Lo screening come setting per la vaccinazione (nelle donne non vaccinate in età target e nelle donne trattate)

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Secondary use/benefits of prophylactic HPV vaccination (ideally given in pre-adolescence)

- Efficacy of HPV vaccines against CIN2+ in 25-45 year old women
- Combinations of HPV vaccination and HPV-based cervical screening in women age 25+
- Does vaccination affect the fate of infections detectable at vaccination?
- Therapeutic vaccines

Un po’ di storia.....

British Journal of Cancer (2012) 107, 1445–1450

www.bjcancer.com

All'inizio vaccinare donne adulte era impensabile (certamente non cost-effective)

Minireview

Human papillomavirus vaccination in low-resource countries: lack of evidence to support vaccinating sexually active women

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Table 1 Benefits and drawbacks associated with human papillomavirus (HPV) vaccination for different age groups in developing countries

	Older girls (14–18 years)	Young women (19–26 years)	Older women (27+ years)
Benefits Compared with vaccinating only girls aged 10–13 years	Slightly reduced but still significant efficacy, depending on the age of sexual debut Shorter time to discernible impact	Protection primarily for those with little or no sexual experience Protection against infection with vaccine HPV type not yet encountered[a]	Small number of women may be protected from late infection or re-infection
Drawbacks Compared with vaccinating only girls aged 10–13 years	Harder to reach (lower school attendance, may have left home) Greatly expanded cohort Reduced cost-effectiveness	Harder to reach (more scattered) and completion of three doses is less likely Greatly expanded cohort Substantially reduced cost-effectiveness	Very large and difficult to reach population to vaccinate Greatly reduced cost-effectiveness Very limited data on efficacy against disease endpoints Probable reduced risk of progression after age 45 years (hormonal changes) Greater delay in benefits compared with screening May reduce screening attendance[b]

Abbreviation: HPV = human papillomavirus. [a]Type 16 is most likely to already be acquired, and type 18 and other oncogenic types (cross-protection) are less common, so limited benefit. [b]May do so even for younger, sexually naïve vaccinees, but they will not be infected by the most common and virulent types when vaccinated (i.e., types 16 and 18) and will have a much smaller risk for cervical cancer.

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EUROGIN 2010 roadmap on cervical cancer prevention

Silvia Franceschi[1], Lynette Denny[2], Kathleen L. Irwin[1*], José Jeronimo[3], Pier Luigi Lopalco[4], Joseph Monsonego[5], Julian Peto[6], Guglielmo Ronco[7], Peter Sasieni[8] and Cosette M. Wheeler[9]

- The simplest intervention in poor countries would be **AFFORDABLE** vaccination against a broad spectrum of HPV types followed at least 2 years later by HPV testing and immediate treatment of all HR HPV infections

- The value of polyvalent vaccination in older women would be, therefore, the possibility of **identifying long-duration HPV infections from a single HPV test.** Any infection with an HR HPV type included in the polyvalent vaccine that is detected 2 years after vaccination could be considered a persistent infection and would therefore justify immediate treatment.

