An Advisory Committee Review
National Advisory Committee on Immunization (NACI)

NACI Literature Review for HPV Immunization of Immunocompromised Populations

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

Immunocompromised populations are at increased risk for HPV infection and for developing HPV-associated cancers. However, additional clarity is required surrounding the immunogenicity and safety outcomes of HPV immunization for immunocompromised populations. To address this information gap, a research question was developed by the National Advisory Committee on Immunization (NACI) human papillomavirus (HPV) Working Group and used to guide a literature review.

A search strategy was developed with a federal Reference Librarian (Health Library) and verified by the NACI HPV Working Group. Three databases (OvidMEDLINE, SCOPUS, Cochrane Library) were queried on March 26, 2015 (updated October 8, 2015). Through this literature review, 27 relevant studies were identified to be rated for quality and included for evidence synthesis. The 27 studies contained reports on immunogenicity, safety, or both, for the use of bivalent or quadrivalent HPV vaccines in immunocompromised populations according to a 3-dose schedule. The type of evidence retrieved on this topic was diverse, including randomized controlled trials, cohort studies, and case reports; the quality of evidence ranged from good to poor.

Only one study described patients with primary (congenital) immunodeficiency, while the rest described patients with secondary (acquired) immunodeficiency. Within the evidence for acquired immunodeficiency, two broad clusters of evidence were apparent: HIV-infected populations, and individuals receiving therapeutic immunosuppression for autoimmune or inflammatory diseases or transplantation. Among the patients undergoing therapeutic immunosuppression, evidence was typically presented according to disease type (e.g. systemic lupus erythematosus, juvenile idiopathic arthritis, solid organ transplant) and rarely stratified by therapeutic modality or dosage. Incomplete datasets and a general lack of control groups made direct comparisons difficult.

Overall, the limited data available on this topic present substantial barriers to the interpretation and potential development of evidence-based recommendations. While immunogenicity may be suboptimal in immunocompromised subgroups (HIV+ and therapeutic immunosuppression), evidence was not sufficient to support specific recommendations for different subgroups. In immunocompromised groups with lower vaccine responses, antibody levels still typically exceeded those resulting from natural infection in immunocompetent individuals. Evidence did not indicate that vaccine safety was different for immunocompromised subgroups compared to immunocompetent, and HPV immunization did not impact CD4 levels or HIV viral load in any study. Evidence at this time does not clearly identify subgroups or immunosuppressive therapies that are associated with lower immune response to HPV vaccine, but evidence suggests that vaccine immunogenicity may be diminished if provided following therapy onset and solid organ transplant.

I. INTRODUCTION

Immunocompromised populations are at increased risk for HPV infection and for developing HPV-associated cancers. International evidence suggests the rates of HPV infection and associated disease are increased in immunocompromised populations including both HIV-infected populations[(1)] and solid organ transplant recipients[(2)]. A meta-analysis found that standardised incidence ratios for HPV-related cancers in these immunocompromised groups ranged from 1.6 to 30 times greater than the general population[(3)]. However, additional clarity is

required surrounding the immunogenicity and safety outcomes of HPV immunization for immunocompromised populations. While there is currently no known correlate for HPV protection following immunization, seroconversion rates and GMTs are often used across groups to compare relative immunity. Through a comprehensive literature review 27 studies were identified for evidence synthesis including reports on immunogenicity, safety, or both.

The primary objectives of this literature review were:

1) To assess the immunogenicity, efficacy, and safety of HPV immunisation for immunocompromised subgroups

2) To establish high risk subgroups or immunosuppressive therapies in the context of HPV immunisation

II. METHODS

II.1 Research question

Do HPV immunization outcomes differ for subgroups of immunocompromised populations?

P (population): immunocompromised populations (different subgroups e.g. HIV-infected, transplant recipients)
I (intervention): HPV vaccination
C (comparison): unimmunized immunocompromised OR immunized immunocompetent
O (outcomes): immunogenicity OR safety OR efficacy

A search strategy was developed with a federal Reference Librarian (Health Library) and verified by the NACI HPV Working Group. Three databases (OvidMEDLINE, SCOPUS, Cochrane Library) were queried on March 26, 2015 (updated October 8, 2015). Language was restricted to English. Full search terms and results flow diagram can be found in Appendix A and B, respectively.

Databases consulted March 26, 2015: OvidMEDLINE (130 results), Scopus (310 results), Cochrane (25 results)

Updated March 26 - October 8, 2015: OvidMEDLINE (12 results), Scopus (22 results), Cochrane (32 results)

Inclusion criteria:
- HPV vaccine recipients with congenital (primary) immunodeficiency
- HPV vaccine recipients with acquired (secondary) immunodeficiency – e.g. immunosuppressive regimes for autoimmune or inflammatory disorders or transplants, HIV infected populations, patients who have undergone chemotherapy or radiation, asplenia.

Exclusion criteria:
- Non-human studies
- Irrelevant titles, abstracts, full text
- Non-English language

Classification of immunodeficient patient populations was drawn from the CIG, Part 3; Vaccination of Specific Populations; Immunization of Immunocompromised Persons. (https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html)

One reviewer (MT) screened the results for relevant studies, individually assessed their quality as per NACI methodology (Appendix C), assigned the level of evidence as per NACI methodology, extracted data into an evidence table, and synthesized evidence into a summary document. Work was reviewed by the NACI HPV Working Group chair and discrepancies were resolved through consensus.

III. RESULTS

III.1 Overview

Through a comprehensive literature review 27 studies were identified for evidence synthesis including reports on immunogenicity, safety, or both. Of the relevant studies that were retrieved, 2 primary groupings were apparent:

1) HIV-infected populations
2) Acquired, therapeutic immunosuppressed populations

Table 1: Result Categories by Disease

	Disease	Number of immunogenicity reports	Number of safety reports
1) HIV-infected populations	HIV-infection	10	9
2) Acquired therapeutic immunosuppression for:	Solid organ transplant	2 + 1 abstract	2
	Juvenile Idiopathic Arthritis (JIA)	3 + 1 abstract	3 + 1 abstract + 1 case report
	Systemic Lupus Erythematosus (SLE)	4	3 + 2 case reports
	Juvenile Dermatomyositis (JDM)	1	1
	Rheumatoid Arthritis (RA)	0	1 case report
	Inflammatory Bowel Disease (IBD)	1	1
	“Steroids or other immunosuppressants”	2	0
3) Congenital immunodeficiency	WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis syndrome) – CXCR4 mutation	1 case report	0

Immunosuppressive regimes were typically reported for patients with acquired therapeutic immunodeficiency (detailed in the evidence table), but unfortunately these studies did not often stratify results according to treatment modality. The extent of effective immunosuppression was not measured or reported in any study, but CD4 counts were typically provided for studies of HIV-infected patients. Cohort study was the predominant experimental design, and most included a low participant number. All studies used bivalent or quadrivalent HPV vaccines with a routine 3-dose schedule, except one study which provided an additional fourth dose. No study used the recently-authorized nine-valent HPV vaccine. The following evidence synthesis outlines relevant findings from these studies, which are also summarized in the evidence table.

III.2 Evidence for immunogenicity in HIV-infected populations

SUMMARY: Of 10 relevant studies identified, only 1 was rated as good quality while 8 were rated as fair and the quality of 1 abstract could not be rated due to limited information. Overall, the majority of HIV-infected subjects in studies had CD4 counts ≥350 cells/μL, uninfected controls were generally not available for comparison, and historical controls were often used. Seroconversion rates and titre responses in these subjects were typically high, but some evidence showed that anti-HPV titre levels trended lower than uninfected historical controls. Adding one additional vaccine dose appeared to improve titre responses and seroconversion rates in one study.

Among HIV-infected subjects with low CD4 levels (≤200 cells/μL), seroconversion rates were significantly lower than in infected subjects with higher CD4 levels; titres were also low, but significant only for HPV6. Similarly, an HIV RNA load >10 000 copies/mL was significantly correlated with low seroconversion rates, while an RNA load >5000 was significantly correlated with low anti-HPV titre responses.

In studies of HIV-infected subjects with varied CD4 levels, HPV vaccination produced good seroconversion rates but anti-HPV titres in HIV-infected groups trended lower than uninfected controls. The viral load or ART-status of subjects and the vaccine type used may be factors. One study also reported that HIV-infected females immunized with the bivalent vaccine CERVARIX® had significantly higher GMTs than those immunized with quadrivalent GARDASIL®.

III.2.1 HIV-infected individuals with CD4 count ≥ 350

Five studies and one abstract have explored the immunogenicity of HPV vaccines in HIV-infected patients with CD4 T cell counts ≥350 cells/μL. Cellular responses to GARDASIL® vaccination were measured in HIV-infected adolescents/adults and uninfected controls (ages 13-27) in a study by Rainone et al.[4], rated as good. All HPV-specific CD4 and CD8 cytokine responses measured were intact in HIV-infected subjects compared to controls, but effector memory CD4 T cell levels were reduced.

In a study rated as fair, Giacomet et al. found that seroconversion rates following GARDASIL® immunization of HIV-infected subjects (ages 13-27) were not significantly different from uninfected controls at 7 months[5]. Similarly, a fair study by Weinberg et al. of HIV-infected children (ages 7-12) with mean CD4+counts of 868 ± 367 cells/μL found that GARDASIL® immunization with 3 scheduled doses resulted in high seroconversion rates (≥97%) for all serotypes 7 months following initial immunization, but 18 months later, they had waned to ≥94% for HPV6, 11, 16 and 76% for HPV18[6]. No uninfected controls were available for comparison. Interestingly, a second group of HIV-infected subjects in this study receiving 4 doses showed 100% seroconversion for all 4 serotypes at 7 months. In a study rated as fair, Kojic et al. found

that seroconversion rates for HIV-1 infected females (ages 13-45) exceeded 91% for all 4 serotypes 7 months after initial vaccination [7], but seroconversion rates and titres were not compared to uninfected controls.

In a study rated as fair, Wilkin et al.[8] studied GARDASIL® immunization in HIV-infected adult males (≥ 18 years) not undergoing ART (CD4 >350 cells/μL) and subjects receiving ART (CD4 ≥200 cells/μL; plasma HIV-1 RNA level <200 copies/mL). Seven months following initial immunization, seroconversion rates in HIV-infected patients exceeded 95% for all serotypes. Similarly, a recent abstract by Brophy et al.[9] that could not be rated describes 100% seroconversion to all 4 serotypes in HIV-infected girls (ages 9-13) at 7 months following immunization with GARDASIL®. However, by 24 months, seroconversion had fallen to 86%, 81% and 70% for HPV 6, 11, and 18 respectively (with 100% for HPV 16), and GMTs for all 4 serotypes were significantly lower in HIV-infected subjects at both 7 and 24 months, compared to age and sex-matched historical controls. Anti-HPV antibody titres were also assessed in several other studies. Wilkin et al. found that CD4 T cell counts, nadir CD4 count, and age were not associated with anti-HPV antibody levels[8]. Similarly, Giacomet et al. found that anti-HPV IgG titres were not significantly different between HIV-infected subjects and uninfected controls in a study as rated fair, although levels trended lower in HIV-infected subjects at months 7, 12, and 18 following initial immunization[5]. CLIA titres were significantly higher 1 month after the final dose of GARDASIL® in a 4-dose group compared to a 3-dose group for all genotypes in a study rated as fair [6].

III.2.2 HIV-infected individuals with CD4 count 201-350

One fair quality study by Kojic et al. compared GARDASIL® responses between HIV-infected females (ages 13-45) stratified by CD4 level. Seven months following initial immunization, HIV-infected women with CD4 counts of 201-350 cells/μL showed seroconversion rates for HPV6, 11, 16 >98%, but HPV18 rates were only 84% [7]. However, these were not significantly different compared to HIV-infected subjects with CD4 counts >350 cells/μL.

III.2.3 HIV-infected individuals with CD4 count ≤ 200, low CD4%, or high viral load

Seven months following initial GARDASIL® immunization, in a study rated as fair, Kojic et al. found that HIV-infected females (ages 13-45) with CD4 counts >350 or 201-350 cells/μL had high seroconversion rates but women with CD4 counts ≤200 cells/μL and an HIV RNA load >10 000 copies/mL, or both had significantly lower correlated seroconversion rates for all 4 serotypes [7]. GMTs were also lower for all serotypes in HIV-infected women with a low CD4 count (≤200 cells/μL), compared to the other groups, but this was significant only for HPV6.

Although Levin et al. studied HIV-infected children (ages 7-12) with mean CD4 counts of 868 (794-942, 95%CI) cells/μL, they also stratified responses based on CD4% nadir and CD4% at screening in a study rated as fair. Levin et al. found that 7 months following initial immunization with GARDASIL®, seroconversion among vaccine recipients was 100% for HPV6, 11, 16, but 90% for HPV18 in the low CD4% stratum (nadir<15; CD4%≥15 at screening). GMTs were not significantly different between groups stratified by CD4%, but titres were lower in HIV-infected vaccine recipients compared to historical data (30-50% lower for HPV6 and 18)[10]. Notably, low HPV-specific antibody levels were significantly correlated with high HIV viral load (>5000 copies/mL vs. <5000 copies/mL).

