

Summary of: WHO Virtual Consultation on the Safety of Adjuvanted Influenza Vaccines

Held by teleconference on June 3 2009 15:30-17:30 CET

A consultation was held by teleconference to review the safety of adjuvanted influenza vaccines. The purpose of this consultation was two-fold:

- (1) To review known and theoretical safety concerns associated with using adjuvants in influenza vaccines;
- (2) To discuss ways to prospectively evaluate vaccine safety.

Participants in the teleconference included vaccine manufacturers, experts in adjuvant development, influenza vaccines and safety evaluation, as well as representatives from regulatory agencies, WHO and other stake-holders.

Introduction (Peter Smith, Chair)

Several adjuvants have been shown to permit dose-reduction and enhanced breadth of immunity for influenza vaccines in clinical studies. In light of the recent outbreak of influenza A (H1N1)_v, there may be a need in the future to immunize large population groups. Adjuvants could potentially expand the supply of available influenza vaccines. While we have no evidence yet of the immunological benefit of adjuvants for vaccines against the H1N1 virus, a discussion of potential safety issues at this stage will facilitate planning and clinical trial design. Many adjuvants are under development, however this consultation will only discuss those that are licensed or have undergone late-stage clinical development with influenza antigens.

WHO has requested this non-confidential consultation to identify known and theoretical safety issues related to the use of adjuvants in pandemic influenza vaccines. The outcomes from this meeting will inform subsequent confidential dialogue between vaccine manufacturers, regulators and governments and will help address risk-benefit considerations by the WHO Global Advisory Committee on Vaccine Safety (GACVS) as well as policy-related recommendations by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).

Severe adverse events associated with unadjuvanted influenza vaccines (Neal Halsey)

Influenza vaccines have been used for more than 60 years comprised of various forms of the influenza antigen, primarily focused on the hemagglutinin protein, in split, subunit, inactivated whole virion, and cold-adapted, live attenuated vaccines. In general, unadjuvanted influenza vaccines have an established record of safety and tolerability in all age groups. However, over many years, there have been notable, albeit rare, serious adverse events (SAEs) either directly or indirectly associated with influenza vaccines. Potential SAEs directly or indirectly associated with influenza vaccines could be related to a number of different issues, including the injection process, vaccine contamination during production or during delivery, replication of a live agent, and normal or aberrant host immune responses to the vaccine or components thereof, including

fever and febrile seizures, immediate or delayed hypersensitivity, oculo-respiratory syndrome, or Guillain-Barre syndrome. There have been reports of coincidental associations between some rare serious adverse events and influenza vaccination including transverse myelitis, serum sickness, and clusters of sudden death in adults, but evidence supporting a causal association is lacking.

In most cases, the incidence of SAEs associated with influenza vaccines have been rare and in some cases hypothesized associations were unfounded. In 1976 there was an increased risk of Guillain-Barre syndrome following the swine influenza vaccine at a rate of approximately 1 per 100,000. There was an hypothesis that the vaccine may have been contaminated with with *C. jejuni*, a known cause of Guillain-Barre syndrome. However, one recent study found no evidence of *C. jejuni* contamination and the causative factor in that vaccine has not been determined.. It is important to note that mass vaccination campaigns will likely result in temporal associations of SAEs and there is a likelihood of many coincidental adverse events to be reported. Participants commented that the community should define and document background rates for conditions such as GBS prior to immunization campaigns so that any occurrence of these can be compared to background. The incidence of such conditions may also be affected by other background events such as other viral or bacterial outbreaks, confounding the situation. In addition, some adverse events with known causal relationships will occur and it will become increasingly challenging to determine higher than expected rates of such occurrences.

Squalene-containing oil-in-water adjuvants (Steve Reed)

Numerous oil-in-water emulsions are known to have adjuvant activity for vaccines, however two (MF59 from Novartis and AS03 from GSK) are in registered influenza vaccines and one other (AF03 from Sanofi Pasteur) has undergone extensive safety testing. While all of these contain squalene or squalene and tocopherol as the oil-phase, their compositions are vastly different and hence safety demonstrated with one can not be extrapolated to the others. Also, while it has been shown that these emulsions induce some APC activation, monocytes migration, and perhaps improved antigen presentation, the precise mechanism of action by which these emulsions cause these effects is not known and hence the safety of emulsions must be viewed on case-by-case basis.

