

Influenza epidemiology in Italy two years after the 2009–2010 pandemic

Need to improve vaccination coverage

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Abbreviations: CDC, Centers For Disease Control and Prevention; CIRI-IT, Inter-University Centre for Research on Influenza and other Transmissible Infections; HA, haemagglutinin; H1N1pdm09, pandemic strain; INFLUNET, Italian influenza surveillance system; NA, neuroaminidase; NIH, National Institute of Health; NIC, National Influenza Center; ILI, influenza-like illness; GPs, general practitioners; WHO, World Health Organization

Since 2000, a sentinel surveillance of influenza, INFLUNET, exists in Italy. It is coordinated by the Ministry of Health and is divided into two parts; one of these is coordinated by the National Institute of Health (NIH), the other by the Inter-University Centre for Research on Influenza and other Transmissible Infections (CIRI-IT). The influenza surveillance system performs its activity from the 42nd week of each year (mid-October) to the 17th week of the following year (late April). Only during the pandemic season (2009/2010) did surveillance continue uninterruptedly. Sentinel physicians – about 1,200 general practitioners and independent pediatricians – send in weekly reports of cases of influenza-like illness (ILI) among their patients (over 2% of the population of Italy) to these centers.

In order to estimate the burden of pandemic and seasonal influenza, we examined the epidemiological data collected over the last 3 seasons (2009–2012). On the basis of the incidences of ILIs at different ages, we estimated that: 4,882,415; 5,519,917; and 4,660,601 cases occurred in Italy in 2009–2010, 2010–2011 and 2011–2012, respectively.

Considering the ILIs, the most part of cases occurred in < 14 y old subjects and especially in 5–14 y old individuals, about 30% and 21% of cases respectively during 2009–2010 and 2010–2011 influenza seasons. In 2011–2012, our evaluation was of about 4.7 million of cases, and as in the previous season, the peak of cases regarded subjects < 14 y (about 29%).

A/California/07/09 predominated in 2009–2010 and continued to circulate in 2010–2011. During 2010–2011 B/Brisbane/60/08 like viruses circulated and A/H3N2 influenza type was sporadically present. H3N2 (A/Perth/16/2009 and A/Victoria/361/2011) was the predominant influenza type-A virus that caused illness in the 2011–2012 season. Many strains of influenza viruses were present in the epidemiological scenario in 2009–2012.

In the period 2009–2012, overall vaccination coverage was low, never exceeding 20% of the Italian population. Among the elderly, coverage rates grew from 40% in 1999 to almost 70% in 2005–2006, but subsequently decreased, in spite of the pandemic; this trend reveals a slight, though constant, decline in compliance with vaccination.

Our data confirm that 2009 pandemics had had a spread particularly important in infants and schoolchildren, and this fact supports the strategy to vaccinate schoolchildren at least until 14 y of age. Furthermore, the low levels of vaccination coverage in Italy reveal the need to improve the catch-up of at-risk subjects during annual influenza vaccination campaigns, and, if possible, to extend free vaccination to at least all 50–64-y-old subjects.

Virologic and epidemiological surveillance remains critical for detection of evolving influenza viruses and to monitor the health and economic burden in all age class annually.

Introduction

Influenza continues to be one of the most common respiratory diseases in the world¹ and, at the same time, poses a potential pandemic threat.² Apart from the serious harm to health and

society that a pandemic may cause, seasonal flu places a heavy burden on both health services and the community.³

The most important influenza viruses that cause epidemic disease in humans are types A and B.⁴ Influenza A viruses are further classified into subtypes according to the characteristics of two

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surface glycoproteins: haemagglutinin (HA) and neuroaminidase (NA). Influenza B viruses are not subdivided into subtypes and, at present, two lineages co-circulate. Influenza viruses display high rates of mutation, which occurs mainly in the external proteins of the envelope, HA and NA. Minor changes in HA and NA can cause an antigenic drift, leading to the emergence of new strains. The antigenic drift of influenza A haemagglutinin is a well-studied evolutionary process, in terms of both the timing and the amino acid location of changes that lead to important antigenic variation.⁵

Influenza A viruses are also subject to antigenic shifts; these are changes of greater magnitude and are responsible for the emergence of new subtypes of influenza viruses, which may result in a widespread pandemic in an immunologically naïve population.⁶

Because of the great variability of influenza virus, the antigen content of vaccines needs to be updated annually. In order to prepare better formulations of influenza vaccines, it is important to monitor both major and minor changes by means of phylogenetic analysis, a strategy that can help to clarify the evolutionary mechanisms of the genome of influenza viruses. In this regard, the WHO has for a long time implemented a virological surveillance system.⁷ Moreover, a network of surveillance coordinated by the Centers For Disease Control and Prevention (CDC) performs influenza surveillance in the US.

