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The complementary roles of Phase 3 trials and post-licensure surveillance in the evaluation of new vaccines

Pier Luigi Lopalco[1] and **Frank DeStefano**[2]

[1]European Centre for Disease Prevention and Control (ECDC) SE-171 83 Stockholm, Sweden

[2]Centers for Disease Control and Prevention Atlanta, Georgia, USA

Abstract

Vaccines have led to significant reductions in morbidity and saved countless lives from many infectious diseases and are one of the most important public health successes of the modern era. Both vaccines' effectiveness and safety are keys for the success of immunisation programmes. The role of post-licensure surveillance has become increasingly recognised by regulatory authorities in the overall vaccine development process. Safety, purity, and effectiveness of vaccines are carefully assessed before licensure, but some safety and effectiveness aspects need continuing monitoring after licensure; Post-marketing activities are a necessary complement to pre-licensure activities for monitoring vaccine quality and to inform public health programmes. In the recent past, the availability of large databases together with data-mining and cross-linkage techniques have significantly improved the potentialities of post-licensure surveillance. The scope of this review is to present challenges and opportunities offered by vaccine post-licensure surveillance. While pre-licensure activities form the foundation for the development of effective and safe vaccines, post-licensure monitoring and assessment, are necessary to assure that vaccines are effective and safe when translated in real world settings. Strong partnerships and collaboration at an international level between different stakeholders is necessary for finding and optimally allocating resources and establishing robust post-licensure processes.

Keywords

vaccine trials; vaccine marketing authorisation; vaccine safety; vaccine effectiveness

Introduction

Since the end of the XVIII century, when the first human prophylactic vaccine was developed, the number of vaccines available for preventing infectious diseases slowly increased until the mid-twentieth century. Antitoxins and bacterial vaccines were mainly developed, but a major breakthrough, represented by the ability to grow viruses in cell cultures, launched a new era for vaccinology [1]. Since then, the number of diseases that can

Corresponding Author: Pier Luigi Lopalco, European Centre for Disease Prevention and Control (ECDC), SE-171 83 Stockholm, Sweden, Office: +46 (0) 8 58 60 12 12, Fax: +46 8 58 60 12 96, pierluigi.lopalco@ecdc.europa.eu.

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be prevented by vaccination increased exponentially. Today, 25 diseases are vaccine preventable [2]. Poliomyelitis, diphtheria, tetanus, pertussis, hepatitis B, *Haemophylus influenzae* type B, measles, mumps, rubella, pneumococcal infections, rotavirus, disease caused by human papillomavirus, and tuberculosis are targeted by childhood vaccination programmes worldwide [3]. Moreover, new technologies in vaccine development dramatically increased the complexity of modern vaccines: synthetic antigens, innovative adjuvants, and conjugated proteins are components of many vaccine products currently in use. Such increased complexity brings important challenges during both the authorization process and the post-marketing phase in terms of assessment of both effectiveness and safety.

Vaccine products reach marketing authorisation after a long development phase that might last as long as 12–15 years [4]. Pre-clinical studies (*in vitro* and *in vivo*) are necessary to select the correct antigenic content so that clinical trials can be designed to be as safe as possible. Phase 1 trials provide preliminary information on vaccine safety in humans and on the dose to be tested in the following clinical trials. They typically involve a limited number of adult volunteers (<100). Candidate vaccines that show promise in pre-clinical evaluation and Phase 1 trials undergo Phase 2 trials in order to further evaluate the dose and safety and immunogenicity. Phase 2 trials usually involve few hundreds of subjects belonging to the final target population of the vaccine (e.g., children for childhood vaccines). Phase 2 studies last until the right dose and vaccine schedule is identified (usually a few years). The final candidate products progress to Phase 3, when they are studied on a larger scale (from many hundreds to many thousands of subjects) to further assess safety and immunogenicity or efficacy against the target disease. Generally, concomitant administration with other vaccine products is also tested in Phase 3 trials, but it can be done even earlier in the development phase [4]. Results from successful vaccine trials are submitted to the regulatory authorities for further evaluation and determination of whether market authorisation should be granted or not..

