ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

RECOMMENDATIONS REGARDING HPV VACCINE DOSAGE

NIAC | 06.09.2022

About NIAC

NIAC membership includes nominees from the RCPI, its Faculties and Institutes, the RCSI, the ICGP, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

NIAC meets to consider new evidence about vaccines and provide advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.

RECOMMENDATIONS

1. A single dose of human papillomavirus (HPV) vaccine is recommended for unvaccinated females and males aged 9-24 years of age.
2. Those aged 25 years and older for whom the vaccine is recommended, or who choose to receive it, require a two dose schedule at 0 and 6-12 months.
3. Those with immunocompromise require a three dose schedule at 0, 2 and 6 months regardless of age.
4. Priority should be given to achieving vaccine uptake of 90% to maximise the effectiveness of a single dose HPV vaccination programme.
5. Enhanced surveillance is required to monitor for the emergence of any replacement serotypes and to detect any decline in HPV9 vaccine effectiveness.

These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about HPV vaccines is evolving and being refined. Recommendations may be updated when more information becomes available.

1. EXECUTIVE SUMMARY

- In females aged 9-45 years, two and three dose HPV vaccination schedules have been shown to provide durable protection for at least a decade following vaccination. Based on immunobridging, similar protection against HPV infection and disease in males is inferred.
- A catch-up HPV vaccination programme for males and females aged 15-24 years was recommended in April 2022, with priority given to those in second level education.
- Following one, two, or three vaccine doses, HPV antibodies reach an early peak followed by a decline to plateau around 18-36 months, and remain stable for at least 11 years.
- HPV antibody levels are significantly lower after one compared with two or three vaccine doses. However, they are several fold higher than those following natural infection. The decline from the peak after one dose is less compared with that after two or three doses.
- Most evidence indicates that in those aged up to 25 years who are immunocompetent there is no significant difference in vaccine effectiveness between those who receive one, two, or three vaccine doses. This is strongly supported by data from randomised controlled trials in those aged up to 20 years.
- Those aged 25-45 years have similar vaccine responses with high seroconversion rates and durable antibody responses, albeit at lower levels for some HPV serotypes than in younger age cohorts.
- For those aged 25 years and older and immunocompetent, available immunogenicity data provide sufficient evidence to support a two dose schedule, consistent with World Health Organization (WHO) recommendations.
- A reduction in the number of doses should enhance the efficiency of the catch-up vaccination programme and could improve vaccine acceptability by the target population.
- A vaccine uptake of the routine HPV vaccination programme of 90% is required to maximise the effectiveness of a single dose schedule. Increasing the numbers vaccinated not only increases individual protection but also improves herd immunity.
- Reduction in the number of vaccine doses is associated with an unlikely risk of a later decline in antibodies to a level associated with reduced effectiveness. Longer term follow up studies of single dose strategy, currently underway, will detect if there is a significant decline in protection which may require an additional vaccine dose at a later date.
- Further risk mitigation can be achieved by HPV infection surveillance. Surveillance is an essential part of the HPV prevention programme to monitor for the emergence of any replacement serotypes. Such surveillance would also serve as an early warning system if protection against HPV9 vaccine effectiveness were to decline.
- There are insufficient data to support a one or two dose schedule for those with immunocompromise regardless of age.

2. BACKGROUND

The HPV vaccination programme commenced in Ireland in 2010 with a three dose HPV vaccine schedule at 0, 2 and 6 months offered to all females aged 12-13 years (first year of second level school).

Since September 2014, a two dose schedule at 0 and 6 months has been recommended for all girls under 15 years of age in the routine HPV vaccination programme. A three dose schedule is recommended for those aged 15 years and older and for those with immunocompromise regardless of age.

Since September 2019, HPV vaccine has been offered to boys and girls in first year of second level school. HPV vaccine coverage in Ireland is currently 79% for one dose and 74% for two dose completion in 2020/21.[1]

On 14 April 2022, NIAC issued updated recommendations for HPV vaccination including catch-up vaccination of unvaccinated females and males under the age of 25 years, with priority given to second level students and females under the age of 25 years.

Evidence suggests that the number of doses in the routine immunisation programme and for some older age groups can be reduced without loss of protection. This document outlines the rationale and evidence for recommendations to reduce the number of HPV vaccine doses required for those who are immunocompetent.

3. HPV VACCINES

The European Medicines Agency (EMA) has authorised HPV vaccines for those aged nine years and older for the prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by the constituent HPV types, and genital warts causally related to specific HPV types.

Three HPV vaccines authorised for use in Ireland:

- HPV2 (Cervarix) targets HPV types 16 and 18
- HPV4 (Gardasil) targets HPV types 6, 11, 16 and 18
- HPV9 (Gardasil 9) targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

HPV9 is the vaccine currently recommended in Ireland.

In June 2020, the Food and Drug Administration (FDA) extended their authorisation of HPV9 vaccine to include the prevention of oropharyngeal and other head and neck cancers in males and females caused by HPV types 16, 18, 31, 33, 45, 52, and 58.

HPV vaccination has been shown to significantly reduce HPV infections[2], anogenital warts[3-5] cervical precancers and cancers,[6,7] with some countries reporting increases in herd immunity.[2,3,8-10] Almost 90% of cervical and anal cancers are caused by HPV strains targeted by HPV9 vaccine. HPV4 and HPV9 vaccines target HPV types associated with over 90% of anogenital warts.

