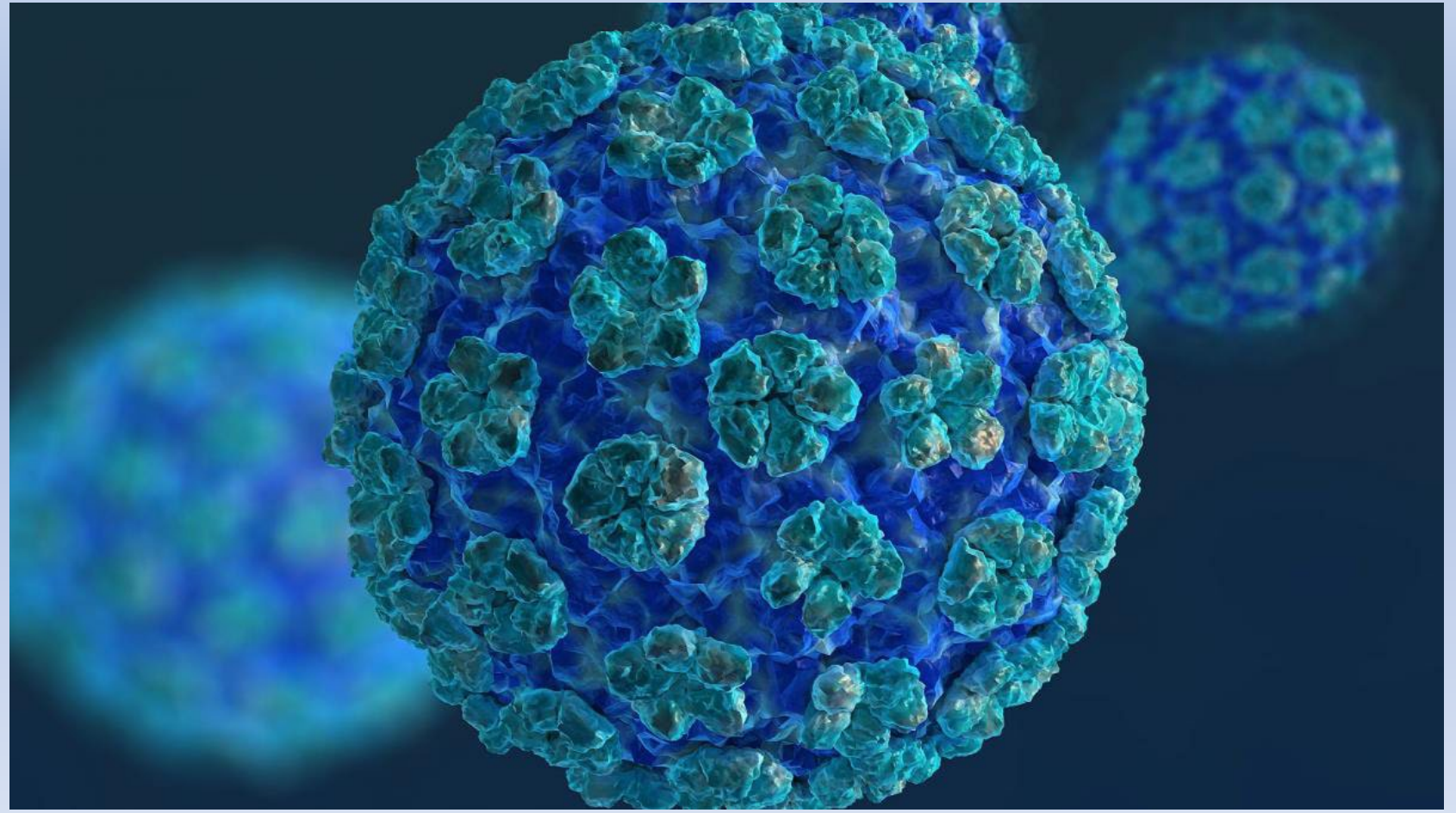


Changing the HPV Landscape with Indigenous Vaccine

CERVAVAC

Dr Hitt Sharma , Serum Institute of India Pvt. Ltd. Pune, India

Background

- The driving force behind the development of **Quadrivalent (6,11,16 & 18) HPV vaccine** was to produce an effective, safe and affordable vaccine for reach out to general public, Private Market/ Immunization program, thereby reducing local and global burden of cervical cancer.
- SIIPL's motto of **supplying life saving vaccines cost effectively,** is supported by its huge manufacturing capacities.
- Till date SIIPL more than 25 products are WHO pre-qualified which is highest in the word by any organization.

