

ORIGINAL ARTICLE

Surveillance of adverse events following immunization with meningococcal group C conjugate vaccine: Tuscany, 2005-2012

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Key words

Adverse events • Meningococcal C conjugate vaccine • Tuscany

Summary

Introduction. Post-licensure vaccine safety studies are essential to identify uncommon events that may be difficult to assess during pre-licensure studies. The aim of our study was to evaluate the safety of serogroup C meningococcal conjugate (MCC) vaccine in Tuscany from 2005 to 2012. **Methods.** All adverse events (AEs) to MCC vaccine notified from 2005 to 2012 were obtained from the regional health authority.

Results. Following 451,570 doses administered, 110 suspected AEs were notified (mean annual reporting rate: 2.8/10,000 doses). The most frequently AE reported was fever (60%), followed by swelling at the injection site (11%) and febrile seizures (10%). Overall, 77.3% of cases were not severe, while 21.8% required hospitalization. Almost four months after the receipt of

the vaccine, a one-year-old infant was diagnosed with a pervasive developmental disorder with disturbance of speech, but any link with the vaccinations received was refuted. Most AEs (80.9%) occurred after co-administration with other vaccines, especially with MMR or MMRV vaccines (42.7%) or the DTPa-HBV-IPV/Hib vaccine (33.7%).

Discussion. Our study confirmed the high level of safety of MCC vaccine in Tuscany: AEs proved rare and all cases had only temporary and self-resolving consequences. As usually only the most severe suspected AEs are reported, the true proportion of AEs requiring hospitalization was most probably overestimated, and it is plausible that most of these cases were in fact only temporally related.

Introduction

Invasive meningococcal disease (IMD), a potentially life-threatening acute disease with a rapid evolution caused by the gram-negative, encapsulated and coffee-bean shaped diplococcus *Neisseria meningitidis*, still represents a global public health challenge, with around 500,000 cases and 50,000 deaths occurring every year worldwide [1]. IMD can be characterized by meningitis, bacteremia, sepsis, pneumonia, or, less commonly, by localized infections such as arthritis, myocarditis, pericarditis and endophthalmitis [2-4]. Prognosis considerably improved after the introduction of antibiotic therapy, but the case fatality rate is still between 5 and 10% in industrialized countries and up to 20% of survivors suffer from lifelong sequelae, such as mental retardation, seizures, bilateral hearing loss, low vision or loss of limbs caused by the tissue necrosis [5]. According to the bacterial capsular antigens, 12 serogroups of *N. meningitidis* have been identified (A, B, C, 29E, H, I, K, L, Y, W135, X and Z), but those most often associated with the disease are serogroups A, B, C, X, Y and W135 [6]. In Europe, most meningococcal disease is caused by B and C serogroups.

Effective vaccination programmes represent the most important tool to fight against the disease. Infections caused by serogroups A, C, Y and W135 can be pre-

vented by polysaccharide vaccines, which, however, are poorly immunogenic in children aged under two years and fail to induce immunological memory in people of any age, or by two types of conjugate vaccines, which allow the induction of immune memory also in children aged under two years [7]. The first, the meningococcal C conjugate (MCC) vaccine, is directed only against type C meningococcus; the capsular polysaccharide antigens are conjugated to an immunogenic protein, either to diphtheria toxoid, or to CRM₁₉₇, a non-toxic mutant of diphtheria toxin, or to tetanus toxoid and may be used after the third month of age. Recently, tetravalent vaccines against the meningococcal groups A, C, W135 and Y, mainly recommended to travellers to Sub-Saharan Africa, have been made available.

In Italy, the previously increasing trend of serogroup C meningococcal disease dramatically declined after the introduction of a universal vaccination programme against *Neisseria meningitidis* serogroup C. Tuscany was the first Italian Region to approve, in 2005, a policy of active offer of MCC vaccine with three doses to all newborns at three, five and 13 months of age, and a catch-up until six years with a single dose. Immunization with MCC vaccine was also recommended for subjects of any age at risk for developing IMD [8]. In July 2008, the newborn schedule turned to a single dose after the first year of age, at around 13 months. Therefore,

presently, at 13-15 months four vaccines are administered: MCC, pneumococcal, hexavalent and MMR or MMRV vaccines [9]. The adoption of the new schedule was established in reason of the high herd immunity created by the vaccination programme, as a result of which the incidence of meningococcal disease was reduced by 80% in children under one year of age, not yet vaccinated [10]. Catch-up of children aged two to six years was maintained by offering a single dose, in order to create a solid immunity in the population. The vaccine is also offered to the 12-14 years age group. With the recognition that on-going post-marketing monitoring is essential in order for the general population to maintain confidence in vaccine safety, the aim of the present study was to evaluate the safety and tolerability of MCC vaccine in Tuscany between 2005 and 2012 through an analysis of the suspected adverse events (AEs) to the MCC vaccine notified to the regional health authority since the inclusion of the MCC vaccination in the recommended vaccination programme.