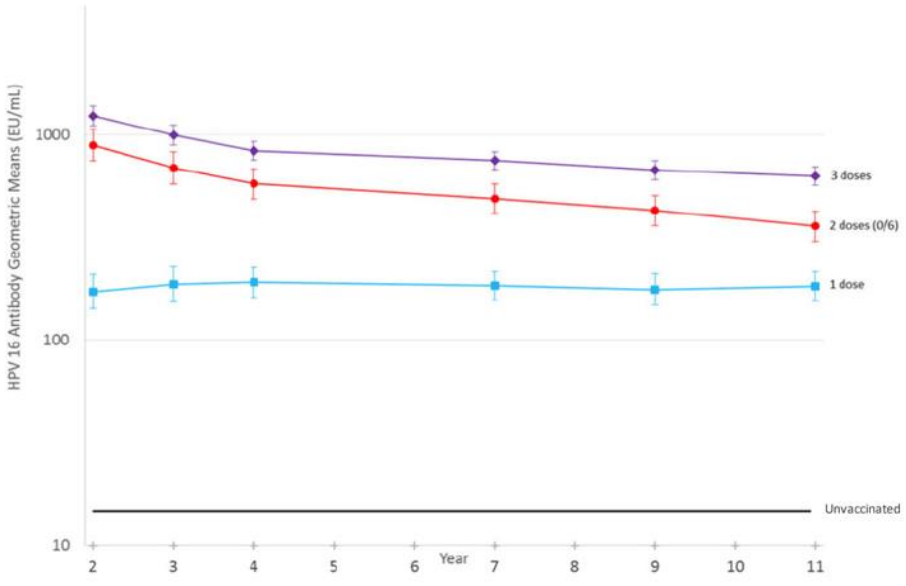
4. EVIDENCE FOR A SINGLE HPV VACCINE DOSE SCHEDULE IN THOSE AGED 9-24 YEARS

HPV antibodies are the primary mediators of vaccine induced protection. However, a defined threshold of immunological protection has not been established. HPV vaccination induces very high rates of seroconversion across gender and age. There is now evidence of a high rate of seroconversion even after one vaccine dose. In general, higher levels of vaccine induced antibodies are seen in younger age cohorts.

Immunogenicity

In women first vaccinated at age 18-25 years, vaccine induced HPV16 and 18 antibody levels, even after one dose, are up to ten times higher than after natural infection and are durable for at least 10 years. (Figure 1)[11]

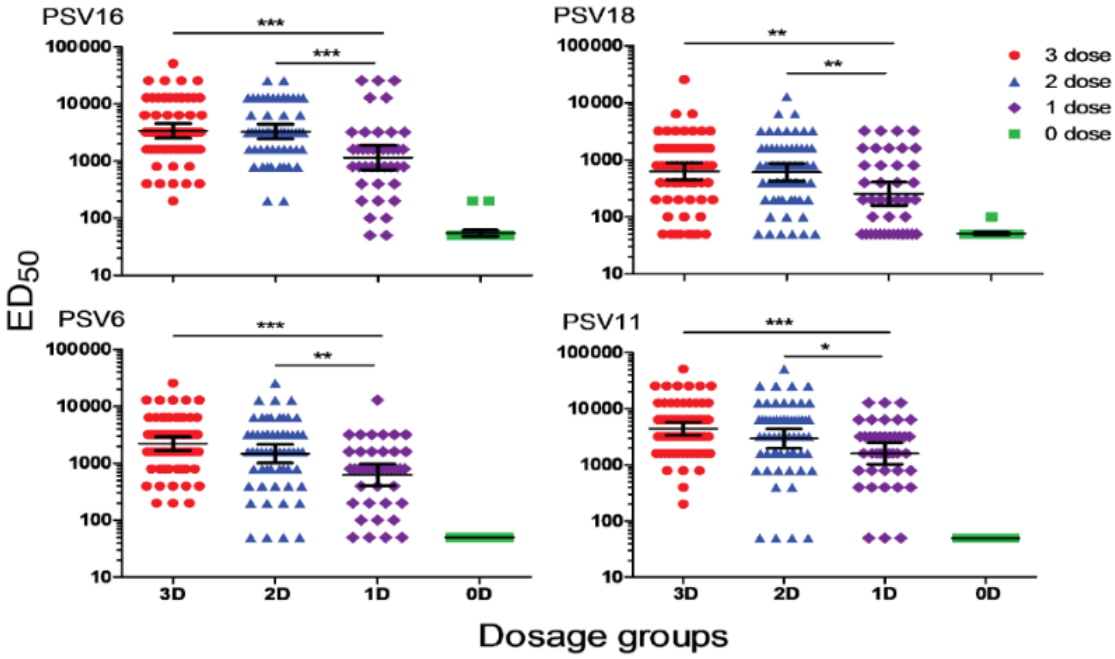
Figure 1. HPV 16 antibody levels after 1, 2, or 3 doses of HPV2 vaccine over 11 years. Source: Kreimer et al.[11]



HPV16 and 18 antibody levels did not qualitatively decline between four and 11 years after vaccination regardless of the number of doses given. All vaccinated women remained seropositive nine and 11 years after vaccination regardless of number of doses received.[11,12] This means that a one or two dose schedule is likely to be as effective as a three dose schedule, as antibody levels were so well sustained over time.

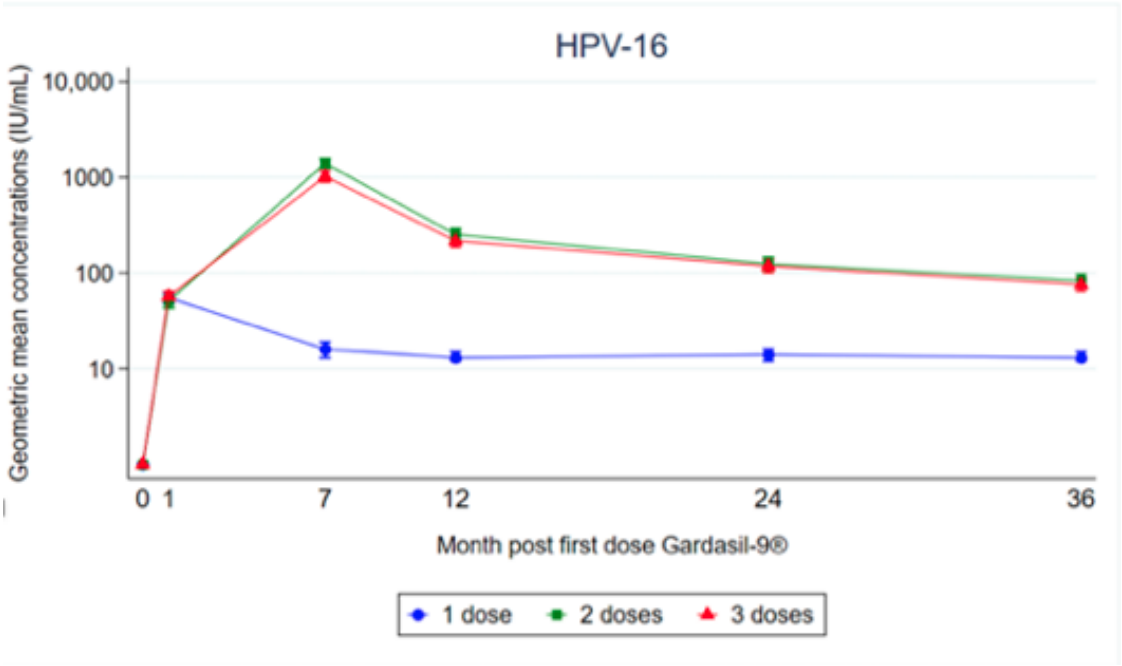
Sustained antibody responses six years following one, two, or three doses of HPV4 vaccine were found in a prospective cohort of 200 Fijian girls who were first vaccinated at 9-12 years. Although one dose recipients had significantly lower antibody titres than two or three dose recipients, titres were 5-30 fold higher than in unvaccinated girls. (Figure 2)[13]

