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Short communication

A mid-term estimate of 2018/2019 vaccine effectiveness to prevent laboratory confirmed A(H1N1)pdm09 and A(H3N2) influenza cases in Sicily (Italy)

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ABSTRACT

Influenza season started in Italy during the month of October 2018, approaching the epidemic peak in January 2019. This report aim to explore the mid-term virologic surveillance data of the 2018–2019 influenza season in Sicily and to estimate the effectiveness of seasonal influenza vaccine (VE) against A(H1N1) pdm09 and A(H3N2) influenza viruses. A test-negative design was used to evaluate influenza VE.

In Sicily, almost all influenza infections were sustained by influenza type A viruses, of which 62.3% were A(H3N2) and 36.3% A(H1N1)pdm09. A reduction of laboratory confirmed influenza cases in Sicilian population immunized against influenza were observed. In particular, an overall significant protective values were observed for any influenza A viruses (Adj-VE = 44.0%; 95%CI: 11.2–64.7%), especially among 15–64 years old age group (Adj-VE = 59.5%; 95%CI: 0.03–83.1) and among the elderly (Adj-VE = 73.6%; 95% CI: 29.4–90.2).

1. Introduction

Influenza season started in Italy during the month of October 2018, approaching the epidemic peak in January 2019 [1]. Influenza A viruses were predominant during the 2018–2019 season in Italy, with A(H1N1)pdm09 viruses responsible for more than half of complicated influenza infections [2].

During the season 2018–2019 in Sicily, quadrivalent influenza vaccine (QIV) and trivalent adjuvanted influenza vaccine (aTIV, provided in elderly adults ≥65 years) were offered to the general population, according to guidelines of the Regional Health Department, which recommend the immunization of the elderly (aged ≥ 65 years), of adults with underlying chronic medical conditions (comorbidities), pregnant women (at second and third trimester of pregnancy), and healthcare workers [3,4]. For the 2018/2019 influenza season in the Northern Hemisphere, the recommended composition provided by the World Health Organization were: an influenza A(Michigan/45/2015[H1N1])pdm09–like virus, an influenza A(Singapore/INFIMH-16-0019/2016[H3N2])–like virus, an influenza B (Colorado/60/2017)–like virus (B/Victoria lineage; updated), and, for quadrivalent vaccines, an additional B virus (Phuket/3073/2013–like virus; B/Yamagata lineage) [5].

This report aim to explore the mid-term virologic surveillance data of the 2018–2019 influenza season in Sicily and to estimate the effectiveness of seasonal influenza vaccine (VE) against A (H1N1)pdm09 and A(H3N2) influenza viruses.

2. Methods

Since the 2009 flu pandemic, the reference laboratory of Sicily (Italy) takes part in the national influenza surveillance network (InfluNet) and contributes to the surveillance of the fourth most populous administrative region of the country, which accounts for more than five million inhabitants. To this purpose, oropharyngeal samples of subjects with Influenza-like illness (ILI) are collected by a network of sentinel general practitioners and pediatricians, covering approximately 2% of the general population [6]. All specimens were molecularly analysed through rtPCR-based protocols according to the Center for Disease Control and

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Prevention for influenza type A viruses (protocols available upon request), and previously published protocols, for the influenza type B viruses [7,8].

Oropharyngeal specimens and epidemiological data were collected from general practitioners and pediatricians involved in the sentinel influenza surveillance network and operating in all the nine Sicilian Local health Units (LHUs: Agrigento, Caltanissetta, Catania, Enna, Messina, Palermo, Ragusa, Siracusa, Trapani). All subjects with Influenza-like illness (ILI), according to European Center for Disease Control and prevention (ECDC) definition (sudden onset of symptoms and at least one systemic symptom among fever or feverishness, malaise, headache, myalgia concomitantly with at least one respiratory symptom such as cough, sore throat or shortness of breath), were enrolled (n = 1225) [9]. Vaccination status, type of vaccine administered and vaccination data were verified and confirmed by community-based practitioners and pediatricians registries. All subjects vaccinated less than 2 weeks before the onset of ILI, newborn younger than 6 months, children younger than 9 years old not compliant with the two-dose recommendation for first influenza vaccination and subjects with unknown vaccination status or unspecified vaccination timing were excluded from the analysis (n = 22, 1.79%).