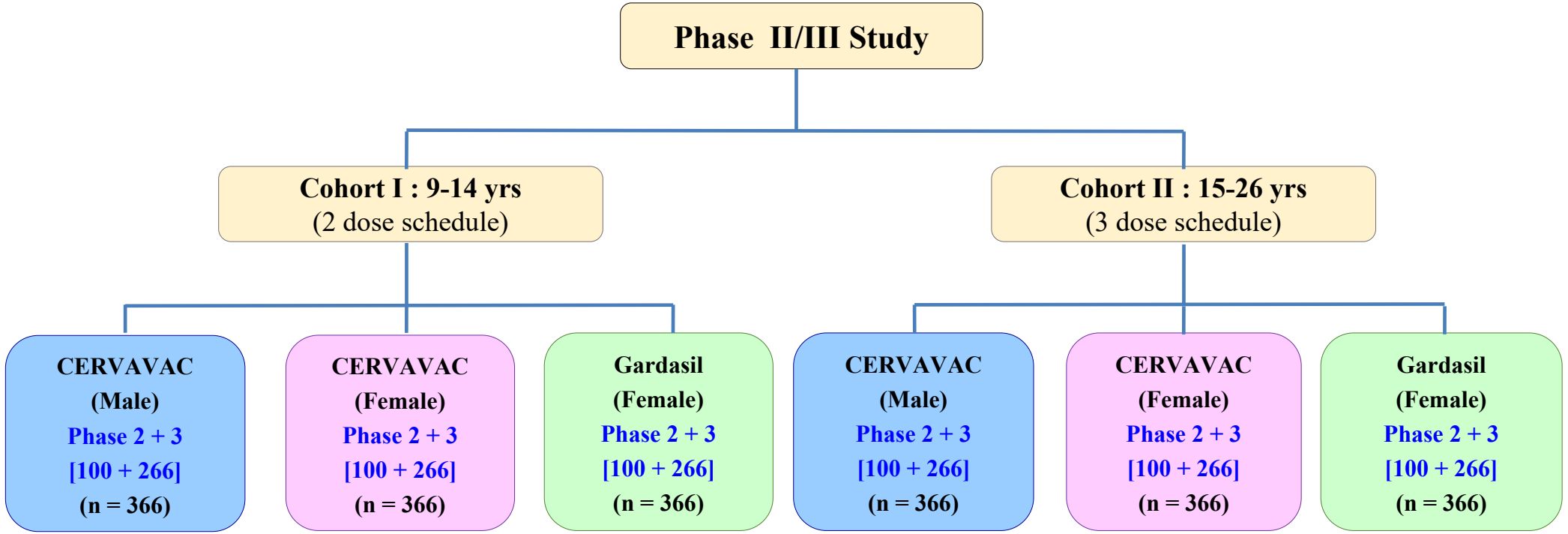
Major Achievements of SII

- ✓ **Covishield & Covovax** : Supplied 2+ Billion Doses
- ✓ **MenAfrivac**: Reduction in deaths due to Men-A in sub Saharan Africa.
- ✓ **Measles**: Averted nearly 22 million deaths
- ✓ **Rubella**: Rubella Eradication in Pan-American Countries
- ✓ **Diphtheria, Tetanus, Pertussis, Hib, HB, ASVS and Antisera** – Uncountable lives saved in the developing world
- ✓ **Tuberculosis** – Over 90% of global BCG supply
- ✓ Oxford **Ebola vaccine** manufactured and shipped in record time by SII to Uganda for WHO Clinical Trial