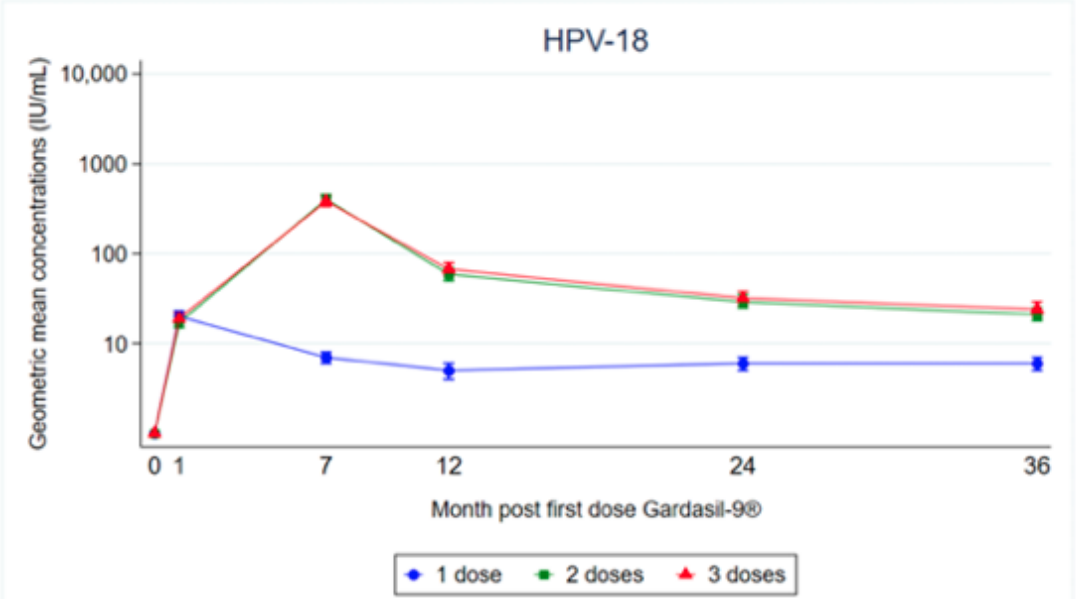
Figure 2. Antibody responses six years following HPV4 vaccination in girls aged 15-19 years. Source: Toh et al.[13]



In a Tanzanian study a single dose of HPV2 or HPV9 vaccine given to girls aged 9-14 years induced seropositivity of greater than 98% and robust immune responses lasted for up to 36 months.[14] As in other studies, antibody levels following one dose were lower than after two or three doses and were associated with a lower peak, but declined less and reached a plateau around month 12 remaining relatively constant thereafter. (Figure 3)[14]

Figure 3. HPV16/18 concentrations over time following a single dose of HPV9 vaccine. Source: Watson-Jones et al.[14]





There was no dose dependant difference in antibody avidity, an indication of strength of binding of antibody to antigen. In immunobridging studies antibody levels were non-inferior to those in three other studies[11,15,16] where one dose efficacy was observed.

In India, HPV antibody levels following one dose of HPV4 vaccine in girls aged 10-18 years were significantly lower than those following two or three doses.[17] However neutralising antibodies were detectable in all subjects. Antibody avidity after one or two doses was similar to that after three doses. The lower antibody levels in one dose recipients were not associated with reduced effectiveness. No persistent HPV infection was detected in any participant over a median follow up of 4.7 years.[17]

Preliminary analysis of an ongoing US non-randomised trial on the immunogenicity of a prime and delayed booster dosing schedule of HPV9 vaccine demonstrated that anti-HPV16 and anti-HPV18 GMTs remained stable and persistent between 12 and 24 months after one dose of HPV9 vaccine. Neutralisation assays, antibody avidity measurements and longer-term immunogenicity evaluations after delayed booster are currently underway.[18,19]

In a systematic review of efficacy and immunogenicity of one compared with two or three HPV vaccine doses involving 7 that included two[12,17] of the above studies, HPV16/18 seropositivity rates were very high following vaccination (97-100%) irrespective of dose schedule. Antibody levels were significantly lower following one dose compared with two or three doses. However, the authors noted that *"whilst levels for two and three-dose arms declined following an initial increase, plateauing thereafter, this trend was typically less pronounced in the one-dose arms, in which levels remained more stable throughout follow-up".*[20]

Overall, the data are consistent in showing that, although antibody levels after one dose are lower than those achieved after two or three doses, they are several fold higher than after infection and are as durable as those following three doses for up to 11 years.

