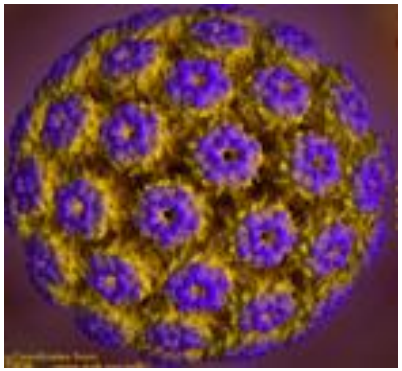
THE POPULATION-LEVEL IMPACT AND HERD EFFECTS OF THE INTRODUCTION OF HPV VACCINATION IN SWEDEN



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In Sweden (10 million people)

Cervical cancer (100% women)

- 500 new cases/year **(**55% HPV-16 and15% HPV-18)
- Around 1 million PAP smears/year (2-4% cellular changes)
- 8000 preventive measures/year

Oropharyngeal squamous cell carcinoma (OSCC) (80% men)

- 400 cases/year ≈ 280 tonsillar- and 120 base of tongue cancer (80% HPV+) and 40 non-tonsillar non base of tongue cancer

- No screening or intervention

Historical interlude – I – from a personal point of view

- The story started in the late 1990s
- HPV and human cancer

- HPV and head neck cancer, in order not to compete with all activity on cervical cancer

- HPV was detected in tonsillar cancer and later in base of tongue cancer (the two major oropharyngeal sites by us)

- HPV was detected in oropharyngeal cancer (OPSCC) by M Gillison

Mellin et al Int J Cancer 2000, Dahlgren et al Int J Cancer 2004. Gillison et al JCO 2000

Tonsillar cancer and base of tongue cancer

1970-2007 (tonsillar cancer study)

- The Swedish Cancer Registry identified 635 patients with tonsillar cancer (ICD-7 145) in the Stockholm area (1970-2002, 2003-2007)
- 335 pre-treatment biopsies were available

Hammarstedt et al., Int J Cancer 119(11) 2620-23, 2006
Näsman et al ., Int J Cancer 125 (2):362-366, 2009

1998-2007 (base of tongue study)

- Swedish Cancer Registry identified 110 patients with base of tongue cancer the Stockholm area between 1998-2007
- 95 pre-treatment biopsies were available

Attner et al., *Int J Cancer. 126(12)2879-84*, 2010

The proportion of HPV(+) tonsillar and base of tongue cancer is increasing and now around 80-90% (in Stockholm) …

Table 1. HPV in tonsillar cancer ICD-7 145.0 between 2000-2007, in Stockholm	
Years	% HPV DNA in the biopsies
1970 -79	23%
1990-99	57%
2006-07	93%

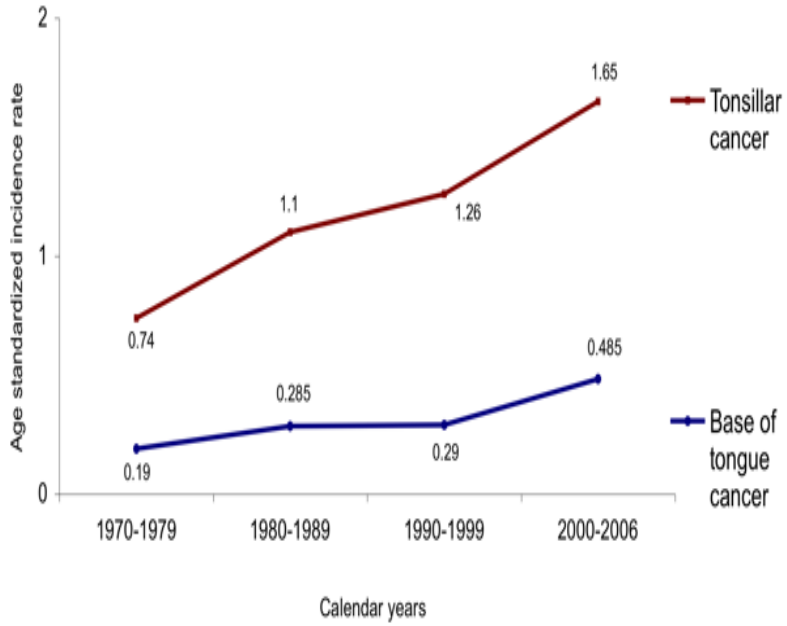
Table 2. HPV base of tongue cancer ICD-10 C01.9 between 1998-2007 in Stockholm	
Years	%HPV DNA in the biopsies
1998-2001	58%
2002-03	75%
2006-07	84%

HPV by PCR with GP5/6 or CPI/GP general primers, HPV 16 type spec primers and sequencing
Of HPV positive cases >90 % were HPV16, > 90% were E6 and/or E7 RNA positive

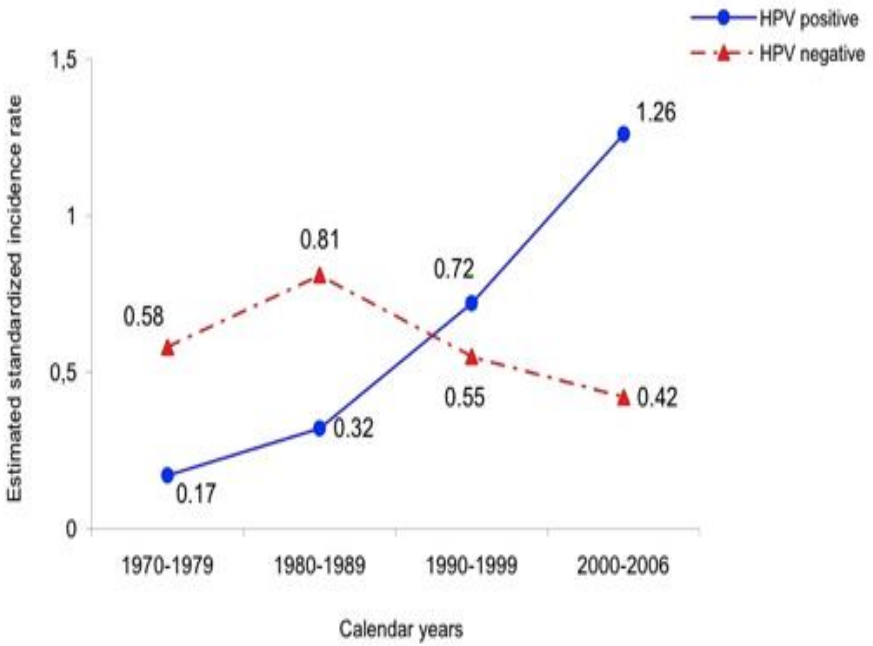
Näsman et al .,Int J Cancer 125 (2) 362, 2009; *Attner et al., Int J Cancer. 15;126(12):2879,2010*