Materials and methods

The notification of a suspected AE following a vaccination is regulated by a Ministerial Decree issued in 2003 [11]: the same procedure and reporting form as in the case of suspected AEs following pharmacological treatments are used. Consistently with Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an AE is a noxious and unintended response to a medicinal product used at normal dosages. A serious adverse reaction is an AE "which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect". The reporting form, filled in by a healthcare worker, is sent to the pharmacovigilance unit of the respective health service, data are registered through the national network of pharmacovigilance and sent to the regional health authority, as well as to the drug or vaccine manufacturer and to the Italian Medicines Agency, within seven days. The information regarding serious AEs are also made available to the European Medicines Agency and to the other EU Member States. The reporting form must include the patient's initials, date of birth, gender, the description and the severity of the event, the effects caused, the name of the suspected drug or vaccine, possible risk factors and information on other vaccines/drugs that may have been co-administered. As for vaccinations, the time of administration and the dose number are also reported, with the specification of the batch number and expiration date [11]. In the reporting form it must be specified whether the AE i) was not severe; ii) was severe requiring hospitalization but followed by resolution; iii) was very severe, possibly with long-term consequences; iv) caused death.

Data regarding all AEs to MCC vaccine from 2005 to 2012, collected by the Regional Health Authority, were obtained after been made anonymous. For each suspected AE the following information were made available: the specific numeric code assigned to the individual; the reporting local health unit; the date of occurrence; the subject's age (due to privacy regulations the date of birth was not available) and gender of the subjects; type, severity and outcome of the reaction; the reporting source (hospital, general practice, primary care, drug store); the contact details of the person who reported the AE; the type of administration and data regarding other vaccines, drugs, herbal or homeopathic products or food supplements that may have been co-administered. Data analysis was performed using descriptive statistics in Microsoft Excel 2010.

Results

From 2005 to 2012, 451,570 doses of conjugate meningococcal C vaccine were administered in Tuscany and, during this period, 110 cases of suspected AEs to the MCC vaccine were notified, with an average annual reporting rate of 2.8/10,000 doses. In Figure 1, the number of doses administered each year and the annual reporting rates are shown. In 2005, the average reporting rate was 1.3/10,000 doses; it increased in the following years until 2008. In that year the schedule was amended to a single dose at 13 months. In 2009, the reporting rate dropped to 1.3/10,000, then an increase of the annual reporting rate, up to 8.0/10,000 doses in 2012, was observed. The vaccine coverage at 24 months progressively increased from 65.8% in 2005, when the policy of active offer of MCC vaccine was introduced, to 90.5% in 2011; in 2012 it was 89.4% (Fig. 2). Females and males were almost equally affected (51% males, 49% females). Given the recommended schedule, AEs mostly affected the youngest age groups: 58.2% of AEs were reported in children

Fig. 1. Number of doses administered per year and average annual reporting rates of suspected adverse events following immunization with MCC vaccine per 10,000 doses administered, Tuscany, 2005-2012.

