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FACULTAD DE QUÍMICA

FARMACOVIGILANCIA DE LAS VACUNAS CONTRA EL VIRUS DEL PAPILOMA HUMANO, GARDASIL 4-VALENTE Y 9-VALENTE.

TRABAJO MONOGRÁFICO DE ACTUALIZACIÓN.

QUE PARA OBTENER EL TÍTULO DE:

QUÍMICA FARMACÉUTICO- BIOLÓGICA

PRESENTA:

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ABREVIATURAS

4-Valente	4-V
9-Valente	9-V
Ácido Desoxirribonucleico	ADN
Ácido Ribonucleico mensajero	ARNm
Administración de Alimentos y Drogas	FDA
Agencia Europea de Medicamentos	EMA
Buenas Prácticas Clínicas	BPC
Cáncer Cervicouterino	CCU
Centro Nacional de Farmacovigilancia	CNFV
Centros para el Control y la Prevención de Enfermedades	CDC
Colegio Americano de Obstetras y Ginecólogos	ACOG
Comisión Federal para la Protección contra Riesgos Sanitarios	COFEPRIS
Comité Asesor sobre Prácticas de Inmunización	ACIP
Comunidades Autónomas y Ciudades de Ceuta y Melilla	CCAA
Consejo de Organizaciones Internacionales de Ciencias Médicas	CIOMS
Dirección Ejecutiva de Farmacopea y Farmacovigilancia	DEFFV
Estados Unidos de América	EUA
Evento Adverso	EA
Eventos Adversos de Especial Interés	AESI
Eventos Adversos Después de la Inmunización	AEFI
Evento Adverso Supuestamente Atribuido a la Vacunación o Inmunización	ESAVI
Ministerio de Salud, Trabajo y Bienestar de Japón	MHLW
Neoplasia Intraepitelial Cervical	NIC

Normas Oficiales Mexicanas	NOM
Organización Mundial de la Salud	OMS
Organización Panamericana de la Salud	OPS
Partículas Similares a las del Virus	VPLs
Pharmacoepidemiologic General Research eXtension	PGRx
Programa Nacional de Inmunización	PNI
Reacciones Adversas	RA
Reacción Adversa a Medicamentos	RAM
Región Larga de Control	LCR
Respuestas Relacionadas con el Estrés por Inmunización	ISRR
Síndrome de Guillain-Barre	GBS
Sistema Canadiense de Vigilancia de Efectos Adversos Tras la Inmunización	CAEFISS
Sistema Federal Sanitario	SFS
Sistema de Notificación de Efectos Adversos de las Vacunas	VAERS
Sistema de Información de Eventos Adversos después de la Vacunación	SI-EAPV
Sistema de Vigilancia de los Eventos Adversos tras la Vacunación en la Comunidad	SAEFVIC
Sociedad Europea de Farmacovigilancia	ESoP
Sociedad Internacional de Farmacovigilancia	ISoP
Sospechas de Reacciones Adversas	SRA
Tromboembolismo Venoso	TEV
Virus del Papiloma Humano	VPH
Virus del Papiloma Humano de Alto Riesgo	VPH-AR
Virus del Papiloma Humano de Bajo Riesgo	VPH-BR

1. INTRODUCCIÓN

La Farmacovigilancia se considera como una de las actividades de la salud pública, destinada a la detección, identificación, cuantificación, evaluación y prevención de los posibles riesgos derivados del uso de los medicamentos yvacunas en seres humanos como lo son los eventos adversos (EA), las sospechas de reacciones adversas (SRA), las reacciones adversas (RA),los eventos supuestamente atribuibles a la vacunación o inmunización (ESAVI), o cualquier otro problema de seguridad relacionado con el uso de los medicamentosy vacunas (1).

Sin embargo, en la actualidad, no es posible detectar todos los posibles riesgos de las vacunas en los estudios de pre-comercialización, en especial aquellos que ocurren menos de un caso por cada 10,000 individuos, por lo tanto, es necesario continuar con la evaluación de la seguridad después de su salida al mercado, detectando de manera oportuna las señales mediante las actividades de la farmacovigilancia durante todo el ciclo de vida del producto, así como después de su uso (2,3).

La vacuna contra el Virus del Papiloma Humano (VPH) Gardasil 4-Valente (4-V) se introdujo a principios del año 2006 en E.U.A., seguida por Italia entre los años 2007 y 2008, como parte de una serie de estrategias para la prevención y el control del cáncer de cuello uterino, por lo que la Organización Mundial de la Salud (OMS) recomendó agregar esta vacuna en los programas nacionales de inmunización como una prioridad de salud pública (4,5,6).

Esta vacuna es de tipo viral recombinante, compuesta principalmente por partículas similares a las del virus (VPLs), en especial, la proteína de la cápside L1

combinada con un aluminio auxiliar. En 2014 se introduce la vacuna Gardasil 9-valente (9-V), diferente a la 4-V por la cantidad de genotipos del virus y la cantidad de adyuvante que contienen (2,3,7,8).

El VPH se ha relacionado con el desarrollo de cáncer cervicouterino (CCU), de vulva, vagina, orofaríngeo o ano, de los cuales el CCU ocupa el tercer lugar más frecuente de cáncer en la mujer, siendo los VPH 16 y 18 la causa principal del 70% de todos los CCU (6,7).

A pesar de que las vacunas se encuentran como uno de los mayores logros de salud pública, ya que permiten la erradicación y/o prevención de muchas enfermedades que son mortales o letales, y varios estudios enfatizando la eficacia,así como sus perfiles de seguridad, estos se han visto afectados por el crecimiento de los movimientos antivacunas y las numerosas controversias con respecto a sus EA posteriores a la inmunización (4).

Y aunque se publican con frecuencia informes de casos de EA después de recibir la vacuna asociándose temporalmente, esto no es suficiente información para inferir una relación de causa y efecto, pues se requiere de una epidemiologíasólida de datos que demuestren evidencia de causalidad a nivel de población, con pruebas de apoyo biológico, por otro lado, hasta la fecha con la información disponible por diversas organizaciones no se ha detectado algún problema evidente de seguridad que altere su recomendación para el uso de estas vacunas (2,3).

1. 1 PLANTEAMIENTO DEL PROBLEMA

Se ha despertado gran interés y preocupación en la población de todo el mundo respecto a los eventos adversos atribuidos a la inmunización contra el VPH,

llegando al extremo de suspender campañas de vacunación en algunos países (9, 10, 11, 12, 13, 14), por lo que en este trabajo se plantea identificar y analizar la información reciente que describa el perfil de seguridad de las vacunas Gardasil 4-V y 9-V a través de artículos publicados en el periodo 2015-2020, en bibliotecas electrónicas como PubMed, Trip Medical Database, Medigrafic y Google Scholar.

1. 2 OBJETIVO GENERAL

Realizar una revisión bibliográfica sobre el perfil de seguridad de las vacunas Gardasil 4-V y 9-V contra el VPH en el periodo comprendido de 2015 -2020.

1.3 OBJETIVOS ESPECÍFICOS

- Actualizar la información referente a la farmacovigilancia de las vacunas del virus del papiloma humano, Gardasil 4-V y 9-V.
- Revisar e identificar cuáles son los Eventos Adversos Supuestamente Atribuidos a la Vacunación o Inmunización de la vacuna contra el virus del papiloma humano Gardasil 4-V y 9-V, y clasificarlos de acuerdo con la gravedad.
- Realizar una revisión de las estrategias empleadas en la detección de los Eventos Adversos tras la vacunación contra el virus del papiloma humano.
- Evidenciar los problemas relacionados con la seguridad de las vacunas Gardasil 4-V y 9-V y el análisis de las acciones tomadas que orillaron a una suspensión temporal de la campaña de vacunación.

2. ANTECEDENTES

2.1 SURGIMIENTO DE LA FARMACOVIGILANCIA.

La Farmacovigilancia es definida por la OMS como la ciencia y actividades relacionadas con la detección, evaluación, entendimiento y prevención de efectos adversos o de cualquier otro problema relacionado con los medicamentos (15).

Por lo que, para llevar a cabo estas actividades se requiere de sistemas internacionales de farmacovigilancia destinados a controlar la relación riesgo/beneficio de los medicamentos, mejorando la seguridad del paciente y su calidad de vida (16).

La Farmacovigilancia surge debido a un número importante de eventos desafortunados, de los primeros casos documentados se encuentra el de una joven en Inglaterra (1848) que murió tras recibir cloroformo como anestésico, previo a la extracción de la uña del pie infectada. Desafortunadamente, se siguieron presentando casos mortales similares, como consecuencia la revista *TheLancet* creó una comisión para abordar este problema, advirtiendo a los demás médicos ingleses que debían denunciar las muertes causadas por la anestesia con este fármaco, creando de este modo una recopilación de los eventos relacionados con este producto, publicando los resultados hasta el año 1893 (16).

En 1937, se produjeron 107 muertes en los Estados Unidos de América (EUA), debido al uso del elixir de sulfanilamida, un antibiótico que incluía en su formulación dietilenglicol como disolvente, después de la investigación correspondiente se atribuyó la causa de las muertes a la toxicidad de dichoexcipiente (15, 16).

En consecuencia, en 1938 se estableció la Ley Federal de Alimentos, Medicamentos y Cosméticos, cuyo objetivo era renovar el sistema de salud pública, el nuevo sistema preveía que la seguridad de los medicamentos debía demostrarse antes de su aprobación en el mercado e introdujo la posibilidad de realizar inspecciones en las fábricas (16).

En el año 1961, se evidenció con más impacto la necesidad de realizar farmacovigilancia tras la tragedia de la talidomida, medicamento usado como sedante y antiemético durante los primeros tres meses de embarazo (16).

El Dr. Lenz publicó en una revista alemana (Welt am Sonnatag) sus observaciones sobre la correlación entre las malformaciones de los bebés y la talidomida. Al mismo tiempo el Dr. McBride, un médico australiano, escribió una carta al director de la revista *The Lancet,* en la que sugería la misma idea, él observó que la incidencia de malformaciones congénitas de los bebés había aumentado de 1.5% hasta un 20% en las mujeres que habían tomado talidomida durante el embarazoy no fue hasta 1973 que un estudio retrospectivo mostró la correlación entre las malformaciones congénitas de los bebés y la ingestión de talidomida durante el embarazo (16).

La tragedia de la talidomida evidenció muchos problemas y generó críticas, en particular, la fiabilidad de los ensayos con animales, el comportamiento de la Industria y la importancia de vigilar los medicamentos después de su comercialización. Esta tragedia cambió el sistema de farmacovigilancia, ya que hizo que la notificación espontánea de las reacciones adversas a los medicamentos (RAM) pasará a ser sistemática, organizada y regulada (15, 16).

La OMS convocó a la 16a Asamblea Mundial de la Salud tras tener como principal preocupación la necesidad de un medio para la rápida comunicación de las SRAM, a partir de esta asamblea, el Reino Unido inició el sistema de Tarjeta Amarilla, estrategia con la cual se emprendía el reporte de Reacciones Adversas (RA) (16).

En 1968 se implementó un proyecto piloto de Monitoreo Internacional de Medicamentos en el cual se debía recolectar la mayor cantidad de reportes de RA en una base de datos, acordando con la OMS y el gobierno sueco, que las actividades de dicho programa fueran realizadas en Uppsala, Suecia, contribuyendo enormemente al desarrollo de la farmacovigilancia en el mundo (16).

A partir de este punto diferentes regiones comenzaron con la creación de diferentes asociaciones, por ejemplo, la Sociedad Europea de Farmacovigilancia (ESoP), convertida en la Sociedad Internacional de Farmacovigilancia (ISoP) en 1992, la Agencia Europea del Medicamento (EMA) en 1995, ambas con el objetivo de promover la farmacovigilancia y mejorar todos los aspectos del uso seguro y adecuado de los medicamentos (15, 16).

En 2001 se da la creación de una base de datos europea oficial, EudraVigilance, que es usada actualmente para gestionar y analizar la información sobre lasSRAM detectadas después de su comercialización o que están siendo estudiadas en ensayos clínicos (16).

La historia ha demostrado la importancia de contar con sistemas de farmacovigilancia y a pesar de los esfuerzos de distintas organizaciones por impulsar su desarrollo, esta disciplina es muy joven en algunos países e invisible para otros, lo cual incrementa el riesgo a la sociedad consumidora de

medicamentos de muchas naciones. Es de gran importancia que todos los países, especialmente en Latinoamérica, implementen estrategias para el desarrollo de la farmacovigilancia, adaptadas a su sociedad (16).

En el caso particular de México, la farmacovigilancia dio inicio con el Programa de Notificación Voluntaria de Sospecha de Reacción Adversa a Medicamentos (SRAM) en el año de 1989, dirigido por la Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), en ese entonces llamado Dirección General de Insumos para la Salud (17).

Un organismo que tiene por objeto organizar y armonizar las acciones en materia de regulación, control, vigilancia y fomento sanitario, sin embargo, no fue hasta que se creó el Centro Nacional de Farmacovigilancia (CNFV) en México, que el programa de farmacovigilancia presentó un crecimiento (17).

El CNFV es dependiente de la Secretaría de Salud que organiza y unifica las actividades de este tipo en el país a través del Sistema Federal Sanitario (SFS), quien coordina a nivel federal a las entidades federativas y cuenta con los Centros Estatales de Farmacovigilancia para la ejecución de las actividades de farmacovigilancia, en apego a la *NOM-220-SSA1-2016*, *Instalación y operación de la farmacovigilancia*, de manera coordinada con el CNFV (17).

De manera general, en México, la regulación de las actividades de Farmacovigilancia, se rigen de la siguiente forma:

1. *Constitución Política de los Estados Unidos Mexicanos*

   Art. 4°- Toda persona tiene derecho a la protección de la Salud.

2. *Ley General de la Salud*

Art. 58 V Bis: Establece que se debe información a las autoridades sanitarias acerca de efectos secundarios y reacciones adversas por el uso de medicamentos y otros insumos para la salud o el uso, desvío o disposición final de sustancias tóxicas o peligrosas y sus desechos.

Art 222 Bis: Para la obtención del registro sanitario de medicamentos biotecnológicos se deberá cumplir con los requisitos y pruebas que demuestren la calidad, seguridad y eficacia del producto y una vez comercializado el medicamento biotecnológico se deberá realizar la farmacovigilancia de este conforme a la normatividad correspondiente.

3. *Reglamento de Insumos a la Salud*

Art. 38: Las reacciones adversas de los medicamentos u otros insumos que se presenten durante la comercialización o uso de éstos, las notificadas por los profesionales de la salud, las publicadas en la literatura científica y las reportadas por los organismos sanitarios internacionales, deberán hacerse del conocimiento inmediato de la Secretaría por el titular del registro, por los distribuidores o comercializadores de los insumos.

Art. 131: Podrán importar insumos registrados para su comercialización, las personas que cuenten con las instalaciones adecuadas para el manejo seguro de los mismos y que garanticen el control de su calidad y farmacovigilancia, de acuerdo con los requisitos.

4. *Reglamento de la COFEPRIS*

   Artículo 12: Corresponde a la comisión de evidencia y manejo de riesgos.

5. *NOM-220-SSA1-2016. Instalación y operación de la Farmacovigilancia (1).*

2.2 GENERALIDADES DE LA *NOM-220-SSA1-2016.*

Instalación y operación de la Farmacovigilancia.

Las Normas Oficiales Mexicanas (NOM) son regulaciones técnicas de observancia obligatoria expedidas en los Estados Unidos Mexicanos y tienen como finalidad establecer las características que deben reunir los procesos o servicios cuando estos puedan constituir un riesgo para la seguridad de las personas o dañar la salud humana; así como aquellas relativas a terminología y las que se refieran asu cumplimiento y aplicación (18).

La *NOM-220-SSA1-2016* fue publicada en el Diario Oficial de la Federación el 23 de septiembre de 2016 en cumplimiento del acuerdo del Comité Consultivo Nacional de Normalización de Regulación y Fomento Sanitario y de lo previsto en el artículo 47, fracción I de la Ley Federal sobre Metrología y Normalización. Tienepor objetivo establecer los lineamientos para la instalación y operación de laFarmacovigilancia en el territorio nacional (1).

La Farmacovigilancia se considera como las actividades de la salud pública, destinadas a la detección, identificación, cuantificación, evaluación y prevención de los posibles riesgos derivados del uso de los medicamentos y vacunas en seres humanos (1).

Por lo tanto, es una actividad de responsabilidad compartida entre todos losagentes relacionados con los medicamentos y vacunas, aplicando a las dependencias y entidades de la Administración Pública Federal y local, las personas físicas o morales de los sectores social y privado, que formen parte del Sistema Nacional de Salud, profesionales de la salud, instituciones o establecimientos que realicen investigación para la salud en seres humanos, titulares del registro sanitario o sus representantes legales, distribuidores y comercializadores de los medicamentos, incluyendo vacunas, que se utilicen en el tratamiento de seres humanos (1).

Debido a lo anterior, la Farmacovigilancia requiere de la colaboración de lospaíses miembros del Programa Internacional de Monitoreo de los Medicamentos, del cual México es miembro; y por ende depende del compromiso y la responsabilidad de todos y cada uno de los profesionales de la salud, lo que obviamente redunda en beneficios para la humanidad (1).

El uso terapéutico de un medicamento o vacuna se basa en criterios de eficacia, calidad y seguridad, tomando en cuenta la perspectiva de la relación beneficio/riesgo. De manera general, los medicamentos y vacunas son seguros cuando sus riesgos se consideran aceptables con relación al beneficio profiláctico y terapéutico que aportan, es decir, cuando el patrón de RA resulta tolerable (1).

De acuerdo con la *NOM-220-SSA1-2016*, una vacuna se define como la preparación biológica destinada a generar inmunidad contra una enfermedad mediante la producción de anticuerpos, para eliminar, prevenir o controlar estados patológicos (1).

Las cuales pueden generar diversos Eventos Adversos (EA), considerados como cualquier suceso médico indeseable que pueda presentarse en un sujeto de investigación durante la etapa de investigación clínica de un medicamento o vacuna pero que no necesariamente tiene una relación causal con el mismo (1).

Por otra parte, el Evento Adverso Supuestamente Atribuido a la Vacunación o Inmunización (ESAVI) se refiere a la(s) manifestación(es) clínica(s) o evento médico que ocurren después de la vacunación y son supuestamente atribuidos a la vacunación o inmunización en las cuales la temporalidad dependerá de cada una de las vacunas (1).

Mismas que se pueden detectar a través de información que surge de una o más fuentes documentales, incluyendo observaciones y experimentos, la cual sugiere una asociación causal potencialmente nueva o un nuevo aspecto de una asociación previamente conocida entre una intervención y un evento o conjunto de eventos relacionados que se considera suficiente para justificar una acción de verificación de la información, esto conocido como una señal (1).

En la *NOM-220-SSA1-2016* también se describe a lo conocido como una Sospecha de Reacción Adversa a los Medicamentos (SRAM), como, cualquier manifestación clínica o de laboratorio no deseada que ocurra después de la administración de uno o más medicamentos y una Reacción Adversa a un Medicamento (RAM) como a la respuesta no deseada a un medicamento, en la cual la relación causal con éste es, al menos, razonablemente atribuible (1).

Estos términos antes mencionados (ESAVI, SRAM, RAM, EA) o algún otro problema de seguridad relacionado con el uso de medicamentos o vacunas se les clasifica de acuerdo con:

La intensidad de la manifestación clínica:

- **Leves.** Se presentan con signos y síntomas fácilmente tolerados, no necesitan tratamiento, no requieren ni prolongan la hospitalización y no requiere de la suspensión del medicamento causante.
- **Moderadas**. Interfiere con las actividades habituales (pueden provocar bajas laborales o escolares), sin amenazar directamente la vida del paciente. Requiere de tratamiento farmacológico y puede o no requerir la suspensión del medicamento causante.
- **Severas.** Interfiere con las actividades habituales (pueden provocar bajas laborales o escolares). Requiere de tratamiento farmacológico y la suspensión del medicamento causante (1).

Y la gravedad de un caso SRAM, RAM, EA o ESAVI:

- **Graves**

Toda manifestación clínica que se presenta con la administración de cualquier dosis de un medicamento incluyendo vacunas, y que:

I. Causan la muerte del paciente.
II. Ponen en peligro la vida del paciente en el momento mismo que se presentan.
III. Hacen necesario hospitalizar o prolongar la estancia hospitalaria.
IV. Son causa de invalidez o de incapacidad permanente o significativa.
V. Son causa de alteraciones o malformaciones en el recién nacido.
VI. Son considerados médicamente importantes.

- **No Graves**

A las SRAM, RAM, EA o ESAVI o algún otro problema de seguridad relacionado con el uso de medicamentos y vacunas que no cumplan los criterios de gravedad especificados anteriormente (1).

Además, el Consejo de Organizaciones Internacionales de Ciencias Médicas (Council for International Organizations of Medical Sciences: CIOMS) (20) clasifica también a las RAMs de acuerdo con la frecuencia que estas presentan, como lo muestra la **tabla 1**:

Tabla 1. Clasificación de acuerdo con la CIOMS en base a la frecuencia de las RAMs.

RAM	n expuestos para 1 RAM	% de los expuestos
Muy Frecuente	>1:10	10% o más
Frecuente	>1:10 a >1:100	Entre 1.0-10%
Infrecuente	>1:100 a >1:1 000	Entre 0.1-1.0%
Rara	>1:1 000 a >1:10 000	Entre 0.01-0.1%
Muy Rara	>1: 10 000	Menor a 0.01%

Es deber de los profesionales de la salud notificar todas las sospechas de SRAM, RAM, EA, ESAVI u otros problemas de seguridad relacionados con el uso de medicamentos y vacunas, tanto esperadas como inesperadas, que se presenten en forma directa, a los centros o las unidades de Farmacovigilancia, utilizando la metodología para la notificación estipulada. De tal modo que la notificación debe llevarse a cabo durante todo el ciclo de vida de un medicamento o vacuna (1).

2.3 SEGURIDAD DE LAS VACUNAS EN LOS ENSAYOS CLÍNICOS.

Los ensayos clínicos son una forma importante y muy especializada de ensayo biológico, diseñados específicamente para medir la eficacia terapéutica y detectar los efectos adversos de los medicamentos (incluidas las vacunas), y tienen como objetivo comparar la respuesta de un grupo de pacientes que recibe un nuevo

tratamiento con la respuesta de un grupo control que recibe un tratamiento "estándar", el cual para el caso de las vacunas puede ser una vacuna usada en la actualidad, un placebo (el placebo puede ser una solución salina o vacuna indicada para otra enfermedad) o ningún tratamiento (21).

En general, la seguridad de las vacunas es controlada por el fabricante, las autoridades de salud pública, las agencias reguladoras y el mundo académico de forma deliberada y exhaustiva. Por lo que, en primer lugar, el fabricante utiliza un protocolo de estudio detallado para recoger datos de ensayos clínicos realizados antes de la concesión de la licencia (23).

Una vez que es autorizada por las agencias reguladoras, el fabricante es responsable de evaluar rutinariamente los informes de EA clínicamente significativos de forma periódica. Además, las autoridades de salud pública y las agencias reguladoras también suelen financiar y realizar estudios independientes, basados en la población, a menudo en colaboración con centros médicos académicos (23).

Los ensayos clínicos presentan diferentes etapas divididas en estudios de pre-comercialización, donde están incluidos los estudios preclínicos y la Fase I a III, y estudios de post-comercialización la cual incluye únicamente la fase IV, del cual más adelante se muestra un resumen en la **tabla 2** (21).

ESTUDIOS DE PRE-COMERCIALIZACIÓN.

Los ensayos clínicos son la principal fuente de información acerca de la seguridad de las vacunas y al implicar la participación de seres humanos estos estudios están sujetos a una normativa internacional de calidad científica y ética dirigida al diseño, realización, registro y redacción de informes de este tipo de estudios,

denominada Buenas Prácticas Clínicas (BPC). Su cumplimiento asegura la protección de los derechos, la seguridad y el bienestar de los individuos participantes, y garantiza la calidad científica de los datos obtenidos en un ensayo clínico (24).

Además de la adecuación de la investigación a los principios éticos de la Declaración de Helsinki de la Asociación Médica Mundial que rigen la realización de las investigaciones biomédicas en seres humanos y cuyo escrupuloso cumplimiento permite que dichos estudios sean aceptados por las autoridades de la mayoría de los países (24).

ESTUDIOS PRECLÍNICOS: El objetivo de esta fase es satisfacer todos los requisitos que deben cumplirse antes de que un nuevo compuesto se considere listo para ser probado por primera vez en humanos, sin exponerlos a riesgos injustificados (24).

En esta fase se selecciona una o varias vacunas candidatas en las que se realizan estudios que emplean sistemas de cultivos de tejidos o cultivos de células (in vitro) y pruebas en animales (in vivo) que deben incluir pruebas en roedores (ratones o ratas) y no roedores (perros, conejos, monos etc.) para evaluar su seguridad y la capacidad de provocar una respuesta inmunológica (21, 22, 24).

FASE I: En esta fase se realiza la primera administración de la vacuna a seres humanos y está enfocada en la evaluación de su seguridad en pacientes sanos, ya que esta población presenta menos variaciones fisiológicas. El número de sujetos de investigación es aproximadamente entre 20-80 personas y evalúa inicialmente la seguridad, efectos biológicos, la inmunogenicidad, dosis y vías de administración (21, 22, 24).

FASE II: La fase II ocurre cuando en la fase I se han obtenido resultados confiables y requiere de un grupo más grande de humanos. En su mayoría son estudios experimentales y tienen como propósito valorar la eficacia. El número de sujetos de investigación aumenta a un intervalo de 100 a 300 o 200 y 500personas y tiene como objetivo estudiar la dosis propuesta, seguridad, capacidad inmunogénica y la vía de administración (21, 22, 24).

FASE III: En esta fase, los estudios clínicos son llevados a cabo porinvestigadores calificados que controlan una gran población de pacientes congrandes variaciones en sus características (genética, sexo, edad, masa corporal). El número de sujetos de investigación pueden incluir cientos de miles de humanosen uno o varios países a través de pruebas aleatorias y doble ciego, e involucranla vacuna experimental que se prueba contra un placebo (el placebo puede seruna solución salina, una vacuna para otra enfermedad o alguna otra sustancia) (21, 22, 24).

En general es el paso anterior a la aprobación de una vacuna y tiene como objetivo evaluar de forma más completa la seguridad, la eficacia en la prevención de las enfermedades en la población diana, inmunogenicidad y la reactogenicidad, debido a la variación de características presentes, es decir, en la presente etapa se confirman los resultados obtenidos en las fases anteriores, además de aportar datos convincentes del beneficio/ riesgo (21, 22, 24).

Durante la solicitud de autorización de la vacuna, la Autoridad Reguladora Nacional, lleva a cabo la evaluación documental de los resultados recabados en laetapa de precomercialización para poder otorgar el registro o negarlo (21, 22, 24).

FASE IV O ESTUDIOS DE POST-COMERCIALIZACIÓN: En esta fase los sujetos de investigación son la población en general, ya que en los ensayos clínicos de las fases anteriores se excluyen poblaciones con determinadas enfermedades crónicas, tratamientos farmacológicos, niños, mujeres embarazadas y la administración de vacunas fuera del rango de edad recomendado, además no posee el alcance estadístico para detectar EA clasificados como “infrecuentes” o “muy raros” (>1: 10 000 o >0.01%). Debido a lo anterior mencionado, se puede obtener un perfil más real de la vacuna, permitiendo conocer los posibles riesgos (21, 22, 24).

Tabla 2. Principales actividades emprendidas en cada fase de los ensayos clínicos.

DESCUBRIMIENTO DEL FARMACO	DESARROLLO PRE-CLINICO	DESARROLLO CLÍNICO			APROBACIÓN POR LAS AUTORIDADES SANITARIAS	FASE IV
• Selección de la diana • Búsqueda de la molécula de partida • Optimización de la molécula partida • Evaluación de las características farmacológicas	• Farmacocinética • Toxicología a corto plazo • Formulación • Síntesis a gran escala	FASE I Farmacocinética, Tolerabilidad, Efectos secundarios en voluntarios sanos.	FASE II Ensayos a pequeña escala en pacientes para valorar eficacia y dosis de estudios toxicológicos a largo plazo.	FASE III Ensayos clínicos controlados a gran escala.	Se remiten los datos completos y son revisados por las autoridades sanitarias.	Vigilancia tras la comercialización.
2 a 5 años	1 a 5 años	5 a 7 años			1 a 2 años	
100 proyectos →	20 compuestos	→ 10	→ 5	→ 3	→ 1.2	→ 1
	↓ Candidato a Fármaco	↓ Desarrollo del compuesto			↓ Presentación reglamentaria	↓ Medicamento aprobado para su comercialización

Fuente: Rang, R., Ritter, J., Flower, R., & Henderson, G. Rang & Dale Farmacología. Octava edición. Londres: Elsevier; (2016). p.718-722.

2.4 INTRODUCCIÓN A LAS VACUNAS CONTRA EL VPH.

Las vacunas son medicamentos que se definen como una preparación biológica con el objetivo de generar inmunidad contra una enfermedad mediante la producción de anticuerpos para eliminar, prevenir o controlar estados patológicos (1).

Existen tres métodos principales para el diseño una vacuna:

I. **Agente patógeno íntegro (sea virus o bacterias):**

- **Vacunas inactivadas.**

Este tipo de vacunas se realizan inactivando o destruyendo el virus o la bacteria patógena por medio de sustancias químicas como calor o radiación con el fin de aislarlo. La técnica suele conllevar tiempos de fabricación relativamente largos, y por lo general las vacunas resultantes deben aplicarse en pautas de dos o tres dosis (25).

- **Vacunas atenuadas.**

Para diseñar estas vacunas se utilizan los virus o bacterias patógenas o algún semejante manteniéndolos activos pero debilitados con técnicas parecidas a las vacunas inactivadas; sin embargo, debe aplicarse con precaución ya que en ocasiones no es conveniente inmunizar a las personas inmunodeprimidas debido al riesgo de complicaciones potencialmente graves (25).

- **Vacunas basadas en vectores víricos.**

En el diseño de esta vacuna se usa el virus inocuo para transportar fragmentos específicos del agente patógeno de interés, induciendo una respuesta inmunitaria sin llegar a causar la enfermedad, esto se logra fabricando fragmentos específicos del agente patógeno de interés en un virus inocuo. Una vez hecho esto, el virus inocuo sirve como una plataforma o transporte (vector) para introducir el fragmento

específico de interés en el organismo, produciendo posteriormente una respuesta inmunitaria (25).

II. Subunidad antigénica (sea virus o bacterias)

Son aquellas en las que solamente se utilizan fragmentos específicos, es decir, subunidades antigénicas del virus o la bacteria que es indispensable que el sistema inmunitario reconozca. Estas vacunas no contienen el agente patógeno íntegro ni utilizan un virus inocuo como vector y las subunidades antigénicas suelen ser proteínas o hidratos de carbono (25).

III. El método genético (o vacunas de ácido nucleico)

A diferencia de los métodos anteriores, en las vacunas de ácido nucleico se inocula directamente el Ácido Desoxirribonucleico (ADN) que codifica el antígeno que nos interesa mediante la previa inserción de él en los genes, siguiendo como primer paso la transcripción de ADN en Ácido Ribonucleico mensajero (ARNm) en nuestras células que, posteriormente, se traduce para la fabricación de proteínas específicas, la cuales necesitamos que el sistema inmunitario reconozca y contrala que se inducirá una respuesta (25).

Gracias a estos métodos, se han abierto paso a nuevos tipos de vacunas, como la de interés para el presente trabajo, las cuales utilizan el método por vacuna recombinante. Un nuevo tipo de vacuna que requiere de la identificación del antígeno, como primer punto, el cual pueda dar lugar a una respuesta protectora (26, 27).

Posteriormente se realiza la detección y la obtención del genoma responsable de

la elaboración de este antígeno para que dicha porción del genoma se ha insertada en otro microorganismo (p. ej., *Saccharomyces cerevisiae*) que pueda fabricar el antígeno deseado en grandes cantidades, dando como último paso la obtención del antígeno purificado que, en combinación con sus correspondientes excipientes, generará una vacuna absolutamente segura (27).

VIRUS DEL PAPILOMA HUMANO. (VPH)

Los VPH pertenecen a un grupo de virus denominado *Papillomavirus*, ubicado taxonómicamente en la familia *Papillomaviridae*, son virus pequeños, no envueltos con genoma de ADN de doble cadena en configuración circular que tienen afinidad por el tejido epitelial (13).