The incidence of tonsillar and base of tongue cancer is increasing in Sweden 1970-2006, due to an HPV epidemic - similar in the US, 2011

Tonsillar and base of cancer



Tonsillar cancer

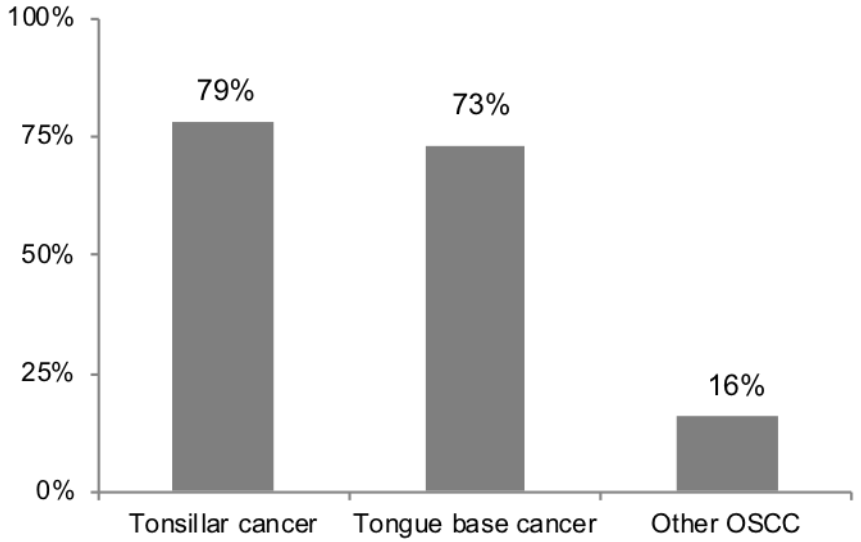


Näsman et al .,Int J Cancer 125 (2) 362, 2009

HPV in OPSCC according to sub-site 2000-2007

2000-2007 the Swedish Cancer Registry identified (ICD9) within the Stockholm County:

- 69 patients with non-tonsillar and base of tongue cancer
- 228 patients with tonsillar cancer
- 89 patients with base of tongue cancer



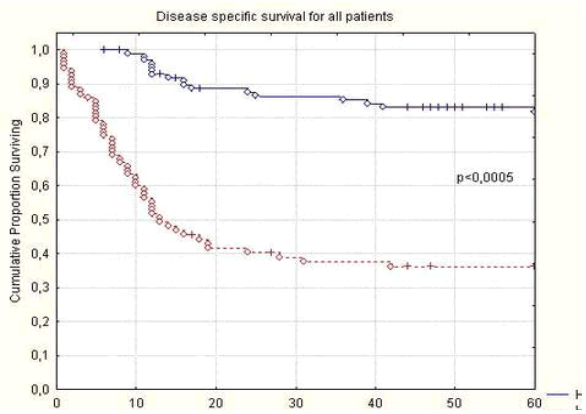
The prevalence of HPV DNA by PCR in tonsillar (79%), and tongue base (73%) OPSCC non-tonsillar, non-tongue base (16%) OPSCC

Marklund et al., Cancer Medicine In press 2012

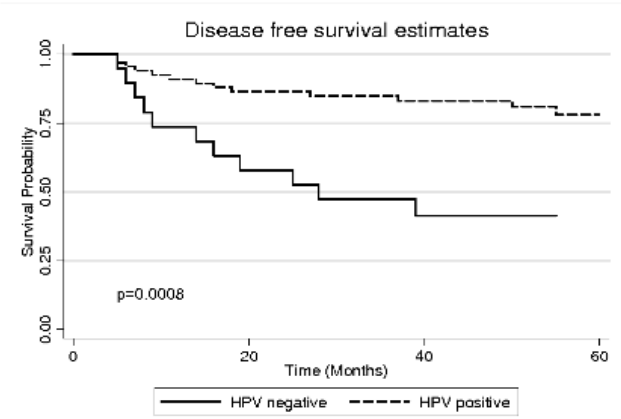
Significant lower fraction of HPV DNA in non-tonsillar, non-tongue base OPSCC compared to tonsillar SCC p=0.00001 and base of tongue SCC p=0.00001.

Patients with HPV-positive tonsillar and base of tongue cancer have a better prognosis than those with HPV negative cancer

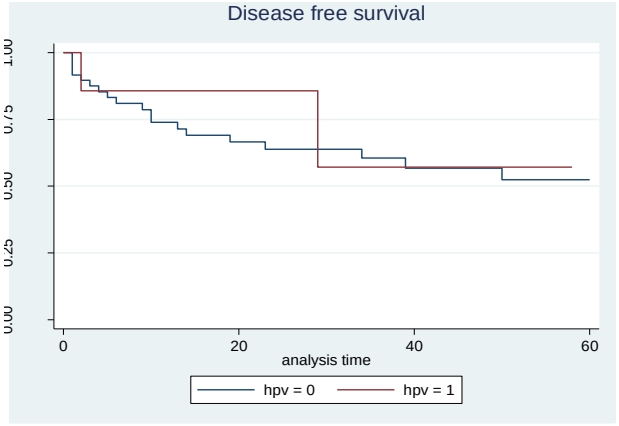
Tonsillar cancer



Base of tongue cancer



Non-tonsillar or non-base of tongue OPSCC



- 70-80% of patients with HPV-positive tonsillar and base of tongue cancer survived 5 years
- 30-40% of the patients with HPV-negative tonsillar and base of tongue cancer survived 5 years

- No difference in survival among patients with HPV positive and negative other OPSCC

Lindquist et al, Mol Onc, 1:350-5, 2007: Dahlgren et al, Int J Cancer 112, 1015-9, 2004 (survival data), Attner et al Int J Cancer, Epub Oct 2011; and Marklund et al., Cancer Medicine In press 2012

Summary – OPSCC per sub-site - 2006-2012

- The proportion of HPV-positive *tonsillar and base of tongue cancer* increased significantly in the Stockholm area between 1970-2007, and 1998-2007 and has continued to increase since then. Similar figures are found in many Western countries.

