

HPV vaccines, lessons learned from a success story

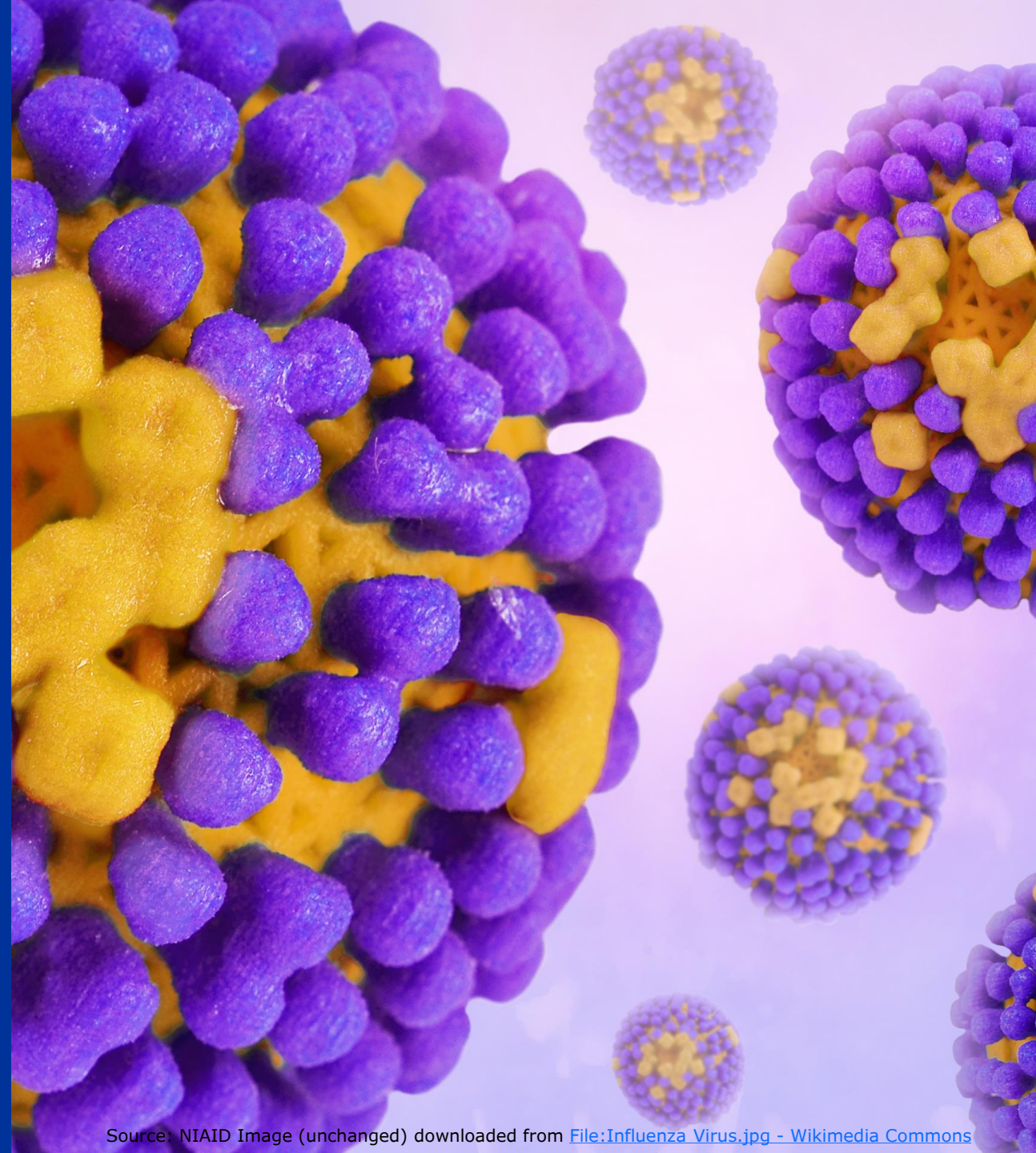
European Immunisation week

28 April 2025

Manuela Mura

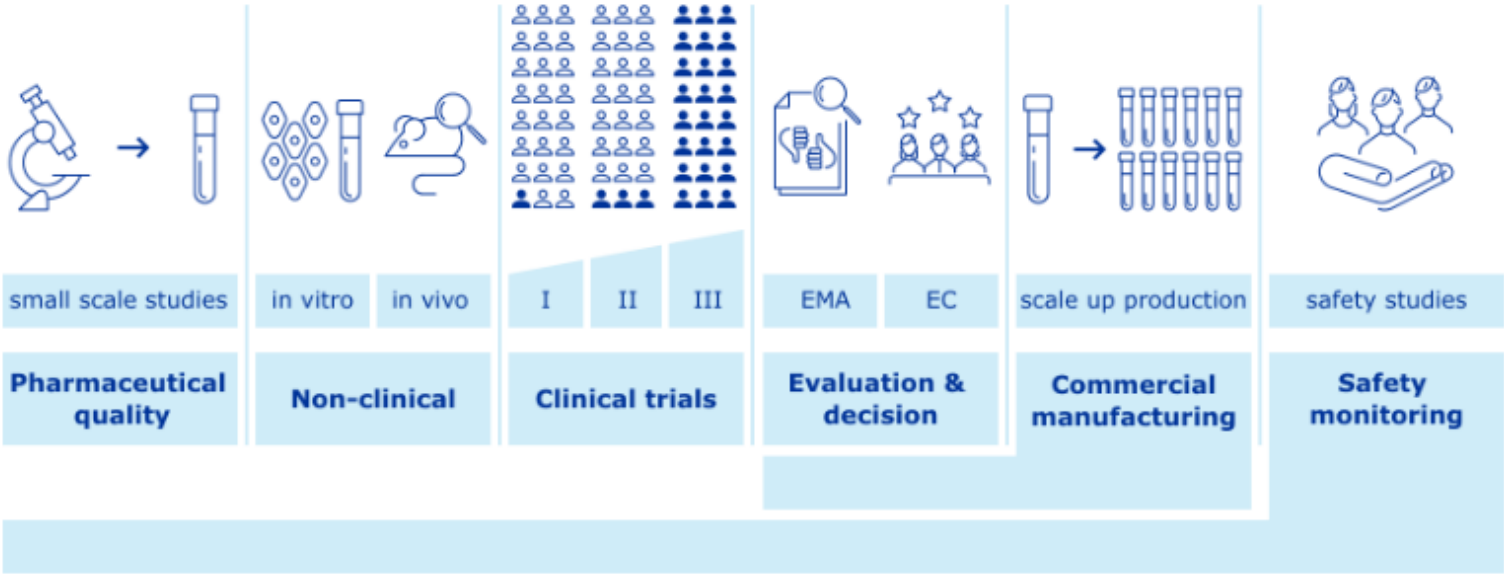
Dept of Health Threats, EMA

Emergency Task Force member



The European Medicines Agency evaluates medicines for EU approval

Vaccine from discovery to the market: 15 years or longer



Evaluates data generated by industry and conclude on the benefit/risk of each medicine

Monitors the effectiveness and safety of medicines across their life cycle

Provides information on medicines to patients and healthcare professionals

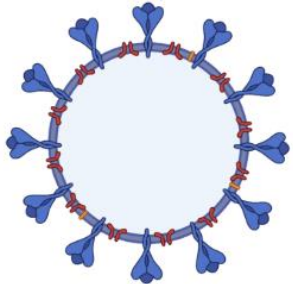
Vaccines to prevent HPV diseases



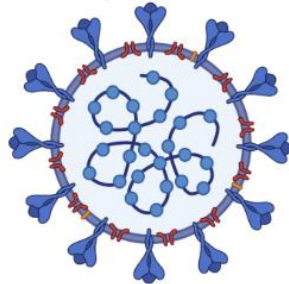
For immunization of individuals from the age of 9 years against:

- Precancers and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types.
- Genital warts (Condyloma acuminata) caused by specific HPV types.