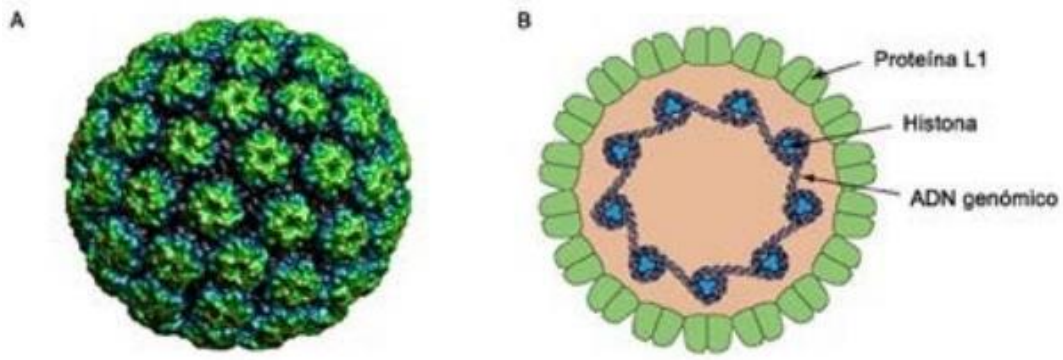

Figura 1. Estructura de los papilomavirus. Se muestra en el inciso A) la imagen en 3D de un virión que ha sido reconstruido por medios informáticos a partir de imágenes obtenidas por microscopía crioelectrónica y de la proteína L1 cristalizada. B) Muestra el diagrama de la cápside del VPH, donde se observa la proteína principal de la cápside, la proteína L1, así como el genoma viral empaquetado con histonas celulares.

El genoma de los *Papillomavirus* se compone de una región de transcripción temprana “E” (Early), que dan origen a proteínas no estructurales, los genes E1, E2, E4, E5, E6 y E7, una región tardía “L” (Late) que dan origen a dos proteínas estructurales los genes L1, L2, y una región larga de control (LCR) la cual es una región reguladora no codificante, ilustradas en la **figura 1 y 2** (13).

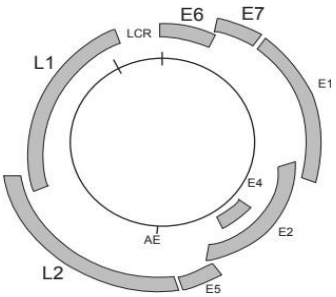

Figura 2. Mapa genómico del genotipo VPH-16. Se destacan en mayor tamaño los genes importantes en la producción de vacunas.

Estos genes tienen diferentes funciones o actividades asociadas, las cuales son mencionadas en la **tabla 3**:

Tabla 3. Proteínas del VPH y funciones asociadas.

TIPO DE PROTEÍNA	NOMBRE	FUNCIÓN O ACTIVIDADES ASOCIADAS
NO ESTRUCTURALES	E1	Tiene funciones de helicasa. Es esencial para la transcripción y replicación.
	E2	Esencial para replicación y transcripción viral, segregación genómica y encapsidación.
	E4	Regula la expresión de genes tardíos, controla la maduración viral y la salida de los viriones
	E5	Estimula la actividad transformante de E6 y E7, promueve la fusión celular generando aneuploidía e inestabilidad cromosómica, contribuye a la invasión de la respuesta inmunitaria.
	E6	Se une e induce la degradación de la proteína supresora de tumores p53, inhibiendo la apoptosis; interactúa con proteínas del sistema inmunitario innato, contribuye a la evasión de la respuesta inmunitaria y a la persistencia del virus; activa la expresión de la telomerasa.
	E7	Se une e induce la degradación de la proteína supresora de tumores pRB; incrementa la actividad de cinasa dependientes de ciclinas; afecta la expresión de genes en la fase S por la interacción directa con factores de transcripción E2F y con histonas desacetilasa; contribuye a la evasión de la respuesta inmunitaria.
ESTRUCTURALES	L1	Proteína principal de la cápside. Reconoce receptores sobre la célula hospedera. Es altamente inmunogénica e induce anticuerpos neutralizantes
	L2	Proteína secundaria de la cápside, participa en la unión del virión a la célula, en su entrada a la célula y su transporte al núcleo, la liberación del genoma y el ensamble de los viriones.

Fuente: Salazar, L., Benavides, M., Boogaard, S., & Marín, Y. (2017). Estrategias latinoamericanas para la vacunación contra el virus del papiloma humano-una revisión temática. Hacia la promoción de la salud, 22(2), 129-143.

Para poder clasificar estos virus se toman en cuenta dos criterios; el primero es el hospedero, ya que se trata de virus altamente específicos de especie; y como segundo criterio, se toman en cuenta las secuencias genéticas, pues permiten la distinción entre diferentes aislamientos de manera detallada y son altamente

conservados. De este modo la secuencia más utilizada para la clasificación de los *Papillomavirus* es la del gen L1 (13).

Cuando las secuencias del gen L1 supera una variación del 10% respecto a tipos virales ya conocidos, se establece un nuevo tipo de *Papillomavirus*, en cambio si la diferencia se encuentra entre los intervalos del 2 al 10 %, se clasifica como un subtipo viral, finalmente, si la diferencia es menor a un porcentaje del 2% se definen como variantes virales (13).

Los *Papillomavirus* forman una familia que contiene un total de 170 miembros y de acuerdo con el Comité Internacional de Taxonomía Viral son agrupados en 16 géneros, estos son nombrados con la terminación *Papillomavirus* y con una letra griega como prefijo, por ejemplo: *Alphapapillomavirus, Betapapillomavirus*, etc (13).

Dentro de cada género existen las especies; dentro del género *Alphapapillomavirus* existen 15 especies, entre ellas el VPH 16, el cual tiene variedades genéticas que pueden ser nombradas con un número diferente (13).

Los *Papillomavirus Humanos* de interés para el presente trabajo, infectan la mucosa del tracto genital, y están ubicados en el género *Alphapapillomavirus*, los cuales se encuentran divididos en dos grupos: los de bajo riesgo (VPH-BR), quese asocian principalmente con verrugas genitales benignas y los de alto riesgo (VPH-AR), que presentan un alto potencial oncogénico y son los agentes etiológicos del CCU (13).

DESARROLLO DE LAS VACUNAS CONTRA EL VPH.

Existen dos tipos de vacunas contra el VPH actualmente; las vacunas terapéuticas, que tienen por objetivo detener el crecimiento de células cancerosas

y reducir el tumor o eliminar las células cancerosas que no han muerto por otras formas de tratamiento, a través del uso de las oncoproteínas E6 y E7, principales blancos, ya que son las más oncogénicas y son esenciales para el mantenimiento del tumor (28).

Y las vacunas preventivas o profilácticas, que impiden el desarrollo del cáncer en las personas sanas, actuando sobre los agentes infecciosos que causan o contribuyen al desarrollo del cáncer, ya que, al conservar su capacidad antigénica, inducen la respuesta del sistema inmune para producir anticuerpos neutralizantes contra el virus (28, 29).

Ambos tipos de vacunas se encuentran ejemplificados en la **tabla 4**, se incluyen características de su composición (antígeno, adyuvante, tipo de VPH al que está dirigido), vía de administración, así como el laboratorio productor (28, 29, 31, 32).

Tabla 4. Características de las actuales vacunas profilácticas y terapéuticas contra el VPH.

	Antígeno	Adyuvante	Tipo de VPH		Vía de aplicación	Farmacéutica productora	Referencias
			Alto Riesgo	Bajo riesgo			
Vacunas Profilácticas							
Cervarix	L1	AS04	16 y 18		IM	Glaxo SmithKline, S.A.	(28)
Gardasil 4V	L1	AAHS	16 y 18	6 y 11	IM	Merck & Co., Inc.	(28, 31)
Gardasil 9V	L1	AAHS	16, 18, 31, 33, 45, 52 y 58	6 y 11	IM	Merck & Co., Inc.	(28, 32)
Vacunas Terapéuticas							
VGX3100	E6/E7	Ninguno	16 y 18		IM	Estudios en Fase II	(28)
TG4001	E6/E7	L2	16		SC	Estudios en Fase II	(28)
GX-188	E6/E7	FIt3L	16 y 18		IM	Estudios en Fase I	(28)
E7-mHsp70	E7	Ninguno	16		IV-IP-IV	Estudios en Fase Pre-Clínica	(28)
Pentarix	E7	TLR3/TLR9	16, 18, 31, 45 y 52		SC	Estudios en Fase Pre-Clínica	(28)

ASO4: lípido A monofosforilado e hidróxido de aluminio; AAHS: sulfato de hidroxifosfato de aluminio amorfo; Fit3L: Ligando de la tirosina quinasa 3 tipo Fms; TLR: receptores tipo Toll; L1: proteína mayor de la cápside; L2: proteína menor de la cápside; E5/E7: oncoproteínas virales; IM: intramuscular; SC: subcutánea; IV: intravenosos; IP: intraperitoneal.

Por ahora la Agencia de Alimentos y Medicamentos de Estados Unidos (Food and Drug Administration: FDA) ha aprobado el uso de tres vacunas profilácticas contra el VPH, la vacuna bivalente (Cervarix®) producida por GlaxoSmithKline Biologicals SA® y la vacuna 4-V (Gardasil®) y 9-V (Gardasil9®) producidas por Merck®, las cuales a finales de 2013 distribuyeron más de 144 millones de dosis solo de la vacuna 4-V y cerca de 41 millones de dosis de la vacuna bivalente a nivelmundial (28).

Debido a que las vacunas 4-V (Gardasil®) y 9-V (Gardasil9®) producidas por Merck® son las de mayor distribución en muchos países (13, 35) se decidió centralizar esta investigación en estas dos vacunas.

El método ocupado para el desarrollo de estas vacunas, es específicamente del tipo viral recombinante, con base en el sistema de Partículas Similares a las del Virus (Virus Like Particles: VLPs) , el cual consiste en clonar la proteína L1 (proteína mayoritaria de la cápside) mediante un sistema de levadura denominado *Saccharomyces cerevisiae*, que es colocado en condiciones óptimas para permitir el autoensamblaje de las VLPs, las cuales poseen características morfológicamente idénticas al virus, pero carentes del genoma viral (2, 3, 7, 8, 10, 28, 29). La vacuna Gardasil 4-V es producida por la farmacéutica Merck & Co, Inc. y fueaprobada para su comercio desde el año 2006 por la FDA, del mismo modo que lavacuna Gardasil 9-V, producida por la misma farmacéutica y aprobada hasta elaño 2014 por la FDA, una nueva versión de la vacuna 4-V desarrollada bajo susmismos principios (31, 32).

Según las fichas técnicas del fabricante (**Anexo 1)**, la vacuna Gardasil 4-V está indicada en niñas, niños, hombres y mujeres de 9 a 26 años, mientras que la

vacuna Gardasil 9-V está indicada en un intervalo más amplio, que indica la misma población, pero con edades que van de los 9 a 45 años (31, 32).

La forma farmacéutica de ambas vacunas es una suspensión de 0,5 mL colocados en un vial de monodosis, es inyectada vía intramuscular, y como cuidados especiales debe mantenerse a una temperatura de entre 2 y 8° C hasta suaplicación (31, 32).

El calendario de administración para la vacuna Gardasil 4-V es: 1er Dosis (día 0), 2da Dosis (2 meses) y 3er Dosis (6 meses) para la población indicada. Mientras que para la vacuna Gardasil 9-V es 1er Dosis (día 0), 2da Dosis (6 meses) y 3er Dosis (12 meses), en caso de tener de 9 a 14 años y 1er Dosis (día 0), 2da Dosis (2 meses) y 3er Dosis (6 meses) para edades mayores de 15 años (31, 32).

Cada envase de suspensión inyectable de 0.5 mL de la vacuna Gardasil 4-V contiene (31) :

Proteína L1 de Papilomavirus humano tipo 6	20 mcg
Proteína L1 de Papilomavirus humano tipo 11	40 mcg
Proteína L1 de Papilomavirus humano tipo 16	40 mcg
Proteína L1 de Papilomavirus humano tipo 18	20 mcg
Aluminio (sulfato hidroxifosfato de aluminio amorfo, suministrado como adyuvante)	225 mcg
Cloruro de sodio	9.56 mg
L-histidina	0.78 mg
Polisorbato 80	50 mcg
Borato de sodio	35 mcg
Proteína de levadura	>7 mcg

Y por cada envase de suspensión inyectable de 0.5 mL de la vacuna Gardasil 9-V contiene (32) :

Proteína L1 de Papilomavirus humano tipo 6	30 mcg
Proteína L1 de Papilomavirus humano tipo 11	40 mcg
Proteína L1 de Papilomavirus humano tipo 16	60 mcg
Proteína L1 de Papilomavirus humano tipo 18	40 mcg
Proteína L1 de Papilomavirus humano tipo 31	20 mcg
Proteína L1 de Papilomavirus humano tipo 33	20 mcg
Proteína L1 de Papilomavirus humano tipo 45	20 mcg
Proteína L1 de Papilomavirus humano tipo 52	20 mcg
Proteína L1 de Papilomavirus humano tipo 58	20 mcg
Aluminio (sulfato hidroxifosfato de aluminio amorfo, suministrado como adyuvante)	500 mcg
Cloruro de sodio	9.56 mg
L-histidina	0.78 mg
Polisorbato 80	50 mcg
Borato de sodio	35 mcg
Proteína de levadura	>7 mcg

Están contraindicadas en hipersensibilidad, incluyendo reacciones alérgicas graves a la levadura (un componente de la vacuna), o después de una dosisprevia de las vacunas, debe tenerse precauciones en enfermedad aguda moderada o grave con o sin fiebre y Trombocitopenia (30, 31, 32).

2.5 VACUNACIÓN CONTRA EL VPH EN DIFERENTES PAÍSES DEL MUNDO.

El VPH es la infección de transmisión sexual más común y la mayoría de las personas son contagiadas poco después de iniciar la actividad sexual con una persona infectada (10) la infección suele ser asintomática y los métodos de barrera no pueden prevenir el riesgo de transmisión por completo, por lo que se ha

evidenciado la necesidad de implementar o mejorar programas de prevención que resulten eficaces (33).

Por ejemplo, algunas proyecciones basadas en las tendencias observadas durante el año 2012 en América Latina (incluyendo México, América Central, América del Sur y el Caribe) estimaron que el número de muertes relacionadas con el CCU aumentaría gradualmente hasta llegar a un 60% a partir de ese año yhasta el 2030 si se seguía con esta tendencia (13).

Fue por esta razón que se implementó un plan de vacunación contra el VPH no solo en esta región, sino en la mayoría de los países del mundo al observar la magnitud del problema que representaba (33).

La disponibilidad de las vacunas contra el VPH da inicio desde el año 2006, con la vacuna Gardasil 4-V, la cual ha demostrado una eficacia profiláctica de casi el 100% contra las infecciones persistentes del tipo vacunal y la neoplasia intraepitelial cervical (NIC) (34).

Demostró ser una vacuna que cuenta con una protección duradera contra la infección y la enfermedad, con evaluaciones primarias de seguridad y un control con revisiones recientes realizadas en 2015 por la Agencia Europea de Medicamentos (EMA) y por el Comité Consultivo Mundial de Seguridad de las Vacunas de la OMS, confirmando la seguridad continua de su uso (34).

Desde abril de 2009, la OMS recomienda que la vacunación contra el VPH se incluya en los programas nacionales de inmunización, siempre y cuando el país constituya una prioridad de salud pública la prevención del CCU, la introducción sea factible, la financiación sostenible y se tenga en cuenta la relación coste-eficacia de las estrategias de vacunación contra el VPH (34).

Afortunadamente, se ha visto un progreso notable en la ampliación de la vacunación contra el VPH en los últimos 10 años, resumen que se puede ilustrar a partir de la **figura 3,** en la que más de 100 países han experimentado ya la administración de la vacuna contra el VPH (34).

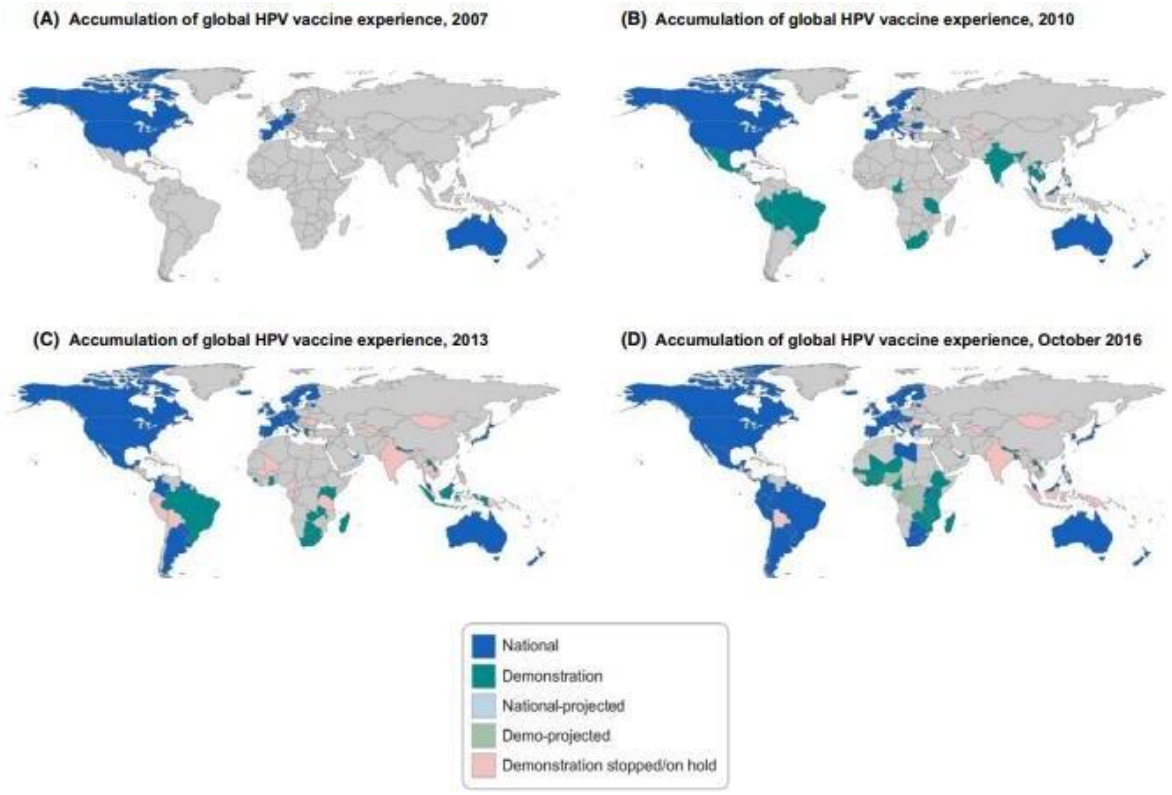

FIGURA 3. (A) Acumulación de la experiencia mundial de la vacuna contra el VPH, 2007. (B) Acumulación de la experiencia mundial de la vacuna contra el VPH, 2010. (C) Acumulación de la experiencia mundial con la vacuna contra el VPH, 2013. (D) Acumulación de la experiencia mundial con la vacuna contra el VPH, octubre de 2016. [La figura en color puede verse en wileyonlinelibrary.com].

La introducción de la vacuna contra el VPH comenzó en los países de altos recursos entre 2008 y 2012 con tres dosis y se centraron en las adolescentes de 12 a 14 años a través de programas escolares, proporcionando la vacuna de forma gratuita o totalmente reembolsable a través de sus programas nacionales de inmunización (34).

Mientras que en países de medianos y bajos ingresos fueron introducidos mediante programas desde el 2007 a 2010 para ilustrar qué tan aceptados y viables serían (34).

A partir de los resultados obtenidos en cada caso, se realizó un resumen en la **tabla 5**, que incluyó variables como la edad de vacunación, la existencia de un consentimiento informado y la cobertura o tasa de vacunación registradas hasta la 3era dosis, así como el año en que se obtuvieron, limitando los datos hasta antes del 2015 (13, 35).

Tabla 5. Tasas de vacunación contra el VPH registradas hasta antes del 2015 en diferentes países del mundo.

AUTOR Y REF	AÑO DE REGISTRO	PAÍS	EDAD DE VACUNACIÓN	CONSENTIMIENTO	TASA DE VACUNACIÓN 3era Dosis
Ministerio de sanidad y servicios e igualdad (35)	**2011**	**E.U.A**	11-12 años	Sin datos.	53%
Salazar L., et al (13)	**2011**	**Perú**	9-15 años	Exige	73.5%
Salazar L., et al (13)	**2013**	**Uruguay**	9-11 años	Exige	Sin datos.
Salazar L., et al (13)	**2011**	**Argentina**	11 años	Exige	50.2%
Salazar L., et al (13)	**2014**	**Brasil**	9-13 años	Exige	Sin datos.
Salazar L., et al (13)	**2012**	**Colombia**	9-11 años	No se exige	22%
Ministerio de sanidad y servicios e igualdad (35)	**2008**	**Panamá**	9-15 años	No se exige	68%
Salazar L., et al (13)	**2013**	**Paraguay**	10-11 años	No se exige	Sin datos.
Ministerio de sanidad y servicios e igualdad (35)	**2009**	**México**	9-12 años	No se exige	67%

Salazar L., et al (13)	**2014**	**Chile**	9-11 años	No se exige	1er. Dosis 67%
Ministerio de sanidad y servicios e igualdad (35)	**2008**	**España**	11-14 años	Sin datos	49.9-98%
Ministerio de sanidad y servicios e igualdad (35)	**2007**	**Australia**	12-13 años	Sin datos	70%
Salazar L., et al (13)	**Sin datos**	**Uganda**	Sin datos	Sin datos	89%
Salazar L., et al (13)	**Sin datos**	**Vietnam**	Sin datos	Sin datos	96%
Ministerio de sanidad y servicios e igualdad (35)	**2007**	**Canadá**	9-13 años	Sin datos	80-85%
Ministerio de sanidad y servicios e igualdad (35)	**2010**	**Reino Unido**	9-18 años	Sin datos	80%

Como se puede observar en la **tabla 5**, los resultados para varios países son alentadores, con resultados de más del 60% de la población objetivo inmunizada, mientras que en otros casos, aun cuando la vacunación contra el VPH representa una oportunidad única para prevenir diversos tipos de cáncer y cuenta con estudios que respaldan su seguridad y eficacia, presentó un descenso, como lo esel caso de Colombia, con una tasa de vacunación correspondiente a un 22% de cobertura para el año 2012 (13) , resultado que representa una seria amenaza para lasalud pública en ese país, que se verá reflejada en los costos sociales y económicos futuros en términos de tratamientos y muertes por cáncer prevenible relacionados con VPH (34).

3. METODOLOGÍA

Se realizó una búsqueda bibliográfica en el idioma español e inglés de las publicaciones de los últimos 5 años (2015-2020) en las bibliotecas electrónicas de PubMed, Trip Medical Database, Lexicomp y Medigraphic, además de usar el buscador Google scholar.

Para PubMed se usaron las palabras clave junto con los operadores; ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ("papillomaviridae"[MeSH Terms] OR "papillomaviridae"[All Fields] OR ("human"[All Fields]) AND "papillomavirus"[All Fields]) OR "human papillomavirus"[All Fields])) AND (HPV [All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]), obteniendo en total de 454 resultados.

Se activaron los filtros para incluir: Ensayo clínico, Metaanálisis, Revisiones sistemáticas, Texto completo gratuito, periodo de publicación (2015-2020), e idioma (inglés y español), obteniendo un total de 261 resultados.

De estos resultados se aplicó un último filtro para incluir las vacunas Gardasil agregando el término: ("Gardasil"[MeSH Terms] OR "Gardasil"[All Fields] al buscador, obteniendo finalmente 16 resultados, seleccionando para el análisis del trabajo 7 artículos según los criterios de inclusión y exclusión.

Para Trip Medical Database se usaron las palabras clave: safety AND gardasil AND vaccine, obteniendo un total de 369 resultados. Se activaron los filtros para incluir artículos en el idioma inglés: Ensayo clínico controlados (5), Revisiones sistemáticas (4), Texto completo gratuito, periodo de publicación (desde 2015),

obteniendo un total de 9 artículos, de los cuales se incluyó 1 artículo para su análisis.

En el caso de la búsqueda en Google scholar se usaron las palabras clave: Seguridad + vacunas + Gardasil, obteniendo 1060 resultados, los cuales después de aplicar los filtros artículos de revisión, así como el rango del periodo 2015- 2020, se obtuvieron 23 artículos, de los cuales se seleccionaron 3 artículos que cumplían con los criterios de inclusión y exclusión.

Para la base de datos de Lexicomp, se realizó la búsqueda de las vacunas Gardasil por separado en el buscador, usando las palabras clave: “quadrivalent vaccine Gardasil” y “nonavalent vaccine Gardasil”, después de esto se analizó únicamente la información relacionada con los porcentajes de los EA presentados en ambas vacunas, para usarlo en el análisis.

Finalmente se realizó una búsqueda manual en Medigraphic mediante las palabras clave: “Vacunas VPH”, la cual incluyó un artículo adicional que cumplió con los criterios de inclusión y exclusión.

Criterios de exclusión: Se excluyeron aquellos artículos que no tuvieran objetivos relacionados con la seguridad de las vacunas Gardasil 4-V y 9-V, o no tuvieran información referente a uno o más puntos de los mencionados anteriormente y aquellos que no fueron publicados dentro del periodo 2015-2020.

Criterios de inclusión: Se incluyeron artículos como Revisiones críticas, Estudios observacionales de tipo descriptivos y retrospectivos, Revisiones sistemáticas, Ensayos clínicos y Revisiones narrativas publicados dentro del periodo 2015-2020

en idioma inglés o español que referencian información relacionada con la seguridad de las vacunas del VPH, Gardasil 4-V y 9-V y que además engloba uno o más de los siguientes puntos:

- Que incluyera estrategias implementadas en la detección de EA de las vacunas Gardasil 4-V y 9-V contra el VPH.
- Que incluyera los EA más frecuentes de las vacunas Gardasil 4-V y 9-V contra el VPH.
- Que incluyera los ESAVI reportados de las vacunas Gardasil 4-V y 9-V contra el VPH.

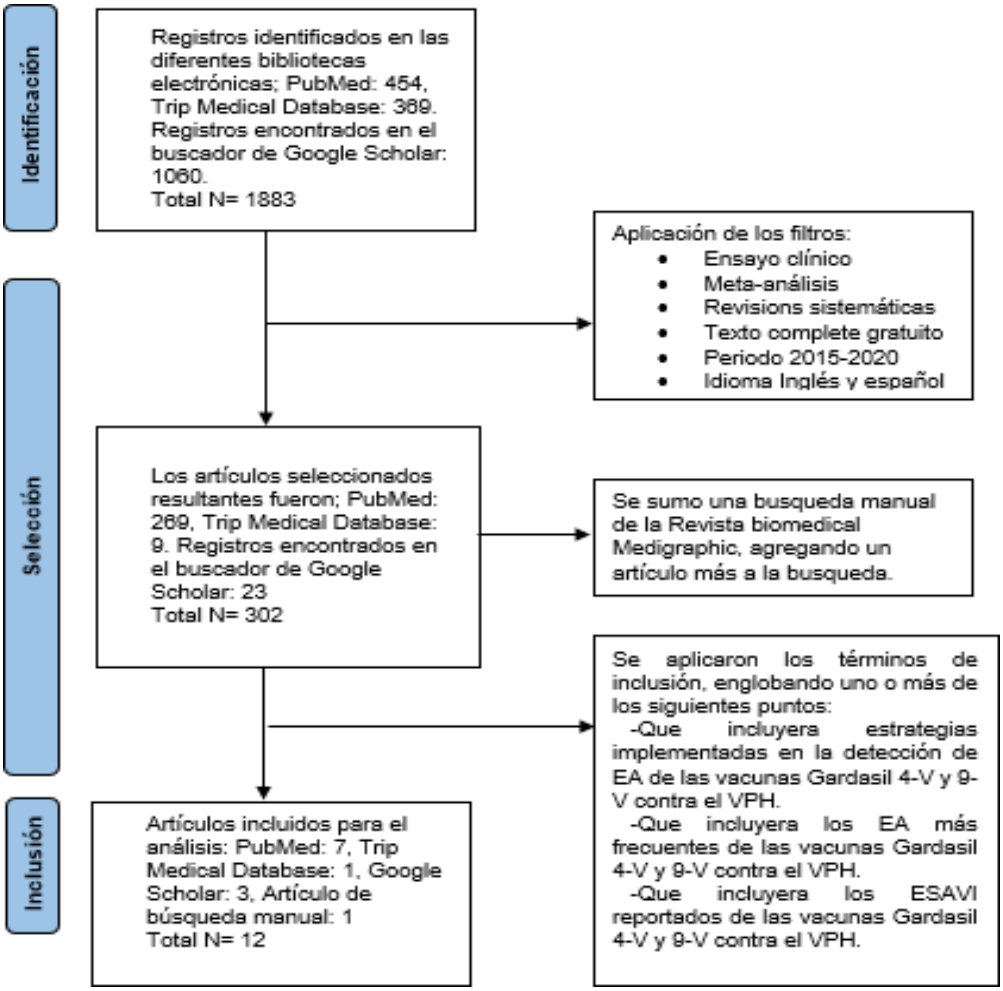

Figura 4. Diagrama de flujo PRISMA flow chart para la búsqueda bibliográfica electrónica.

4. RESULTADOS

De acuerdo con la revisión bibliográfica realizada en este trabajo, se encontraron un total de 1883 artículos de referencia sobre el tema, a los cuales se les aplicaron los criterios de exclusión con los filtros: de idioma (inglés o español), periodo (2015-2020), texto gratuito completo y tipo de artículo (ensayos clínicos, revisiones sistemáticas y metaanálisis), de los cuales se obtuvieron 302 resultados.

Para finalmente seleccionar aquellos artículos que cumplieran con los criterios de inclusión, por ejemplo, que el artículo contara con información relacionada con la seguridad de las vacunas Gardasil 4-V y 9-V, estrategias implementadas para la detección de Eventos Adversos (EA), los EA más frecuentes. Y aquellos que identificaron y clasificaron según el criterio de cada autor por su gravedad los Eventos Adversos Supuestamente Atribuidos a la Vacunación o Inmunización (ESAVI) reportados.

Resultando en total 12 artículos incluidos para el análisis de este trabajo;1 Revisión bibliográfica, 1 Revisión sistemática, 2 Estudios observacionales de tipo retrospectivo y descriptivo, 1 estudio de cohorte prospectiva, 1 ensayo clínico de Fase III, 1 Revisión temática, 4 Revisiones narrativas, y 1 Revisión crítica.

Mismos que se enlistan en la **tabla 6**, con la finalidad de resumir los resultados acerca de la seguridad de las vacunas Gardasil 4-V y 9-V, en donde podemos observar el autor o autores del artículo, año en que fue publicado, país de procedencia, población estudiada, tipo de artículo, así como los resultados finales sobre el perfil de seguridad de las vacunas Gardasil 4-V y 9-V usadas contra el VPH.

Tabla 6. Evidencia de los artículos incluidos para el análisis sobre la seguridad de las vacunas Gardasil 4-V y 9-

Autor y referencia.	Año	País	Tipo de artículo y Población estudiada	Resultados del perfil de seguridad de las vacunas Gardasil
Bonaldo et al. (4)	2019	Estados Unidos de América	Estudio retrospectivo y descriptivo. Hombres y Mujeres.	Los datos en este artículo concuerdan con características previamente descritas de la vacuna y con los resultados de las investigaciones de seguridad llevadas a cabo por las autoridades reguladoras en los últimos años, el perfil de seguridad de las vacunas contra el VPH ha demostrado ser bueno.
Martínez L. et al. (43)	2017	México	Revisión narrativa. Revisión crítica de ensayos aleatorios y series de casos posteriores a la comercialización. Hombres y Mujeres.	De acuerdo con el artículo, en los ensayos aleatorios se encontró un número significativamente mayor de Eventos Adversos Graves (EAG) al comparar las vacunas 4-V y 9-Vcontra el VPH y el placebo de aluminio. No obstante, ninguno de los EAG de ambos estudios se consideró relacionado con las vacunas. En los ensayos preclínicos y lasseries de casos posteriores a la comercialización se describieron síntomas similares tras la vacunación contra el VPH. Sin embargo, debido a que se encontró un preocupante cociente entre el número necesario para vacunar y el número necesario para dañar sobre la vacuna 9-V, se plantearon más dudas sobre la seguridad de la vacuna contra el VPH.
Mauro et al. (10)	2019	Brasil	Estudio retrospectivo y descriptivo. Mujeres.	Los datos encontrados en esteartículo coinciden con los de otros países y corroboran la seguridad de las vacunas contra el VPH.
Phillips et al. (2)	2018	Australia	Revisión narrativa actualizada. Hombres y Mujeres.	Apoyando la posición del Comité Consultivo Mundial sobre Seguridadde las Vacunas (The Global Advisory Committee on Vaccine Safety: GACVS), la EMA y otros grupos de expertos, no se encontró evidencia de ningún problema de seguridad que deba impactar en el uso de los programas de inmunización de esta vacuna en todo el mundo, concluyendo que las vacunas contrael VPH son seguras.

