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The association of adverse events with bivalent human papilloma virus vaccination: A nationwide register-based cohort study in Finland

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ABSTRACT

Background: A bivalent HPV vaccine (*Cervarix*®; HPV2, GlaxoSmithKline) was introduced into the Finnish national vaccination programme (NVP) in November 2013 for girls aged 11–13 years with a catch-up for 14–15 year-olds. We evaluated the association between HPV2 and selected autoimmune diseases and clinical syndromes by conducting a nation-wide retrospective register-based cohort study.
Methods: First life-time occurrences of the relevant ICD-10 codes in girls aged 11–15 years between Nov-2013 and Dec-2016 were obtained from the national hospital discharge register. Population denominators were obtained from the Population Information System and vaccination records from the National Vaccination Register. Registers were linked using unique personal identity codes. Association between HPV2 and 38 selected outcomes were studied using Cox regression, with age as the main time-scale and the first vaccination dose as the time-dependent exposure. The hazard ratios (HR) with 95%CI were assessed according to the time since exposure (entire follow-up, 0-180/181-365/>365 days).
Results: Of 240 605 girls eligible for HPV2 vaccination, 134 615 (56%) were vaccinated. After adjustment for geographical area (6 hospital districts), country of origin (Finnish-born/not) and number of hospital contacts from 9 through 10 years of age, HRs ranged from 0.34 (95%CI 0.11–1.05) to 8.37 (95%CI 0.85–82.54) and HPV2 vaccination was not statistically significantly associated with a higher risk of any outcome during the entire follow-up.
Conclusions: This study found no significantly increased risk for the selected outcomes after the HPV vaccination in girls 11–15 years of age. These results provide valid evidence to counterbalance public scepticism, fears of adverse events and possible opposition to HPV vaccination and consequently can contribute to increase HPV vaccination coverage in Finland as well as elsewhere.

1. Introduction

Concerns about human papillomavirus (HPV) vaccine related adverse events following immunization (AEFIs) are common among the adolescent females, their parents and health professionals around the world [1–4]. These concerns are frequently supported by anti-vaccination groups, spread in social media, and are also caught by the media, which has led to negative publicity about the vaccinations and coverage drop in many countries [5,6].

However, the available pre- and post-licensure data demonstrate acceptable safety of HPV vaccines, and the World Health Organization (WHO) [7] and the European Medicines Agency (EMA) [8] recommend HPV vaccinations to prevent the cervical cancer and other HPV-related diseases.

In November 2013, a school-based HPV vaccination with a bivalent HPV vaccine (*Cervarix*®; HPV2, GlaxoSmithKline) given in three doses (0, 2, 6 months) to 11–13 year-old females and catch-up in 14–15 year-olds was implemented in the Finnish national vaccination programme (NVP). The Finnish Medicine Agency (FIMEA) receives notifications about the AEFIs following the HPV vaccination from healthcare professionals and patients, who are advised to report suspected adverse reactions to vaccines that come to their knowledge. These notifications are intended to

Abbreviations: AEFI, adverse events following immunization; AvoHILMO, the national register of primary health care visits; EMA, European medicines agency; FIMEA, finnish medicine agency; HILMO, national hospital discharge register; HPV, human papillomavirus; ICD-10, international classification of diseases, 10th revision; ICPC-2, international classification of primary care, second edition; NVP, national vaccination programme; NVR, national vaccination register; THL, national institute for health and welfare; WHO, world health organization.

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provide early safety signals, but this passive reporting system is subject to reporting biases and cannot prove causal association with vaccinations.

To evaluate the association of HPV2 with a large number of potential AEFIs, we assessed the baseline incidences of selected outcomes and conducted an observational retrospective nation-wide register-based cohort study.

2. Material and Methods

2.1. Outcomes

We selected potential AEFIs with the diagnoses according to the International Classification of Diseases, Version 10 (ICD-10) [9]. Our selection of the outcomes was based on previous research [6,10,11], media reports on HPV safety and discussions on the use of the ICD-10 codes with clinicians in Finland. We included diagnoses of immunological diseases, disease syndromes of unknown etiology and general symptoms, including the diseases alleged to be AEFIs in the media, such as Guillain-Barré syndrome (GBS) and the non-specific diagnostic entities, such as complex regional pain syndrome (CRPS), chronic fatigue syndrome/systemic exertion intolerance disease (CFS/SEID) and postural orthostatic tachycardia syndrome (POTS). (see Supplementary Table 1 for all outcomes with ICD-10 codes)

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.06.074.

