

UNIVERSAL VARICELLA VACCINATION IN THE SICILIAN PAEDIATRIC POPULATION: RAPID UPTAKE OF THE VACCINATION PROGRAMME AND MORBIDITY TRENDS OVER FIVE YEARS

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Following the licensure of the Oka/Merck varicella vaccine in Italy in January 2003, the Sicilian health authorities launched a universal vaccination programme in all nine Local Health Units. A two-cohort vaccination strategy was adopted to minimise the shift of the mean age of varicella occurrence to older age groups, with the goal of vaccinating with one dose at least 80% of children in their second year of life and 50% of susceptible adolescents in their 12th year of life. Two studies were implemented in parallel to closely monitor vaccination coverage as well as varicella incidence. Overall, the programme achieved its target, with 87.5% vaccine coverage for the birth cohort 2005 and 90.2% for adolescents born in 1995 and 1996. Varicella surveillance data obtained from a total of 28,188 children (0-14 years-old) monitored by family paediatricians showed a decline in incidence rates from 95.7 (95% confidence interval (CI): 72.2-126.8) for 1,000 person-years (PY) in 2004 to 9.0 (95% CI: 6.4-12.6) for 1,000 PY in 2007. In Europe, the only similar experience is the routine childhood varicella vaccination programme in Germany that started in 2004 with a single dose at the age of 11-14 months. The two-cohort universal vaccination programme implemented in Sicily, as well as the network for the surveillance study, can offer a model to other European countries that are considering introducing universal childhood varicella vaccination.

Introduction

Now that many vaccine preventable paediatric diseases have been eliminated or controlled, varicella remains one of the most common childhood diseases. Although varicella-zoster virus (VZV) infections are generally mild and self-limiting in the vast majority of children, complications such as secondary bacterial infections, pneumonia, encephalitis, cerebellar ataxia, transverse myelitis and death, can occur [1].

The incidence of varicella in Italy is believed to approximate the birth cohort, with over 5,300 annual estimated cases per 100,000 children under the age of 15 years [2], 3.5-5% of whom develop

complications such as upper respiratory tract and cutaneous infections [3]. The figures presented in this report illustrate the significant burden of the disease in Sicily both for parents and for health services [4] and support the launch of a universal vaccination programme. Following the licensure of the Oka/Merck varicella vaccine (Varivax®) in Italy in 2001 for use in healthy children, the Sicilian health authorities launched a two-cohort universal vaccination programme. The impact of varicella vaccination was monitored in two studies conducted in parallel, one focusing on vaccination coverage and the other on varicella incidence.

Methods

Coverage study

Sicily (5,015,297 inhabitants in the national census of 1 January 2006) is one of twenty Regions in Italy. Public health policies are established autonomously in the Regions, based on recommendations from the Italian National Health Service. Compulsory and recommended vaccinations are actively offered free of charge to all Sicilian children against diphtheria, tetanus, poliomyelitis, hepatitis B, pertussis, *Haemophilus influenzae* type b, measles, mumps, and rubella. In Italy, childhood vaccinations are mostly performed in Vaccination Centres (VCs). Sicily counts 386 VCs that are part of Health Districts (HDs), themselves part of Local Health Units (LHUs).

Vaccination programme

Universal varicella vaccination was added to the standard childhood vaccination programme in January 2003 and was actively offered free of charge to all children in their second year of life (at about 15 months of age) and to all susceptible adolescents in their 12th year of age, at the time of the measles, mumps and rubella (MMR) vaccination in order to improve parents compliance. Although two vaccines were available, only Varivax® was licensed for universal vaccination at the time and thus selected for the programme. Once the parents consented to the vaccination, varicella vaccine was administered on the same occasion as MMR

vaccine, injected in the counter lateral arm. Following existing recommendations at the start of the programme, one dose of varicella vaccine was administered to every participating child and adolescent.

Public health physicians carried out most of the vaccinations, although paediatricians were the key contacts for counselling and in some cases vaccinated the children themselves. In addition, ad hoc information campaigns in secondary school were performed and susceptible adolescents could also be vaccinated at their own school surgery. Varicella vaccine was also offered free of charge to the siblings of all vaccinated children and to household contacts of varicella cases.

The vaccination target was set at $\geq 80\%$ coverage for children in their second year of life and $\geq 50\%$ for susceptible adolescents. Vaccination coverage was analysed overall, by age group and by birth cohort.

Collection and recording of data

Demographic and vaccination data were collected by VCs and reported monthly to HDs. Data was entered in a protected internet database with varying levels of access, connecting HDs, LHUs and the Regional Public Health Office (RPHO), each of these entities having a different level of access for data entry, data monitoring and analysis. For the few vaccinations performed by family paediatricians (FPs) or other structures, the vaccination data was communicated to the public health system for entry into the database. Quality control of the database was monitored by an external agency through quarterly visits and audits.