- Between 2000-2007 the majority of tonsillar cancer (79%) and base of tongue cancer (73%) was HPV-positive, while a lower proportion (16%) of non-tonsillar non-base of tongue was HPV-positive

- Patients with HPV-positive tonsillar and base of tongue cancer have a better disease specific survival compared to those with HPV-negative cancer, this was not obvious in other OPSCC

Future conclusions in 2007

- In ten years possibly 450 of the around 800-900 head neck cancer patients in Sweden will have HPV-positive tonsillar and base of tongue cancer and have a better prognosis

- We should check HPV prevalence orally, and discuss HPV vaccination of boys not only girls

- We should therefore find options to individualize treatment and not overtreat patients with better prognosis and a different disease (due to treatment intensification for all head and neck cancer the past 10 years).

Historical interlude II – from a personal point of view

- In 2006 there was an FDA approved vaccine against HPV16, 18, 6 and 11
- How was the HPV prevalence situation among youth?
- The Swedish Institute for Infectious Disease Control - collaboration
- The Youth Clinic in the nearby in central Stockholm - collaboration

Studies of genital and oral HPV infection 2008-2011 at a youth clinic in Stockholm before public HPV vaccination

Karolinska Institutet

Initiated 2007*

- Largest youth clinic at the time for 15-23 year old youth in Stockholm, with 8000 visits (5000 young women and 800 young men visit annually) consultations for birth control and sexually transmitted diseases.

- Ethical permissions, for a genital tract and an oral tract study and not having to ask the parents of the involved subjects.

Hammarstedt et al Human papillomavirus infection may account for the increase in tonsillar cancer. Int J Cancer 119(11):2620-2006, Ramqvist et al., Scand J Inf Dis 43 (2) 115-121, 2011 ; Du et al EID 18(9) 1468-1471, 2012

Studies of genital and oral HPV infection at a youth clinic in Stockholm 2008-2011 before public HPV vaccination

Patients and samples

- 544* young women were willing to give a genital sample (self-test or by a midwife)
- 483* young adults, 401 women and 82 men donated a mouth wash sample (diluted listerine/later we used Scope)

*The original number of individuals were 555 and 490 the ones denoted above are the ones with samples with extractable DNA. Less than 5% of the girls had been catch-up vaccinated at the time

Studies of genital and oral HPV infection at a youth clinic in Stockholm 2008-2011

Method

- Luminex based Multiplex assay; (24 HPV types) (Later also HPV 30, 67, 69)

15 High risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82)
3 Putative high risk (26, 53, 66)
6 Low risk (6, 11, 42, 43, 44, 70)

We guessed 20% would be HPV-positive in the genital tract

Studies of genital HPV infection in girls at a youth clinic in Stockholm 2008-2011

