

# The impact of influenza virus B in Italy: myth or reality?

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## Keywords

Influenza impact • Epidemiology • Influenza B • Vaccination • Vaccine mismatch

## Summary

*We describe the burden of influenza B infections in Italy over a 12-year study period. Influenza A and B viruses co-circulated throughout the period, with numbers of influenza B cases approaching or exceeding those of influenza A during three influenza seasons. Influenza B virus infections led to fewer admissions to an intensive care unit (ICU) and a lower mortality rate than influenza A from 2010 to 2015. However, only 16% of those admitted to ICU with influenza B had been immunized. This highlights the need for con-*

*sistent influenza vaccination for identified risk groups. Our study demonstrates that influenza B virus infections are associated with substantial morbidity and that influenza surveillance and interventions including vaccination and treatment are still suboptimal. Our findings have important public health implications. Incorporating virus and epidemiological data will help obtain more accurate estimates of influenza disease burden and result in a better selection of influenza prevention and control strategies.*

## Introduction

The societal burden of seasonal influenza epidemics is quite heavy, with approximately 3-5 million cases and 250,000-500,000 estimated deaths worldwide every year [1] and a large economic impact, which includes both direct and indirect costs [2, 3]. Conventionally, attention has been directed toward influenza A, which accounts for the majority of influenza cases in most seasons [4-7]. However, influenza B can account for a considerable proportion of total cases [8]. Since the 1980s, influenza B viruses have belonged to two antigenically distinct lineages, called the Victoria and Yamagata lineages [9]; this has constituted a challenge for seasonal influenza vaccines, as only one influenza B strain is included in the trivalent vaccine. Studies in the United States have shown that the frequent influenza B vaccine mismatches of recent years have been associated both with substantial increases in cases, hospitalizations and deaths (up to 970,000 cases, with 8200 hospitalizations and 485 deaths annually, in the USA) [10], and with high influenza-related medical costs and costs due to productivity loss [11].

Despite the important role of influenza B, much of the published scientific literature regarding the epidemiology of influenza has focused on influenza A, and we still have a relatively poor understanding of the global epidemiology and disease burden of influenza B. Several studies have reported on the burden of disease attributable to influenza B in a single season, or during consecutive seasons in a single country [12, 13]. In order to improve our understanding of the burden and epidemiology of influenza B, we reviewed the influenza B viruses circulating in Italy from 2000 to 2015.

## Materials and methods

### THE NATIONAL INFLUENZA SENTINEL SURVEILLANCE SYSTEM

In Italy, the Influenza Sentinel Surveillance System (INFLUNET) was implemented nationwide in the 1999-2000 season by the Influnet working group [12]. INFLUNET is based on the voluntary participation of an average of 830 (range 648-902) general practitioners (including paediatricians) per year, covering about 1.5-2% of the national population in all Italian regions. The system aims to monitor the incidence of influenza-like illness (ILI) and to determine the extent, timing and severity of seasonal epidemics. GPs are asked to report ILI cases (defined as acute onset of fever + respiratory symptoms + one of the following symptoms: headache, general discomfort, asthenia) weekly (from week 42 to week 17) using standardized forms. Specific information regarding age (0-14, 15-64, > 64 years) and influenza vaccine status are also collected. We excluded the first years of data collection and focused the analysis on Influnet data collected from the 2005/2006 to 2014/2015 seasons.

### THE NATIONAL VIROLOGICAL SURVEILLANCE SYSTEM

Influenza virological surveillance in Italy is routinely carried out, between week 46 and week 17 of the following year, by the National WHO (World Health Organization) Influenza Centre at the Istituto Superiore di Sanità (NIC-ISS), in collaboration with a network of 15 peripheral laboratories located in 14 of the 21 Italian regions. The main objective of these activities is to rapidly characterize the influenza viruses circulating in

the country and to identify antigenic variants emerging in human populations during the winter season, in order to update the vaccine composition, in collaboration with the WHO and ECDC (European Centre for Disease Prevention and Control). During the virological surveillance period, sampling kits are sent out to a random sample of GPs participating in the INFLUNET surveillance system, who collect throat swabs from the first ILI patients seen each week. Collected swabs are then sent to the regional Reference Laboratories for influenza diagnosis, and the isolated strains are characterized at the Regional Laboratory or directly sent to the NIC-ISS for further molecular and antigenic analyses. Overall results obtained throughout the country are reported to the NIC-ISS weekly by means of web-based electronic forms. Every year, approximately 2000 samples are collected, with a proportion of positive specimens of about 34%. Our analysis included virological surveillance data collected from the 2000/2001 to 2011/2012 seasons.