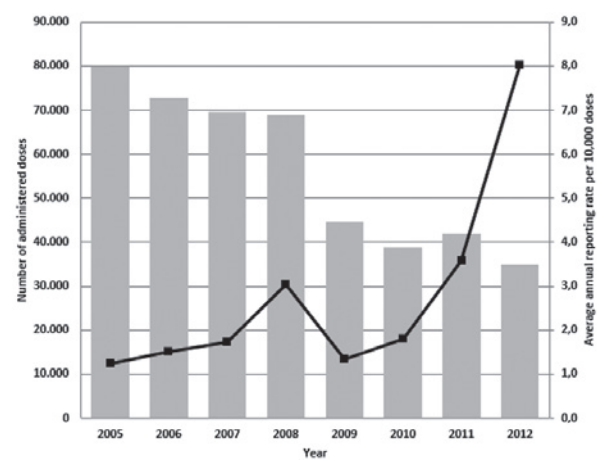
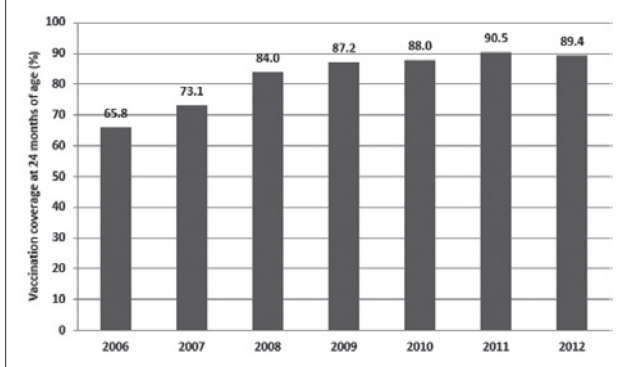
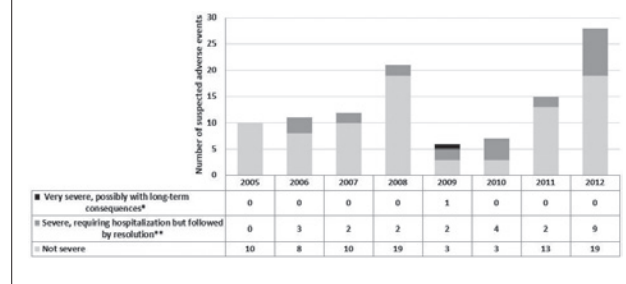


Fig. 2. Vaccination coverage with MCC vaccine at 24 months of age (%), Tuscany, 2006-2012.**Fig. 3.** Number of suspected adverse events following immunization with MCC vaccine by severity of the events, Tuscany, 2005-2012. * Lack of biological plausibility, ** Causal association not demonstrated.

aged one to two years, 15.5% in infants up to one year of age and 13.6% in children aged two to seven years (Tab. I). Most AEs, 25.5% and 19.1% respectively, were recorded in 2012 and 2008.

Overall, the most frequently reported AE was fever (60%), followed by swelling at the injection site (11%). Ten cases of febrile seizures (10%) were reported. Four cases of non-febrile seizures (3.6%) and three cases (2.7%) of unspecified convulsions were also notified. Rash was also common (10%). Other suspected AEs were vomiting (7.2%), diarrhoea, drowsiness, agitation/restlessness (4.5%), lymphadenopathy, persistent crying, pain at the injection site (3.6%). Two cases of thrombocytopenia purpura (1.8%), one of which classified as idiopathic, and one case of ataxia (1%) were also notified.

The majority of suspected AEs to MCC vaccine, 77.3%, were not severe, whereas approximately a fifth (21.8%) were severe and required patients' hospitalization, but were followed by resolution (Fig. 3). Almost half (49%) of total suspected AEs occurred the same day the vaccine was administered, most of these (87%) were not severe. Most febrile seizures (6/10) occurred between six and 11 days after vaccination.

Half of the 24 cases requiring hospitalization occurred after six days from the vaccination.

One third of hospitalized cases (8/24) was admitted to hospital due to convulsions (Fig. 4). Among these, 63% (N = 5) were febrile seizures. A fifth (5/24; 20.8%) were hospitalized for the onset of fever (all in children aged one). Another fifth was hospitalized due to disorders of

the nervous system other than convulsions: two cases of hypotonia (one in a two-year-old; the other, followed by loss of consciousness, was reported in a two-month-old); sleepiness and irritability were notified for a one-year-old; an infant was admitted for absence seizure and hyperpyrexia; finally, a case of ataxia was reported in a one-year-old after concomitant administration with MMRV. The other causes of hospitalization were: development of acute dyspnea or apnea accompanied by fever (n = 2); thrombocytopenic purpura (n = 2; one after co-administration with the MMRV vaccine); giant urticaria (n = 1). In the case of an eight-year-old child, the cause of hospitalization was itchiness at the injection site.

