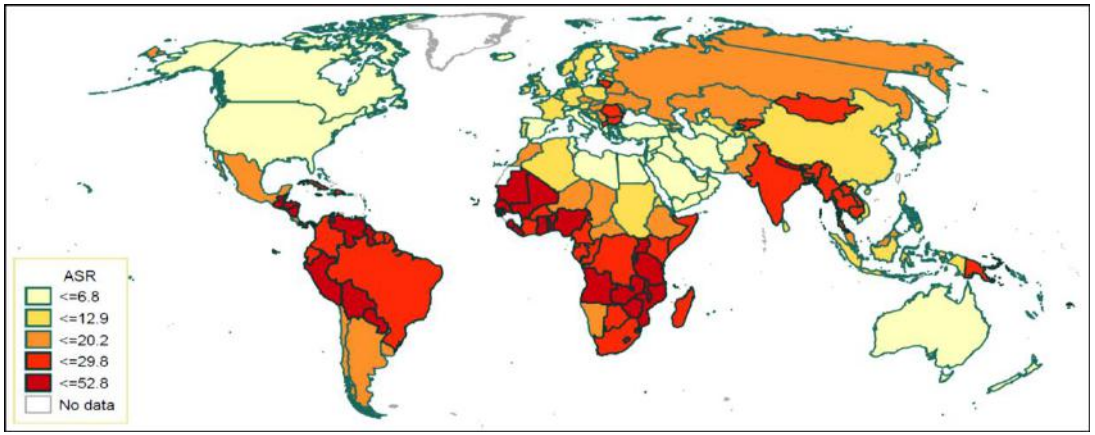
110 years of research

10 years of HPV vaccines & HPV vaccination



FX Bosch
Institut Catala d'Oncologia
Barcelona 2017

Potential conflict of interest

- Research and educational institutional grants:

  GSK, SPMSD, Merck, Qiagen

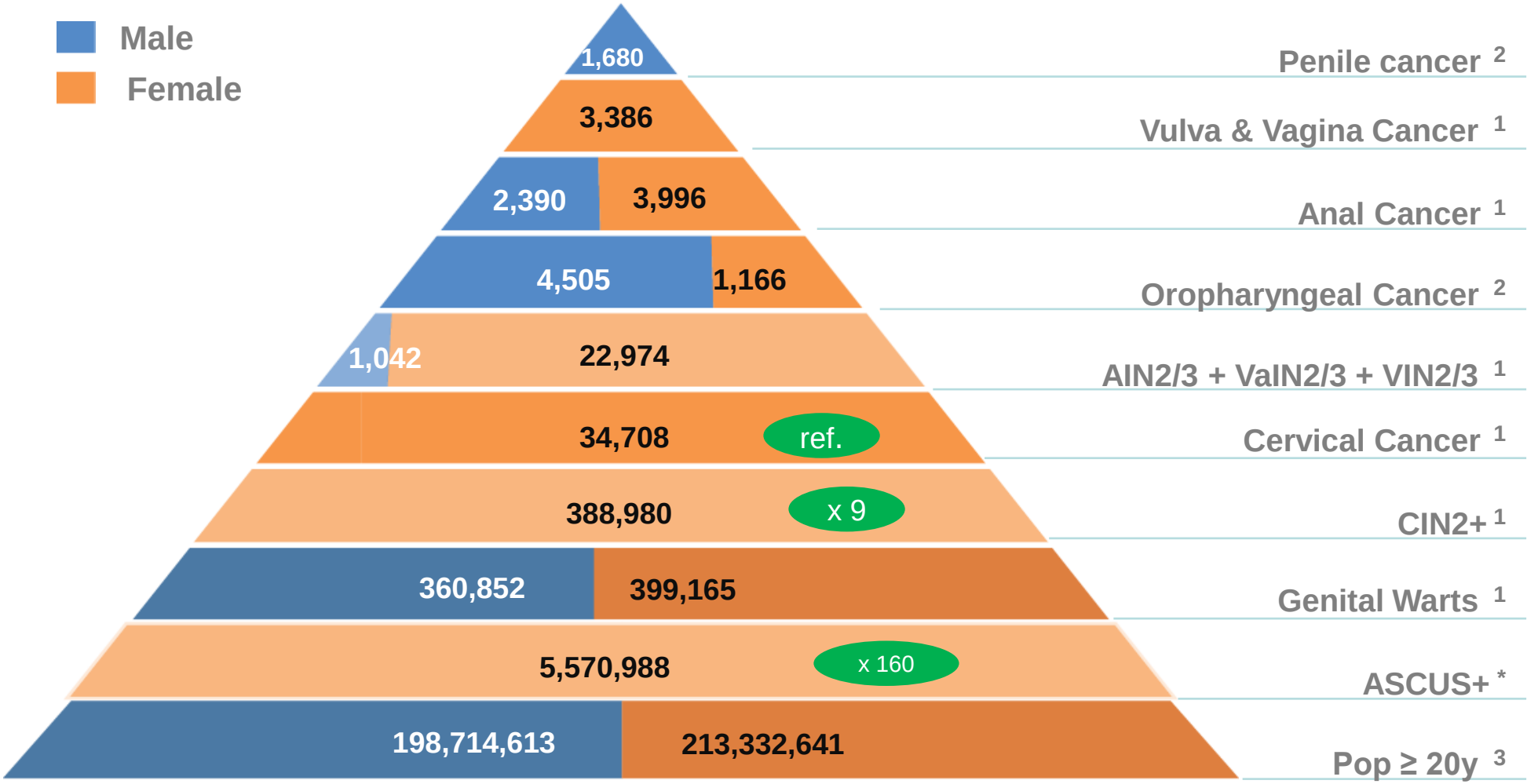
- Personal / speaking / travel grants:

  GSK, SPMSD, Merck, Qiagen, RMS

This presentation is the sole responsibility of the author

European Union HPV-Related Disease Burden, Men and Women :

Annual estimations for Cancers ***(50,000)*** and precancerous lesions ***(6M)***



Europe: 30 countries from European Medicines Agency (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, UK) + Switzerland. * Estimations assuming 3.5% of ASCUS+ among women aged 25-65 years.

