REVIEW

Present situation and new perspectives for vaccination against *Neisseria meningitidis* in Tuscany, Central Italy

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Key words

Neisseria meningitidis • Vaccination strategies • Prevention

Summary

Background. *In Italy one third of bacterial meningitis are caused by Neisseria meningitidis. In March 2005, the Regional Health Authority of Tuscany included the meningococcal serogroup C conjugate (MCC) vaccine in the recommended vaccination program with a schedule of three doses to all newborns at 3, 5 and 13 months of age (from 2008 amended to a single dose at 13 months) and a single catch-up dose until age 6.*
Objective. *To evaluate the impact of the current national and regional immunization strategies against N. meningitidis and to highlight new perspectives for meningococcal disease prevention with the existing tetravalent meningococcal vaccine (ACWY) and with the future incoming meningococcal B vaccines.*
Methods. *Meningitis incidence rates in Italy and in Tuscany were calculated for the period 1994-2011 and 2005-2011,respectively. Immunization coverage with MCC vaccine in Tuscany and vaccination status of meningitis cases were reported. Literature review on meningococcal conjugate vaccine use and recommendation was performed.*
Results. *A decrease in incidence rates of meningococcal meningitis was observed in all age groups involved in the immunization campaign. Immunization coverage with MCC increased progressively year by year in Tuscany. A herd immunity effect was measured in unvaccinated age groups. Since 2006 no cases of invasive meningococcal C infection in vaccinated subjects were observed in Tuscany.*
Conclusions. *Implementation of MCC vaccination in Tuscany was effective in preventing meningococcal C disease, confirming the effectiveness of the vaccine. A new tetravalent (ACWY) conjugate vaccine is now available and its use in all Italian Regions should be considered.*

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Introduction

Meningococcal invasive disease is a life-threatening infection that affects mostly children and adolescents worldwide. It is estimated that around 500,000 cases and 50,000 deaths occur annually worldwide [1]. The case-fatality rate is 7.78% in Europe and 10-14% in the USA, and serious sequelae, including deafness, neurological problems and amputations are possible among survivors [2, 3].

Historical overview of the epidemiology of *N. meningitidis* in Italy

Before 1987 the incidence of meningococcal cases in Italy was over 1/100,000 and has stabilized at around 0.6/100,000 in 1987 [4]. The highest number of cases in 1987 was seen in the 1-4 year-old age group (27%). The highest percentage of the isolates (63%) belonged to serogroup C while 25% belonged to serogroup B [5]. Between 1985 and 1989 in Italy *N. meningitidis* serogroup C dominated. The incidence rate at the end of the Eighties was 0.5/100,000 in the general population. The highest proportion of cases (27%) was seen in subjects 5-14 years old. Forty-four percent of the isolates belonged to serogroup B while 37% belonged to group C [6]. In 1990 a predominance of serogroup B was revealed (72% of the isolates) while 12% belonged to group C. The highest proportion of cases (32%) was observed in subjects 1-4 years old [7]. In 1994, 603 cases of bacterial meningitis were reported in Italy one third of which were due to *N. meningitidis* (33.4%) and occurred in subjects below five years of age (35.7%). The estimated incidence of *N. meningitidis* in Italy was 0.27/100,000. Serogroup B accounted for 62.5% of the serotyped isolates, group C for 23.1%, group A for 7.2%, group W-135 for 3.6%, group Y for 1.8% [8] During 1999-2001, the average incidence was 0.4 cases per 100,000 inhabitants. Serogroup B was predominant and accounted for 75% of the isolates, followed by serogroup C with 24% [9].
In Italy, each year about 900 cases of bacterial meningitis occur, one third are caused by *N. meningitidis*, one third by *S. pneumoniae*, while in the remaining cases either the cause is represented by different bacteria or it remains unknown.

