

인유두종바이러스 예방백신 권고안

2024년 11월 개발: 대한부인종양학회 백신권고안 개정위원회

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발간사

안녕하세요.

2024년도판 "인유두종바이러스 예방백신 권고안"의 발간을 축하드립니다. 이 보고서는 대한한국 여성에서 자궁경부암 예방을 위한 또 하나의 중요한 발걸음이며, 이를 통해 우리의 여성 건강과 공공 보건에 대한 이해를 높일 수 있는 기회가 마련되었다고 봅니다.

인유두종바이러스는 자궁경부암을 포함한 여러 형태의 암과 관련이 있는데, 이를 예방할 수 있는 방법으로 백신의 중요성을 강조하는 것은 아무리 해도 지나치지 않습니다. 특히, 이 권고안에서 다룬 다양한 연령대와 성별에 따른 예방 전략 확대는 많은 분들에게 유익한 가이드는 물론 최적의 임상적 결과를 제공할 것입니다.

인유두종바이러스 예방백신 접종이 청소년기와 젊은 여성에게 가장 효과적이라는 점을 깊이 이해하며, 이 보고서를 통해 백신에 대한 정확한 정보가 확산되어 보다 많은 분들이 예방 접종을 받게 되기를 기원합니다.

대한부인종양학회 백신권고안 개정위원회 이택상 위원장을 비롯 임현지 간사와 모든 개발 위원님들의 노고에 감사드리며, 이 새로운 권고안을 충실히 수용한다면 자궁경부암 및 여타 질환 예방 및 국민 건강 향상에 실질적인 도움이 되리라 확신합니다. 나아가 우리가 함께 건강한 사회를 만들어 나가는 데 기여할 수 있기를 희망합니다.

다시 한번, 최신 "인유두종바이러스 예방백신 권고안" 발간을 축하드립니다!

감사합니다.

2024년 11월 2일 대한부인종양학회 회장 김재원

머리말

자궁경부암은 여성 건강에 심각한 위협을 가하는 암 중 하나로, 인유두종 바이러스(HPV)에 의해 주로 발생합니다. HPV는 성 접촉을 통해 전파되며, 특정 유형의 HPV는 자궁경부암 뿐만 아니라 다른 형태의 암과 생식기 사마귀를 유발할 수 있습니다. 이러한 위협에 대응하기 위해 HPV 백신이 개발되었고, 이는 자궁경부암의 예방에 중요한 역할을 하고 있습니다.

자궁경부암 백신은 특히 청소년기와 젊은 여성에게 접종할 때 가장 효과적이며, 백신 접종을 통해 자궁경부암의 발생률을 현저히 낮출 수 있습니다. 하지만 백신의 중요성에도 불구하고, 많은 사람들이 여전히 백신에 대한 정보 부족과 오해로 인해 접종을 기피하고 있습니다. 이에 따라 자궁경부암 백신의 중요성과 필요성, 그리고 올바른 접종 방법에 대한 명확한 가이드라인이 절실히 필요합니다.

본 가이드라인은 일반인과 의료인 모두를 위한 것으로, 자궁경부암 백신의 접종에 대한 포괄적인 정보를 제공하고자 합니다. 일반인들에게는 백신의 안전성과 효과, 접종 시기 및 방법에 대한 이해를 높이는 데 중점을 두고 있으며, 의료인들에게는 최신 연구 결과와 접종 권장 사항을 기반으로 한 전문적인 지침을 제공합니다. 이를 통해 자궁경부암 예방을 위한 백신 접종률을 향상시키고, 더 많은 여성이 자궁경부암의 위험에서 벗어날 수 있도록 돕는 것이 본 가이드라인의 주된 목적입니다.

부인종양학회는 우리나라 실정에 맞는 인유두종바이러스 예방백신의 올바른 접종을 권고하기 위해 2016년 첫 진료권고안을 개발하였으며, 이어서 2018년 새로 개발된 9가 바이러스 백신에 대한 진료권고안을 추가로 발표하였으며, 2021년도에 중년 여성 및 남성, 원추절제술 시행 이후 백신접종의 효과에 대한 내용이 추가되었습니다. 본 개정안에서는 중년 남성에서의 접종 필요성 및 최근 WHO에서 백신 보급의 확대를 목적으로 한 1회접종에 대한 학회의 입장, 기존 2/4가 백신 기접종자들에 대한 9가 예방백신 추가접종에 대한 권고, 9~14세 청소년들에서 2회접종에 대한 과학적 근거를 보완하는 것을 중점적으로 기술하였습니다. 본 권고안의 개발에 동력을 불어넣어주신 김재원 회장님과 자문 역할을 기꺼이 자청해주신 이재관 부회장님, 개발에 실무역할을 해주신 간사님과 위원님들, 그간 축적된 자료들의 제공에 아낌없는 도움을 주신 MSD 관계자 분들께 사의를 표하는 바입니다.

본 가이드라인은 최신 연구 자료와 전문가들의 의견을 바탕으로 제작되었으며, 과학적 근거를 통해 백신의 안전성과 효과를 강조합니다. 또한, 백신 접종에 대한 사회적 인식을 높이고, 백신에 대한 잘못된 정보와 오해를 바로잡기 위해 노력하고 있습니다. 자궁경부암 예방을 위한 백신 접종은 개인의 건강을 지키는 것은 물론, 전체

사회의 건강 수준을 높이는 중요한 공중보건 활동입니다. 본 가이드라인이 자궁경부암 예방에 기여하고, 더 나아가 건강한 사회를 만드는 데 일조하기를 바랍니다.

다소 부족한 점이 있을 수 있겠지만, 이를 바탕으로 필요한 점들을 수정, 보완하여 나간다면 보다 완벽한 우리의 진료권고안이 될 수 있지 않을까 생각합니다. 이 진료권고안이 앞으로 여러 산부인과 선생님들의 진료에 실질적인 많은 도움이 될 수 있기를 기대합니다.

2024년 10월

대한부인종양학회 백신권고안 개발위원회 위원장 이택상

총론

1) 진료지침의 범위와 목적설정

본 권고안은 국내에 출시된 인유두종바이러스 감염을 예방하기 위한 백신에 관한 내용을 포함하며, 목적은 국내에서 행하는 인유두종바이러스 예방백신 분야의 표준화 및 그 수준의 향상에 있다.

2) 개정위원회 구성 및 회의

근거중심의 인유두종바이러스 예방백신 권고안을 개발하기 위하여 대한부인종양학회에 소속된 전문가들과 체계적 문헌 검색 및 고찰을 담당할 ‘인유두종바이러스 예방백신 권고안 개정 위원회 (이하 위원회)’를 구성하였다 (표 1).

표 1. 인유두종바이러스 예방백신 권고안 개정 위원회 구성

이름	소속	역 할
이택상	서울의대	위 원 장
임현지	차의대	간사
김재원	서울의대	
이재관	고려의대	
민경진	고려의대	
김세익	서울의대	

3) 개발방법

(1) 인유두종바이러스 예방백신 권고안 개발전략

2011년과 2016년, 2021년 세 차례 걸쳐 인유두종바이러스 권고안이 개발된 이후 2가/4가/9가 인유두종바이러스 예방백신의 14세 미만에서의 접종 횟수와, 2가/4가 인유두종바이러스 예방백신 접종 후 9가백신 재접종 관련하여 2022년 12월 WHO의 의견서(position paper)가 새롭게 발표됨에 따라 이번 권고안은 세 가지 예방백신에 대한 최신

내용을 검토하여 업데이트하기로 하였다. 인유두종바이러스 예방백신 권고안 개발의 핵심질문과 개발범위를 위원회의 회의를 통해 도출하였다. 인유두종바이러스 예방백신과 관련된 연구는 PICO(Patient/Problem, Intervention, Comparison, Outcomes) 중 중재 항목이 2가, 4가 및 9가 인유두종바이러스 백신의 사용 유무이며 비교 항목이 중재 항목과 다른 인유두종바이러스 백신 또는 다른 바이러스 백신 또는 위약으로 있기 때문에 핵심 질문을 통합하여 검색하기로 하였다. 인유두종바이러스 예방백신과 관련된 최신 문헌을 체계적으로 검색하고 근거를 평가하여 권고안을 개발하고자 하였다.

(2) 핵심질문 및 분석틀

인유두종바이러스 예방 백신의 효과와 안전성을 평가하기 위하여 핵심질문을 도출하였다. 또한 효과와 관련하여 2회 접종, 백신에 포함되지 않은 유형에 대한 교차 예방 효과 및 중년 여성에서의 효과를 평가하기 위한 핵심질문도 도출하였다. 도출된 핵심질문은 다음 표 2과 같다.

표 2. 권고안 핵심질문

- 핵심질문 1
 - 인유두종바이러스 예방백신 접종 연령 및 접종 횟수는?
- 핵심질문 2
 - 현재 WHO에서 제시하고 있는 9-14세에서의 인유두종바이러스 백신의 1회 접종은 우리나라에서 실행 가능한가?
- 핵심질문 3
 - 이미 HPV에 감염된 경우 인유두종바이러스 예방백신 접종이 효과가 있나?
- 핵심질문 4
 - 원추절제술을 시행 받은 환자에서 인유두종바이러스 예방백신 접종이 인유두종바이러스 관련 질환의 재발을 예방하는 효과가 있나?
- 핵심질문 5
 - 이미 2가/4가 인유두종바이러스 예방백신 접종을 완료한 여성에게 9가 인유두종바이러스 예

방백신 추가접종이 인유두종바이러스 관련 질환의 재발을 예방하는데 도움이 되는가?

인유두종바이러스 예방백신 권고안의 개발 범위(PICO)는 다음 표 3-5와 같이 설정하였다.

표 3. 인유두종바이러스 예방백신 권고안의 개발 범위 1

- P (Population)
 - 9-45세 사이의 여성 및 남성
- I (Intervention)
 - 2가/4가/9가 인유두종바이러스 예방백신을 접종한 중년 여성
- C (Comparison)
 - 백신 종류 별로 구분 (2가/4가 – Placebo, 9가 백신–4가 백신)
- O (Outcome)
 - 백신 종류 별로 구분 (중등도 자궁경부 상피내 종양 이상의 병변 발생률 또는 면역원성의 비교 우위)

표 4. 인유두종바이러스 예방백신 권고안의 개발 범위 2

- P (Population)
 - 15-45세 사이의 여성
- I (Intervention)
 - 자궁경부 병변 치료 후 2가/4가/9가 인유두종바이러스 예방백신을 접종한 여성
- C (Comparison)
 - 자궁경부 병변 치료 후 예방백신을 접종 받지 않은 여성
- O (Outcome)
 - HPV 재감염률 및 중등도 자궁경부 상피내 종양 이상의 병변 발생률

표 5. 인유두종바이러스 예방백신 권고안의 개발 범위 3

- P (Population)
 - 2가/4가 인유두종바이러스 예방백신을 접종한 21-45세 사이의 여성
- I (Intervention)

- 2가/4가 인유두종바이러스 예방백신 접종 후 9가 인유두종바이러스 예방백신을 재접종한 여성
○ C (Comparison)
- 2가/4가 인유두종바이러스 예방백신 접종 후 9가 인유두종바이러스 예방백신을 재접종하지 않은 여성
○ O (Outcome)
- 9가 인유두종바이러스 예방 백신 재접종으로 인한 효과와 안정성

(3) 문헌 검색 전략

문헌 검색은 최근 업데이트된 내용을 검색하기 위하여 각 핵심 질문과 관련된 각각의 PICO에 근거하여 검색식을 구성하였다. 26 - 45세중년 여성에서 각 백신의 효능을 확인하는 검색식과 치료 후 백신의 효능을 확인하는 검색식은 supplement 1에서 참조할 수 있다. 검색은 Ovid-MEDLINE, Ovid-EMbase, Cochrane Library에서 시행하였다. 검색된 문헌은 전체 핵심질문의 선택·배제기준에 따라 문헌 당 2인의 검토자가 독립적으로 문헌 선택·배제를 진행하였다. 1차로 제목과 초록을 보고 선택·배제를 하였으며 1인이라도 선택한 문헌은 원문을 검색하였다. 2차로 원문을 보고 위원들이 선택·배제를 하였으며, 위원들간 일치이 이루어지지 않은 경우 합의를 통해 최종 선택·배제를 결정하였다. 또한, 문헌 검색의 흐름도 역시 supplement 1에서 확인할 수 있다.

(4) 문헌의 질 평가

선정된 문헌에 대해 무작위대조시험인 경우는 Cochrane의 비뚤림 위험도 ROB(risk of bias, ROB)를 이용하여 평가하였고, 비무작위임상시험, 관찰연구인 경우는 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES를 이용하여 질 평가를 수행하였다. 문헌의 질 평가는 2인의 위원이 독립적으로 평가하였고, 문헌의 질 평가가 다른 경우는 두 위원간의 합의를 통해 결정하였다.

(5) 근거요약 및 자료추출

최종 선정된 문헌의 자료추출은 미리 정해 놓은 자료 추출 양식에 맞게 두 명의 실무위원이 독립적으로 자료를 추출하고 상이할 경우 합의를 통해 최종 정리하였다. 근거가 된 연구의 자료추출 요약 내용은 부록에 첨부하였다.

(6) 근거 및 권고의 등급화

선정된 문헌에 대한 근거의 수준은 GRADE (the grading of recommendation, assessment, development and evaluation)에 의해 평가하였다. GRADE에서 근거수준은 연구설계에 따라 우선적으로 결정되는데, 무작위대조시험의 경우 근거 수준이 '높음', 관찰연구인 경우 '낮음', 환자군 연구인 경우 '매우 낮음'으로 분류된다. 체계적 문헌고찰을 통한 근거 평가 결과를 이용하여, ① 비뚤림 위험, ② 비일치성, ③ 비직접성, ④ 비정밀성, ⑤ 출판비뚤림이 있는 경우 각각 근거수준 1등급 혹은 2등급을 낮추었다. 또한 ① 효과의 크기, ② 교란변수의 영향, ③ 양-반응 관계를 고려하여 근거수준을 높였다. 이를 바탕으로 4개의 근거수준으로 구분하였으며 추가로 권위있는 전문가의 임상 경험에 기초한 의견이나 전문가로 구성된 위원회에서 발표된 연구결과나 보고 자료에서 얻은 근거를 바탕으로 하나의 근거 수준을 추가하였다.

I	적절한 연구 디자인의 (bias 가능성 최소화) 대규모 무작위 배정연구 <u>또는</u> 이질성(heterogeneity)이 없는 무작위 배정연구들을 분석한 메타연구를 적어도 1개 이상 근거로 할 때
II	소규모 무작위 배정연구 <u>또는</u> 연구 디자인의 적합성이 다소 떨어지는 대규모 무작위 배정연구 <u>또는</u> 이질성을 가지는 메타연구를 근거로 할 때
III	전향적 코호트 연구를 근거로 할 때
IV	후향적 코호트 연구 <u>또는</u> 환자-대조군 연구를 근거로 할 때
V	대조군이 없는 연구, 증례 보고, 전문가 제언(expert opinions)을 근거로 할 때

권고의 등급 결정은 Grade Group에서 제시한 권고안 도출의 방법론을 적용하였다. 근거의 수준을 기반으로 해당 중재의 적용대상, 위해, 편익, 사회적 개인적 비용, 대상자의 기호를 고려하여 권고의 등급을 결정하였으며 권고의 수준은 5개의 권고 등급으로 구분하였다. 권고 등급의 결정은 해당 위원회 협의를 통해 1차 확정하였으며 공청회를 통해 최종 확정하였다.

A	상당한 임상적 이익을 포함한 효능에 대한 확실한 (strong) 근거가 있어, 강한 수준으로 권고될 때 (strongly recommended)
B	효능에 대한 확실하거나 보통의 (moderate) 근거가 있으나 제한된 임상적 이익으로, 대체적으로 권고될 때 (generally recommended)
C	효능에 대한 근거가 불충분하거나 (insufficient) 위험/불이익을 능가하는 이익이 없어, 선택적으로 권고될 때 (optional)
D	효능에 반대되거나 부작용에 대한 보통의 근거로, 대체적으로 권고되지 않을 때 (generally not recommended)
E	효능에 반대되거나 부작용에 대한 강한 근거로, 절대 권고되지 않을 때 (never recommended)

4) 내외부 검토와 승인과정

권고안 가안을 작성 후 내부 검토 과정을 거쳐 정리된 권고 등급 등에 관한 내용을 1 번의 공청회를 통해 대한부인종양학회 전체 회원의 의견을 확인하였으며, 관련 학회의 경우 의견 확인을 위해 권고안을 회람하고 회신 내용을 확인한 후 회의 내용을 추가 보완하였다. 공청회에서 각 핵심 질문에 대해 Voting 작업을 진행하였으며 권고안 작성에 참여한 위원을 제외하고 참석자의 50% 이상이 찬성할 경우 권고 문구와 권고 등급을 확정하기로 하였다.

5) 진료지침의 적용 및 보급확산

상기 권고안은 대한부인종양학회 전 위원을 포함하여 모든 산부인과 학회 회원들에게 배포 예정이며, 인유두종바이러스 예방 백신을 환자 진료에 이용할 수 있는 관련 학회에도 배포할 예정이다. 또한, 보급 확산을 위해 대한부인종양학회 홈페이지에 게시하여 접근성을 높이려고 한다.

6) 보급전략 및 방법

- 온라인 자료 배포: 2025 년 대한부인종양학회 및 대한산부인과학회 홈페이지에 배포 예정
- 학회 발표; 개정된 권고안은 2024 년 11 월 대한부인종양학회 학술대회에서 발표한다. 상기 권고안에 대해 대한산부인과학회지인 Obstetrics & Gynecology Science 에 투고한다.

인유두종바이러스 예방백신 권고안의 개정사항 요약

1. 소아에서의 인유두종바이러스 예방백신 2회접종과 성인 남성 예방접종 연령의 확대
 - 2가/4가/9가 인유두종바이러스 예방백신은 9-14세 남녀를 대상으로 2회 접종이 가능하며, 그 간격은 6개월이다.
 - 27-45세 남성은 의료진과 상의 후 4가/9가 백신의 3회 접종이 가능하다.
2. 현재 WHO에서 제시하고 있는 9-14세에서의 1회 접종에 대한 의견
 - 우리나라에 도입하기에는 안전성 및 효과에 대한 근거가 부족하므로, 1회 접종의 효과에 대한 명확한 근거가 축적되기 전까지는 2회 접종을 유지한다.
3. 원추절제술을 시행 받은 환자에서 인유두종바이러스 예방백신 접종의 근거/권고수준 상향조정 (IIB/IVB -> IB)
 - 원추절제술을 받은 여성에서 2가/4가/9가 인유두종바이러스 예방백신 투여는 해당하는 바이러스 아형의 감염을 예방하여 인유두종바이러스 관련 질환 재발의 위험을 낮출 수 있으므로 접종을 권고한다.
4. 이미 2가/4가 인유두종바이러스 예방백신 접종을 완료한 여성에서 9가 인유두종바이러스 예방백신 재접종에 대한 권고 추가
 - 9가 인유두종바이러스 예방백신 추가접종은 추가적인 바이러스 아형의 감염 위험을 낮출 수 있으므로 재접종을 권고한다.