1. Hartwig et al. submitted; 2. Forman et al .2012 Vaccine; 3. World Population Prospects 2012 Revision

bi-valent HPV vaccine (Cervarix)

16	18	
60µg	40µg	ASO4-AL

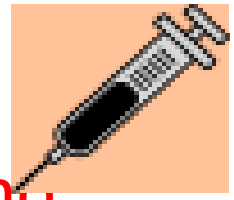
quadri-valent HPV vaccine (Gardasil)

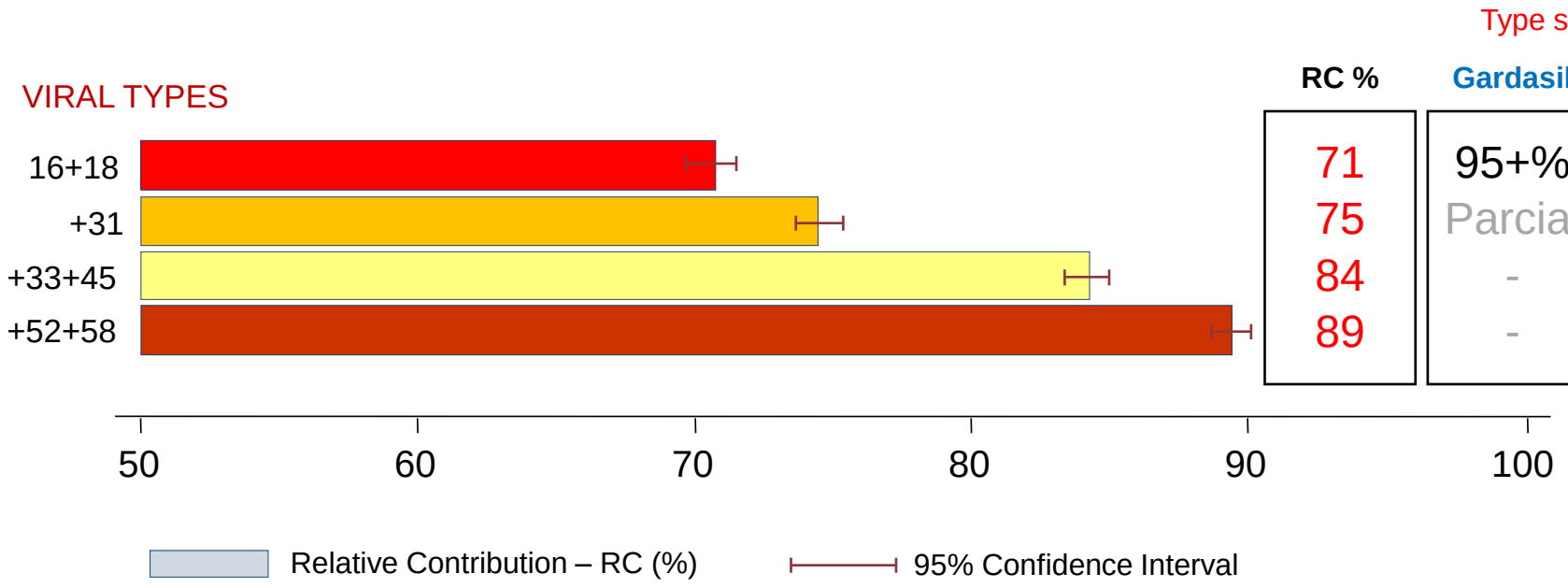
6	11	16	18	
20µg	40µg	40µg	20µg	AAHS 250

nine-valent HPV vaccine (Gardasil 9)

6	11	16	18	31	33	45	52	58	
30µg	40µg	60µg	40µg	20µg	20µg	20µg	20µg	20µg	AAHS 500

HPV type-specific contribution to cervical cancer and potential for prevention of existing vaccines



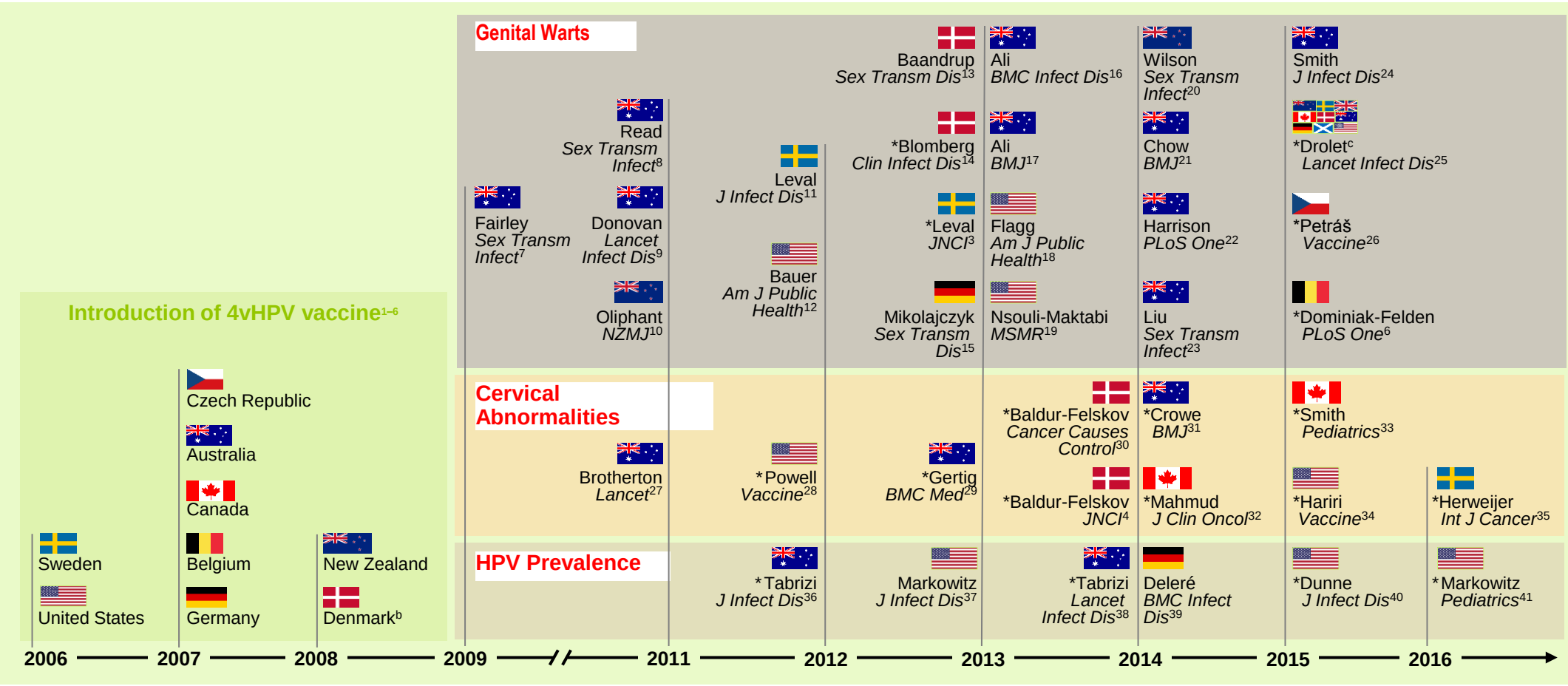


Type specific Vaccine efficacy

RC %	Gardasil	Cervarix	Gardasil9
71	95+%	95+%	95+%
75	Parcial	Parcial	95+%
84	-	Parcial	95+%
89	-	?	95+%

