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Human Papillomavirus (HPV) Vaccines as an Option for Preventing Cervical Malignancies: (How) Effective and Safe?

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Abstract: We carried out a systematic review of HPV vaccine pre- and post-licensure trials to assess the evidence of their effectiveness and safety. We find that HPV vaccine clinical trials design, and data interpretation of both efficacy and safety outcomes, were largely inadequate. Additionally, we note evidence of selective reporting of results from clinical trials (i.e., exclusion of vaccine efficacy figures related to study subgroups in which efficacy might be lower or even negative from peer-reviewed publications). Given this, the widespread optimism regarding HPV vaccines long-term benefits appears to rest on a number of unproven assumptions (or such which are at odd with factual evidence) and significant misinterpretation of available data. For example, the claim that HPV vaccination will result in approximately 70% reduction of cervical cancers is made despite the fact that the clinical trials data have not demonstrated to date that the vaccines have actually prevented a single case of cervical cancer (let alone cervical cancer death), nor that the current overly optimistic surrogate marker-based extrapolations are justified. Likewise, the notion that HPV vaccines have an impressive safety profile is only supported by highly flawed design of safety trials and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities). We thus conclude that further reduction of cervical cancers might be best achieved by optimizing cervical screening (which carries no such risks) and targeting other factors of the disease rather than by the reliance on vaccines with questionable efficacy and safety profiles.

Keywords: HPV vaccines, Gardasil, Cervarix, adverse reactions, vaccine efficacy, vaccine safety, conflict of interests.

INTRODUCTION

Cervical cancer is a serious disease, affecting almost half a million women world-wide on an annual basis [1]. Almost 90% of cervical cancer deaths occur in developing countries which have an insufficient medical infrastructure to fully implement regular Papanicolaou (Pap) screening programmes. In contrast, in developed countries cervical cancer mortality rates are very low (1.4-1.7/100,000 women) [2]. Nonetheless, further prevention of cervical cancer mortality by means of prophylactic human papillomavirus (HPV) vaccination seems like a convenient and attractive option for both developed and developing countries.

HPV is a necessary, although not sufficient, etiological factor in cervical cancer pathogenesis [3]. Although there are over 100 types of HPV, only 15 are oncogenic (high-risk HPVs) [4, 5]. Persistent infection with oncogenic HPV(s) can cause precancerous lesions and ultimately lead to cervical cancer [3, 6-8]. Thus, *if* over a lifespan, one could prevent the development of HPV-related precancerous lesions, then interventions to treat them would not be necessary and the development of most cervical cancers could theoretically be eliminated. This exciting goal was the very premise that lead the U.S. Food and Drug Administration (FDA) to fast-track the approval of Merck's Gardasil [9, 10], the first "cervical cancer vaccine" [11]. Later in 2009, the FDA also approved Cervarix, the HPV vaccine manufactured by GlaxoSmithKline [12]. Both Gardasil and Cervarix are designed to prevent infections with high-risk HPV-16 and HPV-18 [7, 13] that cause the majority of cervical cancers [4, 7, 10]. In addition, Gardasil targets low risk HPV-6 and HPV-11 [14] which although rarely detected in high-grade cervical lesions, cause the majority of anogenital warts [15].

Ever since gaining the FDA's approval in 2006, Merck has been heavily criticized for their overly aggressive marketing strategies and lobbying campaigns aimed at promoting Gardasil as a mandatory vaccine [16-19]. Subsequently, questions have been raised as to whether it was appropriate for vaccine manufacturers to partake in public health policymaking process when their conflicts of interests are so obvious [18-20]. Some of their advertising campaign slogans, such as "worldwide, cervical cancer is the second leading cause of cancer death in women" and, "your daughter could become one less life affected by cervical cancer", seemed more designed to promote fear of the disease (thus likely increasing vaccine uptake), rather than evidence-based decision making about the potential benefits of the vaccine [18]. Although, conflicts of interests do not necessarily mean that the product itself is faulty, marketing claims should be carefully examined against factual science data.

Clinical trials for both vaccines appear to indicate that they are 100% effective against persistent infections with HPV-16 and HPV-18, which together according to World Health Organization's statistics, contribute to approximately 70% of all cervical cancers [1, 21]. Scientists and public health officials have thus quickly assumed that HPV vaccination of all girls before sexual debut could prevent approximately 70% of all cases of cervical cancer [22-26]. Consequently, most countries around the world have implemented, or are striving to implement, universal HPV vaccination [2, 27, 28]. The confidence in HPV vaccine efficacy has even led to executive orders making HPV vaccination a mandatory for 11- to 12-year-old girls as a condition to enter school in some U.S. states [17]. In the midst of mixed optimism (and official mandates) however, some crucial questions still remained unanswered. Namely, (1) duration of protective immunity; (2) efficacy against oncogenic HPV strains not covered by the vaccine; (3) possibility of increased frequency of

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infection with these types; (4) efficacy in women acquiring multiple HPV types; (5) effects in women with pre-existing HPV infections; and (6) probability of serious adverse reactions (ADRs) [2, 20, 22, 26, 29-32].

In order to answer the questions regarding long-term effectiveness of HPV vaccines (i.e., prevention of cervical cancer), it is crucial to emphasize that all conclusions derived from clinical trials were based on extrapolations from a rather complex set of surrogate markers [26, 27]. Explicitly, the proportion of cancers associated with HPV-16 and HPV-18 types targeted by the vaccines as surrogate for the proportion of cancers avoided, HPV infections and precancerous cervical intraepithelial neoplasia (CIN) grade 1-3 lesions as surrogates for cancer and ≥15 year old girls and women in their mid to late twenties as surrogates for 9 to12 year old girls [14, 33-37].

Since the primary aim of HPV vaccination is to prevent cervical cancers [7], careful assessment of surrogate variable adequacy (i.e., whether they accurately measure what they are purport to measure), is essential in determining whether or not any meaningful clinical benefit can be expected from HPV vaccines.

HPV VACCINE EFFICACY: GENERAL CONSIDERATIONS FOR USING SURROGATE MARKERS IN INTERPRETING TRIAL RESULTS

To determine if a new drug actually provides a real benefit to patients can often take a very long time. This real benefit (i.e., preventing mortality from a serious disease or significantly increasing life expectancy) is known as a "clinical outcome." Thus, in cases where disease progression is slow, it is most practical to use surrogate endpoints which are an indirect or substitute measurement that is meant to represent a clinically meaningful outcome [38]. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval (as was in the case of Gardasil). Notably, approval of a drug based on such endpoints is given on the condition that post-licensure clinical trials verify the anticipated clinical benefit [38].

HPV INFECTIONS AND PRECANCEROUS LESIONS SURROGATES

The progression from acquisition of HPV infection to invasive cervical cancer is very slow, taking anywhere from 20 to 40 years [6, 7, 13, 20, 39]. Given that persistent infection with HPV is necessary for cervical cancers to occur, the use of HPV infections and HPV related CIN 1-3 precancerous lesions as cervical cancer surrogates seems perfectly valid. However, while HPV infection is very common, with nearly a fifth of all women of screening age infected, less than 8% of screened women have associated cytologic abnormalities [40-43]. More importantly, it is well known that 70% of cytologically expressed infections will resolve within one year and more than 90% of HPV will resolve within two to three years [44-47]. Of these unresolved HPV infections, only 5% will eventually progress to pre-cancerous CIN 2/3 lesions [48].

Thus, because the vast majority of HPV infections regress within three years, they are a poor surrogate marker for determining cervical cancer progression. Notably, the validity of CIN 2 being a cancer precursor is also questionable due to high misclassification rates [49, 50], and poor intra- and inter-observer reproducibility in diagnosis [50, 51], as well as high regression rates in adolescent women aged 13 to 24 years (38% of CIN 2 resolve after one year, 63% after two and 68% after three years [52]). According to Castle *et al.* [50] CIN 2 is the least reproducible of all histopathologic diagnoses and may in part reflect sampling error.

While CIN 3 is a more reliable marker for cancer progression than CIN 2, the use of this marker is not without caveats. First, CIN 3 lesions are heterogeneous. For example, there are early small lesions and old advanced lesions and it is hard to determine what proportion of these small lesions, which serve as clinical endpoints in current studies, would persist to become large, advanced CIN 3 lesions) [48]. Secondly, the progression of CIN 3 to invasive cancer is relatively slow [39], with some CIN 3 regressing to normal epithelium [53]. It takes five years for 20% of the large visible CIN 3 lesions to progress to invasive cancer. After 30 years, 40% of CIN 3 lesions have become cervical cancer [39].

In summary, what is clear from the above data is that the incidence of HPV infection and incidence of cervical cancer should not be considered as equal since cervical cancer will not develop in most women who are infected even with high-risk HPVs. Similarly, cervical cancer will not develop in 68% of women diagnosed with CIN 2 [52]) and almost half of those diagnosed with CIN 3 [39]. Finally, because there are at least 15 types of high-risk HPVs, infection with other high-risk HPVs associated with cervical cancer also needs to be considered in determining the real benefits of HPV vaccination [26, 30]. Thus, the overall (global) efficacy of HPV vaccines, that is reduction of CIN 2/3 due to all high-risk types rather than just HPV-16/18, would be the most relevant measure outcome both for the individual patient and in terms of overall public health benefits.

THE EFFICACY OF THE QUADRIVALENT HPV VACCINE GARDASIL

The quadrivalent HPV vaccine Gardasil (HPV4; Gardasil, Merck & Co, Inc.) [14], was the first HPV vaccine licensed for use in females aged 9 through 26 years. Gardasil received a *Fast Track* approval by the FDA following a six-month priority review process. In order to gain approval, a *Fast Track* drug must demonstrate the following: (1) show superior effectiveness to existing treatments (if such are available); (2) avoid serious side effects of an available treatment; (3) improving the diagnosis of a serious disease where early diagnosis results in an improved outcome; and (4) decrease a clinically significant toxicity of an accepted treatment [38].

RESULTS FROM CLINICAL TRIALS SUBMITTED TO THE U.S. FDA FOR LICENSING APPROVAL

Efficacy Against HPV-6/11/16/18 Related CIN 2/3+ Lesions

The FDA's licensing approval for Gardasil was largely based on efficacy and safety results from three double-blind, randomized, placebo-controlled trials, a phase II Study 007 and two phase III trials, FUTURE I and FUTURE II (both of which included a 3 year follow-up of study participants) [54]. These studies were designed, sponsored and conducted by the vaccine manufacturer [14, 33, 54].