인유두종바이러스 예방백신 권고안의 요약

1. 핵심질문 1: 인유두종바이러스 예방백신 접종연령 및 접종횟수는?
 - 2가 인유두종바이러스 예방백신의 접종대상은 9-45세 사이의 여성, 9-25세 사이의 남성이다.
 - 근거/권고수준: 9-45세 여성 (IA), 9-25세 남성 (IIC)
 - 4가/9가 인유두종바이러스 예방백신의 접종대상은 9-45세 사이의 여성 및 9~26세 남성이다. 단, 27-45세 남성은 의료진과 상의 후 접종이 가능하다.
 - 근거/권고수준: 9-26세 여성 및 남성 (IA), 27-45세 여성 (IIIB)
 - 2가/4가/9가 인유두종바이러스 예방백신은 9-14세 남녀를 대상으로 2회 접종이 가능하며, 그 간격은 6개월이다.
 - 근거/권고수준: 9-14세 남성 및 여성 2회접종 (IB)
2. 핵심질문 2: 현재 WHO에서 제시하고 있는 9-14세에서의 인유두종바이러스 백신의 1회 접종은 우리나라에서 실행 가능한가?
 - 우리나라에 도입하기에는 안전성 및 효과에 대한 근거가 부족하므로, 1회 접종의 효과에 대한 명확한 근거가 축적되기 전까지는 2회 접종을 유지한다.
3. 핵심질문 3: 이미 인유두종바이러스에 감염된 경우 예방백신 접종이 효과가 있나?
 - 이미 HPV에 감염된 여성에서 2가/4가/9가 인유두종바이러스 예방백신 투여는 감염되지 않은 인유두종바이러스 아형의 감염 위험을 낮출 수 있으므로 접종을 권고한다.
 - 근거/권고수준: IIB
4. 핵심질문 4: 원추절제술을 시행 받은 환자에서 인유두종바이러스 예방백신 접종이 인유두종바이러스 관련 질환의 재발을 예방하는 효과가 있나?
 - 원추절제술을 받은 여성에서 2가/4가/9가 인유두종바이러스 예방백신 투여는 해당하는 바이러스 아형의 감염을 예방하여 인유두종바이러스 관련 질환 재발의 위험을 낮출 수 있으므로 접종을 권고한다.
 - 근거/권고수준: IB
5. 핵심질문 5: 이미 2가/4가 인유두종바이러스 예방백신 접종을 완료한 여성에게 9가 인유두종바이러스 예방백신 추가접종이 도움이 되는가?

- 9가 인유두종바이러스 예방백신 추가접종은 추가적인 바이러스 아형의 감염 위험을 낮출 수 있으므로 재접종을 권고한다.
 - 근거/권고수준: IIB

I. 서론

고위험 인유두종 바이러스는 자궁경부, 질, 외음부, 음경, 항문 및 구인두암 발생과 관련이 있으며, 전체 암의 5-10%의 원인이 된다 (1). 특히 자궁경부암이 인유두종바이러스와 관련된 암의 80%를 차지한다 (2). 인유두종바이러스는 전세계적으로 유병율이 약 11%인 가장 흔한 성매개 질환으로, 지속적인 인유두종바이러스 감염이 자궁경부 전암병변과 암발생의 주요원인이다 (3, 4). 고위험 인유두종바이러스에 대한 예방적인 백신접종은 자궁경부암 전암병변과 자궁경부암은 물론 구인두암, 항문암, 음경암과 같이 남성에서 발생하는 암도 예방할 수 있다 (5-8).

현재까지 4가 (가다실), 2가 (서바릭스), 9가 (가다실 9) 세 종류의 인유두종바이러스 예방백신이 승인되었다. 이들은 자궁경부암의 약 70%와 다른 인유두종바이러스 관련 종양의 원인이 되는 HPV 16, 18형 감염을 예방할 수 있다 (6, 9-16). 또한 4가 백신은 생식기 사마귀 원인의 90%를 차지하는 HPV 6, 11형을 추가로 예방할 수 있다 (17). 가장 최근에 도입된 9가백신은 이 네 가지 HPV 유형과 함께 추가로 다섯개 유형의 고위험 인유두종바이러스 31, 33, 45, 52, 58형을 추가로 예방할 수 있다 (18).

대한부인종양학회에서 2011년 및 2016년, 2021년에 자궁경부암 예방백신 임상권고안을 개정하였으며 (19, 20), 9가 백신이 새로이 국내에 도입됨에 따라 9가 백신에 대한 권고안을 2019년에 발표하였고 (8), 2021년 중년 여성에 대한 권고 대상을 확장하였다 (21).

이러한 학계의 권고로 인하여 권고대상에서의 인유두종바이러스 백신 접종률은 점차 증가하고 있으며, 2016년부터 건강여성 첫걸음 클리닉 사업을 통해 인유두종바이러스 백신을 국가예방접종프로그램에 포함시켜 만 12-13세 여아를 대상으로 국가 예방접종 프로그램이 시행되고 있다. 그러나, 현재 증가하는 접종률에도 불구하고, 국내에서는 WHO에서 제시한 자궁경부암의 퇴치를 도달하는 목표에 아직 도달하지 못하고 있다. 호주는 남녀 모두에게 적극적인 인유두종바이러스 백신 접종 권고와 이른 국가예방접종프로그램 도입으로, 2028년 이전 자궁경부암을 퇴치할 첫번째 국가로 예상되고 있다. 우리나라도 자궁경부암의 퇴치를 위한 국제적인 예방 전략에 맞추어, 좀더 적극적인 국내 권고의 필요성이 있어 권고안을 개정하게 되었다.

II. 핵심질문

1. 핵심 질문 1: 인유두종바이러스 예방백신 접종연령 및 접종횟수는?

대한부인종양학회는 2016년에 3회 접종의 적정연령은 4가 백신은 9-26세 여성, 2가 백신은 9-25세 여성으로 권고하였다 (22). 또한 2019년 9가백신의 3회 접종의 적정연령은 9-26세 여성으로 권고하였고 (8), 2021년 9가 백신의 3회 접종의 적정연령은 9-45세 여성 및 9-26세 남성으로 확대 권고하였다. 본 권고안에서는 중년남성에서의 접종의 필요성 및 9-14세 여성 및 남성에서 2회 접종의 효과에 대해 조사하였다.

(1) 2, 4가 백신

2009년에 발표된 임상시험에서는 24-45세 여성을 대상으로 4가 백신을 접종하였을 때, HPV 6/11/16/18형과 관련된 감염 또는 질환 예방은 90.5% (95% CI, 73.7-97.5%)로 확인되었으며, 이 중 HPV 16/18형 관련 질환 예방은 83.1% (95% CI, 50.6-95.8)로 관찰되었다 (23). 첫 백신을 접종한 지 48개월 뒤 HPV 6/11/16/18형에 대한 혈청 항체 양성률은 각각 91.5%, 92.0%, 97.4%, 47.9% 였으며, 심각한 부작용은 관찰되지 않았다 (23, 24). 1,610명을 대상으로 약 10년 간 장기추적검사를 진행한 결과, 27-45세 여성에서 HPV 6/11/16/18형 관련 질환에 대해 최대 10년 (중앙값 8.9년) 동안 지속적인 보호 효과를 보였고 혈청 항체 반응 또한 10년 간 유지되는 것을 확인할 수 있었다 (25). 접종횟수에 관한 연구에서 4가 백신의 경우 만 9-13세 여아 2회 접종군을 이전에 백신 효과가 입증된 만 16-26세 여성 3회 접종군과 비교하였을 때, 인유두종바이러스 항체 형성이 열등하지 않았다 (26).

9-15세 남성에서 4가 백신 접종 10년후 시행한 HPV 6/11/16형에 대한 혈청 검사에서 89.96% 항체 양성으로 관찰되었으며, 항체 역가는 13-15세 남성에 비해 9-12세 남성에서 16-42% 더 높은 것으로 나타났다 (5). 16-26세 남성에서는 HPV 6/11/16/18형에 대한 항문상피내종양 2,3과 침형 콘딜로마 발생이 per protocol 분석에서 각각 74.9% (95%CI, 8.8-95.4%), 90.4% (95%CI, 69.2-98.1%) 감소하였으며, 백신과 관련된 심각한 부작용은 없었다(5, 6, 27). 또한 9-45세 남성에서 백신을 3회 접종 후 1개월에 혈청을 분석하였을 때, 4가지 HPV 유형 모두에 대해 남성 100%가 항체 형성을 보였다 (28). 본 연구결과들을 근거로 2017년 항문암에 대한 적응증이 추가되었다.

26-55세 여성에게 2가 백신 3회 접종 후 연령별로 나누어 HPV 16/18형과 관련된 6개월 지속 감염 또는 경증 자궁경부상피이형성증을 예방하는 효과를 분석하였을 때, 26-35세 연령군에서는 83.5% (95% CI, 45.0-96.8), 36-45세 연령군에서는 77.2% (95% CI, 2.8-96.9)로 의미 있게 나타났으나, 46-55세 연령군에서는 효과가 없었다 (29). 또한 HPV 16/18형에 대한 항체 역가와 항체 지속기간이 18-26세와 비교하여 27-35세, 36-45세 여성에서 감소하는 것으로 나타났다 (30). 여러 연구에서 심각한 부작용이나 안정성에 문제는 없었다. 접종 횟수에 대한 연구에서 2가 HPV 백신의 경우 9-14세 여아 2회 접종군과 15-25세 연령의 3회 접종군을 비교하였을 때, 만 9-14세 여아 2회 접종군에서의 인유두종바이러스 항체 형성이 열등하지 않았다 (31). 10-18세 남성을 대상으로 2가 백신을 접종한후 7개월후 항체양성은 100% 였으며 심각한 부작용은 없었다 (7).

현재 우리나라를 비롯하여 범 세계적으로 9가 백신이 개발되어 상용화되고 있는 상황에서 2가, 4가 백신의 역할은 축소되고 있으나, 아직 국내에서 국가필수예방접종(NIP)에 포함되어 활용되고 있는 관계로 권고안의 유지가 필요하다. 2가백신의 경우 현재 국가필수예방접종에서 제외되어 있으며 추후 상용화 지속여부의 확인 후에 차후 권고안 개정 시 이에 대한 반영이 필요할 것으로 보인다. 위 연구결과들에 근거하여 2가 및 4가 백신에 대한 접종을 다음과 같이 권고한다.

- 2가 인유두종바이러스 예방백신의 접종대상은 9-45세 사이의 여성 (IA), 9-25세 사이의 남성 (IIc) 이다.
- 4가 인유두종바이러스 예방백신의 접종대상은 9-45세 사이의 여성 및 9-26세의 남성이다. (9-26세 여성 및 남성 (IA); 27-45세 여성 (IIIB)).
- 2가, 4가 백신 모두 9-14세에서 2회접종을 권고하며, 2회 접종 의 간격은 최소 6개월로 접종한다. 15세 이상의 경우 종전과 같이 3회접종을 권고한다 (IB).

(2) 9가 백신

16-45세 여성에서 9가 백신의 면역원성과 안전성을 평가하였으며, 접종 7개월에 HPV 6/11/16/18/31/33/45/52/58형에 대한 항체 역가는 27-45세 여성이 16-26세 여성에 비해 0.60-0.67 정도로

열등하지 않았다. 또한 27-45세 여성에서 모든 HPV 유형에 대한 항체양성율은 99% 이상으로 나타났으며, 백신과 관련된 심각한 부작용은 보고되지 않았다 (32).

HPV 9가 백신을 접종한 16-26세의 젊은 남성에서 항체 면역원성과 안전성을 입증하기 위하여 동일 연령의 젊은 여성의 결과와 비교한 연구가 이루어졌다. 연구에는 이성애자 남성 1,106명(HM), 동성애자 남성 313명(MSM) 및 아직 HPV 예방접종을 받지 않은 젊은 여성 1,101명이 참여하였다. 아홉 가지 아형에 대한 항체의 평균 역가는 HM의 경우 여성에 비해 열등하지 않았으나, MSM의 경우 HM과 여성에 비해 낮았다 (33). 안전성 측면에서 남성과 여성 모두에서 심각한 백신 관련 부작용은 보고되지 않았다.

또한 성인에서 HPV 감염 시점을 모델링한 연구에 따르면 HPV 고위험 유형에 감염되는 연령이 여성의 25%에서 35세 이상이고 남성의 29%에서 27~45세인 것으로 나타났다 (34, 35). 따라서, 인유두종바이러스 관련 질병 전파를 방지하기 위하여 성인 남녀 모두에서 인유두종바이러스 예방접종을 적극 권장해야 할 필요가 있다.

단, 중년 남성에서 서양의 안전성에 기반한 근거와는 별도로 국내에서는 4가, 9가 백신의 허가가 아직 없는 상태이며 권고사항은 허가사항에 기반하여 권고할 필요가 있는 바, 27세 이상 남성에서의 접종은 의료진과의 충분한 상의 후 접종할 것을 권고한다.

접종횟수에 관한 연구에서 만 9-14세 여아 2회 접종군의 마지막 접종 4주 후 시행한 인유두종바이러스 항체 검사에서 0, 6개월 및 0, 12개월 2회 접종군 모두 3회 접종군에 비해 항체가가 열등하지 않음을 확인할 수 있었다. 특히 0, 6개월 2회 접종군에 비해 0, 12개월 2회 접종군이 HPV 45형을 제외하고 8가지 HPV 형에 대한 항체가가 더 높게 관찰되었다. 따라서 14세 이전에 백신을 접종하는 것이 접종 완료에 필요한 비용을 절약할 수 있어 경제적 측면에서 긍정적이며 인유두종바이러스에 감염되기 전에 예방할 수 있어 더욱 효과적이다 (36).

위 연구결과를 근거로 권고안은 다음과 같이 결정되었다

- 9가 인유두종바이러스 예방백신의 접종대상은 9-45세 사이의 여성 및 9-26세 사이의 남성이다. (9-26

세 여성 및 남성 (IA); 27-45세 여성 (IIIB))

단, 27세 이상의 남성의 경우 의료진과 충분히 상의 후 접종한다.

- 9-14세에서 2회 접종이 가능하며, 그 간격은 최소 6개월이다. 15세 이상의 경우 종전과 같이 3회접종을 권고한다 (IB).

표 1. 백신 종류, 성별 및 나이에 따른 접종권고안 요약

백신의 종류	첫 접종 나이	접종횟수	접종일정
2가/4가/9가	만 9-14세	2회	0, 6-12개월
2가*	여성: 만 15-45세 남성: 만 15-25세	3회	0, 1, 6개월
4가/9가	여성: 15-45세 남성: 15-26세 (27-45세 남성은 의료진과 상의 후 접종 가능)	3회	0, 2, 6개월

* 2가 백신은 현재 국가암예방접종사업에서 제외된 상태

2. 핵심질문 2: 현재 WHO에서 제시하고 있는 9-14세에서의 인유두종바이러스 백신의 1회 접종은 우리나라에서 실행가능한가?

WHO의 예방접종 전문가 전략 자문 그룹(Strategic Advisory Group of Experts on Immunization, SAGE)에서는 전 세계 인유두종바이러스 예방백신 접종률이 13%에 불과한 것의 원인으로 백신에 대한 낮은 접근성과 2회 접종의 어려움 및 상대적으로 비싼 가격 등을 꼽았다. 따라서 예방접종의 보편화와 접종 스케줄을 완료하는 것을 장려하기 위해, 2022년 4월 WHO는 9-20세 여성에서는 1회 혹은 2회 접종, 21세 이상에서는 6개월 간격으로 2회 접종하는 것을 권고한다고 발표하였다 (37).

영국과 호주는 2023년부터 WHO와 비슷한 권고수준으로 인유두종바이러스 백신의 권고안을 개정하였다. 이 두 국가는 인유두종바이러스 백신 국가 예방접종 프로그램을 비교적 조기에 도입하여 이미 16년이상 시행해 왔고, 남성접종도 함께 시행하고 있는 국가이다.

국내에서는 2016년부터 인유두종바이러스 백신을 국가예방접종프로그램에 포함시켜 만 12-13세 여성 청소년을 대상으로 무료 접종을 시행하고 있으며, 최근 17세까지 대상을 확대하였다. WHO의 경우 저개발국가를 고려하여 백신자원의 효율적인 분배에 초점을 맞추어 권고안을 개정하였으나 우리나라의 실정에는 맞지 않으며, 아직 인유두종바이러스 백신 1회 접종을 우리나라에 도입하기에는 안전성 및 효과에 대한 근거가 부족하므로, 1회 접종의 효과에 대한 명확한 근거가 축적되기 전까지는 현재의 권고사항을 유지하는 것으로 위원회에서 결정하였다.

3. 핵심 질문 3: 이미 인유두종바이러스에 감염된 경우 예방백신 접종이 효과가 있나?

3상 무작위 배정 임상연구에 따르면 연구 시작 시점에서 HPV 16/18형에 감염되어 있는 여성에서 2가 백신 투여 시, 감염되어 있지 않은 HPV 유형에 의한 자궁경부 상피내 종양 2단계 이상 발병에 대한 백신 효능은 90% (31.8-99.8) 이었다 (38). 또한 HPV 16번 양성인 27-45세 중년여성을 4가 백신 접종 군 5명, 비접종군 5명으로 나누어 비교한 결과, 백신 접종군에서 항체역가 24-930배 상승하였고 memory B cell 수 또한 3-27배 증가하였다 (39). 9가 백신의 경우 연구 시작시점에서 HPV 6/11/16/18형에 양성이지만 HPV 31/33/45/52/58형에 음성인 여성에서 이 5가지 HPV유형으로 인한 자궁경부 질환 발생률이 현저히 감소하였다 (모든 등급 95.1%, 고등급 91.1%). 비슷하게 HPV 31/33/45/52/58형에 양성이지만 HPV 6/11/16/18형에 음성인 경우에도 이 4가지 HPV유형에 의한 자궁경부 질환 발생률은 역시 크게 감소하였다 (모든 등급 97.4%, 고등급 95.8%) (12).

위 결과를 통해 권고안은 다음과 같이 결정되었다.

- 이미 HPV에 감염된 여성에서 2가/4가/9가 인유두종바이러스 예방백신 투여는 감염되지 않은 인유두종바이러스 아형의 감염 위험을 낮출 수 있으므로 접종을 권고한다 (IIB).

4. 핵심 질문 4: 원추절제술을 시행 받은 환자에서 인유두종바이러스 예방백신 접종이 인유두종바이러스 관련 질환의 재발을 예방하는 효과가 있나?

