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Research paper

Quadrivalent human papillomavirus vaccination and non-targeted infectious disease hospitalisation: Population-based self-controlled case series analysis

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SUMMARY

Background: Claims of non-live vaccines having deleterious effects on non-targeted infectious disease and mortality among females persists. The majority of the available evidence is from West Africa and consists of observational studies and the interpretation and implications are controversial. Results from high-income countries have been conflicting. We evaluated the association between a human papillomavirus vaccine, a non-live vaccine primarily administered to pre-adolescent females, and non-targeted infectious disease in a high-income country.

Methods: We constructed a nationwide cohort of all Danish females 10 to 29 years of age during 2007 to 2016 with information on quadrivalent human papillomavirus vaccination status and infectious disease hospital contacts using national registers. Nested in this cohort, we conducted a self-controlled case series (SCCS) analysis comparing the rates of hospitalisation in a 90-day main risk period following the latest vaccination to reference period rates with adjustment for age and season.

Findings: We included 853,879 Danish-born females aged 10 to 29 years of age during the 2007 to 2016 study period in the study cohort. We identified a total of 65,293 infectious disease hospitalisations among 50,599 participants; 46,955 cases among 37,003 participants vaccinated during follow-up were included in the SCCS analysis. There was no statistically significantly increased risk of infectious disease hospitalisation in the 90-day main risk period (rate ratio 0.92, 95% CI 0.88 to 0.95).

Interpretation: Reassuringly, our large well-controlled study does not support that human papillomavirus vaccination increases the risk of non-targeted infectious disease in any clinically meaningful way. While our study does not provide evidence against adverse effects of other non-live vaccines, it does provide evidence against the claim that all non-live vaccines increase risk of heterologous infections in females.

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1. Introduction

It has been suggested that non-live vaccines increase the susceptibility of females to non-targeted infections [1]. Today, non-live vaccines are widely used and the majority of modern vaccine development focuses on non-live vaccines. Thus, the claim of increased risk of non-targeted infections following commonly used vaccines has significant implications for global health. One of the earliest observations of potential detrimental effects of non-live vaccines was a report from Guinea-Bissau in West Africa. Kristensen and colleagues observed 72% increased mortality among children vaccinated with the diphtheria-tetanus-whole cell pertussis (DTwP) vaccine compared to unvaccinated children [2]. In a recent systematic meta-analysis of vaccines and childhood mortality, 17 studies evaluating DTwP vaccination was identified [3]. Seven studies were excluded due to "very high risk of bias", and the meta analysis of the remaining 10 studies yielded a mortality rate ratio of 1.38 (95% confidence interval, 0.92-2.08). The selection of which studies to include have been challenged. In a reanalysis of 8 of the 17 studies, a mortality rate ratio of 2.00 (95% CI, 1.50-2.67) was reported [4]. Similar controversy exist with respect to whether a possible risk is more pronounced in females. The 2016 meta-analysis reported a male:female ratio of relative risks of 0.72 (95% CI, 0.46-1.14) [3]. Among children with DTwP as their last vaccine, other researchers reported a female:male ratio of 1.53 (95% CI, 1.21-1.93) [5]. Other non-live vaccines have been linked to increased mortality in females, but this has primarily been

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Research in context

Evidence before this study

A new paradigm for vaccinology which incorporates non-specific effects of vaccines to a greater degree has been proposed (Lancet Infect Dis. 2020 Oct;20(10):e274-e283). One of the so-called emerging principles of this paradigm is the claim of deleterious effects in females of non-live vaccines. The majority of evidence on non-specific effects of vaccines, including non-live vaccines, comes from observational studies of mortality in low-income countries. In a 2016 systematic review (*BMJ*. 2016;355: i5170), clinical trials and observational studies on the association between BCG, DTP and measles containing vaccines and childhood mortality were identified. Sixty-eight articles reporting results from 34 birth cohorts were reviewed. The conclusion for DTP was that the vaccine may increase all-cause mortality and that this non-specific effect may be more pronounced in females. However, no increase and no female: male difference were also compatible with the results and could not be discounted with any certainty. To identify articles reporting studies on vaccination and nontargeted infectious disease, we searched PubMed for the following terms "vaccination nontargeted infectious disease" and "vaccination 'non-specific effects' infections" which revealed a number of studies of vaccination and non-targeted infectious diseases in high-income countries. However, none of these studies was on human papillomavirus vaccination. We did identify a recent systematic review of MMR vaccination and infectious disease hospitalisation in high-income countries; 3 studies of MMR vs DTaP as the latest vaccine and 2 studies of MMR alone vs. MMR+DTaP together (Human Vaccines & Immunotherapeutics. 2020; 16:3, 490-498). DTaP may increase risk or MMR may reduce risk, however, the risk of bias was high in all of the included studies.