MF59 is the most widely evaluated of these emulsions: given to over 26 thousand people of all ages in over 44 clinical trials with follow-up for up to 200 days in most cases. In addition, over 40 million doses of Flud, an influenza vaccine containing MF59 and approved in 1997 for older adults in 26 countries, have been distributed and evaluated in various high risk and immune-suppressed groups and no safety signals of significance have been reported publicly. MF59 has been evaluated in clinical trials with influenza antigens in over 20,000 elderly, 6,000 adults and 700 children. While increased local reactogenicity has been observed, there has been no detectable increase in autoimmune disease, cardiovascular diseases, serious adverse events, hospitalizations, or death associated with the use of the adjuvanted influenza vaccine.

AS03 has been evaluated in 45,000 individuals. An integrated summary of safety from 15,400 subjects with a 6-month follow up suggests an increase in local reactogenicity, however no increase in immune-mediated events above background rates. AF03 has been evaluated for

safety in two phase 1 trials in adults involving 513 volunteers. No safety signals have been reported.

One topic related to safety of oil-in-water emulsions that has been debated was the concern of inducing anti-squalene antibodies. This has been reviewed by the GACVS¹ on vaccine safety who found the concern to be unjustified, but noted that the experience of squalene-containing vaccines has been primarily in older age-groups and recommended that as squalene-containing vaccines are introduced in other age-groups, careful post-marketing follow up to detect any vaccine-related adverse events needs to be performed. It was pointed out by participants that background anti-squalene antibodies vary from population to population, possibly as a function of diet.

There was some discussion on the potential of lowering the amount of squalene used and perhaps empirical determination of the dose currently used in influenza vaccines. There does seem to be data that has been generated showing that it is possible to reduce the squalene content and achieve a similar level of immunogenicity. However, the manufacturers stressed the importance of the safety database generated with the current dose of squalene and very limited safety data exists with lower amounts and it is difficult to determine if the immune response is altered in other ways by using a lower dose.

Other adjuvants (Masato Tashiro)

There are other adjuvants either licensed or under immediate consideration for use in influenza vaccines, including aluminium salts, and to a much lesser extent virosomes and polyoxidonium.

Aluminium salts (alum; referring to the various salts including hydroxide and phosphate) are widely used in vaccines and rare SAEs associated with this adjuvant family are well documented and have been the subject of numerous safety reviews. Aluminium salts have been extensively evaluated in numerous vaccines, but are less frequently used in formulation of influenza vaccines compared to other vaccines. Aluminium salts are included in approved seasonal (whole-cell seasonal vaccine produced in Hungary) and several vaccines against novel human influenza viruses (e.g. H5N1). No safety signals have appeared in clinical trials in all ages.

Polyoxidonium is a poly-electrolyte polymer used as an immunostimulator in the Grippol influenza vaccine approved and distributed in Russia. A signal of possible safety concerns (allergy, angioedema) arose during a campaign in 2006 however a direct causal relationship has not been concluded².

Virosomes are used in an approved seasonal influenza vaccine (Invivax). No safety concerns have been detected following parenteral administration, however again, the number of doses evaluated and distributed are small compared to those of other discussed adjuvants.

Discussion

¹ <http://www.who.int/wer/2006/wer8128.pdf>

² http://www.who.int/wer/2007/wer8228_29.pdf

The floor was then opened for discussion. A variety of general issues were discussed, including the need for careful clinical studies not only to show the safety of adjuvanted influenza vaccines, but also to demonstrate in parallel immunological benefit in various age groups with differing levels of pre-existing antibodies to the vaccine strain. While there is potential dose-sparing effect of adding adjuvants to pandemic influenza vaccines, there could also be sufficient levels of protective immunity raised by unadjuvanted vaccines if the population or portion thereof is already primed against the pandemic virus strain. It was recommended that dose-ranging studies both with and without adjuvant be conducted to better understand the benefit of adding an adjuvant.

Some concern were raised on the use of squalene-containing adjuvants in all age groups, due to limited experience with these products in children. These adjuvants must therefore be introduced carefully into these groups. In particular there are no data at all on the safety of squalene-adjuvanted vaccines in the very young (under 6 months).