In Italy, too, a similar network has existed since 2000.⁸ This network had previously been tested (1999–2000). The Italian sentinel surveillance of influenza, INFLUNET, is coordinated by the Ministry of Health and is divided into two parts; one of these is coordinated by the National Institute of Health (NIH), the other by the Inter-University Centre for Research on Influenza and other Transmissible Infections (CIRI-IT). The surveillance system used the collaboration of the regional departments of health, general practitioners (GPs) and pediatricians and university laboratories of reference.⁹ The Italian system of surveillance monitors the evolution of seasonal influenza, and was upgraded during the 2009 pandemic. Furthermore, in Rome the National Influenza Center (NIC) of the WHO coordinates Virological Surveillance.¹⁰

The pandemic caused by influenza A (H1N1) pdm09 struck Italy in two waves. The first occurred between the end of October 2009 and the month of December of the same year, the second one between February and April 2011.¹¹ Although the virus did not prove to be particularly aggressive, it has been estimated that it caused about five million cases in Italy during the first wave.¹² Furthermore, Dawood FS et al. recently estimated that the respiratory and cardiovascular mortality associated with the 2009 influenza A H1N1 pandemic was 15 times higher than reported laboratory-confirmed deaths, and that these deaths mainly involved people under 65 y. In addition, a high influenza mortality rate in children has sometimes been recorded in other countries.^{13,14}

Although the pandemic vaccine had been available in Italy since October 2009, inappropriate management of the vaccination campaign by Italian leaders made compliance with vaccination very poor.^{15,16} Consequently, in addition to the cost that Italian society had to bear because of the poor response to

vaccination, both the image of decision-makers and the public's perception of vaccines were undermined.

It therefore seemed useful to analyze, in the light of the epidemiological trend of influenza during the 2009–2012 period, the consequences of the pandemics and the mistakes made by decision-makers. Furthermore, we studied vaccine coverage in the general population and in subjects older than 65 y; the vaccine coverage rate expresses the degree of compliance of the public with influenza vaccination. Finally, an attempt was made to formulate predictions concerning the influenza epidemic of the 2012–2013 winter. The results obtained are reported in this article.

Results

Figure 1 shows the incidence of influenza-like illness (ILI) in Italy in 2009–2012. As can be seen, the 2009 pandemic began early – in late autumn – and peaked in November, when the incidence reached a value of about 13 cases per 1,000 people. In the following season, the influenza epidemic began late in December 2010 and peaked in January (about 11 cases per 1,000 inhabitants). In 2011–2012, the incidence curve was temporally similar to that of 2010–2011, but peaked at about 10 cases per 1,000 inhabitants, a slightly lower value than in the previous season.

On the basis of the incidence of ILIs at different ages, we estimated that: 4,882,415; 5,519,917; and 4,660,601 cases occurred in Italy in 2009–2010, 2010–2011 and 2011–2012, respectively.

Figure 2 reports the age distribution of the incidence of ILIs in 2009–2012. During the pandemics, most cases occurred among subjects aged 0–4 and 5–14 y, and particularly among schoolchildren and adolescents. Furthermore, considering the incidence of ILIs, we estimated that most cases involved < 14-y-old subjects, and especially those aged 5–14 y (about 30% and 21% of cases during the 2009–2010 and 2010–2011 influenza seasons, respectively). In 2011–2012, our estimate was of about 4.7 million cases, and, as in the previous season, the peak of cases regarded subjects aged < 14 y (about 29%).

The incidence curve of cases in 2009–2012 and the frequency of the different types and subtypes of influenza viruses identified are reported in **Figure 3**.

In 2009/2010 influenza season the predominant circulating virus was the pandemic A(H1N1)pdm09.

A/H3N2 strains, antigenically closely related to A/Brisbane/10/07 variant, and B viruses were only sporadically isolated.

In 2010/2011 winter A(H1N1)pdm09 viruses still predominated. A/H3N2 viruses, belonging to A/Perth/16/2009 antigenic variant, were very rarely detected, as well as influenza B strains, which co-circulated, but at a very low level.