Brief Study Design - Phase 2/3

- **Partially Double-blind, Multi-centre, Randomized, Active Controlled.**
- Gardasil® as a active comparator Vs CERVAVAC.
- **Two age cohorts**
  - ✓ Cohort 1- Aged 9-14 yrs (2 dose – 0 and 6 M)
  - ✓ Cohort 2- Aged 15-26 yrs (3 dose – 0, 2 and 6M)
- **3 Arms in each age cohort**
  - ✓ **CERVAVAC** (6, 11, 16, 18) – Male
  - ✓ **CERVAVAC** (6, 11, 16, 18) - Female
  - ✓ Gardasil (6, 11, 16, 18) – Female
- Multicentric study carried out in 12 premier institutes/hospitals in India.
- The study is being supervised by WHO-IARC, BMGF (scientific and technical support) and funded by DBT-BIRAC.
- Clinical Trial registered at : CTRI/2018/06/014601

Cohort-wise Subject Allocation



Total sample size planned for the study (Phase-II / III) : 2196 [Phase-II : 600; Phase-III: 1596]

Phase II – Objectives

1. To assess the reactogenicity and safety of SIIPL qHPV vaccine in 9-14 and 15-26 years cohort.
2. Determination of assay method for immunogenicity testing for Phase-III part.
   - Phase II clinical samples were tested by three different assays
     1. ELISA
     2. Multiplexed ELISA on MSD platform
     3. Pseudovirion Based Neutralization Assay (PBNA).
   - Correlation of ELISA and Multiplexed ELISA on MSD platform was established with PBNA.
   - Both assays ELISA & ELISA-MSD had shown a high Correlation **(>0.9)** with the PBNA Assay.
   - Multiplex ELISA on MSD platform was finalized as it is more sensitive assay, has high throughput capacity and tests more samples in parallel for different HPV types simultaneously.
   - The total number of subjects required for the primary immunogenicity analysis was calculated based on SD of the finalized assay.

Primary Objectives

- To demonstrate the immunogenic non-inferiority one month after the last dose i.e. at 7 month

Sr. No.	CERVAVAC	Gardasil
1	**Girls (9-14 yrs)** **2 doses**	**Women (15-26 yrs)** **3 doses**
2	**Boys (9-14 yrs)** **2 doses**	**Women (15-26 yrs)** **3 doses**
3	**Women (15-26 yrs)** **3 doses**	**Women (15-26 yrs)** **3 doses**
4	**Men (15-26 yrs)** **3 doses**	**Women (15-26 yrs)** **3 doses**

1. Summary of GMT - Girls 9-14 yrs receiving 2 Doses of CERVAVAC Vs Women 15-26 yrs receiving 3 Doses of Gardasil

	Girls of age 9-14 years receiving 2 doses of CERVAVAC			Women of age 15-26 years receiving 3 doses of Gardasil			Comparison between SIIPL-qHPV and Gardasil
HPV types	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	GMT Ratio (98.75% CI) by using ANCOVA
Type 6	350	0.0648 (0.0510, 0.0773)	304.1654 (270.8461, 341.5835)	338	0.0639 (0.0516, 0.0791)	154.5933 (137.3779, 173.9660)	1.9675 (1.6674, 2.3217)
Type 11	350	0.0379 (0.0299, 0.0481)	339.1310 (302.9058, 379.6885)	338	0.0386 (0.0309, 0.0482)	208.6625 (186.0035, 234.0818)	1.6253 (1.3833, 1.9095)
Type 16	350	0.0763 (0.0593, 0.0981)	1340.1700 (1189.3734, 1510.0855)	338	0.0903 (0.0703, 0.1160)	706.1694 (625.3952, 797.3761)	1.8978 (1.6006, 2.2503)
Type 18	350	0.2001 (0.1612, 0.2483)	528.0761 (462.2296, 603.3028)	338	0.2183 (0.1814, 0.2627)	244.5019 (213.5135, 279.9880)	2.1598 (1.7860, 2.6119)

✓ In 9-14 yrs old girls Geometric Mean Fold Rise (GMFR) for all 4 serotypes is > 1000 fold.

