approximately 3–6 months after the transplantation, but still remains unknown.

Up to now, few studies has been published evaluating the efficacy of two doses of mRNA-based COVID-19 vaccines in liver transplant patients.<sup>30</sup> Antibody-responses ranged between 47.5%<sup>28</sup>

and 81%.<sup>31</sup> The efficacy of a third dose of COVID-19 vaccine has been evaluated in two studies. In a study with 30 patients with suboptimal response, a third dose increased antibody titers in one third of patients who had negative antibody titers and in all patients who had low-positive antibody titers.<sup>32</sup> In another study with 59 non-responders to two doses of vaccine, a third dose achieved a serological response in 26 (44%) and an increase in antibodies titers among those with previous response were seropositive at 4 weeks after the third dose.<sup>33</sup>

The French Society of Gastroenterology has recently proposed a third dose of vaccine in liver transplant recipients. A 4-week interval between the second and third dose of the BioNTec/Pfizer and Moderna vaccines was suggested.<sup>34</sup>

## UEG's main recommendations

### Healthcare delivery/organization

- When adapting or easing measures, national governments should take into account the latest clinical data to inform policies and guidelines and ensure citizens' protection and support.
- Resumption and maintenance of endoscopic activity is crucial for screening programs, mortality and prognosis of digestive disorders. Elective procedures performance must be balanced with the need to protect healthcare and patients.
- More data are needed to better assess the short and long-term effects of lockdowns on cancer screening, diagnosis and staging across Europe.

### COVID-19 vaccination

- The variability in national vaccination schemes, epidemiological settings and vaccine coverage rates should not affect the prioritization of immunocompromised patient groups.
- The introduction of booster doses should be evidence-based. Antibody titer determination after vaccination in vulnerable populations such as patients with IBD under immunosuppressive treatment, patients with digestive malignancies under treatment, as well as transplant recipients is needed along with further research to determine the optimal titer cut-off.

### EU health capacity

- We support the European Commission's goal of [building a European Health Union](#) and affirm the need to reinforce the mandates of the European Centre for Disease Control and Prevention (ECDC) and the European Medicines Agency to facilitate a strong and coordinated Union-level response to health crises.
- The revision of the ECDC mandate should not miss the opportunity of expanding the agency's mandate to include activities in the


area of noncommunicable diseases. This is particularly important considering the interlinks between communicable and non-communicable diseases amplified by the SARS-CoV-2 pandemic.

## KEYWORDS

cirrhosis, colorectal cancer screening, COVID-19, inflammatory bowel disease, liver transplantation, obesity, vaccination

## CONFLICT OF INTEREST

I have no conflicts with regards to the manuscript.

Markus Peck-Radosavljevic<sup>1</sup> 

Patrizia Burra<sup>2</sup>

Maria Buti Ferret<sup>3</sup>

Pierluigi Fracasso<sup>4</sup>

Luigi Ricciardiello<sup>5</sup> 

Thomas Seufferlein<sup>6</sup>

Philippe Van Hootegem<sup>7</sup>

Monique van Leerdam<sup>8</sup>

Shira Zelber-Sagi<sup>9</sup>

UEG Public Affairs Committee

<sup>1</sup>*Innere Medizin & Gastroenterologie (IMuG), Klinikum Klagenfurt am Worthersee, Klagenfurt, Austria*

<sup>2</sup>*Department of Surgery, Oncology and Gastroenterology, Multivisceral Transplant Unit, Padua University Hospital, Italy*

<sup>3</sup>*Liver Unit, Hospital Universitario Valle Hebrón, Barcelona, Spain*

<sup>4</sup>*Department of Gastroenterology, Ospedale Sandro Pertini, Rome, Italy*

<sup>5</sup>*Department of Medical and Surgical Sciences, Università degli Studi di Bologna, Bologna, Italy*

<sup>6</sup>*Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany*

<sup>7</sup>*Department of Internal Medicine and Division of Gastroenterology and Hepatology, Sint-Lucas General Hospital, Brugge, Belgium*

<sup>8</sup>*Netherlands Cancer Institute, Amsterdam, The Netherlands*

<sup>9</sup>*School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel*

## Correspondence

Markus Peck-Radosavljevic, Innere Medizin & Gastroenterologie (IMuG), Klinikum Klagenfurt am Worthersee, Feschnigstrasse 11, 9020 Klagenfurt, Austria.

Email: [markus@peck.at](mailto:markus@peck.at)

## DATA AVAILABILITY STATEMENT

Not available.