Added value

Ours is the first study of a human papillomavirus vaccine and non-targeted infectious disease. The human papillomavirus vaccine is a subunit vaccine administered primarily to pre-adolescent girls. Thus, our finding of no clinically meaningful association does not support a paradigm encompassing the idea that all non-live vaccines increase susceptibility to infections in females.

Implications

The claim that all non-live vaccines enhance susceptibility to unrelated infections in females is of great concern. Non-live vaccines are used extensively in both low-, middle- and high-income countries around the world, and the global health impact would be devastating if this claim was true. It is of vital importance to vaccination programs and to global health, that such hypotheses are tested. Our study does not rule out that other non-live vaccines increase risk of heterologous infection. We need more studies of non-specific effects of different non-live vaccines, from diverse settings around the world and from different research groups.

in the form of re-analyses of studies not originally designed to test such hypotheses [1]. These observations from low to middle-income countries, where childhood mortality is high and infectious disease morbidity is significant, does not necessarily translate directly into deleterious effects in high-income countries due to much lower infectious disease mortality. Observations from high-income countries on deleterious effects in the form of non-targeted infectious disease susceptibility are rarer and conflicting [6]. The human papillomavirus (HPV) vaccines are non-live adjuvanted vaccines based on virus-like particles primarily administered to pre-adolescent girls [7]. While there is no evidence that HPV vaccines increase susceptibility to non-targeted infectious disease in females, no studies have, to the best of our knowledge, been conducted. However, to maintain public and professional support in vaccination, any safety concerns must be addressed rigorously. In particular, HPV immunization programs have struggled with suboptimal uptake in many countries due to spurious safety concerns perpetuated by both social- and professional media [8,9]. Since the HPV vaccine effectively protects against cervical cancer [10]. the obvious implications of spurious safety concerns are needless suffering and loss of lives. In this study, we addressed the concern that the quadrivalent HPV (qHPV) vaccine, a non-live vaccine, increases the risk of non-targeted infectious disease susceptibility in females. We conducted a self-controlled case series (SCCS) study [11] of the association between the qHPV vaccine and non-targeted infectious disease hospitalisation nested in a nationwide cohort of Danish females aged 10-29 years in 2007-16.

2. Methods

2.1. Study cohort

Since 1968, all Danish inhabitants have been assigned a unique person identifier which is used in national administrative, demographic and health registers [12]. This allows for the creation of large nationwide cohorts with individual-level and longitudinal information on relevant exposures, outcomes and covariates. We took advantage of these opportunities to construct a study cohort of all Danish-born females 10-29 years of age in the study period 2007-2016 with information on HPV vaccination status and possible hospitalisations due to infectious diseases. The study was approved by the Danish Data Protection Agency (internal compliance journal number, 21/00893). Ethical approval is not required for register-based research in Denmark.

2.2. Vaccination

The qHPV vaccine (Gardasil®, Merck Sharp and Dohme) has been available for purchase in Denmark since late 2006. It was introduced in the free Danish childhood immunization program for 12- year old girls in January 2009. Catch-up vaccination of 13-15 year-old girls preceded this introduction in October 2008 and was later also offered to 20-27 year-old women in August 2012 (corresponding to the 1985-1992 birth cohorts). A 3-dose schedule was originally used with the second and third doses administered 2 and 6 months, respectively, after the first dose. A 2-dose schedule was later introduced in August 2014 for girls given the first dose at 12-13 years of age. The bivalent vaccine (bHPV, Cervarix®, GlaxoSmithKline) replaced the quadrivalent vaccine in February 2016. We obtained information on dates of HPV vaccination in the study cohort from the Danish vaccination register [13]. This register comprises both HPV vaccinations administered as part of the free national childhood immunization program and HPV vaccinations privately purchased and administered outside of the program for individuals not eligible for the national program. However, the large majority of the HPV vaccinations in our study are from the national program ensuring a high degree of completeness since general practitioners, who are responsible for the program vaccinations, must report to ensure reimbursement of costs.

