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REVIEW ARTICLE

Human papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they at odds?

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All drugs are associated with some risks of adverse reactions. Because vaccines represent a special category of drugs, generally given to healthy individuals, uncertain benefits mean that only a small level of risk for adverse reactions is acceptable. Furthermore, medical ethics demand that vaccination should be carried out with the participant's full and informed consent. This necessitates an objective disclosure of the known or foreseeable vaccination benefits and risks. The way in which HPV vaccines are often promoted to women indicates that such disclosure is not always given from the basis of the best available knowledge. For example, while the world's leading medical authorities state that HPV vaccines are an important cervical cancer prevention tool, clinical trials show no evidence that HPV vaccination can protect against cervical cancer. Similarly, contrary to claims that cervical cancer is the second most common cancer in women worldwide, existing data show that this only applies to developing countries. In the Western world cervical cancer is a rare disease with mortality rates that are several times lower than the rate of reported serious adverse reactions (including deaths) from HPV vaccination. Future vaccination policies should adhere more rigorously to evidence-based medicine and ethical guidelines for informed consent.

Key words: Cervarix, cervical cancer, Gardasil, HPV vaccines, informed consent, vaccine adverse reactions

Key messages

- To date, the efficacy of HPV vaccines in preventing cervical cancer has not been demonstrated, while vaccine risks remain to be fully evaluated.
- Current worldwide HPV immunization practices with either of the two HPV vaccines appear to be neither justified by long-term health benefits nor economically viable, nor is there any evidence that HPV vaccination (even *if* proven effective against cervical cancer) would reduce the rate of cervical cancer beyond what Pap screening has already achieved.
- Cumulatively, the list of serious adverse reactions related to HPV vaccination worldwide includes deaths, convulsions, paraesthesia, paralysis, Guillain–Barré syndrome (GBS), transverse myelitis, facial palsy, chronic fatigue syndrome, anaphylaxis, autoimmune disorders, deep vein thrombosis, pulmonary embolisms, and cervical cancers.
- Because the HPV vaccination programme has global coverage, the long-term health of many women may be at risk against still unknown vaccine benefits.
- Physicians should adopt a more rigorous evidence-based medicine approach, in order to provide a balanced and objective evaluation of vaccine risks and benefits to their patients.

Introduction

In 2002 the US Food and Drug Administration (FDA) stated that vaccines represent a special category of drugs aimed mostly at healthy individuals and for prophylaxis against diseases to which an individual may never be exposed (1). This, according to the FDA,places significant emphasis on vaccine safety (1). In other words, contrary to conventional drug treatments aimed at management of existing, oftentimes severe and/or advanced disease conditions, in preventative vaccination a compromise in efficacy for the benefit of safety should not be seen as an unreasonable expectation. Furthermore, physicians are ethically obliged to provide an accurate explanation of vaccine risks and benefits to their patients and, where applicable, a description of alternative courses of treatment. This in turn enables patients to make a fully informed decision with regard to vaccination. For example, the Australian guidelines for vaccination emphasize that for a consent to be legally valid, the following element *must* be satisfied: 'it [consent] can *only* be given after the relevant vaccine (s) and their potential risks and benefits have been explained to the individual' (emphasis added) (2). Likewise, the United Kingdom (UK) guidelines pertaining to vaccination practices state that subjects must be given

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adequate information on which to base their decision on whether to accept or refuse a vaccine (3). This includes having a clear explanation on vaccine risks and side-effects (3).

Surprisingly, in the United States (US), there are no governmental requirements for informed consent for vaccination (4). Such an omission leaves the door open to a failure to obtain informed consent. Nonetheless, there are regulatory agencies such as the US FDA which are empowered to assure that only demonstrably safe and effective vaccines reach the market.In addition, health authorities (i.e. US Centers for Disease Control and Prevention (CDC)) are expected to provide expert advice concerning the benefits and risks related to particular drugs, including vaccines. When these official bodies are not able to provide their normal regulatory oversight and/or if financial interests take precedence over public health, significant problems in true informed consent guidelines can occur.

What is known about the currently licensed human papillomavirus (HPV) vaccines? What are their benefits, and what are their risks? While medical authorities in a number of countries, including the US, strongly advocate their use, some members of the public have become increasingly sceptical for a variety of reasons. The key question posed by such sceptics is this: Is it possible that HPV vaccines have been promoted to women based on inaccurate information? The present article examines the evidence in order to answer this critical question.

Can the currently licensed HPV vaccines prevent cervical cancer?

