

Reply to: Epidemiological evidence for an association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy

To the Editor,

We read with great interest the paper by Marín-Hernández and colleagues on the potential interplay between seasonal influenza vaccination and COVID-19 outcome in Italy.¹ The authors, using data on vaccination in adults older than 65 years published in 1999, found a moderate/strong negative correlation between vaccination and COVID-19-related deaths: they calculate that each unit of percentage individuals vaccinated against influenza would result in a 0.3450 decrease in mortality.

ASST Grande Ospedale Metropolitano Niguarda is one of the largest hospitals in the Lombardy Region, the area mainly involved in the first COVID-19 outbreak in Europe, with in-hospital mortality above 10% and with an excess of deaths higher than 20% compared with the previous 5 years.² We cross-sectionally evaluated 893 patients admitted to our hospital between February and May 2020 with a diagnosis of COVID-19. Follow-up ended in September 2020. Demographic and clinical information was obtained from the hospital's electronic patient records. Data about flu immunizations were retrieved from the Agency of Health Protection which manages public vaccinations in Lombardy.

The study population had a median age of 64 years (interquartile range [IQR], 52–77; 49.8% was older than 65), males were 553 (61.9%) and 385 individuals (43.1%) had a severe or critical disease as defined according to the Chinese guidelines.³ Charlson Comorbidity Index (CCI) was ≥ 5 in 232 subjects (26.0%). Two hundred thirteen individuals (23.9%) received flu vaccination between October and December 2019. The in-hospital mortality was 21.2%.

Vaccine status had only a limited impact on disease severity (41.5% of unvaccinated and 48.4% of vaccinated individuals had severe or critical disease, $p = .076$). In the Cox univariate analysis, flu vaccination was significantly associated with death (hazard ratio [HR], 1.934; 95% confidence interval, 1.108–2.062; $p = .009$), but, after adjusting for age, sex, and CCI, such an association went lost in the Cox multivariable regression (HR, 0.948; 95% confidence interval, 0.689–1.304; $p = .742$).

Some studies suggested potential benefits from influenza vaccination, but they have been performed in other geographical areas where the case fatality rate was not comparable with what registered in Northern Italy.^{4,5} Several mathematical models were developed to predict a beneficial effect but clinical validation is still missing.^{6,7}

Amato and colleagues reported a relationship between the flu vaccine and a reduced spread and disease severity in Italy.⁸ In this paper, data about vaccination were not related to the 2019/2020 season and the analyses were adjusted for epidemiological and economic factors but not for clinical issues.

Other risk factors—especially age—seem to play a major role rather than flu vaccination. Published literature generally provides analyses in populations older than 65 years, but the elderly could not be all grouped together as clinical evolution might be diverse in different age classes.⁹ Additionally, the high mortality rate observed in the Lombardy Region might be distinctive of this first outbreak and could not be compared with studies performed elsewhere.

Although influenza vaccination is strongly recommended for clinical, epidemiological, and management issues,¹⁰ our data do not support its beneficial effect in terms of COVID-19-related disease severity and mortality in Italy.

CONFLICT OF INTERESTS



The authors declare that there are no conflict of interests.

PEER REVIEW TRANSPARENT

The peer review history for this article is available at <https://publons.com/publon/10.1002/jmv.26841>

DATA AVAILABILITY STATEMENT

Our data are available for external review if requested.

Roberto Rossotti¹ 
Silvia Nerini Molteni²
Marino Faccini³
Massimo Puoti^{1,4} 

¹Department of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

²Chemical-Clinical and Microbiological Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

³Agency for Health Protection of Metropolitan Area of Milan (ATS), Milan, Italy

⁴School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy

Correspondence

Roberto Rossotti, Department of Infectious Diseases, ASST Grande
Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore 2,
20162 Milan, Italy.

Email: roberto.rossotti@ospedaleniguarda.it

ORCID

Roberto Rossotti  <http://orcid.org/0000-0003-4965-8789>

Massimo Puoti  <https://orcid.org/0000-0003-3278-7138>

REFERENCES

1. Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy [published online ahead of print June 9, 2020]. *J Med Virol*. <https://doi.org/10.1002/jmv.26120>
2. Alicandro G, Remuzzi G, La Vecchia C. COVID-19 pandemic and total mortality in the first six months of 2020 in Italy. *Med Lav*. 2020;111:351-353.
3. Lin L, Li TS. [Interpretation of "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection by the National Health Commission (Trial Version 5)".] *Zhonghua Yi Xue Za Zhi*. 2020;100(11):805-807. <https://doi.org/10.3760/cma.j.cn112137-20200205-00199>
4. Zanettini C, Omar M, Dinalankara W, et al. Influenza vaccination and COVID19 mortality in the USA. *medRxiv*. 2020. <https://doi.org/10.1101/2020.06.24.20129817>
5. Fink G, Orlova-Fink N, Schindler T, et al. Inactivated trivalent influenza vaccination is associated with lower mortality among patients with Covid-19 in Brazil [published online ahead of print December 11, 2020]. *BMJ Evid Based Med*. [10.1136/bmjebm-2020-111549](https://doi.org/10.1136/bmjebm-2020-111549)
6. Li Q, Tang B, Bragazzi NL, Xiao Y, Wu J. Modeling the impact of mass influenza vaccination and public health interventions on COVID-19 epidemics with limited detection capability. *Math Biosci*. 2020;325:108378.
7. Thindwa D, Garcia Quesada M, Liu Y, et al. Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality. *Vaccine*. 2020;38:398-5401.
8. Amato M, Werba JP, Frigerio B, et al. Relationship between influenza vaccination coverage rate and COVID-19 outbreak: an Italian ecological study. *Vaccines*. 2020;8:535.
9. Karagiannidis C, Mostert C, Nentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med*. 2020;8:853-862.
10. Maltezou HC, Theodoridou K, Poland G. Influenza immunization and COVID-19. *Vaccine*. 2020;38:6078-6079.