2.2. Data sources

The population denominators were obtained through the Finnish Population Information System [12] with information on the personal identity code (PIC), sex, age, death, immigration to Finland, date of birth and area of residence. The individual follow-up times for each citizen were used in the cohort study and average yearly age-and sex-specific population estimates for the baseline calculations.

Exposure data on vaccinations was obtained from the Finnish National Vaccination Register (NVR), available since 2011 at the THL. Exposure time started on the day of the first dose of HPV vaccine regardless of receiving following doses. The NVR includes information on PIC, sex, age, date of birth, the date, type and dose of HPV vaccine, and hospital district information. Based on the NVR records, the first-dose vaccine uptake has ranged by birth cohorts between 64 and 73% in females and 0% in males [13]. Before the HPV introduction into the NVP, approximately 30,000 doses were administered since 2006 on girls/parents' own initiative at own cost. Persons who have been vaccinated in clinical trials before the NVP are not included in this study (birth cohorts born 1992–1995) [14]. Based on the national sales data, approximately 5400 doses were sold outside of the NVP between 2013 and 2016. With a 3-dose schedule, the number of HPV vaccinated (of any age) was 1800 during this time period [15].

Outcome data was obtained from the national hospital discharge register (HILMO) with the individual information for all hospital visits including outpatient visits and inpatient hospitalizations. Since 1996 HILMO contains comprehensive records on inpatients with ICD-10 codes and since 1998 also outpatient visits. The basic variables include PIC, area of residence, ICD-10 codes, admission, discharge, and outpatient visit dates. We have previously used this register for a baseline study of the GBS, CFS/SEID and POTS [16].

Data on confounding variables were obtained from the Finnish Population Information System on the geographical area and country of origin, and from HILMO on the number of hospital visits from 9 through 10 years of age.

To assess the primary health care resource use in vaccinated and non-vaccinated females from 9 through 10 years of age, we used the National Register of Primary Health Care Visits (AvoHILMO). Since 2011, AvoHILMO contains records on outpatient care from all public health care centers in Finland with assigned ICD-10 codes or the International Classification of Primary Care, Second edition (ICPC-2) codes [17].

We used the unique and permanent PIC number allocated to all permanent inhabitants of Finland to link information from the different national registers.

The study was approved by the Institutional review board of THL and the permission to use the data was provided by the register controller at THL.

3. Statistical analysis

First, we calculated annual baseline incidence rates per 100,000 person-years (IRs) for 65 selected outcomes in female and male populations of age 11–15 years residing in Finland during 2002–2016. We also evaluated incidence rate ratio (IRR) with 95% confidence intervals (95%CI) comparing sex-specific IRs in the pre-vaccination (PreV) period from January 2009 through October 2013, with the post-vaccination period (PostV) from November 2013 through December 2016.

We then carried out a nation-wide population-based observational retrospective register cohort study, comparing the risk of the outcomes between females exposed and not exposed to HPV2. Given the low number of the cases for some outcomes studied in the baseline analyses, we included only outcomes with at least 5 vaccinated cases for further assessment in the cohort study, resulting in a total of 38 outcomes. We defined the outcome as the first occurrence of the ICD-10 diagnosis in any discharge notification in any position (first and secondary diagnoses collected).

The cohort included all individuals eligible for HPV2 through the NVP during the PostV period, i.e. females of age 11–15 years and residing in Finland (n = 240,650). Follow-up started from the 11-year birthday or 1 November 2013, whichever came last. The females in the cohort were followed until the first outcome diagnosis, death, 16th birthday, or 31 December 2016, whichever came first. Subjects with any life-time occurrence of the outcome diagnosis before the start of the follow-up were excluded from the specific outcome analysis. To ensure complete information on medical history from HILMO, we excluded females who immigrated to Finland later than they turned 2 years (n = 13,433), and also those who were vaccinated with the first HPV2 dose (n = 9) before and those vaccinated with the quadrivalent HPV vaccine (*Gardasil*™, Merck and Co., n = 57) during the follow-up time.

