


**Open issues with last wave of COVID-19 pandemic: a commentary regarding frail patients and non-responders to vaccination in clinical practice**

***Problemi aperti con l'ultima ondata della pandemia COVID-19: un commento sui pazienti fragili e sui non rispondenti alla vaccinazione nella pratica clinica***

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**Abstract**

The year 2021 was next to finish and the year 2022 began and the world fighting the pandemic due to SARS-CoV-2. The clinical scenario is now really different from the onset of pandemic after first waves of vaccinations campaign. Severe lung failures are less frequent the vaccination campaign and because the presence of COVID-19 variant' of concern that seem to be less virulent, in particular B.1.1.529 (Omicron), severe lung failures may be found in anti Vax people and in immunocompromised patients because immunological toward SARS-CoV-2. Furthermore, because the presence of less virulent lately, we are observing more frequently patients with positive nasopharyngeal swab to SARS-CoV-2 and with acute medical diseases but without interstitial pneumonia COVID-19. These unfortunately induce frequent difficulties to the internal and external triage system, also to the collocation and distribution of patients positive to SARS-CoV-2 or without COVID-19 into the hospital.

## Abstract

*L'anno 2021 era prossimo alla fine e l'anno 2022 è iniziato e il mondo sta combattendo la pandemia dovuta alla SARS-CoV-2. Lo scenario clinico è ora molto diverso dall'inizio della pandemia dopo le prime ondate di campagne di vaccinazione. Le gravi insufficienze polmonari sono meno frequenti con la campagna di vaccinazione e perché la presenza della variante COVID-19' di preoccupazione che sembra essere meno virulenta, in particolare B.1 .1.529 (Omicron)., gravi insufficienze polmonari possono essere riscontrate in persone anti-Vax e in pazienti immunocompromessi perché immunologici verso il SARS-CoV-2. Inoltre, a causa della presenza di varianti meno virulente, ultimamente si osservano più frequentemente pazienti con tampone nasofaringeo positivo al SARS-CoV-2 e con patologie mediche acute ma senza polmonite interstiziale COVID-19. Ciò purtroppo comporta frequenti difficoltà al sistema di triage interno ed esterno, nonché alla collocazione e distribuzione dei pazienti positivi al SARS-CoV-2 o senza COVID-19 in ospedale.*

**Keywords:** covid-19; pandemic; triage; vocs; antivax; immunocompromised patients

**Summary:** [1. Background.](#) – [2. Anti-SARS-CoV-2 vaccines, frail immunocompromised patients and non-responder to vaccines.](#) – [3. Variants of concerns of SARS-CoV-2.](#) – [4. Non vaccinated individuals, anti Vax and related extra troubles.](#) – [5. People with positive nasopharyngeal swab to SARS-CoV-2but without COVID-19.](#) – [6. Evolution to adequate approaches to Ventilating COVID-19.](#) – [7. High flow nasal cannula \(HFNC\).](#) – [8. COVID-19 induced stress in hospital workers.](#) – [9. Conclusion.](#)

### 1. Background.

Since the year 2021 was next to finish year 2022 began SARS-CoV-2 is still ongoing with different diffusion in the population (e.g., travelers, schools and so on) compared to the begin of outbreak in which lockdown was carried out. Together to personal cautions and environmental chances (e.g. use of face mask as far as access to public area to a reduced number of people as far as cleaning of hands) the onset of vaccination campaign reduced month after month the number of infected patients with severe lung failure and of course morbidity, mortality and hospitalization rate for COVID-19.

Yet, there are still several in the management of subjects affected by COVID-19 in particular when hospitalization is required. The presence of different viral variant of concerns (VOCs), the type of intensive therapeutic support (in particular ventilatory support) and the induced stress to hospital workers are those that require still a daily discussion, while antiviral and antithrombotic pharmacological supports raised a common agreement between physicians.

These are the hottest topics of daily clinical management of last wave of pandemic, mainly related to the risk to develop severe COVID-19 for non-responders to vaccination, antiVAX peoples and immunocompromised patients

(ICP) as far as the diffusion of less virulent viral variants.

Actually, in fact, these items are daily discussed in clinical practice, not only because they are current but also because their discussion in the Literature is poor, so inducing a possible varied attitude of each physician. Therefore, we focused our attention on these items and their this brief report that is next to be published nearly after 2 years from the of.