Available vaccines against *N. meningitidis*

Five major groups of *N. meningitidis* (A, B, C, Y and W135) are responsible for most meningococcal diseases. Vaccination is the main tool in the fight against meningococcal meningitis. Infections caused by serogroups A, C, Y and W135 can be prevented by polysaccharide vaccines, which however are not effective in younger children, especially under 2 years of age,

in whom a T-cell dependent immunity is not induced and a long-term immunological memory cannot be elicited.
Currently conjugate vaccines for the prevention of *N. meningitidis* serotype C infection are available. MCC vaccines were developed in the late 1990s, after the successful experience with *Haemophilus influenzae* and pneumococcal conjugate vaccines [10]. United Kingdom was the first country to introduce the vaccination in 1999 [11]. Due to the success of the immunization programme, in 2000 the vaccine was also introduced into national publicly funded routine immunization programmes in Ireland and Spain; in 2002 in Iceland, in Belgium and in the Netherlands; in 2006 in Portugal, Greece and Germany [12].

Vaccination strategies in Italy and Tuscany

In Italy the Ministry of Health entitles Regions and Autonomous Provinces to implement different meningococcal vaccination policies according to the local epidemiology and priorities. In the Italian National Vaccine Plan 2012-2014 MCC vaccination was recommended for infants between 13 and 15 months of age and for adolescents (11-18 years) [13]. Since 2003, the MCC vaccine in Tuscany was offered to subjects at risk in all age groups and it was accessible to all subjects in co-payment.
Tuscany was the first Region to approve and include the conjugate meningococcus C (MCC) vaccination in the recommended vaccination program with a schedule of three doses to all newborns at 3, 5 and 13 months of age (from 2008 amended to a single dose at 13 months) and a single catch-up dose until age 6 [14].
Recently (March 2010), a quadrivalent conjugate vaccine against serogroups A, C, Y, W-135, was authorized in European Union and it is now indicated for active immunisation of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitidis groups A, C, W135 and Y, to prevent invasive disease [15].

The purpose of this study was to evaluate the impact of the current national and regional immunization strategies against *N. meningitidis* and to highlight new perspectives for meningococcal disease prevention with the existing tetravalent meningococcal vaccine (ACWY) and with the future incoming meningococcal B vaccines.

Methods

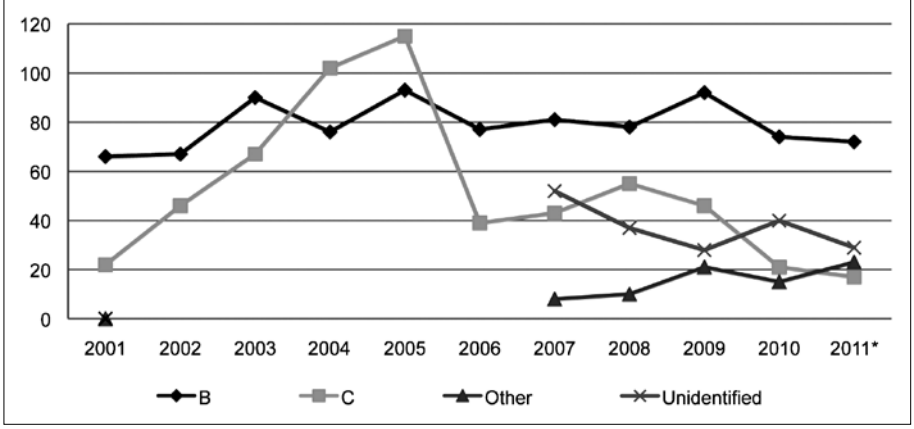
Data collection

Data collection started in 2009 and ended in February 2012. The Regional Health Authority provided surveillance data on IBD:

- notification of meningitis cases by etiologic agent and year of notification
- immunization coverage at 24 months of age, by birth cohort.

Incidence rates were calculated by age groups: < 1 year; 1-4 years; 5-14 years; 15-20 years; 21-30 years; 31-49 years; 50-64 years; ≥ 65 years.
In order to calculate incidence data for meningitis cases the number of notified cases in Tuscany was divided by the resident Tuscan population in the same age groups [16].
Italian surveillance data were obtained by means of the SIMI (Infectious Diseases Information System) database and incidence rates were calculated on the resident Italian population [17].
The SIMI provides passive notification data; it is based on the notifications filled by the local public health units on the basis of the medical reports received. To calculate the vaccination coverage, the number of vaccinated children (numerator) was derived from the coverage database of the 12 regional local health care units, whereas the total number of children eligible for vaccination in each age group (denominator), was obtained from the census data from the same areas.