Gardasil's manufacturer, Merck, states on their website that 'Gardasil does more than help prevent cervical cancer, it protects against other HPV diseases, too.' Merck further claims that 'Gardasil does not prevent all types of cervical cancer' (5). Similarly, the US CDC and the FDA claim that 'This [Gardasil] vaccine is an important cervical cancer prevention tool that will potentially benefit the health of millions of women' (6) and 'Based on all of the information we have today, CDC recommends HPV vaccination for the prevention of most types of cervical cancer' (7). All four of these statements are at significant variance with the available evidence as they imply that Gardasil can indeed protect against some types of cervical cancer.

At present there are no significant data showing that either Gardasil or Cervarix (GlaxoSmithKline) can prevent any type of cervical cancer since the testing period employed was too short to evaluate long-term benefits of HPV vaccination. The longest follow-up data from phase II trials for Gardasil and Cervarix are 5 and 8.4 years, respectively (8–10), while invasive cervical cancer takes up to 20–40 years to develop from the time of acquisition of HPV infection (10–13). Both vaccines, however, are highly effective in preventing HPV-16/18 persistent infections and the associated cervical intraepithelial neoplasia (CIN) 2/3 lesions in young women who had no HPV infection at the time of first vaccination (13–15). Nonetheless, although cervical cancer may be caused by persistent exposure to 15 out of 100 extant HPVs through sexual contact (11), even persistent HPV infections caused by 'high-risk' HPVs will usually not lead to immediate precursor lesions, let alone in the longer term to cervical cancer.The reason for this is that as much as 90% HPV infections resolve spontaneously within 2 years and, of those that do not resolve, only a small proportion may progress to cancer over the subsequent 20–40 years (10,11,16–18). Moreover, research data show that even higher degrees of atypia (such as CIN 2/3) can either resolve or stabilize over time (19). Thus, in the absence of long-term follow-up data, it is impossible to know whether HPV vaccines can indeed prevent *some* cervical cancers or merely postpone them. In addition, neither of the two vaccines is able to clear existing HPV-16/18 infections, nor can they prevent their progression to CIN 2/3 lesions (20,21). According to the FDA, 'It is *believed* that prevention of cervical precancerous lesions is highly *likely* to result in the prevention of those cancers' (emphasis added) (22). It would thus appear that even the FDA acknowledges that the long-term benefits of HPV vaccination rest on assumptions rather than solid research data.

Gardasil and Cervarix: do the benefits of vaccination outweigh 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 (6,23,24). Moreover, the US CDC maintains that Gardasil is 'an important cervical cancer prevention tool' and therefore 'recommends HPV vaccination for the prevention of most types of cervical cancer' (6,7). However, the rationale behind these statements is unclear given that the primary claim that HPV vaccination prevents cervical cancer remains unproven. Furthermore, in the US, the current age-standardized death rate from cervical cancer according to World Health Organization (WHO) data (1.7/100,000) (Table I), is 2.5 times lower than the rate of serious adverse reactions (ADRs) from Gardasil reported to the Vaccine Adverse Event Reporting System (VAERS) (4.3/100,000 doses distributed) (Table II). In the Netherlands, the reported rate of serious ADRs from Cervarix per 100,000 doses administered (5.7) (Table II) is nearly 4-fold higher than the age-standardized death rate from cervical cancer (1.5/100,000) (Table I).

Although it may not be entirely appropriate to compare deaths alone from cervical cancer to serious ADRs from HPV vaccines, it should be re-emphasized that (in accordance with FDA guidelines) the margin of tolerance for serious ADRs for a vaccine with uncertain benefits needs to be very narrow, especially when such vaccine is administered to otherwise healthy individuals (1).HPV vaccination, even *if* proven effective as claimed, is targeting 9–12 year old girls to prevent approximately 70% of cervical cancers, some of which may cause death at a rate of 1.4–2.3/100,000 women in developed countries with effective Pap smear screening programmes (Table I). For a vaccine designed to prevent a disease with such a low death rate, the risk to those vaccinated should be minimal. Further, according to some estimates, HPV vaccination would do little to decrease the already low rate of cervical cancer in countries with regular Pap screening (10). Thus, any expected benefit from HPV vaccination will notably drop in the setting of routine Pap screening. Accordingly, the risk-to-benefit balance associated with HPV vaccination will then also become less favourable. On the other hand, in developing countries where cervical cancer deaths are much higher and Pap screening coverage low (Table I), the potential benefits of HPV vaccination are significantly hampered by high vaccine costs (25).