## 2. Anti-SARS-CoV-2 vaccines, frail immunocompromised patients and non-responder to vaccines.

The subpopulation that actually could develop a severe COVID-19 may be in people that do not develop effective immunological protection against SARS CoV2 and people that did not perform vaccination for any rea-son.

The advent of anti-SARS-CoV-2 vaccines, in fact, changed the natural history of pandemic inducing efficacy in protecting humans against SARS-CoV-2 infection and COVID-19 around the world.<sup>1</sup> The rate of hospitalization for COVID-19 decreased since vaccinations against SARS-CoV-2 a relevant number of people in each country.<sup>2</sup> In this setting, approved COVID-19 vaccines included Pfizer/BioNTech BNT162B2,<sup>3</sup> Moderna mRNA-1273<sup>4</sup> and AstraZeneca recombinant adenoviral ChAdOx1-S in western Countries,<sup>5</sup> while other type of vaccines anti SARS-CoV-2 have been used in Russia and China.<sup>6</sup>

Yet, as for all vaccinations, mild side effects to vaccines are not usual (e.g. including pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain).<sup>7 8</sup> Regarding this topic, the agrees with these recommendations and clarifies that there is no contraindication to administer these vaccines to allergic patients who do not have a history of an allergic reaction to any of the vaccine components.<sup>9</sup> Furthermore, the rate of responder to vaccinations varies from

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<sup>1</sup> R L Soiza, C Scicluna, EC Thomson, 'Efficacy and safety of COVID-19 vaccines in older people', (2021) 50, Age and Ageing, 279-283.

<sup>2</sup> MW Tenforde, WH Self, et al., 'Influenza and Other Viruses in the Acutely Ill (IVY) Network. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity', (2021) 326 JAMA, 2043-2054.

<sup>3</sup> FP Polack, SJ Thomas et al., 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine', (2020) 383 N Engl J Med, 2603-2615.

<sup>4</sup> LR Baden, HM El Sahly et al., 'Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine', (2021) 384 N Engl J Med., 403-416.

<sup>5</sup> M Voysey, SAC Clemens et al., 'Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK', (2021) 397 Lancet, 99-111.

<sup>6</sup> Drugs and Lactation Database (LactMed). Bethesda (MD): National Library of Medicine (US); 2006-. COVID-19 vaccines, 25/01/2022, Available at: <https://www.ncbi.nlm.nih.gov/sites/books/NBK501922/>.

<sup>7</sup> RA Mohammed, RM Garout et al., 'A Survey on the Side Effects of Pfizer/BioNTech COVID-19 Vaccine Among Vaccinated Adults in Saudi Arabia', (2021) 13 Cureus, 19222.

<sup>8</sup> Y Solomon, T Eshete, et al., 'COVID-19 Vaccine: Side Effects After the First Dose of the Oxford AstraZeneca Vaccine Among Health Professionals in Low-Income Country: Ethiopia', (2021) 14 'J Multidiscip Healthc', 2577-2585.

<sup>9</sup> M Sokolowska, T Eiwegger et al, 'EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines', (2021) 76 Allergy, 1629-1639.

90% of Chadox1- Ncov- 95% of BNT162b2 in clinical trials.<sup>10 11</sup> Therefore, 5-10% of population may result at risk to develop infection although anti-SARS-CoV-2, based on data of clinical trials.

Yet, first clinical trials were made on general population with exclusion of immunocompromised patients,<sup>12 13</sup> for this reason a group of frail patients (e.g. immunocompromised patients) were tested for anti-SARS-CoV-2 in a different trial.<sup>14</sup> In this study, antibody response to the Pfizer-BioNTech vaccine was highly variable among different immunocompromised patients; so, individual recommendations should be provided when chronic diseases associated to immunosuppression states as far as infection induced by HIV<sup>15</sup> as far as malignancies<sup>16</sup> as far as chronic intake of immuno-suppressive drugs for any reason are present.

These last two categories of subjects (i.e. non-responders to vaccines and immunocompromised patients) represent frail categories that may be still infected by SARS-CoV-2 develop severe infection nevertheless the pre-vious vaccination and actually they represent a category that have not large space in the Literature with focused studies on outcomes.