2.3. Infectious disease hospitalisation

Study outcomes in the form of infectious disease hospitalisation was ascertained from the Danish National Patient Register [14]. This register comprises individual-level information on hospital contacts. Assigned diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10). We did not include contacts for ambulatory care or emergency department visits. We included information on 'upper respiratory infections', 'lower respiratory infections', 'gastrointestinal infections' and 'other infections' – see Supplementary table S1 for the specific ICD-10 codes used. Both primary and secondary diagnoses were considered. Date of admission was used as the event date. Each study cohort participant could contribute with more than one study outcome hospitalisation. We defined a new hospitalisation as one that occurred at least 2 days after the latest discharge date. The time between admission and discharge was excluded.

2.4. Statistical analysis

We followed study cohort participants from age 10 or 1 January 2007, whichever event came later, until age 30, 1 January 2017, emigration, death or disappearance from the registers, whichever event came first. We censored participants receiving other HPV vaccines than the qHPV vaccine at the date of vaccination. Vaccination with 1, 2 or 3 doses of qHPV vaccine was considered a time-varying variable. Our primary outcome was any infectious disease hospitalisation. Secondary outcomes were 'upper respiratory infections', 'lower respiratory infections', 'gastrointestinal infections' and 'other infections'. From the resulting number of cases and follow-up we estimated incidence rates of infectious disease hospitalisation according to age, calendar period, season and time since the latest vaccination.

We conducted a SCCS analysis [11] of the association between qHPV vaccination and infectious disease hospitalisation among all infectious disease hospitalisations occurring among participants vaccinated during follow-up in the study cohort. SCCS analysis has been widely used in vaccine safety research for the study of hypotheses of acute or short-term effects of vaccination. The main benefit of the method is the self-controlling aspect, whereby time-periods are compared within study participants eliminating the need to adjust for confounders, which do not vary during the study period such as many lifestyle- and socioeconomic factors or comorbidity [15]. We predefined a main risk period of interest as the first 90 days after the latest vaccination. Thus, each case could contribute up to 270 days of follow-up to the main risk period (if vaccinated three times). We refer to Figure S1 for schematic representation of how follow-up time is partitioned for our SCCS analysis. Risk period status was assessed chronologically with the current exposure taking precedent in the case of potential overlapping. We used conditional Poisson regression to estimate incidence rate ratios with 95% confidence intervals according to vaccination status. In the main risk period analysis the referent group comprised unvaccinated follow-up and follow-up occurring more than 90 days after the latest vaccination. Since individuals are unlikely to adhere to a vaccination appointment if sick, we excluded the 7 days preceding a vaccination. We also excluded time spent hospitalized due to a study outcome, since another study outcome cannot occur in this period by design. We adjusted rate ratios for age (1-year categories) and season (1-month categories).

A number of assumptions must be fulfilled for the SCCS method to provide valid estimates in our setting [16]. Study outcomes should not be associated with mortality and should not influence the future risk of exposure. To investigate the validity of the first assumption we plotted frequencies of outcomes against days since diagnosis in the actual study and days since diagnosis in the study without right censoring. To investigate the validity of the second assumption, we plotted the number of outcomes per 100,000 vaccinated study participants according to time before and after vaccination.

We also estimated incidence rate ratios using Poisson regression in the full study cohort with the same age and season adjustment as in the SCCS analysis.

Statistical analyses and data management were conducted using R version 4.0.2 (R Core Team, 2020). We used the SCCS package available from https://cran.r-project.org/web/packages/SCCS/index.html for the SCCS analyses.

2.5. Role of funding agency

The funding body had no role in the study design; collection, analysis, and interpretation of the data; writing of the manuscript; or the decision to submit it for publication. All authors are independent from the funding agencies.

3. Results

We included 853,879 Danish-born females aged 10 to 29 years of age during the 2007 to 2016 study period in the study cohort. Study participants were followed for 5,887,092 person-years. During the study, 13,496 participants were lost to follow-up (12,444 due to emigration, 962 due to death, 90 due to unexplained disappearance from the national registers) and 11,330 were censored at the time of vaccination with HPV vaccines other than the qHPV vaccine. In the study cohort, 502,269 participants were vaccinated with 1,344,915 doses of qHPV vaccine. In girls aged 10-17, qHPV vaccines were administered at a median age of 12.9 years (Interquartile Range [IQR], 2.0) and in women aged 18-29, vaccines were administered at a median age of 23.9 (IQR 4.2). We identified a total of 65,293 infectious disease hospitalisations among 50,599 participants. 'Other infections' were the most common cause of hospitalisation (n=30,131 hospitalisations) followed by 'upper respiratory infections' (n=19,557), 'lower respiratory infections' (n=8,862) and 'gastrointestinal infections' (n=8,406).

