Uptake of Papanicolaou testing by HPV vaccination status

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Abstract

Background: Although the annual incidence of cervical cancer in Israel is relatively low (5.4 per 100,000), the Ministry of Health recommends human papillomavirus (HPV) vaccination among females and males at 8th grade as part of the national childhood immunization program. It is unclear whether young Israeli women who initiated HPV vaccination are more likely than unvaccinated women to report having a Papanicolaou (Pap) test later in life.

Objectives: To evaluate the impact of the HPV vaccine on cervical cancer screening program and to examine if uptake of Pap testing differed across subgroups of age and income by vaccination status.

Methods: Design and settings: This retrospective cohort analysis was carried out at Maccabi Healthcare Services (MHS), a 2.3-million-enrollee, integrated-care provider in Israel. From all women immunized with at least one dose of HPV vaccine from its introduction in Israel in June 2007 to Dec. 2018, we excluded those who had a Pap test prior to vaccination, as well as women who were no longer members of MHS on Dec. 2018. Over 20,000 eligible vaccinated women were individually matched with non-vaccinated MHS members on a one-to-one basis by exact birth year, socioeconomic level, and district of residence. Exposure: HPV immunization was collected from the women's electronic medical records (EMR), as well as information on demographic factors (date of birth, district of residence, enumeration area), body mass index, and if ever smoked cigarettes. Socioeconomic status was categorized according to the poverty index of the member's enumeration area. Main outcome: Data on the uptake of Pap smears were extracted from MHS central laboratory, and the number of Pap smears for each woman during the study period was counted. Statistical analysis: We started follow-up at the date of purchase of first vaccination dose and then followed them forward until Pap test or Dec. 2018, whichever occurred first. We used Cox proportional hazards regression, with days of follow-up as the time scale.

Results: Proportion of women having Pap test was significantly higher among HPV vaccinated women (27%) compared to 22% of non-vaccinated (aHR=1.34; 95%CI: 1.29-1.41). Adherence of Pap smear tests among vaccinated women was significantly higher compared to non-vaccinated women across all relevant age groups.

Conclusions: We found no indication for lower adherence with Pap tests among women who were immunized with HPV vaccine than in the past.

Background

- Cervical cancer is caused by oncogenic types of HPV.
- In Israel, HPV vaccinations are recommended for females and males at 8th grade.
- The HPV vaccine is ineffective against non-vaccine oncogenic type or in patients with prior infections. As such, cervical cancer screening is still essential for cancer prevention.
- Guidelines in Israel recommend Pap testing at 3-year intervals from age 25, regardless of HPV vaccination status.
- Two HPV vaccines are available in Israel (Cervarix®, Glaxo Smith Kline; and Gardasil®, Merck that was introduced in Israel June 2007). Vaccination was opportunistic, as it was not covered by the National Health Insurance Act. At first it was indicated for females aged 9 to 26 years; since 2012 it was expanded to females aged 9 to 45 years.
- Recent literature has indicated that women who initiated HPV vaccination were more likely than unvaccinated women to report having a Pap test in the previous 3 years.

Objectives

- We aimed to evaluate the impact of the HPV vaccine on a cervical cancer screening program in Israel and to examine if uptake of Pap testing differed across subgroups of age and income by vaccination status.

Methods

- Using the database of MHS, which covers 25% of the total population in Israel, we identified a total of 47,690 women immunized with at least one dose of HPV vaccine from its introduction in Israel in June 2007 to December 2018.
- Excluded from the study were women who had a Pap test prior to vaccination (n=24,642), as well as women who were no longer members of MHS on December 2018 (n=2,121). All eligible vaccinated women (n=20,904) were individually matched with non-vaccinated MHS members on a one-to-one basis by exact birth year, socioeconomic level, and district of residence.
- Data on the uptake of Pap smears were extracted from MHS central laboratory, and the number of Pap smears for each woman during the study period was counted.
- We collected information on demographic factors, body mass index, poverty index, and smoking.
- Retrospective follow-up was from date of purchase of first HPV vaccination dose through date of first Pap test or December 2018, whichever occurred first.

Results

- Characteristics of study population are given in Table 1
- Cumulative rates of Pap screening tests among women vaccinated with HPV by the end of follow-up was higher (26.8%) as compared to non-vaccinated females (22.4%)
- Cumulative rates of Pap screening tests by HPV vaccination status among women aged 15-24 years and 25-34 years at HPV vaccination are given in Figures 1 and 2, respectively.
- In a multivariable model, HPV vaccination was associated with a significantly (P<0.001) higher likelihood (adjusted HR= 1.34; 1.29-1.41) for performing HPV screening test as compared to non-vaccinated females.