Vaccine efficacy and effectiveness

Efficacy and effectiveness against HPV infection

A US cross-sectional study examined the prevalence of HPV infection among women who received between none and three doses of HPV4 vaccine. Infection with HPV type 6, 11, 16, or 18 was significantly less prevalent among women who received one, two or three doses of HPV vaccine compared with unvaccinated women. There was no significant difference in prevalence by number of doses received.[21]

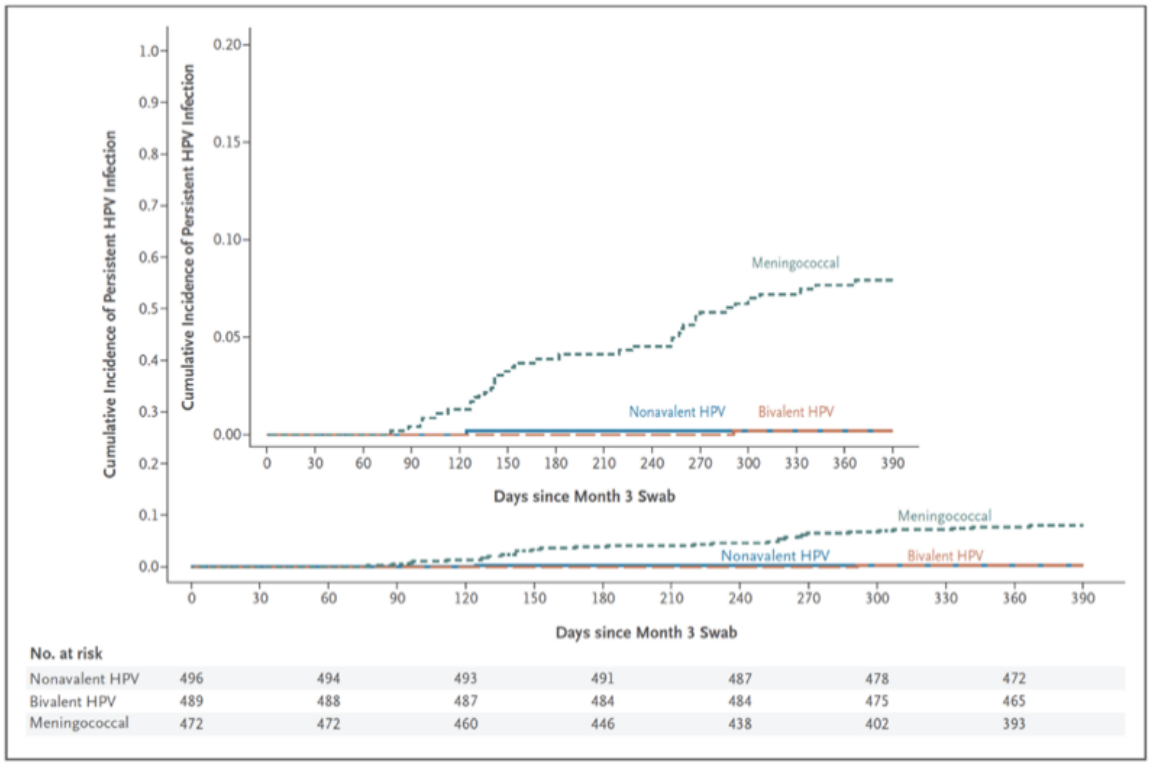
A Mongolian retrospective paired cohort study published in 2020 found that one dose of HPV4 vaccine given at age 11-17 years reduced HPV16 and 18 prevalence by 92% in vaccinated compared with unvaccinated participants (1.1% versus 15.4%) six years post vaccination. In subgroup analysis 90% of vaccinated women remained seropositive for HPV16 and 58% seropositive for HPV18 after six years with neutralising antibody levels five and twofold higher than unvaccinated women. Lower rates of seropositivity at 90% and 58% compared with other studies were postulated to be related to small sample size as measured by the HPV pseudovirion neutralisation assay.[22]

A Costa Rican randomised controlled trial in women aged 18-25 years found no difference in vaccine efficacy against incident HPV16 and HPV18 infection in those vaccinated with one, two, or three doses of HPV2 vaccine after a median follow-up of 11.3 years. Vaccine efficacy against prevalent HPV16 or 18 infection was 80% among three dose, 84% among two dose, and 82% among one dose women.[11,12,23]

In India, over 20,000 girls were enrolled in a randomised controlled trial to compare two or three doses of HPV4 vaccine in unmarried girls aged 10-18 years. Over 60% were aged under 16 years. Following temporary suspension of HPV vaccine trials in India, the study was converted to a prospective cohort study comparing those who had already received one, two or three doses of HPV4 vaccine and an unvaccinated control group. In 2021, the investigators reported that ten years post vaccination vaccine efficacy against persistent HPV16 and 18 infection was similar at 95%, 93% and 93% in cohorts receiving one, two or three doses.[15]

In Kenya, an ongoing prospective randomised controlled trial is comparing one dose HPV9 or HPV2 vaccine with meningococcal vaccination in 2,275 females aged 15-20 years. Over the initial 18 months of the study, one dose of HPV9 or HPV2 vaccine was highly effective in preventing persistent HPV16/18 infection, with vaccine efficacy of 97.5% for both vaccines. (Figure 4)[16]

Figure 4: Cumulative incidence of persistent HPV16/18 infection in single HPV2 or HPV4 vaccine recipients compared with meningococcal vaccination over 18 months. Source: Barnabas et al.[16]