Fig. 1. Cases of *N. meningitidis* by serogroup B and C in Italy, by year (2001-2011*) (*) data for 2011 are updated to 24 February 2012.



Results

Italy and Tuscany

In Italy a shift in prevalence from serogroup C to serogroup B isolates was observed during the Nineties and up to 2003. In the years 2004 and 2005 isolates of serogroup C have exceeded those of serogroup B (Fig. 1).
The proportion of serogroup C isolates was over 50% for both 2004 and 2005 and decreased to about 20% in 2011 (Tab. I).

Since 2006 the annual number of *N. meningitidis* cases has remained under 200 ranging between 141 and 187 cases corresponding to incidence values between 0.31 and 0.23 (Fig. 2) [17].
The highest incidence rates of meningitis cases due to any causal agents in Tuscany from 2005 to 2011 were calculated in infants, ranging from 3.2/100.000 in 2005 to 9.3/100.000 in 2010. An incidence rate of 5.1/100.000 was registered in subjects of 1-4 years in 2005, a value that gradually decreased the following three years but increased in 2009 and in 2010, still remaining lower than in 2005 (3.9/100.000 and 2.3/100.000, respectively). As far as subjects aged 5-14 years are concerned, the highest incidence rate was reached in 2005 (2.1/100.000), and became around 1/100.000 in 2010 and 1.6/100.000 in 2011.
The incidence rate in subjects of 15-20 years was nearly 1.7/100.000 between 2005 and 2009. In 2011 it was 0.5/100.000. No cases were registered in 2010. In subjects older than 20 a decrease in meningitis C incidence was registered in the period of observation.
All serogroup C cases observed since 2006 occurred in unvaccinated subjects.
Immunization coverage at 24 months of age with MCC increased progressively year by year in Tuscany. During the six-year period it improved from 68% in 2006 to 90.5% in 2011. Results are reported in Table II.

Tab. I. Proportion of meningitis caused by serogroups C on the total of *N. meningitidis* isolates in Italy, by year (2991-2011*) (*) data of 2011 are provisional and updated to February 2012.

	Neisseria meningitidis serogroup C	total isolated meningococci	Percentage of C/ (C+B+unidentified)
2001	22	88	25,0
2002	46	113	40,7
2003	67	157	42,7
2004	102	178	57,3
2005	115	208	55,3
2006	39	116	33,6
2007	43	124	34,7
2008	55	133	41,4
2009	46	138	33,3
2010	21	95	22,1
2011*	17	89	19,1

Fig. 2. Incidence of meningitis cases in Italy, by year (2005 – 2011*). (*) data of 2011 are provisional and updated to February 2012. [17] Population data source: [16].