We used Cox regression to study the association of HPV2 and the selected outcomes. Crude and adjusted hazard ratios (HRs) and 95%CIs were estimated for each outcome. We used stratified Cox models with birth cohorts as strata and age in years as the main time scale. The 95%CIs and Wald tests were used to test for significance of the effects in the model. Vaccination status (first dose) was used as time-dependent covariate and the exposed follow-up time started at the date of the vaccination. We assessed the hazards for the selected outcomes according to the time since the first vaccination exposure, i.e. 0–180 days, 181–365 days, more than 365 days and entire follow-up (overall). In addition, we did sensitivity analysis, excluding subjects living in communities with incomplete reporting of vaccination data to the NVR (<2% of the population) [18].

All models were adjusted for hospital district (N = 6), country background (born abroad or in Finland) and number of any

hospital visits or admissions (0; 1;2; 3–4; 5–6; ≥7) two years before the scheduled vaccination, i.e. when the females were 9–10 years of age.

The number of primary healthcare visits (0; 1;2; 3–4; 5–6; ≥7) at 9–10 years of age included physical visits in outpatient, school, student and work health services. The significance in distribution of health care use between vaccinated and non-vaccinated was tested by the Wilcoxon-type trend test.

For the data analysis we used the Stata software package, Version 15 (USA: StataCorp LP) and the R software package [19].

4. Results

Out of a total of 240,605 persons followed over 453,676 person-years during PostV period in females aged 11–15 years, we identified 3730 cases for the 65 outcomes. The IRs spanned from 0.0 (acute rheumatic fever, autoimmune hemolytic anemia and Reiteŕs disease) to 250.8 per 100,000 person-years (asthma). For 8 outcomes a significant IRR between PostV and PreV was observed (Fig. 1, Supplementary Table 2). However, for 5 outcomes, a similar increase was observed among males, for 1 outcome (celiac disease) significance was very weak and for the remaining 2 outcomes (other paralytic syndromes and polyarteritis nodosa), the number of cases was very low. Moreover, except for the unspecified illnesses, an increasing trend of the IR was observed already before 2013.

There was no significant increase of the IRs in the PostV for the CRPS, GBS and POTS but the CFS/SEID showed an increase (IRR 2.0). However, a similar increase was observed in males (IRR 2.1) (Fig. 2).

The characteristics of our cohort, females aged 11–15 years eligible for the HPV2 vaccination in the NVP from November 2013 through December 2016, are shown in Table 1. Of 240,605 eligible females, 134,615 (55.9%) were vaccinated with variations among the birth cohorts: year 1997 (4.8%); 1998 (59.5%); 1999 (63.1%); 2000 (65.6%); 2001 (65.8%); 2002 (71.0%); 2003 (68.3%); 2004 (63.5%); 2005 (0.4%). The Northern Finland had the lowest HPV2 coverage (48.3%) and coverage was higher among Finnish born females (57.2%) compared to non-Finnish (37.6%). The vaccinated group had had less hospital and primary healthcare visits compared to the non-vaccinated group ($p < 0.001$).

The adjusted HRs for the entire follow-up ranged from 0.34 (95%CI 0.11–1.05) to 8.37 (95%CI 0.85–82.54) across the 38 outcomes among the vaccinated in relation to the unvaccinated, of which 17 had an overall adjusted HR equal or above one. However, the 95%CIs and the overall Wald test ($p > 0.05$) showed that HPV2 was not significantly associated with an increased risk for any of the 38 outcomes (Fig. 3).

There were in total 4 outcomes for which the adjusted HR was statistically significantly below one for the overall period (CFS/SEID, epilepsy and recurrent seizures, Henoch-Schonleiń s purpura, malaise/fatigue) and for 3 additional outcomes in other exposure windows (autism, idiopatic thrombocytopenic purpura, and other hyperthyroidism). There were 3 outcomes for which the adjusted HRs in other exposure windows were above one, but all 3 outcomes had very low numbers in vaccinated (N = 5 or 6) and therefore wide 95%CIs: GBS (HR = 32.17, 95%CI 1.59–652.4) within more than 365 days, myositis (HR = 7.46, 95%CI 1.00–55.39) and pancreatitis (HR = 20.28, 95%CI 1.66–247.9) within 181–366 days after the vaccination. However, the overall Wald tests for the HRs being equal to one when comparing all exposure-periods (simultaneous test) were not significant ($p = 0.9$, $p = 0.2$ and $p = 0.7$, respectively) (see Supplementary Table 3 for HRs in all outcomes).

