Vaccine 35 (2017) 3041–3049

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Challenges in conducting post-authorisation safety studies (PASS): A vaccine manufacturer's view

Catherine Cohet *, Dominique Rosillon, Corinne Willame, Francois Haguinet, Marie-Noëlle Marenne, Sandrine Fontaine, Hubert Buyse, Vincent Bauchau, Laurence Baril [1]

GSK Vaccines, Wavre, Belgium

ARTICLE INFO

Article history:
Received 14 November 2016
Received in revised form 13 April 2017
Accepted 20 April 2017
Available online 29 April 2017

Keywords:
Vaccine
Safety
Adverse event
Pharmacoepidemiology
PASS
Challenges

ABSTRACT

Post-authorisation safety studies (PASS) of vaccines assess or quantify the risk of adverse events following immunisation that were not identified or could not be estimated pre-licensure. The aim of this perspective paper is to describe the authors' experience in the design and conduct of twelve PASS that contributed to the evaluation of the benefit-risk of vaccines in real-world settings. We describe challenges and learnings from selected PASS of rotavirus, malaria, influenza, human papillomavirus and measles-mumps-rubella-varicella vaccines that assessed or identified potential or theoretical risks, which may lead to changes to risk management plans and/or to label updates. Study settings include the use of large healthcare databases and *de novo* data collection. PASS methodology is influenced by the background incidence of the outcome of interest, vaccine uptake, availability and quality of data sources, identification of the at-risk population and of suitable comparators, availability of validated case definitions, and the frequent need for case ascertainment in large databases. Challenges include the requirement for valid exposure and outcome data, identification of, and access to, adequate data sources, and mitigating limitations including bias and confounding. Assessing feasibility is becoming a key step to confirm that study objectives can be met in a timely manner. PASS provide critical information for regulators, public health agencies, vaccine manufacturers and ultimately, individuals. Collaborative approaches and synergistic efforts between vaccine manufacturers and key stakeholders, such as regulatory and public health agencies, are needed to facilitate access to data, and to drive optimal study design and implementation, with the aim of generating robust evidence.

1. Introduction

Whilst most common drug adverse reactions are identified during clinical development, rare adverse events (AEs) may remain undetected or unconfirmed until post-marketing use [1]. Unlike most drugs, vaccines are administered to healthy individuals, including young children and vulnerable populations such as individuals with underlying medical conditions or immunosuppression, pregnant women, and the elderly. Vaccine safety profiles may change over time through expanded use in real-world settings and their systematic monitoring is a continuous process performed in consultation with regulatory authorities. Post-authorisation safety studies (PASS) are the ultimate step of the iterative process of pharmacovigilance [2]. They identify, characterise or quantify an identified, potential or theoretical safety hazard; confirm the safety profile of an authorised product; or measure the effectiveness of risk mitigation measures under real-world conditions and contribute to the benefit-risk evaluation of medicinal products [3]. Important improvements to monitoring requirements for vaccine safety have been made over the last decade (Fig. 1) and have impacted how vaccine manufacturers conduct PASS. In Europe, PASS are defined in the guideline on Good Pharmacovigilance Practices, which has contributed to improving the quality and transparency of PASS while introducing additional procedural steps [3–6]. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance has provided an opportunity to improve post-licensure research through methodological standards, checklists and a study register [7]. Similar but more limited guidance exists in the United States (US) [8]; here we will refer to all post-authorisation safety studies using 'PASS' as a generic term,

* Corresponding author at: GSK, Avenue Fleming 20, 1300 Wavre, Belgium.
E-mail addresses: catherine.x.cohet@gsk.com (C. Cohet), dominique.x.rosillon@gsk.com (D. Rosillon), corinne.x.willame@gsk.com (C. Willame), Francois.F.Haguinet@gsk.com (F. Haguinet), Marie-Noelle.Marenne@gsk.com (M.-N. Marenne), Sandrine.X.Fontaine@gsk.com (S. Fontaine), Hubert.X.Buyse@gsk.com (H. Buyse), Vincent.G.Bauchau@gsk.com (V. Bauchau), laurencebaril1@gmail.com (L. Baril).
[1] At the time of manuscript development.

http://dx.doi.org/10.1016/j.vaccine.2017.04.058
0264-410X/

whether they were conducted in Europe or globally, and regardless of the regulatory agency which mandated them. PASS designs are influenced by numerous factors including vaccine uptake, target population, validity of exposure and outcome data, availability of surveillance systems and relevant data sources, availability of covariate data to address bias and confounding, and methodological and operational feasibility (Table 1). The aim of this manuscript is to illustrate these challenges through the description of PASS that contributed to important updates to the safety profile at various stages of the vaccine lifecycle.

2. Selected examples of PASS

The main results and primary challenges of each selected PASS is shown in Table 2.