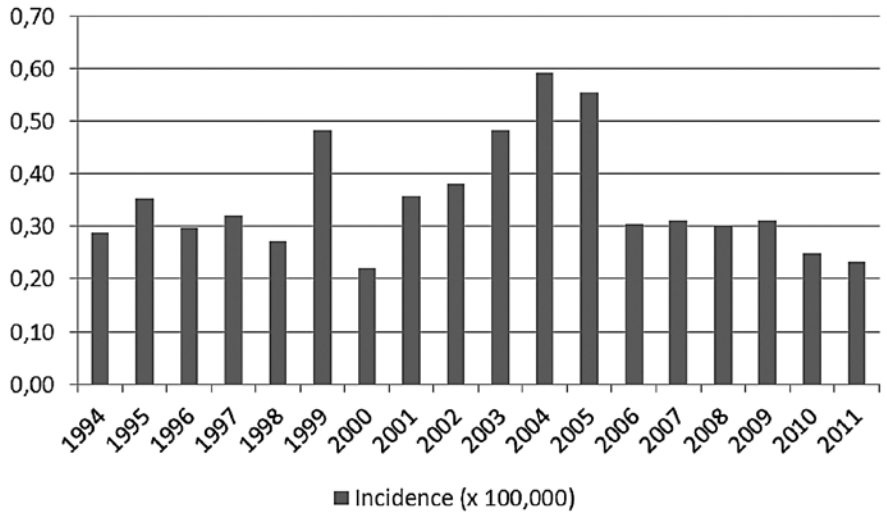


Fig. 3. Cases of *N. meningitidis* by serogroup B and C in Tuscany, by year (2001-2011*) (*) data for 2011 are updated to January 2012).

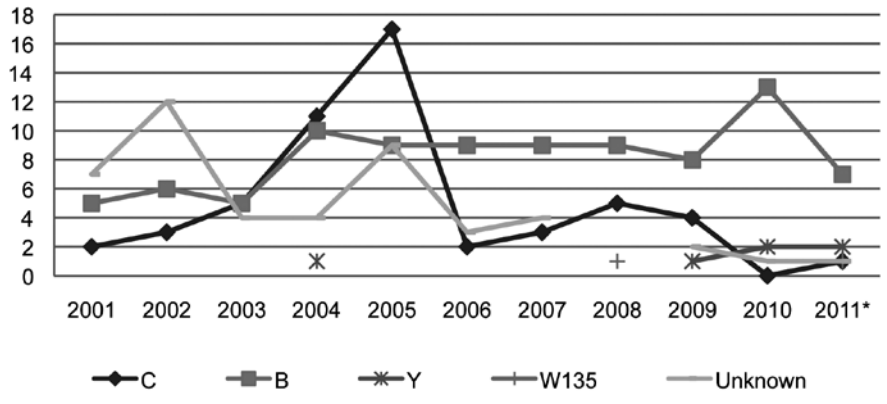
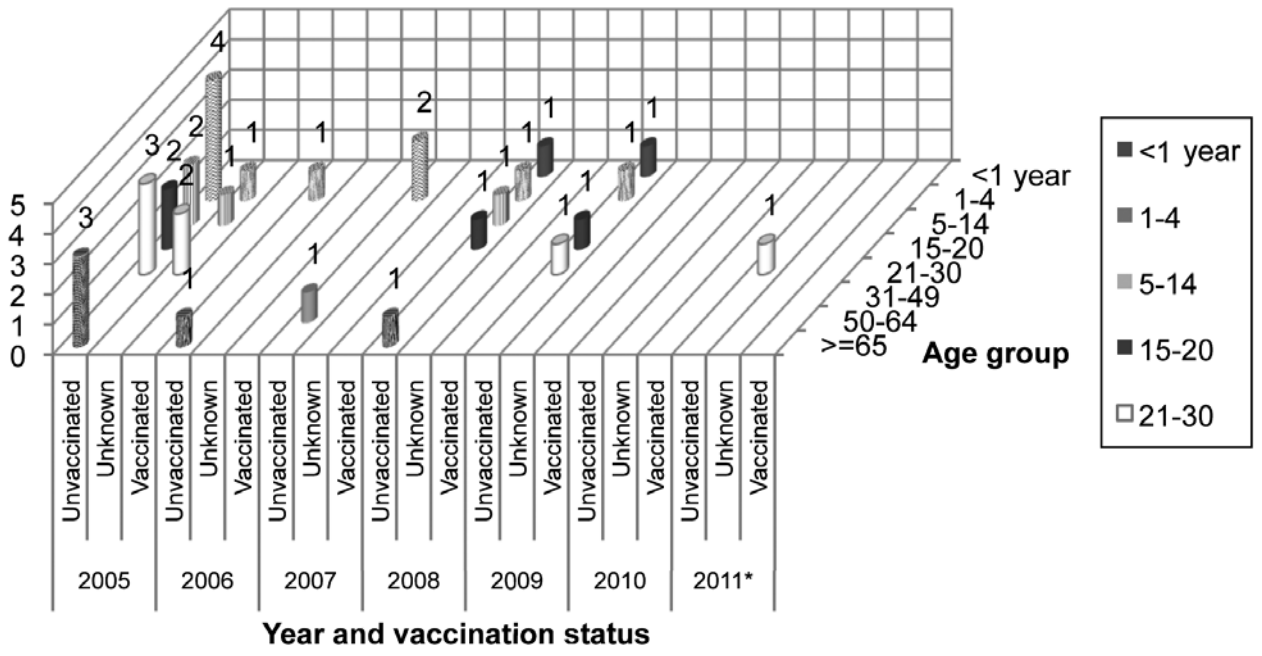


