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RESEARCH PAPER

Trends of influenza B during the 2010–2016 seasons in 2 regions of north and south Italy: The impact of the vaccine mismatch on influenza immunisation strategy

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ABSTRACT

Influenza A and B viruses are responsible for respiratory infections, representing globally seasonal threats to human health. The 2 viral types often co-circulate and influenza B plays an important role in the spread of infection.

A 6-year retrospective surveillance study was conducted between 2010 and 2016 in 2 large administrative regions of Italy, located in the north (Liguria) and in the south (Sicily) of the country, to describe the burden and epidemiology of both B/Victoria and B/Yamagata lineages in different healthcare settings.

Influenza B viruses were detected in 5 of 6 seasonal outbreaks, exceeding influenza A during the season 2012–2013. Most of influenza B infections were found in children aged $\leq$ 14 y and significant differences were observed in the age-groups infected by the different lineages. B/Victoria strains prevailed in younger population than B/Yamagata, but also were more frequently found in the community setting. Conversely, B/Yamagata viruses were prevalent among hospitalized cases suggesting their potential role in the development of more severe disease.

The relative proportions of viral lineages varied from year to year, resulting in different lineage-level mismatch for the B component of trivalent influenza vaccine.

Our findings confirmed the need for continuous virological surveillance of seasonal epidemics and bring attention to the adoption of universal influenza immunization program in the childhood. The use of tetravalent vaccine formulations may be useful to improve the prevention and control of the influenza burden in general population.

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Introduction

Influenza A and B are major causes of respiratory infections in human and contribute to increase morbidity and mortality globally.[1-6] The clinical presentation of influenza A seems to be comparable to that of influenza B;[7,8] this latter, like influenza A, can lead to severe complications and death in both pediatric and adult populations.[9-11] Despite similar clinical phenotypes, the 2 viral types appear considerably dissimilar in their propensity for genetic reassortment as a consequence of differences in the corresponding host reservoirs.

In fact, influenza A viruses have been isolated from various species including humans and this have contributed to viral heterogeneity, generating various subtypes which have the potential to cause human pandemics.[12]

Conversely, influenza B virus is supposed to have evolved almost exclusively as human pathogen and this has limited the generation of new strains by reassortment, leading to scarse pandemic potential, although its presence has been confirmed in throat swab obtained from seal,[13,14] and detected in nasal swabs from domestic pigs by real-time reverse transcription PCR and sequencing.[15]

Influenza B viruses are not formally classified into subtypes. However, 2 antigenically and genetically distinct major lineages are universally recognized, which evolved since 1983 from the first isolate B/Lee/40,[16] actually referring to B/Victoria/2/87 and B/Yamagata/16/88 strains, henceforth termed the Victoria and Yamagata lineages, respectively.

From a public health point of view, vaccination is the primary measure to prevent influenza and reduce its impact in the population. For decades, licensed trivalent seasonal influenza vaccines have contained 2 type A strains (A/H1N1 and A/H3N2) and one of the 2 known divergent influenza B lineages, which have also been shown to circulate simultaneously. In this context, it has represented a challenge in terms of vaccine efficacy and effectiveness, because of the limited cross protection between the 2 influenza B lineages,[17,18] and the degree of

