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High seroprevalence of multiple high-risk human papillomavirus types among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands

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ABSTRACT

Background: Incidence and mortality of human papillomavirus (HPV)-related cancers differs geographically, with high rates in Caribbean countries. Seroepidemiological data provide information on lifetime cumulative HPV exposure and contributing risk factors, but has not been available yet for Caribbean Netherlands (CN), comprising the islands Bonaire, St. Eustatius and Saba. Therefore, a cross-sectional population-based serosurveillance study was performed in this (recently girls-only HPV-vaccinated) population in 2017.
Methods: Blood samples from participants (n = 1,823, 0–90 years) were tested for seven high-risk (hr)-HPV-specific IgG-antibodies using a VLP-based multiplex-immunoassay. Risk factors for HPV-seropositivity were analysed among persons unvaccinated aged $\geq$ 15 years who ever had sex (n = 1,080).
Results: Among unvaccinated individuals aged $\geq$ 15 years, overall seropositivity was high (34%), with over half of them being seropositive for $\geq$ 2 hr-HPV types, and HPV16 and 52 being most prevalent (13%). Seroprevalence was substantial higher in unvaccinated women (51%) than men (18%), predominantly peaking in women aged 20–59 years, and was highest on St. Eustatius (38%). Besides age and sex, sexual risk factors were associated with HPV-seropositivity.
Conclusions: In accordance with the Caribbean region, seroprevalence of multiple hr-HPV types was high in CN. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted pathogen in men and women worldwide, approximately infecting 80% of people at some time. Over 200 different HPV genotypes have been identified, of which 40 can infect the genital tract [1]. Persistent infection with high-risk (hr)-HPV types can lead to anogenital- and oropharyngeal cancers, of which cervical cancer is the most prevalent. Annually, 680,000 HPV-related cancers are estimated to occur worldwide, including 570,000 cervical cancer cases [2]. Hr-HPV types 16 and 18 are mostly detected in women and thereby responsible for 70% of all cervical cancer cases [3].

Incidence and mortality of HPV-related diseases differ geographically. For cervical cancer this can largely be explained by presence of organized prevention programs. Caribbean countries, that mostly lack vaccination and cervical cancer screening programs, have a higher than world average incidence and mortality

Abbreviations: (a)OR, (adjusted) odds ratio; *BMI*, body mass index; *CI*, confidence interval; *CN*, Caribbean Netherlands; *GMC*, geometric mean concentration; *HPV*, Human papillomavirus; *hr*, high-risk; *IQR*, interquartile range; *IU*, international units; *ln*, natural logarithmic; *LU*, Luminex units; *METC*, Medical Ethics Committee; *PIVA-V*, population registry of the Dutch overseas territories; *Ref*, reference category *RIVM*, National Institute for Public Health and the Environment of the Netherlands; *STD*, sexual transmittable disease(s); *VLP*, virus-like-particle.

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rate with 15.2 and 8.5 per 100,000, respectively, whereas, e.g., in Western Europe this is below average with 6.8 and 2.1 per 100,000, respectively [2,4,5]. In Caribbean Netherlands (CN) – consisting of the three Dutch overseas municipalities Bonaire, St. Eustatius and Saba, comprising a diverse ethic population of ~ 25,000 people – HPV-vaccination has been included in the National Immunization Program since 2013. The quadrivalent vaccine was introduced on St. Eustatius and Saba in 2013, and bivalent vaccine on all three islands in 2015 (two doses for girls aged 9/10 years of age), with coverage in 2018 ranging between 28 and 67% across islands [6]. A population-based cervical cancer screening program, however, has not been introduced in CN thus far.

Insight into the population-based HPV serostatus provides information on age- and sex-specific lifetime cumulative HPV exposure and past infections of (vaccine-relevant) circulating genotypes, and can be linked to contributing risk factors. Moreover, these insights can serve as a guide for policymakers in their development of future HPV preventive programs, such as consideration of a population-based cervical cancer screening or as a baseline for future evaluation of the vaccination program. For instance, by estimating vaccine uptake (since vaccine-induced antibody levels are far higher than after natural infection), and monitoring changes in epidemiological dynamics of HPV infection after vaccination, including (indirect) herd effects in those ineligible for vaccination (by comparing age- and gender-specific serological profiles pre- and post-vaccination) as well as impact on other HPV types by the vaccine used (cross-protection/replacement) [7]. However, such data have not been available for CN yet; hence, by means of a representative serosurveillance study conducted in this (recently girls-only HPV-vaccinated) population in 2017 for the first time, we describe the seroprevalence of seven hr-HPV types (16, 18, 31, 33, 45, 52, 58) and associated risk factors for HPV-seropositivity.

2. Materials and methods

2.1. Study design and sample collection

A cross-sectional population-based serosurveillance study (Health Study Caribbean Netherlands) was conducted by the National Institute for Public Health and the Environment of the Netherlands (RIVM) in mid-2017. Details of the survey methods, data collection and inclusion have been described previously [8]. Briefly, on Bonaire, St. Eustatius and Saba, an age-stratified sample, with age strata 0–11, 12–17, 18–34, 35–59 and 60–89 years, was randomly drawn from the population registry (PIVA-V, January 1, 2017). A total of 7,768 eligible individuals were invited. All procedures performed were in accordance with the 1964 Declaration of Helsinki and its later amendments. The Medical Ethics Committee Noord-Holland in the Netherlands approved the study (METC number: M015-022), and, prior to participation, signed informed consent was obtained from all participants aged $\geq$ 12 years and, if < 18 years of age, also from their parents or legal guardians. In total, 1,900 participants were included in this study (response rate 24.5%).

Participants donated a blood sample – via a finger- or heel prick using the dried blood spot (DBS) method on air-dried filter paper (Whatman® 903 protein saver cards) – and completed a questionnaire on sociodemographics, sexual behaviour (from 15 years of age) and other factors possibly related to HPV infection. Information on HPV-vaccination was collected via vaccination certificates or, if unavailable, retrieved from the local public health department if obtainable. Women up till 30 years of age without any documented vaccination record were considered vaccinated if their antibody concentration was within a range of vaccinated adolescent girls from a large cohort measured at the same laboratory (i.e., HPV16 $\geq$ 100 Luminex units (LU)/mL and HPV18 $\geq$ 50 LU/mL (Hoes et al.; submitted)).