Demonstration of effectiveness may be derived from clinical endpoint efficacy studies. In some cases, immunogenicity data may be sufficient for a demonstration of effectiveness and clinical endpoint efficacy data are not required. Whether immunogenicity data provide sufficient evidence of effectiveness depends on the strength of evidence that the immune response endpoints predict clinical protection and whether there are sufficiently validated assays to measure those endpoints. In such cases, immunogenicity is considered a good proxy for vaccine efficacy. This is the case for certain new Hib, Td, or Hepatitis B vaccines since for these diseases there are scientifically well-accepted immunological markers that predict protection and that can be reliably measured in a validated assay..

After marketing authorisation has been granted, Phase 4 trials and other post-licensure surveillance activities can be carried out. Their scope is primarily to assess long-term effectiveness and potential safety concerns that were not statistically significant in Phase 3 trials but merit monitoring in the post licensure setting. Vaccine effectiveness assessed during the post-marketing phase is the result of direct vaccine efficacy combined with herd immunity. Phase 4 studies are very often an integral part of the authorisation process in terms of post-marketing action required by the regulatory agencies to the vaccine

manufacturers. Phase 4 studies are complemented by other post-licensure surveillance activities that are carried out by different agents (public health institutions, universities, research groups) as part of their public health mission.

The role of post-licensure surveillance has become increasingly important during the last decades. New methodologies have been developed to enhance efficiency and feasibility of post-licensure surveillance [5,6]. More recently, availability of large databases opened a new season for post-licensure surveillance by using cross-linkage and data-mining technologies [7].

The scope of this review is to present challenges and opportunities offered by vaccine post-licensure surveillance; and to discuss how, under the current authorisation framework in the US and EU, post-licensure surveillance can best complement Phase 3 trials.

The European and U.S. authorisation and public health frameworks for vaccine products

In the U.S., regulation of vaccines and other biological products began with the enactment of the Biologics Control Act of 1902 following an immunization safety incident in which several children died after receiving diphtheria antitoxin that had been contaminated with tetanus toxin [10]. The authority to control biologics evolved and was strengthened with the passage of additional laws and regulations in subsequent years. One of the major laws was enacted as a result of another vaccine safety tragedy -- the “Cutter incident” in 1955, in which some batches of polio vaccine had been inadequately inactivated, resulting in polio in several vaccine recipients and their contacts [11]. As a result, the U.S. Congress directed the creation of a new division at the National Institute of Health (NIH) for the regulation of biological products (Division of Biological Standards). Currently, regulatory authority for licensure (i.e., market authorisation) of vaccines rests with the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. The process of regulation and testing of vaccines has been previously reviewed by Baylor and Midthun [10]. Recommendations for routine use of vaccines are issued by the Centers for Disease Control and Prevention (CDC), with guidance from its Advisory Committee on Immunization Practices [12].

In the U.S., programs to systematically monitor vaccine safety in the post-licensure setting began in the late 1970s. Established by CDC in 1978, the Monitoring System for Adverse Events Following Immunizations (MSAEFI) collected reports of adverse events in children who received publicly funded vaccines [13]. The National Childhood Vaccine Injury Act (NCVIA) of 1986 was landmark legislation that established the Vaccine Injury Compensation Program and the Vaccine Adverse Event Reporting System (VAERS), which replaced MSAEFI in 1990.

In Europe, the European Medicines Agency (EMA) was established in 1995 as a decentralised agency of the European Union (EU) for the evaluation of medicines for use in member countries. Thanks to a centralised procedure, pharmaceutical companies may submit one single marketing-authorisation (MA) application to the EMA. Scientific

evaluation of the MA is carried out by *scientific committees* coordinated by the EMA. The Committee for Medicinal Products for Human Use (CHMP), the Paediatric Committee (PDCO) and the Pharmacovigilance Risk Assessment Committee (PRAC) are those more involved with vaccine products. Committees' members are nominated by the medicines regulatory authorities of the EU Member States, so that geographical representativeness is granted and national interests represented. Representatives of patients and healthcare-professionals may also be part of the committees. Ad hoc *working parties* are also established in order to provide recommendations to the scientific committees for certain specific issues. In particular, a Vaccine Working Party has been operational since 2005.