### 3. Variants of concerns of SARS-CoV-2.

Besides its ability to ensure replication by host cells, any type of virus in its cycle is able to do a high number of genome mutations that might induce its prolonged survival versus the immunization of the general population. These mechanisms are mainly responsible of the epidemiological trend that each viral infection assumes: epidemic, pandemic, endemic. Similar course has been described for other viruses as influenza virus spp. SARS-CoV-2 seems to live a similar biological evolution.<sup>17</sup> Several viral variants have been identified in these last 2 years: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), B.1.427, B.1.429 (Epsilon), P.2 (Zeta), B.1.525 (Eta), P.3 (Theta), B.1.526 (Iota), B.1.617.1 (Kappa) and last identified B.1.1.529 (Omicron) have been

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<sup>10</sup> V Naranbhai, WF Garcia-Beltran et al., 'Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COV2.S COVID-19 vaccines' [2021] *J Infect Dis.*, jiaab593.

<sup>11</sup> MN Ramasamy, AM Minassian et al., 'Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial', (2021) *396 Lancet*, , 1979-1993.

<sup>12</sup> F Polack, SJ Thomas et al, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine', (3) 2603-2615.

<sup>13</sup> M Voysey, SAC Clemens et al., 'Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK', (5) 99-111.

<sup>14</sup> G Rahav, Y Lustig et al., 'BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: A prospective cohort study', (2021) *41 EclinicalMedicine*, 101158.

<sup>15</sup> I Levy, A Wieder-Finesod et al., 'Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people living with HIV-1', (2021) *27 Clin Microbiol Infect.*, 1851-1855.

<sup>16</sup> N Shem-Tov, R Yerushalmi et al., 'Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in haematopoietic stem cell transplantation recipients', [2021] *Br J Haematol.*, 884-891.

<sup>17</sup> JA Plante, BM Mitchell, KS Plante, K Debbink, SC Weaver, VD Menachery, 'The variant gambit: COVID-19's next move', (2021) *29 Cell Host Microbe*, 508-515.

identified as the protagonists of SARS CoV2 outbreak and of concern (VOCs).<sup>18</sup>  
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In last months, in fact, B.1.617.2 (Delta) and B.1.1.529 (Omicron) VOCs have been the most common identified in patients positive to nasopharyngeal swabs(NPS)around the world. Yet, from a clinical point of view, nevertheless the presence of several VOCs actually we are not detecting a strong increase of morbidity or mortality or hospitalization rate or admission in ICU of patients positive to NPS if vaccinated,<sup>20 21</sup> while the increase of hospitalization rate is still significant for patients that did not perform anti-SARS CoV2 vaccination.

#### 4. Non vaccinated individuals, anti Vax and related extra troubles.

Although vaccination campaign was planned around the world and quickly started in western countries because suggested by each government and health authorities, there is a piece of population that result non-vaccinated. Usually, non-vaccinated individuals are younger than vaccinated people (e.g. under age 50), have lower levels of education, than those who were vaccinated and/or adhere to anti-Vax campaign. Anti-vax cultural campaign in fact represents a great obstacle to the completion of vaccination program.

Since vaccination campaign anti SARS-CoV-2was planned, vaccine hesitancy begun parallel and sometimes it has been associated to strong anti vax cultural campaign.<sup>22</sup> The management of anti vax campaign was based mainly to misinformation and disinformation by social media, personal blog and interview or word of mouth.<sup>23</sup> Usually, anti vax strategy is based on the organization of narratives according to themes or rhetoric appealing to the vulnerability of frail categories.

Yet, from a clinical point of view the presence of anti vax subjects is relevant because the rate of vaccines does not raise the herd different places in the world, (while other regions of the globe reached >90% of vaccination of eligible people);<sup>24 25</sup> in those regions, a constant presence of the virus is present and for this a constant hospitalization people that COVID-19.

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<sup>18</sup> M Prajapat, V Handa et al, 'Update on geographical variation and distribution of SARS-nCoV-2: A systematic review', (2021) 53 Indian J Pharmacol., 310-316.

<sup>19</sup> L VanBlargan, J Errico et al, 'An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies', (2022) 28 Nat Med, 490–495.

<sup>20</sup> D Follmann, J Fintzi et al., 'A Deferred-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group Is Vaccinated', (2021) 174 Ann Intern Med., 1118-1125.

<sup>21</sup> EV Robilotti, K Whiting et al., 'Clinical and Genomic Characterization of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) Infections in mRNA Vaccinated Health Care Personnel in New York City', (2022) 75 Clinical Infectious Diseases, e774–e782.