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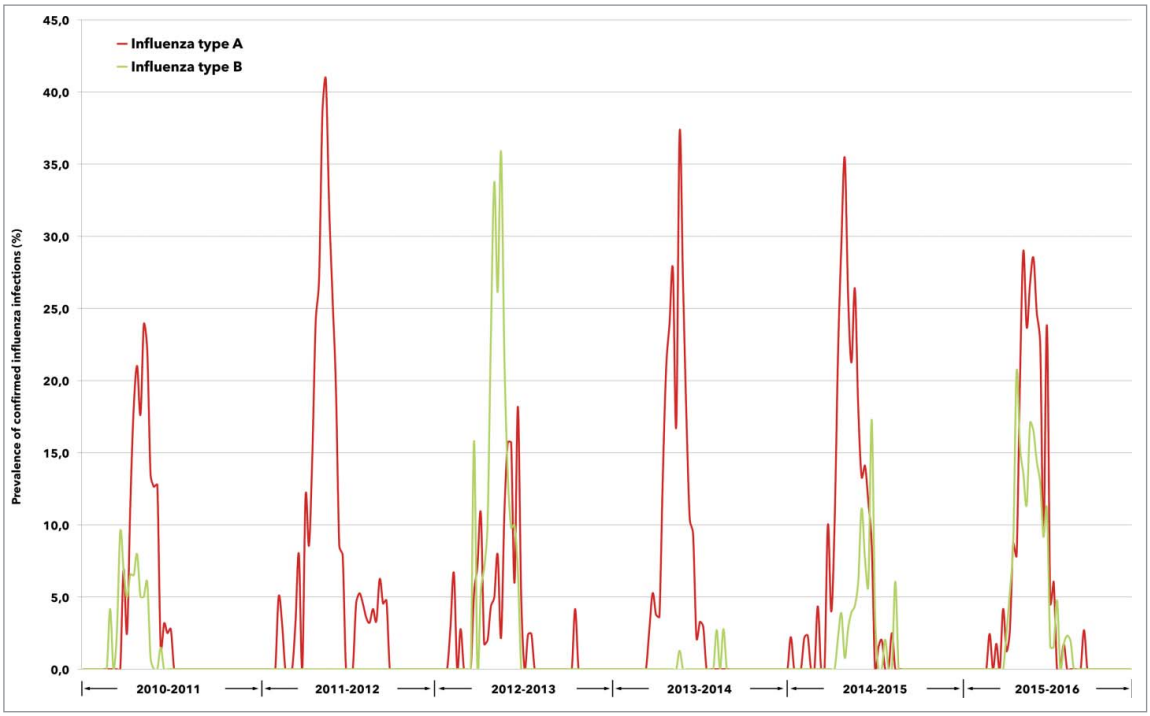

Figure 1. Prevalence of confirmed influenza A and B infections between 2010 and 2016, according to annual epidemic.

mismatch of seasonal vaccines in respect to circulating influenza B virus strains.[19,20] These factors make difficult the yearly production of influenza vaccines and force to continuously update the correct B component, determining an increasing interest in production of quadrivalent vaccines that include both antigenic variants of influenza B viruses. Nevertheless, the potential benefits afforded by these vaccines, in terms of reduced burden and outcomes of seasonal influenza illness, are still hampered by different reasons which prevent their adoption to a large-scale context.

Data regarding the circulation in Italy of influenza B strains belonging to different lineages are quite sparse and limited.[21-24] The present retrospective surveillance study aimed to improve the knowledge of the burden and epidemiology of influenza B during annual outbreaks among patients with influenza-like illness (ILI) in either community or hospital contexts over the period 2010–2016. The mismatch ratio between seasonal circulating and vaccine included influenza B strains was also analyzed.

Results

Epidemiology of influenza viruses between 2010 and 2016

During the 6-year study period, influenza A and B viruses co-circulated in almost all seasonal epidemics, with the exclusion of the season 2011–2012 when influenza B was not detected at all in the regions included in the study. Influenza A strains exceeded influenza B in 4 seasons (2010–2011, 2013–2014, 2014–2015, and 2015–2016), with different timing of peak activity, while influenza B viruses significantly prevailed for most of the season 2012–2013 (Fig. 1).

A total of 14,212 specimens were collected and laboratory tested from subjects with ILI symptoms (Table 1). Despite the natural fluctuation in ILI incidence rates reported in Italy between 2010 and 2016, the total number of respiratory samples collected in Liguria and Sicily, for influenza detection and genotyping, progressively increased year after year through a significant improvement of the virological surveillance system.

Overall, 13.2% (n = 1,874/14,212) were confirmed influenza cases, of which 70.2% (n = 1,315/1,874) and 29.8% (n = 559/1,874) were influenza A and B infections, respectively.

As described in Table 2, roughly 3 quarters of identified influenza B cases (n = 422/559) were from general population (community-based infections), sampled by family practitioners during outpatient visits, whereas 24.5% (n = 137/559) were from hospitalized patients; no gender differences were found (data not shown).

Influenza B infection was widely distributed between age-groups, with a clear predominance in children and teenagers; the median age was 9.0 y and, altogether, subjects aged ≤ 14 y sustained more than 60% of total influenza B infections, recording the highest prevalence in age-group 5–9 y.

