Advs Exp. Medicine, Biology - Neuroscience and Respiration (2017) 35: 93–100
DOI 10.1007/5584_2017_69

Published online: 21 July 2017

# Vaccine Effectiveness against Influenza in 2015/16 in Hospital and Ambulatory Medical Care Facilities: Polish Results of the European *I-MOVE+* Multicenter Study

Iwona Paradowska-Stankiewicz, Monika R. Korczyńska, Katarzyna Cieślak, Dorota Kowalczyk, Karol Szymański, and Lidia B. Brydak

**Abstract**

Influenza vaccination is the best measure available to prevent seasonal influenza infection. The majority of studies on vaccine effectiveness in the 2015/16 season conducted in the European *I-MOVE+* Project, show that a match between the circulating influenza strains in the general public and those included in the vaccine for the Northern Hemisphere was low to moderate. As part of *I-MOVE+*, Poland has implemented a case control negative study design and molecular biology methods, such as real time RT-PCR, to assess the vaccine match and effectiveness. The research described herein consisted of two major influenza vaccine effectiveness investigations conducted in Poland in the 2015/16 season. The general practice part of the study included 228 cases consisting of 159 type A, 65 type B, and 4 coinfections (types A + B), and 312 negative control cases. The hospital study part included 26 cases consisting of 21 type A, 2 type B, and 3 coinfections, and 13 negative control cases. The data were collected from patients of all ages recruited by 46 volunteering doctors in 15 Poland's provinces and three hospitals, respectively. In both study parts, only were seven patients and 12 control subjects vaccinated. Low vaccine coverage, a major limitation of the Polish study, makes the calculation of vaccine effectiveness for the Polish population hardly applicable statistically. Despite the crudeness of data, they were included

I. Paradowska-Stankiewicz (✉) and M.R. Korczyńska
Department of Epidemiology, Surveillance for Vaccine Preventable Diseases Unit, National Institute of Public Health – National Institute of Hygiene, 24 Chocimska Street, 00-791 Warsaw, Poland
e-mail: istankiewicz@pzh.gov.pl

K. Cieślak, D. Kowalczyk, K. Szymański, and L.B. Brydak
Department of Influenza Research, National Influenza Center, National Institute of Public Health- National Institute of Hygiene, 24 Chocimska Street, 00-791 Warsaw, Poland

into the common European analysis. The overall vaccine effectiveness amounted to 21.0% (95% CI: 74–122). It was somehow better for type B virus: 53.9% (95% CI: 47–87) and type A virus: 23.6% (95% CI: 83–185). A larger sample size is needed to achieve a desired interpretation of results on influenza vaccine effectiveness in Poland.

**Keywords**
Age • General population • Influenza • Vaccination • Vaccine coverage rate • Vaccine effectiveness

## 1 Introduction

Influenza is an infectious disease with an important public health impact at the global level. Annual epidemics of seasonal influenza represent a significant burden on society. The emergence and dominance of circulating influenza viruses are variable and difficult to predict. Therefore, influenza surveillance plays an important role in disease prevention (Blank et al. 2012; Council of the European Communities 2009). Studies on influenza vaccine effectiveness coordinated by the EpiConcept (I-Move in Europe 2016; Kissling and Valenciano 2016) and ECDC (2016) have been conducted in the EU since 2007. The main goals of those studies have been to assess a match between the circulating viral strains and those included in the vaccine as well as vaccine effectiveness in the general public. Poland has joined these studies as of the 2010/11 epidemic season. Recently, the country has implemented a case control negative study design and molecular biology methods within the European *I-MOVE+* Multicenter project on influenza vaccine effectiveness.