III.2.4 HIV-infected individuals with CD4 count mixed or not described

In a randomized controlled trial rated as fair, Denny et al. found that CERVARIX® immunization of HIV-infected women with mixed CD4 counts resulted in 100% seroconversion to both HPV16 and 18 at 7 and 12 months[11]. However, the HIV-infected subjects had GMTs approximately half those of uninfected controls, although statistical comparisons were not provided.

Kahn et al. found that GARDASIL® immunization of HIV-infected females (ages 16-23) with mixed CD4 counts resulted in seroconversion rates exceeding 92% for all 4 serotypes at 7 months, but HPV seroconversion in non-ART HIV-infected females was significantly lower than in historical controls[12]. There was also a trend towards lower GMTs in subjects with HIV RNA load ≥400 copies/mL (which was significant for HPV11) but no relationship to CD4 levels was observed in this study, rated as fair.

Finally, in a study rated as fair, Toft et al.[13] compared responses to GARDASIL® or CERVARIX® in HIV-infected adults (>18 years old). Both vaccines caused similar anti-HPV16 GMTs at 7 and 12 months post-enrolment, but anti-HPV18 GMTs were significantly higher in CERVARIX® compared to GARDASIL® recipients at 7 months. Within the HIV-infected female subset, CERVARIX® recipients had significantly higher GMTs than GARDASIL® recipients for both HPV16 and 18 at 7 and 12 months.

III.3 Evidence for immunogenicity in acquired therapeutic immunodeficiency

SUMMARY: Of 11 relevant studies identified, only 3 were rated as good quality while 4 were rated as fair, 2 were rated as poor quality, and the quality of 2 abstracts could not be rated due to limited information. Overall, patients receiving therapeutic immunosuppression for transplant or autoimmune or inflammatory disorders often respond to HPV vaccination, but seroconversion rates and titre responses can be significantly lower than in healthy controls. Some evidence suggests that certain treatment modalities have a greater impact than others, but there is insufficient evidence to specifically identify high-risk treatments in the context of HPV immunization.

III.3.1 Solid organ transplant

Two studies rated as fair quality, and one abstract, explored the immunogenicity of quadrivalent HPV vaccination in solid organ transplant recipients. Gomez-Lobo et al.[14] found that a small group of children and adolescents (ages 9-17) receiving immunosuppressive therapy for solid organ transplants responded well to the GARDASIL® vaccine. All patients who completed the 3-dose series had seroconverted to all 4 serotypes 7 months following initial immunization, and GMTs for all serotypes were similar to historical control data. However, the only liver transplant recipient appeared to have relatively low anti-HPV6 and 16 GMTs. No comparison was made between different treatment modalities.

Conversely, Kumar et al.[15] found that both seroconversion rates and anti-HPV antibody responses in adult transplant recipients immunized with GARDASIL® were low compared to historical controls published in other studies. There was a trend towards lower response rates in patients immunized within the first year post-transplant, and lung transplant recipients had significantly lower titres than other transplant types at 7 months following initial immunization. Notably, median Tacrolimus levels were significantly lower in responders compared to non-responders (6.4 vs. 9.4 µg/mL), suggesting that Tacrolimus levels may interfere with HPV vaccine responses.

A recent abstract by Nailescu et al.[16] did not include sufficient detail to be rated for quality, but their results suggest that seroconversion rates and GMTs are lower in pediatric and adolescent kidney transplant recipients who received the GARDASIL® vaccine ≥6 months post-transplant compared to those who were immunized prior to kidney transplant. Immunosuppressive regimes were not detailed in this abstract.

III.3.2 Juvenile Idiopathic Arthritis (JIA)

Four studies examined the immunogenicity of HPV vaccination in patients treated for JIA. Two of these studies evaluating seroconversion in JIA patients found similar rates to healthy controls following immunization, and both were rated as good [17][18].

A prospective controlled cohort study by Heijstek et al.[17] found that all female adolescent JIA patients (ages 12-18) and healthy controls immunized with bivalent CERVARIX® had seroconverted to HPV16 and 18 at 7 months following initial vaccination, and all but one JIA patient maintained seroconversion at 12 months. However, HPV16 and HPV18-specific memory B cell levels in a sample of JIA participants were lower than in controls at 3, 7, and 12 months, despite similar responses kinetics. Methotrexate did not significantly affect HPV16 or 18 antibody levels, and all methotrexate patients were seropositive at 12 months. However, anti-HPV antibody levels appeared lower in patients receiving anti-TNFα therapy, but not significantly.

Esposito et al.[18] found that JIA adolescent females (ages 12-15) immunized with CERVARIX® had similar anti-HPV18 antibody levels to healthy controls, but significantly lower anti-HPV16 levels at 7 months; no difference was observed between treatment modalities.

In a study rated as poor quality, Akikusa and Crawford[19] found that GARDASIL® responses measured opportunistically were similar for all 4 serotypes in adolescent and adult female patients with pediatric rheumatic diseases [JIA (n=28); SLE (n=6); Juvenile dermatomyositis (n=2); Scleroderma (n=1); Sjogren's disease (n=1)] compared to historical control titres. However, when compared to healthy historical controls, a non-significant trend was observed for lower anti-HPV 6, 11, 16 titres in patients receiving high dose corticosteroids (>2.0 mg/kg/day), or biological agents, or a combination of DMARD and corticosteroids, or a combination of DMARDs, but the specific data were not reported.

An abstract by Singer et al.[20] suggests that female JIA patients (ages 6-26) had anti-HPV antibody levels comparable to healthy controls following GARDASIL® immunization, but the immunosuppressive regimes were not outlined and there was not sufficient information provided to rate the quality of this study.

III.3.3 Systemic Lupus Erythematosus (SLE)

Four studies of varying quality examined the immunogenicity of HPV vaccination in patients treated for SLE. Of the three studies evaluating seroconversion, two [21][22] (rated fair and poor) found rates similar to healthy controls following immunization; while Mok et al.[23], in a study rated as good, noted that seroconversion was deficient in SLE patients 7 and 12 months post-vaccination compared to controls, but rates exceeded 76% for all serotypes.

In their cohort study of adult females (ages 18-35), Mok et al.[23] also found that anti-HPV titres post-GARDASIL® vaccination were generally lower in patients on immunosuppressive medications. Combined immunosuppression with prednisolone and mycophenolate mofetil was

associated with significantly lower titres and seroconversion rates (33%) for HPV6 and HPV18 at 12 months, with significantly lower HPV16 titres at 7 months. Similarly, Heijstek et al.[21] found that anti-HPV16 and 18 Ab geometric mean concentrations (GMCs) were lower in SLE patients compared to healthy controls at 3, 7, 12 months following CERVARIX® vaccination, but not significantly lower. In a small open-label cohort study of medicated SLE patients, rated as poor quality, one subject who received rituximab between doses 2-3 had no antibody response to HPV6 and HPV18 at month 7, with low responses to HPV11 and HPV16 (titres 75 and 65 mMu/mL)[22].

III.3.4 Other therapeutic immunosuppression

One study of IBD patients, rated as fair, found that seroconversion rates for IBD patients immunized with GARDASIL® exceeded 94% for all 4 serotypes, while anti-HPV GMTs 7 months post-immunization were similar to or exceeded historic healthy controls[24]. Interestingly, patients receiving immunomodulators (not further characterized) had significantly lower HPV6 mean titres compared to patients receiving TNF-α inhibitor therapy, but both were similar to historical healthy control titres for HPV6. All other serotypes were similar. Early results of this study were also reported in an abstract[25].

One study, rated as fair, including 6 Juvenile Dermatomyositis (JDM) patients showed that anti-HPV16 and 18 GMCs were significantly lower for JDM patients compared to healthy controls at 7 months, but similar to controls 12 months post-enrolment[21]. These effects did not appear related to immunosuppressive medication, as un-medicated JDM patients experienced similar responses.

In the GARDASIL® product monograph and unpublished manufacturer data on file, which could not be rated due to limited details, it was reported that small subgroups of girls and women, aged 9-26 or 27-45 years, receiving “steroids or other immunosuppressants” had similar GMTs for all 4 HPV types at 7 months following immunization compared to vaccine recipients without steroids or other immunosuppressants.

III.4 Evidence for immunogenicity in congenital immunodeficiency

The only study to explore immunogenicity outcomes following HPV vaccination in patients with primary immunodeficiency was a fair quality case report of a 12 year old female patient with WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis syndrome) resulting from a CXCR4 mutation[26]. Overall, GARDASIL® vaccination elicited detectable titres and neutralizing anti-HPV responses in the WHIM patient, but titres appeared much lower than in healthy immunized adults. Statistical comparisons were not possible. Two months after dose 3, the WHIM patient had detectable titres at 400 for HPV6, 11, 16 and titers at 100 for HPV18. In healthy adults, titres ranged from 6,400 – 102,400 for all 4 serotypes.

III.5 Evidence for safety in HIV-infected populations

SUMMARY: Overall, HPV vaccination of HIV-infected patients was safe and well-tolerated. Furthermore, HPV immunization did not affect CD4 levels or HIV viral load in any study. Unfortunately, most studies did not include uninfected immunized controls, or HIV-infected unimmunized controls, for comparison. Of the 9 relevant studies identified, 3 were rated as good quality, 5 were rated as fair, and the quality of 1 abstract could not be rated due to limited information. Some studies suggest that local reactions were more common in HIV-infected subjects than uninfected controls, and one study, rated as good, suggests that local reactions

were more common with CERVARIX® than with GARDASIL®. SAEs were uncommon, and only 1 SAE was considered possibly associated with immunization.

Nine studies, rated as good and fair quality, have explored the safety of HPV vaccination in HIV-infected patients. In a study with GARDASIL® among persons aged 13-27 by Rainone et al., rated as good quality, no significant safety issues were associated with vaccination [4]. Kojic et al.[7] reported on GARDASIL®-related symptoms from HIV-1 infected females (ages 13-45) 24-48h post-vaccine, and no significant safety issues were identified. No uninfected controls were available for comparison, and the study was rated as fair. The most common adverse event was pain, but other common events included neurological, gastrointestinal, and skin-related. Two deaths occurred that were unrelated to vaccination: 1 from lymphoma and 1 from meningitis. One participant had an allergic reaction, and 1 participant developed a grade 3 fever. Sixteen participants had grade 1 (or higher) fever reported during post-vaccination follow-up, and 3 participants experienced grade 2 injection site reactions. Overall, 17% of participants experienced grade 3 or higher adverse events, 11% experienced grade 3 or higher signs and symptoms, and 8% experienced grade 3 or higher laboratory abnormalities.

In an abstract that could not be rated due to limited information, Vandriel et al. observed that HIV-infected girls and women had fewer AEs following GARDASIL® immunization compared to HIV-negative historical controls[27]. In their sample of 350 girls and women, 36 SAEs were reported but only 1 (encephalopathy) was possibly related to the vaccine and it resolved without sequelae.

In a study rated as fair, Giacomet et al.[5] found an overall trend for higher local and systemic events in HIV-infected subjects compared to HIV-negative controls following GARDASIL® immunization (ages 13-27), but the study was underpowered and did not allow for direct comparisons between groups. No SAEs were reported.

In a study rated as good, Toft et al.[13] compared vaccine-related symptoms following GARDASIL® or CERVARIX® immunization in HIV-infected adults (>18 years old). No SAEs were reported, and both vaccines were well-tolerated with few mild systemic reactions (influenza-like symptoms, headache, nausea). Injection site reactions were the most common overall, and they were significantly more frequent in the CERVARIX® group than in the GARDASIL® group (91.1% vs 69.6%; P = 0.02).

Denny et al.[11] reported similar adverse events for HIV-infected women (ages 18-25) immunized with CERVARIX® compared to HIV-infected women receiving an alum control immunization, or uninfected controls in a study rated as good. Vaccine administration did not alter CD4+ cell counts in HIV-infected HPV-immunized subjects compared to HIV-infected alum controls. The overall incidence of solicited local and general adverse events was similar in HIV-infected and HIV-negative vaccinated women, and most solicited local and general adverse events were of mild or moderate intensity and resolved spontaneously. SAEs were reported by 6 subjects, and none were related to vaccination. No subjects withdrew due to SAEs, and no deaths were reported.

In a study rated as fair, Kahn et al.[12] found that GARDASIL® immunization of HIV-infected females (ages 16-23) was safe and well-tolerated, and reactions were similar to historical healthy controls. One SAE was reported for fatigue, but this was not related to vaccination.

In a double blind randomized controlled trial of HIV-infected children (ages 7-12) rated as fair quality, Levin et al.[10] reported that AEs were infrequent and their occurrence was similar in both

GARDASIL® and placebo recipients. Injection site reactions were significantly more common in vaccine recipients compared to placebo controls, but no SAEs were reported. Importantly, AEs did not differ between groups stratified by CD4%. Furthermore, CD4 status and viral load were not altered by vaccination.