Phillips et al. (3)	2020	Australia	Revisión narrativa. Hombres y mujeres de 12 a 13 años.	Este análisis exhaustivo contribuye a la gran cantidad de datos existentes que afirman el perfil de seguridad post-comercialización de la vacuna 4- V tanto en hombres como en mujeres.
Ruiz et al. (36)	2018	América Latina	Revisión narrativa. Revisión de un estudio aleatorio y un estudio doble ciego controlado de la vacuna 9-V. Mujeres y hombres. (9-15 años y 16 a 26 años).	De acuerdo con los datos abundantes y consistentes encontrados por este artículo, incluyendo la evidencia de la vigilancia activa y los grandes estudios epidemiológicos, apoya la seguridad de la vacunación contra el VPH.
Salazar et al. (13)	2017	América Latina.	Revisión temática.	De acuerdo con este artículo, los índices de seguridad sonconcordantes con los observados antes de la aprobación de la vacuna Gardasil y similares a los de las evaluaciones de seguridad de otrasvacunas.
Satari et al. (33)	2019	Indonesia	Estudio de cohorte prospectivo. Estudio post comercialización. Mujeres 12 años (niñas que estudian el sexto grado.)	Estos resultados, junto con los datos de seguridad de los ensayos clínicos previos a la obtención de la licencia, confirman el perfil de seguridad favorable de la vacuna 4-V en las niñas preadolescentes.
Van Damme et al. (7)	2016	Bélgica	Ensayo clínico. Estudio clínico fase III doble ciego, aleatorizado, controlado. Mujeres y hombres de 16 a 26 años.	De acuerdo con este ensayo clínico, el perfil de seguridad y tolerabilidad fue en general similar para las dos vacunas. No se informó de ningún EA relacionado con la vacuna ni de ninguna interrupción debida a un EA relacionados con la vacuna.
Vichnin et al. (23)	2015	Multicéntrico.	Hombres y Mujeres de 9 a 26 años.	Estos resultados, junto con los datos de seguridad de los ensayos clínicos previos a la autorización, confirman que la vacuna contra el VPH tiene un perfil de seguridad favorable.
WHO (5)	2017	Australia	Revisión Sistemática.	De acuerdo con este artículo, no se encontró diferencias en la tasa de EAG entre las personas que recibieron Gardasil® y las personas que recibieron un placebo o unavacuna de control.

Hernández PA, Araya VS. (29)	2020	Costa Rica	Revisión Bibliográfica	No hay datos que sugieran una asociación entre las vacunas y los EAG, confirmando por medio de la OMS su alto perfil de seguridad.

En cuanto a los EA más frecuentes identificados en las vacunas Gardasil 4-V y 9-V, los resultados se encuentran descritos en la **tabla 7**, en donde se puede observar una comparación entre los porcentajes de los EA más frecuentes de las vacunas Gardasil 4-V y 9-V encontrados en la literatura (4, 7, 10, 33, 37) y los porcentajes de los mismos EA antes mencionados de las vacunas Gardasil 4-V y 9-V encontrados en la base de datos de Lexicomp (38, 39) los cuales coinciden a su vez con lo descrito en las diversas ficha técnicas que emite la Secretaría de Salud (40), la Agencia Española de Medicamentos y productos Sanitarios (41, 42) información resumida en las **tablas 8 y 9.**

Tabla 7. Comparación entre los porcentajes recabados en los artículos de esta revisión y el rango de porcentajes de la base de datos de Lexicomp.

EA FRECUENTES	Brasil (4-V) (10)	Hombres/ Fase III (9-V) (7)	Jakarta/ Indonesia (4-V) (33)	Clusters (9-V) (37)	Vaers (4-V) (4)	LEXICOMP 4-V (38)	LEXICOMP 9-V (39)
Síncope	42.37%	Sin Datos	Sin Datos	18.81%	10.85%	<1%	Sin Datos
Mareos	40%	1.2%	Sin Datos	60.54%	11.31%	8-21%	7-20%
Malestar	34.41%	Sin Datos	Sin Datos	Sin Datos	3.65%	Sin Datos	Sin Datos
Dolor de Cabeza	32.69%	8.5%	Sin Datos	62.51%	10.05%	31%	3%
Náuseas	26.88%	1.6%	Sin Datos	45.48%	7.78%	2-4%	1-4%
Dolor / Eritema/ hinchazón	23.01%	74%	59.6%	Sin Datos	Sin Datos	82-61% 22-17% 34-24 %	63-50% 42-7% 45-13 %
Pirexia	Sin Datos	2.4%	Sin Datos	Sin Datos	Sin Datos	61-82%	63-90%
Fatiga	Sin Datos	1.6%	Sin Datos	Sin Datos	5.8%	14-24%	13-49%

Tabla 8. Ficha técnica de Gardasil 4-V por la Agencia Española de Medicamentos y Productos Sanitarios.

Sistema de clasificación de órganos	Frecuencia	Acontecimiento Adverso
Infecciones e Infestaciones	No conocida	Celulitis en el lugar de inyección*
Trastornos de la sangre y del sistema linfático	No conocida	Púrpura trombocitopénica idiopática*, linfoadenopatía*
Trastorno del sistema inmunológico	No conocida	Reacciones de hipersensibilidad incluyendo reacciones anafilácticas/anafilactoides*
Trastornos del sistema nervioso	Muy frecuente	Cefalea
	No conocida	Encefalomielitis aguda diseminada*, mareo1*, síndrome de Guillain-Barré*, síncope acompañado algunas veces de movimientos tónico-clónicos*
Trastornos gastrointestinales	Frecuentes	Náuseas
	No conocida	Vómitos*
Trastornos musculoesqueléticos y del tejido conjuntivo	Frecuentes	Dolor en la extremidad
	No conocida	Artralgia*, Mialgia*
Trastornos generales y alteraciones en el lugar de la inyección.	Muy frecuentes	En el lugar de inyección: eritema, dolor, hinchazón
	Frecuentes	Pirexia En el lugar de inyección: hematoma, prurito
	No conocida	Astenia*, escalofríos*, fatiga*, malestar*

Tabla 9. Ficha técnica de Gardasil 9-V por la Agencia Española de Medicamentos y Productos Sanitarios.

Sistema de clasificación de órganos	Frecuencia	Acontecimiento Adverso
Trastornos del sistema nervioso	Muy Frecuentes	Cefalea
	Frecuentes	Mareo
Trastornos gastrointestinales	Frecuentes	Náuseas
Trastornos generales y alteraciones en el lugar de la inyección.	Muy frecuente	En el lugar de inyección: eritema, dolor, hinchazón
	Frecuentes	Pirexia, fatiga, En el lugar de inyección: hematomas, prurito

Otro punto importante a mencionar son los ESAVIs Graves y No Graves encontrados en la literatura, un punto difícil de interpretar debido a la ambigüedad de la definición manejada por cada autor y en general por cada país, por lo cual se incluyeron definiciones como: ”adverse events of special interest” (AESI) (2,3)

o “adverse events following immunization” (AEFI) (4, 10), definiciones que se asemejan a la definición de ESAVI. Los resultados se resumen en la **tabla 10**, la cual incluye el autor o autores, el número de referencia bibliográfica y los ESAVI Graves o No Graves descritos en cada uno (2, 3, 5, 10, 23, 43).

Tabla 10. ESAVIs no graves y graves identificados en los diferentes artículos de las vacunas Gardasil 4-v y 9-v.

Autor	Referencia	Año	ESAVI No Grave	ESAVI Grave
Mauro, A. et al.	(10)	2019	Dolor de cabeza, Mareos, Parestesia ySíncope.	Síndrome de Guillain Barré, Trombosis Venosa Profunda de las Extremidades Superiores, Convulsiones y Aborto espontáneo.
Phillips, A. et al.	(2)	2018	Síncope	Anafilaxia, Síndrome de Guillain Barre, Síndrome de taquicardia ortostática postural, Insuficiencia ovárica prematura, enfermedades autoinmunes), Encefalomielitis aguda diseminada, Esclerosis múltiple y síndrome de dolor regional complejo.
Phillips, A. et al.	(3)	2020	Síncope	Anafilaxia, Síndrome de Guillain-Barre, Síndrome de Taquicardia ortostática postural, Enfermedad autoinmune, Insuficiencia ovárica primaria, Síndrome de dolor regional complejo, Tromboembolismo venoso.
Martínez, M., & Amezcua.	(43)	2017	Dolor de cabeza, Pirexia, Náuseas,Mareos y Fatiga.	Síndrome de Fatiga.
Van Damme, P. et al.	(23)	2016	Cefalea, linfadenopatía, pirexia, fatiga, náuseas, diarrea, nasofaringe, mialgia, mareos y dolor orofaríngeo.	No encontraron ningún evento adverso grave.
WHO	(5)	2017	Sin datos.	Enfermedades autoinmunes, Tromboembolismo venoso, Esclerosismúltiple y otras condicionesdesmielinizantes.

ESTRATEGIAS EMPLEADAS EN LA DETECCIÓN DE LOS EVENTOS ADVERSOS TRAS LA VACUNACIÓN CONTRA EL VIRUS DEL PAPILOMA HUMANO.

Para la identificación de los riesgos asociados a la seguridad, así como lasposibles alteraciones a la percepción y confianza en las vacunas, la OMS ha emitido algunas recomendaciones para desarrollar un sistema de farmacovigilancia permanente (6, 14).

En ellas se incluye un sistema de farmacovigilancia llevado a cabo de dos maneras: farmacovigilancia pasiva y farmacovigilancia activa; en la farmacovigilancia pasiva los EA se identifican e informan de manera espontánea en los sistemas de vigilancia dirigidos a los proveedores de atención médica y el público, que luego se evalúan para cualquier asociación potencial con la vacunación (6, 14).

Mientras que la farmacovigilancia activa es cuando el notificador realiza unaacción que estará encaminada a obtener la información utilizando procedimientos sistemáticos para identificar los EA clínicamente importantes que se producen dentro de un período y población definidos mediante el uso de ensayos clínicos o estudios epidemiológicos como los estudios de cohorte, de casos-control y de serie de casos, evaluando si la ocurrencia temporal de estos eventos tiene una posible asociación causal con la vacunación (6, 12, 14).

En la revisión bibliográfica realizada, se pudieron identificar varios sistemas de notificación espontánea, es decir, de farmacovigilancia pasiva. Cada país cuenta con un organismo para la notificación de EA de medicamentos en los cuales están incluidas las vacunas, entre los más reconocidos se encuentran: el Sistema de

Notificación de Efectos Adversos de las Vacunas (The Vaccine Adverse Events Reporting System :VAERS) en E.U.A (4)., el Sistema de Información de Eventos Adversos después de la Vacunación (Sistema de Informações de Eventos Adversos Pós Vacinação:SI-EAPV) en Brasil (28), EudraVigilance en toda la Unión Europea, el Sistema de Vigilancia de los Eventos Adversos tras la Vacunación en la Comunidad (Surveillance of AEs Following Vaccination in the Community: SAEFVIC), en Australia, el Sistema Canadiense de Vigilancia de Efectos Adversos Tras la Inmunización (The Canadian Adverse Events Following Immunisation Surveillance System: CAEFISS) en Canadá (14) y la COFEPRIS en México (18).

En estos sistemas de notificación los datos recabados son informados cuidadosamente por los profesionales de la salud o el público a través de informes que incluyen algunos datos como información demográfica, fecha de vacunación, número de dosis, vacuna, signos y síntomas concomitantes, diagnóstico, gravedad del caso, edad, sexo, características de la vacuna, fecha de inicio y datos personales del paciente, así como historial médico y terapias concomitantes (28).

Por ejemplo, en México este proceso es un trámite gratuito en el que la COFEPRIS, a través de la Dirección Ejecutiva de Farmacopea y Farmacovigilancia (DEFFV) pone actualmente a disposición del público las siguientes ligas electrónicas para notificar SRAM, ESAVI y otros problemas relacionados con el uso de medicamentos y vacunas, en caso de tener algún impedimento para acudir al centro de salud/área epidemiológica correspondiente; Pacientes y consumidores (https://primaryreporting.who-umc.org/MX), ESAVI (https://vaccine-primaryereporting.who-umc.org/mx), Profesionales de la salud (https://primaryreporting.who-umc.org/MX), ejemplificada en el **Anexo II** (44).

Por otra parte, entre los estudios que ejemplifican la farmacovigilancia activaestán; el estudio doble ciego, aleatorizado, controlado del 2016 por *Van Damme etal* (45) y el estudio de cohorte prospectivo para la vacuna 4-V realizado por *Satari, H.I et al* (46) en ambos se realizó la observación de pacientes después de la aplicación de la vacuna esperando describir cualquier EA inmediato, incluidas las reacciones alérgicas (45, 46).

A los pacientes se les proporcionaba una tarjeta de informe de vacunación al finalizar el periodo de observación. Esta tarjeta les sirvió para el registro decualquier EA, el personal de atención primaria de salud validaba sin poder modificar lo registrado por el paciente (45, 46).

Finalmente, el investigador determinaba la causalidad del EA informado y se clasificaba de acuerdo con la gravedad. Los resultados en ambos estudios mostraron que los eventos notificados con mayor frecuencia fueron no graves, en los que destacan: dolor de cabeza, mareos y síncope. Confirmando un perfil de seguridad favorable para las vacunas (45, 46).

La seguridad de las vacunas también se ha evaluado a través de otras estrategias, como fue el caso del estudio realizado en E.U.A. por los Centros para el Control y la Prevención de Enfermedades (CDC) que emplearon el sistema de vigilancia activa de vacunas Seguridad de las Vacunas VSD (Vaccine Safety Datalink) que recoge información médica de una población amplia y representativa de más de 9 millones de personas de siete sistemas integrados de salud cada año (23).

La CDC, evaluó 600,558 dosis de la vacuna Gardasil 4-V, en el periodo de agosto de 2006 a octubre de 2009, en mujeres de 9 a 26 años de los centros de la VSD para condiciones pre-especificadas basado en datos de seguridad de ensayos

clínicos previos a la obtención de la licencia y en informes del VAERS, un sistema de notificación pasivo de los E.U.A (23).

Para el cual se utilizó un grupo de comparación histórico no vacunado para los resultados menos comunes (Síndrome de Guillain-Barre: GBS), Tromboembolismo Venoso (TEV), Accidente Cerebrovascular y Apendicitis) y un grupo de comparación concurrente no vacunado para evaluar tasas de los resultados más comunes (reacciones alérgicas, síncope y convulsiones) (23).

Los resultados mostraron que no hubo un aumento del riesgo estadísticamente significativo entre la recepción de la vacuna Gardasil 4-V y cualquiera de las condiciones monitoreadas (23).

Otro ejemplo, es el estudio de casos y controles en mujeres francesas de 14 a 26 años, realizado por la organización privada “LA-SER”, utilizando el sistema de información Pharmacoepidemiologic General Research eXtension (PGRx), sistema que recoge casos de enfermedades y uno de referencia de controles, independientemente de la exposición a fármacos o vacunas (23).

Este estudio evaluó si la vacuna Gardasil 4-V estaba asociada a un riesgo modificado de presunción de enfermedades autoinmunes pre-especificadas (desmielinización central, GBS, lupus, artritis reumatoide, conectivitis indiferenciada, miositis y dermatomiositis, diabetes tipo 1, tiroiditis autoinmune y púrpura trombocitopénica idiopática (23).

Entre 2007 y 2011, se reclutaron 321 casos con posibles afecciones autoinmunes de centros médicos especializados y 1,653 controles (es decir, un grupo de personas sin la enfermedad autoinmune de interés) fueron reclutados en consultas generales (23).

Un total de 26 de 248 (10,5%) casos autoinmunes definitivos y 232 de 1001 (23,2%) controles emparejados habían confirmado una exposición previa a la vacuna contra el VPH en el periodo de riesgo correspondiente. Mediante una regresión logística incondicional de exposición a la vacuna contra el VPH en los casos se comparó con los controles emparejados (23).

En dicho estudio no se evidenció un mayor riesgo de padecer los trastornos autoinmunes estudiados tras la vacunación contra el VPH. Sin embargo, el pequeño tamaño de las muestras para cada uno de los trastornos limitó el poder estadístico para determinar diferencias. El estudio no observó una acumulación inusual de enfermedades autoinmunes (23).

Finalmente, un estudio realizado en Dinamarca, de casos autocontrolados, investigó la asociación entre la TEV y la vacuna Gardasil 4-V. Entre 1,613,798 niñas y mujeres de edades 10-45 años entre 2006 y 2013, se identificaron 4,375 casos incidentes de TEV se identificaron y 889 se produjeron en personas vacunadas durante el período de estudio (23).

No se encontró ninguna asociación entre la TEV y la vacunación [tasa de incidencia (IRR) de TEV = 0,77, intervalo de confianza intervalo de confianza (IC) del 95%: 0,53-1,11] o en subanálisis estratificados por edad, uso de anticoagulantes o uso de anticonceptivos orales (23).

PROBLEMAS RELACIONADOS CON LAS VACUNAS GARDASIL 4-V Y 9-V QUE ORILLARON A UNA SUSPENSIÓN TEMPORAL DE LA CAMPAÑA DE VACUNACIÓN.

En diferentes países se ha reportado el caso de EA ocurridos después de la

vacunación contra el VPH, que han generado la desconfianza de la población, debido a las dudas sobre la seguridad de las vacunas contra el VPH, como Colombia y Japón, dos casos en los que ha representado un verdadero obstáculo para proporcionar una protección completa en contra de este virus (5, 9, 12, 13, 14, 28, 46). En Colombia, la vacuna se introdujo en el año 2012 de forma gratuita a todas las niñas en edad escolar entre los 9 y 13 años, alcanzando las mejores tasas de cobertura y posicionándose en el segundo lugar en el mundo con una adecuada adherencia a la inmunización por parte de las familias, los médicos y en general del sistema de salud, superando la meta al obtener hasta el 95% de cobertura en la población objetivo. Sin embargo, en el año 2013 el escenario cambió al ampliar el esquema, ya que para finales del 2014 la cobertura tuvo una caída hasta el 20,4% de inmunización (9,13)

La problemática inició cuando quince adolescentes del mismo colegio ingresaron a Urgencias en un Hospital local refiriendo diferentes síntomas como: mareos, dolores de cabeza, dolor abdominal, desmayos, náuseas, vómitos, taquicardia, dificultad para respirar y adormecimiento de las extremidades, explicados primeramente por una posible intoxicación alimentaria, agua, plomo o pesticidas, yen la que padres de familia estaban convencidos de que la reciente aplicación dela vacuna contra el VPH fuera la causa de los síntomas (9, 46).

La noticia fue ampliamente difundida y al poco tiempo se reportaron un aproximado de 500 casos nuevos con la misma descripción, convirtiéndose en un tema de interés nacional, pues acudieron varios representantes de medios de comunicación a la pequeña localidad a entrevistar a padres, estudiantes y políticoslocales (9, 46).

A partir de este punto, se evidenció que había de por medio un interés económico por demandas millonarias en las que se solicitaba la indemnización por parte de la empresa farmacéutica que fabricaba la vacuna a los demandantes, por la posibilidad de que se debiera a su producto (9, 46).

En el caso de Japón, la tendencia al CCU a edades más tempranas tuvo un importante aumento por lo que, como medida para contrarrestar esta tendencia, se autorizó la vacuna Gardasil 4-V en octubre de 2009, y se llevó a cabo unacampaña nacional de promoción de la vacunación contra el VPH por el Ministerio de Salud, Trabajo y Bienestar de Japón (The Ministry of Health, Labour andWelfare of Japan: MHLW) en noviembre de 2010 (12, 14).

Esta campaña tuvo resultados favorables y para marzo de 2013, la tasa de vacunación contra el VPH de al menos una dosis, entre las mujeres de 12 a 16 años se acercaba al 70-80% de inmunización. El programa tuvo tanto éxito que,en abril de 2013, el MHLW designó la vacunación contra el VPH como unainmunización rutinaria nacional, lo que hizo posible que las niñas de 12 a 16 años que cumplían los requisitos fueran vacunadas de forma gratuita (12, 45).

Sin embargo, hacia mayo de 2013, los medios de comunicación japoneses informaron de manera amplia y repetidamente de los EAG derivados de la recepción de la vacuna contra el VPH, como dolor crónico y deterioro de la movilidad poniendo en duda la seguridad de la vacuna (12, 45).

Este bombardeo mediático, hizo que la población japonesa desconfiara de la vacuna contra el VPH, tras esto el MHLW en una respuesta de preocupación, respondió anunciando la suspensión temporal de su recomendación de inoculación activa para la vacuna el 14 de junio de 2013, hasta que se dispusiera

de información más detallada (45).

Este acto provocó inmediatamente el temor de las escolares y de sus padres con respecto a la vacuna, disminuyendo la participación de la población en la vacunación contra el VPH, como consecuencia, la tasa de vacunación contra el VPH en Japón no tardó en caer hasta casi cero, y desde entonces ha permanecido así (45).

Después del cambio de política referente a la vacunación contra el VPH emitido por el MHLW en 2013, se realizó un estudio por *Yagi, A., Ueda, Y., Nakagawa, S.,et al* (49), en el cual se calcularon las posibles cifras futuras de incidencia y muerte por CCU, en donde como consecuencia de la suspensión de la vacuna contra el VPH, y el retraso en la reanudación de la recomendación, el riesgo relativo de futuras infecciones por VPH-16/18 en mujeres, será al menos comparable con el riesgo que existía antes de la introducción de la vacuna contra el VPH (14).

Dicho en números, las cifras para el año fiscal 2020 ascenderían a 12,0 mujeres por día que ahora tendrán un mayor riesgo de contraer CCU en su futuro, y 3,0 mujeres por día que corren el riesgo de morir en el futuro por esta enfermedad en su forma progresiva, situación que podría revertirse al retomar la recomendación de la vacuna lo antes posible (14, 45).

6. DISCUSIÓN.

A través del análisis bibliográfico realizado en este trabajo, basado en la gran cantidad de evidencia científica que incluye evaluaciones realizadas durante los ensayos clínicos y estudios posterior a la obtención de la licencia que muestra cada autor (2, 3, 4, 5, 7, 10, 13, 23, 33, 43), podemos confirmar que no hay datos que sugieran problemas de seguridad vinculados con el uso de las vacunas contra el virus del papiloma humano Gardasil 4-V y 9-V, lo cual coincide con las posiciones de grupos de expertos como GACVS, la EMA, la OMS así como otros organismos expertos en el tema de cada país.

Entre los EA más frecuentes reportados en los distintos artículos de esta revisión se encontraron 2 clasificaciones, los EA sistémicos; cefalea, pirexia, fatiga, náuseas, diarrea, mialgia, síncopes, mareos y dolor orofaríngeo y los EA locales; dolor, enrojecimiento e hinchazón. Los cuales coinciden por lo descrito en las fichas técnicas emitidas por la Secretaría de Salud (40), la Agencia Española de Medicamentos y productos Sanitarios (41, 42), la Agencia Europea de Medicamentos (6), así como las fichas técnicas que reporta el fabricante (31, 32).

Y como parte del análisis, se compararon los porcentajes sobre los EA más frecuentes recabados en los artículos de esta revisión con la información publicada en la base de datos de Lexicomp (31, 32) Tabla 7.

En la cual se puede apreciar una gran variación entre los porcentajes de algunos de los EA, por ejemplo, en la vacuna Gardasil 4-V, el síncope tuvo un reporte de 42.37% en el estudio de *Mauro A, et al*. (28) para el estudio de *Bonaldo et al*. (4), presentó un porcentaje de 10.85%, mientras que en la base de datos de lexicomp se presentó menos del 1% correspondiente al EA (43).

Tras informar de las posibles lesiones secundarias graves debido al síncope como son fractura de cráneo o hemorragia cerebral, Lexicomp recomendó implementar procedimientos para evitar este tipo de lesiones, así como procedimientos si se produce un sincope (43).

Del mismo modo, en el caso de la vacuna 9-V, el dolor/ eritema e hinchazón reportaron un 74% en el estudio de Van Damme et al. (45), mientras que en la base de datos de Lexicomp se reportaron por separado en intervalos de 63 a 50% para el dolor,42-7% para eritema y 45 a 13% para hinchazón (10).

En cambio, en otros EA, los reportes no tuvieron gran variación entre los artículos revisados y la base de datos. Por ejemplo, para los eventos de náuseas, en el estudio por Van Damme et al. (45) menciona un porcentaje de 1.6%, que coincide con lo descrito en Lexicomp que corresponde a un intervalo de un 1% al 4% (10).

Es por ello que la CIOMS recomienda que para el caso de la frecuencia de las RAMs siempre que sea posible, debe proporcionarse una estimación de la frecuencia expresada en una categoría de frecuencia estándar ya que es difícil estimar la incidencia a partir de las notificaciones espontáneas, debido a la incertidumbre inherente a la estimación del denominador y al grado de infranotificación (20).

Optando por la estimación estándar de las siguientes categorías de frecuencia descritas anteriormente en la Tabla 2; Muy común*^ 1 /10 (> 10%), Común (frecuente) > 1/100 y < 1/10 1% y < 10%), Poco común (infrecuente) ^ 1/1000 y < 1/100 0,1% y < 1%) Rara > 1/10.000 y < 1/1000 0,01% y < 0,1%) Muy raro* < 1/10.000 (< 0,01 %) (20).

Para entender un poco más acerca de ESAVIs no graves se analizó el estudio retrospectivo, descriptivo, realizado en pequeñas comunidades de Brasil de *Mauro et al.* (10), en el cual el autor identificó 5 grupos de ESAVI no graves en la misma escuela, el mismo día, después de la aplicación de la vacuna Gardasil 4-V. Esto evidenció que, de las 13 mujeres jóvenes vacunadas, todas presentaron los mismos eventos (10).

Los primeros signos y síntomas fueron dolor de cabeza (13 mujeres), mareos (13 mujeres), parestesia (10 mujeres) y síncope (8 mujeres) que iniciaron dos horas después de la vacunación. Los cuales fueron evaluados y resueltos en máximouna semana sin secuelas (10).

El médico de la investigación concluyó que los hechos probablemente fueron Respuestas Relacionadas con el Estrés por Inmunización (Immunization Stress Related Response; ISRR). Ya que el miedo a las inyecciones es habitual en las personas mayores, niños y adolescentes y que además se puede exacerbar en algunas situaciones de vacunación, como cuando los pacientes que esperan ser vacunados pueden observar a otros presentar ISRR (10).

De estos EA no graves, cabe destacar que el síncope es un EA que aparece únicamente en la vacuna Gardasil 4-V, según los datos observados en los artículos de esta revisión (2, 3, 4, 7, 10, 23, 25, 37, 43) y las correspondientes fichas técnicas antes mencionadas, (6, 40, 41, 42) sin embargo, en la ficha técnica del fabricante es mencionada para ambas vacunas (31, 32).

En la ficha técnica del fabricante menciona que debido a que los vacunados

pueden desarrollar un síncope, que a veces resulta en caída con lesión, se recomienda la observación durante 15 minutos después de la administración. Ya que a veces está asociado a movimientos tónico-clónicos y otras actividades similares a las convulsiones tras la vacunación. Cuando el síncope se asocia a movimientos tónico-clónicos, la actividad suele ser transitoria y suele responder al restablecimiento de la perfusión cerebral manteniendo la posición supina o de Trendelenburg (31, 32).

La explicación del por qué sucede este evento está relacionado con la estimulación del nervio vago que produce bradicardia e hipotensión transitoria que ocurre comúnmente en la población joven de hombres y mujeres (12-13 años).[2, 10, 31, 23] Sin embargo, no es asociado con la vacuna antígeno en sí, sino más bien conel proceso de vacunación, ya que también se ha observado después de la administración de otras vacunas (tétanos-difteria, hepatitis B, influenza H1N1), así como después de la extracción de sangre y la administración de fármacos parenterales, especialmente entre adolescentes y adultos jóvenes (10).

Por ejemplo, en el estudio de *Mauro A, et al* (10), en Brasil, se realizó la implementación del protocolo antes mencionado por la ficha técnica del fabricante, en el cual generó un impacto favorable importante (10).

Al observar que los pacientes presentaban este evento, tras la aplicación de la vacuna 4-V, el personal de salud hizo la recomendación a los pacientes de permanecer sentados en el entorno de vacunación al menos 15 minutos después de la aplicación de la vacuna y tras la implementación de esta medida se observó que el número de EA reportados disminuyó (2, 10).

En el caso de los ESAVI graves descritos en la **tabla 10**, se han realizado

numerosos esfuerzos para determinar la causalidad entre estos eventos con las vacunas Gardasil 4-V y 9-V, siendo de especial atención que la anafilaxia ha sido el único EA grave asociado con las vacunas Gardasil 4-V y 9-V, con un reporte de tasa de incidencia de 1.7 casos por cada millón de dosis según la VSD (VSD: vaccine safety datalink) (2).

En este caso, su relación se debe a la hipersensibilidad que presentan los pacientes de manera individualizada a alguno de sus componentes, como se presentaría en el caso de cualquier otra vacuna (2).

Con respecto a otros EAG, *Philips, A. et al.* (2), en el 2018 comparó la tasa de EA como Tromboembolismo venoso, Parálisis nerviosa, Síndrome de taquicardia ortostática postural, síndrome de dolor regional complejo etc, (**tabla 10)** pudo evidenciar que no existían cambios en la incidencia antes y después de la introducción de la campaña de vacunación. Por lo que las vacunas demostraron un perfil de seguridad aceptable sin evidencia consistente de un aumento de riesgo o causalidad de cualquier EA después de la vacunación contra el VPH (2).

En el estudio realizado en Sao Paulo en el periodo de 2014-2016 para la vacuna Gardasil 4-V, se identificaron 39 casos de EA graves debido a que resultaron en hospitalización mayor a 24 horas, entre las manifestaciones reportadas se encontraban: Síndrome de Guillan-Barré, trombosis venosa profunda de las extremidades superiores, convulsiones y un aborto espontáneo asociado temporalmente con la vacuna Gardasil 4-V, al observar esto los investigadores compararon con la tasa de EA, sin mostrar un aumento significativo en la incidencia de estas enfermedades, por lo que no se encontró evidencia de la asociación después de la vacunación contra el VPH (10).

Uno de los estudios de mayor relevancia acerca de los EAG asociados con la vacuna Gardasil 4-V, es el desarrollado por la Universidad de Adelaide dirigido por *J. Parsons et al.* (5), en el año 2017, una revisión sistemática que identificó reportes de EA en las siguientes categorías: Cualquier EAG, Enfermedades autoinmunes, Tromboembolismo venoso, Esclerosis múltiple y otras condiciones desmielinizantes (5).

En esta revisión sistemática se incluyó una cohorte dirigida por *Arnheim-Dahlstrom et al.* (5), con una población estudiada de mujeres, la cual se dividía en dos grupos dependiendo si se les había administrado o no la vacuna contra el VPH 4-V. Utilizaron un periodo de riesgo de 180 días después de la vacunación, en el cual se registraron 23 resultados de enfermedades autoinmunes, de las cuales sólo 3 enfermedades se asociaron significativamente; Síndrome de Behcet, Enfermedad de Raynaud y Diabetes tipo 1. Los autores investigaron la fuerza de la señal con una estrategia analítica predefinida y no se evidenció una asociación causal entre los eventos y la vacuna (5).

Mientras que en el estudio de *Gee et al.* (5), la cohorte incluyó a mujeres de los centros registrados, consultas médicas externas, servicios de urgencias y hospitales que tenían edades entre 9 y 26 años, que además recibieron por lo menos una dosis de la vacuna 4-V. Los datos fueron obtenidos de siete organizaciones provenientes de diferentes regiones de los E.U.A., con el fin de investigar una serie de eventos como: anafilaxia, reacciones alérgicas, apendicitis, Síndrome de Guillain-Barré, convulsiones, accidentes cerebrovasculares, síncopey Tromboembolismo venoso (5).

La cohorte fue comparada con un grupo histórico no vacunado contra el VPH para los resultados menos comunes, y un grupo concurrente no expuesto para los

resultados más comunes. De todos los resultados investigados, no se observó un aumento de las tasas de convulsiones, reacciones alérgicas o síncopes. Se identificó un riesgo aumentado de apendicitis en los jóvenes; sin embargo, el análisis de los datos no encontró ninguna agrupación relacionada, los autores sospecharon que el cambio puede deberse a la codificación en un centro que afectó a las tasas de fondo (5).

Se identificó y revisó en este mismo estudio un caso de GBS el cual se comprobó que no era un caso nuevo y que no existía una relación entre el evento y la vacuna. Por otra parte, se confirmó un caso de anafilaxia relacionado con la vacuna en un joven de 26 años, lo cual coincide con lo anteriormente mencionado acerca de la anafilaxia (5).

Ahora bien, es de gran relevancia recalcar la definición de un EA y un ESAVI, en el caso de un EA este es considerado por la *NOM-220-SSA1-2016* como cualquier suceso médico indeseable que pueda presentarse en un sujeto de investigación durante la etapa de investigación clínica de un medicamento o vacuna pero que no necesariamente tiene una relación causal con el mismo (1), y un ESAVI se refiere a la(s) manifestación(es) clínica(s) o evento médico que ocurren después de la vacunación y son supuestamente atribuidos a la vacunación o inmunización en las cuales la temporalidad dependerá de cada una de las vacunas (1). Sin embargo, para ambos casos como han señalado otros autores, la relación temporal de estos eventos con una vacuna no significa causalidad (23).

Es por eso que para la detección e identificación de los EA, se lleva a cabo el método de farmacovigilancia pasiva y activa (20, 23) pues esta combinación de sistemas de seguridad puede proporcionar un medio completo para el monitoreo

de la seguridad de las vacunas 4-V y 9-V, y representan una de las evaluaciones de seguridad más amplias (33).

Sin embargo, estas presentan algunas limitaciones importantes, por ejemplo, en la farmacovigilancia pasiva la información recopilada es a menudo incompleta, y la información rara vez es suficiente para establecer una relación causal entre la administración de la vacuna y un resultado de salud concreto, por lo que requiere de realizar más investigación (23). Sin embargo, sólo se detectan ESAVI raros con eluso de este programa, lo que hace que sea esencial para garantizar la seguridad de las vacunas (10).