In the 2015/16 influenza season in Europe, circulation of influenza type A viruses predominated over type B. The A(H1N1)pdm09 virus was found in the majority of infected patients in intensive care units. Studies on influenza vaccine effectiveness conducted in the 2015/16 season in the European *I-MOVE+* project have shown that a match between the circulating vaccine strains and those included in the vaccine for the Northern Hemisphere was low to moderate. The goal of this report is to present the findings of the Polish part of the *I-MOVE+* study on influenza vaccine effectiveness in the 2015/16 epidemic season.

## 2 Methods

This study was approved by a local Ethics Committee of the National Influenza Center, National Institute of Public Health- National Institute of Hygiene in Warsaw, Poland and was conducted in accord with the principles of the Declaration of Helsinki for Human Research. The adult participants and legal guardians in case of children gave informed written consent to be included in the study. All participants were interviewed using a standardized questionnaire to collect data on clinical, epidemiological, and descriptive information, including the date of illness onset, the date of swabbing, the vaccination status, and the presence of any chronic health conditions. The study on the influenza vaccine effectiveness conducted in the 2015/16 season in Poland consisted of two major parts; the general practice part and the hospital part. The former was based on the collaboration with 46 volunteering general practitioners (GP) from 28 ambulatory medical care facilities from across the country, representing 15 Voivodship Sanitary Epidemiological Stations. There were 540 patients in this study part, 226 men and 314 women. Each GP recruited at least 5 patients selected for the study. The later part was conducted in three regional hospitals; two in

central and one in southern Poland and included 40 patients; 15 men and 25 women.

Nasopharyngeal swab specimens were collected from persons suffering from influenza-like illness (ILI) or acute respiratory illness. The specimens were tested for influenza viruses by real-time reverse transcription polymerase chain reaction (RT-PCR). Detection of a specific viral nucleic acid was considered a positive influenza diagnosis. The control group consisted of patients who did not meet the definition of ILI and had negative influenza RT-PCR results. All specimens were transported to the laboratory with the attached information concerning the date of general practitioner's visit and the date of swabbing. The participants of both ILI and non-influenza illness were stratified by age to the following groups: 0–14, 15–64, and 65+ years old.

## 2.1 Laboratory Elaboration

Laboratory elaboration consisting of virus detection, typing, and subtyping was conducted in the Department of Influenza Research of the National Influenza Center in the National Institute of Public Health – National Institute of Hygiene in Warsaw, Poland, and in Voivodship Sanitary Epidemiological Stations.

Influenza virus RNA was isolated using a Maxwell 16 Viral Total Nucleic Acid Purification Kit (Promega Corporation; Madison, WI) from 200 μl of clinical samples suspended in phosphate-buffered saline, according to the manufacturer's instructions for low elution volume cartridges. The RNA was eluted with 50 μl of RNAse-free water.

Real-time RT-PCR was performed with a Light Thermocycler 2.0 System (Roche Diagnostics; Rotkreuz, Switzerland) according the method described previously (Hallmann-Szelińska et al. 2016). Briefly, reactions were conducted in capillary tubes of 20 μl volume using 0.5 μl (20 nM) of primers and 0.5 μl (5 nM) of probes for each reaction. The reaction mixture consisted of $MgSO_4$, bovine serum albumin (BSA), RNase-free $H_2O$, and SuperScript® III/Platinum® *Taq* Mix (Invitrogen by Life Technologies – Thermo Fisher Scientific, Carlsband, CA), and was incubated with 5 μl of RNA sample in each capillary tube. RNA from the 2015/16 vaccine viruses: A/California/7/2009(H1N1)pdm09 and A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 were introduced as positive controls. The negative control constituted RNase-free water. Before DNA amplification, RNA templates were reverse transcribed (at 50 °C for 30 min) to obtain the corresponding cDNA. Subsequently, cDNA was subjected to denaturation (one cycle at 95 °C for 2 min), followed by further steps of denaturation (95 °C; 15 s), annealing (55 °C; 30 s), and extension (72 °C; 20 s) repeated in 45 cycles.