The scientific committee that is in charge of evaluating a MA application appoints a *rapporteur* to lead the assessment. The rapporteur is supported by an assessment team and can ask for a peer-reviewed process in order to improve the scientific validity of the process. National authorities that provide the staff for the process are remunerated by the EMA. Opinions and recommendations presented by the rapporteur are usually adopted in plenary sessions of the scientific committees. If consensus cannot be achieved, the final position is reached through a vote. On the basis of EMA scientific assessment, the European Commission may grant a MA issuing a legally binding EU-wide decision. Vaccines that are authorised through this centralised process can be marketed in any country of the EU and European Economic Area (EEA - including Iceland, Norway and Liechtenstein).

Specific post-authorization measures (PAM) may be identified by EMA's committees during the scientific assessment phase and are strictly regulated within a legislative framework [8]. PAM are not intended to promote premature authorization of medicinal products, but are necessary when the manufacturer needs to produce additional data on safety and/or efficacy to complement data produced in the pre-authorization phase [9]. Post-authorization safety studies (PASS), either active studies or meta-analyses, may be carried out as part of PAM. In addition, post-authorization efficacy/effectiveness studies may be required as part of the *risk management plan* submitted by the manufacturer as part of the application file.

Methodological aspects of Phase 3 trials: strengths and limitations

Phase 3 trials are considered the gold standard to assess vaccine efficacy in the pre-authorisation phase. Well-designed double/triple blinded, randomised, controlled trials (RCT) provide a very robust estimate of vaccine efficacy under standard conditions. Nevertheless, some strengths of RCTs can turn into limitations from a public health perspective. First of all, in RCTs vaccines are provided under very strict experimental conditions in terms of cold chain, schedule, administration technique, etc; standard conditions are necessary for experimental purposes and are also needed in the marketing authorisation framework, but they may not be strictly adhered to in practice during daily vaccination activities. Moreover, in RCTs controlled conditions are pursued as much as possible and efficacy estimates in vaccinated individuals may not be influenced by herd immunity; whereas, the real life impact of vaccination is affected by herd immunity, which is indeed highly desired under a public health perspective. Post-licensure effectiveness evaluation is useful both for vaccines that have been evaluated in pre-licensure clinical VE

trials as well as those for which pre-licensure effectiveness was based on immunogenicity data. In addition, very rare adverse events usually cannot be identified during RCTs, due to natural limitations in terms of sample size and study power. [10],[11].

Definitely, RCTs represent the best way to assess vaccine efficacy and safety, but the information they can provide needs to be supplemented to support public health decision making post-licensure. In particular, RCTs are sometime limited by sample size constraints in their ability to evaluate risks for very rare adverse events.

Methodologies for post-licensure surveillance

Effectiveness assessment

Vaccine effectiveness can be defined as the ability of a vaccine to prevent specific outcomes in a “real life” situation. Assessing vaccine effectiveness is necessary in order to establish the actual benefit of the vaccination in the field. Vaccine effectiveness estimates may significantly differ from vaccine efficacy measured during vaccine trials. In fact they may be influenced by several factors that are summarised in Table 1.

Several methodologies have been developed for assessing vaccine effectiveness in the field, each of them presenting strengths and limitations [5,6,12–19]. Strengths and limitations of some of those methodologies that have been extensively used in the recent past are summarised in Table 2.

Vaccine effectiveness measured in the field may provide evidence for decision making that may not be available at the time of marketing authorisation. Herd immunity effects, degree of matching with circulating strains, impact of waning immunity, and changes in microbial ecology induced by vaccination are some of the conditions that can be analysed only by means of post-licensure surveillance. The ability to address such issues represents an evident added value of post-licensure surveillance and makes post-licensure surveillance a valuable complement to Phase 3 studies.

Safety assessment

Passive surveillance of adverse events following immunisation (AEFI) and adverse events of special interest (AESI) is mandatory after vaccine marketing both in the US and EU. Passive spontaneous reporting systems can be valuable for identifying potential new safety concerns (i.e., “signals”), but they are subject to several limitations that limit their utility for causality assessment (Table 3).

