harmful (adverse event), occurring with any combined MMR vaccine given independently compared with no vaccination, or placebo or vaccines containing one or two component antigens.

Findings: We identified 110 articles possibly satisfying our criteria and included 20. MMR is associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, similar incidence of other adverse effects compared to placebo and is likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints and aseptic meningitis (mumps Urabe strain-containing MMR). Exposure to MMR is unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps Jeryl-Lynn strain-containing MMR). Moderate to high risk of bias is present in 16 out of 20 studies. The conclusions of eight studies are undermined by selection bias, 15 by missing definitions for all adverse events and 19 by incomplete vaccine exposure details. Systematic reviewing methods can be applied to evidence of safety of vaccines and are an aid in interpreting the evidence.

Interpretation: The design and reporting of safety outcomes in MMR vaccine studies, both pre and post-marketing, are largely inadequate. The evidence of adverse events following immunization with MMR cannot be separated from its role in preventing the target diseases.

S004. Passive surveillance of adverse events following immunization in the Netherlands

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Monitoring of adverse drug reactions of vaccines is a specialized field within pharmacovigilance, which requires specific knowledge and expertise. These relate to specific product characteristics and to the use of vaccines. Vaccines commonly are administered by the parenteral route to healthy persons—often healthy infants—for infectious disease prophylaxis in government endorsed programs.

Effective prophylaxis depends on high vaccine uptake and coverage. Success of the treatment is not readily recognizable in the individual whereas the inevitable adverse events are. This situation puts a strong claim on safety and postmarketing surveillance of vaccines. One of the characteristics which distinguishes vaccines from other drugs is the fierce public scrutiny and debate, partly driven by well organized consumer groups, where the benefit-risk balance is concerned. This constant public and media attention makes post-marketing surveillance of Adverse Events Following Immunization [AEFI] is a unique playground within pharmacovigilance.

Pre-registration safety testing and post-marketing safety surveillance are hampered by lack of consistent case-definitions. Moreover the MEDDRA classification for adverse reactions does not meet the needs for AEFI case definitions. In the Brighton Collaboration international vaccine experts are trying to reach scientific sound case-definitions for AEFI.

Pharmacovigilance of AEFI is differently organized in different countries: passive post-marketing safety surveillance of vaccines is conducted by the regular national pharmacovigilance centre or conducted by a separate dedicated pharmacovigilance organization for vaccines. Some of these separate pharmacovigilance organizations for vaccines undertake active post-marketing safety surveillance by database linkage of vaccination records and medical records.

In the Netherlands a special centre for the monitoring of vaccinations of the national childhood immunization program is operated by the National Institute of Public Health and the Environment [RIVM] and all other vaccinations [occupational, travelers] are monitored by the Netherlands Pharmacovigilance Centre [Lareb]. Although both systems are complementary, differences in procedures and methods exist between them. These relate to the method of notification, the data entered into the database, the coding of AEFI, and the processing of AEFI-reports. Annual numbers of AEFI-reports of vaccines to RIVM are about 30% of the number of total annual ADR-reports of all marketed drugs to Lareb. Pro's and con's of this bi-central organization of passive pharmacovigilance of AEFI will be discussed.

S005. Integrating quantitative signal detection in daily practice

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The primary aim of spontaneous reporting systems (SRS) is signal detection i.e. the timely detection of unknown adverse drug reactions (ADRs). Generally this is carried out by a systematic manual review of every report sent to a SRS. Case reports or case series are highly sensitive in picking up qualitative signals. On the other hand, they are limited in their ability to provide quantitative information. Statistical analysis of the data sets of a SRS, or quantitative signal detection, can provide this additional information concerning a possible relationship between a drug and an ADR. Despite the increasing popularity of these new approaches, application of these approaches is still no routine. We describe the place of quantitative signal detection and the way it is applied at the Netherlands Pharmacovigilance Centre Lareb. The extent to which this association between ADR and suspected drug stands out in respect to its background frequency in the database, is calculated using a 'reporting odds ratio' as a measure of disproportional. Three different approaches can be distinguished. Firstly