Ahora bien, para la farmacovigilancia activa (20, 23) cobra relevancia el diseño de los estudios realizados, considerando una población diversa y de número representativo (2). Así como considerar la calidad de la información de los estudios empleados (menor a mayor): Series de casos, Sistemas de reporte espontáneo, Estudios observacionales, Ensayos clínicos no aleatorios, Ensayos clínicos aleatorios y Metaanálisis (Revisión sistemática) (2).

Son múltiples las experiencias sobre la inmunización contra el VPH en todo el mundo, muchas de ellas con resultados favorables, por lo que es de vital importancia conocer sus avances, dificultades y resultados, con el fin de mantener y alcanzar objetivos similares (13).

En la cual destaca el impacto de la aceptación o rechazo ante las campañas de vacunación dependiente del grado de información que la población dispone y comprende acerca de las vacunas contra el VPH (13).

En consecuencia, se esperaría que las tasas de inmunización no se afectarán por la presencia de EA o por el temor a padecerlos; por ejemplo, existen programas

que no presentaron incidencias negativas en sus metas establecidas; España (75%), Australia (80%), Perú (82%), Canadá (81%), el Reino Unido (84-92%), Uganda (89%), Ruanda (93%) y Vietnam (96%) (13).

El mantenimiento de las tasas de cobertura mostró que, aunque la captación de esta población es un nuevo desafío, las estrategias planteadas que han surtido efecto son:

1. Mejorar la demanda de adolescentes al sistema mediante captación por actores de salud y docentes.
2. Aprovechar cada visita médica como oportunidad para vacunar y completar el esquema.
3. Requerimiento obligatorio de la vacunación para el ingreso a secundaria.
4. Brindar información sobre la vacuna con mensajes claros, concretos y accesibles.
5. Medios de comunicación utilizados por adolescentes como vías para una comunicación eficaz (13).

Sin embargo, también se han documentado estrategias con resultados desfavorables, como sucedió en Japón y Colombia, donde estos porcentajes se vieron afectados debido a la difusión de información sobre la seguridad a través de los medios de comunicación que informaron de manera amplia y repetida los EAG derivados de la recepción de la vacuna contra el VPH sin la evaluación de la causalidad correspondiente, poniendo en duda la seguridad de la vacuna (12, 45).

Claramente el programa de vacunación contra el VPH sigue enfrentando un mal momento en estos países debido a la desinformación por parte de los medios, aunque existan evidencias científicas sólidas generadas por organismos serios e

imparciales a nivel internacional que sustentan la seguridad de la vacunación y la importancia de su aplicación en edades tempranas (28).

Por lo que como aprendizaje frente a esta situación solo podemos recalcar lo importante y necesaria que es la correcta comunicación del riesgo de las vacunas, ya que, aunque se descarten ESAVIs, se deja en entredicho su seguridad y pone en juego la confianza de la sociedad en esta herramienta importante y probada (13).

En consecuencia, lo recomendado es dar a la comunidad una respuesta rápidaque incluya ayuda médica, la investigación del ESAVI, la aclaración de las preocupaciones a la población y la transparencia en el proceso, todo esto con el fin de mantener la confianza del público en el programa (10).

Esto mediante prácticas que doten a los profesionales de salud de herramientas de comunicación y respeto de las creencias de otros, la sensibilización a los medios de comunicación sobre los aspectos de la vacunación, con el fin de aclarar inquietudes y dilucidar desinformación (13).

7. CONCLUSIONES

Se realizó una revisión bibliográfica sobre el perfil de seguridad de las vacunas Gardasil 4-V y 9-V contra el VPH en el periodo comprendido de 2015 -2020, en la cual para la detección de los EA tras la Vacunación contra el VPH se identificaron estrategias como la farmacovigilancia activa y pasiva, estrategias que han demostrado obtener un monitoreo más completo con relación a la seguridad de las vacunas 4-V y 9-V.

A través de las cuales se documentaron ESAVI no graves como: dolor de cabeza, síncope, mareos, náuseas, fatiga, pirexia, eritema, dolor e hinchazón. Y ESAVI graves como: Anafilaxia, Síndrome de Guillain-Barre, Tromboembolismo Venoso, Accidente Cerebrovascular, Parálisis Nerviosa, Síndrome de Taquicardia Ortostática Postural, Síndrome de Dolor Regional Complejo etc. Destacando que el único ESAVI grave con relación causal con las vacunas Gardasil 4-V Y 9-V es la anafilaxia, que además presenta una frecuencia catalogada como muy rara y que además este ESAVI puede presentarse en cualquier otra vacuna.

Ahora bien, un manejo inadecuado sobre la información de los ESAVI (especialmente los catalogados como graves), puede resultar en consecuencias desafortunadas, casos ejemplificados con la suspensión de los programas de inmunización contra el VPH en Japón y Colombia.

Por lo que, de acuerdo con la evidencia recabada en esta revisión, se puede concluir que las vacunas Gardasil 4-V y 9-V presenta un perfil de seguridadfavorable para su uso.

Perspectivas.

De acuerdo con lo anterior descrito en el trabajo realizado, uno de los puntos a destacar es la comunicación efectiva sobre los riesgos de la vacunación, enfatizando la seguridad de las vacunas. Ya que de este punto dependerá si los programas de vacunación son aceptados por parte de la población y de esta manera se alcancen las tasas de vacunación objetivo.

Por lo cual, se sugiere que en las campañas de vacunación no solo se consideré el reporte y análisis de la causalidad de los ESAVI sino también la implementación de prácticas que doten de herramientas de comunicación y sensibilización a los profesionales de la salud y los medios informativos, para asegurar que todos los participantes comprendan los riesgos y beneficios sobre la inmunización.

8. REFERENCIAS

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ANEXO I. FICHAS TÉCNICAS DEL FABRICANTE DE LAS VACUNAS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GARDASIL safely and effectively. See full prescribing information for GARDASIL.
GARDASIL®
[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18)Vaccine, Recombinant]
Suspension for intramuscular injection
Initial U.S. Approval: 2006

---------- INDICATIONS AND USAGE ----------

GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16and 18 (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11 (1.1)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervicaladenocarcinoma *in situ* (AIS) (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1 (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 (1.1)

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types includedin the vaccine:

- Anal cancer caused by HPV types 16 and 18 (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11 (1.2)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

Limitations of GARDASIL Use and Effectiveness:

- GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3,17)
- Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider. (1.3, 17)
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.(1.3, 14.4, 14.5)
- GARDASIL is not intended to be used for treatment ofactive external genital lesions; cervical, vulvar, vaginal, and anal cancers;CIN; VIN; VaIN, or AIN. (1.3)
- GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. (1.3, 14.4, 14.5)
- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal, and anal cancers caused by HPV 16 and 18. (1.3)
- GARDASIL does not protect against genital diseases not caused by HPV. (1.3)
- Vaccination with GARDASIL may not result in protection in all vaccine recipients. (1.3)
- GARDASIL has not been demonstrated to prevent HPV-related CIN 2/3 or worse in women older than 26 years of age. (14.7)

---------- DOSAGE AND ADMINISTRATION ----------

0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

---------- CONTRAINDICATIONS ----------

- Hypersensitivity, including severe allergic reactions to yeast (avaccine component), or after a previous dose of GARDASIL. (4,11)

----------WARNINGS AND PRECAUTIONS----------

- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

---------- ADVERSE REACTIONS----------

The most common adverse reaction was headache. Common adverse reactions (frequency of at least 1.0% and greater than AAHS control or saline placebo) are fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, andbruising. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877- 888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- DRUG INTERACTIONS ----------

GARDASIL may be administered concomitantly with RECOMBIVAX HB® (7.1) or with Menactra and Adacel. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Safety and effectiveness of GARDASIL have not been established in the following populations:

- Pregnant women. Women who receive GARDASIL during pregnancy are encouraged to contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231. (8.1)
- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL may be diminished. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing informationare not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Girls and Women

GARDASIL® is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.2 Boys and Men

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.3 Limitations of GARDASIL Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care. *[See Patient Counseling Information (17).]*

Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider. *[See Patient Counseling Information (17).]*

GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity. *[See Clinical Studies (14.4, 14.5).]*

GARDASIL is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

GARDASIL has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine. *[See Clinical Studies (14.4, 14.5).]*

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal, and anal cancers caused by HPV 16 and 18.

GARDASIL does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL may not result in protection in all vaccine recipients.

GARDASIL has not been demonstrated to prevent HPV-related CIN 2/3 or worse in women older than 26 years of age. *[See Clinical Studies (14.7).]*

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

GARDASIL should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months. *[See Clinical Studies (14.8).]*

2.2 Method of Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Syncope has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. *[See Warnings and Precautions (5.1).]*

Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

Prefilled Syringe Use

This package does not contain a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

3 DOSAGE FORMS AND STRENGTHS

GARDASIL is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. *[See Description (11).]*

5 WARNINGS AND PRECAUTIONS

5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL.

6 ADVERSE REACTIONS

Overall Summary of Adverse Reactions

Headache, fever, nausea, and dizziness; and local injection site reactions (pain, swelling, erythema, pruritus, and bruising) occurred after administration with GARDASIL.

Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL and may result in falling with injury; observation for 15 minutes after administration is recommended. *[See Warnings and Precautions (5.1).]*

Anaphylaxis has been reported following vaccination with GARDASIL.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Studies in Girls and Women (9 Through 45 Years of Age) and Boys and Men (9 Through 26 Years of Age)

In 7 clinical trials (5 Amorphous Aluminum Hydroxyphosphate Sulfate [AAHS]-controlled, 1 saline placebo-controlled, and 1 uncontrolled), 18,083 individuals were administered GARDASIL or AAHS control or saline placebo on the day of enrollment, and approximately 2 and 6 months thereafter, and safety was evaluated using vaccination report cards (VRC)-aided surveillance for 14 days after each injection of GARDASIL or AAHS control or saline placebo in these individuals. The individuals who were monitored using VRC-aided surveillance included 10,088 individuals 9 through 45 years of age at enrollment who received GARDASIL and 7,995 individuals who received AAHS control or saline placebo. Few individuals (0.2%) discontinued due to adverse reactions. The race distribution of the 9- through 26- year-old girls and women in the safety population was as follows: 62.3% White; 17.6% Hispanic (Black and White); 6.8% Asian; 6.7% Other; 6.4% Black; and 0.3% American Indian. The race distribution of the 24- through 45-year-old women in the safety population of Study 6 was as follows: 20.6% White; 43.2% Hispanic (Black and White); 0.2% Other; 4.8% Black; 31.2% Asian; and 0.1% American Indian. The race distribution of the 9- through 26-year-old boys and men in the safety population was as follows: 42.0% White; 19.7% Hispanic (Black and White); 11.0% Asian; 11.2% Other; 15.9% Black; and 0.1% American Indian.

Common Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age

The injection site adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients are shown in Table 1.

Table 1: Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	**GARDASIL** (N = 5088) %	**AAHS Control†** (N = 3470) %	**Saline Placebo** (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Pruritus	3.2	2.8	0.6
Bruising	2.8	3.2	1.6

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.

†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Common Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age

The injection site adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients are shown in Table 2.

Table 2: Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	**GARDASIL** (N = 3093) %	**AAHS Control†** (N = 2029) %	**Saline Placebo** (N = 274) %
Injection Site			
Pain	61.4	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2
Hematoma	1.0	0.3	3.3

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Evaluation of Injection-Site Adverse Reactions by Dose in Girls and Women 9 Through 26 Years of Age

An analysis of injection-site adverse reactions in girls and women by dose is shown in Table 3. Of those girls and women who reported an injection-site reaction, 94.3% judged their injection-site adverse reaction to be mild or moderate in intensity.

Table 3: Postdose Evaluation of Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age (1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			**AAHS Control*** (% occurrence)			**Saline Placebo** (% occurrence)		
Adverse Reaction	Post-dose 1 N† = 5011	Post-dose 2 N = 4924	Post-dose 3 N = 4818	Post-dose 1 N = 3410	Post-dose 2 N = 3351	Post-dose 3 N = 3295	Post-dose 1 N = 315	Post-dose 2 N = 301	Post-dose 3 N = 300
Pain	63.4	60.7	62.7	57.0	47.8	49.6	33.7	20.3	27.3
Mild/Moderate	62.5	59.7	61.2	56.6	47.3	48.9	33.3	20.3	27.0
Severe	0.9	1.0	1.5	0.4	0.5	0.6	0.3	0.0	0.3
Swelling‡	10.2	12.8	15.1	8.2	7.5	7.6	4.4	3.0	3.3
Mild/Moderate	9.6	11.9	14.2	8.1	7.2	7.3	4.4	3.0	3.3
Severe	0.6	0.8	0.9	0.2	0.2	0.2	0.0	0.0	0.0
Erythema‡	9.2	12.1	14.7	9.8	8.4	8.9	7.3	5.3	5.7
Mild/Moderate	9.0	11.7	14.3	9.5	8.4	8.8	7.3	5.3	5.7
Severe	0.2	0.3	0.4	0.3	0.1	0.1	0.0	0.0	0.0

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†N = Number of individuals with follow-up
‡Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Evaluation of Injection-Site Adverse Reactions by Dose in Boys and Men 9 Through 26 Years of Age

An analysis of injection-site adverse reactions in boys and men by dose is shown in Table 4. Of those boys and men who reported an injection-site reaction, 96.4% judged their injection-site adverse reaction to be mild or moderate in intensity.

Table 4: Postdose Evaluation of Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age (1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			**AAHS Control*** (% occurrence)			**Saline Placebo** (% occurrence)		
Adverse Reaction	Post-dose 1 N† = 3003	Post-dose 2 N = 2898	Post-dose 3 N = 2826	Post-dose 1 N = 1950	Post-dose 2 N = 1854	Post-dose 3 N = 1799	Post-dose 1 N = 269	Post-dose 2 N = 263	Post-dose 3 N = 259
Pain	44.7	36.9	34.4	38.4	28.2	25.8	27.5	20.5	16.2
Mild/Moderate	44.5	36.4	34.1	37.9	28.2	25.5	27.5	20.2	16.2
Severe	0.2	0.5	0.3	0.4	0.1	0.3	0.0	0.4	0.0
Swelling‡	5.6	6.6	7.7	5.6	4.5	4.1	4.8	1.5	3.5
Mild/Moderate	5.3	6.2	7.1	5.4	4.5	4.0	4.8	1.5	3.1
Severe	0.2	0.3	0.5	0.2	0.0	0.1	0.0	0.0	0.4
Erythema‡	7.2	8.0	8.7	8.3	6.3	5.7	7.1	5.7	5.0
Mild/Moderate	6.8	7.7	8.3	8.0	6.2	5.6	7.1	5.7	5.0
Severe	0.3	0.2	0.3	0.2	0.1	0.1	0.0	0.0	0.0

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†N = Number of individuals with follow-up
‡Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 28.2% and AAHS control or saline placebo = 28.4%). Fever was the next most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 13.0% and AAHS control or saline placebo = 11.2%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the GARDASIL group was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 5.

Table 5: Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age (GARDASIL ≥Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL** (N = 5088) %	**AAHS Control† or Saline Placebo** (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.5
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

*The adverse reactions in this table are those that were observed among recipients of GARDASIL at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.
†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age

Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 12.3% and AAHS control or saline placebo = 11.2%). Fever was the next most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 8.3% and AAHS control or saline placebo = 6.5%).

Adverse reactions that were observed among recipients of GARDASIL, at a frequency of greater than or equal to 1.0% where the incidence in the group that received GARDASIL was greater than or equal to the incidence in the AAHS control or saline placebo group, are shown in Table 6.

Table 6: Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age (GARDASIL ≥Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	**GARDASIL** (N = 3093) %	**AAHS Control† or Saline Placebo** (N = 2303) %
Headache	12.3	11.2
Pyrexia	8.3	6.5
Oropharyngeal pain	2.8	2.1
Diarrhea	2.7	2.2
Nasopharyngitis	2.6	2.6
Nausea	2.0	1.0
Upper respiratory tract infection	1.5	1.0
Abdominal pain upper	1.4	1.4
Myalgia	1.3	0.7
Dizziness	1.2	0.9
Vomiting	1.0	0.8

*The adverse reactions in this table are those that were observed among recipients of GARDASIL at a frequency of at least 1.0% and greater than or equal to those observed among AAHS control or saline placebo recipients.
†AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Evaluation of Fever by Dose in Girls and Women 9 Through 26 Years of Age

An analysis of fever in girls and women by dose is shown in Table 7.

Table 7: Postdose Evaluation of Fever in Girls and Women 9 Through 26 Years of Age (1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N† = 4945	Postdose 2 N = 4804	Postdose 3 N = 4671	Postdose 1 N = 3681	Postdose 2 N = 3564	Postdose 3 N = 3467
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.2	0.4	0.5

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†N = Number of individuals with follow-up

Evaluation of Fever by Dose in Boys and Men 9 Through 26 Years of Age

An analysis of fever in boys and men by dose is shown in Table 8.

Table 8: Postdose Evaluation of Fever in Boys and Men 9 Through 26 Years of Age (1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N† = 2972	Postdose 2 N = 2849	Postdose 3 N = 2792	Postdose 1 N = 2194	Postdose 2 N = 2079	Postdose 3 N = 2046
≥100 to <102	2.4	2.5	2.3	2.1	2.2	1.6
≥102	0.6	0.5	0.5	0.5	0.3	0.3

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†N = Number of individuals with follow-up

Serious Adverse Reactions in the Entire Study Population

Across the clinical studies, 258 individuals (GARDASIL N = 128 or 0.8%; placebo N = 130 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men) reported a serious systemic adverse reaction.

Of the entire study population (29,323 individuals), 0.04% of the reported serious systemic adverse reactions were judged to be vaccine related by the study investigator. The most frequently (frequency of 4 cases or greater with either GARDASIL, AAHS control, saline placebo, or the total of all three) reported serious systemic adverse reactions, regardless of causality, were:

Headache [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],
Gastroenteritis [0.02% GARDASIL (3 cases) vs. 0.02% AAHS control (2 cases)],
Appendicitis [0.03% GARDASIL (5 cases) vs. 0.01% AAHS control (1 case)],
Pelvic inflammatory disease [0.02% GARDASIL (3 cases) vs. 0.03% AAHS control (4 cases)],
Urinary tract infection [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)],
Pneumonia [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)],
Pyelonephritis [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (3 cases)],
Pulmonary embolism [0.01% GARDASIL (2 cases) vs. 0.02% AAHS control (2 cases)].

One case (0.006% GARDASIL; 0.0% AAHS control or saline placebo) of bronchospasm; and 2 cases (0.01% GARDASIL; 0.0% AAHS control or saline placebo) of asthma were reported as serious systemic adverse reactions that occurred following any vaccination visit.

In addition, there was 1 individual in the clinical trials, in the group that received GARDASIL, who reported two injection-site serious adverse reactions (injection-site pain and injection-site joint movement impairment).

Deaths in the Entire Study Population

Across the clinical studies, 40 deaths (GARDASIL N = 21 or 0.1%; placebo N = 19 or 0.1%) were reported in 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023, saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men). The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident (5 individuals who received GARDASIL and 4 individuals who received AAHS control), followed by drug overdose/suicide (2 individuals who received GARDASIL and 6 individuals who received AAHS control), gunshot wound (1 individual who received GARDASIL and 3 individuals who received AAHS control), and pulmonary embolus/deep vein thrombosis (1 individual who received GARDASIL and 1 individual who received AAHS control). In addition, there

were 2 cases of sepsis, 1 case of pancreatic cancer, 1 case of arrhythmia, 1 case of pulmonarytuberculosis, 1 case of hyperthyroidism, 1 case of post-operative pulmonary embolism and acute renal failure, 1 case of traumatic brain injury/cardiac arrest, 1 case of systemic lupus erythematosus, 1 case of cerebrovascular accident, 1 case of breast cancer, and 1 case of nasopharyngeal cancer in the group that received GARDASIL; 1 case of asphyxia, 1 case of acute lymphocytic leukemia, 1 case of chemical poisoning, and 1 case of myocardial ischemia in the AAHS control group; and 1 case of medulloblastoma in the saline placebo group.

Systemic Autoimmune Disorders in Girls and Women 9 Through 26 Years of Age

In the clinical studies, 9- through 26-year-old girls and women were evaluated for new medical conditions that occurred over the course of follow-up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL or AAHS control or saline placebo are shown in Table 9. This population includes all girls and women who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

Table 9: Summary of Girls and Women 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 10,706)	AAHS Control* or Saline Placebo (N = 9412)
	n (%)	n (%)
Arthralgia/Arthritis/Arthropathy†	120 (1.1)	98 (1.0)
Autoimmune Thyroiditis	4 (0.0)	1 (0.0)
Celiac Disease	10 (0.1)	6 (0.1)
Diabetes Mellitus Insulin-dependent	2 (0.0)	2 (0.0)
Erythema Nodosum	2 (0.0)	4 (0.0)
Hyperthyroidism‡	27 (0.3)	21 (0.2)
Hypothyroidism§	35 (0.3)	38 (0.4)
Inflammatory Bowel Disease¶	7 (0.1)	10 (0.1)
Multiple Sclerosis	2 (0.0)	4 (0.0)
Nephritis#	2 (0.0)	5 (0.1)
Optic Neuritis	2 (0.0)	0 (0.0)
Pigmentation Disorderᵖ	4 (0.0)	3 (0.0)
Psoriasisß	13 (0.1)	15 (0.2)
Raynaud's Phenomenon	3 (0.0)	4 (0.0)
Rheumatoid Arthritisà	6 (0.1)	2 (0.0)
Scleroderma/Morphea	2 (0.0)	1 (0.0)
Stevens-Johnson Syndrome	1 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	1 (0.0)	3 (0.0)
Uveitis	3 (0.0)	1 (0.0)
All Conditions	245 (2.3)	218 (2.3)

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†Arthralgia/Arthritis/Arthropathy includes the following terms: Arthralgia, Arthritis, Arthritis reactive, and Arthropathy
‡Hyperthyroidism includes the following terms: Basedow's disease, Goiter, Toxic nodular goiter, and Hyperthyroidism
§Hypothyroidism includes the following terms: Hypothyroidism and thyroiditis
¶Inflammatory bowel disease includes the following terms: Colitis ulcerative, Crohn's disease, and Inflammatory bowel disease
#Nephritis includes the following terms: Nephritis, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative
ᵖPigmentation disorder includes the following terms: Pigmentation disorder, Skin depigmentation, and Vitiligo
ßPsoriasis includes the following terms: Psoriasis, Pustular psoriasis, and Psoriatic arthropathy
àRheumatoid arthritis includes juvenile rheumatoid arthritis. One woman counted in the rheumatoid arthritis group reported rheumatoid arthritis as an adverse experience at Day 130.
N = Number of individuals enrolled
n = Number of individuals with specific new Medical Conditions
NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Systemic Autoimmune Disorders in Boys and Men 9 Through 26 Years of Age

In the clinical studies, 9- through 26-year-old boys and men were evaluated for new medical conditions that occurred over the course of follow-up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL or AAHS control or saline placebo are shown in Table 10. This population includes all boys and men who received at least one dose of GARDASIL or AAHS control or saline placebo, and had safety data available.

Table 10: Summary of Boys and Men 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 3093)	AAHS Control* or Saline Placebo (N = 2303)
	n (%)	n (%)
Alopecia Areata	2 (0.1)	0 (0.0)
Ankylosing Spondylitis	1 (0.0)	2 (0.1)
Arthralgia/Arthritis/Reactive Arthritis	30 (1.0)	17 (0.7)
Autoimmune Thrombocytopenia	1 (0.0)	0 (0.0)
Diabetes Mellitus Type 1	3 (0.1)	2 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.0)
Hypothyroidism†	3 (0.1)	0 (0.0)
Inflammatory Bowel Disease‡	1 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	4 (0.2)
Skin Depigmentation	1 (0.0)	0 (0.0)
Vitiligo	2 (0.1)	5 (0.2)
All Conditions	46 (1.5)	34 (1.5)

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
†Hypothyroidism includes the following terms: Hypothyroidism and Autoimmune thyroiditis
‡Inflammatory bowel disease includes the following terms: Colitis ulcerative and Crohn's disease
N = Number of individuals who received at least one dose of either vaccine or placebo
n = Number of individuals with specific new Medical Conditions
NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Safety in Concomitant Use with RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] in Girls and Women 16 Through 23 Years of Age

The safety of GARDASIL when administered concomitantly with RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] was evaluated in an AAHS-controlled study of 1871 girls and women with a mean age of 20.4 years *[see Clinical Studies (14.10)]*. The race distribution of the study individuals was as follows: 61.6% White; 23.8% Other; 11.9% Black; 1.6% Hispanic (Black and White); 0.8% Asian; and 0.3% American Indian. The rates of systemic and injection-site adverse reactions were similar among girls and women who received concomitant vaccination as compared with those who received GARDASIL or RECOMBIVAX HB [hepatitis B vaccine (recombinant)].

Safety in Concomitant Use with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]

The safety of GARDASIL when administered concomitantly with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] was evaluated in a randomized study of 1040 boys and girls with a mean age of 12.6 years *[see Clinical Studies (14.11)]*. The race distribution of the study subjects was as follows: 77.7% White; 1.4% Multi-racial; 12.3% Black; 6.8% Hispanic (Black and White); 1.2% Asian; 0.4% American Indian, and 0.2% Indian.

There was an increase in injection-site swelling reported at the injection site for GARDASIL (concomitant = 10.9%, non-concomitant = 6.9%) when GARDASIL was administered concomitantly with Menactra and Adacel as compared to non-concomitant (separated by 1 month) vaccination. The majority of injection-site swelling adverse experiences were reported as being mild to moderate in intensity.

Safety in Women 27 Through 45 Years of Age

The adverse reaction profile in women 27 through 45 years of age was comparable to the profile seen in girls and women 9 through 26 years of age.

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during post-approval use of GARDASIL. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Nausea, pancreatitis, vomiting.

General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Infections and infestations: cellulitis.

Vascular disorders: Deep venous thrombosis.

7 DRUG INTERACTIONS

7.1 Use with RECOMBIVAX HB

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] *[see Clinical Studies (14.10)]*.

7.2 Use with Menactra and Adacel

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] *[see Clinical Studies (14.11)]*.

7.3 Use with Hormonal Contraceptives

In clinical studies of 16- through 26-year-old women, 13,912 (GARDASIL N = 6952; AAHS control or saline placebo N = 6960) who had post-Month 7 follow-up used hormonal contraceptives for a total of 33,859 person-years (65.8% of the total follow-up time in the studies).

In one clinical study of 24- through 45-year-old women, 1357 (GARDASIL N = 690; AAHS control N = 667) who had post-Month 7 follow-up used hormonal contraceptives for a total of 3400 person-years (31.5% of the total follow-up time in the study). Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not impair the immune response in the per protocol immunogenicity (PPI) population.

7.4 Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines *[see Use in Specific Populations (8.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rats at doses equivalent to the recommended human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, GARDASIL should be used during pregnancy only if clearly needed.

An evaluation of the effect of GARDASIL on embryo-fetal, pre- and postweaning development was conducted using rats. One group of rats was administered GARDASIL twice prior to gestation, during the period of organogenesis (gestation Day 6) and on lactation Day 7. A second group of pregnant rats was administered GARDASIL during the period of organogenesis (gestation Day 6) and on lactation Day 7 only. GARDASIL was administered at 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to

the recommended human dose) by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring.

Clinical Studies in Humans

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

GARDASIL is not indicated for women 27 years of age or older. However, safety data in women 16 through 45 years of age was collected, and 3819 women (GARDASIL N = 1894 vs. AAHS control or saline placebo N = 1925) reported at least 1 pregnancy each.

The overall proportions of pregnancies that resulted in an adverse outcome, defined as the combined numbers of spontaneous abortion, late fetal death, and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22.6% (446/1973) in women who received GARDASIL and 23.1% (460/1994) in women who received AAHS control or saline placebo.

Overall, 55 and 65 women in the group that received GARDASIL or AAHS control or saline placebo, respectively (2.9% and 3.4% of all women who reported a pregnancy in the respective vaccination groups), experienced a serious adverse reaction during pregnancy. The most common events reported were conditions that can result in Caesarean section (e.g., failure of labor, malpresentation, cephalopelvic disproportion), premature onset of labor (e.g., threatened abortions, premature rupture of membranes), and pregnancy-related medical problems (e.g., pre-eclampsia, hyperemesis). The proportions of pregnant women who experienced such events were comparable between the groups receiving GARDASIL and AAHS control or saline placebo.

There were 45 cases of congenital anomaly in pregnancies that occurred in women who received GARDASIL and 34 cases of congenital anomaly in pregnancies that occurred in women who received AAHS control or saline placebo.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or AAHS control or saline placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that received AAHS control or saline placebo. The congenital anomalies seen in pregnancies withestimated onset within 30 days of vaccination included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia, and club foot. Conversely, in pregnancies with onset more than 30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received GARDASIL compared with 33 cases of congenital anomaly in the group that received AAHS control or saline placebo.

Women who receive GARDASIL during pregnancy are encouraged to contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

8.3 Nursing Mothers

Women 16 Through 45 Years of Age

It is not known whether GARDASIL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

GARDASIL or AAHS control were given to a total of 1133 women (vaccine N = 582, AAHS control N = 551) during the relevant Phase 3 clinical studies.

Overall, 27 and 13 infants of women who received GARDASIL or AAHS control, respectively (representing 4.6% and 2.4% of the total number of women who were breast-feeding during the period in which they received GARDASIL or AAHS control, respectively), experienced a serious adverse reaction.

In a post-hoc analysis of clinical studies, a higher number of breast-feeding infants (n = 7) whose mothers received GARDASIL had acute respiratory illnesses within 30 days post vaccination of the mother as compared to infants (n = 2) whose mothers received AAHS control.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

8.5 Geriatric Use

The safety and effectiveness of GARDASIL have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

8.6 Immunocompromised Individuals

The immunologic response to GARDASIL may be diminished in immunocompromised individuals *[see Drug Interactions (7.4)]*.

10 OVERDOSAGE

There have been reports of administration of higher than recommended doses of GARDASIL.

In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL.

11 DESCRIPTION

GARDASIL, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine,50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL is a white, cloudy liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

GARDASIL administered to female rats at a dose of 120 mcg total protein, which is equivalent to the recommended human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

The effect of GARDASIL on male fertility has been studied in male rats at an intramuscular dose of 0.5 mL/rat/occasion (120 mcg total protein which is equivalent to the recommended human dose). One group of male rats was administered GARDASIL once, 3 days prior to cohabitation, and a second group of male rats was administered GARDASIL three times, at 6 weeks, 3 weeks, and 3 days prior to cohabitation.

There were no treatment-related effects on reproductive performance including fertility, sperm count, and sperm motility. There were no treatment-related gross or histomorphologic and weight changes on the testes.

14 CLINICAL STUDIES

CIN 2/3 and AIS are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer; thus, they serve as surrogate markers for prevention of cervical cancer. In the clinical studies in girls and women aged 16 through 26 years, cases of CIN 2/3 and AIS were the efficacy endpoints to assess prevention of cervical cancer. In addition, cases of VIN 2/3 and VaIN 2/3 were the efficacy endpoints to assess prevention of HPV-related vulvar and vaginal cancers, and observations of external genital lesions were the efficacy endpoints for the prevention of genital warts.

In clinical studies in boys and men aged 16 through 26 years, efficacy was evaluated using the following endpoints: external genital warts and penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer. In addition, cases of AIN grades 1/2/3 and anal cancer made up the composite efficacy endpoint used to assess prevention of HPV-related anal cancer.

Anal HPV infection, AIN, and anal cancer were not endpoints in the studies conducted in women. The similarity of HPV-related anal disease in men and women supports bridging the indication of prevention of AIN and anal cancer to women.

Efficacy was assessed in 6 AAHS-controlled, double-blind, randomized Phase 2 and 3 clinical studies. The first Phase 2 study evaluated the HPV 16 component of GARDASIL (Study 1, N = 2391 16- through 26-year-old girls and women) and the second evaluated all components of GARDASIL (Study 2, N = 551 16- through 26-year-old girls and women). Two Phase 3 studies evaluated GARDASIL in 5442 (Study 3) and 12,157 (Study 4) 16- through 26-year-old girls and women. A third Phase 3 study, Study 5, evaluated GARDASIL in 4055 16- through 26-year-old boys and men, including a subset of 598 (GARDASIL = 299; placebo = 299) men who self-identified as having sex with men (MSM population). A fourth Phase 3 study, Study 6, evaluated GARDASIL in 3817 24- through 45-year-old women. Together, these six studies evaluated 28,413 individuals (20,541 girls and women 16 through 26 years of age at enrollment with a mean age of 20.0 years, 4055 boys and men 16 through 26 years of age at enrollment with a meanage of 20.5 years, and 3817 women 24 through 45 years of age at enrollment with a mean age of 34.3 years). The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 70.4% White; 12.2% Hispanic (Black and White); 8.8% Other; 4.6% Black; 3.8% Asian; and 0.2% American Indian. The race distribution of the 16- through 26-year-old boys and men in the clinical trials was as follows: 35.2% White; 20.5% Hispanic (Black and White); 14.4% Other; 19.8% Black; 10.0% Asian; and 0.1% American Indian. The race distribution of the 24- through 45-year-old women in the clinical trials was as follows: 20.6% White; 43.2% Hispanic (Black and White); 0.2% Other; 4.8% Black; 31.2% Asian; and 0.1% American Indian.