<sup>22</sup> F Pandolfi, L Franza et al., 'The Importance of Complying with Vaccination Protocols in Developed Countries: "Anti-Vax" Hysteria and the Spread of Severe Preventable Diseases', (2018) 25 Curr Med Chem., 6070-6081.

<sup>23</sup> D Gori, F Durazzi et al., 'Mis-tweeting communication: a Vaccine Hesitancy analysis among twitter users in Italy', (2021) 92 Acta Biomed., e2021416.

<sup>24</sup> V Naranbhai, WF Garcia-Beltran et al., 'Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COVID-19 vaccines', (10) 593.

<sup>25</sup> N Shem-Tov, R Yerushalmi et al., 'Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in haematopoietic stem cell transplantation recipients', (14) 884-891.

Although, a clear rate of hospitalization, morbidity and mortality of anti vax people is still lacking in the Literature, actually severe COVID-19 usually affect mainly anti vax subjects or ICP that did not develop anti SARS-CoV-2 protective antibodies after vaccination. So, we may postulate that this wave of the end of year is less strong than others because we are in a post vaccination era,<sup>26 27</sup> and actually the clinical situation of lung failure due to severe COVID-19 is mainly related to anti vax people<sup>28</sup> or ICP that did not develop an efficacy of the immune system after vaccines.

## 5. People with positive nasopharyngeal swab to SARS-CoV-2 but without COVID-19.

For the reasons exposed in previous paragraphs, VOCs with less pathogenicity and virulence and/or the increased immunological power induced by vaccines, there is an evidence that the number of hospitalizations for severe COVID-19 in western countries is not high as in first waves.<sup>29 30</sup> The high risk for endemic series of COVID-19 is actual for ICP or for anti vax people. Yet, ICP and anti vax peoples may raise nearly 10-15% of population,<sup>31 32</sup> so the presence of the virus is still strong in our life. On the other hand, environmental and climatic conditions greatly the transmission of infectious diseases SARS, as far as for other virus, there are evidences for which climatic factors as cold weather in winter season, are most important for their transmission.<sup>33</sup> Important factor in the winter is that humans spend more time indoors than outdoor also in common areas or crowded areas. This usually comes with less ventilation and less personal space, probably due to the density of households (e.g. schools are considered locus of much infectious disease transmission).<sup>34</sup> So, in these last times, frequently we are observing people positive to NPS but without lung dysfunction and that may require the need of hospitalization for reasons other than suspected COVID-19 (e.g. trauma or other acute medical illness).

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<sup>26</sup> D Follmann, J Fintzi et al., 'A Deferred-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group Is Vaccinated', (19) 1118-1125.

<sup>27</sup> EV Robilotti, K Whiting et al., 'Clinical and Genomic Characterization of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) Infections in mRNA Vaccinated Health Care Personnel in New York City', (20) e774–e782.

<sup>28</sup> F Pandolfi, L Franza et al., 'The Importance of Complying with Vaccination Protocols in Developed Countries: "Anti-Vax" Hysteria and the Spread of Severe Preventable Diseases', (21) 6070-6081.

<sup>29</sup> F Pandolfi, L Franza et al., 'The Importance of Complying with Vaccination Protocols in Developed Countries: "Anti-Vax" Hysteria and the Spread of Severe Preventable Diseases', (Curr Med Chem. 2018) ibid 6070-6081.

<sup>30</sup> D Gori, F Durazzi et al., 'Mis-tweeting communication: a Vaccine Hesitancy analysis among twitter users in Italy', (22) e2021416.

<sup>31</sup> V Naranbhai, WF Garcia-Beltran et al., 'Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COVS COVID-19 vaccines', (10) jjab593.

<sup>32</sup> N Shem-Tov, R Yerushalmi et al., 'Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in haematopoietic stem cell transplantation recipients', (14) 884-891.

<sup>33</sup> S Chen, K Prettner et al., 'Climate and the spread of COVID-19', (2021) 11 Sci Rep., 9042.

<sup>34</sup> E Larosa, O Djuric et al., 'Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study', (2020) 25 Euro Surveill., 2001911.

