Estimating the Impact of a Gender-Neutral Quadrivalent Human Papillomavirus Vaccination Program in all HPV6/11/16/18-Related Diseases in Brazil With a Higher Vaccine Coverage Rate

Batista, PM[1]; Moreira, TNF[1]; Yen, GP[2]; Pavelyev, A[2a]; Haas LC[1]; Monsanto H[3]; Parellada C[1]

[1]MSD Brazil, São Paulo, SP, Brazil, [2]Merck & Co., Inc., Kenilworth, NJ, USA, [3]Center for Observational and Real-World Evidence (Carolina, Puerto Rico), Merck & Co., Inc., Kenilworth, NJ, USA

[a]Author working under contract with HCL America, Inc., Sunnyvale, CA, USA.

BACKGROUND

Human papillomavirus (HPV) infection can lead to the development of cervical, vulvar, and vaginal cancer in women; penile cancer in men; and genital warts (GW), recurrent respiratory papillomatosis (RRP), and anal and head and neck cancer in both sexes.[1]

The burden of HPV-related disease is high in both genders in Brazil (**Table 1**) and could be prevented through primary prevention interventions.[1-6]

In 2014, Brazil introduced a publicly funded female-only HPV vaccination program with the quadrivalent (6,11,16,18) HPV vaccine (4vHPV) and expanded it to include boys in 2017.[7]

The 2013-2018 cumulative vaccine coverage rate (VCR) was first dose (D1) 70.3%/second dose (D2) 49.9% for females aged 9-15 years and D1-42.3%/D2-20.1% for males aged 11-14 years.

Table 1. 2018 Burden of Disease of HPV-related Cases in Brazil and HPV Attribution[3]

		Burden of Disease		HPV Attribution Fraction (%)	Relative Contribution	
		Incidence[a]	Mortality		6/11	16/18
Female	Genital warts[b]	600	–	100.0%	90.0%	–
	RRP[c]	1.12	0.0531	100.0%	90.0%	–
	Cervical[d]	15.2	8.2	78.0%	–	68.2%
	Vaginal[d]	0.51	0.21	24.9%	–	63.7%
	Vulvar[d]	1.6	0.40	24.9%	–	72.6%
	Anal[d]	1.8	0.25	88.0%	–	87.0%
	Oral cavity[d]	3.0	1.5	2.2%	–	84.9%
	Oropharynx[d]	0.76	0.24	30.8%	–	84.9%
	Larynx[d]	1.3	0.34	2.4%	–	84.9%
Male	Genital warts[b]	600	–	100.0%	90.0%	–
	RRP[c]	1.35	0.0635	100.0%	90.0%	–
	Penile[d]	0.9	0.39	50.0%	–	70.2%
	Anal[d]	0.52	0.25	88.0%	–	87.0%
	Oral cavity[d]	6.4	3.1	2.2%	–	84.9%
	Oropharynx[d]	1.9	1.1	30.8%	–	84.9%
	Larynx[d]	4.0	2.1	2.4%	–	84.9%

[a]Crude rate per 100,000 persons; [b]Brazil arm HIM study; [c]Assumption based on literature data. [d]Extracted from Globocan 2018.

OBJECTIVE

The aim of this analysis is to assess the epidemiologic and economic impact of increasing the VCR for the existing gender-neutral 4vHPV program in Brazil.

METHODS

- A validated HPV-type dynamic transmission model[8-11] was adapted to simulate GNV two-dose 4vHPV vaccination in the 9- to 14-year-old female cohort and 11- to 14-year-old male cohort for the prevention of HPV-related cervical cancer, cervical lesions (CIN-1/2/3), vaginal, vulvar, penile, anal, and head and neck cancers as well as GW and RRP, over a 100 year timeframe in Brazil.
- The predicted health outcomes included HPV 6/11/16/18-related disease cases and deaths averted, direct healthcare cost avoided by vaccination, direct healthcare costs prevented, and incremental cost-effectiveness ratios (ICERs).
- The model compared current first and second dose VCRs in Brazil (D1-80% and D2-50% in females; D1-50% and D2-20% in males) with the same VCR scenario for both genders (30% VCR increase in males).
- Brazilian-specific data were used in the model and consisted of demographic, epidemiological, screening, and economic parameters (**Tables 1** and **2**).[1-6,12-16]
- The model assumed a 100-year time-horizon, lifelong immunity following vaccination, herd immunity, ongoing cytology screening, and a discount rate of 5% for costs and benefits.
- Incremental cost-effectiveness ratios (ICER) were calculated by dividing the difference in accumulated costs by the QALY gained.
  - There is no official cost-effectiveness threshold in Brazil. The WHO definition of cost-effectiveness was used to define the threshold of highly cost-effective (ICER below 1 GDP per capita or US$8,920.8 for Brazil) and cost-effective from 1-3 GDP per capita (less than US$26,762.4).[17-18]
- The Brazilian national health database (DATASUS) was used to estimate the HPV-related disease costs.[16] The costs were converted from local currency (reais) to US dollars (exchange rate on May 31, 2019; 1 US $=3.92 reais).[19]