The test-negative design, commonly used as preferred method in observational studies, was used to evaluate influenza VE [10,11].

For the estimate of the test negative vaccine effectiveness, cases were identified as individuals that had a laboratory confirmed diagnosis of influenza during the 2018/2019 season and controls as subjects without laboratory confirmed diagnosis of influenza enrolled during the 2018/2019 with symptoms of ILI. Moreover, all subjects with an interval between onset of symptoms and oropharyngeal specimen collection ≥8 days (n = 98, 8.0%) were subsequently excluded from the analysis [11,12].

The VE estimates were obtained by comparing the odds ratio (OR) of vaccination between cases and controls (1 – OR × 100) [10].

Crude and AdjVE analysis for sex, comorbidities and for calendar time (week of symptom onset of ILI) were performed for age groups and all influenza A subtypes, with a particular focus on VE for A(H1N1) and A(H3N2) viruses.

The approval of the Palermo Ethical Committee 1 (session of the 29th of April 2019, protocol number: 04/2019) was obtained.

3. Results

3.1. Surveillance data

Between week 42 of 2018 and week 6 of 2019 (October 15, 2018 to February 10, 2019), a total of 1105 samples were obtained from community-based sentinel general practitioners and pediatricians. Overall, 39.6% (n = 438) of samples resulted positive for influenza viruses, with a peek at week 4 of 2019 (Fig. 1).

Almost all influenza infections were sustained by influenza type A viruses, of which of which 62.3% were A(H3N2), 36.3% A(H1N1) pdm09, 1.4% A (without subtypes) (data not shown in table).

Table 1 reports the main characteristics of ILI subjects enrolled and of laboratory confirmed influenza A cases from the Sicilian sentinel surveillance system. Most of them (n = 708; 64.1%) belonged to the pediatrician area, followed by 308 subjects aged 15–64 years and 89 ≥ 65 years old. Over 19% of enrolled population (n = 218) had at least one comorbidity.

No substantial differences of influenza positivity rates by age groups, sex and comorbidities were observed (Table 1).

Among test-negative controls, 3.7% of children aged 7 months-14 years, 13.2% of subjects aged 15–64 years and 69.2% of subjects ≥65 years old were vaccinated against influenza (Table 2).

Comparing influenza positive and negative cases with influenza vaccination receipt, higher vaccination rates in laboratory-confirmed negative subjects were observed in the age groups 15–64 years old (13.2% *vs.* 6.3%) and ≥65 years old (69.2% *vs.* 45.9%) and among subjects with comorbidities (41.5% *vs.* 26.8%) (Table 2).