On the contrary, 2011/2012 influenza season was characterized by a widespread activity of A/H3N2 viruses, which prevailed over B strains and A(H1N1)pdm09 strains. The results of the antigenic characterization of A/H3N2 viruses isolated in this winter showed that, early in the influenza season, strains closely related to the A/Perth/16/2009 variant prevailed. Later in the season, an increasing number of viruses proved to be more

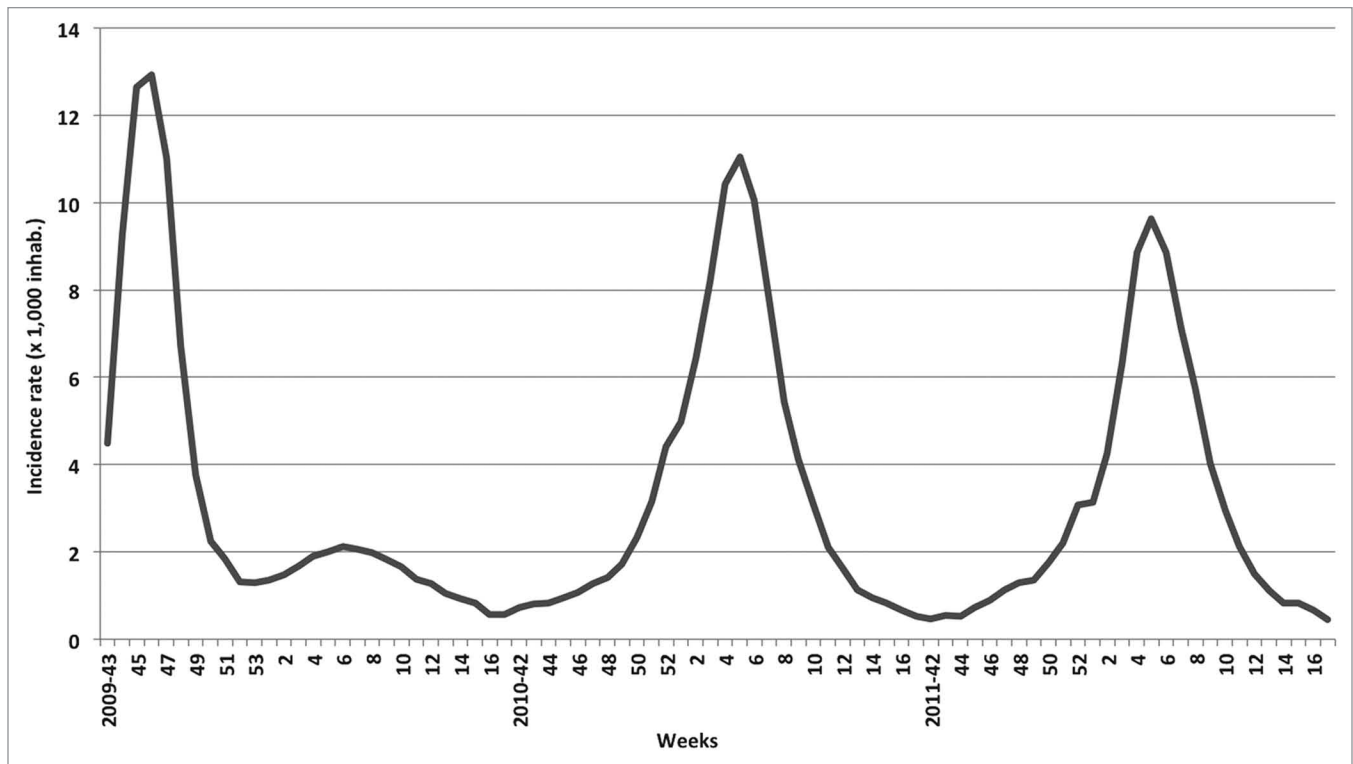


Figure 1. Influenza Like Illness incidence rate (x 1,000 inhabitants) during 2009–2012 influenza seasons in Italy.

closely related to the new variant A/Victoria/361/2011. Influenza B virus belonging to the two lineages, B/Victoria/2/87 and B/Yamagata/16/88, co-circulated in 2011–2012. However, most of these strains belonged to the B/Yamagata lineage (closely related to the B/Wisconsin/1/2010 variant).

Figure 4 shows the incidence of ILI per 1,000 inhabitants in Italy from 1999 to 2012. The highest peak coincides with the emergence of new H3N2 variants, such as the A/Fujian/411/2002 variant in 2004.

Figure 5 reports the coverage rates of vaccination against influenza from 1999 to 2011. Overall coverage was low, never exceeding 20% of the population. Among the elderly, coverage rates grew from 40% in 1999 to almost 70% in 2005–2006, but subsequently decreased, in spite of the pandemic; this trend reveals a slight, though constant, decline in compliance with vaccination.