The primary objective of the larger FUTURE II trial was to determine the safety and efficacy of Gardasil in preventing cervical cancers due to HPV-16 and 18 following administration of a three-dose regimen among women who had no evidence of previous infection with HPV (per protocol population, PPP; Table **1**). Efficacy was also evaluated under variable vaccine dose intervals and in all vaccinated subjects including those who violated study protocols (modified intent-to-treat populations; MITT; Table **1**). The FUTURE I trial was primarily aimed at investigating the safety and efficacy in reducing the incidence of CIN, adenocarcinoma in situ (AIS), or cervical cancer related to all four HPV types covered by the vaccine. Other primary endpoints in the FUTURE I trial included the incidence of HPV-6/11/16/18 related external genital warts, vulvar and vaginal intraepithelial neoplasia and vulvar and vaginal cancers [54]. For the purpose of this review we will limit our discussion to Gardasil efficacy against HPV-6/11/16/18 related CIN 2/3.

FUTURE I trial included a total of 5455 female participants aged 16 to 24 years. FUTURE II included a larger study population of 12,167 females aged 15-26 years. A total of 78% and 87% and of all subjects enrolled in FUTURE I and II respectively met the criteria for the PPP for the primary study endpoint efficacy analysis [54]. Overall, vaccine efficacy against HPV-16/18 or HPV-6/11/16/18 related CIN 2/3 was high in all three randomised trials,

Table 1. Gardasil HPV Quadrivalent Vaccine. Summary of Efficacy Data in Relation to Primary Clinically Relevant Endpoints. Results Obtained from Three Pre-licensure trials (FUTURE I, FUTURE II and Study 007 [54]) and a Post-licensure Study (Villa *et al.* [55]). The Per Protocol Population (PPP) Served for Analysis of Prophylactic Efficacy under Optimal Conditions and the Modified Intent-to-treat populations (MITT) for Analysis of Prophylactic Efficacy under Suboptimal Vaccine Dose Uptake Conditions. Underline Denotes Global Vaccine Efficacy (Reduction of Pre-cancerous Lesions due to All High-risk HPVs, the Most Relevant Measure Outcome for Overall Public Health Benefits). Red Denotes Wide CI Range.

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (95% CI)	p-value	Time of follow-up
Pre-licensure: FUTURE II (phase III trial) [54]								
HPV-16/18-related								
CIN 2/3+	*PPP*[1]	5301	0	5258	21	**100%** (75.8 to 100)	n.d.	*3 years*
HPV-6/11/16/18-related								
CIN 2/3+		5383	0	5370	22	**100%** (81.1 to 100)	n.d.	
HPV-16/18-related								
CIN 2/3+	*MITT-2*[2]	5736	1	5766	36	**97.2%** (83.4 to 99.9)	n.d.	
HPV-16/18-related								
CIN 2/3+	*MITT-3*[4]	5947	68	5973	116	**40.9%** (19.7 to 56.9)	n.d.	
Any HPV type-related								
CIN 2/3+	*PPP*	3899	44	3703	49	**14.4%** (<0 to 44.3)	n.d.	
Any HPV type-related								
CIN 2/3+	*RMITT-2*[3]	3789	32	3826	51	**36.5%** (<0 to 60.5)	n.d.	
Pre-licensure: combined efficacy analysis: FUTURE I, FUTURE II, (phase III) and Study 007 (phase II) [54]								
HPV-6/11/16/18-related								
CIN 2/3+	*MITT-2*	8625	1	8673	69	**98.5%** (91.6 to 100)	n.d.	*3 years*
HPV-6/11/16/18-related								
CIN 2/3+	*MITT-3*	8814	118	8846	186	**36.3%** (19.4 to 49.9)	n.d.	
Any HPV type-related								
CIN 2/3+	*PPP*	5685	75	5457	87	**16.9%** (<0 to 39.8)	n.d.	
Any HPV type-related								
CIN 2/3+	*RMITT-2*	5638	59	5701	96	**37.9%** (13.2 to 55.9)	n.d.	
Any HPV type-related								
CIN 2/3+	*MITT-3*	8814	287	8846	328	**12.2%** (<0 to 25.3)	n.d.	

(Table 1) Contd.…

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (95% CI)	p-value	Time of follow-up
Post-licensure: phase II trial, Villa *et al*. [55]								
HPV-16/18-related								
CIN 1-3	*PPP*	235	0	233	3	**100%** (<0 to 100)	n.d.	*5 years*
HPV-16/18-related								
CIN 1-3	*MITT*[5]	258	0	256	7	**100%** (30.8 to 100)	n.d.	

[1]**Per Protocol Population (PPP)**: Received all 3 doses of vaccine or placebo, were seronegative and HPV DNA negative on PCR analysis for vaccine targeted HPV types (6/11/16/18) at day 1 and had no major protocol violations. Were included even if results on cervical cytologic examination at day 1 were abnormal.
[2]**Modified Intent-to-treat population 2 (MITT-2)**: Received at least one dose of vaccine or placebo, were seronegative and HPV DNA negative on PCR analysis for vaccine targeted HPV types (6/11/16/18) at day 1 and were included even if protocol violations were present. Were included even if results on cervical cytologic examination at day 1 were abnormal.
[3]**Restricted Modified Intent-to-treat population 2 (RMITT-2)**: Received at least one dose of vaccine or placebo, were seronegative and HPV DNA negative on PCR analysis for vaccine targeted HPV types (6/11/16/18) at day 1 and were included even if protocol violations were present. Had normal results on cervical cytologic examination at day 1.
[4]**Modified Intent-to-treat population 3 (MITT-3)**: Received at least one dose of vaccine or placebo, Were included even if they had infection or disease associated with HPV-6, HPV-11, HPV-16, or HPV-18 (i.e., CIN) and were included even if protocol violations were present. Were included even if results on cervical cytologic examination at day 1 were abnormal.
[5]**Modified Intent-to-treat population (MITT):** corresponds to MITT-2.

ranging from 97.2-100% in the PPP and various MITT cohorts (Table **1**). The exception was the MITT-3 cohort where vaccine efficacy was only 36.3 to 40.9% (Table **1**). These latter results can possibly be explained by the fact that this cohort (unlike others) included women who had abnormal results on cervical cytologic examination at day 1. Altogether, these results suggest that although the vaccine may in short-term prevent abnormal Pap-smears, it is ineffective in clearing existing HPV lesions.

Efficacy Against CIN 2/3+ Lesions Related to Any HPV Type

HPV-6/11/16/18 related CIN 2/3 vaccine efficacy data cited above are insufficient to determine the real capacity of Gardasil to prevent future cervical cancers, the primary reason for which it received *Fast Track* approval by the FDA [38]. Because of the possibility of infections with HPV types not covered by the vaccine and/or multiple infections including these types, any meaningful assessment of a true prophylactic value from HPV vaccination, which would likely result in a *real* clinical benefit (i.e., a global reduction of the cervical cancer burden), needs to include analysis of vaccine efficacy against CIN 2/3+ caused by *all* relevant (high risk) HPVs in the PPP cohort. These data do in fact exist and cast doubt about the Gardasil's overall prophylactic potential. Specifically, the capacity of Gardasil to prevent CIN 2/3+ associated with any HPV type in the PPP was only 14.4% (95% CI <0 to 44.3) in the FUTURE II trial and 16.9% (95% CI <0 to 39.8) in the combined efficacy analysis which included results from FUTURE I, II and 007 trials (Table **1**). In the various MITT cohorts, reduction of CIN 2/3+ lesions due to any HPV type was comparably low (12.2 to 37.9%) and with similarly wide 95% CI (<0 to 25.3, <13.2 to 55.9; Table **1**). Notably, such wide 95% CI values make it unlikely that the observed, at best low-to-modest overall reduction of CIN 2/3+, was a real effect attributable to the HPV vaccine. It is further interesting to note that the official publication of the FUTURE II trial in *NEJM* [33] did not cite figures of vaccine effectiveness in the PPP cohort against CIN 2/3+ due to any HPVs. These data are however available from documents Merck submitted to the U.S. FDA for licensing purposes [54]. Such selective reporting of clinical trial results precludes an objective and independent assessment of Gardasil's true prophylactic value.

Efficacy Against HPV-6/11/16/18 Related CIN 2/3+ Lesions in Women with Prior History of HPV-6/11/16/18 Infection

Another example of selectively reported data, missing from the *NEJM* publications of FUTURE I and II trials [14, 33], pertain to Merck's "important concerns" regarding administration of Gardasil to women with pre-existing HPV-6/11/16/18 infections. Namely, "the potential of Gardasil to enhance cervical disease" [54]. Results from the FUTURE I trial submitted to the FDA do in fact show that Gardasil had an observed efficacy of -33 to - 44.6% in subjects who were already exposed to HPVs targeted by the vaccine (Table **2**). Notably, data from the combined efficacy analysis which included FUTURE I, II and Study 007 were also consistent with Merck's concern regarding the potential of Gardasil to exacerbate cervical disease in this particular subgroup of women (vaccine efficacy -11.6%; 95% CI <0 to 20.6; Table **2**).

POST-LICENSURE VACCINE EFFICACY DATA

Regarding Gardasil's potential to reduce cervical cancer incidence (at least in those individuals with no evidence of prior infections), current post-licensure results on long-term preventative vaccine efficacy were less than encouraging, as only combined efficacy against HPV-16/18 related CIN 1-3 lesions was reported [55]. Not only was there no efficacy data on prevention against other HPV types, but the combined 100% efficacy pertaining to reduction of HPV-16/18 related CIN 1-3 (Table **1**) was of no value in determining the true long-term prophylactic potential of the vaccine. The reason for this is that in the natural course of cervical cancer, only a small fraction of CIN 1 lesions will progress to CIN 2 lesions and likewise, only a small fraction of CIN 3 lesions will eventually progress to cervical cancer. Specifically, a review of the literature from 1950-1992, showed that as much as 60% of CIN 1 lesions regressed, 30% persisted, 10% progressed to CIN 3, and only 1% progressed to invasive cancer [53]. Therefore, in any female population, there will be many more CIN 1 lesions than all CIN 2s, CIN 3s and cervical cancers put together. CIN 1 however is neither an adequate marker of cervical cancer progression nor an adequate surrogate endpoint for assessing long-term clinical benefits in HPV vaccine trials.