#### SURVEILLANCE OF LABORATORY-CONFIRMED SEVERE CASES

A web-based data collection form for the surveillance of severe confirmed hospitalised cases and deaths due to pandemic influenza was drawn up in mid-September 2009. Since then, regional and local authorities have filled in forms during the influenza season (October-April); the data are analysed weekly at the national level (by the ISS and the Ministry of Health). Our analysis included virological surveillance data collected from the 2010/2011

to 2014/2015 seasons, as all confirmed cases during the 2009/2010 season were due to A/H1N1pdm09 virus.

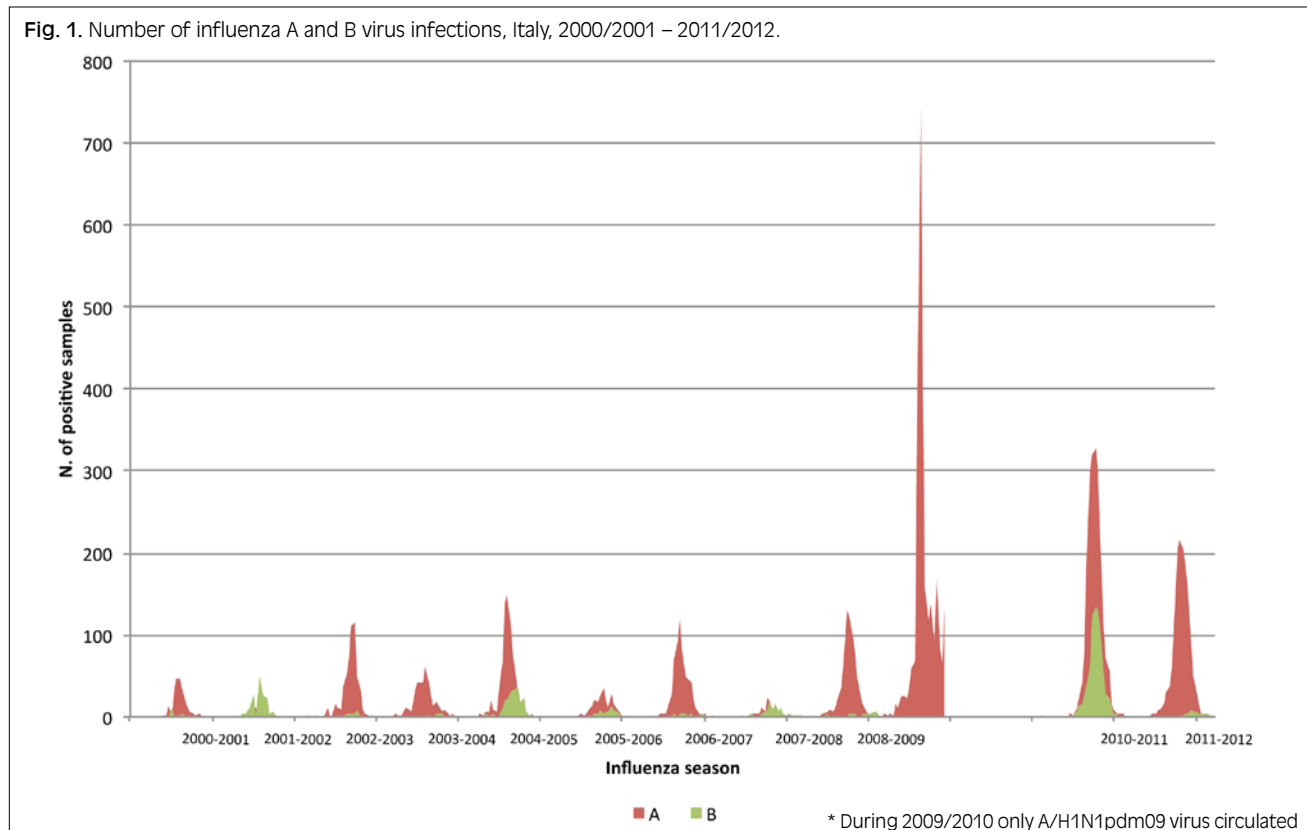
## Results

From the 2005/2006 to 2014/2015 seasons, an estimated average number of approximately 4,800,000 ILI cases were reported to the surveillance system (Tab. I). Most were in the 0-5-year age-class. The national database that was used for the analysis included 40,000 ILI cases, with testing of samples from cases that occurred between 2000/2001 and 2011/2012. During the study period, several waves of infections by influenza A and B viruses were observed in Italy

