

Assessing Vaccines and Vaccination Programmes in the Field

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Abstract

Background: The impact of universal vaccination programmes in terms of reduction of disease burden is not questioned very much in the scientific community. Nevertheless assessing safety and efficacy of vaccination products in the field is an essential part of the success of any vaccination programme. In addition to that, there are several aspects of vaccination programmes that have to be evaluated and carefully assessed in order to improve the overall quality of vaccination programmes.

Methods: Several different epidemiological methods have been developed during the last decades for these purposes. A critical review of innovative epidemiological methods used for assessing vaccines in the field was undertaken.

Results: Availability of innovative methods and progress made in the field of health informatics allow easy evaluation of large volumes of information.

Conclusions: In addition to scientific and technical support, political commitment is required in order to increase the amount of resources available for public health professionals. International organisations can play an important role at the EU level.

Key words: vaccines, vaccination programmes, safety, effectiveness, Europe

Introduction

Vaccination is one of the most effective public health preventive tools. Universal vaccination programmes have had a tremendous impact in terms of reduction of disease burden. Smallpox eradication has been without any doubt the biggest success, but many other success stories can be described. In the United States, universal childhood vaccination has resulted in the elimination of smallpox, polio, diphtheria, and measles and has led to an over 95% reduction in morbidity for other targeted diseases [1]. Similar achievements have been reached in most western European countries.

On the other hand it is not always evident – both to the general public and to health care professionals – the amount of effort that was required to reach these goals and how difficult it is to maintain such an effective immunisation programme.

The same applies to newly introduced vaccination programmes. Having a good – effective and safe – vaccine on the market is the first critical step but it does not guarantee the success of an immunisation programme.

In this environment monitoring activities

represent a crucial part. Assessing efficacy and safety of vaccine products as well as assessing the effectiveness of the whole vaccine programme are different aspects that require strict methodologies and thorough experience in order to be addressed properly.

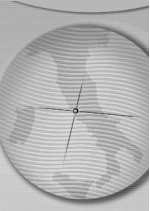
In this short review the main methods used to assess vaccines and vaccination programmes in the field are described.

Assessing vaccine products in the field

Efficacy and safety of vaccine products are carefully assessed before marketing authorisation by regulatory authorities is given. Pre-marketing evaluation is usually carried out by the way of randomised clinical trials (RCT).

Populations involved in RCTs can vary greatly. The number of subjects to be enrolled in a RCT depends on several factors but it is mainly determined by the expected statistical power that the results should have in relation to specific end points (efficacy to protect against specific severity levels of the disease, occurrence of specific adverse events, etc.).

Just as an example, anti-rotavirus vaccines – that have been recently authorised in the EU through



the European Medicine Agency (EMA) centralised procedure - have been tested in 18 large clinical trials involving about 140,000 subjects (including placebo and control groups) [2,3]. Furthermore, additional clinical data is then collected after the manufacturers have been granted marketing authorisation. In the case of anti-rotavirus vaccines the high number of subjects enrolled in the RCTs was mainly due to the feared risk of an increased number of cases of intussusceptions after vaccination. Higher risk of intussusception was the cause of the withdrawal from the market of the previous anti-rotavirus vaccine Rotashield [4].

The link between the Rotashield vaccine and higher risk of intussusception was detected in the US in a post-marketing surveillance setting. Being a very rare event, intussusception was not detected during pre-authorisation studies.

Efficacy of vaccines towards different end points (infection, mild or severe disease, sequelae, death) is also assessed in pre-authorisation settings by the means of RCTs. But efficacy measured in prelicensure studies - when conditions of use of the vaccine are strictly controlled - is not automatically comparable with efficacy in a post-marketing setting, under normal conditions of use.

Several different methods are available to evaluate both safety and efficacy in the field [5-7]. We will briefly describe some of those.

Vaccine safety assessment in post-marketing settings

There are several epidemiological methods that can be used to assess vaccine safety after marketing a vaccine product. Excluding cohort studies because of their cost and their poor feasibility in a post-marketing setting, case-control studies are well known methods to be performed at population level.

Nevertheless, the need for an external control group still represents a constraint when a timely answer is required to respond to a public health problem - like a serious adverse event following immunisation (AEFI). In addition, external controls need to be selected very carefully in order to avoid possible biases.

For this reason, during recent years several epidemiologic methods have been developed for investigating causality between vaccination and rare adverse events that require data collection only from cases. A nice review of these "case-only" methods was carried out by Farrington in 2004 [7].

Table 1 summarises the main features of these

methods, detailed descriptions can be obtained by referring to Farrington's article.

Case-only methods provide powerful epidemiological tools, especially when there is the need to respond rapidly and effectively to emerging problems, like rumours of unexpected AEFI. Nevertheless, there are factors that are critical in making optimal use of such methods, first of all access to good data on cases. Computerised data-linkage between different data sources (vaccine registries, pharmacovigilance data, hospital discharge records, etc.) can dramatically improve the performance of such studies.

Vaccine effectiveness assessment

Vaccine effectiveness can be defined as the efficacy of a vaccine product measured under normal condition of use.