Table 2. Evaluation of the Potential of Gardasil HPV Quadrivalent Vaccine to Enhance Cervical Disease in Subjects Who Had Evidence of Persistent Infection with Vaccine-relevant HPV Types Prior to Vaccination. Results Obtained from Three Pre-licensure Double-blind Randomized, Placebo-controlled Trials (FUTURE I, FUTURE II and Study 007) were Listed in Merck's report to the U.S. FDA Vaccines and Related Biological Products Advisory Committee (*VRBPAC Background Document on Gardasil HPV Quadrivalent Vaccine* [54]) but Excluded from Official Peer-reviewed Trials' Publications [14, 33].

Endpoint		Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (95% CI)	p-value	Time of follow-up
FUTURE I: *Subjects who were PCR positive and seropositive for relevant HPV types at day 1*								
HPV-6/11/16/18-related CIN 2/3+		156	32	137	19	**-44.6%** (<0 to 8.5)	n.d.	*3 years*
FUTURE I: *Subjects who were PCR positive and/or seropositive for relevant HPV types at day 1*								
HPV-6/11/16/18-related CIN 2/3+		685	48	664	35	**-33.7%** (<0 to 15.3)	n.d.	
FUTURE II: *Subjects who were PCR positive and seropositive for relevant HPV types at day 1*								
HPV-6/11/16/18-related CIN 2/3+		398	42	430	48	**5.4%** (<0 to 39.0)	n.d.	*3 years*
Combined efficacy analysis, FUTURE I, FUTURE II and Study 007: *Subjects who were PCR positive and seropositive for relevant HPV types at day1*								
HPV-6/11/16/18-related CIN 2/3+		568	75	580	69	**-11.7%** (<0 to 20.6)	n.d.	*3 years*

GARDASIL EFFICACY: RESULT SUMMARY AND IMPLICATIONS FOR CERVICAL CANCER PREVENTION

According to the U.S. FDA, a drug that receives *Fast Track* designation is eligible for *Accelerated Approval*, which is, "approval on an effect on a surrogate, or substitute endpoint *reasonably likely* to predict clinical benefit" [38] [emphasis added]. The *Accelerated Approval*, which is temporary, is expressly designed to get drugs on the market before they demonstrate any "real" benefit. Nonetheless, the *Accelerated Approval* based on a surrogate endpoint (i.e., CIN 1-3), is given on the condition that post-marketing clinical trials (otherwise known as phase IV trials) verify the anticipated clinical benefit. If however the confirmatory phase IV trials do not show that the drug provides real clinical benefit, "FDA has regulatory procedures in place that could lead to removing the drug from the market" [38].

During the longest reported follow-up of Gardasil trial participants (5 years) the vaccine was found to be 100% efficacious against persistent HPV-16/18 infections and CIN 1-3 lesions (Table **1**) [55]. However, the significance of these results is questionable at best for two major reasons, first being the low number of cases and correspondingly, wide 95% CI (Table **1**). In other words, the vaccine prevented 1.3% and 2.7% of all CIN 1-3 lesions in the PPP and MITT cohorts respectively (0/235 in the vaccine versus 3/233 in the control group in the PPP cohort and the corresponding 0/258 versus 7/256 in the MITT cohort; Table **1**). However, as explained above, reporting a combined efficacy against CIN 1-3 gives a highly misleading impression about the true clinical value of the vaccine, given that the vast majority of the lesions within this population would have comprised of CIN 1 lesions. CIN 1s, as discussed above, are a completely inadequate surrogate endpoint for assessing long-term clinical benefits of any HPV vaccine due to their benign nature as well as high frequency of regression [7, 53].

Thus, with regard to efficacy, Gardasil ultimately fails to satisfy the FDA's criteria for *Fast Track* approval [38] as the vaccine fails to show superior efficacy to Pap screening. In spite of this, the vaccine manufacturer as well as medical authorities worldwide continue to promote Gardasil as if indeed, it already had received phase IV confirmatory trials approval (demonstrated efficacy against cervical cancer). For example, Merck states that, "Gardasil does more than help prevent cervical cancer" [56], while the U.S. health authorities describes Gardasil as a "life-saving vaccine" [57]. However, in light of Merck's limited 5-year follow-up data these claims are demonstrably inaccurate. Finally, although results from pre-licensure trials indicate >97% vaccine effectiveness against HPV-6/11/16/18 related CIN 2/3+ lesions, the corresponding figures against CIN 2/3+ caused by all HPV types are mostly well below 40% (Table **1**).

Taken together, these data indicate that vaccination with Gardasil is unlikely to have any notable impact in reducing the global cervical cancer burden, at least not beyond what Pap screening has already accomplished [7, 13]. Moreover, Merck's pre-licensure data submitted to the FDA suggest that Gardasil can only be used as a prophylactic vaccine and not for treating pre-existing HPV infections nor pre-existing pre-cancerous lesions [54].

In conclusion, Merck's HPV vaccine Gardasil fails to meet a single one of the four criteria required by the U.S. FDA for *Fast Track* approval [38]. Indeed, the contrary situation exists: the vaccine has not, to date, prevented a single case of cervical cancer, let alone cervical cancer death, nor has it improved the diagnosis of a serious disease. Moreover, Gardasil may exacerbate cervical cancer

disease in women with pre-existing HPV-6/11/16/18 infections (Table **2**). For these reasons, it is neither more effective nor safer than Pap screening combined with the loop electrosurgical excision procedure (LEEP).

THE EFFICACY OF THE BIVALENT HPV VACCINE CERVARIX

On October 16, 2009, the U.S. FDA licensed bivalent HPV vaccine (HPV2; Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years [12]. Cervarix licensure was based on efficacy and safety data obtained in two randomized, double-blind, controlled clinical trials in females aged 15 to 25 years, including a phase IIb trial (mean follow up 27 months and 6.4 years respectively [37, 58]) and a phase III trial (PATRICIA study, mean follow-up 34.9 months [34]). Since licensure, data from the continuing phase II trial [37] became available showing safety and efficacy after 7.3 years of follow-up analysis [36]. These studies were entirely designed and sponsored by the vaccine manufacturer who also co-ordinated data analysis, interpretation and writing of study reports [34, 37, 58]).

PRE-LICENSURE VACCINE EFFICACY DATA

Efficacy Against HPV-16/18 Related CIN 2/3+ Lesions After 2.9 Years of Follow-up

The primary objective of the phase III PATRICIA trial was to assess vaccine efficacy against CIN 2+ lesions associated with HPV-16 and HPV-18 in women who received three vaccine doses, were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding HPV type and did not violate the study protocol (according to protocol population for efficacy, ATP-E) [34]. The PATRICIA study included 18,644 females, followed for a mean of 34.9 months (2.9 years). Combined efficacy against HPV-16 /18 related CIN 2+ was 92.9% (96.1% CI 79.9 to 98.3; $p<0.0001$) and 94.5% (96.1% CI 86.2 to 98.4; $p<0.0001$) in the ATP-E, and total vaccinated cohort for efficacy (TVC-E; all women who were given at least one vaccine dose and had normal or low-grade cytology at baseline) respectively (Table **3**). Overall however, Cervarix was much less efficacious against HPV-16 and HPV-18 associated CIN 3+ lesions, the more diagnostically reliable and clinically relevant endpoint than CIN 2 [7]. For example, in the ATP-E cohort, the combined efficacy against HPV-16 /18 related CIN 3+ was 80.0% (96.1% CI 0.3 to 98.1; $p<0.0221$), while separately, efficacy against HPV-16 related CIN 3 did not reach statistical significance despite 67.2% vaccine efficacy (96.1% CI -97.1 to 97.2; $p<0.1749$).

It is important to note that with the increase in lesion severity, the 96.1% CI become much wider (i.e., compare the CI values for vaccine efficacy between HPV-16 and HPV-18 related CIN 2+ and CIN 3+ respectively in ATP-E and TVC-E cohorts; Table **3**). This is because a large proportion of CIN 2 either regresses or stabilizes over time [52], thus resulting in far fewer cases of CIN 3+ compared to CIN 2+ in the placebo groups. For example, in the ATP-E placebo cohort there were 56 cases of HPV-16/18 related CIN 2+ but only 10 cases of HPV-16/18 related CIN 3+ amongst 7312 women. The corresponding numbers in the ATP-E vaccine group were 4 cases of CIN 2+ and 2 of CIN 3+ among 7344 women (Table **3**). Thus, vaccine efficacy against HPV-16/18 related CIN 3+ was 80% with 96.1% CI 0.3 to 98.1 ($p<0.0221$). In essence however, the percentage of CIN 3+ in the HPV vaccine group was 0.03% versus 0.14% in the placebo group. In other words, PATRICIA trial results showed that Cervarix prevented a mere 0.11% of a subgroup of HPV related CIN 3+ lesions, namely those associated with HPV-16 or HPV-18.

Efficacy Against CIN 2/3+ Lesions Related to Any High-risk HPV After 2.9 Years of Follow-up

Vaccine efficacy against CIN 2+ lesions associated with other high-risk HPVs in the ATP-E cohort ranged between 14.3 to 100%, with overall very wide 96.1% CI (Table **3**; note that no results are reported for efficacy against CIN 3+ related to other high-risk HPVs in this cohort). On the other hand, in the TVC cohort, the combined efficacy against CIN 3+ lesions related to all 14 oncogenic HPVs investigated was only 33.4% (96.1% CI 9.1 to 51.5; $p<0.0058$).

Finally, Cervarix reduced the rate of CIN 3+ related excision procedures in the TVC and TVC-naive cohorts by 24.7% (96.1% CI 7.4 to 38.9; $p=0.0035$) and 68.8% (96.1% CI 50.0 to 81.2; $p<0.0001$) respectively, after 2.9 years of follow-up (Table **3**). TVC-naive cohort included women who were given at least one vaccine dose and at baseline had normal cytology, were DNA negative for all 14 oncogenic HPV types investigated, and were seronegative for HPV-16 /18. Because this cohort was representative of young girls before their sexual debut, the data pertaining to vaccine efficacy in reducing the rate of CIN 3+ related excision procedures (68.8%) are the most relevant in terms of assessing the prophylactic efficacy of Cervarix in this trial.