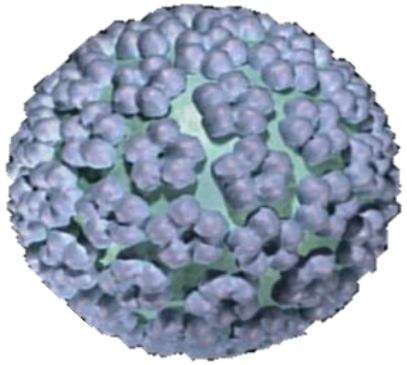
de Sanjosé S et al. Lancet Oncol, 2010
Serrano B et al. Infect Ag Cancer, 2012
Schiller J et al Vaccine 30 S 5 2012
Lehtinen M et al. Nat Rev Clin Oncol. 10 2013

Effectiveness and Impact of 4vHPV Vaccine in Vaccination Programs demonstrated in numerous publications: Selected Reports



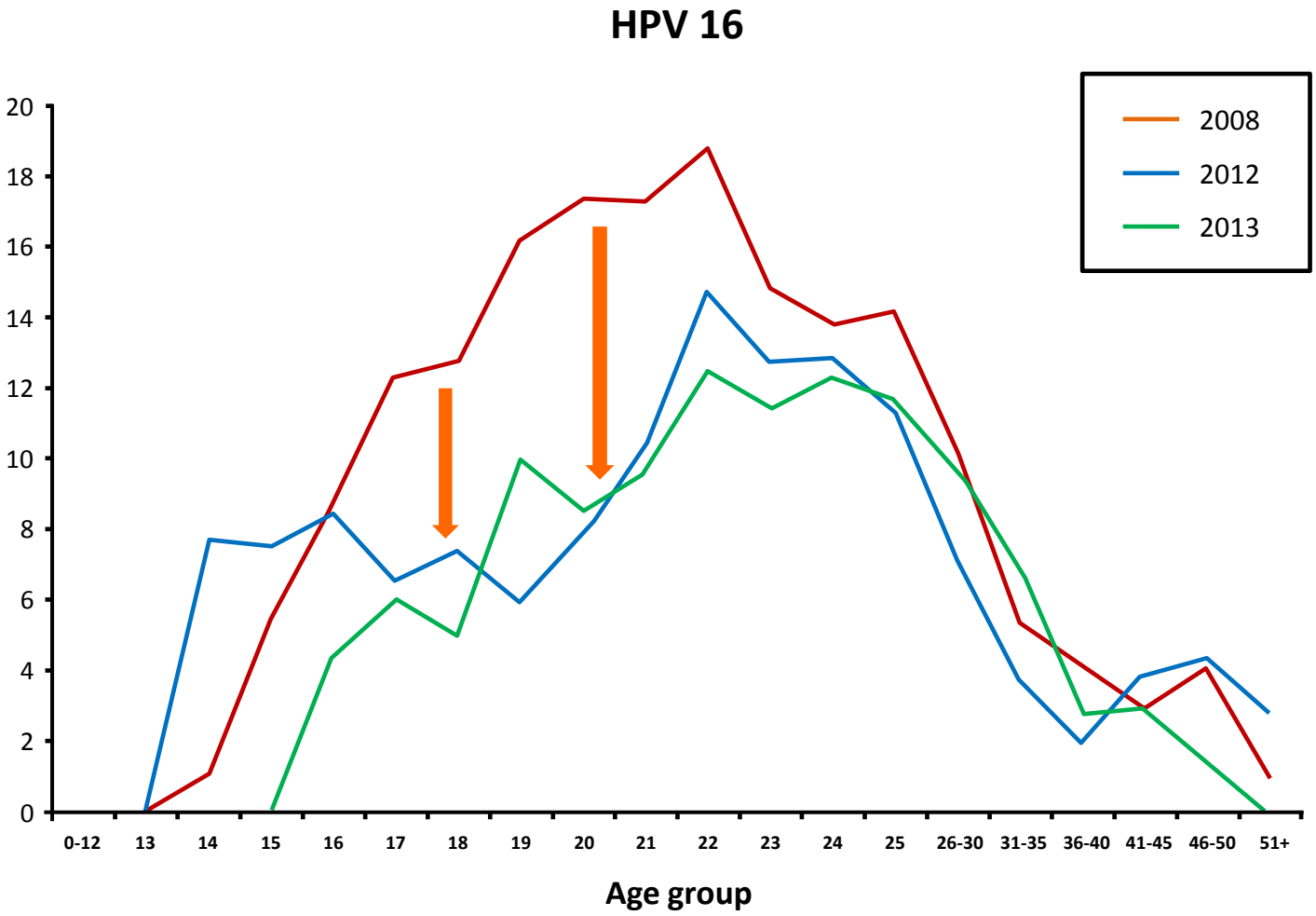
*Study links effectiveness data to vaccination status. [a]Includes reports published in the peer-reviewed scientific literature, and does not encompass reports at scientific conferences. [b]Beginning on February 1, 2016 the childhood vaccination program switched to the 2vHPV vaccine.[42] [c]Meta-analysis of data from 20 studies in 9 countries (United States, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada, and Germany), including both 4vHPV vaccine and 2vHPV vaccine.[25]

OUTCOME HPV INFECTIONS



STI registries and serum banks in Sweden.
Specimens tested for HPV
before and after HPV vaccine introduction