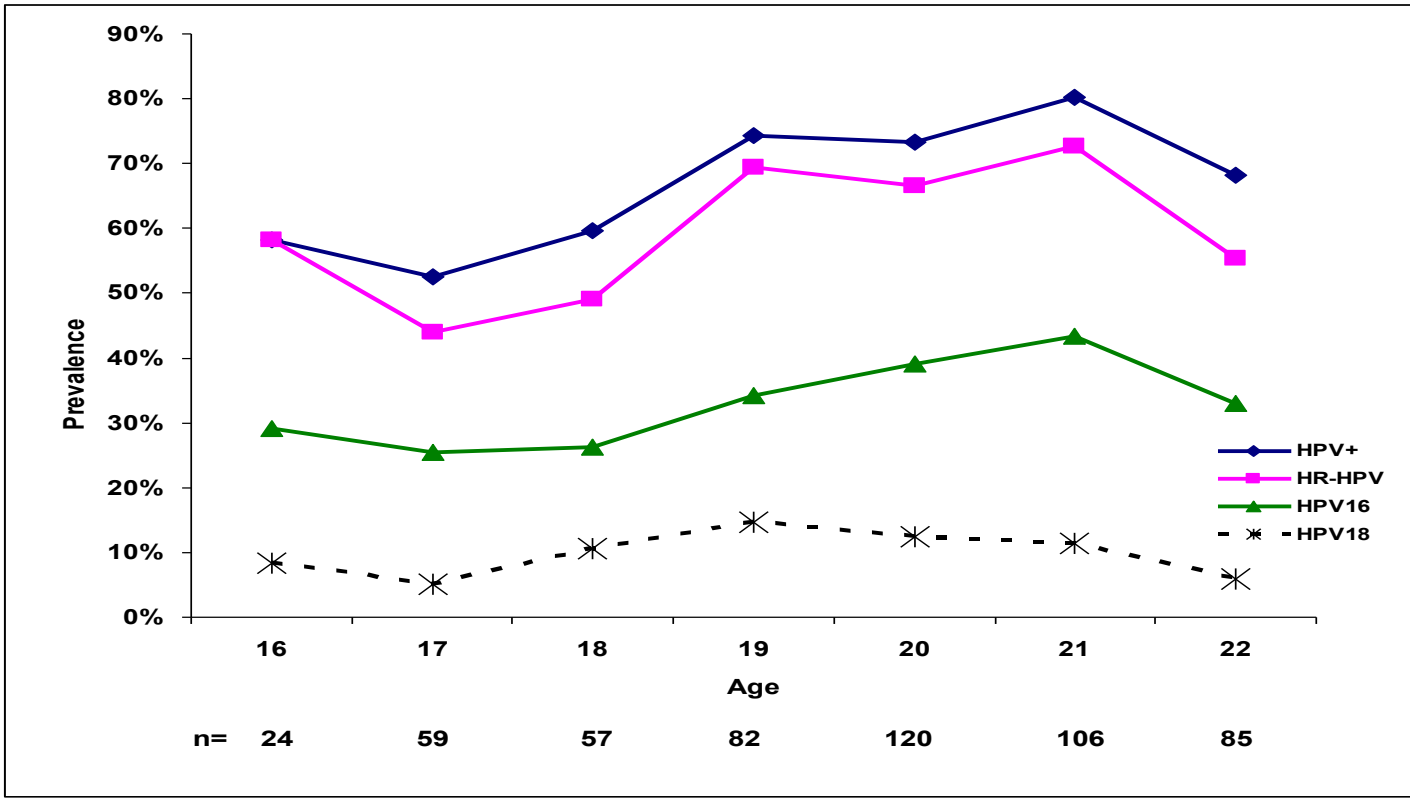


Figure 2

Ramqvist et al., Scand J Inf Dis 43 (2) 115-121, 2011

High risk HPV was common in the genital tract of young women at a youth clinic in Stockholm 2008-2011

- **Cervical tract HPV prevalence**

- 70% HPV positive
- 62% High risk HPV positive
- 35% HPV16 positive

- Infection with high risk HPV16 was very common

Ramqvist et al., Scand J Inf Dis 43 (2) 115-121, 2011

High risk HPV was common in the oral tract of youth and genital tract of young women at a youth clinic in Stockholm 2008-2011

Oral tract HPV prevalence

- 9.3% (45/483) HPV positive (9.2% in women; 9.8% in men)
- 7.2% (35/483) High risk HPV positive
- 3.6 % (14/483) HPV16 positive

Du J et al., EID 18(9) 1468-1471, 2012

Oral HPV infection was more common in women with as compared to those without a genital HPV infection

- 129/174 (74.1%) of the women with donating both genital and oral samples had genital HPV infection

- 17.1% (22/129) of the women with genital HPV had oral HPV infection and HPV concordance was observed.

- 4.4% (2/45) of the women without a genital HPV had oral HPV infection (p=0.043)

Historical interlude III

- HPV vaccination was introduced gradually
- 2010 it was free of charge for 10-12 year old girls
- 2012 it was introduced into the school based vaccination program for 10-12 year old girls
- 2012 a catch up vaccination program was available for women up to 26 years of age in Stockholm (similar but not identical in other counties)

Oral HPV prevalence in youth at high schools in one municipality in Sweden 2013

Students and samples (Life style questionnaire study)

- 175 boys and 160 girls, 17-21 years (mean age 18 years) donated mouth samples,
- 64% of the women were HPV vaccinated, in average at 17 years of age
- Sexual debut average was around 15. 2 years for girls and 15,4 years for boys

Method

- Luminex based Multiplex assay; (27 HPV types)

Results

- 1.8% of the oral samples were HPV positive (3.1% of the girls and 0.6% of the boys)
- 4/6 girls with HPV positive samples had been HPV-vaccinated

Grün N et al., Inf Dis 47: 57-61, 2015

Follow up of HPV prevalence in youth at the youth clinic 2013-2014

Patients and samples

- 211 young women gave a genital sample (self-test or by a midwife)
- 287 young adults, 200 women and 87 men donated a mouth wash sample

Method

- Luminex based Multiplex assay; (27 HPV types)

