

## Editorials

## The remarkable impact of bivalent HPV vaccine in Scotland

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## Linked research

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland

## Linked opinion

Bivalent HPV vaccine in Scotland is having a considerable and sustained effect

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## Re: Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of

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## Re: Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century, with key publications starting in 1999 [3-6]. We now have increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary

supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements (and sun exposure) to combat the high prevalence of vitamin D deficiency in Scotland [11-23].

Vitamin D supplementation has been the subject of several placebo-controlled trials documenting anti-inflammatory, antiviral, and anticancer effects. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" in which they summarized, "In conclusion, vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism, plasma NO, TAC, GSH and MDA levels." In 2018, Vahedpoor and colleagues [39] published "Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3" in which they noted, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity; use of nutritional supplements that contain or potentiate vitamin D had started to increase in the population by 2003. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially misleading, especially when these authors make no account whatsoever of the national program for vitamin D supplementation which started in the same time-frame. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

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**Competing interests:** Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, and the human microbiome. Dr Vasquez has served as a consultant to Biotics Research Corporation.

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