For the unspecified illnesses, which increased during the post-vaccination periodthe overall adjusted HR (HR = 0.66, 95%CI 0.48–0.90) was lower than one in the cohort analysis. None of the 8 outcomes with significant increase of IRs in females in the PostV period compared to PreV period (Fig. 1) was associated with the HPV2.

The sensitivity analysis by excluding municipalities with incomplete reporting of the vaccination data did not change the estimates of our HRs.

5. Discussion

This was the first safety evaluation in Finland after the HPV2 vaccine was introduced into the NVP, evaluating the risk of the pre-selected outcomes. In this nation-wide population-based cohort study, exposure to HPV2 was not associated with increased occurrence of the evaluated autoimmune diseases and other clinical syndromes.

Our results are in line with many other studies, which showed no risk for AEFIs following HPV2 vaccination in studies before licensure [20–22] and after [23–25], including large population-based cohort studies on HPV2 [6,11] and studies on quadrivalent

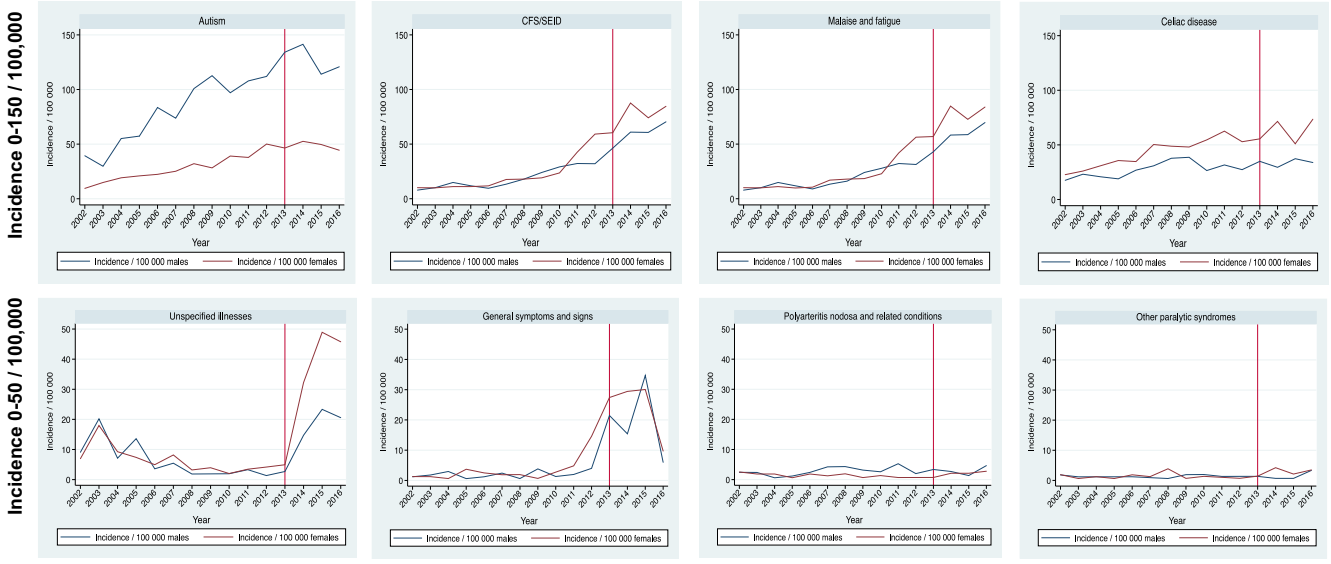

Fig. 1. Incidence rates per 100,000 person-years in females 11–15 years, Finland, 2002–2016. Outcomes (n = 8) with significant increases of the incidence rates in the post-vaccination period. Vertical line indicates year 2013 when HPV vaccination was introduced in the national vaccination programme in Finland.

