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Evaluation of a vaccination strategy by serosurveillance data: The case of varicella

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Serological studies have many important epidemiologic applications. They can be used to investigate acquisition of various infections in different populations, measure the induction of an immune response in the host, evaluate the persistence of antibody, identify appropriate target groups and the age for vaccination. Serological studies can also be used to determine the vaccine efficacy. Since 1995 a varicella vaccine is available and it has been recommended in several countries (e.g. USA, Australia, Canada, Costa Rica, Ecuador, etc.). Nevertheless few varicella seroprevalence studies in countries that adopted an URV are available. It is related to the relatively recent introduction of the vaccination and to the lack of structured and collaborative surveillance systems based on serosurvey at national or regional level. Varicella seroprevalence data collected before the introduction of vaccination strategies allowed to establish the age of vaccination (e.g., indicated the opportunity to offer the vaccine to Italian susceptible adolescents). In the post-vaccination era, seroprevalence data demonstrated vaccine as immunogenic and excluded an increase of the age of infection linked to the vaccination strategy. New seroprevalence studies should be performed to answer to open questions, such as the long-term immunity and the change of the herpes zoster epidemiological pattern related to the vaccine.

Keywords: age of infection, epidemiological pattern, immunogenicity of vaccines, mathematical model, seroprevalence data

Abbreviations: URV; Universal Routine Vaccination.

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Introduction

Data on the proportion of the population that is immune or has been infected with a specific microorganism have many important epidemiologic applications. These include the identification of susceptible groups in the population, the evaluation of health programs (e.g., vaccine uptake), and the use of these data in mathematical modeling to predict outbreaks.[1-3]

Cross-sectional antibody prevalence studies were originally used as research tools to investigate acquisition of various infections in different populations. For example, in the early 1950s many surveys of antibody to poliomyelitis were conducted in different countries. These contributed greatly to the understanding the epidemiology of the infection.[4,5]

Seroconversion is useful to measure the induction of an immune response in the host and, in the absence of disease, indicates the persistence of antibody and immunity. Before beginning an immunization program, these studies can help to identify appropriate target groups and age for vaccination.[6] This is actually crucial, because a lot of countries recently assumed the Health Technology Assessment methodology to evaluate the introduction of new vaccines.[7]

Serological studies can also be used to determine a vaccine's efficacy.[8] Studies that monitor changes in the prevalence of antibody following the introduction of vaccination programs demonstrate their epidemiological impact.[9,10] The need to continue serological surveillance following the introduction of vaccination has been highlighted by mathematical models of disease transmission, which have demonstrated that gradual accumulation of susceptible subjects could lead to resurgence of disease after many years of low incidence.[11,12]

In countries where a continuous inflow of refugees from developing countries

(e.g. Central Africa) is noted, serological studies can show lack of immunization or inadequate vaccination coverage level.[11]

Varicella Vaccination Strategies: a Global Overview

In 1995, a varicella vaccine was licensed in the United States for use among healthy children aged >12 months, adolescents, and adults. At that time, the Advisory Committee on Immunization Practices (ACIP) recommended routine varicella vaccination of children aged 12–18 months, catch-up vaccination of susceptible children aged 19 months-12 years, and vaccination of susceptible persons who have close contact with persons at high risk for serious complications (e.g., health-care workers and family contacts of immunocompromised persons). The schedule included one dose of vaccine for children aged 12 months-12 years and 2 doses, 4–8 weeks apart, for persons aged ≥13 years.[14]

In 1998, WHO advocated routine childhood immunization against varicella in countries where the disease is a relatively important public health and socio-economic problem, where the vaccine is affordable and where sustained high (85–90%) vaccination coverage can be achieved. Additionally, WHO advocated recommendation of the vaccine in any country to adolescents and adults without a history of varicella, in particular to those at increased risk of contracting or spreading the infection.[15] In 1999, ACIP updated the recommendations to include child care and school entry requirements, use of the vaccine after exposure and for outbreak control, use of the vaccine for certain children infected with human immunodeficiency virus (HIV), and vaccination of adolescents and adults at high risk for exposure or transmission.[16]

In 2007, ACIP adopted new recommendations regarding the use of varicella vaccines that include the implementation of a routine 2-dose varicella vaccination program for children, with the first dose administered at age 12–15 months and the second dose at age 4–6 years; a second dose catch-up varicella vaccination for children, adolescents, and adults who previously had received 1 dose; routine vaccination of all healthy persons aged >13 years without evidence of immunity; prenatal assessment and postpartum vaccination; expanding the use of the varicella vaccine for HIV-infected children with age-specific CD4+T lymphocyte percentages of 15%–24% and adolescents and adults with CD4+T lymphocyte counts >200 cells/μL; and establishing middle school, high school, and college entry vaccination requirements.[17] The recommended age of 4–6 years for the second dose of varicella vaccine was supported by the epidemiology of varicella during the mature one-dose program, with low incidence and few outbreaks among preschool aged children and higher incidence and more outbreaks among school-aged children.

