

## HPV vaccination: for women of all ages?

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The discovery of human papillomavirus (HPV) DNA in cervical cancer by Harald zur Hausen sparked 30 years of research that established that persistent cervical infection by certain HPV genotypes causes cervical cancer. This research has led to revolutionary technical advances for the prevention of cervical cancer: prophylactic HPV vaccination and sensitive molecular HPV testing for screening. These promising technologies can be used to complement or enhance established cervical cancer prevention programmes, and to provide robust solutions in low-resource settings without screening programmes.<sup>1</sup>

In *The Lancet*, Rachel Skinner and colleagues<sup>2</sup> report the results of a randomised clinical trial comparing bivalent HPV 16/18 vaccination (n=2881) with placebo control (n=2871) in women aged older than 25 years, which is above the recommended age range of 9–26 years—the US Centers for Disease Control and Prevention targets vaccination at girls aged 11–12 years and catch-up vaccination in those aged 13–26 years.<sup>3</sup> The mean follow-up in the study was 40.3 months. HPV 16/18 vaccination induced enduring, high-titre anti-HPV 16 and anti-HPV 18 antibodies. In the according-to-protocol cohort for efficacy, HPV 16/18 vaccination was highly efficacious at preventing 6-month persistent HPV infection or cervical intraepithelial neoplasia grade 1

lesions or more severe diagnoses (CIN1+) caused by the targeted HPV genotypes (HPV 16 and HPV 18) compared with placebo (0.11 vs 0.58 cases per 100 woman-years; vaccine efficacy 81.1%, 97.7% CI 52.1–94.0). HPV 16/18 vaccination also protected against 6-month persistent infection by non-targeted HPV genotypes HPV 31 (79.1%, 27.6–95.9) and HPV 45 (76.9%, 18.5–95.6).

In the total vaccinated cohort, HPV 16/18 vaccination was only partly effective at preventing 6-month persistent HPV infection or CIN1+ caused by HPV 16 and HPV 18 compared with placebo (0.89 vs 1.59 cases per 100 woman-years; vaccine efficacy 43.9%, 97.7% CI 23.9–59.0). In terms of safety, HPV 16/18 vaccination increased the risk of injection-site symptoms (2443 [85%] of 2881 patients vs 1910 [67%] of 2871 patients) and general solicited symptoms (1878 [65%] vs 1659 [58%]), but, importantly, did not increase the risk of serious adverse events (285 [10%] vs 267 [9%]), and there were no differences in pregnancy outcomes, including the proportion of normal infants (257 [72%] vs 250 [70%]). Overall, HPV 16/18 vaccination was safe and, when given to HPV-naive women, highly effective.

However, when the benefits of HPV vaccination with either the bivalent or quadrivalent HPV vaccine in older (aged 25 years and older) and younger (aged younger than 25 years) cohorts of women are compared, the benefit of vaccinating younger women is greater than that of vaccinating older women in the intention-to-treat populations (table). Even within the younger cohorts, the effectiveness of HPV vaccination in the total vaccinated cohort decreases with increasing age.<sup>6,7</sup> Although preventing incident, persistent HPV infection will reduce the future risk of CIN2+,<sup>8,9</sup> the risk of CIN2+ after 1 year of HPV persistence decreases with increasing age,<sup>10</sup> suggesting that the long-term effect of preventing persistent HPV infection by HPV vaccination might also lessen with increasing age at vaccination. There are women at all ages who will benefit from prophylactic HPV vaccination, but the proportion of women who will benefit decreases with age.

Rationally, to extend HPV vaccination to older women, cost-effectiveness must be taken into account. To approach the cost-effectiveness achieved by vaccinating younger women, the cost of vaccination would need to be reduced, or subsequent screening reduced or

