

Impact of vaccination programs against measles, varicella and meningococcus C in Italy and in Tuscany and public health policies in the last decades

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Keywords

Vaccination program • Measles • Varicella • *Neisseria meningitidis* type C • Italy

Summary

*The World Health Organization (WHO) has established specific targets for control, elimination or eradication of some vaccine preventable infectious diseases, which were periodically updated. In Italy, WHO recommendations have been endorsed and implemented over time, through the national and regional health prevention plans. The aim of the study was to assess the impact of the immunization practices against measles, varicella and *Neisseria meningitidis* type C (Men C) in Italy and in Tuscany Region, during the last decades, by analyzing national and regional surveillance databases. Benefits of vaccination strategies were discussed from different points of view (clinical, epidemiological, economic, ethical, social and communicative). The implementation of measles, varicella and Men C vaccination, caused a considerable*

decrease of incidence rates over the years in Italy and in Tuscany too. However, in the last years, notifications of measles and Men C cases in subjects not targeted by immunization campaigns, in Italy and in Tuscany, are a cause for concern for public health and for the achievement of the elimination goals. Achieving and maintaining high vaccine coverage guarantees a decrease in the incidence of serious diseases and their clinical and economic consequences, but it is necessary to strengthen surveillance system of infectious diseases in order to monitor epidemiological trends. Moreover, outreach campaigns are necessary to raise awareness in the general population and create the culture of prevention with the same nationwide health goals for all.

Introduction

Vaccination is one of the most successful health interventions ever introduced in the history of medicine and, together with the modern hygiene practices and the use of antibiotics, has contributed significantly to decrease infectious diseases. All over the world, introduction of universal vaccination resulted in an overall net reduction of infectious diseases, the main cause of mortality in children in the past and, currently, in developing countries. Indeed, the World Health Organization (WHO) estimates that 1.5 million deaths each year could be averted thanks to vaccinations that provide protection against infectious diseases. However, in 2013 nearly 22 million children missed out the opportunity to be adequately protected against vaccine preventable diseases, resulting in a significant infant mortality, particularly in developing countries. Globally, under-five mortality rate has decreased by 53%: it has dropped from 91 deaths per 1000 live births in 1990 to 43 deaths per 1000 live births in 2015 [1, 2]. According to the “Global Vaccine Action Plan 2011-2020” published by WHO, vaccines will prevent 25 million deaths during the current decade [3]. However, transmission of infectious diseases could be reduced, only achieving and maintaining high level of vaccination coverage (VC). The WHO has set specific targets for the control, elimination or eradication of dif-

ferent infectious diseases (i.e. measles and polio), which were periodically updated.

In Italy, these targets have been included in all the National Health Plans approved in the last decade. In particular, in the National Plan for Vaccine Prevention 2017-2019, specific goals for immunization against Measles, Varicella and Meningococcal C diseases were defined [4]:

- achieving and maintaining VC for one dose of MMR (measles, mumps, rubella) $\geq 95\%$ within 2 years of age and two doses of MMR $\geq 95\%$ in children aged 5-6 years and adolescents (11-18 years);
- achieving and maintaining VC $\geq 95\%$ for meningococcal C vaccination in newborns and adolescents (11-18 years) within 2 years of age;
- achieving and maintaining VC $\geq 95\%$ for one dose of varicella vaccination within 2 years of age and two doses of varicella vaccination $\geq 95\%$ in children of 5-6 years of age.

In Tuscany, health authorities adopted specific vaccination strategies against measles, *Neisseria meningitidis* C (Men C) and varicella, in different times, in order to reduce the burden of those diseases at regional level and contribute to the achievement of national objectives.

The aim of this study was to assess the impact of the regional vaccination program in Italy and in Tuscany by analyzing and comparing national and regional inci-

dence data on measles, Men C and varicella before and after the introduction of the specific recommendations for immunization up to 2010. Moreover, we added some considerations on the current epidemiological data of measles and Men C cases observed in the last years at the regional and national level.

Benefits of vaccination practices in the field of public health were discussed from different points of view: clinical, epidemiological, economic, ethical, social and communicative.

The impact of vaccination programs was assessed by analyzing epidemiological surveillance data of these three infectious diseases in Italy and in Tuscany. The discussion is supported by specific searches carried out on "PubMed" database. A consultation of national and international official websites (WHO, UNICEF, Ministry of Health, National Institute of Health - ISS Epicentro) was also performed in order to retrieve recommendations on vaccines and vaccination policy in other Italian regions or EU countries.