POST-LICENSURE VACCINE EFFICACY DATA

Long-term Follow-up Data on Vaccine Efficacy Against Cytological Abnormalities Related to HPV-16/18 and Other High-risk HPVs

Although the reduction in the rate of excision procedures due to CIN 3+ lesions in the TVC-naive cohort was highly significant after 2.9 years (96.1% CI 50.0 to 81.2; $p<0.0001$)[34], long-term follow-up data from the ongoing phase II trials [36, 37] were much less persuasive. First, the results from both the 6.4 year [37] and the 7.3 year follow-up trials [36] showed only vaccine efficacy against CIN 2+, which not only has a highly substantial frequency of regression (up to 68% after three years in women aged 12 to 24 years [52], the same age group tested in Cervarix trials), but is also a rather poor and unreliable prognostic marker for cervical cancer progression [7, 50]. Second and more importantly, in both studies the 96.1% CI were extremely wide thus making it unlikely that the vaccine had any *real* significant effect in reducing the frequency of CIN 2+ lesions [emphasis added]. Note also that the manufacturer did not report the corresponding p-values for vaccine efficacy analysis (Tables **4** and **5**).

Furthermore, as shown previously in Table **3**, it is possible to obtain a 100% vaccine efficacy against CIN 2+ without a true significant effect (i.e., HPV-45 related CIN 2+; 96.1%CI -67.8 to 100; $p=0.0619$) due to a very rare occurrence of these lesions (i.e., 4/7745 in the placebo versus 0/7782 in the vaccine group). A similar result is seen after a 7.3 year follow-up with only 3/212 cases of HPV-16/18 related CIN 2+ in the placebo group versus 0/219 in the HPV vaccine group (100% efficacy; 96.1% CI -129.8 to 100; Table **5**). Finally, vaccine efficacy against CIN 2+ related to any high-risk HPV type (including HPV-16 and 18) after 7.3 years, which is the most clinically relevant of the reported endpoints from the longest to date HPV vaccine trial, was only 40.6% (96.1% CI -106.0 to 84.7; Table **5**).

Similar to observations from the 2.9 year PATRICIA trial, overall in the 7.3 year follow-up study [36], Cervarix was more efficacious against HPV-16/18 related persistent infections and cytological abnormalities than against those associated with all high-risk types combined (including HPV-16/18; Table **5**). Additionally, in both long-term follow-up studies [36, 37] as was the

Table 3. Cervarix HPV Bivalent Vaccine. Summary of Efficacy Data in Relation to Primary Clinically Relevant Endpoints, Obtained after 2.9 Years of Follow-up in a Double-blind Randomized, Placebo-controlled Phase III PATRICIA Trial [34]). The According to Protocol Population for Efficacy (ATP-E) Served for Analysis of Prophylactic Efficacy under Optimal Conditions and the Total Vaccinated Cohort (TVC) for Analysis of Prophylactic Efficacy under Suboptimal Vaccine Dose Uptake Conditions [34]. Underline Denotes the Most Relevant Measure Outcomes for Overall Public Health Benefits. Red Denotes Wide CI Range.

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
CIN 2+								
HPV-16/18	*ATP-E*[1]	7344	4	7312	56	**92.9%** (79.9 to 98.3)	<0.0001	*2.9 years*
HPV-16		6303	2	6165	46	**95.7%** (82.9 to 99.6)	<0.0001	
HPV-18		6794	2	6746	15	**86.7%** (39.7 to 98.7)	0.0013	
CIN 3+								
HPV-16/18		7344	2	7312	10	**80.0%** (0.3 to 98.1)	0.0221	
HPV-16		6303	2	6165	6	**67.2%** (-97.1 to 97.2)	0.1749	
HPV-18		6794	0	6746	5	**100%** (-19.3 to 100)	0.0307	
CIN 2+								
HPV-16/18	*TVC-E*[2]	8040	5	8080	91	**94.5%** (86.2 to 98.4)	<0.0001	*2.9 years*
HPV-16		6921	3	6923	73	**95.9%** (87.0 to 99.3)	<0.0001	
HPV-18		7455	2	7480	24	**91.6%** (64.6 to 99.2)	<0.0001	
CIN 3+								
HPV-16/18		8040	2	8080	22	**90.9%** (60.8 to 99.1)	<0.0001	
HPV-16		6921	2	6923	16	**87.5%** (43.8 to 98.8)	0.0013	
HPV-18		7455	0	7480	7	**100%** (24.2 to 100)	0.0156	
CIN 2+								
HPV-31	*ATP-E*	7583	2	7599	25	**92.0%** (66.0 to 99.2)	<0.0001	*2.9 years*
HPV-33		7720	12	7706	25	**51.9%** (-2.9 to 78.9)	0.0332	
HPV-45		7782	0	7745	4	**100%** (-67.8 to 100)	0.0619	
HPV-52		7461	12	7414	14	**14.3%** (-108.1 to 65.4)	0.7000	

(Table 3) Contd.…

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
HPV-58		7709	6	7702	17	**64.5%** (1.5 to 89.2)	0.0225	
HPV-31/33/45/52/58		7862	30	7853	64	**53.0%** (24.7 to 71.3)	0.0004	
Any oncogenic type except HPV-16/18		7863	50	7853	109	**54.0%** (34.0 to 68.4)	<0.0001	
Any oncogenic HPV type		7863	54	7853	142	**61.9%** (46.7 to 73.2)	<0.0001	
CIN 3+								
HPV-16/18	*TVC*[3]	8667	43	8682	65	**33.6%** (-1.1 to 56.9)	0.0422	*2.9 years*
Any oncogenic HPV type		8667	77	8682	116	**33.4%** (9.1 to 51.5)	0.0058	
Reduction in number of colposcopy referrals		8667	1107	8682	1235	**10.4%** (2.3 to 17.8)	0.0055	
Reduction in number of cervical excisions		8667	180	8682	240	**24.7%** (7.4 to 38.9)	0.0035	
CIN 3+								
HPV-16/18	*TVC-Naive*[4]	5449	0	5436	13	**100%** (64.7 to 100)	<0.0001	*2.9 years*
Any oncogenic HPV type		5449	3	5436	23	**87.0%** (54.9 to 97.7)	<0.0001	
Reduction in number of colposcopy referrals		5449	354	5436	476	**26.3%** (14.7 to 36.4)	<0.0001	
Reduction in number of cervical excisions		5449	26	5436	83	**68.8%** (50.0 to 81.2)	<0.0001	

[1]**According to Protocol Population for Efficacy (ATP-E)**: Women who were given three vaccine doses, had normal or low-grade cytology at baseline, me*et all* eligibility criteria, and complied with the protocol procedures.
[2]**The Total Vaccinated Cohort for Efficacy (TVC-E)**: all women who were given at least one vaccine dose and had normal or low-grade cytology at baseline.
[3]**The Total Vaccinated Cohort (TVC)**: included all women who were given at least one vaccine dose, irrespective of other criteria, and was intended to represent the general population of young women, including those who are sexually active. These women were a diverse population, including those with evidence of current or previous HPV infection and with abnormal low-grade or high-grade cytology (the TVC-E sub-cohort included only women with either normal or low-grade cytology).
[4]**The Total Vaccinated Naive Cohort (TVC-naive)**: women who were given at least one vaccine dose, and at baseline had normal cytology, were DNA negative for all 14 oncogenic HPV types investigated, and were seronegative for HPV-16 and HPV-18. This cohort was representative of young girls before their sexual debut.

case in the PATRICIA trial, the CI tended to increase with the increase in lesion severity, due to a notable reduction in the number of cases in the control group (i.e., compare 96.1% CI for ASC-US through to CIN 2+ in Tables **4** and **5**). Thus, after 7.3 years, the number of HPV-16/18 related ASC-US, LSIL, CIN 1+ and CIN 2+ in the vaccinated group was 1,1,0 and 0 compared to 27,16,7 and 3 in the placebo group (each group consisting of a total of ~ 200 women). As with the Gardasil trials (Tables **1** -**2**), the real significance of these results is open to speculation due to the failure of the vaccine manufacturer to report p-values (Tables **4**-**5**).

CERVARIX EFFICACY: RESULT SUMMARY AND IMPLICATIONS FOR CERVICAL CANCER PREVENTION

In summary, the results on Cervarix efficacy against CIN 2+ (the primary clinically relevant endpoint for which data were available from all three randomised trials; Table **6**), make it evident that the global vaccine efficacy (reduction of CIN 2+ due to all high-risk HPVs) fell sharply over time. Thus, after 7.3 years, the global vaccine efficacy was not only very low (40.6%), but also with extremely wide 96.1% CI (−106.0 to 84.7). The 96.1% CI values related to efficacy against HPV-16/18 related CIN 2+ were similarly

Table 4. Cervarix HPV Bivalent Vaccine. Summary of Efficacy Data in Relation to Primary Clinically Relevant Endpoints, Obtained after 6.4 Years of Follow-up in a Double-blind Randomized, Placebo-controlled Trial [37]. Underline Denotes the Most Relevant Measure Outcomes for Overall Public Health Benefits. Red Denotes Wide CI Range

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
HPV-16/18-related								
≥ASC-US[1]	*TVC*	505	2	497	54	**96.7%** (87.3 to 99.6)	n.d.	*6.4 years*
≥LSIL[2]		505	2	497	34	**94.6%** (78.8 to 99.4)	n.d.	
CIN 1+		481	0	470	15	**100%** (73.4 to 100)	n.d.	
CIN 2+		481	0	470	9	**100%** (51.3 to 100)	n.d.	
Any oncogenic HPV type-related								
≥ASC-US	*TVC*	505	118	497	162	**35.4%** (17.6 to 49.5)	n.d.	*6.4 years*
≥LSIL		505	62	497	93	**39.4%** (15.6 to 56.8)	n.d.	
CIN 1+		505	20	497	38	**50.3%** (12.5 to 72.6)	n.d.	
CIN 2+		505	5	497	17	**71.9%** (20.6 to 91.9)	n.d.	

[1]ASC-US: atypical squamous cells of undetermined significance
[2] LSIL: low-grade squamous intraepithelial lesion

Table 5. Cervarix HPV Bivalent Vaccine. Summary of Efficacy Data in Relation to Primary Clinically Relevant Endpoints, Obtained after 7.4 Years of Follow-up in a Double-blind Randomized, Placebo-controlled Trial [36]. Underline Denotes the Most Relevant Measure Outcomes for Overall Public Health Benefits. Red Denotes Wide CI range

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
HPV-16/18-related								
Incident infection	*ATP-E*	193	3	175	43	**94.5%** (82.9 to 98.9)	n.d.	*7.3 years*
6-month persistent infection		193	0	175	17	**100%** (79.5 to100)	n.d.	
12-month persistent infection		193	0	175	9	**100%** (55.7 to 100)	n.d.	
Any oncogenic HPV type-related								
Incident infection		179	80	158	86	**26.6%** (−0.7 to 46.5)	n.d.	
6-month persistent infection		179	47	158	49	**18.8** (−23.7 to 46.8)	n.d.	