Virus-Like Particle:
No genome. Has at least some
of the viral proteins.



Virion:
Has genome and all viral
proteins



VLPs do not contain no viral DNA, cannot infect cells, reproduce or cause disease.

HPV vaccines showed high efficacy and safety in large pivotal clinical trials

- Approx 21,000 women and 4100 men aged 16 to 26 years tested in placebo-controlled, double-blind, randomised Phase 3 clinical studies (Gardasil)
- Efficacy demonstrated by assessing how many people with warts or precancers in the placebo group vs. the vaccinated group (people negative for prior or existing HPV infection)



Disease	HPV type (Gardasil)	2 years	4 years	11-14 years
AIS/CIN2/3	16-18	100% (0/53)	98% (2/112)	No cases (6-11-16-18)
Any lesions	16-18	85%	--	--
Any lesions	6-11-16-18	89%	--	--
Precancers - warts	6-11-16-18	90% (3/32)	--	No cases (6-11-16-18)

Cervical Intraepithelial Neoplasia (CIN) and adenocarcinoma in situ (AIS) known to be immediate precursors of invasive cervical cancer, thus used as a surrogate for cervical cancer.

https://www.ema.europa.eu/en/documents/product-information/gardasil-epar-product-information_en.pdf

Estimating efficacy based on blood markers

- HPV vaccine efficacy mediated by antibodies
- Antibodies to the virus in the blood of 9–15-year-olds are superior to 16–26-year-olds where efficacy was demonstrated



Table 6: Immunogenicity bridging between 9- to 15-year-old girls and 16- to 26-year-old women (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Girls (Protocols 016 and 018)		16- to 26-Year-Old Women (Protocols 013 and 015)	
	n	GMT (95 % CI)	n	GMT (95 % CI)
HPV 6	915	929 (874, 987)	2631	543 (526, 560)
HPV 11	915	1303 (1223, 1388)	2655	762 (735, 789)
HPV 16	913	4909 (4548, 5300)	2570	2294 (2185, 2408)
HPV 18	920	1040 (965, 1120)	2796	462 (444, 480)

GMT- Geometric mean titre in mMU/ml (mMU = milli-Merck units)

On the basis of this **immunogenicity bridging**, the efficacy of Gardasil in boys & girls is inferred.

- no cases of HPV diseases observed through more than 10 years after vaccination in boys and girls

HPV vaccines have a documented safety record

Common side effects (usually mild and temporary):

- Pain, redness, or swelling in the arm where the shot was given
- Fever, headache or feeling tired
- Nausea
- Muscle or joint pain

Warnings:

- Not recommended in pregnancy, if taken no reason to be alarmed
- Rare life-threatening allergic reactions as after any vaccination.
- Fainting may be caused by any injected vaccines

Very rare side effects:

- The risk of Guillain-Barré syndrome (GBS) is extremely rare

What happens to my side effects report?

Keeping MEDICINES safe

If side effects are unusual a flag is raised and EU experts take an even closer look. This can lead to a change in how the medicine is prescribed.

You can play a role in making medicines safer by reporting side effects directly to your national medicines authority.

EUROPEAN MEDICINES AGENCY
An agency of the European Union

Reports are sent to EudraVigilance, the European database of suspected side effects
<http://www.adrreports.eu/>

Independent research shows reduction in precancers and cancer rates since vaccination started

- The US CDC HPV-Impact Project monitored women through Pap test during 2008–2022