2.2. Serological measurements

Blood samples were air-shipped to the laboratory of the RIVM and stored instantly at −80 °C awaiting analyses. For the detection of HPV-specific IgG-antibodies levels against HPV L1 virus-like-particle (VLP) 16, 18, 31, 33, 45, 52, 58, a VLP-based multiplex-immunoassay was used, as previously described [9] (VLPs were kindly donated by MSD (Merck & Co, Inc, Kenilworth, NJ)). In short, following standard protocol, a 3.2 mm (1/8 in.) punch was taken from the DBS and incubated in phosphate-buffered-saline containing 0.2% Tween-20 and 1% bovine serum albumin (i.e., assay buffer) at 4 °C overnight on a shaker to release serum, resulting in a 1:200 dilution [10,11]. If detection was out of range, samples were further diluted to 1:20,000 in assay buffer. HPV-specific antibodies were detected using R-phycoerythrin conjugated goat anti-human IgG after incubation with VLP-conjugated beads (Bio-Rad Laboratories, Hercules, CA). Blanks, four in-house controls and a standard were used consistently. HPV-specific IgG-antibodies were analyzed using the Bioplex200 system and software (Bio-Rad Laboratories, Hercules, CA), measured in arbitrary LU/mL (and for HPV16 and 18 converted to international units (IU)/mL by dividing LU/mL by 2.8 and 3.3, respectively). Samples were assumed to be seropositive above cutoffs determined via a method by Frey et al. [12] (with 99% one-sided t-values based on n = 215 controls, aged 1–6 years from the present study), namely: HPV16: $\geq$ 9 LU/mL, HPV18: $\geq$ 15 LU/mL, HPV31: $\geq$ 9 LU/mL, HPV33: $\geq$ 11 LU/mL, HPV45: $\geq$ 27 LU/mL, HPV52: $\geq$ 19 LU/mL, HPV58: $\geq$ 17 LU/mL.

2.3. Statistical analyses

Data were analysed in SAS v.9.4 (SAS Institute Inc., Cary, NC) and R v.3.6. Overall seroprevalence and geometric mean concentrations (GMC) for IgG-antibodies against the seven hr-HPV types among the total population were estimated. These data were weighted, taking into account island, sex, age group, country of birth (and for Bonaire neighbourhood too), in order to match the population distribution of each island as of January 1, 2017. Differences in seroprevalence of HPV-specific antibodies between islands, sex and age were determined by estimating the parameters of the beta distribution of these seroprevalence rates using the methods of moments [13]. Risk ratios, their corresponding 95% confidence intervals (CI) and p values were estimated by Monte Carlo simulations of both seroprevalence estimates. Differences in the GMC between islands, sex and age were identified by calculating the differences in logarithmic (ln)-concentrations and tested via a t-test. Age-specific seroprevalence, GMC and 95% CI were determined for CN, per islands and sex, and stratified for HPV-vaccination. Seroprevalence for 'any' or 'all' hr-HPV-type(s) refer to the seven hr-serotypes that have been measured in this study. Statistically significance was set at $p < 0.05$.

Risk factors were determined for hr-HPV-seropositivity among sexual active and HPV-unvaccinated participants from 15 years of age. Generalized estimating equations with an exchangeable correlation structure was used. Each hr-HPV type was treated as a separate endpoint accounting for multiple antibodies against hr-HPV types per person and ultimately estimating the exposure effect on hr-HPV-seropositivity as a whole. Risk factors included in the model were: island, sex, age group, ethnicity, residency in CN, educational level, smoking, alcohol consumption, body mass index (BMI), having a steady partner, age at sexual debut, sexual partners, sexual preference, condom use, oral contraceptive use, history of sexual transmittable disease(s) (STD) (note: participants

with missing values for a specific variable were allocated to a missing category). In univariate analyses, all variables were adjusted for multiple hr-HPV types, and sex and age group thereby taking into account the survey design. Variables in univariate analyses with a $p < 0.10$ were included in the multivariate analysis and backward selection (dropping variables one-by-one manually) was then used to identify risk factors in which a $p < 0.05$ was considered statistically significant associated. Crude and adjusted odds ratios (ORs) and 95% CIs were estimated as well as unweighted seroprevalence and 95% CI for all studied factors.

3. Results

3.1. Study characteristics

Sociodemographic study characteristics have been described in-depth elsewhere [8]. Shortly, 1,823 persons, aged 3 months to 90 years, donated a blood sample from which HPV-specific IgG-antibodies could be determined and filled-out the questionnaire (Table1). There were 820 (45%) men and 1003 (55%) women, and in accordance with the sampling, the largest part resided on Bonaire (n = 1,124 (62%), followed by St. Eustatius (n = 478 (26%)) and Saba (n = 221 (12%)). Most people originated from the Dutch overseas territories (comprising CN, Aruba, Curaçao and St. Maarten) and Suriname (n = 1,309, 72%), followed by Latin America and other non-Western countries (n = 280, 16%), and indigenous Dutch & other Western countries (n = 221, 12%). People from the Dutch overseas territories and Suriname were relatively often present in the study sample of St. Eustatius (82%), whereas this was the case for those from indigenous Dutch and other Western countries (22%) and Latin America and other non-Western countries (16%) on Saba – following their population composition [14]. In total, 102 women were vaccinated against HPV (n = 73, 27 and 2 in age groups 9–14, 15–19 and 20–29 years, respectively), with relatively most on St. Eustatius (n = 40 (8%)) and Saba (n = 17 (8%)), as routine HPV-vaccination was introduced two years earlier than on Bonaire.

Questions related to sexual behavior were completed from age 15 years (n = 1,209). Sixty percent reported to have a steady partner and 84% ever had sexual intercourse. Among the latter, median age of sexual debut was 17 years (interquartile range (IQR) 16–19). Men had an earlier sexual debut (17 (IQR: 15–18)) than women (18 (16–20)), being lowest for men on St. Eustatius (16 (IQR: 14–18) and Saba (16 (IQR: 15–18). Overall, 16% reported to have had ≥ 5 lifetime sexual partners. For Saba this percentage (26%) was higher than Bonaire (15%) and St. Eustatius (12%), however, nearly 50% of participants did not complete this question (mostly on St. Eustatius (62%)). Five percent had a self-reported history of a STD (chlamydia was most reported (n = 35), followed by gonorrhea (n = 15)), being highest on Saba (11%).

3.2. Seroprevalence and GMC

3.2.1. Overall seroprevalence and GMC in CN

Seroprevalence for any of the seven hr-HPV types in CN (0–90 years, n = 1,823) was 31.3% (95% CI 28.6–34%) and amounted to 29.7% (95% CI 26.9–32.4) in those unvaccinated (n = 1,721). GMCs for all hr-types in vaccinated individuals were significantly higher than in unvaccinated individuals, especially for vaccine types HPV16 (GMCs of 246.8 vs. 0.56 IU/mL, respectively) and HPV18 (74.7 vs. 0.74 IU/mL, respectively) (all $p < 0.0001$) (Fig. 1). Focusing on unvaccinated participants from age 15 years (n = 1,180), overall seroprevalence was 34% (95% CI 30.8–37.3), and antibodies against HPV16 and 52 were detected mostly (both 13.1%), followed by HPV58, HPV18, HPV31, HPV45 and HPV33 (8.9–12.7%) (Table2a). Over half of those seropositive were positive for ≥ 2 hr-HPV types and a small proportion (2%) was positive for all hr-types.

3.2.2. Overall seroprevalence and GMC, by sex and island

Among those unvaccinated from age 15 years, seroprevalence for any hr-HPV type was significantly higher in women (51.4%) than in men (18.1%) (Table2a). The same accounted for hr-type specific GMCs (all $p < 0.0001$) and hr-type specific seroprevalence, and this sex difference was observed on all islands. HPV16 and 52 were most common in women (20%), and HPV58 (8%), 16 and 52 (both 7%) in men. Women were over 3-fold more often seropositive against ≥ 2 hr-HPV types than men (28.8 vs. 8.8%), yet seropositivity against all hr-types did not differ between sexes.

