

M-M-RVAXPRO® and crying

Introduction

It is known that vaccination can lead to a variety of non-specific reactions that can be attributed to the (painful) injection or a systemic reaction to the injected solution. A frequently reported, non-specific reaction is crying. Crying after vaccination may arise directly in response to the injection, but children may also cry as a reaction to general malaise, fever and pain due to a local injection site reaction. It is known that symptoms such as fever and malaise often emerge 5-12 days after vaccination with the MMR vaccine. This latency period is explained by the fact that the live attenuated pathogens in the vaccine need some days to replicate themselves and to establish an immune response. A local injection site reaction, however, occurs often within 24 hours after vaccination. Parents often consider crying shortly after vaccination as an expected and logical response to the injection. Crying due to malaise following vaccination several days after the administration, is sometimes troubling for parents because it is not always clear why the child is crying. The concern that arises because of this crying, is often reason for a doctor's visit. It is important that health care professionals and executors of the national vaccination program are able to inform and explain to parents that crying with a certain latency after vaccination falls within the expected pattern based on the characteristics of the MMR vaccine. Though it should be kept in mind that besides the general malaise also other, more severe underlying adverse events can cause the crying. At this moment crying is not listed as an event that can occur following immunization in the official product information of the MMR vaccine M-M-RVAXPRO® [1]. The disclosure of this adverse event in the official product information, may lead to more awareness among health care professionals concerning the features of this reaction following immunization with M-M-RVAXPRO®, allowing them to better inform parents about this reaction.

Reports

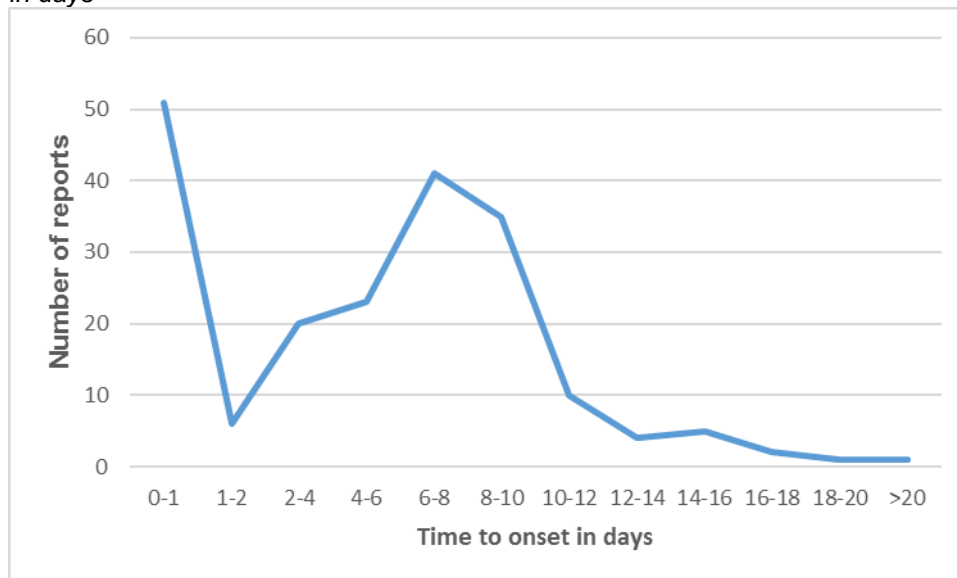
From the first of June 2010 until the fifth of February 2016, the Netherlands Pharmacovigilance Center Lareb received 327 reports of MedDRA® Preferred Term (PT) 'Crying' (preferred term) following immunization with the MMR vaccine. The preferred term 'Crying' includes reports that concern the lower level terms 'Crying'; 'Crying abnormal'; 'High-pitched crying'; 'Inconsolable crying'; 'Uncontrollable crying' and 'Persistent crying'.

Table 1. Number of reports on the preferred term crying classified by lower level term

Lower level term	Number of reports
Crying	223
Inconsolable crying	83
Persistent crying	9
Crying abnormal	9
Crying uncontrollable	3

The reported time between vaccination with the MMR vaccine and the onset of crying (LLT) is shown in the chart below. The peak of day 1 until 2 probably corresponds with crying due to the injection and the onset of an injection site reaction. The peak between 6 to 10 days corresponds with the time to onset of malaise and other adverse events that are based on the activation of live attenuated pathogens in the MMR vaccine.

Figure 1. Number of reports on crying (LLT) in association with MMR vaccination, with a time to onset in days



Time to onset: time between vaccination and the onset of the crying

Other sources of information

SmPC

Except for the product information of the HPV vaccine 'Cervarix®' and the MMR vaccine 'M-M-RVAXPRO®', (abnormal) crying is listed as an adverse event following immunization (AEFI) in the product information of all vaccines that are being given in het National Immunization Program [2-7].

Vaccination coverage

The vaccination coverage in the Netherlands concerning the MMR vaccination of infants has been around 95% for years. [8] When you take into account the number of newborns in the Netherlands per year, 171,000 infants are vaccinated with this vaccine yearly [8,9].

Databases

On the 27th of June 2016, the WHO database of the Uppsala Monitoring Centre (Vigilyze™) contained 2359 reports on crying associated with Measles, Mumps and Rubella vaccines. Lareb is not able to determine disproportionality.

Discussion and conclusion

The Dutch Pharmacovigilance Center Lareb received 327 reports of crying associated with the MMR vaccine M-M-RVAXPRO®. In 297 reports a clear time to onset could be determined. In 29% of the cases (85 of the 297 reports) the crying occurred ≤ 24 hours after vaccination. In 30 of these cases an injection site reaction (swelling, redness, pain) was also reported. 71% Of the reports (212 of 297) concern crying with a time to onset of more than 24 hours. As shown in figure 1, the majority of the crying occurred 6 to 10 days after vaccination. This latency period appears to correspond with the time to onset of general malaise that often occurs after the MMR vaccination. This malaise usually occurs 5 to 12 days after administration of this vaccine and children recover from it several days after onset. Crying shortly after the injection is most likely a response to the vaccination or due to the occurrence of an injection site reaction (pain, swelling). It should be noted that infants and young children may cry for a wide variety of reasons not causally related to vaccinations. Health care professionals should be aware of the fact that crying with a latency of 5 to 12 days of the MMR vaccination can be related to the vaccination.

References

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2. College ter Beoordeling van Geneesmiddelen. SmPC Cervarix suspensie voor injectie Humaan papillomavirusvaccin [Typen 16, 18] (Recombinant, met adjuvans, geadsorbeerd). (version date: 2016, access date: 29-6-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf.

3. College ter Beoordeling van Geneesmiddelen. SmPC Infanrix-IPV, suspensie voor injectie Difterie, tetanus, pertussis- (acellulair, component) (Pa) en poliomyelitis-(geïnactiveerd) (IPV) vaccin. (version date: 23-12-2015, access date: 29-6-2016) <http://db.cbg-meb.nl/IB-teksten/h34568.pdf>.
4. College ter Beoordeling van Geneesmiddelen. SmPC Boostrix suspensie voor injectie in voorgevulde spuit. Difterie, tetanus en pertussis (acellulaire component) vaccin (geadsorbeerd, gereduceerde antigeeninhoud). (version date: 17-10-2013, access date: 27-6-2016) <http://db.cbg-meb.nl/IB-teksten/h35121.pdf>.
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