It should be noted that for any vaccine the number of doses that are eventually administered is lower than the number of doses that are distributed. Thus, calculations based on the latter tend to under-estimate the rate of vaccine-associated ADRs (Figure 1). Supporting this interpretation, we show in Table II and Figure 1 that for any of the two HPV vaccines, the reported rate of ADRs per 100,000 doses administered is very similar across different countries and approximately seven times higher than that

Table I. Key data on cervical cancer, HPV-16/18 prevalence, and cervical cancer prevention strategies in 22 countries. Data sourced from the World Health Organization (WHO)/Institut Catala d'Oncologia (ICO) Information Centre on HPV and cervical cancer (105).

Country	Incidence per 100,000 women (age-standardized)	Mortality per 100,000 women (age-standardized)	Mortality ranking among all cancers (all ages)	Pap screening coverage (%)	HPV-16/18 prevalence in women with low-/high-grade lesions/cervical cancer (%)	HPV vaccine introduced
Australia	4.9	1.4	17th	60.6 (All women aged 20–69 y screened every 2 y)	3.8/44.6/76.2	Yes
Netherlands	5.4	1.5	16th	59.0 (All women aged > 20 y screened every 5 y)	1.5/61.6/87.9	Yes
US	5.7	1.7	15th	83.3 (All women aged > 18 y screened every 3 y)	7.7/55/76.6	Yes
France	7.1	1.8	15th	74.9 (All women aged 20–69 y screened every 2 y	7.6/63.4/75.6	Yes
Canada	6.6	1.9	14th	72.8 (All women aged 18–69 y screened every 3 y; Annual if at high risk)	11.8/56.2/74.3	Yes
Spain	6.3	1.9	15th	75.6 (All women aged 18–65 y screened every 3 y	2.3/46.9/55.9	Yes
UK and Ireland	7.2	2	16th	80 (All women aged 25–64 y screened every 5 y)	2.4/61.9/79.1	Yes
Israel	5.6	2.1	14th	34.7 (All women aged 18–69 y screened every 3 y)	2.2/44.8/68.5	Yes
Germany	6.9	2.3	13th	55.9 (Women aged 20–49 y screened every 5 y)	1.4/54.1/76.8	Yes
China	9.6	4.2	7th	16.8 (All women aged 18–69 y screened every 3 y)	2.3/45.7/71	No
Viet Nam	11.5	5.7	4th	4.9 (All women aged 18–69 y screened every 3 y)	2.1/33.3/72.6	Yes
Russia	13.3	5.9	7th	70.4 (All women aged 18–69 y screened every 3y)	9.3/56/74	Yes
Brazil	24.5	10.9	2nd	64.8 (All women aged 18–69 y screened every 3 y)	4.3/54/70.7	Yes
Thailand	24.5	12.8	2nd	37.7 (All women aged 15–44 y ever screened	4.1/33.3/73.8	Yes
Pakistan	19.5	12.9	2nd	1.9 (All women aged 18–69 y screened every 3 y)	6/59.3/96.7	Yes
South Africa	26.6	14.5	2nd	13.6 (All women aged 18–69 y screened every 3 y	3.6/58.4/62.8	Yes
India	27	15.2	1st	2.6 (All women aged 18–69 y screened every 3 y)	6/56/82.5	Yes
Cambodia	27.4	16.2	1st	None	3.2/33.3/72.6	Yes
Nepal	32.4	17.6	1st	2.4 (All women aged 18–69y screened every 3 y	6/59.3/82.3	No
Nigeria	33	22.9	2nd	None	4.7/41.3/50	Yes
Ghana	39.5	27.6	1st	2.7 (All women aged 18–69 y screened every 3 y)	4.6/41.3/50	Yes
Uganda	47.5	34.9	1st	None	6.7/37.9/74.1	Yes

calculated from the number of distributed doses. The latter calculations also show a comparable range across several countries (Figure 1). Given that government-official vaccine surveillance programmes routinely rely on passive reporting (26), the rate of ADRs from HPV and other vaccines may be further under-estimated. According to some estimates, only 1–10% of the ADRs in the US are reported to VAERS (27).

The lack of data on serious ADRs in countries where routine HPV vaccination for young women is recommended and strongly promoted (Table II) greatly hampers our understanding about the

Table II. Summary of adverse reactions (ADRs) from HPV vaccines Gardasil and Cervarix. Note that the US FDA Code of Federal Regulation defines a serious adverse drug event as 'any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect' (106).