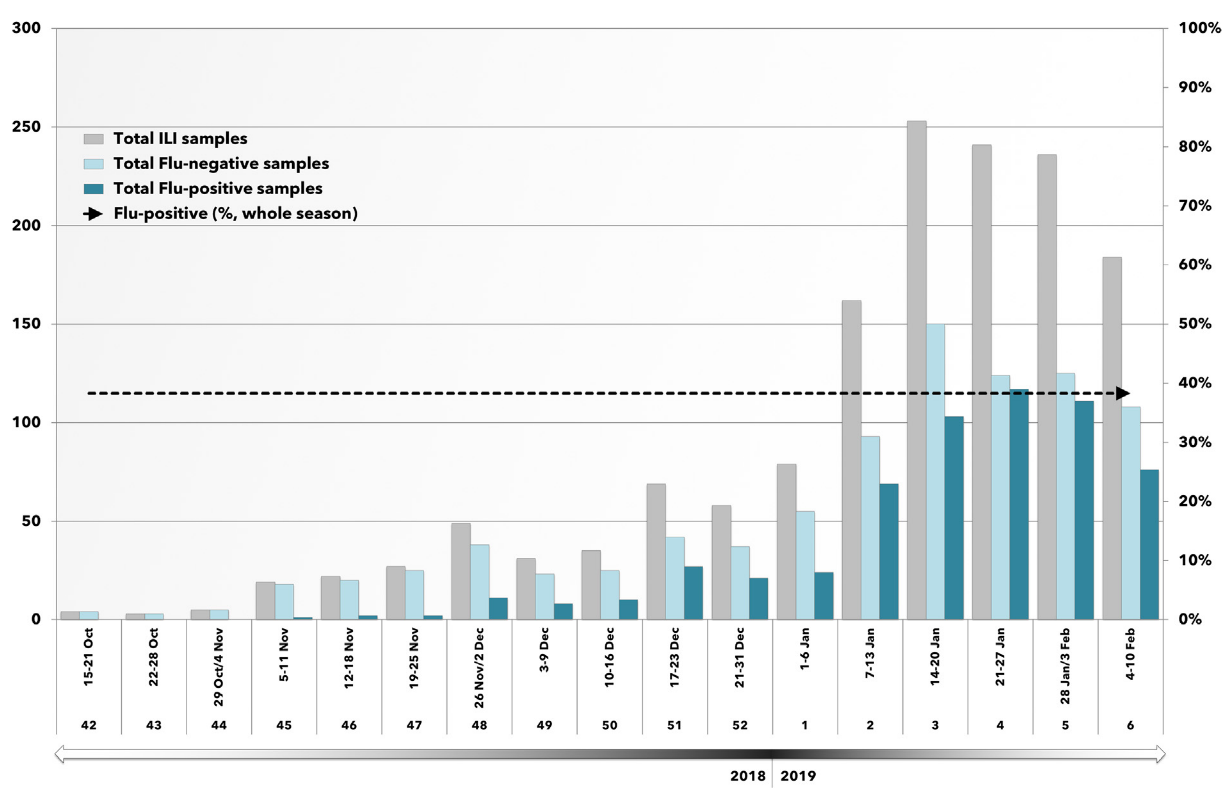

Fig. 1. Overview of Influenza Surveillance Activity in Sicily (Italy) from October 15th, 2018 to February 10th, 2019.

Table 1
Characteristics of the 1105 ILI subjects enrolled and of laboratory confirmed influenza A cases, according to sub-types, between October 15th, 2018 and February 10th, 2019 in Sicily (Italy).

Characteristics	Overall n = 1105	Laboratory confirmed influenza A cases (39.6%) n (%)	Influenza sub-types of laboratory confirmed cases n	
			Influenza A(H3N2)	Influenza A(H1N1)pdm09
Age-groups				
7 months-14 years	708	275 (38.8%)	173	99
15–64 years	308	126 (40.9%)	75	48
≥65 years	89	37 (41.5%)	25	12
Sex				
Male	574	236 (41.1%)	149	84
Female	531	202 (38.0%)	124	75
Comorbidities				
Yes	218	83 (38.1%)	55	26
No	887	355 (40.0%)	218	133

Table 2
Characteristics of the 1,105 ILI subjects enrolled by general practitioners and pediatricians between October 15th, 2018 and February 10th, 2019 in Sicily (Italy), according to influenza positivity and influenza vaccination receipt.