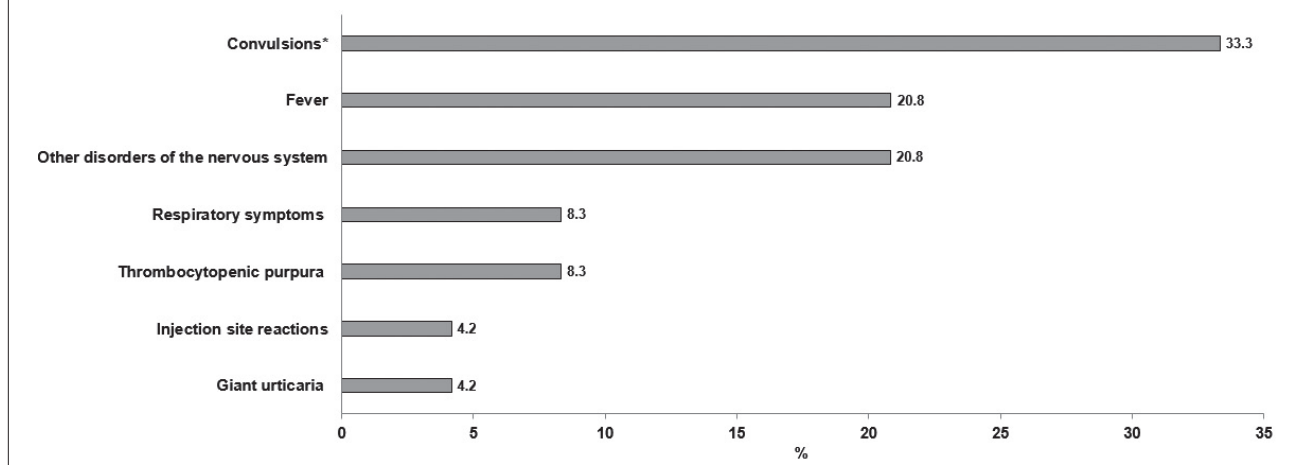
In 2009, one suspected AE was classified as "very severe, possibly with persistent consequences": it was the case of a one-year-old infant, for whom a pervasive developmental disorder with disturbance of speech was reported about four months after the administration of the MCC vaccine. According to the recommendations of the regional vaccination plan, the child was vaccinated with MMRV and MCC vaccines in March and with the 7-valent pneumococcal conjugate vaccine in April and in June. Any causal correlation with the MCC vaccine or with the other vaccines administered simultaneously or afterwards was refuted by the paediatrician, due to the lack of biological plausibility, and an autism spectrum disorder was hypothesized instead. The physician, however, was still not completely certain about the diagnosis as of July 2014.

Tab. I. Suspected AEs following immunization with MCC vaccine by age groups and year, Tuscany, 2005-2012.

Age groups	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	Suspected AEs 2005-2012 N (%)
< 1	2 (20)	5 (45.5)	4 (33.3)	4 (19.0)	0 (0)	0 (0)	1 (6.7)	1 (3.6)	17 (15.5)
1-2	3 (30)	2 (18.2)	6 (50.0)	11 (52.4)	5 (83.3)	2 (28.6)	12 (80)	23 (82.1)	64 (58.2)
2-7	4 (40)	3 (27.3)	2 (16.7)	1 (4.8)	0 (0)	2 (28.6)	1 (6.7)	2 (7.1)	15 (13.6)
7-14	1 (10)	1 (9.1)	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	1 (3.6)	4 (3.6)
> 14	0 (0)	0 (0)	0 (0)	4 (19.0)	1 (16.7)	3 (42.9)	1 (6.7)	1 (3.6)	10 (9.1)
TOTAL N (%) *	10 (9.1)	11 (10.0)	12 (10.9)	21 (19.1)	6 (5.4)	7 (6.4)	15 (13.6)	28 (25.5)	110 (100)

* % on the total suspected AEs reported between 2005 and 2012.

Fig. 4. Causes of hospitalization following MCC vaccine in Tuscany (2005-2012). * Five cases of convulsions out of eight were febrile seizures.



Most suspected AEs (89/110; 80.9%) occurred the same day of co-administration with other vaccines. Three vaccines, MCC included, were co-administered in 7.3% of AEs and a fourth vaccine was administered in one case (0.9%). The most common associations were those with the MMRV or the MMR vaccines (42.7%) and those with the hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio/Haemophilus influenzae b (DTPa-HBV-IPV/Hib) vaccine (33.7%) (Fig. 5). The majority of suspected AEs following co-administration with another vaccine (57%) occurred between 2009 and 2012, i.e. after the switch, in 2008, to a single dose at 13 months, age in which, according to the regional schedule, children are also immunized against MMR or MMRV. All ten cases of febrile seizures occurred after co-administration with other vaccines: five after MMR vaccine, two after MMRV vaccine, two after the DTPa-HBV-IPV/Hib vaccine, and one after the varicella virus vaccine. In Figure 6, the suspected AEs reported following co-administration of MCC with MMR or MMRV vaccines and the vaccination coverage at 24 months for measles and/or varicella containing vaccines are shown.