Wilkin et al.[8] examined GARDASIL® vaccination in HIV-1 infected males (≥ 18 years old) with or without ART therapy. Vaccination did not result in changes to CD4 cell counts or HIV-1 RNA levels in either group. Grade 2 reactions related to vaccination occurred in 5% of participants, including one with recurrent tinnitus possibly related to vaccination - in this case the 3rd dose was withheld. Grade 1, and 2 local reactions were observed after dose 1 (18%), dose 2 (17%), and dose 3 (12%). Unfortunately, no controls were available for direct comparison and the study was rated as fair quality. There were no SAEs associated with vaccination.

III.6 Evidence for safety in acquired therapeutic immunodeficiency

SUMMARY: Of 13 relevant publications identified, 3 were case reports. Only 4 studies were rated as good quality while 3 were rated as fair, 5 were rated as poor quality, and 1 abstract could not be rated. Overall, HPV vaccination of patients receiving therapeutic immunosuppression for transplant or autoimmune or inflammatory disorders was safe and well-tolerated. Incomplete datasets and a general lack of control groups make direct safety comparisons difficult. Some case reports indicate a flare or new onset of autoimmune disease, but larger cohort studies indicate that these diseases are not adversely affected by HPV immunization.

III.6.1 Solid organ transplant

Two cohort studies rated as fair quality have explored the safety of HPV vaccination in solid organ transplant recipients. Kumar et al.[15] found that the GARDASIL® vaccine was safe and well-tolerated in 47 adult solid organ transplant recipients (ages 18-35) with various immunosuppressive regimes. No acute rejection was observed, and vaccine-associated adverse events were similar to historical control data. In a small study by Gomez-Lobo et al.[14], acute rejection was observed in 6 of 14 adolescent kidney transplant recipients (ages 9-17) immunized with GARDASIL®, and the study was concluded early due to this factor. However, analysis of data from a similar age cohort of unvaccinated transplant recipients indicated similar rejection levels. A relationship between treatment modality and acute rejection was not explored.

III.6.2 Juvenile Idiopathic Arthritis (JIA)

Four studies and 1 case report have explored the safety of HPV vaccination in JIA patients. Heijstek et al.[17] found that CERVARIX® immunization of adolescent females (ages 12-18) with various immunosuppressive therapies was safe and well-tolerated in a study rated as good. Redness and bruising at the injection site were reported more frequently by healthy controls, and the frequency of general symptoms was comparable in patients and controls. SAEs occurred more often in JIA patients (16%) compared to healthy controls (2%), but these were not considered related to immunization due to pre-existing conditions and events associated with JIA disease or treatment. Importantly, JIA disease activity significantly improved at 7 and 12 months following initial immunization.

Similarly, in another study rated as good, Esposito et al.[18] report that the frequency of local or systemic reactions following CERVARIX® immunization was not significantly different between adolescent female JIA patients (ages 12-15) and healthy controls; and JIA disease activity was

not affected by immunization 12 months following initial immunization. An abstract by Singer et al.[20] also indicates that no SAEs were observed following GARDASIL® immunization of females with JIA (ages 9-26), but there was not sufficient information provided to rate the quality of this study.

In a cohort study rated as poor, Akikusa and Crawford[19] noted in their analysis of 38 female adolescents and adults with paediatric rheumatic diseases (including 28 with JIA) that one JIA patient experienced a disease flare associated with quadrivalent HPV immunization. The patient had active disease and was being treated with etanercept and methotrexate during immunization. The event occurred 2 days post-dose 3 and lasted 6 weeks, resolving with physiotherapy. No other SAEs were reported, and it should be noted that opportunistic enrolment did not allow for prospective monitoring of events or responses immediately following immunization; un-immunized JIA controls were not available for comparison of disease flare rates. One case report[28], rated as poor quality, indicates enthesitis JIA a few days following bivalent HPV immunization, but no immunosuppressive therapy was described.

III.6.3 Systemic Lupus Erythematosus (SLE)

Three studies and 2 case reports have addressed the safety of HPV immunization in SLE patients receiving various immunosuppressive therapies. In a study rated as good, Mok et al.[23] reported that GARDASIL® immunization of adult female SLE patients (ages 18-35) was safe and well-tolerated. The most common AE was erythema and pain at the injection site (5%), and no differences were observed between SLE patients and healthy controls within 12 months following immunization. Furthermore, there was no increase of SLE disease activity index (SLEDAI) associated with vaccination in SLE patients. Similarly, Heijstek et al.[21] reported no change in SLEDAI scores from 6 adolescents with SLE (ages 12-18) following CERVARIX® immunization, but this study did not report on SAEs and was rated as poor quality. Soybilgic et al.[22] observed a significant reduction of SLEDAI following GARDASIL® immunization of SLE patients (ages 16-26) receiving hydroxychloroquine and other immunosuppressive medications, although the study was rated as poor quality due to a low sample size and lack of control groups.

Two case reports, one rated as good[29] and one rated as poor quality[30], reported SLE or RA disease flares in adults following HPV immunization in patients receiving a range of immunosuppressive treatments.

III.6.4 Inflammatory Bowel Disease (IBD)

Jacobson et al.[24] present an open-label cohort study, rated as fair, combining prospective and retrospective subjects with IBD (ages 9-26) who were immunized with GARDASIL® and compared to historical healthy control data. Immunosuppression included TNF-α inhibitor and immunomodulator therapies. In the prospective cohort, 5 SAEs were reported: 2 hospitalized for IBD exacerbations, 1 for pneumonia, 1 for ovarian torsion secondary to endometriosis, 1 for acute sinus pain. The 2 patients reporting IBD exacerbation showed active colitis 2 weeks prior to study, and all SAEs were believed to be unrelated to vaccination. Minor adverse events possibly relating to vaccination included leg pain (1), diarrhea (1), rash on chin (1), abdominal pain (2), swelling and severe arm pain (1).

IV. EVIDENCE GAPS

IV.1 Overview

Limited evidence is available on the topic of HPV vaccination for immunocompromised populations, and very few of these are RCTs. Studies that do explore immunization in these populations rarely stratify results based on immunosuppressive therapy or functional immune status.

IV.2 Research priorities

Evaluation of immune status (e.g. CD4 counts) for vaccine recipients undergoing immunosuppressive therapy would allow better identification of risk groups for vaccine failure:

- Direct comparison and stratification of immunosuppressive therapies in vaccine recipients;
- Follow up of vaccinated immunocompromised subjects to evaluate long-term immunity and secondary vaccine failure;
- Evaluation of additional doses to improve potentially the immunogenicity in immunocompromised populations;
- Further direct comparisons of vaccination before and after transplantation;
- Evaluation of 9-valent HPV vaccine in immunocompromised populations.

V. DISCUSSION

The limited data available on this topic present significant barriers to the interpretation and potential development of evidence-based recommendations. The lack of control groups often resulted in a lower quality of evidence, and the sample sizes from most relevant studies were relatively small. Moreover, where control groups were included, many referred only to previously published historical control data. Taken together, although statistical comparisons were not always performed, studies indicated that among HIV-infected groups, those with lower CD4 counts or higher viral loads tended to experience the most pronounced immunogenicity deficits.

Among the patients undergoing therapeutic immunosuppression, it was not possible to organise evidence according to treatment modality or dosage, as most studies did not stratify results by treatment. Evidence was typically presented by disease type (e.g. systemic lupus erythematosus, juvenile idiopathic arthritis, solid organ transplant). Accordingly, studies were grouped by disease type in this literature review, but an ideal dataset would have enabled the grouping of results by treatment modality or effective immunosuppression.

VI. CONCLUSIONS

Immunogenicity may be suboptimal in immunocompromised subgroups (HIV+ and therapeutic immunosuppression), but evidence is not sufficient to support specific recommendations for different subgroups. In immunocompromised groups with lower vaccine responses, antibody levels still typically exceed those resulting from natural infection in immunocompetent

individuals. Evidence does not indicate that vaccine safety is different for immunocompromised subgroups.

Evidence at this time does not clearly identify high risk subgroups or immunosuppressive therapies, but evidence suggests that vaccine immunogenicity may be diminished if provided following therapy onset and solid organ transplant.

VII. LIST OF ABBREVIATIONS

Abbreviation	***Term***
AE	Adverse event
ART	Antiretroviral therapy
CD4	Cluster of differentiation 4
CIG	Canadian Immunization Guide
DMARD	Disease-modifying anti-rheumatic drug
GMC	Geometric mean concentration
GMT	Geometric mean titre
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IBD	Inflammatory Bowel Disease
JIA	Juvenile Idiopathic Arthritis
NACI	National Advisory Committee on Immunization
PM	Product monograph
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
SLE	Systemic Lupus Erythematosus
TNFα	Tumor necrosis factor alpha

VIII. ACKNOWLEDGMENTS

This literature review was prepared by: Dr. Matthew Tunis and Dr. S. Deeks and approved by NACI.

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Appendix A: Search strategy and results

Outlined below are the search terms formatted for the respective databases; this list was developed in collaboration with a librarian at the Health Library. Please note the Medline table for a breakdown of search concepts.

OvidMEDLINE

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present (March 26, 2015)

Table 2: Search Strategy

#	Searches	Results
1	Papillomavirus Vaccines/	4 433
2	((("HPV" or papillomavirus) adj4 (vaccin* or immuniz* or immunis* or innocul*)) or (gardasil or cervarix)).tw.	5 843
3	1 or 2	6 762
4	((vaccin* or immuniz* or immunis* or innocul*) adj5 (effective* or efficac* or immunogenic* or safe*)).tw.	42 947
5	(protect* or immunogenic* or antibod* or seroconver* or seropositiv* or seronegativ* or titre or titres or titer or titers or gmt or gmc or noninferior* or non-inferior* or wart* or cin3* or cin2* or cin1* or infect*).tw.	2 363 316
6	humans/ or (child* or boy or girl or boys or girls or infant* or toddler* or kid or kids or preschool* or pre?school* or teen or teens or teenager* or youth or youths or pre?teen* or preteen* or men or man or mens or mans or woman or womans or women or womens or adulthood* or people or peoples or person or persons or human or humans or subject or subjects or participant* or patient*).tw.	15 034 875
7	Immunocompromised Host/ or exp Autoimmune Diseases/ or Transplants/ or Rheumatology/ or Rheumatic Diseases/ or HIV Infections/ or Acquired Immunodeficiency Syndrome/ or Steroids/ or Radiotherapy/ or (immunocompromi* or immunosuppress* or immunodeficien* or rheumatol* or transplant* or HIV or chemotherap* or radiation or steroid* or autoimmun* or auto?immun* or biologic or biologics).tw.	1 913 223
8	3 and 4 and 5 and 6 and 7	130

(Papillomavirus Vaccines/ or ((("HPV" or papillomavirus) adj4 (vaccin* or immuniz* or immunis* or innocul*)) or (gardasil or cervarix)).tw.) and ((vaccin* or immuniz* or immunis* or innocul*) adj5 (effective* or efficac* or immunogenic* or safe*)).tw. and (protect* or immunogenic* or antibod* or seroconver* or seropositiv* or seronegativ* or titre or titres or titer or titers or gmt or gmc or noninferior* or non-inferior* or wart* or cin3* or cin2* or cin1* or infect*).tw. and (humans/ or (child* or boy or girl or boys or girls or infant* or toddler* or kid or kids or preschool* or pre?school* or teen or teens or teenager* or youth or youths or pre?teen* or preteen* or men or man or mens or mans or woman or womans or women or womens or adulthood* or people or peoples or person or persons or human or humans or subject or subjects or participant* or patient*).tw.) and (Immunocompromised Host/ or exp Autoimmune Diseases/ or Transplants/ or Rheumatology/ or Rheumatic Diseases/ or HIV Infections/ or Acquired Immunodeficiency Syndrome/ or Steroids/ or Radiotherapy/ or (immunocompromi* or immunosuppress* or

immunodeficien* or rheumatol* or transplant* or HIV or chemotherap* or radiation or steroid* or autoimmun* or auto?immun* or biologic or biologics).tw.)