Fig. 4. Cases of *N. meningitidis* serogroup C in Tuscany by age group and vaccination status (2005-2011*). (*) data for 2011 are updated to January 2012.



The immunization coverage with MCC vaccine by birth cohort ranged from 49% to 68% (average 58.1%) in 2006, for the cohort of subjects born in 2001 and in 2004, respectively and it ranged from 61% to 87% (average 75.3%) in 2009, for the cohort of subjects born in 2000 and in 2006, respectively (Tab. III).

Tab. II. Vaccination coverage with MCC vaccine at 24 months of age (%) in Tuscany, 2006-2011.

Year	Vaccination coverage at 24 months of age (%)
2006	67.9
2007	72.8
2008	83.8
2009	87.2
2010	88
2011	90.5

Tab. III. Vaccination coverage with Men C vaccine in Tuscany, by birth cohort (2006-2009).

	2006 (%)	2007 (%)	2008 (%)	2009 (%)
Born in 2000	50.3	55.5	59.5	61.3
Born in 2001	48.7	59.2	63.8	65.0
Born in 2002	54.4	63.1	69.7	72.0
Born in 2003	64.4	69.2	74.0	75.6
Born in 2004	67.9	73.3	78.3	80.4
Born in 2005	63.1	72.8	84.0	85.2
Born in 2006		64.7	83.8	87.2
Average	58.1	65.4	73.3	75.3

The catch-up immunization of children under 6 years in Tuscany allowed to increase immunization coverage in four years (2006-2009) by a minimum of 11%, for subjects born in 2000 and in 2003, to a maximum of 23% for children born in 2005 and 2006. The highest immunization coverage values are registered in younger children.

Discussion and conclusions

In Italy the number of serogroup C meningococcal cases decrease gradually after the introduction of the MCC vaccine.

According to ICONA 2008 survey in Tuscany immunization coverage with MCC vaccine at 24 months of age was 64.3% (IC95%: 55.6% -73.0%), which is lower than the official routine immunization coverage reported in this study (Tab. II). In Italy, immunization coverage with MCC vaccine are very low in children at 24 months of age (36.9%). Children immunized with a cycle of three doses in the first year of life were 5.6%, while 31.3% received one dose in the second year of life. Immunization coverage for children "at risk" was 29.9%. ICONA survey reported a value of 21.4% (IC95%: 14.7%-28.1%), for Tuscan adolescents (16 years old) which is higher than the Italian adolescents immunization coverage (16.0%; IC95%:14.2%-17.8%). As far as concern MCC vaccination coverage in Italy there is generally a high regional variability: five regions reported an immunization coverage between 20 and 72%, while in all the other regions the coverage is lower than 10%. As long as MCC vaccine will be underused in Italy, cases of meningitis will continue to occur and incidence rates will maintain high, especially in those age groups more affected by the disease [18].

Invasive Meningococcal Disease (IMD) cases in 2005 and 2008 reported to the National Meningococcal Surveillance System showed an incidence of 0.5 and 0.3 per 100,000 inhabitants, respectively. While the incidence due to serogroup B continued to be stable, IMD incidence due to serogroup C has decreased since 2006, particularly among infants [19].

