

**Letters to Editor****H1N1 Influenza among Hematological Patients: Monocentric Influenza Cases from 2011 to 2016****Keywords:** Influenza A, Hematological diseases, Vaccines.**Published:** March 1, 2017**Received:** December 19, 2016**Accepted:** January 23, 2017**Citation:** Metafuni E., Santangelo R., Chiusolo P., Laurenti L., Sorà F., Giammarco S., Sica S. H1N1 influenza among hematological patients: monocentric influenza cases from 2011 to 2016. *Mediterr J Hematol Infect Dis* 2017, 9(1): e2017024, DOI: <http://dx.doi.org/10.4084/MJHID.2017.024>This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Dear Editor,**

We read with interest the paper by La Torre et al.,¹ which conducted two systematic reviews and a meta-analysis to summarize the results of scientific works about influenza and pneumococcal vaccines in onco-hematological patients. We paid specific attention to influenza vaccine results. The protection rate of H1N1 vaccine resulted in 31% and 30% after the first dose and booster dose, respectively. Protection rate of H3N2 and influenza B first dose was 42.6% and 39.6%, respectively. Considering the response rate, the pooled prevalence for H1N1 was 30% and 35% after the first dose and booster dose, respectively. The response rate for H3N2 was 21.7% after first dose and 24% after booster dose. Finally, the response rate for influenza B was 23.6% after the first dose and 29% after booster dose. Only a minority of patients experienced adverse events, most of them were mild and did not require treatment. Even though influenza vaccine elicits a low response rate among onco-hematological patients, particularly in those who received transplantation, splenectomy or rituximab, it is an inexpensive intervention with few side effects. However, the first vaccine dose induces a small response, and the booster dose induces additional antibodies. Therefore, it is recommended to vaccinate these patients twice,² and the higher immunogenicity of adjuvated vaccines may be the way to improve response rate.³ To further decrease influenza risk, also household members and care providers should receive vaccination.⁴

Patients with hematological malignancies presented an increased susceptibility to influenza because of their underlying disease or treatment associated immunodeficiency.⁵ Recently, we evaluated the trend of influenza cases in our center from 2011 to 2016 (**Figure 1**), according to patients adherence to vaccine campaign. Our hematology unit is composed of a section for non-transplant hematological patients (22 beds), another section for autologous and allogeneic stem cell transplantation (SCT) (8 beds) and an outpatient clinic. Visitors can access to the unit only during visiting hours, one visitor at the time for patients by wearing the mask. Moreover, in the transplant unit visitor must wear mask, gown, headdress and gloves. Patients were advised to receive influenza vaccine, in the influenza season, available for risk categories by our Minister of Health. In addition, care workers and patients' family members were strictly encouraged to perform seasonal influenza vaccine to reduce possible sources of infection both at home and in the hospital. Throughout the influenza season, all patients were tested for influenza viruses at the admission to the ward and in the case of symptoms development for hospitalized patients and outpatients. We documented the first outbreak of H1N1 influenza in 2011, when, despite recommendations, the percentage of general population submitted to vaccination in our region Lazio was of 18.9%.⁶ Since that, fragile patients were strongly advised to adhere to vaccination campaign that was entrusted to family doctors and