Another major topic of discussion was the need to conduct careful post-marketing surveillance to be able to quickly identify and report adverse events when they occur. Challenges to doing this include the need to identify specific conditions that should be monitored as well as to establish common case definitions to be used globally to identify and collect valuable information in real-time during mass vaccinations campaigns. Conditions that were suggested included GBS, demyelinating diseases and also immediate hypersensitivity and ocular/respiratory syndrome. Clinicians need to receive background information on various conditions that need close monitoring; expect many false concerns to be raised as well. A need for a coordinated approach to post market surveillance was expressed. It was suggested that a group such as GACVS could take a lead in this role and provide guidance for working on common protocols.

The challenge was raised on the need to have some portion of the population serve as a control to enable the evaluation of the risk/benefit ratio and of potential safety issues observed during mass vaccination. It will however be very difficult to monitor for background incidence if everyone is receiving the vaccine at once. This might be addressed by active surveillance in the general population, but it might be extremely difficult to do this reliably. This issue clearly needs careful consideration.

Participants attempted to address the question of an appropriate period of safety follow-up. While many SAEs would likely fall within a 6 to 8 weeks window, the use of new adjuvants may bring uncertainties and risks that have not yet been identified. However, monitoring for 6 to 12 months would be a challenge. After further discussion, no objections were raised to monitoring for 6 to 8 weeks after vaccination. However it was pointed out that while SAEs such as GBS have typically occurred within this window, it is not known whether the use of adjuvants could modify the time period to occurrence of vaccine related SAEs.

There was considerable discussion on the use of adjuvanted influenza vaccines in very young children and in cases of early pregnancy. Adjuvants are known to have an effect on cytokine regulation and the impact of this in very young children and early stage pregnancy has not yet been studied. Regulatory agencies currently focus on antibody responses and not as much on cytokine responses in vaccinated subjects.

Some participants proposed that adjuvanted vaccines might also be contra-indicated if a vaccinee has a history of prior GBS. Seasonal influenza vaccines currently have notes of caution for use in such persons. A similar approach might be considered to reduce the risk for subsequent episodes of GBS. Research on the role of anti-gM1 antibodies in GBS and the possibility of influenza vaccines to modify such immune responses is currently being considered. Such research may contribute to an improved understanding of potential causality and risk with adjuvanted influenza vaccines.

There is limited data available on the safety of concomitant administration of seasonal vaccine with an adjuvanted pandemic vaccine, and it was suggested that this be addressed in upcoming clinical trials. Novartis has data in over 1,000 people who were given a dose of adjuvanted pandemic vaccine at the same time as their seasonal vaccine. In their experience, there was no detectable interference between the two vaccines. GSK indicated that while they have not evaluated concomitant delivery, they have evaluated adjuvanted pandemic vaccines in subjects who were pre-vaccinated with seasonal vaccine.

Summary

A WHO virtual consultation was held with over 60 experts on regulatory, manufacturing, immunology, virology, clinical and policy to discuss the safety of adjuvanted influenza vaccines. Following a brief overview of currently licensed or late-stage influenza vaccines with and without adjuvants and a review of adverse events that have been associated with such vaccines, participants discussed various topics related to the safety of such vaccines and of their widespread use in mass vaccination campaigns against an H1N1v pandemic virus. While it was noted that there have been rare cases of SAEs with influenza vaccines in the past, there is currently no clinical experience to assess the risk or benefit of using adjuvanted or non-adjuvanted H1N1 vaccines. Clinical studies are the only way to address such questions. Careful studies with harmonized trial design, case definition and post-marketing monitoring are planned and will be initiated soon. The WHO could play an important role in facilitating such activities through the GACVS. Unknown risks exist in certain age and risk groups where limited data exists with adjuvanted influenza vaccines and methods for introducing vaccines into these groups should proceed cautiously. Furthermore, the need for a population control group to monitor for baseline events to be able to identify an increased incidence of SAEs in vaccine recipients remains an unresolved challenge. Overall, no significant safety concern or barriers to evaluating or using adjuvanted vaccines for the current H1N1 vaccine were raised.

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