Evaluation of the impact of vaccination in Tuscany and in Italy: the clinical-epidemiological value

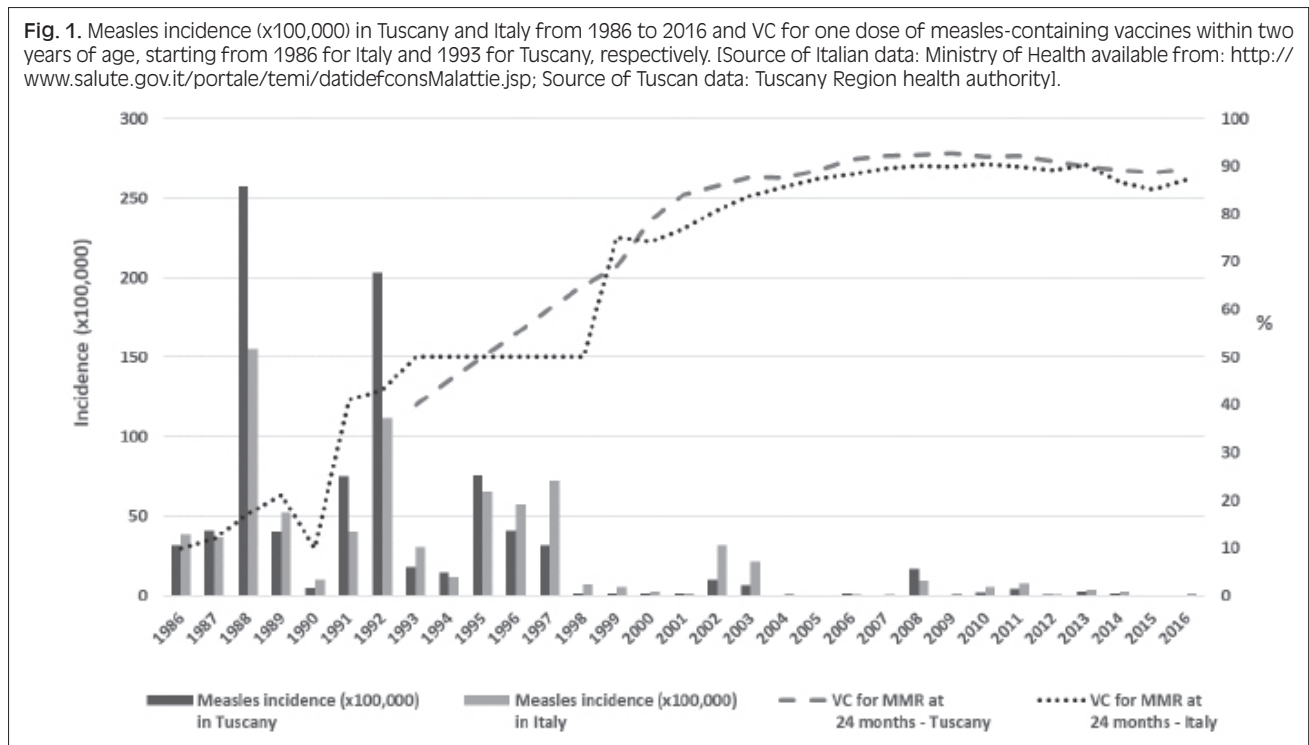
MEASLES

In Italy, the introduction of measles (M) and measles-mumps-rubella (MMR) vaccination determined a significant decrease in the number of cases and deaths due to MMR over time. Figure 1 shows the trend of measles incidence in Tuscany and Italy from 1986 to 2016 and VC for one dose of measles-containing vaccines within two

years of age. Noteworthy, the increase of immunization coverage at 24 months of age, that reached in 2010 the value of 91% and 92% in Italy and in Tuscany, respectively, corresponds to a drastic decrease in the number of measles cases and of incidence rates too (1.4 and 0.7 per 100,000 in Italy and Tuscany, respectively in 2010). Moreover, in 2010 MMR immunization coverage with 2 doses reached almost 70% at 6, 12 and 15 years of age [5]. According to the ICONA study 2008, vaccination coverage in Italian adolescents (16 years) was 91% for 1 dose of MMR and 75% for 2 doses [6], in line with the Tuscan VC data.