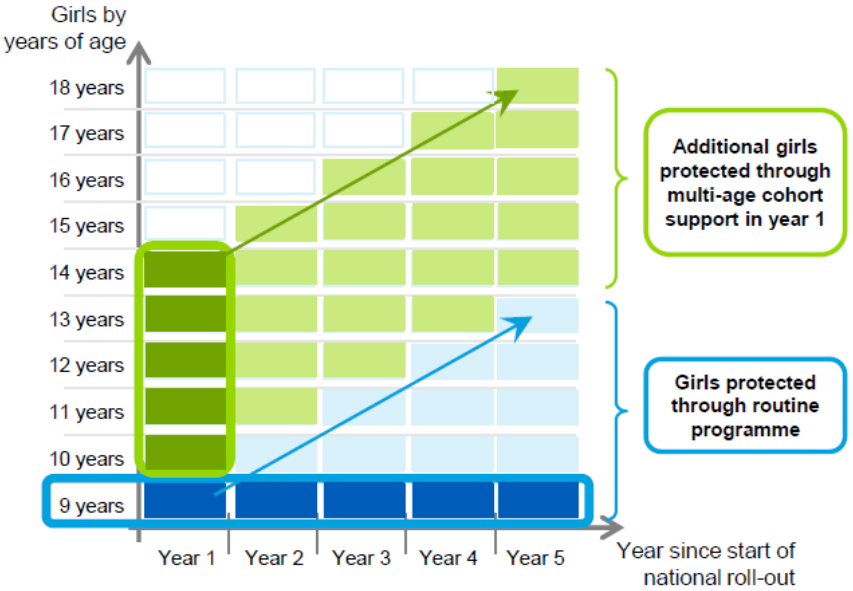
…..AND AN OPPORTUNITY TO FURTHER REDUCE CERVICAL CANCER BURDEN

OK!

Multi-age cohort recommended by SAGE 2016

- HPV vaccination for **multi-age cohort**:
  - 9-14 yrs cost effective using 2 dose schedules
  - Cohorts >15 yrs: reduced incremental cost-effectiveness (requires 3-dose, more girls/women already infected)
- **Direct impact** expected to scale proportionally with number of age cohorts
- Additional **indirect benefit (herd immunity)** expected
- Incremental cost for additional cohort expected to benefit from **economies of scale**

Higher and faster impact if one-time support for up to 5 additional age cohorts is given



SAGE meeting scheduled for October 20th, 2016

Gavi The Vaccine Alliance

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Randomised clinical trial of the quadrivalent vaccine of 3819 women age 24-45 years (Castellsague et al, 2011)

- On account of the rarity of CIN2+ in HPV-naïve women, primary efficacy endpoint was the combined incidence of persistent infection, CIN, and external genital lesions related to HPV 6/11/16/18.
- The efficacy against the combined endpoint after 4 years of follow-up was statistically significant in both per-protocol-for-efficacy and intention-to-treat (ITT) populations, the CIN2+ outcomes in the ITT population based primarily on infection

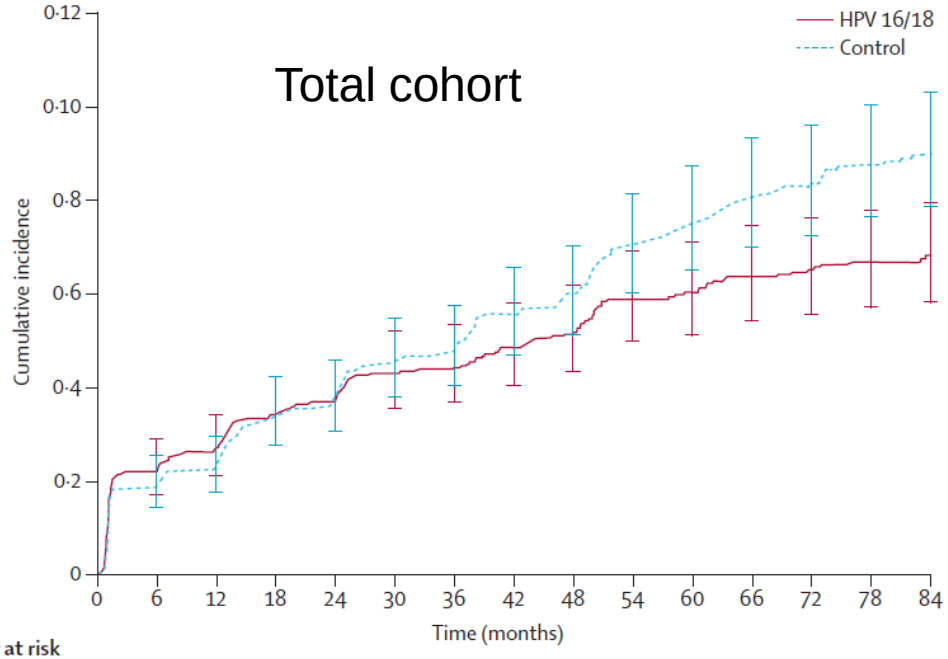
Table 3 Cases of CIN 2/3 or worse due to vaccine and non-vaccine HPV types by baseline infection status in the ITT population