Vaccine	Country	Total *n* ADRs(ref.)	Doses*n*(ref.)	Total *n* ADRs/100,000 doses	Total *n* serious ADRs(ref.)	Total *n* serious ADRs/100,000 doses
Gardasil	US	18,727 (7)	35,000,000[a] (7)	54	1,498 (7)	4.3
	France	1,700 (34)	4,000,000[a] (34)	43	na	–
	Australia	1,534 (39)	6,000,000[a] (39)	26	91[c](26,28,29)	1.5[c]
	Ireland	314 (33)	90,000[b] (33)	349	na	–
Cervarix	Netherlands	575 (32)	192,000[b] (32)	299	575 (32)	5.7
	UK	8,798 (23)	3,500,000[b] (23)	251	na	–

na = not available.
[a]Doses distributed.
[b]Doses administered.
[c]Excluding 2010 data(unavailable at the time of writing of this report).

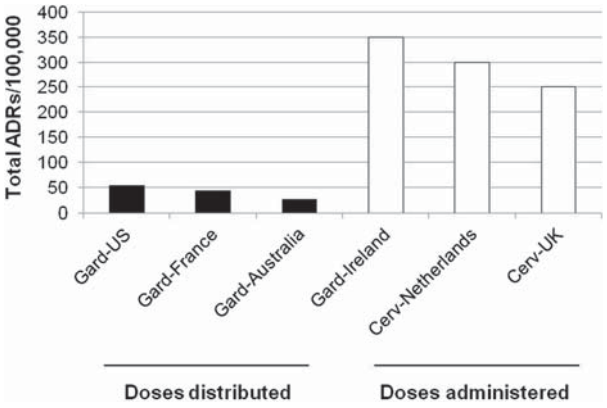

Figure 1. The rate of adverse reactions (ADRs) from Gardasil and Cervarix reported through various government-official vaccine surveillance programmes. For the data source, see Table II.

overall safety of the various HPV vaccination programmes. Nonetheless, analysis of the UK Medicines and Healthcare products Regulatory Agency (MHRA) vaccine safety data shows that there may be valid reasons for concern. For example, the total number of ADRs reported for Cervarix appears to be 24–104 times higher than that reported for any of the other vaccines in the UK immunization schedule (Figure 2).

Official reports on adverse events following immunization (AEFI) in Australia also raise concerns (26). In 2008, Australia reported an annual AEFI rate of 7.3/100,000, the highest since 2003, representing an 85% increase compared with AEFI rate from 2006 (26). This increase was almost entirely due to AEFIs reported following the commencement of the national HPV vaccination programme for females aged 12–26 years in April 2007 (705 out of a total of 1538 AEFI records). Thus, nearly 50% of all AEFIs reported during 2007 were related to the HPV vaccine. Moreover, HPV vaccine was the only suspected vaccine in 674 (96%) records, 203 (29%) had causality ratings of 'certain' or 'probable', and 43 (6%) were defined as 'serious'. The most severe AEFIs reported following HPV vaccination were anaphylaxis and convulsions. Notably, in 2007, 10 out of 13 reported anaphylaxis (77%) and 18 out of 35 convulsions (51%) occurred in women following HPV vaccination (26). During 2008, the HPV vaccine was still the number one vaccine on the list of AEFIs in Australia, with 497 records (32% of all AEFIs), and accountable for nearly 30% of convulsions (13 out of 43) (28). During 2009, the Australian reported AEFI rate for adolescents decreased by almost 50% (from 10.4 to 5.6/100,000) (29). This decline in AEFI rates was attributed to a reduction in the numbers of HPV vaccine-related reports, following cessation of the catch-up component of the HPV programme(29). Namely, the percentage of AEFIs related to HPV vaccines was only 6.4 in 2009 (29) compared to 50 in 2007 (26). In spite of the overall significant decrease in AEFI rate, the percentage of convulsions attributable to the HPV vaccine remained comparable between 2007 and 2009 (51% (26) and 40% (29), respectively).

Cumulatively, the list of serious ADRs related to HPV vaccination in the US, UK, Australia, Netherlands, France, and Ireland includes deaths, convulsions, syncope, paraesthesia, paralysis, Guillain–Barré syndrome (GBS), transverse myelitis, facial palsy, chronic fatigue syndrome, anaphylaxis, autoimmune disorders, deep vein thrombosis, pulmonary embolisms, and pancreatitis (23,24,26,28–35).