Grün N et al., Inf Dis 47: 57-61, 2015

Follow up of oral HPV prevalence in youth at the youth clinic 2013-2014

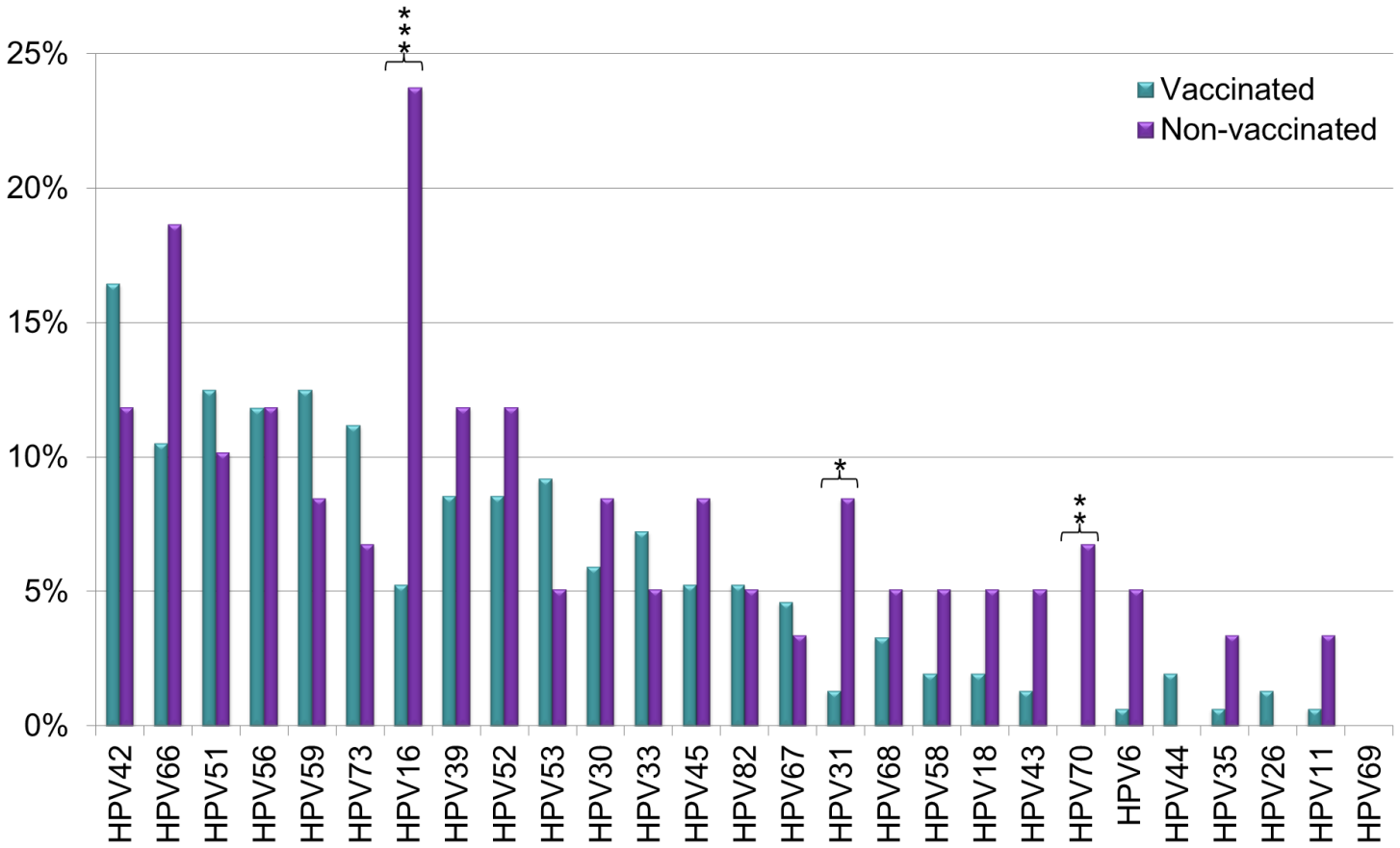
Oral HPV prevalence

- 4/287 (1.4%) of the youth (87 men, 200 women) had oral HPV positive (HPV16,51,52,59) samples, all 4 were women and all had genital HPV infection and in this cohort 75% of the women were HPV vaccinated, before or after sex debut

- This was significantly lower than that reported before i.e. 9.3%

- It was similar to that reported in 2013 in third grade high school students in a middle sized community in Sweden

Follow up of cervical HPV prevalence at the youth clinic 2013-2014



- 211 cervical samples; 73% of the women were HPV vaccinated b/a sex debut

Cervical HPV prevalence in women at the youth clinic 2013-2014

- HPV16 was significantly less common in the vaccinated than the non-vaccinated group, and similar trends were also found for HPV18, 6 and 11, but these were not statistically significant

- In addition, HPV31 and 70 (HPV16 and HPV18 like) were all significantly less common in the vaccinated than the non-vaccinated group

- Common cervical HR-HPV types were HPV 51, 56, 59, 73,16, 39, 52 and 53 – of which some are included in the new HPV vaccines

Oral HPV prevalence in youth at the youth clinic 2013-2015

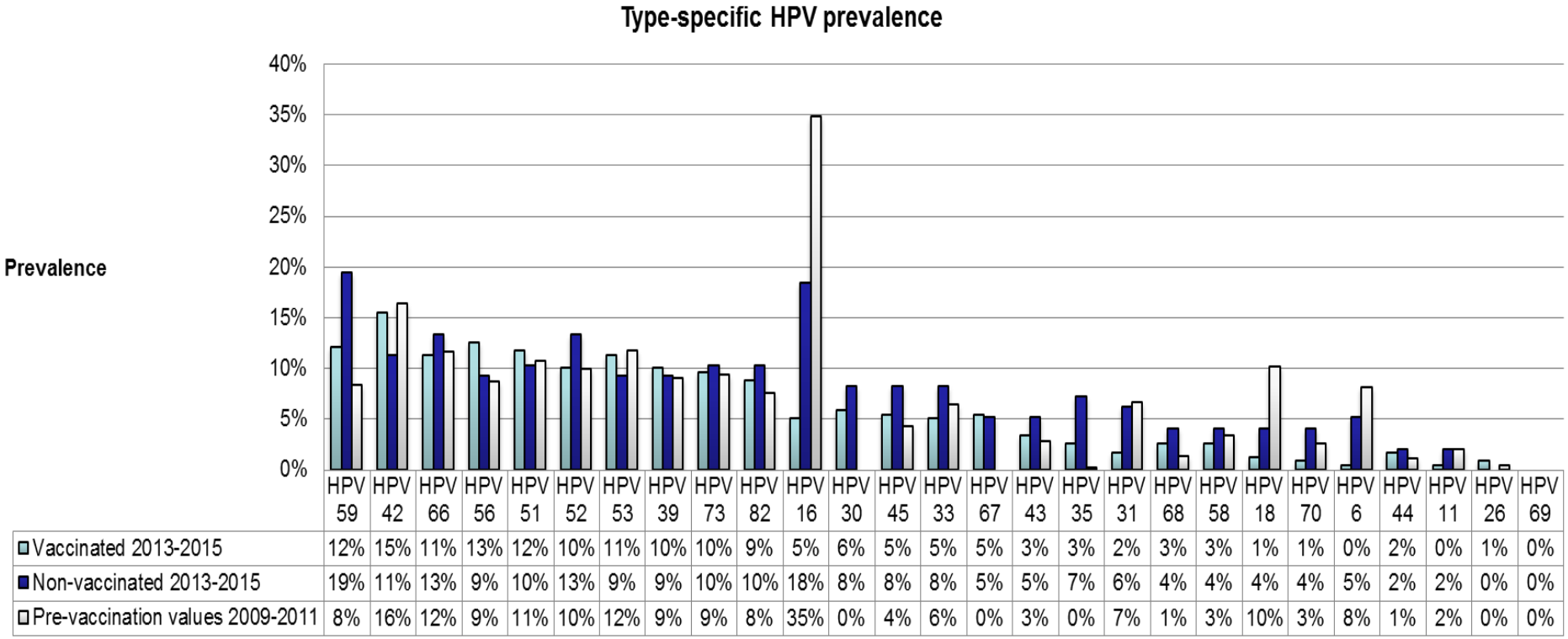
Patients, methods, results

- 7/457 (1.5%) of the youth (122 men 335 women) had oral HPV positive samples, 3 were men and 4 were women and all had genital HPV infection and in this cohort 71% of the women were HPV vaccinated, before or after sex debut