(Table 5) Contd.…

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
12-month persistent infection		179	27	158	29	**19.4%** (−41.0 to 54.1)	n.d.	
HPV-16/18-related								
≥ASC-US[1]	*TVC*	224	1	219	27	**96.7%** (79.9 to 99.9)	n.d.	*7.3 years*
≥LSIL[2]		224	1	219	16	**94.2%** (62.8 to 99.9)	n.d.	
CIN 1+		219	0	212	7	**100%** (34.4 to 100)	n.d.	
CIN 2+		219	0	212	3	**100%** (−129.8 to 100)	n.d	
Any oncogenic HPV type-related								
≥ASC-US	*TVC*	224	48	219	70	**40.5%** (12.9 to 59.7)	n.d.	*7.3 years*
≥LSIL		224	27	219	52	**53.9%** (25.3 to 72.2)	n.d.	
CIN 1+		219	6	212	18	**69.0%** (18.5 to 89.9)	n.d.	
CIN 2+		219	5	212	8	**40.6%** (−106.0 to 84.7)	n.d.	

[1]ASC-US: atypical squamous cells of undetermined significance
[2] LSIL: low-grade squamous intraepithelial lesion

very wide after both long-term follow-ups thus making any true significant beneficial effect attributable to the vaccine unlikely (Table **6**). Had the corresponding data for CIN 3+ lesions been available, vaccine efficacy figures would have probably been even lower. Due to a small study population size there were in fact no occurrences of CIN 3+ cases in the placebo group after both 6.4 and 7.3 year follow-ups [36, 37]. The lack of CIN 3+ cases in these trials reflects the well known facts about the natural course of cervical cancer, namely, that of a slowly progressing disease with only a small fraction of precancerous CIN 2+ lesions progressing to CIN 3+ grade (15-20% [52, 53]).

Altogether, the above observations indicate that although Cervarix can substantially reduce the incidence of abnormal CIN 2/3+ cytologies, it is unlikely to have any *real* significant benefit in reducing the overall frequency of cervical cancers (at least not in countries with regular screening programs), yet this is the primary aim for which the vaccine was developed. Indeed, according to Harper and Vierthaler [7], prophylactic HPV vaccination will have little cancer reducing effect in the general screened population, but may prevent cervical cancer among those with no screening opportunities. Harper and Vierthaler further noted that, "Modeling indicates that HPV vaccination [with Cervarix] will prevent potentially 17% of the abnormal Pap tests based on current knowledge of HPV type distribution and only a very few cancers that Pap testing would not have detected, *not enough to lower the population incidence of cervical cancer lower than what screening already accomplishes*" [emphasis added]. Finally, like Gardasil, Cervarix has no therapeutic benefit given that it does not cause regression of pre-existing HPV-16/18 infections or associated lesions [7].

HPV VACCINE SAFETY

Benefits of HPV Vaccination Versus the Risks

Currently, governmental health agencies worldwide state that HPV vaccines are "safe and effective" and that the benefits of HPV vaccination outweigh the risks [59-61]. However, our previous analysis has shown that in developed countries the current age-standardized death rate from cervical cancer is several folds lower than the reported rate of serious ADRs from HPV vaccines [2]. Although it may not be entirely appropriate to compare deaths alone from cervical cancer to serious ADRs from HPV vaccines, it should be emphasized that (in accordance with U.S. FDA guidelines), the margin of tolerance for serious ADRs for a vaccine with uncertain long-term benefits needs to be very narrow, especially when such a vaccine is intended for healthy young individuals [62]. HPV vaccination, even *if* proven effective against actual cervical cancers, is targeting 9 to 12 year old girls to prevent a yet undetermined proportion of these cancers, some of which *may* cause death at a rate of 1.4 to 2.3/100,000 women in developed countries [2, 31]. For a vaccine designed to prevent a disease with such a low death rate, the risk to those vaccinated should be minimal [31]. Given that it is unlikely that HPV vaccination would decrease the already low incidence of cervical cancers in developed countries

Table 6. Cervarix Efficacy Against CIN 2+ Lesions, the Primary Clinically Relevant Endpoint for which Data Were Available from Pre and Post-licensure Clinical Trials (Including the Longest Reported Follow-up Trial) [34, 36, 37]. Underline Denotes the Most Relevant Measure Outcomes for Overall Public Health Benefits. Red Denotes Wide CI range

Endpoint	Population	Vaccine Total n cases		Placebo Total n cases		Vaccine efficacy (96.1% CI)	p-value	Time of follow-up
CIN 2+								
HPV-16/18	*ATP-E*	7344	4	7312	56	**92.9%** (79.9 to 98.3)	<0.0001	*2.9 years*
Any oncogenic HPV type		7863	54	7853	142	**61.9%** (46.7 to 73.2)	<0.0001	
HPV-16/18	*TVC-E*	8040	5	8080	91	**94.5%** (86.2 to 98.4)	<0.0001	*2.9 years*
HPV-16/18	*TVC*	481	0	470	9	**100%** (51.3 to 100)	n.d.	*6.4 years*
Any oncogenic HPV type		505	5	497	17	**71.9%** (20.6 to 91.9)	n.d.	
HPV-16/18	*TVC*	219	0	212	3	**100%** (−129.8 to 100)	n.d	*7.3 years*
Any oncogenic HPV type		219	5	212	8	**40.6%** (−106.0 to 84.7)	n.d.	

with good Pap screening practices [7, 13], any expected benefit from HPV vaccines will be significantly limited in such settings [22]. Accordingly, the risk-to-benefit balance associated with HPV vaccination will then also become less favourable [2].

The situation in developing countries is on the other hand more complex than in the developed world where there seems to be little need for a HPV vaccine given the success of Pap screening programs. Although HPV vaccination seems like an attractive option for countries with high rates of cervical cancer, two facts related to vaccine risks and benefits need to be considered before decisions are made about recommending them to young women. First in terms of safety, lack of adequate health care is a significant concern. A review of the U.S. Vaccine Adverse Event Reporting System (VAERS) reports shows that many life-threatening outcomes resulting from Gardasil & Cervarix have been mitigated simply due to quick access to emergency room (ER) facilities and immediate action of health professionals. In a country which does not have such medical infrastructure (i.e., India [32]), the magnitude of vaccine-related adverse outcomes could be much more severe. Second, the effectiveness of the vaccine could be lower in girls with immune-compromising diseases associated with poor socioeconomic status, such as severe anaemia, chronic illnesses or HIV infections [63].

Passive Vaccine Surveillance Systems Safety Data and Case Reports

Since 2006, the U.S. VAERS received a total of 20,663 ADRs from HPV vaccines, 8% of which were serious (1592), including 73 deaths, 348 life-threatening ADRs and 581 events which resulted in permanent disability (Table **7**). Notably, compared to all other vaccines given to females aged 6 to 29 years (the target group for HPV vaccines), Gardasil and Cervarix alone were associated with over 60% of all serious ADRs (including 63.8% of all deaths and 64.8% of all life-threatening reactions). Moreover, 82% cases of permanent disability in females under 30 years of age were also attributed to HPV vaccines (Table **8**).

Table 7. Summary of Adverse Reactions (ADRs) Following Vaccination with Gardasil and Cervarix in the U.S. Reported to VAERS [72] in the Post-licensure Period (June 2006 to March 2012).

Total	20,663
Serious	1592
Deaths	73
Life-threatening	348
Permanently disabled	581
Prolonged hospitalization	208
Emergency room visit	9332

Cumulatively, the list of serious ADRs related to HPV vaccination in the U.S., U.K., Australia, Netherlands, France and Ireland includes deaths, convulsions, paralysis, paraesthesia, demyelinating diseases of the central nervous system (i.e., multiple sclerosis and acute disseminating encephalomyelitis), Guillain-Barre´ syndrome (GBS), transverse myelitis, facial palsy, chronic fatigue syndrome, anaphylaxis, autoimmune disorders, deep vein thrombosis, pulmonary embolisms, pancreatitis, visual impairments and spontaneous abortions [59, 61, 64-73]. Of particular interest is that the U.S. VAERS received 438 reports of abnormal Pap smears, 143 reports of cervical dysplasia and 16 reports of cervical cancers related to

Table 8. Age-adjusted Rate of ADRs Related to Gardasil and Cervarix in Comparison to All Other Vaccines in the U.S. Reported to VAERS from 2006 to 2012). VAERS Internet Database [72] was Searched Under the Following Criteria: Gender (Female) and Age (16 to 29 Years).

Events	HPV Vaccines	All Vaccines	% ADRs Due to HPV Vaccines
All	14,596	31,532	46.3
Serious	1259	2043	61.6
Deaths	37	58	63.8
Life-threatening	284	438	64.8
Permanently disabled	464	564	82.3
Prolonged hospitalization	171	226	75.7
Emergency room visit	6870	12,843	53.5

Gardasil in the post-licensure period (2006-2012) [72]. These cases likely confirm Merck's concern about "the potential of Gardasil to enhance cervical disease in subjects who had evidence of persistent infection with vaccine-relevant HPV types prior to vaccination" [54].

It may be thus appropriate to ask whether it is worth risking death or a disabling life-long neurodegenerative condition such as GBS at a pre-adolescent age for a vaccine that has only a theoretical potential to prevent cervical cancer, a disease that may develop 20 to 40 years after exposure to HPV, when the same can be prevented with regular Pap screening [74]? Moreover, in contrast to HPV vaccination, a procedure which uses a speculum to take cells from the cervix does not carry a risk of death or neurological or autoimmune complications. Neither is LEEP which is used to remove high-grade CIN 2/3 lesions in women who test positive on a Pap screen a risk for such serious ADRs.

A report to a passive government-based vaccine surveillance system does not by itself prove that the vaccine caused an ADR. However, the unusually high frequency of reports of ADRs related to HPV vaccines (Table **8**; Fig. (**1**)), as well as their consistent pattern (i.e. with only minor deviations, nervous system-related disorders rank the highest in frequency followed by general/administration site conditions and gastrointestinal disorders; Fig. (**2**)) point to a potentially causal relationship. Nonetheless, the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) regards the entire group of system class disorders shown in Fig. (**2**) as unrelated to HPV vaccination. According to the Agency "These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination" [59, 75]. However, the fact that a similar pattern of system class ADRs to that in the U.K. is also observed in at least two other countries argues against such over-simplistic conclusions and suggests the opposite, namely that a causal relationship with the HPV vaccine exists. Also of note, the total number of ADRs reported for Cervarix in the U.K. appears to be 24 to 104 times higher than that reported for any of the other vaccines in the U.K. immunization schedule (Fig. (**1**)).