2가 백신에 대한 무작위배정 임상시험의 post hoc 분석 연구에서 15-25세 여성을 대상으로 백신접종 후 자궁경

부의 병변 제거수술을 시행한 환자에서 자궁경부 상피내종양 2단계 이상 병변 재발에 대한 백신 효능을 보았을 때 88.2% (95% CI, 14.8-99.7) 이었다 (40). 하지만 다른 연구에서는 백신 효능이 없었다 (41). 위의 2개의 연구가 포함된 메타연구(2가 백신 연구 2개, 4가백신 연구 3개) 에서는, 원추절제술 등 치료 전 백신접종의 백신 효능 (자궁경부 상피내종양 2단계 이상) 은 교차비 0.4 (95% CI, 0.21-0.78), 치료 후 백신접종은 교차비 0.28 (95% CI, 0.14-0.56) 으로 모두 백신접종이 자궁경부 병변의 재발에 효과가 있는 것으로 나타났다 (42).

자궁경부 상피내종양 1-3으로 진단되어 원추절제술 등 치료를 받은 312명을 대상으로 4가 백신 투약군과 위약군으로 무작위 배정을 하여 24개월 추적관찰을 한 연구에서 백신의 효능 (자궁경부 상피내 종양 1-3의 재발) 은 58.7%로 위약군과 비교하여 통계적으로 유의하게 낮았다 (43). 자궁경부 상피내 종양 2단계로 원추절제술을 시행한 환자를 대상으로 한 전향적 환자 대조군 연구에서도 백신을 접종한 환자에서 고등급 자궁경부 상피내 종양 발생 위험을 81.2% (95% CI, 34.3-95.7) 감소시키는 것으로 나타났다 (44). 20-45세 한국여성을 대상으로 한 후향연구에서는 고등급 자궁경부 상피내 종양으로 진단받고 원추절제술을 시행한 환자가 4가 백신을 맞았을 경우 재발이 감소하였고 (백신 접종 2.5%; 백신 미접종 7.2%), 백신 미접종 군에서 통계적으로 유의하게 고등급 자궁경부 상피내 종양 재발 위험이 증가하는 것으로 나타났다 (위험비=2.84; 95% CI 1.335-6.042) (45).

9가 백신을 포함한 후향연구에서 원추절제술을 시행한 여성에게 백신접종(2가 19.6%; 4가 4.6%; 9가 64.1%)을 시행했을 때 비접종군에 비해 지속 또는 재발한 고등급 상피내종양 발생율이 낮았고 (3.3% vs. 10.7%, $p=0.015$), 병변에 대한 위험이 통계적으로 유의하게 감소하였다 (교차비 0.2, 95% CI, 0.1-0.7) (46).

또한 2023년 8월 발표된 메타분석에서는 원추절제술을 받은 여성에서 2가/4가/9가 백신을 접종한 것에 대한 20개의 연구가 포함되었다. 자궁경부 상피내 종양 2단계 이상 병변의 재발에 대한 백신의 효과는 HPV 아형에 상관없이 69.5% (95% CI, 54.7-79.5)으로 나타났으며, 특히 첫번째 접종을 원추절제술 받은 이후에 접종한 환자군에서 78.1% (95% CI, 68.7-84.7)로 가장 높은 백신 효과를 보였다 (47).

위 결과를 통해 권고안은 다음과 같이 결정되었다.

- 원추절제술을 받은 여성에서 2가/4가/9가 인유두종바이러스 예방백신 투여는 해당하는 바이러스 아형의 감염을 예방하여 인유두종바이러스 관련 질환 재발의 위험을 낮출 수 있으므로 접종을 권고한다 (IB).

5. 핵심질문 5: 이미 2가/4가 인유두종바이러스 예방백신 접종을 완료한 여성에게 9가 인유두종바이러스 예방백신 추가접종이 인유두종바이러스 관련 질환의 재발을 예방하는 데에 도움이 되는가?

2010년부터 2011년 사이에 진행된 연구에서 기존에 4가 백신을 접종한 12-26세 여성을 대상으로 9가 백신 3회 접종에 대한 안전성과 면역원성을 평가하였다. 그 결과, 9가 백신을 재 접종 받은 여성에서 높은 면역원성을 관찰할 수 있었다. HPV 백신 4가를 3회 접종 후 HPV 백신 9가를 3회 접종한 그룹에서 HPV 6/11/16/18형에 대한 항체 역가는 HPV 백신 4가를 접종한 그룹보다 높게 나타났다. 한편, HPV 31/33/45/52/58형에 대한 항체 역가는 HPV 백신 9가를 재 접종 받은 군에서 4가를 접종 받지 않고 9가를 접종한 군보다 낮게 나타났다 (48). 이 경우 국소 이상반응에서 주사 부위의 통증, 부종 및 홍반이 위약군보다 많이 보고되었으나 전신적 이상반응에서는 유의한 차이가 없었다 (49).

2006년부터 2011년까지 18-79세(중양나이; 44세)의 한국인 여성 60,775명을 대상으로 HPV genotype 검사를 시행한 결과, 고위험군 HPV 감염 여성에서 흔히 관찰되는 HPV 유형은 HPV 16, 52, 58형 순으로 확인되었다 (50). 이는 WHO에서 발표한 한국의 2023년 HPV 및 HPV 관련 암에 대한 레포트의 내용과 일치하는 결과이다 (51). 따라서, 인유두종 바이러스의 역학을 고려하였을 때 한국에서도 2가/4가 백신 기접종자에게 9가 백신의 추가접종은 HPV 52, 58형 예방에 대한 미충족 수요를 채워줌으로써 충분한 임상적인 유익이 있을 것으로 판단된다.

- 이미 2가/4가 백신 접종을 완료한 여성에서 9가 백신 추가접종은 추가적인 바이러스 아형의 감염 위험을 낮출 수 있으므로 재접종을 권고한다 (IIB).

III. 고찰

본 권고안에서는 백신 2회 접종군에서 3회 접종군에 비하여 인유두종바이러스 관련 질환의 예방효과가 열등하지 않다는 임상시험의 결과를 토대로 9세-14세의 여아 및 남아에서는 2가/4가/9가 백신의 2회 접종을 권고하고 있다 (22, 52, 53).

본 권고안에서는 백신 접종의 남성대상자의 연령 확대에 대한 논의가 있었으나 종전과 같이 종전 권고안과 동일하게 4가/9가 백신 접종의 남성대상자가 9-26세를 유지하였으며 다만 27세 이상의 연령에서 제한된 연구결과에 근거하여 의사와 상의하여 접종할 수 있다는 단서를 추가하였다. 이는 4가 백신의 경우 27-45세 사이 남성을 대상으로 한 임상시험은 하나뿐이며, 150명에 불과한 소수의 9-45세 남성을 대상으로 백신의 면역성원과 안전성을 평가한 결과이므로 그 근거가 충분치 않기 때문이다 (28). 또한 9가 백신의 경우도 마찬가지로 27-45세 사이 남성에서 면역원성에 대한 직접적인 비교연구가 있는 것이 아니고 인유두종 바이러스 고위험 유형 감염에 취약한 연령대라는 것을 고려한 것으로 백신 접종의 직접적인 효과에 대한 근거가 불충분하다 (34, 35). 따라서 현재 국내 FDA에서는 중년 남성에서의 인유두종바이러스 접종에 대한 허가가 이루어져 있지 않은 상태이며, 추가적인 남성 대상 연구결과에 따라 이에 대한 적응증 및 접종대상 확대가 필요할 것으로 보인다. 현재 인유두종바이러스 관련 남성질환에 해당하는 구인두암 관련된 3상 이중맹검, 무작위 3환자대조군 연구가 진행되고 있으며, 2026년에 1차 분석을 앞두고 있다. 이 결과에 따라 권고안이 업데이트될 것으로 생각된다.

본 권고안에서 이미 인유두종바이러스에 감염된 환자에서 백신 접종이 감염되지 않은 다른 아형의 예방에 도움을 줄 수 있다고 권고하고 있다. 이 부분은 오해의 여지가 있을 수 있어 명확한 설명이 필요하다. 여러 임상연구에서 백신 접종이 이미 감염된 인유두종바이러스를 제거하는 데에는 도움이 되지 않는 것으로 나타났으므로 해당환자에게 접종 시 이에 대해 충분히 설명이 필요하다 (12, 38, 39). 또한 최근 메타분석에서 이미 원추절제술을 시행한 환자에서 HPV 백신 접종이 자궁경부 상피내 종양 2단계 이상 병변의 재발을 예방하는 데에 유익한 효과가 있음을 설득력 있게 보여주었으나, 원추절제술 이전에 백신접종을 시작하는 것이 원추절제술 후 접종을 시작

하는 것에 비하여 더 나은 예후를 보이는 지는 아직 확실하지 않다 (47). 마찬가지로 이미 2가/4가 인유두종바이러스 예방접종을 완료한 사람이라도 다른 아형에 대한 감염을 예방하기 위해서 9가 백신을 추가접종 할 수 있다. 그러나 4가 백신을 접종 후 9가 백신을 추가 접종하는 경우 HPV 6/11/16/18형에 대한 항체 역가는 9가 백신만 접종한 군보다 높게 나타났지만, 다른 다섯가지 고위험 아형 (HPV 31/33/45/52/58형)에 대해서는 4가 백신 접종 후 9가 백신을 추가 접종하는 것보다 9가 백신만 3회 접종하는 것이 항체 역가가 높게 나타나므로, 이에 대한 설명이 필요할 것으로 보인다 (48).

인유두종바이러스 백신의 안정성 관련하여, 다발성 경화증과 기타 중추신경계 탈수초성 질환, 길랑-바레 증후군, 신경계 질환, 정맥 혈전색전증 및 자가면역 질환의 발생 등에 대해서는 관찰 연구와 무작위배정 임상연구에서 연관성이 관찰되지 않았다 (54-57). 또한 최근 발표된 한국 11-14세 여아에 대한 빅데이터 연구에서 하시모토 갑상선염, 류마티스 관절염, 악성 두통을 포함한 33개의 심각한 합병증과 백신접종과 연관성이 없는 것으로 나타났다 (58).

향후 국내 특이적인 역학과 성별 특이적인 질병 특성을 고려하여 남녀가 모두 적극적으로 백신을 접종 받는다 면 우리나라도 빠른 시일내에 자궁경부암의 퇴치국으로 거듭날 것이다.

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Supplement 1. 문헌 검색의 검색식과 흐름도

표 1. 인유두종바이러스 예방백신 권고안 검색식

1) 여성에서 인유두종바이러스 예방백신 효능을 확인하기 위한 검색식

검색엔진	연번	검색식	검색결과
MEDLINE	#1	Cervical[tiab] OR Cervix[tiab] OR Vaginal[tiab] OR Vagina[tiab] OR Vulvar[tiab] OR Vulva[tiab]	351,239
	#2	cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] OR Adenocarcinoma[tiab] OR Adenocarcinomas[tiab]	2,611,066
	#3	1 AND 2	115,999
	#4	((("Genital Neoplasms, Female"[Mesh:NoExp]) OR "Uterine Cervical Neoplasms"[Mesh]) OR "Vaginal Neoplasms"[Mesh]) OR "Vulvar Neoplasms"[Mesh]	97,544
	#5	3 OR 4	149,627
	#6	((("Papillomaviridae"[Mesh:NoExp]) OR "Alphapapillomavirus"[Mesh]) OR "Papillomavirus Infections"[Mesh]) OR "HPV L1 protein, Human papillomavirus" [Supplementary Concept]	47,201
	#7	Papillomaviridae[tiab] OR Alphapapillomavirus[tiab] OR Alphapapillomaviruses[tiab] OR papillomavirus[tiab] OR Wart[tiab] OR Warts[tiab] OR "Condylomata Acuminata"[tiab] OR "HPV L1 protein"[tiab] OR "Papilloma viridae"[tiab] OR "Alphapapilloma virus"[tiab] OR "Alphapapilloma viruses"[tiab] OR "papilloma virus"[tiab]	50,010
	#8	6 OR 7	62,745
	#9	Gardasil[tiab] OR "HPV L1 vaccine" OR "HPV Vaccines"[tiab] OR "HPV Vaccine"[tiab] OR "Papillomavirus Vaccines"[tiab] OR "Papillomavirus Vaccine"[tiab] OR Nonavalent[tiab]	6,650
	#10	("human papillomavirus vaccine L1, type 6,11,16,18" [Supplementary Concept]) OR "Papillomavirus Vaccines"[Mesh]	7,898
	#11	Cervarix[tiab] OR "HPV L1 vaccine" OR "HPV Vaccines"[tiab] OR "HPV Vaccine"[tiab] OR "Papillomavirus Vaccines"[tiab] OR "Papillomavirus Vaccine"[tiab] OR Bivalent[tiab]	14,356
	#12	("human papillomavirus vaccine L1, type 16,18" [Supplementary Concept]) OR "Papillomavirus Vaccines"[Mesh]	7,898
	#13	9 OR 10 OR 11 OR 12	17,686
	#14	5 AND 13	5,440
	#15	5 AND 8	25,888
	#16	Vaccines[tiab] OR Vaccine[tiab]	237,129
	#17	15 AND 16	5,288
	#18	14 OR 17	6,459
	#19	18 NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms])	4,987
	#20	19 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term]))	4,980
	#21	20 AND "Middle Aged"[Mesh]	1,241

검색엔진	연번	검색식	검색결과
EMbase	#1	cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR cancers:ab,ti OR malignancy:ab,ti OR carcinomas:ab,ti OR neoplasms:ab,ti OR Adenocarcinoma: ab,ti OR Adenocarcinomas:ab,ti	38,845
	#2	Cervical:ab,ti OR Cervix:ab,ti OR Vaginal:ab,ti OR Vagina:ab,ti OR Vulvar:ab,ti OR Vulva:ab,ti	465,612
	#3	1 AND 2	2,245
	#4	'female genital tract cancer'/de OR 'uterine cervix cancer'/exp OR 'vagina cancer'/exp OR 'vaginal intraepithelial neoplasia'/exp OR 'vulva cancer'/exp	119,032
	#5	3 OR 4	119,919
	#6	'Papilloma virus'/de OR 'Alphapapillomavirus'/exp OR 'papillomavirus infection'/exp OR 'Wart virus'/exp	76,256
	#7	Papillomaviridae:ab,ti OR Alphapapillomavirus:ab,ti OR Alphapapillomaviruses:ab,ti OR papillomavirus:ab,ti OR Wart:ab,ti OR Warts:ab,ti OR 'Condylomata Acuminata':ab,ti OR 'HPV L1 protein':ab,ti OR 'Papilloma viridae':ab,ti OR 'Alphapapilloma virus':ab,ti OR 'Alphapapilloma viruses':ab,ti OR 'papilloma virus':ab,ti	59,172
	#8	6 OR 7	85,074
	#9	Gardasil:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Nonavalent:ab,ti	8,396
	#10	Gardasil:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Quadrivalent:ab,ti	9,890
	#11	Cervarix:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Bivalent:ab,ti	16,955
	#12	'Wart virus vaccine'/exp	13,934
	#13	9 OR 10 OR 11 OR 12	25,574
	#14	5 AND 13	6,415
	#15	5 AND 8	25,360
	#16	Vaccines:ab,ti OR Vaccine:ab,ti	276,742
	#17	15 AND 16	5,004
	#18	14 OR 17	7,379
	#19	18 NOT ('conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	4,361
	#20	19 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de)	3,216
	#21	20 AND 'Middle Aged'/exp	141

검색엔진	연번	검색식	검색결과
Cochrane	#1	Cervical OR Cervix OR Vaginal OR Vagina OR Vulvar OR Vulva:ab,ti,kw	35,498
	#2	cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms OR Adenocarcinoma OR Adenocarcinomas:ab,ti,kw	189,831
	#3	1 AND 2	7,606
	#4	MeSH descriptor: [Genital Neoplasms, Female] this term only	338
	#5	MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees	2,031
	#6	MeSH descriptor: [Vaginal Neoplasms] explode all trees	56
	#7	MeSH descriptor: [Vulvar Neoplasms] explode all trees	100
	#8	4-7/OR	2,441
	#9	MeSH descriptor: [Papillomavirus Infections] explode all trees	1,046
	#10	MeSH descriptor: [Alphapapillomavirus] explode all trees	221
	#11	MeSH descriptor: [Papillomaviridae] this term only	368
	#12	9-11/OR	1,159
	#13	Papillomaviridae OR Alphapapillomavirus OR Alphapapillomaviruses OR papillomavirus OR Wart OR Warts OR "Condylomata Acuminata" OR "HPV L1 protein" OR "Papilloma viridae" OR "Alphapapilloma virus" OR "Alphapapilloma viruses" OR "papilloma virus":ab,ti,kw	3,284
	#14	12 OR 13	3,284
	#15	Gardasil OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Nonavalent :ab,ti,kw	916
	#16	Gardasil OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Quadrivalent :ab,ti,kw	1,405
	#17	Cervarix OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Bivalent :ab,ti,kw	1,249
	#18	MeSH descriptor: [Papillomavirus Vaccines] explode all trees	324
	#19	15-18/OR	1,787
	#20	3 OR 8	7,883
	#21	20 AND 19	425
	#22	Vaccines OR Vaccine:ab,ti,kw	22,506
	#23	20 AND 14 AND 22	487
	#24	23 OR 21	516
	#25	24/trials	510
	#26	MeSH descriptor: [Middle Aged] this term only	309,679
#26	25 AND 26	34	