Cochrane Library

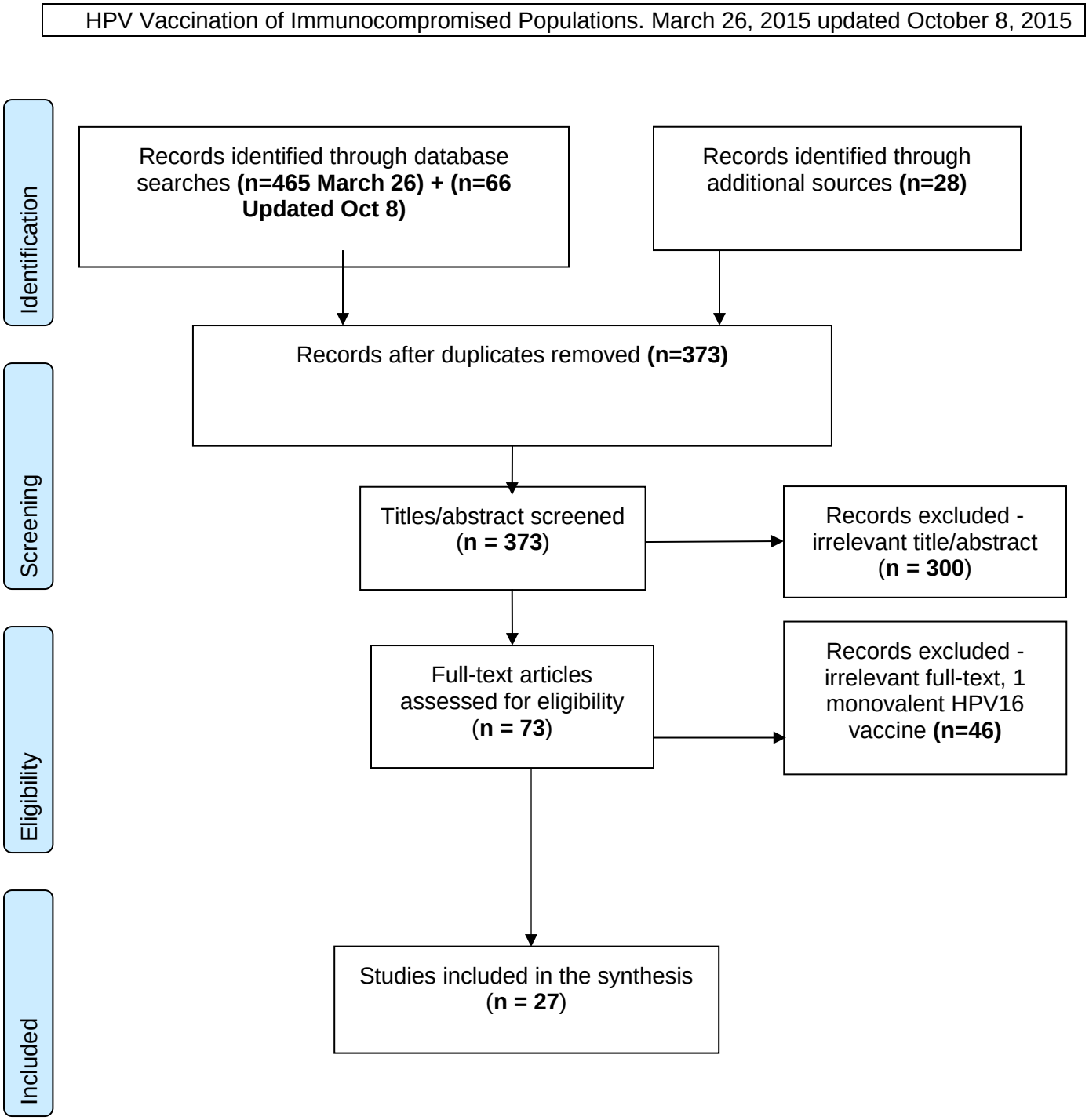
#1 (((HPV or Papillomavirus) and (Vaccin* or immuniz* or immunis* or innocul*)) or (Gardasil or Cervarix)):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Immunocompromised Host] explode all trees
#3 (immunocompromi* or immunosuppress* or immunodeficien* or rheumatol* or transplant* or HIV or chemotherap* or radiation or steroid* or autoimmun* or auto?immun* or biologics):ti,ab,kw (Word variations have been searched)
#4 (#2 or #3) and #1
(25 Results)

SCOPUS

((TITLE-ABS-KEY(("HPV" OR papillomavirus) W/4 (vaccin* OR immuniz* OR immunis* OR innocul*)) OR TITLE-ABS-KEY(gardasil OR cervarix))) AND (TITLE-ABS-KEY((vaccin* OR immuniz* OR immunis* OR innocul*) W/5 (effective* OR efficac* OR immunogenic* OR safe*))) AND (TITLE-ABS-KEY((protect* OR immunogenic* OR antibod* OR seroconver* OR seropositiv* OR seronegativ* OR titre OR titres OR titer OR titers OR gmt OR gmc OR noninferior* OR non-inferior* OR wart* OR cin3* OR cin2* OR cin1* OR infect*))) AND (TITLE-ABS-KEY(child* OR boy OR girl OR boys OR girls OR infant* OR toddler* OR kid OR kids OR preschool* OR pre?school* OR teen OR teens OR teenager* OR youth OR youths OR pre?teen* OR preteen* OR men OR man OR mens OR mans OR woman OR womans OR women OR womens OR adulthood* OR people OR peoples OR person OR persons OR human OR humans OR subject OR subjects OR participant* OR patient*)) AND (TITLE-ABS-KEY((immunocompromi* OR immunosuppress* OR immunodeficien* OR rheumatol* OR transplant* OR HIV OR chemotherap* OR radiation OR *steroid OR autoimmun* OR auto?immun* OR biologic OR biologics))) AND (LIMIT-TO(DOCTYPE,"re") OR LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"cp")) AND (LIMIT-TO(LANGUAGE,"English") OR LIMIT-TO(LANGUAGE,"French"))

310 Document Results

Appendix B: Flow diagram



Appendix C: Level of evidence based on research design and quality (internal validity) rating of evidence

Table 3. Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 4. Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Appendix D: Summary of evidence related to immunogenicity

Evidence for immunogenicity in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Rainone, V. *et al.*, 2015[4]	GARDASIL®	Longitudinal prospective nonrandomized, controlled, open-label clinical study Pediatric infectious disease clinic at L. Sacco Hospital, University of Milan, Italy.	*n*=46 HIV-infected males (20) and females (26) (13–27 years old); *n*=46 age-matched HIV-negative controls for comparison.	Acquired: HIV infection Clinically asymptomatic, $CD4^+$ count ≥350 cells/mm^3, good compliance to HAART, ≥ two suppressed HIV-RNA periods (<37 copies/ml) during 6 months prior to enrolment	Cellular responses to vaccination were measured 0, 3, 7 or 12 months post-enrolment. Overall, cellular responses to immunization were similar between HIV-infected participants and healthy controls. Naïve and central memory CD4 and CD8 T cells were increased in both groups at 3 months post-enrolment, as well as activated CD4 and CD8 T cells. Effector memory CD4 T cells were reduced 7 months post-enrolment in HIV-infected patients but not healthy controls. Otherwise, no differences in CD4 or CD8 changes were observed between HIV-infected patients and healthy controls following immunization. HPV-specific IL-2 and IFNγ-secreting CD4 T cells (and IFNγ-secreting CD8 T cells) were significantly elevated in both groups at 3 and 48 months. HPV-specific TNFα, perforin and granzyme B-expressing CD8 T cells were also increased.	II-2	Good

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

<table>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Source of immunodeficiency</th><th>Summary of Relevant Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td>Brophy, J. et al., 2015[9] [Abstract]</td><td>GARDASIL®</td><td>Open label, multi-centered study</td><td>n=32 HIV-infected 9-13 year old girls
n=260 HIV-negative age-matched historical control girls</td><td>Acquired:
HIV infection

Median (IQR) baseline CD4 Cells/µL 692 (547-929)
59% had suppressed viral load (<50 copies)</td><td>Vaccine responses were measured 0, 7, 12, 18, and 24 months post-enrolment.

100% of HIV-infected girls receiving 3 doses of Gardasil had seroconverted at month 7. HIV-infected girls with suppressed viral load had significantly higher GMTs compared to unsuppressed subjects. GMTs for all 4 serotypes were significantly lower in HIV-infected girls compared to age-matched historical controls at months 7 and 24, and appeared to decline more rapidly.

Below are GMTs at month 7:
<table>
<tr><th>HPV type</th><th>HIV+ GMT (95%CI)</th><th>HIV- historical GMT (95%CI)</th></tr>
<tr><td>6</td><td>844 (546-1304)</td><td>1856 (1571-2192)</td></tr>
<tr><td>11</td><td>971 (651-1468)</td><td>2096 (1869-2350)</td></tr>
<tr><td>16</td><td>4924 (3402-7128)</td><td>7640 (6561-8896)</td></tr>
<tr><td>18</td><td>703 (408-1212)</td><td>1703 (1489-1946)</td></tr>
</table>
GMTs at month 24:
<table>
<tr><th>HPV type</th><th>HIV+ GMT (95%CI)</th><th>HIV- historical GMT (95%CI)</th></tr>
<tr><td>6</td><td>122 (60-249)</td><td>359 (315-410)</td></tr>
</table></td><td>II-2</td><td>N/A (Assessment pending publication of complete results)</td></tr>
</table>

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
					11: 114 (57-229); 422 (369-483) 16: 688 (374-1264); 1739 (1519-1992) 18: 71 (31-164); 267 (219-324)		
Kojic, E.M. *et al*., 2014 [7]	GARDASIL®	Phase II Open-label non-randomized single arm study USA, Brazil, South Africa	*n*=315 females with documented HIV-1 infection (13-45 years old);	Acquired: HIV infection Stratified by CD4 level: Stratum A, *n*=127 >350 Cells/µL Stratum B, *n*=95 201-350 Cells/µL Stratum C, *n*=93 ≤200 Cells/µL	Vaccine responses were measured 0 and 7 months post-enrolment. Women completing 3-dose series from stratum A and B showed good seroconversion rates, but women with HIV RNA load >10 000 copies/mL and/or CD4 count ≤200 cells/µL (stratum C) had significantly lower correlated seroconversion rates for all 4 serotypes. Listed below are % seroconversion (95%CI) HPV type 6: Stratum A >350 Cells/µL 96.3 (87.3–99.5); Stratum B 201-350 Cells/µL 100.0 (92.9-100.0); Stratum C ≤200 Cells/µL 84.4 (70.5–93.5) 11: 97.7 (91.9–99.7); 98.3 (90.9-100.0); 91.9 (82.2–97.3) 16: 98.5 (92.0-100.0); 98.2 (90.4-100.0); 92.9 (82.7–98.0) 18: 91.0 (82.4–96.3); 84.5 (74.0–92.0); 75.4 (62.7–85.5) Within Stratum C, (≤200 Cells/µL), seroconversion was lower for HPV6, 11, 16, 18 in women with viral RNA >400 copies/mL (73% 77%, 81%, 56%) compared to <400 copies/mL (89%, 97%, 100%, 91%); significant for HPV11, 16, 18.	II-2	Fair (No healthy controls for comparison of seroconversion and titres)

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

<table>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Source of immunodeficiency</th><th>Summary of Relevant Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>GMTs from intention to treat were also lower for all serotypes in Stratum C women compared to A or B, significant only for HPV6.

Listed below are GMTs mMU/mL (95%CI)

<table><tr><th>HPV type</th><th>Stratum A >350 Cells/µL</th><th>Stratum B 201-350 Cells/µL</th><th>Stratum C ≤200 Cells/µL</th></tr><tr><td>6</td><td>462 (321–667)</td><td>349 (242–504)</td><td>137 (82–229)</td></tr><tr><td>11</td><td>477 (362–627)</td><td>417 (287–607)</td><td>205 (129–327)</td></tr><tr><td>16</td><td>1200 (871–1654)</td><td>1117 (746–1672)</td><td>571 (328–994)</td></tr><tr><td>18</td><td>175 (126–243)</td><td>171 (115–255)</td><td>94 (59–149)</td></tr></table></td><td></td><td></td></tr>
<tr><td>Giacomet, V. et al., 2014 [5]</td><td>GARDASIL®</td><td>18 month prospective non-randomized controlled open-label clinical study

Pediatric infectious disease clinic at L. Sacco Hospital, University of Milan, Italy.</td><td>n=46 HIV-infected males (20) and females (26) (13–27 years old);

n=46 age-matched HIV-negative controls for comparison.</td><td>Acquired:
HIV infection

Clinically asymptomatic, CD4+ count ≥350 cells/mm^3, good compliance to HAART, ≥ two suppressed HIV-RNA periods (<37 copies/ml) during 6 months prior to enrolment</td><td>Vaccine responses were measured 0, 1, 3, 7, 12, 18 months post-enrolment.

Total HPV-specific seroconversion rates 7 months post-enrolment not significantly different between HIV-infected subjects (0.85, 95%CI 0.75-0.95) and HIV-negative controls (0.91, 95%CI 0.83-0.99)

Anti-HPV IgG titres not significantly different between HIV-infected subjects and controls, but trended lower in HIV-infected subjects at months 7, 12, 18.