In the daily clinical practice, the clinical management of these peoples in emergency department<sup>35 36</sup> they require hospitalization for acute medical illness different from COVID-19 but they result positive to screening with NPS or with antigen molecular testing that are suggested and used in several triage systems.<sup>37</sup>

In this cases, when possible, it could be useful a “grey area” in the Hospital in which peoples asymptomatic for COVID-19 positive to NPS may be observed also for other medical illness included the needs of any type of surgery.<sup>38</sup> A similar organization of contumacies areas in hospital in which patients with COVID-19 were admitted also to surgical areas for any surgical reason has been experienced during pandemic<sup>39 40</sup> and should be again considered until the number of patients positive to is considerable the de-created virulence of VOCs of SARS-CoV-2 the relevant number of vaccinated peoples actually reducing the needs of ICU for ARDS increasing the needs for hospitalization for other reasons.

## 6. Evolution to adequate approaches to Ventilating COVID-19.

Since December 2019, Coronavirus disease 2019 (COVID-19) rapidly became a public health emergency requiring hospitalization in approximately 14% of infected patients.<sup>41</sup> It manifests itself with severe acute hypoxemic respiratory failure in nearly 30% of hospitalized patients requiring oxygen and non-invasive respiratory support and intensive care unit (ICU) admission in approximately 5% of cases.<sup>42</sup> The percentage of patients requiring non-invasive respiratory support varied greatly among the studies, ranging from 11% to 96%, with higher rate in China, and lower rate in North America and Italy (11%). The mortality rate in patients requiring advanced respiratory support ranged from 62% to 97%; main reasons for this range is related to different aspects as overbooking of clinical areas as far as unavailable ventilator support for all patients and so on. Additionally, nearly 25% of patients that needed advanced support in critical condition for long time before to have a full clinical improvements.<sup>43</sup>

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<sup>35</sup> J Zhang, L Zhou et al., ‘Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics, (2020) 8 Lancet Respir Med., e11-e12.

<sup>36</sup> P Di Micco, M Imparato, MT Iannuzzo, A Fontanella, ‘Lesson learned by covid-19 outbreak: multilevel triage strategies in patients admitted to the emergency room in southern Italy’, (2021) 15 Italian Journal of Medicine, 1445.

<sup>37</sup> J Dinnes, JJ Deeks et al., ‘Cochrane COVID-19 Diagnostic Test Accuracy Group. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection’, (2021) 3 Cochrane Database Syst Rev., CD013705.

<sup>38</sup> A Hogan, ‘COVID-19 and emergency surgery’, (2020) 107 Br J Surg., e180.

<sup>39</sup> A Hogan COVID-19 and emergency surgery, in Br J Surg., 2020, Vol. 107, e180.

<sup>40</sup> B De Simone, E Chouillard et al., ‘Emergency surgery during the COVID-19 pandemic: what you need to know for practice’, (2020) 102 Ann R Coll Surg Engl., 323-332.

<sup>41</sup> A Hogan COVID-19 and emergency surgery, (28) 107 e180.

<sup>42</sup> A Hogan COVID-19 and emergency surgery, (Br J Surg. 2020) ibid 107 -180.

<sup>43</sup> C Crimi, A Noto et al., ‘Noninvasive respiratory support in acute hypoxemic respiratory failure associated with COVID-19 and other viral infections’, (2020) 86 Minerva Anesthesiol., 1190-1204.

Brusasco et al. suggest, based on their experience, that several subjects with moderate-to-severe ARF due to COVID-19 may be amenable to high flow oxygen support or to continuous airway pressure (CPAP) support, even if gas exchange and radiological findings at thoracic CT could be suggestive of other invasive mechanical ventilation or even extracorporeal oxygenation as far as in other clinical pictures of ARDS.<sup>44</sup> Pathophysiological mechanisms occurring during COVID-19 are different from other form of ARDS because an overlapping of different mechanisms (i.e. infective, inflammatory, and prothrombotic mechanisms). After first observations in few intubated patients it has been suggested that acute respiratory failure (ARF) in COVID-19 may be different from typical ARDS for a relatively conserved respiratory mechanics despite comparably severe shunt (PaO<sub>2</sub> / FIO<sub>2</sub>) and CT abnormalities.<sup>45</sup> In particular, lungs alterations induced by COVID-19 showed ventilation-perfusion mismatch although lung compliance is kept. Patients with COVID-19, in fact, and ARDS typically have severe hypoxemia and frequently hypocapnia with relatively well-preserved lung mechanics. In-deed, it was reasonable to assume that patients with COVID-19 benefited from CPAP therapy. Yet, many patients with COVID-19 and severe respiratory failure frequently were obese and for this reasons may have risk factors for a global lung failure because underlying lung dysfunctions as obstructive sleep apnea and hypoventilation obesity syndrome.