The incidence rate of meningococcal disease in Italy is currently among the lowest in Europe with 200-300 cases per year (0.25/100,000 in 2010) [20]. In Tuscany the proportion of serogroup C isolates represented about 20% of meningococcal cases in 2011. A constant decrease of Men C cases was observed after the introduction of MCC vaccination.

In Italy, as in Tuscany, an increase in the isolation of serogroup Y and sporadic isolation of serogroup W-135 was observed since 2001.

Variations over time of meningococcal serogroups were observed in many countries. From the mid-90s, serogroup Y has spread in the United States to become the predominant serogroup in 2007 (Y: 37%; C: 29%; B: 25% and W-135: 9%). From 1998 to 2006 the percentage of *N. meningitidis* serogroup Y isolated from patients with IMD in Italy has increased. Before 2005 the proportion of serogroup Y isolates ranged between 0 and 4% of the total strains sent to the National Reference Laboratory (NRL) at the Istituto Superiore di Sanità, but an increase up to 7% was observed during 2006. Molecular characteristics of invasive serogroup Y in Italy will be helpful to monitor the spread of this serogroup in the next years [21].

Serogroup W-135 has begun to be present in significant percentage worldwide. The origin of the spread of *N. meningitidis* serogroup W-135 began in Saudi Arabia with the pilgrimage to Mecca in 2000. A spread in Africa and globally with the return of pilgrims was observed in the following period. Recently W-135 has become endemic in South Africa and has spread from Africa to Europe, Asia and North America [22-24].

N. meningitidis bacteria are characterized by a dynamic epidemiology whose determinants are: recombination between different serogroups, through genetically determined mechanisms and international travels, which promote the spread of different serotypes [25, 26]. These two factors contribute to determine an unpredictable epidemiology.

During 2003-2005 a study was performed in Italy to compare the phenotypic characteristics of meningococcal isolates from the two age groups most at risk of developing invasive meningococcal disease (children aged <4 years and adolescents aged 15-19 years) with those from other age groups in order to assess whether strategies for treatment and prevention implemented elsewhere can also be applied in Italy. Serogroup C was found to have replaced serogroup B as the predominant serogroup since 2004. A dramatic increase, from 50.9% to 87.4%, in the circulation of strains with decreased susceptibility to penicillin was observed especially among serogroup C isolates, without great differences in terms of distribution among the different age groups. In contrast, a greater percentage of serogroup B isolates with reduced susceptibility to penicillin was isolated from children and adolescents than from other age groups. The circulation of meningococci with decreased susceptibility to penicillin needs continuous monitoring in order to determine vaccination strategies [27].

A strong correlation between the serum bactericidal antibodies and antibodies to the polysaccharide capsule of C exists. A seroepidemiological study was performed in Italy in 2003-2004 and a total of 577 sera were collected in 17 of the 20 Italian Regions. The geometric mean titre of bactericidal antibodies (SBA GMT) was low in subjects under 1 year of age, significantly increased in 1-9-year-old children and decreased in adolescents and young adults. According to this survey meningococcus C has the highest probability of spreading among 1-4, 8-10 and 14-17-year-old subjects in Italy [28].

Besides, studies of meningococcal carriage are a good tool in improving knowledge on the epidemiology of meningococcal disease. In a sample of students from the University of Bari the circulation of *N. meningitidis* was investigated. The nasopharyngeal swabs of 583 university students were collected and 12 carriers were identified (2%). Nine isolates proved auto-agglutinable, the other strains belonged to serogroups B, W135 and Y. No type C serogroup strain was detected and this could be right associated to immunization policies providing meningococcal serogroup C conjugate vaccines for newborns and adolescents in Puglia. The shifting pattern of *N. meningitidis* serogroups circulating in healthy carriers could support the adoption of quadrivalent meningococcal conjugate vaccines to pre-adolescents and adults [29].