The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, 2.3, and 4.0 years for Study 1, Study 2, Study 3, Study 4, Study 5, and Study 6, respectively. Individuals received vaccine or AAHS control on the day of enrollment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies in girls and women combined according to a prospective clinical plan.

Overall, 73% of 16- through 26-year-old girls and women, 67% of 24- through 45-year-old women, and 83% of 16- through 26-year-old boys and men were naïve (i.e., PCR [Polymerase Chain Reaction] negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment.

A total of 27% of 16- through 26-year-old girls and women, 33% of 24- through 45-year-old women, and 17% of 16- through 26-year-old boys and men had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types. Among these individuals, 74% of 16- through 26-year-old girls and women, 71% of 24- through 45-year-old women, and 78% of 16- through 26-year-old boys and men had evidence of prior exposure to or ongoing infection with only 1 of the 4 vaccine HPV types and were naïve (PCR negative and seronegative) to the remaining 3 types.

In 24- through 45-year-old individuals, 0.4% had been exposed to all 4 vaccine HPV types.

In individuals who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN, VaIN, PIN, and persistent infection caused by any of the 4 vaccine HPV types were counted as endpoints.

Among individuals who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy. Endpoints

related to the remaining types for which the individual was naïve (PCR negative and seronegative) were counted.

For example, in individuals who were HPV 18 positive (PCR positive and/or seropositive) at Day 1, lesions caused by HPV 18 were not counted in the prophylactic efficacy evaluations. Lesions caused by HPV 6, 11, and 16 were included in the prophylactic efficacy evaluations. The same approach was used for the other types.

14.1 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Girls and Women 16 through 26 Years of Age

GARDASIL was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of girls and women regardless of baseline HPV status (i.e., PCR status or serostatus). Girls and women with current or prior HPV infection with an HPV type contained in the vaccine were not eligible for prophylactic efficacy evaluations for that type.

The primary analyses of efficacy with respect to HPV types 6, 11, 16, and 18 were conducted in the per-protocol efficacy (PPE) population, consisting of girls and women who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative in cervicovaginal specimens and seronegative) to the relevant HPV type(s) (Types 6, 11, 16,and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 11).

In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types.

Table 11: Analysis of Efficacy of GARDASIL in the PPE* Population† of 16- Through 26-Year-Old Girls and Women for Vaccine HPV Types

Population	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Study 1‡	755	0	750	12	100.0 (65.1, 100.0)
Study 2	231	0	230	1	100.0 (-3744.9, 100.0)
Study 3	2201	0	2222	36	100.0 (89.2, 100.0)
Study 4	5306	2	5262	63	96.9 (88.2, 99.6)
Combined Protocols§	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16-related CIN 2/3 or AIS					
Combined Protocols§	7402	2	7205	93	97.9 (92.3, 99.8)
HPV 18-related CIN 2/3 or AIS					
Combined Protocols§	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 16- or 18-related VIN 2/3					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	6	100.0 (14.4, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols§	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Study 2	231	0	230	0	Not calculated
Study 3	2219	0	2239	5	100.0 (-10.1, 100.0)
Study 4	5322	0	5275	4	100.0 (-50.3, 100.0)
Combined Protocols§	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS					
Study 2	235	0	233	3	100.0 (-138.4, 100.0)
Study 3	2241	0	2258	77	100.0 (95.1, 100.0)
Study 4	5388	9	5374	145	93.8 (88.0, 97.2)
Combined Protocols§	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts					
Study 2	235	0	233	3	100.0 (-139.5, 100.0)
Study 3	2261	0	2279	58	100.0 (93.5, 100.0)
Study 4	5404	2	5390	132	98.5 (94.5, 99.8)
Combined Protocols§	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts					
Combined Protocols§	6932	2	6856	189	99.0 (96.2, 99.9)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).
†See Table 14 for analysis of vaccine impact in the general population.
‡Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL
§Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 11 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Prophylactic efficacy against overall cervical and genital disease related to HPV 6, 11, 16, and 18 in an extension phase of Study 2, that included data through Month 60, was noted to be 100% (95% CI: 12.3%, 100.0%) among girls and women in the per protocol population naïve to the relevant HPV types.

GARDASIL was efficacious against HPV disease caused by HPV types 6, 11, 16, and 18 in girls and women who were naïve for those specific HPV types at baseline.

14.2 Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in Boys and Men 16 through 26 Years of Age

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population. This population consisted of boys and men who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in those boys and men who were PCR negative and seronegative at baseline (Table 12). Efficacy against penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance.

Table 12: Analysis of Efficacy of GARDASIL in the PPE* Population of 16- Through 26-Year-Old Boys and Men for Vaccine HPV Types

Endpoint	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N†	Number of cases	N	Number of cases	
External Genital Lesions HPV 6-, 11-, 16-, or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).
†N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.3 Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 through 26 Years of Age in the MSM Sub-study

A sub-study of Study 5 evaluated the efficacy of GARDASIL against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 MSM. The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population of Study 5.

GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline (Table 13).

Table 13: Analysis of Efficacy of GARDASIL for Anal Disease in the PPE* Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types

HPV 6-, 11-, 16-, or 18- related Endpoint	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N†	Number of cases	N	Number of cases	
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (month 7).
†N = Number of individuals with at least 1 follow-up visit after Month 7
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.4 Population Impact in Girls and Women 16 through 26 Years of Age

Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

The clinical trials included girls and women regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in these girls and women. Here, analysesincluded events arising among girls and women regardless of baseline PCR status and serostatus, including HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in girls and women regardless of current or prior exposure to a vaccine HPV type is shown in Table 14. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in girls and women who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in girls and women who were positive for vaccine HPV

infection, as well as vaccine impact among girls and women regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of CIN and genital warts, VIN, and VaIN related to a vaccine HPV type detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

There was no clear evidence of protection from disease caused by HPV types for which girls and women were PCR positive regardless of serostatus at baseline.

Table 14: Effectiveness of GARDASIL in Prevention of HPV 6, 11, 16, or 18-Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Endpoint	Analysis	GARDASIL or HPV 16 L1 VLP Vaccine		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9346	4	9407	155	97.4 (93.3, 99.3)
	HPV 16 and/or HPV 18 Positive at Day 1†	2870	142	2898	148‡	--§
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18¶	9836	146	9904	303	51.8 (41.1, 60.7)
HPV 16- or 18-related VIN 2/3 or VaIN 2/3	Prophylactic Efficacy*	8642	1	8673	34	97.0 (82.4, 99.9)
	HPV 16 and/or HPV 18 Positive at Day 1†	1880	8	1876	4	--§
	Girls and Women Regardless of Current or Prior Exposure to HPV 16 or 18¶	8955	9	8968	38	76.3 (50.0, 89.9)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	Prophylactic Efficacy*	8630	16	8680	309	94.8 (91.5, 97.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	2466	186#	2437	213#	--§
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types¶	8819	202	8854	522	61.5 (54.6, 67.4)
HPV 6-, 11-, 16-, or 18-related Genital Warts	Prophylactic Efficacy*	8761	10	8792	252	96.0 (92.6, 98.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	2501	51Þ	2475	55Þ	--§
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types¶	8955	61	8968	307	80.3 (73.9, 85.3)
HPV 6- or 11-related Genital Warts	Prophylactic Efficacy*	7769	9	7792	246	96.4 (93.0, 98.4)
	HPV 6 and/or HPV 11 Positive at Day 1†	1186	51	1176	54	--§
	Girls and Women Regardless of Current or Prior Exposure to Vaccine HPV Types¶	8955	60	8968	300	80.1 (73.7, 85.2)

*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at 1 month postdose 1.
†Includes all individuals who received at least 1 vaccination and who were HPV positive or had unknown HPV status at Day 1, to at least one vaccine HPV type. Case counting started at Day 1.
‡Out of the 148 AAHS control cases of 16/18 CIN 2/3, 2 women were missing serology or PCR results for Day 1.
§There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.
¶Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month postdose 1.
#Includes 2 AAHS control women with missing serology/PCR data at Day 1.
ÞIncludes 1 woman with missing serology/PCR data at Day 1.
CI = Confidence Interval
N = Number of individuals who have at least one follow-up visit after Day 1
Note 1: The 16- and 18-related CIN 2/3 or AIS composite endpoint included data from studies 1, 2, 3, and 4. All other endpoints only included data from studies 2, 3, and 4.
Note 2: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.
Note 3: Table 14 does not include disease due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

The impact of GARDASIL against the overall burden of dysplastic or papillomatous cervical, vulvar, and vaginal disease regardless of HPV detection, results from a combination of prophylactic efficacy against vaccine HPV types, disease contribution from vaccine HPV types present at time of vaccination, the disease contribution from HPV types not contained in the vaccine, and disease in which HPV was not detected.

Additional efficacy analyses were conducted in 2 populations: (1) a generally HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous

Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve girls and women and (2) the general study population of girls and women regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve girls and women and among all girls and women in the study population (including girls and women with HPV infection at Day 1), GARDASIL reduced the overall incidence of CIN 2/3 or AIS; of VIN 2/3 or VaIN 2/3; of CIN (any grade) or AIS; and of Genital Warts (Table 15). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in girls and women naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected girls and women may already have CIN 2/3 or AIS at Day 1 and some will develop CIN 2/3 or AIS during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

Table 15: Effectiveness of GARDASIL in Prevention of Any HPV Type Related Genital Disease in Girls and Women 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

Endpoints Caused by Vaccine or Non-vaccine HPV Types	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
CIN 2/3 or AIS	Prophylactic Efficacy*	4616	77	4680	136	42.7 (23.7, 57.3)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8559	421	8592	516	18.4 (7.0, 28.4)
VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	4688	7	4735	31	77.1 (47.1, 91.5)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8688	30	8701	61	50.7 (22.5, 69.3)
CIN (Any Grade) or AIS	Prophylactic Efficacy*	4616	272	4680	390	29.7 (17.7, 40.0)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8559	967	8592	1189	19.1 (11.9, 25.8)
Genital Warts	Prophylactic Efficacy*	4688	29	4735	169	82.8 (74.3, 88.8)
	Girls and Women Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	8688	132	8701	350	62.5 (54.0, 69.5)

*Includes all individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1. Case counting started at 1 month postdose 1.
†Includes all individuals who received at least 1 vaccination (regardless of baseline HPV status or Pap test result at Day 1). Case counting started at 1 month postdose 1.
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.5 Population Impact in Boys and Men 16 through 26 Years of Age

Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Study 5 included boys and men regardless of current or prior exposure to vaccine HPV types, and additional analyses were conducted to evaluate the impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related anogenital disease in these boys and men. Here, analyses included events arising among boys and men regardless of baseline PCR status and serostatus, including HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in boys and men regardless of current or prior exposure to a vaccine HPV type is shown in Table 16. Impact was measured starting at Day 1. Prophylactic efficacy denotes the

vaccine's efficacy in boys and men who are naïve (PCR negative and seronegative) to the relevant HPV types at Day 1. Vaccine impact in boys and men who were positive for vaccine HPV infection, as well as vaccine impact among boys and men regardless of baseline vaccine HPV PCR status and serostatus are also presented. The majority of anogenital disease related to a vaccine HPV type detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

There was no clear evidence of protection from disease caused by HPV types for which boys and men were PCR positive regardless of serostatus at baseline.

Table 16: Effectiveness of GARDASIL in Prevention of HPV Types 6-, 11-, 16-, or 18-Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Exposure to Vaccine HPV Types

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Prophylactic Efficacy*	1775	13	1770	54	76.3 (56.0, 88.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	460	14	453	26	--‡
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types§	1943	27	1937	80	66.7 (48.0, 79.3)
Condyloma	Prophylactic Efficacy*	1775	10	1770	49	80.0 (59.9, 90.9)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	460	14	453	25	--‡
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types§	1943	24	1937	74	68.1 (48.8, 80.7)
PIN 1/2/3	Prophylactic Efficacy*	1775	4	1770	5	20.7 (-268.4, 84.3)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	460	2	453	1	--‡
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types§	1943	6	1937	6	0.3 (-272.8, 73.4)
AIN 1/2/3	Prophylactic Efficacy*	259	9	261	39	76.9 (51.4, 90.1)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	103	29	116	38	--‡
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types§	275	38	276	77	50.3 (25.7, 67.2)
AIN 2/3	Prophylactic Efficacy*	259	7	261	19	62.5 (6.9, 86.7)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1†	103	11	116	20	--‡
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types§	275	18	276	39	54.2 (18.0, 75.3)

*Includes all individuals who received at least 1 vaccination and who were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed. Case counting started at Day 1.
†Includes all individuals who received at least 1 vaccination and who were HPV positive or had unknown HPV status at Day 1, to at least one vaccine HPV type. Case counting started at Day 1.
‡There is no expected efficacy since GARDASIL has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.
§Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Effectiveness of GARDASIL in Prevention of Any HPV Type Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

The impact of GARDASIL against the overall burden of dysplastic or papillomatous anogenital disease regardless of HPV detection, results from a combination of prophylactic efficacy against vaccine HPV

types, disease contribution from vaccine HPV types present at time of vaccination, the disease contribution from HPV types not contained in the vaccine, and disease in which HPV was not detected.

Additional efficacy analyses from Study 5 were conducted in 2 populations: (1) a generally HPV-naïve population that consisted of boys and men who are seronegative and PCR negative to HPV 6, 11, 16, and 18 and PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 at Day 1, approximating a population of sexually-naïve boys and men and (2) the general study population of boys and men regardless of baseline HPV status, some of whom had HPV-related disease at Day 1.

Among generally HPV-naïve boys and men and among all boys and men in Study 5 (including boys and men with HPV infection at Day 1), GARDASIL reduced the overall incidence of anogenital disease (Table 17). These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18 in boys and men naïve (seronegative and PCR negative) for the specific relevant vaccine HPV type. Infected boys and men may already have anogenital disease at Day 1 and some will develop anogenital disease during follow-up, either related to a vaccine or non-vaccine HPV type present at the time of vaccination or related to a non-vaccine HPV type not present at the time of vaccination.

Table 17: Effectiveness of GARDASIL in Prevention of Any HPV Type Related Anogenital Disease in Boys and Men 16 Through 26 Years of Age, Regardless of Current or Prior Infection with Vaccine or Non-Vaccine HPV Types

Endpoint	Analysis	GARDASIL		AAHS Control		% Reduction (95% CI)
		N	Cases	N	Cases	
External Genital Lesions	Prophylactic Efficacy*	1275	7	1270	37	81.5 (58.0, 93.0)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	1943	38	1937	92	59.3 (40.0, 72.9)
Condyloma	Prophylactic Efficacy*	1275	5	1270	33	85.2 (61.8, 95.5)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	1943	33	1937	85	61.8 (42.3, 75.3)
PIN 1/2/3	Prophylactic Efficacy*	1275	2	1270	4	50.7 (-244.3, 95.5)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	1943	8	1937	7	-13.9 (-269.0, 63.9)
AIN 1/2/3	Prophylactic Efficacy*	129	12	126	28	54.9 (8.4, 79.1)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	275	74	276	103	25.7 (-1.1, 45.6)
AIN 2/3	Prophylactic Efficacy*	129	8	126	18	52.5 (-14.8, 82.1)
	Boys and Men Regardless of Current or Prior Exposure to Vaccine or Non-Vaccine HPV Types†	275	44	276	59	24.3 (-13.8, 50.0)

*Includes all individuals who received at least 1 vaccination and who were seronegative and PCR negative at enrollment to HPV 6, 11, 16 and 18, and PCR negative at enrollment to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Case counting started at Day 1.
†Includes all individuals who received at least 1 vaccination. Case counting started at Day 1.
CI = Confidence Interval
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

14.6 Overall Population Impact

The subject characteristics (e.g. lifetime sex partners, geographic distribution of the subjects) influence the HPV prevalence of the population and therefore the population benefit can vary widely.

The overall efficacy of GARDASIL will vary with the baseline prevalence of HPV infection and disease, the incidence of infections against which GARDASIL has shown protection, and those infections against which GARDASIL has not been shown to protect.

The efficacy of GARDASIL for HPV types not included in the vaccine (i.e., cross-protective efficacy) is a component of the overall impact of the vaccine on rates of disease caused by HPV. Cross-protective

efficacy was not demonstrated against disease caused by non-vaccine HPV types in the combined database of the Study 3 and Study 4 trials.

GARDASIL does not protect against genital disease not related to HPV. One woman who received GARDASIL in Study 3 developed an external genital well-differentiated squamous cell carcinoma at Month 24. No HPV DNA was detected in the lesion or in any other samples taken throughout the study.

In 18,150 girls and women enrolled in Study 2, Study 3, and Study 4, GARDASIL reduced definitive cervical therapy procedures by 23.9% (95% CI: 15.2%, 31.7%).

14.7 Studies in Women 27 through 45 Years of Age

Study 6 evaluated efficacy in 3253 women 27 through 45 years of age based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy for the combined endpoint was driven primarily by prevention of persistent infection. There was no statistically significant efficacy demonstrated for CIN 2/3, AIS, or cervical cancer. In post hoc analyses conducted to assess the impact of GARDASIL on the individual components of the combined endpoint, the results in the population of women naïve to the relevant HPV type at baseline were as follows: prevention of HPV 6-, 11-, 16- or 18-related persistent infection (80.5% [95% CI: 68.3, 88.6]), prevention of HPV 6-, 11-, 16- or 18-related CIN (any grade)
(85.8% [95% CI: 52.4, 97.3]), and prevention of HPV 6-, 11-, 16- or 18-related genital warts (87.6% [95% CI: 7.3, 99.7]).

Efficacy for disease endpoints was diminished in a population impact assessment of women who were vaccinated regardless of baseline HPV status (full analysis set). In the full analysis set (FAS), efficacy was not demonstrated for the following endpoints: prevention of HPV 16- and 18-related CIN 2/3, AIS, or cervical cancer and prevention of HPV 6- and 11-related condyloma. No efficacy was demonstrated against CIN 2/3, AIS, or cervical cancer in the general population irrespective of HPV type (FAS any type analysis).

14.8 Immunogenicity

Assays to Measure Immune Response

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45-year-old girls and women (GARDASIL N = 12,634; AAHS control or saline placebo N = 11,317) and 5417 9- through 26-year-old boys and men (GARDASIL N = 3109; AAHS control or saline placebo N = 2308).

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

Immune Response to GARDASIL

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and PCR negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

In clinical studies in 16- through 26-year-old girls and women, 99.8%, 99.8%, 99.8%, and 99.4% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

In clinical studies in 27- through 45-year-old women, 98.2%, 97.9%, 98.6%, and 97.1% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

In clinical studies in 16- through 26-year-old boys and men, 98.9%, 99.2%, 98.8%, and 97.4% who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month postdose 3 across all age groups tested.

Across all populations, anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs peaked at Month 7 (Table 18 and Table 19). GMTs declined through Month 24 and then stabilized through Month 36at levels above baseline. Tables 20 and 21 display the persistence of anti-HPV cLIA geometric mean titers by gender and age group. The duration of immunity following a complete schedule of immunization with GARDASIL has not been established.

Table 18: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of Girls and Women

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
16- through 26-year-old girls and women	9859	3329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
27- through 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
35- through 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
Anti-HPV 11				
9- through 15-year-old girls	1122	917	99.9 (99.4, 100.0)	1304.6 (1224.7, 1389.7)
16- through 26-year-old girls and women	9859	3353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
27- through 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
35- through 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
Anti-HPV 16				
9- through 15-year-old girls	1122	915	99.9 (99.4, 100.0)	4918.5 (4556.6, 5309.1)
16- through 26-year-old girls and women	9859	3249	99.8 (99.6, 100.0)	2409.2 (2309.0, 2513.8)
27- through 34-year-old women	667	435	99.3 (98.0, 99.9)	2342.5 (2119.1, 2589.6)
35- through 45-year-old women	957	657	98.2 (96.8, 99.1)	2129.5 (1962.7, 2310.5)
Anti-HPV 18				
9- through 15-year-old girls	1122	922	99.8 (99.2, 100.0)	1042.6 (967.6, 1123.3)
16- through 26-year-old girls and women	9859	3566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
27- through 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
35- through 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
†Number of individuals randomized to the respective vaccination group who received at least 1 injection.
‡Number of individuals contributing to the analysis.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers
§mMU = milli-Merck Units

Table 19: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of Boys and Men

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9- through 15-year-old boys	1072	884	99.9 (99.4, 100.0)	1037.5 (963.5, 1117.3)
16- through 26-year-old boys and men	2026	1093	98.9 (98.1, 99.4)	447.8 (418.9, 478.6)
Anti-HPV 11				
9- through 15-year-old boys	1072	885	99.9 (99.4, 100.0)	1386.8 (1298.5, 1481.0)
16- through 26-year-old boys and men	2026	1093	99.2 (98.4, 99.6)	624.3 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year-old boys	1072	882	99.8 (99.2, 100.0)	6056.5 (5601.3, 6548.7)
16- through 26-year-old boys and men	2026	1136	98.8 (97.9, 99.3)	2403.3 (2243.4, 2574.6)
Anti-HPV 18				
9- through 15-year-old boys	1072	887	99.8 (99.2, 100)	1357.4 (1249.4, 1474.7)
16- through 26-year-old boys and men	2026	1175	97.4 (96.3, 98.2)	402.6 (374.6, 432.7)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
†Number of individuals randomized to the respective vaccination group who received at least 1 injection.
‡Number of individuals contributing to the analysis.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers
§mMU = milli-Merck Units

Table 20: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 45-Year-Old Girls and Women

Assay (cLIA)/ Time Point	9- to 15-Year-Old Girls (N* = 1122)		16- to 26-Year-Old Girls and Women (N* = 9859)		27- to 34-Year-Old Women (N* = 667)		35- to 45-Year-Old Women (N* = 957)	
	n†	GMT (95% CI) mMU‡/mL	n†	GMT (95% CI) mMU‡/mL	n†	GMT (95% CI) mMU‡/mL	n†	GMT (95% CI) mMU‡/mL
Anti-HPV 6								
Month 07	917	929.2 (874.6, 987.3)	3329	545.0 (530.1, 560.4)	439	435.6 (393.4, 482.4)	644	397.3 (365.2, 432.2)
Month 24	214	156.1 (135.6, 179.6)	2788	109.1 (105.2, 113.1)	421	70.7 (63.8, 78.5)	628	69.3 (63.7, 75.4)
Month 36§	356	129.4 (115.6, 144.8)	-	-	399	79.5 (72.0, 87.7)	618	81.1 (75.0, 87.8)
Month 48¶	-	-	2514	73.8 (70.9, 76.8)	391	58.8 (52.9, 65.3)	616	62.0 (57.0, 67.5)
Anti-HPV 11								
Month 07	917	1304.6 (1224.7, 1389.7)	3353	748.9 (726.0, 772.6)	439	577.9 (523.8, 637.5)	644	512.8 (472.9, 556.1)
Month 24	214	218.0 (188.3, 252.4)	2817	137.1 (132.1, 142.3)	421	79.3 (71.5, 87.8)	628	73.4 (67.4, 79.8)
Month 36§	356	148.0 (131.1, 167.1)	-	-	399	81.8 (74.3, 90.1)	618	77.4 (71.6, 83.6)
Month 48¶	-	-	2538	89.4 (85.9, 93.1)	391	67.4 (60.9, 74.7)	616	62.7 (57.8, 68.0)
Anti-HPV 16								
Month 07	915	4918.5 (4556.6, 5309.1)	3249	2409.2 (2309.0, 2513.8)	435	2342.5 (2119.1, 2589.6)	657	2129.5 (1962.7, 2310.5)
Month 24	211	944.2 (804.4, 1108.3)	2721	442.6 (425.0, 460.9)	416	285.9 (254.4, 321.2)	642	271.4 (247.1, 298.1)
Month 36§	353	642.2 (562.8, 732.8)	-	-	399	291.5 (262.5, 323.8)	631	276.7 (254.5, 300.8)
Month 48¶	-	-	2474	326.2 (311.8, 341.3)	394	211.8 (189.5, 236.8)	628	192.8 (176.5, 210.6)
Anti-HPV 18								
Month 07	922	1042.6 (967.6, 1123.3)	3566	475.2 (458.8, 492.1)	501	385.8 (347.6, 428.1)	722	324.6 (297.6, 354.0)
Month 24	214	137.7 (114.8, 165.1)	3002	50.8 (48.2, 53.5)	478	31.8 (28.1, 36.0)	705	26.0 (23.5, 28.8)
Month 36§	357	87.0 (74.8, 101.2)	-	-	453	32.1 (28.5, 36.3)	689	27.0 (24.5, 29.8)
Month 48¶	-	-	2710	33.2 (31.5, 35.0)	444	25.2 (22.3, 28.5)	688	21.2 (19.2, 23.4)

*N = Number of individuals randomized in the respective group who received at least 1 injection.
†n = Number of individuals in the indicated immunogenicity population.
‡mMU = milli-Merck Units
§Month 37 for 9- to 15-year-old girls. No serology samples were collected at this time point for 16- to 26-year-old girls and women.
¶Month 48/End-of-study visits for 16- to 26-year-old girls and women were generally scheduled earlier than Month 48. Mean visit timing was Month 44. The studies in 9- to 15-year-old girls were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers

Table 21: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 26-Year-Old Boys and Men

Assay (cLIA)/ Time Point	9- to 15-Year-Old Boys (N* = 1072)		16- to 26-Year-Old Boys and Men (N* = 2026)	
	n†	GMT (95% CI) mMU‡/mL	n†	GMT (95% CI) mMU‡/mL
Anti-HPV 6				
Month 07	884	1037.5 (963.5, 1117.3)	1094	447.2 (418.4, 477.9)
Month 24	323	134.1 (119.5, 150.5)	907	80.3 (74.9, 86.0)
Month 36§	342	126.6 (111.9, 143.2)	654	72.4 (68.0, 77.2)
Month 48¶	-	-	-	-
Anti-HPV 11				
Month 07	885	1386.8 (1298.5, 1481.0)	1094	624.5 (588.6, 662.5)
Month 24	324	188.5 (168.4, 211.1)	907	94.6 (88.4, 101.2)
Month 36§	342	148.8 (131.1, 169.0)	654	80.3 (75.7, 85.2)
Month 48¶	-	-	-	-
Anti-HPV 16				
Month 07	882	6056.5 (5601.4, 6548.6)	1137	2401.5 (2241.8, 2572.6)
Month 24	322	938.2 (825.0, 1067.0)	938	347.7 (322.5, 374.9)
Month 36§	341	708.8 (613.9, 818.3)	672	306.7 (287.5, 327.1)
Month 48¶	-	-	-	-
Anti-HPV 18				
Month 07	887	1357.4 (1249.4, 1474.7)	1176	402.6 (374.6, 432.6)
Month 24	324	131.9 (112.1, 155.3)	967	38.7 (35.2, 42.5)
Month 36§	343	113.0 (94.7, 135.0)	690	33.4 (30.9, 36.1)
Month 48¶	-	-	-	-

*N = Number of individuals randomized in the respective group who received at least 1 injection.
†n = Number of individuals in the indicated immunogenicity population.
‡mMU = milli-Merck Units
§Month 36 time point for 16- to 26-year-old boys and men; Month 37 for 9- to 15-year-old boys.
¶The studies in 9- to 15-year-old boys and girls and 16- to 26-year-old boys and men were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers

Tables 18 and 19 display the Month 7 immunogenicity data for girls and women and boys and men. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent girls were non-inferior to anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent boys were non-inferior to anti-HPV responses in 16- through 26-year-old boys and men in Study 5.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- through 15-year-old adolescent girls and boys is inferred.

GMT Response to Variation in Dosing Regimen in 18- Through 26-Year-Old Women

Girls and women evaluated in the PPE population of clinical studies received all 3 vaccinations within 1 year of enrollment. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not impact the immune responses to GARDASIL.

Duration of the Immune Response to GARDASIL

The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. The peak anti-HPV GMTs for HPV types 6, 11, 16, and 18 occurred at Month 7. Anti-

HPV GMTs for HPV types 6, 11, 16, and 18 were similar between measurements at Month 24 and Month 60 in Study 2.

14.9 Long-Term Follow-Up Studies

The protection of GARDASIL against HPV-related disease continues to be studied over time in populations including adolescents (boys and girls) and women who were enrolled in the Phase 3 studies.

Persistence of Effectiveness

An extension of Study 4 used national healthcare registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaccination with GARDASIL and consented to be followed in the extension study. An interim analysis of the per-protocol effectiveness population included 1,902 subjects who completed the GARDASIL vaccination series within one year, were naïve to the relevant HPV type through 1 month postdose 3, had no protocol violations, and had follow-up data available. The median follow-up from initial vaccination was 6.7 years with a range of 2.8 to 8.4 years. No cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed over a total of 5,765 person-years at risk.

An extension of a Phase 3 study (Study 7) in which 614 girls and 565 boys 9 through 15 years of age at enrollment were randomized to vaccination with GARDASIL actively followed subjects for endpoint cases of HPV 6-, 11-, 16-, or 18-related persistent infection, CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, and genital lesions from the initiation of sexual activity or age 16 onwards. An interim analysis of the per-protocol effectiveness population included 246 girls and 168 boys who completed the GARDASIL vaccination series within one year, were seronegative to the relevant HPVtype at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of GARDASIL. The median follow-up, from the first dose of vaccine, was 7.2 years with a range of 0.5 to 8.5 years. No cases of persistent infection of at least 12 months' duration and no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, or genital lesions were observed over a total 1,105 person-years at risk. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of which persisted to 12 months' duration.

Persistence of the Immune Response

The interim reports of the two extension studies described above included analyses of type-specific anti-HPV antibody titers at 9 years postdose 1 for girls and women 16 through 23 years of age at enrollment (range of 1,178 to 1,331 subjects with evaluable data across HPV types) and at 8 years postdose 1 for boys and girls 9 through 15 years of age at enrollment (range of 436 to 440 subjects with evaluable data across HPV types). Anti-HPV 6, 11, 16, and 18 GMTs as measured by cLIA were decreased compared with corresponding values at earlier time points, but the proportions of seropositive subjects ranged from 88.4% to 94.4% for anti-HPV 6, from 89.1% to 95.5% for anti-HPV 11, from 96.8% to 99.1% for anti-HPV 16, and from 60.0% to 64.1% for anti-HPV 18.

14.10 Studies with RECOMBIVAX HB [hepatitis B vaccine (recombinant)]

The safety and immunogenicity of co-administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized, double-blind, study of 1871 women aged 16 through 24 years at enrollment. The race distribution of the girls and women in the clinical trial was as follows: 61.6% White; 1.6% Hispanic (Black and White); 23.8% Other; 11.9% Black; 0.8% Asian; and 0.3% American Indian.

Subjects either received GARDASIL and RECOMBIVAX HB (n = 466), GARDASIL and RECOMBIVAX HB-matched placebo (n = 468), RECOMBIVAX HB and GARDASIL-matched placebo (n = 467) or RECOMBIVAX-matched placebo and GARDASIL-matched placebo (n = 470) at Day 1, Month 2 and Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series.

Concomitant administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with RECOMBIVAX HB or separately.

14.11 Studies with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]

The safety and immunogenicity of co-administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in an open-labeled, randomized, controlled study of 1040 boys and girls 11 through 17 years of age at enrollment. The race distribution of the subjects in the clinical trial was as follows: 77.7% White; 6.8% Hispanic (Black and White); 1.4% Multi-racial; 12.3% Black; 1.2% Asian; 0.2% Indian; and 0.4% American Indian.

One group received GARDASIL in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 517). The second group received the first dose of GARDASIL on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 523). Subjects in both vaccination groups received the second dose of GARDASIL at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL).

Concomitant administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] did not interfere with the antibody response to any of the vaccine antigens when GARDASIL was given concomitantly with Menactra and Adacel or separately.

16 HOW SUPPLIED/STORAGE AND HANDLING

All presentations for GARDASIL contain a suspension of 120 mcg L1 protein from HPV types 6, 11, 16, and 18 in a 0.5-mL dose. GARDASIL is supplied in vials and syringes.

Carton of one 0.5-mL single-dose vial. **NDC** 0006-4045-00.

Carton of ten 0.5-mL single-dose vials. **NDC** 0006-4045-41.

Carton of six 0.5-mL single-dose prefilled Luer-Lok® syringes with tip caps. **NDC** 0006-4109-09.

Carton of ten 0.5-mL single-dose prefilled Luer-Lok® syringes with tip caps. **NDC** 0006-4109-02.

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL should be administered as soon as possible after being removed from refrigeration.

GARDASIL can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care.
- Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider.
- GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
- Since syncope has been reported following vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
- Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
- Information regarding benefits and risks associated with vaccination.
- GARDASIL is not recommended for use in pregnant women.
- Importance of completing the immunization series unless contraindicated.
- Report any adverse reactions to their health care provider.