- This was significantly lower than that reported before i.e. 9.3%

- It was similar to that reported in 2013 in third grade high school students in a middle sized community in Sweden

Cervical HPV prevalence in women at the youth clinic 2013-2015



	HPV 59	HPV 42	HPV 66	HPV 56	HPV 51	HPV 52	HPV 53	HPV 39	HPV 73	HPV 82	HPV 16	HPV 30	HPV 45	HPV 33	HPV 67	HPV 43	HPV 35	HPV 31	HPV 68	HPV 58	HPV 18	HPV 70	HPV 6	HPV 44	HPV 11	HPV 26	HPV 69
Vaccinated 2013-2015	12%	15%	11%	13%	12%	10%	11%	10%	10%	9%	5%	6%	5%	5%	5%	3%	3%	2%	3%	3%	1%	1%	0%	2%	0%	1%	0%
Non-vaccinated 2013-2015	19%	11%	13%	9%	10%	13%	9%	9%	10%	10%	18%	8%	8%	8%	5%	5%	7%	6%	4%	4%	4%	4%	5%	2%	2%	0%	0%
Pre-vaccination values 2009-2011	8%	16%	12%	9%	11%	10%	12%	9%	9%	8%	35%	0%	4%	6%	0%	3%	0%	7%	1%	3%	10%	3%	8%	1%	2%	0%	0%

- 338 cervical samples; 71% of the women were HPV vaccinated b/a sex debut

Cervical HPV prevalence in women at the youth clinic 2017-2018

Patients and samples

- 121 cervical samples; 77% of the women were HPV vaccinated before or after sex debut

Methods

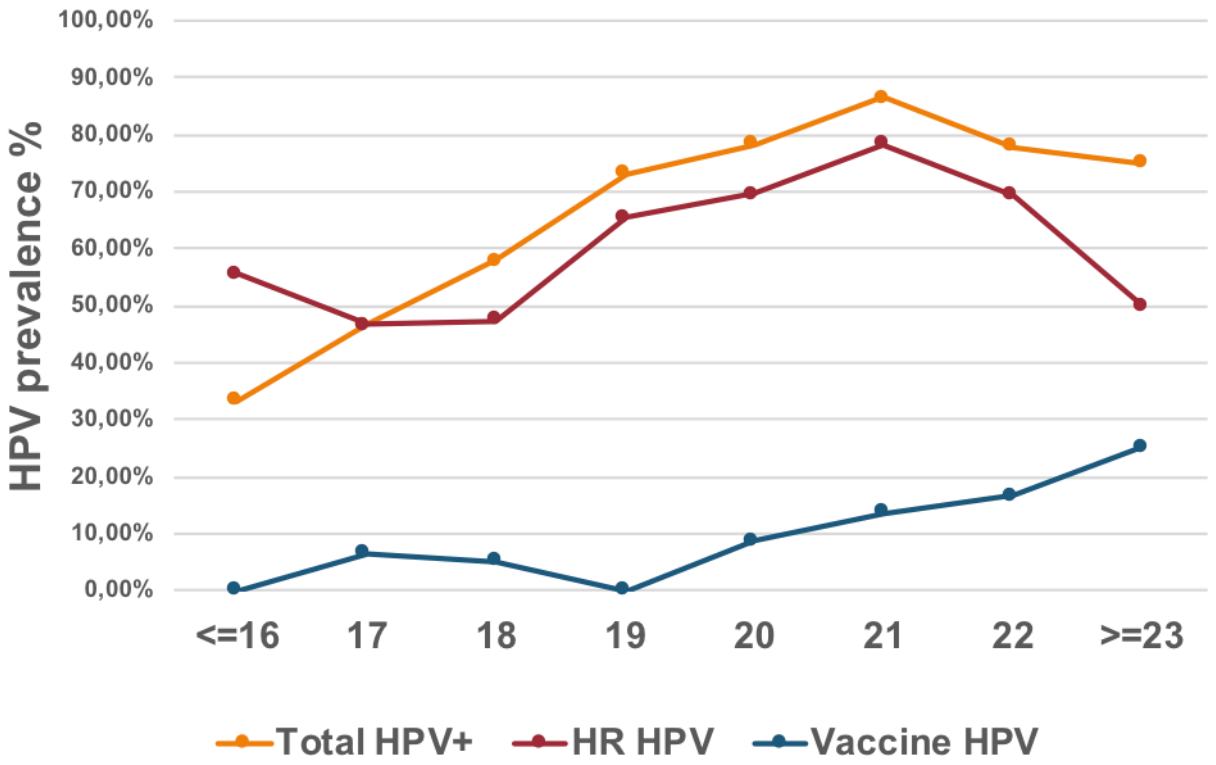
- A Luminex based multiplex assay was used for HPV-detection, 27 HPV types

Ährlund-Richter A et al, Front Cell Infect Microbiol. 2019 Mar 20;9:59..