Target population for data analysis

The target population for data analyses for the period 2003-2007 included:

all children aged 12-23 months (100% of the resident population in this age group),

all susceptible adolescents aged 11-12 years (18% of the resident population in this age group).

Susceptibility to varicella was based on self-reported negative history for the disease. Although there are limitations associated with parental reporting (e.g. under- or overestimation of disease occurrence), these limitations are usually accepted in observational epidemiological surveillance studies.

The denominator for coverage rate was calculated using resident population numbers according to the National Institute of Statistics (ISTAT, data as of 1 January 2006) and prevalence of VZV, extrapolated using known Italian VZV seroprevalence data by age range [5].

Surveillance study

Varicella surveillance was performed through a sentinel network of randomly selected FPs in order to describe age-specific varicella incidence rates among children 0-14 years after the introduction of the universal vaccination programme, as well as age-specific related complications. FPs offer a unique surveillance opportunity since every child in Italy is registered with an FP from birth until the age of 14 years. Thus, each FP has a precise paediatric population under their care (between 800 and 1,000 children) and their public health duty includes routine control visits that are perfect opportunities for offering vaccination, for disease control and surveillance. Of the 844 FPs operating in Sicily, 30

were randomly selected to participate in the study. The number of FPs from each LHU was balanced by resident population and geographical location (urban versus rural) with at least one FP from each of the nine LHUs. Computations of incident cases and person-year (PY) computation were recorded prospectively from March 2005 and retrospectively (based on physicians records) for the period from January 2003 to February 2005. This could result in some degree of underreporting for the retrospective period, although it is noteworthy that most of the physicians participating in the study had already been involved in active infectious diseases surveillance before the start of the study.

All children registered with the 30 sentinel FPs were proposed participation into the study. Informed parental consent was

TABLE

Number of children vaccinated against varicella, by birth cohort, Sicily, 2003-2007

Birth cohort	1995-1996	1997-2004	2005
Vaccinated children	8,839	152,308	35,123
Resident children*	108,958	410,652	50,202
Susceptible children**	19,613	nd	50,202

nd: not done.

*National Institute of Statistics data (ISTAT) data as of 1 January 2006.

**Estimated based on published seroprevalence data [5].

FIGURE 1

Coverage rates for varicella vaccination of children, by birth cohort (2001-2005), Sicily

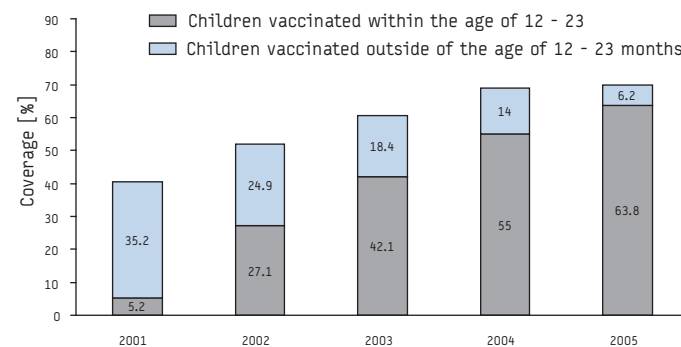
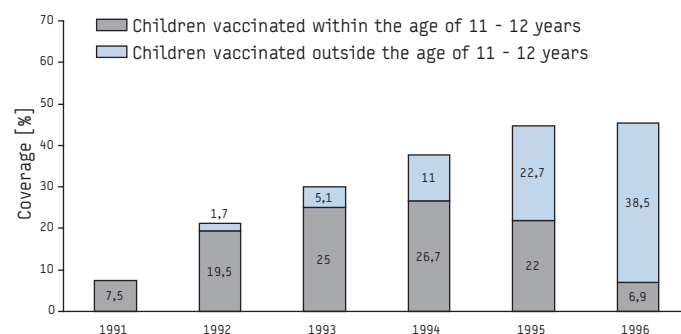


FIGURE 2

Coverage rates for varicella vaccination of adolescents, by birth cohort (1991-1996), Sicily



requested. The at-risk population (denominator) included all children susceptible to varicella who were followed by participating FPs. The PY contribution of each child followed up was calculated using information from the FPs' records. This was done for the active surveillance period of the study (2005 to 2007), as well as for the years 2003 and 2004 using information in the FPs' records

FIGURE 3
Overall coverage rates of varicella vaccination in children 12-23 months, by Local Health Unit, Sicily, 2003-2007