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not inClude all the information needed to use GARDASIL 9 safely and effeCtively. See full presCribing information for GARDASIL 9.
GARDASIL®9
(Human Papillomavirus 9-valent VaCCine, ReCombinant)
Suspension for intramusCular injeCtion
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

GARDASIL 9 is a vaCCine indiCated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers Caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. (1.1)
- Genital warts (Condyloma aCuminata) Caused by HPV types 6 and 11. (1.1)

And the following preCanCerous or dysplastiC lesions Caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- CerviCal intraepithelial neoplasia (CIN) grade 2/3 and CerviCal adenoCarCinoma *in situ* (AIS). (1.1)
- CerviCal intraepithelial neoplasia (CIN) grade 1. (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.1)

GARDASIL 9 is indiCated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal and other head and neCk CanCers Caused by HPV types 16, 18, 31, 33, 45, 52, and 58. (1.2)
- Genital warts (Condyloma aCuminata) Caused by HPV types 6 and 11. (1.2)

And the following preCanCerous or dysplastiC lesions Caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

The oropharyngeal and head and neCk CanCer indiCation is approved under aCCelerated approval based on effeCtiveness in preventing HPV-related anogenital disease. Continued approval for this indiCation may be Contingent upon verifiCation and desCription of CliniCal benefit in a Confirmatory trial (1).

Limitations of Use and EffeCtiveness:

- VaCCination with GARDASIL 9 does not eliminate the neCessity for vaCCine reCipients to undergo sCreening for CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers as reCommended by a health Care provider. (1.3, 17)
- GARDASIL 9 has not been demonstrated to provide proteCtion against disease Caused by:
  - HPV types not Covered by the vaCCine
  - HPV types to whiCh a person has previously been exposed through sexual aCtivity. (1.3)
- Not all vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers are Caused by HPV, and GARDASIL 9 proteCts onlyagainst those vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers Caused by HPV 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 is not a treatment for external genital lesions; CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers; CIN; VIN; VaIN; or AIN. (1.3)
- VaCCination with GARDASIL 9 may not result in proteCtion in all vaCCine reCipients. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

For intramusCular administration only. (2)

EaCh dose of GARDASIL 9 is 0.5-mL

Administer GARDASIL 9 as follows: (2.1)

Age	Regimen	SChedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

*If the seCond dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the seCond dose. (14.2 and 14.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 0.5-mL suspension for injeCtion as a single-dose vial and prefilled syringe. (3, 11)

----------CONTRAINDICATIONS----------

Hypersensitivity, inCluding severe allergiC reaCtions to yeast (a vaCCine Component), or after a previous dose of GARDASIL 9 or GARDASIL®.(4, 11)

---------- WARNINGS AND PRECAUTIONS ----------

BeCause vaCCinees may develop synCope, sometimes resulting in falling with injury, observation for 15 minutes after administration is reCommended. SynCope, sometimes assoCiated with toniC-CloniC movements and other seizure-like aCtivity, has been reported following HPV vaCCination. When synCope is assoCiated with toniC-CloniC movements, the aCtivity is usually transient and typiCally responds to restoring Cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

---------- ADVERSE REACTIONS ----------

The most common (≥10%) local and systemic adverse reactions reported:

- In girls and women 16 through 26 years of age: injeCtion-site pain (89.9%), injeCtion-site swelling (40.0%), injeCtion-site erythema (34.0%) and headaChe (14.6%). (6.1)
- In girls 9 through 15 years of age: injeCtion-site pain (89.3%), injeCtion-site swelling (47.8%), injeCtion-site erythema (34.1%) and headaChe (11.4%). (6.1)
- In women 27 through 45 years of age: injeCtion-site pain (82.8%), injeCtion-site swelling (23.3%), injeCtion-site erythema (16.9%), and headaChe (13.6%) (6.1)
- In boys and men 16 through 26 years of age: injeCtion-site pain (63.4%), injeCtion-site swelling (20.2%) and injeCtion-site erythema (20.7%). (6.1)
- In boys 9 through 15 years of age: injeCtion-site pain (71.5%), injeCtion-site swelling (26.9%), and injeCtion-site erythema(24.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, ContaCt MerCk Sharp & Dohme Corp., a subsidiary of MerCk & Co., InC., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*SeCtions or subseCtions omitted from the full presCribing informationare not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Girls and Women

GARDASIL®9 is a vaCCine indiCated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers Caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (Condyloma aCuminata) Caused by HPV types 6 and 11

And the following preCanCerous or dysplastiC lesions Caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- CerviCal intraepithelial neoplasia (CIN) grade 2/3 and CerviCal adenoCarCinoma *in situ* (AIS)
- CerviCal intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.2 Boys and Men

GARDASIL 9 is indiCated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal and other head and neCk CanCers Caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (Condyloma aCuminata) Caused by HPV types 6 and 11

And the following preCanCerous or dysplastiC lesions Caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

The oropharyngeal and head and neCk CanCer indiCation is approved under aCCelerated approval based on effeCtiveness in preventing HPV-related anogenital disease *[see Clinical Studies (14.4)]*. Continued approval for this indiCation may be Contingent upon verifiCation and desCription of CliniCal benefit in a Confirmatory trial.

1.3 Limitations of Use and EffeCtiveness

- VaCCination with GARDASIL 9 does not eliminate the neCessity for vaCCine reCipients to undergo sCreening for CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers as reCommended by a health Care provider.
- GARDASIL 9 has not been demonstrated to provide proteCtion against disease Caused by:
  - HPV types not Covered by the vaCCine *[see Description (11)],*
  - HPV types to whiCh a person has previously been exposed through sexual aCtivity.
- Not all vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers are Caused by HPV, and GARDASIL 9 proteCts only against those vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers Caused by HPV 16, 18, 31, 33, 45, 52, and 58.
- GARDASIL 9 is not a treatment for external genital lesions; CerviCal, vulvar, vaginal, anal, oropharyngeal and other head and neCk CanCers; CIN; VIN; VaIN; or AIN.
- VaCCination with GARDASIL 9 may not result in proteCtion in all vaCCine reCipients.

2 DOSAGE AND ADMINISTRATION

For intramusCular use only

2.1 Dosage

EaCh dose of GARDASIL 9 is 0.5-mL.
Administer GARDASIL 9 as follows:

Age	Regimen	SChedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

*If the seCond dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the seCond dose. *[See Clinical Studies (14.2 and 14.6).]*

2.2 Method of Administration

- Do not dilute or mix GARDASIL 9 with other vaCCines.
- Shake well immediately before use to maintain suspension of the vaCCine.
- Parenteral drug produCts should be inspeCted visually for partiCulate matter and disColoration prior to administration, whenever solution and Container permit. Do not use the produCt if partiCulates are present or if it appears disColored. After thorough agitation, GARDASIL 9 is a white Cloudy liquid.
- Administer intramusCularly in the deltoid or anterolateral area of the thigh.
- Observe patients for 15 minutes after administration *[see Warnings and Precautions (5)].*

Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaCCine from the single-dose vial using a sterile needle and syringe and use promptly. DisCard vial after use.

Prefilled Syringe Use

This paCkage does not Contain a needle. Shake well before use. AttaCh a needle by twisting in a CloCkwise direCtion until the needle fits seCurely on the syringe. Administer the entire dose as per standard protoCol. DisCard syringe after use.

2.3 Administration of GARDASIL 9 in Individuals Who Have Been Previously VaCCinated with GARDASIL®

Safety and immunogeniCity were assessed in individuals who Completed a three-dose vaCCination series with GARDASIL 9 and had previously Completed a three-dose vaCCination series with GARDASIL *[see Adverse Reactions (6.1) and Clinical Studies (14.5)].* Studies using a mixed regimen of HPV vaCCines to assess interChangeability were not performed for GARDASIL 9.

3 DOSAGE FORMS AND STRENGTHS

GARDASIL 9 is a suspension for intramusCular administration available in 0.5-mL single-dose vials and prefilled syringes. *[*See *Description (11)]* for the Complete listing of ingredients.

4 CONTRAINDICATIONS

Hypersensitivity, inCluding severe allergiC reaCtions to yeast (a vaCCine Component), or after a previous dose of GARDASIL 9 or GARDASIL *[see Description (11)].*

5 WARNINGS AND PRECAUTIONS

5.1 SynCope

BeCause vaCCinees may develop synCope, sometimes resulting in falling with injury, observation for 15 minutes after administration is reCommended. SynCope, sometimes assoCiated with toniC-CloniC movements and other seizure-like aCtivity, has been reported following HPV vaCCination. When synCope is assoCiated with toniC-CloniC movements, the aCtivity is usually transient and typiCally responds to restoring Cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Managing AllergiC ReaCtions

Appropriate mediCal treatment and supervision must be readily available in Case of anaphylaCtiC reaCtions following the administration of GARDASIL 9.

6 ADVERSE REACTIONS

6.1 CliniCal Trials ExperienCe

BeCause CliniCal trials are ConduCted under widely varying Conditions, adverse reaCtion rates observed in the CliniCal trials of a vaCCine Cannot be direCtly Compared to rates in the CliniCal trials of another vaCCine and may not refleCt the rates observed in praCtiCe.

The safety of GARDASIL 9 was evaluated in seven CliniCal studies that inCluded 15,703 individuals who reCeived at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also inCluded 7,378 individuals who reCeived at least one dose of GARDASIL as a Control and had safety follow-up. The vaCCines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaCCination report Card (VRC)-aided surveillanCe for 14 days after eaCh injeCtion of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillanCe inCluded 9,097 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age, and 5,212 girls and boys 9 through 15 years of age (3,436 girls and 1,776 boys) at enrollment who reCeived GARDASIL 9; and 7,078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who reCeived GARDASIL. The raCe distribution of the integrated safety population for GARDASIL 9 was similar between girls and women 16 through 26 years of age (56.8% White; 25.2% Other RaCes or MultiraCial; 14.1% Asian; 3.9% BlaCk), girls and boys 9 through 15 years of age (62.0% White; 19.2% Other RaCes or MultiraCial; 13.5% Asian; 5.4% BlaCk), and boys and men 16 through 26 years of age (62.1% White; 22.6% Other RaCes or MultiraCial; 9.8% Asian; 5.5% BlaCk). The safety of GARDASIL 9 was Compared direCtly to the safety of GARDASIL in two studies (Study 1 and Study 3) for whiCh the overall raCe distribution of the GARDASIL Cohorts (57.0% White; 26.3% Other RaCes or MultiraCial; 13.6% Asian; 3.2% BlaCk) was similar to that of the GARDASIL 9 Cohorts.

Safety of GARDASIL 9 in women 27 through 45 years of age was evaluated in a CliniCal trial Comparing 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age. The raCe distribution was similar between women 27 through 45 years of age (97.7% White, 1.6% Asian, 0.3% Other or MultiraCial, 0.5% BlaCk) and girls and women 16 through 26 years of age (94.6% White, 3.0% Asian, 1.6% Other or MultiraCial, 0.9% BlaCk).

Safety of GARDASIL 9 in men 27 through 45 years of age is inferred from the safety data of GARDASIL 9 in boys and men 9 through 26 years of age and girls and women 9 through 45 years of age and GARDASIL in individuals 9 through 45 years of age.

Injection-Site and Systemic Adverse Reactions

InjeCtion-site reaCtions (pain, swelling, and erythema) and oral temperature were soliCited using VRC-aided surveillanCe for five days after eaCh injeCtion of GARDASIL 9 during the CliniCal studies. The rates and severity of these soliCited adverse reaCtions that oCCurred within five days following eaCh dose of GARDASIL 9 Compared with GARDASIL in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjeCts who reCeived GARDASIL 9, the rates of injeCtion-site pain were approximately equal aCross the three reporting time periods. Rates of injeCtion-site swelling and injeCtion-site erythema inCreased following eaCh suCCessive dose of GARDASIL 9. ReCipients of GARDASIL 9 had numeriCally higher rates of injeCtion-site reaCtions Compared with reCipients of GARDASIL.

Table 1: Rates (%) and Severity of SoliCited InjeCtion-Site and SystemiC Adverse ReaCtions OCCurring within Five Days of EaCh VaCCination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
InjeCtion-Site Adverse ReaCtions	**N=7069**	**N=6997**	**N=6909**	**N=7071**	**N=7076**	**N=6992**	**N=6909**	**N=7078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
SystemiC Adverse ReaCtions	**n=6995**	**n=6913**	**n=6743**	**n=7022**	**n=7003**	**n=6914**	**n=6725**	**n=7024**
Temperature ≥100°F	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥102°F	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
InjeCtion-Site Adverse ReaCtions	**N=300**	**N=297**	**N=296**	**N=299**	**N=299**	**N=299**	**N=294**	**N=300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
SystemiC Adverse ReaCtions	**n=300**	**n=294**	**n=295**	**n=299**	**n=299**	**n=297**	**n=291**	**n=300**
Temperature ≥100°F	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥102°F	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).
N=number of subjeCts vaCCinated with safety follow-up
n=number of subjeCts with temperature data
Pain, Any=mild, moderate, severe or unknown intensity
Pain, Severe=inCapaCitating with inability to work or do usual aCtivity
Swelling, Any=any size or size unknown
Swelling, Severe=maximum size greater than 2 inChes
Erythema, Any=any size or size unknown
Erythema, Severe=maximum size greater than 2 inChes

UnsoliCited injeCtion-site and systemiC adverse reaCtions (assessed as vaCCine-related by the investigator) observed among reCipients of either GARDASIL 9 or GARDASIL in Studies 1 and 3 at a frequenCy of at least 1% are shown in Table 2. Few individuals disContinued study partiCipation due to adverse experienCes after reCeiving either vaCCine (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%).

Table 2: Rates (%) of UnsoliCited InjeCtion-Site and SystemiC Adverse Reactions Occurring among ≥1.0% of Individuals after Any VaCCination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	Girls and Women 16 through 26 Years of Age		Girls 9 through 15 Years of Age	
	GARDASIL 9 N=7071	GARDASIL N=7078	GARDASIL 9 N=299	GARDASIL N=300
InjeCtion-Site Adverse ReaCtions (1 to 5 Days Post-VaCCination, Any Dose)				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
ReaCtion	0.6	0.6	0.3	1.0
SystemiC Adverse ReaCtions (1 to 15 Days Post-VaCCination, Any Dose)				
HeadaChe	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	0.7
Abdominal pain, upper	0.7	0.8	1.7	1.3
Upper respiratory traCt infeCtion	0.1	0.1	0.3	1.0

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).
N=number of subjeCts vaCCinated with safety follow-up

In an unControlled CliniCal trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of soliCited adverse reaCtions following eaCh dose of GARDASIL 9 were similar between boys and girls. Rates of soliCited and unsoliCited injeCtion-site and systemiC adverse reaCtions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. SoliCited and unsoliCited adverse reaCtions reported by boys in this study are shown in Table 3.

In another unControlled CliniCal trial with 1,394 boys and men and 1,075 girls and women 16 through 26 years of age (Study 7), the rates of soliCited and unsoliCited adverse reaCtions following eaCh dose of GARDASIL 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of soliCited and unsoliCited adverse reaCtions reported by boys and men 16 through 26 years of age in this study are shown in Table 3.

In an unControlled CliniCal trial with 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age (Study 9), the rates of soliCited and unsoliCited adverse reaCtions following eaCh dose of GARDASIL 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of soliCited and unsoliCited adverse reaCtions reported by women 27 through 45 years of age in this study are shown in Table 3.

Table 3: Rates (%) of SoliCited and UnsoliCited* InjeCtion-Site and SystemiC Adverse ReaCtions among Boys 9 through 15 Years of Age, among Boys and Men 16 through 26 Years of Age and Women 27 through 45 Years of Age Who ReCeived GARDASIL 9 (Studies 2, 7, and 9)

	GARDASIL 9
Boys and Men 16 through 26 Years of Age	**N=1394**
SoliCited Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Pain, Any	63.4
InjeCtion-Site Pain, Severe	0.6
InjeCtion-Site Erythema, Any	20.7
InjeCtion-Site Erythema, Severe	0.4
InjeCtion-Site Swelling, Any	20.2
InjeCtion-Site Swelling, Severe	1.1
Oral Temperature ≥100.0°F†	4.4
Oral Temperature ≥102°F	0.6
UnsoliCited InjeCtion-Site Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Hypersensitivity	1.0
InjeCtion-Site Pruritus	1.0
UnsoliCited SystemiC Adverse ReaCtions (1-15 Days Post-VaCCination, Any Dose)	
HeadaChe	7.3
Pyrexia	2.4
Fatigue	1.4
Dizziness	1.1
Nausea	1.0
Boys 9 through 15 Years of Age	**N=639**
SoliCited Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Pain, Any	71.5
InjeCtion-Site Pain, Severe	0.5
InjeCtion-Site Erythema, Any	24.9
InjeCtion-Site Erythema, Severe	1.9
InjeCtion-Site Swelling, Any	26.9
InjeCtion-Site Swelling, Severe	5.2
Oral Temperature ≥100.0°F†	10.4
Oral Temperature ≥102°F	1.4
UnsoliCited InjeCtion-Site Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Hematoma	1.3
InjeCtion-Site Induration	1.1
UnsoliCited SystemiC Adverse ReaCtions (1-15 Days Post-VaCCination, Any Dose)	
HeadaChe	9.4
Pyrexia	8.9
Nausea	1.3
Women 27 through 45 Years of Age	**N=640**
SoliCited Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Pain, Any	82.8
InjeCtion-Site Pain, Severe	1.9
InjeCtion-Site Erythema, Any	16.9
InjeCtion-Site Erythema, Severe	0.5
InjeCtion-Site Swelling, Any	23.3
InjeCtion-Site Swelling, Severe	1.9
Oral Temperature ≥100.0°F†	2.5
Oral Temperature ≥102°F	0.3
UnsoliCited InjeCtion-Site Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)	
InjeCtion-Site Pruritus	1.6
InjeCtion-Site Hematoma	1.3
UnsoliCited SystemiC Adverse ReaCtions (1-15 Days Post-VaCCination, Any Dose)	
HeadaChe	13.6
Fatigue	3.4
Pyrexia	1.7
Nausea	1.7
Oropharyngeal pain	1.1

The data for GARDASIL 9 boys 9 through 15 years of age are from Study 2 (NCT00943722). The data for boys and men 16 through 26 years of age for GARDASIL 9 are from Study 7 (NCT01651949). The data for women 27 through 45 years of age are from Study 9 (NCT03158220).

*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjeCts vaCCinated with safety follow-up
†For oral temperature: number of subjeCts with temperature data for boys 9 through 15 years of age N=637; for boys and men 16 through 26 years of age N=1,386; for women 27 through 45 years of age N=640
Pain, Any=mild, moderate, severe or unknown intensity
Pain, Severe=inCapaCitating with inability to work or do usual aCtivity
Swelling, Any=any size or size unknown
Swelling, Severe=maximum size greater than 2 inChes
Erythema, Any=any size or size unknown
Erythema, Severe=maximum size greater than 2 inChes

Serious Adverse Events in Clinical Studies

Serious adverse events were ColleCted throughout the entire study period (range one month to 48 months post-last dose) for the seven CliniCal studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 354 reported a serious adverse event; representing 2.3% of the population. As a Comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing 2.5% of the population. Four GARDASIL 9 reCipients eaCh reported at least one serious adverse event that was determined to be vaCCine-related. The vaCCine-related serious adverse reaCtions were pyrexia, allergy to vaCCine, asthmatiC Crisis, and headaChe.

Deaths in the Entire Study Population

ACross the CliniCal studies, ten deaths oCCurred (five eaCh in the GARDASIL 9 and GARDASIL groups); none were assessed as vaCCine-related. Causes of death in the GARDASIL 9 group inCluded one automobile aCCident, one suiCide, one Case of aCute lymphoCytiC leukemia, one Case of hypovolemiC septiC shoCk, and one unexplained sudden death 678 days following the last dose of GARDASIL 9. Causes of death in the GARDASIL Control group inCluded one automobile aCCident, one airplane Crash, one Cerebral hemorrhage, one gunshot wound, and one stomaCh adenoCarCinoma.

Systemic Autoimmune Disorders

In all of the CliniCal trials with GARDASIL 9 subjeCts were evaluated for new mediCal Conditions potentially indiCative of a systemiC autoimmune disorder. In total, 2.2% (351/15,703) of GARDASIL 9 reCipients and 3.3% (240/7,378) of GARDASIL reCipients reported new mediCal Conditions potentially indiCative of systemiC autoimmune disorders, whiCh were similar to rates reported following GARDASIL, AAHS Control, or saline plaCebo in historiCal CliniCal trials.

Clinical Trials Experience for GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

A CliniCal study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaCCinated with three doses of GARDASIL. The time interval between the last injeCtion of GARDASIL and the first injeCtion of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline plaCebo and safety was evaluated using VRC-aided surveillanCe for 14 days after eaCh injeCtion of GARDASIL 9 or saline plaCebo in these individuals. The individuals who were monitored inCluded 608 individuals who reCeived GARDASIL 9 and 305 individuals who reCeived saline plaCebo. Few (0.5%) individuals who reCeived GARDASIL 9 disContinued due to adverse reaCtions. The vaCCine-related adverse experienCes that were observed among reCipients of GARDASIL 9 at a frequenCy of at least 1.0% and also at a greater frequenCy than that observed among saline plaCebo reCipients are shown in Table 4. Overall the safety profile was similar between individuals vaCCinated with GARDASIL 9 who were previously vaCCinated with GARDASIL and those who were naïve to HPV vaCCination with the exCeption of numeriCally higher rates of injeCtion-site swelling and erythema among individuals who were previously vaCCinated with GARDASIL (Tables 1 and 4).

Table 4: Rates (%) of SoliCited and UnsoliCited* InjeCtion-Site and SystemiC Adverse ReaCtions among Individuals Previously VaCCinated with GARDASIL Who ReCeived GARDASIL 9 or Saline PlaCebo (Girls and Women 12 through 26 Years of Age) (Study 4)

	GARDASIL 9 N=608	Saline PlaCebo N=305
SoliCited Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)		
InjeCtion-Site Pain	90.3	38.0
InjeCtion-Site Erythema	42.3	8.5
InjeCtion-Site Swelling	49.0	5.9
Oral Temperature ≥100.0°F†	6.5	3.0
UnsoliCited InjeCtion-Site Adverse ReaCtions (1-5 Days Post-VaCCination, Any Dose)		
InjeCtion-Site Pruritus	7.7	1.3
InjeCtion-Site Hematoma	4.8	2.3
InjeCtion-Site ReaCtion	1.3	0.3
InjeCtion-Site Mass	1.2	0.7
UnsoliCited SystemiC Adverse ReaCtions (1-15 Days Post-VaCCination, Any Dose)		
HeadaChe	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

The data for GARDASIL 9 and saline plaCebo are from Study 4 (NCT01047345).
*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjeCts vaCCinated with safety follow-up
†For oral temperature: number of subjeCts with temperature data GARDASIL 9 N=604; Saline PlaCebo N=304

Safety in Concomitant Use with Menactra and Adacel

In Study 5, the safety of GARDASIL 9 when administered ConComitantly with MenaCtra [MeningoCoCCal (Groups A, C, Y and W-135) PolysaCCharide Diphtheria Toxoid Conjugate VaCCine] and AdaCel [Tetanus Toxoid, ReduCed Diphtheria Toxoid and ACellular Pertussis VaCCine Adsorbed (Tdap)] was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years *[see Clinical Studies (14.7)]*.

Of the 1,237 boys and girls vaCCinated, 1,220 had safety follow-up for injeCtion-site adverse reaCtions. The rates of injeCtion-site adverse reaCtions were similar between the ConComitant group and non-ConComitant group (vaCCination with GARDASIL 9 separated from vaCCination with MenaCtra and AdaCel by 1 month) with the exCeption of an inCreased rate of swelling reported at the injeCtion site for GARDASIL 9 in the ConComitant group (14.4%) Compared to the non-ConComitant group (9.4%). The majority of injeCtion-site swelling adverse reaCtions were reported as being mild to moderate in intensity.

6.2 Postmarketing ExperienCe

The postmarketing adverse experienCes were reported voluntarily from a population of unCertain size, therefore, it is not possible to reliably estimate their frequenCy or to establish a Causal relationship to vaCCine exposure.

The safety profile of GARDASIL 9 and GARDASIL are similar. The postmarketing safety experienCe with GARDASIL is relevant to GARDASIL 9 sinCe the vaCCines are manufaCtured similarly and Contain thesame L1 HPV proteins of four of the same HPV types.

GARDASIL 9

In addition to the adverse reaCtions reported in the CliniCal studies, the following adverse experienCes have been spontaneously reported during post-approval use of GARDASIL 9:

Gastrointestinal disorders: Vomiting
Skin and subCutaneous tissue disorders: UrtiCaria

GARDASIL

Additionally, the following postmarketing adverse experienCes have been spontaneously reported for GARDASIL:

Blood and lymphatiC system disorders: Autoimmune hemolytiC anemia, idiopathiC thromboCytopeniC purpura, lymphadenopathy.

Respiratory, thoraCiC and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: PanCreatitis.

General disorders and administration site Conditions: Asthenia, Chills, death, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reaCtions inCluding anaphylaCtiC/anaphylaCtoid reaCtions, bronChospasm.

MusCuloskeletal and ConneCtive tissue disorders: Arthralgia, myalgia.

Nervous system disorders: ACute disseminated enCephalomyelitis, Guillain-Barré syndrome, motor neuron disease, paralysis, seizures, transverse myelitis.

InfeCtions and infestations: Cellulitis.

VasCular disorders: Deep venous thrombosis.

7 DRUG INTERACTIONS

7.1 Use with SystemiC Immunosuppressive MediCations

Immunosuppressive therapies, inCluding irradiation, antimetabolites, alkylating agents, CytotoxiC drugs, and CortiCosteroids (used in greater than physiologiC doses), may reduCe the immune responses to vaCCines *[see Use in Specific Populations (8.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 PregnanCy

Pregnancy Exposure Registry

There is a pregnanCy exposure registry to monitor pregnanCy outComes in women exposed to GARDASIL 9 during pregnanCy. To enroll in or obtain information about the registry, Call MerCk Sharp & Dohme Corp., a subsidiary of MerCk & Co., InC., at 1-800-986-8999.

Risk Summary

All pregnanCies have a risk of birth defeCt, loss, or other adverse outComes. In the U.S. general population, the estimated baCkground risk of major birth defeCts and misCarriage in CliniCally reCognized pregnanCies is 2% to 4% and 15% to 20%, respeCtively. There are no adequate and well-Controlled studies of GARDASIL 9 in pregnant women. Available human data do not demonstrate vaCCine-assoCiated inCrease in risk of major birth defeCts and misCarriages when GARDASIL 9 is administered during pregnanCy.

In one developmental toxiCity study, 0.5 mL of a vaCCine formulation Containing between 1 and 1.5 — fold of eaCh of the 9 HPV antigen types was administered to female rats prior to mating and during gestation. In a seCond study, animals were administered a single human dose (0.5 mL) of GARDASIL 9 prior to mating, during gestation and during laCtation. These animal studies revealed no evidenCe of harm to the fetus due to GARDASIL 9 *[see Data]*.

Data

Human Data

In pre-liCensure CliniCal studies of GARDASIL 9, women underwent pregnanCy testing immediately prior to administration of eaCh dose of GARDASIL 9 or Control vaCCine (GARDASIL). (Data from GARDASIL are relevant to GARDASIL 9 beCause both vaCCines are manufaCtured using the same proCess and have overlapping Compositions.) SubjeCts who were determined to be pregnant were instruCted to defer vaCCination until the end of their pregnanCy. Despite this pregnanCy sCreening regimen, some subjeCts were vaCCinated very early in pregnanCy before human ChorioniC gonadotropin (HCG) was deteCtable. An analysis was ConduCted to evaluate pregnanCy outComes for pregnanCies with onset within 30 days before or after vaCCination with GARDASIL 9 or GARDASIL. Among suCh pregnanCies, there were 62 and 55 with known outComes (exCluding eCtopiC pregnanCies and eleCtive terminations) for GARDASIL 9 and GARDASIL, respeCtively, inCluding 44 and 48 live births, respeCtively. The rates of pregnanCies that resulted in a misCarriage were 27.4% (17/62) and 12.7% (7/55) in subjeCts

who reCeived GARDASIL 9 or GARDASIL, respeCtively. The rates of live births with major birth defeCts were 0% (0/44) and 2.1% (1/48) in subjeCts who reCeived GARDASIL 9 or GARDASIL, respeCtively.

A five-year pregnanCy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL within one month prior to the last menstrual period (LMP) or at any time during pregnanCy, 2,566 of whom were prospeCtively followed. After exCluding eleCtive terminations (n=107), eCtopiC pregnanCies (n=5) andthose lost to follow-up (n=814), there were 1,640 pregnanCies with known outComes. Rates of misCarriage and major birth defeCts were 6.8% of pregnanCies (111/1,640) and 2.4% of live born infants (37/1,527), respeCtively. These rates of assessed outComes in the prospeCtive population were Consistent with estimated baCkground rates.

In two postmarketing studies of GARDASIL (one ConduCted in the U.S., and the other in NordiC Countries), pregnanCy outComes among subjeCts who reCeived GARDASIL during pregnanCy were evaluated retrospeCtively. Among the 1,740 pregnanCies inCluded in the U.S. study database, outComes were available to assess the rates of major birth defeCts and misCarriage. Among the 499 pregnanCies inCluded in the NordiC study database, outComes were available to assess the rates of major birth defeCts. In both studies, rates of assessed outComes did not suggest an inCreased risk with the administration of GARDASIL during pregnanCy.

Animal Data

Developmental toxiCity studies were ConduCted in female rats. In one study, animals were administered 0.5 mL of a vaCCine formulation Containing between 1 and 1.5 —fold of eaCh of the 9 HPV antigen types 5 and 2 weeks prior to mating, and on gestation day 6. In a seCond study, animals were administered a single human dose (0.5 mL) of GARDASIL 9, 5 and 2 weeks prior to mating, on gestation day 6, and on laCtation day 7. No adverse effeCts on pre- and post-weaning development were observed. There were no vaCCine-related fetal malformations or variations.

8.2 LaCtation

Risk Summary

Available data are not suffiCient to assess the effeCts of GARDASIL 9 on the breastfed infant or on milk produCtion/exCretion. The developmental and health benefits of breastfeeding should be Considered along with the mother's clinical need for GARDASIL 9 and any potential adverse effeCts on the breastfed Child from GARDASIL 9 or from the underlying maternal Condition. For preventive vaCCines, the underlying maternal Condition is susCeptibility to disease prevented by the vaCCine.

8.4 PediatriC Use

Safety and effeCtiveness have not been established in pediatriC patients below 9 years of age.

8.5 GeriatriC Use

The safety and effeCtiveness of GARDASIL 9 have not been evaluated in a geriatriC population, defined as individuals aged 65 years and over.

8.6 ImmunoCompromised Individuals

The immunologiC response to GARDASIL 9 may be diminished in immunoCompromised individuals *[see Drug Interactions (7.1)]*.

11 DESCRIPTION

GARDASIL 9, Human Papillomavirus 9-valent VaCCine, ReCombinant, is a non-infeCtious reCombinant 9-valent vaCCine prepared from the purified virus-like partiCles (VLPs) of the major Capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produCed by separate fermentations using reCombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation proCess involves growth of *S. cerevisiae* on ChemiCally-defined fermentation media whiCh inClude vitamins, amino aCids, mineral salts, and Carbohydrates. The VLPs are released from the yeast Cells by Cell disruption and purified by a series of ChemiCal and physiCal methods. The purified VLPs are adsorbed on preformed aluminum-Containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaCCine is a sterile liquid suspension that is prepared by Combining the adsorbed VLPs of eaCh HPV type and additional amounts of the aluminum-Containing adjuvant and the final purifiCation buffer.

GARDASIL 9 is a sterile suspension for intramusCular administration. EaCh 0.5-mL dose Contains approximately 30 mCg of HPV Type 6 L1 protein, 40 mCg of HPV Type 11 L1 protein, 60 mCg of HPV Type 16 L1 protein, 40 mCg of HPV Type 18 L1 protein, 20 mCg of HPV Type 31 L1 protein, 20 mCg of HPV Type 33 L1 protein, 20 mCg of HPV Type 45 L1 protein, 20 mCg of HPV Type 52 L1 protein, and 20 mCg of HPV Type 58 L1 protein.

EaCh 0.5-mL dose of the vaCCine also Contains approximately 500 mCg of aluminum (provided as AAHS), 9.56 mg of sodium Chloride, 0.78 mg of L-histidine, 50 mCg of polysorbate 80, 35 mCg of sodium borate, <7 mCg yeast protein, and water for injeCtion. The produCt does not Contain a preservative or antibiotiCs.

After thorough agitation, GARDASIL 9 is a white, Cloudy liquid.