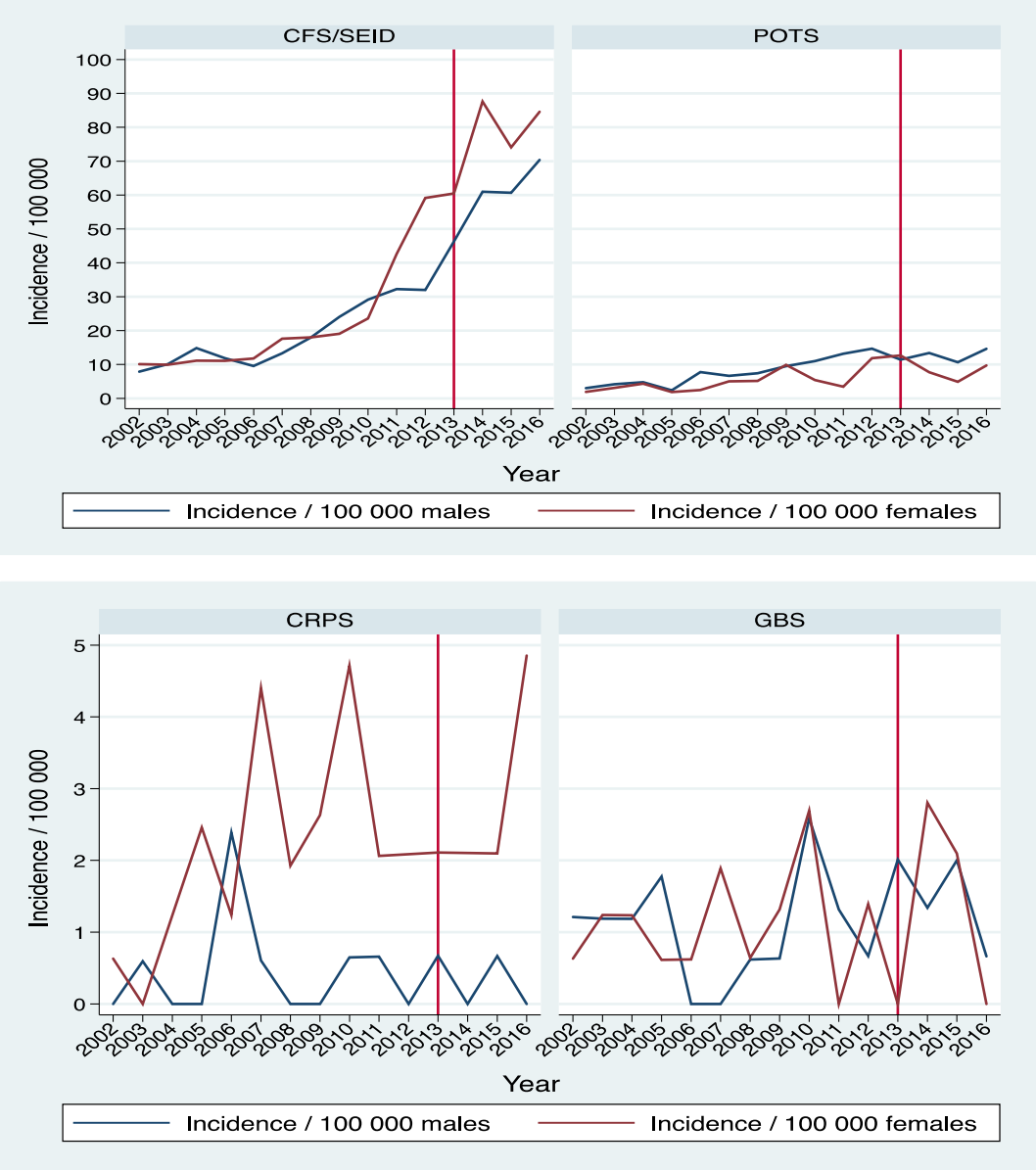

Fig. 2. Incidence rates per 100,000 person-years of Guillain-Barré syndrome (GBS), Complex Regional Pain Syndrome (CRPS), Chronic Fatique Syndrome /Systemic Exertion Intolerance Disease (CFS/SEID) and Postural Orthostatic Tachycardia Syndrome (POTS) in females and males of 11–15 years, years 2002–2016.

(HPV4) vaccine [10,26–27]. However, although multiple studies and reviews by the EMA [8] and the WHO [7] confirm the safety of HPV vaccines, due to limited evidence, the causal link is still being discussed [28–29]. Two French studies have found an association of GBS with the HPV4 vaccine [6,11], while others did not [30–31]. In our study, only a low number of GBS cases was detected. The results were statistically non significant, but after more than 365 days the adjusted HR was substantially increased, but with very wide 95%CIs: (HR = 32.17, 95%CI 1.59–652.4). The period during which any true increase would be expected is in the first 6–8 weeks after the vaccination.