## ORCID

Markus Peck-Radosavljevic  <https://orcid.org/0000-0002-0597-2728>

Luigi Ricciardiello  <https://orcid.org/0000-0003-2568-6208>

## REFERENCES

- Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: the current evidence. *United European Gastroenterol J.* 2020 Jun;8(5):509–19. <https://doi.org/10.1177/2050640620924157>
- Magro F, Abreu C, Rahier JF. The daily impact of COVID-19 in gastroenterology. *United European Gastroenterol J.* 2020 Jun;8(5):520–7. Epub 2020 Apr 11. <https://doi.org/10.1177/2050640620920157>
- Konturek PC, Harsch IA, Neurath MF, Zopf Y. COVID-19—more than respiratory disease: a gastroenterologist's perspective. *J Physiol Pharmacol.* 2020;71(2). <https://doi.org/10.26402/jpp.2020.2.02>
- Chai N, Mei Z, Zhang W, Du C, Wang X, Li L, et al. Endoscopy works during the pandemic of coronavirus COVID-19: recommendations by the Chinese Society of Digestive Endoscopy. *United European Gastroenterol J.* 2020 Aug;8(7):798–803. Epub 2020 Jul 2. <https://doi.org/10.1177/2050640620930632>
- Magro F, Nuzzo A, Abreu C, Libânio D, Rodriguez-Lago L, Pawlak K, et al. COVID-19 in gastroenterology: where are we now? Current evidence on the impact of COVID-19 in gastroenterology. *United European Gastroenterol J.* 2021 Jun 30;9(7):750–65. <https://doi.org/10.1002/ueg2.12115>
- Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet.* 2020;395:912–20. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8)
- Gralnek IM, Hassan C, Beilenhoff U, Antonelli G, Ebigbo A, Pellisé M, et al. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and COVID-19: an update on guidance during the post-lockdown phase and selected results from a membership survey. *Endoscopy.* 2020;52(10):891–8. <https://doi.org/10.1055/a-1213-5761>
- Boškoski I, Costamagna G. Gastrointestinal endoscopy and the COVID-19 pandemic: urgent issues in endoscopic retrograde cholangio-pancreatography and endoscopic training. *United European Gastroenterol J.* 2020 Jul;8(6):743–4. <https://doi.org/10.1177/2050640620926324>
- Sud A, Jones M, Broggio J, Scott S, Loveday C, Torr B, et al. Quantifying and mitigating the impact of the COVID-19 pandemic on outcomes in colorectal cancer. *medRxiv.* 2020. <https://doi.org/10.1101/2020.04.28.20083170>
- Ricciardiello L, Ferrari C, Cameletti M, Gaianni F, Buttitta F, Bazzoli F, et al. Impact of SARS-CoV-2 pandemic on colorectal cancer screening delay: effect on stage shift and increased mortality. *Clin Gastroenterol Hepatol.* 2021 Jul;19(7):1410–17. <https://doi.org/10.1016/j.cgh.2020.09.008>
- Naja F, Hamadeh R. Nutrition amid the COVID-19 pandemic: a multi-level framework for action. *Eur J Clin Nutr.* 2020;74(8):1117–21. <https://doi.org/10.1038/s41430-020-0634-3>
- Pellegrini M, Ponzo V, Rosato R, Scumaci E, Goitre I, Benso A, et al. Changes in weight and nutritional habits in adults with obesity during the 'Lockdown' period caused by the COVID-19 virus emergency. *Nutrients.* 2020;12(7):2016. <https://doi.org/10.3390/nu12072016>
- Górska P, Górna I, Miechowicz I, Przysławski J. Changes in eating behaviour during SARS-CoV-2 pandemic among the inhabitants of five European countries. *Foods.* 2021;10(7):1624. <https://doi.org/10.3390/foods10071624>
- Shanmugam H, Di Ciaula A, Di Palo DM, Molina-Molina E, Garruti G, Faienza MF, et al. Multiplying effects of COVID-19 lockdown on metabolic risk and fatty liver. *Eur J Clin Invest.* 2021;51(7):e13597. <https://doi.org/10.1111/eci.13597>
- Vu TT, Rydland KJ, Achenbach CJ, Van Horn L, Cornelis MC. Dietary behaviors and incident COVID-19 in the UK Biobank. *Nutrients.* 2021;13(6):2114. <https://doi.org/10.3390/nu13062114>