For this reason, the clinical approach to therapeutic ventilation changed during pandemic week after week: at first, attempts were made to establish timing for intubating patients when it was not too late but was unsuccessful.<sup>46</sup> Furthermore, non-invasive positive pressure ventilation treatment with CPAP and bilevel positive airway pressure (BiPAP) are considered as or masks have been used commonly in Italy during the COVID-19 pandemic with good results but one of the most common trouble regarding the appropriate choice of interface was related to the compliance and

Yet, guidelines' recommendations on the use of non-invasive ventilation (NIV) in COVID-19 are of discussion.<sup>47</sup> Conflicting recommendations possible complications ARF bacterial or fungal overlapping.<sup>48</sup> On the other hand, invasive mechanical ventilation was considered after four days of unsuccessful CPAP.<sup>49 50 51</sup>

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<sup>44</sup> C Brusasco, F Corradi et al., 'Continuous positive airway pressure in Covid-19 patients with moderate-to-severe respiratory failure', (2020) 57 Eur Respir J., 2002524.

<sup>45</sup> L Gattinoni, S Coppola et al., 'Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome', (2020) 201 Am. J. Respir. Crit. Care Med., 1299-1300.

<sup>46</sup> MJ Tobin, F Laghi, A Jubran, 'Caution about early intubation and mechanical ventilation in COVID-19', (2020) 10 Ann. Intensive Care', 78.

<sup>47</sup> Y Solomon, T Eshete, B Mekasha, W Assefa, 'COVID-19 Vaccine: Side Effects After the First Dose of the Oxford AstraZeneca Vaccine Among Health Professionals in Low-Income Country: Ethiopia', (8) 2577-2585.

<sup>48</sup> C Crimi, A Noto et al., 'Non invasive respiratory support in acute hypoxemic respiratory failure associated with COVID-19 and other viral infections', (30) 1190-1204.

<sup>49</sup> C Crimi, A Noto et al., 'Noninvasive respiratory support in acute hypoxemic respiratory failure associated with COVID-19 and other viral infections, (Minerva Anestesiol. 2020) ibidem 1190-1204.

<sup>50</sup> C Brusasco, F Corradi et al, 'Continuous positive airway pressure in Covid-19 patients with moderate-to-severe respiratory failure', (31) 2002524.

<sup>51</sup> CC Dobler, MH Murad, ME Wilson, 'Noninvasive Positive Pressure Ventilation in Patients With COVID-19', (2020) 95 Mayo Clin Proc., 2594-2601.



## 7. High flow nasal cannula (HFNC).

Although, as we described, the deadliest complication of patients affected by COVID-19 is severe acute respiratory failure that occurs in patients with bilateral pneumonia, the progressive adherence to vaccination reduced the number of patients requiring respiratory support further data are emerging in last weeks and will be analyzed after the end of this wave. improved in with COVID-19 with high flow nasal cannula (HFNC) as .

HFNC refers to high-flow, potentially oxygenated gas, warmed and humidified to body temperature, provided via nasal cannula at maximum flows varying from 40 to 80 L / min depending on the device. It is a fairly recent technology that has emerged in recent years, with increasing evidence hypoxemic and hypercapnic. The warm and humidification also improve to maintain hydration and mobility of secretions and to preserve mucociliary work.<sup>52</sup>

The tolerance of the interface is extremely high in particular if compared to the use of mask or helmet used for ARF. many reports are emerging on the use of HFNC in patients with COVID-19, actually there insufficient to establish the effectiveness of HFNC compared with NIV in COVID-19. Some patients, in fact, fail to oxygenate adequately with HFNC and go on to improve with the helmet, presumably because of the helmet's greater positive airway pressure. in many other cases, HFNC successful when the helmet fails. The available reports to date suggest that HFNC provides high concentrations of oxygen to the patients who cannot reach conventional devices.<sup>53 54</sup>

However, HFNC can reduce intubation in subjects with COVID-19, the length of intensive care unit stays and has been used also for patients treated at home.

So, due to a limited number of ventilators available in hospitals during first waves of pandemic, the use of HFNC has been demonstrated as a good option to use before during hypoxemic phases of disease. Furthermore, WHO guide clarify that HFNC does not create a wide dispersion of exhaled air and should be associated with a low risk of transmission of respiratory viruses to hospital workers and not only.<sup>55</sup>

Based on current, NIV was considered as alternative to early intubation choice of the type of NIV derived from case-by-case decision-making in account characteristics the presence of comorbidities such as obstructive apneas, heart failure, pre-existing severe lung disease. , in we further therapeutic HFNC<sup>56</sup> in awake proning in.