Discussion

The first cases of influenza caused by A(H1N1)pdm09 virus (A/California/07/09) occurred in Italy in April–May 2009. These cases were imported into Italy by students who had spent a period of study in United Kingdom, where the pandemic occurred earlier than in the countries of continental Europe.¹⁷ In Italy, the epidemic peaked between late October and December 2009 (46th week, incidence of ILI of 12.9‰). We have estimated that in 2009 the virus caused about 4.9 million cases, especially among school-age (5–15 y) subjects (about 30% of cases). The global economic burden of the 2009 pandemic in Italy, calculated on

the cumulative incidence of ILIs at different ages, has been estimated as € 2,300,000,000.¹⁸

Our results show that the A/California/07/09 virus also circulated widely in the winter of 2010–2011; indeed, about 67% of isolates in Italy were closely related to the H1N1pdm09 strain. In the same season, this virus co-circulated with B strains (about 27% of isolates) and H3N2 (about 2.3% of isolates). In 2010–2011 the curve of the winter epidemic peaked at the end of January 2011 (5th week), and the influenza season displayed a very long epidemic period (14 weeks). Although the H1N1pdm09 strain did not generally cause very severe disease, a disproportionate mortality rate was sometimes observed in young children.^{19–21}

Regarding H3N2 strains, they were rarely isolated in 2009–2010, and were closely related to A/Brisbane/10/07 variant. While the isolation of H3N2 strains closely related to the A/Perth/16/2009 variant occurred in the next season, and predominated in the winter of 2011–2012. Specifically, while strains belonging to the A/Perth/16/2009 variant prevailed in the first part of 2011–2012, the new variant A/Victoria/361/2011 emerged in the second part.

Regarding virological characteristics of B isolates in Italy in 2009–2012, the NIC's data show that B strains mostly belonging to the lineage B/Victoria/2/87 (B/Brisbane/60/08) were present in the 2009–2010 pandemic scenario. In the following season, isolations of B strains were more frequent than H3N2 isolations; again, they belonged to the B/Victoria/2/87 lineage (B/Brisbane/60/2008). By contrast, in 2011–2012, B strains (3.5% of Italian isolates) belonging to the B/Yamagata lineage (closely related to the B/Wisconsin/1/2010 variant) were mostly