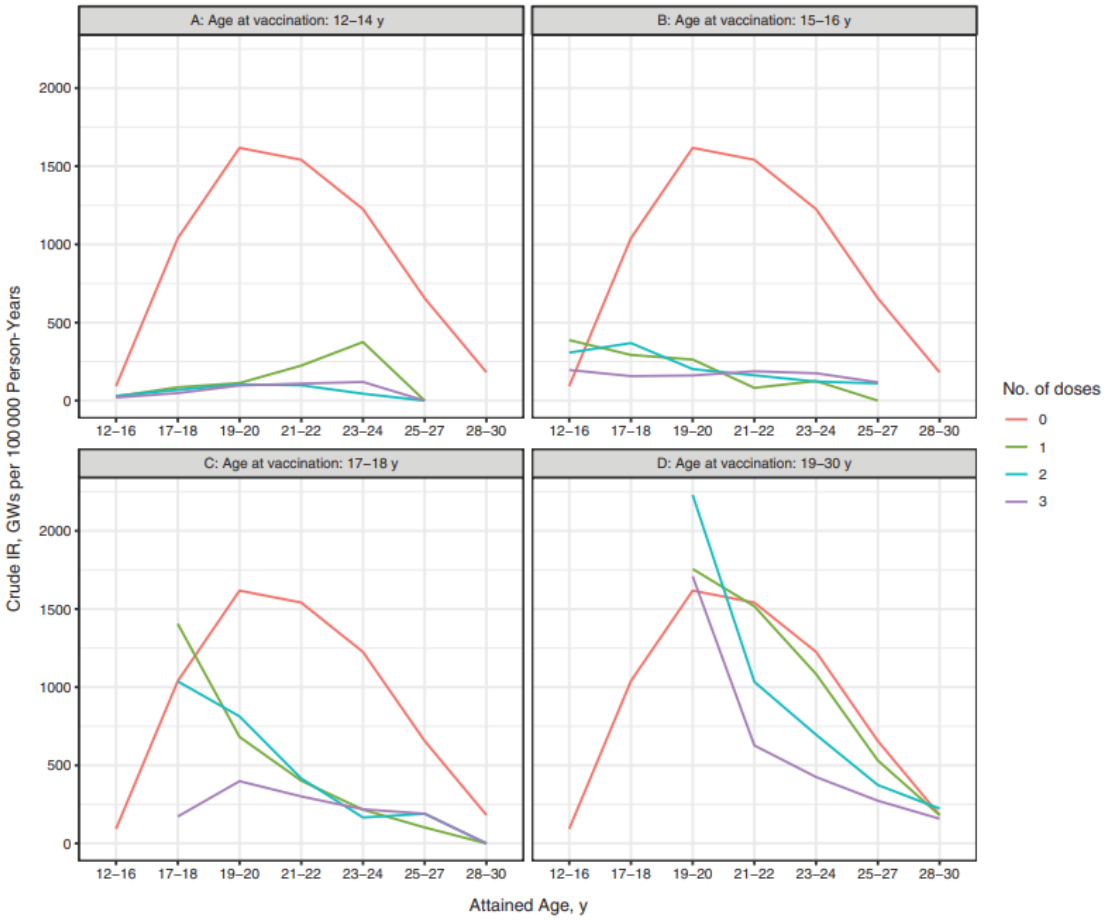


Effectiveness against anogenital warts

In 2018 a US retrospective cohort study concluded that one, two and three doses of HPV4 vaccine were similarly effective against anogenital warts in adolescents aged 15-19 years, irrespective of gender. The hazard ratio of anogenital warts for the three dose vaccine was 0.58, compared with 0.65 and 0.67 for the one and two dose groups respectively.[24]

A Danish retrospective cohort study published with over one million female participants aged 12-19 years at time of vaccination concluded that one or two doses of HPV4 vaccine was associated with substantial protection against anogenital warts in girls vaccinated aged 16 years or younger. In those vaccinated over 16 years of age, increased vaccine effectiveness was seen with each additional vaccine dose. For those aged over 19 years, only three doses provided statistically significant protection. However, the significantly higher incident rates of genital warts in those 17-18 years of age at first follow up suggested a higher baseline prevalence of HPV infection after which the rates decreased steeply with age. The lack of detectable difference in the oldest age group is also likely due to higher baseline prevalence of HPV infection and the development of herd immunity, as incidence rates in the unvaccinated also declined over time. This could lead to an underestimation of vaccine effectiveness. One dose effectiveness approached that of two or three doses over time, leading the authors to conclude that a reduced dose schedule may be favourable in countries with high vaccine coverage. (Figure 5)[25]

Figure 5. Crude incidence of genital warts by attained age and by vaccine dose number 0, 1, 2, and 3. Incidence rates are presented for those vaccinated at 12-14 (A), 15-16 (B), 17–18 (C) and >19 (D) years. Source: Baandrup et al.[25]



Effectiveness against cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ (AIS)

In a US test-negative case control study, women with HPV16/18 positive CIN2+ (vaccine-type cases) were compared with those with HPV16/18 negative CIN2+ (controls) with respect to their vaccination history 24 months or more before diagnosis. Overall vaccine effectiveness was 47%, 55% and 74% for one, two, and three doses with higher estimates (59-83%) for those born in 1987-1994 (median age at vaccination 23 years) compared with those born 1979-1986 (median age of vaccination 19 years). Vaccine effectiveness was significantly higher with three doses. When women who had received any vaccine dose during the 24 month buffer period were excluded from analysis the effectiveness of a single vaccine dose increased to 65%. Baseline difference in cohort characteristics between those receiving one and three doses were noted.[26]

In a Danish nationwide cohort study of all women aged 17-25 years who were vaccinated at 16 years or younger, there was no difference in vaccine effectiveness against CIN3 after one (62%),

two (62%) or three (63%) vaccine doses. Results were similar for CIN2. No evidence of loss of effectiveness with reduction in dose number was found. The lower effectiveness rates than might be anticipated from initial clinical trials was attributed to the older age of the cohort related to likely age at sexual debut.[27]