For seven severe cases that required hospitalization, data concerning the outcomes are missing. The causes of hospitalization for these cases were: febrile seizures ($n = 3$); unspecified convulsions ($n = 1$); hypotonia ($n = 1$); idiopathic thrombocytopenic purpura ($n = 1$); and, finally, hyperpyrexia ($n = 1$). All other cases were followed by improvement or complete resolution.

Discussion

The development of the meningococcal serogroup C conjugated vaccine was prompted by the increasing number of serogroup C infections in the 1990s, especially in children under two years: these were cases that could not be prevented on account of the poor immunogenicity granted for this age group by the already available polysaccharide vaccine. The safety and the immunogenicity

of MCC vaccine had been clearly evaluated in several pre-licensure trials [12-14]. The first country to implement a national MCC immunization programme, in November 1999, was the UK, where, in less than one year and a half, each individual aged under 18 years was immunised. The Committee on Safety of Medicines Expert Working Group assessed the MCC vaccine safety profile during this immunisation campaign and concluded for its extremely favourable risks/benefits balance [15]. Post-licensure surveillance of vaccine safety is essential in order to identify uncommon events that may be difficult to assess during pre-licensure studies, when, usually, the small sample size and the relatively short period of observation only allow to describe the most common and expected AEs. Furthermore, the effects on susceptible individuals that might eventually become the target of vaccination strategies, such as subjects with medical conditions, are not commonly evaluated in pre-licensure studies [16]. Research in vaccine safety can help to maintain public confidence in immunizations and to prevent the decrease of vaccination coverage, the return of previously under control infectious diseases, as well as avoidable deaths [17]. As a matter of fact, at the present time, vaccinations are at risk to become victims of their own success, especially in Western Europe, where some illnesses against which vaccines offer protection (e.g. haemophilus influenzae infections or diphtheria) have become so sporadic that even health professionals sometimes fail to appreciate the potential of one of the most successful tools for protecting the public's health, and anti-vaccine movements have gained popularity in recent decades. When, very rarely, true severe adverse reactions to immunizations do arise, they are generally short-lived and can be treated under the circumstances in which vaccines are nowadays administered. However, although vaccines are recognized as the most effective and safest medical and public health interventions [18], second only to the development of safe water resources [19], yet, very rarely, they may cause severe AEs. It is therefore important to timely identify such events, so that regulatory actions can be promptly taken in order

Fig. 5. Suspected adverse events following immunization with MCC vaccine in co-administration with other vaccines, Tuscany, 2005-2012.