Characteristics	Influenza positive (n = 438)		Influenza negative (n = 667)	
	Not vaccinated	Vaccinated n (%)	Not vaccinated	Vaccinated n (%)
Age-groups				
7 months-14 years	267	8 (2.9)	417	16 (3.7)
15–64 years	118	8 (6.3)	158	24 (13.2)
≥65 years	20	17 (45.9)	16	36 (69.2)
Sex				
Male	218	18 (7.6)	306	32 (9.5)
Female	187	15 (7.4)	285	44 (13.4)
Comorbidities				
Yes	60	22 (26.8)	79	56 (41.5)
No	344	12 (3.4)	512	20 (53.7)

3.2. Vaccine effectiveness estimates

In Table 3 are reported the test negative VE estimates for both the A viruses and for A(H3N2) and A(H1N1)pdm09. Crude VEs by age-group (15–64 and over 65 years old), gender and comorbidities were analyzed. Finally, the overall test-negative VE for subjects 15–64 and ≥65 years old were estimated, adjusting by sex, age groups, comorbidities and for calendar time (week of symptom onset) with a logistic regression model.

No substantial differences of VE adjusting for sex, comorbidities and calendar time in comparison to crude VE were observed.

The overall adjusted VE estimates (adj-VE) was significantly protective against influenza A viruses (44.0%; 95% CI: 11.2–64.7). The adj-VE showed similar protective values for A(H3N2) viruses (40.7%; 95% CI: −1.0–65.3) and A(H1N1)pdm09 viruses (34.1%; 95% CI: −27.8–66.1). In particular, a significant protective value of adj-VE were observed for any influenza A among 15–64 years old age-group (59.5%; 95% CI: 0.03–83.1), and among the elderly (73.6%; 95% CI: 29.4–90.2).

4. Discussion

To date, the virological surveillance of influenza in Sicily showed the exclusive circulation of influenza type A viruses, with a clear predominance of A(H3N2) over A(H1N1)pdm09, conflicting to the interim reports of the 2018–2019 influenza surveillance conducted in USA, Canada and in six European Countries (93%, 74%, 58 to <80% of A(H1N1)pdm09 proportion, respectively) [13–15].

Among 1105 surveilled subjects, pediatric patients prevailed (64.1%). This data is consistent with International and National influenza-like illness surveillance reports that yearly demonstrated a higher prevalence in the age classes >7 months-4 years and 5–14 years [1,16].

Table 3
Crude and adjusted test-negative VE influenza estimate (95% CI) for any influenza type A, influenza A(H3N2) and influenza A(H1N1)pdm09, according to age groups.

Vaccine effectiveness (test-negative)	Overall (n = 1,105)		7 months–14 years old (n = 708)		15–64 years old (n = 308)		≥65 years old (n = 89)	
	Crude VE (95% CI)	Adjusted VE*	Crude VE (95% CI)	Adjusted VE*	Crude VE (95% CI)	Adjusted VE*	Crude VE (95% CI)	Adjusted VE*
Any influenza A	**36.2 (2.0 to 58.3)**	**44.0 (11.2 to 64.7)**	20.9 (−87.3 to 66.6)	26.0 (−78.4 to 69.3)	55.4 (−2.9 to 80.7)	**59.5 (0.03 to 83.1)**	62.8 (9.4 to 84.3)	**73.6 (29.4 to 90.2)**
Influenza A(H3N2)	33.7 (−9.8 to 60.0)	40.7 (−1.0 to 65.3)	38.7 (−81.9 to 79.4)	31.9 (−108.1to 77.7)	58.8 (−21.7 to 86.1)	66.7 (−0.01 to 89.0)	48.2 (−32.0 to 79.7)	51.6 (−26.1 to 81.6)
Influenza A(H1N1)pdm09	28.6 (−33.3 to 61.8)	34.1 (−27.8 to 66.1)	−23.8 (−270.1 to 58.6)	−5.2 (−319.8 to 65.4)	46.9 (−81.8 to 84.5)	34.0 (−136.7 to 81.6)	56.9 (−48.6 to 87.5)	72.5 (−4.1 to 92.8)

Bold characters identified the significant (p-value < 0.05) values of VE and related 95% CI.
* Adjusted by sex, age groups comorbidities and for week of symptom onset (calendar time).

The higher risk of acquiring influenza-like illness during the first years of life could be related also with a very low influenza vaccination coverage commonly reported in Italy and, in part, due to the lack of national recommendations that not suggest influenza vaccination in children without comorbidities [4].

