Rapid & routine detection of vaccine safety signals

Robert Davis, Center for Health Research, Kaiser Permanente Georgia, Atlanta, USA

The link found in 1999 between rotavirus vaccine and intussusception, along with the association observed later between rofecoxib and heart disease, substantially increased interest in developing ways to perform effective post-marketing safety surveillance for vaccines and drugs. This talk will provide a historical overview of the issues faced while trying to develop the means of performing rapid, yet routine monitoring for vaccines in the CDC Vaccine Safety Datalink project. At first, a major challenge arose simply in orienting the large amounts of data such that it could be prepared easily and shared routinely on a weekly basis. At the same time, the data needed to contain enough detail and specificity as to allow its use for multivariate modeling. Once the data became available for use in analyses, the original models used Sequential Probability Ratio Testing (SPRT) to test for vaccine safety signals. However, it soon became apparent that temporal trends in coding and in the completeness of data collection threatened the accuracy of the results. It was only after these secular trends were accurately controlled that the SPRT processes performed well, and were then used to assess the safety of both rotavirus vaccine and the new acelluar pertussis-containing combination vaccines. Attempting to extend the use of SPRT to examine the safety of influenza vaccine, however, uncovered a fundamental limitation to this method, related to an excess dependence on prior knowledge of vaccine risk. Given that the level of the risk – for rare serious adverse events - of most vaccines are not well known before licensure, it was clear that there was the need to modify the SPRT process, leading to the development of the maximum likelihood estimate (maxSPRT). Currently maxSPRT is used by the VSD for performing surveillance on new vaccines licensed in the United States, while work continues on identifying the best ways to optimize the statistical approach to monitoring for vaccine safety. Other new methods under development will also be presented, including ‘case-based’ methods which reduce data requirements substantially; their strengths and limitations will be discussed. Ongoing challenges – such as how to decide which outcomes to screen for, and how to minimize ‘mission creep’ when performing surveillance – will be discussed using real-life examples.