CD4 levels remained stable during the study period (mean 780 cells/mm^3, SD 280).</td><td>II-2</td><td>Fair
(No reporting of titres/seroconversion rates for distinct HPV serotypes)</td></tr>
</table>

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
Denny, L. *et al.,* 2013[11]	CERVARIX®	Partially-blind, partially-randomised, placebo-controlled trial Phase I/II Single centre in Cape Town, Republic of South Africa	*n*=120 **HIV-** infected women (18-25 years old); *n*=30 HIV-negative women (18-25 years old) At month 12: *n*=42 **HIV+/HPV imm**; *n*=37 HIV+/alum control, *n*=22 HIV-/HPV imm	Acquired: HIV infection HIV^{+}/HPV imm *CD4^{+} cells/mm^{3}* <200 (3.3%) 200-500 (57.4%) >500 (39.9%)	Vaccine responses were measured 0, 2, 7, and 12 months post-enrolment. High proportion of baseline HPV16 and 18 seropositive levels prior to immunization in all groups (50%-85.4%). 100% of HPV-immunized subjects were seropositive following 2nd dose of vaccine, sustained at 12 months post-enrolment. GMTs were much lower (approximately 50%) in immunized HIV-positive subjects compared to HIV-negative controls at 7 and 12 months, statistical comparisons not provided. Despite this, HIV-negative GMTs at 12 months still 16-24-fold higher than published natural infection levels. Anti-HPV16 and 18 GMTs peaked at 7 months in both immunized groups. Listed below are GMTs EL.U/mL (95%CI)	I	Fair (No statistical comparison of GMTs or CD4 responses; no stratification of responses according to CD4 level)

Assessment	HPV type	**HIV positive**	**HIV negative**
7 months	16	3558.2 (2723.6-4648.6)	8168.8 (6341.0-10,523.5)
	18	1945.8 (1451.4-2608.6)	3703.0 (2502.5-5479.4)
12 months	16	748.1 (520.0-1076.3)	2793.6 (2087.8-3738.0)

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
					<table><tr><td></td><td>18</td><td>343.1 (236.2-498.2)</td><td>1021.3 (627.4-1662.6)</td></tr></table> HPV-specific CD4+ T cells were increased in both immunized groups (HIV-positive and negative) compared to un-immunized HIV-positive controls, and sustained at 12 months (no statistical analysis provided).		
Kahn, J.A. *et al.*, 2013[12]	GARDASIL®	Phase II, open-label, multicenter trial 14 sites in USA and Puerto Rico	*n*=30 HIV-infected females with ART *(antiretroviral therapy)* *n*=69 HIV-infected females non-ART (16-23 years old). *n*=267 healthy age-matched controls from historical published data	Acquired: HIV infection *ART group* *$CD4^+$ cells/mm^3 at enrolment:* <200 (3.3%) 200-349 (16.7%) ≥350 (80.0%) *Viral copies/mL* <400 (93.3) 400-999 (3.3%) 1000-9999 (3.3%) 10000-99999 (0%) ≥100 000 (0%) *Non-ART group* *$CD4^+$ cells/mm^3 at enrolment:* <200 (0%) 200-349 (11.6%) ≥350 (88.4%) *Viral copies/mL* <400 (17.4%)	Vaccine responses were measured 0, 4, and 7 months post-enrolment. Overall, vaccine responses were better in HIV-infected patients receiving ART compared to the non-ART group, while GMT levels in the ART group were similar to historical controls. Seroconversion exceeded 92% in all groups for all serotypes at 7 months post-enrolment. Non-ART seroconversion significantly lower than historical controls for HPV18 (92.3% versus 100%). 7 months post-enrolment anti-HPV GMTs in the non-ART group were lower than the ART group, significant lower for HPV16 and 18. Non-ART group anti-HPV16 and 18 GMTs significantly lower than historical controls. Listed below are GMTs: mMU/mL (95%CI)	II-2	Fair (relies on historical control data)

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
				400-999 (23.2%) 1000-9999 (43.5%) 10000-99999 (13.0%) ≥100 000 (2.9%)	<table><tr><th>HPV type</th><th>ART</th><th>Non-ART</th><th>Healthy historical controls</th></tr><tr><td>6</td><td>1294 (334–2255)</td><td>658 (313–1002)</td><td>582 (527–643)</td></tr><tr><td>11</td><td>1522 (526–2518)</td><td>727 (485–970)</td><td>697 (618–785)</td></tr><tr><td>16</td><td>5046 (2338–7755)</td><td>2393 (1252–3534)</td><td>3892 (3324–4558)</td></tr><tr><td>18</td><td>979 (302–1655)</td><td>463 (247–679)</td><td>801 (694–925)</td></tr></table> Trend towards lower GMTs in subjects with HIV RNA load ≥400 copies/mL (significant for HPV11) but no relationship to CD4 levels.		
Toft, L. *et al.*, 2013[13]	GARDASIL® vs. CERVARIX®	Randomized, double-blind trial Aarhus University Hospital, Denmark	*n*=92 randomized (46 CERVARIX®, 46 GARDASIL®) HIV-seropositive patients >18 years old. Patients stratified by sex and use of HAART.	Acquired: HIV infection	Vaccine responses were measured 0, 7, 12 months post-enrolment. Both vaccines caused similar anti-HPV16 GMTs at 7 and 12 months post-enrolment. Anti-HPV18 GMTs were significantly higher in CERVARIX® compared to GARDASIL® recipients at 7 months (GMT ratio 4.31; 95%CI 2.21–8.40) and 12 months (GMT ratio 4.15; 95%CI 1.95–8.84). Ab responses in GARDASIL® recipients not different between sexes, but female CERVARIX® recipients had 3.16-fold higher GMTs than men (95%CI 1.56-6.40) at 7 months, and 4.43-fold (95% CI, 1.85- 10.6) at 12 months. GMTs in female CERVARIX® recipients	I	Fair (No reporting of seroconversion rates)

Evidence for immunogenicity in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					significantly greater than GARDASIL® for both HPV16 and 18 at 7 and 12 months.		
Weinberg, A. *et al.*, 2012[6]	GARDASIL® 3-dose vs. 4-dose	Open-label randomized trial Location not specified	*n*=99 (4-dose group) *n*=31 (3-dose group) HIV-infected children (7-12 years old)	Acquired: HIV infection Mean $CD4^+$count= 868 ± 367 All but 2 receiving HAART	Vaccine responses measured 1 and 18 months after final vaccine dose (3rd or 4th). 1 month post-dose 3 seroconversion occurred in 97%-100% for all serotypes. 18 months post-dose 3 seroconversion was sustained at ≥94% for HPV6, 11, 16 and 76% for HPV18. In 4-dose group, seroconversion was 100% for all serotypes at 1 month post-dose 4. CLIA titres were significantly higher 1 month after final dose in the 4-dose group compared to 3-dose group for all genotypes. Oral secretions were tested for HPV-16 or 18 specific IgG and IgA 1 month post-dose 3. 69% of participants developed HPV16 IgG, and 39% of participants developed HPV18 IgG mucosal antibodies. No respondents developed HPV-specific mucosal IgA. Members of 4-dose group did not appear to be assessed for mucosal antibodies. 60% and 52% of participants developed cytotoxic T lymphocytes (CTLs) for HPV16 and 31, respectively,	II-2	Fair (no healthy controls for comparison)

Evidence for immunogenicity in HIV-infected populations

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
					1 month post-dose 3. Fourth dose of vaccine did not improve these CTL numbers.		
Levin, M.J. *et al.*, 2010[10]	GARDASIL®	Double blind, RCT Location not specified	*n*=126 HIV-infected children (7-12 years old) [*n*=96 GARDASIL immunized *n*=30 placebo controls]	Acquired: HIV infection Mean CD4 count = 868 (794-942, 95%CI) cells/mm^3 Subjects stratified by CD4% nadir and CD4% at screening: <u>*Group 1*</u>*:* - CD4% nadir<15; - CD4%≥15 at screening *[mean 29.1% (26.5-31.6 95%CI)]* <u>*Group 2*</u>: - CD4% nadir≥15; - CD4%≥15, <25 at screening *[mean 33.6% (30.7-36.4 95%CI)]* <u>*Group 3*</u>: - CD4% nadir≥25; - CD4% ≥25 at screening *[mean 38.7% (36.6-40.8 95%CI)]*	Vaccine responses were measured 0 and 7 months post-enrolment. At month 7, seroconversion among vaccine recipients was 100% for HPV6, 11, 16, but 90% for HPV18 in Group 1 (low CD4%). GMTs were not significantly different between Groups (stratified by CD4%) of vaccine recipients. Titres were lower in HIV-infected vaccine recipients compared to historical data (30-50% lower for HPV6 and 18). Below are GMTs (95%CI): HPV type / **HIV infected** / **Historical controls** 6 / 535 (387-379) / 1053 (974-1138) 11 / 1321 (1025-1702) / 1587 (1469-1715) 16 / 4987 (3685-6751) / 6444 (5840-7110) 18 / 845 (547-1306) / 1558 (1416-1716) Low HPV-specific antibody levels were significantly correlated with high HIV viral load (>5000 copies/mL vs. <5000 copies/mL).	I	Fair (Relies on historical healthy control data for comparison)

Evidence for immunogenicity in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Wilkin, T. *et al.*, 2010[8]	GARDASIL®	Single arm open label, pilot trial 8 centers in USA.	*n*=100 HIV-1-infected males ≥ 18 years old.	Acquired: HIV infection <u>ART recipients</u> CD4 ≥200 cells/µL plasma HIV-1 RNA level <200 copies/mL <u>No ART</u> CD4 >350 cells/µL	Vaccine responses were measured 0 and 7 months post-enrolment. 7 months post-enrolment, seroconversion rates in HIV-infected patients were as follows: HPV6: 98% HPV11: 99% HPV16: 100% HPV18: 95% CD4 cell counts, nadir CD4 count, and age were not associated with anti-HPV antibody levels. Positive HPV-DNA detection by anal swab at enrolment was associated with lower antibody levels post-vaccine for HPV11, 16, and 6. ART use during vaccination was associated with higher post-vaccine anti-HPV16 and HPV18 antibody levels.	II-2	Fair (No controls available for comparison)

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Immunogenicity in transplant recipients							
Nailescu, C. *et al.*, 2015 [Abstract] [16]	GARDASIL®	Cohort study with limited details (abstract)	*n*=8-10 kidney transplant recipients ≥6 months post-transplant (post-KT).	Immunosuppression not described in abstract.	Vaccine responses were measured at 0 and 7 months post-enrolment. All pre-KT immunized subjects seroconverted to all 4 serotypes, but in post-KT immunized subjects the	II-2	*N/A (Assessment pending publication of complete results)*

Evidence for immunogenicity in acquired therapeutic immunodeficiency

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
			n=11 girls and boys (>9 years old) pre-kidney transplant (pre-KT)		seroconversion rates did not exceed 80% for any serotype. Only 60% of post-KT subjects seroconverted to HPV18 which was significantly lower than the pre-KT group. Post-KT immunized subjects had significantly lower GMTs for all 4 serotypes compared to pre-KT subjects. Seroconversion rates (%) at 7 months: HPV type / **Pre-KT** (n=11) / **Post-KT** (n=10) 6: 100 / 70 11: 100 / 70 16: 100 / 80 18: 100 / 60 GMTs at 7 months: HPV type / **Pre-KT** (n=11) / **Post-KT** (n=8) 6: 225 (68-2038) / 105 (0-622) 11: 1281 (292-2824) / 76 (0-4540) 16: 3781 (426-9179) / 129.5 (0-6975) 18: 693 (21-5456) / 13.5 (0-999)		

<table>
<tr><th colspan="8">Evidence for immunogenicity in acquired therapeutic immunodeficiency</th></tr>
<tr><th colspan="8">STUDY DETAILS</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Source of immunodeficiency</th><th>Summary of Relevant Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td>Gomez-Lobo, V. et al., 2014[14]</td><td>GARDASIL®</td><td>Cohort study

Patients recruited from CNMC and MedStar Georgetown University Hospital, USA.</td><td>n=17 solid organ transplant recipients (9-17 years old) on stable immunosuppression, >6 months post-transplant.

Only n=9 completed vaccine series (n=7 kidney; n=2 liver).

n=855 healthy controls from previous studies used for comparison.</td><td>Acquired: Immunosuppressive therapy post-solid organ transplant: Mycophenolate mofetil (88.9%); Tacrolimus (77.7%); Prednisone (44.4%); Cyclosporin (14.3%) Listed as % of completed subjects</td><td>Vaccine responses were measured 0, 3 and 7 months post-enrolment.

All transplant patients completing 3-dose series were seropositive 7 months post-enrolment.
After 2 doses of vaccine, 5 of 7 kidney recipients and 1 of 1 liver recipient seroconverted, which is comparatively low to healthy controls in literature.

GMTs for all serotypes similar overall in transplant recipients compared to historical control data. HPV6 and HPV16 GMTs appeared lower in liver transplant recipient compared to historic controls, but sample size was low and no statistical comparison performed.