For all four categories of infectious diseases, the youngest participants had the lowest incidence rates (Fig. 1). 'Other infections' peaked around the age of 18, 'upper respiratory infections' at 17, 'lower respiratory infections' at 29 and 'gastrointestinal infections' at the age of 25 years (Fig. 1). Marked seasonal changes in rates were observed for 'gastrointestinal infections' peaking during summer and 'upper'- and 'lower respiratory infections' peaking during winter (Fig. 1). Rates of 'lower respiratory infections' varied to a greater degree according to study year than the other outcomes (Fig. 1). Rates according to time since vaccination showed no pattern of increases in the immediate periods following vaccination (Fig. 1).

In the full study cohort of 853,879 females, the incidence rate ratio for all infections was 0.89 (0.85 to 0.93) comparing the main risk period to the referent period.

In the SCCS analysis, 37,003 study participants vaccinated during follow-up experienced 46,955 hospitalisations. Among participants, only 1.5% had a hospital contact for cancer, diabetes, or juvenile arthritis in the 5 years before study start. In the main risk period, 2496 hospitalisations occurred during 21,965 person-years of follow-up. A total of 230.2 person-years of follow-up, corresponding to 0.07% of all follow-up in the study, constituted time between admission and discharge, and was excluded. Vaccinated follow-up was primarily from girls and younger women (Fig. 2). There was no statistically significantly increased risk of infectious disease hospitalisation in the main risk period (rate ratio0.92, 95% CI 0.88 to 0.95) (Table 1). There was no dose-specific differences in this effect – p=0.71 for a test of homogeneity of the main risk period estimate for the 1st, 2nd and 3rd dose. Similarly, no increased risks were observed for 'upper respiratory infections' (rate ratio 0.94, 95% CI 0.87 to 1.01), 'lower respiratory infections' (0.85, 0.75 to 0.96), 'gastrointestinal infections' (0.89, 0.79 to 1.01) and 'other infections' (0.92, 0.86 to