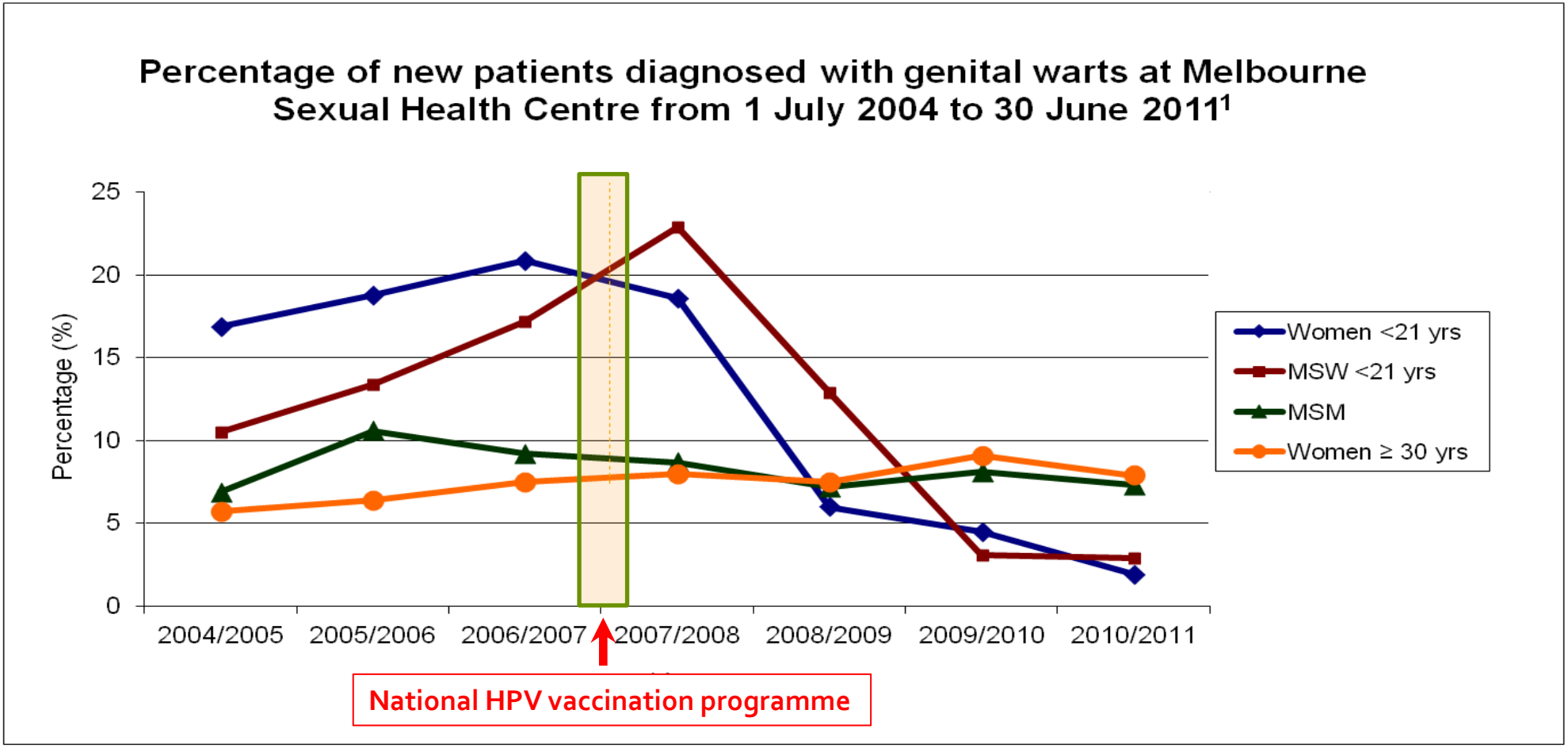
HPV16 prevalence according to age in genital swabs with or without urine from women.



Söderlund-Strand A, et al. Cancer Epidemiol, Biomarkers & Prevention. 23(12):2757-64.

Outcome: Genital warts

AUSTRALIA: POPULATION IMPACT ESTIMATES ON GENITAL WARTS



Declines in under 21 years of age: women from **18.6% to 1.9%** heterosexual men from **22.9% to 2.9%**

Around 93% reduction of GW – this has been seen also in other countries

1. Read et.al., *Sex Transm Infect* 2011; 87:544e547. doi:10.1136/sextrans-2011-050234

OUTCOME: CIN 3 - CARCINOMA IN SITU

Decline in pre-cancer now impacting up to 30 years

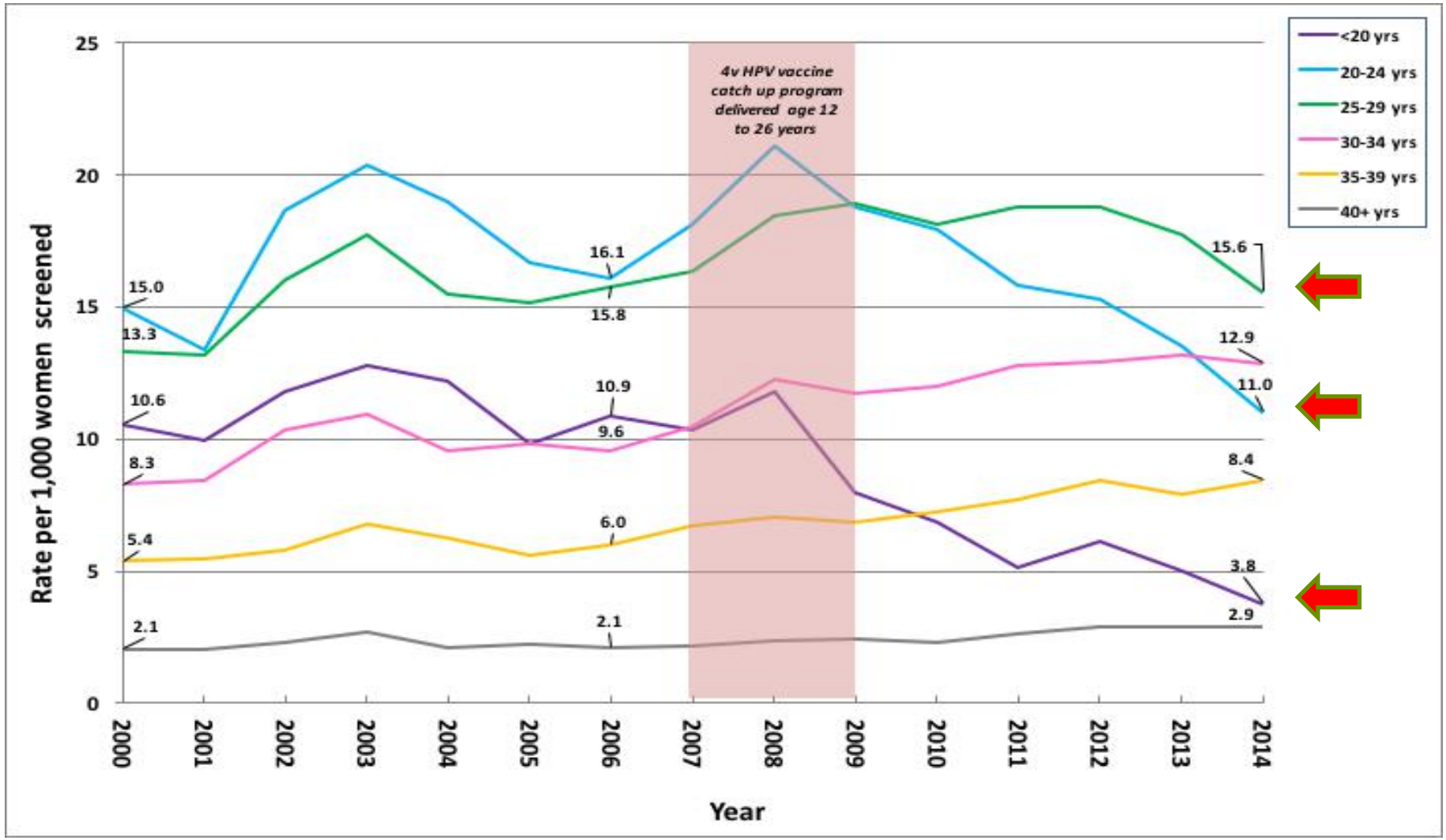


Figure 1: Trends in prevalence rates of high grade histologically confirmed cervical abnormalities (CIN2+)* diagnosed in Victorian women, Australia, by age group, 2000-2014

Source: Brotherton et al. Med J Aust 2016

Expected results 2017 +

- Reduction of *cervical cancer* (2/3 years)
- Reduction in *RRP* (in 4 / 9 valent vaccine users)
- Reduction on *other HPV related cancers* (vulva, vagina, anal, oropharynx) (at least one decade)
- Reduction of *other* cancers (?)