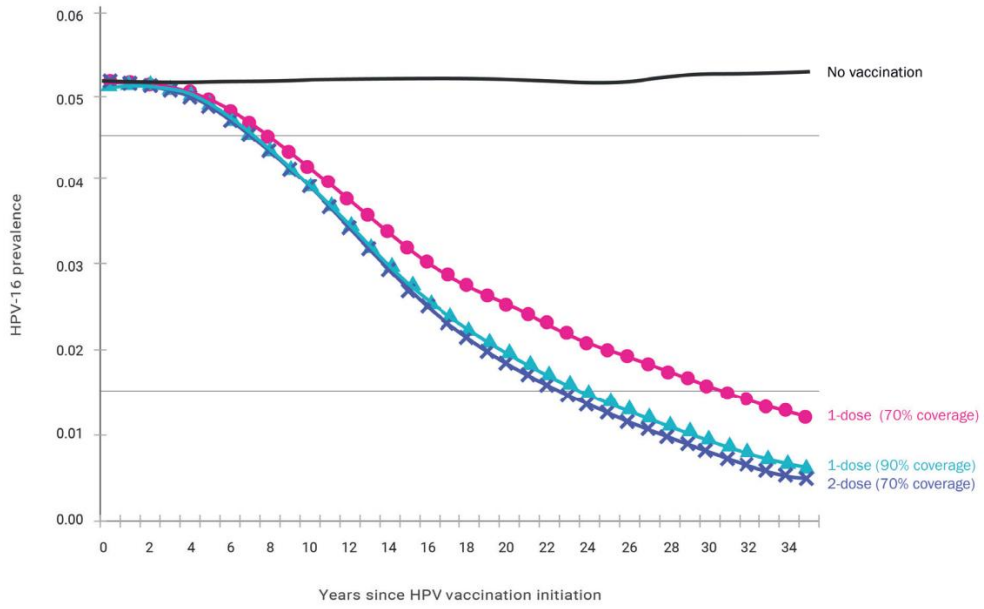
An Australian cohort study assessed the effectiveness of HPV4 vaccine administered to girls aged 12-15 years against CIN2/CIN3/AIS/cancer for up to seven years post vaccination by number of doses. The adjusted hazard ratio was significantly lower for all dose groups compared to unvaccinated women 0·65, 0.6 and 0·59 for one, two and three doses respectively, with no significant difference between dose groups. One dose of HPV4 vaccine had comparable effectiveness to two or three doses in preventing high–grade disease in a high coverage setting in women vaccinated between the ages of 12 and 15 years.[8]

Further data on single dose HPV vaccination are anticipated over the next three years.

Modelling study

Based on a US population, modelling of the impact of routine vaccination of girls aged 12 years was carried out assuming 80% efficacy for one compared with two doses and that two doses provided 100% lifetime protection against HPV16/18. At thirty year post vaccination, two doses were projected to achieve an 85% reduction in HPV16, whereas one dose achieved 70%. This difference was projected to be almost completely offset if one dose vaccine coverage increased to 90% (Figure 6). The study projected that if vaccine coverage could be improved by introduction of a single dose regimen, any potential reduction in efficacy of one rather than two doses may be offset.[28]

Figure 6. Model-projected HPV16 prevalence in females over time. Source: Kim.[28]

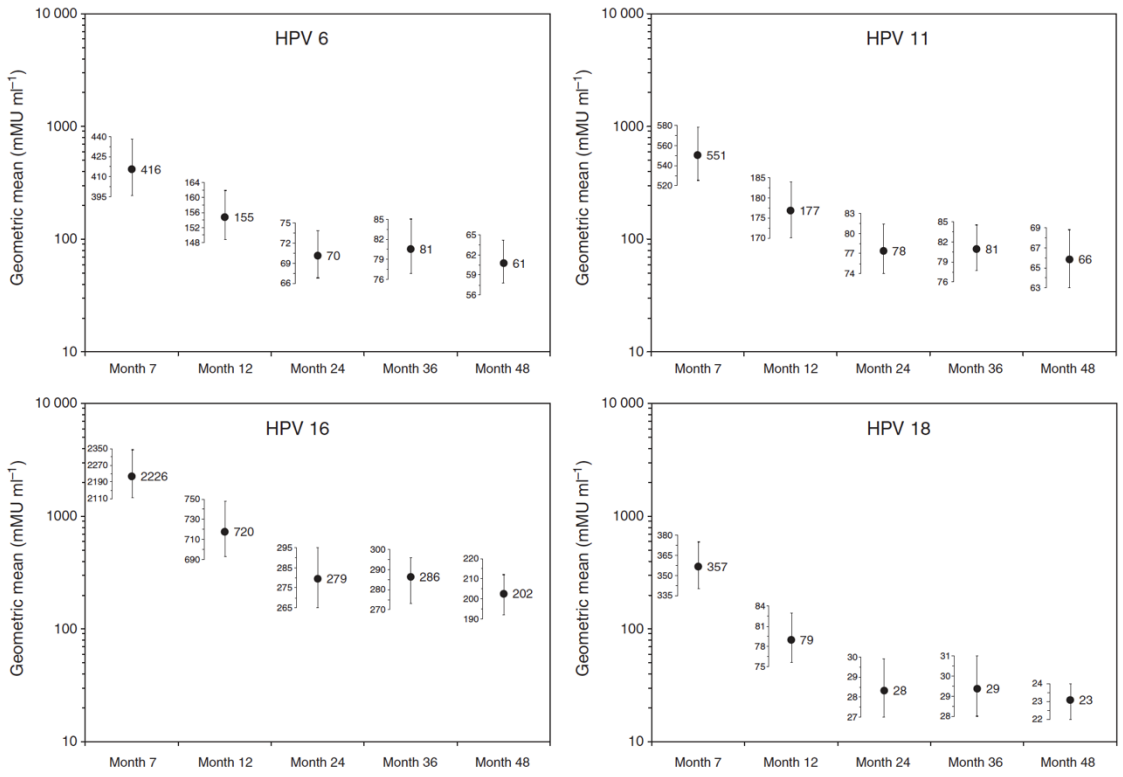


5. EVIDENCE FOR A TWO DOSE SCHEDULE FOR THOSE AGED 25 YEARS AND OLDER

Studies on a single dose schedule for mid-life individuals are not available. However similar patterns of HPV vaccine induced antibody responses are seen in different age and gender cohorts. Robust and durable vaccine responses in females from age 9-45 years and in males aged 27-45 years have been found.[5,29-31]

Munoz et al found high seroconversion rates with no difference by age group and that vaccine induced antibody responses against HPV6, 11, 16 and 18 were similar in women aged 24-34 and 35-45 years. However antibody responses in those aged 25-45 years while comparable for HPV16 were somewhat lower for HPV6, 11, and 18 than those seen in women aged 16-23 years.[29] In later follow-up, the end of study report showed that vaccine efficacy at four years against persistent HPV6/11/16/18 infection and disease was maintained at 89%. (Figure 7)[30]

Figure 7: Immunogenicity of HPV4 vaccines in those aged 24-45 years over 48 months. Source: Castellsagué et al.[30]