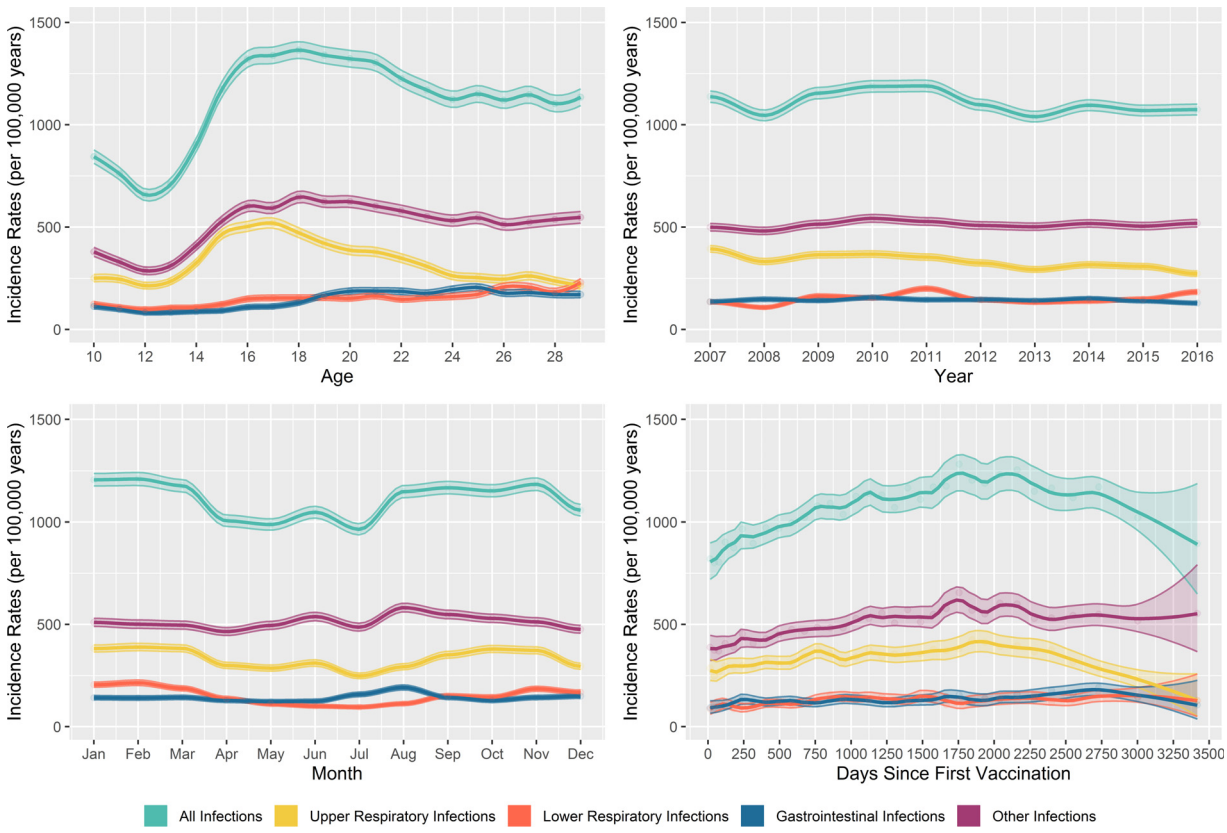

Fig. 1. Line plots (smoothed using local polynomial regression) of infectious disease hospitalisation rates according to age, calendar year, month, and days since first quadrivalent human papillomavirus vaccination among Danish females 10 to 29 years of age during 2007 to 2016.