THE ANTI HPV VACCINE SPECIFICITY

Trump taps vaccine skeptic Robert F. Kennedy Jr. to launch review

President-elect Trump has some doubts about the current vaccine policy, Kennedy says

Thomson Reuters Posted: Jan 10, 2017 2:57 PM ET | Last Updated: Jan 11, 2017 8:44 AM ET

General considerations

- HPV vaccines have arrived at a time in which ***concerns about safety***, surveillance and vaccination programs are of great importance.
  - i.e. crisis with the avian flu vaccines, rotavirus, adjuvants, other.

- Generalized ***adolescent vaccination*** is relatively new in the calendar.
  - Group psychogenic responses (Australia, Colombia, Spain).
  - Limited tradition in vaccinating adolescents (i.e. school vs clinics)

- ***Social image*** of public institutions and corporations (even WHO) is under scrutiny and significant challenge.

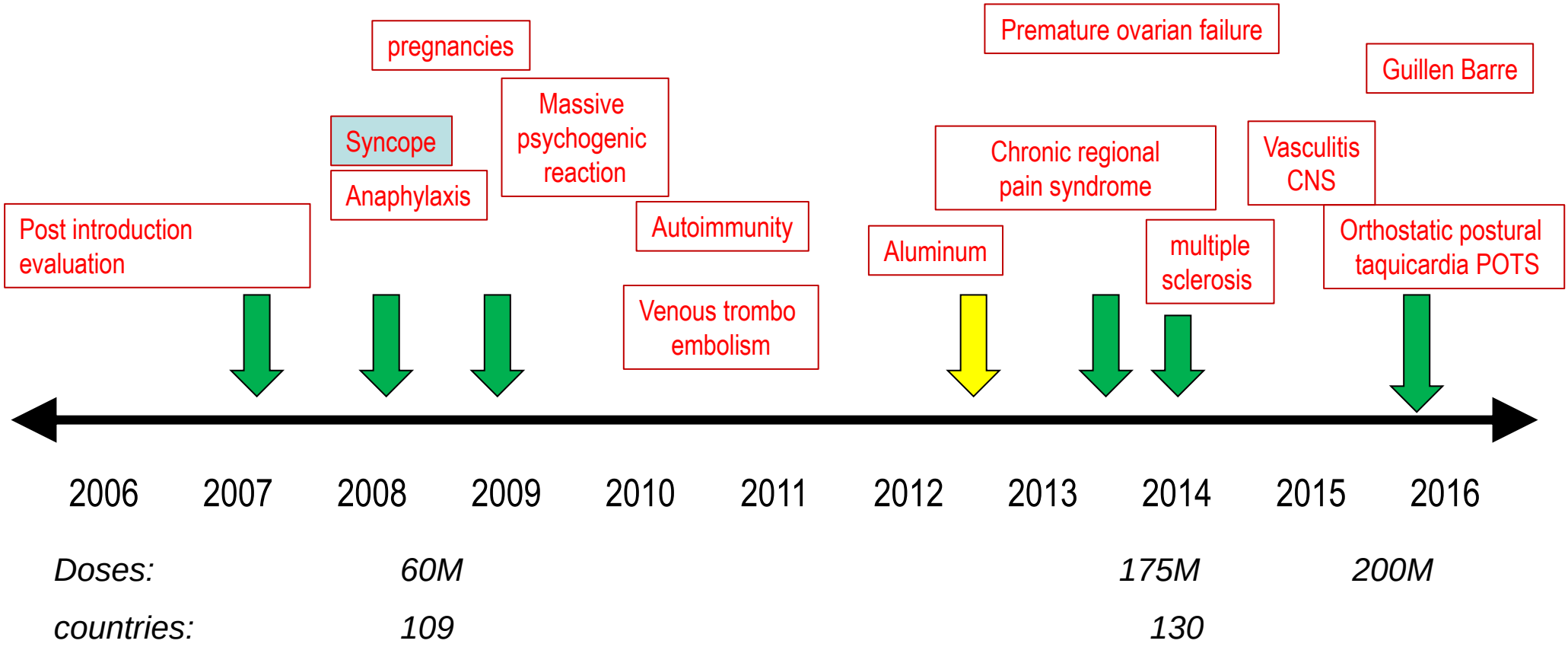
General considerations (2)

- **HPV vaccines** have a special aura:

  - ***Long interval*** between exposure and disease. Distorted perception of risk over time. Pediatricians *vs*. gynecologists *vs*. oncologists
  - ***Sexual behavior*** connotations, ethical considerations, religious involvement.
  - ***One gender*** vaccination recommendations.
  - ***New technology*** in manufacturing.
  - Very active ***anti-vaccine*** movements; internet amplified.

Reports of the global committee on safety of vaccination in relation to the HPV vaccine (GACVS 2007/15) / Strategic Advisory Group of Experts in immunization (SAGE)

World Health Organization



Original Article
Journal of INTERNAL MEDICINE
doi: 10.1111/joim.12535

Incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease after quadrivalent human papillomavirus vaccination: a cohort study