2.1. Introducing a new vaccine when there is an identified risk with a similar vaccine

2.1.1. Rotavirus vaccines and intussusception (IS)

After marketing of the first tetravalent rhesus-human reassortant rotavirus vaccine (*RotaShield*, Wyeth, Pennsylvania, US), an increased risk of IS in infants was observed during the first week after immunisation. The vaccine was subsequently withdrawn [9]. In view of this identified risk, the safety of new rotavirus vaccines had to be assessed. In large pre-licensure studies of *Rotarix* (GSK, Wavre, Belgium) and *Rotateq* (Merck, Kenilworth, NJ, US), no increased IS risk was observed [10,11]. At the time of first *Rotarix* registration in Latin America, GSK committed to the European Medicines Agency (EMA) to conduct a study in Mexico, one of the first countries to include rotavirus vaccination in their national vaccination calendar. A prospective self-controlled case-series built on the active IS surveillance already in place, on the fact that *Rotarix* was the only rotavirus vaccine distributed, and on the opportunity of a large sample size because of mass immunisation. An attributable risk of 3–4 additional IS cases per 100,000 vaccinated infants was observed. A temporal risk increase was observed within 7 days after the first dose [12]. The warning was updated in the Prescribing Information (PI). In addition, at the time of US approval, the US Food and Drug Administration (FDA) requested a PASS in a US population. A cohort study was conducted using the Optum Research Database and the HealthCore Integrated Research Database, two large US health insurance plans [13]. Although IS is a rare outcome, case definition and background incidence data were available. A large vaccinated cohort was matched to a concurrent and a historical cohort of infants having received an inactivated poliovirus vaccine. IS cases were confirmed by medical chart review. No increased risk was observed in the 0–59-day risk period following *Rotarix*. However, the study was not powered to assess the risk of IS during the 7 days following vaccination. As several studies since *Rotarix* and *Rotateq* registration suggested an increased risk 7 days' post-vaccination, meta-analyses were conducted to obtain risk estimates associated with two doses, and to assess whether the risk is brand-specific or rather a class effect. The meta-analyses confirmed an association with IS 7 days after the first dose, and to a lesser extent after the second dose; the risk appeared similar for both vaccines [14,15]. Considering accumulated evidence and the well-documented benefit of the vaccines, the benefit-risk of rotavirus vaccines remains favourable [16].

2.1.2. Measles-mumps-rubella-varicella (MMRV) vaccine and febrile convulsion (FC)

During the clinical development of the combined live-attenuated MMRV vaccine (*Priorix tetra,* GSK) the incidence of fever after the first, but not the second, vaccine dose was 1.5-fold higher compared to measles-mumps-rubella (MMR) and varicella (MMR+V) vaccines administered separately [17]. A post-marketing study with Merck's *ProQuad* showed an increased risk of FC after MMRV as compared to MMR vaccination [18]. This was considered a potential signal for *Priorix tetra* and a cohort study based on hospitalisation claims was conducted in the German Pharmacoepidemiological Research Database in children between 9 and 30 months of age, building on the equivalent use of the two antigen combinations, MMR and MMR+V, in Germany. The study compared those who had received a first dose of MMRV to those who received MMR and/or MMR+V [19]. The case definition of FC was based on billing codes. Since medical chart review was not possible, definitions of varying sensitivity and specificity were used. Other challenges included incomplete country coverage of the database and no access outside of academic groups. Risk of misclassification of exposure or outcome had been mitigated by pre-planned feasibility assessments. An increase in the cumulative incidence of FC within 5–12 days after the first dose of *Priorix tetra* compared to MMR/MMR+V was observed, equating to one additional case of FC per 2747 subjects vaccinated. Although the results did not indicate a change in benefit-risk for *Priorix tetra* as a first dose, a warning was added to the PI [20].

2.2. Investigating a potential risk identified prior to licensure

2.2.1. AS04-adjuvanted human papillomavirus (HPV) vaccine and spontaneous abortion (SA)

The AS04-HPV-16/18-vaccine (*Cervarix*, GSK) is indicated in young women to prevent premalignant genital lesions and cervical cancer. An analysis of two Phase III studies could not rule out an increased risk of SA in women unexpectedly exposed during early pregnancy [21] and the FDA requested a PASS to investigate these findings. The design had to consider low vaccine exposure in pregnant women and how to identify SA events and their corresponding risk windows [22]. After cancelling a prospective study in the US due to low vaccine uptake leading to insufficient sample size, a retrospective cohort study was conducted in the United Kingdom (UK), which had achieved high coverage as part of the national immunisation programme. The study used the Clinical Practice Research Datalink (CPRD), a large representative healthcare database of general practitioners with adequate medical and immunisation records, and a mother–baby link [23]. Feasibility assessment showed that only a fraction of HPV vaccinations were recorded, therefore only pregnancies in vaccinated women were included. Outcomes were compared between pregnancies where vaccination occurred near pregnancy onset (from 30 days before, to 90 days after any vaccine dose) and pregnancies where vaccination occurred long before (between 120 days and 18 months after the last vaccine dose). The remote vaccination in this referent cohort was to mitigate the incomplete vaccination records, increasing comparability. Patient profiles, including free text, were reviewed by experts blinded to vaccination status. Observed SA rates were consistent with published background rates and there was no evidence of an increased risk of SA or other pregnancy outcomes in young women inadvertently exposed around gestation compared to other women [24]. In light of these data, the benefit-risk of *Cervarix* remains favourable.

2.3. Investigating a theoretical risk

2.3.1. HPV vaccine and autoimmune diseases

In view of the theoretical concern that vaccine adjuvants could trigger the onset or exacerbation of autoimmune diseases in susceptible individuals [25,26] the FDA requested a PASS to investigate the risk of neuroinflammatory/ophthalmic and other autoimmune diseases within 12 months following the first *Cervarix*