



**CHMP Vaccine Working Party
Chairman: R Dobbelaer**

**VWP Conclusions from the Workshop on Co-administration of Vaccines
held on 31 Jan-1 Feb 2006**

The Workshop concentrated on issues regarding co-administration of vaccines (i.e. the administration of more than one vaccine at the same visit to a healthcare facility). It was recognised that in many instances co-administration involves giving a combination vaccine (i.e. a vaccine that contains multiple antigens) with monovalent vaccine(s) and/or another combination vaccine(s). The Workshop also considered how data derived from the administration of a combination vaccine might be used to support recommendations for concomitant administration of vaccines that collectively administer the same antigens as those included in the combination product.

General points

Vaccination schedules, particularly the crowded schedules applied during infancy that commonly require concomitant administrations of two or more vaccines, are becoming increasingly complex. The use of combination vaccines and the concomitant administration of vaccines both involve trade-offs between achieving some protection against a range of infectious diseases within a short timeframe and the possible negative effects of immune interference phenomena on the magnitude and/or quality of the immune response. Particular problems can arise when such trade-offs are applied to infant immunisation regimens due to the added complexities posed by immature immune systems. However, similar considerations for schedules and interference apply to concomitant vaccine administration in the more immunologically mature older children, adolescents and adults.

If immune interference with respect to one or more antigens is observed this may or may not be clinically important and has to be balanced against the need to provide immunisation at appropriate schedules that encourage good compliance. In many instances the importance, if any, of immune interference phenomena can only be evaluated during well-conducted post-marketing programmes that estimate vaccine effectiveness.

There are very real constraints on Companies regarding obtaining experimental data pre-licensure or post-licensure for every possible vaccine co-administration scenario that might be of interest across the EU. Therefore, there is always likely to be a need for further exploration of immune interference phenomena with specific co-administrations and at particular schedules to be performed in the post-marketing period. Such studies would most likely be performed by Public Health (PH) authorities with the capacity and infrastructure to obtain reliable data. Companies are encouraged to collaborate with PH authorities in acquiring such data.

Ideally, PH authorities should be aware of the possible issues related to concomitant administration of the vaccines of interest to the national and/or local situation before immunisation programs are set. However, it is unlikely that all the questions will already be answered before co-administration is implemented. For this reason it is essential that emerging evidence of potentially clinically significant interactions is brought to the attention of PH authorities since this could trigger modifications of existing schedules. Such data should be shared across the international PH community. Since it may take some time before results are published, establishing a mechanism for confidential pre-publication sharing of important findings across the EU would be optimal.

The establishment of vaccine registries in the EU (e.g. that record details of populations immunised, products used [including batch number] and immunisation schedule) would be an important tool for evaluation of the safety and effectiveness of concomitant use of vaccines.

Regarding clinical studies to assess co-administration and the reflection of the data in SPCs:

- Studies that explore the effects of vaccine co-administration should focus on safety and immunogenicity. The various study designs that might be used to assess the effects of co-administration and the evaluation and interpretation of immune responses are covered in general in EMEA/CHMP/VWP/164653/2005.
- The assessment of immunogenicity should be based primarily on measurement of functional immune responses using validated assays. An assessment of the cellular response should be performed whenever relevant to the type of vaccine/disease to be prevented.
- Ideally the immune responses with respect to each antigen that is co-administered should be adequate (e.g. as judged by any available surrogate markers for clinical protection) and should be non-inferior to the responses seen when the vaccines are administered alone to a similar population.
- The design and interpretation of co-administration studies (whether primary series or booster doses are evaluated) should take into account the absolute age and/or time post-vaccination by which it is considered necessary to achieve protection. In some instances, such as for co-administration of vaccines that contain polysaccharide antigens conjugated to protein carrier molecules, studies should take into account the possibility that the dose(s) and type(s) of conjugate vaccines co-administered in the primary series may have important effects on the response to booster doses of each conjugate construct.
- If a specific concomitant administration results in lower antibody responses to an antigen than seen with time-separated administrations predicting the clinical implications is not straightforward. For example if there has been satisfactory induction of immune memory during the primary series this may be sufficient to provide ongoing protection at least up to the time of a booster dose. However, it has become clear that for some infections, such as those due to rapidly invasive organisms, there is a need to maintain a minimal amount of circulating antibody for continued protection. Therefore, low post-primary antibody levels, with or without a rapid decay in concentrations in the ensuing months, may have important implications for the timing of booster doses even when satisfactory priming has been demonstrated.
- The timing of booster doses of individual vaccines, regardless of any immune interference that might have been observed on co-administration during primary series, should be based on post-primary antibody kinetics and any available efficacy and/or effectiveness data. Data already available or being generated with one or both vaccines given alone that might assist an assessment of the implications of immune interference for continued protection could also be used to identify the need for and timing of boosters.