Problems linked to the cold chain, to bad injection practices, bad compliance to the schedule, interference with other vaccine products that were not investigated in the RCTs, but also different characteristics of the population can affect the actual efficacy of the vaccine.

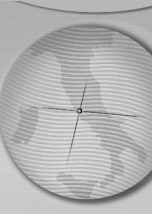
Similarly to what has been described before, several methodological issues have been used in the past in order to evaluate vaccine efficacy in the field - i.e. effectiveness.

A nice review of these methods was written by Orenstein in 1988 [6].

Serologic studies (both seroprevalence and seroconversion studies) are a good proxy of vaccine effectiveness, and they are the only studies that can provide good information about the real level of protection against an infectious disease in the population. This is particularly true when serology represents a good correlate of protection. In any case, serologic studies can show the real effect of a vaccination programme in a large population and they can highlight the population subgroups that require urgent intervention.

Very recently a seroprevalence study conducted in several European countries showed how the proportion of population seronegative for measles antibodies was not compatible with the levels of vaccine coverage reported by some European countries. Such discrepancies could be explained either by problems in the administration of the vaccine or by issues related to the data collection systems [8]. Similarly, the results of a seroprevalence study performed in ten European countries could show the impact of the universal vaccination programme against hepatitis B [9].

Disadvantages of the serologic studies are



mainly due to difficulties in interpreting antibody data, but easiness and low cost are two major advantages.

Analytical methods can be usefully utilised to assess vaccine effectiveness: cohort and case-control studies have been used in several instances to evaluate the effectiveness of vaccine products. Many variants of the basic analytical methods have been developed in order to limit the effect of potential biases during observational studies.

An interesting approach was developed using secondary attack rates in households. In fact households can be considered mini-cohorts where exposure does not vary a lot. The first case and coprimary cases in each household are discarded - since these persons were exposed outside the household; all secondary (or even tertiary) cases are included in the evaluation. The study population will therefore consist of all secondary/tertiary cases and the rest of the households that did not get ill. The total population from the different households can be analysed as a large cohort of vaccinated and unvaccinated people and risk ratio can be calculated comparing incidence of disease among vaccinated and unvaccinated persons.

An interesting method - the screening method - developed in the early '80s has been used for assessing the effectiveness of measles vaccines [10]. It is based on the known relationship between vaccine coverage, vaccine effectiveness and proportion of vaccinated subjects among disease cases; knowing two of these parameters allows for the calculation of the third [5]. Precise estimates of vaccine coverage and vaccination status of the cases are essential in order to obtain a good estimate of vaccine effectiveness.

Even if the screening method cannot be relied upon for precise estimate of effectiveness, nevertheless it can be extremely useful to highlight potential problems related to unexpected low vaccine effectiveness. Moreover, it is very easy to perform and it is based only on analysis of data that are currently collected for other reasons - usually from administrative databases.

Assessing vaccination programmes

Efficacy and safety are very important aspects related to the use of vaccines. As discussed before, they are not only pre-requisites for marketing authorisation, but are important parameters to be evaluated and assessed in the field in a post-marketing setting.

On the other hand, the success of a vaccination

programme is not only linked to the quality of the vaccine product in use. Availability of a safe and effective vaccine is only the first step for reaching the desired goal that can be control, elimination or even eradication of the targeted disease. Very high vaccination coverage is always needed in order to make any vaccination programme really effective.

In this perspective evaluation of vaccine programmes is necessary in order to assess the progress and to implement any needed intervention aimed at improving the performance of the programme. Finally, evaluation is also needed in order to assess the outcomes of the programme and to check if and when all planned goals have been reached.

Both qualitative and quantitative evaluations can be performed (see text box)

Quantitative (*outcomes evaluation*)

- Vaccination coverage
- Disease burden (incidence, hospitalisation, disability, mortality)

Qualitative (*process evaluation*)

- Quality Assurance
- Customer satisfaction
- Sustainability

Evaluation of vaccination coverage is essential, as vaccination coverage is the best proxy of the effectiveness of the programme itself. On the other hand, it is even more important to assess the programme in terms of impact on the burden of disease.

Availability of reliable data is extremely important in order to assess the real impact of the programme on the burden of the targeted disease.

Under this aspect, quality of surveillance plays a central role. Unfortunately, limited resources in public health often result in the impossibility of starting new surveillance systems or improving the quality of the existing ones. Very often vaccination programmes start without having had any opportunity to assess its impact because of the lack of baseline data. Moreover, very often surveillance systems are not flexible enough to adapt to new needs coming from the establishment of new vaccination programmes (lack of information on circulating strains, vaccination status of cases, etc.).

Such information can also be used for communication with the public as well as health care professionals. Notably during the recent past there have been many examples of vaccination programmes that have been jeopardised by rumours of alleged AEFI (measles, mumps, rubella,

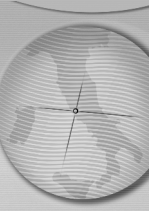
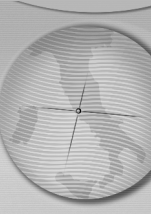


Table 1. Case-only methods for assessing causality between vaccination and unexpected AEFI. Source: Farrington CP, Vaccine, (22) 2004.