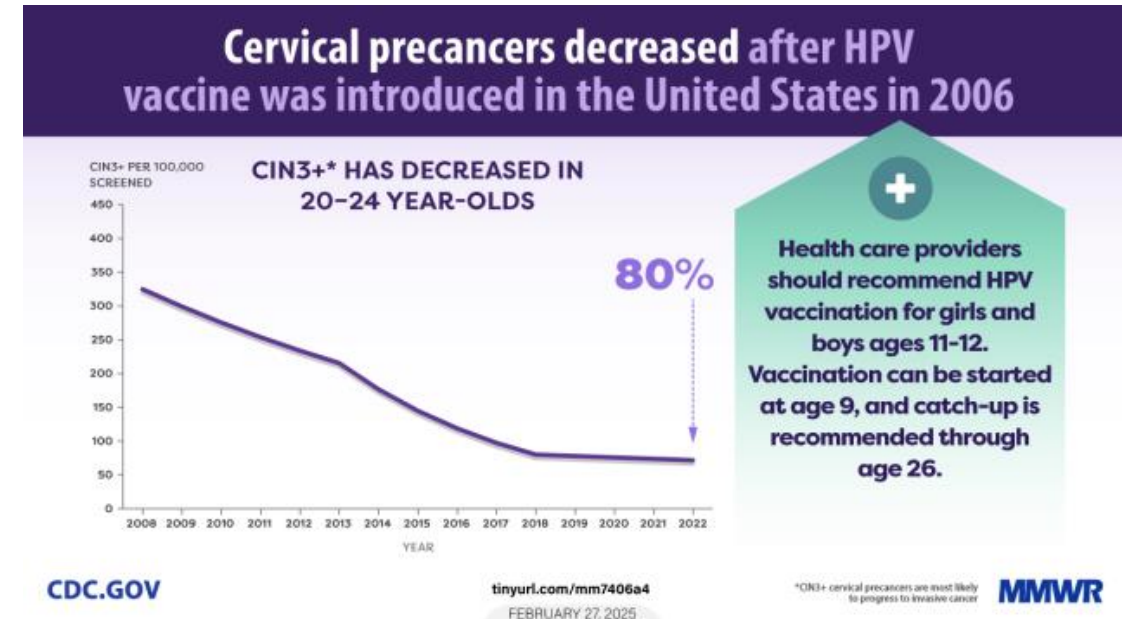
[Trends in Cervical Precancers Identified Through Population-Based Surveillance — Human Papillomavirus Vaccine Impact Monitoring Project, Five Sites, United States, 2008–2022 | MMWR](#)

- 58 studies in 9 countries (2007 and 2016): ↓90% for HPV infection, ↓90% for genital warts, ↓45% for low-grade precancers, and ↓85% for high-grade precancers.

[Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience | Clinical Infectious Diseases | Oxford Academic](#)

- A Danish study on 870,000 women aged 17-30 years in 2006-2029 show **reduction of cervical cancer by 86%** in women vaccinated at 16 years (68% in 17-19 years)

[Real-World Effectiveness of Human Papillomavirus Vaccination Against Cervical Cancer | JNCI: Journal of the National Cancer Institute | Oxford Academic](#)



European Public Assessment Report



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Home > Medicines > Gardasil 9

Gardasil 9

human papillomavirus 9-valent vaccine (recombinant, adsorbed)

Medicine Human



✓ **Authorised**
This medicine is authorised for use in the European Union

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Overview

This is a summary of the European public assessment report (EPAR) for Gardasil 9. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Gardasil 9.

For practical information about using Gardasil 9, patients should read the package leaflet or contact their doctor or pharmacist.

Expand section

Collapse section

What is Gardasil 9 and what is it used for?

How is Gardasil 9 used?

How does Gardasil 9 work?

What benefits of Gardasil 9 have been shown in studies?

Product information



Gardasil 9 : EPAR - Product information

English (EN) (420.49 KB - PDF)

First published: 03/07/2015 Last updated: 11/10/2024

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News on Gardasil 9

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

20/11/2015

Review concludes evidence does not support that HPV vaccines cause CRPS or POTS

05/11/2015

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 6-9 July 2015

13/07/2015

EMA to further clarify safety profile of human papillomavirus (HPV) vaccines

13/07/2015

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 23-26 March 2015

27/03/2015

Human papillomavirus vaccines

More information on Gardasil 9

Retrospective cohort study evaluating effectiveness of GARDASIL™ against adult-onset recurrent respiratory papillomatosis in Norway - post-authorisation study