Official reports from vaccine safety surveillance systems in Australia also indicate an unusually high proportion of ADRs due to HPV vaccines [68]. In 2008, Australia reported an annual ADR rate of 7.3/100,000, the highest since 2003, representing an 85% increase compared with ADR rate from 2006. This increase was almost entirely due to ADRs reported following the commencement of the national HPV vaccination programme for females aged 12 to 26 years in April 2007 [68]. Moreover, HPV vaccine was the only suspected vaccine in 96% records, 29% had causality ratings of "certain" or "probable" and 6% were defined as "serious". The most severe ADRs reported following HPV vaccination were anaphylaxis and convulsions. Moreover, in 2007, 10 out of 13 reported anaphylaxis (77%) and 18 out of 35 convulsions (51%) occurred in women following HPV vaccination [68].

Finally, matching the safety data from various government-based passive vaccine surveillance systems worldwide [59, 61, 64-72], is an increasing number of case reports documenting similar serious ADRs following HPV vaccination (i.e., autoimmune diseases [76, 77], nervous system disorders including multiple sclerosis [78-80], acute disseminated encephalomyelitis [81-83], opsoclonus-myoclonus syndrome (characterized by ocular ataxia and myoclonic jerks of the extremities) [84], brachial neuritis [85] and vision loss [86], pancreatitis [87], anaphylaxis [88], postural orthostatic tachycardia syndrome [89] and death [90, 91]). Cumulatively, the above observations suggest that the risks of HPV vaccination have not been fully evaluated in pre-licensure clinical trials. A review of pre-licensure HPV vaccine safety data discussed below indeed confirms this concern.

Clinical and Post-Clinical Trials Safety Data

Pre-licensure safety evaluation of Gardasil presented in Merck's package insert and the U.S. FDA product approval information [92] shows that compared to the saline placebo, those women receiving the aluminum-containing placebo reported approximately 2 to 5 times more injection-site ADRs. On the other hand, the proportion of injection site ADRs reported in the Gardasil-treatment group was comparable to that of the aluminum "control" group. Thus, Merck's own data seem to indicate that a large proportion of ADRs from the HPV vaccine were due to the effect of the aluminum adjuvant. In spite of these observations, in assessing serious ADRs, the manufacturer pooled the results from the study participants who received the saline placebo with those who received the aluminum-containing placebo and presented them as one "control" group. The outcome of this procedure was that Gardasil and the aluminum "control" group had exactly the same rate of serious ADRs (2.3%) [2]. Thus at best, Gardasil was shown to be as safe as its potentially neuroimmunotoxic constituent aluminum.

Clinical trials on Cervarix also used an aluminum adjuvant-containing placebo [34, 36, 37] despite the fact that research accumulated in the last few decades strongly implicates these compounds in various neurological and autoimmune disorders in both humans and animals [93-102]. In this regard, in an analysis of ADRs of potential autoimmune etiology in a large integrated safety database of ASO4-adjuvanted vaccines (including Cervarix), Verstraeten *et al.* [103] found no evidence of an increase in relative risk

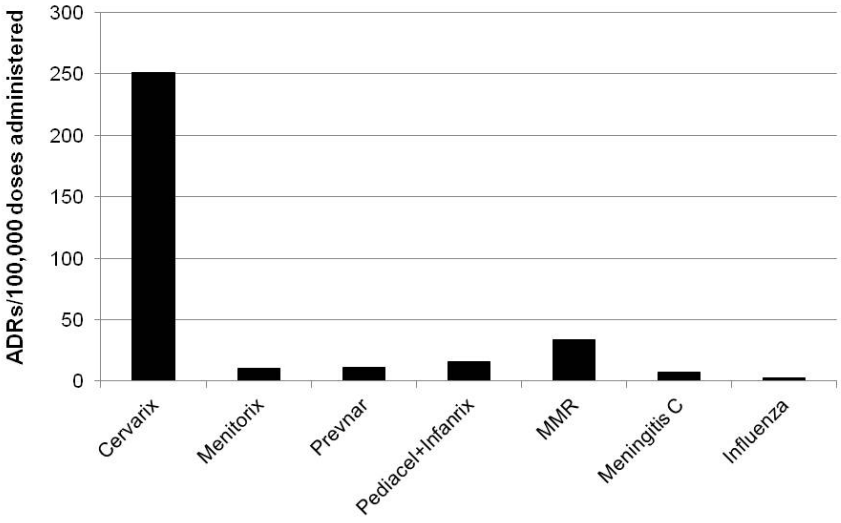

Fig. (1). The rate of adverse reactions (ADRs) from Cervarix compared to that of other vaccines in the UK immunization schedule. Data sourced from the report provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the Joint Committee on Vaccination and Immunisation in June 2010 [59].

of autoimmune disorders. Nonetheless, the authors acknowledged that, "It is important to note that none of these studies were set up primarily to study autoimmune disorders." If the purpose of the study was indeed to assess ADRs of "potential autoimmune etiology", as the title itself clearly states [103], then the study should have been designed to detect them. All of the eight authors of the ASO4 safety study are employees of GlaxoSmithKline (GSK), the manufacturer of Cervarix [103]. These authors noted that, "our search of the literature found no studies conducted by independent sources on this subject" and "All studies included in this analysis were funded by GSK Biologicals, as was the analysis itself. GSK Biologicals was involved in the study design, data collection, interpretation and analysis, preparation of the manuscript and decision to publish" [103]. Given that vaccines can trigger autoimmune disorders [93, 104-106], a more rigorous safety assessment than that provided by the GSK-sponsored study would appear to have been warranted.

The Verstraeten *et al*. [103] study was further cited as evidence for Cervarix safety in the publication of the phase III PATRICIA trial [34]. The safety outcomes in the TVC cohort of this trial however showed that out of over 9000 women in the vaccine group, 8% reported a serious event (the same rate of serious ADRs as that obtained from the U.S. VAERS), 32% reported a medically significant condition (defined as an ADR that prompted a visits to the ER or to the physician), 9% reported a spontaneous abortion and 3% reported a new-onset chronic disease (Table **9**). Notably, women in the aluminum-adjuvant "placebo control" group reported exactly the same rate of ADRs for all of the investigated conditions including those mentioned above (Table **9**). The only fact clear from these observations is that the true evidence of Cervarix safety remains concealed by the use of a potentially toxic pseudo-placebo. On the other hand, the only demonstrated benefit from Cervarix in the same trial consisted of 0.24% reduction in HPV-16/18 related CIN 3+ lesions, and a 1.05% reduction in a number of cervical excision procedures in the TVC-naive cohort (representative of girls before their sexual debut, the primary target population for prophylactic HPV vaccination; Table **9**).

If the vaccine is indeed responsible for the above observed rate of serious adverse outcomes, the medical community should seriously question the rationale of its global use in young women (currently, in use in over 100 countries [7]), especially since the long-term cervical cancer-preventative potential of the vaccine remains uncertain. Finally, because of the unusually high-frequency and severity of Cervarix-suspected ADRs reported to various vaccine safety databases Figs. (**1** and **2**), the rationale behind its global use is even more dubious from a public health perspective.

Most recently, the *Journal of Internal Medicine* published a safety study on autoimmune conditions following the routine use of Gardasil which failed to identify any significant autoimmune safety concerns [107]. This study was sponsored by Merck and conducted as a post-licensure commitment to the FDA, the European Medicines Agency (EMA) and other regulatory authorities to help evaluate the autoimmune safety of the vaccine [107]. In particular, the authors noted that, "well-designed postlicensure safety studies for newly approved vaccines facilitate *proper* evaluation of their autoimmune safety" [emphasis added]. The study population for the autoimmune surveillance by the Merck's research team thus included 189 629 women of diverse ethnical and socio-economic background, 99% of whom were in the recommended age range for HPV vaccination (9 to 26 years) [107]. Nonetheless, two potential biases might have influenced the outcome of the safety analysis. First, the study included all women who received at least one dose of Gardasil, thus making this particular population sample less sensitive for detection of serious ADRs, as such events are likely to occur less frequently if fewer doses of the vaccine are administered. Since the authors did not report how many women actually completed the recommended three-dose HPV vaccination regimen, it is impossible to know what proportion of the study population was actually at high-risk from vaccine-related serious ADRs. Second, the Safety Review Committee (SRC) which reviewed all safety data included a general paediatrician/clinical epidemiologist, a perinatologist/teratologist, a vaccinologist, a paediatric rheumatologist and a pharmacoepidemiologist [107]. Given that the autoimmune conditions of interest that were examined by this expert Committee included (1) rheumatologic/autoimmune disorders; (2) autoimmune endocrine conditions; and (3) autoimmune neurological/ophthalmic disorders [107], the question should be asked about why Merck's research team failed to recruit an expert panel with such expertise to match more closely their study's task? If in fact, the study aimed to facilitate *proper* evaluation of autoimmune safety of Gardasil? It is thus surprising to note the absence of an immunologist/autoimmunologist, neurologist and ophthalmologist from the SRC especially