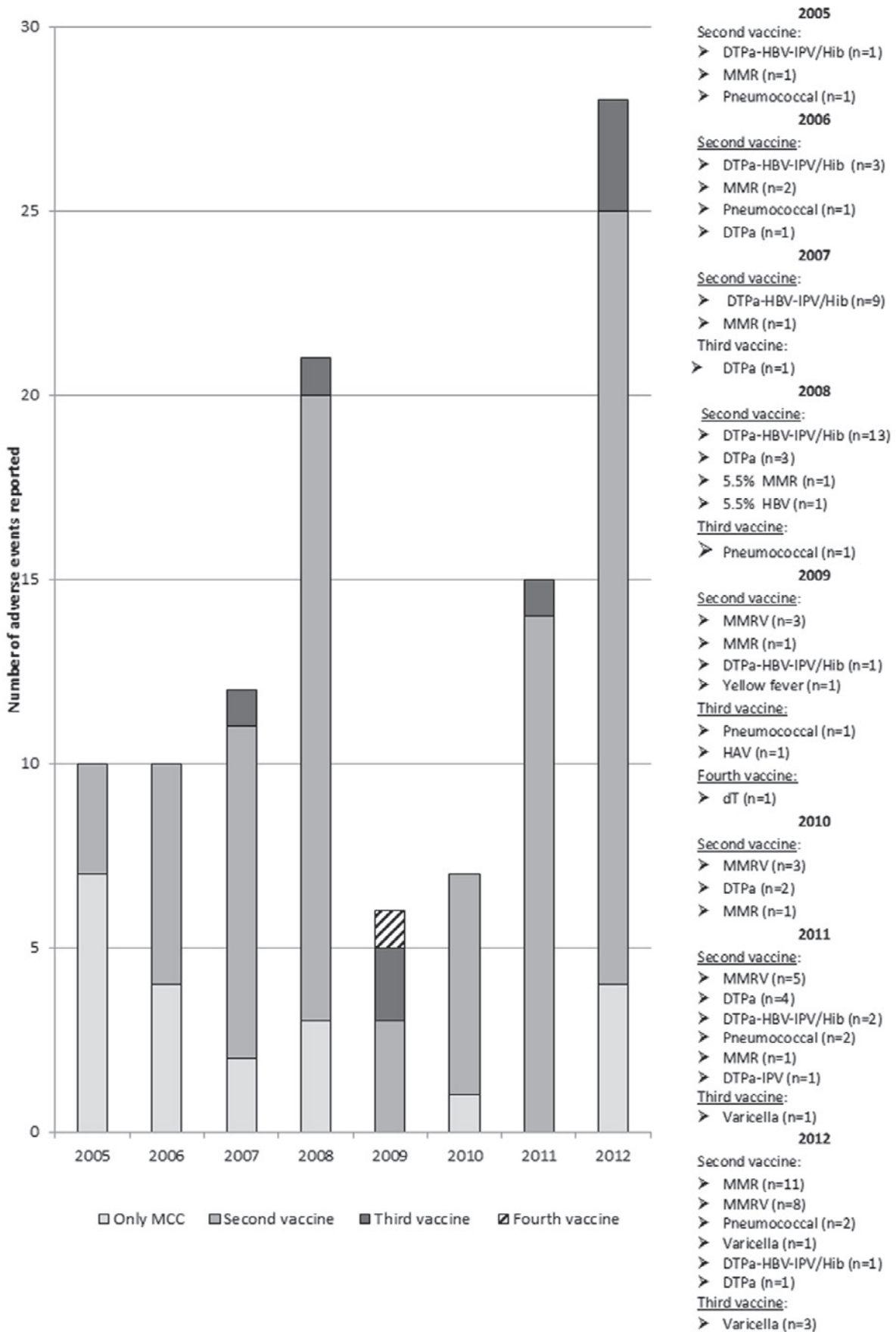
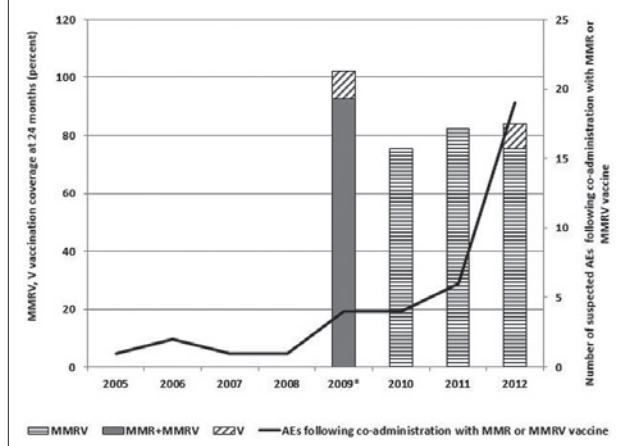


Fig. 6. Suspected adverse events following MCC vaccination co-administered with MMR or MMRV vaccine, and MMRV, MMR, V vaccination coverage at 24 months of age, Tuscany, 2009-2012. * For 2009, the vaccine coverage at 24 months is beyond 100%, because the information obtained by the regional authority regarded the combined MMR/MMRV vaccine coverage (separate data were not available) and about the monovalent varicella (V) vaccine coverage: these two values partly overlap, as MMR and V vaccines could be administered simultaneously in the same day.



to ensure that vaccines continue to have the desirable safety and quality profiles.