Table 2. Cost Parameters per Episode-of-Care[16]

Parameter	Costs (US $)	Parameter	Costs (US $)
CIN 1	132.30	Penile cancer	1,911.35
CIN 2/3	218.98	Anal cancer	1,896.42
Cervical cancer	2,849.60	Head & Neck cancer	2,774.40
VaIN 2/3	113.26	Genital warts	86.03
Vaginal cancer	3,261.15	RRP	542.55
Vulvar cancer	2,334.85		

CIN, cervical intraepithelial neoplasia; RRP, recurrent respiratory papillomatosis; VaIN, vaginal intraepithelial neoplasia
Since DATASUS does not provide costs by cancer stage, a weighted average cost of each disease considering all procedures (surgery, chemotherapy, and radiotherapy) performed in the 2014-2018 period according to the ICD-10 was calculated.

RESULTS

With a 30% VCR increase in males compared to the current program VCR, the model predicted at year 100 the following outcomes:

HPV-related Disease
- **Figure 1** shows the greater and earlier reduction of HPV 6/11-related diseases (GW and RRP), starting few years after simulation as well as a significant decrease in the incidence rates related to HPV 16/18 after 25-30 years (**Figure 1, Table 3**).
- A total of 58,227 avoided cancer cases: 27,097 cervical cancer (CC) cases and 31,130 non-CC cases (8,864 in females and 22,266 in males). (**Table 3**).

HPV-related Deaths
- A total of 26, 934 avoided deaths: 15,757 in females and 11,177 in males (**Table 3**).

Direct Healthcare Costs
- US$134.6 million of HPV 6/11/16/18 direct medical health care costs avoided over 100 years, driven by HPV6/11-related treatment costs (**Figure 2**).

ICER
- Under the model assumptions, a GNV 4vHPV program with a 30% increase in males VCR was found to be a highly cost-effective strategy compared with the base case (ICER of US $ 702 per QALY).

Table 3. Estimated HPV 6/11/16/18-related Disease Cases and Deaths Averted and Respective Percentage Incidence Reduction with VCR D1-80%/D2-50% Among females and males Compared with the Current Vaccination Program (D1-80%/D2-50% for females and D1-50%/D2-20% for males) Over 100 Years

		Avoided Cases		Avoided Deaths	
		Frequency	Percent	Frequency	Percent
Female	Cervical cancer	27.097	4.2	13.178	3.6
	CIN 1 – related to HPV 6/11	53.498	7.2	-	-
	CIN 1 – related to HPV 16/18	77.066	7.1	-	-
	CIN 2/3	260.694	6.5	-	-
	Head and Neck cancer	2.997	4.3	1.194	4.0
	Anal cancer	4.529	4.5	622	4.2
	Vaginal cancer	472	3.8	149	3.5
	VaIN 2/3	827	4.2	-	-
	Vulvar cancer	866	3.6	296	3.4
	GW	3,136,968	10.7	-	-
	RRP	7.086	11.4	318	10.3
Male	Head and Neck cancer	16.982	10.4	8.155	9.8
	Anal cancer	3.081	9.8	1.479	9.4
	Penile cancer	2.203	13.2	881	12.6
	GW	7,345,305	20.2	-	-
	RRP	14.888	17.4	662	15.9

D1, first dose; D2, second dose; GNV, gender-neutral vaccination; CC, cervical cancer; CIN, cervical intraepithelial neoplasia; GW, genital warts; RRP, recurrent respiratory papillomatosis.

Figure 1. Estimated Percentage Reduction of 6/11/16/18 HPV-related Diseases Incidence With VCR D1-80%/D2-50% Among Females and Males Compared with Current Vaccination Program (D1-80%/D2-50% for females and D1-50%/D2-20% for males) over 100 Years