The incidence of measles in Italy in 2005 reached a historic low of 0.2 cases per 100,000 inhabitants (108 cases). In the period 2003-2007 there was an improvement in immunization coverage for the first dose of MMR within 24 months (from 84% in 2003 to 90% in 2007), and a special surveillance system for measles and rubella cases was established at regional and national level, in order to laboratory confirm suspected cases. Moreover, in the same period, the second dose of MMR vaccine at 5-6 years was definitively introduced. However, in Italy outbreaks of measles still occur and serious complications (such as pneumonia, encephalitis and deaths) are reported [7, 8]. From July 2009 to September 2010 the incidence of measles was 3.6 cases per 100,000 inhabitants, with 2,151 cases in 15 regions (of which 42% laboratory-confirmed). The average age of cases was 18 years and 92% of the cases involved unvaccinated people. A large percentage of subjects (36%) required hospitalization [9].

The trends of measles incidence rates in Tuscany reflect the national one. The VC for MMR in children aged 24 months in Tuscany gradually increased since 2000 and



the 2002-03 epidemic of measles occurred in Italy, had a less impact in Tuscany than into the other Italian regions. In fact, only 330 and 218 cases were notified in 2002 and in 2003, respectively [10]. In the following years, a marked reduction in incidence was still observed, with only 3-55 cases reported in 2007 and 2006, but a peak of 600 cases occurred in 2008 (16.3 cases/100,000). The age group most affected was that of young adults (75%), confirming the achievement of optimal vaccination coverage in younger subjects, target of the vaccination program. Moreover, in the last years, a high susceptibility to measles in young adults in Tuscany was discovered [5]. In 2017, an epidemic of measles occurred in Italy and in Tuscany too. At national level 4,885 cases and 4 deaths were reported from 1 January 2017, including infants and adults (median age: 27 years). It involved especially unvaccinated subjects (88%) or subjects vaccinated with a single dose (6%), causing a high percentage of complications (35%) and a large number of hospitalizations (44%). Moreover, 315 cases occurred among health care workers [8]. From January 1 to April 30, 2018, 18 regions have reported to the national integrated measles and rubella surveillance system 1,258 cases of measles, including 4 deaths [11]. These evidences reflect the expected epidemiological shift of the mean age of infection towards older age groups caused by the missed goals of vaccination coverage in childhood. Improvement of vaccination coverage can be reached through additional vaccination strategies in hard-to-reach subjects (adolescents or adults) who are not included in the routine vaccination offer [12].