The aim of the present study was to evaluate the safety and tolerability of MCC vaccine in Tuscany since its introduction into the regional immunization programme, through an analysis of the suspected AEs reported between 2005 and 2012. Due to privacy regulations, data were obtained anonymized, but we could assess the reporting rate per doses administered. Our findings confirmed the high level of safety and tolerability of the vaccine in Tuscany: AEs proved to be rare, the average annual reporting rate being 2.8/10,000 doses. The increase of the reporting rates after 2009 reflects the transition from a three-dose to a single-dose schedule and the subsequent decreased denominators. The events notified were not severe in nearly four-fifths of the cases. All suspected AEs for whom the information on the outcome was available proved to be temporary and self-resolving. For the one severe suspected AE with probable permanent disability, any causal relationship with the vaccines administered around the time of the onset of symptoms (pervasive developmental disorder with disturbance of speech) was conclusively ruled out by the paediatrician, due to the lack of biological plausibility. As for the most severe AEs registered, it is important to highlight that all febrile seizures registered occurred following co-administration with MMR, MMRV, DTPa-HBV-IPV/Hib or varicella vaccines. The risk of febrile seizures, generally occurring seven to 10 days after immunization, particularly increases with MMR or MMRV vaccines: up to 3.4 additional cases per 10,000 children [20, 21] and 5.8 additional cases per 10,000 doses [22], respectively, have been described in the literature. Results from our study indeed confirmed the post-vaccine “peak period” for febrile convulsions incidence.

One of the two cases of thrombocytopenic purpura that were registered can be put in causal correlation with the MMRV vaccine, since it occurred after co-administration with this vaccine, and while there is no evidence of an increased risk in children following immunization with MCC [23], idiopathic thrombocytopenic purpura is a recognized adverse event of measles-containing vaccines [24]: in the literature up to 1 case per 22,300 doses have been reported in association with these vaccines [25-30]. Also the case of ataxia in one-year-old infant, which resulted in complete resolution, could be related to MMRV vaccine: it occurred after co-administration with this vaccine and transient ataxia has been, very rarely, reported after MMRV vaccinations in post-marketing surveillance studies [31, 32].

Conclusions

Since usually only the most severe AEs are reported, the suspected AEs that required inpatient hospitalization (21.8%) in all likelihood overestimated the true proportion of severe AEs. Most of these observed cases may be unrelated to the immunization, but have a temporal association with it. The increase in the reporting rate in the last two years of our period of observation (2011-2012) is indeed noteworthy: it followed the publication of a study, in 2010, pointing at an increased risk for febrile seizures in subjects immunized with the MMRV vaccine [33], which contributed to focus widespread attention on the problem of adverse events following immunizations. The findings of the present study, which confirmed the high level of safety of the MCC vaccine, can contribute to support public health professionals in addressing parents’ concerns regarding the safety profile of the vaccines recommended in our national and regional immunization programmes.

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References

- [1] Wilder-Smith A. *Meningococcal vaccine in travelers*. *Curr Opin Infect Dis* 2007;20:454-60.
- [2] European Centre for Disease Prevention and Control. *Surveillance of invasive bacterial diseases in Europe, 2011*. Stockholm 2013.
- [3] Jafri RZ, Ali A, Messonnier NE, et al. *Global epidemiology of invasive meningococcal disease*. *Popul Health Metr* 2013;11:17.
- [4] World Health Organization. *Meningococcal vaccines: WHO position paper, November 2011*. *Wkly Epidemiol Rec* 2011;47:521-40.
- [5] Bonanni P, Bechini A, Boccalini S, et al. *Epidemiologia e prevenzione delle malattie infettive*. In: *Igiene e Sanità Pubblica*. 2012. pp. 355-447.