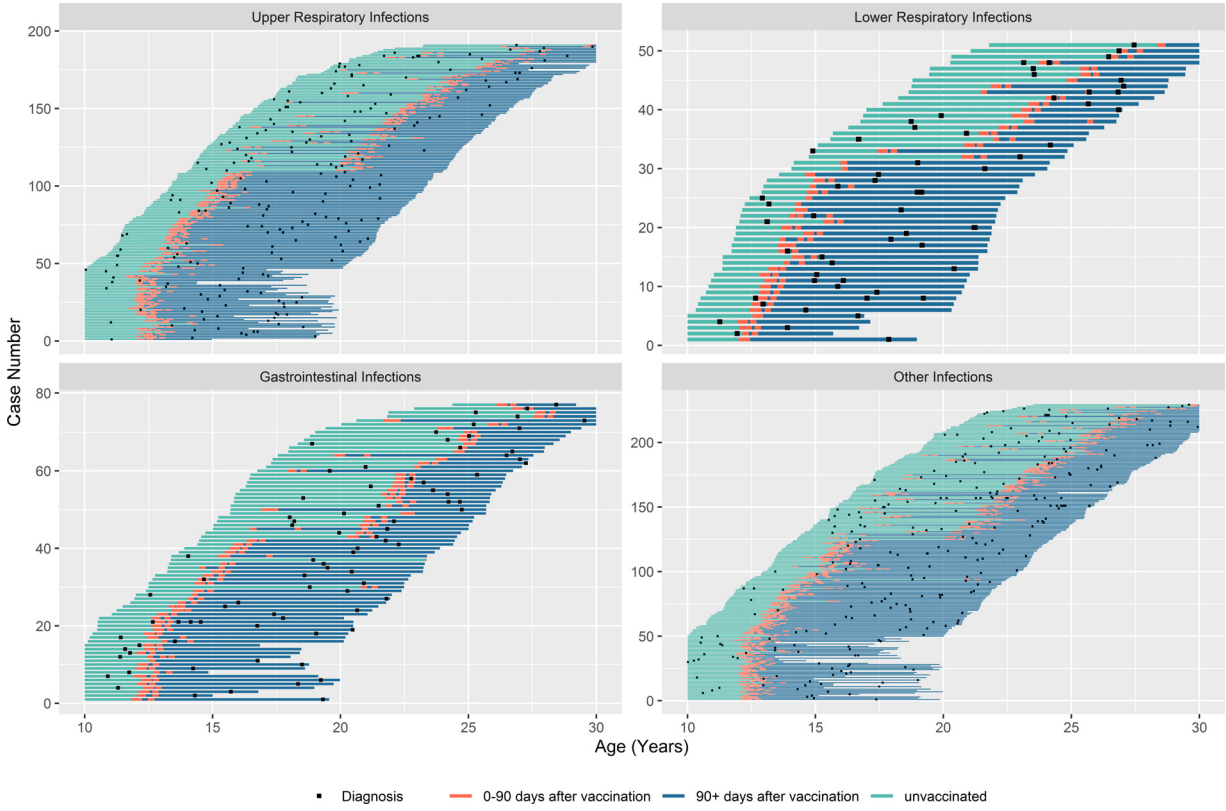

Fig. 2. Infectious disease hospitalisation- and quadrivalent human papillomavirus vaccination history among Danish females 10 to 29 years of age during 2007 to 2016 with at least one infectious disease hospitalisation (750 randomly sampled individuals out of 37,003). Each line represents the time spent in the study for one participant colored according to vaccination history and with black dots representing the timing of the hospitalizations that the participant has contributed to the SCCS analysis.

Table 1
Self-controlled case series analysis of quadrivalent human papillomavirus vaccination and rate of infectious disease hospitalisation among Danish females 10-29 years of age in 2007-2016.

Risk Period	Number of cases	Person-Years	Crude Rate Ratio (95% CI)	Adjusted* Rate Ratio (95% CI)
Any Infections				
Reference period†	44349	320473	1 (Reference)	1 (Reference)
0-90 days after vaccination	2496	21965	0.80 (0.77-0.83)	0.92 (0.88-0.95)
Upper Respiratory Infections				
Reference period†	14382	118755	1 (Reference)	1 (Reference)
0-90 days after vaccination	846	8164	0.83 (0.78-0.89)	0.94 (0.87-1.01)
Lower Respiratory Infections				
Reference period†	5120	35706	1 (Reference)	1 (Reference)
0-90 days after vaccination	281	2460	0.78 (0.69-0.88)	0.85 (0.75-0.96)
Gastrointestinal Infections				
Reference period†	5556	47602	1 (Reference)	1 (Reference)
0-90 days after vaccination	314	3237	0.81 (0.72-0.91)	0.89 (0.79-1.01)
Other Infections				
Reference period†	20393	151974	1 (Reference)	1 (Reference)
0-90 days after vaccination	1116	10357	0.78 (0.73-0.83)	0.92 (0.86-0.98)

* Adjusted for calendar month and age in 1-year categories.
† Comprising unvaccinated follow-up and follow-up from the period 91+ days after vaccination.

0.98) (Table 1). Since in particular upper- and lower respiratory infections vary with season in our study (Fig. 1), we conducted tests of homogeneity of effects across season for these outcomes. We found no support for the hypothesis that the main risk period effect varied according to season (p=0.40 for upper respiratory infections and p=0.20 for lower respiratory infections).

In sensitivity analyses, main risk periods of 30 or 60 days (instead of 90 days) following the last vaccination was also not associated with increased risk of infectious disease hospitalisation (rate ratio 0.91, 95% CI 0.85 to 0.97, and0.91, 0.87 to 0.95, for 30 and 60 days, respectively)(Table 2). Alternative risk periods following the first 90 days after vaccination also revealed no increased risks (Table 2). Excluding different periods immediately before and after the risk period had little impact (Table 2). No increased risk was observed when only including the first hospitalisation for each study participant (rate ratio 0.93, 95% CI 0.89 to 0.98) or when comparing the main 90-day risk period to the period 91 days or more after the latest vaccination (0.90, 0.86 to 0.94). When stratifying by age, we found no support for different main risk period estimates (test of homogeneity, p=0.46). In both girls aged 10 to 17 years and women aged 18 to 29 years, qHPV vaccination was not associated with the rate of hospitalisation in the main risk period (rate ratio 0.93, 95% CI 0.88 to 0.99 and rate ratio0.90, 0.84 to 0.95, respectively). Sensitivity analyses for each infectious disease category yielded similar results (Supplementary table S2). Considering any HPV vaccination as the exposure in contrast to qHPV only, yielded identical results, main risk period estimate for all infections, rate ratio 0.92 (95% CI, 0.88 to 0.95). Only considering primary diagnoses yielded a main risk period estimate for all infections of rate ratio 0.93 (95% CI, 0.89 to 0.98). Including possible measles, mumps, rubella vaccination in the study period as a time-varying variable in the SCCS analysis had little impact, all infections, rate ratio 0.92 (95% CI, 0.88 to 0.96). Only including admissions lasting more than 24 hours yielded an all infections, rate ratio of 0.90 (95% CI, 0.84 to 0.95). Requiring 10 days out of hospital instead of 2 days for a registration to count as a new admission, yielded an all infections, rate ratio of 0.92 (95% CI 0.88 to 0.96).