## 2.2 Statistical Elaboration

Influenza vaccine effectiveness (VE), a single percentage value estimating the reduction in risk provided by the vaccine in laboratory-confirmed ILI, was calculated as 1 – OR; where OR is the odds ratio for acquiring influenza infection in vaccinated *versus* unvaccinated patients with laboratory confirmed ILI. Logistic regression analysis was used to calculate the adjusted OR and its correspondent 95% confidence interval (CI). The statistical analysis was performed with a commercial Stata 12 package (StataCorp LLC; College Station, TX).

# 3 Results

In the general practice part of the study, there were 228 influenza positive and 312 negative control cases. The positive cases consisted of 159 influenza type A, including 136 A/H1N1/pdm09 and 23 type A unsubtyped, 65 type B, and four type A + B co-infections. The second hospital part included 26 cases consisting of 21 type A, 3 type B, and 2 co-infections, and 14 control cases.

Among all 540 patients investigated, there were 35 persons aged 65+, with positive influenza results in 12 of them. These positive results

**Table 1** Positive influenza type A and B cases and negative control cases in the *I-MOVE+* Polish study among ambulatory medical care facilities during the 2015/16 epidemic season

| | | Positive influenza cases (n = 228) | Negative control cases (n = 312) |
|---|---|---|---|
| | | n (%) | n (%) |
| Age-groups (year) | 0–4 | 19 (8.3) | 38 (12.2) |
| | 5–14 | 35 (15.4) | 35 (11.2) |
| | 15–64 | 162 (71.1) | 216 (69.2) |
| | 65+ | 12 (5.3) | 23 (7.4) |
| Gender | Male | 94 (41.2) | 132 (42.3) |
| | Female | 134 (58.8) | 180 (57.7) |
| Vaccination | Yes | 7 (3.1) | 12 (3.8) |
| | No | 221 (96.9) | 300 (96.2) |
| Influenza type | A/H1N1/pdm09 | 136 (59.6) | – |
| | A/H3N2/ | 0 (0) | – |
| | A unsubtyped | 23 (10.1) | – |
| | B/A co-infection | 1 (0.4) | – |
| | B Yam/A co-infection | 0 (0) | – |
| | B Vic/A co-infection | 3 (1.3) | – |
| | B Yamagata | 0 (0) | – |
| | B Victoria | 9 (3.9) | – |
| | B unknown | 56 (24.6) | – |
| Any chronic condition, including obesity and pregnancy | Yes | 42 (18.4) | 62 (19.9) |
| | No | 186 (81.6) | 250 (80.1) |
| Belongs to target group for vaccination | Yes | 121 (53.1) | 177 (56.7) |
| | No | 107 (46.9) | 135 (43.3) |

were typed/subtyped as follows: nine cases of A/H1N1/pdm09, one case of influenza type A unsubtyped, and two cases of influenza type B. A descriptive summary of *I-MOVE+* findings from both GP ambulatory and hospital medical care facilities is presented in Tables 1 and 2, respectively.

Virological characteristics of weekly specimens during the 2015/16 season showed that influenza type A virus predominated in the circulation. The collection of samples started in Week 2 (W2), according to the International Organization for Standardization (ISO) week-numbering. The seasonal peak took place in W6, confirming a typical course of the epidemic curve (Fig. 1). In the hospital part of the study, severe acute respiratory infections (SARI) cases predominated in W8 and W9, still providing a significant number of influenza cases down to W14 (Fig. 2).

## 4 Discussion

The 2015/16 influenza season in Europe was characterized by a high degree of antigenic and genetic mismatch between the circulating type A viruses and the vaccine strains consisting of A/California/7/2009(H1N1)pdm09 clade NYMC X-181 and A/Switzerland/9715293/2013 (H3N2) clade NIB-88, recommended for the Northern Hemisphere in the season.

