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## COVID-19: Time to embrace MDI+ valved-holding chambers!



### To the Editor:

Because of the great transmissibility of the virus causing coronavirus disease 2019 (COVID-19), the use of small-volume nebulizers (SVNs) in these days may constitute a serious hazard.

There is much evidence that pressurized albuterol metered-dose inhalers (pMDIs) with valved-holding chambers (VHCs) are efficient, effective, and associated with less side effects than SVNs for the treatment of obstructive pulmonary exacerbations.<sup>1,2</sup> VHCs help to ensure aerosol delivery in infants and toddlers (3-5 years) and in the elderly or cognitively impaired by means of facemasks and tidal breathing. In older children, adolescents, and adults, aerosols should be inhaled by means of the VHC mouthpiece and well-defined respiratory maneuvers designed to maximize deposition of medical aerosol particle (mass median aerodynamic diameter 1-5  $\mu\text{m}$ ) in the lower respiratory tract.<sup>3</sup>

In contrast to many other countries that have replaced SVN bronchodilator therapy with pMDIs with VHCs, the United States has continued to use SVN in asthma and chronic obstructive pulmonary disease.

The main impetus for continuing to use SVNs was perceived financial considerations. Because the MDI unit used to cost about \$200 and had to be single-patient use (not reimbursed), it was “clearly more cost-effective” to use the SVN. However, this is true only if one considers the devices and not the true cost of the longer emergency department and often intensive care unit stay. Recent studies showed a significant cost saving with MDIs/VHCs because patients improved faster, were sent home more quickly, and could be taught in the emergency department to use the MDIs/VHCs, thus decreasing early readmission.<sup>4,5</sup>

VHCs have numerous additional advantages including an up to 80% decrease in the upper respiratory tract deposition of inhaled medication, and generation of significantly smaller particles that better penetrate into the lung periphery.<sup>3</sup> Furthermore, they are totally self-contained and do not require an external, expensive, and bulky source of energy.

The current COVID-19 pandemic has been shown to require much greater infection control not only with proven infected persons but even more in unknown, as yet undiagnosed, or asymptomatic COVID-19 carriers.

With continuously operating SVNs, aerosols are released into the room air throughout exhalation. The risk of transmission further increases because SVNs generate a large, potentially “respirable” aerosol mass propelled over a greater distance than the natural dispersion pattern.<sup>6</sup> Recent reports indicated that the coronavirus may be disseminated by airborne transmission.<sup>7-9</sup> Furthermore, the aerosol particles generated by SVNs can

stimulate patients’ or by-standers’ cough reflex, further increasing the risk of spreading the disease.

The change from SVNs to MDIs/VHCs has been going on in Canada for many years. Given the current pandemic of COVID-19, Canadians have further restricted the delivery of aerosol by nebulizers, with Global Initiative for Asthma<sup>10</sup> and many other international authorities following suit. On April 8, 2020, the Food and Drug Administration approved the first generic albuterol inhaler in the United States. This is a major step that promises to make pMDIs/VHCs increasingly favored over SVNs for treating reversible airflow obstruction. It is our view that caregivers worldwide should also adopt the conversion from SVNs to pMDIs/VHCs for bronchodilator therapy.

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## The bimodal SARS-CoV-2 outbreak in Italy as an effect of environmental and allergic causes



### To the Editor:

We read with attention the very recent Editorial by Navel et al<sup>1</sup> in the latest issue of the *Journal*. The topic intrigued us because we are currently investigating how come Italy is cropped into 2 great coronavirus disease 2019 (COVID-19)-infected macro

