**Reviews and Meta-Analysis**

**Twenty years of universal vaccination against hepatitis B in Italy: achievements and challenges**

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**Significance for public health**

This study is a historical overview on the global impact of vaccination against hepatitis B. Viral hepatitis B is a leading cause of acute and chronic liver disease, including cirrhosis and liver cancer. Hepatitis B is the most effective measure to control and prevent hepatitis B and its long-term sequelae. According to the WHO, 179 countries have currently implemented universal vaccination programmes worldwide, and Italy was one of the first countries to introduce a universal strategy of hepatitis B vaccination. On the whole, a significant reduction in newly acquired hepatitis B, carrier rate, and hepatitis B-related mortality has been observed in countries where vaccination has been implemented. In Italy, universal vaccination started in infants as well as adolescents in 1991 with an outstanding record of safety and efficacy. Data collected from Italy and elsewhere clearly show the success of this vaccination in terms of public health since its implementation has dramatically contributed to the saving of lives, prevention of suffering, and savings to the community at large.

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**Abstract**

Viral hepatitis B is a vaccine-preventable disease. Vaccination has proved to be safe and highly effective in reducing the incidence, the carrier rate and HBV-related mortality on a global scale. In Italy, universal vaccination against hepatitis B started in 1991 in infants as well as in adolescents, providing an outstanding record of safety and effectiveness. Within a few years, over 95% coverage was consistently reported. Today, some 17 million people are immune against hepatitis B and their immunity has been shown to be long-lasting. At present, no booster is required in healthy vaccinated people to sustain protection. Surveillance data from Italy have shown a clear overall decline in hepatitis B among successfully vaccinated individuals. Furthermore, a generation of children and young people (at present cohorts ranging from 0 to 32 years) is emerging with practically no markers of HBV infection. Italy's vaccination programme has resulted in substantial progress towards the prevention and control of hepatitis B. The vaccination programme must continue. Maintaining mandatory vaccination of infants and increasing HBV vaccination coverage in high-risk groups, including households of HBsAg carriers as well as immigrants, remains a priority for the future.

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**Introduction**

Viral hepatitis type B is still a major public health problem on a global scale. Infection with hepatitis B virus (HBV) can progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma (HCC), which ranks as the third cause of cancer deaths worldwide.

Vaccination is the most effective measure to control and prevent hepatitis B in terms of both cost-effectiveness and benefit-cost ratios. Safe and effective vaccines have been available since the early 1980s when the so-called plasma-derived vaccines were first introduced and then largely replaced by yeast-derived recombinant DNA vaccines in the mid-1980s.

Strategies of vaccination were initially targeted toward groups at increased behavioural (e.g., injecting drug users, sexually active homosexual men, people with multiple sexual partners), professional (e.g., health-care workers) risk of infection, to patients like haemophiliacs and those on dialysis maintenance, and to babies born to hepatitis B surface antigen (HBsAg) positive mothers. Failure of such policies of vaccination to reduce the impact of hepatitis B in the population at large led to the WHO recommendation that all countries introduce a policy of universal infant or adolescent (or both if economically feasible) hepatitis B vaccination integrated into their national immunisation programme. At present, 179 countries worldwide have so far implemented this recommendation or are planning to do. In the WHO European region, UK and Scandinavian countries still do not advocate universal vaccination and have opted (on economic grounds) for targeted vaccination focussed on well-defined risk groups.

Globally, several hundred million vaccinations have been administered worldwide so far, with an outstanding record of safety and efficacy. Vaccination against hepatitis B is well tolerated. Local side effects are generally mild and confined to symptoms at the site of injection, while systemic reactions are uncommon. A number of case reports from France in 1998 and thereafter raised concern that hepatitis B vaccination may lead to new cases or relapses of multiple sclerosis or other neurological disorders, but no clear causal link was established.

There is evidence to indicate that anti-HBs (hepatitis B surface antibodies) seroprotection (concentration ≥10 mIU/mL) rates are close to 100% in healthy children and over 95% in healthy adults, and that protective antibodies are long-lasting since they may persist for at least 15-20 years. Vaccinees who have lost antibody usually show a rapid anamnestic response when boosted. This means that the immunological memory outlasts antibody detection providing protection against clinical disease and the development of carrier state.

Thus, current evidence shows that there is no need for a booster in the general population. However, some long-term protection studies have recently shown an increasing number of people with no evidence of boostability (failure to respond to a booster); the reason for this finding and its significance should be further investigated.

Vaccination has been proved to reduce the incidence, carrier rates, and mortality related to hepatitis B. In Taiwan, where mass vaccination of newborns was first introduced in 1984, the HBsAg carrier rates among children dropped from 9.8% in the year prior immunisation to 0.6% in 2004. Furthermore, the annual average incidence of HCC declined significantly after the implementation of vaccination, demonstrating that hepatitis B vaccine can prevent a major human cancer. Likewise, in other hyperendemic countries such as the Gambia, Malaysia and Alaska, vaccination has clearly proven to be very effective.
The Italian vaccination programme and its impact

A vaccine against hepatitis B was first introduced in Italy in 1981 for the immunisation of haemodialysis patients and their staff. In 1983, a selective programme started using the vaccine in targeted campaigns among at-risk populations. The results encouraged a broader introduction of the vaccine and in 1988 a decree identified subjects at increased risk for hepatitis B to whom vaccination would be offered free of charge. Then, in 1991, a law was passed mandating the universal vaccination of infants and 12-year-old adolescents (restricted to the first 12 years of the implementation of the vaccination law) on a national scale. This programme also includes mandatory screening for HBsAg of pregnant women in order to identify babies in need of treatment with hepatitis B immune globulins (HBIG) and vaccine at birth, and recommendation for vaccination of high-risk groups free of charge. By the end of 2003, the first infant cohort vaccinated in 1991 reached the age (12 years) at which adolescent vaccination was programmed. Thus, in 2004, vaccination of 12-year-old adolescents was stopped and that of infants maintained.