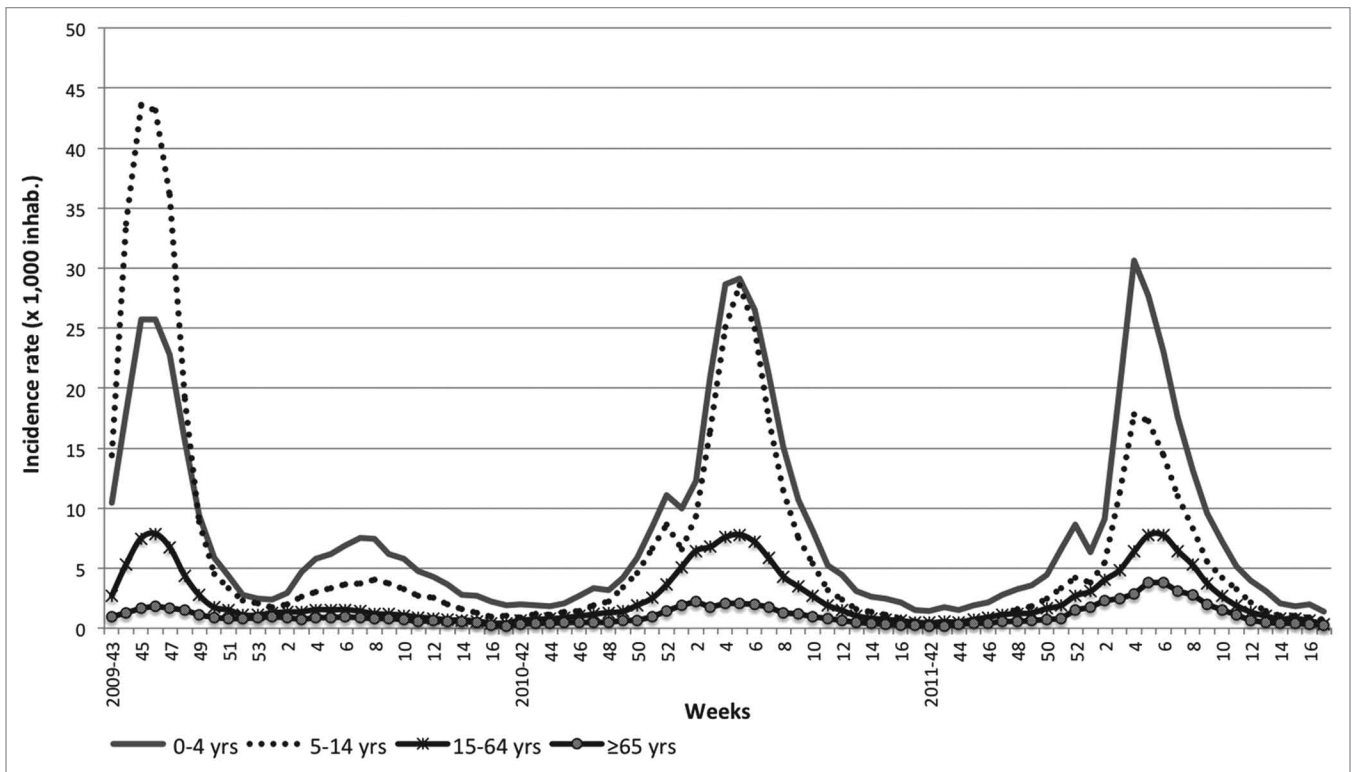


Figure 2. Influenza Like Illness incidence rate (x 1,000 inhabitants) during 2009–2012 influenza seasons in Italy, by age class.

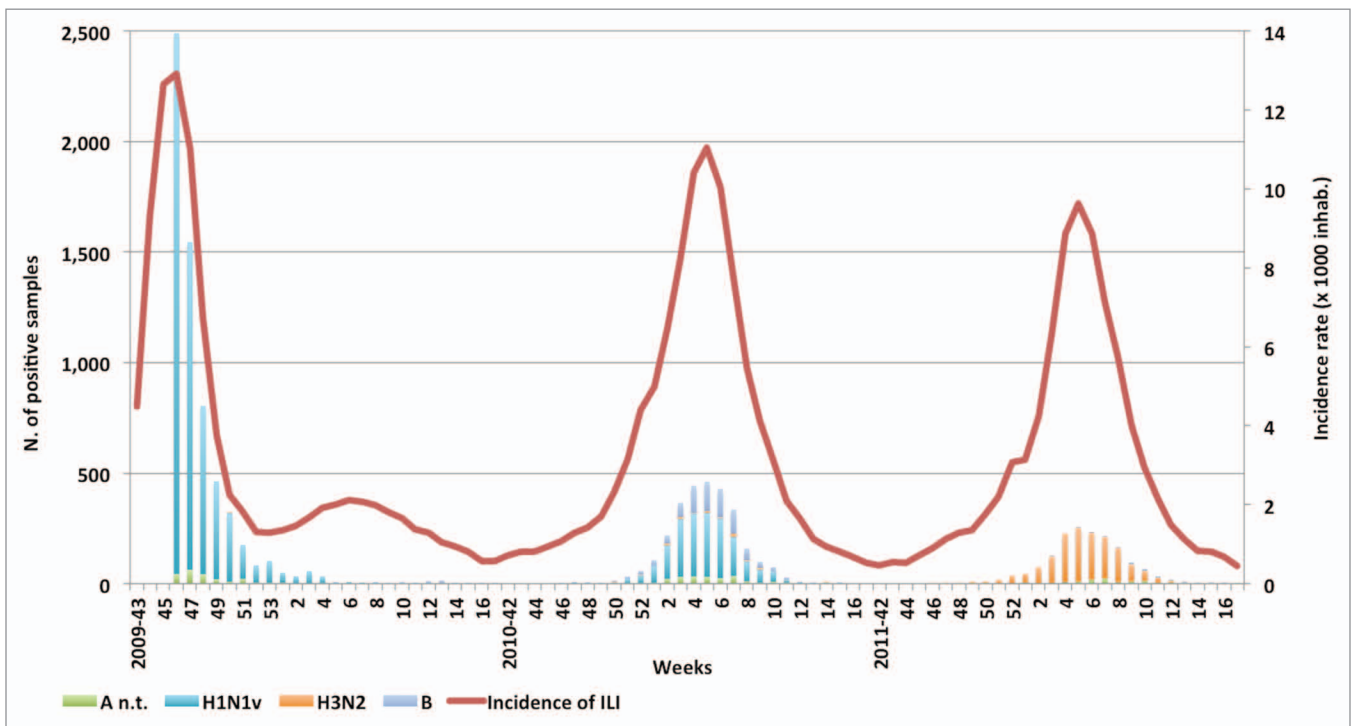


Figure 3. Influenza Like Illness incidence rate (x 1,000 inhabitants) and influenza laboratory confirmed cases during 2009–2012 influenza seasons in Italy.