- The risk of immunological interference to occur with co-administration of vaccines is maximal in early life (< 6 months of age) and decreases with increasing age.
- Taking into account the need for administration of multiple antigens within a short timeframe and the changes that occur in the infant immune system in the first months of life there should be a detailed pre-licensure assessment of the effects of co-administration for vaccines intended for use in primary infant immunisation series.
- If no immune interference is observed in young persons (e.g. infants or toddlers) it is unlikely to occur at later ages and therefore some extrapolation of data might be allowed.
- There is evidence that results obtained with accelerated schedules have the potential to be extrapolated to more relaxed schedules but not *vice versa*. For example, studies that employ the EPI (6, 10, 14 weeks) and 2, 3 and 4-month schedules may sometimes pick up immune interference phenomena that are not observed, or are observed to a lesser extent, when the schedule is more relaxed and immune responses after the final dose are generally greater (e.g. 2, 4 and 6 months or 3, 5 and 12 months). However, other factors may also play an important part in the immune responses observed to at least some antigens (e.g. due to effects of maternal antibody in infants and different background immunological stimuli at all ages).
- Studies in which vaccines are given concomitantly to boost previously primed individuals should take into account vaccination history (including type and dose of antigens administered), probability of pre-booster natural exposure and/or baseline serological status when selecting subjects for study and when interpreting the results.
- In principle, if no potentially clinically significant immune interference between antigens is seen with a combination vaccine when administered in a specific age group at a chosen schedule then no immunogenicity problems would be expected following co-administration of vaccines that collectively deliver the same antigens under the same conditions. Therefore, it may be possible to use data derived from the clinical development programme for a combination vaccine to support statements regarding co-administration of certain vaccines if all products are derived from the same manufacturer. More general extrapolations of data (i.e. between different manufacturer's products) could only be allowed if supported by detailed and robust justifications.
- Safety data obtained with a combination vaccine may not predict the local and general reactogenicity that might occur on co-administration of vaccines that collectively deliver the same antigens. Therefore, the available safety data from use of the combination vaccine and from each vaccine that is to be co-administered should be reviewed to assess whether any particular problems might be expected.
- Co-administration of vaccines to travellers very shortly before departure, even with use of condensed schedules, might affect time to onset of achieving protective levels. Ideally, co-administrations at the commonest potential schedules should be explored pre-licensure. Additional data to cover a wider range of scenarios would have to be obtained from further studies in the post-licensure period. However, it has to be acknowledged that it may fall to PH authorities and /or the military to conduct studies at schedules of most interest for particular situations. Studies should take into account factors that may modify the immune response such as type of malarial chemoprophylaxis and level of stress that may be encountered. Such data could be supplemented by information from independent organisations (e.g. traveller's medicine associations).
- The SPC should mention the extent of the available data on specific co-administration scenarios. If there are no data on a specific type of administration that is likely to be often

necessary then this should be mentioned. However, there is no need to preclude or advise caution about co-administrations for which there are no data unless there is other evidence available to suggest that there might be a problem.

- Extrapolation of data on co-administration with a specific product from one MAH to similar vaccines from other MAHs may be acceptable for those types of vaccines (e.g. MMR, HAV) for which there are already data to indicate that a significant interaction is very unlikely to occur.
- Whenever the available data indicate that assumptions about the effects of co-administration cannot be made any claims proposed for the SPC must be supported by a clinical study. For example, experience has shown that extrapolations cannot be made from data with one MAH's conjugated polysaccharide vaccine to other similar vaccines intended to prevent the same disease, even if the same carrier protein is used. These vaccines do not behave uniformly and the conjugate protein in combinations with the molecular characteristics of the polysaccharide may influence the likelihood of interactions.