It may be thus appropriate to ask whether it is worth risking death or a disabling lifelong neurodegenerative condition such as GBS at a preadolescent age for a vaccine that has only a theoretical potential to prevent cervical cancer, a disease that may develop 20–40 years after exposure to HPV, when, as Harper noted, the same can be prevented with regular Pap screening (36)?

It is also of note that in the post-licensure period (2006–2011), the US VAERS received 360 reports of abnormal Pap smears, 112 reports of cervical cancer dysplasia, and 11 reports of cervical cancers related to HPV vaccines (35). In a report to the FDA (37), Merck expressed two 'important concerns' regarding administration of Gardasil to girls with pre-existing HPV-16/18 infection. One was 'the potential of Gardasil to enhance cervical disease', and the other 'was the observations of CIN 2/3 or worse cases due to HPV types not contained in the vaccine'. According to Merck, 'These cases of disease due to other HPV types have the potential to counter the efficacy results of Gardasil for the HPV types contained in the vaccine.' Table 17 in Merck's report to the FDA shows that Gardasil had an observed efficacy rate of –44.6% in subjects who were already exposed to 'relevant HPV types' (37). If, as implied by Merck's own submission, Gardasil may exacerbate

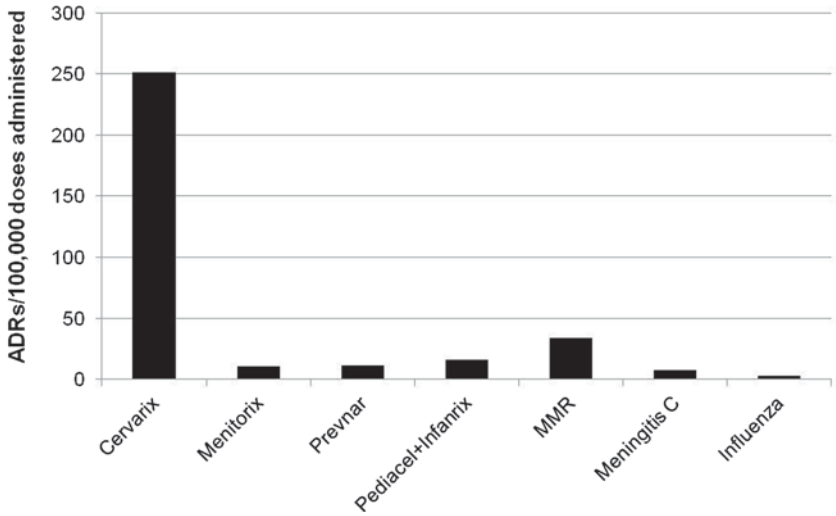

Figure 2. The rate of adverse reactions (ADRs) from Cervarix compared to that of other vaccines in the UK immunization schedule. Data sourced from the report provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the Joint Committee on Vaccination and Immunisation in June 2010 (23).

the very disease it is supposed to prevent, why do the US FDA and the CDC allow for preadolescent girls and young women to be vaccinated with Gardasil without prescreening them for HPV-16/18 infections?

Side-effects from HPV vaccines: are they a minor concern?

According to governmental health agencies worldwide, including the US CDC, Health Canada, the Australian Therapeutic Goods Administration (TGA), the UK MHRA, and the Irish Medicines Board (IMB), the vast majority of adverse reactions from either Gardasil or Cervarix are non-serious (6,23,24,38,39). These sources further state that most participants report brief soreness at the injection site, headache, nausea, fever, and fainting (6,23,24,38,39). Moreover, the UK MHRA and the US FDA and the CDC maintain that fainting is common with vaccines (especially among adolescents) and hence not a reason for concern (6,23). Specifically, the UK MHRA states that '"Psychogenic events" including vasovagal syncope, faints and panic attacks can occur with any injection procedure' and that 'such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbances, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.' (23).

The VAERS data show that since 2006 when it was first approved, Gardasil has been associated with 18,727 adverse reactions in the US alone, 8% of which were serious (1498) including 68 deaths (Table II). A report to any passive vaccine surveillance system does not by itself prove that the vaccine caused an ADR. Systematic, prospective, controlled trials are needed to establish or reject causal relationships with regard to drug-related adverse reactions of any type. Nevertheless, the unusually high frequency of reports of ADRs related to HPV vaccines (Figure 2), as well as their consistent pattern (i.e. with only minor deviations, nervous system-related disorders rank the highest in frequency across different countries, followed by general/administration site conditions and gastrointestinal disorders) (Figure 3), indicates that the risks of HPV vaccination may not have been fully evaluated in clinical trials. Indeed, in their analysis of ADRs of potential autoimmune aetiology in a large integrated safety database of ASO4 adjuvanted vaccines (a novel adjuvant system composed of 3-O-desacyl-4-monophosphoryl lipid A and aluminum salts used in Cervarix), Verstraeten et al. (40) acknowledge 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 aetiology', as the title itself clearly states (40), 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 (40). 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' (40).