Tab. I. Distribution of estimated influenza-like illness cases and cumulative incidence by season, Italy, 2005/2006 – 2014/2015.

Season	Peak week	Cumulative incidence	Estimated ILI cases
2005/2006	12	3.9	2,400,000
2006/2007	5	5.7	3,700,000
2007/2008	7	6.9	4,700,000
2008/2009	4	7.2	4,100,000
2009/2010	46	9.7	5,600,000
2010/2011	5	10.3	5,400,000
2011/2012	5	8.6	5,000,000
2012/2013	6	10.5	6,200,000
2013/2014	6	7.8	4,500,000
2014/2015	4	10.8	6,300,000

Fig. 1. Number of influenza A and B virus infections, Italy, 2000/2001 – 2011/2012.



(Fig. 1). In detail, 11,488 influenza cases were confirmed in the study period: 9,842 influenza A cases and 1,646 influenza B cases. Influenza A and B viruses co-circulated during most influenza seasons, with numbers of influenza B infections approaching or exceeding those of influenza A virus during three seasons in the study period considered (2001/02, 2007/08 and 2012/13). The number of samples tested for influenza viruses by PCR in Italy increased by a factor of 1.5 over this period, from an average of 2,774 per season in the period 2000-2007 to an average of 4,312 per season in 2008-2012. Influenza B appeared to be relatively more frequent among older children; A(H1N1)pdm2009 among young and older adults, and A(H3N2) among the elderly. On average, the proportion of influenza B cases on the total of tested samples was 23% (range < 1-78%) (Fig. 2).

### SEVERITY OF INFLUENZA B

From 2010/2011 to 2014/15, on a total of 1,545 severe confirmed influenza cases reported to the surveillance system (Tab. I), 102 were confirmed influenza B virus-infected individuals admitted to ICU; 2 were pregnant (both in the third trimester); 7 needed extracorporeal membrane oxygenation (ECMO) treatment, and 24 died. The median age was 63 years (range 0-92), 58 were male, and 16 were vaccinated almost 15 days before symptom onset. The median age of the individuals who died was 76 (range 39-85). Of the 102 severe influenza B patients, 73 belonged to groups recommended for vaccination (65 years and older or a clinical risk group), but only 16 had

actually received the seasonal influenza vaccination. Most of the influenza B cases were reported during the 2012/2013 season, when the B virus co-circulated with the A/H1N1pdm09.

### Discussion

Our results on influenza B virus infections in Italy are timely, in view of the recent introduction of a tetravalent influenza vaccine containing influenza B viruses of both the Victoria and Yamagata lineages. Our study reveals that influenza B virus was the predominant overall cause of influenza in two of the 13 influenza seasons from 2000/01 through 2012/13. However, circulation of the B virus during the inter-pandemic season was always demonstrated. Similar patterns of influenza B virus circulation have been described in the US, Europe and Hong Kong [12-13]. In Italy, the proportion of influenza B cases in the study period averaged 23% (range < 1-78%), a value similar to the European (23% (1-60%)) and US (24% (< 1-44%)) averages [14].