We checked the SCCS assumption that outcomes should not increase mortality by plotting frequencies of outcomes against days since diagnosis in the study and days since diagnosis in the study with no right censoring, respectively. Visual inspection revealed a

Table 2
Sensitivity analyses of the association between quadrivalent human papillomavirus vaccination and infectious disease hospitalisation among Danish females 10-29 years of age in 2007-2016.

	Number of cases	Person-Years	Adjusted* Rate Ratio (95% CI)
Main SCCS analysis of all infections	2496	21965	0.92 (0.88-0.95)
Alternative risk periods †			
0-30 days risk period after vaccination	930	8392	0.91 (0.85-0.97)
0-60 days risk period after vaccination	1814	16256	0.91 (0.87-0.95)
0-90 days risk period after vaccination	2532	22529	0.91 (0.87-0.95)
91-180 days risk period after vaccination	2675	22297	0.97 (0.93-1.01)
181-365 days risk period after vaccination	4541	36078	1.00 (0.96-1.03)
366+ days risk period after vaccination	24434	173273	1.03 (0.99-1.07)
Alternative pre- and post-exposure exclusion periods			
14 days pre-exposure excluded	2446	21377	0.92 (0.88-0.96)
14 days pre- and 14 days post-exposure excluded	2046	17591	0.93 (0.89-0.98)
7 days post-exposure excluded	2313	20065	0.93 (0.89-0.97)
0-90 days risk period after vaccination vs referent period excluding 7 days pre-exposure stratified by age			
10-17 years old	1358	12306	0.93 (0.88-0.99)
18-29 years old	1138	9659	0.90 (0.84-0.95)
0-90 days risk period after vaccination vs referent period excluding 7 days pre-exposure considering only first events	2002	21964	0.93 (0.89-0.98)
0-90 days risk period after vaccination vs referent period comprising only 91+ days after vaccination	2514	15573	0.90 (0.86-0.94)
0-90 days risk period after vaccination vs referent period excluding 7 days pre-exposure, but including time between admission and discharge	2496	21976	0.92 (0.88-0.95)

* Adjusted for calendar month and age in 1-year categories and excluding time between admission and discharge and the 7 days prior to vaccination unless otherwise stated.
† Referent period includes the 7 day pre-exposure period.

high-degree of overlap suggestive of minimal bias (Supplementary figure S2). We also checked the assumption that outcomes should not influence future vaccination propensity. In a plot of the number of outcomes per 100,000 vaccinated study participants according to time before and after vaccination, we did not observe consistent patterns suggestive of changes in vaccination propensity after outcome (Supplementary figure S3). We observed a clear dip in the incidence of lower respiratory infections in the 7-days before vaccination. However, this period is already excluded from our analyses.

4. Discussion

In a self-controlled case series analysis of 46,955 infectious disease hospitalisations we found no support for the hypothesis that qHPV vaccination, a non-live vaccine administered to females, increases the risk of non-targeted infectious diseases.

While not implausible, the biological underpinnings of non-targeted effects of vaccines are not well established [17,18]. The evidence is strongest for beneficial non-specific effects of Bacillus Calmette-Guérin in particular where cross-reactive T-cells or training of innate immunity has been put forward as explanations [19].

A recent systematic review concluded that studies of non-targeted immunological effects were heterogeneous in design and quality, and that the clinical implications were unclear due to a lack of research linking immunological variables to clinical endpoints [20].