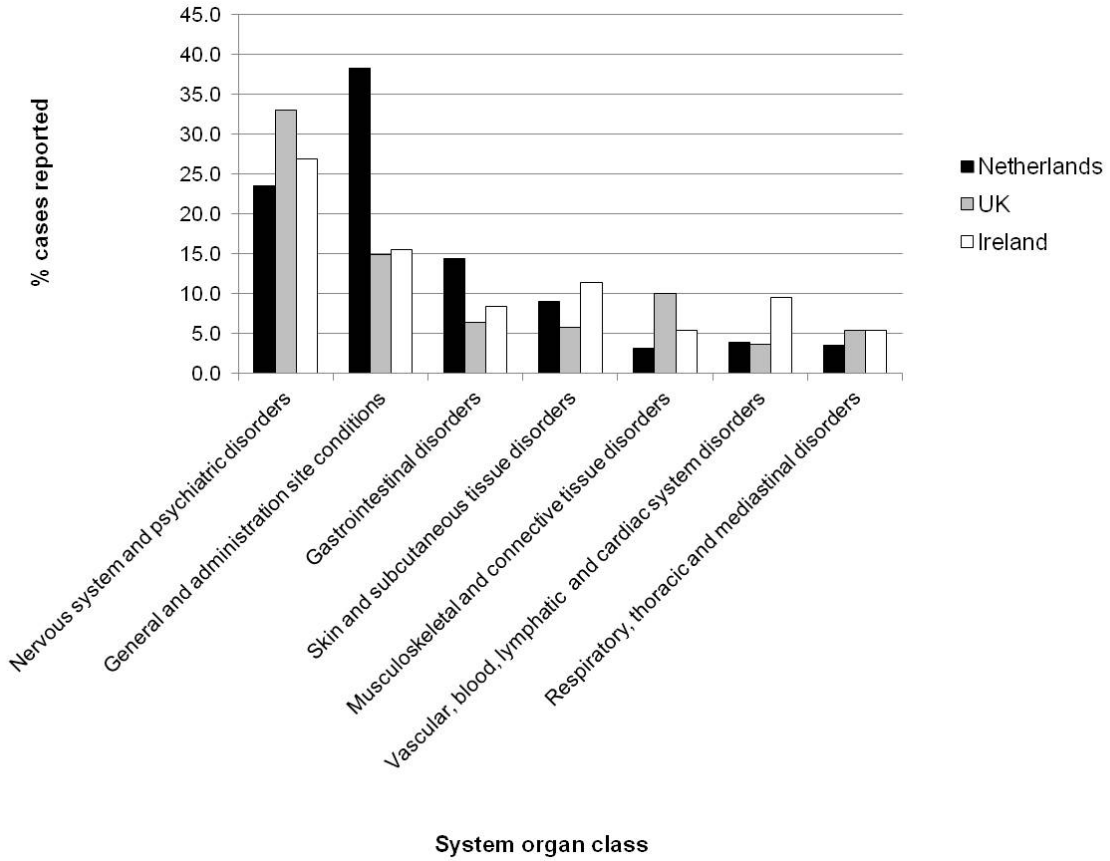

Fig. (2). Percentages of reported ADRs associated with HPV vaccines for each system organ class. Data sourced from the Database of the Netherlands Pharmacovigilance Centre Lareb [66], the UK Medicines and Healthcare products Regulatory Agency (MHRA) [75] and the Irish Medicines Board (IMB) [61]. The most commonly reported ADRs in the nervous system and psychiatric disorders class were headache, syncope, convulsions, dizziness, hypoaesthesia, paraesthesia, lethargy, migraine, tremors, somnolence, loss of consciousness, dysarthria, epilepsy, sensory disturbances, facial palsy, grand mal convulsion, dysstasia, dyskinesia, hallucination and insomnia.

since such experts were in fact present at a latter stage, in the analysis of case reports selected by the SRC [107].

As demonstrated repeatedly in the scientific literature, inadequately designed research cannot be used to reliably evaluate the safety of any drug [108, 109]. It is thus clear that no meaningful conclusions on Gardasil and Cervarix safety is possible from studies designed to generate Type 2 errors (false negatives). The poor design of existing vaccine safety and efficacy trials may be a reflection of the fact that in the past two decades the pharmaceutical industry gained an unprecedented control over the evaluation of its own products [110, 111]. As noted by Angell, "Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer" [110].

COST-EFFECTIVENESS ANALYSES: CAN HPV VACCINATION ADD VALUE TO EXISTING SCREENING PROGRAMMES?

Although approximately 275,000 women die annually from cervical cancer worldwide , almost 88% of these deaths occur in developing countries with inadequate or inexistent Pap screening programmes [1, 2]. In developing countries, such programmes helped to achieve a 70% reduction in the incidence of cervical cancer over the last five decades [13, 17, 29, 35]. Conversely, in Finland, when women stopped attending Pap screens, a 4-fold increase in cervical cancer occurred within 5 years from screening cessation [112, 113].

It is further important to emphasize that HPV vaccination, even if proven effective against actual cervical cancers, would not make Pap screening obsolete, given that the current HPV vaccines guard only against two out of 15 high-risk HPVs. Various researchers have expressed concerns regarding the possibility that HPV vaccinated women might be less inclined to participate in screening programmes [29, 114]. Such outcomes would in turn compromise timely specialist referral of cases harbouring precancerous lesions, especially those related to HPV types other than 16/18 [114]. Moreover, HPV vaccination in countries with good screening coverage could worsen the incidence of cervical cancer if the population participation in the routine cytology screening drops below 70% [115], as has already been observed [35, 116]. Thus, even with HPV vaccines, Pap screens are needed and in fact indispensable for successful management of cervical cancers [35]. Because of this, any meaningful analysis of HPV vaccination cost-effectiveness needs to take in account current screening procedures.

Several mathematical cost-effectiveness models have thus been developed in order to evaluate the impact of HPV vaccination either alone or in combination with screening (compared to screening programmes alone), on cervical cancer incidence and mortality. As shown in Table **10**, the vast majority of analyses have concluded that HPV vaccination is cost-effective but only under the most favourable assumptions, namely, (1) vaccine efficacy of 95 to 100% against HPV-16/18, corresponding to approximately 70% reduction of cervical cancers (despite the fact that careful scrutiny of clinical trials data as discussed above does not support such over-simplistic

Table 9. Comparison of Risks Versus Benefits from Cervarix based on Data Obtained After 2.9 Years of Follow-up in the Phase III PATRICIA Trial [34]

Safety Data			Efficacy Data			
ADR type	**ADRs reported (%)**		**Endpoint**	**Cases/Total n (% cases)**		**Cases prevented by the vaccine (%)**
	Vaccine	***Placebo***		***Vaccine***	***Placebo***	
• *Total serious*	**8**	**8**	• *CIN 3+ (HPV-16/18), ATP-E*	2/7344 (0.03)	10/7312 (0.14)	**0.11**
• *Medically significant condition*	**32**	**32**	• *CIN 3+ (HPV-16/18), TVC*	43/8667 (0.5)	43/8667 (0.75)	**0.25**
• *New-onset chronic disease*	**3**	**3**	• *CIN 3+ (Any HPV type), TVC*	77/8667 (0.89)	116/8667 (1.34)	**0.45**
• *New-onset autoimmune disease*	**<1**	**<1**	• *Cervical excisions, TVC*	180/8667 (2.08)	240/8682 (2.76)	**0.69**
• *Pregnancy outcomes*						
Normal infant	**62**	**63**	• *CIN 3+ (HPV-16/18), TVC-naive*	0/5449 (0.48)	13/5436 (1.53)	**0.24**
Abnormal infant						
Congenital anomaly	**<1**	**<1**	• *CIN 3+ (Any HPV type), TVC-naive*	3/5449 (0.48)	23/5436 (1.53)	**0.37**
Medically significant condition	**<1**	**<1**	• *Cervical excisions, TVC-naive*	26/5449 (0.48)	83/5436 (1.53)	**1.05**
Spontaneous abortion	**9**	**9**				

surrogate marker-based extrapolations); (2) lifelong protection from three vaccine doses (even though follow-up data does not extend beyond 5 to 8 years; Tables **1**-**6**); (3) high-vaccination coverage of preadolescent girls (a population for which efficacy data are still scarce, as most HPV vaccine clinical trials recruited young women >15 years of age [34, 36, 37, 54]) and; (4) no decrease in life quality due to vaccine-related serious adverse events (despite the fact that such conclusions can only be supported by highly flawed designs of existing safety trials). Regarding the latter, the study conducted by Mexican researchers states that "Because published data show that the vaccine has no or only slight minor side effects of minimal clinical importance, side effects were not considered in the simulation model" [117].

Overall in most settings, the cost-effectiveness of the vaccination strategy was highly sensitive to cervical cancer incidence, age of vaccination, duration of vaccine efficacy, and cost of vaccination (Table **10**). The low incidence of cervical cancer in developed countries with routine screening implies a limited maximum effect of HPV vaccination. In these countries high coverage is essential for the vaccine to be potentially cost-effective. In the Netherlands however, the country with the lowest morbidity from cervical cancer, HPV vaccination is not cost-effective even under favourable assumptions (e.g. that three HPV vaccine doses provide lifelong protection against 70% of all cervical cancers). Under less favourable assumptions (protection against 50% of cancers and additional booster doses) HPV vaccination is not cost-effective even if the price per vaccine dose was € 0. On the other hand, in developing countries where cervical cancer deaths are much higher, the potential benefits of HPV vaccination are significantly hampered by high vaccine costs, even under conditions of low vaccination coverage (e.g., Mexico; Table **1**).

As a result of favourable cost-effectiveness projections, most countries included HPV vaccines in national vaccination programmes [27]. Specifically, Cervarix and Gardasil are currently approved for use in over 100 countries worldwide [7, 28], with many more countries awaiting approval from their respective regulatory agencies [28]. However, is it rational that vaccine policy decisions be based on conclusions derived from an uncritical acceptance of flawed estimates on vaccine safety and long-term protective efficacy?

OTHER OPTIONS FOR REDUCING THE BURDEN OF CERVICAL CANCER

We have previously shown that HPV-16/18 prevalence in women with high-grade lesions and those with cervical cancer is not a significant contributing factor to high cervical cancer mortality in developing countries ($p=0.07$ to 0.19), but rather it is the lack of, or insufficient, Pap screening coverage that appears to be the key factor ($p<0.0001$) [2]. These observations do not dispute that infection with oncogenic HPVs is the primary prerequisite for cervical cancer. They do however point to other cofactors as necessary determinants of both disease progression and outcome. For example, chronic inflammation, immune system suppression due to suboptimal hygiene and/or nutrition, smoking, long-term use of oral contraceptives (OC) and multiple sexual partners conducive to sexually transmitted diseases have all been implicated as main HPV cofactors in increasing the risk of cervical carcinogenesis [3, 6, 118, 119]. Most of these cofactors appear to act through various immuno-suppressing mechanisms, thus increasing the likelihood of HPV infection becoming persistent, the latter a major prerequisite for cervical cancer progression cancer [3, 6-8].