St. Eustatius displayed a higher seropositivity against any hr-HPV types (38.4%) as compared to Bonaire (33.4%) and Saba (33.1%) (Table2b), and this was due to a higher seropositivity in both men (23.0%) and (unvaccinated) women (55.7%) on this island. Overall GMCs for all hr-types were also highest on St. Eustatius, and significantly higher for HPV16, 18, 31, 33 and 58 as compared to Bonaire, and for HPV33 and 58 compared to Saba (all $p < 0.05$). Also, with exception of HPV52 – which was highest on Bonaire – seropositivity against all other six hr-types was highest on St. Eustatius (with HPV16, 31 and 58 being highest), attributable to higher seroprevalence in men as compared to Bonaire and Saba. Interestingly, seropositivity against all hr-types on St. Eustatius was higher for men (6.8%) than women (1.6%), whereas this was not the case on the other islands.

3.2.3. Age-specific seroprevalence and GMC in CN

In accordance with age of sexual debut, a sharp increase in seropositivity, i.e., a step-up, was observed from 6% in the 0–8 year-olds to 21.1% and 35.6% in the unvaccinated age groups 15–19 and 20–29 years respectively, with similar rise in GMC for all hr-types (Figs. S1 and 1). Both GMC and seroprevalence peaked in age group 30–39 years (37.8%), remained stable up till age group 50–59 years and declined in persons of 60 years and above to levels comparable to that of 15–19 year-olds.

3.2.4. Age-specific seroprevalence and GMC, by sex and island

Unvaccinated women had a substantially higher HPV seroprevalence for any hr-type as compared to men between 15 and 74 years of age (Fig. 2). Likewise, a sex difference in seroprevalence and GMC for all seven hr-types was observed for age groups 20–74 years. Although the step-up among adolescents was noticeable among both men and women, it was most pronounced in women in whom seroprevalence increased considerably from 18.8% (in 9–14 years) to 39.8% in 15–19 years, and almost reached 60% in those aged 20–29 years – with greatest step-up seen for HPV33 and HPV52. In women aged 20–39 years, seroprevalence was highest (all > 25%) for HPV16, 18, 31 and 52. Remarkably, seropositivity for HPV58 in women rose gradually with age, peaking at 50–59 years (23%), and being highest among all seven hr-types in that age group. In men, highest seroprevalence was observed in 15–19 year-olds for all seven hr-types, with rates being similar to women in that age group for HPV45, HPV52 and HPV58.

Seroprevalence was remarkably high for any hr-type in 65–90 year-olds on St. Eustatius (45%) as compared to Bonaire (24%; p = 0.008) and Saba (29%; p = 0.13). This was primarily due to HPV16, 18 and 58 which were all > 15% in this age group (Fig. S2). Also, GMCs were significantly higher (data not shown). Specifically, besides women demonstrating a higher seroprevalence in this age group on St. Eustatius, men in particular had a higher seroprevalence as compared to those on the other islands (Fig. 3) – with HPV16 and 58 being even higher in men than women on St. Eustatius (Fig. S3). Interestingly, among the unvacci-

Table 1
Sociodemographic and sexual behaviour characteristics of participants with a blood sample for HPV IgG antibody determination in the Health Study Caribbean Netherlands, by island[a].

Sociodemographic characteristic	Bonaire *n* (%) *n* = 1,124 (61.7)	St. Eustatius *n* (%) *n* = 478 (26.2)	Saba *n* (%) *n* = 221 (12.1)	Total *n* (%) *n* = 1,823
Sex				
Men	503 (44.8)	221 (46.2)	96 (43.4)	820 (45.0)
Women	621 (55.2)	257 (53.8)	125 (56.6)	1,003 (55.0)
Age groups, years				
0–14	373 (33.2)	183 (38.3)	58 (26.2)	614 (33.7)
15–24	125 (11.1)	53 (11.1)	22 (10.0)	200 (11.0)
25–34	110 (9.8)	62 (13.0)	24 (10.9)	196 (10.7)
35–44	78 (7.0)	34 (7.1)	25 (11.3)	137 (7.5)
45–64	259 (23.0)	90 (18.8)	52 (23.5)	401 (22.0)
65–90	179 (15.9)	56 (11.7)	40 (18.1)	275 (15.1)
Ethnicity*				
Dutch overseas territories & Suriname	799 (71.2)	384 (82.1)	126 (57.5)	1,309 (72.3)
Indigenous Dutch & other Western countries	143 (12.7)	30 (6.4)	48 (21.9)	221 (12.2)
Latin America & other non-Western countries	181 (16.1)	54 (11.5)	45 (20.6)	280 (15.5)
(Maternal) educational level[b]				
High	170 (15.1)	68 (14.2)	85 (38.4)	323 (17.7)
Middle	297 (26.4)	126 (26.4)	45 (20.4)	468 (25.7)
Low	570 (50.7)	232 (48.5)	80 (36.2)	882 (48.4)
Unknown	87 (7.7)	52 (10.9)	11 (5.0)	150 (8.2)
HPV vaccination[c]				
Yes	45 (4.0)	40 (8.4)	17 (7.7)	102 (5.6)
No	1,079 (96.0)	438 (91.6)	204 (92.3)	1,721 (94.4)
Among participants from 15 years of age *(n_{total} = 1,209)*				
Steady partner				
Yes	458 (61.0)	178 (60.3)	89 (54.6)	725 (60.0)
No	264 (35.1)	91 (30.9)	60 (36.8)	415 (34.3)
Unknown	29 (3.9)	26 (8.8)	14 (8.6)	69 (5.7)
Ever had sexual intercourse				
Yes	631 (84.0)	249 (84.4)	140 (85.9)	1,020 (84.3)
No	77 (10.3)	12 (4.1)	11 (6.7)	100 (8.3)
Unknown	43 (5.7)	34 (11.5)	12 (7.4)	89 (7.4)
Among participants from 15 years of age who had sexual intercourse *(*i.e.*, excluding those without) (n_{total} = 1109)*				
Median age at sexual debut	18 (16–20)	17 (15–18)	18 (16–19)	17 (16–19)
Age at sexual debut				
< 18	213 (31.6)	94 (33.2)	57 (37.5)	364 (32.8)
≥ 18	233 (34.6)	67 (23.7)	63 (41.5)	363 (32.7)
Does not want to answer	87 (12.9)	45 (15.9)	12 (7.9)	144 (13.0)
Unknown	141 (20.9)	77 (27.2)	20 (13.6)	238 (21.5)
Lifetime sexual partners				
1	110 (16.3)	22 (7.8)	26 (17.1)	158 (14.3)
2–4	150 (22.3)	53 (18.7)	27 (17.8)	230 (20.7)
≥ 5	102 (15.1)	34 (12.0)	40 (26.3)	176 (15.9)
Unknown	312 (46.3)	174 (61.5)	59 (38.8)	545 (49.1)
Ever had sexual transmitted disease				
Yes	30 (4.5)	12 (4.2)	16 (10.5)	58 (5.2)
No	644 (96.6)	271 (95.8)	136 (89.5)	1,051 (94.8)

Missing: ethnicity n = 13.