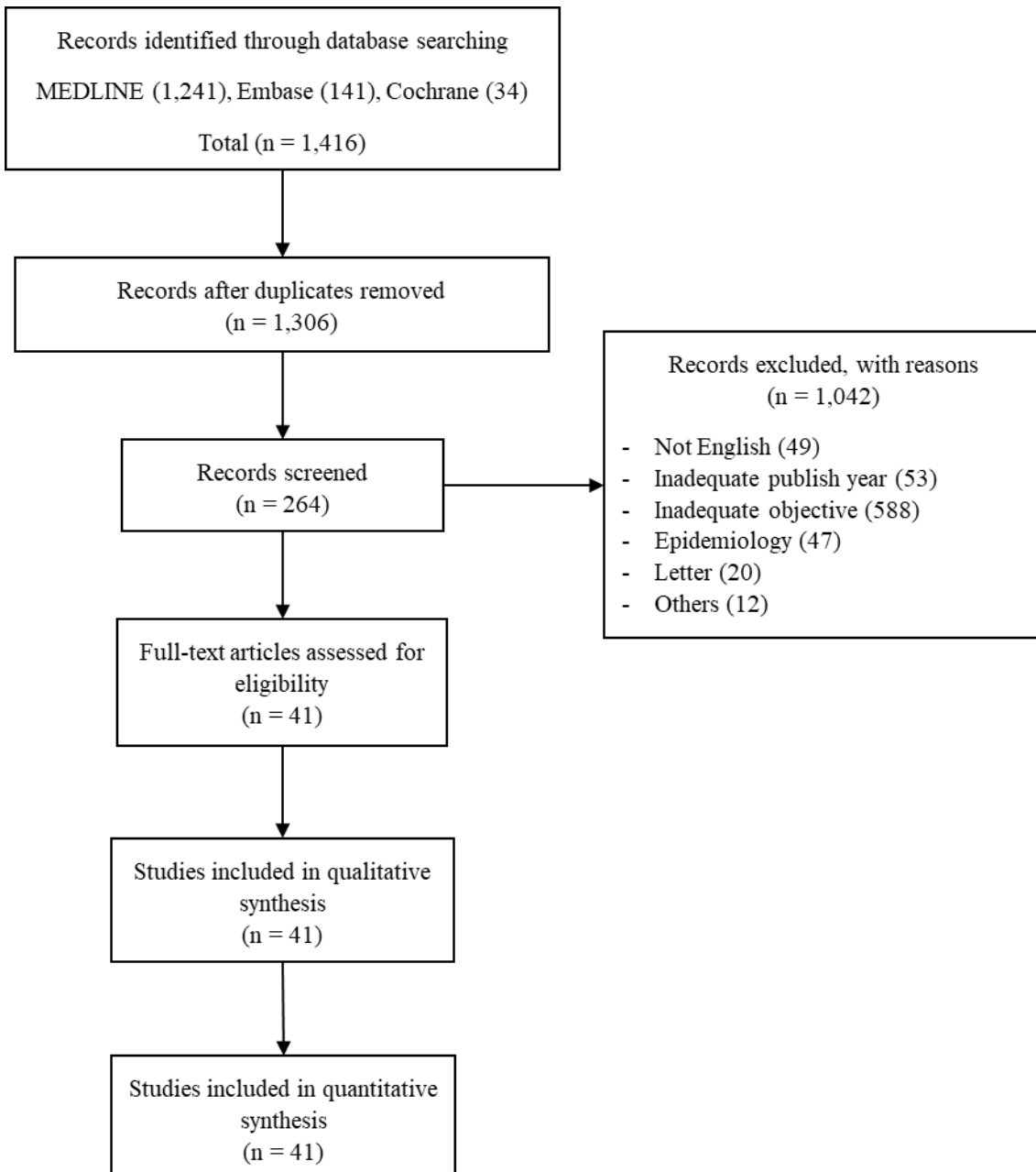


그림 1. 문헌 검색 흐름도 (여성)

2) 치료 후 백신 접종

검색엔진	연번	검색식	검색결과
MEDLINE	#1	Cervical[tiab] OR Cervix[tiab]	251,786
	#2	cancer[tiab] OR malignant[tiab] OR carcinoma[tiab] OR neoplasm[tiab] OR cancers[tiab] OR malignancy[tiab] OR carcinomas[tiab] OR neoplasms[tiab] OR Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] OR neoplasia[tiab]	2,632,728
	#3	1 AND 2	106,912
	#4	"Genital Neoplasms, Female"[Mesh:NoExp] OR "Uterine Cervical Neoplasms"[Mesh] OR "Cervical Intraepithelial Neoplasia"[Mesh]	88,360
	#5	3 OR 4	134,550
	#6	"Conization"[Mesh] OR "Electrosurgery"[Mesh] OR conization*[tiab] OR conisation*[tiab] OR electrosurger*[tiab] OR electrosurgical[tiab] OR treatment*[tiab] OR therap*[tiab]	6,153,261
	#7	((("Papillomaviridae"[Mesh:NoExp]) OR "Alphapapillomavirus"[Mesh]) OR "Papillomavirus Infections"[Mesh]) OR "HPV L1 protein, Human papillomavirus" [Supplementary Concept]	47,230
	#8	Papillomaviridae[tiab] OR Alphapapillomavirus[tiab] OR Alphapapillomaviruses[tiab] OR papillomavirus[tiab] OR Wart[tiab] OR Warts[tiab] OR "Condylomata Acuminata"[tiab] OR "HPV L1 protein"[tiab] OR "Papilloma viridae"[tiab] OR "Alphapapilloma virus"[tiab] OR "Alphapapilloma viruses"[tiab] OR "papilloma virus"[tiab]	50,051
	#9	7 OR 8	62,789
	#10	Gardasil[tiab] OR "HPV L1 vaccine" OR "HPV Vaccines"[tiab] OR "HPV Vaccine"[tiab] OR "Papillomavirus Vaccines"[tiab] OR "Papillomavirus Vaccine"[tiab] OR Nonavalent[tiab]	6,659
	#11	("human papillomavirus vaccine L1, type 6,11,16,18" [Supplementary Concept]) OR "Papillomavirus Vaccines"[Mesh]	7,905
	#12	Cervarix[tiab] OR "HPV L1 vaccine" OR "HPV Vaccines"[tiab] OR "HPV Vaccine"[tiab] OR "Papillomavirus Vaccines"[tiab] OR "Papillomavirus Vaccine"[tiab] OR Bivalent[tiab]	14,368
	#13	("human papillomavirus vaccine L1, type 16,18" [Supplementary Concept]) OR "Papillomavirus Vaccines"[Mesh]	7,905
	#14	10 OR 11 OR 12 OR 13	17,700
	#15	5 AND 6 AND 14	961
	#16	5 AND 6 AND 9	5,472
	#17	Vaccines[tiab] OR Vaccine[tiab]	237,361
	#18	16 AND 17	1,195
	#19	15 OR 18	1,362
	#20	19 NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms])	811
	#21	20 NOT (animals[Mesh] NOT (humans[Mesh] AND animals[Mesh]))	699
	#22	21 AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR "Young Adult"[Mesh])	173

검색엔진	연번	검색식	검색결과
EMbase	#1	cancer:ab,ti OR malignant:ab,ti OR carcinoma:ab,ti OR neoplasm:ab,ti OR cancers:ab,ti OR malignancy:ab,ti OR carcinomas:ab,ti OR neoplasms:ab,ti OR Adenocarcinoma: ab,ti OR Adenocarcinomas:ab,ti OR neoplasia:ab,ti	111,867
	#2	Cervical:ab,ti OR Cervix:ab,ti	326,817
	#3	1 AND 2	16,154
	#4	'female genital tract cancer'/de OR 'uterine cervix cancer'/exp OR 'uterine cervix carcinoma in situ'/de	112,279
	#5	3 OR 4	116,045
	#6	'uterine cervix conization'/de OR electrosurgery/de OR conization*:ab,ti OR conisation*:ab,ti OR electrosurger*:ab,ti OR electrosurgical:ab,ti OR treatment*:ab,ti OR therap*:ab,ti	8,440,498
	#7	'Papilloma virus'/de OR 'Alphapapillomavirus'/exp OR 'papillomavirus infection'/exp OR 'Wart virus'/exp	76,343
	#8	Papillomaviridae:ab,ti OR Alphapapillomavirus:ab,ti OR Alphapapillomaviruses:ab,ti OR papillomavirus:ab,ti OR Wart:ab,ti OR Warts:ab,ti OR 'Condylomata Acuminata':ab,ti OR 'HPV L1 protein':ab,ti OR 'Papilloma viridae':ab,ti OR 'Alphapapilloma virus':ab,ti OR 'Alphapapilloma viruses':ab,ti OR 'papilloma virus':ab,ti	59,244
	#9	7 OR 8	85,173
	#10	Gardasil:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Nonavalent:ab,ti	8,413
	#11	Gardasil:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Quadrivalent:ab,ti	9,911
	#12	Cervarix:ab,ti OR 'HPV L1 vaccine' OR 'HPV Vaccines':ab,ti OR 'HPV Vaccine':ab,ti OR 'Papillomavirus Vaccines':ab,ti OR 'Papillomavirus Vaccine':ab,ti OR Bivalent:ab,ti	16,980
	#13	'Wart virus vaccine'/exp	13,959
	#14	10 OR 11 OR 12 OR 13	25,610
	#15	5 AND 6 AND 14	1,391
	#16	5 AND 6 AND 9	6,323
	#17	Vaccines:ab,ti OR Vaccine:ab,ti	277,223
	#18	16 AND 17	1,334
	#19	15 OR 18	1,852
	#20	19 NOT ('conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	1,059
	#21	20 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de)	635
	#22	21 AND (child/exp OR adolescent/de OR 'young adult'/de)	122

검색엔진	연번	검색식	검색결과
Cochrane	#1	(Cervical OR Cervix):ab,ti,kw	21,035
	#2	(cancer OR malignant OR carcinoma OR neoplasm OR cancers OR malignancy OR carcinomas OR neoplasms OR Adenocarcinoma OR Adenocarcinomas OR neoplasia):ab,ti,kw	191,181
	#3	1 AND 2	6,602
	#4	MeSH descriptor: [Genital Neoplasms, Female] this term only	338
	#5	MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees	2,039
	#6	MeSH descriptor: [Cervical Intraepithelial Neoplasia] explode all trees	554
	#7	4-6/OR	2,498
	#8	#3 OR #7	6,888
	#9	[mh Conization] OR [mh Electrosurgery] OR (conization* OR conisation* OR electrosurger* OR electrosurgical OR treatment* OR therap*):ab,ti,kw	998,371
	#10	MeSH descriptor: [Papillomavirus Infections] explode all trees	1,062
	#11	MeSH descriptor: [Alphapapillomavirus] explode all trees	222
	#12	MeSH descriptor: [Papillomaviridae] this term only	375
	#13	10-12/OR	1,176
	#14	(Papillomaviridae OR Alphapapillomavirus OR Alphapapillomaviruses OR papillomavirus OR Wart OR Warts OR "Condylomata Acuminata" OR "HPV L1 protein" OR "Papilloma viridae" OR "Alphapapilloma virus" OR "Alphapapilloma viruses" OR "papilloma virus"):ab,ti,kw	3,303
	#15	13 OR 14	3,303
	#16	(Gardasil OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Nonavalent):ab,ti,kw	925
	#17	(Gardasil OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Quadrivalent):ab,ti,kw	1,415
	#18	(Cervarix OR "HPV L1 vaccine" OR "HPV Vaccines" OR "HPV Vaccine" OR "Papillomavirus Vaccines" OR "Papillomavirus Vaccine" OR Bivalent):ab,ti,kw	1,260
	#19	MeSH descriptor: [Papillomavirus Vaccines] explode all trees	328
	#20	16-19/OR	1,800
	#21	8 AND 9 AND 20	220
	#22	8 AND 9 AND 15	597
	#23	(Vaccines OR Vaccine):ab,ti,kw	22,592
	#24	22 AND 23	274
	#25	21 OR 24	282
	#26	25/trials	279
	#27	[mh Child] OR [mh Adolescent] OR [mh "Young Adult"]	161,005
	#28	26 AND 27	88

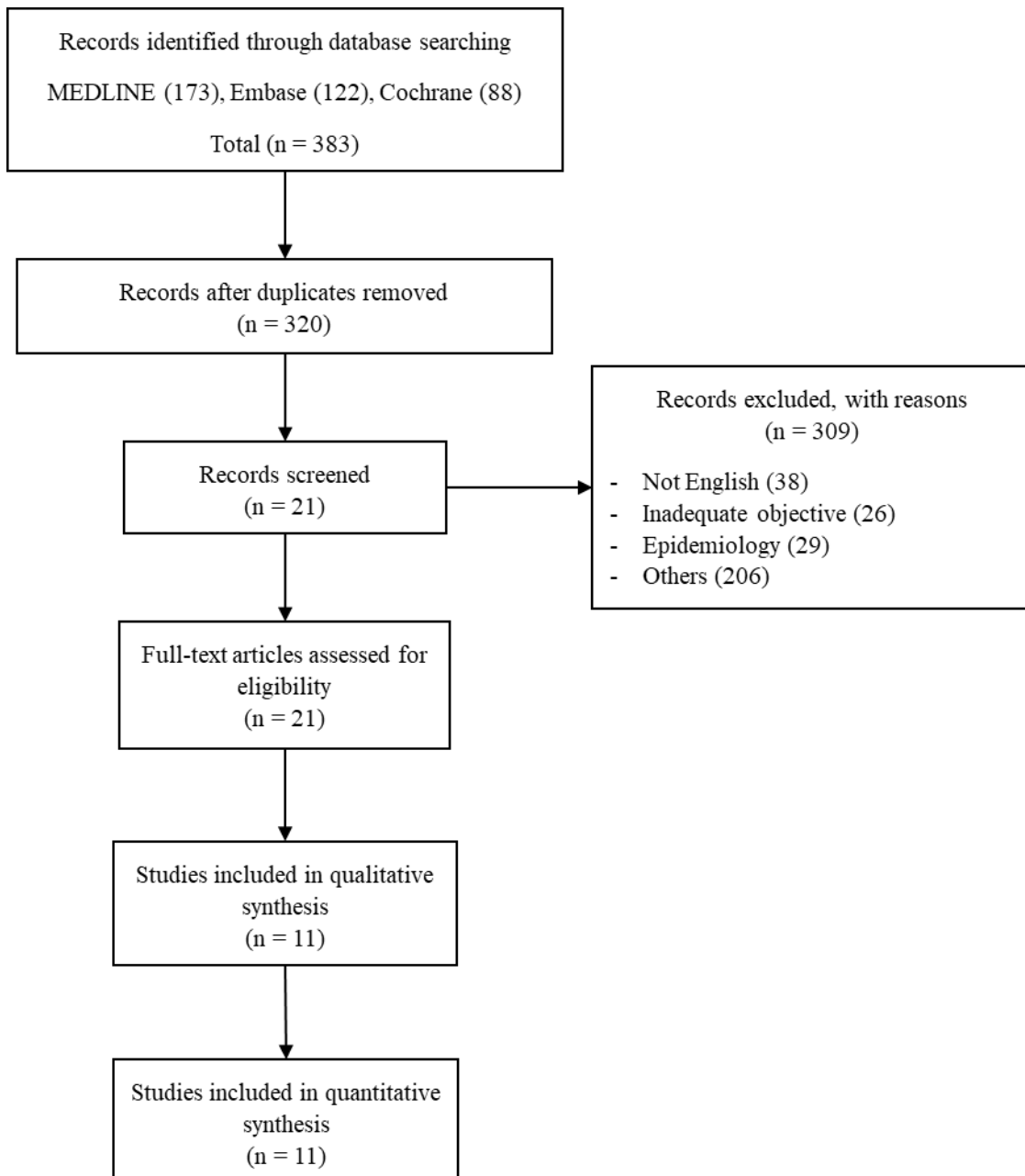


그림 2. 문헌 검색 흐름도 (치료 후 백신 접종)

Supplement 2.

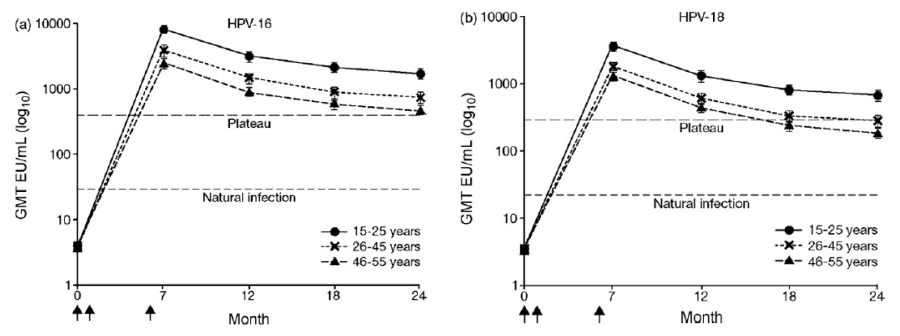
Evidence Table of Key Question 1

인유두종바이러스 예방백신 3회 접종 연령은? (남녀 모두 포함)

KQ 1. 2가

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Paavonen et al. 2007, 2009 (59, 60) PATRICIA study	phase III double-blind, randomised controlled trial CIN2+ incidence	women aged 15–25 years	1) Inclusion (i) Healthy women aged 15–25 years who reported no more than six lifetime sexual partners before study enrolment (ii) Women who agreed to adequate contraception over the vaccination period	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Efficacy and Immunogenicity - Vaccine efficacy against CIN2+ containing HPV16/18DNA ① In overall population: 92.9% (96.1% CI 79.9–98.3) ② Per protocol population: 98.1% (96.1% CI 88.4–100) 2. Adverse Events No clinically meaningful differences were noted in safety outcomes between the study groups.
Draper et al. 2013 (61)	A Randomized, Observer-Blinded Immunogenicity Trial Immuno-bridging	12–15 year old girls	1) Inclusion (i) 12–15 year old girls (ii) written informed consent	- Control Group: Gardasil - Study Group: Cervarix	1. Efficacy and Immunogenicity - Serum-neutralizing antibody responses against non-vaccine HPV types were broader and of higher magnitude in the Cervarix, compared to the Gardasil - Cervarix having a median 2.5 (inter-quartile range, 1.7–3.5) fold higher geometric mean HPV-specific IgG ratio in serum and genital samples than Gardasil (p=0.0047)
Einstein et al. 2009, 2014 (30, 62)	Follow-up from months 12–24 in a Phase III randomized study Immuno-bridging	healthy women aged 18–45 years	1) Inclusion (i) Healthy women aged 18–45 years (ii) Participants were required to have an intact cervix (iii) A negative urine pregnancy test	- Control Group: Gardasil - Study Group: Cervarix	1. Efficacy and Immunogenicity - seropositivity rates of neutralizing antibodies (nAbs) were, across all age strata, 100% (HPV-16/18 vaccine) and 97.5–100% (HPV-6/11/16/18 vaccine) for HPV-16, and 99.0–100% (HPV-16/18 vaccine) and 72.3–84.4% (HPV-6/11/16/18 vaccine) for HPV-18. - geometric mean titers (GMTs) were 2.4–5.8- fold higher for HPV-16 and 7.7–9.4-fold higher for HPV-18 with the HPV-16/18 vaccine vs. the HPV-6/11/16/18 vaccine.