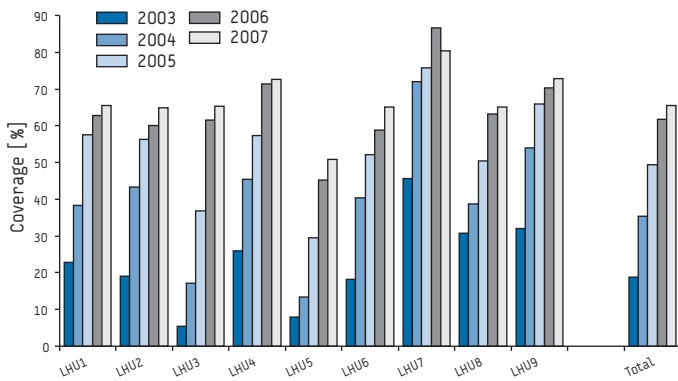


FIGURE 4
Annual varicella incidence rates per age group, sentinel FP network, Sicily, 2003-2007

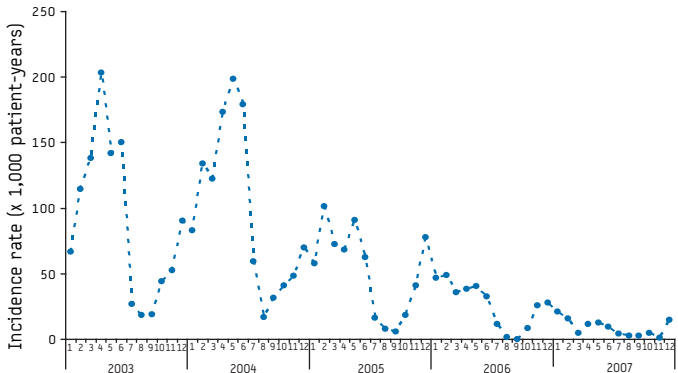
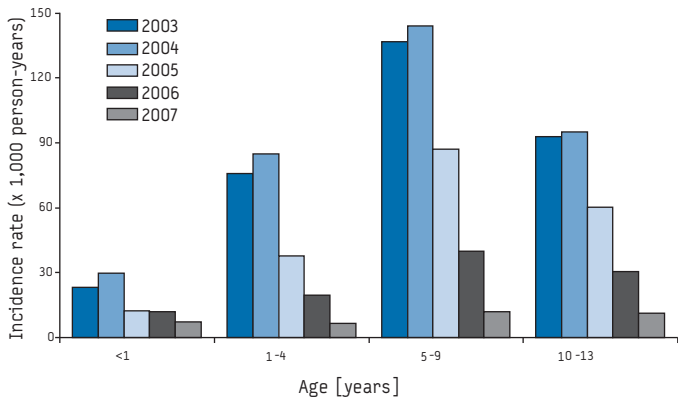


FIGURE 5
Annual varicella incidence rates per age group, sentinel FP network, Sicily, 2003-2007



to obtain 'historical' rates for the period between the introduction of the vaccine in Sicily (2003) and the implementation of the study (2005).

Results

A total of 225,642 children vaccinated during the study period (1 January 2003 to 31 December 2007) were taken into consideration for the analysis, as presented in the Table.

The coverage rate for children born in 2005 was 70.0% (Figure 1), while that of susceptible adolescents born in 1995 and 1996 was 45.1% (Figure 2).

The overall coverage rate for 2007 was 65.5% in children 12-23 months (range 50.9-80.5%), as shown in Figure 3, and 12.1% in adolescents 11-12 years of age (range 5.1-40.9%).

Varicella surveillance data were obtained from a total of 28,188 children at the age of 0-14 years (the 86.7% of the registered children for whom informed parental consent was obtained). Of those, 21,568 susceptible children were taken into account for the calculation of varicella incidence. The varicella incidence rates per month in 0-14 year-old children are presented in Figure 4.

Annual incidence rates declined from 95.7 (95% confidence interval (CI): 72.2-126.8) for 1,000 PY in 2004 to 9.0 (95% CI: 6.4-12.6) for 1,000 PY in 2007. The incidence of varicella declined in all age groups (Figure 5).

A total of 22 cases of breakthrough varicella (occurring more than six weeks after vaccination) were reported. Ten cases occurred in 1-4 year-old children, nine cases in the age group of 5-9 year-olds and three cases in 10-13 year-old children. No case required hospitalisation. In addition, seven herpes zoster cases were reported among vaccinated children: three in 1-4 year-old children, three cases in 5-9 year-olds and one case in the age group of 10-13 year-olds.