[a] Dutch overseas territories include the islands: Bonaire, Saba and St. Eustatius (i.e., Caribbean Netherlands), and Aruba, Curaçao and St. Maarten. Within ethnic group indigenous Dutch and other Western countries, n = 147 (66%) were indigenous Dutch. Within ethnic group Latin America and other non-Western countries, n = 261 (93%) were born in Latin America.

[b] Maternal educational level was used for participants 0-11y, active education was used for participants 12-25y, and highest accomplished educational level was used for participants > 25y. Low = no education, primary school, pre-vocational education (VMBO), lower vocational education (LBO/MBO-1), lower general secondary education (MAVO/VMBO). Middle = intermediate/ secondary vocational education (MBO-2–4), higher/senior vocational education (HAVO), pre-university education (VWO/Gymnasium); High = higher professional education (HBO), University BSc., University MSc., Doctorate.

[c] *n* = 71 women were vaccinated against HPV according to the vaccination registry and *n* = 31 without vaccination records were highly likely to be vaccinated based on IgG antibody concentration and age, see method section for detailed definition (in age groups 9–14, 15–19 and 20–29*n* = 73, 27 and 2 women were vaccinated, respectively).

nated 9–17 year-olds on Saba no one was seropositive for any hr-type.

3.3. Risk factors for hr-HPV-seropositivity

Risk factors for hr-HPV-seropositivity were investigated in HPV-unvaccinated sexually active participants from age 15 years (n = 1,080) (Table3). In univariate analyses the following variables were significantly associated with HPV-seropositivity: sex, age group, number of lifetime sexual partners and in the preceding year, and history of STD. In multivariate analysis, female sex was found to be the most pronounced determinant, followed by the number of lifetime sexual partners (2–4 and ≥ 5 vs. 1), being 25–34 years of age (vs. 15–24) and having a history of STD.

4. Discussion

For the first time we describe the seroepidemiology of IgG-antibodies against the hr-HPV types 16, 18, 31, 33, 45, 52 and 58 in the population of Caribbean Netherlands, situated in a region with a high incidence of HPV-related cancers [2,4,5]. Seropositivity for multiple hr-HPV types was high in the unvaccinated popula-

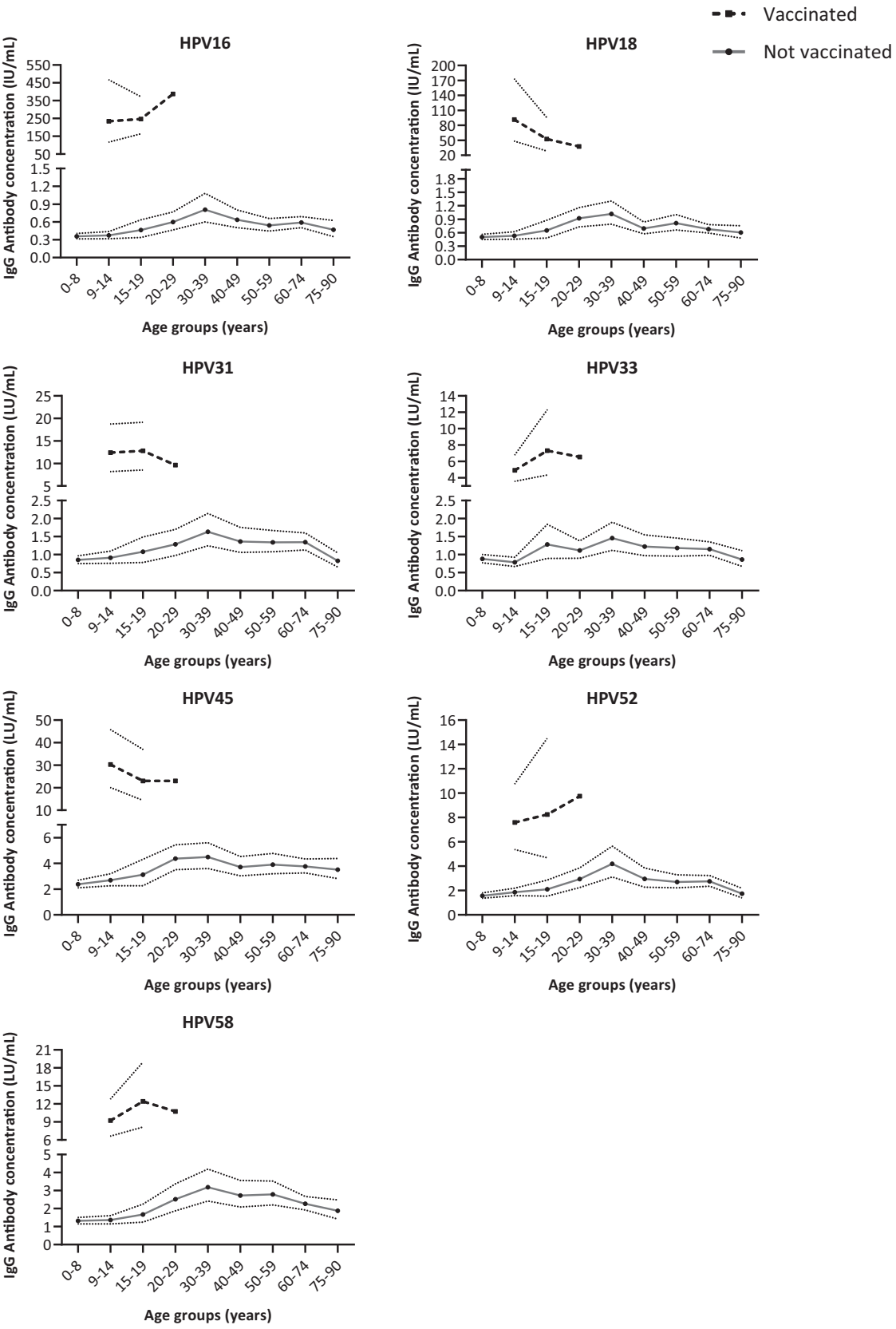

Fig. 1. Age-specific geometric mean concentration (GMC) (with 95% confidence intervals (CI)) of seven high-risk types human papillomavirus (HPV) IgG antibodies in the general population of Caribbean Netherlands, 2017, by HPV vaccination. Note: 95% CI was not provided for vaccinated participants in age group 20–29 years due to the low number of participants in this group.