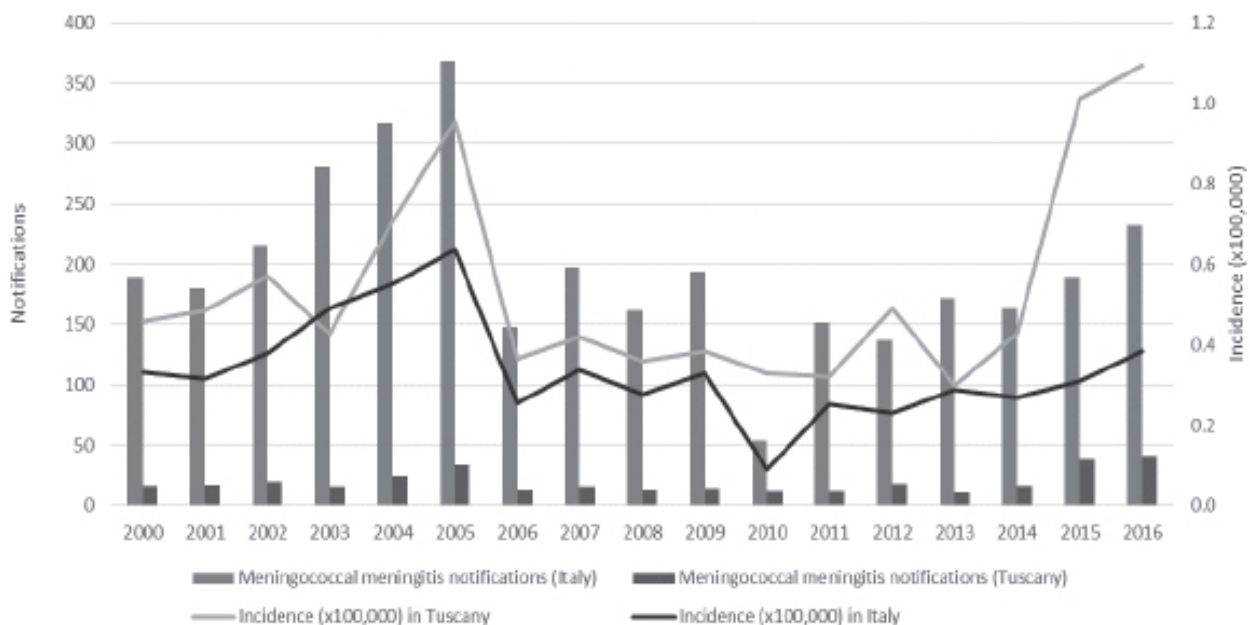
NEISSERIA MENINGITIDIS TYPE C

Although Italy, in the period 1994-2012, faced the lowest incidence rates for invasive meningococcal diseases

(IMD) compared to other European countries, 3,929 cases of IMD have been notified to the surveillance system of Invasive Bacterial Diseases (MIB), and 2,280 cases (58.0%) were typed. Serogroup B has always been the most common, accounting for 60.3% (1,375 cases) of cases typed, followed by serogroup C (33%, 760 cases) [13]. On the other hand, serogroup C isolates progressively increased from 1994 to 2005 at national level [14, 15]. Figure 2 shows meningococcal meningitis notifications and incidence in Tuscany and Italy from 2000 to 2016.

In Tuscany, since 2006 a clear reduction in the number of Men C cases was observed, probably related to the introduction of conjugate vaccines against Men C in the regional immunization program. Since 2003, monovalent polysaccharide conjugate vaccination against Men C in Tuscany was offered to subjects at risk of all ages and it was accessible to all the other people in co-payment. Tuscany was the first Italian region to include Men C vaccination in the universal immunization program. Since 2005, three doses of vaccine were offered free of charge to children at 3, 5 and 13 months of age and one catch-up dose for children up to 6 years of age. Starting from 2008, the vaccination schedule was amended, and a single dose at 13 months of age to all infants was recommended [16]. In 2010, the goal of the Tuscany Region was to achieve a vaccination coverage of 80% [17]. Immunization coverage at 24 months of age, with monovalent vaccine against meningococcal C, progressively increased year after year, from 68% in 2006 to 90.5% in 2011. In 2006 vaccination coverage by birth cohort was 49% for children born in 2001 and 68% for children born in 2004, similarly in 2009 vaccination coverage was 61% for children born in 2000 and 87% for children

Fig. 2. Meningococcal meningitis notifications and incidence (x 100,000) in Tuscany and Italy from 2000 to 2016. [Source of Italian data: Ministry of Health available from: <http://www.salute.gov.it/portale/temi/datidefconsMalattie.jsp>. Source of Tuscan data: Tuscany Region health authority].



born in 2006 [14]. All cases of Men C observed from 2006 to 2011 occurred in unvaccinated subjects [15]. However, in 2015-2016 the incidence of IMD in Tuscany increased, and some cases occurred in subjects vaccinated 8 years before the symptoms onset [18]. For this reason, the Tuscany Region adopted a new vaccination strategy, to give protection to all adolescents already vaccinated and adults. Tuscany Region will monitor the epidemiological situation and the impact of this campaign will be visible in the coming years [19].

VARICELLA

In Italy, according to the National Plan for Vaccine Prevention 2012-2014, the decision to recommend the universal vaccination varicella (UVV) in children has been postponed to 2015, for the 2014 birth cohort, when surveillance data on the impact of vaccination programs, already active in some Italian Regions, including Tuscany, will be available [4].