		qHPV vaccine		Placebo	
Causal HPV type in CIN 2/3	**Baseline HPV status**	**Cases**	**Rate**	**Cases**	**Rate**
Any type	Any	62	0.9	51	0.7
Vaccine type(s)[a]		21	0.3	27	0.4
	Day 1-negative for causal type	3	<0.1	8	0.1
	Day 1-positive for causal type	18	3.9	19	4.7
Non-vaccine type(s)[b]		40	0.6	25	0.4
	Day 1-negative for causal type	13	0.2	4	0.1
	Day 1-positive for causal type	30	2.3	22	1.8
Unknown type	Any	9	0.1	9	0.1

Abbreviations: CIN = cervical intraepithelial neoplasia; qHPV = quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine; ITT = intention to treat. The sum of the vaccine type-, non-vaccine type-, and unknown type-related cases is not equal to the any type-related cases as some subjects can have both vaccine type- and non-vaccine type-related CIN 2/3 or worse. [a]Vaccine type(s) = 6, 11, 16, or 18. [b]Non-vaccine type(s) = 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59.

Efficacy, safety of HPV16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up, Wheeler et al, Lancet Inf, 2016

CIN1+, all women



Number at risk															
HPV 1/18	2733	2663	2603	2353	2490	2444	2353	2238	2130	1976	1950	1898	1833	1718	1209
Control	2735	2671	2626	2554	2501	2443	2327	2185	2079	1913	1883	1820	1760	1661	1172
Cumulative															
HPV 16/18	0	61	74	93	102	116	119	129	137	152	155	162	165	168	170
Control	0	53	63	93	102	123	129	147	157	178	189	200	205	213	217

Per protocol analyses

In 25-45 yr old women
Efficacy against CIN2+ (1 vs 6 cases):
84% (96% CI: -47 to100)
49 cases (-6-to 125) prevented per 100,000 woman-years