Table 2
Weighted seroprevalence for seven high-risk HPV types and combinations in the total population of Caribbean Netherlands among those unvaccinated[a] and from 15 years of age, by sex (**a**) and island (**b**).

a)	Seroprevalence (95% CI) Overall *n* = 1,180		Men *n* = 505 (42.8%)		Women *n* = 675 (57.2%)		*P* value[b]
High-risk HPV types							
HPV16	13.1	(11.0–15.2)	6.8	(4.4–9.3)	19.9	(16.5–23.3)	**<0.0001**
HPV18	11.8	(9.7–13.8)	5.6	(3.3–7.9)	18.5	(15.1–21.9)	**<0.0001**
HPV31	10.9	(9.0–12.8)	5.6	(3.4–7.9)	16.3	(13.5–19.7)	**<0.0001**
HPV33	8.9	(7.1–10.8)	6.0	(3.5–8.5)	12.2	(9.4–14.9)	**0.001**
HPV45	9.4	(7.6–11.3)	5.3	(3.1–7.5)	13.9	(11.0–16.9)	**<0.0001**
HPV52	13.1	(10.8–15.4)	7.1	(4.3–9.9)	19.7	(16.2–23.2)	**<0.0001**
HPV58	12.7	(10.5–14.9)	7.5	(4.7–10.3)	18.4	(14.9–21.8)	**<0.0001**
HPV combinations							
HPV16 and 18	5.5	(4.1–7.0)	3.9	(2.1–5.7)	7.4	(5.2–9.5)	**0.02**
HPV16 or 18	19.3	(16.8–21.9)	8.5	(5.8–11.3)	31.1	(27.1–35.1)	**<0.0001**
Positive for 1 or more high-risk HPV types	34	(30.8–37.3)	18.1	(14.0–22.2)	51.4	(47.1–55.7)	**<0.0001**
Positive for 2 or more high-risk HPV types	18.1	(15.5–20.6)	8.8	(5.8–11.8)	28.1	(24.3–32.0)	**<0.0001**
Positive for 7 high-risk HPV types	2.0	(1.1–3.0)	2.3	(0.8–3.8)	1.8	(0.6–2.9)	0.61

b)	**Seroprevalence (95% CI) Bonaire** *n*=744 (63.0%)		**St. Eustatius** *n*=278 (23.6%)		**Saba** *n*=158 (13.4%)	
High-risk HPV types						
HPV16	**11.4**[st]	(9.0–13.8)	**20.7**[bo]	(15.0–26.4)	18.3	(11.5–25.2)
HPV18	11.3	(8.9–13.7)	15.2	(10.3–20.2)	11.0	(5.7–16.3)
HPV31	**9.6**[st]	(7.4–11.8)	**16.4**[bo]	(11.2–21.5)	14.9	(9.0–20.8)
HPV33	8.3	(6.2–10.5)	12.5	(7.8–17.2)	9.2	(4.5–14.0)
HPV45	8.9	(6.7–11.0)	12.6	(7.9–17.3)	9.9	(5.0–14.8)
HPV52	13.7	(11.0–16.4)	10.6	(6.3–15.0)	11.3	(6.1–16.4)
HPV58	12.3	(9.7–14.9)	16.6	(11.3–21.8)	10.0	(5.1–15.1)
HPV combinations						
HPV16 and 18	**4.9**[st]	(3.4–6.5)	**8.2**[bo]	(4.2–12.2)	7.4	(3.0–11.9)
HPV16 or 18	17.7	(14.8–20.6)	27.7	(21.5–33.9)	21.9	(14.6–29.2)
Positive for 1 or more high-risk HPV types	33.4	(29.6–37.3)	38.4	(31.7–45.1)	33.1	(24.8–41.3)
Positive for 2 or more high-risk HPV types	17.7	(14.7–20.7)	20.8	(15.4–26.3)	17.0	(10.7–23.3)
Positive for 7 high-risk HPV types	1.5	(0.5–2.6)	4.4	(0.8–7.9)	3.4	(0.3–6.6)

CI=confidence interval.
[a] *n* = 29 women were vaccinated (of which *n* = 12 according to the registry and *n* = 17 without vaccination records highly likely to be vaccinated (based on IgG antibody concentration and age, see method section for detailed definition)).
[bo] Statistically significant different ($p < 0.05$) between men and women in bold type.
[st] Statistically significant different from St. Eustatius ($p < 0.05$) in bold type.

tion, with antibody responses against HPV16 and 52 being detected mostly. In general, women had a nearly 3-fold higher seroprevalence compared to men, predominantly peaking in women aged 20–59 years. Seropositivity for six hr-types was highest on St. Eustatius, which was particularly attributable to older men. Besides age and sex, risk factors related to sexual behavior were found to be associated with HPV-seropositivity in unvaccinated participants from age 15 years.

The incidence of cervical cancer is high in Caribbean countries. Recent estimations on Suriname and neighbouring island Curaçao revealed that incidence is 22.4 and 13.4 per 100,000, respectively [15,16], whereas this is lower in the Netherlands (7.5 per 100,000) [17]. Despite this high incidence, only few studies have been conducted on HPV seroepidemiology in the Caribbean region; data which is key in developing preventive programs. In CN, over one third of the unvaccinated population from age 15 years was seropositive against any hr-HPV type measured, and over half of them had detectable antibodies against multiple hr-types. HPV16 and 52 were the most common hr-types (both 13%), followed by 58, 18 and 31. These observations are within a broad range found in (the few) other studies conducted in the Caribbean region [18–20], with exception of Jamaica where an even higher seroprevalence (50%) was found for HPV16 [21]. Conversely, seropositivity in CN was higher as compared to Western countries [22–25], for instance in the Netherlands [9,26]; a country in which girls-only vaccination has been introduced since 2009 and population-based cervical screening has been in place since 1996. Still, prior to vaccination, seroprevalence in the Netherlands was lower than the present estimates in CN, with higher rates among people from Latin America and Caribbean descent [9], similar to the present study.

HPV-specific antibodies could already be detected in young children who are not likely to be sexually active which is in accordance with other population studies [24,27]. This implies that the route of HPV-transmission is not only by sexual contact, but also for instance via vertical or horizontal transmission and autoinoculation [28]. Further, participants who had been vaccinated displayed an significant antibody response against hr-HPV vaccine types 16 and 18 as well as against the non-vaccine types. This cross-reactivity has been observed by others [29–32]. Interestingly, no one was HPV-seropositive among the unvaccinated 9–17 year-olds on Saba. Although HPV-vaccination was introduced for 9 year-old girls on Saba in 2013 and vaccine coverage has been high since a herd effect due to vaccination might seem too early. As ~ 25% of this total age group on Saba responded in this study and the included numbers are low, future serosurveillance studies in CN should shed more light on this observation. Similar findings were not observed on the other islands; which might be explained by a lower vaccination coverage and very recent introduction of HPV-vaccination on Bonaire (two years prior to this study in 2015).