In Tuscany, UVV with two doses of quadrivalent Measles-Mumps-Rubella-Varicella (MMRV) vaccine is recommended for children 13-15 months and 5-6 years old since July 2008 [15]. UVV, was also endorsed by the 2010 and 2014 regional immunization schedules [20-21]. The introduction of UVV in Tuscany and in other seven Italian Regions in two doses for all newborns achieved remarkable results up to 2014 [22]. The high immunization coverage at 24 months of age (84% with one dose in 2012) was rapidly achieved in Tuscany, thanks to the drawing effect of the trivalent MMR vaccine coverage, close to 90%. Data on VC for varicella in 2016 was about 30% at the national level, because there was not a national recommendation since the launch of the new National Prevention Plan (2017-2019). While

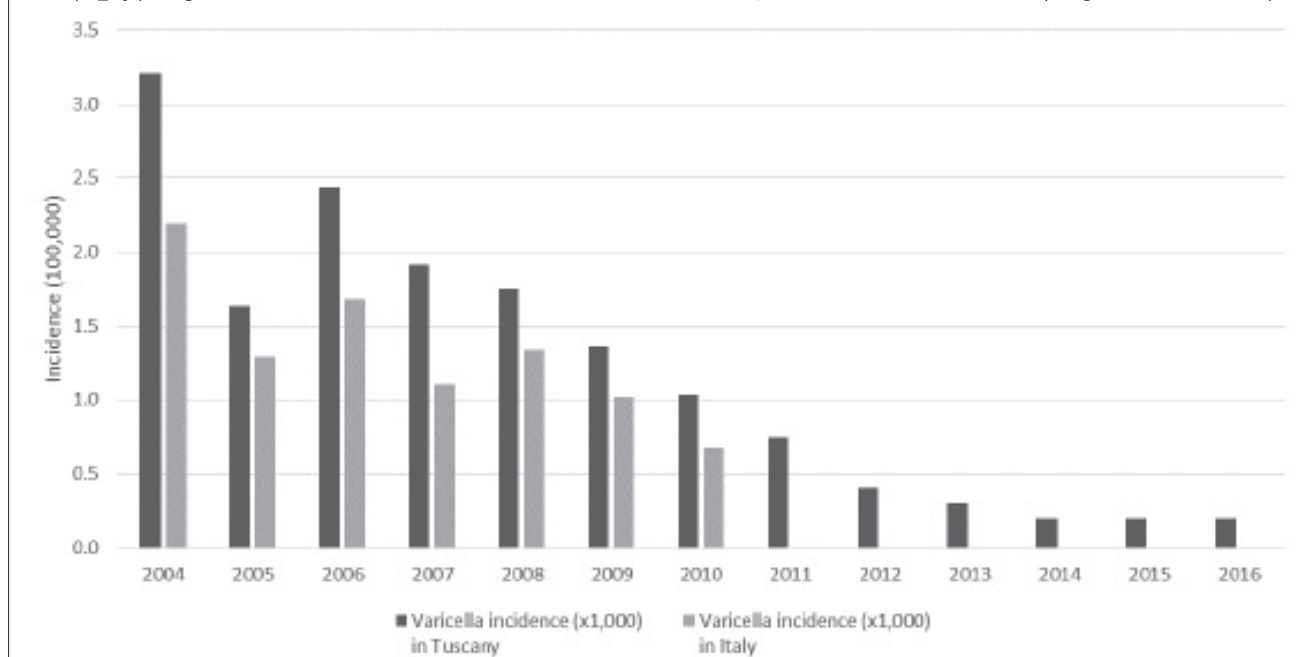
in the regions which have already introduced UVV, VC reached values between 65% and 86% [23]. Incidence rates of varicella cases decreased in the period 2004-2016 in Tuscany in all age groups (Fig. 3).

The degree of varicella underreporting in Italy, in individuals from 6 months to 20 years of age, in 2002 was 7.7 (95% CI 7.4-7.9). Underreporting was greater in older age groups and in southern Italy [24]. In Italian Central regions the underreporting rate is lower than in the South (about 5.4), this could explain the higher incidence values registered in Tuscany compared to the national average rate, from 2004 to 2010. National varicella notification data from 2011 to 2016 are not available in the surveillance system. (Fig. 3). Even at European level, existing surveillance systems are affected by underreporting and under-ascertainment [25].

Noteworthy, in Tuscany UVV has had a remarkable impact both in clinical-epidemiological and economic aspect. The introduction of universal varicella vaccination with MMRV in Tuscany has also resulted in a significant reduction of varicella-related hospitalisations, especially in subjects under 15 years of age and a total reduction of related costs. The UVV in Tuscany led to savings amounting to Euro 613,121 (Euro 153,280/year) already after four years of UVV implementation [26].