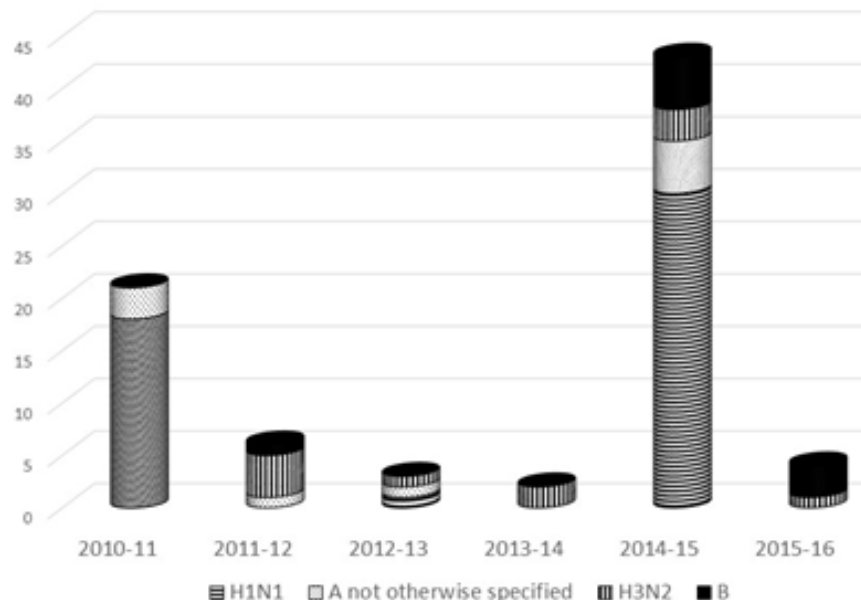


Figure 1. Illustration shows influenza cases in our department from 2011 to 2016. *Season 2010-11 (21)*: 18 cases of influenza H1N1 and 3 cases of influenza A non-otherwise specified; *Season 2011-12 (6)*: 4 cases of influenza H3N2, 1 case of influenza A and 1 case of influenza B; *Season 2012-13 (2)*: 1 case of influenza H1N1 and 1 case of concomitant influenza A and B; *Season 2013-14 (2)*: 2 cases of influenza H3N2; *Season 2014-15 (43)*: 30 cases of influenza H1N1, 3 cases of Influenza H3N2, 5 cases of influenza A non-otherwise specified and 5 cases of influenza B; *Season 2015-16 (4)*: one case of influenza H3N2 and 3 cases of influenza B.

was focused on elderly, immunocompromised and chronic diseases affected people. Because of a major percentage of vaccine coverage, in the following years, few cases of influenza infections were registered. Unfortunately, in the 2014-2015 season, we fell in a broader A flu outbreak, most likely due to the lack of adherence of patients, care workers and family members to influenza vaccination program, with a fall in vaccine administration down to 14% in region Lazio.⁶ The incidence of influenza cases in Italy in this season was the highest registered since 2009 pandemic, with up to 10.6 cases every 1000 observed in the central weeks of the season.⁷ In Italy, at least two episodes determined a drastic reduction of adherence to vaccination campaign in the last years. In 2013 several batches of influenza vaccines were temporarily taken off the market and in 2014 an alert on sudden deaths after influenza vaccines had an impressive echo on social media. Despite the prompt response of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee concluding that there was no evidence of an association between the reported deaths and the vaccine, flu vaccination has decreased by 80%, resulting in an estimated decrease of 25-30% on the overall 2014 national immunization campaign.⁸

Between December 2014 to March 2015 we diagnosed forty-three cases of influenza in 35

hospitalized patients and 8 outpatients: H1N1 in 30 cases (69.8%), influenza A not-otherwise specified in 5 cases (11.6%), H3N2 in 3 cases (7%) and influenza B in 5 cases (11.6%). Only three patients had received influenza vaccination, two of them developed influenza B infection and another one H1N1 influenza with mild symptoms. Patients' characteristics as age, underlying disease and status are reported in **Table 1**. All outpatients were screened for influenza infection because of respiratory symptoms development, while only 20 (57.1%) of the hospitalized patients presented already symptoms at admission: asthenia in one case, only fever in 5 cases, fever and diarrhea in one case, cough in 6 cases, and both fever and cough in 7 cases. The others 15 patients developed respiratory symptoms during the hospital stay. The overall median duration of hospitalization was 13 days (range, 2 to 90), and median time to swab positivization was 4 days (range, 1 to 27) after admission. At the date of swab positivity, patients showed median neutrophils and lymphocytes count of $1.89 \times 10^9/L$ (range, 0.01 to 17.96) and $0.45 \times 10^9/L$ (range, 0.01 to 23.77), respectively. All of them received oseltamivir administration within 24-48 hours from symptoms development. Twenty-five patients (58.1%) presented abnormal radiological study ranging from isolated small opacity to extensive and bilateral pulmonary involvement with pleural effusion.

Table 1 Season 2014-2015. Patient's characteristics.

Patients	43
Sex M/F	22/21
Median age (range) years	53 (23-84)
Hospitalized	35 (81.4%)
Outpatients	8 (18.6%)
Diagnosis	1 AA/PNH 1 megaloblastic anemia 1 APS 1 ITP/CVID 2 HL 3 ALL 1 CLL 8 AML 1 CML 10 NHL 11 MM 1 MPD 2 MDS
Chemotherapy	27 (62,8%)
Allogeneic SCT	7 (16.3%)
Autologous SCT	5 (11,6%)
No therapy	2 (4,65%)
Steroids/Eculizumab	2 (4,65%)
H1N1v	30 (69,8%)
Influenza A	5 (11,6%)
H3N2	3 (7%)
Influenza B	5 (11,6%)

Seventeen patients (39.5%) developed hypoxia requiring oxygen therapy. Seven patients (41.2%) were supported with Venturi mask while three patients (17.6%) required C-PAP mask support. The other seven patients (41.2%) presented a severe respiratory impairment requiring orotracheal intubation and were transferred in Intensive Care Unit. Two of them also required extracorporeal membrane oxygenation (ECMO)

support to manage the severe acute respiratory distress, unfortunately unsuccessfully. Cumulative mortality incidence in the study's group was 23.3% (10/43), while it was 58.8% among the hypoxemic patients (10/17). Death cause was attributable to a refractory and progressive respiratory distress leading to pulmonary failure in a half of the cases, while a multi organ failure (MOF) sepsis-driven was responsible for death in the remaining cases.