Community-based B infections were found in subjects substantially younger than hospitalized patients (median age, years: 8 *vs.* 51; $p < 0.001$), and a comparison of age-stratified prevalences showed a significant inverse correlation between the 2 healthcare settings (Figure S1).

Influenza B lineage information was collected during the entire study period. Basing on subtyping pooled data available from the 2 regions, Victoria-lineage viruses were more represented than those belonging to the Yamagata-lineage over the entire study period, accounting for 59.8% (n = 298/498) and 40.2% (n = 200/498) of cases, respectively (Table 3).

Table 1. Number of specimens tested, influenza cases, and relative percentages attributable to influenza A and B virus subtypes. Period: 2010-2016.

Influenza season	ILI incidence rate (x 1,000)*	Number of specimens tested	Influenza cases	Influenza A	Influenza B
Total [n (%), % by row]		**14,212**	**1,874 (13.2)**	**1,315 (70.2)**	**559 (29.8)**
2010-2011	11.1	2,228	273 (12.2)	210 (76.9)	63 (23.1)
2011-2012	9.6	1,658	192 (11.6)	192 (100.0)	0
2012-2013	10.0	1,961	227 (11.6)	73 (32.2)	154 (67.8)
2013-2014	6.6	2,234	162 (7.2)	159 (98.1)	3 (1.9)
2014-2015	10.9	2,705	335 (12.4)	270 (80.6)	65 (19.4)
2015-2016	6.1	3,426	685 (20.0)	411 (60.0)	274 (40.0)

*National influenza-like illness (ILI) incidence rate at the epidemic peak. Source: InfluNet, influenza sentinel surveillance network, Italy.

On average, individuals infected with Victoria-lineage viruses were significantly younger than those presenting a Yamagata-lineage infection (median age, years: 8.0 *vs.* 12.0; $p < 0.001$), reflecting the age-distribution observed among total B cases.

Both influenza B lineages contributed to the 2010–2016 epidemics. Victoria-lineage strains predominated in the seasons 2010–2011 (77.1% *vs.* 22.9%) and 2015–2016 (97.4% *vs.* 2.6%), while in 3 consecutive seasonal outbreaks between 2012 and 2015, almost all infections were sustained by viruses belonging to the Yamagata-lineage.

On the whole, according to the different population groups collected in the 2 regions, the proportion of influenza B found in the community was consistently higher than that observed among hospitalized patients. Nevertheless, the relative frequencies of the 2 lineages varied between healthcare settings, showing a wider spread of Victoria strains in the general population (63.9% *vs.* 36.1% for Victoria- and Yamagata-lineage, respectively), than that documented in ILI subjects with severe respiratory symptoms requiring an hospital admission (37.7% *vs.* 62.3% for Victoria- and Yamagata-lineage, respectively). In our study, a Yamagata-lineage infection represented an independent risk factor for a complicated influenza outcome (hospital-based *vs.* community-based management, OR = 2.95; 95%CI: 1.78 - 4.67).

Finally, for each season, the extent of lineage-level mismatch between influenza B strains circulating in our geographic areas and those included in vaccine formulation for the Northern Hemisphere was evaluated.

During the 6 post pandemic seasons reported in the present study, the degree of mismatch was quite similar, when observed at the regional level. Pooled data depicted in Fig. 2, documented a low degree of B mismatch in 5 consecutive seasons (range: 0–22.9%) between 2010 and 2015, while the circulation of B viruses belonging to the opposite lineage of the vaccine strain was exceptionally high (97.4%) during the last analyzed season (2015–2016).

Discussion

In this study, we analyzed the epidemiology and seasonal patterns of 559 influenza B infections identified among 14,212 subjects with ILI symptoms monitored during the surveillance seasons 2010–2016 in Liguria and Sicily, 2 Italian administrative regions located in the northern part and in the southern part of the country, where the influenza virological surveillance is seasonally performed as part of the national network (InfluNet).

Our findings revealed that types A and B influenza viruses almost always co-circulated throughout the study period and confirmed the important role of influenza type B virus in the spread of infection in the population.

On average, influenza B viruses accounted for 29.8% of total laboratory confirmed infections, and it was in the range of other European countries such as Finland[18] and UK.[6,25] In our setting, influenza B cases followed year-to-year fluctuations in prevalence and the highest value was observed in 2012–2013 (67.8%), a season characterized by a significant influenza B activity in the whole European region.[26]

Table 2. Age distribution of influenza B infections, according to community and hospital settings. Period: 2010-2016.