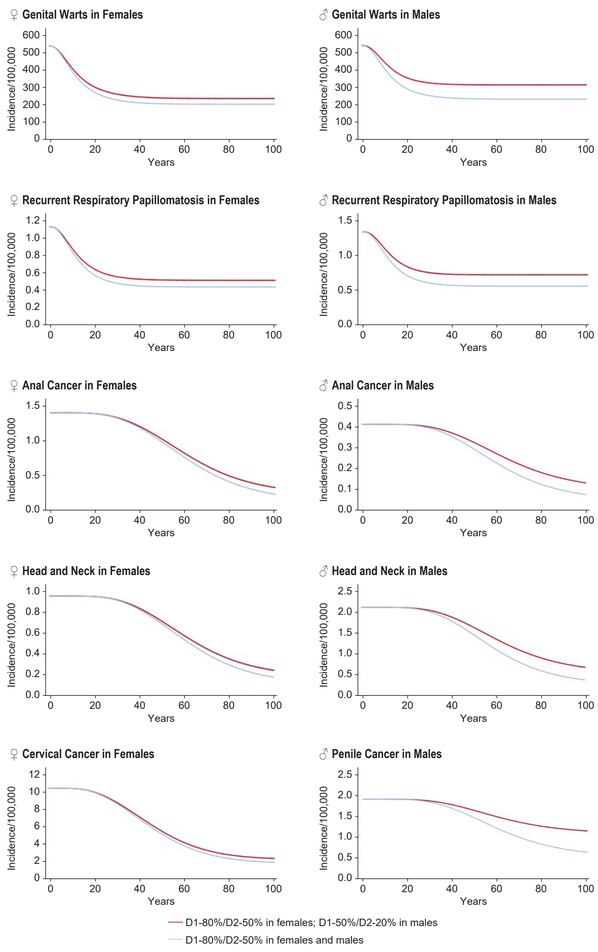
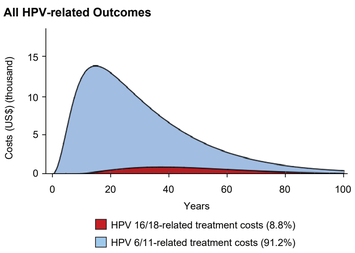


Figure 2. Estimated Direct Health Care Costs Avoided with GNV VCR (D1-80%/D2-50% for females/males) Compared with the Current Vaccination Program (D1-80%/D2-50% for females and D1-50%/D2-20% for males) over 100 Years



D1, first dose; D2, second dose; CC, cervical cancer; GW, genital warts; HPV, human papillomavirus; VCR, vaccine coverage rate.

LIMITATIONS

Currently, HPV vaccines are not indicated for the prevention of penile cancer, RRP, and head and neck cancers.

Model does not assess possible changes to CC screening methods over the course of 100 years.

Direct medical costs related to outpatient visits, potential complications, and palliative care are not included in the model. This may result in cost underestimation of treatment.

Indirect costs were not taken into consideration.

CONCLUSIONS

- In Brazil, a model-based analysis suggests a GNV 4vHPV vaccination program with higher VCR in males relative to the current VCR is projected to:
  - Provide earlier and greater cumulative reductions in all HPV 6/11/16/18-related diseases in both genders
  - Be a highly cost-effective strategy

References

1. Bruni L, et al. Human Papillomavirus and Related Diseases in Colombia. Summary Report 10 December 2018. Available at: https://hpvcentre.net/statistics/reports/COL.pdf. Accessed March 30, 2019.
2. da Silva RJC, et al. *Braz J Infect Dis.* 2017;21(4):376-385.
3. Globocan 2018. Available at: http://gco.iarc.fr/today/home. Accessed April 1, 2019.
4. World Health Organization. Accelerating Cervical Cancer Elimination. Available at: http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_28-en.pdf. Accessed March 30, 2019.
5. de Martel C, et al. *Int J Cancer.* 2017;141(4):664-670.
6. Wang X, et al. Recurrent respiratory papillomatosis: a systematic literature review. Available from: https://ipvc2018.org/. Accessed April 1, 2019.
7. Brazil. Ministério da Saúde. Available at: http://portalarquivos2.saude.gov.br/images/pdf/2018/marco/14/Informe-T--cnico-HPV-MENINGITE.pdf. Accessed April 1, 2019.
8. Dasbach EJ, et al. *Epidemiol Rev.* 2006;28:88-100.
9. Elbasha EH, et al. *Emerg Infect Dis.* 2007;13(1):28-41.
10. Insinga RP, et al. *Bull Math Biol.* 2008;70(8):2126-2176.
11. Ortiz AP, et al. *PLoS One.* 2017;12(11):e0184540.
12. Instituto Brasileiro de Geografia e Estatística (IBGE). Population. Available at: https://www.ibge.gov.br/estatisticas/sociais/populacao.html. Accessed March 30, 2019.
13. Barbosa RM, et al. *Rev Saude Publica.* 2008;42(Suppl 1):21-33.
14. dos Santos AV, et al. *Asian Pac J Cancer Prev.* 2019;20(4):1019-1024.
15. Oliveira MM, et al. *Rev Bras Epidemiol.* 2018;21: e180014.
16. DATASUS. Available at: http://datasus.saude.gov.br/informacoes-de-saude. Accessed March 30, 2019.
17. World Health Organization. Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health. Geneva: World Health Organization; 2001. Available at: https://apps.who.int/iris/handle/10665/42435.
18. The World Bank. 2018 Brazil GDP per capita. Available from https://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed August 24, 2019.
19. Banco Central do Brasil. Exchange Rate in May 31, 2019. Available at: https://www.bcb.gov.br.

Disclosure

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Presented at Virtual ISPOR 2020; May 18-20.