✓ NI is demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio CI is above 0.5

2. Summary of GMT - Boys 9-14 yrs receiving 2 Doses of CERVAVAC Vs Women 15-26 yrs receiving 3 Doses of Gardasil

	Boys of age 9-14 years receiving 2 doses of CERVAVAC			Women of age 15-26 years receiving 3 doses of Gardasil			Comparison between SIIPL-qHPV and Gardasil
HPV types	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	GMT Ratio (98.75% CI) by using ANCOVA
Type 6	349	0.0666 (0.0557, 0.0796)	288.1297 (255.5136, 324.9092)	338	0.0639 (0.0516, 0.0791)	154.7922 (137.0038, 174.8901)	1.8614 (1.5684, 2.2092)
Type 11	349	0.0412 (0.0332, 0.0511)	305.0051 (270.6547, 343.7152)	338	0.0386 (0.0309, 0.0482)	208.8504 (184.9720, 235.8113)	1.4604 (1.2316, 1.7316)
Type 16	349	0.1012 (0.0803, 0.1277)	1155.9445 (1019.3383, 1310.8581)	338	0.0903 (0.0703, 0.1160)	711.9284 (626.5208, 808.9787)	1.6237 (1.3571, 1.9426)
Type 18	349	0.2188 (0.1789, 0.2676)	440.7087 (385.1323, 504.3051)	338	0.2183 (0.1814, 0.2627)	245.4037 (213.9905, 281.4283)	1.7959 (1.4819, 2.1764)

- ✓ In 9-14 yrs old Boys Geometric Mean Fold Rise (GMFR) for all 4 serotypes is > 1000 fold.
- ✓ NI is demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio CI is above 0.5

3. Summary of GMT - Women 15-26 yrs receiving 3 Doses of CERVAVAC Vs Women 15-26 yrs receiving 3 Doses of Gardasil

	Women of age 15-26 years receiving 3 doses of CERVAVAC			Women of age 15-26 years receiving 3 doses of Gardasil			Comparison between SIIPL-qHPV and Gardasil
HPV types	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	GMT Ratio (98.75% CI) by using ANCOVA
Type 6	343	0.0741 (0.0597, 0.0920)	142.6141 (126.7748, 160.4323)	338	0.0639 (0.0516, 0.0791)	155.0237 (137.6865, 174.5438)	0.9200 (0.7783, 1.0874)
Type 11	343	0.0487 (0.0388, 0.0613)	122.1572 (108.6290, 137.3702)	338	0.0386 (0.0309, 0.0482)	209.0347 (185.7242, 235.2709)	0.5844 (0.4946, 0.6905)
Type 16	343	0.1119 (0.0845, 0.1482)	544.0063 (486.0548, 608.8671)	338	0.0903 (0.0703, 0.1160)	713.5528 (637.0103, 799.2926)	0.7624 (0.6497, 0.8947)
Type 18	343	0.2484 (0.2009, 0.3070)	277.7217 (243.4136, 316.8655)	338	0.2183 (0.1814, 0.2627)	246.4908 (215.8307, 281.5063)	1.1267 (0.9343, 1.3587)

✓ In 15-26 yrs old Women GMFR for all 4 serotypes is > 1000 fold.

✓ NI is demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio CI is above 0.5