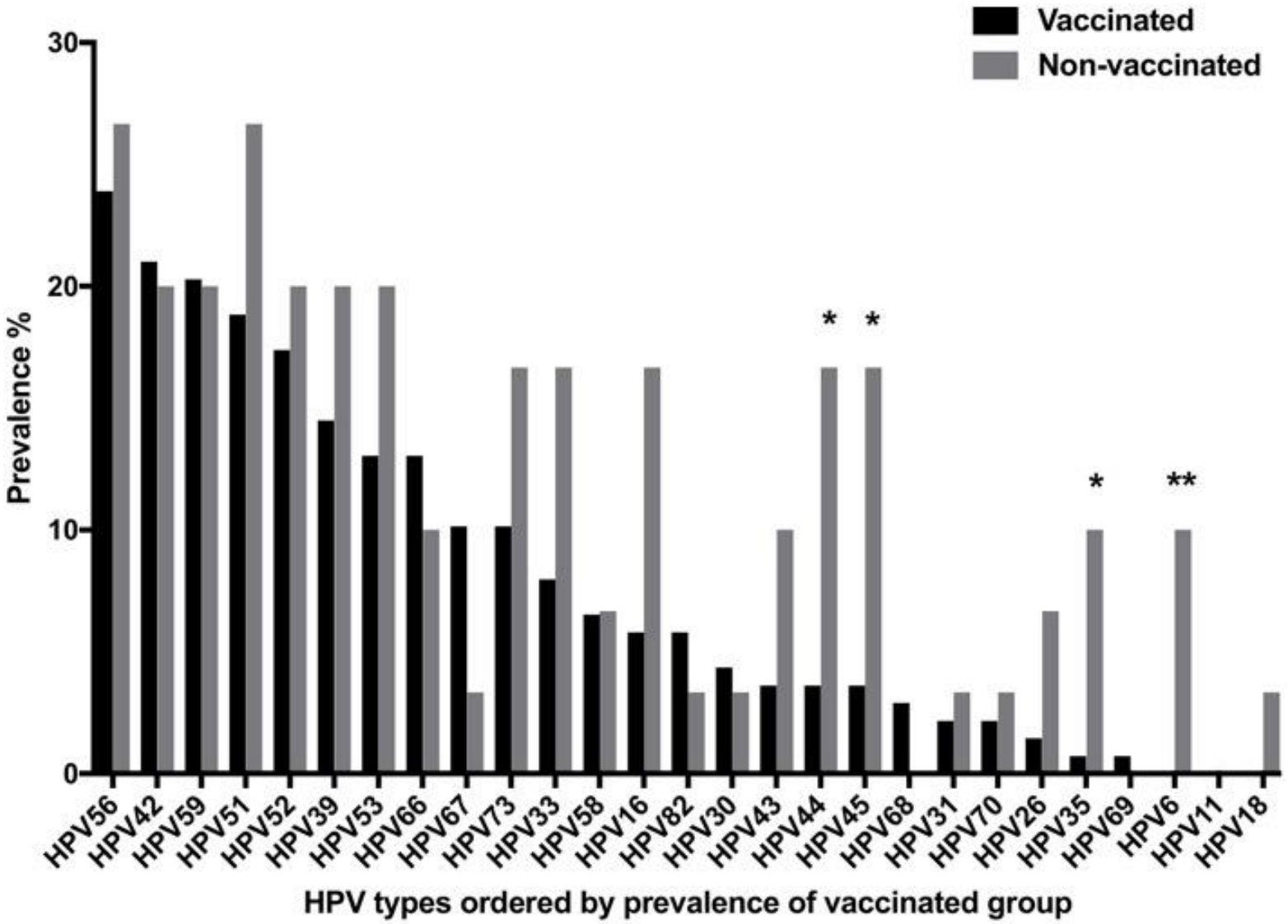
Cervical HPV prevalence in women at the youth clinic 2017-2018