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<sup>52</sup> P Imitazione, GE Polistina et al., 'Acute Respiratory Failure in COVID-19 Pneumoniae: The Best Interface for an Optimal Management - A South Italian Experience', (2020) 21 Turk Thorac J., 289-290.

<sup>53</sup> A Gürün Kaya, M Öz et al., 'High flow nasal cannula in COVID-19: a literature review', (2020) 68 Tuberk Toraks, 168-174.

<sup>54</sup> A Annunziata, A Coppola et al., 'Home Management of Patients with Moderate or Severe Respiratory Failure Secondary to COVID-19, Using Remote Monitoring and Oxygen with or without HFNC', (2021) 10 Pathogens, 413.

<sup>55</sup> JP Frat, R Coudroy, N Marjanovic, AW Thille, 'High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure', (2017) 5 Ann. Transl. Med., 297.

<sup>56</sup> A Agarwal, J Basmaji et al., 'High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission', (2020) 67 Can J Anaesth., 1217-1248.

## 8. COVID-19 induced stress in hospital workers.

Since pandemic was declared by WHO, it generated stress throughout the population. Specialists were involved since the begin of pandemic to promote a series of messages that can be used in communications to support mental and psychosocial stress of each citizen.<sup>57 58</sup> Yet, although the induced stress was identified soon the consumption of antipsychotic drugs increased. Furthermore, the psychosocial and professional stress touched in early phase also hospital workers<sup>59</sup> because the increased risk to develop COVID-19 and the related risk of morbidity and mortality. Furthermore, several experts and international meetings have been planned to rehab mental wellbeing of hospital workers and to prevent further psychological disorders.<sup>60</sup>

## 9. Conclusion.

Despite the maximum therapeutic effort some patients evolve unfavorably when affected by COVID-19. Usually these patients are frail because the presence of underlying diseases as cardiovascular diseases and/or immunopathological diseases as reported since first epidemiological reports from China<sup>61 62</sup> on the other hand, the presence of immunocompromised patients (i.e. patients that perform immunosuppressive drugs for any reason) and anti-vax people represent potential targets of perpetuate endemic SARS CoV2 contagion. We are still looking for a feature that can identify and distinguish the different evolutions, but the use of green pass linked to previous vaccination against SARS CoV2 is a useful step to identify easily patients more or less at risk to develop severe COVID-19 actually.

Comorbidities such as obesity, systemic arterial hypertension, chronic lung disease and respiratory failure, cardiovascular disease are associated with severe COVID-19.<sup>63</sup> Furthermore, COVID 19 can develop into a life-threatening hyperinflammatory disease and still currently the scientific world seeks to better understand productive immune responses against SARS-CoV-2 virus and immunopathological mechanisms that trigger the severe and lethal disease.<sup>64</sup>

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<sup>57</sup> A Anwar, M Malik, V Raees, A Anwar, 'Role of Mass Media and Public Health Communications in the COVID-19 Pandemic', (2020) 12 Cureus, e10453.

<sup>58</sup> A Sarangi, W Amor et al., 'Social Media Reinvented: Can Social Media Help Tackle the Post-Pandemic Mental Health Onslaught?', (2022) 14 Cureus, , e21070.

<sup>59</sup> S Hassamal, F Dong et al., 'The Psychological Impact of COVID-19 on Hospital Staff', (2021) 22 West J Emerg Med., 346-352.

<sup>60</sup> J Raudenská, V Steinerová et al., 'Occupational burnout syndrome and post-traumatic stress among healthcare professionals during the novel coronavirus disease 2019 (COVID-19) pandemic', (2020) 34 Best Pract Res Clin Anaesthesiol, 553-560.

<sup>61</sup> J Li, DQ Huang, B Zou et al., 'Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes', (2021) 93 J Med Virol., 1449-1458.

<sup>62</sup> Z Zheng, F Peng, B Xu et al., 'Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis', (2020) 81 J Infect., e16-e25.

<sup>63</sup> Y Zhou, J Chi et al., 'Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19)', (2021) 37 Diabetes Metab Res Rev., e3377.

<sup>64</sup> P Brodin, 'Immune determinants of COVID-19 disease presentation and severity', (2021) 27 Nat Med., 28-33.