Population-based retrospective nested case-control study evaluating effectiveness of GARDASIL™/GARDASIL™9 against adult-onset recurrent respiratory papillomatosis (AoRRP) in Sweden, Denmark, and Norway (V503-088) - post-authorisation study

DARWIN EU® Effectiveness of Human Papillomavirus Vaccines (HPV) to prevent cervical cancer - post-authorisation study



HPV vaccines - a success story for vaccination

Nobel Price for HPV-mediated carcinogenesis
Harald zur Hausen
(1936 - 2023)



1960s

Herpes
simplex
virus 2
suspected

1979

isolated the 1st
virus DNA
from genital
warts, HPV-6.
HPV-11 from a
laryngeal
papilloma

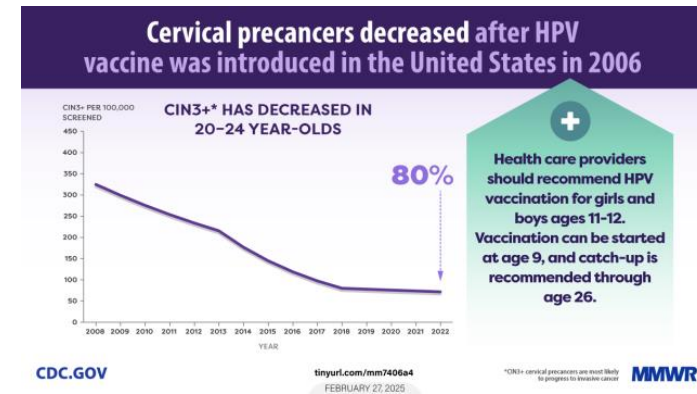
1983

HPV-16
isolated, in
1984 HPV-18
DNA.



2006

First HPV
vaccine
authorised



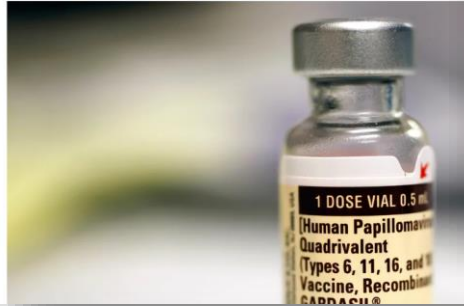
Slow vaccine uptake and low coverage amid public concerns mostly related to safety

TREATMENTS

Early Push To Require The HPV Vaccine May Have Backfired

JULY 14, 2015 - 3:58 PM ET

By Robin Marantz Henig



The most widely used vaccine, sold under the brand name Gardasil, protects against **nine strains** of human papillomavirus (the original version protected against four strains) that together account for about 90 percent of cervical cancer in the U.S., as well as a large proportion of vulvar cancer, anal cancer and genital warts. But according to the CDC's **most recent data** from 2013, just 37.6 percent of American teenage girls have received all three doses of the HPV vaccine, and just 13.9 percent of American teenage boys.

to language that cast the HPV vaccine as "a vaccine that would introduce sexual activity in young women, that would inappropriately introduce promiscuity," says Sarah

"If they had waited until it was recommended for both boys and girls, that would have made a big difference," says Gollust, who was not involved in the study. "No other vaccine is required for just one gender, so it felt like there was something different about this one."

Common misconceptions rectified:

- No proof HPV vaccines cause reproductive problems, e.g. infertility or primary ovarian insufficiency
- No link with Postural orthostatic tachycardia syndrome (POTS) or Complex regional pain syndrome (CRPS).
- No increased risk of Chronic fatigue syndrome

The EMA Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review

The screenshot displays the EMA website's interface for the HPV vaccine review. At the top, the EMA logo and navigation menu are visible. The main heading reads "Human papillomavirus vaccines - Cervarix, Gardasil, Gardasil 9, Silgard - referral". Below this, a timeline shows the progression from "Procedure started" to "European Commission final decision". A sidebar on the left lists "Page contents" including Overview, Key facts, All documents, News, Related information, and Topics. The "Overview" section is highlighted, containing a summary of the review.