In the years 2009-2011 vaccination has had an overall rate of reported adverse reactions of 6/10,000 doses administered (45 cases out of 77,938 doses). Only 15 cases of adverse reactions were classified as serious, but without permanent damage [27]. Future UVV adoption in all Italian regions should be monitored with attention in order to avoid a possible shift of cases to adolescence or adulthood.

Figure 3. Varicella incidence in Tuscany from 2004 to 2016 and in Italy in the period 2004-2010. (Source of Italian data: Notification data 2004-2007: <http://www.epicentro.iss.it/problemi/varicella/epid.asp> and notification data 2008-2010: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=812&area=Malattie%20infettive&menu=vuoto; Source of Tuscan data: Tuscany Region health authority).



Evaluation of the impact of vaccination: economic, ethical, social and communicative aspects

Immunization programs are different between Italian Regions, and sometimes these differences occur even into the same regional territories, resulting in a great heterogeneity of prevention practices at national level. In the most recent years Italian Regions have started to move towards a common strategy, but an open debate on health prevention policies to be adopted, is still going on.

Concerning the previous mentioned example of measles in Tuscany, increased vaccination coverage in children reduces the risk to contract the disease. In fact, vaccination coverage at 24 months of age has greatly improved in recent years at the national level; although, VC targets have not yet reached, differences in VC between Italian Regions are reducing. The increasing susceptibility to measles in young adults suggests the importance to establish vaccine strategies focused on this age group [12]. Moreover, in 2017 measles cases occurred in health care workers in Italy. In this professional group, immunization status to measles (and to other infectious diseases, such as rubella and varicella or pertussis) should be monitored. Not only for their direct protection, but also for the protection of the patients they care during their work; in particular in case of patients at risk of complications (i.e. pregnant women, newborns or immunocompromised subjects). It is fundamental to assess the impact of the immunization programs, through the monitoring of the VC trends and incidence rates. However, further efforts are needed to collect coverage and notification data in a standardized way in all regions, in order to obtain reliable surveillance figures and to plan and evaluate immunization programs.

High level of immunization coverage and disease incidence reduction have also been obtained in Tuscany with the extended use of monovalent meningococcal C conjugate vaccine (MCV). However, recent cases of meningococcal C meningitis occurred in Tuscany even in vaccinated subjects, highlighting the need to re-evaluate the current vaccination policies for all adolescent. Regional health authorities recommended the administration of a second dose of meningococcal C vaccine between 6 and 9 years, to counter the loss of immunity conferred by the first dose of vaccine, administered in the second year of life [28, 29], and a third dose of MCV was recommended even in adolescence [19].

Previous results about the UVV in Tuscany shown the social importance of vaccination as a preventive method, which can advantage not only the individual, but also the entire community. For many vaccines is possible to obtain a herd protection through the achievement of high immunization coverage in the target population to protect susceptible or vulnerable people inside the community, this represents the additional social value of vaccination [30]. Indeed, immunization allows the control and containment of circulation of microorganisms responsible of many infectious diseases. Vaccination has the advantage

of providing protection to the whole community, resulting in a significant impact on the population's health in terms of infectious diseases control and reduction of disease burden (morbidity, mortality, use of medical care, hospitalizations), as well as on the decrease of costs attributed to the infectious diseases themselves [31]. In Tuscany the high level of varicella VC (84% in 2012) resulted in a significant decline in varicella notifications, from 33,114 (2004–2007) to 13,184 cases (2009–2012), and also of hospitalisations, from 584 (pre-vaccination period) to 325 (vaccination period). The hospitalisation rate was 4.1 per 100,000 before the introduction of vaccination, which dropped to 2.2 per 100,000 in the vaccination period [26]. These results obtained in Tuscany with UVV are similar to those achieved in other Italian regions. Sicily, which was the first Italian Region to offer free UVV to children at 15 months of life and to all susceptible adolescents in the twelfth year of age, since January 2003, quickly reached a rate of vaccination coverage equal to 65.5% in children (12–23 months) and 12.1% in adolescents (11–12 years) after 2 years. In the same period, the incidence rate of varicella decreased from 95.7 / 1,000 person-years in 2004 to 9.0 / 1,000 person-years in 2007 in pediatric population (0–13 years) [32, 33]. Since January 2005, Veneto Region has offered free UVV to children at 14 months of age, a second dose to 6 years old children and a catch-up program for 12-year-old children. Moreover, three years after the adoption of the varicella vaccination program in Veneto, an increase in vaccination coverage (78.6% in the cohort of 2008) and a clear decrease in the incidence of varicella in children (0–14 years) has been observed [34–36]. In the general population, the number of varicella cases in 2011 reduced by almost 85% compared to 2006 (from 13,700 cases to about 2,090 cases) [37]. Vaccination strategies can be implemented differently in each Regions depending on their needs, infrastructure and healthcare budget. However, ensuring high coverage remains the critical success factor for significant prevention of varicella when introducing varicella vaccination in the national immunisation programme [38].