Discussion

Varicella vaccination is not yet routine in Europe despite the availability of VZV vaccines in at least 14 European countries [6]. In general, selected high-risk groups, such as healthcare workers, susceptible adults, and immunocompromised patients are targeted for vaccination. Although the epidemiology of varicella in Europe is similar to that observed in the prevaccine era in the United States, Germany remains the only country that has incorporated the VZV vaccine nationwide in the routine immunisation schedule as a single dose at the age of 11-14 months, starting from July 2004 [7].

Sicily was the first Italian region to introduce universal varicella vaccination in its childhood vaccination programme in 2003 and to date, only three other Italian regions have a similar programme for varicella. The model adopted by the Sicilian health authorities took into account the peculiarities of the age-specific varicella seroprevalence in Italy. Indeed, the reproduction numbers and herd immunity thresholds can have a profound impact on susceptibility patterns and disease transmission and thus have important implications for the design and implementation of varicella vaccination programmes in a given country [6]. Standardised serological surveillance established for eight-vaccine preventable diseases [8,9] showed striking variations in the rate of VZV transmission in different European countries. While seroprevalence

for varicella at the age of five years was high in some countries (97% in the Netherlands, 86% in Israel, 81% in Belgium), but very low in Italy, with only 38% of children seropositive for VZV antibodies [5]. Within Italy, however, VZV is circulating more intensely in the southern part of the country and affects people at an earlier age [4]. No clear explanations can be given for the relatively low seroprevalence of varicella antibodies across all age groups in the Italian population. Nevertheless, these data provide a good rationale for varicella vaccination in early childhood and adolescence in a population relatively less well protected by natural immunity compared to other European countries.

The programme Sicily was taken up rapidly, with increasing coverage rates in both cohorts over time. Although significant differences were initially observed between LHUs, the figures became more uniform over the years. The average coverage rates were 65.5% for children in their second year of life and 12.1% for adolescents at the age of 11-12 years. A steady uptake of the programme was observed between 2003 and 2007, and the programme's target was achieved, with 87.5% coverage for the birth cohort 2005 and 90.2% for adolescents born in 1995-1996. The introduction of the combined MMR-VZV vaccine is expected to modify the acceptance of varicella vaccination and could further increase coverage rates [10] in view of the MMR vaccination rates of up to 85% currently attained in all Sicilian LHUs.

Vaccination of young children before the peak age of varicella prevalence can have a significant impact on the incidence of the disease, as already demonstrated in the United States (US), where universal childhood vaccination was introduced in 1995. In Sicily, the main targeted cohort (children at the age of 15 months) was selected based on the fact that infection in Sicily occurs at an earlier age compared to the rest of the country. After the launch of the varicella vaccination programme, a steady decrease in varicella incidence was observed, reaching 9.0 for 1,000 PY during the last year of observation (2007), a number well below the national estimate of 70 for 1,000 PY. So far, this strategy has proven very effective and breakthrough disease has been rare (only 22 cases reported in the surveyed population). Low levels of circulating VZV in early childhood warrant better protection of susceptible adults and adolescents and can limit the potential shift of the disease towards older age that is generally put forward as a risk of universal varicella vaccination in childhood. The possible need for booster doses in adolescents and adults cannot be excluded, although the two-dose vaccination regimen currently proposed for all ages seems to lower the risk of breakthrough varicella in vaccinated children considerably. Good coverage rates in susceptible adolescents will be an additional barrier against the shift of the disease to older age. Clearly, the dynamics of disease epidemiology after the start of the vaccination programme will need further assessment and one key element will be the observed incidence of breakthrough disease.

Another potential risk that has limited the uptake of varicella vaccination in Europe is the possible increase in the incidence of herpes zoster. Our data show a very low number of herpes zoster cases in the surveyed population. Unfortunately, virological data were not available for these latter cases, although virological typing (differentiating between the Oka/Merck vaccine strain and the wildtype virus) had been made available to participating physicians for a number of complications or breakthrough cases. Longer follow-up is required, as well as more consistent data on the background rates of herpes zoster in the general paediatric population.

Overall, long-term surveillance is needed to evaluate the effectiveness of the programme over time, and the progressive introduction of the second dose of varicella vaccine in early childhood, as already recommended in the US [11], will have to be closely monitored. Nevertheless, very good results have already been obtained in the five years of universal varicella vaccination with one dose, as shown by the very low incidence of the disease in all age groups in 2007, including those not targeted by the vaccination programme. Close collaboration between public health services and family paediatricians also proved effective.

The two-cohort universal vaccination programme implemented in Sicily, as well as the network for the surveillance study, can offer a model to other European countries that are considering introducing universal childhood varicella vaccination.

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Conflict of interest statement:

LR Biasio is Medical and Development Director of Sanofi Pasteur MSD.

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