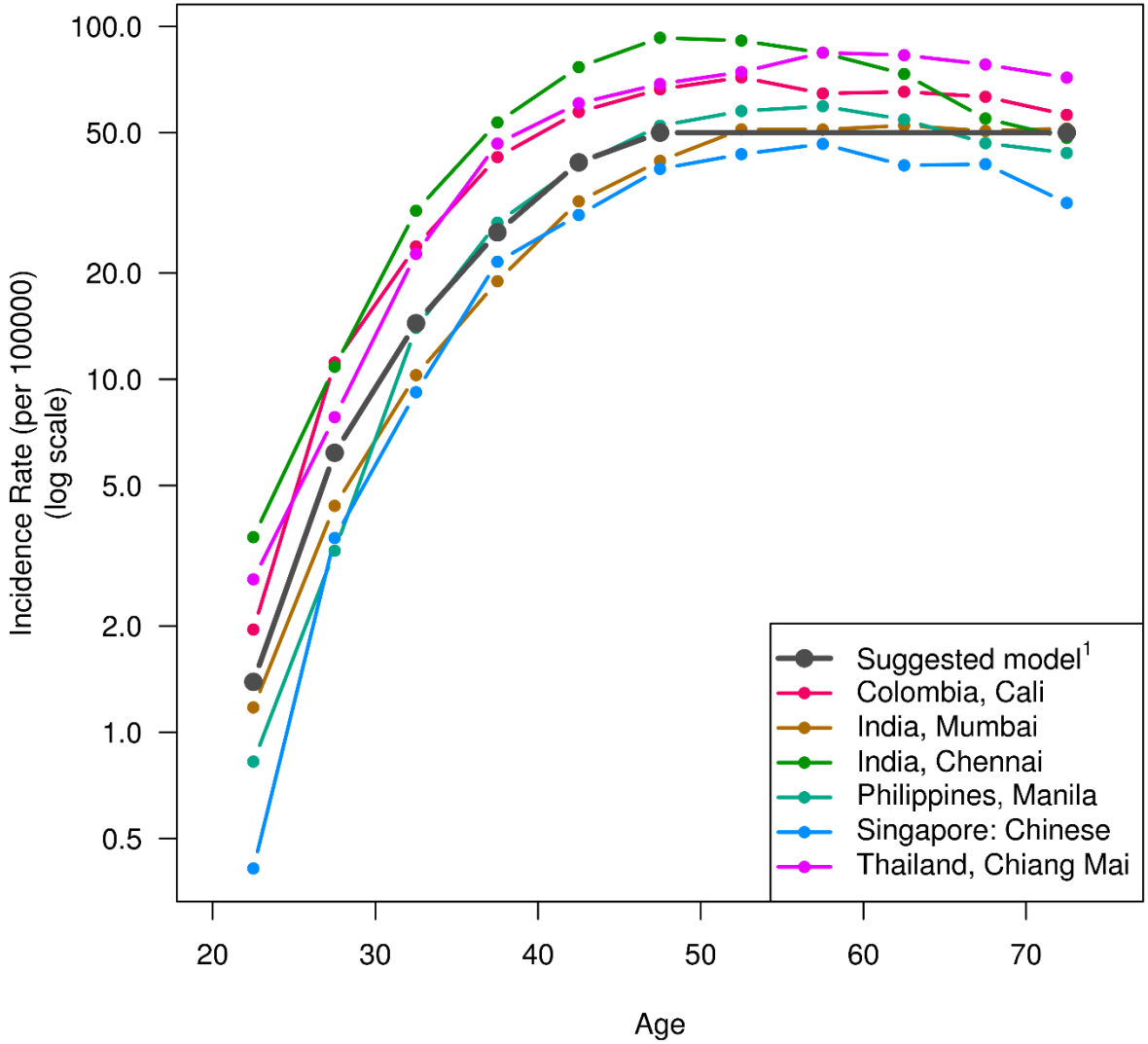
In 15-25 yr old women
Efficacy against CIN2+ (1 vs 97 cases:
99% (95% CI: 94 to 100)
~470 cases prevented per 100,000 woman-years

Similarly, in Castellsague et al, 2011 there were 1 CIN2+ in the vaccine group and 6 in the placebo group, non-signif. difference. Efficacy 835 (-37 to 100)

Vaccines efficacy against CIN2+ in 25-45 year old women
Conclusions, 1

- HPV vaccines prevent HPV infections and CIN1 at any age
- Randomized controlled trial (about 4,000/5,000 women) were too small to find a significant difference in CIN2
- CIN2+ cumulative incidence was much rarer at age >25 than in younger women
- Most cervical cancers derives from early HPV infection and and long-duration CIN2+