Also influenza vaccination rates in the age classes 15–64 years old (10.4%), the elderly (59.5%) and subjects with comorbidities (35.8%), were similar to data reported at National and Regional level during previous influenza seasons, supporting the representativeness of the population enrolled [17].

This mid-term influenza VE report showed an overall 44% reduction of laboratory confirmed influenza cases in Sicilian general population. To best of our knowledge, this paper represents one of the most updated report in Europe and in the World, particularly estimating a VE for influenza A(H3N2) viruses due to the prevalent circulation of these sub-types during the 2018–2019 influenza season in our Region.

At the same time, VE estimates for A(H1N1)pdm09 influenza viruses among the elderly was similar than that reported during previous influenza seasons [18] and consistent with the interim report conducted in Canada [14].

Conversely, the VE observed in the early report of the 2018–2019 season in the United States for the A(H1N1)pdm09 was higher among children and adults, differently from that observed in our population, where the influenza A(H1N1)pdm09 VE substantially increased with age [13].

The VE estimates were also higher from that observed in a recent metanalysis reporting a VE of 25% (95%CI: 6–40%) in reducing outpatient laboratory-confirmed cases of influenza among the elderly [19].

The 2018–2019 seasonal influenza epidemic, according to the trend of the epidemic curve observed from the 3rd to the 6th weeks of 2019, seems to be descending. In Sicily the number of ILI cases expected within the end of 2018–2019 influenza season should decrease, and the mid-season estimates from our network could be considered consistent with final VE data referring to the whole season [20].

Some limits could affect this analysis. As first limitation, our VE estimates a mid term value that could be just a bit different from that measured at the end of influenza epidemics. However it should be noted that, in both the national and regional surveillance systems, from the 3rd to the 6th weeks of 2019 epidemic curve started a descending slope, suggesting that more than half of the total ILI for this influenza season have been included in our analysis. For this reason, the mid-season estimates from our network could be considered consistent with final VE data of the 2018/2019 influenza season [20].

As second point, the different characteristics of influenza viruses circulation and influenza season duration across the Northern Hemisphere should be taken into account. In particular, the other mid-term reports evidenced an earlier start of influenza circulation during the last weeks of 2018 and an anticipated peak in comparison with European data [13,14,16]. Moreover, analyzing the virus circulation, in our context a prevalence of A(H3N2) viruses represented at time a unique event and this situation could have determined an overall VE different from that measured in other countries.

Finally, the study was carried out with a sample of subjects enrolled throughout the regional sentinel system of influenza and thus, as well as in other similar studies, it could be not fully representative of the population. The limited sample size could also affect the strength of some VE estimates, especially for age-groups and for subtype, for the small number of vaccinated subjects.

5. Conclusions

The Sicilian mid-term VE estimate represents, to our knowledge, the first data on influenza vaccine effectiveness for the current season in Italy and one of the first VE estimates for influenza A(H3N2) viruses.

The observed VEs confirmed the protective role of vaccination in prevent laboratory confirmed cases of influenza, especially among the elderly and subjects with comorbidities, that represent the categories at higher risk for influenza correlated complications.

Finally, our data support not only the effectiveness of the influenza vaccines against influenza A(H1N1)pdm09, as already confirmed in Canada and United States [13,14], but also a significant protective effect of vaccination against A(H3N2) viruses.

Finally, the high incidence of influenza infections in the age class ≥7 months–14 years old, confirmed by the European surveillance data, should represent a suggestion for Italian Public health Authorities for routine influenza vaccine administration in healthy children.

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Declaration of Competing Interest

The authors declare that they have no competing interests

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Authors' contributions

Conception and design of the study: FT, FV and CC; laboratory investigation and data acquisition: FT and GMEC; data analysis: CC, VR and EA; drafting the article: CC and FT; draft revision and final approval of the version submitted: FV, EA and VR.

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