Listed below are GMTs
<table>
<tr><th>HPV type</th><th>Kidney transplant (n=7)</th><th>Liver transplant (n=1)</th><th>Healthy historical controls (n=850-855)</th></tr>
<tr><td>6</td><td>1056</td><td>158</td><td>1001</td></tr>
<tr><td>11</td><td>1303</td><td>1882</td><td>1269</td></tr>
<tr><td>16</td><td>6872</td><td>824</td><td>5168</td></tr>
<tr><td>18</td><td>1619</td><td>1616</td><td>1064</td></tr>
</table>
No comparison between immunosuppressive treatment modalities.</td><td>II-2</td><td>Fair (only 53% study completion rate – study was concluded early due to ethical/safety concerns for AR in kidney recipients; low sample size; relies on historic control data for comparisons; no statistical comparisons performed)</td></tr>
<tr><td>Kumar, D. et al., 2013[15]</td><td>GARDASIL®</td><td>Cohort study

Outpatient</td><td>n=47 adult solid organ transplant recipients (18-</td><td>Acquired: Immunosuppressive therapy post-solid</td><td>Vaccine responses measured 0, 7 and 12 months post-enrolment.</td><td>II-2</td><td>Fair (no immunocomp</td></tr>
</table>

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
		clinics at University of Alberta Hospital, Canada.	35 years old). 3 months post-transplant on stable immunosuppressive therapy (no change 1 month).	organ transplant: Calcineurin-inhibitors (91.5% of total) with 93% of these on Tacrolimus; mycophenolate mofetil (87.5% of total) with 52.4% of these on high-dose (≥2g/day); Prednisone (76.6%); Sirolimus (6.4%)	Overall, responses were low compared to controls published in other studies. Seroconversion to at least one serotype was 76.3% (95%CI 62.8-89.8%) in 3-dose patients. Titres were low for all 4 serotypes (6, 11, 16, 18) 12 months after initial vaccination (14.7, 32.6, 36.4, 11.3 mMU/L respectively) compared to immunocompetent subjects in other published trials. Lung transplant recipients had significantly lowest titres 7 months after initial vaccination. There was a trend towards lower response rate in patients <1 year post-transplant. Median Tacrolimus levels were significantly lower in responders compared to non-responders (6.4 vs. 9.4 µg/mL).		etent or untreated transplant control groups for direct statistical comparison)
Immunogenicity in JIA populations							
Heijstek, M.W. *et al.*, 2014[17]	CERVARIX®	Prospective controlled observational cohort study Patients of a Paediatric rheumatology unit, Netherlands.	*n*=123; 68 females with stable JIA (12-18 years old). 55 healthy female controls (12-18 years old).	Acquired: Immunosuppressive therapy for Juvenile Idiopathic Arthritis (JIA): methotrexate (36%); NSAIDs (54%); other disease-modifying anti-rheumatic drugs (9%); anti-TNFα (13%); anti-IL-1 (1%); oral steroids (0%)	Vaccine responses measured 0, 3, 7 and 12 months post-enrolment. All JIA patients and healthy controls were seropositive for HPV16 and 18 by 7 months post-enrolment. At 12 months, all subjects (except one JIA patient) remained seropositive to both serotypes. HPV16 and HPV18–specific memory B cell responses also examined in randomized sample of participants at 3, 7, and 12 months. Kinetics of	II-2	Good

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					responses similar in JIA patients and controls (peak at 7 months); but magnitude of responses appeared lower in JIA patients 7 and 12 months post-enrollment. 5 JIA patients, 2 controls showed no memory Bcell response to HPV16. 3 JIA patients, 1 control showed no memory Bcell response to HPV18. Methotrexate did not significantly affect HPV16 or 18 antibodies levels, and all methotrexate patients were seropositive at 12 months. Anti-HPV Ab concentrations appeared lower in anti-TNFα patients, but difference not significant (low *n*).		
Esposito, S. *et al.,* 2014[18]	CERVARIX®	Cohort study Patients of a Pediatric Rheumatology Unit in Milan, Italy.	*n*=42; 21 females with stable JIA (12-15 years old). 21 healthy female controls of similar age.	Acquired: Immunosuppressive therapy for Juvenile Idiopathic Arthritis (JIA): Disease-modifying anti-rheumatic drugs (71.4%); NSAIDs (47.6); etanercept (28.6%); methotrexate (23.8%)	Vaccine responses measured 0, 6 and 7 months post-enrolment. No difference in seroconversion rates compared to healthy controls 7 months after first dose. JIA patients showed significantly lower HPV16 Nab ED_{50} GMT (6834.38) compared to healthy controls (12,177.48) at 7 months; no significant difference in HPV18 titres. No difference in immunogenicity between treatment modalities.	II-2	Good
Akikusa, J.D. and Crawford, N.W., 2014[19]	Quadrivalent	Cohort study One centre in Australia	*n*=38 females 11.8-24.7 years old (median 14.5)	Acquired: Immunosuppressive therapy for Paediatric rheumatic diseases:	Vaccine responses measured opportunistically at 0.9-23.1 months (median 1.4 months) post-dose 3.	II-2	Poor (no stratification of results by

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
			Paediatric rheumatic diseases (PRD); JIA (*n*=28); SLE (*n*=6); Juvenile dermatomyositis (*n*=2); Scleroderma (*n*=1); Sjogren's disease (*n*=1)	No therapy or NSAIDs only (7.9%); single disease modifying anti-rheumaric drug (DMARD) or low-dose corticosteroids (45%); high dose corticosteroids (>2.0 mg/kg/day) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs (47%)	Vaccine titres in PRD patients were not significantly different from historical controls for all 4 serotypes. Seroconversion rates not assessed due to lack of pre-vaccine samples. A non-significant trend was observed for lower anti-HPV 6, 11, 16 titres in patients receiving [high dose corticosteroids (>2.0 mg/kg/day) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs] compared to historic controls – but data not provided in study.		disease or therapy type; pre-vaccine titres not assessed; statistical methods not described)
Singer, N. *et al.*, 2014 [Abstract][20]	GARDASIL®	Cohort study Number of centers unknown	*n*=28 females with **JIA** (9-26 years old)	Immunosuppression not described in abstract.	Vaccine responses measured 0, 7 and 12 months post-enrolment. All but one participant showed HPV-specific GMTs comparable to controls for all 4 serotypes.	II-2	*N/A (Assessment pending publication of complete results)*
Immunogenicity in SLE populations							
Mok, C.C. *et al.,* 2013[23]	GARDASIL®	12 month cohort study One centre in Hong Kong, China	*n*=100; 50 adult females with SLE on stable immunosuppressive therapy within 3 months of entry, 50 healthy controls (18-35 years old). 50 additional SLE	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE): prednisone (70%); hydroxychloroquine (66%); azathioprine (48%); mycophenolate mofetil (18%);	Vaccine responses measured 0, 7 and 12 months post-enrolment. Deficiencies in seroconversion and titres were noted in SLE patients. Seroconversion was lower than controls at 7 and 12 months post-vaccine, but exceeded 74% in all serotypes. Listed below are % seroconversion rates	II-2	Good

Evidence for immunogenicity in acquired therapeutic immunodeficiency

STUDY DETAILS

Study	*Vaccine*	*Study Design*	*Participants*	*Source of immunodeficiency*	*Summary of Relevant Findings*	*Level of Evidence*	*Quality*
			controls were accessed through clinic for disease flare/safety comparisons.	ciclosporin A (4%); tacrolimus (10%); methotrexate (6%)	<table><tr><th>Assessment</th><th>HPV type</th><th>SLE patients</th><th>Controls</th></tr><tr><td rowspan="4">7 months</td><td>6</td><td>74</td><td>96</td></tr><tr><td>11</td><td>76</td><td>95</td></tr><tr><td>16</td><td>92</td><td>98</td></tr><tr><td>18</td><td>76</td><td>93</td></tr><tr><td rowspan="4">12 months</td><td>6</td><td>82</td><td>98</td></tr><tr><td>11</td><td>89</td><td>98</td></tr><tr><td>16</td><td>95</td><td>98</td></tr><tr><td>18</td><td>76</td><td>80</td></tr></table> Anti-HPV titres post-vaccination were generally lower in patients on immunosuppressive medications. Combined immunosuppression with prednisolone and mycophenolate mofetil was associated with significantly lower titres and seroconversion for HPV6 (33%) and HPV18 (33%) at 12 months, and significantly lower HPV16 titres (211 mMU, IQR 2100) at 7 months.		
Heijstek *et al.*, 2013[21]	CERVARIX®[J]	Prospective controlled observational study Pediatric rheumatology unit, University Medical Center Utrecht, Netherlands	*n*=61; 6 SLE patients; 6 JDM patients; 49 healthy controls (12-18 years old).	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE) or Juvenile Dermatomyositis (JDM): glucocorticosteroids (*n*=6); hydroxychloroquine (*n*=2); methotrexate (*n*=2); azathioprine (*n*=1);	Vaccine responses measured 0, 3, 7, 12 months post-enrolment. All subjects seropositive for HPV16 and 18 after completing 3 dose series, except for 1 JDM patient (not on immunosuppressive therapy). HPV16 and 18 Ab GMC were lower for SLE patients compared to healthy controls at 3, 7, 12 months, but not significant. HPV16 and 18 Ab GMCs were	II-2	Fair (small treatment group sample size).

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
				mycophenolate mofetil (*n*=1)	significantly lower for JDM patients compared to healthy controls at 7 months, but similar to controls 12 months post-enrolment. Kinetics of response dramatically different between JDM patients and controls. Effects did not appear related to immunosuppressive medication, as unmedicated patients experienced similar responses.		
Soybilgic, A. *et al.,* 2013[22]	GARDASIL®	Open-label, prospective, pre-post intervention cohort study University of Chicago rheumatology clinics, USA.	*n*=27 patients with SLE on stable immunosuppressive therapy (12-26 years old).	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE): hydroxychloroquine (100%); prednisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%)	Vaccine responses measured 0, 7 months post-enrolment. Seroconversion exceeded 94% for all serotypes at 7 months post-vaccine. One patient who received rituximab between doses 2-3 had no Ab response to HPV6 and HPV18 at month 7, with low responses to HPV11 and HPV16 (titres 75 and 65 mMU/mL). No comparison of titer levels.	II-2	Poor (small sample size – only 20 completed study. No immunocompetent or untreated SLE control groups for comparison of immunogenicity or disease scores. No titer comparisons).
Akikusa, J.D. and Crawford, N.W., 2014[19]	Quadrivalent	Cohort study One centre in Australia	*n*=38 females 11.8-24.7 years old (median 14.5) Paediatric rheumatic diseases (PRD); JIA (*n*=28); SLE (*n*=6); Juvenile	Acquired: Immunosuppressive therapy for Paediatric rheumatic diseases: No therapy or NSAIDs only (79%); single disease modifying anti-rheumatic drug	Vaccine responses measured opportunistically at 0.9-23.1 months (median 1.4 months) post-dose 3. Vaccine titres in PRD patients were not significantly different from historic controls for all 4 serotypes. Seroconversion rates not assessed due to lack of pre-vaccine samples.	II-2	Poor (no stratification of results by disease or therapy type; pre-vaccine titres not assessed;

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
			dermatomyositis (*n*=2); Scleroderma (*n*=1); Sjogren's disease (*n*=1)	(DMARD) or low-dose corticosteroids (45%); high dose corticosteroids (>2.0 mg/kg/day) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs (47%)	A non-significant trend was observed for lower anti-HPV 6, 11, 16 titres in patients receiving [high dose corticosteroids (>2.0 mg/kg/day) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs] compared to historic controls – but data not provided in study.		statistical methods not described)
Immunogenicity in IBD populations							
Jacobson, D.L. *et al.,* 2013[24]	GARDASIL®	Open-label prospective and retrospective cohort study Patients at Children's Hospital Boston or Maine Medical Center, USA.	*n*=37 prospective (33 completed) and *n*=15 retrospective patients with IBD: Crohn's disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC), (9-26 years old). Compared to historic healthy control data.	Acquired: immunosuppressive therapy for IBD: *Prospective (n=37)* TNF-α inhibitor (51%); Immunomodulator (49%) *Retrospective (n=15)* TNF-α inhibitor (67%); Immunomodulator (33%)	Vaccine responses measured 0, 7 months post-enrolment for prospective cohort. Response measured upon enrolment for retrospective cohort (0.5-27.2 months post-3rd dose vaccination) to assess long-term response. Historic healthy controls measured at month 7. Upon completion of 3-dose series, all prospective cohort participants were seropositive for HPV6, 11, 16; but 6% (2/33) did not seroconvert to HPV18. Overall, GMTs of prospective cohort IBD patients 7 months post-enrolment were similar to or exceeded historic healthy controls for all 4 serotypes. Prospective patients with TNF-α inhibitor therapy had significantly higher HPV6 mean titres (1511; 95%CI 955, 2393) compared to patients with Immunomodulators (788; 95%CI 526,	II-2	Fair (relies on historic healthy control data for comparison, non-inferiority not assessed)

Evidence for immunogenicity in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					1180) but both were similar to historical healthy control titres for HPV6 (545.2 age 16-26, 929.2 age 9-15). All other serotypes were similar. Retrospective (previously immunized) patients were all seropositive for HPV6, 11, 16, but 40% (6/15) were seronegative for HPV18 (titer <24, cLIA assay). Ab titres by cLIA showed significant negative correlation between titer levels and months following dose 3 for HPV6, 11, 18 but not 16; suggesting that response decreases over first year post-vaccine.		