areas, an upstream (Northern) zone and a downstream (Central-Southern) zone, with respect to the river Po. More recent data from the Italian Ministry of Health assessed that the 7 regions in the Northern macro area account for about 79.81% of the whole severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive population. This singular circumstance fits perfectly with the observation that the Central-Southern part, downstream the Po, is completely surrounded by Mediterranean. Fundamental insights come from past studies conducted in our Academy, where the authors assessed that the Italian population in the Central-Southern part of the peninsula has a higher risk to be affected by chronic airway allergy, that is, asthmatic disease, compared with more rainy-cold Northern regions.<sup>2</sup> The peninsular part of Italy is exactly the portion of the country with only about one-fifth (21.19%) of COVID-19-positive subjects and also being endowed with the largest near-coastal environment. The latter is particularly enriched in troposphere ozone (O<sub>3</sub>), which is a well-known risk factor for asthmatic allergy disorders, particularly during sunlight exposure in warm season.<sup>3</sup> The role of O<sub>3</sub> in pulmonary physiology and airway allergy might be particularly intriguing to shed light on the progress of COVID-19, particularly in such circumstance described by the authors, that is, following a reduction in the anthropic pollutants.<sup>1</sup> So far, very few associations were established between SARS-CoV-2 and subjects with asthma, although it is observed that the prevalence of asthma in severe patients with COVID-19 is lower than in the general adult population.<sup>4</sup> Moreover, some reports have shown that, particularly in elder subjects with hypertension-derived cardiovascular disease, the expression of angiotensin-converting enzyme 2 (ACE2) is reduced, whereas, on the contrary, in people predisposed to develop asthmatic symptoms, the expression of ACE2 was much higher and exerting a protective role against the COVID-19 exacerbation, which otherwise should lead to interstitial bilateral pneumonia and lung fibrosis.<sup>5</sup> Finally, Central-Southern Italy is characterized by a higher frequency of ACE I/D polymorphism in the II allele compared with the Northern macro area, which has a prevalence in the DD allele, usually linked with a higher risk for cardiovascular disease.<sup>6</sup>

Although lockdown with its drastic reduction in engine exhausts has decreased airborne urban pollutants<sup>1</sup> such as particulate matter  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>), NO<sub>2</sub>, SO<sub>2</sub>, CO, and O<sub>3</sub>, the coexistence of O<sub>3</sub> high levels and PM<sub>10</sub> low levels is associated with a low COVID-19 incidence odds ratio (OR). Furthermore, it is well known that in Italy urban pollutants decrease from inland to offshore and near the coastal environment and are associated with interstitial pneumonia.<sup>7</sup>

On the basis of several publicly available data from government's environmental, health, and statistical institutions for the latest 3 years, we calculated that the Northern regions have an OR of 11.44 (95% CI, 10.707-12.238) for COVID-19 incidence risk in subjects living in inland areas with PM<sub>10</sub> levels of greater than or equal to 40  $\mu\text{g}/\text{m}^3$  and NO<sub>2</sub> levels of greater than or equal to 40  $\mu\text{g}/\text{m}^3$  for at least 3 months/y, whereas the Central-Southern regions, including major islands, have an OR of 0.97 (95% CI, 0.898-1.068) with same values in the same time course; that is, there is no relevant risk association between the onset of COVID-19 following SARS-CoV-2 infections and major urban pollutants. Furthermore, we calculated from data of the Italian Government "Institute of STATistics" (ISTAT) and the National Institute of Health that the OR of COVID-19 risk incidence in subjects with asthma living permanently in Northern inland

macro area was 1.44 (95% CI, 1.395-1.488), whereas in the Central-Southern macro area (including Sardinia and Sicily), the OR was 0.76 (95% CI, 0.721-0.807). This result is in agreement with the latitude dependency in asthma prevalence in Italy and assesses that asthma is not a risk factor for COVID-19.<sup>2</sup> According to our opinion, one possible leading factor in the paradoxical bimodal distribution of COVID-19 cases in Italy, very high in the Northern part and slightly modest in the Central-Southern part, is not only the favorable genetic endowment of ACE I/D polymorphism but also the presence of environmental O<sub>3</sub>, because ozone, besides being a nontoxic asthma trigger, is able to modulate the pulmonary microbiome, thus assessing the correct cross-talk between airway bacteria and the immune surveillance of lung physiology, whereas PM<sub>10</sub> alters this interrelationship.<sup>5-7</sup> It is possible therefore to suggest that the increasing asthma prevalence from North to South is a sign of the different impact of the troposphere ozone in Italy.

The article by Navel et al offered us the opportunity to boost current research about COVID-19 in Italy, trying to shed light on the unusual COVID-19 distribution, which might even drive the political decision about lockdown and "Fase-2", if taking into consideration both allergy and environmental issues.

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## Reply



To the Editor:

We read with considerable interest the relevant comment of Chirumbolo and Bjørklund<sup>1</sup> concerning our recent Editorial.<sup>2</sup> The authors discussed the complex link between the prevalence of coronavirus disease 2019 (COVID-19) in Italy and the geographic zones of a peninsula location, air pollution related to different climates, and allergic diseases of the respiratory