isolated. This alternation of B variants, which are particularly important for children, amply justifies the fact that in the US a quadrivalent live attenuated influenza vaccine has been prepared and approved.^{22,23}

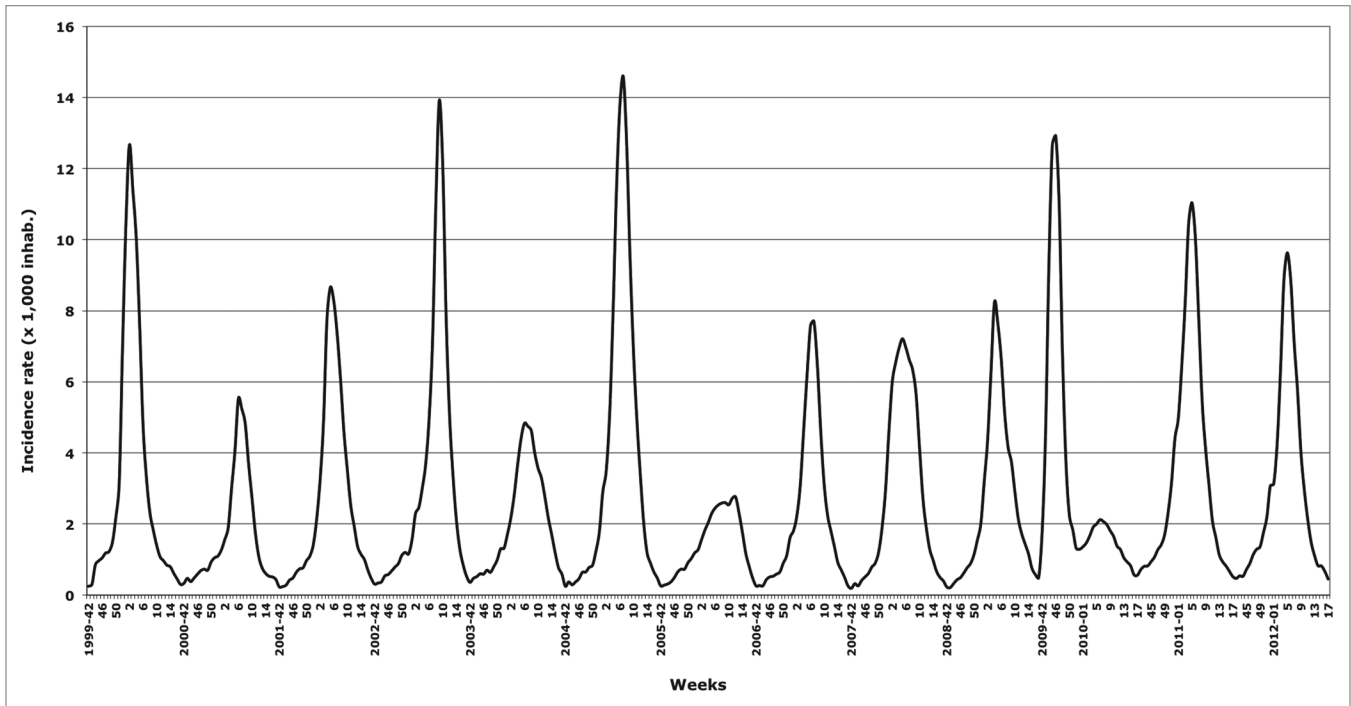


Figure 4. Weekly morbidity per ILI (x 1,000 inhabitants) from 1999–2000 to 2011–2012 influenza seasons in Italy.