Female sex was the strongest predictor for being HPV-seropositive and women had a substantial higher overall seroprevalence than men in the total CN-population (51% vs. 18%). Seroprevalence (and GMC) rose quickly in adolescents and young

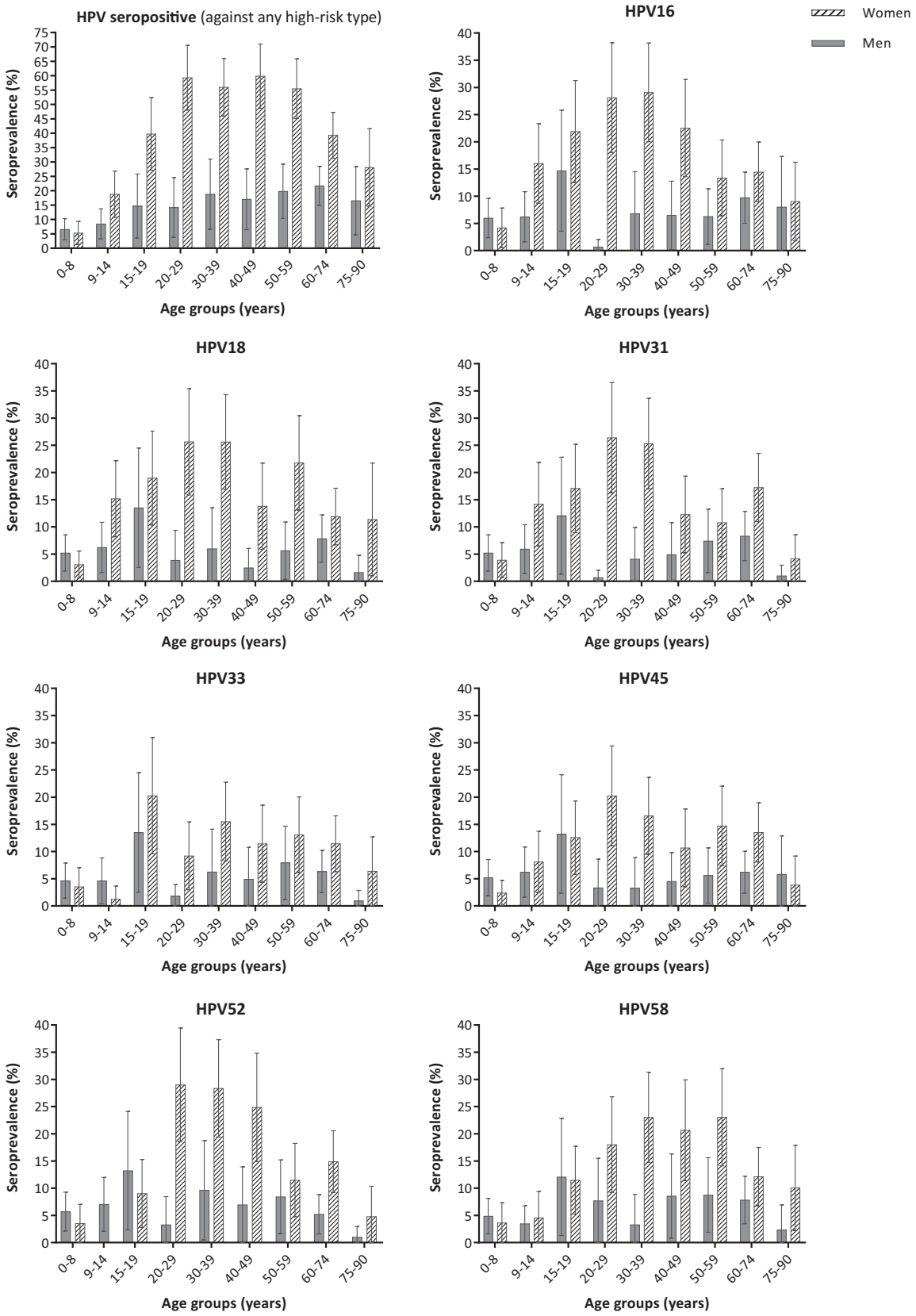

Fig. 2. Age-specific seroprevalence (%) (with 95% confidence intervals) of any high-risk type and seven high-risk types human papillomavirus (HPV) IgG antibodies in the unvaccinated general population of Caribbean Netherlands, 2017, by sex.

adult women, corresponding to the age of sexual debut. This steep increase is in line with other studies [9,19,24,33], and highlights the necessity to promote early education on HPV-vaccination and safe(r) sexual practices to prevent STDs in general. From age

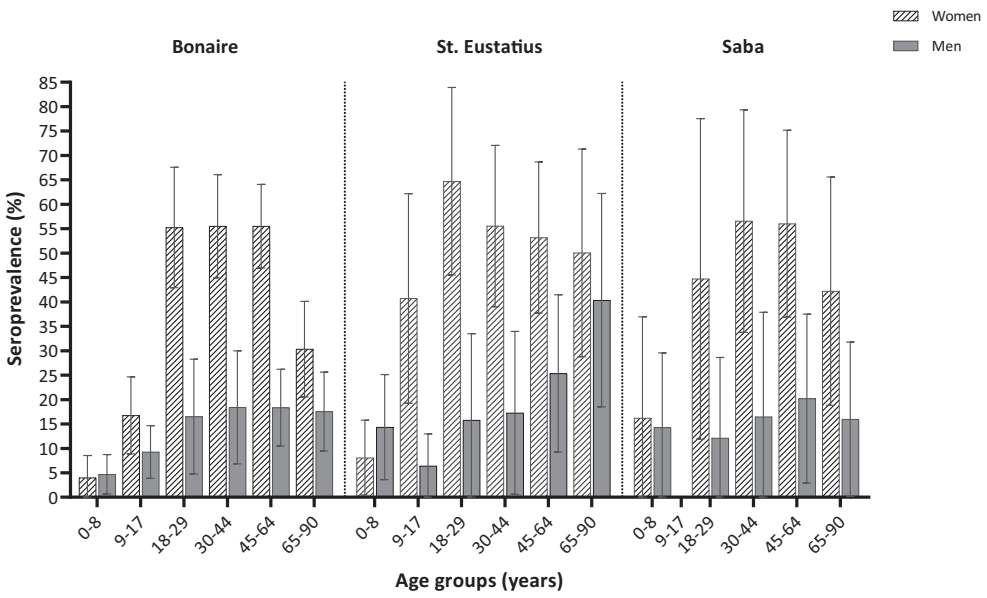

Fig. 3. Age-specific seroprevalence (%) (with 95% confidence intervals) of any high-risk type human papillomavirus (HPV) IgG antibodies in the unvaccinated general population of Bonaire, St. Eustatius and Saba, 2017, by sex.

60 years, seroprevalence decreased to rates comparable to 15–19 year-olds, possibly as a result of antibody waning or due to a cohort effect, i.e., decreasing sexual behavior over time, as earlier hypothesized [22]. Although the dissimilarity between sexes is in accordance with other studies, it was more pronounced than observed in other countries [9,22]. After stratifying sexual risk behavior by sex, women were shown to have similar patterns as men (data not shown). It should be noted, however, that questions regarding sexual behavior were among the least well-completed, especially by men. Self-reporting of sexual behavior could lead to bias due to social desirability and this was also illustrated by our risk factor analysis for some variables (e.g., the missing category for lifetime sexual partners had the highest OR). It is known from literature, however, that Caribbean men more often report about multiple partnerships than women [34]. This could result in increased exposure to (multiple) HPV types in both sexes when compared to other populations. Subsequently, the fact that women display a substantial higher seroprevalence in this population might be explained by the different site of entry of the infection between sexes. As mucosal surfaces are infected in women predominantly, a detectable humoral immune response is more likely to be expected as compared to an infection at epithelial surfaces which mainly occur in men, as suggested by Desai and colleagues [22]. Hence, although increased sexual behavior in men will result in increased seropositivity, it will probably not be so pronounced as in women.