Appendix E: Summary of evidence related to safety

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Rainone, V. *et al.*, 2015[4]	GARDASIL®	Longitudinal prospective nonrandomized, controlled, open-label clinical study Pediatric infectious disease clinic at L. Sacco Hospital, University of Milan, Italy.	*n*=46 HIV-infected males (20) and females (26) (13–27 years old); *n*=46 age-matched HIV-negative controls for comparison.	Acquired: HIV infection Clinically asymptomatic, CD4+ count ≥350 cells/mm^3, good compliance to HAART, ≥ two suppressed HIV-RNA periods (<37 copies/ml) during 6 months prior to enrolment	No significant safety issues identified. Refer to [Giacomet, V. *et al.*, 2014, *Vaccine*] for more details	II-2	Good
Vandriel, S. *et al.*, 2015 [27][Abstract]	GARDASIL®	Multi-centre study	*n*=57 HIV-infected girls (<18 years old) *n*=293 HIV-infected women. All 350 received 3 doses of vaccine	Acquired: HIV infection	Vaccine-related symptoms reported up to 30 days after each dose of vaccine. No significant safety issues identified. Most common AE local injection-site reactions (32%), pain (31%), redness (5%), swelling (5%). Systemic AEs occurred in 19% of subjects. 36 SAEs reported, only 1 possibly related to vaccine (encephalopathy) which resolved without sequelae. No HIV-negative controls available for direct comparison, but AEs were lower compared to historical HIV-negative controls.	N/A	*N/A (Assessment pending publication of complete results)*

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Kojic, E.M. *et al*., 2014[7]	GARDASIL®	Phase II Open-label non-randomized single arm study USA, Brazil, South Africa	*n*=315 females with documented HIV-1 infection (13-45 years old);	Acquired: HIV infection Stratified by CD4 level: <u>Stratum A</u>, *n*=127 >350 Cells/µL <u>Stratum B</u>, *n*=95 201-350 Cells/µL <u>Stratum C</u>, *n*=93 ≤200 Cells/µL	Vaccine-related symptoms assessed 24-48h post-vaccine. No significant safety issues identified. Most common adverse event was pain; other common events include neurological, gastrointestinal, skin related. Two deaths unrelated to vaccine from stratum A (1 lymphoma and 1 meningitis). One participant in stratum B had allergic reaction; 1 participant from stratum C developed grade 3 fever. Sixteen participants had grade 1 or higher fever reported during post-vaccination follow-up. Three participants from stratum C experienced grade 2 injection site reactions. Overall, 17% of participants experienced grade 3 or higher adverse events, 11% grade 3 or higher signs and symptoms, and 8% grade 3 or higher laboratory abnormalities.	II-2	Fair (No healthy or untreated HIV-infected control groups for direct comparison)
Giacomet, V. *et al.*, 2014[5]	GARDASIL®	18 month prospective non-randomized controlled open-label clinical study Pediatric	*n*=46 HIV-infected males (20) and females (26) (13–27 years old); *n*=46 age-matched HIV-	Acquired: HIV infection Clinically asymptomatic, CD4+ count ≥350 cells/mm^3, good compliance to HAART, ≥ two	Overall trends for higher local and systemic events in HIV-infected subjects compared to HIV-negative controls. Local events: Pain (18.8% HIV- / 32.6% HIV+) Erythema (5.8% HIV- / 11.3% HIV+)	II-2	Fair (underpowered for direct comparisons between groups)

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
		infectious disease clinic at L. Sacco Hospital, University of Milan, Italy.	negative controls for comparison.	suppressed HIV-RNA periods (<37 copies/ml) during 6 months prior to enrolment	Edema (7.2% HIV- / 7.8% HIV+) Induration (10.1% HIV- / 12.8% HIV+) Systemic events: Fever (0% HIV- / 2.8% HIV+) Malaise (1.4% HIV- / 7.1% HIV+) Headache (2.2% HIV- / 13.5% HIV+) No SAEs reported.		
Toft, L. *et al.*, 2013[13]	GARDASIL® vs. CERVARIX®	Randomized, double-blind trial Aarhus University Hospital, Denmark	*n*=92 randomized (46 CERVARIX®, 46 GARDASIL®) HIV-seropositive patients >18 years old.	Acquired: HIV infection Patients stratified by sex and use of HAART.	Vaccine-related symptoms assessed up to 15 days post-vaccine. No SAEs reported in this study. Both vaccines well-tolerated with very few mild systemic reactions (influenza-like symptoms, headache, nausea). Injection site pain most common reaction. Injection site reactions more common in CERVARIX group than in GARDASIL group (91.1% vs 69.6%; P = 0.02). No sex-related differences in injection site reactions.	I	Good
Denny, L. *et al.,* 2013[11]	CERVARIX®	Partially-blind, partially-randomised, placebo-controlled trial Phase I/II Single centre in Cape Town,	*n*=120 HIV-infected women (18-25 years old); *n*=30 HIV-negative women (18-25 years old)	Acquired: HIV infection HIV$^+$/HPV imm - 3.3% subjects with CD4$^+$<200cells/mm^3 - 57.4% subjects with CD4$^+$200-500 cells/mm^3	Vaccine administration did not alter CD4$^+$ cell counts in HIV+ HPV-immunized subjects compared to HIV+ alum controls. Overall incidence of solicited local and general adverse events similar in HIV-positive and HIV-negative vaccinated women. Most solicited	I	Good

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
		Republic of South Africa At month 12: *n*=42 HIV+/HPV imm; *n*=37 HIV+/alum control, *n*=22 HIV-/HPV imm		- 39.3% subjects with $CD4^+$>500 cells/mm^3	local and general adverse events were mild or moderate intensity and resolved spontaneously. Grade 3 pain reported following 1.9% of doses in HIV+/HPV group, and 1.2% of doses in the HIV-/HPV group. No Grade 3 local solicited events in HIV+/alum control group. Most commonly reported unsolicited adverse events were headache (19.7%, 23.7% and 13.3%, respectively) and upper respiratory tract infection (16.4%, 16.9% and 23.3%). SAEs reported by 6 subjects (no more than 3 per group), none related to vaccine. No subjects withdrew due to SAEs, no deaths.		
Kahn, J.A. *et al.*, 2013[12]	GARDASIL®	Phase II, open-label, multicenter trial 14 sites in USA and Puerto Rico	*n*=30 HIV-infected females with ART *n*=69 HIV-infected females non-ART (16-23 years old). *n*=267 healthy age-matched controls from historical published data	Acquired: HIV infection *ART (antiretroviral therapy) group* *$CD4^+$ cells/mm^3 at enrolment:* <200 (3.3%) 200-349 (16.7%) ≥350 (80.0%) *Viral copies/mL* <400 (93.3) 400-999 (3.3%) 1000-9999 (3.3%) 10000-99999 (0%)	Vaccine was safe and well-tolerated. 48.5% of HIV-infected participants reported at least 1 local or systemic reaction. Most common local reaction was pain (26.3%). Fever was most common systemic reaction (12.1%), followed by headache (15.2%). These were similar to historical healthy control levels. One SAE reported for fatigue, not related to vaccine.	II-2	Fair (relies on historical control data for comparison)

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
				≥100 000 (0%) *<u>Non-ART group</u>* *$CD4^+$ cells/mm^3 at enrolment:* <200 (0%) 200-349 (11.6%) ≥350 (88.4%) *Viral copies/mL* <400 (17.4%) 400-999 (23.2%) 1000-9999 (43.5%) 10000-99999 (13.0%) ≥100 000 (2.9%)			
Levin, M.J. *et al.*, 2010[10]	GARDASIL®	Double blind, RCT	*n*=126 HIV-infected children (7-12 years old) [*n*=96 GARDASIL immunized *n*=30 placebo controls]	Acquired: HIV infection Mean CD4 count = 868 (794-942, 95%CI) cells/mm^3 Subjects stratified by CD4% nadir and CD4% at screening: *<u>Group 1</u>:* - CD4% nadir<15; - CD4%≥15 at screening *[mean 29.1% (26.5-31.6 95%CI)]* *<u>Group 2</u>*: - CD4% nadir≥15;	Vaccine safe and well-tolerated. AEs infrequent and their occurrence was similar in vaccine and placebo recipients, but injection site reactions were significantly more common in vaccine recipients compared to placebo controls. AEs did not differ between groups stratified by CD4%. Within 14 days of first HPV immunization: 25% reported Grade 1 symptoms; 29% reported Grade 2 symptoms; 5% reported Grade 3 symptoms; 2% reported Grade 4 symptoms No SAEs reported. CD4 status and viral load not	I	Fair (No comparison to healthy vaccine recipients)

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
				- CD4%≥15, <25 at screening *[mean 33.6% (30.7-36.4 95%CI)]* <u>*Group 3*</u>: - CD4% nadir≥25; - CD4% ≥25 at screening *[mean 38.7% (36.6-40.8 95%CI)]*	altered by vaccination.		
Wilkin, T. *et al.*, 2010[8]	GARDASIL®	Single arm open label, pilot trial 8 centers in USA.	*n*=100 HIV-1-infected males ≥ 18 years old.	Acquired: HIV infection <u>ART recipients</u> CD4 ≥200 cells/µL plasma HIV-1 RNA level <200 copies/mL (mean CD4 514 cells/µL at enrolment) <u>No ART</u> CD4 >350 cells/µL (mean CD4 544 cells/µL at enrolment)	No Grade 3, 4, or 5 events related to vaccination. Grade 2 reactions related to vaccination occurred in 5% of participants, including one with recurrent tinnitus possibly related to vaccination - in this case 3rd dose was withheld. Grade 1, 2 local reactions observed after dose 1 (18%), dose 2 (17%), and dose 3 (12%). CD4 cell counts in ART patients were similar before vaccination (514 cells/µL) and at 12 weeks (558 cells/µL) post-enrolment. CD4 cell counts in non-ART patients were similar before vaccination (544 cells/µL) and at 12 weeks (517 cells/µL) post-enrolment. HIV-1 RNA levels were also similar before and after vaccination for	II-2	Fair (No controls available for comparison)

Evidence for safety in HIV-infected populations							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					both groups.		

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Safety in transplant recipients							
Gomez-Lobo, V. *et al.*, 2014[14]	GARDASIL®	Cohort study Patients recruited from CNMC and MedStar Georgetown University Hospital, USA.	*n*=17 solid organ transplant recipients 9-17 years old on stable immunosuppression, >6 months post-transplant. Only *n*=9 completed vaccine series (*n*=7 kidney; *n*=2 liver). *n*=855 healthy controls from previous studies used for comparison.	Acquired: Immunosuppressive therapy post-solid organ transplant: Mycophenolate mofetil (88.9%); Tacrolimus (77.7%); Prednisone (44.4%); Cyclosporin (14.3%) Listed as % of completed subjects	Adverse event measurement timeframe was not indicated. Adverse events included fever (4), swelling and pain at the injection site (3), acne (1), cough (1), pneumonia (1), diarrhea (1), and headache (1); none requiring hospitalization. Study was concluded early due to ethical/safety concerns for acute rejection (AR) in kidney recipients. Six of 14 (42.8%) kidney transplant recipients developed AR (3.6 ± 3.4) months following last dose of vaccine. Of 7 with complete vaccination, one had AR 8 months after completion. Of 7 with incomplete vaccination, five had AR after (2.6 ± 1.8) months of receiving vaccination. Mean COV% of tacrolimus level was 44.5% Analysis of data from similar age cohort of unvaccinated transplant recipients indicated similar rejection	II-2	Poor (only 53% study completion rate – study was concluded early due to ethical/safety concerns for AR in kidney recipients; low sample size; significantly underpowered to assess relationship between vaccination and AR)