	Influenza B infections		
	Total [n (%)]	Community-based [n (%)]	Hospital-based [n (%)]
	559	**422 (75.5)**	**137 (24.5)**
Age (years) [median (IQR)]	9.0 (33)	8.0 (8)*	51.0 (48)*
Age groups (years) [n (%), % by column]			
≤4	98 (17.5)	85 (20.1)	13 (9.5)
5–9	182 (32.6)	172 (40.8)	10 (7.3)
10–14	66 (11.8)	61 (14.4)	5 (3.6)
15–19	24 (4.3)	21 (5.0)	3 (2.2)
20–34	38 (6.8)	23 (5.4)	15 (11.0)
35–49	46 (8.2)	26 (6.2)	20 (14.7)
50–64	46 (8.2)	18 (4.3)	28 (20.4)
65–85	53 (9.5)	15 (3.6)	38 (27.7)
>85	6 (1.1)	1 (0.2)	5 (3.6)

*$p < 0.001$

Table 3. Proportion of influenza B infections, according to viral lineage (pooled data from Liguria and Sicily). Period 2010-2016.

	Victoria-lineage	Yamagata-lineage
Influenza B infections [n (%), % by row], n = 498	**298 (59.8)**	**200 (40.2)**
Age (years) [median (IQR)]	8.0 (9.0)*	12.0 (40.0)*
Age groups (years) [n (%), % by column]		
≤4	57 (19.1)	32 (16.0)
5–9	124 (41.6)	54 (27.0)
10–14	44 (14.8)	20 (10.0)
15–19	13 (4.3)	10 (5.0)
20–34	20 (6.7)	11 (5.5)
35–49	10 (3.4)	27 (13.5)
50–64	10 (3.4)	25 (12.5)
65–85	20 (6.7)	15 (7.5)
>85	0	6 (3.0)
Influenza season [n (%), % by row]		
2010-2011	27 (77.1)	8 (22.9)
2011-2012	0	0
2012-2013	5 (3.9)	122 (96.1)
2013-2014	0	1 (100.0)
2014-2015	0	62 (100.0)
2015-2016	266 (97.4)	7 (2.6)
Healthcare settings [n (%), % by row]**		
Community-based	269 (63.9)	152 (36.1)
Hospital-based	29 (37.7)	48 (62.3)

*$p < 0.001$
**OR=2.95 (95%CI: 1.78 - 4.67). Hospital-based setting as reference group.

It has been widely highlighted the role of influenza disease as a determinant of excess mortality in the elderly,[27-29] irrespective of genotype and subtype.

On the other hand, children and adolescents have been shown to be crucial in the spread of the virus in the community, experiencing some of the highest rates of influenza infection during seasonal epidemics[18,30] and, in this regard, it has been suggested that influenza B viruses could be transmitted with a higher reproductive number (R_0) in younger age population.[31]

It is well known that influenza type B, when present as seasonal circulating virus within a geographic area, mainly occurs among younger persons than influenza A and school-aged children reflect the highest proportion of influenza B cases,[18,19,25,32-34] as further confirmed in the present study among children aged 5–9 y.

In accordance, Harvala and colleagues[6] revealed higher rates of influenza B detections in Scottish children under the age of 5 y during the season 2012–2013, although a considerable circulation of B strains were also observed in adults.

In Shanghai, the age distribution of B infections documented between 2009 and 2014 was higher among young outpatients (6–17 years) seeking hospital medical care for ILI,[33] and similar findings were reported in a population study conducted in Southern China between 2009 and 2010.[35]