Human papillomavirus vaccines - Cervarix, Gardasil, Gardasil 9, Silgard - referral

Referral Human

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Overview

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

On 19 November EMA completed its review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. In line with its initial recommendations, EMA confirmed that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

The Agency's review included published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States. The Agency's Pharmacovigilance Risk Assessment Committee (PRAC) was responsible for the initial review. In reaching its recommendations, it also consulted a group of leading experts in the field, and took into account detailed information received from a number of patient groups that also highlighted the impact these syndromes can have on patients and families.

The review recognised that more than 80 million girls and women worldwide have now received these vaccines, and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer (cancer of the neck of the womb, which is responsible for over 20,000 deaths in Europe each year) and various other cancers and conditions caused by HPV. The benefits of HPV vaccines therefore continue to outweigh the known side effects. The safety of these vaccines, as with all medicines, will continue to be carefully monitored and will take into account any future new evidence of side effects that becomes available.

Take home messages

- Even successful vaccines such as HPV, possibly leading to eradication of HPV-related cancers, show slow/limited uptake and coverage
- Main reasons mostly related to lack of (access to) information, lack of understanding, misinformation
- Fear of safety effects linked to vaccination, mistrust in HCPs and authorities

What can EMA do:

- ✓ Enhance (social) listening to better understand concerns, communication voids, misinformation, and tackle them more proactively
- ✓ Respond to public queries, engage with media and the public
- ✓ Enhanced transparency /easy to find info – **improved benefit/risk communication**
- ✓ **Support timely generation of independent reliable evidence of safety and effectiveness**



The EMA supports more research on safety and effectiveness of vaccines

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Vaccine Monitoring Platform

The Vaccine Monitoring Platform (VMP) is a collaboration between the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) aiming to generate real-world evidence (RWE) on the safety, effectiveness and use of vaccines in the European Union (EU) and the European Economic Area (EEA).

Human Vaccines

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Role

Composition

Research agenda

The VMP enables EMA and ECDC to coordinate and oversee EU-funded, independent **post-authorisation studies** on vaccine use, safety, and effectiveness. These studies are conducted in EU and EEA countries.

EMA and ECDC established the VMP in May 2022, in accordance with the [Regulation on EMA's Reinforced Role \(Regulation \(EU\) 2022/123\)](#) and [ECDC's extended mandate Regulation \(EU\) 2022/2370](#).

The VMP is an important milestone for the European Commission's [European Health Union initiative](#).

EMA's participation is based on its formal role in preparing for and managing the response to health emergencies,

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Data Analysis and Real World Interrogation Network (DARWIN EU)

Human Data on medicines

The European Medicines Agency (EMA) and the [European Medicines Regulatory Network](#) established a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the European Union (EU). This capability is called the Data Analysis and Real World Interrogation Network (DARWIN EU®).

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Key figures

How Darwin EU uses data for the benefit of patients

Interaction with the European Health Data Space

EMA's role

Darwin EU Coordination Centre

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Data partners

Darwin EU studies



DARWIN EU

Darwin EU delivers **real-world evidence** from across Europe on diseases, populations and the uses and performance of medicines.

This enables EMA and national competent authorities in the [European medicines regulatory network](#) to use these data whenever needed throughout the lifecycle of a medicinal product.

Darwin EU supports regulatory decision-making by:

- providing a source of high-quality, validated real-world data on the uses, safety and efficacy of medicines;
- addressing specific questions by carrying out high-quality, non-interventional **studies**, including developing scientific protocols, interrogating relevant data sources and interpreting and reporting study results;
- expanding the Heads of Medicines Agency (HMA)-EMA catalogue of **real-world data sources** for use in medicines regulation and the HMA-EMA catalogue of **real-world data studies**.

The range of approved **healthcare databases** enabling distributed data access via Darwin EU will evolve and expand over time.



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Thank you

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