Some studies reported association of HPV vaccines with the CFS/SEID [2,32], CRPS [33] and POTS [2,32–34], while others, in line with our results, did not [35–37]. The CFS/SEID was negatively associated with the HPV2 in our study.

A major strength of this study was that we included individual level data of the entire population in Finland with data from all hospitals in Finland and thus reduced the risk of selection bias. Furthermore, the national health insurance assures equal access to care for all Finnish citizens and persons permanently residing in Finland. We took the whole history of the subjects into account as we included only the first incident life-time occurrence of the diagnosis. The HILMO and NVR registers are considered close to complete due to the mandatory reporting and because HPV2 are administered through the public school-based system. Some subjects without vaccination records, and considered unexposed in this study, may have been vaccinated in the private health care before the NVP, or could be missed due to incomplete reporting. After the NVP, it is highly unlikely that females eligible for the free NVP would pay for the expensive vaccination; this is supported by our sensitivity analysis excluding subjects from municipalities with incomplete reporting which did not change the results.

We also evaluated baseline sex-specific incidence rates of a large number of outcomes (n = 65). Although increases of the IRs for some outcomes after the HPV2 introduction were observed, no significant association with HPV2 was found in the cohort study. Therefore, these increases most likely happened due to other causes, by changes in the diagnostic practices or by chance alone.

Table 1
Characteristics of females of age 11–15 years eligible for HPV vaccination through the Finnish national vaccination programme in the period 1 November 2013 to 31 December 2016, N = 240 605.

	Received HPV vaccine		Not received HPV vaccine	
	n	%	n	%
Females eligible for vaccination	134,615	100	105,990	100
Age (years) at first vaccine dose, mean, y (SD)	12.9 (1.21)	–	–	–
Age				
11	9885	7.3	–	–
12	58,898	43.8	–	–
13	23,305	17.3	–	–
14	22,534	16.7	–	–
15	19,993	14.9	–	–
Birth cohort				
1997	225	0.2	4465	4.2
1998	17,900	13.3	12,186	11.5
1999	18,861	14.0	11,033	10.4
2000	19,155	14.2	10,059	9.5
2001	19,102	14.2	9939	9.4
2002	20,313	15.1	8279	7.8
2003	20,073	14.9	9324	8.8
2004	18,878	14.0	10,866	10.2
2005	108	0.1	29,839	28.2
1st dose by year[a]				
2013	20,597	15.3	–	–
2014	69,698	51.8	–	–
2015	22,139	16.4	–	–
2016	22,181	16.5	–	–
Number of doses			–	–
1st	134,615	100	–	–
2nd	111,897	83.1	–	–
3rd	103,027	76.5	–	–
Country background				
Finnish	128,645	95.6	96,079	90.6
Non-Finnish	5970	4.4	9911	9.4
University hospital district				
HUS (Southern Finland)	49,605	36.9	32,437	30.6
KYS (Eastern Finland)	22,267	16.5	12,550	11.8
OYS (Northern Finland)	16,776	12.5	17,973	17.0
TAYS (Central Finland)	28,291	21.0	26,131	24.7
TYKS (Western Finland)	17,363	12.9	12,675	12.0
Unknown	313	0.2	4224	4.0
Number of hospital visits[b]				
0	95,846	71.2	75,061	70.8
1	14,313	10.6	10,847	10.2
2	7036	5.2	5540	5.2
3–4	7224	5.4	5540	5.2
5–6	3242	2.4	2625	2.5
7 or more	6954	5.2	6377	6.0
Number of primary healthcare visits[c]				
0	0	0	0	0
1	9594	7.1	5664	5.3
2	13,023	9.7	9382	8.9
3–4	24,611	18.3	19,163	18.1
5–6	16,859	12.5	13,746	12.9
7 or more	70,528	52.4	58,035	54.8

[a] Year 2013 includes 1 November 2013 to 31 December 2013.
[b] Registered in HILMO 2 years prior females were 11 years old.
[c] Registered in AvoHILMO 2 years prior females were 11 years old.