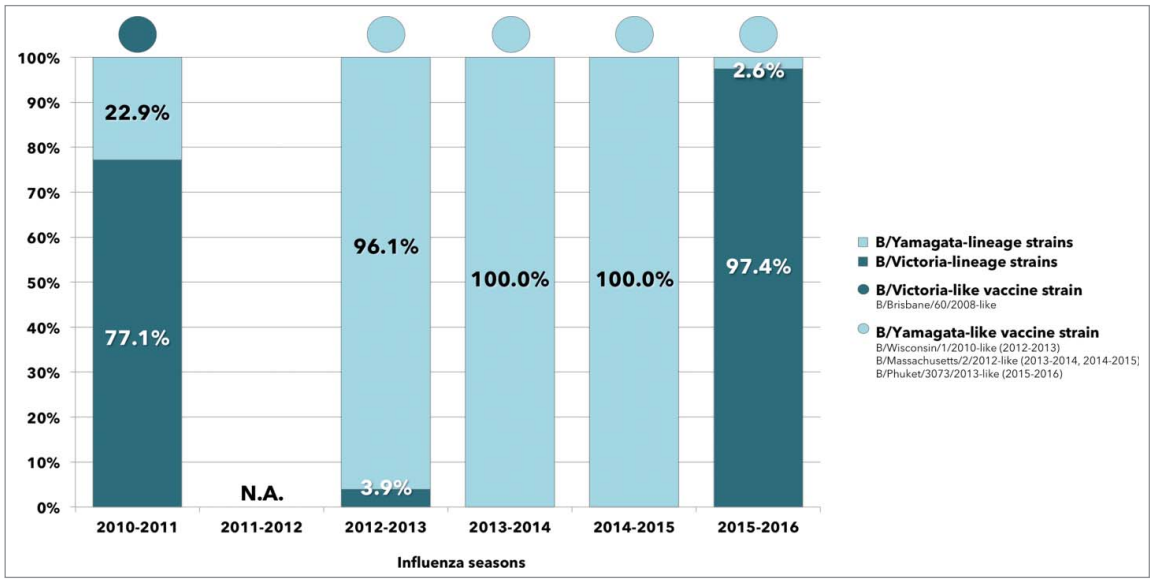

Figure 2. Relative frequencies of lineage-level matched and mismatched influenza B virus infections identified between 2010 and 2016, compared with the vaccine strain for the Northern Hemisphere and according to annual epidemic (pooled data from Liguria and Sicily).

Our results evidenced that ILI subjects infected by influenza B, in the context of the general population, were significantly younger than those admitted to hospital and an inverse correlation was found between the 2 healthcare settings, by comparison of age-stratified prevalences. Although, to our knowledge, no direct comparisons between the 2 population groups have been previously reported in the literature, studies conducted either in the general population[36] or in the hospital setting[6,35] highligthed, on average, an older age of patients in this latter group. According to other authors, no correlation was observed between influenza B infection and gender.[34,37,38]

During the study period, different patterns of Yamagata- and Victoria-lineage B viruses were observed, albeit with similar trend between the 2 Italian regions. The distinct evolutionary viral variants of influenza B spread as single lineage or co-circulated among each season.

The 2010–2011 influenza outbreak demonstrated the co-circulation of both B lineages in our geographic areas, but with the preponderance of Victoria-lineage viruses, and a similar scenario was depicted in Europe[39] and elsewhere worldwide, with the exception of China where Yamagata-lineage strains predominated.[40] Conversely, Victoria-lineage viruses were almost completely replaced by influenza strains belonging to the alternative lineage in the season 2012–2013, reflecting the trend obsderved in other European countries,[6,41] as well as in the Southern Hemisphere.[42] Notably, a lineage swap was documented in Italy since 2013[43] and this epidemiological feature of B lineages was also evidenced in other countries such as Malaysia.[44]

Moreover, an heterogenous distribution has been reported by age-group. Some authors from China and Malaysia as well as from Europe[35,38,44] revealed stark differences in age among B infected patients, reporting a trend toward a higher proportion of Victoria-lineage sustained infections in children and teenagers than those caused by either Yamagata-lineage viruses, suggesting an intrinsic different transmissibility of the 2 lineages.[42] Nevertheless, a limited variation in age susceptibility to different influenza B variants was found in Australia,[36] while Mosnier and co-authors,[34] in France, and Harvala and colleagues,[6] in Scotland, did not find any relationship.

In light of published data, the potential association between viral lineage and age of infected patients is still debated. It may be likely correlated with the local epidemiology of specific geographic region, as a result of a difference in background population immunity. Interestingly, Vijaykrishna and colleagues[42] recently proposed that age difference between Victoria- and Yamagata-lineage infections is thought to be due to differences in the molecular aspects of cellular dynamics which help the viruses to infect the epithelium of the respiratory tract, while more attractive hypotheses are consistent with a higher basic reproductive number (R_0) of the Victoria-lineage viruses, which altogether might reduce the mean age of lineage-specific infections.