For example, chronic inflammation downregulates cell-mediated immune responses, and high rates of cervical cancer are known to coincide with endemic and epidemic cervicitis [120]. Chronic inflammation may also increase cervical cancer risk is *via* reactive oxygen species-mediated genotoxicity. Consistent with

Table 10. Summary of Mathematical Modelling Analyses on Cost-effectiveness of HPV Vaccination Programmes Either Alone or in Combination with Screening versus Screening Programmes Alone. Underline Denotes Most Clinically-relevant Model-based Assumptions

Country	Cervical Cancer Incidence/Mortality Per 100,000 (Age Standardized	Comparison	Assumptions	Conclusion	Policy Decision
Netherlands [22]	5.4/1.5	Screening plus vaccination vs screening alone	Favourable assumptions: — lifelong immunity/protection — <u>prevents 70% of cervical cancers</u> (associated with HPV-16/18 only) — no side effects, — 3 doses administered to all women regardless of their risk of cervical cancer starting from age 12 Less favourable assumptions: — prevents 50% of cervical — cancers (associated with HPV-16/18 only) — 5 boosters — 50% coverage	Vaccination is not cost-effective Vaccination is not cost-effective even if the price per vaccine dose was € 0.	HPV vaccine included in national vaccination schedules
United States [24]	5.7/1.7	Screening plus vaccination vs screening alone	Favourable assumptions: — lifelong immunity/protection — <u>prevents 50-100% of cervical cancers</u> (associated with HPV-16/18 only) among girls and women without a previous history of those infections — 75% vaccination coverage of the pre-adolescent population (i.e., starting at age 12) — 3 vaccine doses — side effects were not considered Less favourable assumptions: — as above but with duration of immunity of only 10 years	Vaccination is cost-effective Vaccination provided only 2% marginal improvement in the reduction in the risk of cervical cancer	HPV vaccine included in national vaccination schedules
Canada [126]	6.6/1.9	Screening plus vaccination vs screening alone	— lifelong immunity/protection — the proportion of individuals protected following immunization is 100% — 95% reduction in susceptibility to HPV-16/18 corresponding to a reduction of 24% of CIN 1, 47% of CIN 2/3 and <u>62% of cervical cancers</u> — natural history of disease is unaltered following vaccine failure or loss of vaccine-induced immunity — model based on vaccinating a cohort of 100,000 12-year-old girls with 3 vaccine doses	Vaccination is cost-effective	HPV vaccine included in national vaccination schedules

(Table 10) Contd….

Country	Cervical cancer incidence/mortality per 100,000 (age standardized	Comparison	Assumptions	Conclusion	Policy decision
United Kingdom [23]	7.2/2	Screening plus vaccination vs screening alone	Favourable assumptions — lifelong immunity/protection — 98% reduction in susceptibility to HPV-16/18 corresponding to a reduction of 35% of CIN 1, 55% of CIN 2/3 and 70% of cervical cancers — 85% vaccination coverage — 3 doses administered to a cohort of 100,000 12-year-old girls Less favourable assumptions: — as above but with duration of immunity of only 10 years	Vaccination is cost-effective Vaccination is not cost-effective	HPV vaccine included in national vaccination schedules
Belgium [25]	9.4/2.7	Screening plus vaccination vs screening alone	Favourable assumptions — lifelong immunity/protection — 100% reduction in susceptibility to HPV-16/18 corresponding to a reduction of 35% of CIN 1, 55% of CIN 2/3 and 75% of cervical cancers — 80% vaccination coverage — 3 doses administered to 12-year-old girls — side effects were not considered Less favourable assumptions: — as above but with duration of immunity of only 20 years	Vaccination is cost-effective Vaccination is not cost-effective	HPV vaccine included in national vaccination schedules
Mexico [117]	19.2/9.7	Vaccination vs screening alone	— lifelong immunity/protection — vaccine efficacy 95% corresponding to a 60% reduction in HPV-16/18-associated invasive cervical cancers and CIN 3 — minimum 30% vaccination coverage — 3 doses administered to 12-year-old girls — side effects were not considered — a cost of $45 USD per vaccinated girl (approximately $15/dose)	Vaccination is cost-effective	HPV vaccine included in national vaccination schedules
Thailand [127]	24.5/12.8	Vaccination vs screening alone	Favourable assumptions: — lifelong immunity/protection — 100% efficacy resulting in 55% reduction in lifetime risk of cervical cancer — 80% vaccination coverage — 3 doses administered to girls prior to 12 years of age — side effects were not considered — a cost of 10 international dollars (I$, a currency that provides a means of translating and comparing costs among countries) per vaccinated girl (approximately I$ 2/dose) or less	Vaccination is cost-effective	HPV vaccine included in national vaccination schedules

(Table 10) Contd….

Country	Cervical cancer incidence/mortality per 100,000 (age standardized	Comparison	Assumptions	Conclusion	Policy decision
			Less favourable assumptions: — as above but with 15% lower vaccine efficacy	Vaccination is not cost-effective even at a price of I$10 per vaccinated girl	
India [63]	27/15.2	Vaccination vs screening alone	Favourable assumptions: — lifelong immunity/protection — 50 to 100% reduction in susceptibility to HPV-16/18 corresponding to a mean reduction of 44% of cervical cancers (range 28 to 57%) — 70% vaccination coverage — 3 doses administered to girls prior to 12 years of age — side effects were not considered — a cost of I$10 per vaccinated girl (approximately I$ 2/dose) Less favourable assumptions: — as above but with a cost of I$20 or above per vaccinated girl	Vaccination is cost-effective Vaccination is not cost-effective	HPV vaccine included in national vaccination schedules

these observations, nonsteroidal anti-inflammatory drugs, targeting the cycloxygenase-2 pathways, were found to decrease the risk of cervical cancer [121]. Likewise, diets high in antioxidant nutrients such as vitamin E, which can neutralize the potentially genotoxic by-products of inflammation-induced oxidative stress, were also found to be protective against high-grade cervical neoplasia and cancer [120].

Smoking could also increase cervical cancer *via* genotoxic mechanisms [3]. In addition, Szarewski *et al*. [122] demonstrated a direct significant link between heavy smoking and persistent HPV infections (p=0.02) in conjunction with a significantly altered balance of immune cells in the cervix. OC may increase the risk of HPV persistence by increasing viral productivity [3] which is consistent with the epidemiological evidence showing a stronger association of longer-duration OC use and cervical cancer [123]. In summary, given the above, it seems likely that the reduction in the burden of cervical cancer globally might be achieved by targeting other cofactors for this disease in concurrence with regular screening programmes.

CONCLUSION

Cervical cancer is a very slowly progressing cancer which can be, and thus far has been, effectively prevented by regular Pap screening [2, 7]. The high death rates from this disease remain in developing countries and are primarily due to (1) detection at very late stages of the disease (2) the lack of screening and treatment facilities and (3) suboptimal nutrition and hygiene and consequently compromised immunity of affected women disease [32]. Contrary to much of the assertions from the vaccine manufacturers, as well as strong recommendations from health agencies worldwide [2, 26], currently, there is no evidence that vaccination with either Gardasil or Cervarix would have any notable impact in reducing the cervical cancer burden, at least not in countries with regular screening programs [7, 13]. Furthermore, unlike screening and LEEP, HPV vaccines offer no therapeutic benefits as they cannot cause regression of pre-existing HPV-16/18 infections or associated lesions [7, 54]. On the contrary, Gardasil may exacerbate cervical cancer disease in women with pre-existing HPV-6/11/16/18 infections (Table **2**).

Although countries with the heaviest cervical cancer burden (i.e., India, Thailand) could in theory benefit from HPV vaccination (providing long-term clinical benefits were actually demonstrated), Pap screens would still be needed as they are indispensable for successful management of cervical cancers [32]. Researchers in the West continually stress the importance of regular screens for HPV vaccinated women, in the absence of which, cervical cancer rates would likely increase despite vaccination [7, 35]. Thus, before a HPV vaccine programme is even contemplated, regular Pap screening practices need to be established. However, with effective screening, there is little need for a HPV vaccine since vaccination is unlikely to reduce the mortality from cervical cancer beyond what Pap screening can accomplish [7, 13]. Therefore, further reduction of cervical cancer burden worldwide might be best achieved by optimizing cervical screening and targeting other factors of the disease, at least until truly safe and effective HPV vaccines are developed.

The current widespread misconceptions regarding the long-term benefits of HPV vaccination appear to have resulted from (1) significant misinterpretation of clinical trials data (i.e., invalid and premature extrapolations from (often dubious) surrogate markers such as CIN 2); and (2) biased and selective reporting of clinical trial results (i.e., reporting combined efficacy against CIN 1-3 or CIN 2/3, failure to report p-values, exclusion of certain efficacy figures from official clinical trials publications, such as those related to study subgroups in which efficacy might be lower or even negative, e.g., those with pre-existing HPV-16/18 infections). While all of these factors give an inaccurate and misleading picture of overall effectiveness of HPV vaccines, exclusion of negative efficacy figures from peer-reviewed publications (Table **2**) additionally precludes an objective and independent assessment of their true prophylactic value.

Of further concern are misleading opinions on HPV vaccine safety, based solely on manufacturer-sponsored, type-2 error-biased clinical trials designs. Of even greater concern however is the fact that such opinions are propagated by world's leading public health authorities [2]. On the other hand, the unusually high frequency and severity, as well as the consistency of the patterns of HPV-vaccine suspected ADRs reported to various vaccine safety databases (Table **8**, Figs. (**1** and **2**)), raise significant concerns about the overall safety of HPV vaccination programmes. In particular, as many as 8% of all ADRs reported to U.S. VAERS (Table **7**) as well as those identified in pre-licensure clinical trials on HPV vaccines have been classified as serious [34]. Noteworthy, compared to all other vaccines in the U.S. VAERS database, Gardasil and Cervarix alone are associated with over 60% of all serious ADRs reports, including 82% cases of permanent disability in females under 30 years of age (Table **8**). Because HPV vaccination is currently implemented in over 100 countries worldwide [7, 28], the long-term health of many young women may be unnecessarily at risk against still unknown vaccine benefits. While 15-year old preadolescents are at zero risk of dying from cervical cancer, they are faced with a risk of death and a permanently disabling lifelong autoimmune or neurodegenerative condition (Tables **7**-**8**) from vaccines which thus far have not prevented a single case of cervical cancer, let alone cervical cancer death. Yet, cancer prevention is the primary aim for which HPV vaccines were designed [7, 9, 12, 124]. For vaccines with uncertain benefits designed to prevent a disease that is already preventable by Pap screening and LEEP which carry no such risks, the risk to those vaccinated should be negligible [31]. Finally, the HPV vaccination-favourable conclusions produced by various cost-effectiveness model analyses (Table **10**) can only be considered as valid as the erroneous presuppositions from which they were derived.

In conclusion, exclusive adherence to inadequately conducted studies sponsored by vaccine manufacturers and uncritical acceptance of their results as a base of vaccine policy decision-making should be discontinued. Such practices do not serve public health interests, nor are they likely to reduce the levels of cervical cancer. Unfortunately, as noted by Gerhardus and Razum, the "unwarranted confidence in the new [HPV] vaccines led to the impression that there was no need to actually evaluate their effectiveness" [26].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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