Given that vaccines can trigger autoimmune disorders(41–44), a more rigorous safety assessment than that provided by the GSK-sponsored study would appear to have been warranted.

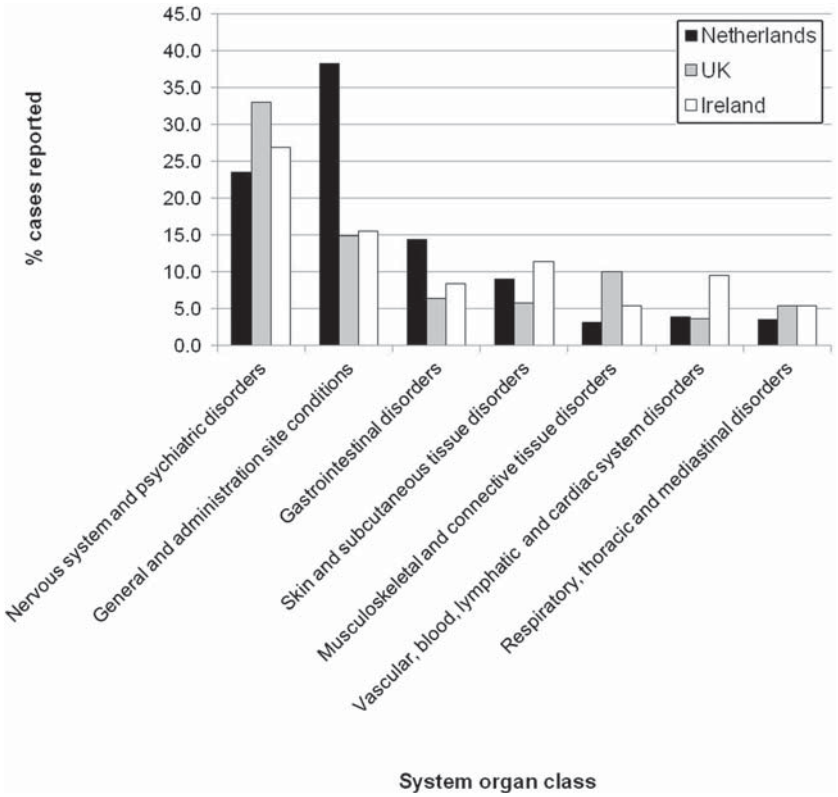

Figure 3. Percentages of reported ADRs associated with HPV vaccines for each system organ class. Data sourced from the Database of the Netherlands Pharmacovigilance Centre Lareb (32), the UK Medicines and Healthcare products Regulatory Agency (MHRA) (62), and the Irish Medicines Board (IMB) (24). The 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.

Meanwhile, independent scientific reports have linked HPV vaccination with serious ADRs, including death (45,46), amyotrophic lateral sclerosis (ALS) (45), acute disseminated encephalomyelitis (ADEM) (47–49), multiple sclerosis (MS) (50–52),opsoclonus-myoclonus syndrome (OMS) (which is characterized by ocular ataxia and myoclonic jerks of the extremities)(53), orthostatic hypotension (54), brachial neuritis (55), vision loss (56), pancreatitis (57), anaphylaxis (58), and postural tachycardia syndrome (POTS)(59).

ADEM and MS are serious demyelinating diseases of the central nervous system that typically follow a febrile infection *or* vaccination (49,50,60). Both disorders are also thought to be triggered by an autoimmune mechanism (50). Clinical symptoms include rapid onset encephalopathy, multifocal neurologic deficits, demyelinating lesions, optic neuritis, seizures, spinal conditions, and variable alterations of consciousness or mental status (47,49,60). Regarding POTS, the reported case had no other relevant factors or eventspreceding the symptoms onset apart from Gardasil vaccination (59). POTS is defined as the development of orthostatic intolerance (61). According to Blitshteyn, 'It is probable that some patients who develop POTS after immunization with Gardasil or other vaccines are simply undiagnosed or misdiagnosed, which leads to underreporting and a paucity of data on the incidence of POTS after vaccination in literature' (59). Patients with POTS typically present with complaints of diminished concentration, tremulousness, dizziness and recurrent fainting, exercise intolerance, fatigue, nausea and loss of appetite (59,61). Such symptoms may be incorrectly labelled as panic disorders or chronic anxiety. Notably, symptoms of POTS appear to be among the most frequent ADRs reported after vaccination with HPV vaccines (6,23,24,39). In spite of this, health authorities worldwide do not regard these outcomes as causally related to the vaccine (6), but rather as 'psychogenic events' (23,39).