The distribution of Victoria- and Yamagata-lineage strains differed by healthcare setting. Victoria-lineage viruses were mostly responsible for a milder influenza disease in the general population, while a greater proportion of infections detected in hospital were sustained by viruses belonging to the Yamagata-lineage. Of note, this was not biased by age, suggesting that Yamagata-lineage viruses on average could be responsible of more complicated infections. However, the limited number of patients with these characteristics in our data set and the potential bias due to the different population characteristics and surveillance systems in the 2 regions prevent us from drawing conclusions.

Finally, our findings evidenced that the level of B vaccine mismatch varied during the 6 seasons, with the highest impact observed in 2015–2016.

In a study by Heikkinen et al. (2014) conducted in Finland, a similar proportion of lineage-level mismatched B viruses was observed, although over a different time slot that partially overlapped our study period; in Australia, a mismatch >60% occurred in over one-third seasons between 2001 and 2014,[36] while a 10-year influenza surveillance conducted in Northern Italy[23] highlighted the occurrence of B vaccine mismatch in 5 seasons between 2004 and 2014.

The potential impact of vaccine-mismatch on influenza virus epidemiology has been broadly investigated and several findings highlighted the effect of seasonal vaccine mismatch on influenza epidemiology, particularly among those age-groups that preferentially sustain the circulation of influenza B virus. The lack of availability of vaccination data in our study population limit our possibility to draw any inference on this topic. However, as reported by other authors, the magnitude of the impact of seasonal vaccine mismatch on influenza epidemiology depends on several factors, including the annual effectiveness of the vaccine and the annual population vaccine coverage, but also on factors such as the overall burden of influenza during a given season and the proportion of each influenza B virus lineage circulating.[28]

On the basis of the results shown in this and other studies, it is evident how much important could be the impact of B vaccine mismatch in terms of efficacy of trivalent influenza vaccines in general population, given the global impact of influenza B, the undemonstrated cross-reactivity of trivalent vaccines against the 2 influenza B lineages and, more importantly, the unability to predict the seasonal epidemiology of influenza viruses. It seems quite clear that the real-life efficacy of influenza vaccines could be significant improved by a broader adoption of quadrivalent formulations, expecially in children.[18,28,45]

Furthermore, it seems a logical consequence that children and adolescents might benefit most from the implementation of specific vaccine-based preventive measures, which may have the potential to reduce the burden of disease in both vaccinated and unvaccinated individuals.

Additionally, benefits may also include contraction in absenteeism due to the need for parents to take time of work to care for sick children,[46,47] and reduced pressure on health care services during seasonal peak in influenza activity.[48,49]

Nevertheless, despite previous assumptions, only USA and Canada among large developed countries, and some rare exceptions in Europe such as Finland, Latvia and United Kingdom, actually recommend the influenza vaccination of healthy children providing the vaccine free of charge.[50]

Resistance to implementing vaccination programmes on healthy children may found possible explanations in the limited evidence for the field efficacy of inactivated and live attenuated

vaccines in younger children, among whom the risk of complication is the greatest,[51,52] the level of uptake which programmes would be able to achieve,[53] and the additional resources required to expand seasonal influenza vaccination campaigns.

Of course this study suffer of some limitations. First, only 2 Italian regions were included in the virological surveillance campaign and the formal representativeness of this population is unknown. Moreover, different population settings, either from the Northern part or the Southern part of Italy, contributed to the population study and this may have locally biased the results. However, basing on the reports from the National surveillance network, we are reasonably confident that, on average, our settings have adequately represented the epidemiology and burden of influenza B strains in Liguria and Sicily during the 6 seasons studied.

The unpredictability of influenza viruses continues to represent a major challenge to health systems. Nevertheless, vaccination remains the most effective preventive measure in reducing the incidence and severity of disease, although the coverage rates in Italy[54] and other European countries[55] remain suboptimal. In particular, during the study period, coverage rates for influenza vaccination decreased at Italian level from 62.4% to 49.9% and from 17.9% to 13.9% in subjects aged $\geq$ 65 y and in general population, respectively, and a similar trend was registered in the 2 considered Italian regions.[54]

The increased use of childhood vaccination is an opportunity for reducing the considerable burden of infection in this age group and it may play a pivotal role in the spread of the virus in the community, also supported by the adoption of quadrivalent vaccines in universal immunization programmes against influenza.