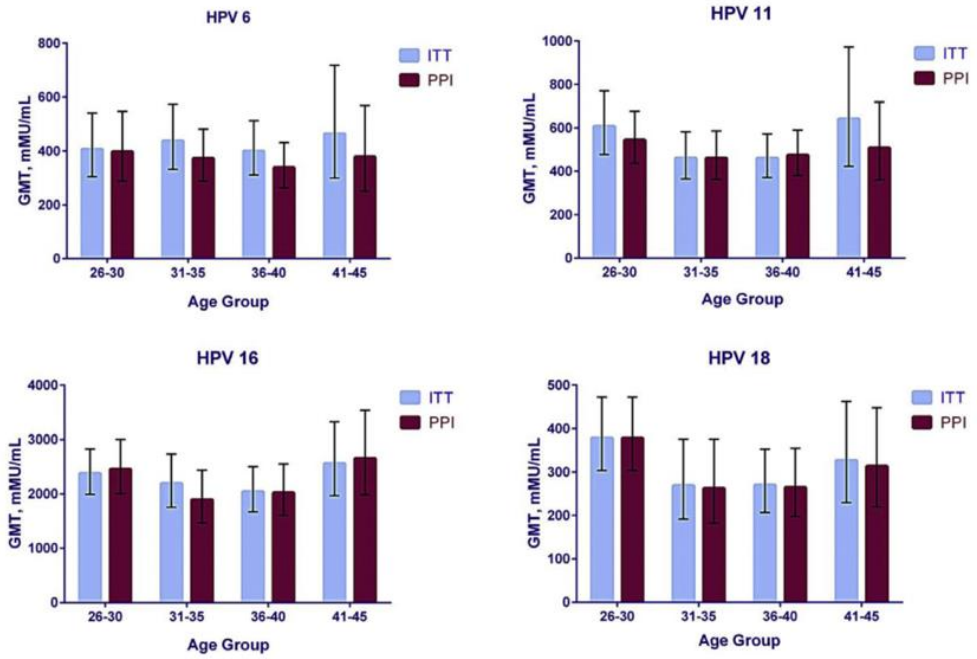


In a seven month immunogenicity study of three doses of HPV9 vaccine in females aged 16-26 and 27-45 years, more than 99% participants seroconverted to all nine HPV types by month seven in both age groups. While an age-related decline in antibody levels was found, non-inferiority

criteria were met for antibody levels in those aged 27-45 years compared with those aged 16-26 years for HPV16/18/31/33/45/52/58. The authors concluded that the data supports bridging HPV9 vaccine efficacy findings in women 16-26 years to women 27-45 years of age.[31]

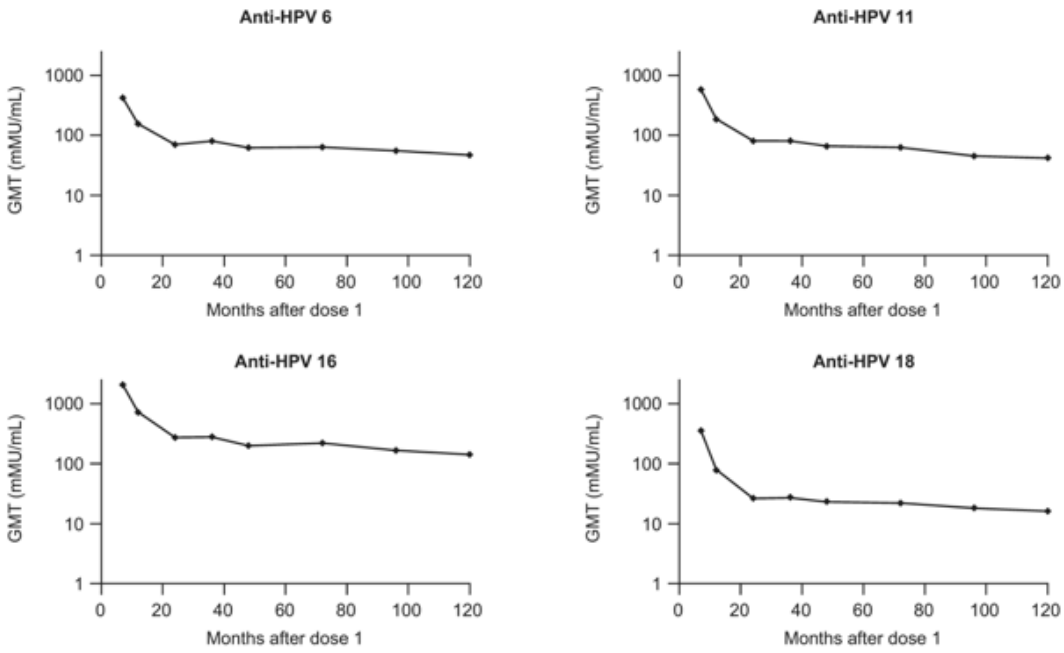
The immunogenicity of HPV4 vaccine was studied in 150 mid-adult males aged 27-45 years. Seroconversion was 100% for each of the four serotypes. Robust antibody responses were found and were comparable to those in younger men. (Figure 8)[32]

Figure 8: HPV4 vaccine immunogenicity (month 7) by age group in the intention to treat (ITT) analysis and per protocol immunogenicity (PPI) populations. Source: Giuliano et al.[32]



Long term follow up of female participants aged 27-45 years in a placebo-controlled study, HPV4 vaccine demonstrated durable protection against the combined endpoint of HPV6/11/16/18 related, high grade, cervical dysplasia and genital warts for up to 10 years. (Figure 9)[5]

Figure 9. Longitudinal anti-HPV6/11/16/18 antibodies among LTFU-study participants who received HPV4 vaccine at age 27-45 years in the FUTURE III Base study (PPI population). Source: Maldonado et al.[5]



In a post-hoc cross study analysis the immunogenicity of HPV vaccine in individuals aged 27-45 years, was non-inferior to those in males and females aged 16-26 years.[5]

6. INTERNATIONAL RECOMMENDATIONS

World Health Organization (WHO)

On 11 April 2022, the WHO Strategic Advisory Group of Experts on Immunization (SAGE)[33] recommended updating HPV vaccine dose schedules as follows:

- one or two dose schedule for girls aged 9-14 years
- one or two dose schedule for young women aged 15-20 years
- two doses six months apart for women 21 years and older.[34]

Those with immunocompromise, including those with HIV, should receive three doses if feasible.