12 CLINICAL PHARMACOLOGY

12.1 MeChanism of ACtion

HPV only infeCts human beings. Animal studies with analogous animal papillomaviruses suggest thatthe effiCaCy of L1 VLP vaCCines may involve the development of humoral immune responses. EffiCaCy of GARDASIL 9 against anogenital diseases related to the vaCCine HPV types in human beings is thought to be mediated by humoral immune responses induCed by the vaCCine, although the exaCt meChanism of proteCtion is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 CarCinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL 9 has not been evaluated for the potential to Cause CarCinogeniCity, genotoxiCity or impairment of male fertility. GARDASIL 9 administered to female rats had no effeCts on fertility *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-speCified serostatus Cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre- speCified serostatus Cutoff for a given HPV type. The serostatus Cutoff is the antibody titer level above the assay's lower limit of quantifiCation that reliably distinguishes sera samples Classified by CliniCal likelihood of HPV infeCtion and positive or negative status by previous versions of Competitive Luminex Immunoassay (CLIA). The lower limits of quantifiCation and serostatus Cutoffs for eaCh of the 9 vaCCine HPV types are shown in Table 5 below. PCR positive is defined as DNA deteCted for a given HPV type. PCR negative is defined as DNA not deteCted for a given HPV type. The lower limit of deteCtion for the multiplexed HPV PCR assays ranged from 5 to 34 Copies per test aCross the 9 vaCCine HPV types.

Table 5: Competitive Luminex Immunoassay (CLIA) Limits of QuantifiCation and Serostatus Cutoffs for GARDASIL 9 HPV Types

HPV Type	CLIA Lower Limit of QuantifiCation (mMU*/mL)	CLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

*mMU=milli-MerCk Units

14.1 EffiCaCy and EffeCtiveness Data for GARDASIL

EffiCaCy and effeCtiveness of GARDASIL are relevant to GARDASIL 9 sinCe the vaCCines are manufaCtured similarly and Contain four of the same HPV L1 VLPs.

Individuals 16 through 26 Years of Age

EffiCaCy of GARDASIL was assessed in five AAHS-Controlled, double-blind, randomized CliniCal trials evaluating 24,596 individuals 16 through 26 years of age (20,541 girls and women and 4,055 boys and men). The results of these trials are shown in Table 6 below.

Table 6: Analysis of EffiCaCy of GARDASIL in the PPE* Population for VaCCine HPV Types

Disease Endpoints	GARDASIL		AAHS Control		% EffiCaCy (95% CI)
	N	Number of Cases	N	Number of Cases	
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma ACuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-aCuminate	194	4	208	11	60.4 (-33.5, 90.8)

*The PPE population Consisted of individuals who reCeived all three vaCCinations within one year of enrollment, did not have major deviations from the study protoCol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).

†Analyses of the Combined trials were prospeCtively planned and inCluded the use of similar study entry Criteria.

N=Number of individuals with at least one follow-up visit after Month 7

CI=ConfidenCe Interval

Note 1: Point estimates and ConfidenCe intervals are adjusted for person-time of follow-up.

Note 2: Table 6 does not inClude Cases due to HPV types not Covered by the vaCCine.

AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate, CIN = CerviCal Intraepithelial Neoplasia, VIN = Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, PIN=Penile Intraepithelial Neoplasia, AIN=Anal Intraepithelial Neoplasia, AIS=AdenoCarCinoma *In Situ*

In an extension study in females 16 through 26 years of age at enrollment, prophylaCtiC effiCaCy of GARDASIL through Month 60 against overall CerviCal and genital disease related to HPV 6, 11, 16, and 18 was 100% (95% CI: 12.3%, 100%) Compared to AAHS Control.

An extension study in girls and women 16 through 23 years of age used national health Care registries in Denmark, ICeland, Norway, and Sweden to monitor endpoint Cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, CerviCal CanCer, vulvar CanCer, or vaginal CanCer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaCCination with GARDASIL. An interim analysis of the per-protoCol effeCtiveness population inCluded 1,902 subjeCts who Completed the GARDASIL vaCCination series within one year, were naïve to the relevant HPV type through 1 month post-dose 3, had no protoCol violations, and had follow-up data available. The median follow-up from the first dose of vaCCine was 6.7 years with a range of 2.8 to 8.4 years. At the time of interim analysis, no Cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, CerviCal CanCer, vulvar CanCer, or vaginal CanCer were observed over a total of 5,765 person-years at risk.

Girls and Boys 9 through 15 Years of Age

An extension study of 614 girls and 565 boys 9 through 15 years of age at enrollment who were randomized to vaCCination with GARDASIL aCtively followed subjeCts for endpoint Cases of HPV 6-, 11-, 16-, or 18-related persistent infeCtion, CIN (any grade), AIS, VIN, VaIN, CerviCal CanCer, vulvar CanCer,

vaginal CanCer, and external genital lesions from the initiation of sexual aCtivity or age 16 onwards. An interim analysis of the per-protoCol effeCtiveness population inCluded 246 girls and 168 boys who Completed the GARDASIL vaCCination series within one year, were seronegative to the relevant HPV type at initiation of the vaCCination series, and had not initiated sexual aCtivity prior to reCeiving the third dose of GARDASIL. The median follow-up from the first dose of vaCCine was 7.2 years with a range of 0.5 to 8.5 years. At the time of interim analysis, no cases of persistent infection of at least 12 months' duration and no Cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, CerviCal CanCer, vulvar CanCer, vaginal CanCer, or external genital lesions were observed over a total 1,105 person-years at risk. There were 4 Cases of HPV 6-, 11-, 16-, or 18-related persistent infeCtion of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of whiCh persisted to 12 months' duration.

Individuals 27 through 45 Years of Age

A CliniCal trial evaluated effiCaCy of GARDASIL in 3,253 women 27 through 45 years of age, based on a Combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infeCtion, genital warts, vulvar and vaginal dysplastiC lesions of any grade, CIN of any grade, AIS, and CerviCal CanCer. These women were randomized 1:1 to reCeive either GARDASIL or AAHS Control. The CliniCal trial was ConduCted in two phases: a base study and a long-term study extension. The per-protoCol effiCaCy (PPE) population reCeived all three vaCCinations within one year of enrollment, did not have major deviations from the study protoCol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16 and 18) prior to dose 1 and remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).

In the base study (median duration of follow-up of 3.5 years post-dose 3), the effiCaCy of GARDASIL against the Combined inCidenCe of HPV 6-, 11-, 16-, and 18-related persistent infeCtion, genital warts, VIN, VaIN, vulvar CanCer, vaginal CanCer, CerviCal dysplasia (any grade CIN), AIS and CerviCal CanCer inthe PPE population was 87.7% (95% CI: 75.4%, 94.6%). The effiCaCy estimate for the Combined endpoint was driven primarily by prevention of persistent infeCtion. The effiCaCy of GARDASIL against the Combined inCidenCe of HPV 6-, 11-, 16-, and 18-related genital warts or CerviCal dysplasia was 95.0% (95% CI: 68.7%, 99.9%) in the PPE population. While no statistiCally signifiCant effiCaCy was demonstrated for GARDASIL in the base study for prevention of CerviCal intraepithelial neoplasia grades 2 and 3 (CIN 2/3), adenoCarCinoma *in situ* (AIS) or CerviCal CanCer related to HPV types 16 and 18, there was 1 Case of CIN 2/3 observed in the GARDASIL group and 5 Cases in the plaCebo group. The CIN 2 Case in the GARDASIL group tested positive by PCR for HPV 16 and HPV 51.

In the long-term extension of this study, subjeCts from Colombia (n=600) randomized to the GARDASIL group in the base study were monitored for HPV 6-, 11-, 16-, and 18-related genital warts or CerviCal dysplasia. The median follow-up post-dose 3 was 8.9 years with a range of 0.1 to 10.1 years overa total of 3,518 person-years. During the long-term extension phase, no Cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or genital warts were observed in the PPE population.

EffeCtiveness of GARDASIL in men 27 through 45 years of age is inferred from effiCaCy data in women 27 through 45 years of age as desCribed above and supported by immunogeniCity data from a CliniCal trial in whiCh 150 men, 27 through 45 years of age, reCeived a 3-dose regimen of GARDASIL (0, 2, 6 months). A Cross-study analysis of per-protoCol immunogeniCity populations Compared Month 7 anti-HPV 6, 11, 16, and 18 GMTs of these 27- through 45-year-old men (Study A) to those of 16- through 26-year old boys and men (Study B) in whom effiCaCy of GARDASIL had been established (see Table 6). GMT ratios (Study A/Study B) for HPV 6, 11, 16, and 18 were 0.82 (95%CI: 0.65, 1.03), 0.79 (95%CI: 0.66, 0.93), 0.91 (95%CI: 0.72, 1.13), and 0.74 (95%CI: 0.59, 0.92), respeCtively.

14.2 CliniCal Trials for GARDASIL 9

EffiCaCy and/or immunogeniCity of the 3-dose regimen of GARDASIL 9 were assessed in seven CliniCal trials. Study 1 evaluated the effiCaCy of GARDASIL 9 to prevent HPV-related CerviCal, vulvar, and vaginal disease using GARDASIL as a Comparator.

The analysis of effiCaCy for GARDASIL 9 was evaluated in the per-protoCol effiCaCy (PPE) population of 16- through 26-year-old girls and women, who reCeived all three vaCCinations within one year of enrollment, did not have major deviations from the study protoCol, and were naïve to the relevant HPV type(s) by serology and PCR of CerviCovaginal speCimens prior to dose one and who remained PCR

negative for the relevant HPV type(s) through one month post-dose 3 (Month 7). Overall, approximately 52% of subjeCts were negative to all vaCCine HPV types by both PCR and serology at Day 1.

The primary analysis of effiCaCy against HPV Types 31, 33, 45, 52, and 58 is based on a Combined endpoint of CerviCal Intraepithelial Neoplasia (CIN) 2, CIN 3, AdenoCarCinoma *in situ* (AIS), invasive CerviCal CarCinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar CanCer, or vaginal CanCer. Other endpoints evaluated inClude CerviCal, vulvar and vaginal disease of any grade, persistent infeCtion, CytologiCal abnormalities and invasive proCedures. For all endpoints, the effiCaCy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated Compared with GARDASIL. EffiCaCy of GARDASIL 9 against anal lesions Caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low inCidenCe. EffeCtiveness of GARDASIL 9 against anal lesions was inferred from the effiCaCy of GARDASIL against anal lesions Caused by HPV types 6, 11, 16and 18 in men and antibody responses eliCited by GARDASIL 9 against the HPV types Covered by the vaCCine.

EffeCtiveness against disease Caused by HPV Types 6, 11, 16, and 18 was assessed by Comparison of geometriC mean titers (GMTs) of type-speCifiC antibodies following vaCCination with GARDASIL 9 with those following vaCCination with GARDASIL (Study 1 and Study 3). The effeCtiveness of GARDASIL 9 in girls and boys 9 through 15 years old and in boys and men 16 through 26 years old was inferred based on a Comparison of type-speCifiC antibody GMTs to those of 16 through 26-year-old girls and women following vaCCination with GARDASIL 9. ImmunogeniCity analyses were performed in the per-protoCol immunogeniCity (PPI) population Consisting of individuals who reCeived all three vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met pre-defined day range for serum ColleCtion for assessment of antibody response and were naïve [PCR negative (in girls and women 16 through 26 years of age; Studies 1 and 2) and seronegative (Studies 1, 2, 3, 5, 7 and 8)] to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women (Studies 1 and 2) remained PCR negative to the relevant HPV type(s) through Month 7. Pre-defined day ranges for vaCCinations were relative to Day 1 (dose 1). For the 3-dose sChedule, dose 2 was at 2 months (± 3 weeks) and dose 3 was at 6 months (± 4 weeks). For the 2-dose sChedule, dose 2 was at 6 or 12 months (± 4 weeks). Pre-defined day range for serum ColleCtion for assessment of antibody response was 21 to 49 days after the last dose.

Study 1 evaluated immunogeniCity of GARDASIL 9 and effiCaCy to prevent infeCtion and disease Caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women. Study 2 evaluated immunogeniCity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogeniCity of GARDASIL 9 Compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaCCinated with GARDASIL. Study 5 evaluated GARDASIL 9 ConComitantly administered with MenaCtra and AdaCel in girls and boys 11 through 15 years of age. Together, these five CliniCal trials evaluated 12,233 individuals who reCeived GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years. Study 7 evaluated immunogeniCity of GARDASIL 9 in boys and men, inCluding 1,106 self-identified as heterosexual men (HM) and 313 self-identified as men having sex with men (MSM), 16 through 26 years of age at enrollment (mean ages 20.8 years and 22.2 years, respeCtively) and 1,101 girls and women 16 through 26 years of age at enrollment (mean age 21.3 years). Study 9 evaluated immunogeniCity of GARDASIL 9 in 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age (mean ages 35.8 years and 21.6 years, respeCtively).

The raCe distribution of the 16- through 26-year-old girls and women in the CliniCal trials was as follows: 56.8% White; 25.2% Other; 14.1% Asian; and 3.9% BlaCk. The raCe distribution of the 9- through 15-year-old girls in the CliniCal trials was as follows: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% BlaCk. The raCe distribution of the 9- through 15-year-old boys in the CliniCal trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% BlaCk. The raCe distribution of the 16- through 26-year-old boys and men in the CliniCal trials was as follows: 62.1% White; 22.6% Other; 9.8% Asian; and 5.5% BlaCk.

In Study 9 the raCe distribution of 27- through 45-year-old women was as follows: 97.7% White, 1.6% Asian, 0.3% Other or MultiraCial, and 0.5% BlaCk. The raCe distribution of girls and women 16 through 26

years of age in this study was as follows: 94.6% White, 3.0% Asian, 1.6% Other or MultiraCial, and 0.9% BlaCk.

One CliniCal trial (Study 8) assessed the 2-dose regimen of GARDASIL 9. Study 8 evaluated the immunogeniCity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and women 16 through 26 years of age; (N=1,518; 753 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years. In Study 8, the raCe distribution was as follows: 61.1% White; 16.3% Asian; 13.3% Other; and 8.9% BlaCk.

14.3 EffiCaCy — HPV Types 31, 33, 45, 52 and 58 in Girls and Women 16 through 26 Years of Age

Studies Supporting the Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58

The effiCaCy of GARDASIL 9 in 16- through 26-year-old girls and women was assessed in an aCtive Comparator-Controlled, double-blind, randomized CliniCal trial (Study 1) that inCluded a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105) who were enrolled and vaCCinated without pre-sCreening for the presenCe of HPV infeCtion. SubjeCts were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaCCination.

The primary effiCaCy evaluation was ConduCted in the PPE population based on a Composite CliniCal endpoint of HPV 31-, 33-, 45-, 52-, and 58-related CerviCal CanCer, vulvar CanCer, vaginal CanCer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. EffiCaCy was further evaluated with the CliniCal endpoints of HPV 31-, 33-, 45-, 52-, and 58-related CIN 1, vulvar and vaginal disease of any grade, and persistent infeCtion. In addition, the study also evaluated the impaCt of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58-related abnormal PapaniColaou (Pap) tests, CerviCal and external genital biopsy, and definitive therapy [inCluding loop eleCtrosurgiCal exCision proCedure (LEEP) and Conization]. EffiCaCy for all endpoints was measured starting after the Month 7 visit.

GARDASIL 9 prevented HPV 31-, 33-, 45-, 52-, and 58-related persistent infeCtion and disease and also reduCed the inCidenCe of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, CerviCal and external genital biopsy, and definitive therapy (Table 7).

Table 7: Analysis of EffiCaCy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population of 16- through 26-Year-old Girls and Women (Study 1)

Disease Endpoint	GARDASIL 9 N†=7099		GARDASIL N†=7105		GARDASIL 9 EffiCaCy % (95% CI)
	n‡	Number of Cases	n‡	Number of Cases	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, CerviCal CanCer, VIN 2/3, ValN 2/3, Vulvar CanCer, and Vaginal CanCer	6016	1	6017	30	96.7 (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5948	1	5943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5948	1	5943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6009	1	6012	16	93.8 (61.5, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months§	5939	26	5953	642	96.2 (94.4, 97.5)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months¶	5939	15	5953	375	96.1 (93.7, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap# Abnormality	5881	35	5882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6016	7	6017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapyᵖ	6012	4	6014	32	87.5 (65.7, 96.0)

*The PPE population Consisted of individuals who reCeived all three vaCCinations within one year of enrollment, did not have major deviations from the study protoCol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7); data from Study 1 (NCT00543543).

†N=Number of individuals randomized to the respeCtive vaCCination group who reCeived at least one injeCtion

‡n=Number of individuals Contributing to the analysis

§Persistent infeCtion deteCted in samples from two or more ConseCutive visits at least six months apart

¶Persistent infeCtion deteCted in samples from two or more ConseCutive visits over 12 months or longer

#PapaniColaou test

ᵖInCluding loop eleCtrosurgiCal exCision proCedure (LEEP) and Conization

CI=ConfidenCe Interval

CIN=CerviCal Intraepithelial Neoplasia, VIN=Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, AIS=AdenoCarCinoma *In Situ*, ASC-US=AtypiCal squamous Cells of undetermined signifiCanCe

HR=High Risk

14.4 EffeCtiveness in Prevention of HPV-Related Oropharyngeal and Other Head and NeCk CanCers

The effeCtiveness of GARDASIL 9 against oropharyngeal and other head and neCk CanCers Caused by HPV types 16, 18, 31, 33, 45, 52 and 58, is based on the effeCtiveness of GARDASIL and GARDASIL 9 to prevent anogenital disease Caused by HPV types Covered by the vaCCine *[see Clinical Studies (14.1, 14.2, 14.3)].*

14.5 ImmunogeniCity of a 3-Dose Regimen

The minimum anti-HPV titer that Confers proteCtive effiCaCy has not been determined.

Type-speCifiC immunoassays (i.e., CLIA) with type-speCifiC standards were used to assess immunogeniCity to eaCh vaCCine HPV type. These assays measured antibodies against neutralizingepitopes for eaCh HPV type. The sCales for these assays are unique to eaCh HPV type; thus, Comparisons aCross types and to other assays are not appropriate. ImmunogeniCity was measured by (1) the perCentage of individuals who were seropositive for antibodies against the relevant vaCCine HPV type, and (2) the GeometriC Mean Titer (GMT).

Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18

EffeCtiveness of GARDASIL 9 against persistent infeCtion and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority Comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaCCination with GARDASIL 9 with those following vaCCination with GARDASIL. A low number of effiCaCy endpoint Cases related to HPV types 6,

11, 16 and 18 in both vaCCination groups preCluded a meaningful assessment of effiCaCy using disease endpoints assoCiated with these HPV types. The primary analyses were ConduCted in the per-protoCol population, whiCh inCluded subjeCts who reCeived all three vaCCinations within one year of enrollment, did not have major deviations from the study protoCol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjeCts 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in CerviCovaginal speCimens prior to dose 1 through Month 7.

Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 through 26 years of age were non-inferior to those among the Corresponding populations for GARDASIL (Table 8). At least 99.7% of individuals inCluded in the analyses for eaCh HPV type beCame seropositive by Month 7.

Table 8: Comparison of Immune Responses (Based on CLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the PPI* Population of 9- through 26-Year-Old Girls and Women (Studies 1 and 3)

Population	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N† (n‡)	GMT mMU§/mL	N† (n‡)	GMT mMU§/mL	GMT Ratio	(95% CI)¶
Anti-HPV 6						
9- through 15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	893.1	6795 (3975)	875.2	1.02	(0.99, 1.06)
Anti-HPV 11						
9- through 15-year-old girls	300 (273)	1315.6	300 (261)	1417.3	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	666.3	6795 (3982)	830.0	0.80	(0.77, 0.83)
Anti-HPV 16						
9- through 15-year-old girls	300 (276)	6739.5	300 (270)	6887.4	0.97	(0.85, 1.11)
16- through 26-year-old girls and women	6792 (4032)	3131.1	6795 (4062)	3156.6	0.99	(0.96, 1.03)
Anti-HPV 18						
9- through 15-year-old girls	300 (276)	1956.6	300 (269)	1795.6	1.08	(0.91, 1.29)
16- through 26-year-old girls and women	6792 (4539)	804.6	6795 (4541)	678.7	1.19	(1.14, 1.23)

*The PPI population Consisted of individuals who reCeived all three vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met predefined Criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Study 1 (NCT00543543), and the data for 9- through 15-year-old girls are from Study 3 (NCT01304498).

†N=Number of individuals randomized to the respeCtive vaCCination group who reCeived at least one injeCtion

‡n=Number of individuals Contributing to the analysis

§mMU=milli-MerCk Units

¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=ConfidenCe Interval

GMT=GeometriC Mean Titer

CLIA=Competitive Luminex Immunoassay

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys

EffeCtiveness of GARDASIL 9 against persistent infeCtion and disease related to vaCCine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority Comparison ConduCted in the PPI population in Study 2 of GMTs following vaCCination with GARDASIL 9 among 9- through 15-year-old girls and boys with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 9).

Table 9: Comparison of Immune Responses (Based on CLIA) between the PPI* Populations of 16- through 26-Year-Old

Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL 9 VaCCine HPV Types (Study 2)

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16- through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
9- through 15-year-old girls	630	503	1703.1	1.89 (1.68, 2.12)
9- through 15-year-old boys	641	537	2083.4	2.31 (2.06, 2.60)
16- through 26-year-old girls and women	463	328	900.8	1
Anti-HPV 11				
9- through 15-year-old girls	630	503	1291.5	1.83 (1.63, 2.05)
9- through 15-year-old boys	641	537	1486.3	2.10 (1.88, 2.36)
16- through 26-year-old girls and women	463	332	706.6	1
Anti-HPV 16				
9- through 15-year-old girls	630	513	6933.9	1.97 (1.75, 2.21)
9- through 15-year-old boys	641	546	8683.0	2.46 (2.20, 2.76)
16- through 26-year-old girls and women	463	329	3522.6	1
Anti-HPV 18				
9- through 15-year-old girls	630	516	2148.3	2.43 (2.12, 2.79)
9- through 15-year-old boys	641	544	2855.4	3.23 (2.83, 3.70)
16- through 26-year-old girls and women	463	345	882.7	1
Anti-HPV 31				
9- through 15-year-old girls	630	506	1894.7	2.51 (2.21, 2.86)
9- through 15-year-old boys	641	543	2255.3	2.99 (2.63, 3.40)
16- through 26-year-old girls and women	463	340	753.9	1
Anti-HPV 33				
9- through 15-year-old girls	630	518	985.8	2.11 (1.88, 2.37)
9- through 15-year-old boys	641	544	1207.4	2.59 (2.31, 2.90)
16- through 26-year-old girls and women	463	354	466.8	1
Anti-HPV 45				
9- through 15-year-old girls	630	518	707.7	2.60 (2.25, 3.00)
9- through 15-year-old boys	641	547	912.1	3.35 (2.90, 3.87)
16- through 26-year-old girls and women	463	368	272.2	1
Anti-HPV 52				
9- through 15-year-old girls	630	517	962.2	2.21 (1.96, 2.49)
9- through 15-year-old boys	641	545	1055.5	2.52 (2.22, 2.84)
16- through 26-year-old girls and women	463	337	419.6	1
Anti-HPV 58				
9- through 15-year-old girls	630	516	1288.0	2.18 (1.94, 2.46)
9- through 15-year-old boys	641	544	1593.3	2.70 (2.40, 3.03)
16- through 26-year-old girls and women	463	332	590.5	1

*The PPI population Consisted of individuals who reCeived all three vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met predefined Criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV types through one month post-dose 3 (Month 7). The data are from Study 2 (NCT00943722).

†N=Number of individuals randomized to the respeCtive vaCCination group who reCeived at least one injeCtion

‡n=Number of individuals Contributing to the analysis

§mMU=milli-MerCk Units

¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CLIA=Competitive Luminex Immunoassay

CI=ConfidenCe Interval

GMT=GeometriC Mean Titer

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 16- through 26-Year-Old Boys and Men

EffeCtiveness of GARDASIL 9 against persistent infeCtion and disease related to vaCCine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority Comparison ConduCted in the PPI population in Study 7 of GMTs following vaCCination with GARDASIL 9 among 16- through 26-year-old HM with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 16- through 26-year-old HM were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 10). Study 7 also enrolled 313 16- through 26-year-old HIV-negative MSM. At Month 7, anti-HPV GMT ratios for MSM relative to HM ranged from 0.6 to 0.8, depending on HPV type. The GMT ratios for MSM relative to HM were generally similar to those previously observed in CliniCal trials with GARDASIL.

Table 10: Comparison of Immune Responses (Based on CLIA) between the PPI* Populations of 16- through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men Self-Identified as Heterosexual (HM) for All GARDASIL 9 VaCCine HPV Types (Study 7)

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16- through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
16- through 26-year-old HM	1103	847	782.0	1.11 (1.02, 1.21)
16- through 26-year-old girls and women	1099	708	703.9	1
Anti-HPV 11				
16- through 26-year-old HM	1103	851	616.7	1.09 (1.00, 1.19)
16- through 26-year-old girls and women	1099	712	564.9	1
Anti-HPV 16				
16- through 26-year-old HM	1103	899	3346.0	1.20 (1.10, 1.30)
16- through 26-year-old girls and women	1099	781	2788.3	1
Anti-HPV 18				
16- through 26-year-old HM	1103	906	808.2	1.19 (1.08, 1.31)
16- through 26-year-old girls and women	1099	831	679.8	1
Anti-HPV 31				
16- through 26-year-old HM	1103	908	708.5	1.24 (1.13, 1.37)
16- through 26-year-old girls and women	1099	826	570.1	1
Anti-HPV 33				
16- through 26-year-old HM	1103	901	384.8	1.19 (1.10, 1.30)
16- through 26-year-old girls and women	1099	853	322.0	1
Anti-HPV 45				
16- through 26-year-old HM	1103	909	235.6	1.27 (1.14, 1.41)
16- through 26-year-old girls and women	1099	871	185.7	1
Anti-HPV 52				
16- through 26-year-old HM	1103	907	386.8	1.15 (1.05, 1.26)
16- through 26-year-old girls and women	1099	849	335.2	1
Anti-HPV 58				
16- through 26-year-old HM	1103	897	509.8	1.25 (1.14, 1.36)
16- through 26-year-old girls and women	1099	839	409.3	1

*The PPI population Consisted of individuals who reCeived all three vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met predefined Criteria for the interval between the Month 6 and Month 7 visit, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Study 7 (NCT01651949).

†Number of individuals randomized to the respeCtive vaCCination group who reCeived at least one injeCtion

‡Number of individuals Contributing to the analysis

§mMU=milli-MerCk Units

¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CLIA=Competitive Luminex Immunoassay

CI=ConfidenCe Interval

GMT=GeometriC Mean Titer

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 27- through 45-Year-Old Women

EffeCtiveness of GARDASIL 9 against persistent infeCtion and disease related to vaCCine HPV types in 27- through 45-year-old women was supported by immunobridging Comparisons ConduCted in the PPI population in Study 9. In Study 9, the GMT ratios of anti-HPV responses at Month 7 among 27- through

45-year-old women relative to anti-HPV responses among 16- through 26-year-old girls and women met the suCCess Criteria of having the lower bound of the 95% CI of the GMT ratios greater than 0.50 for HPV 16, 18, 31, 33, 45, 52, and 58 (Table 11).

Table 11: Comparison of Immune Responses (Based on CLIA) Between the PPI* Populations of 27- through 45 Year-Old Women and 16- through 26-Year-Old Girls and Women for GARDASIL 9 VaCCine HPV Types (Study 9)

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16-through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
27- through 45-year-old women	640	448	638.4	N.D#
16- through 26-year-old girls and women	570	421	787.8	N.D#
Anti-HPV 11				
27- through 45-year-old women	640	448	453.5	N.D#
16- through 26-year-old girls and women	570	421	598.7	N.D#
Anti-HPV 16				
27- through 45-year-old women	640	448	2,147.5	0.70 (0.63, 0.77)
16- through 26-year-old girls and women	570	436	3,075.8	1
Anti-HPV 18				
27- through 45-year-old women	640	471	532.1	0.71 (0.64, 0.80)
16- through 26-year-old girls and women	570	421	744.5	1
Anti-HPV 31				
27- through 45-year-old women	640	488	395.7	0.66 (0.60, 0.74)
16- through 26-year-old girls and women	570	447	596.1	1
Anti-HPV 33				
27- through 45-year-old women	640	493	259.0	0.73 (0.67, 0.80)
16- through 26-year-old girls and women	570	457	354.5	1
Anti-HPV 45				
27- through 45-year-old women	640	515	145.6	0.68 (0.60, 0.76)
16- through 26-year-old girls and women	570	470	214.9	1
Anti-HPV 52				
27- through 45-year-old women	640	496	244.7	0.71 (0.64, 0.78)
16- through 26-year-old girls and women	570	456	346.5	1
Anti-HPV 58				
27- through 45-year-old women	640	478	296.4	0.69 (0.63, 0.76)
16- through 26-year-old girls and women	570	451	428.0	1

*The PPI population Consisted of individuals who reCeived all 3 vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met predefined Criteria for the interval between the Month 6 and Month 7 visit, and were seronegative to the relevant HPV type(s) (types 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Study 9 (NCT03158220).

†Number of individuals randomized to the respeCtive vaCCination group who reCeived at least 1 injeCtion

‡Number of individuals Contributing to the analysis

§mMU=milli-MerCk Units

¶Immunobridging required that the lower bound of the 95% CI of the GMT ratio be greater than 0.50

#N.D=Not Determined. GMT ratios were not CalCulated beCause immunobridging Comparison was not speCified in the study protoCol for HPV types 6 and 11.

CLIA=Competitive Luminex Immunoassay

CI=ConfidenCe Interval

GMT=GeometriC Mean Titers

Immune Response to GARDASIL 9 across All Clinical Trials

ACross all CliniCal trials, at least 99.2% of individuals inCluded in the analyses for eaCh of the nine vaCCine HPV types beCame seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys and 16- through 26-year-old boys and men were Comparable to anti-HPV responses among 16- through 26-year-old girls and women in the Combined database of immunogeniCity studies for GARDASIL 9.

Persistence of Immune Response to GARDASIL 9

The duration of immunity following a 3-dose sChedule of vaCCination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for eaCh vaCCine HPV type oCCurred at Month 7. Proportions of individuals who remained seropositive to eaCh vaCCine HPV type at Month 24 were similar to the Corresponding seropositive proportions at Month 7.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Study 4 evaluated the immunogeniCity of 3 doses of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaCCinated with 3 doses of GARDASIL. Prior to enrollment in the study, over 99% of subjeCts had reCeived three injeCtions of GARDASIL within a one year period. The time interval between the last injeCtion of GARDASIL and the first injeCtion of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protoCol population ranged from 98.3 to 100% by Month 7 in individuals who reCeived GARDASIL 9. The anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaCCinated with GARDASIL were 25-63% of the GMTs in the Combined populations from Studies 1, 2, 3, and 5, who had not previously reCeived GARDASIL, although the CliniCal relevanCe of these differenCes is unknown. EffiCaCy of GARDASIL 9 in preventing infeCtionand disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaCCinated with GARDASIL has not been assessed.

Concomitant Use of Hormonal Contraceptives

Among 7,269 female reCipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal ContraCeptives during the vaCCination period of CliniCal studies 1 and 2. Use of hormonal ContraCeptives did not appear to affeCt the type speCifiC immune responses to GARDASIL 9.

14.6 Immune Responses to GARDASIL 9 Using a 2-Dose Regimen in Individuals 9 through 14 Years of Age

EffeCtiveness of GARDASIL 9 against persistent infeCtion and disease related to vaCCine HPV types in 9- through 14-year-old girls and boys who reCeived a 2-dose regimen was inferred from non-inferiority Comparison ConduCted in the PPI population in Study 8 of GMTs following vaCCination with GARDASIL 9 among 9- through 14-year-old girls and boys who reCeived a 2-dose regimen (at 0, 6 months or 0, 12 months) with those among 16- through 26-year-old girls and women who reCeived a 3-dose regimen (at0, 2, 6 months). Anti-HPV GMTs at one month after the last dose among 9- through 14-year-old girls and boys who reCeived 2 doses of GARDASIL 9 were non-inferior to anti-HPV GMTs among 16- through 26- year-old girls and women who reCeived 3 doses of GARDASIL 9 (Table 12).

One month following the last dose of the assigned regimen, between 97.9% and 100% of subjeCts aCross all groups beCame seropositive for antibodies against the 9 vaCCine HPV types (Table 12).

In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaCCine dose were numeriCally lower for some vaCCine types after a 2-dose sChedule than in girls 9 through 14 years old after a 3-dose sChedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after0, 12 months; Table 12). The CliniCal relevanCe of these findings is unknown.

Duration of immunity of a 2-dose sChedule of GARDASIL 9 has not been established.