The limitation of this study is that the register data were not validated; we used routine vaccination data and diagnoses as set by the treating physicians. However, we consider the exposure data, i.e. vaccinations, highly specific, with a low number of false positives. On the other hand, for the outcome data we have probably some misclassification including both false positive and false negative outcomes. Especially the ill-defined syndromes (CFS/SEID, CRPS, POTS) with overlapping clinical features can be underreported because these are misdiagnosed or not diagnosed at all. To be as precise as possible in the selection of the ICD-10 codes for these outcomes, we had multiple discussions on the use of codes with the Finnish clinicians. We decided for a broad definition to identify cases in a sensitive manner to ensure adequate number of cases and to evaluate the public health impact of the potential adverse outcomes. Therefore, we also included the ICD-10 codes from the R-chapter with symptoms without specific diseases codes. Misclassification of the outcome may thus result in false positive diagnoses which may mask true associations due to poor specificity of the outcome. All the HRs for the ill-defined syndromes were below one, and therefore any misclassification should be major to mask any potential true association. While for most of the diagnoses any potential misclassification is likely symmetric

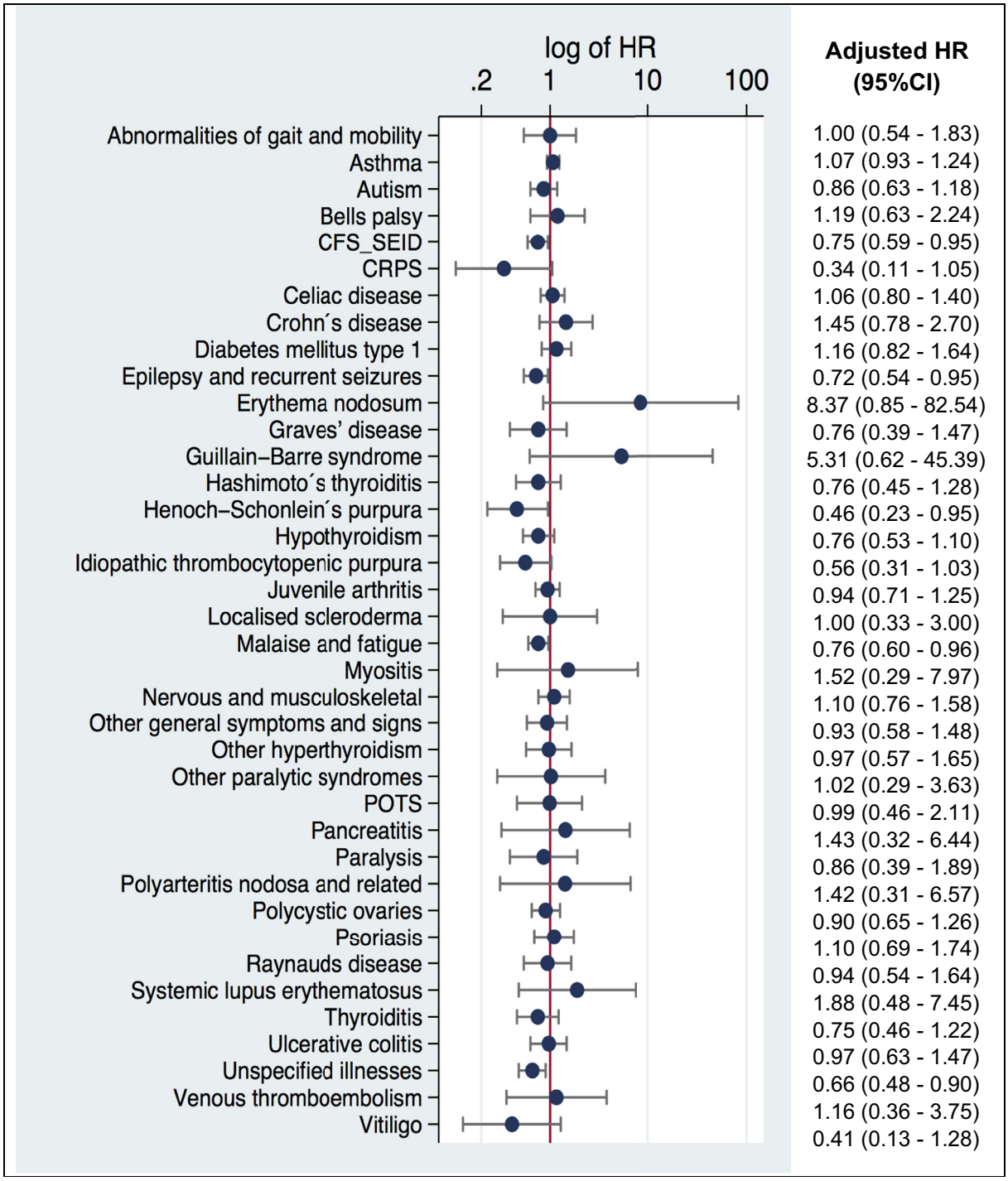

Fig. 3. Association between HPV vaccine and 38 outcomes, overall adjusted hazard ratios (HRs) with 95% confidence intervals (95%CI) in females of age 11–15 years in Finland, November 2013 to December 2016.

between the vaccinated and non-vaccinated, the above-mentioned ill-defined syndromes have been associated with vaccinations by the media, and therefore, vaccinated subjects might have been diagnosed more commonly with these syndromes resulting in false positive results due to bias; however, this was not observed in our results.

Another limitation was that the less severe cases diagnosed and treated in the outpatient settings only were missed. We did not include primary care data because the diagnostic coding was not consistent (both ICD-10 codes and ICPC-2 codes have been used) during the follow-up periods across the country and it did not include the private outpatient care.

In vaccine safety studies it is important to consider also the previous medical history of the subjects [38]. We observed that females with more frequent hospital and primary healthcare visits were less likely to be vaccinated, in line with the Norwegian study [35], although the proportions of visits between the vaccinated and non-vaccinated were not very different. Those with unexplained or serious illness might more likely object to the vaccination, which may result in the healthy vaccinee bias [39]. We observed 5 of