UK

The UK Joint Committee on Vaccination and Immunisation (JCVI) reviewed immunogenicity and effectiveness data for two and three dose HPV vaccine schedules. On 5 August 2022, they released new HPV vaccine schedule recommendations as follows:

- One dose for all routine vaccination of those aged less than 25 years
- Two doses for those aged 25 years and older in their men who have sex with men (MSM) programme
- Three doses for those who are immunosuppressed and those known to be HIV positive.[35]

7. DISCUSSION

The COVID-19 pandemic caused disruption to the Irish HPV vaccination programme, with a reduction in HPV coverage among adolescents. Enhancing routine vaccine uptake and providing a catch-up programme should be prioritised to reduce the incidence of HPV infection, anogenital warts, associated pre-cancers, cervical, and oropharyngeal cancers.

HPV vaccines are very safe and effective for males and females. Strategies that enable broader coverage by HPV vaccine, irrespective of gender and across the ages can increase the numbers of individuals protected and also contribute to an acceleration and strengthening of herd immunity. Increasing the numbers of those vaccinated may mitigate any potential reduction in vaccine effectiveness associated with reduction in number of doses received.

While there is no established threshold of HPV antibody titre that indicate protection, antibodies are a key component in the protection against persistent infection and HPV disease. Lower antibody levels following one dose compared with two or three doses do not necessarily correlate with a loss of protection and antibody levels induced by a three-dose schedule may be several fold higher than necessary for protection.

High seroconversion rates and the durability of vaccine induced antibody responses are remarkably consistent across studies irrespective of age or number of vaccine doses received. Although some observational studies have shown that antibodies, especially HPV18 antibodies, in older age cohorts are somewhat lower than in younger cohorts and that levels following a single dose are lower than following two or three doses, they are several fold higher than following natural infection. In prospective cohorts and randomised trials no difference in vaccine effectiveness against infection was detected over periods extending to 11 years.

The protective benefits of HPV vaccination are documented for individuals receiving one, two or three doses of vaccine. While some studies have reported higher effectiveness against CIN2+ of a three compared with a one or two dose schedule[26,36] differences in study outcomes are likely due to confounding by older age at vaccination, higher prevalent infection, potential behavioural

differences between those receiving one compared to three doses and the impact of evolving herd immunity, all of which could result in underestimation of vaccine effectiveness. There is good evidence from randomised controlled trials and prospective cohorts that in those aged under 25 years antibody responses are strong and durable over time. The preponderance of available evidence in women aged under 25 years indicate that a single HPV vaccine dose is as effective as three doses in preventing HPV infection for at least 11 years.

The excellent immunogenicity of the HPV vaccines is related to the virus like particle configuration that more closely resembles natural infection in the presentation of antigens than some other vaccines. This is considered to account for the durable immunogenicity in the younger age cohorts. Similar results might be anticipated for those aged 25 years and older, however data on single dose in these cohorts is not yet available.

B cell memory responses, an essential component of durable protection, decline with age. Therefore, a two dose schedule with an interval of at least six months is preferable for those aged 25 years and older with the second dose given within 12 months of the first. Recommendations for this may change as further information becomes available.

There is now sufficient evidence to reduce the number of doses from three to one in those aged nine to 24 years of age without compromising vaccine efficacy. WHO recommends the option of one dose for those aged up to 21 years[34] but the UK recommends one dose for those aged up to 25 years[35] as evidence suggests vaccine efficacy will not differ in those aged 22-24 years. This reduces the number of vaccine doses required, facilitates service users, and is likely to improve uptake.

Modelling suggests that improving single dose HPV vaccine uptake to 90% can offset any potential long term reduction in vaccine effectiveness. Enabling HPV vaccination of a greater number will further reduce the HPV associated disease burden on the health service. There may also be short and long term health economic benefits.

Reduction in the number of vaccine doses may be associated with an unlikely risk of a later decline in antibody to a level associated with reduced effectiveness. Several long term follow up studies of single dose strategy are underway and will yield more definitive results in the coming years, well ahead of any potentially significant decline in protection. This would permit catch up with an additional vaccine dose if required.

Further risk mitigation can be achieved by HPV infection surveillance. Enhanced surveillance is a necessary part of the HPV prevention programme to monitor for the emergence of replacement serotypes. Such surveillance would also serve as an early warning system if protection against HPV9 vaccine types were to decline.

8. RECOMMENDATIONS

RECOMMENDATIONS
1. A single dose of human papillomavirus (HPV) vaccine is recommended for unvaccinated females and males aged 9-24 years of age. 2. Those aged 25 years and older for whom the vaccine is recommended, or who choose to receive it, require a two dose schedule at 0 and 6-12 months. 3. Those with immunocompromise require a three dose schedule at 0, 2 and 6 months regardless of age. 4. Priority should be given to achieving vaccine uptake of 90% to maximise the effectiveness of a single dose HPV vaccination programme. 5. Enhanced surveillance is required to monitor for the emergence of any replacement serotypes and to detect any decline in HPV9 vaccine effectiveness. These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about HPV vaccines is evolving and being refined. Recommendations may be updated when more information becomes available.

APPENDIX 1. NIAC HPV VACCINE RECOMMENDATIONS

<table>
<tr><th>Age</th><th>Current</th><th>Updated recommendation</th></tr>
<tr><td>9 –14 years</td><td>Two doses
6-12 months apart</td><td>One dose</td></tr>
<tr><td>15–24 years</td><td rowspan="3">Three doses
at 0, 2, and 6 months.

All three doses should be given within 12 months.</td><td>One dose</td></tr>
<tr><td>25 years and older</td><td>Two doses
at least 6 months apart.

Second dose should be given within 12 months.</td></tr>
<tr><td>Immunocompromised (any age)</td><td>Three doses
at 0, 2, and 6 months.

All three doses should be given within 12 months.</td></tr>
</table>

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- NIAC members
- NIAC SpR Research Panel
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