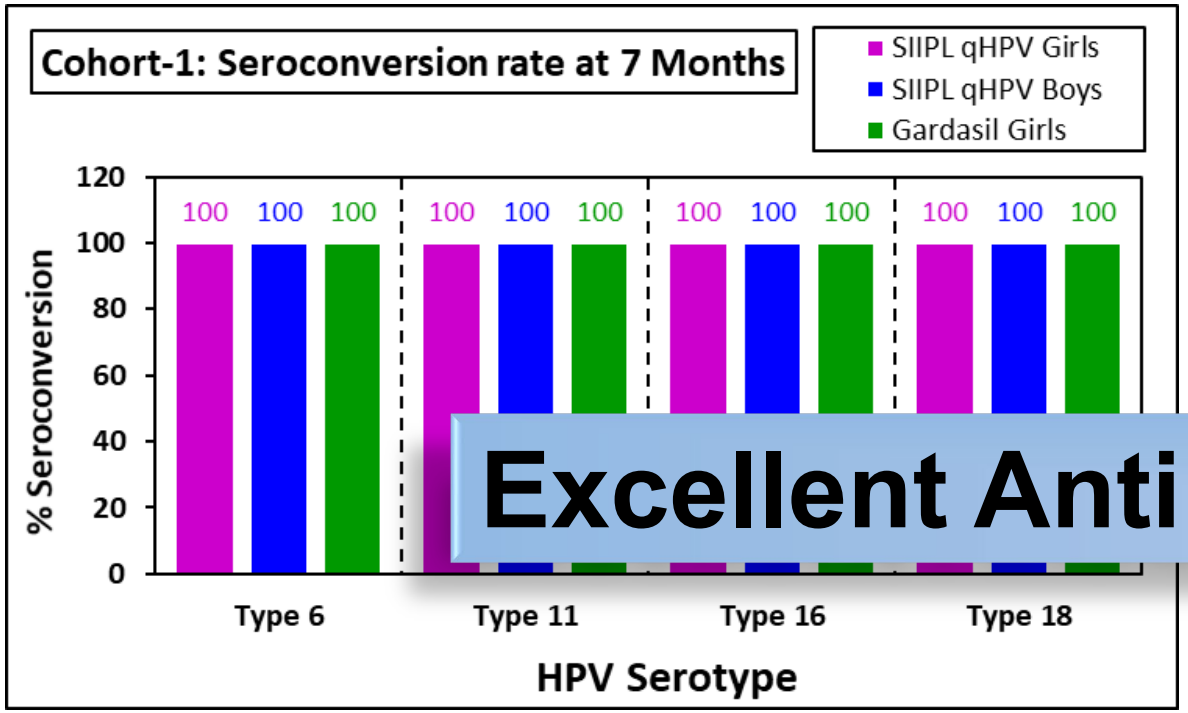
4. Summary of GMT - Men 15-26 yrs receiving 3 Doses of CERVAVAC Vs Women 15-26 yrs receiving 3 Doses of Gardasil