	n	Mean follow-up in months	Mean age in years (SD)	CIN2+ cases	Rate of CIN2+	Efficacy (CI*)
<b>Bivalent vaccine</b>						
Skinner et al (2014) <sup>2†</sup>						29.1% (-22.5 to 59.6)
Vaccine	2740	44.3	37.0 (7.2)	32	0.3	
Placebo	2737	44.3	37.0 (7.3)	45	0.4	
Lehtinen et al (2012) <sup>4</sup>						60.7% (49.6 to 69.5)
Vaccine	8694	47.4	20.0 (3.1)	90	0.3	
Placebo	8708	47.4	20.0 (3.1)	228	0.7	
<b>Quadrivalent vaccine</b>						
Castellsagué et al (2011) <sup>5†</sup>						22.4% (-42.5 to 58.3)
Vaccine	1911	48.0	34.3 (6.3)	21	0.3	
Placebo	1908	48.0	34.3 (6.3)	27	0.4	
Kjaer et al (2009) <sup>6</sup>						51.5% (40.6 to 60.6)
Vaccine	8823	42.0	20.0 (2.0)	142	0.5	
Placebo	8860	42.0	20.0 (2.0)	293	1.0	

CIN2+=cervical intraepithelial neoplasia grade 2 or more severe diagnoses. \*CIs are 95% CIs for all studies apart from Skinner and colleagues' study,<sup>2</sup> which used 97.7% CIs. †The studies in older women<sup>2,5</sup> were not powered for a CIN2+ endpoint.

**Table: Comparison of the effectiveness of bivalent (HPV 16/18) and quadrivalent (HPV 6/11/16/18) vaccines against CIN2+ caused by the targeted HPV genotypes in older and younger age groups (intention-to-treat cohort, or equivalent)**

eliminated in older women. Two novel strategies that integrate vaccination and screening in older women have been proposed to reduce the need for screening, but need validation. First, a vaccinate and screen strategy,<sup>11</sup> in which women would be vaccinated and then screened 1 year after vaccination for the presence of high-risk HPV in the cervix. Any woman who tests positive for high-risk HPV at follow-up will very likely have persistent high-risk HPV from a pre-existing HPV infection present at the time of vaccination and be at high risk of having or developing CIN2+,<sup>8,9</sup> and could therefore be managed aggressively. Second, a screen and vaccinate strategy,<sup>12</sup> in which women would first be screened for high-risk HPV, with those who test positive given follow-up management or treatment and not being vaccinated, and those who test negative being vaccinated.

In both scenarios, vaccinated, low-risk women are protected against acquisition of new infections by the highest risk HPV genotypes, and might need screening either never again or at a much lower frequency than if not vaccinated. Both approaches, if validated, are promising, especially for low-resource settings in which several rounds of screening might not be financially sustainable. These approaches might be best realised with the next generation HPV vaccine that targets nine HPV genotypes,<sup>13</sup> including HPV 16, HPV 18, and five additional high-risk HPV genotypes, and is predicted to prevent 85–90% of cervical cancer,<sup>14</sup> but more data for its efficacy, duration, and safety are needed.

Additionally, long-term data will need to be collected to ensure that low-risk women are adequately protected with such strategies. We do not know whether re-emergence of latent or quiescent HPV infections,<sup>15</sup> for which HPV vaccination presumably would not offer protection, leads to a substantial risk of cervical cancer. Also, the weaker high-risk HPV genotypes not targeted by any of the three HPV vaccines are the ones most likely to be identified in cervical cancers in older women.<sup>14,16</sup> Collection of data to support these strategies will be challenging because of the fewer events in older than in younger women, as predicted and noted by Skinner and colleagues,<sup>2</sup> and the need for very long follow-up to ensure safety against cervical cancer.

Skinner and colleagues<sup>2</sup> affirm that prophylactic HPV vaccination is safe and prevents the acquisition of target HPV genotypes at any age, and that any woman could benefit from HPV vaccination. However,

cost-effectiveness and available resources need to be taken into account in the decision to extend HPV vaccination to any subgroups other than young women, within the context of optimising the allocation of resources to achieve the maximum health benefits to the entire population. In the end, it is easy to rationalise doing more and gaining the incremental reduction in cervical cancer for countries that can afford it without consideration of cost or cost-effectiveness. However, perfection could be the enemy of the good.

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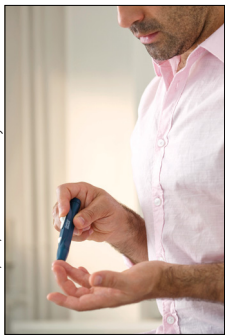
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PEC has received commercial human papillomavirus (HPV) tests for research at reduced or no cost from Roche, Qiagen, Norchip, and mtm. He has been compensated as a member of a Merck data and safety monitoring board for HPV vaccines, and has consulted for BD, Gen-Probe/Hologic, Roche, Cepheid, ClearPath, Guided Therapeutics, and GE Healthcare. KMS declares no competing interests.