In Europe, there are considerable differences in the state of vaccination against seasonal influenza in populations at risk of a severe and complicated course of influenza. The target 75% coverage of vaccination recommended by the Council of the European Union (2009) is seldom met. The UK and the Netherlands are the only two countries that have reached or nearly reached this target level in the elderly. Vaccination may

**Table 2** Positive influenza type A and B cases and negative control cases in the *I-MOVE+* Polish study among ambulatory medical care facilities during the 2015/16 epidemic season

| | | Positive influenza cases (n = 26) n (%) | Negative control cases (n = 14) n (%) |
|---|---|---|---|
| Age-groups (year) | 65–79 | 16 (61.5) | 10 (71.4) |
| | 80+ | 10 (38.5) | 4 (28.6) |
| Gender | Male | 7 (26.9) | 8 (57.1) |
| | Female | 19 (73.1) | 6 (42.9) |
| Vaccination | Yes | 1 (3.8) | 0 (0) |
| | No | 25 (96.2) | 14 (100) |
| Influenza type | A/H1N1/ | 16 (61.5) | – |
| | A/H3N2/ | 0 (0) | – |
| | A unsubtyped | 5 (19.2) | – |
| | B Yam + A/H3N2/ co-infection | 1 (3.9) | – |
| | B Vic + A/H3N2/ co-infection | 1 (3.9) | – |
| | B unknown | 3 (11.5) | – |
| Hospital ward | Internal medicine | 7 (26.9) | 9 (64.3) |
| | Emergency department | 0 (0) | 0 (0) |
| | Intensive care unit | 0 (0) | 2 (14.3) |
| | Pulmonary diseases | 0 (0) | 0 (0) |
| | Cardiology | 16 (61.5) | 2 (14.3) |
| | Infectious diseases | 0 (0) | 0 (0) |
| | Geriatrics | 0 (0) | 0 (0) |
| | Others | 3 (11.6) | 1 (7.1) |

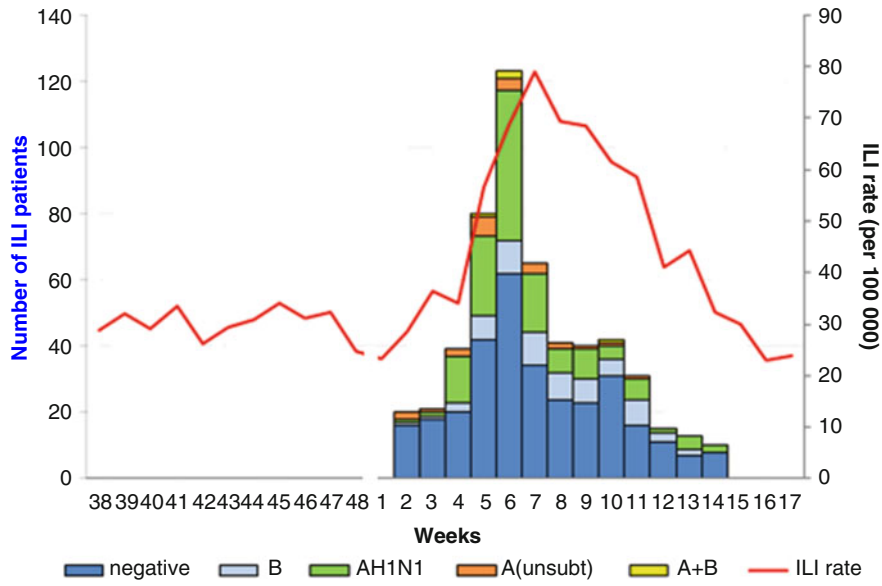


**Fig. 1** Virological characteristics of nasopharyngeal swab specimens collected in the general practice facilities within the *I-MOVE+* study distributed by the week number during the 2015/16 influenza epidemic season in Poland; week-numbering is in accordance with the International Organization for Standardization (ISO) system