Karolinska Institutet

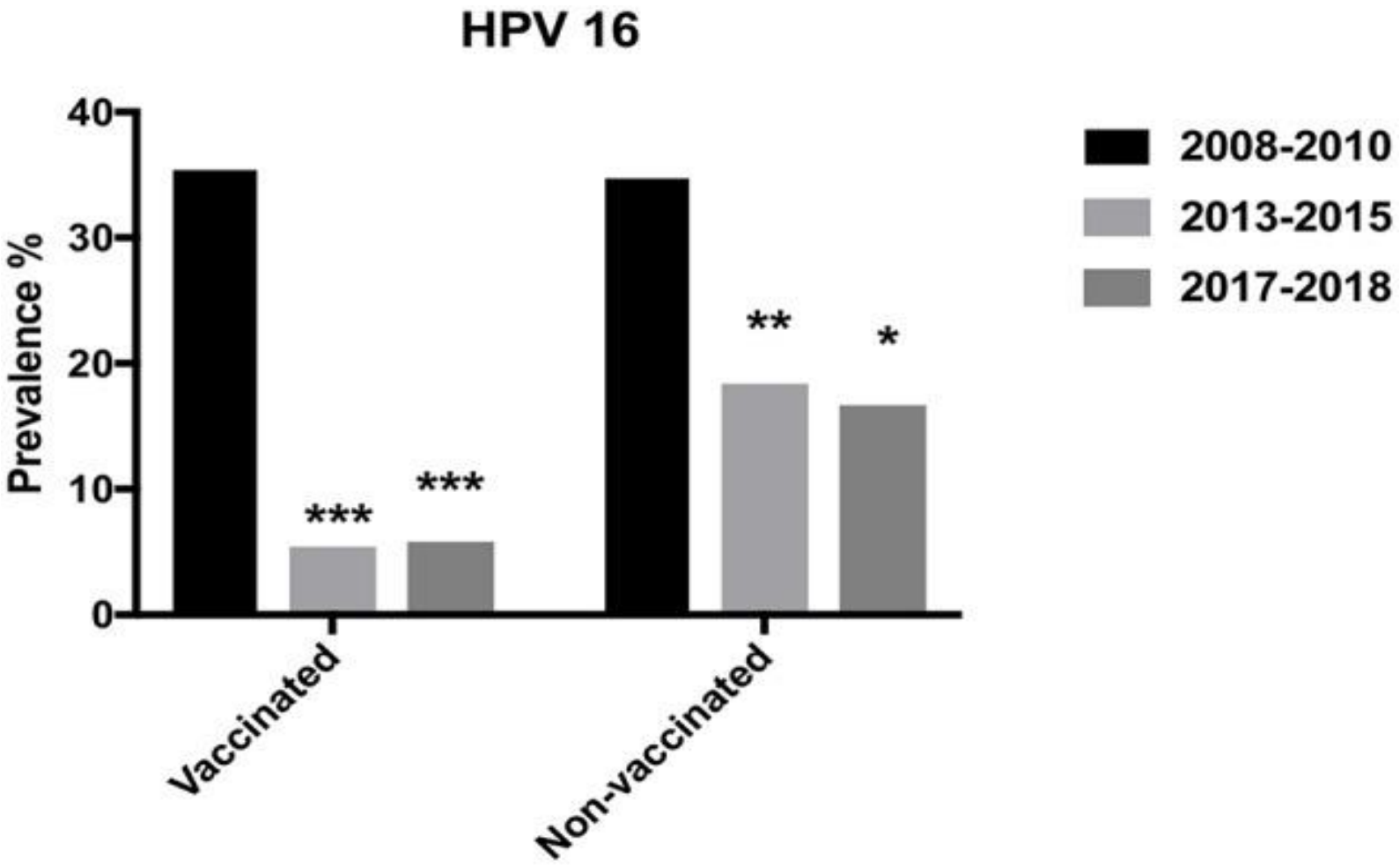
Data by age



Cervical HPV prevalence in women at the youth clinic 2017-2018



Cervical HPV prevalence in women at the youth clinic 2008-2018



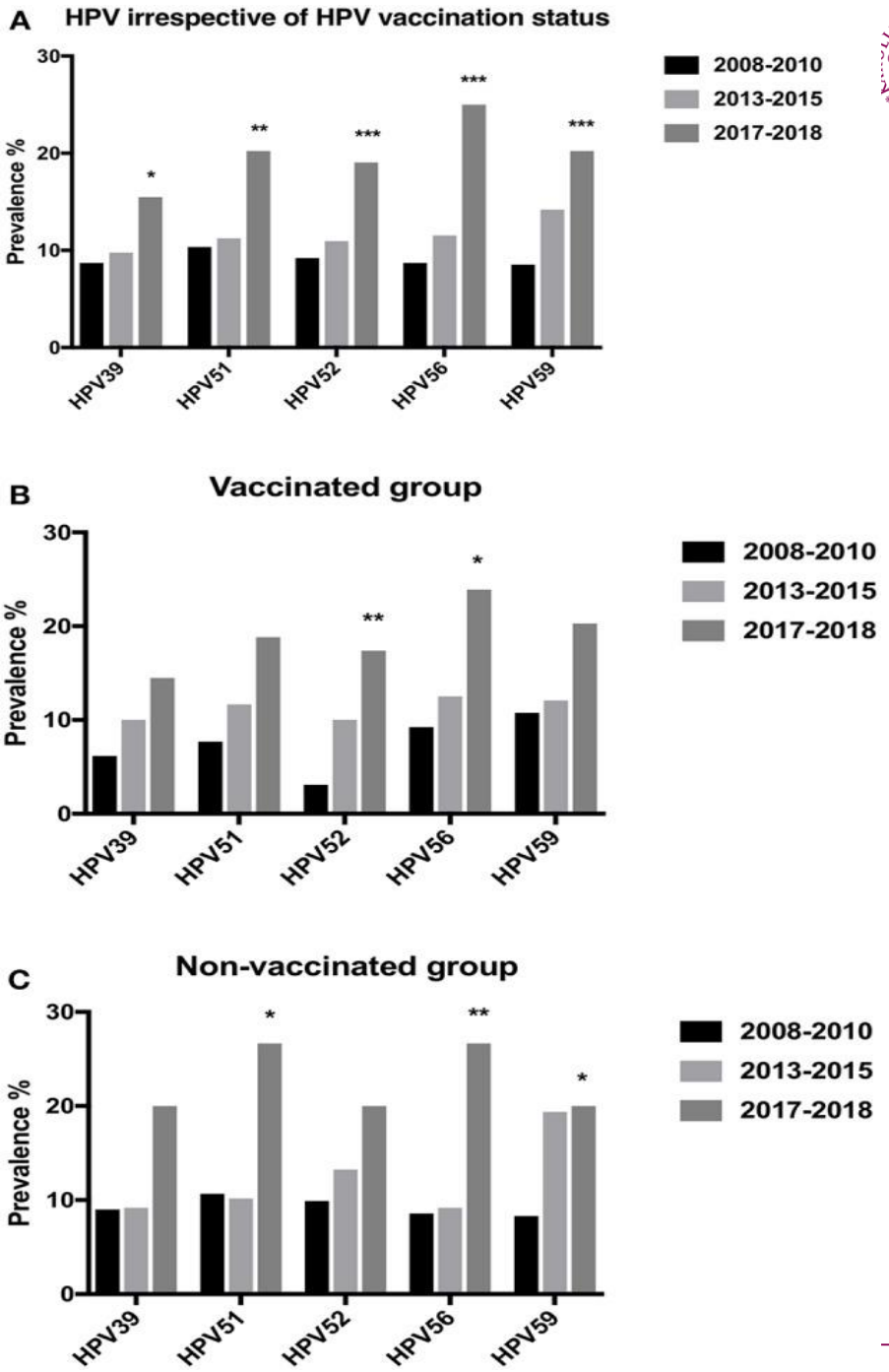
Cervical HPV prevalence in women at the youth clinic

HR HPV39, 51, 52, 56 and 59 have increased in prevalence

The nonavalent vaccine includes: HPV16, 18, 31, 33, 45, 52 and 58 6 and 11

So..HPV39, 51, 56 and 59 may still present a risk

And according to previous data together they may account for around 10% of all cervical cancer



Summary (Stockholm youth clinic data):

2008-2011

- Cervical HPV infection, including HPV16 was frequent (34%) in women
- Oral HPV infection was similar in men and women (9-10%)

2013-2015

- Cervical HPV16 infection dropped considerably in vaccinated (5%) compared to non-vaccinated (18%) women and this was lower than that 2008-2011 (35%)
- Oral HPV infection had decreased considerably (from 9.3% to 1.5%)

2017-2018

- Cervical HPV16 infection dropped considerably in vaccinated (5.8%) compared to non-vaccinated (16.7%) women and lower than that 2008-2011 (35%)

Summary (Stockholm youth clinic data and a systematic review and meta-analysis):

2017-2018[1]

- Cervical HPV16,18, and others have dropped considerably in vaccinated and non-vaccinated individuals

- However, HR HPV39, 51, 56 and 59 still remain and may present a risk despite the introduction of the nonavalent vaccine

2019[2]*

- Cervical HPV16,18, and others have dropped considerably on the population level and CIN II has decreased

** Drolet et al, Lancet. 2019 Aug 10;394(10197):497-509*

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