Vaccination currently is the only concrete preventive drug against this fearsome enemy.

## Interdisciplinary Dialogue Chart

ANNA ANITA MOLLO 

Issues covered:	Legal relevance profiles:
<p><u>Anti-SARS-CoV-2 vaccines</u></p> <p>Paragraph: 1, 2 e 3</p>	<p>3. Compulsory vaccination:</p> <ul style="list-style-type: none"> <li>- constitutional admissibility of the obligation</li> <li>- unequal treatment of persons and professional categories</li> <li>- compulsory vaccination of health personnel and related</li> </ul> <p>2. Protecting of vulnerable's health</p> <ul style="list-style-type: none"> <li>- minors</li> <li>- people with disabilities</li> <li>- people with previous illnesses</li> <li>- the elderly</li> </ul> <p>3. Protecting the mental health of citizens and health personnel</p> <p>4. Imbalances and deficiencies in the NHS:</p> <ul style="list-style-type: none"> <li>- structural deficiencies in pandemic management</li> <li>- lack of adequate space and healthcare personnel for the treatment and care of other diseases during the pandemic period</li> </ul> <p><b>Law</b></p> <ul style="list-style-type: none"> <li>• Artt. 2, 3, 32 Cost.</li> <li>• D.L. 1° aprile 2021, n. 44</li> </ul> <p><b>Case Law</b></p> <ul style="list-style-type: none"> <li>• C. Cost., 9 febbraio 2023, sentenze nn. 14, 15 e 16</li> </ul> <p><b>Soft Law</b></p> <ul style="list-style-type: none"> <li>• <u>Opinion CNB 28 maggio 2020</u></li> <li>• <u>UNESCO International Bioethics Committee and World Commission on the Ethics of Scientific Knowledge and Technology, Statement on COVID-19: Ethical Considerations from a Global</u></li> </ul>

	<u>Perspective, 26 March 2020.</u>
<u>Anti-VAX</u> Paragraph 9	1. Disinformation e fake news 2. Completeness and transparency of information from institutions, ethics committees, social media 2. Relationship between science, information and protection of the individual 3. Prohibition of discrimination against vaccinated persons  <b>Law</b> <ul style="list-style-type: none"> <li>• Reg. UE 2021/953</li> <li>• Reg. UE 2022/2065</li> </ul> <b>Soft Law</b> <ul style="list-style-type: none"> <li>• <u>OMS, Infodemics and health misinformation: a systematic review of reviews, 2022</u></li> <li>• <u>ECDC, Countering online vaccine misinformation in EU/EEA, 2021</u></li> </ul>
<u>Green pass linked to previous vaccination against SARS CoV2 as a useful step to identify easily patients more or less at risk to develop severe COVID-19 actually.</u> Paragraph 9	1. Data protection of vaccinated and non-vaccinated patients. 2. Use of contact tracing apps and related processing of personal data  <b>Law</b> <ul style="list-style-type: none"> <li>• Reg. UE 679/2016</li> <li>• Dir. 2002/58/CE</li> </ul> <b>Soft law</b> <ul style="list-style-type: none"> <li>• eHealth Network Mobile applications to support contact tracing in the EU's fight against COVID-19 Common EU Toolbox for Member States</li> <li>• <u>Linee-guida04/2020 sull'uso dei dati di localizzazione e degli strumenti per il tracciamento dei contatti nel contesto dell'emergenza legata al COVID-19</u></li> </ul>
<u>Main pharmaceutical companies producing vaccines</u> Paragraph 2	1. Contracts for the production and sale of vaccines; 2. APAs, advance purchase agreements between pharmaceutical companies and EU Member States; 3. Pharmacovigilance: reporting of possible adverse reactions of vaccines;

	<p>4. Identifying the liable party for vaccine damage</p> <p>5. Right to compensation and damages</p> <p><i>Law</i></p> <ul style="list-style-type: none"><li>• Artt. 2043 e 2050 c.c.</li><li>• D.l. 27 gennaio 2022, n. 4 che ha modificato la l. 210/1992</li></ul> <p><i>Case Law</i></p> <ul style="list-style-type: none"><li>• Cons. Stato 7045/2021</li></ul> <p><i>Soft Law</i></p> <ul style="list-style-type: none"><li>• <u>Communication from the commission.</u> <u>Eu strategy for covid-19 vaccines.</u></li></ul>
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