38 outcomes inversely associated with the HPV2, a phenomenon reported also elsewhere [10,23]. The observed reduced risk among the HPV2 vaccinated females might have happened because they might have had better baseline health or healthier lifestyle. We aimed to reduce the healthy vaccinee bias by adjusting for the number of hospital visits. In addition, we adjusted our estimates for the baseline factors, including age and hospital geographic area. However, inclusion of primary healthcare visits was not included in the model as it did not affect the estimates. Additional adjustments might reduce potential confounding further, but we did not have individual data on these. Additionally, we excluded the subjects diagnosed with the outcome of interest before the study follow-up. This should reduce the probability of healthy vaccinee bias, although the incident cases might have had other prior diagnoses which might also cause healthy vaccinee bias despite adjustment for prior hospital visits. As in any observational study, residual confounding may be present. We did however use the best available information on healthcare utilization (Finnish national hospital discharge register), which includes all inpatient and outpatient visits in all Finnish hospitals. A true protective effect may be possible [40] although, to date, the findings about the non-specific effects of vaccines are controversial after live vaccines and have been observed mainly for infectious diseases [41].

The associations found could be also due to the alfa error because of multiplicity testing bias [42], which was unavoidable because we studied so many outcomes. We tried to reduce the bias by using Wald (simultaneous tests) for different periods after vaccination but did not use the Bonferroni correction because it may result in too conservative estimates [43] and could hide some weak signals that we aimed at finding in this explorative analysis. On the other hand, most of the outcome event numbers were small resulting in inadequate power to detect any potential true associations. Therefore, we need to await further accumulation of follow-up data.

6. Conclusions

No significant association between the bivalent HPV vaccine and risk of multiple AEFIs was observed. This large nationwide study supports other studies on the safety of the HPV vaccination and conclusions made by EMA [12] and WHO [11]. Our results can serve as a source of information for communication by the Finnish public health authorities to improve public acceptance of the vaccination and consequently contribute to higher HPV immunization coverage and lower HPV-related disease burden in Finland.

Conflict of interest statement

Authors are employed by National Institute for Health and Welfare which has received research funding from GlaxoSmithKline and Pfizer, Inc. AAP and ER are co-investigators in these studies.

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Authorship/Contributions

Jozica Skufca have made contributions to design of the study, analysis of the data and drafting the article. Miia Artama, Arto A. Palmu and Hanna Nohynek have made substantial contributions to the conception and design of the study. Jukka Ollgren made substantial contributions to analysis of data and Esa Ruokokoski to acquisition of data. All authors contributed to the interpretation of the results, revising the manuscript for important intellectual content, and accepted the submission for publication. Therefore, we need to await further accumulation of follow-up data to get more information on the associations.

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