Latency period of crying following MMR vaccination
What do spontaneous AEFI-reports show?

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Introduction
The Netherlands has an extensive national immunisation programme to protect children against a number of infectious diseases. At the age of 14 months and 9 years, children get a combined vaccination against mumps, measles and rubella (MMR). Like every other vaccination, the vaccination against MMR may lead to a variety of non-disease-specific reactions that can be attributed to the (painful) injection or a local or systemic reaction. A frequently reported, non-specific reaction following vaccination, is crying directly after vaccination. In the cases reported to the Netherlands Pharmacovigilance Centre Lareb crying following MMR vaccination occurred with variable latency periods. Pyrexia and rash are the most frequently co-reported adverse events.

Objectives
To analyse the number of reports and the latency period of crying after immunisation with a live attenuated MMR vaccine and to determine if there is a difference between the first (at 14 months) and second vaccination moment (at 9 years). The second objective is to visualise in what way the latency periods of crying, pyrexia and rash are related to each other.

Methods
Reports submitted to the Netherlands Pharmacovigilance Centre Lareb between 1 June 2010 and 22 February 2017 with the MedDRA Preferred Term ‘crying’ following immunisation with a MMR vaccine were included. For all reported episodes the latency period was analysed and the vaccination moment was determined. Of the reports in which crying was co-reported with rash and/or pyrexia, the latency period of these co-reported reactions was determined.

Results
Latency period of crying: Two distinct incidence peaks are visible in figure 1 and 2. The first incidence peak of crying is seen in the 24 hours following vaccination. The second peak occurs between the fifth and twelfth day after vaccination, with a majority of reports with a latency period of seven to eight days. The latency period of the second peak is consistent with the time to onset of a viremia caused by replication of the live attenuated viral particles in the MMR vaccine. When you compare crying after the first and second vaccination moment, it is notable that after the second MMR vaccination moment, only one incidence peak is visible which occurs on the first day after vaccination. The absence of a second peak can be explained by the fact that after the second MMR vaccination, adverse reactions are less likely to occur, while the viremia after the second vaccination gets sufficiently suppressed by the immune response that is established through the first vaccination.

Relation between latency period of crying, rash and pyrexia: rash was co-reported in 115 of the 396 reported cases of crying. Pyrexia was co-reported in 302 cases. The latency period of pyrexia follows a similar pattern to that of crying. The latency period of rash shows less distinct peaks. This can be explained by the fact that rash is often not directly detected by parents and rash due to other causes (and therefore with other latency periods) occurs frequently in young children.

Conclusion
- Crying shortly after vaccination is an expected and logical response to the (painful) injection or to the onset of a local injection site reaction which leads to discomfort.
- After MMR vaccination, crying also can occur after 5-12 days, which corresponds with the latency period of the viremia, caused by replication of the live attenuated pathogens in the vaccine.
- After the second MMR vaccination, crying after 5-12 days is less likely to occur while the viremia is sufficiently suppressed by the immune response established through the first vaccination.
- The latency period of pyrexia follows a similar pattern to that of crying, but that of rash shows less distinct peaks.
- Although one should stay alert for other causes for crying, health care professionals should inform parents that crying 5 to 12 days after the first vaccination with the MMR vaccine may be expected.