More generally, the reduction over time of the incidence of vaccine-preventable diseases thanks to the increase of the immunization coverage and the loss of risk perception related to damages caused by infectious diseases in the general population, has fostered a tendency to question the real need of vaccines [39]. Moreover, in recent years refusal to vaccinations based on ideological and cultural convictions has gradually emerged [40], sometimes it is associated with a high (and often unfounded) perception of the risk of possible vaccination consequences (side effects, adverse reactions). The doubts and beliefs that often lead to the choice to vaccinate or not to vaccinate should be discussed with health professionals, in order to establish a trusting relationship and provide accurate, clear, complete, and up to date information. Therefore, counseling is the best strategy to guarantee that adherence or non-adherence to vaccination result from an aware choice [41]. Evidence suggests that personalized and targeted counseling, combined with a

good health service delivery, could increase vaccination coverage even among adults [42].

The decrease of the burden of disease due to vaccination strategies corresponded in Tuscany to an overall reduction of hospitalizations and consequently a decrease in the health costs related to hospitalizations and to the management of patients. Different Italian studies report that in case of a varicella hospitalization, the average cost per patient is around 2,050 euros. Azzari et al. in their study shown that the real hospitalization costs due to varicella are about 30-40% higher than those calculated with the Diagnosed Related Group (DRG) [43]. Vaccinations have also a significant economic impact that is higher than the costs supported by the National Health Service related to treatment, and included indirect costs generated for the whole society (loss of work days for the assistance to an infectious person). A good vaccination strategy could contribute to create a healthy population which is able to determine the classic engines of economic growth: a better education, a more qualified employment and technological progress, as well as international appraisal [44].

According to the latest estimates of the WHO-UNICEF, even if immunization coverage for childhood diseases is over 94% in the European Region, globally at least 24 million of children are not protected by vaccinations and in each country, there are high risk groups of population that continue to be susceptible to some diseases despite the obvious advantages of vaccinations. In the 2008-2009 measles outbreaks occurred in some European countries (Austria, Bosnia-Herzegovina, Bulgaria, France, Germany, Italy, Poland and Spain), the majority of cases were reported in people who had not been vaccinated for philosophical reasons or who were part of migrant groups with limited access to immunization services. Inequalities in the access to vaccination services are due to the different socio-economic conditions between countries or even inside a single country. However, even in countries with high Gross National Product (GNP) and high investment on health services and opportunities, there were large outbreaks with a high incidence of vaccine preventable diseases, mostly due to the influence in the general population of anti-vaccination movements, which often, are the cause of the limited vaccination acceptance. For example, in 2009, for the first time, 95% of measles reported cases were from people residing in EU countries with high socio-economic level (65% from Western Europe) [45].

The harmonization process of vaccination practices at national level should take into account an equal accessibility to healthcare services, territorial differences, the effectiveness of vaccinations strategies, moreover communicative solutions to contrast the overcome resistance in the population should be proposed and realized. The achievement and maintenance of high vaccination coverage, including high risk people, can guarantee a decrease in the incidence rates of infectious diseases and of their complications. For this reason it is important to sensitize the entire population implementing extraordinary immunization campaigns; trying to overcome territorial dif-

ferences; strengthening all types of surveillance, making communication campaigns both for the population and for health professionals, involving health professionals in the empowerment process of the general population.

Conclusions

In conclusion, all the evidences reported in this study confirm that public health vaccination policies, such as the ones adopted in Tuscany for the prevention of measles, meningococcal C diseases and varicella, have a high clinical, epidemiological, economic and ethical impact on the society. Vaccination programs should be constantly monitored and updated to reach high protective level of immunity inside the community, with particular attention to susceptible subjects or high risk groups.

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Authors' contributions

AB, MC, EP, ET, CL, GB, PB, SB. All authors contributed equally to this paper.

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