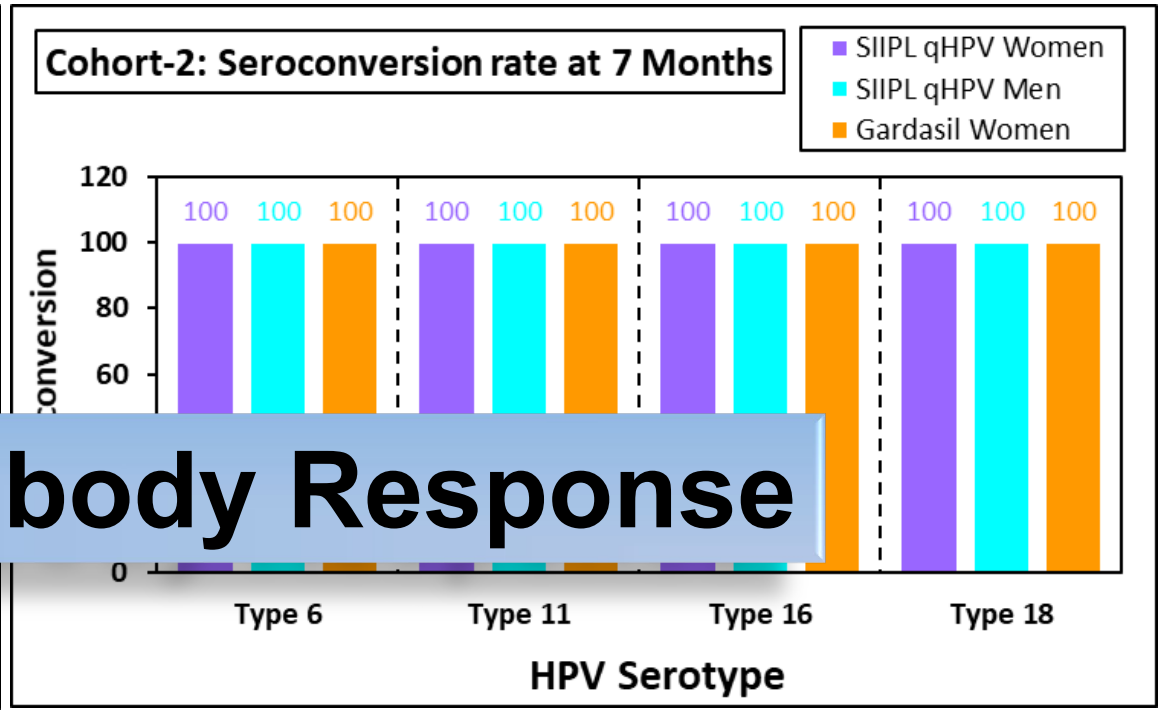
	Men of age 15-26 years receiving 3 doses of SIIPL-qHPV vaccine			Women of age 15-26 years receiving 3 doses of Gardasil			Comparison between SIIPL-qHPV and Gardasil
HPV types	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	n	Pre vaccination GMT of IgG (98.75% CI)	Post vaccination GMT of IgG (98.75% CI)	GMT Ratio (98.75% CI) by using ANCOVA
Type 6	347	0.0671 (0.0543, 0.0829)	137.3243 (121.2377, 155.5454)	338	0.0639 (0.0516, 0.0791)	154.7782 (136.4220, 175.6044)	0.8872 (0.7430, 1.0594)
Type 11	347	0.0420 (0.0332, 0.0532)	107.6912 (95.3429, 121.6388)	338	0.0386 (0.0309, 0.0482)	208.8346 (184.5911, 236.2622)	0.5157 (0.4336, 0.6133)
Type 16	347	0.1015 (0.0774, 0.1331)	548.9574 (486.5658, 619.3494)	338	0.0903 (0.0703, 0.1160)	712.3065 (630.3424, 804.9286)	0.7707 (0.6490, 0.9151)
Type 18	347	0.2271 (0.1832, 0.2814)	265.5901 (230.9204, 305.4650)	338	0.2183 (0.1814, 0.2627)	245.9150 (213.4184, 283.3597)	1.0800 (0.8850, 1.3180)

✓ In 15-26 yrs old Men GMFR for all 4 serotypes is > 1000 fold.

✓ NI is demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio CI is above 0.5

Seroconversion at 7 months





Excellent Antibody Response

Serotypes	HPV 6	HPV 11	HPV 16	HPV 18
Cut-off Values	0.197 AU/mL	0.152 AU/mL	0.333 IU/mL	0.695 IU/mL

Ref : Use Of Children's Sera To Establish Negative Cut-off Values For Hpv Serology Assays .Gitika Panicker, Ira Rajbhandari, Julia M. Denniss, Elizabeth R. Unger. Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, GA, USA

Solicited Adverse Events Girls/Women

Protocol Specified Term	Cohort 1			Cohort 2		
	CERVAVAC (Girls) (N=369) n (%)	Gardasil (Girls) (N=369) n (%)	p-value	CERVAVAC (Women) (N=411) n (%)	Gardasil (Women) (N=408) n (%)	p-value
Local						
Vaccination site erythema	7 (1.9)	5 (1.4)	0.7726	10 (2.4)	11 (2.7)	0.8291
Vaccination site pain	146 (39.6)	147 (39.8)	1.0000	178 (43.3)	193 (47.3)	0.2618
Vaccination site swelling	8 (2.2)	17 (4.6)	0.1018	16 (3.9)	20 (4.9)	0.5005
Vaccination site Pruritus	16 (4.3)	6 (1.6)	0.0490	20 (4.9)	19 (4.7)	1.0000
Systemic						
Nausea	17 (4.6)	14 (3.8)	0.7142	22 (5.4)	39 (9.6)	0.0237
Pyrexia	3 (0.8)	11 (3.0)	0.0551	6 (1.5)	3 (0.7)	0.5054
Pain in extremity	44 (11.9)	34 (9.2)	0.2812	60 (14.6)	62 (15.2)	0.8447
Dizziness	15 (4.1)	15 (4.1)	1.0000	41 (10.0)	39 (9.6)	0.9064
Headache	41 (11.1)	51 (13.8)	0.3159	80 (19.5)	100 (24.5)	0.0914