Materials and methods

Case definition

The enrollment criteria for surveillance cases were in accordance to the operative protocol of the Italian Influenza Epidemiological and Virological Surveillance Network.[56] A case of ILI was defined as one individual with sudden onset of at least one of the following systemic symptoms: fever ($\geq$ 37.5°C), general discomfort or asthenia, headache, muscle pain, and at least one of the respiratory symptoms between cough, sore throat, and shortness of breath.

Study population and retrospective data collection

We analyzed all available clinical and virological data, collected during 6 consecutive post-pandemic influenza seasons over the period 2010–2016, from week 42 to week 17 of the following year, in 2 different Italian administrative regions located in the South (Sicily) and in the North (Liguria) of the country, where 2 regional reference laboratories for the influenza surveillance belonging to the FluNet have been active for all the study period.

All surveillance data are aggregated at a regional level, shared at a national level on a weekly basis, and ultimately flow into the World Health Organization's (WHO) global influenza program.

Each year, several pediatricians and general practitioners contribute to the community-based influenza surveillance, while both pediatric and adult hospitals allow the monitoring of ILI patients admitted with severe respiratory distress, potentially correlated with influenza infection.

More specifically, the Ligurian influenza surveillance system essentially collected data from both hospital inpatients and outpatients (99.0%; n = 11,008/11,120), while the influenza virological surveillance in Sicily resulted mostly oriented to general population (70.2%; n = 2,172/3,092).

Anonymised data on birthdate, sex, date of ILI onset, outcomes were gathered from each ILI cases.

Routine testing and influenza virus genotyping

Oropharyngeal samples were obtained from each patient and transported to the regional reference laboratories by using Virocult swabs (MWE, Medical Wire).

Viral RNA was extracted using QIAamp Viral RNA extraction kit (QIAGEN) according to the manufacturer's suggested protocol and the RNA was eluted from the spin column in 60 μL of elution buffer. Eluted RNA was divided into aliquots and stored immediately at -80°C until further use. Each sample was tested by one-step real-time RT-PCR for the presence of influenza virus RNA (protocols available on request), and influenza B positive samples were genotyped using lineage-specific multiplex one-step real-time RT-PCR according the "WHO protocols for molecular diagnosis of influenza virus"[57] using a QuantStudio 7 Flex Real-Time PCR system (Applied Biosystem).

Seasonal mismatch with trivalent vaccine B lineage

Data on the circulation of different lineages of influenza B viruses in Sicily and Liguria were retrieved during each season.

The extent of vaccine mismatch against influenza B viruses was estimated by comparing the information concerning the B lineage antigens contained in the trivalent vaccine for the Northern Hemisphere, as recommended by the WHO, and the proportion of circulating B viruses belonging to different lineages.

The level of B vaccine mismatch was defined as the percentage ratio between the proportions of mismatched and matched influenza B viruses per year of surveillance.

Data managements and statistical analysis

Descriptive statistics were used to summarize each of the sociodemographic and clinical variables included in the data set (counts, percentages, median and interquartile range, as appropriate).

The study population was arbitrarily subdivided into 9 different age groups, categorizing children/teenagers into 4 groups ($\leq$ 4, 5–9, 10–14, and 15–19 years) and adults/elderly into 5 groups (20–34, 35–49, 50–64, 65–85, and >85 years).

Median values were compared using the Mann-Whitney U test. All of the analyses with p-values of 0.05 or less were considered to be statistically significant (2 tailed). Data were

processed with the STATA MP statistical software package v14.1 for Apple™ (StataCorp).

Abbreviation

ILI Influenza-like illness

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Authors' contributions

AO and FT were involved in the conception and design of the studies. AO, GMEC, FP, GC, CA, CT, and PC collected clinical and epidemiological data. AO and FT analyzed and interpreted the results. AO, FT, FV, and FA were involved in drafting the manuscript or revising it critically for important intellectual content. All authors had full access to the data and approved the manuscript before it was submitted by the corresponding author.

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