

Disease-related adverse events following non-live vaccines: Analysis of the WHO Global ICSRs database, VigiBase

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It has been recently suggested the existence of a vaccine-specific reporting bias for which some non-live vaccines may be preferentially reported as the suspected cause of the disease or symptoms/signs related to the disease they should prevent (Oka's et al., 2011). Therefore, the application of disproportional measures for signal detection purposes to post-marketing surveillance databases may generate false associations. The aim of this study was to analyze the WHO Global Individual Case Safety Report (ICSR) database, VigiBase (Lindqvist, 2008), in order to explore this newly described reporting bias in greater detail and to verify whether it can generate potentially misleading signals of disproportionate reporting (SDRs). All vaccines reports entered into VigiBase between 1990 and 2011 were extracted. Suspected duplicates (Noren et al., 2007) and reports of vaccination failure were removed. Twelve non-combined non-live vaccines were chosen for analysis. To retrieve reports of interest, a selection of MedDRA preferred terms (PTs) was performed. Per each of the 12 infectious diseases related to the non-live vaccines tested, two distinct groups of terms were selected: '*disease-specific AEFIs*' and '*disease/organ related conditions*'. Therefore, 24 vaccine-events pairs were obtained and referred to as 'misleading combinations'. A descriptive analysis of the reports retrieved was performed. The reporting rate distribution of the 24 groups of selected PTs per vaccine included in the study was observed. To verify whether the combinations retrieved could generate potentially misleading SDRs, the Reporting Odds Ratio (ROR) with 95% confidence intervals was calculated considering all the other vaccine reports as the background (Bate et al., 2009). A total of 627,165 reports were analyzed. Among ICSRs containing a 'misleading combination', healthcare professionals were the most frequently noted (17%), though reporter type was unknown in 72% of the remaining reports. The reporting rate distribution showed that for 16 out of 24 group of terms tested the highest reporting frequency was reached in association with the vaccine representing the relevant 'misleading combination' (in 10 out of 12 cases among *disease-specific AEFIs* and 6 out of 12 cases among *disease/organ related conditions*). The ROR application resulted in 21 SDRs out of 24 'misleading combinations' tested (11 out of 12 and 10 out of 12 in the *disease-specific AEFIs* group and *disease/organ related conditions* respectively). Findings from this study support the existence of a vaccine-specific reporting bias. Since this phenomenon may result in potentially misleading SDRs, professionals involved in vaccine safety surveillance should also consider the influence of this vaccine-specific reporting bias during the validation of such disproportional associations.

Oka's et al. (2011). *Vaccine*. 29, 6321-26

Lindqvist (2008). *Drug Information Journal*. 42, 409-19.

Noren et al. (2007). *Data Mining and Knowledge Discovery*. 14, 305-28.

Bate et al. (2009). *Pharmacoepidemiol. Drug Saf.* 18, 427-36