Solicited Adverse Events Boys/Men

Protocol Specified Term	Cohort 1			Cohort 2		
	CERVAVAC (Boys) (N=369) n (%)	Gardasil (Girls) (N=369) n (%)	p-value	CERVAVAC (Men) (N=381) n (%)	Gardasil (Women) (N=408) n (%)	p-value
Local						
Vaccination site erythema	7 (1.9)	5 (1.4)	0.7726	7 (1.8)	11 (2.7)	0.4803
Vaccination site pain	106 (28.7)	147 (39.8)	0.0019	77 (20.2)	193 (47.3)	<0.0001
Vaccination site swelling	8 (2.2)	17 (4.6)	0.1018	8 (2.1)	20 (4.9)	0.0354
Vaccination site Pruritus	6 (1.6)	6 (1.6)	1.0000	2 (0.5)	19 (4.7)	0.0002
Systemic						
Nausea	10 (2.7)	14 (3.8)	0.5345	5 (1.3)	39 (9.6)	<0.0001
Pyrexia	4 (1.1)	11 (3.0)	0.1147	7 (1.8)	3 (0.7)	0.2102
Pain in extremity	21 (5.7)	34 (9.2)	0.0918	17 (4.5)	62 (15.2)	<0.0001
Dizziness	3 (0.8)	15 (4.1)	0.0069	8 (2.1)	39 (9.6)	<0.0001
Headache	23 (6.2)	51 (13.8)	0.0008	24 (6.3)	100 (24.5)	<0.0001

Summary

- CERVAVAC has demonstrated a robust antibody response.
- 100% seroconversion was reported across all 4 vaccine types (Serotypes 6, 11, 16, 18).
- Geometric Mean Fold Rise (GMFR) for all 4 HPV serotypes is > 1000 fold across all age cohorts and gender.
- Adverse Events reported were predominantly mild to moderate in intensity and recovered completely.
- No vaccine related Serious Adverse Event was reported.
- Overall incidence of AEs with CERVAVAC is within acceptable limits and in line with the product label of the comparator viz., Gardasil.
- The immunogenicity and safety data supports the use of SIIPL qHPV vaccine in 9-26 years male and females in a mass vaccination campaign and immunization programmes.

A “Silver Bullet” for Cervical Cancer

EDITORIAL | VOLUME 23, ISSUE 10, P1233, OCTOBER 2022

HPV vaccination in south Asia: new progress, old challenges

The Lancet Oncology

Published: October, 2022 • DOI: https://doi.org/10.1016/S1470-2045(22)00567-8 •

Check for updates

In a promising advance in its fight against cervical cancer, India has recently launched its first locally produced version of the human papillomavirus (HPV) vaccine. The quadrivalent Cervavac vaccine, which protects against the virus strains most likely to cause cancer of the cervix, vagina, and vulva, among others, was developed jointly by the Serum Institute of India and the Indian Government's Department of Biotechnology. Following positive data from a large phase 2/3 clinical trial, marketing authorisation was granted by the Drugs Controller General of India on July 12, 2022, for female and male individuals aged 9–26 years, with the vaccine officially launched on Sept 1. Cervavac costs 200–400 rupees (€5) per dose, making it much more affordable than existing licensed HPV vaccines. Heralded as a huge step forward, could this be the silver bullet for cervical cancer control, both in India and other low-income and middle-income countries?