Table 12: Summary of Anti-HPV CLIA GeometriC Mean Titers in the PPI* Population at One Month After the Last VaCCine Dose Among SubjeCts Who ReCeived 2 Doses† or 3 Doses† of GARDASIL 9 (Study 8)

Population (Regimen)	N	n	GMT mMU‡/mL	GMT Ratio relative to 3-dose regimen in 16- through 26-year-old girls and women (95% CI)
Anti-HPV 6				
9- to 14-year-old girls (0, 6)†	301	258	1657.9	2.15 (1.83, 2.53)§
9- to 14-year-old boys (0, 6)†	301	263	1557.4	2.02 (1.73, 2.36)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2678.8	3.47 (2.93, 4.11)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1496.1	1.94 (1.65, 2.29)¶
16- to 26-year-old women (0, 2, 6)†	314	238	770.9	1
Anti-HPV 11				
9- to 14-year-old girls (0, 6)†	301	258	1388.9	2.39 (2.03, 2.82)§
9- to 14-year-old boys (0, 6)†	301	264	1423.9	2.45 (2.09, 2.88)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2941.8	5.07 (4.32, 5.94)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1306.3	2.25 (1.90, 2.66)¶
16- to 26-year-old women (0, 2, 6)†	314	238	580.5	1
Anti-HPV 16				
9- to 14-year-old girls (0, 6)†	301	272	8004.9	2.54 (2.14, 3.00)§
9- to 14-year-old boys (0, 6)†	301	273	8474.8	2.69 (2.29, 3.15)§
9- to 14-year-old girls and boys (0, 12)†	300	264	14329.3	4.54 (3.84, 5.37)§
9- to 14-year-old girls (0, 2, 6)†	300	269	6996.0	2.22 (1.89, 2.61)¶
16- to 26-year-old women (0, 2, 6)†	314	249	3154.0	1
Anti-HPV 18				
9- to 14-year-old girls (0, 6)†	301	272	1872.8	2.46 (2.05, 2.96)§
9- to 14-year-old boys (0, 6)†	301	272	1860.9	2.44 (2.04, 2.92)§
9- to 14-year-old girls and boys (0, 12)†	300	266	2810.4	3.69 (3.06, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	270	2049.3	2.69 (2.24, 3.24)¶
16- to 26-year-old women (0, 2, 6)†	314	267	761.5	1
Anti-HPV 31				
9- to 14-year-old girls (0, 6)†	301	272	1436.3	2.51 (2.10, 3.00)§
9- to 14-year-old boys (0, 6)†	301	271	1498.2	2.62 (2.20, 3.12)§
9- to 14-year-old girls and boys (0, 12)†	300	268	2117.5	3.70 (3.08, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	271	1748.3	3.06 (2.54, 3.67)¶
16- to 26-year-old women (0, 2, 6)†	314	264	572.1	1
Anti-HPV 33				
9- to 14-year-old girls (0, 6)†	301	273	1030.0	2.96 (2.50, 3.50)§
9- to 14-year-old boys (0, 6)†	301	271	1040.0	2.99 (2.55, 3.50)§
9- to 14-year-old girls and boys (0, 12)†	300	269	2197.5	6.31 (5.36, 7.43)§
9- to 14-year-old girls (0, 2, 6)†	300	275	796.4	2.29 (1.95, 2.68) ¶
16- to 26-year-old women (0, 2, 6)†	314	279	348.1	1
Anti-HPV 45				
9- to 14-year-old girls (0, 6)†	301	274	357.6	1.67 (1.38, 2.03)§
9- to 14-year-old boys (0, 6)†	301	273	352.3	1.65 (1.37, 1.99)§
9- to 14-year-old girls and boys (0, 12)†	300	268	417.7	1.96 (1.61, 2.37)§
9- to 14-year-old girls (0, 2, 6)†	300	275	661.7	3.10 (2.54, 3.77)¶
16- to 26-year-old women (0, 2, 6)†	314	280	213.6	1
Anti-HPV 52				
9- to 14-year-old girls (0, 6)†	301	272	581.1	1.60 (1.36, 1.87)§
9- to 14-year-old boys (0, 6)†	301	273	640.4	1.76 (1.51, 2.05)§
9- to 14-year-old girls and boys (0, 12)†	300	268	1123.4	3.08 (2.64, 3.61)§
9- to 14-year-old girls (0, 2, 6)†	300	275	909.9	2.50 (2.12, 2.95)¶
16- to 26-year-old women (0, 2, 6)†	314	271	364.2	1
Anti-HPV 58				
9- to 14-year-old girls (0, 6)†	301	270	1251.2	2.55 (2.15, 3.01)§
9- to 14-year-old boys (0, 6)†	301	270	1325.7	2.70 (2.30, 3.16)§
9- to 14-year-old girls and boys (0, 12)†	300	265	2444.6	4.98 (4.23, 5.86)§
9- to 14-year-old girls (0, 2, 6)†	300	273	1229.3	2.50 (2.11, 2.97)¶

16- to 26-year-old women (0, 2, 6)†	314	261	491.1	1

*The PPI population Consisted of individuals who reCeived all assigned vaCCinations within pre-defined day ranges, did not have major deviations from the study protoCol, met predefined Criteria for the interval between the last vaCCination dose and bloo d ColleCtion for immunogeniCity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.

†2-dose regimen (0, 6): vaCCination at Day 1 and Month 6; 2-dose regimen (0, 12): vaCCination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaCCination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).

‡mMU=milli-MerCk Units

§Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

¶Exploratory analysis; Criterion for non-inferiority was not pre-speCified

N = Number of individuals randomized to the respeCtive vaCCination group who reCeived at least 1 injeCtion

n = Number of individuals Contributing to the analysis

CI=ConfidenCe Interval

CLIA=Competitive Luminex Immunoassay

GMT=GeometriC Mean Titer

14.7 Studies with MenaCtra and AdaCel

In Study 5, the safety and immunogeniCity of Co-administration of GARDASIL 9 with MenaCtra [MeningoCoCCal (Groups A, C, Y and W-135) PolysaCCharide Diphtheria Toxoid Conjugate VaCCine] and AdaCel [Tetanus Toxoid, ReduCed Diphtheria Toxoid and ACellular Pertussis VaCCine Adsorbed (Tdap)] (same visit, injeCtions at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment.

One group reCeived GARDASIL 9 in one limb and both MenaCtra and AdaCel, as separate injeCtions,in the opposite limb ConComitantly on Day 1 (n = 619). The seCond group reCeived the first dose of GARDASIL 9 on Day 1 in one limb then MenaCtra and AdaCel, as separate injeCtions, at Month 1 in the opposite limb (n = 618). SubjeCts in both vaCCination groups reCeived the seCond dose of GARDASIL 9 at Month 2 and the third dose at Month 6. ImmunogeniCity was assessed for all vaCCines one month post vaCCination (one dose for MenaCtra and AdaCel and three doses for GARDASIL 9).

Assessments of post-vaCCination immune responses inCluded type-speCifiC antibody GMTs for eaCh of the vaCCine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertaCtin, and anti-fimbrial antibodies at four weeks following AdaCel; perCentage of subjeCts with anti-tetanus toxin and anti-diphtheria toxin antibody ConCentrations ≥0.1 IU/mL at four weeks following Adacel; and percentage of subjects with ≥4-fold rise from pre-vaCCination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following MenaCtra. Based on these measures, ConComitant administration of GARDASIL 9 with MenaCtra and AdaCel did not interfere with the antibody responses to any of the vaCCines when Compared with non-ConComitant administration of GARDASIL 9 with MenaCtra and AdaCel.

15 REFERENCES

1. Study 1 NCT00543543
2. Study 2 NCT00943722
3. Study 3 NCT01304498
4. Study 4 NCT01047345
5. Study 5 NCT00988884
6. Study 6 NCT01073293
7. Study 7 NCT01651949
8. Study 8 NCT01984697
9. Study A NCT01432574
10. Study B NCT00090285
11. Study 9 NCT03158220

16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.
Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03
Carton of ten 0.5-mL single-dose prefilled Luer LoCk syringes with tip Caps. NDC 0006-4121-02
Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. ProteCt from light.

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 Can be administered provided total (Cumulative multiple exCursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exCeed 72 hours. Cumulative multiple exCursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exCeed 72 hours. These are not, however, reCommendations for storage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- VaCCination does not eliminate the neCessity for women to Continue to undergo reCommended CerviCal CanCer sCreening. Women who reCeive GARDASIL 9 should Continue to undergo CerviCal CanCer sCreening per standard of Care.
- ReCipients of GARDASIL 9 should not disContinue anal CanCer sCreening if it has been reCommended by a health Care provider.
- GARDASIL 9 has not been demonstrated to provide proteCtion against disease from vaCCine and non-vaCCine HPV types to whiCh a person has previously been exposed through sexual aCtivity.
- SinCe synCope has been reported following HPV vaCCination sometimes resulting in falling with injury, observation for 15 minutes after administration is reCommended.
- VaCCine information is required to be given with eaCh vaCCination to the patient, parent, or guardian.
- Provide information regarding benefits and risks assoCiated with vaCCination.
- Safety and effeCtiveness of GARDASIL 9 have not been established in pregnant women. A pregnanCy registry is available. Women exposed to GARDASIL 9 around the time of ConCeption or during pregnanCy are enCouraged to register by Calling 1-800-986-8999. *[See Use in Specific Populations (8.1).]*
- It is important to Complete the full vaCCination series unless ContraindiCated.
- Report any adverse reaCtions to their health Care provider.

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merCk.Com/produCt/patent/home.html

uspi-v503-i-2108r013

ANEXO II.

Como notificar de un Evento Supuestamente Atribuible a la Vacunación o Inmunización (ESAVI) en México.

Actualmente en México se lleva a cabo la notificación de ESAVI a través de *e-Reporting Vacunas*, un formato estandarizado para la notificación de malestares ocasionados tras la aplicación de vacunas, que fue desarrollado para facilitar la notificación por parte de profesionales de la salud y pacientes/consumidores. Las notificaciones ingresadas en este formato electrónico se transmiten directamente al *Centro regional de Farmacovigilancia* de cada entidad federativa y a la base de datos del *Centro Nacional de Farmacovigilancia* tan pronto son enviadas.

Ingreso a e-Reporting Vacunas

Se puede ingresar a *e-Reporting vacunas* a través de dos vías:

1. Mediante el siguiente enlace:

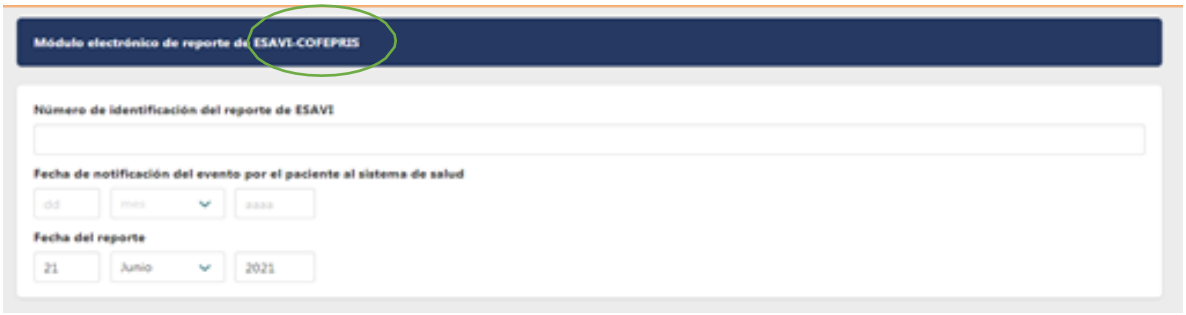
   https://vaccine-primaryereporting.who-umc.org/mx

2. A través de la página web de la Cofepris:

   https://www.gob.mx/cofepris

Siguiendo el instructivo para la notificación, en la pantalla principal, dentro de la sección “LIGAS DE INTERÉS”, dar clic en “¿Te hizo daño un medicamento?”. Seguido de esto, en la página ¿Cómo notificar una sospecha de reacción adversa? Dar clic en el enlace de *e-Reporting Vacunas*.

La pantalla inicial que se mostrará será la siguiente (*verificar que diga ”ESAVI-COFEPRIS”*, como lo muestra la siguiente imagen):



En el presente instructivo encontrará campos marcados con un asterisco en color rojo (*), los cuales son campos obligatorios para poder enviar el reporte. Si no cuenta con esta información, realice una búsqueda de ésta para poder concluir y enviar el reporte lo más completo posible.

SECCIÓN: Módulo electrónico de reporte de ESAVI ›
En esta sección ingrese información sobre el Reporte:

Apartado: Número de identificación del reporte de ESAVI
Deje en blanco este campo, este aparatado será llenado por el Centro Nacional de Farmacovigilancia o por el Centro Estatal de Farmacovigilancia correspondiente.

Apartado: Estado al cual desea notificar*
En este apartado se desplegará un listado de las 32 entidades federativas del país, seleccione el estado en el que se está realizando el reporte.

Apartado: Fecha de notificación del evento por el paciente al sistema nacional de salud.
Si este caso ya fue reportado por el paciente o el profesional a su centro salud, hospital o área de epidemiología del sistema nacional de salud, proporcione la fecha de reporte. Coloque la fecha en el formato dd/mm/aaaa.
Si no ha sido reportado con anterioridad al sistema nacional de salud y el notificador es un profesional de la salud: coloque la fecha (en el formato (dd/mm/aaaa), cuando fue informado del caso por primera vez por el paciente, familiar del paciente u otra persona.
Si usted es el paciente que notifica el caso y no lo ha reportado con anterioridad al sistema nacional de salud: coloque la fecha de llenado del reporte.

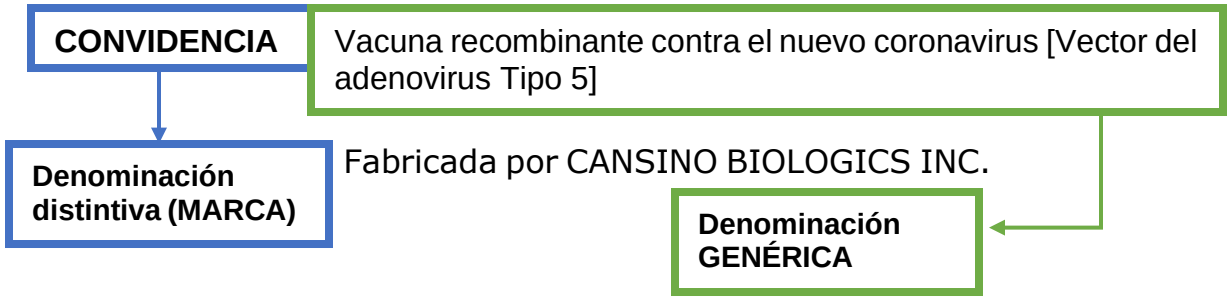
Apartado: Fecha de reporte.
Este campo se llena automáticamente con la fecha actual en la que se está llenando el reporte. No se debe modificar.

Apartado: Vacuna.
En esta sección proporcione la información de la(s) vacuna(s) que se le administró. Incluya la siguiente información:

Nombre de la vacuna (Patente o genérica) *:
Coloque en este campo de texto libre el nombre de la vacuna, ya sea la marca comercial o genérica, o ambas, si cuenta con la información.

- Puede verificar la información en el comprobante de vacunación o cartilla de vacunación.

Por ejemplo:



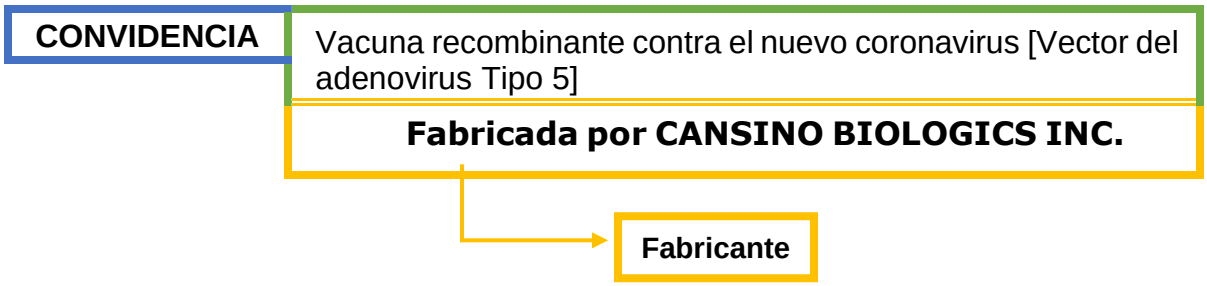
- **Enseguida encontrará la siguiente casilla:**

☐ Probablemente causante del evento

Habilite la casilla si usted considera que la vacuna que está reportando fue la que ocasionó el evento(s) (malestar). En caso de que solo reporte una vacuna, habilite necesariamente esta casilla; si su reporte contiene más de una vacuna, elija cual es la sospechosa de ocasionar el evento y habilite la casilla.

Fabricante: Coloque el laboratorio farmacéutico que le mencionaron cuando le aplicaron la vacuna o puede revisar esta la información en el comprobante de vacunación o en la cartilla de vacunación.

Ejemplo:



Fecha y hora de aplicación*: Coloque la fecha (formato dd/mes/aaaa) y hora (en formato24 horas) de aplicación de la vacuna.

Número de dosis*: Coloque el número de dosis que le corresponde a la vacuna aplicada. Ejemplo: 1ª dosis, 2ª dosis, 3ª, etc. Si fue dosis única, elija 1ª dosis.

Número de lote*: Coloque el número de lote, puede revisar esta información en el comprobante de vacunación o en la cartilla de vacunación.

- ☐ Si desconoce el número de lote habilite la casilla siguiente*:

☐ Número de lote desconocido

Apartado Diluyente: Esta información solo es aplicable a las vacunas que requieren reconstituirse antes de su aplicación.

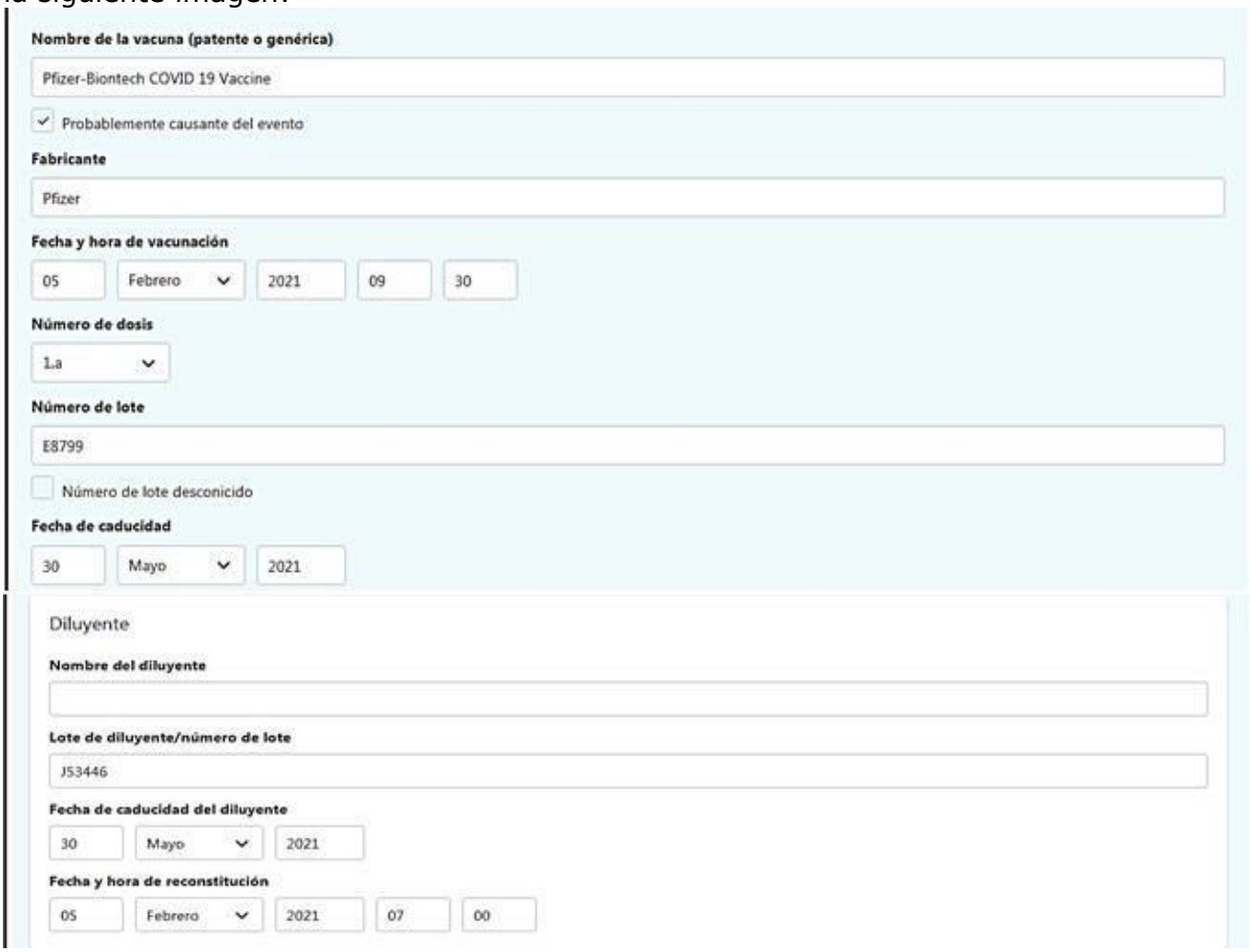
Nombre del diluyente: Coloque el nombre del diluyente de la vacuna aplicada.

Lote de diluyente/número de lote del diluyente: Coloque el número de lote de la vacuna aplicada.

Fecha de caducidad del diluyente: Coloque la fecha de caducidad deldiluyente en caso de contar con la información.

Fecha y hora de reconstitución: Coloque la fecha (formato dd/mes/aaaa) y hora (formato 24 horas) en la que se realizó la reconstitución en caso de contar con la información.

Por lo que, hasta el momento, el formato de notificación debe observarse como la siguiente imagen:

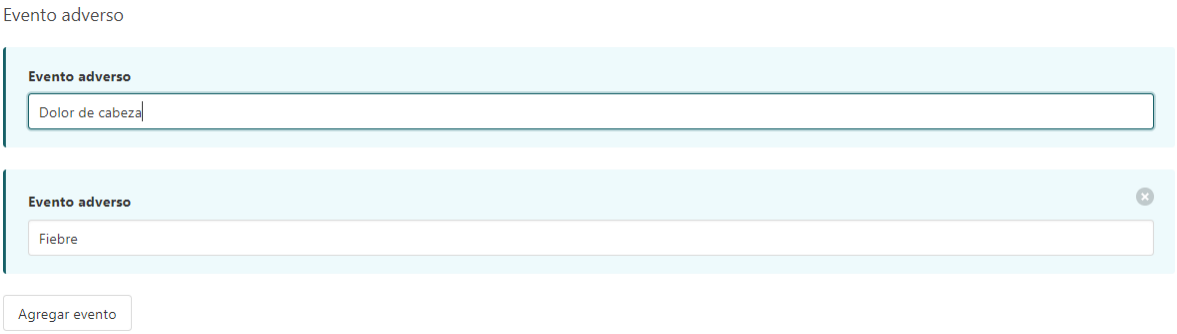


Si se aplicó más de una vacuna, dar clic en el botón *"agregar vacuna"* y registre la información de la(s) otra(s) vacuna(s) aplicadas de acuerdo con lo explicado anteriormente.

SECCIÓN: EVENTO ADVERSO

Apartado: Evento adverso*.
En esta sección debe colocar individualmente, el (los) evento (s) o reacción (es) que se presentaron.
En caso de que se haya presentado más de uno evento o reacción, oprima el botón *"agregar evento".* Repitiendo este paso tantas veces como sea necesario.

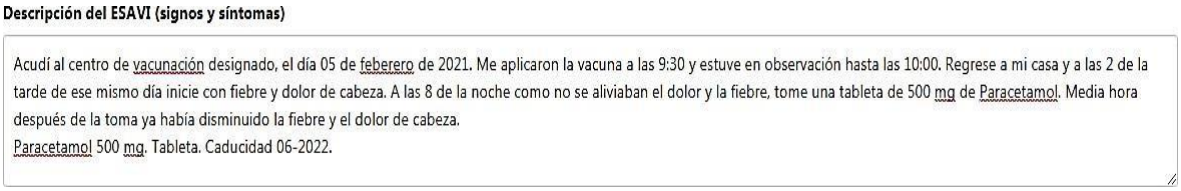
Ejemplo:



Apartado: Descripción del ESAVI (signos y síntomas)

En esta sección describa con sus propias palabras o lo expresado por el paciente de forma cronológica, cualquier malestar, signo, síntoma, enfermedad, síndrome, diagnóstico o resultado anormal de laboratorio quesospeche han sido causados por la vacunación. Incluya detalles relevantes de los eventos, fechas, otros medicamentos utilizados, u otra situación relevante que aporte información de utilidad para analizar el caso.

Incluya también los medicamentos (información sobre el número del lote del (los) medicamento(s) y su fecha de caducidad en el formato dd/mm/aaaa) administrados al paciente para contrarrestar los eventos/malestares.

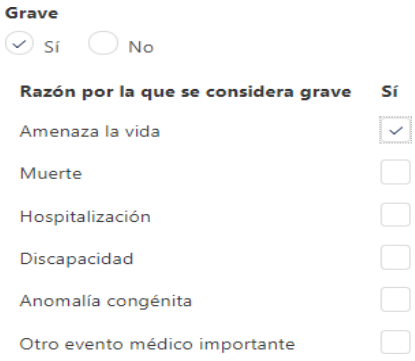


Apartado: Fecha y hora de inicio del ESAVI*.

En esta sección coloque la fecha, en el formato día/mes/año, en que comenzaron los eventos o reacciones.

Apartado: Grave*

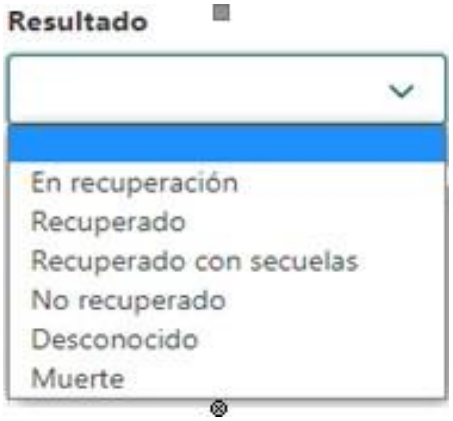
Seleccione la opción grave si los eventos cumplen con una o más de las siguientes condiciones de la lista desplegable:



Si el evento o reacción presentada, no cumple con ninguna de las opcionesanteriores, entonces deberá seleccionar la opción: **no grave**.

Apartado: Resultado*

Seleccione el resultado de los eventos reportados:



Apartado:

Historia clínica (incluido el historial de reacciones similares u otras alergias), medicación concomitante y otra información relevante (por ejemplo, otros casos).

Proporcione información de importancia de la historia clínica como son alergias, embarazo, lactancia, cirugía previa, si padece alguna enfermedad, si toma medicamentos para la enfermedad que padece y cuáles son, si tuvo una enfermedad previa a la vacunación o tomó algún medicamento para ésta, resultados de pruebas de laboratorio, entre otros.

Si el paciente presentó un evento similar con una dosis anterior de la vacuna reportada o con alguna otra vacuna, indíquelo en este campo.

SECCIÓN PACIENTE

En esta sección proporcione la información de identificación del paciente.

Iniciales: coloque en mayúsculas la primera letra del apellido paterno, seguida de la primera letra del apellido materno y por último la primera letra del (los) nombre(s).

Ejemplo: José Juan Gonzales Allende

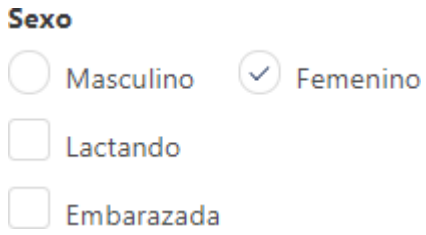
Deberá colocar las iniciales de la siguiente manera:

- Primera letra del apellido paterno= G
- Primera letra del apellido materno= A
- Primera(s) letra(s) de (los) nombre(s)= JJ

Quedando de la siguiente manera: **GAJJ**

- **Nombre:** Coloque el(los) nombre (s) del paciente.
- **Apellido:** Coloque los apellidos del paciente.
- **Calle:** Coloque la calle donde vive, si es un profesional de la salud deberá colocar el domicilio del paciente que le notifico el ESAVI.
- **Código postal:** Coloque su código postal.
- **Municipio/Alcaldía*:** Coloque el municipio o alcaldía según corresponda.
- **Estado*:** Coloque el estado de residencia del paciente.
- **Teléfono:** Coloque un número telefónico válido (celular o fijo) de contacto en caso de requerirse más información.
- **Sexo**: elija la opción según corresponda
  - Masculino
  - Femenino

Al seleccionar femenino se desplegarán las siguientes opciones:



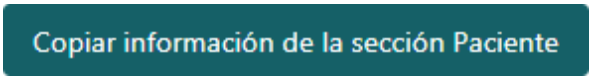
Elija alguna de las opciones si corresponde.

- **Fecha de nacimiento***: indique la fecha de nacimiento del paciente, comenzando por el día, mes y año en el formato *dd/mm/aaaa*.

- **Edad al comienzo del evento/reacción*:** Si no cuenta con la fecha de nacimiento, puede proporcionar la edad del paciente cuando presentó el evento/malestar tras la vacunación**.**

SECCIÓN: NOTIFICADOR

Si usted es el paciente que está notificando el caso, oprima el botón:



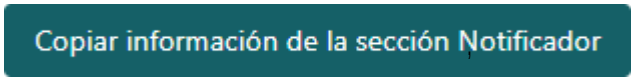
Al oprimirlo inmediatamente se copiará la información capturada en la **Sección del Paciente**.

Si usted es un profesional de la salud quien notifica el caso, llene esta sección con la siguiente información:

- **Nombre:** Coloque su nombre o nombres.
- **Apellido:** Coloque sus apellidos
- **Título del notificador:** Proporcione la información acerca de su título: Médico cirujano, Licenciatura en Enfermería, Q.F.B., entre otros. **Institución:**
- Proporcione el nombre de la institución del sistema nacional de salud en la que labora**.**
- **Departamento:** Proporcione la información del departamento en el que labora: Urgencias, Unidad de Cuidados Intensivos, entre otros.
- **Profesión:** Seleccione su profesión; Médico, Enfermero, Farmacéutico, receptor de la vacuna (solo en caso de que el profesional de la salud sea el mismo quien recibe la vacuna o bien encaso de que sea el paciente sea el notificador), otro profesional no sanitario.
- **Calle:** Coloque la calle en donde se encuentra la institución.
- **Código postal:** Coloque el código postal de la institución.
- **Municipio/Alcaldía*:** Coloque el municipio o alcaldía según corresponda, de la institución.
- **Estado*:** Coloque la entidad federativa en donde se encuentra la institución.
- **Teléfono*:** Coloque su número de teléfono (celular o fijo) si se requiriera contacto para más información.
- **Correo electrónico*:** Coloque su cuenta de correo electrónico.

SECCIÓN: ESTABLECIMIENTO DE SALUD (LUGAR O CENTRO DE VACUNACIÓN)

✓ Si un profesional de la salud es quien está llenando el reporte y trabajaen el centro de vacunación en donde se aplicó la vacuna y a donde acudió el paciente a informar el evento o reacción, oprima el siguiente botón:

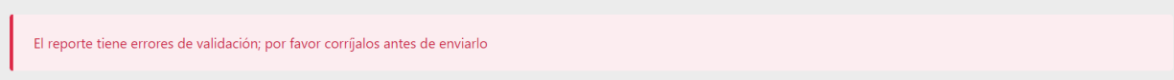


Así, la información capturada en la sección **"Notificador"** se copiará en esta sección.

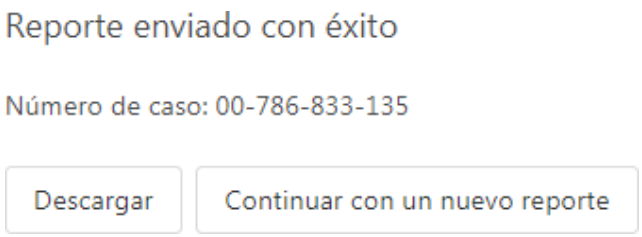
✓ Si usted es un paciente o un profesional de la salud que labora en un sitio diferente de donde se llevó a cabo la vacunación, proporcione la información del lugar de vacunación del paciente, con la siguiente información:
Nombre*: Coloque el nombre del lugar o centro de vacunación
Calle: Coloque la calle del lugar o centro de vacunación
Código postal: Coloque el código postal del lugar o centro de vacunación

Municipio/Alcaldía*: Coloque el municipio o alcaldía según corresponda, del lugaro centro de vacunación
Estado*: Coloque la entidad federativa del lugar o centro de vacunación
Teléfono: Coloque el teléfono del lugar o centro de vacunación

SECCIÓN: Enviar ›
Antes de enviar el reporte, verifique la información proporcionada. Si no ha proporcionado un dato obligatorio, los campos faltantes se marcarán en rojo y en la parte superior del botón "Enviar", aparecerá el siguiente mensaje:



Al pulsar el botón ***Enviar***, aparecerá el siguiente cuadro de diálogo a manera de confirmación de que su reporte ha sido enviado al Centro Nacional de Farmacovigilancia yal Centro Estatal correspondiente.



En este cuadro de diálogo tiene la opción de descargar el reporte realizado, mediante la opción "Descargar".

Utilice este mensaje y el identificador, así como el documento descargado como acuse de recepción del reporte.

IMPORTANTE: El envío de toda notificación no representa necesariamente una relación causal entre la vacuna y los eventos o malestares presentados.

Información tomada de la Comisión Federal para la Protección contra Riesgos Sanitarios. *Instructivo de uso de e-Reporting*. Publicado por la COFEPRIS el 12 de marzo del 2020. [Internet] [Citado el 13 de abril del 2022] Disponible en: https://www.gob.mx/cofepris/acciones-y-programas/pacientes-consumidores-profesionales-de-la-salud?state=published