HPV-seropositivity for any hr-type was highest on St. Eustatius, followed by Saba and Bonaire, and seroprevalence (and GMC) for all measured hr-types, except HPV52, was highest on St. Eustatius too. Both women and men displayed higher seroprevalence rates on St. Eustatius as compared to the other islands, and particularly rates in men from 65 years of age were higher – predominantly due to HPV16 and 58. Increased sexual behavior on St. Eustatius most likely explains the difference between islands in general, and specifically among men. For instance, on this island, highest proportion for seropositivity against all seven hr-types was found in men as well as lowest age of sexual debut (16 years of age). The questionnaire data could not confirm this for other sexual risk factors, probably due to the high number of missing values for these variables on St. Eustatius.

Various potential risk factors for HPV-seropositivity were investigated in this study. Beside female sex, and being a young adult (25–34 years), increased number of lifetime sexual partners and a history of STD are in line with other studies [19,20,35,36]. Literature has been inconsistent on the influence of other factors, such as smoking, condom use, BMI and oral contraceptive use [18,19,36–40]. In this study, all these factors were not associated in our multivariate analysis, suggesting no relationship with HPV-seropositivity.

This study is subject to potential limitations. A direct comparison between HPV-serology studies is hindered by the use of different assays and methods [41]. Due to logistical reasons, we made use of the DBS-method in this study to collect our samples, and although we eluted these via a standardized and validated protocol, marginal difference with serum samples might not be inconceivable. Also, international standardization for all hr-HPV types, which has already been done for HPV16 and 18 and applied in this study, could help to overcome this difficulty in future studies. Direct comparison of data was possible with the population-based study performed in the Netherlands [9,26], which was conducted, measured and analyzed in a similar way. Additionally, our cutoffs were determined via a statistically valid and widely used method in the field of immunoassays. Moreover, in particular men aged 18–34 years were relatively hard to include in our study; a common phenomenon in population-based studies [8,42]. Hence, especially on the smaller islands St. Eustatius and Saba, this limits stratifying for multiple variables, and due to possible loss of power one should not exclude potential related bias. To minimize this, we have weighted our sample on a set of sociodemographic characteristics corresponding to the island's population at the time of enrollment. Further, we cannot draw firm conclusions on the rate of current HPV infections in this study as not all infected persons will develop a quantifiable antibody response, seroconversion might be delayed or HPV DNA has been cleared [43]. Likewise, risk factors for HPV-seropositivity do not necessarily reflect determinants for current HPV-infections.

Our findings are of great importance for policy implications. Firstly, girls in CN are currently vaccinated twice at age 9/10 years and this age is justifiable by the observed step-up in seroprevalence of multiple (vaccine-relevant) hr-types in those 15–19 years,

Table 3
Risk factor analysis for any high-risk type HPV IgG seropositivity among sexual active and unvaccinated participants from 15 years of age in the Health Study Caribbean Netherlands[a].

Potential risk factor for any high-risk type HPV seronegativity	*n* (%) *n* = 1,080	% HPV seropositive (95% CI)	Univariate Crude OR[b] (95% CI)	*P* value[c]	Multivariate aOR[b] (95% CI)	*P* value[c]
Island				0.61		
Bonaire	672 (62.2)	37.5 (33.8–41.2)	Ref.			
St. Eustatius	261 (24.2)	39.5 (33.5–45.4)	1.12 (0.85–1.47)			
Saba	147 (13.6)	37.4 (29.6–45.2)	1.14 (0.81–1.61)			
Sex				**<0.0001**		**<0.0001**
Men	461 (42.7)	19.5 (15.9–23.1)	Ref.		Ref.	
Women	619 (57.3)	51.7 (47.8–55.6)	**2.94 (2.19–3.94)**		**3.34 (2.49–4.49)**	
Age group, years				**<0.0001**		**0.0007**
15–24	102 (9.4)	31.4 (22.4–40.4)	Ref.		Ref.	
25–34	189 (17.5)	54.0 (46.9–61.1)	**1.74 (1.09–2.80)**		**1.68 (1.04–2.73)**	
35–44	134 (12.4)	38.1 (29.8–46.3)	0.93 (0.55–1.57)		0.92 (0.54–1.59)	
45–64	383 (35.5)	37.6 (32.7–42.5)	0.99 (0.62–1.57)		1.00 (0.62–1.61)	
65–90	272 (25.2)	29.8 (24.3–35.2)	0.71 (0.43–1.17)		0.77 (0.46–1.28)	
Ethnicity				0.26		
Dutch overseas territories[d] and Suriname	675 (62.5)	37.9 (34.3–41.6)	Ref.			
Indigenous Dutch and other Western countries	178 (16.5)	32.0 (25.2–38.9)	0.85 (0.60–1.20)			
Latin America and other non-Western countries	227 (21.0)	42.7 (36.3–49.2)	1.18 (0.89–1.58)			
Resident of Caribbean Netherlands since, years of age				0.37		
0–10	529 (49.0)	38.4 (34.2–42.5)	Ref.			
11–17	25 (2.3)	44.0 (24.5–63.5)	1.23 (0.64–2.34)			
18–39	286 (26.5)	38.8 (33.2–44.5)	0.83 (0.62–1.11)			
≥ 40	189 (17.5)	34.4 (27.6–41.2)	0.92 (0.66–1.29)			
Missing	51 (4.7)	39.2 (25.8–52.6)	1.46 (0.79–2.69)			
Educational level[e]				0.90		
High	225 (20.8)	39.6 (33.2–46.0)	Ref.			
Middle	236 (21.9)	39.4 (33.2–45.7)	0.98 (0.68–1.40)			
Low	520 (48.1)	35.6 (31.5–39.7)	1.08 (0.81–1.45)			
Missing	99 (9.2)	43.4 (33.7–53.2)	1.05 (0.69–1.60)			
Current smoking				0.93		
Yes	163 (15.1)	33.1 (25.9–40.4)	Ref.			
No	888 (82.2)	39.0 (35.8–42.2)	0.93 (0.65–1.33)			
Missing	29 (2.7)	34.5 (17.2–51.8)	0.95 (0.40–2.26)			
Drunk alcohol in preceding year				0.33		
Yes	651 (60.3)	39.3 (35.6–43.1)	Ref.			
No	381 (35.3)	36.5 (31.6–41.3)	0.84 (0.66–1.07)			
Missing	48 (4.4)	31.3 (18.1–44.4)	0.85 (0.45–1.64)			
Body Mass Index				0.27		
Underweight	15 (1.4)	33.3 (9.4–57.2)	0.94 (0.41–2.13)			
Normal weight	280 (22.9)	32.1 (26.7–37.6)	Ref.			
Overweight	352 (32.6)	38.1 (33.0–43.1)	**1.39 (1.01–1.91)**			
Obesity	357 (33.1)	43.1 (38.0–48.3)	1.30 (0.96–1.77)			
Missing	76 (7.0)	35.5 (24.7–46.3)	1.12 (0.67–1.88)			
Steady partner				0.22		
Yes	689 (63.8)	38.9 (35.3–42.5)	Ref.			
No	327 (30.3)	35.8 (30.6–41.0)	1.03 (0.79–1.35)			
Missing	64 (5.9)	39.1 (27.1–51.0)	**1.70 (1.02–2.83)**			
Age at sexual debut, years				0.13		
< 18	356 (33.0)	42.1 (37.0–47.3)	**1.39 (1.04–1.85)**			
≥ 18	359 (33.2)	37.3 (32.3–42.3)	Ref.			
Does not want to answer	140 (13.0)	37.1 (29.1–45.2)	1.34 (0.93–1.92)			
Missing	225 (20.8)	32.9 (26.7–39.0)	1.25 (0.88–1.76)			
Lifetime sexual partners				**<0.0001**		**<0.0001**
1	155 (14.4)	26.5 (19.5–33.4)	Ref.		Ref.	
2–4	225 (20.8)	38.7 (32.3–45.0)	**1.89 (1.25–2.85)**		**1.85 (1.22–2.79)**	
≥ 5	171 (15.8)	43.9 (36.4–51.3)	**2.42 (1.57–3.72)**		**2.24 (1.44–3.48)**	
Missing	529 (49.0)	39.1 (35.0–43.3)	**2.91 (1.99–4.24)**		**2.88 (1.97–4.19)**	
Sexual preference				0.81		
Heterosexual	812 (75.2)	37.3 (34–40.6)	Ref.			
Homosexual	14 (1.3)	35.7 (10.6–60.9)	1.03 (0.43–2.45)			
Bisexual	32 (3.0)	56.3 (39.0–73.5)	1.09 (0.65–1.84)			
Does not want to answer	74 (6.8)	37.8 (26.8–48.9)	1.35 (0.84–2.16)			
Missing	148 (13.7)	37.8 (30.0–45.7)	1.11 (0.77–1.61)			
Sexual partners preceding year				**0.043**		
0	244 (22.6)	32.0 (26.1–37.8)	Ref.			
1	557 (51.6)	41.7 (37.6–45.8)	**1.51 (1.09–2.10)**			
≥ 2	70 (6.5)	40.0 (28.5–51.5)	1.33 (0.79–2.26)			
Does not want to answer	48 (4.4)	29.2 (16.3–42.0)	1.51 (0.73–3.13)			
Missing	209 (14.9)	34.4 (28.0–40.9)	**1.81 (1.19–2.75)**			
Condom use last sexual intercourse				0.67		
Yes	166 (15.4)	38.0 (30.6–45.3)	Ref.			