In summary, it appears that many medical authorities may have been too quick to dismiss a possible link between HPV vaccines and serious ADRs by relying heavily on data provided by the vaccine manufacturers rather than from independent research. The UK MHRA states that 'The vast majority of suspected ADRs reported to MHRA in association with Cervarix vaccine continue to be related to either the signs and symptoms of recognized side effects listed in the product information or to the injection process and not the vaccine itself (i.e. "psychogenic" in nature such as faints)' (23). It is interesting to note that the entire group of system class disorders shown in Figure 3 is regarded as unrelated to the HPV vaccine by the MHRA. 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' (23,62). However, the fact that a similar pattern of system class ADRs to that in the UK has also been observed in at least two other countries argues against the MHRA conclusion and suggests the opposite, namely a causal relationship with the HPV vaccine (Figure 3).

Safety assessment of HPV vaccines in clinical trials: was it adequate?

A double-blinded, placebo-controlled trial is considered the 'gold standard' for clinical trials as it is thought to prevent potential researchers' biases from distorting the conduct of a trial and/or the interpretation of the results (63). Biases, however, may still occur due to selective publication of findings from within such trials, subject selection factors (inclusion/exclusion criteria), as well as placebo choices. With regard to the latter, according to the FDA, a placebo is 'an inactive pill, liquid, or powder that has no treatment value' (63). It is therefore surprising thus to note that no regulations govern placebo composition, given that certain placebos can influence trial outcomes (64). Specifically, placebo composition can, in principle, be manipulated to produce results that are favourable to the drug either in terms of safety or efficacy (64).

The clinical trials for Gardasil and Cervarix used an aluminum-containing placebo (15,20,40,65–69). Both HPV vaccines, like many other vaccines, are adjuvanted with aluminum in spite of well documented evidence that aluminum can be highly neurotoxic (70–72). Moreover, current research strongly implicates aluminum adjuvants in various neurological and autoimmune disorders in both humans and animals (41,73–80). It is thus becoming increasingly clear that the routine use of aluminum as a placebo in vaccine trials is not appropriate (80,81).

Notably, safety data for Gardasil presented in Merck's package insert and the FDA product approval information (82) show that compared to the saline placebo, those women receiving the aluminum-containing placebo reported approximately 2–5 times more injectionsite ADRs. On the other end, the proportion of injection site ADRs reported in the Gardasil treatment group was comparable to that of the aluminum 'control' group (Table III). 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.

For the assessment of serious conditions, 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 conditions (2.3%) (Table IV).

In a recent meta-analysis of safety and efficacy of HPV vaccines, seven trials enrolling a total of 44,142 females were evaluated (83). Two main populations of women were defined in these trials: those who received three doses of the HPV vaccine or the aluminum-containing placebo within a year (denoted as the per-protocol population (PPP)), and those who received at least one injection of the vaccine or the placebo within the same period (intention-to-treat population (ITT)). While HPV vaccine efficacy was evaluated in both PPP and ITT cohorts, vaccine safety was primarily evaluated in the ITT cohort (83). Although ITT analysis is 'conservative' for assessment of treatment benefits (since dropouts may occur), it is 'anti-conservative' for assessment of ADRs, because ADRs will occur

Table III. Injectionsite adverse reactions (ADRs) reported in Gardasil clinical trials among 8878 female participants aged 9–26 years, 1–5 days post-vaccination(82).

ADR type	Gardasil ($n = 5088$)%	Aluminum (AAHS)[a] ($n = 3470$)%	Saline placebo ($n = 320$)%	Gardasil/saline	Gardasil/AAHS	AAHS/saline
Pain	83.9	75.4	48.6	1.7	1.1	1.6
Swelling	25.4	15.8	7.3	3.5	1.6	2.2
Erythema	24.7	18.4	12.1	2.0	1.3	1.5
Pruritus	3.2	2.8	0.6	3.5	1.1	4.7
Bruising	2.8	3.2	1.6	1.8	0.9	2.0

[a]AAHS Control = amorphous aluminum hydroxyphosphate sulfate.