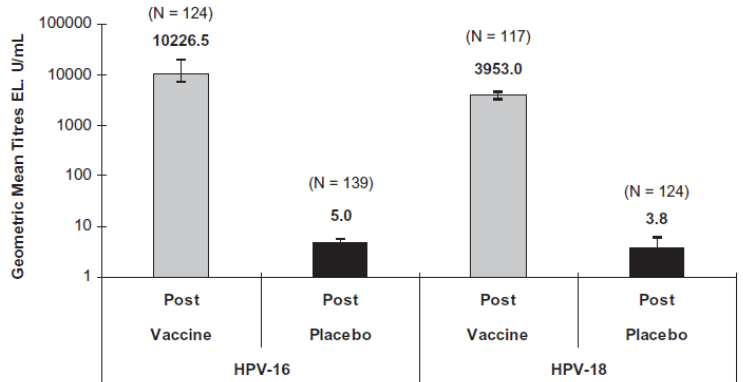
(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Harper et al. 2006 (63)	follow-up from a randomised control trial Incident infection Persistent infection for 6 months or 12 months CIN incidence	women between 15–25 years of age	1) Inclusion (i) healthy women aged 15–25 years (ii) no more than six sexual partners (iii) no history of an abnormal Pap test or ablative or excisional treatment of the cervix (iv) cytology negative (v) seronegative for HPV-16 and HPV-18 antibodies	- Control Group: placebo - Study Group: Cervarix	1. Efficacy and Immunogenicity - vaccine efficacy against HPV-16 and HPV-18 endpoints ① Incident infection, 96.9% (95% CI 81.3–99.9) ② Persistent infection: 6 month - 94.3 (63.2–99.9); 12 month - 100% (33.6–100) - vaccine efficacy of 100% (42.4–100) against CIN lesions associated with vaccine types 2. Adverse Events - good long-term safety profile.
Schwarz et al. 2009, 2011, 2015 (64-66)	Phase III, non-randomised, open-label clinical trial Antibody (GMT) Levels / Adverse events	women aged 15–55 years	1) Inclusion (i) Women between 15 and 55 years of age (ii) using adequate contraception (iii) negative pregnancy test	Three groups - age 15–25 - age 26–45 - age 46–55	1. Efficacy and Immunogenicity - seropositivity : 100%  2. Adverse Events - well tolerated in overall population

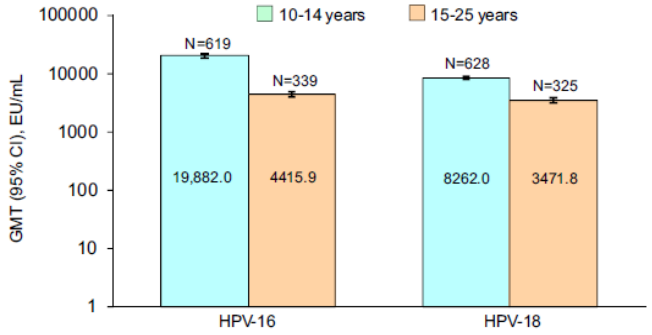
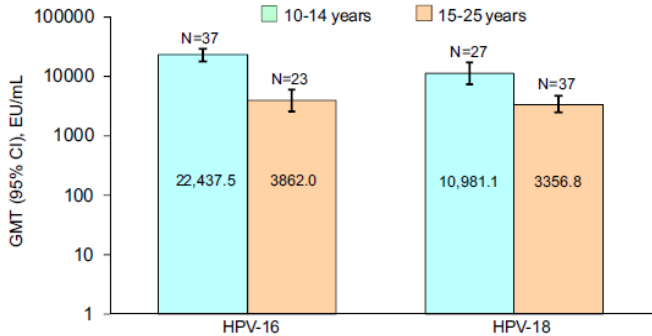
(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results																																
Petaja et al. 2009 (7)	phase I/II, observer-blind, parallel-group, randomized study Antibody (GMT) Levels / Adverse events	Healthy males aged 10 to 18 years	1) Inclusion (i) Boys aged 10 to 18 years	- Control Group: hepatitis B vaccine - Study Group: Cervarix	<p>1. Efficacy and Immunogenicity</p> <p>- seropositivity : 100%</p> <table border="1"> <caption>GMT (EU/mL) Data from Chart</caption> <thead> <tr> <th>HPV Type</th> <th>Group</th> <th>n</th> <th>GMT (EU/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-16</td> <td>Boys 10-18 years-old</td> <td>163</td> <td>~20,000</td> </tr> <tr> <td>Women 15-25 years-old</td> <td>359</td> <td>~8,000</td> </tr> <tr> <td rowspan="2">HPV-18</td> <td>Boys 10-14 years-old</td> <td>79</td> <td>~25,000</td> </tr> <tr> <td>Girls 10-14 years-old</td> <td>143</td> <td>~15,000</td> </tr> <tr> <td rowspan="2">HPV-16</td> <td>Boys 10-18 years-old</td> <td>150</td> <td>~8,000</td> </tr> <tr> <td>Women 15-25 years-old</td> <td>364</td> <td>~3,000</td> </tr> <tr> <td rowspan="2">HPV-18</td> <td>Boys 10-14 years-old</td> <td>72</td> <td>~10,000</td> </tr> <tr> <td>Girls 10-14 years-old</td> <td>141</td> <td>~7,000</td> </tr> </tbody> </table> <p>2. Adverse Events</p> <p>- The reactogenicity profiles of the HPV-16/18 AS04 and HBV vaccines were similar</p>	HPV Type	Group	n	GMT (EU/mL)	HPV-16	Boys 10-18 years-old	163	~20,000	Women 15-25 years-old	359	~8,000	HPV-18	Boys 10-14 years-old	79	~25,000	Girls 10-14 years-old	143	~15,000	HPV-16	Boys 10-18 years-old	150	~8,000	Women 15-25 years-old	364	~3,000	HPV-18	Boys 10-14 years-old	72	~10,000	Girls 10-14 years-old	141	~7,000
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HPV-18	Boys 10-14 years-old	72	~10,000																																		
	Girls 10-14 years-old	141	~7,000																																		
Romanowski et al. 2009 (67)	double-blind, randomised, placebo-controlled study CIN2+ incidence Incident infection/Persistent infection for 12 months	Women aged 15–25 years	1) Inclusion (i) Healthy young women (aged 15–25 years) (ii) normal cervical cytology (iii) HPV-16 and HPV-18 seronegative	- Control Group: placebo - Study Group: Cervarix	<p>1. Efficacy and Immunogenicity</p> <p>- vaccine efficacy against HPV-16 and HPV-18 endpoints</p> <p>① Incident infection, 95.3% (95% CI 87.4–98.7)</p> <p>② Persistent infection: 12 month - 100% (81.8–100)</p> <p>- vaccine efficacy against CIN2+ lesions associated with HPV16/18: 100% (51.3–100)</p> <p>- vaccine efficacy against CIN2+ lesions independent of HPV DNA: 71.9% (20.6–91.9)</p> <p>2. Adverse Events</p> <p>- similar between groups</p>																																

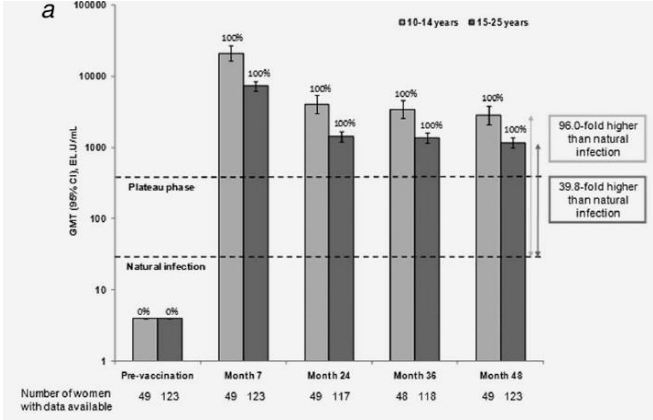
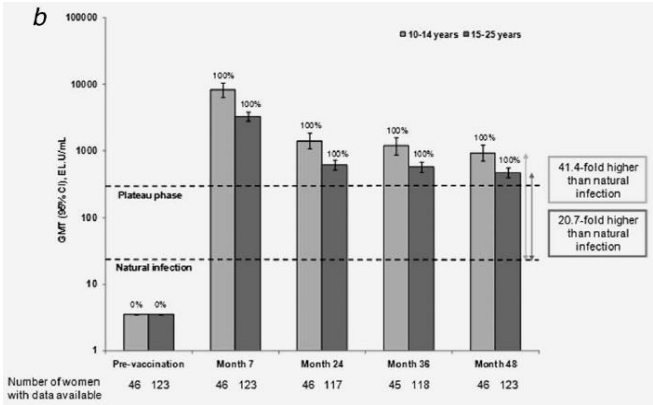
(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results																		
Konno et al. 2010 (68, 69)	Phase 2 Double-Blind, Randomized Controlled Trial Persistent infection for 6 months CIN1+ incidence Adverse events	women aged 20 to 25 years	1) Inclusion (i) Japanese healthy woman aged 20 to 25 years (ii) negative urine pregnancy test (iii) contraception (iv) intact cervix	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Efficacy and Immunogenicity - vaccine efficacy against HPV-16 and HPV-18 endpoints: Persistent infection: 6 month - 100% (95% CI 71.3-100) - vaccine efficacy against CIN1+ lesions associated with 14 oncogenic HPV: 64.9% (4.9-89.0) 2. Adverse Events - acceptable safety profile																		
Bhatla et al. 2010 (70)	double-blind, randomized (1:1), controlled parallel group trial Antibody (GMT) level Adverse events	healthy Indian women aged 18-35 years old	1) Inclusion (i) Indian healthy woman aged 18 to 35 years (ii) negative urine pregnancy test (iii) contraception (iv) intact cervix	- Control Group: placebo - Study Group: Cervarix	1. Efficacy and Immunogenicity - seropositivity : 100%  <table border="1"> <caption>Geometric Mean Titres ELU/mL</caption> <thead> <tr> <th>HPV Type</th> <th>Group</th> <th>N</th> <th>Geometric Mean Titres ELU/mL</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-16</td> <td>Post Vaccine</td> <td>124</td> <td>10226.5</td> </tr> <tr> <td>Post Placebo</td> <td>139</td> <td>5.0</td> </tr> <tr> <td rowspan="2">HPV-18</td> <td>Post Vaccine</td> <td>117</td> <td>3953.0</td> </tr> <tr> <td>Post Placebo</td> <td>124</td> <td>3.8</td> </tr> </tbody> </table> 2. Adverse Events - similar in both groups	HPV Type	Group	N	Geometric Mean Titres ELU/mL	HPV-16	Post Vaccine	124	10226.5	Post Placebo	139	5.0	HPV-18	Post Vaccine	117	3953.0	Post Placebo	124	3.8
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Medina et al. 2010 (71)	Randomized, Controlled Trial Antibody (GMT) levels Adverse events	healthy girls, aged 10–14 years	1) Inclusion - healthy girls, aged 10– 14 years 2) exclusion (i) immunodeficiency, (ii) history of allergic disease (iii) known acute or chronic clinically significant neurologic, hepatic, or renal functional abnormality	- Control Group: hepatitis A vaccine - Study Group: Cervarix	<p>1. Efficacy and Immunogenicity</p> <p>- seropositivity : 100%</p> <p>A Initially seronegative participants</p>  <table border="1"> <caption>Data for Chart A: Initially seronegative participants</caption> <thead> <tr> <th>HPV Type</th> <th>Age Group</th> <th>N</th> <th>GMT (95% CI), EU/mL</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-16</td> <td>10-14 years</td> <td>619</td> <td>19,882.0</td> </tr> <tr> <td>15-25 years</td> <td>339</td> <td>4,415.9</td> </tr> <tr> <td rowspan="2">HPV-18</td> <td>10-14 years</td> <td>628</td> <td>8,262.0</td> </tr> <tr> <td>15-25 years</td> <td>325</td> <td>3,471.8</td> </tr> </tbody> </table> <p>B Initially seropositive participants</p>  <table border="1"> <caption>Data for Chart B: Initially seropositive participants</caption> <thead> <tr> <th>HPV Type</th> <th>Age Group</th> <th>N</th> <th>GMT (95% CI), EU/mL</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HPV-16</td> <td>10-14 years</td> <td>37</td> <td>22,437.5</td> </tr> <tr> <td>15-25 years</td> <td>23</td> <td>3,862.0</td> </tr> <tr> <td rowspan="2">HPV-18</td> <td>10-14 years</td> <td>27</td> <td>10,981.1</td> </tr> <tr> <td>15-25 years</td> <td>37</td> <td>3,356.8</td> </tr> </tbody> </table> <p>2. Adverse Events</p> <p>- similar in both groups</p>	HPV Type	Age Group	N	GMT (95% CI), EU/mL	HPV-16	10-14 years	619	19,882.0	15-25 years	339	4,415.9	HPV-18	10-14 years	628	8,262.0	15-25 years	325	3,471.8	HPV Type	Age Group	N	GMT (95% CI), EU/mL	HPV-16	10-14 years	37	22,437.5	15-25 years	23	3,862.0	HPV-18	10-14 years	27	10,981.1	15-25 years	37	3,356.8
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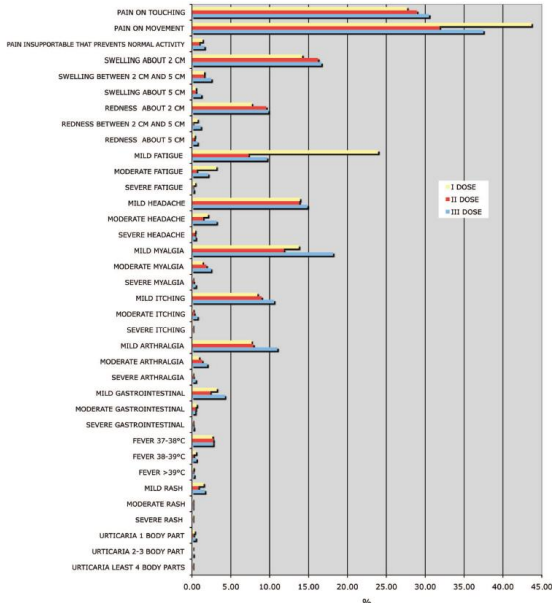
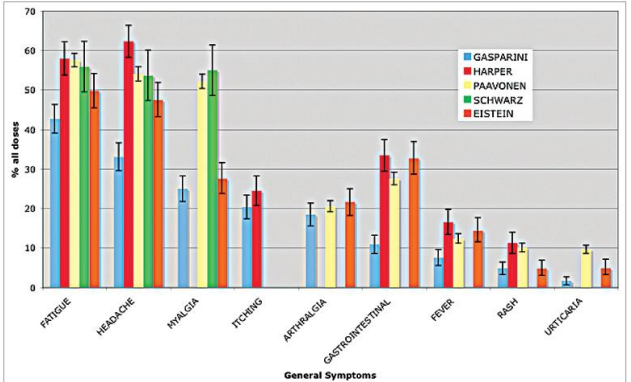
(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Petaja et al. 2011 (72)	phase III, open, multicentric, follow-up study Antibody (GMT) levels Adverse events	young women aged 10–25 years	1) Inclusion (i) healthy women aged 10–25 years (ii) no more than six sexual partners (iii) contraception (iv) no pregnancy		1. Efficacy and Immunogenicity - seropositivity : 100% HPV 16  HPV 18  2. Adverse Events - acceptable safety profile

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results																								
Garcia-Sicilia et al. 2010 (73)	Randomized open, 3 parallel study Antibody (GMT) levels Adverse events	Healthy girls and young women aged 10–18 years	1) Inclusion (i) healthy women aged 10–18 years (ii) contraception (iii) no pregnancy	Three group - Cerviarix only - Cervarix and dTpa-IPV - dTpa-IPV only	<p>1. Efficacy and Immunogenicity</p> <p>- seroconversion: HPV 16 (coadministration: 99.5% // HPV vaccine only 100%), HPV 18 (coadministration: 99.5% // HPV vaccine only 100%)</p> <table border="1"> <caption>HPV-16 GMT (EU/mL)</caption> <thead> <tr> <th>Group</th> <th>GMT (EU/mL)</th> <th>Seroconversion (%)</th> </tr> </thead> <tbody> <tr> <td>HPV</td> <td>18965.1</td> <td>100%</td> </tr> <tr> <td>HPV+dTpa-IPV</td> <td>15608.0</td> <td>99.5%</td> </tr> <tr> <td>dTpa-IPV</td> <td>14214.1</td> <td>100%</td> </tr> </tbody> </table> <table border="1"> <caption>HPV-18 GMT (EU/mL)</caption> <thead> <tr> <th>Group</th> <th>GMT (EU/mL)</th> <th>Seroconversion (%)</th> </tr> </thead> <tbody> <tr> <td>HPV</td> <td>6902.4</td> <td>100%</td> </tr> <tr> <td>HPV+dTpa-IPV</td> <td>6596.8</td> <td>99.5%</td> </tr> <tr> <td>dTpa-IPV</td> <td>5147.4</td> <td>100%</td> </tr> </tbody> </table> <p>2. Adverse Events</p> <p>- coadministration was well tolerated.</p>	Group	GMT (EU/mL)	Seroconversion (%)	HPV	18965.1	100%	HPV+dTpa-IPV	15608.0	99.5%	dTpa-IPV	14214.1	100%	Group	GMT (EU/mL)	Seroconversion (%)	HPV	6902.4	100%	HPV+dTpa-IPV	6596.8	99.5%	dTpa-IPV	5147.4	100%
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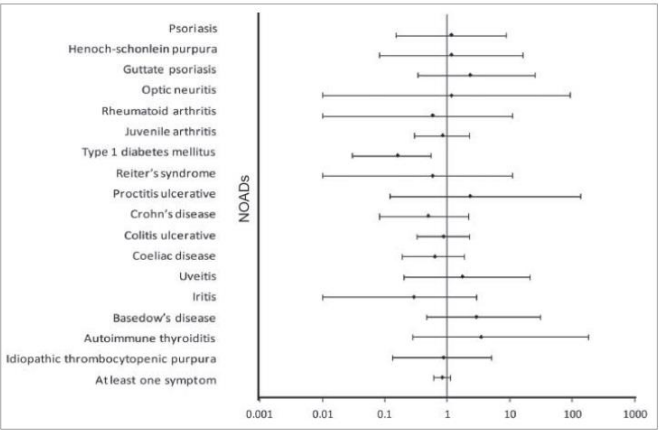
(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Gasparini et al. 2011 (74)	An Italian post-licensure study Adverse events	female subjects aged between 12 and 26 years	1) Inclusion (i) female subjects aged between 12 and 26 years (ii) 4,600 subjects who had begun the vaccination cycle in 2008 and 2009		<p>1. Adverse Events</p> <p>- No serious adverse events were observed.</p>  <p>- better tolerability of the vaccine in comparison with the data from some controlled clinical studies</p> 

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Pedersen et al. 2012 (75)	randomized, open, controlled, parallel group study Antibody (GMT) level	Healthy girls aged 9–15 years	1) Inclusion (i) healthy women aged 9–15 years (ii) contraception (iii) no pregnancy	Three group - Cerviarix only - Cervarix and HAB (hepatitis A and B) - HAB only	<p>1. Efficacy and Immunogenicity</p> <p>- seroconversion: 100% in each group</p> <p>2. Adverse Events</p> <p>- No vaccine-related serious adverse events were reported</p>
Wheeler et al. 2016 (76)	phase 3, double-blind, randomised controlled trial Persistent infection for 6 months CIN1+	healthy women older than 25 years	1) Inclusion (i) healthy women older than 25 years (ii) contraception (iii) no pregnancy	- Control Group: placebo - Study Group: Cervarix	<p>1. Efficacy and Immunogenicity</p> <p>- vaccine efficacy against HPV-16 and HPV-18 endpoints</p> <p>① Persistent infection 6 months or CIN1+: 90.5% (96.2% CI 78.6-96.5)</p> <p>- vaccine efficacy against HPV-31 endpoints</p> <p>① Persistent infection 6 months or CIN1+: 65.8% (24.9-85.8)</p> <p>- vaccine efficacy against HPV-45 endpoints</p> <p>① Persistent infection 6 months or CIN1+: 70.7% (34.2-88.4)</p> <p>- vaccine efficacy of 100% (42.4–100) against CIN lesions associated with vaccine types</p> <p>2. Adverse Events</p> <p>- Serious adverse events: 5 (0.2%) in vaccine group, 8 (0.3%) in control group</p>