- [6] Stephens DS. *Biology and pathogenesis of the evolutionarily successful, obligate human bacterium Neisseria meningitidis*. *Vaccine* 2009;27(Suppl 2):B71-7.
- [7] Trotter CL, Ramsay ME. *Vaccination against meningococcal disease in Europe: review and recommendations for the use of conjugate vaccines*. *FEMS Microbiol Rev* 2007;31:101-7.
- [8] Giunta Regionale Regione Toscana. DGR n. 379 del 7/03/2005. *Direttive in materia di vaccinazioni e indirizzi per la stesura del nuovo calendario regionale delle vaccinazioni*. Modifiche alla delibera G.R. 24.11.2003 n°1249. 2005.
- [9] Giunta Regionale Regione Toscana. DGR n. 1020 del 27-12-2007. *Aggiornamento direttive regionali in materia di vaccinazioni*. Revoca delibere n. 1249 del 24/11/2003, n.379 del 7/3/2005 e n.1060 del 10/10/2000. Modifica delibera n. 1386 del 17/12/2001. 2008.
- [10] Regione Toscana DGR n. 1020 del 27/12/2007. *Aggiornamento direttive regionali in materia di vaccinazioni*. Revoca delibere n. 1249 del 24/11/2003, n.379 del 7/3/2005 e n.1060 del 10/10/2000. Modifica delibera n. 1386 del 17/12/2001. BURT n. 2 del; 9.01.200.
- [11] Ministero della Salute. *Decreto 12 Dicembre 2003, Nuovo modello di segnalazione di reazione avversa a farmaci e vaccini*. 2003.
- [12] Miller E, Salisbury D, Ramsay M. *Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story*. *Vaccine* 2001;20(Suppl 1):S58-67.
- [13] Richmond P, Borrow R, Goldblatt D, et al. *Ability of 3 different meningococcal C conjugate vaccines to induce immunologic memory after a single dose in UK toddlers*. *J Infect Dis* 2001;183:160-3.
- [14] MacLennan JM, Shackley F, Heath PT, et al. *Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants: a randomized controlled trial*. *JAMA* 2000;283:2795-801.
- [15] Medicines Control Agency. *Report of the Committee on Safety of Medicines Expert Working Group on Meningococcal Group C Conjugate Vaccines*. 2002.
- [16] Australian Government. Department of Health. *Therapeutic Goods Administration. Reporting medicine and vaccine adverse events*.
- [17] Lakshman R, Jones I, Walker D, et al. *Safety of a new conjugate meningococcal C vaccine in infants*. *Arch Dis Child* 2001;85:391-7.
- [18] Andre FE, Booy R, Bock HL, et al. *Vaccination greatly reduces disease, disability, death and inequity worldwide*. *Bull World Health Organ* 2008;86:140-6.
- [19] Plotkin S, Plotkin S. *A short history of vaccination*. In: Plotkin S, Orenstein W, Offit P, editors. *Vaccines*. Philadelphia: Elsevier-Saunders 2013, pp. 1-13.
- [20] Barlow WE, Davis RL, Glasser JW, et al. *The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine*. *N Engl J Med* 2001;345:656-61.
- [21] Farrington P, Pugh S, Colville A, et al. *A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines*. *Lancet* 1995;345:567-9.
- [22] MacDonald SE, Dover DC, Simmonds KA, et al. *Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study*. *CMAJ* 2014;186:824-9.
- [23] Andrews N, Stowe J, Miller E, et al. *Post-licensure safety of the meningococcal group C conjugate vaccine*. *Hum Vaccin* 2007;3:59-63.
- [24] Maglione MA, Das L, Raaen L, et al. *Safety of vaccines used for routine immunization of U.S. children: a systematic review*. *Pediatrics* 2014;134:325-37.
- [25] France E, Glanz J, Xu S, et al. *Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children*. *Pediatrics* 2008;121:e687-92.
- [26] Andrews N, Stowe J, Miller E, et al. *A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark*. *Vaccine* 2012;30:3042-6.
- [27] Rajantie J, Zeller B, Treutiger I, et al. *Vaccination associated thrombocytopenic purpura in children*. *Vaccine* 2007;25:1838-40.
- [28] Black C, Kaye JA, Jick H. *MMR vaccine and idiopathic thrombocytopenic purpura*. *Br J Clin Pharmacol* 2003;55:107-11.
- [29] Miller E, Waight P, Farrington CP, et al. *Idiopathic thrombocytopenic purpura and MMR vaccine*. *Arch Dis Child* 2001;84:227-9.
- [30] Jonville-Béra AP, Autret E, Galy-Eyraud C, et al. *Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional pharmacovigilance centres and pasteur-mérieux sérums et vaccins*. *Pediatr Infect Dis J* 1996;15:44-8.
- [31] GlaxoSmithKline. *PRIORIX-TETRA® Combined measles, mumps, rubella and varicella vaccine, live, attenuated. Product monograph*. Mississauga, Ontario: 2014.
- [32] Knuf M, Zepp F, Meyer CU, et al. *Safety, immunogenicity and immediate pain of intramuscular versus subcutaneous administration of a measles-mumps-rubella-varicella vaccine to children aged 11-21 months*. *Eur J Pediatr* 2010;169:925-33.
- [33] Klein NP, Lewis E, Baxter R, et al. *Measles-containing vaccines and febrile seizures in children age 4 to 6 years*. *Pediatrics* 2012;129:809-14.

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