After MCC vaccine introduction in infants and adolescents, meningococcus serogroup B have been responsible of most cases of IMD in Italy. MenB vaccines can contribute to containing meningococcal disease. There is still no universal vaccine available against the serogroup B, which is a major cause of invasive disease [30]. The development of MenB vaccines has focused on subcapsular antigens as outer membrane vesicles (OMVs) [31]. Several candidate OMV vaccines have been tested in large-scale efficacy studies in Norway, Cuba, Brazil, Chile and New Zealand. Protection rate of 57.2% was observed in Norwegian secondary school students, but in other countries a variation in estimated vaccine efficacy by age was observed [32, 33]. The serum bactericidal antibody (SBA) titres of sera collected from toddlers and school children, pre- and post-vaccination, with a hexavalent OMV vaccine has been evaluated in phase I and II trials with promising results. The numbers of subjects with SBA titres of < 4, 4 and > or = 8 varied greatly between the different strains. On the basis of genotypic data and potential cross-reactivity, the MenB vaccine has the potential to protect against a significant proportion of MenB disease in England and Wales [34]. On the other hand, none of the subtypes included in the hexavalent outer membrane vesicle (OMV) vaccine that is currently being evaluated in the UK [31] was significantly represented among group B isolates circulating in Italy [27].

Another approach to develop MenB vaccines is "reverse vaccinology" which consists in the use of genomics for vaccine development. More than 600 universal, cross-reac-

tive antigens have been identified sequencing the genome of *N. meningitidis* through "reverse vaccinology" and successfully tested as recombinant protein vaccines [33, 35].

What is the possible integration of a Men B vaccine in the Italian calendar?

The vaccine in a more advanced stage of testing (early stage 3) is currently assessed under schedule 2, 4, 6 months and 2, 3, 4 months. There will be a likely future trial with schedule 3, 5, 12 months. But the insertion of this new vaccine may result in two risks (1) a drop of vaccine coverage for all vaccines in case of the introduction of new appointments in the first year of life, (2) lack of acceptance by parents in case of return to 3 injections per session (hexavalent, pneumococcal conjugate and meningo B vaccines).

Given all experience gained in this field, the development of a universal vaccine for prevention of group B meningococcal disease looks promising. Selection of strains representative of the global epidemiological situation will be of outmost importance, defining criteria and revising such strain collections is currently ongoing and will be a key element in developing and evaluating new protein based vaccines in the time to come [35].

Conclusions

Where applied with routine childhood programs + catch-up in children and adolescents, meningococcal C conjugate vaccines have demonstrated high effectiveness in preventing invasive disease in both vaccinated and in non-immunized subjects, thanks to the herd immunity effect.

A new tetravalent (ACWY) conjugate vaccine is now available, the use of which in place of the conjugate C dose for adolescent and for children over 2 years of age should be considered.

In Italy the administration of a single MCC dose to 11-18 years adolescents is now recommended in subjects who have not been vaccinated in childhood. The objectives of the National Prevention Plan 2012-2014 for meningococcal vaccination are: achieving and maintaining in newborns and adolescents (11-18 years) vaccination coverage ≥ 95%. Targets are still too far to be reached.

In Italy vaccination policies are characterized by high regional heterogeneity. Some Regions offer the same vaccination free to all newborns and others only to risk groups, besides differences within the same Region can be observed, for different behaviors of each Local Health Unit. According to our result MCC vaccination was effective in Tuscany to prevent Men C disease and all Italian Regions should introduce this vaccination in order to protect their population. To date, a universal vaccination programme is implemented free of charge in 17 out of 21 Regions (81%) for meningococcal C vaccine. Nine of these Regions also provide immunization to susceptible adolescents. Italian Regions are moving towards a common vaccination strategy concerning pneumococcal and meningococcal C vaccine [36].

It is expected that incoming meningococcal B vaccines are tested with 2+1 schedule, now increasingly common in European countries for invasive bacterial diseases; their inclusion in the already crowded childhood immunization schedule should be carefully evaluated in its coverage implications and acceptability.

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Abbreviations: MCC = meningococcal serogroup C conjugate vaccine; MenB = meningococcal serogroup B vaccine; IBD = invasive bacterial disease; IMD = Invasive meningococcal disease; SBA = serum bactericidal antibody

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