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## GLP-1 receptor agonists and basal insulin in type 2 diabetes



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Drug development is a slow process, and understanding how best to deploy new treatments even slower. In *The Lancet*, Conrad Eng and colleagues<sup>1</sup> report the findings from their systematic review and meta-analysis of evidence about the combination of glucagon-like peptide-1 (GLP-1) receptor agonists and basal insulin in type 2 diabetes.

In 1992, two scientific breakthroughs led to the commercial development of GLP-1 agonists. First, GLP-1 (7-37)amide, the active fragment of GLP-1, was shown to have antihyperglycaemic activity in type 2 diabetes, against a background of insulin infusion.<sup>2</sup> Second, exendin-4 was discovered in the saliva of the Gila monster, a venomous lizard, and recognised to have structural similarity to GLP-1.<sup>3,4</sup> This xenopeptide was resistant to degradation and reduced glucose in animals, eventually becoming the first GLP-1 agonist, exenatide.<sup>4</sup>

The initial phase 2 study of a GLP-1 agonist was done in 1999, a single-masked, 5 day random-order crossover design of exenatide or saline given twice daily.<sup>4</sup> Six of the 24 patients were insulin-treated and assessed in our research unit; any insulin formulation, dose, or schedule was acceptable. Eligible participants were switched to bedtime basal insulin titrated to a fasting blood glucose value of less than 10 mmol/L for at least 3 consecutive days. When the first insulin-treated patient received the initial dose of exenatide and underwent a liquid meal challenge, the bedside glucose analyser showed no change in the patient's blood glucose for 5 h. This response in an insulin-deficient patient was inconceivable, and it was assumed that there had been a miscalculation of meal volume or malfunction of the glucose analyser. However, the pattern was the usual response for the entire study.

Exenatide twice-daily gained regulatory approval in 2005. Due to concerns that insulin-associated hypoglycaemia would raise questions about the safety of exenatide, a formal study of GLP-1 agonists with

basal insulin was not started until 2008.<sup>5</sup> Participants were treated with optimised insulin glargine plus exenatide or placebo twice daily. Compared with the placebo group, patients in the exenatide group had a 0.7% greater reduction in glycated haemoglobin (HbA<sub>1c</sub>), similar rates of hypoglycaemia, and weight loss as opposed to weight gain.

Since that report in 2011, there has been an explosion of interest in the combination of GLP-1 receptor agonists with insulin and eventual regulatory approval as documented by Eng and colleagues.<sup>1</sup> Of the 2905 studies identified, the investigators assessed 15, which together enrolled 4348 participants. Compared with basal insulin alone, a GLP-1 agonist plus basal insulin provided substantially greater HbA<sub>1c</sub> lowering (−0.44% vs basal insulin; 95% CI −0.60 to −0.29) with similar rates of hypoglycaemia and a mean reduction in weight of −3.22 kg (−4.90 to −1.54). Compared with full basal-bolus insulin regimens, a GLP-1 agonist plus basal insulin gave a clinically insignificant reduction in HbA<sub>1c</sub> (−0.1% [−0.17 to −0.02]), but with a lower relative risk of hypoglycaemia (0.67 [0.56–0.80]) and a reduction in mean weight of −5.66 kg (−9.8 to −1.51). Eng and colleagues appropriately point out many limitations to the available studies; that said, the consistency of the findings suggests a robust conclusion.

Several questions remain. First, do shorter-acting GLP-1 agonists with their unparalleled efficacy on postprandial glucose provide unique advantages over long-acting GLP-1 agonists combined with basal insulin? There are no adequate trials to answer this question, but it seems that the differences are probably small. A second issue tangential to the focus of the systematic review is whether there is a role for long-acting GLP-1 agonists combined with prandial insulin (injected or inhaled). Findings from the AWARD-4 study suggest that once-weekly dulaglutide, a GLP-1 agonist, combined with a

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