O. Grönlund[1], E. Herweijer[1], K. Sundström[2] & L. Arnheim-Dahlström[1]

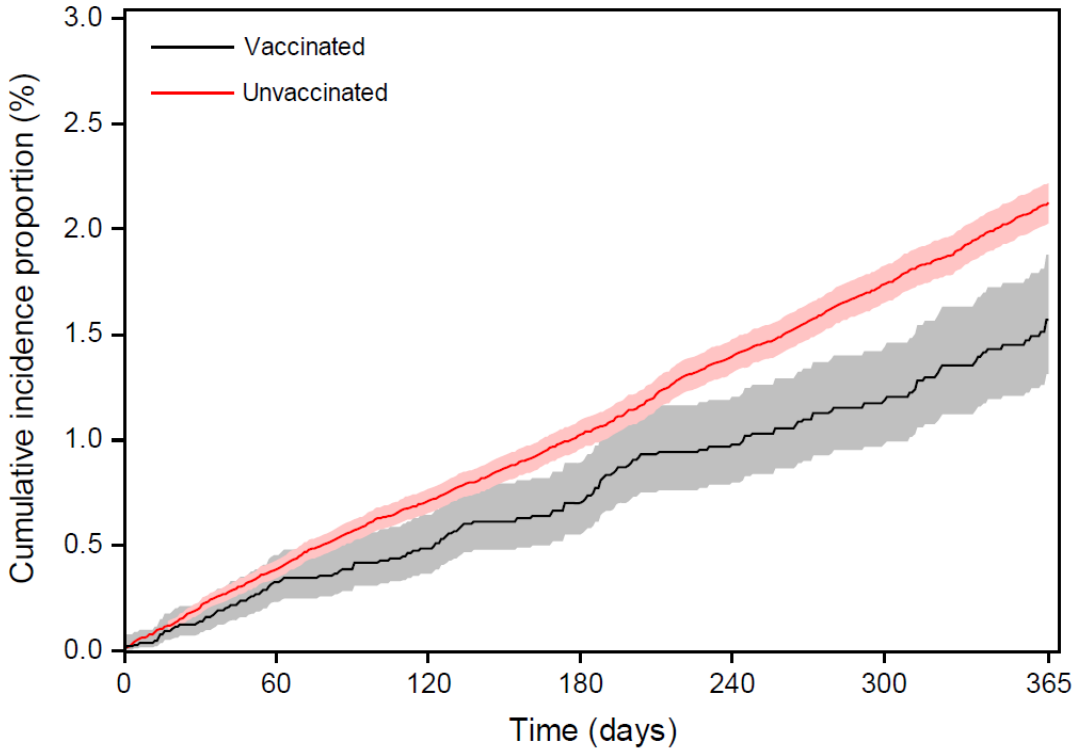
From the [1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; and [2]Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

70,265 women (10-30) with one of 49 pre specified autoimmune diseases (AID) in 2006-12: 16% received at least one dose of HPV vaccine in Sweden

Incidence of second AID in vaccinated: 15.8 x 1000 py

Incidence of second AID in non vaccinated: 22.1 x1000 py

Cumulative incidence (%) of autoimmune diseases in recipients of 1 dose of 4vHPV vaccine compared to an aged matched non-vaccinated group. 1-year follow up IRR: 0.77 (0.65-0.93) p=0.006



Grolund O. J Internal medicine 2016

HEALTH PROFILE ASSOCIATED WITH REPORTED SIDE EFFECTS AFTER VACCINATION : DENMARK LINKAGE STUDY

2 year before vaccination	Multivariate OR	95 % CI
Consultation GP/Other	**1.91**	1.15 - 3.16
Physiotherapy / chiropractor /related treatments	**2.13**	1.64 - 2.76
Psychologists /psychiatrists / related treatments	**1.87**	1.31- 2.66
Hospital contact / digestive	**1.57**	1.01- 2.45
Hospital contact / musculoskeletal and connective	**1.56**	1.09 - 2.23
Hospital contact / ill defined	**1.77**	1.27 - 2.48
Hospital contact / injuries	**1.51**	1.18 - 1.93

Molbak et al. PLOS one 2016

Communica nt and a

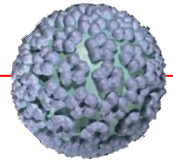
POTENTIAL NEW INDICATIONS FOR HPV VACCINATION / SCREENING

PROPHYLACTIC
(prevent new infections and transmission)

- Adult women
  - *To 26, 30,* 45+…
- Males
  - To 18, 50+…
- Infants (EPI)
- Two/One doses

AS PART OF THERAPY
(interrupt reinfections and prevent transmission)

- HPV + women found in screening
- Post treatments in CIN lesions
- RRP
- GW and survivors of HPV related cancers
- Therapeutic / mixed vaccines



HIGH RISK GROUPS
(selective vaccination)

- HIV cohorts / MSM
- Transplants & immunosuppressed
- Autoimmune patients
- STI clinics
- Partners of HPV+
- Migrants / marginal
- Abused children

Searching for the right combinations of vaccination and screening for cervical cancer prevention : The *HPV FASTER* project

FX Bosch
Institut Catala d'Oncologia

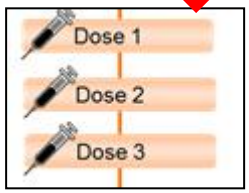
NEW OPTIONS UNDER RESEARCH FOR A *NON-INFERIOR LIFETIME PROTECTION*

Women 25-65

ONE HPV SCREENING

♣Two doses
♣ One dose

♣ First dose with first screen



1 / 2 visits?

X 5 / 7/ 10y

7 to 9 visits

At each round 3-5% follow up required

Both arms should offer *similar level* of high protection

BUT

Much *lower global costs*
Greater *compliance* (2 / 3 visits)
Lower burden on the *clinical health services*

Only opportunity

Individual option

Two doses vs. Three doses

- Price reduction of the program
  - Logistics simplification
- Improve vaccination coverage