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					levels.		
Kumar, D. *et al.*, 2013[15]	GARDASIL®	Cohort study Outpatient clinics at University of Alberta Hospital, Canada.	*n*=47 adult solid organ transplant recipients (18-35 years old). 3 months post-transplant on stable immunosuppressive therapy (no change 1 month). Local and systemic reactions assessed 48h and 7 days post vaccine for each dose, up to 1 year.	Acquired: Immunosuppressive therapy post-solid organ transplant: Calcineurin-inhibitors (91.5% of total) with 93% of these on Tacrolimus; mycophenolate mofetil (87.5% of total) with 52.4% of these on high-dose (≥2g/day); Prednisone (76.6%); Sirolimus (6.4%)	Vaccine safe and well-tolerated. After first dose, injection site tenderness was most common reaction (22.2%). After second dose, tenderness (2.2%) and fever (2.2%) most common. By third dose, no local or systemic reactions occurred. Other adverse events in 1 year post-enrolment include CMV viremia, CMV enteritis, lymphoma, unanticipated pregnancy. 3 female patients diagnosed with LSIL at 14, 36, and 36 months post-immunization, all were seronegative for HPV18 after vaccination.	II-2	Fair (No immunocompetent or untreated transplant control groups for direct comparison)
Safety in JIA populations							
Heijstek, M.W. *et al.*, 2014[17]	CERVARIX®	Prospective controlled observational cohort study Patients of a Paediatric rheumatology unit, Netherlands	*n*=123; 68 females with stable JIA (12-18 years old). 55 healthy female controls (12-18 years old).	Acquired: Immunosuppressive therapy for Juvenile Idiopathic Arthritis (JIA): NSAIDs (54%); methotrexate (36%); other disease-modifying anti-rheumatic drugs (9%); anti-TNFα (13%); anti-IL-1 (1%); oral steroids (0%)	Vaccine safe and well-tolerated. Reactions measured for 2 weeks following each immunization. Redness and bruising at injection site reported more frequently by healthy controls. Frequency of general symptoms was comparable in patients and controls. SAEs occurred more often in JIA patients (16%) compared to healthy controls (2%), but these were not considered related to immunization due to pre-existing conditions and	II-2	Good

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					events associated with JIA disease or treatment. JIA disease activity (measured by JADAS-27) did not worsen, but significantly improved at 7 and 12 months post-enrolment. Vaccination did not negatively affect JIA disease, including cases with methotrexate (*n*=24) or anti-TNFα (*n*=9).		
Esposito, S. *et al.,* 2014[18]	CERVARIX®	Cohort study Patients of a Pediatric Rheumatology Unit in Milan, Italy	*n*=42; 21 females with stable JIA (12-15 years old). 21 healthy female controls of similar age.	Acquired: immunosuppressive therapy for Juvenile Idiopathic Arthritis (JIA): Disease-modifying anti-rheumatic drugs (71.4%); NSAID (47.6); etanercept (28.6%); methotrexate (23.8%)	Vaccine safe and well-tolerated. Reactions measured for 2 weeks following each immunization. Frequency of local reactions not statistically different between patients and healthy controls: 42.9 versus 42.8% after first dose; 47.6 versus 28.6% after second and 42.8 versus 38.1% after third dose. Incidence of systemic reactions marginal, not statistically different between the groups: 14.3 versus 4.8% after first dose; 9.5 versus 4.8% after second and 4.8 versus 4.8% after third dose. No serious adverse events, fever, or rash were noted from any group. In JIA patients, no change in JADAS-27 scores or laboratory test results up to 12 months post enrolment.	II-2	Good

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Akikusa, J.D. and Crawford, N.W., 2014[19]	Quadrivalent	Cohort study One centre in Australia	*n*=38 females 11.8-24.7 years old (median 14.5 years old) Paediatric rheumatic diseases (PRD); JIA (*n*=28); SLE (*n*=6); Juvenile dermatomyositis (*n*=2); Scleroderma (*n*=1); Sjogren's disease (*n*=1)	Acquired: Immunosuppressive therapy for Paediatric rheumatic diseases: No therapy or NSAIDs only (79%); single disease modifying anti-rheumaric drug (DMARD) or low-dose corticosteroids (45%); high dose corticosteroids (>2.0 mg/kg/day) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs (47%)	One JIA patient experienced disease flare in left hip associated with immunization. Pt had active disease and was being treated with etanercept and methotrexate during immunization. Event occurred 2 days post-dose 3 and lasted 6 weeks, resolving with physiotherapy. No other SAEs were reported.	II-2	Poor (opportunistic enrolment did not allow for prospective monitoring of events/responses immediately following immunization; no un-immunized controls available for comparison).
Singer, N. *et al.*, 2014 [Abstract][20]	GARDASIL®	Cohort study Number of centers unknown	*n*=28 females with JIA (9-26 years old)	Immunosuppression not described in abstract.	No SAEs observed at time of publication. AEs included local and systemic events.	II-2	*N/A (Assessment pending publication of complete results)*
Safety in SLE populations							
Mok, C.C. *et al.,* 2013[23]	GARDASIL®	12 month cohort study One centre in Hong Kong, China	*n*=100; 50 adult females with SLE on stable immunosuppressive therapy within 3 months of entry, 50 healthy controls (18-35 years	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE): prednisone (70%); hydroxychloroquine (66%); azathioprine	Vaccine safe and well-tolerated. The most common AE was erythema and pain at injection site (5%). No differences were observed between SLE patients and healthy controls within 12 months post-immunization. No increase of SLE disease activity	II-2	Good

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
			old). 50 additional SLE controls were accessed through clinic for disease flare/safety comparisons.	(48%); mycophenolate mofetil (18%); ciclosporin A (4%); tacrolimus (10%); methotrexate (6%)	index following vaccination in SLE patients. 10 SLE flares occurred during 12-month follow up, not significantly different than rate in unimmunized SLE controls.		
Soybilgic, A. *et al.,* 2013[22]	GARDASIL®	Open-label, prospective, pre-post intervention cohort study University of Chicago rheumatology clinics, USA.	*n*=27 patients with SLE on stable immunosuppressive therapy (12-26 years old).	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE): hydroxychloroquine (100%); prenisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%)	Vaccine safe and well-tolerated. No increase in SLE disease activity index (SLEDAI). In fact, significant reduction of SLEDAI observed post-vaccine (4.49, SD 2.8) compared to pre-vaccine (6.14, SD 3.7).	II-2	Poor (small sample size – only 20 completed study. No immunocompetent or untreated SLE control groups for comparison of immunogenicity or disease scores)
Heijstek *et al.*, 2013[21]	CERVARIX®	Prospective controlled observational study Pediatric rheumatology unit, University Medical Center Utrecht, Netherlands	*n*=61; 6 SLE patients; 6 JDM patients; 49 healthy controls (12-18 years old).	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE) or Juvenile Dermatomyositis (JDM): glucocorticosteroids (*n*=6); hydroxychloroquine (*n*=2); methotrexate (*n*=2); azathioprine (*n*=1);	For SLE patients, SLEDAI low prior to (range 0-8) and following (range 0-12) immunization. All JDM patients were in remission before and after immunization. No reporting on SAE.	II-2	Poor (small treatment group sample size; no unimmunized controls for comparison; no reporting on SAE).

Evidence for safety in acquired therapeutic immunodeficiency							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
				mycophenolate mofetil (*n*=1)			
Safety in IBD populations							
Jacobson, D.L. *et al.,* 2013[24]	GARDASIL®	Open-label prospective and retrospective cohort study Patients at Children's Hospital Boston or Maine Medical Center, USA.	*n*=37 prospective (33 completed) and *n*=15 retrospective patients with IBD: Crohn's disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC), (9-26 years old). Compared to historical healthy control data.	Acquired: immunosuppressive therapy for IBD: Prospective (*n*=37) TNF-α inhibitor (51%); Immunomodulator (49%) Retrospective (*n*=15) TNF-α inhibitor (67%); Immunomodulator (33%)	Vaccine considered safe and well-tolerated. In prospective cohort, 5 SAEs reported: 2 hospitalized for IBD exacerbations, 1 for pneumonia, 1 for ovarian torsion secondary to endometriosis, 1 for acute sinus pain. The 2 reports of IBD exacerbation showed active colitis 2 weeks prior to study, all SAEs believed to be unrelated to vaccination. Minor adverse events deemed possibly relating to vaccine included leg pain (1), diarrhea (1), rash on chin (1), abdominal pain (2), swelling and severe arm pain (1). Most common local reaction in prospective cohort was soreness at injection site (52% post-dose 3).	II-2	Fair (No immunocompetent or untreated IBD control groups used for direct comparison).

Appendix F: Summary of evidence related to case reports

Case Reports							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
Immunogenicity							
Handisurya, A. *et al.*, 2010[26]	GARDASIL®	case report	*n*=1 female (12 years old) with WHIM syndrome, mutation in CXCR4 Comparison population = 3 immunocompetent adults (28-49 years old)	Congenital: WHIM Syndrome (CXCR4 mutation)	Samples collected at enrolment and 8 weeks after dose 3. Overall, vaccination elicited detectable titer and neutralizing anti-HPV responses in WHIM patient, but titres appeared much lower than responses in 3 immunocompetent adults. 2 months post-dose 3, anti-HPV antibodies detectable in WHIM patient and all 3 comparison adults for all 4 serotypes. WHIM patient had detectable titres at 400 for HPV6, 11, 16 and titres at 100 for HPV18. In comparison adults, titres ranged from 6,400 – 102,400 for all 4 serotypes. Neutralization of pseudovirions with serum 2 months post-dose 3 occurred in WHIM patient with anti-HPV6 titer of 50, compared to 1600-25600 in immunocompetent adults. Neutralization with anti-HPV11 titer 400, compared to 1600-6400 in immunocompetent adults. Neutralization with anti-HPV16 titer 200, compared to 1600-6400 in immunocompetent adults. No neutralization of HPV18	III	Fair (no direct comparison statistically possible between WHIM patient and controls)

Case Reports							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					PsVs occurred with serum from WHIM patient or immunocompetent adults. Cellular responses (PBMC proliferation) were detected *in vitro* in WHIM patient and immunocompetent adults in response to GARDASIL® vaccine at months 2, 6, and 8 post-enrolment.		
Safety							
Akioka, S., 2014[28]	Bivalent HPV vaccine	Case report	*n*=1 female JIA patient (15 years old).	No previous immunosuppressive therapy was described.	Patient had history of intermittent buttock pain and lumbago 2 years pre-vaccination. A few days after first dose, pt had persistent pain with joint swelling, spreading to multiple sites following subsequent vaccine doses. Pt was diagnosed with enthesitis JIA, clinical phenotype polyenthesitis. Investigators state it was unclear whether vaccination uncovered underlying disease, or aggravated disease which had been previously overlooked.	III	Poor (No summary of total SAEs or local reactions; immune status of pt not clear).
Gatto, M. *et al.,* 2013[29]	GARDASIL®	Case reports	*n=1* female (19 years old) with history of SLE *n=5* other cases also reported with onset of new SLE	Acquired: immunosuppressive therapy for Systemic Lupus Erythematosus (SLE): Maintenance therapy of low-dose hydroxychloroquine and vitamin D, flares treated with	SLE patient in full clinical remission prior to immunization, maintenance therapy of low-dose hydroxychloroquine and vitamin D. Minor symptoms reported following 1st vaccine dose: mild arthralgia, dyspnea (no abnormalities on chest x-ray), cervical lymphadenopathy, skin rash. Symptoms resolved following prednisone therapy (40mg/day) tapering down with	III	Good

Case Reports							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
				corticosteroids	time. Patient experienced SLE flare 10 days following 2nd dose of vaccine: very notable malar rash, severe skin rash, cervical lymphadenopathy of more than 3 cm, alopecia, leucopenia, elevated ESR, decreased complement levels. Symptoms resolved following increased corticosteroid dose and belimumab.		
Soldevilla, H.F. *et al.,* 2012[30]	"HPV vaccine" – valency not specified	Case report	*n=1* female (58 years old) with history of SLE, in remission for 8 years *n*=1 female (45 years old) with history of RA, in remission for 1 year	Patient#1 N/A Patient#2 Acquired: immunosuppressive therapy for Rheumatoid Arthritis (RA): Maintenance therapy of methotrexate and low-dose steroid.	Patient#1 received 2 doses of HPV vaccine, followed by severe SLE flare 3 months later. Patient#1 was hospitalised for malar and scalp rashes, fever, easy fatigability, cervical lymph nodes, gross hematuria and pallor. Work up disclosed severe anemia and thrombocytopenia, azotemia, transaminitis, hypocomplementemia, and active nephritis, with SLEDAI score of 15. Despite aggressive management, patient#1 died in hospital 1 day after admission. Patient#2 received HPV vaccine (number of doses not reported), followed by new SLE disease activity 4 months later. Patient#2 presented with intermittent fever, generalized	III	Poor (type of HPV vaccine not disclosed; timeline of doses not clear)

Case Reports							
STUDY DETAILS							
Study	***Vaccine***	***Study Design***	***Participants***	***Source of immunodeficiency***	***Summary of Relevant Findings***	***Level of Evidence***	***Quality***
					weakness, oral ulcers, alopecia, malar rash, photosensitivity, arthritis, intestinal pseudo-obstruction, ascites and behavioral changes. Infectious and metabolic work-ups all negative. MRI showed vasculitic lesions on frontal and parietal lobes. Cerebrospinal fluid examination was normal, did not grow any microorganisms. Abdominal ultrasound showed ascites. Further tests showed hypocomplementemia, elevated ESR, proteinuria with active urine sediments, positive ANA at 1:320 (homogeneous pattern), with positive antibodies against dsDNA, Ro/SSA, La/SSB and histone. Patient#2 improved following pulse methylprednisolone and was maintained on prednisone and hydroxychloroquine.		