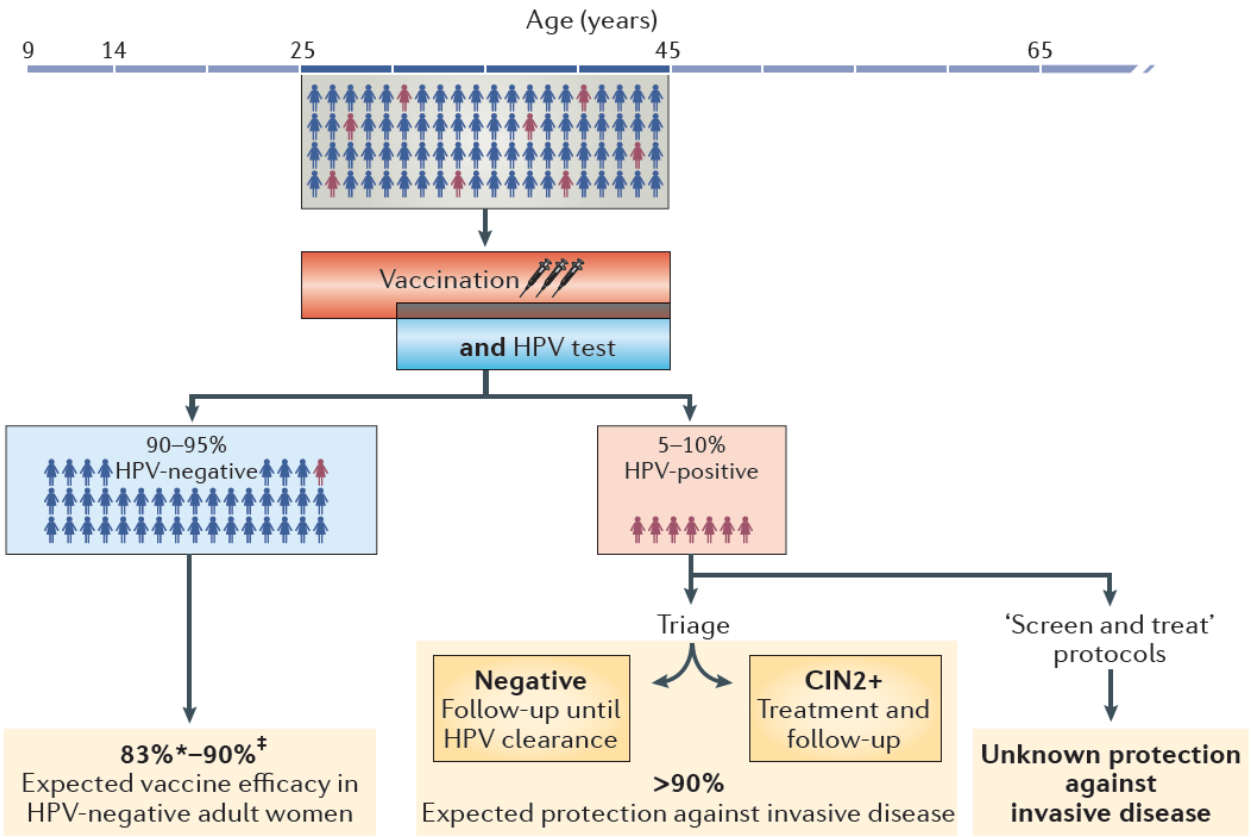
Cervical cancer incidence rates in unscreened populations
(Plummer et al, BJC, 2012)



Plummer, Peto, Franceschi 2012

The HPV-FASTER core concept and the rationale for combined HPV screening and vaccination of women up to 45–50 years of age,

Bosch et al, Nat Rev, 2016



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HPV vaccination and HPV-based cervical screening in women age 25+

Conclusions, 2

- Different interesting combinations of HPV screening and HPV vaccination are conceivable
- Cost-effectiveness depends from the feasibility, the cost of screening and vaccines, and the upper age limit of study women (the older the worse)
- The restriction of the offer of HPV vaccination to HPV-negative women is debatable
- A key question is how much cervical screening will be reduced in vaccinated women? This decision will challenge many stakeholders in addition to us experts (society, health professional, women)

Does vaccination affect the fate of infections detectable at vaccination?

- Some reports have suggested a possible benefit of vaccination versus the recurrence of genital lesions after excisional treatment of prevalent disease irrespective of the HPV type in the lesion
- Joura et al, BMJ, 2012: Efficacy of 4-Valent against CIN2+ 60 days or more post-surgery for a first lesion against for subsequent 64.9% (20.1% to 86.3%).
- Garland et al, IJC, 2016: Efficacy of 2-Valent against CIN2+ 60 days or more post-surgery for a first lesion was 88.2%(95% CI: 14.8, 99.7)

CAVEAT: 60-day was chosen to maximise the follow up time while minimizing the risk of capturing residual disease.