Table 1 : Characteristics of study population by HPV vaccination status

		Not vaccinated (n=20904)		Vaccinated (N=20904)	
		n	%	n	%
Age at index date	Years	19.68	(3.88)	19.23	(4.58)
BMI	kg/M²	23.56	(4.98)	23.08	(4.41)
Smoking*	Current	1655	8.31%	1507	7.28%
	Past	208	1.05%	197	0.95%
	Never	18041	90.64%	18999	91.77%
SES , Median (IQR)		7	(6-9)	7	(6-9)
District	North	3338	16.0%	3338	16.0%
	Sharon	5428	26.0%	5428	26.0%
	South	2467	11.8%	2467	11.8%
	Center	5316	25.4%	5316	25.4%
	Shfela	4355	20.8%	4355	20.8%
Pap	No	16222	77.6%	15298	73.2%
	Yes	4682	22.4%	5606	26.8%

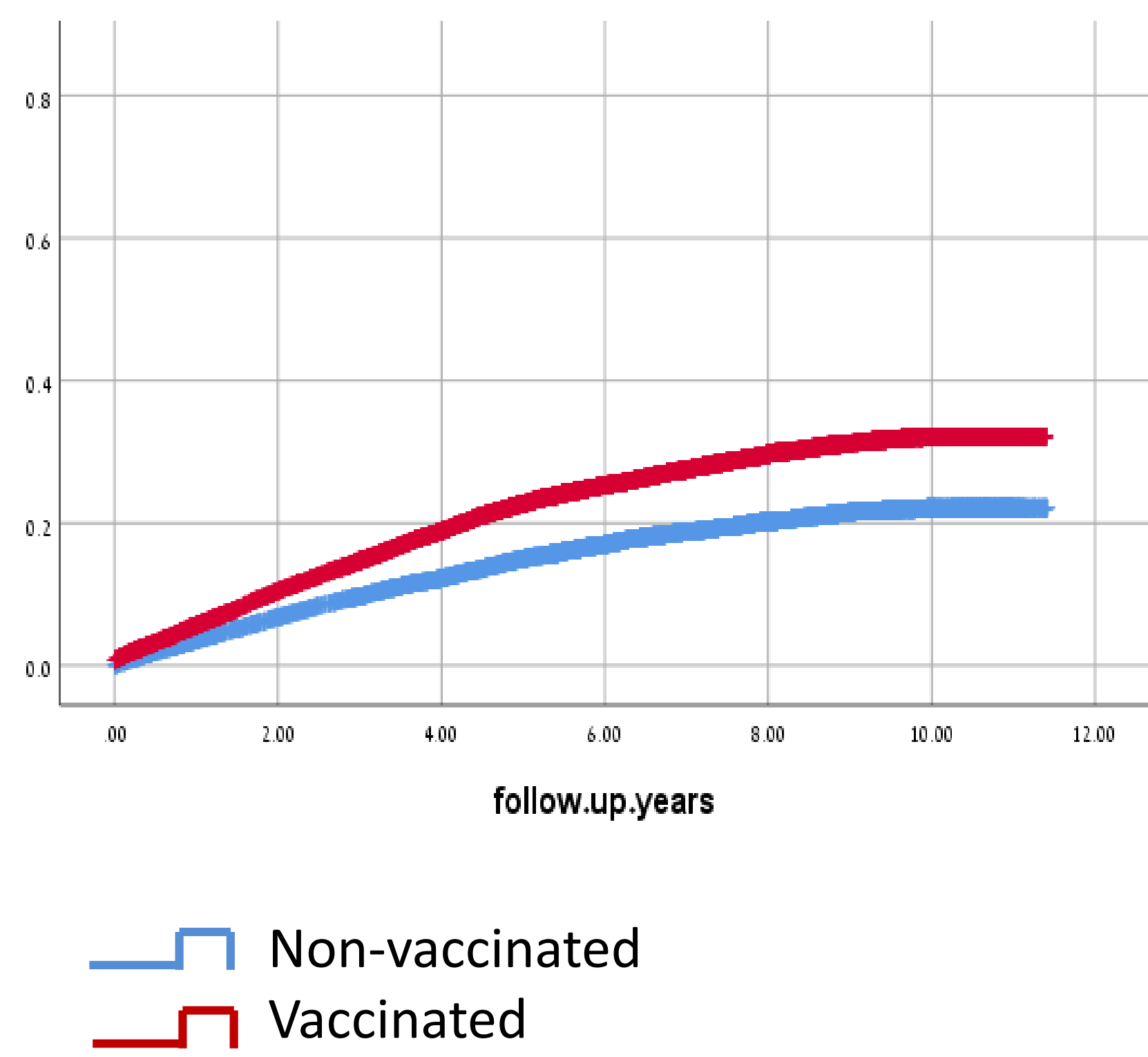**Fig. 1: Cumulative rate of Pap screening tests, by HPV vaccination status (age: 15-24y)**