After US, several countries outside Europe (Australia, Canada, Costa Rica, Ecuador, Israel, New Zealand, Oman, Panama, Qatar, Saudi-Arabia, South Korea, Taiwan, the United Arab Emirates, Uruguay) have introduced routine varicella vaccination during the last 2 decades.[18,19]

Currently varicella vaccine recommendations in the EU/EEA are heterogeneous: in 2012 only 5 countries (Germany, Latvia, Greece, Cyprus, Luxemburg) universally recommend varicella vaccination for children at national level and 2 countries (Spain and Italy) at regional level. Seventeen countries (including the 2 with regional universal recommendation) recommended nationwide vaccination for susceptible teenagers and/or risk groups only. In seven countries there is no specific recommendation for varicella vaccination (Bulgaria, Czech Republic, Hungary, Portugal, Romania, Slovakia, Sweden).[20]

Evidence from countries that have implemented universal varicella vaccination of infants demonstrates a significant and sustained decrease in the burden of varicella. In the US this has been demonstrated for more than 15 years now. However to influence the decision regarding the implementation of the vaccine a better post-vaccination surveillance and epidemiological research is needed to fill the knowledge gaps, that include duration of vaccine-induced immunity, need for further doses, impact of vaccination coverage, risk of increasing complications due to varicella following shifts in the mean age of infection following vaccine introduction, risk of complication in breakthrough varicella adult cases occurring several decades after vaccination and potential increases in Herpes Zoster incidence following varicella vaccination.[21]

To reach the post-marketing surveillance objective, serosurveillance studies are mandatory.

Varicella Seroprevalence Studies in the Vaccination Era

United States first issued recommendations for universal varicella vaccination; during the 10 years following the introduction of vaccination, thanks to the progressive increase in vaccination coverage from 27% to 88%, the population sero-epidemiological pattern changed. The data collected by NHANES (an ad hoc surveillance system) for 1999–2004, compared with the same survey performed through 1988–1994, showed no changes of varicella seroprevalence between the 2 periods in children of 6–11 years (86.0% in NHANES III vs. 88.9% in NHANES 1999-2004, p = 0:10), while a significant seroprevalence increase was reported for 12-to-19-year-old (93.2% vs. 97.2% in NHANES III in NHANES 1999-2004, $P < 0.0001$) and for 20-to-29-year-old (95.5% vs. 97.3% in NHANES III in NHANES 1999-2004, $P < 0.05$); a decrease in 30-39-year-old (98.9% in NHANES III vs. 97.3% in NHANES 1999-2004, $P < 0.001$). No changes were observed for 40-49-year-olds subjects.[22]

In Australia, before the introduction of vaccination, approximately 240,000 varicella cases occurred each year with a seroprevalence of 83% in children aged 10 to 14 years.[23] After the introduction of the vaccination recommendation in 2003 for all susceptible subjects (among children, adolescents and adults) and in 2005 for people at risk, no changes in the sero-epidemiological pattern of the disease were described even if the achieved vaccination coverage was low.[24]

As regards Europe, in 2001 the European Network of sero-epidemiology (ESEN2) was established to standardize the procedures for serological surveillance of 8 vaccine-preventable diseases in 22 European countries. A seroprevalence survey of varicella performed in 11 European countries in 2001 showed that over 50% of young children had antibodies to VZV by 5 years of age in all countries except in Italy, where only 38% of children were varicella sero-positive. Over 90% of adolescents aged between 10 and 15 years were sero-positive for VZV in all countries, except in Italy where only 78% of 15 year olds had antibodies to VZV.[25]

The evidence of an high proportion of susceptibles sustained the decision of the Italian Ministry of Health to introduce the active offer of varicella vaccine to adolescents with a negative anamnesis of varicella in 2005.[26]

A study by Ueno-Yamamoto et al. compared the seroprevalence of varicella in Japan between the pre- (1977-81) and the post-vaccine (2001–2005) eras, to assess the influence of optional immunization and to estimate the current susceptible population. The overall prevalence of antibodies to VZV was 66.5% in 1977-81 and 74.2% in 2001–2005; the difference in prevalence between the 2 periods was statistically significant for all age groups except the <1 year olds. Authors concluded that increasing seroprevalence of varicella could have occurred as a result of limited vaccination.[27]

Tafuri et al. evaluated the pattern of immunity/susceptibility for varicella in Apulian (Italy) adults by a seroprevalence survey carried out 6 years after the introduction of universal routine vaccination (URV), in order to assess if vaccination strategy had any impact on the susceptibility pattern in the older age group who is not involved in the vaccination strategy. URV did not seem to have any impact on susceptibility among adults and in particular authors did not find any cluster of susceptible subjects among young adults. Furthermore in the vaccination era, the average age of infection doesn't seem to shift among adults and then an increase of cases of complicated varicella related to the URV could be excluded.[28]

Expert Commentary

Few varicella seroprevalence studies in countries that adopted an URV are available. This is related to the relatively recent introduction of the vaccination and to the lack of structured and collaborative surveillance systems based on serosurvey at national or regional level.

However the "varicella vaccine case study" seems to confirm the need of serosurveillance surveys in designing and monitoring vaccination programs.

Varicella seroprevalence data collected before the introduction of vaccination strategies allowed to establish the age of vaccination; e.g., studies sustained the priority of the varicella vaccination in Italian adolescents. Data demonstrated that the vaccine is immunogenic, because in nations with URV and high vaccination coverage, a large proportion of vaccine target population was found to be immune.

Data from countries that adopted URV excluded an increase of the age of infection linked to the vaccination strategy. There is still little evidence of the long-term vaccine efficacy, in particular for a 2 dose strategy[29]; therefore this topic has to be examined in depth in future large population studies.

Serosurveillance studies in countries that adopted universal mass vaccination could clarify the role of the varicella vaccination in modifying the zoster epidemiology. A mathematical model carried out by Brisson et al in 2010[30] showed that a 2 dose-varicella vaccine schedule may have the detrimental short-term effect of increasing zoster incidence; however, in the long-term, zoster incidence is predicted to decline more significantly under a 2-dose strategy as there will be a lower proportion of individuals with a history of VZV infection. In these model, percentage of persons who become temporarily protected after varicella vaccination are considered; as future seroprevalence studies could add new evidences on this parameter, the results of the Brisson model will be again adjusted and updated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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