The vast majority of influenza cases among our patients during the 2014-2015 season were due to H1N1v rather than H3N2, opposite to that reported by several authors for the same season. Even if we thought that lack of vaccination was the main responsible for this new influenza outbreak, we could not exclude a virus neuraminidase inhibitor resistance conferred by amino acid substitution.⁹

In order to limit the influenza infection and nosocomial spread, our hospital organized a vaccination planning for care workers, in ward patients and outpatients increasing awareness and vaccination rate. Considering the results observed in the last season, it seems that our effort was able to avoid a new outbreak of influenza in our department.

Acknowledgements. This study was supported by Centro di Ricerca sulle Cellule Staminali Emopoietiche e le Terapie Cellulari, Università Cattolica del Sacro Cuore in Rome.

Elisabetta Metafuni¹, Rosaria Santangelo², Patrizia Chiusolo¹, Luca Laurenti¹, Federica Sorà¹, Sabrina Giammarco¹ and Simona Sica¹.

¹Hematology Department, Fondazione Policlinico Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.

²Microbiology Department, Fondazione Policlinico Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.

Competing interests: The authors have declared that no competing interests exist.

Correspondence to: Simona Sica, Hematology Department, Fondazione Policlinico Agostino Gemelli, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli, 8 00168 Rome, Italy, Tel: +39 0630155300, Fax +39 063017319. E-mail: simona.sica@unicatt.it

References:

1. La Torre G, Mannocci A, Colamesta V, D'Egidio V, Sestili C, Spadea A. Influenza and Pneumococcal Vaccination in Hematological Malignancies: a Systematic Review of Efficacy, Effectiveness, and Safety. *Mediterr J Hematol Infect Dis*. 2016 Sep 1;8(1):e2016044. <https://doi.org/10.4084/MJHID.2016.044>
2. Ide Y, Imamura Y, Ohfuji S, Fukushima W, Ide S, Tsutsumi C, Koga M, Maeda K, Hirota Y. Immunogenicity of a monovalent influenza A(H1N1)pdm09 vaccine in patients with hematological malignancies. *Hum Vaccin Immunother*. 2014;10(8):2387-94. <https://doi.org/10.4161/hv.29094> PMID:25424946 PMCid:PMC4896784
3. Cherif H, Höglund M, Pauksens K. Adjuvanted influenza a (H1N1) 2009 vaccine in patients with hematological diseases: good safety and immunogenicity even in chemotherapy-treated patients. *Eur J Haematol*. 2013 May;90(5):413-9. Epub 2013 Mar 18. <https://doi.org/10.1111/ejh.12094>
4. Engelhard D, Zakay-Rones Z, Shapira MY, Resnick I, Averbuch D, Grisariu S, Dray L, Djian E, Strauss-Liviatan N, Grotto I, Wolf DG, Or R. The humoral immune response of hematopoietic stem cell transplantation recipients to AS03-adjuvanted A/California/7/2009 (H1N1)v-like virus vaccine during the 2009 pandemic. *Vaccine*. 2011 Feb 17;29(9):1777-82

- <https://doi.org/10.1016/j.vaccine.2010.12.113> PMID:21216315
5. Lalayanni C, Sirigou A, Iskas M, Smias C, Sakellari I, Anagnostopoulos A. Outbreak of novel influenza A (H1N1) in an adult haematology department and haematopoietic cell transplantation unit: clinical presentation and outcome. *J Infect.* 2010;61(3):270-2. <https://doi.org/10.1016/j.jinf.2010.06.013> PMID:20600296
 6. Vaccinazione antinfluenzale in Italia. Stagioni 2000-2001/2015-2016. Ministero della Salute. http://www.salute.gov.it/imgs/C_17_tavole_19_allegati_itemAllegati_0_fileAllegati_itemFile_3_file.pdf
 7. Epicentro. Istituto Superiore di Sanità. Bollettino epidemiologico settimanale delle sindromi influenzali. 1/2015. http://www.epicentro.iss.it/problemi/influenza/FluNews/FluNews_2015-4.pdf
 8. Signorelli C, Odone A, Conversano M, Bonanni P. Deaths after Fluad flu vaccine and the epidemic of panic in Italy. *BMJ.* 2015;350:h116. <https://doi.org/10.1136/bmj.h116> PMID:25589037
 9. Hurt AC, Besselaar TG, Daniels RS, Ermetal B, Fry A, Gubareva L, Huang W, Lackenby A, Lee RT, Lo J, Maurer-Stroh S, Nguyen HT, Pereyaslov D, Rebelo-de-Andrade H, Siqueira MM, Takashita E, Tashiro M, Tilmanis D, Wang D, Zhang W, Meijer A. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2014-2015. *Antiviral Res.* 2016 Aug;132:178-85. <https://doi.org/10.1016/j.antiviral.2016.06.001> PMID:27265623