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29 April 2025

cc	Prof Ellen Crushell	Deputy CMO, DOH
	Ms Michael Duffy	Head of Unit, DOH
	Ms Pauline Brady	CMO Office, DOH
	Dr Máirín Ryan	Director of Health Technology Assessment and Deputy CEO, HIQA
	Dr Patricia Harrington	Deputy Director, Health Technology Assessment Directorate, HIQA

RE: Rationale for 4 in 1 vaccine minimum interval recommended in the updated primary childhood catch-up schedule

Dear Mary,

I am writing regarding your request that NIAC outline the rationale for minimum intervals for the 4 in 1 (DTaP/IPV - diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine) vaccine recommended in the updated primary childhood catch-up schedule.

Introduction of 4th dose of 6 in 1 vaccine at 13 months

The 6 in 1 vaccine includes diphtheria, *Haemophilus influenzae* b (Hib), hepatitis B (hepB), acellular pertussis, inactivated polio and tetanus vaccines. The rationale for a 6 in 1 booster in the second year of life was previously outlined in detail in NIAC's recommendation in February 2023.¹ In summary NIAC recommended that a 4th dose of 6 in 1 be given at 13 months of age:

- To replace the Hib/Men C vaccine as manufacture was due to be discontinued. While a monovalent Hib vaccine is available, the 6 in 1 also targets Hib and can boost protection to Hib as well as to diphtheria, hepatitis B, inactivated polio, acellular pertussis, and tetanus.
- To bring Ireland in line with the EU/EAA and other countries recommending a booster dose of 6 in 1 vaccine in the second year of life.
- To remove the gap of four years between the primary 6 in 1 series and a 4 in 1 booster at school entry, which is associated with waning of immunity prior to boosting and leading to susceptibility to breakthrough infections.
- To bring Ireland in line with the WHO recommendation for a pertussis booster dose in the second year of life ≥ 6 months after last primary dose.²

NIAC recommended the scheduled time for the 4th dose be at 13 months, as this is seven months after the scheduled 3rd dose of the primary series of 6 in 1 vaccine, which is in keeping with schedules for the US³ (at 15-18 months); Canada⁴ (at 12-23 months, usually 18 months); and Australia⁵ (at 18

months). These countries also follow the 2, 4, and 6 month schedule for the primary series of the 6 in 1 vaccine that Ireland follows. The minimum interval and age in catch-up schedules recommended by the US, Canada, and Australia – where a 4th dose is given in the second year of life – are six months after the 3rd dose in the primary series and a minimum age of 12 months.^{3,4,5}

In determining the timing of the 4th dose of 6 in 1, NIAC considered the following: *“The requirement for three injections at each of the 12 and 13 month visits in the updated schedule could impact its acceptability among parents/carers. An alternative schedule that confers similar benefits in terms of protection and might be associated with reduced reactogenicity at the 13 month visit would be to give a monovalent Hib vaccine at 13 months concomitantly with MenC and PCV vaccines (no reduction in number of injections) and give the 6 in 1 at a separate additional 15-18 month visit. The reliance on the monovalent Hib vaccine incorporates an additional risk in terms of security of vaccine supply. It would also involve an extra health care visit and further time commitment from the parent/carer. Taking into consideration the need for an extra GP visit, the additional intrusion into the daily schedule and time off work required, the alternative requiring an extra clinic visit is considered a less favourable option. A schedule that requires fewer health care visits is more likely to be associated with higher vaccine uptake. A period of enhanced surveillance for potential adverse events following the change could provide reassurance with regard to the acceptability and tolerability of the schedule.”*¹

Delays in the routine 6 in 1 vaccine schedule

NIAC recommends that the Primary Childhood Immunisation Programme (PCIP) should prioritise children getting their vaccines on time every time, as the immunisation schedule is designed, via combination vaccines and a series of vaccine doses at the optimal time, to protect children from serious diseases when they are most vulnerable.

However, we understand from colleagues in the National Immunisation Office (NIO) that the 6-month interval between dose 3 and dose 4 could be problematic from an implementation perspective if a child receives their 6 month vaccines late, as it is important that the remaining vaccines due at 13 months are not delayed to allow the 4th dose of 6 in 1 vaccine to be given at the same time. Therefore, an extra GP visit to give the 4th 6 in 1 vaccine will be required for some children on catch-up schedules due to this minimum interval (i.e. children who have their 3rd dose of 6 in 1 vaccine at ≥ 12 months of age).

Third dose of 6 in 1 given at <12 months of age

If a child is delayed in their 6 in 1 schedule such that they have their 3rd dose after six months but before 12 months **they should resume the recommended schedule** and have their 4th dose of 6 in 1 vaccine as scheduled at least 4 weeks after the 3rd dose of 6 in 1 vaccine and at the same time as other vaccines due at 13 months as long as those vaccines are complying with their minimum intervals. For example, if the second dose of PCV13 is given later than six months there is a requirement of a minimum interval of 8 weeks between dose 2 and dose 3, and dose 3 to be given at ≥ 12 months of age.

Third dose of 6 in 1 given at ≥ 12 months of age

If a child is delayed in their 6 in 1 schedule such that they have their 3rd dose of 6 in 1 vaccine at ≥ 12 months the requirement to give a dose of Hib vaccine in the second year of life will be met and, as hepatitis B vaccine series will be completed, the 4th dose of 6 in 1 at 13 months is not required.

However, a booster dose of 4 in 1 (DTaP/IPV) is recommended at least 6 months after the 3rd dose of 6 in 1 (delayed until ≥ 12 months) as part of their catch-up schedule. The administration of other vaccines due at 13 months should not be delayed because of the required minimum interval for 4 in 1 catch-up.

For catch-up of delayed vaccinations (where the 3rd dose of 6 in 1 vaccine is given at ≥ 12 months), the minimum interval between the 3rd and 4th dose is 6 months, as this is a booster dose and a more prolonged interval between primary series and booster dose improves duration of protection.

Following the introduction of a 4th dose of 6 in 1 into the primary childhood schedule for children born on or after 1st October 2024, NIAC Chapter 2 guidelines on catch-up schedules for those with delayed immunisation, or late entrants to Irish healthcare system, were updated.⁶ Included in this guidance is a recommendation that if the 3rd dose of 6 in 1 (DTaP/HepB/Hib/IPV) is given at ≥ 12 months of age, then the 4th dose may be given as 4 in 1 (DTaP/IPV), as children over 12 months of age require only one dose of Hib vaccine and hepatitis B series is completed on the 3rd dose, so a 6 in 1 vaccine is not required.

In this instance, the boosting effect of the 4th dose confers adequate protection until the next 4 in 1 booster in Junior infants. As such, if the 4th dose is delayed until the child is aged ≥ 3 years and 4 months, the booster dose at Junior Infants can be omitted and another booster would not be required until 12-13 years. This is similar to the US³ - *“at age 4 years or older and at least 6 months after dose 3”*; Canada⁷ – *“after fourth birthday”* and Australia⁸ - *“dose 4 received at >3.5 years of age, then dose 5 is not needed”*. The UK⁹ recommends a 4th dose at three years and four months, as a pre-school booster, with the next booster due in adolescence. Children from the UK are the most common group presenting for transition to the Junior Infant schools immunisation programme in Ireland where this situation arises.

Finally, the 4 in 1 (DTaP/IPV) vaccine is not routinely provided by the HSE to general practice. As such, if the 4 in 1 vaccine is not available for this 4th dose, NIAC recommends that a 6 in 1 vaccine may be used.

Kind regards,



Dr Edina Moylett
NIAC Chair

References

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