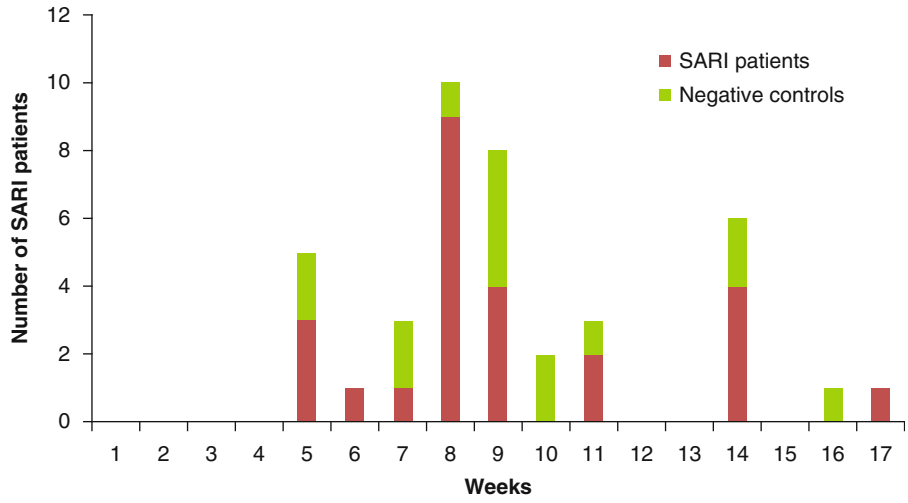


**Fig. 2** Severe acute respiratory infections (SARI) in hospitals involved in the *I-MOVE+* study distribution by the week number during the 2015/16 influenza epidemic season in Poland; week-numbering is in accordance with the International Organization for Standardization (ISO) system

reduce the risk of infection by influenza viruses by 70–80% in healthy adults and by 30–70% in the elderly (Centers for Disease Control and Prevention 2013). The implementation of vaccination programs against influenza is cost-effective, taking into account the reduction in morbidity and mortality due to the disease and its complications. It should be noted that vaccine effectiveness may vary depending on the season. The relevance of vaccine strains circulating in the population in previous years does not provide cross-protection (ECDC 2016; Grohskopf et al. 2014; Council of the European Communities 2009). In Poland, influenza vaccine coverage in the 2015/16 epidemic season was dismally low, amounting to barely 3.55% of the population. This low coverage has persisted for years in both general population and subpopulations or age-groups at high risk such as the immunocompromised, children, or pregnant women. A somehow better vaccination coverage, amounting to 6–8%, concerns the elderly, which may stem from the vaccination cost reimbursement currently used in this population group. It thus may be presumed that the Polish population, as a whole, is outstandingly susceptible to influenza infection and complications. The death toll due to influenza infection amounted to 140 cases in the 2015/16 season in Poland. That pointedly demonstrates a high price paid by the society in terms of hospitalizations, work absenteeism, and overall medical care.

Vaccine coverage data are part of the calculation of vaccine effectiveness (VE). A low value of vaccine coverage makes the calculation of VE for the Polish population statistically inapplicable. The overall VE amounted to 21.0% (95% CI: 74–122). It was somehow better for type B virus: 53.9% (95% CI: 47–87) and type A virus: 23.6% (95% CI: 83–185). Despite the crudeness of these data, they were included into the common European analysis. The European analysis has shown that the adjusted VE was low to moderate for A/H1N1/pdm09: overall 33.1% and by the age-groups: 31.7%, 42.5%, and 10.0% among 0–14, 15–64, and 65+ years-old individuals, respectively. The Italian studies show a good VE against A/H1N1/pdm09 and B viruses and the lack of VE against A/H3N2/virus due to the antigenic mismatch between the circulating A/H3N2/and the respective 2014/15 vaccine strain (Rizzo et al. 2016). The I-MOVE Multicenter Case-Control Study has confirmed a moderate VE against A/H1N1/pdm09 and B viruses, and a low VE against A/H3N2/2014/2015 virus in the 2014/15 epidemic season; the latter was

consistent with a reported mismatch between the circulating and vaccine strains (Valenciano et al. 2016). In contrast, Pebody et al. (2016) have reported moderate to good levels of protection, amounting to overall adjusted end-of-season VE of 52.4% in children in the UK. The country was in the third season of introducing universal pediatric influenza vaccination with a quadrivalent live attenuated influenza vaccine. These results may be viewed as a reassurance of the efficacy of modern influenza immunization programs in modern health protection and care.