Method	Description	Pros	Cons
Ecological Studies	Undertaken at population level, without stratifying on individual exposures. It can be done comparing adverse event rates in populations with different vaccination coverage, or in a pre- and post-campaign situation.	Very easy if AEFI surveillance data are available. The studies can achieve a good power.	Difficult to look for confounders. Impossible to adjust for individual characteristics.
Case-coverage	Uses exposure information from individuals supplemented by coverage data at population level. Same approach as the screening method for assessing vaccine effectiveness. Ex: compare vaccination coverage for MMR in a group of children with autism and MMR vaccination coverage in the whole country.	Only information required is the vaccine status of the individuals with AEFI and the average vaccine coverage in the general population	May produce bias when the population for which coverage data are available is not exactly the same from which the cases come
Case-crossover	Patients serve as their own controls. The method compares time periods before and after the exposure in the same subject. Time periods before vaccination are used as control.	It provide a reliable effect estimate without requiring external controls. All individual-level confounders are automatically controlled for.	The underlying probability to be vaccinated should be the same in all interval periods.
Case-control case series	Like the case-crossover method, it uses cases as their own controls, but its logic derives from cohort rather than case-control design: the incidence of the suspected adverse event in a "risk period" window (let's say two weeks after vaccination) is compared with the incidence in "not-risk" periods. The final measure is relative risk.	It has the same power as a cohort method, sharing all the advantages of a case-crossover study.	Valuable only for acute adverse events occurring within defined (short) time periods after vaccination.



hepatitis B) or have had their effectiveness questioned (influenza, hepatitis B). Only the availability of timely and reliable information can support effective communication.

Conclusions

In conclusion, assessing the impact and the quality of vaccine programmes should be always considered an essential part of their implementation. Both epidemiological methods and technical tools are easily and readily available for health care professionals. Political commitment is needed in order to put in place the resources necessary for this purpose at both the national and international level.

So far, safety and effectiveness in a post-marketing setting have been assessed for many vaccines. On the other hand, a coordinated approach to evaluating vaccination programmes – including safety, effectiveness, and impact assessment at the same time – is largely lacking both at national and international levels.

During the last years, the European Centre for Disease Prevention and Control (ECDC) has devoted substantial resources in order to improve the overall EU capacity in the field of evaluation of vaccination programmes.

In this regard, two specific networks have been implemented, namely VENICE II [11] and VAESCO

[12] both focusing on different aspects including vaccine safety and the overall performance of vaccination programmes.

In particular, the VENICE II project's general aim is to collect and share information on national vaccination programmes through a network of professionals with the final goal of improving the overall performance of the immunisation systems. The project is also providing information on the impact of newly introduced vaccinations and is collecting information at the sub-national level for selected vaccination programmes. The main tool used by VENICE network consists of a web-based system that allows quick EU-wide surveys. Reports are publicly available of the VENICE web site [11].

The VAESCO project focuses on the assessment of vaccine safety. It provides standard methods to be used at the national level for causality assessment between vaccination and adverse events and it will soon start a pilot project in selected regions for monitoring vaccine safety through data linkage between large databases.

Improved collaboration between ECDC and other relevant partners like EMEA, European Commission and the WHO European Office has allowed for an international umbrella to support, with coordinated initiatives, all the challenges that the European Member States have to face in the field of vaccination programmes.

References

- 1) CDC. Achievements in Public Health, 1900-1999 Impact of Vaccines Universally Recommended for Children – United States, 1990-1998. *MMWR*, 1999; 48(12):243-248
- 2) EMEA. European Public Assessment Report for Rotarix, Scientific Aspects. Available from: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/rotarix/063906en6.pdf> [Accessed on 09/09/2009].
- 3) EMEA. European Public Assessment Report for Rotateq, Scientific Aspects. Available from: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Rotateq/066906en6.pdf> [Accessed on 09/09/2009].
- 4) Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR Morb Mortal Wkly Rep*. 1999; 48(27):577-81.
- 5) Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. *Bull WHO*. 1985;63:1055-68.
- 6) Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. *Epidemiol Rev* 1988;10:212-41.
- 7) Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine* 2004; 22(15-16):2064-70.
- 8) Andrews N, Tischer A, Siedler A et al. Towards elimination: measles susceptibility in Australia and 17 European countries. *Bull World Health Organ* 2008; 86(3):197-204.
- 9) Nardone A, Anastassopoulou CG, Theeten H et al. A comparison of hepatitis B seroepidemiology in ten European countries. *Epidemiol Infect* 2009;137(7):961-9.
10. Centers for Disease Control and Prevention. Measles vaccine efficacy – United States. *Morb Mortal Wkly Rep* 1980; 29:470-472.
- 11) VENICE II project website. Available from: <http://venice.cineca.org> [Accessed on 09/09/2009].
- 12) VAESCO project website. Available from: <http://www.vaesco.net> [Accessed on 09/09/2009].