Table 3 (*continued*)

Potential risk factor for any high-risk type HPV seronegativity	*n* (%) *n* = 1,080	% HPV seropositive (95% CI)	Univariate Crude OR[b] (95% CI)	*P* value[c]	Multivariate aOR[b] (95% CI)	*P* value[c]
No	613 (56.7)	37.7 (33.8–41.5)	0.81 (0.58–1.13)			
Does not want to answer	58 (5.4)	29.3 (17.6–41.0)	0.88 (0.46–1.69)			
Missing	243 (22.5)	40.7 (34.6–46.9)	0.87 (0.59–1.28)			
Oral contraceptive use last sexual intercourse				0.47		
Yes	117 (10.8)	49.6 (40.5–58.6)	1.32 (0.95–1.85)			
No	626 (58.0)	36.1 (32.3–39.9)	Ref.			
Does not want to answer	51 (4.7)	29.4 (16.9–41.9)	1.02 (0.55–1.90)			
Missing	286 (26.5)	38.8 (33.2–44.5)	1.09 (0.82–1.44)			
Ever had sexual transmitted disease				**0.01**		**0.02**
Yes	55 (5.1)	65.5 (52.9–78.0)	**1.68 (1.18–2.39)**		**1.64 (1.12–2.40)**	
No	1,025 (94.9)	36.5 (33.5–39.4)	Ref.		Ref.	

Abbreviations: *aOR*, adjusted odds ratio; *CI*, confidence interval; *OR*, odds ratio; *Ref.*, reference category.

[a] *n* = 100 participants had not been sexual active, and *n* = 29 women were vaccinated (of which *n* = 12 according to the registry and *n* = 17 without vaccination records highly likely to be vaccinated (based on IgG antibody concentration and age, see method section for detailed definition)).

[b] Crude odds ratios were a priori adjusted for HPV high-risk type, sex and age group and significant (a)ORs are marked in bold type.

[c] *P* values were determined by means of Chi-Square tests for GEE analysis, and significant *p* values (< 0.1 in univariate and < 0.05 in multivariate analysis) are marked in bold type.

[d] Dutch overseas territories include the islands: Bonaire, Saba and St. Eustatius (i.e., Caribbean Netherlands), and Aruba, Curaçao and St. Maarten.

[e] Active education was used for participants 15-25y, and highest accomplished educational level was used for participants > 25y. Low = no education, primary school, pre-vocational education (VMBO), lower vocational education (LBO/MBO-1), lower general secondary education (MAVO/VMBO). Middle = intermediate/ secondary vocational education (MBO-2–4), higher/senior vocational education (HAVO), pre-university education (VWO/Gymnasium); High = higher professional education (HBO), University BSc., University MSc., Doctorate.

which is indicative for the age of HPV-exposure in this population. Secondly, in June 2019 the Dutch Health Council advised to expand the National Immunization Program by offering the HPV vaccine also to boys [44]. As the burden of HPV-related cancers among men is substantial in the Caribbean region [2] and HPV-seropositivity among men was shown to be significant too, a sex-neutral vaccination program in CN will lead to direct benefit of the male population. Thirdly, the high seroprevalence of multiple hr-types among adult women indicate towards a relative high-risk of (precursors of) HPV-related cancers and thereby underlines the need to consider routine cervical screening in CN and the potential value of a catch-up campaign.

Incidence of HPV-related cancers is high in the Caribbean region, and comprehensive and locally responsive cancer care is particularly challenging due to commonly under-resourced health-care systems, as highlighted by Spence and colleagues recently [45]. Besides the policy implications addressed, this study will be able to serve as a baseline for future investigations assessing the impact of a potential cervical cancer screening program and (catch-up) vaccination programs in CN by estimating vaccine uptake and monitoring epidemiological dynamics of HPV infection in the population (i.e., direct and indirect effects as well as impact on circulating HPV types) [7]. Few seroprevalence studies have been conducted in this region and we hereby would like to emphasize the need for serosurveillance data since that would be the first step in developing evidence-based public health policy and could eventually prevent HPV-infections and associated diseases as a whole.

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6. Authors' contributions

RV coordinated and executed the Health Study Caribbean Netherlands, collected and processed the data, analysed epidemiological data, interpreted the results, and designed and wrote the manuscript.

HP supervised the laboratory analyses, interpreted the results, and designed and wrote the manuscript.

LT conducted the laboratory analyses, read the manuscript and provided valuable comments.

AJJ, SBK, KH contributed to acquisition of data, read the manuscript and provided valuable comments.

HdM interpreted the results, supervised the design of the manuscript, read the manuscript and provided valuable comments.

FvdK was principal investigator of the present study, interpreted the results, supervised the design of the manuscript, read the manuscript and provided valuable comments.

All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.02.017.

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