## 5 Conclusions

- Studies on vaccine effectiveness are a useful epidemiological and microbiological tool for the assessment of influenza vaccine effectiveness in prevention against infection.
- Influenza vaccine coverage is dismally low, amounting to a few percentage points, in the general population in Poland.
- Overall vaccine effectiveness in the epidemic 2015/16 season in Poland amounted to a low 21.0% (95% CI: 74–122). It was somehow better for type B virus: 53.9% (95% CI: 47–87) and type A virus: 23.6% (95% CI: 83–185).
- Low vaccine coverage, making the calculation of vaccine effectiveness statistically inapplicable, was a major limitation of the Polish study. Nonetheless, the Polish results were included inti the European *I-MOVE+* Multicenter Study.

**Acknowledgements** We are grateful to the EpiConcept and ECDC for giving an opportunity to carrying out the study in Poland. Supported in part by the I-MOVE+ Project and H2020 funds.

**Conflicts of Interest** The authors declare no conflicts of interest in relation to this article.

## References

Blank P, Schwenkglenks M, Szucs TD (2012) The impact of European vaccination policies on seasonal influenza vaccination coverage rates in the elderly. Hum Vaccin Immunother 8(3):328–335

Centers for Disease Control and Prevention (2013) Seasonal influenza (flu). https://www.cdc.gov/flu/pastseasons/1314season.htm. Accessed on 16 May 2017

Council of the European Communities (2009) Proposal for a Council Recommendation on Seasonal Influenza Vaccination. https://ec.europa.eu/health/ph_threats/com/Influenza/docs/seasonflu_rec2009_en.pdf. Accessed on 8 May 2017

Council of the European Union. State of play on implementation of the Council Recommendation of 22 December 2009 on seasonal influenza

ECDC (2016) European Centre for Disease Prevention and Control. Seasonal Influenza Vaccine Effectiveness, 2005–2016. https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Accessed on 9 May 2017

Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR, Karron RA, Walter EB, Centers for Disease Control and Prevention (2014) Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2014–15 influenza season. MMWR Morb Mortal Wkly Rep 63(32):691–697

Hallmann-Szelińska E, Bednarska K, Korczyńska M, Paradowska-Stankiewicz I, Brydak LB (2016) Virological characteristics of the 2014/2015 influenza season based on molecular analysis of biological material derived from I-MOVE study. Adv Exp Med Biol 921:81–86

I-Move in Europe (2016) https://sites.google.com/site/epiflu/. Accessed on 9 May 2017

Kissling E, Valenciano M (2016) Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study. Euro Surveill 21(6). doi:10.2807/1560-7917.ES.2016.21.6.30134

Pebody R, Warburton F, Ellis J, Andrews N, Potts A et al (2016) Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. Euro Surveill 21(38). doi:10.2807/1560-7917.ES.2016.21.38.30348

Rizzo C, Bella A, Alfonsi V, Puzelli S, Palmieri AP et al (2016) Influenza vaccine effectiveness in Italy: age, subtype-specific and vaccine type estimates 2014/15 season. Vaccine 34(37):3102–3108

Valenciano M, Kissling E, Reuss A, Rizzo C, Gherasim A et al (2016) Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A (H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case-Control Study, Europe 2014/15. Euro Surveill 21(7). doi:10.2807/1560-7917.ES.2016.21.7.30139