Most likely prevented diseases were due to infections not present at vaccination

Prior HPV-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial, 18,644 young women, Garland et al, IJC, 2016

Table 3. Vaccine efficacy against subsequent histopathologically confirmed disease and cytological abnormalities in women who underwent surgical treatment for a first lesion during the study

Endpoint	Interval since surgery for first lesion	HPV type in lesion	Group	*N*	Cases	Rate (95% CI)[1]	Efficacy (95% CI)
CIN2+	≥60 days	Irrespective of HPV DNA	Vaccine	190	1	0.24 (0.01–1.32)	88.2% (14.8 to 99.7)
			Control	264	9	2.01 (0.92–3.81)	
		HPV-16/18	Vaccine	190	0	0.00 (0.00–0.87)	100% (−63.1 to 100)
			Control	265	4	0.87 (0.24–2.24)	
CIN1+	≥60 days	Irrespective of HPV DNA	Vaccine	190	12	2.91 (1.50–5.08)	42.6% (−21.1 to 74.1)
			Control	264	22	5.07 (3.18–7.68)	
		HPV-16/18	Vaccine	190	0	0.00 (0.00–0.87)	100% (26.1 to 100)
			Control	265	7	1.55 (0.62–3.19)	
LSIL	≥60 days	Irrespective of HPV DNA	Vaccine	101	27	13.40 (8.83–19.50)	−30.5% (−142.7 to 29.0)
			Control	110	21	10.27 (6.36–15.70)	
		HPV-16/18	Vaccine	160	1	0.29 (0.01–1.61)	89.5% (21.6 to 99.8)
			Control	163	8	2.75 (1.19–5.41)	
HSIL	≥60 days	Irrespective of HPV DNA	Vaccine	159	0	0.00 (0.00–1.04)	100% (−59.4 to 100)
			Control	215	4	1.07 (0.29–2.74)	
		HPV-16/18	Vaccine	174	0	0.00 (0.00–0.95)	100% (−3950.4 to 100)
			Control	234	1	0.25 (0.01–1.38)	

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Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment, Hildesheim et al, AJOG, 2016

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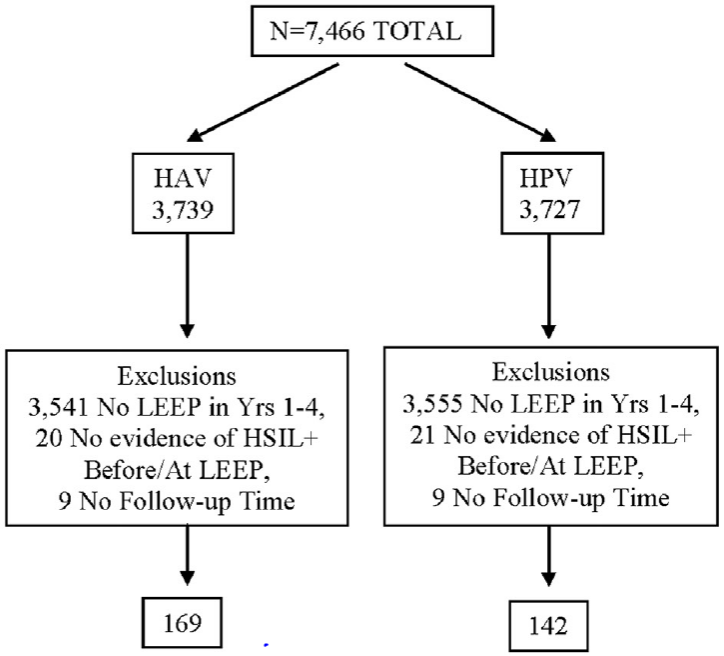

Analysis according to HPV type (present/absent before treatment)

No significant effect of 2-Valent on clearance of HPV infections or incidence of cytologic/ histologic abnormalities associated with human papillomavirus types present at enrolment.