16. UEG Press Release: World digestive health day 2021: the European obesity crisis. <https://ueg.eu/a/275> (2021). Accessed 27 Oct 2021.
17. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Implication of nonalcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis. *J Hepatol.* 2020;73:451–3. <https://doi.org/10.1016/j.jhep.2020.03.044>
18. ESMO Statements for vaccination against COVID-19 in patients with cancer. <https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination> (2020). Accessed 27 Oct 2021.
19. van der Veldt AAM, Oosting SF, Dingemans AMC, Fehrmann RSN, GeurtsvanKessel C, Jalving M, et al. COVID-19 vaccination: the VOICE for patients with cancer. *Nat Med.* 2021;27:568–9. <https://doi.org/10.1038/s41591-021-01240-w>
20. European Society of Medical Oncology Press Release: Most solid tumour patients recently given chemotherapy and/or immunotherapy will achieve an adequate antibody response to COVID-19 vaccination. <https://oncologypro.esmo.org/oncology-news/daily-news/voice-sars-cov-2-vaccination-effective-during-solid-tumour-treatment> (2021). Accessed 27 Oct 2021.
21. ESMO Congress 2021 Press Release: <https://www.esmo.org/newsroom/press-office/the-evidence-is-in-covid-vaccines-do-protect-patients-with-cancer> (2021). Accessed 27 Oct 2021.
22. Scaldaferrì F, Pugliese D, Privitera G, Onali S, Lopetuso LR, Rizzatti G, et al. Impact of COVID-19 pandemic on the daily management of biotechnological therapy in inflammatory bowel disease patients: reorganisational response in a high-volume Italian inflammatory bowel disease centre. *United European Gastroenterol J.* 2020 Aug;8(7):775–81. Epub 2020 May 21. <https://doi.org/10.1177/2050640620929133>
23. Wellens J, Colombel JF, Satsangi JJ, Wong SY. SARS-CoV-2 vaccination in IBD: past lessons, current evidence, and future challenges. *J Crohns Colitis.* 2021;15(8):1376–86. <https://doi.org/10.1093/ecco-jcc/jjab046>
24. Siegel CA, Melmed GY, McGovern DP, Rai V, Krammer F, Rubin DT, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut.* 2021;70(4):635–40. <https://doi.org/10.1136/gutjnl-2020-324000>
25. Marjot T, Webb GJ, Barritt AS, Ginès P, Lohse AW, Moon AM, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. *Lancet Gastroenterol Hepatol.* 2021;6(3):156–8. [https://doi.org/10.1016/S2468-1253\(21\)00008-X](https://doi.org/10.1016/S2468-1253(21)00008-X)
26. Aggeletopoulou I, Davoulou P, Konstantakis C, Thomopoulos K, Triantos C. Response to hepatitis B vaccination in patients with liver cirrhosis. *Rev Med Virol.* 2017;27(6):e1942. <https://doi.org/10.1002/rmv.1942>; McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. *J Infect Dis.* 2000;181(2):757–60. doi:10.1086/315245.
27. Wang J, Hou Z, Liu J, Gu Y, Wu Y, Chen Z, et al. Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHES2101): a multicenter study. *J Hepatol.* 2021;75(2):439–441.
28. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol.* 2021;75(2):435–8. <https://doi.org/10.1016/j.jhep.2021.04.020>
29. Gardiner A, Liu K, Bonnichsen M, Joshi V, Davis RJ, Strasser SI. Immunity to vaccine-preventable viral infections in Australians being evaluated for liver transplantation. *Transplantation.* 2019;103(11):2318–22. <https://doi.org/10.1097/TP.0000000000002722>
30. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *J Am Med Assoc.* 2021;325(21):2204–6. <https://doi.org/10.1001/jama.2021.7489>
31. Strauss AT, Hallett AM, Boyarsky BJ, Ou MT, Werbel WA, Avery RK, et al. Antibody response to severe acute respiratory syndrome-coronavirus-2 messenger RNA vaccines in liver transplant recipients. *Liver Transplant.* 2021. Epub ahead of print. <https://doi.org/10.1002/lt.26273>
32. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med.* 2021;174(9):1330–2. <https://doi.org/10.7326/L21-0282>
33. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med.* 2021;385(7):661–2. <https://doi.org/10.1056/NEJMc2108861>
34. Société Nationale Française de Gastro-Entérologie, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif, d'Hépatologie, FFdCDSF Recommandations de la SNFGE, du GETAID, de la FFCD et de l'AFEF pour la vaccination contre le SARS-CoV-2 des patients atteints de maladies chroniques de l'appareil digestif. 2021 <https://www.snfge.org/recommandations>. Accessed 27 Oct 2021.