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Lehtinen et al. 2016 (77)	large community-randomized controlled trial Adverse events	girls and boys aged 12–15	1) Inclusion (i) girls and boys aged 12–15	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Adverse Events - the observed incidences (per 100,000 person-years) of serious adverse events (SAEs) possibly related to vaccination ① Vaccine group: 54.3 (95% CI 34.0-82.1) ② HBV group: 64.0 (43.2-91.3) - risk of the occurrence of new-onset autoimmune disease (NOADs) 
Lehtinen et al 2017 (78)	cluster-randomised follow-up study CIN3+ incidence	Clinical trial participants aged 16–17 years	1) Inclusion (i) girls and boys aged 16-17	- Control Group: unvaccinated population aged 18-19 - Study Group: clinical trial participant aged 16-17	1. Efficacy and Immunogenicity - vaccine efficacy against CIN3+ lesion: 66% (95% CI 8-88)
Zhu et al. 2019 (79)	phase II/III, randomised, controlled trial HPV16/18-associated CIN2+ incidence Adverse events	Chinese women aged 18-25 years	1) Inclusion (i) healthy women aged 18-25 years (ii) no pregnancy	- Control Group: placebo - Study Group: Cervarix	1. Efficacy and Immunogenicity - vaccine efficacy against HPV-16/18-associated CIN2+: 87.3% (95% CI 5.5-99.7) - Cross-protective efficacy against incident infection with HPV 31/33/45: 59.6% (39.4-73.5), 42.7% (15.6-61.6), 54.8% (19.3-75.6) 2. Adverse Events - Serious adverse events: 1.9% in vaccine group, 2.7% in control group

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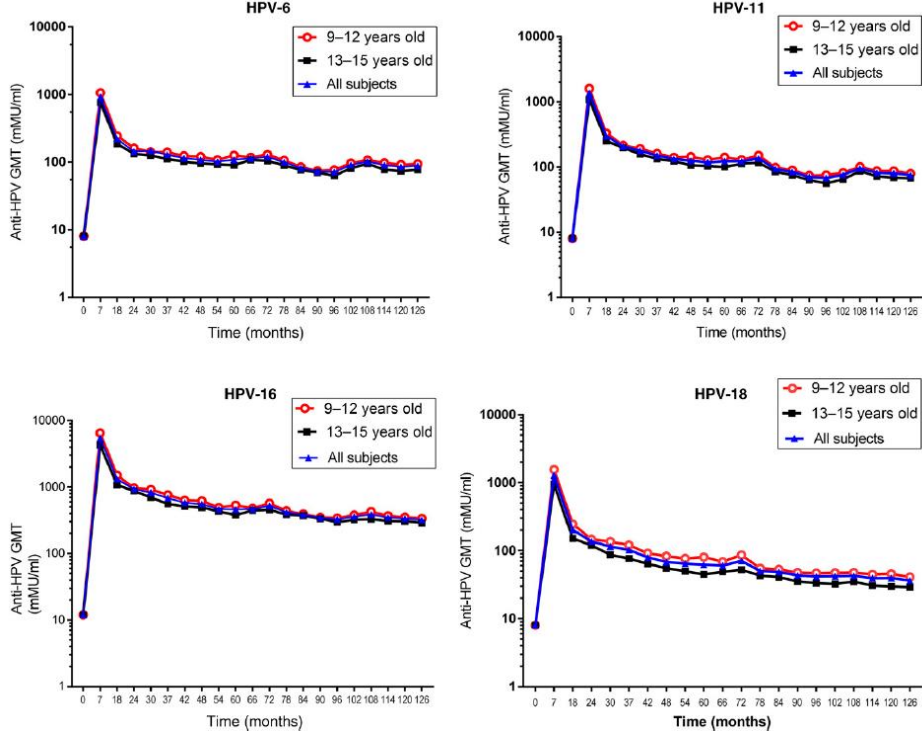
ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Chen et al. 2019 (80)	Phase 3, randomized, double-blind, placebo-controlled clinical trial Adverse events	Chinese women 20–45 years of age	1) Inclusion (i) women were 20–45 years of age (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: placebo - Study Group: qHPV vaccine	1. adverse events - 926 (61.8%) qHPV vaccine recipients and 856 (57.1%) placebo recipients - Injection-site AEs: qHPV vaccine vs placebo (37.6% vs 27.8%) - systemic AEs : similar between qHPV and placebo
Wei et al. 2019 (81)	Phase 3, randomized, double-blind, placebo-controlled clinical trial CIN2+ incidence	Chinese women 20–45 years of age	1) Inclusion (i) women were 20–45 years of age (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: placebo - Study Group: qHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against CIN2+ associated with HPV 16/18: 100% (95% CI 32.3-100) - Vaccine efficacy against CIN1+ associated with HPV 6/11/16/18: 100% (70.9-100) - Vaccine efficacy against persistent infection associated with HPV 16/18 ① 6/12 months: 91.6% (66.0-99.0) ② 30/78 months: 97.5% (85.1-99.9) - Vaccine efficacy against cytology abnormalities associated with HPV6/11/16/18: 94.0% (81.5-98.8)
Herweijer et al. 2016 (82)	A population-based study CIN2+ incidence	girls and young women aged 13–29	1) Inclusion (i) all 13 to 30 year old girls and young women that were resident in Sweden		1. Efficacy and Immunogenicity - Vaccine efficacy against CIN2+ initiating vaccination before age 17: 75% - Vaccine efficacy against CIN2+ initiating vaccination at ages 17-19: 46% - Vaccine efficacy against CIN2+ initiating vaccination at ages 20-29: 22%

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Kjaer et al. 2020 (83) 12 year F/U report	randomized, double-blind, placebo-controlled study CIN2+ incidence Antibody(GMT) level	Young women aged 16-23 years	1) Inclusion (i) women were 16–23 years of age (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: placebo - Study Group: qHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against CIN2+ for >12 years: 100% (95% CI 94.7-100) - seropositivity: >90% (HPV 6/11/16), 52% (HPV 18)
Kjaer et al. 2018 (84) 10 year F/U report	randomized, double-blind, placebo-controlled clinical trial CIN2+ incidence Antibody(GMT) level	women between the ages of 15 and 26 years	1) Inclusion (i) women were 15–26 years of age (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: placebo - Study Group: qHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against CIN2+ for 10 years: >90%

Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk (95% Confidence Interval)	Vaccine Effectiveness ^a (%)
HPV16/18-related CIN2+	2084	0	13c794.9	0.0 (0.0-0.0)	100
By time since day 1 of base study					
4 years or less	1930	0	803.5	0.0 (0.0–0.5)	
>4 to 6 years	2083	0	4119.9	0.0 (0.0–0.1)	
>6 to 8 years	2037	0	3978.7	0.0 (0.0–0.1)	
>8 to 10 years	1914	0	3393.1	0.0 (0.0–0.1)	
>10 to 12 years	1333	0	1479.0	0.0 (0.0–0.2)	
>12 to 14 years	124	0	20.6	0.0(0.0–17.9)	
By HPV type					
HPV16-related CIN2+	1787	0	11 809.9	0.0 (0.0-0.0)	
HPV18-related CIN 2+	1981	0	13115.5	0.0 (0.0-0.0)	
By lesion type					
CIN 2	2084	0	13 794.9	0.0 (0.0-0.0)	
CIN 3	2084	0	13 794.9	0.0 (0.0-0.0)	
Adenocarcinoma in situ	2084	0	13 794.9	0.0 (0.0-0.0)	
Cervical cancer	2084	0	13 794.9	0.0 (0.0-0.0)	

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Ferris et al. 2017 (5) 10 year F/U report	randomized, double-blind, placebo controlled, multicenter study Antibody (GMT) level	9- to 15-year-old boys and girls	1) Inclusion (i) healthy women aged 9–15 years (ii) contraception (iii) no pregnancy	- Control Group: placebo - Study Group: qHPV vaccine	1. Efficacy and Immunogenicity - seropositivity for 10 years post-vaccination: 89-96% (HPV 6/11/16) - preadolescents (9-12 years) had 16-42% higher geometric mean titers at 10 years compared with adolescents (13-15 years)  2. adverse events - No new serious adverse events

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results																																																																																																									
Castellsague' et al. 2011 (24)	Randomised, placebo-controlled, double-blind safety, immunogenicity, and efficacy study (Protocol 019)	3819 women between the ages of 24 and 45 years	Inclusion Criteria 1) not pregnant 2) not undergone hysterectomy 3) effective contraception 4) no history of genital warts or CIN/cancer	- Control: placebo - Study: qHPV vaccine	1) Vaccine efficacy per protocol - Against the combined incidence of persistent infection, CIN/EGL related to HPV6/11/16/18: 88.7% (95% CI: 78.1, 94.8) 2) Efficacy received at least 1 dose (seropositive and DNA negative): 66.9% (95% CI: 4.3, 90.6) 3) Seropositivity at month 48 - 91.5, 92.0, 97.4, 47.9% to HPV 6/11/16/18 4) Adverse events: no serious vaccine-related AE																																																																																																									
Munoz et al. 2009 (23)	a randomised, double-blind trial CIN incidence	women aged 24-45 years	1) Inclusion (i) women were 24-45 years of age (ii) contraception (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: placebo - Study Group: qHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against disease or infection related to HPV 6, 11, 16, and 18: 90.5% (95% CI 73.7-97.5) - Vaccine efficacy against disease or infection related to HPV 16 and 18 alone: 83.1% (50.6-95.8) <table border="1" data-bbox="1070 635 1848 933"> <thead> <tr> <th rowspan="2"></th> <th colspan="3">Vaccine (n=1910)</th> <th colspan="3">Placebo (n=1907)</th> <th rowspan="2">Efficacy (95% CI)</th> <th rowspan="2">p value</th> </tr> <tr> <th>n</th> <th>Cases</th> <th>Rate</th> <th>n</th> <th>Cases</th> <th>Rate</th> </tr> </thead> <tbody> <tr> <td colspan="9">Per-protocol population*</td> </tr> <tr> <td>HPV 6/11/16/18-related (all women)</td> <td>1615</td> <td>4</td> <td>0.1</td> <td>1607</td> <td>41</td> <td>1.5</td> <td>90.5% (73.7 to 97.5)</td> <td><0.0001</td> </tr> <tr> <td> Women aged 24-34 years</td> <td>792</td> <td>2</td> <td>0.2</td> <td>792</td> <td>24</td> <td>1.8</td> <td>91.8% (67.1 to 99.1)</td> <td>--</td> </tr> <tr> <td> Women aged 35-45 years</td> <td>823</td> <td>2</td> <td>0.1</td> <td>815</td> <td>17</td> <td>1.3</td> <td>88.6% (51.9 to 98.7)</td> <td>--</td> </tr> <tr> <td>HPV 16/18-related (all women)</td> <td>1601</td> <td>4</td> <td>0.1</td> <td>1579</td> <td>23</td> <td>0.9</td> <td>83.1% (50.6 to 95.8)</td> <td>0.0001</td> </tr> <tr> <td> Women aged 24-34 years</td> <td>784</td> <td>2</td> <td>0.2</td> <td>774</td> <td>13</td> <td>1.0</td> <td>85.0% (33.8 to 98.4)</td> <td>--</td> </tr> <tr> <td> Women aged 35-45 years</td> <td>817</td> <td>2</td> <td>0.1</td> <td>805</td> <td>10</td> <td>0.7</td> <td>80.6% (9.1 to 97.9)</td> <td>--</td> </tr> <tr> <td>HPV 6/11-related (all women)</td> <td>1329</td> <td>0</td> <td>0.0</td> <td>1323</td> <td>19</td> <td>0.9</td> <td>100% (79.0 to 100)</td> <td><0.0001</td> </tr> <tr> <td> Women aged 24-34 years</td> <td>636</td> <td>0</td> <td>0.0</td> <td>653</td> <td>12</td> <td>1.1</td> <td>100% (63.7 to 100)</td> <td>--</td> </tr> <tr> <td> Women aged 35-45 years</td> <td>693</td> <td>0</td> <td>0.0</td> <td>670</td> <td>7</td> <td>0.6</td> <td>100% (33.6 to 100)</td> <td>--</td> </tr> </tbody> </table> 2. adverse events - No new serious adverse events		Vaccine (n=1910)			Placebo (n=1907)			Efficacy (95% CI)	p value	n	Cases	Rate	n	Cases	Rate	Per-protocol population*									HPV 6/11/16/18-related (all women)	1615	4	0.1	1607	41	1.5	90.5% (73.7 to 97.5)	<0.0001	Women aged 24-34 years	792	2	0.2	792	24	1.8	91.8% (67.1 to 99.1)	--	Women aged 35-45 years	823	2	0.1	815	17	1.3	88.6% (51.9 to 98.7)	--	HPV 16/18-related (all women)	1601	4	0.1	1579	23	0.9	83.1% (50.6 to 95.8)	0.0001	Women aged 24-34 years	784	2	0.2	774	13	1.0	85.0% (33.8 to 98.4)	--	Women aged 35-45 years	817	2	0.1	805	10	0.7	80.6% (9.1 to 97.9)	--	HPV 6/11-related (all women)	1329	0	0.0	1323	19	0.9	100% (79.0 to 100)	<0.0001	Women aged 24-34 years	636	0	0.0	653	12	1.1	100% (63.7 to 100)	--	Women aged 35-45 years	693	0	0.0	670	7	0.6	100% (33.6 to 100)	--
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Giuliano et al. 2015 (28)	Single arm, prospective cohort study	Men aged 27-45 years	Inclusion 1) male 2) 27-45 years old, 3) completed four years of follow-up in the HPV Infection in Men (HIM) natural history study	Single arm	100% of men seroconverted to each of the four HPV vaccine components The vaccine was generally well-tolerated. Antibody responses to vaccine did not differ by age group or sexual orientation, regardless of HPV type, and were significantly higher at Month 7 among men who entered the trial seropositive for HPV 6 or 11.																																																																																																									

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Mikamo et al. 2019 (85)	randomized, double-blind trial combined incidence of HPV6/11/16/18-related persistent anogenital infection	Japanese men (aged 16–26 years)	Inclusion criteria - Heterosexual men: have exclusively female sexual partners and 1–5 lifetime sexual partners at the time of enrollment - MSM: have exclusively male sexual partners and 1–5 lifetime sexual partners at the time of enrollment	- Control: placebo - Study: qHPV vaccine	1. Efficacy against HPV6/11/16/18-related persistent infection - Interim 83.3% (95% CI 24.9 to 98.2) / Final: 85.9% (95% CI 52.7 to 97.3) - 2 cases in placebo group vs. non in vaccine group 2. Vaccine-related AE - 60.8% in qHPV vaccine group vs. 56.5% in placebo group - Mild to moderate injection-site pain, erythema, and swelling. Injection-site pain and swelling

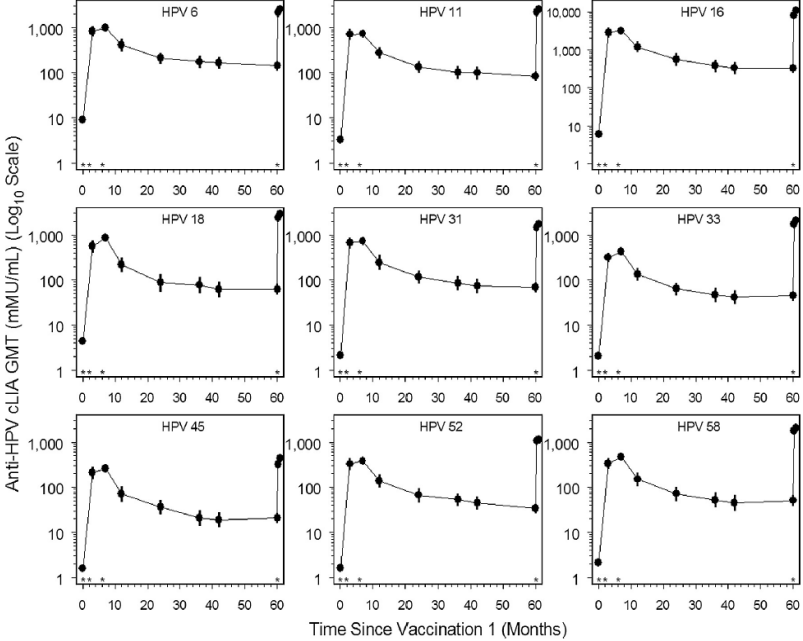
KQ 1. 9가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Garland et al. 2017 (86)	a randomized, double-blinded, qHPV vaccine-controlled efficacy study (study 001) and an immunogenicity study (study 002)	young women aged 16–26 years (study 001) and girls and boys aged 9–15 years (study 002)	1) Inclusion (i) all Asian participant from study 001, 002	- Control Group: qHPV vaccine (study 001), - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against persistent infection associated with HPV 31/33/45/52/58: 90.4-100% - seroconversion: >97.9% of participant 2. Adverse Events - most were mild to moderate
Giuliano et al. 2019 (12)	Analysis with three international, randomized, double-blind studies	women aged 16–26 years	1) Inclusion (i) women aged 16–26 years (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: Historic placebo - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against of HSIL related to 9 HPV types: 98.2% (95% CI 93.6-99.7) - reduction of cervical surgery related to 9 HPV types: 97.8% (93.4-99.4)
Ruiz-Sternberg et al. 2018 (87)	Analysis with 2 international studies including a randomized, double-blinded, controlled trial	young women aged 16–26 years (study 001) and girls and boys aged 9–15 years (study 002)	1) Inclusion (i) all Asian participant from study 001, 002	- Control Group: qHPV vaccine (study 001), - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against of HSIL related to HPV 31/33/45/52/58 types: 92.3% (95% CI 54.4-99.6) - seroconversion at month 7: >99% of participant - Anti-HPV antibody responses following vaccination were higher among girls and boys than in young women
Huh et al. 2017 (88)	A randomised, double-blind trial	women aged 16–26 years	1) Inclusion (i) women aged 16–26 years (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: qHPV vaccine - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - Vaccine efficacy against of HSIL related to HPV 31/33/45/52/58 types: 97.4% (95% CI 85.0-99.9) - incidence of HSIL related to HPV 31/33/45/52/58 types (per 10000 person-years): 0.5 in 9vHPV vs 19.0 in qHPV - Anti-HPV antibody responses were non-inferior in the 9Vhpv versus qHPV group 2. Adverse Events - no clinical meaningful difference

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Joura et al. 2015 (89)	A randomized, international, double-blind, phase 2b–3 study	women aged 16–26 years	1) Inclusion (i) women aged 16–26 years (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: qHPV vaccine - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - incidence of HSIL irrespective of HPV types: 14.0 per person-years - incidence of HSIL related to HPV 31/33/45/52/58 types (per 1000 person-years): 0.1 in 9vHPV vs 1.6 in qHPV - Vaccine efficacy against of HSIL related to HPV 31/33/45/52/58 types: 96.7% (95% CI 80.9-99.8) - Anti-HPV antibody responses to HPV 6,11,16, 18 were non-inferior in the 9Vhpv versus qHPV group 2. Adverse Events - Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group
Vesikari et al. 2015 (18)	A Randomized, Double-Blind, Phase III Study	9–15-Year-Old Girls	1) Inclusion (i) girls aged ≥ 9 to <16 years (ii) good physical health (iii) virgins (iv) not planning to become sexually active through month 7 of the study	- Control Group: qHPV vaccine - Study Group: 9vHPV vaccine	1. Efficacy and Immunogenicity - Anti-HPV antibody responses to HPV 6,11,16, 18 elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine - seroconversion: >99% of participant 2. Adverse Events - similar safety outcomes - Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group
Castellsague et al. 2015 (90)	an international, multi-centered, immunogenicity and tolerability study (Protocol V503-003) Immuno-Bridging	young men (16–26 years of age) vs. young women (16–26 years of age)		- Control: 16-26 years of women - Study: 16-26 years of men	The GMT for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 for HM - non-inferior to those of women at Month 7 For all vaccine HPV types, Month 7 GMTs were numerically lower in MSM than in HM Over 99.5% of subjects were seropositive at Month 7 for each vaccine HPV type Administration of 9vHPV vaccine to both 16–26 year old men and women was generally well tolerated.