Before the mandatory vaccination, a wealth of published epidemiological and clinical data on the national burden of the disease and those collected by the National Surveillance System for Acute Viral Hepatitis (SEIEVA) prepared the ground by studiously tracking the presence of hepatitis B in the country, emphasizing the need to urgently implement control and preventive measures.

Take-up of the vaccine was rapid and within a few years over 95% coverage was consistently reported. Today, some 17 million young people are immune against hepatitis B and their immunity has been shown to be long-lasting. Data collected prior- and post-vaccination by SEIEVA, clearly show that rates of hepatitis B virus infection fell dramatically. Although the decline in incidence of hepatitis B had started before the mandatory introduction of the vaccine as a result of improving socioeconomic conditions, demographic changes (smaller families), better hygiene and the changes in risky behaviour resulting from anti-AIDS campaigns, refinement in blood screening, and adoption of universal precautions in medical settings, the vaccine ensured that the efforts made towards elimination of the disease were worthwhile. Since the mandatory introduction of universal hepatitis B vaccination, the incidence of the disease has fallen from 5.1 per 100,000 inhabitants in 1991 to 0.9 cases per 100,000 in 2010. The decline was even more remarkable in 15-24-year-old individuals where incidence per 100,000 dropped from 17 to less than 0.5 in the same period of time. Furthermore, prevalence of markers of HBV infection (HBsAg and/or anti-HBc) declined dramatically after the introduction of the vaccination programme. In addition to the decline of hepatitis B, cases of hepatitis delta, which depends on the presence of the hepatitis B virus, are now rarely reported.

Cases of hepatitis B in vaccinated individuals have rarely been reported to SEIEVA and they were generally confined to those who did not complete the vaccination schedule properly. Infections caused by HBV-mutants, including the prototype glycine to arginine substitution G145R (first identified in Italy some 25 years ago in babies born to HBsAg carriers mothers and treated at birth with HBIG and vaccine), are very occasionally the causes of breakthrough infections in successfully vaccinated people. Despite the initial concern that these S-gene mutants could evade vaccine-induced immunity and infect vaccinated people, for the moment, they are not known to pose a public health threat.

The issue of hexavalent vaccines

In 2000, two hexavalent vaccines (Hexacav, Sanofi Pasteur MSD and Infanrix, Glaxo Smith Kline) were licensed in Europe for vaccinating children against diphtheria, pertussis, poliomyelitis, hepatitis B, and invasive infections caused by Haemophilus influenzae b. In 2005, Hexacav was suspended by the European Medicines Agency (EMA) due to concerns about long-term protection against hepatitis B. No action was taken over Infanrix since immunogenicity of its hepatitis B component did not raise equal concern. Until suspension, approximately 10 million doses of Hexacav had been distributed globally, of which almost 90% were used for immunisation of infants in Germany, Austria, and Italy. So the crucial question was whether infants vaccinated with Hexacav were protected or required a booster vaccination to sustain immunity. A large randomised, multicentre study carried out in Italy showed that five years after primary immunisation, Hexacav albeit less immunogenic than Infanrix, induced immune memory. Therefore, it can be inferred that if such vaccinated children are exposed to HBV, the immune memory rapidly induces a vigorous anamnestic response that prevents acute disease and the development of a chronic carrier state. In other words, even children who have lost protective antibody concentrations may still maintain T-cell memory that is able to trigger anti-HBs production by B cells following activation by revaccination or by natural exposure to HBV. Thus, the main message from this finding is that routine booster doses of vaccine do not seem necessary to sustain immunity in children primed with hexavalent vaccines. However, additional follow up is needed to see whether immunological memory persists during adolescence and adulthood, when risk of HBV exposure does significantly increase, or whether a booster may be needed later in life to maintain lifelong protection.

Conclusions and what the future holds

Vaccination has proved successful in Italy. Our findings compare well with data reported in previously highly endemic countries (e.g. Taiwan, the Gambia, Alaska) where the impact of vaccination in terms of reduction in incidence, in carrier rate, and in HBV-related mortality has been highly impressive.

Economic analyses show enormous benefits to the country at large as well as to individuals, and projections up to 2060 indicate that elimination of hepatitis B will have paid for itself and covered the costs of the campaigns many times over.

The Italian vaccination programme must continue until every generation has been immunized. Increasing the HBV vaccination coverage in high-risk-groups, including households of HBsAg carriers and immigrants coming from highly endemic countries, must be a priority. New antiviral treatments are being introduced, offering hope to the 600,000 or so people (mainly over the fifth decade of life) who remain carriers of HBV in the country (compared with 2 million 20 years ago) and those who still contract the disease. The success of Italy’s hepatitis B vaccination programme should pave the way for the introduction of new vaccines both nationally and in other countries, as well as reinvigorating existing campaigns against vaccine-preventable diseases.
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Key words: HBV, hepatitis B, vaccination, long-term immunity.

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Conflict of interest: the authors declare no conflicts of interest.

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