T0

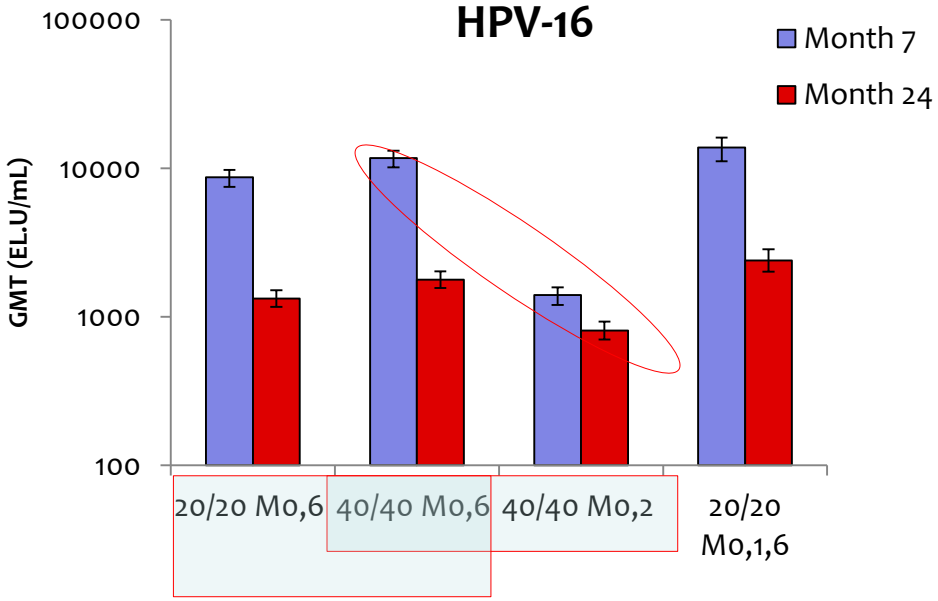
T1-2

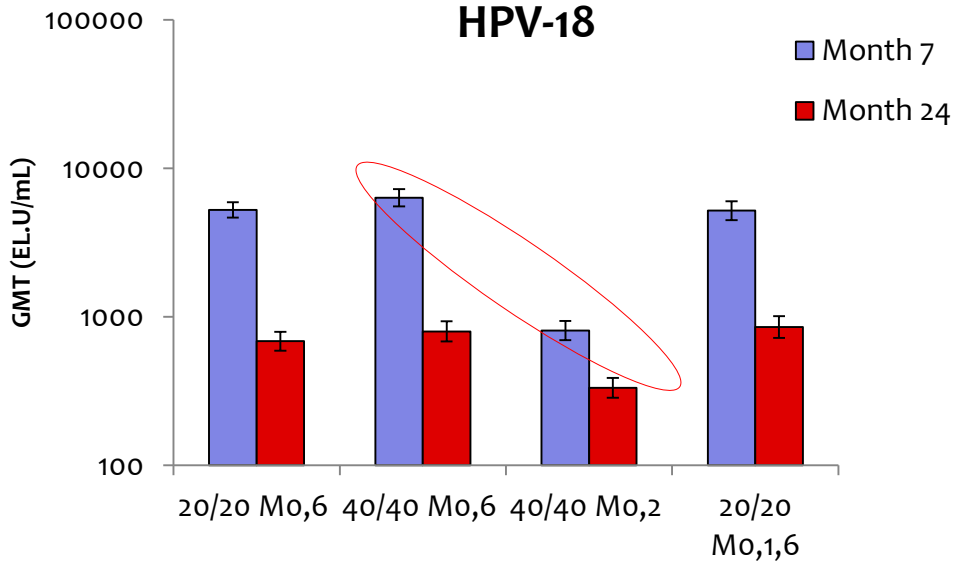
T6-12

Immunogenicity: 9–25 years, seronegative at baseline

(ATP immunogenicity cohort, Month 24)

- All subjects were seropositive one month after vaccination (Month 7) and up to Month 24 for both antigens





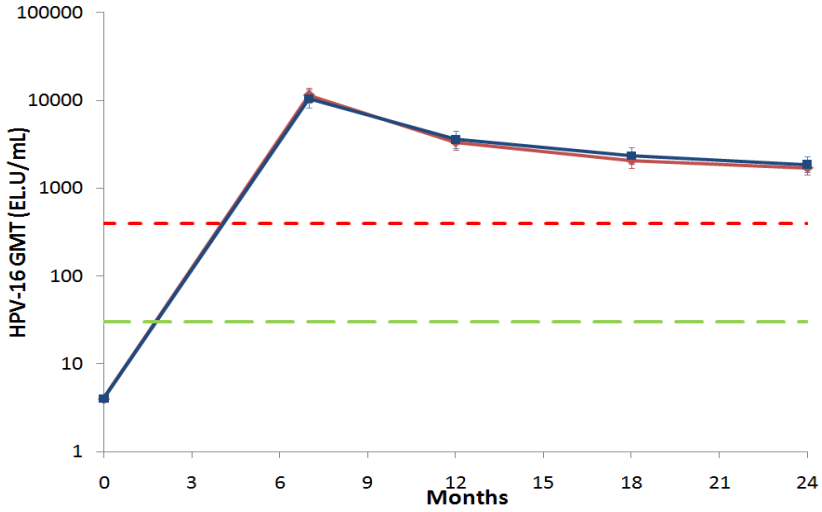
ATP = according to protocol, **GMT** = geometric mean titre, error bars represent 95% confidence intervals

Antibody kinetics

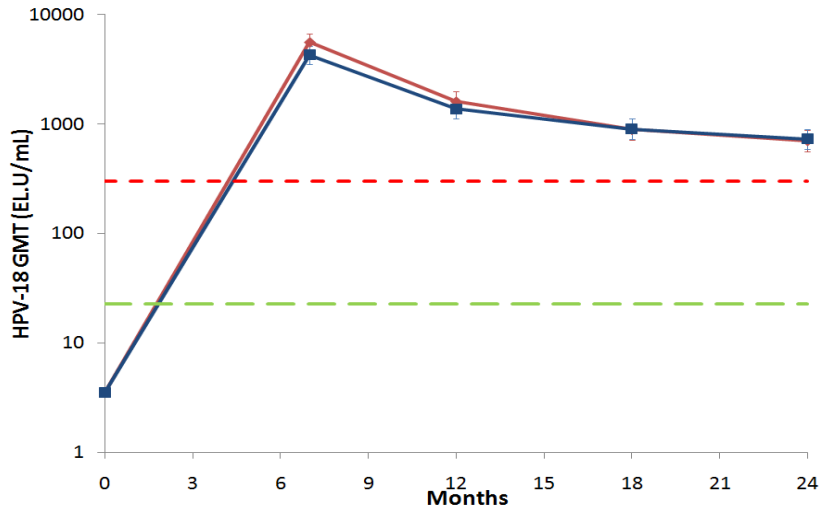
(ATP immunogenicity cohort, Month 24)

- Antibody kinetics were similar between the 2-dose M0,6 (9–14 years) and 3-dose M0,1,6 (15–25 years) groups

HPV-16



HPV-18



20/20 M0,6 (9–14 years)
Plateau
20/20 M0,1,6 (15–25 years)
Natural infection

ATP = according to protocol, **GMT** = geometric mean titre, **natural infection** = subjects who had cleared infection had GMTs of 29.8 (HPV-16) and 22.7 EL.U/mL (HPV-18) in Study HPV-008; **plateau** = GMTs at the plateau level in Study HPV-007 (Month 45-50 time point) were 397.8 (HPV-16) and 297.3 EL.U/mL (HPV-18)

FDA Approvals:

Vaccine type	Female	Male	Age
Cervarix[1]	Cervix	No indication	9 – 25 years
Gardasil[2]	Cervix, Vulva, Vagina, Anal, Genital Warts	Anal, Genital Warts	9 – 26 years
Gardasil 9[3]	Cervix, Vulva, Vagina, Anal, Genital Warts	Anal, Genital Warts	9 – 26 years

EMA Approvals:

Vaccine type	Female	Male	Age
Cervarix[4]	Cervix, Vulva, Vagina, Anal	Anal	> 9 years
Gardasil[5]	Cervix, Vulva, Vagina, Anal, Genital Warts	Anal, Genital Warts	> 9 years
Gardasil 9[6]	Cervix, Vulva, Vagina, Anal, Genital Warts	Anal, Genital Warts	> 9 years

1. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf - Last accessed on 16.08.2016
2. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf - Last accessed on 16.08.2016
3. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf - Last accessed on 16.08.2016
4. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf - Last accessed on 16.08.2016
5. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf - Last accessed on 16.08.2016
6. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf - Last accessed on 16.08.2016

Posology of HPV Vaccines

VACCİNE TYPE	FDA	EMA
Cervarix[1,4]	**3 Doses** (0, 1, 6 months)	**9-14 Years:** **2 Doses** *The second dose given between 5 and 13 months after the first dose** **+15 Years:** **3 Doses** (0, 1, 6 months)
Gardasil[5]	**3 Doses** (0, 2, 6 months)	**9-13 Years:** **2 Doses** (0, 6 months)*** **+14 Years:** **3 Doses** (0, 2, 6 months)****
Gardasil 9[6]	**3 Doses** (0, 2, 6 months)	**9-14 Years:** **2 Doses***** *The second dose should be administered between 5 and 13 months after the first dose* **+15 Years:** **3 Doses** (0, 2, 6 months)****

** If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered*
*** If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose*
**** If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered*
***** The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period*
****** If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.*

MALE HPV VACCINATION:

Further increase protection of women by interrupting transmission
protect vaccinated males against hpv-induced cancers

QUADRIVALENT HPV VACCINE EFFICACY STUDIES IN MEN

Vaccine efficacy against EGL, (mostly GW) in men	Vaccine efficacy against anal intraepithelial lesions in MSM
 **90.6% (70-98)**	 **77.5% (40-93)**
Giuliano *et al.* NEJM 2011 Per protocol cohorts	Palefsky *et al* . NEJM 2011 Per protocol cohorts

COST BENEFIT BALANCE: GENERAL CONSIDERATIONS

Include males

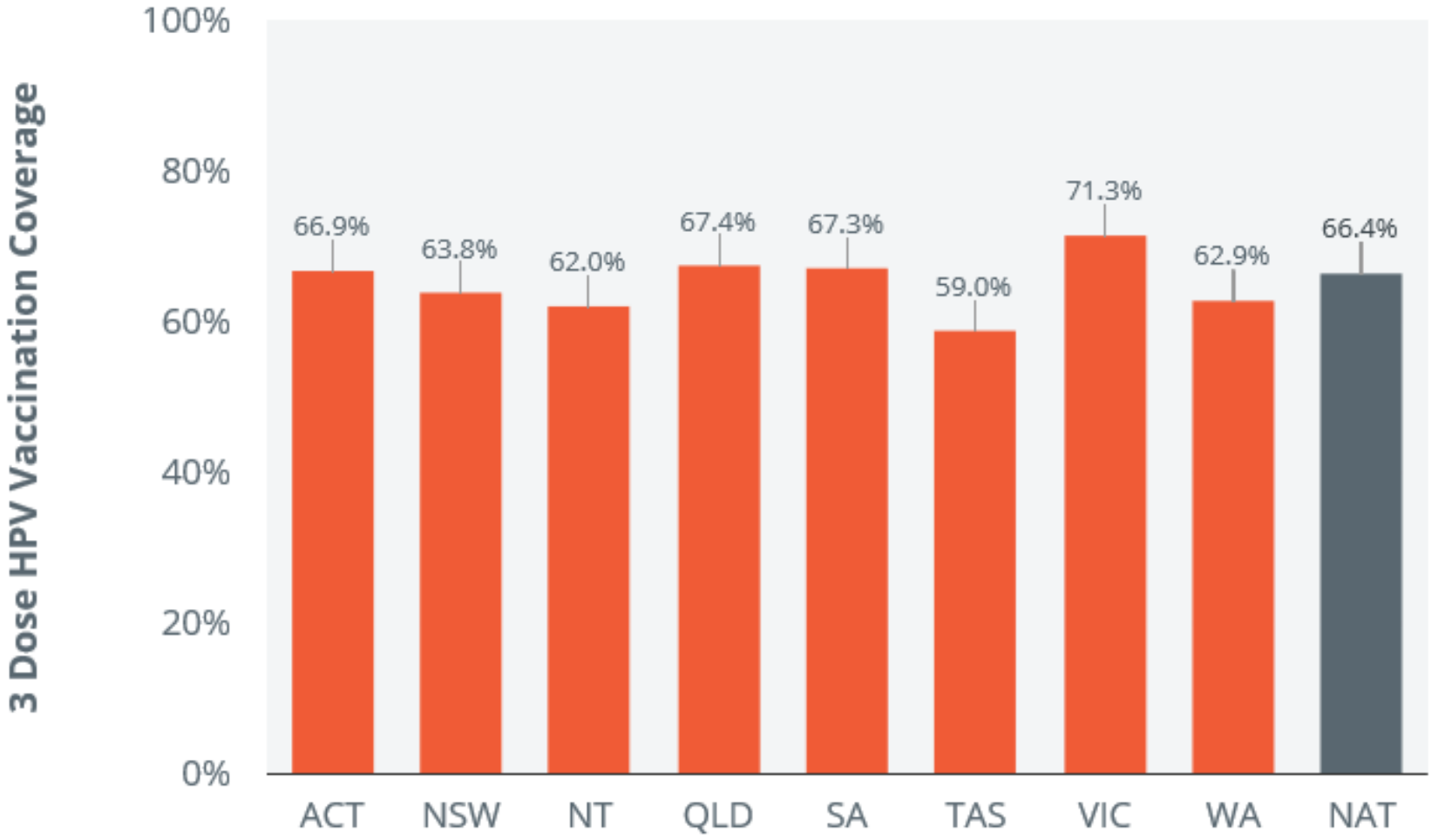
- Recognition of the HPV etiology of significant number of cancers in males
- Impact of GW's & global burden of disease / health services requirements
- Trends in sexual practices in many countries
- Interrupting the transmission chain to other partners
- *Powerful herd effects and program resilience if both genders are included*

Australia, US, Canada, Austria

- Highest burden of severe disease is in women
- Herd immunity may be sufficient if high female vaccination rates are achieved (stable populations)
- High cost of the vaccine

Women only

HPV vaccination coverage estimates in Australia for boys aged 15



Potential roles of pediatricians in HPV vaccination

- **Safety net** for female routine vaccination campaigns
  - Identify non / insufficiently vaccinated girls (30%+)
  - Vaccination catch up (**sisters and boys**)
- **Awareness** on the vaccination offer: what protection is granted (HPV) and what protection is not offered (HSV…)
- Introduction of **screening** practices (in collaboration with gynecologists)
- Permanent **safety** vigilance
- General advice to **families** (vaccination of adult women & mothers)

Gracias colegas