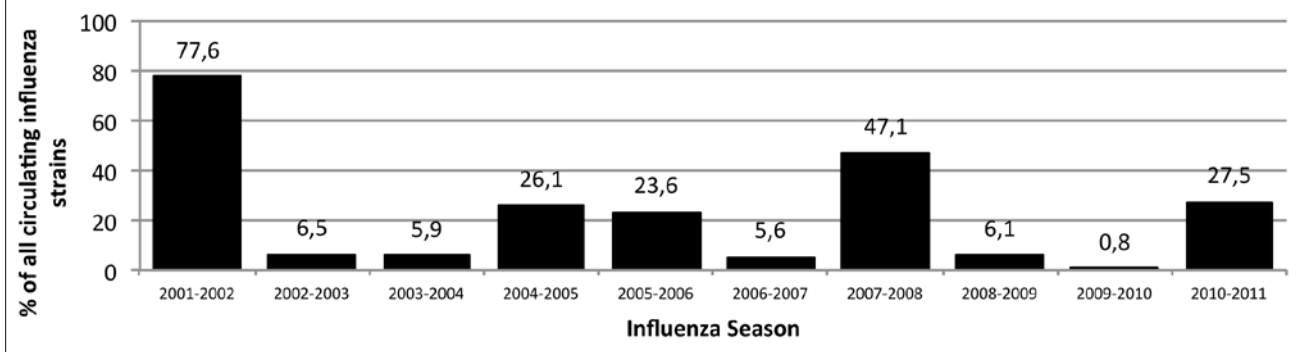
In our study, < 1% of all ILI cases are tested for influenza each season, and very few B viruses were antigenically and genetically characterized, thus reducing the opportunity to identify the co-circulation of the two lineages in Italy. However, evidence from two Northern Italian regions clearly demonstrated a complete or partial mismatch in the 2001/2002, 2004/2005, 2005/2006, 2007/2008, 2008/2009, 2010/2011, and 2011/2012 seasons; this was almost always due to co-circulation of the two lineages [15-17].

Influenza is generally recognised as an important disease which causes high excess mortality among the elderly, although children have been shown to play an important role in its transmission [18-19]. Unlike the influenza A(H3N2) virus, the B virus predominantly infects children and young adults and is generally recognised as a mild influenza virus [20]. Data on severe influenza B virus infections and mortality are limited. A large study conducted in the US reported that 25% of all influenza-related mortality could be attributed to influenza B virus [21]. This is higher than the percentage seen in the present study, in which influenza B in-

Tab. II. Distribution of confirmed severe cases, by influenza virus, Italy, 2010/2011 – 2014/2015.

Season	A/H1N1v	A/H3N2	A/non sub-typed	B	Total
2010/2011	517	0	11	10	538
2011/2012	7	33	1	1	42
2012/2013	143	8	7	61	219
2013/2014	61	23	7	1	92
2014/2015	494	87	44	29	654
Total	1,222	151	70	102	1,545

Fig. 2. Influenza B circulation as a proportion of the total percentage of all circulating influenza strains, Italy 2001/2002 – 2010/2011 seasons.



fections accounted for 6% of all influenza virus-related deaths (24/428) during the period considered, but is similar to figures reported for Scotland [22]. Among those admitted to ICU with influenza B infections, 7% needed ECMO treatment, 2% were pregnant, and 23.5% died.

Influenza immunisation is recommended in Italy for specific groups with an increased risk of complications following influenza infection (e.g. > 65 years old, > 6 months with chronic conditions, healthcare personnel, pregnant women in their second or third trimester etc.) [23]. Only 16% of those treated in ICU who should have been vaccinated had received the seasonal influenza vaccine, and 70% of those treated in ICU were included in the target categories of national recommendations.

The magnitude of the problem created by mismatching between circulating influenza B strains and the influenza B lineage contained in the vaccine varies by season. The most striking recent examples occurred during the 2005-2006 and 2007-2008 seasons. In 2005-2006, the influenza B component of the northern hemisphere influenza vaccine was of the B/Yamagata lineage, but 81-91% of the circulating influenza B viruses antigenically characterized in the US and Europe were of the B/Victoria lineage, and influenza B was found in 34-60% of all samples [14]. Similarly, in 2007-2008, the influenza B component of the vaccine was of the B/Victoria lineage, but 98-99% of the circulating influenza B viruses characterized in the US and Europe belonged to the B/Yamagata lineage [14].

Unfortunately, as very few B influenza viruses in Italy were genotyped, information on the antigenic characteristics of circulating B viruses was not available at the national level.

Our study demonstrates that influenza B virus infections are associated with substantial morbidity and that influenza surveillance and interventions including vaccination and treatment are still suboptimal. Our findings have important public health implications. Incorporating viral and epidemiological data will help obtain more accurate estimates of influenza disease burden and result in a better selection of strategies for influenza prevention and control [25].

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