There are no observational studies of the association between HPV vaccines and non-targeted infectious disease. However, one study on other non-specific outcomes did report a reduced risk of all-cause mortality among HPV vaccinated girls corresponding to a rate ratio of 0.52 [21]. Most vaccines used in childhood immunization schedules in high-income countries today are subunit vaccines in the form of toxoid vaccines, conjugate vaccines and recombinant vaccines. The HPV vaccines are recombinant subunit vaccines. Garly and colleagues conducted a cohort study of Hepatitis B vaccine, also a recombinant subunit vaccine, nested in a trial of measles vaccine in Guinea-Bissau [22]. The researchers observed a mortality rate ratio of 2.27 (95% CI, 1.31-3.94) associated with Hepatitis B vaccination in girls. Several studies have attempted to evaluate the effect of other commonly used subunit vaccines on off-target infectious disease hospitalisation in high-income settings with conflicting results. Two Danish studies have reported increased risks of infectious disease hospitalisation after the third dose of diphtheria-tetanus-acellular pertussis vaccine both as the last vaccine received and together with measles-mumps-rubella vaccination [23,24]. However, in another Danish study, no increased risks of infectious disease hospitalisation in the three months following vaccination with non-live vaccines was observed [25]. These Danish studies differ in analytical approaches and where the Sørup studies mainly compares schedules, the Hviid study compares vaccinated and unvaccinated children with direct adjustment for other vaccinations. Children not adhering to the recommended schedule or unvaccinated children are likely selected populations, a limitation for all three Danish studies. However, the Hviid study did take advantage of changes in the schedule during the study period, and utilized both children unvaccinated by choice and by study design. Furthermore, Danish researchers have reported reduced mortality for more doses of the DTaP vaccine received compared with fewer [26]. In a U.S. study evaluating live vaccines and non-live vaccines, infectious disease hospitalisation risk was lower following vaccination with live vaccines than following non-live vaccines [27]. However, a Dutch study reported a protective effect of receiving a fourth DTaP vaccine compared to three, and a self-controlled case series study from England reported no increased risk among children receiving MMR vaccine together with an inactivated vaccine compared to children receiving MMR alone [28,29].

We utilized the self-controlled case series design nested in a large nationwide cohort with independent ascertainment of vaccinations and hospitalisations. The nationwide cohort reduces concern about selection and recall bias and the self-controlling nature of the case series reduces concerns about confounding by eliminating all time-invariant confounding. We cannot completely discount time-variant confounding if healthcare seeking behavior or admission thresholds vary with time. However, HPV vaccination status is unlikely to be associated with changes in healthcare seeking behavior or admission thresholds in individual study participants.

We chose a main risk period of 90 days. The choice of a relatively short risk period in contrast to an unvaccinated vs vaccinated comparison allows for better capture of acute deleterious effects. Many of the previous studies have relatively short follow-up in the 90 days to 12 mo. range [3,19]. However, risk periods following the first 90 days after the last vaccination, also did not reveal any increased risks suggesting no negative long term effects either. We utilized hospitalisations as study outcomes, which will capture infectious diseases of a more serious nature that are not readily handled by the general practitioner and are admitted to the hospital setting for diagnosis, observation or treatment. Thus, we cannot exclude that the qHPV vaccine is associated with increased risk of less serious infectious disease outside of the hospital setting. We included both primary and secondary diagnoses. Consequently, we included infections, occurring in subjects with primary diagnoses unrelated to infections, which would not normally themselves be sufficient cause for admission. However, HPV vaccination is unlikely to be related to other primary diagnoses than those related to HPV infection. We included both children and adults in our study in contrast to many previous studies, which have included only infants and toddlers. HPV vaccines are not used in the youngest children, and we cannot exclude that deleterious effects only occur in age groups not included in our study. However, in age-stratified analyses, there was no support for an increased risk in 10 to 17 year old females in our study. We did observe reduced risks of several study outcomes in the main risk period. Although we cannot exclude a casual effect, another possible explanation for these findings are a possible increased probability of being vaccinated following hospitalisation.

Claims of serious deleterious effects of non-live vaccines, especially when administered to females, have persisted for several decades. Non-live vaccines are used all over the world and the public health impact would be devastating if these claims were true. However, most of the observational research supporting deleterious effects comes from West Africa and caution is warranted in the interpretation of these studies [30–32]. Reassuringly, our large well-controlled study of a non-live vaccine in the form of qHPV vaccine administered to females in a high-income country does not support that qHPV vaccination increases the risk of non-targeted infectious disease in any clinically meaningful way and consequently does not support the claim that all non-live vaccines increase risk of heterologous infections in females.

Contributors

AH conceived and supervised the study. AL conducted the statistical analyses. AH obtained data and funding. AH drafted the original Article. AL contributed to the editing of the Article. All authors read and approved the final Article. AH and AL both had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

The data consists of personal histories of health events, which we cannot share due to privacy concerns.

Declaration of Interests

We declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100189.

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