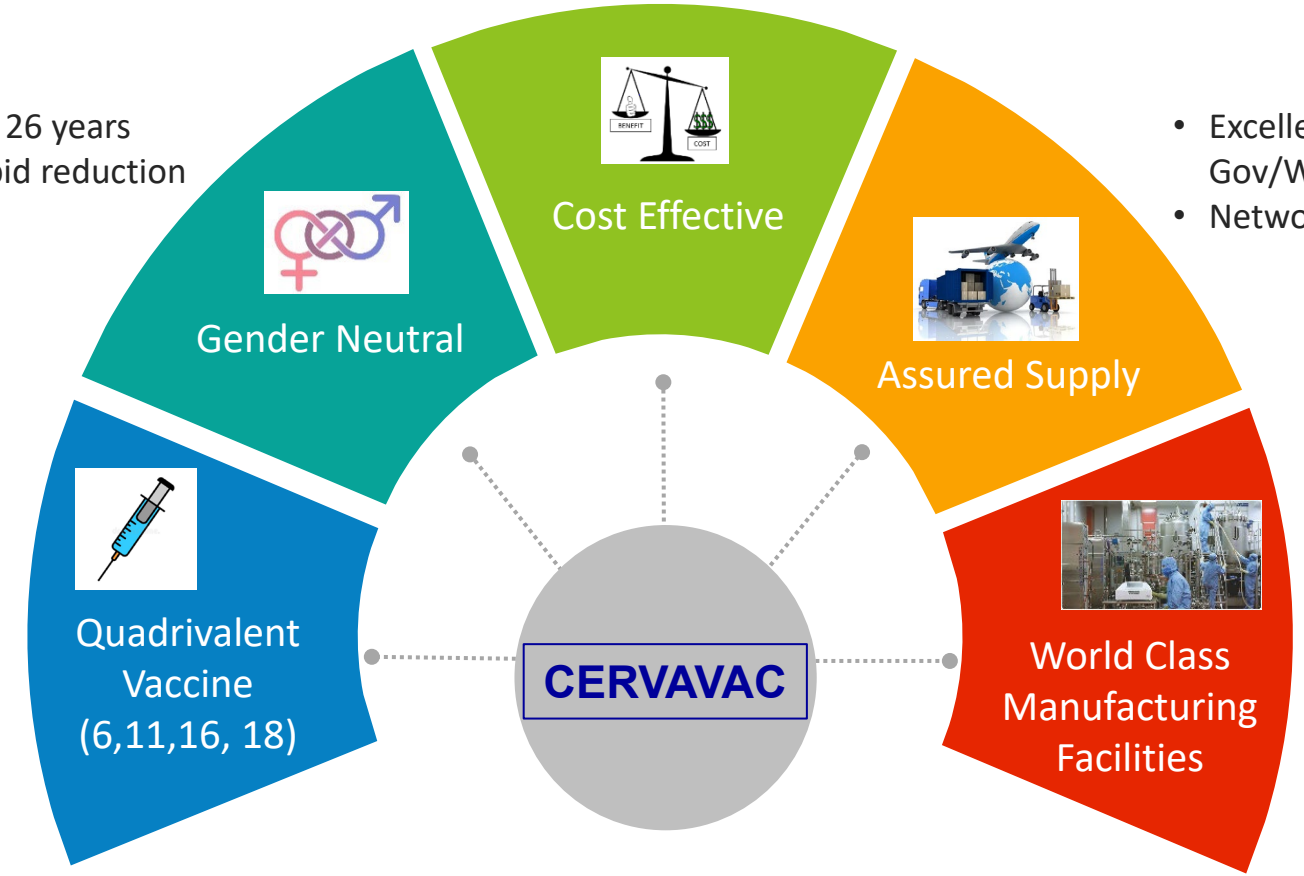
The Lancet Oncology; October, 2022

CERVAVAC - Sustainable, High Volume, High Quality, Cost Effective HPV Vaccine

- Most Affordable
- Remove the inequity in Access to HPV Vaccination

- Boys and Men - 9 to 26 years
- Facilitate a more rapid reduction in HPV prevalence.

- Excellent Track Record for Gov/WHO/UNICEF/GAVI supply
- Network & reach to 170+ countries



- India's First Indigenous HPV vaccine
- Licensed in Q2 2022

- Fully Automated close loop system
- Dedicated facilities & dedicated manpower for HPV manufacturing

Worldwide Public Private Partnership Collaboration

We can’t afford to lose one more life to a preventable, curable disease. And that means ensuring that a lack of supply of HPV vaccines to lower-income countries does not become the only barrier to this ambitious, but highly feasible, goal of eliminating cervical cancer – for good.