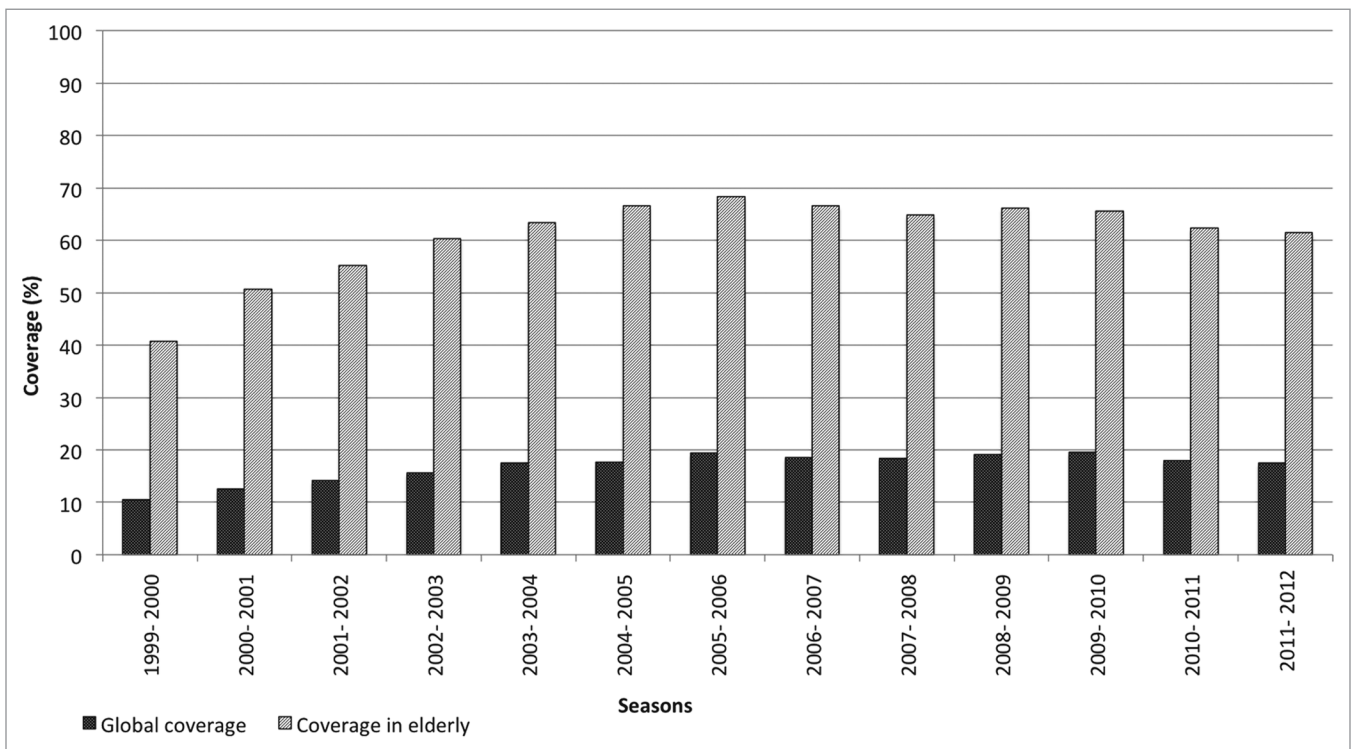


Figure 5. Influenza vaccination coverage in the general population and the elderly (per 100 inhabitants) during 1999–2012 influenza seasons in Italy.

With regard to vaccine coverage, the Italian Ministry of Health has also recently confirmed that it is necessary to achieve high coverage in risk groups. It has therefore set the minimum target for coverage at 75% and the optimal target at 95%.²⁴

Overall coverage is still far too low, particularly among non-elderly high-risk subjects. In the elderly, although coverage increased significantly from 1999 to 2006, since 2007 it has slowly declined. In the Liguria Region, for instance, we observed a decrease in coverage from 65.7% in 2008/09 to 58% in the 2011/12 influenza season (unpublished data). This decline was probably due in part to the mistakes made during the vaccination campaign for the 2009 pandemic. These can be summarized as follows:

- An inappropriate communication campaign by the leadership, which tended to substantially minimize the potential severity of the disease;

- Frequent changes in ministerial guidelines on who should be vaccinated as a priority;

- A lack of systematic training of GPs, pediatricians and obstetricians;

- The lack of an economic incentive for these professionals to vaccinate their patients.

In conclusion:

- The 2009 pandemic determined a high incidence of ILIs, though this was lower than the incidence recorded in 1999–2000 and in 2004–2005, when new variants of H3N2 emerged.²⁷ It was also lower than in 2002–2003, when H3N2 viruses co-circulated with B strains and, after an absence of 10 y, a B/Victoria variant re-emerged;²⁵

- The incidence of ILIs in 2010–2011, when H1N1pdm09 sustained a second pandemic wave, was moderate;

- Many strains of influenza viruses were present in the epidemiological scenario in 2009–2012. However, it is interesting to note that seasonal H1N1, which circulated in previous years, was practically absent in that period;

- The 2009 pandemic virus seems to have saturated the reservoir of susceptibility;