The Vaccine Adverse Event Reporting System, co-managed by CDC and FDA, is the US spontaneous reporting system for adverse events after vaccination [20]. VAERS accepts reports from healthcare providers, manufacturers, vaccine recipients, and others. Healthcare providers are required to report AEs listed in the VAERS Table of Reportable Events following Vaccination and are encouraged to report other clinically significant AEs after vaccination. Reported AEs are entered into a database and coded using Medical Dictionary for Regulatory Activities (MedDRA) terms. Physicians and scientists at FDA and CDC regularly review the VAERS reports and conduct periodic safety assessments. FDA has

regulatory requirements to conduct scheduled safety assessments of specific vaccines. De-identified VAERS data also are available for viewing and analysis by the public.

All drugs that are centrally authorised in the EU – vaccines included – are subject to mandatory passive surveillance of adverse events at the European level. Individual reports of adverse events are managed through the EudraVigilance system [21]. Both reports from studies carried out by the manufacturers and spontaneous reports by healthcare professionals and regulatory agencies are captured by the system. Data from EudraVigilance are published in the European database of suspected adverse drug reaction reports [22]. Individual suspected-side-effect reports sorted by age group, sex, type of suspected side effect and outcome, can be viewed by any external user. No pharmacovigilance system specific for a vaccine product is in place in the EU.

Assessment of passive AEFI reports is carried out by the EMA regularly, according to the risk management plan. Routine analysis of EudraVigilance reports - for detecting any potential signal - is performed at least monthly; for some medicines, including some vaccines, it is done bi-weekly.

While AEFI passive surveillance is quite effective for signal detection purposes, formal epidemiologic studies are needed for causality assessment. In addition to traditional methodologies, such as cohort and case-control studies, case-only methods have been developed in order to improve feasibility of AEFI causality assessment in pharmacovigilance settings [23]. Case-only studies provide the great advantage of using cases as their own control group, avoiding the need to select external controls. Case-only methods are particularly advantageous for assessment of rare AEFI and in situations of possible indication bias (e.g., certain vaccines that may be indicated for particular high risk groups).

Analytical studies for AEFI causality assessment are facilitated by the availability of large databases collecting information on any event of medical interest in large cohorts of vaccinees. Large databases and cross-linkage techniques have allowed the recent development of new kinds of analyses that would have been impossible a few decades ago. The US Vaccine Safety Datalink (VSD) is the oldest such database infrastructure for monitoring vaccine safety. Recognizing the need for a flexible, timely and robust system to evaluate vaccine safety and supplement information provided by VAERS, CDC established VSD in 1990 to conduct post-marketing vaccine safety evaluations in defined populations [24]. As a collaboration between CDC and several large health care organizations, VSD conducts population-based monitoring and research on important immunization safety questions. VSD has the capacity to address a wide array of safety issues, including monitoring new vaccines in children and adults and conducting timely evaluations of new vaccine safety signals. The aggregate population across all sites is sufficiently large so that risk can be assessed for rare adverse events. Data from approximately 9.3 million individuals are available annually, including 2.1 million children and 7.2 million adults. VSD has cumulative information on more than 21 million individuals who have collectively received over 134 million vaccine doses. Building on the VSD model, FDA has recently established the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system that

links data from several large health insurance companies. PRISM is integrated within the Mini-Sentinel project [25] and enhances the national capacity for vaccine safety monitoring by assembling vaccination and outcomes data on an additional large population [26].

In Europe, the VAESCO consortium has been initiated and sponsored by the ECDC with the aim of improving the sensitivity and timeliness of vaccine safety monitoring systems [27]. Large database linkage has been successfully used by VAESCO partners on several occasions [28–30].