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Guevara et al. 2017 (91)	open-label extension of the pivotal efficacy study	young women 16–26 years of age	1) Inclusion (i) women aged 16–26 years (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: qHPV vaccine - Study Group: 9vHPV vaccine	1. Immunogenicity - seropositivity at 5 years post-vaccination: > 77.5-100% - Geometric mean titers at 1 week and 1 month post-dose 4 were 1.25–4.10 and 1.65–4.88-fold higher than levels observed 1 month following the completion of the three-dose primary series 
Petersen et al. 2017 (92)	A combined analysis of five phase III clinical trials	girls and boys 9–15 years of age and young women 16–26 years of age			1. Immunogenicity - Geometric mean titers were higher in girls and boys than in young women

(To be continued)

ID	Study Design / Primary Endpoints	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Signorelli et 2017 (93)	Meta-analysis	매우 다양			1. Efficacy and Immunogenicity - females aged 16–26 years for risk reduction against HSIL= 96.7% (95% CI 80–99.8)
Van Damme et al. 2016 (94)	a double-blind, randomized, controlled, with qHPV vaccine, immunogenicity and safety study of the 9vHPV vaccine Antibody (GMT) level	young men 16–26 years of age	Inclusion Criteria 1) in three countries (Belgium, Germany, and the Netherlands) 2) in good physical health 3) had a history of no more than five lifetime female and no male sexual partners	- Control: qHPV vaccine - Study: 9vHPV vaccine	1. The HPV 6/11/16/18 immune responses elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine. 2. All participants receiving the 9vHPV vaccine seroconverted for HPV 31/33/45/52/58. 3. The 9vHPV and qHPV vaccines showed comparable safety profiles.

KQ 1. Overall

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results																																																												
Setiawan et al. 2016 (95)	Meta-analysis two quadrivalent vaccine studies and eight bivalent-vaccine studies conducted in Asian countries	<table border="1"> <tr> <td>Authors</td> <td>Kang, 2007 (30)</td> <td>Konno, 2009 (31)</td> <td>Kim, 2010 (32)</td> <td>Bhatla, 2010 (33)</td> </tr> <tr> <td>Country</td> <td>Korea</td> <td>Japan</td> <td>Korea</td> <td>India</td> </tr> <tr> <td>Protocol number</td> <td>-</td> <td>NCT00316693</td> <td>NCT00290277</td> <td>NCT00344032</td> </tr> <tr> <td>Funding source</td> <td>Merck & Co Inc</td> <td>GSK</td> <td>GSK</td> <td>GSK</td> </tr> <tr> <td>Gender</td> <td>Female</td> <td>Female</td> <td>Female</td> <td>Female</td> </tr> <tr> <td>Patient age</td> <td>9-23</td> <td>20-25</td> <td>10-14</td> <td>18-35</td> </tr> </table> <table border="1"> <tr> <td>Ngan, 2010 (34)</td> <td>Kim, 2011 (35)</td> <td>Khatun, 2012 (36)</td> <td>Li, 2012 (37)</td> <td>Lim, 2013 (38)</td> <td>Zhu, 2014 (39)</td> </tr> <tr> <td>China (Hong Kong)</td> <td>Korean</td> <td>Bangladesh</td> <td>China</td> <td>Malaysia</td> <td>China</td> </tr> <tr> <td>NCT00306241</td> <td>NCT00485732</td> <td>-</td> <td>-</td> <td>NCT00345878</td> <td>NCT00779766</td> </tr> <tr> <td>GSK</td> <td>GSK</td> <td>Grameenphone Ltd</td> <td>Merck & Co Inc</td> <td>GSK</td> <td>GSK</td> </tr> <tr> <td>Female 18-35</td> <td>Female 15-25</td> <td>Female 9-13</td> <td>Female and male 9-45</td> <td>Female 18-35</td> <td>Female 18-25</td> </tr> </table>	Authors	Kang, 2007 (30)	Konno, 2009 (31)	Kim, 2010 (32)	Bhatla, 2010 (33)	Country	Korea	Japan	Korea	India	Protocol number	-	NCT00316693	NCT00290277	NCT00344032	Funding source	Merck & Co Inc	GSK	GSK	GSK	Gender	Female	Female	Female	Female	Patient age	9-23	20-25	10-14	18-35	Ngan, 2010 (34)	Kim, 2011 (35)	Khatun, 2012 (36)	Li, 2012 (37)	Lim, 2013 (38)	Zhu, 2014 (39)	China (Hong Kong)	Korean	Bangladesh	China	Malaysia	China	NCT00306241	NCT00485732	-	-	NCT00345878	NCT00779766	GSK	GSK	Grameenphone Ltd	Merck & Co Inc	GSK	GSK	Female 18-35	Female 15-25	Female 9-13	Female and male 9-45	Female 18-35	Female 18-25	<p>1) Inclusion</p> <p>Women who got Gardasil or Cervarix</p>	<p>- Control Group: unvaccinated</p> <p>- Study Group: vaccinated</p>	<p>1. Immunogenicity</p> <p>- HPV16/18 specific antibody conversion rate</p> <p>① uninfected population: HPV 16 risk ratio (RR) 85.69; (95% CI 31.51-233.04); HPV 18 RR 62.77 (37.4-105.51)</p> <p>② combined population (infected + uninfected): HPV16 RR 8.60 (6.95-10.64); HPV 18 RR 8.13 (5.96-11.11)</p> <p>2. Adverse Events</p> <p>- favorable safety profile</p>
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Artemchuk et al. 2019 (96)	Maternity Cohort STUDY	females aged 16-17 years	<p>1) Inclusion</p> <p>Women who got Gardasil or Cervarix</p>		<p>1. Efficacy and Immunogenicity</p> <p>- The median antibody levels were higher among Cervarix recipients 7-12 years post vaccination ($P < .0001$)</p> <p>**빨간점: cervarix, 파란점: Gardasil</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>A HPV-16</p> </div> <div style="text-align: center;"> <p>B HPV-18</p> </div> </div>																																																												

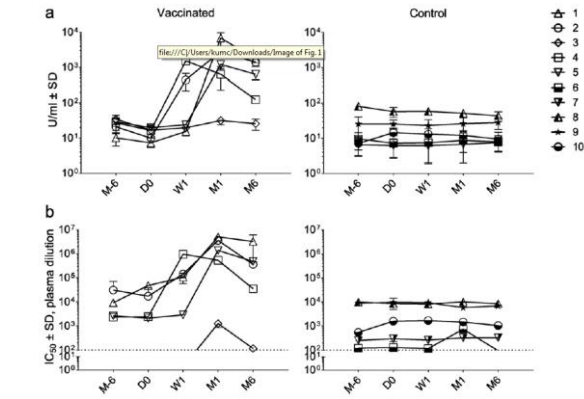
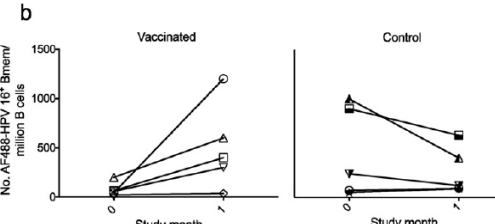
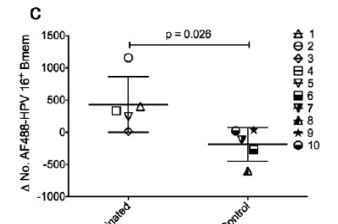
(To be continued)

<p>Dilley et al. 2020 (97)</p>	<p>A Society of Gynecologic Oncology Evidence-based Review</p>			<p>The World Health Organization (WHO) currently endorses a 3-dose schedule for those aged 15 years or older</p> <p>For those who do not receive the vaccine before after 15, vaccination is recommended in women aged 15-26 and men aged 15-21 in a three dose series with an expanded recommendation for high risk subsets of men through age 26</p> <p>FDA approved to expand the range of eligible patients for the nonavalent (9vHPV) vaccine to women and men from age 27 to 45 for the prevention of HPV-related cancers and diseases</p>																																																																																																										
<p>Arbyn et al. 2018 (98)</p>	<p>Meta-analysis</p>	<p>Randomized trials addressing vaccine efficacy typically enrolled young women (15–26 years) or mid-adult women (24–45 years).</p>	<p>women who received at least one dose or three doses of bivalent or quadrivalent HPV vaccine</p>	<p>1. Efficacy and Immunogenicity</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>hr HPV DNA- ≥ 1 dose</th> <th>HPV16/18 DNA- 3 doses</th> <th>Regardless of HPV ≥ 1 dose</th> </tr> </thead> <tbody> <tr> <td colspan="4">Age group 15-26</td> </tr> <tr> <td colspan="4">High-grade intraepithelial neoplasia associated with HPV16/18</td> </tr> <tr> <td>1</td> <td>CIN2+ 0.01 (0.00 to 0.05)^{b2q1} [Fig1] ⊕⊕⊕⊕</td> <td>0.07 (0.03 to 0.15)^{b4q2} [Fig2a] ⊕⊕⊕⊕</td> <td>0.46 (0.37 to 0.57)^{b1q2} [F3a] ⊕⊕⊕⊕</td> </tr> <tr> <td>2</td> <td>CIN3+ 0.01 (0.00 to 0.10)^{b1q1} ⊕⊕⊕⊕</td> <td>0.07 (0.02 to 0.29)^{b1q2} ⊕⊕⊕⊕</td> <td>0.55 (0.45 to 0.67)^{b1q1} ⊕⊕⊕⊕</td> </tr> <tr> <td>3</td> <td>AIS+ 0.10 (0.01 to 0.82)^{b1q1} ⊕⊕⊕</td> <td>0.12 (0.02 to 0.70)^{b1q2} ⊕⊕⊕</td> <td>0.36 (0.17 to 0.78)^{b1q1} ⊕⊕⊕</td> </tr> <tr> <td colspan="4">Any high-grade intraepithelial neoplasia irrespective of HPV types</td> </tr> <tr> <td>4</td> <td>CIN2+ 0.33 (0.25 to 0.43)^{b2} ⊕⊕⊕⊕ 0.57 (0.44 to 0.76)^{r1} 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<tr> <td>No protection: 1 included in CI</td> <td></td> </tr> <tr> <td>Adverse protection: RR>1 and 1 excluded from CI</td> <td></td> </tr> </tbody> </table>	Outcome	hr HPV DNA- ≥ 1 dose	HPV16/18 DNA- 3 doses	Regardless of HPV ≥ 1 dose	Age group 15-26				High-grade intraepithelial neoplasia associated with HPV16/18				1	CIN2+ 0.01 (0.00 to 0.05) ^{b2q1} [Fig1] ⊕⊕⊕⊕	0.07 (0.03 to 0.15) ^{b4q2} [Fig2a] ⊕⊕⊕⊕	0.46 (0.37 to 0.57) ^{b1q2} [F3a] ⊕⊕⊕⊕	2	CIN3+ 0.01 (0.00 to 0.10) ^{b1q1} ⊕⊕⊕⊕	0.07 (0.02 to 0.29) ^{b1q2} ⊕⊕⊕⊕	0.55 (0.45 to 0.67) ^{b1q1} ⊕⊕⊕⊕	3	AIS+ 0.10 (0.01 to 0.82) ^{b1q1} ⊕⊕⊕	0.12 (0.02 to 0.70) ^{b1q2} ⊕⊕⊕	0.36 (0.17 to 0.78) ^{b1q1} ⊕⊕⊕	Any high-grade intraepithelial neoplasia irrespective of HPV types				4	CIN2+ 0.33 (0.25 to 0.43) ^{b2} ⊕⊕⊕⊕ 0.57 (0.44 to 0.76) ^{r1} ⊕⊕⊕⊕	0.40 (0.25 to 0.64) ^{b2q1} ⊕⊕⊕⊕	0.70 (0.58 to 0.85) ^{b2q1} [F4a] ⊕⊕⊕⊕	5	CIN3+ 0.08 (0.03 to 0.23) ^{b2} ⊕⊕⊕⊕ 0.54 (0.36 to 0.82) ^{r1} ⊕⊕⊕⊕	-	0.55 (0.43 to 0.71) ^{b2} [Fig4] ⊕⊕⊕⊕ 0.81 (0.69 to 0.96) 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Evidence Table of Key Question 2

이미 HPV에 감염된 경우 예방백신 접종이 병변의 재발을 예방하는 효과가 있나?

KQ 2. 4가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Scherer et al. 2016 (39)	Randomized unblinded pilot study	healthy women, aged 27–45 years	1) Inclusion (i) healthy women, aged 27–45 years (ii) ≥ five heterosexual lifetime partners (iii) HPV 16 seropositive	- Control Group: unvaccinated group - Study Group: qHPV vaccine	1. Immunogenicity - Single vaccine dose boosted ① Ab levels 24- to 930-fold (median 77-fold)  ② memory B cell numbers 3- to 27-fold (median 6-fold).  

KQ 2. 2가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Szarewski et al. 2011 (38)	phase III double-blind, randomised controlled trial	women aged 15–25 years	1) Inclusion (i) Healthy women aged 15–25 years who reported no more than six lifetime sexual partners before study enrolment (ii) Women who agreed to adequate contraception over the vaccination period (iii) women were not screened for HPV exposure before study entry	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Efficacy and Immunogenicity - women HPV-16/18 DNA negative but with serological evidence of previous HPV-16/18 infection (seropositive) <ul style="list-style-type: none"> ① Vaccine efficacy against persistent infection: 6 month – 72.3% (95% CI 53.0–84.5) ② Vaccine efficacy against CIN1+: 67.2% (10.9-89.9) ③ Vaccine efficacy against CIN2+: 68.8% (-28.3-95.0) - women with no evidence of current HPV-16/18 infection (DNA negative), regardless of their baseline HPV-16/18 serological status <ul style="list-style-type: none"> ① Vaccine efficacy against persistent infection: 6 month – 88.7% (85.7-91.1) ② Vaccine efficacy against CIN1+: 89.1% (81.6-94.0) ③ Vaccine efficacy against CIN2+: 92.4% (84.0-97.0) - In women who were DNA positive for one vaccine type: the vaccine was efficacious against the other vaccine type. 2. Adverse Events - well tolerated in overall population