- The co-circulation of two lineages of influenza virus type B justifies the development of quadrivalent vaccines;

- Our data confirm that the 2009 pandemic had a particularly heavy impact on infants and schoolchildren. This fact supports the strategy of vaccinating schoolchildren up to at least 14 y of age, also against seasonal influenza. This policy, which is consistent with the findings of the Tecumseh study published by Monto AS et al. in 1969,²⁶ was implemented by Japanese Health Authorities in 1962–1987.²⁷ The Japanese policy of vaccinating schoolchildren against influenza has progressively recently been promoted in the US, where now influenza vaccination is universally recommended;²⁸

- The low levels of vaccination coverage in Italy reveal the need to improve the catch-up of at-risk subjects during annual influenza vaccination campaigns, and, if possible, to extend free vaccination to at least all 50–64-y-old subjects,²⁹ given that in Italy influenza vaccination is currently offered free of charge to persons over 64 y of age, and only to subjects at risk under this age;³⁰ indeed, vaccinating 50–64-y-olds would both raise the level of coverage of at-risk subjects and reduce the loss of productivity caused by influenza.³¹

- With regard to the provisions of the 2012–2013 influenza epidemic in the Northern Hemisphere, also taking into account

the epidemiology of the disease in the Southern Hemisphere in June–September 2012, it is possible to forecast a co-circulation of influenza H3N2 and B viruses, while probably there will be no spread of the H1N1 viruses, neither seasonal nor pandemic.³²

- Finally, in the light of the experience gained during the 2009 pandemic, the state, regional authorities and physicians should be better coordinated; this would involve enlisting the support of the professional unions of those chiefly engaged in carrying out vaccination campaigns, in order to agree upon appropriate professional training and adequate incentives.

Materials and Methods

Epidemiological and virological surveillance. The influenza surveillance system performs its activity from the 42nd week of each year (mid-October) to the 17th week of the following year (late April). Only during the pandemic season (2009/10) did surveillance continue uninterruptedly. GPs and pediatricians report ILI cases to the CIRI-IT and NIH Centers weekly. The electronic data form for each subject includes birth year, sex and status of influenza vaccination.

The definition of ILI comprises: abrupt onset of fever ($> 38^{\circ}\text{C}$), one or more respiratory symptoms (non-productive cough, sore throat, rhinitis) and one or more systemic symptoms (myalgia, headache and severe malaise).³ With regard to the diagnosis of ILI in infants and children, physicians are reminded that the presentation of influenza is often nonspecific in these subjects and that its manifestations may include abrupt onset of high fever, coryza, cough, sore throat, vomiting and diarrhea (particularly in breastfeeding infants), abdominal pain, fatigue, headache, red eyes and conjunctivitis (particularly at preschool age) and myalgia.³³ The classic symptoms often associated with influenza in adults are not easily identified in children. In 2004, Friedman MJ et al. performed a study which enabled them to conclude that the triad of cough, headache and pharyngitis was a very good predictor of influenza infection in children.³⁴

Since 1999, the data have been analyzed, validated and processed in order to calculate total incidence and incidence by age-group (0–14; 15–64 and > 64 y). Since the 2003/2004 season, the 0–14-y age-group has been subdivided into two groups (0–4 and 5–14 y).

To maximize the accuracy of the analysis (in particular, to ensure documentation of the number of subjects monitored during the week) the zero-reporting method was used, whereby doctors were also required to report the absence of cases among the patients.

From 1999 to 2008, the number of people monitored in Italy accounted for 1.6% of the population; since the 2009/10 influenza season, this percentage has risen to 2%.

The baseline weekly incidence of 2 per 1,000 marked the epidemic threshold. To define the epidemic threshold, a period of 13 y (1999–2012) was considered. In this manner, a background level was calculated as an average weekly incidence over a six-week period before the first virus isolation and a six-week period after the last isolation.³ Subsequently, the epidemic threshold was calculated to be the background level +3 standard deviations.

The results of the ILI surveillance performed by the CIRI-IT were aggregated with data from the NIH in order to construct the global national epidemiological scenario. The results were published weekly on line.³⁵⁻³⁷ Virological surveillance was performed by the network of Regional reference laboratories. The identification and isolation of virus strains was performed according standard procedures.³⁸ The results of virological surveillance were collected and aggregated by the Italian NIC in Rome. The NHI collected data on influenza vaccination coverage; every year, all Italian regional authorities inform the NHI

of the total number of doses of vaccine administered, both by the vaccination services of Local Health Agencies and by physicians or pediatricians.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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