Illustrative case studies of the added value of post-licensure surveillance

Effectiveness of Acellular Pertussis vaccines

Acellular pertussis vaccine trials have represented one of the biggest public investments in the history of vaccine development. By the mid-1980's the US NIH, worried about the increasing public concern about the safety of cellular pertussis vaccines, boosted research on acellular vaccines [31]. Large acellular pertussis trials were conducted in the 1990's, assessing safety and efficacy of DTaP vaccines in infants [32,33]. Efficacy estimates from the Phase 3 trials were very consistent, showing protective efficacy of more than 80% in children vaccinated with acellular vaccines; on the other hand efficacy of cellular vaccines was very variable. Moreover, acellular vaccines showed much higher tolerability [34]. As a consequence, beginning in the late 1990's acellular vaccines rapidly replaced cellular vaccines both in the US and in Europe and vaccine coverage against pertussis increased [35]. Notwithstanding high coverage rates, resurgence of pertussis has been recently reported both in the US and in Europe; in particular, high incidence rates have been reported in adolescents and young adults as well as small infants [36–39]. The increase has been attributed to different factors, including earlier than expected waning of immunity; a shift of pertussis circulation in those age groups not covered by vaccination and subsequent transmission to unvaccinated infants; and possible vaccine failure due to emergence of *Bordetella pertussis* mutant strains [38,40–44]. Whatever the reason, the resurgence of pertussis indicates a need for a revision of current pertussis vaccination strategies guided by a thorough assessment of pertussis epidemiology and vaccine effectiveness. The unexpected resurgence of pertussis in some countries, however, is not in contradiction with the reported high vaccine efficacy after Phase 3 trials. Even in the presence of high individual efficacy after primary vaccination [32,33] and reasonably good sustained efficacy after 5 years [45,46], infant vaccination alone seems to be far from sufficient to stop the overall circulation of *Bordetella pertussis*. Alternative strategies including adolescent/adult vaccination [39,47–49] and vaccination in pregnancy [50]have been implemented in many countries. In order to inform new vaccination strategies and to better understand the reasons behind pertussis resurgence, both disease and vaccine post-licensure surveillance are paramount [51–54].

Effectiveness of Influenza vaccines

Immunogenicity and safety of influenza vaccines is systematically assessed by means of Phase 3 trials for MA purposes. Unfortunately, due to the frequent drifts and shifts of influenza viruses, pre-licensure trials, carried out for regulatory purposes, do not always

anticipate the impact of influenza vaccination public health campaigns. Several systematic reviews of the literature reported limited impact of influenza vaccination in children below 2 years, healthy adults, and the elderly [55–57]. Mismatch between vaccine and circulating strains is one of the most important factors for low influenza vaccine effectiveness. Thus, influenza vaccine effectiveness should be routinely measured in order to better understand the role and impact of vaccination strategies under different epidemiological circumstances. For this purpose, the US Flu VE Network [58] was established and the I-MOVE network was established in Europe in 2007. Repeated estimates of influenza vaccine effectiveness have been provided by I-MOVE throughout different influenza seasons [18]. Not surprisingly, one of the highest vaccine effectiveness estimates (71.9%; 95% confidence interval 45.6–85.5) has been reported during the 2009–10 season, when the pandemic A(H1N1)pdm09 virus was the almost exclusive circulating strain and was well matched to the vaccine strain [19]. Unfortunately, effectiveness estimates, in the best case scenario, are available a few months after the influenza season is over and may not be applicable to the next season (i.e., because of strain changes). Nevertheless, continuing evaluation of influenza vaccine effectiveness can provide important information for public health decisions in terms of vaccine effectiveness in different age groups, the added value of adjuvants, and the effectiveness of different vaccine types. Increasing knowledge on the impact of influenza vaccination is of high value for public health.

European Experience: Pandemrix and Narcolepsy

In August 2010 public health authorities in Finland and Sweden reported an increase of cases of narcolepsy in children and adolescents, suggesting a potential association with Pandemrix vaccination. Eight influenza A(H1N1)pdm09 vaccines were licensed for use in Europe during the 2009 pandemic, but Pandemrix was the most frequently used vaccine in Europe: based on EMA estimates, more than 30.5 million people were vaccinated with Pandemrix in the EU/EEA [59]. In Finland and Sweden, Pandemrix was the only vaccine used for the pandemic vaccination campaign.

Narcolepsy is a rare neurological disorder characterized by inability to regulate sleep-wake cycles normally. The primary symptom is excessive daytime sleepiness. Narcolepsy predominantly affects adolescents and young adults, and very rarely children under 16 years of age. Sudden onset of short episodes of muscle tone loss, known as cataplexy, may occur as part of the neurological disorder [60]. Abnormal immunological response to different antigens, combined with specific genetic patterns, is suspected to be the trigger for narcolepsy [61,62].