Partial and nonsignificant protective effect of vaccination against new infections absent before treatment

Does vaccination affect the fate of infections detectable at vaccination?

CONCLUSIONS, 3

- Findings reinforce the notion that HPV vaccination is prophylactic and does not provide secondary benefit to HPV carriers
- No differences: 1) in rates of viral clearance or progression among women infected at the time of vaccination; 2) rates of post-LEEP infections and/or disease after vaccination
- The vaccine is likely to protect against *de novo* HPV infection with vaccine HPV types and some cross-protection against non-vaccine HPV types
- Other mechanisms (boosting of cellular adaptive and innate immune responses) are still unclear

Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial, **Trimble et al, Lancet, 2015**

Promising but a long-way to go to have an efficacious and affordable therapeutic vaccine

In this phase 2, randomised, double-blind, placebo-controlled clinical trial in women with HPV-16-positive or HPV-18-positive CIN2/3, both histopathological regression and concomitant histopathological regression and viral clearance were significantly greater after therapeutic vaccination with VGX-3100 compared with placebo. Both findings confirmed our hypotheses that therapeutic vaccination with this combination of synthetic plasmids targeting HPV-16 and HPV-18 E6 and E7 delivered by electroporation with the CELLECTRA device would cause histopathological regression and clearance of the infecting HPV genotype(s) in women with HPV-16-positive or HPV-18-positive CIN2/3. Furthermore, immune responses in peripheral blood (both CD8+ T cell and antibody) and cervical tissue correlated with both histopathological regression and concomitant histopathological regression with viral clearance.

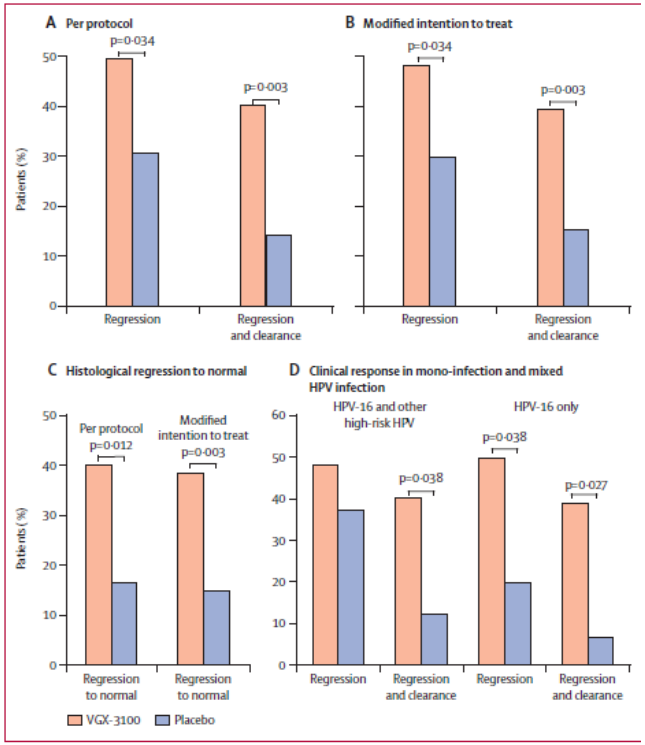

Figure 2: **Clinical efficacy**
Percentage of patients with histopathological regression or concomitant histopathological regression and viral clearance at week 36 in VGX-3100 and placebo groups in (A) the per-protocol analysis and (B) the modified intention-to-treat analysis. (C) Histopathological regression to normal for per-protocol and modified intention-to-treat analyses. (D) Effect of mixed infections including HPV-16 (left) compared with HPV-16 mono-infection (right) on rates of histopathological regression and viral clearance. HPV=human papillomavirus.

ANTI-VIRAL TOPICAL TREATMENTS WOULD BE VERY USEFUL TOO