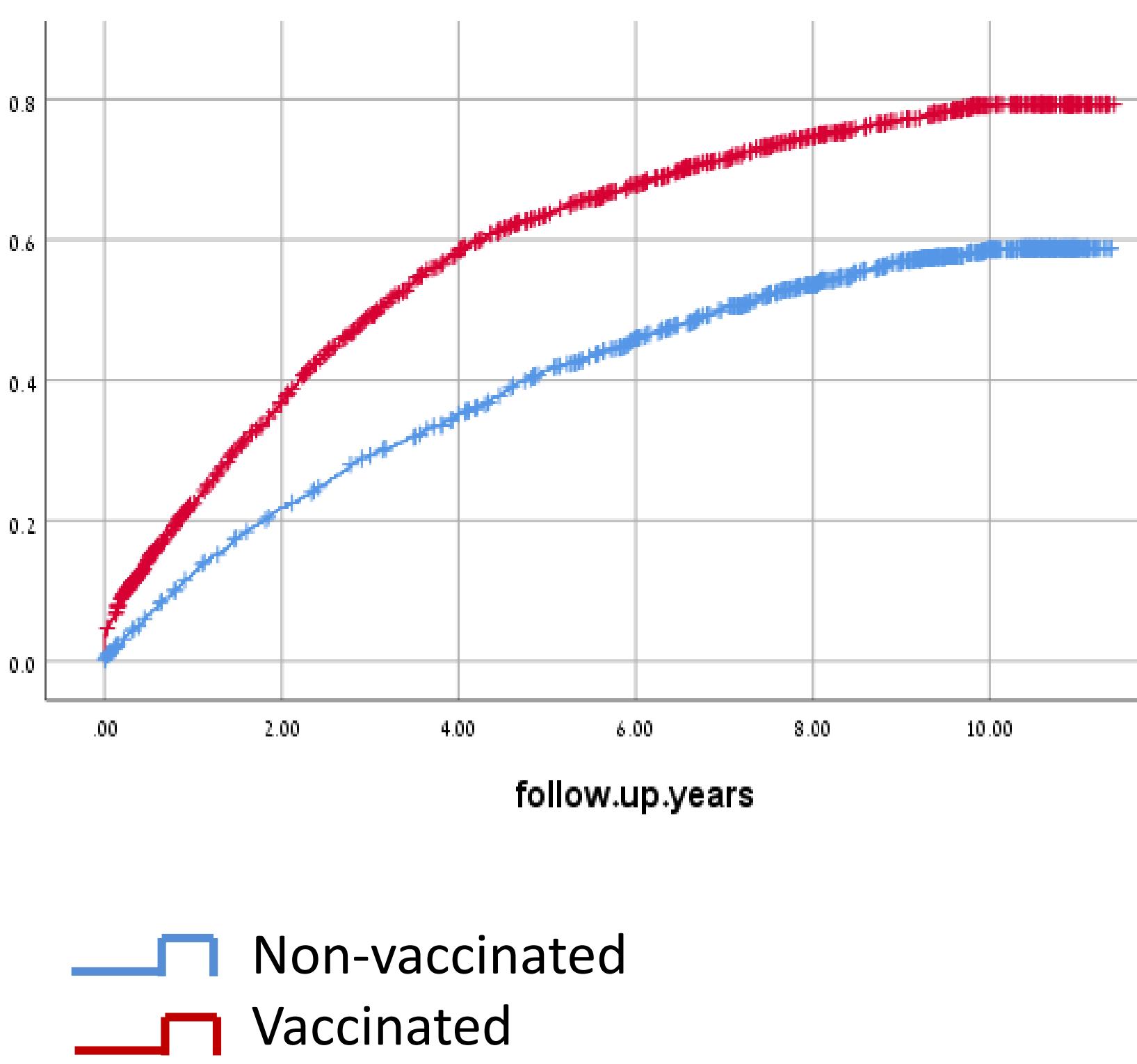**Fig. 2: Cumulative rate of Pap screening tests, by HPV vaccination status (age: 25-34y)**

Non-vaccinated
Vaccinated

Table 2: Cox Proportional hazards model for Pap smear test

		p	HR	95% CI Lower	95% CI Upper
Smoking	Never		1 (ref.)		
	Current	.087	.93	.86	1.01
	Past	.038	1.20	1.01	1.43
BMI	Per 1 kg/m2	<0.001	1.01	1.01	1.02
Birth year	Per year	<0.001	.85	.84	.86
HPV Vaccinated	Yes vs. no	<0.001	1.34	1.29	1.41

Conclusions

We found no indication for lower adherence with Pap tests among women who were immunized with HPV vaccine than in the past. These results are supported by reports of the U.S. National Health Interview Survey that indicate young women who had not initiated HPV vaccination have lower uptake of Pap test compared to women who had initiated vaccination.