The VAESCO consortium, supported by the ECDC, coordinated a multinational investigation to assess the causality relationship between narcolepsy and Pandemrix [27]. Eight European countries (Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the United Kingdom) participated in a case-control study using a common protocol, common case report forms, and a common Brighton Collaboration case definition. This study confirmed a strong statistical association between Pandemrix and onset of narcolepsy in children and adolescents in Finland and Sweden [59], in line with independent analyses

carried out by national authorities [63–66]. Further studies, carried out at national levels in Norway, Ireland, and England identified an association in those countries as well [67–69].

In conclusion, after the signal raised in Finland and Sweden, a strong association between narcolepsy and influenza A(H1N1)pdm09 vaccination has been established in some European countries, but not in others and nowhere else outside Europe. It is still unknown if the vaccine was the cause of the neurological disorder or if it was just the trigger speeding up disease onset in individuals who would otherwise have developed narcolepsy later. This will become clear in the coming years, as results become available from studies in other countries as well as research on the pathogenic mechanisms of narcolepsy that has been stimulated by this event. In this episode, post-licensure surveillance was demonstrated to be effective in detecting a signal of a serious AEFI at national levels, and international collaboration has been extremely fruitful for the following signal assessment.

Rotashield and intussusception

The first vaccine designed to prevent rotavirus infection (Rotashield® – Wyeth Lederle Vaccines, Philadelphia, PA) was voluntarily withdrawn from the US market by the manufacturer in 1999 due to an increased risk of intussusception among infants receiving the vaccine [70]. The identification and investigation of this safety problem provides an excellent illustration of a post-licensure vaccine safety monitoring system that worked well to inform vaccination policy. In the pre-licensure trials for Rotashield®, a small increase in the number of cases of intussusception had been observed, but the results were not statistically significant. As a result, FDA and CDC were on the alert to closely monitor for intussusception after Rotashield® was licensed in the US in August 1998 and subsequently recommended for universal infant immunization in March 1999. By May 1999, nine cases of intussusception had been reported to VAERS following Rotashield®, whereas VAERS had received only 3 reports of intussusception following all vaccines administered from 1990 to 1998. In response to the VAERS signal, along with other data, CDC initiated two confirmatory studies and suspended the recommendation for Rotashield® vaccination pending the results of those studies. The first study was initiated in VSD and expanded to include 10 large medical care organizations. Using the computerized databases of the participating medical care organizations, with chart confirmation of intussusception cases, a cohort study was conducted that found a large increased risk of intussusception associated with Rotashield® vaccination; the highest relative risk of 31 occurred during days 3–7 after the first dose [71]. The second study was a large case-control study conducted in 19 states, which also found a strong association with Rotashield® with a peak relative risk of 36 at 3–7 days after the first dose [72]. As a result of these findings, in October 1999 the manufacturer stopped marketing the vaccine and ACIP withdrew its recommendation for the vaccine.

Two new rotavirus vaccines were subsequently licensed following large pre-licensure trials that did not find an increased risk of intussusception. In post-licensure monitoring, however, a small increased risk of intussusception was detected for both vaccines [73,74]. Post licensure data have also documented large benefits of rotavirus vaccination in terms of reductions in hospitalizations, ER visits, and in some cases, deaths from diarrhea [75]. Thus,

policy makers have continued to recommend the current rotavirus vaccines for childhood immunization programs.

Conclusion

Pre-licensure activities form the foundation for the development and licensure of effective and safe vaccines. Pre-licensure activities, including the pivotal Phase 3 trials, cannot be replaced by post-licensure monitoring systems. Post-licensure monitoring and assessment, however, are necessary adjuncts to pre-licensure activities to assure that vaccines are effective when translated from the somewhat idealized clinical trial setting to wider population groups in real world settings. After licensure, robust vaccine safety monitoring systems are essential for providing assurance of the safety of vaccines and rapidly identifying and responding to potential safety problems, particularly rare health conditions that pre-licensure trials may not have had the power to detect. Currently, spontaneous reporting systems serve as the principal mechanisms for the early identification of potential vaccine safety problems. Spontaneous reporting systems, however, have many limitations, with under-reporting being foremost among them. Possible technological advances could be employed to improve reporting completeness and accuracy, including application of Web-based and text messaging technologies to make reporting easier and more accurate.

