Australian Government

Department of Health and Ageing

IMMUNISATION

Chief Medical Officer

Guidance on revaccination where HPV vaccine doses have been given at less than recommended minimum intervals January 2009

The Chief Medical Officer has provided the following guidance to assist immunisation providers in making a decision on whether to revaccinate a person who has received doses of HPV vaccine at less than the recommended minimum intervals. The guidance has been developed in consultation with the National Centre for Immunisation Research and other immunisation experts, based on currently available evidence.

Principles:

- The minimum dosage intervals for HPV vaccination recommended in the Australian Immunisation Handbook are: 1 month between doses 1 and 2; and 3 months between doses 2 and 3 ie a total interval between doses 1 and 3 of 4 months. In keeping with other vaccines in Australia, valid vaccination is considered to have occurred where first and second doses have been given 27 or more days apart and second and third doses have been given 84 or more days apart ie a total interval of 111 or more days .
- Every effort should be made to adhere to the recommended dose intervals as efficacy data for the HPV vaccines are based on them. However, where receipt of three doses of bivalent or quadrivalent HPV vaccine is documented, the risk of an immune response sufficiently suboptimal to result in clinically significant reduction in protection against HPV infection is low.
- The highest risk of suboptimal response would be where there was a shorter than minimum recommended interval between *both* Dose 1 and 2 *and* Dose 2 and 3 (ie a total of less than 111 days between Dose 1 and Dose 3). This would be particularly the case where there was less than 14 days between dose 1 and dose 2 *and* less than 60 days between dose 2 and dose 3 (ie less than 74 days between dose 1 and dose 3).

Based on these principles, the following is recommended:

- *Gap between the first and third dose is 111 days or longer*: Although there may be quantifiable differences in the mean antibody titre achieved in the short term, repeat vaccination is not justified for any recipient of 3 doses across this time interval.
- *Gap between the first and third doses is 74 to 111 days* - depending on the age of the recipient, public health practitioners should judge the balance of risks and benefits of re-vaccination. For those aged 15 years and under, among whom antibody responses to 2 doses are similar to 3 doses in older females, repeat vaccination would not generally be justified. If given, the fourth dose should be at least 6 months after the recorded date of the third dose.
- *Gap between the first and third doses less than 74 days* - it would be prudent to give a fourth dose at least 6 months after the recorded date of the third dose.

Policy Rationale

Background

The schedule recommended by manufacturers differs for the quadrivalent (0,2,6 months and bivalent (0,1,6 months) HPV vaccines. Although data to confirm this for HPV vaccines are lacking, from first principles delayed administration, especially of the third dose, is expected to give at least comparable, and most likely superior, immune responses and additional doses will not be indicated.

With respect to accelerated schedules, 0,1, 4 months is listed as acceptable by the Australian Immunisation Handbook in the context of school-based administration, with minimum intervals of 1 month and 3 months between first and second and second and third doses respectively. However, no statement is made as to the need for an additional dose should vaccine be administered at a shorter inter-dose interval. Internationally, only the United States of America specifically recommends repeat administration of doses given too early.

In a large program it is inevitable that doses will be given earlier than the minimum recommended intervals. If this occurs, the alternatives range from a conservative approach, under which all doses administered earlier than 27[1] days after dose 1 or 84 days[2] after dose 2 are repeated, to a risk-based approach, where an additional dose is given only under circumstances where the risk of an inadequate immune response is unacceptably high.

Risk of inadequate response with less than minimum dosage intervals

Dose one to dose two interval

The available data show that a minimum interval of 30 days results in immune responses comparable to longer intervals. An interval as short as 15 days has been studied for the bivalent vaccine but data are not available.

Dose two to dose three interval

For the quadrivalent vaccine, available data show a non-significant trend to higher mean antibody levels when the third dose is given a minimum of 106 versus a minimum of 80 days following the second. However these lower mean titres were still many orders of magnitude higher than seen after natural infection.

Importance of age

In girls 10-15 years, antibody responses following two doses of quadrivalent vaccine were higher than those after three doses in 16-23 year old women.

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1 *As per ACIR guidelines for other vaccines*

2 *3 months is taken as equivalent to 12 weeks or 84 days*

Lack of direct correlation between antibody level and protection

Although antibody is important for protection, no threshold below which protection against infection wanes has been identified. Data on response to subsequent HPV exposure are not available, but antibody levels achieved even in the worst case scenario are many-fold higher than those seen after natural infection.

Conclusion

Although efficacy data, and also immunogenicity data for more extreme scenarios, are lacking for accelerated schedules, the key determinant of immune response is likely to be the nature of the vaccine course as a whole. Thus, although intervals between dose 1 and 2 of less than 30 days may be associated with lower pre-dose 3 antibody levels, as long as the interval is at least 14 days and a third dose is administered, the available data suggest that adequate protection will be achieved. Similarly, the robust responses to a third dose across the range of studied lower dose intervals following dose 2 suggest that quite gross variations from this would be needed to adversely affect antibody responses to a degree which was clinically significant. Overall, the risk of a response inadequate for protection against HPV infection following receipt of 3 doses across a wide range of dosing intervals seems likely be very low in the short to medium term. Thus, the case for re-vaccination following administration of dose 2 or 3 at less than the recommended minimum interval, given the cost, inconvenience and potential for higher rates of at least local reactions, seems weak under most scenarios.