KQ 2. 9가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results																																															
Giuliano et al. 2019 (12)	Combined study of two RCTs	women aged 16–26 years	1) Inclusion (i) women aged 16–26 years (ii) 1–4 lifetime sexual partners (iii) no history of genital warts or cervical disease, active cervical disease	- Control Group: Historic placebo - Study Group: 9vHPV vaccine	<p>1. Efficacy and Immunogenicity</p> <p>- The reduction of incidence of cervical disease related to HPV 31, 33, 45, 52, or 58 among women positive at baseline for HPV 6, 11, 16, or 18 but negative for HPV 31, 33, 45, 52, and 58: any grade: 95.1%, 8.3 versus 168.3/10,000 person-years; high grade, 91.1%; 8.3 versus 93.4/10,000 person-years</p> <p>- The reduction of incidence of cervical disease related to HPV 6, 11, 16, or 18 among women negative at baseline for HPV 6, 11, 16, and 18 but positive for HPV 31, 33, 45, 52, or 58: any grade: 97.4%, 3.9 versus 154.4/10,000 person-years; high grade: 95.8%, 3.9 versus 93.7/10,000 person-years</p> <p>Table 5 Effect of 9vHPV vaccine on the reduction in incidence of cervical, vulvar, and vaginal disease; cervical biopsy; and definitive therapy procedures stratified by baseline HPV status (mITT population).</p> <table border="1"> <thead> <tr> <th rowspan="3">Endpoint</th> <th colspan="2">Day 1 PCR-positive to ≥1 of the indicated HPV types</th> <th colspan="2">Percent risk reduction^a (95% CI)</th> </tr> <tr> <th rowspan="2">HPV 6, 11, 16, or 18</th> <th rowspan="2">HPV 31, 33, 45, 52, or 58</th> <th colspan="2">[incidence rate (95% CI)^b 9vHPV (N = 6997); historic placebo (N = 8748)]</th> </tr> <tr> <th>Related to HPV 6, 11, 16, or 18</th> <th>Related to HPV 31, 33, 45, 52, or 58</th> </tr> </thead> <tbody> <tr> <td rowspan="6">Cervical disease, any grade</td> <td rowspan="3">No</td> <td>No</td> <td>99.0 (96.4–99.8) [1.1 (0.1–3.9); 106.4 (93.3–120.9)]</td> <td>96.9 (93.4–98.7) [3.2 (1.2–7.0); 104.3 (91.3–118.6)]</td> </tr> <tr> <td>Yes</td> <td>97.4 (85.6–99.9) [3.9 (0.1–22.0); 154.4 (110.8–209.5)]</td> <td>18.9 (–4.8–37.7) [420.9 (342.8–511.4); 519.1 (434.3–615.6)]</td> </tr> <tr> <td>No</td> <td>–2.2 (–32.7–20.7) [511.9 (423.0–614.0); 501.0 (416.7–597.3)]</td> <td>95.1 (81.9–99.1) [8.3 (1.0–30.0); 168.3 (121.8–226.7)]</td> </tr> <tr> <td rowspan="3">Yes</td> <td>Yes</td> <td>24.5 (–0.6–43.4) [663.4 (534.8–813.6); 879.1 (721.1–1061.3)]</td> <td>13.3 (–15.0–35.4) [682.3 (551.4–835.0); 787.0 (638.9–959.1)]</td> </tr> <tr> <td>No</td> <td>100 (96.1–100) [0.0 (0.0–2.0); 49.4 (40.6–59.6)]</td> <td>95.3 (88.4–98.4) [2.1 (0.6–5.5); 45.8 (37.4–55.6)]</td> </tr> <tr> <td>Yes</td> <td>95.8 (76.9–99.8) [3.9 (0.1–22.0); 93.7 (60.6–138.3)]</td> <td>6.8 (–32.6–34.6) [254.2 (195.3–325.2); 272.7 (213.4–343.4)]</td> </tr> <tr> <td rowspan="4">High-grade cervical disease</td> <td rowspan="2">No</td> <td>Yes</td> <td>–2.3 (–40.9–25.8) [333.6 (264.1–415.8); 326.2 (259.8–404.3)]</td> <td>91.1 (67.5–98.5) [8.3 (1.0–30.0); 93.4 (59.9–139.0)]</td> </tr> <tr> <td>Yes</td> <td>12.7 (–24.3–38.7) [455.2 (352.0–579.1); 521.4 (404.9–661.0)]</td> <td>–14.4 (–67.3–21.4) [462.9 (358.7–587.9); 404.5 (303.0–529.1)]</td> </tr> <tr> <td rowspan="2">Yes</td> <td>No</td> <td>94.9 (90.6–97.4) [5.3 (2.5–9.8); 103.1 (90.2–117.3)]</td> <td>98.2 (90.5–99.9) [0.5 (0.0–3.0); 29.4 (22.7–37.4)]</td> </tr> <tr> <td>No</td> <td>92.4 (76.4–98.0)</td> <td>51.1 (–27.5–83.1)</td> </tr> </tbody> </table>	Endpoint	Day 1 PCR-positive to ≥1 of the indicated HPV types		Percent risk reduction ^a (95% CI)		HPV 6, 11, 16, or 18	HPV 31, 33, 45, 52, or 58	[incidence rate (95% CI) ^b 9vHPV (N = 6997); historic placebo (N = 8748)]		Related to HPV 6, 11, 16, or 18	Related to HPV 31, 33, 45, 52, or 58	Cervical disease, any grade	No	No	99.0 (96.4–99.8) [1.1 (0.1–3.9); 106.4 (93.3–120.9)]	96.9 (93.4–98.7) [3.2 (1.2–7.0); 104.3 (91.3–118.6)]	Yes	97.4 (85.6–99.9) [3.9 (0.1–22.0); 154.4 (110.8–209.5)]	18.9 (–4.8–37.7) [420.9 (342.8–511.4); 519.1 (434.3–615.6)]	No	–2.2 (–32.7–20.7) [511.9 (423.0–614.0); 501.0 (416.7–597.3)]	95.1 (81.9–99.1) [8.3 (1.0–30.0); 168.3 (121.8–226.7)]	Yes	Yes	24.5 (–0.6–43.4) [663.4 (534.8–813.6); 879.1 (721.1–1061.3)]	13.3 (–15.0–35.4) [682.3 (551.4–835.0); 787.0 (638.9–959.1)]	No	100 (96.1–100) [0.0 (0.0–2.0); 49.4 (40.6–59.6)]	95.3 (88.4–98.4) [2.1 (0.6–5.5); 45.8 (37.4–55.6)]	Yes	95.8 (76.9–99.8) [3.9 (0.1–22.0); 93.7 (60.6–138.3)]	6.8 (–32.6–34.6) [254.2 (195.3–325.2); 272.7 (213.4–343.4)]	High-grade cervical disease	No	Yes	–2.3 (–40.9–25.8) [333.6 (264.1–415.8); 326.2 (259.8–404.3)]	91.1 (67.5–98.5) [8.3 (1.0–30.0); 93.4 (59.9–139.0)]	Yes	12.7 (–24.3–38.7) [455.2 (352.0–579.1); 521.4 (404.9–661.0)]	–14.4 (–67.3–21.4) [462.9 (358.7–587.9); 404.5 (303.0–529.1)]	Yes	No	94.9 (90.6–97.4) [5.3 (2.5–9.8); 103.1 (90.2–117.3)]	98.2 (90.5–99.9) [0.5 (0.0–3.0); 29.4 (22.7–37.4)]	No	92.4 (76.4–98.0)	51.1 (–27.5–83.1)
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			Related to HPV 6, 11, 16, or 18	Related to HPV 31, 33, 45, 52, or 58																																																
Cervical disease, any grade	No	No	99.0 (96.4–99.8) [1.1 (0.1–3.9); 106.4 (93.3–120.9)]	96.9 (93.4–98.7) [3.2 (1.2–7.0); 104.3 (91.3–118.6)]																																																
		Yes	97.4 (85.6–99.9) [3.9 (0.1–22.0); 154.4 (110.8–209.5)]	18.9 (–4.8–37.7) [420.9 (342.8–511.4); 519.1 (434.3–615.6)]																																																
		No	–2.2 (–32.7–20.7) [511.9 (423.0–614.0); 501.0 (416.7–597.3)]	95.1 (81.9–99.1) [8.3 (1.0–30.0); 168.3 (121.8–226.7)]																																																
	Yes	Yes	24.5 (–0.6–43.4) [663.4 (534.8–813.6); 879.1 (721.1–1061.3)]	13.3 (–15.0–35.4) [682.3 (551.4–835.0); 787.0 (638.9–959.1)]																																																
		No	100 (96.1–100) [0.0 (0.0–2.0); 49.4 (40.6–59.6)]	95.3 (88.4–98.4) [2.1 (0.6–5.5); 45.8 (37.4–55.6)]																																																
		Yes	95.8 (76.9–99.8) [3.9 (0.1–22.0); 93.7 (60.6–138.3)]	6.8 (–32.6–34.6) [254.2 (195.3–325.2); 272.7 (213.4–343.4)]																																																
High-grade cervical disease	No	Yes	–2.3 (–40.9–25.8) [333.6 (264.1–415.8); 326.2 (259.8–404.3)]	91.1 (67.5–98.5) [8.3 (1.0–30.0); 93.4 (59.9–139.0)]																																																
		Yes	12.7 (–24.3–38.7) [455.2 (352.0–579.1); 521.4 (404.9–661.0)]	–14.4 (–67.3–21.4) [462.9 (358.7–587.9); 404.5 (303.0–529.1)]																																																
	Yes	No	94.9 (90.6–97.4) [5.3 (2.5–9.8); 103.1 (90.2–117.3)]	98.2 (90.5–99.9) [0.5 (0.0–3.0); 29.4 (22.7–37.4)]																																																
		No	92.4 (76.4–98.0)	51.1 (–27.5–83.1)																																																

Evidence Table of Key Question 3

원추절제술을 시행받은 경우 예방백신 접종이 병변의 재발을 예방하는 효과가 있나?

KQ 3. 2가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results																																																							
Garland et al. 2016 (40)	Post-hoc analysis from RCT (PATRICIA)	women aged 15–25 years	1) Inclusion (i) Healthy women aged 15–25 years who reported no more than six lifetime sexual partners before study enrolment (ii) Women who agreed to adequate contraception over the vaccination period	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Efficacy and Immunogenicity - vaccine efficacy against subsequent HPV-related CIN2+ 60 days or more post-surgery: 88.2% (95% CI 14.8-99.7) - Vaccine efficacy against CIN11 associated with HPV-16 and/or HPV-18 after surgical therapy: 100% (95% CI 26.1-100) - vaccine efficacy against CIN11 irrespective of HPV genotype in the lesion: 42.6% (95% CI -22.1- 74.1)																																																							
Hildesheim et al. 2016 (41)	Post-hoc analysis from RCT (Costa Rica HPV Vaccine Trial)	women aged 18–25 years	2 groups of women. The first group : were infected with 1 or more of 12 oncogenic HPV types (defined herein), and who were randomized, vaccinated The second group: were randomized and vaccinated, who at some time during follow-up received LEEP treatment for cervical precancer,	- Control Group: hepatitis A vaccine - Study Group: Cervarix	1. Efficacy and Immunogenicity - Vaccine efficacy against HSIL+ after LEEP: -163.3% (95% CI -742-18) Impact of HPV-16/18 vaccination on recurrence of HPV infections and cervical lesions after LEEP (continued) <table border="1"> <thead> <tr> <th rowspan="2">HPV types</th> <th rowspan="2">Outcome</th> <th colspan="5">Overall analysis</th> <th colspan="3">Analysis restricted to newly detected HPV infections after treatment</th> </tr> <tr> <th>Arm</th> <th>Total no. events (# Prevalent/ # Incident)</th> <th>No. person-years</th> <th>Rate per 1000</th> <th>% vaccine efficacy</th> <th>95% CI</th> <th>Rate per 1000</th> <th>% vaccine efficacy (incident)</th> <th>95% CI (incident)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">HSIL+</td> <td rowspan="2"></td> <td>HPV</td> <td>10</td> <td>348</td> <td>28.7</td> <td rowspan="2">-163.3%</td> <td rowspan="2">[-742, 18]</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Ctrl</td> <td>4</td> <td>367</td> <td>10.9</td> <td></td> <td></td> <td></td> </tr> <tr> <td rowspan="2">CIN2+</td> <td rowspan="2"></td> <td>HPV</td> <td>3</td> <td>362</td> <td>8.3</td> <td rowspan="2">-55.5%</td> <td rowspan="2">[-834, 74]</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Ctrl</td> <td>2</td> <td>375</td> <td>5.3</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	HPV types	Outcome	Overall analysis					Analysis restricted to newly detected HPV infections after treatment			Arm	Total no. events (# Prevalent/ # Incident)	No. person-years	Rate per 1000	% vaccine efficacy	95% CI	Rate per 1000	% vaccine efficacy (incident)	95% CI (incident)	HSIL+		HPV	10	348	28.7	-163.3%	[-742, 18]				Ctrl	4	367	10.9				CIN2+		HPV	3	362	8.3	-55.5%	[-834, 74]				Ctrl	2	375	5.3			
HPV types	Outcome	Overall analysis						Analysis restricted to newly detected HPV infections after treatment																																																				
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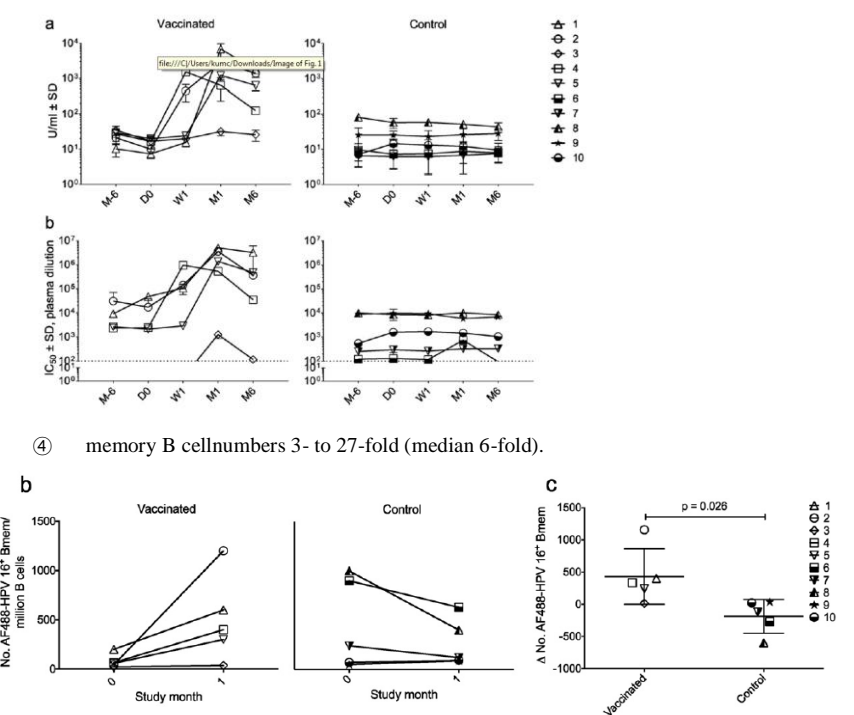
(To be continued)

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Bartels et al. 2020 (42)	Meta-analysis	5 studies comprising 2912 patients	1) inclusion (i) females 15 years or older having undergone surgical treatment for CIN (ii) reports on the outcome measure of recurrence of histologically proven CIN2+ post vaccination	- Control Group: placebo or unvaccinated group - Study Group: vaccinated group	1. Efficacy and Immunogenicity - incidence of CIN2+ in vaccinated group compared to control group: odd ratio (OR) 0.34 (95% CI 0.21-0.54) ① Pre-treatment vaccination: OR 0.4 (0.21-0.78) ② Adjuvant vaccination: OR 0.28 (0.14-0.56)
Del Pino et al. 2020 (46)	Retrospective study	265 women	1) Inclusion (i) History of Conization (ii) CIN (iii) f/u up to at least 24 months	- Jan 2013 to Jul 2017: 2v or 4vHPV vaccines - after Jul 2017: 9vHPV vaccine	Not distinguished by vaccine type (2v: 19.6%, 4v: 4.6%, 9v: 64.1%, unknown: 11.8%) 153 (57.7%) women accepted vaccination (vaccinated group) 112 (42.3%) refused the vaccine (non-vaccinated group) Persistent/recurrent HSIL - in vaccinated group: 3.3% - in non-vaccinated group: 10.7%, p = 0.015 HPV vaccination: reduced risk of persistent/recurrent HSIL (OR 0.2, 95%CI: 0.1-0.7, p = 0.010)

KQ 3. 4가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results																
Karimi-Zarchi et al. 2019 (43)	randomized controlled trial	women with histologically confirmed residual/recurrent CIN 1 or high-grade CIN (CIN 2-3)	1) Inclusion i) age 21-45 years ii) not pregnant iii) no abnormal results on a previous cervical smear test iv) no more than four sexual partners v) histologically confirmed residual/recurrent CIN 1 or high-grade CIN (CIN 2-3) vi) treated by conservative treatment.	- Control Group: no vaccine - Study Group: qHPV	1. Efficacy and Immunogenicity - Vaccine efficacy against CIN1-3: 58.7% (p=0.018) 2. Adverse Events - no serious adverse effects related to vaccination																
Ghelardi et al. 2018 (44)	prospective case-control study	women treated for CIN2+	1) Inclusion (i) Women underwent conization due to CIN2+	- Control Group: unvaccinated group (NV group) - Study Group: vaccinated group (V group)	1. Efficacy - HPV infection clearance rate at 6 months: 15.1% in V group vs 18.6% in NV group (p=0.387) - CIN2+ recurrence: <div style="text-align: center;"> <p>Cumulative incidence vs Time (months)</p> <table border="1"> <caption>CDR irrespective of causal HPV type (CIN2+)</caption> <thead> <tr> <th></th> <th>V-group</th> <th>NV-group</th> <th>% risk reduction in rate with vaccine</th> </tr> </thead> <tbody> <tr> <td>No. of evaluable women</td> <td>172</td> <td>172</td> <td></td> </tr> <tr> <td>No. of women with CDR</td> <td>2</td> <td>11</td> <td>81.2%</td> </tr> <tr> <td>recurrence rate (%)</td> <td>1.2</td> <td>6.4</td> <td>[95% CI: 34,3-95,7]</td> </tr> </tbody> </table> </div>		V-group	NV-group	% risk reduction in rate with vaccine	No. of evaluable women	172	172		No. of women with CDR	2	11	81.2%	recurrence rate (%)	1.2	6.4	[95% CI: 34,3-95,7]
	V-group	NV-group	% risk reduction in rate with vaccine																		
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recurrence rate (%)	1.2	6.4	[95% CI: 34,3-95,7]																		

(To be continued)

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Scherer et al. 2016 (39)	Randomized unblinded pilot study	healthy women, aged 27–45 years	1) Inclusion (i) healthy women, aged 27–45 years (ii) ≥ five heterosexual lifetime partners (iii) HPV 16 seropositive	- Control Group: unvaccinated group - Study Group: qHPV vaccine	1. Immunogenicity - Single vaccine dose boosted ③ Ab levels 24- to 930-fold (median 77-fold)  ④ memory B cell numbers 3- to 27-fold (median 6-fold).
Kang et al. 2013 (45)	Retrospective chart review	748 patients aged 20–45 years with histologically-confirmed CIN2–3 who had been treated by LEEP	Inclusion Criteria (a) histologically-confirmed CIN2–3 by LEEP (b) patients in whom both pre- and post-LEEP HR-HPV test results from the HPV DNA chip test and the hybrid capture II assay (c) patients who have not received the qHPV vaccine or the bHPV vaccine before diagnosis with CIN2–3 (d) patients who were followed for a minimum of 2 years		1. 36 (4.9%) patients developed recurrence - 9 patients (2.5%) in vaccination group vs. 27 patients (7.2%) in non-vaccination group 2. In patients infected with HPV 16 and/or 18 - 5 patients (2.5%) in vaccination group vs. 18 patients (8.5%) in non-vaccination group

KQ 3. 9가

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Del Pino et al. 2020 (46)	Retrospective study	265 women	1) Inclusion (i) History of Conization (ii) CIN (iii) f/u up to at least 24 months	- Jan 2013 to Jul 2017: 2v or 4vHPV vaccines - after Jul 2017: 9vHPV vaccine	Not distinguished by vaccine type (2v: 19.6%, 4v: 4.6%, 9v: 64.1%, unknown: 11.8%) 153 (57.7%) women accepted vaccination (vaccinated group) 112 (42.3%) refused the vaccine (non-vaccinated group) Persistent/recurrent HSIL - in vaccinated group: 3.3% - in non-vaccinated group: 10.7%, p = 0.015 HPV vaccination: reduced risk of persistent/recurrent HSIL (OR 0.2, 95%CI: 0.1–0.7, p = 0.010)

Evidence Table of Key Question (추가사항)

2가 백신과 9가 백신의 혼합 접종은 효과가 있나?

ID	Study Design	Participant	Inclusion & Exclusion Criteria	Intervention	Results
Gilca et al. 2018 (99)	randomised controlled trial Antibody (GMT) levels	371 girls and boys aged 9-10 years	1) Inclusion 1) no immunosuppression; 2) no coagulation problems; 3) no previous HPV vaccination; 4) no allergy to any vaccine component, and 5) not planning to move away from the Quebec City area during the next three years	(I) two doses of 9vHPV (II) a mixed schedule of 2vHPV + 9vHPV or 9vHPV + 2vHPV with a 6 month interval	<p>1. Efficacy and Immunogenicity</p> <p>The figure contains two bar charts. The top chart, titled 'Seropositivity', shows the percentage of participants with detectable antibodies for nine HPV types (HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58). The y-axis ranges from 0 to 120. For each type, three bars represent different schedules: 9vHPV * 2 (blue), 9vHPV in 1st + 2vHPV in 2nd (orange), and 2vHPV in 1st + 9vHPV in 2nd (grey). All bars are at approximately 100%. The bottom chart, titled 'GMT level', shows the Geometric Mean Titer on a logarithmic scale from 1 to 10,000. For each type, the same three schedules are compared. The 9vHPV * 2 schedule (blue) consistently shows the highest GMT levels, often exceeding 1,000, while the mixed schedules (orange and grey) show lower GMT levels, generally below 100.</p> <p>2. Adverse events - no differences between 2vHPV and 9vHPV</p>