An optimal vaccine safety monitoring system must include a capability to rapidly conduct formal epidemiologic evaluations of potential safety problems identified from spontaneous reporting systems or other sources. This function can be most readily served by the establishment of standing infrastructures of large linked healthcare databases, such as the VSD project. The diffusion of electronic health records and the capability to link records across health data systems and immunization registries may allow the expansion of populations that could be included in post-licensure epidemiologic evaluations of vaccine safety.

New technologies and innovative epidemiological methods also can be beneficial to improve post-licensure assessment of vaccine effectiveness and impact on population health. Data on disease epidemiology, disease burden, vaccine coverage, vaccination status of disease cases are necessary for effectiveness and impact assessment. Those data are usually available in different databases hosted by different public health agencies. Strong partnerships between regulatory and public health authorities as well as academia and vaccine manufacturers would be necessary to facilitate such activities. Moreover, due to the large sample size required for those kinds of studies, international collaboration and coordination is paramount. The legal regulatory framework also plays a crucial role: enhancing the importance of post-licensure surveillance in the regulatory process could facilitate allocation of adequate resources and foster collaboration among all involved stakeholders.

Vaccines are one of the most important public health successes of the modern era. They have led to significant reductions in morbidity and saved countless lives from many infectious diseases. The success of vaccination programs depends on both vaccines' effectiveness and their safety. Robust systems to monitor and evaluate vaccines after they are licensed and are widely administered are critical to maintaining the public’s confidence

in and acceptance of vaccines, as well as to assure that the vaccines are providing the level of protection and safety anticipated when they were licensed.

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Table 1

Factors affecting vaccine effectiveness

● Host Factors
○ Age
○ Presence of conditions/co-morbidities that may either affect immune response or influence individual disease susceptibility
○ Previous exposure to antigen
○ Interference due to co-administered vaccines or other drugs
● Logistic issues
○ Schedule compliance
○ Cold chain
○ Administration issues
● Epidemiological factors
○ Force of infection
○ Herd immunity
○ Mismatch with circulating strains
○ Emergence of new viral/bacterial variants

Table 2

Some strengths and limitations of different methodologies for assessing vaccine effectiveness.

Method	Strengths	Limitations
Screening method	• Use of routinely collected data • Rapid and not expensive	• Suboptimal accuracy and completeness of routinely collected data • Does not provide precise estimates of vaccine effectiveness
Outbreak investigation	• Good estimates provided under certain circumstances (closed communities, low disease incidence in the past, high attack rates) • During community-wide outbreaks cluster sampling can be performed	• Control programmes during the outbreak can severely interfere • Exposure can be different among vaccinees and non-vaccinees
Coverage survey method	• Similar approach as in outbreak investigation, but does not require any actual outbreak • Similar resources required as for coverage survey	• Exposure can be different among vaccinees and non-vaccinees • Can be used only in endemic areas • Recall bias may affect the accuracy of case ascertainment
Secondary attack rates in households or clusters	• Bias due to different exposure among vaccinees and non-vaccinees is reduced	• Small number of children available • Families should be followed-up for a time longer than the incubation period • Method of secondary attack rates in clusters is less rigorous
Case-control studies	• Good use of resources • Useful when access to data from clinics is easier than access to vaccination records	• Correct selection of controls is crucial to limit bias • Potential confounders must be seriously addressed
Time-series analysis	• Use of routinely collected data • May evaluate both direct and indirect (herd immunity) vaccination effects	• Limits of any ecological approach
Indirect cohort design	• More efficient than cohort studies • Suitable for rare diseases (pneumococcal infections)	• May under-estimate vaccine effectiveness because cross protection against non-vaccine types cannot be controlled

Table 3

Some strengths and limitations of spontaneous reporting systems.

Strengths	Limitations
• Rapid signal detection (hypothesis generation)	• Reporting bias (e.g., underreporting, stimulated reporting) routinely collected data
• Cover large population	• Inconsistent data quality and completeness
• Can detect rare adverse events	• Lack of unvaccinated comparison group
• Relatively inexpensive	• Not designed to assess if a vaccine caused an adverse event