Table IV. Number of girls and women aged 9–26 years who reported a condition potentially indicative of a systemic autoimmune disorder after enrolment in Gardasil clinical trials (82).

Condition	Gardasil ($n = 10,706$) n (%)	Aluminum (AAHS) [a]($n = 9412$) n (%)
Arthralgia/arthritis/arthropathy	120 (1.1)	98 (1.0)
Autoimmune thyroiditis	4 (0.0)	1 (0.0)
Coeliac disease	10 (0.1)	6 (0.1)
Insulin-dependent	2 (0.0)	4 (0.0)
Diabetes melitus insulin-dependent	2 (0.0)	2 (0.0)
Erythema nodosum	27 (0.3)	21 (0.2)
Hyperthyroidism	35 (0.3)	38 (0.4)
Hypothyroidism	7 (0.1)	10 (0.1)
Inflammatory bowel disease	2 (0.0)	4 (0.0)
Multiple sclerosis	2 (0.0)	5 (0.1)
Nephritis	2 (0.0)	0 (0.0)
Optic neuritis	4 (0.0)	3 (0.0)
Pigmentation disorder	13 (0.1)	15 (0.2)
Psoriasis	3 (0.0)	4 (0.0)
Raynaud's phenomenon	6 (0.1)	2 (0.0)
Rheumatoid arthritis	2 (0.0)	1 (0.0)
Scleroderma/morphea	1 (0.0)	0 (0.0)
Stevens–Johnson syndrome	1 (0.0)	3 (0.0)
Sytemic lupus erythematosus	3 (0.0)	1 (0.0)
Uveitis	3 (0.0)	1 (0.0)
Total	245 (2.3)	218 (2.3)

less frequently if fewer doses of the vaccine are administered. Thus, such a selection procedure may explain why the meta-analysis found the risk-to-benefit ratio to be in favour of the HPV vaccines (83).

The seven trials included in the meta-analysis were all sponsored by the vaccine manufacturers (14,15,20,65–69). In a lengthy report of potential conflicts of interests of the FUTURE II trial study group (15), the majority of authors declared 'receiving lecture fees from Merck, Sanofi Pasteur, and Merck Sharp & Dohme'. In addition, 'Indiana University and Merck have a confidential agreement that pays the university on the basis of certain landmarks regarding the HPV vaccine.' In the 2009 *JAMA* editorial (11), Haug noted that 'When weighing evidence about risks and benefits, it is also appropriate to ask who takes the risk, and who gets the benefit. Patients and the public logically expect that only medical and scientific evidence is put on the balance. If other matters weigh in, such as profit for a company or financial or professional gains for physicians or groups of physicians, the balance is easily skewed. The balance will also tilt if the adverse events are not calculated correctly.'

Are there safe and effective alternatives to HPV vaccination?

Although approximately 275,000 women die annually from cervical cancer worldwide, almost 88% of these deaths occur in developing countries. Such disproportion of cancer deaths may be surprising given that the prevalence of HPV-16/18 in women with cervical cancer is equal in both developing and developed countries (71.0% and 70.8%, respectively) (Table V). Furthermore, HPV-16 and HPV-18 are the most oncogenic of all HPV subtypes and increasingly dominant with increasing severity of cervical cancer lesions (Table I) (84). Nonetheless, analysis of WHO data in Figure 4 shows that HPV-16/18 prevalence in women with high-grade lesions as well as cervical cancer is not a significant promoter of high cervical cancer mortality in developing countries ($P = 0.07$–0.19), but rather it is the lack of or insufficient Pap screening coverage ($P < 0.0001$). These data do not dispute that HPV-16/18 infection is a primary prerequisite for cervical cancer. However, they do point to other co-factors as necessary determinants of both disease progression and outcome (85).

The efficacy of regular Pap screening procedures in developed countries is further emphasized by the fact that such programmes helped to achieve a 70% reduction in the incidence of cervical cancer over the last five decades (10,12,86,87). Conversely, in Finland, when women stopped attending Pap screens, a 4-fold increase in cervical cancer occurred within 5 years from screening cessation (88,89).

It should be emphasized that HPV vaccination does not make Pap screening obsolete, especially since the current HPV vaccines guard only against 2 out of 15 oncogenic HPV strains. Harper noted that if HPV-vaccinated women stopped going for Pap smears, the incidence rate of cervical cancer would increase (36,86). A similar concern was also raised by French and Canadian researchers who suggested the possibility that vaccinated women might be less inclined to participate in screening programmes (87,90). Such outcomes would in turn compromise timely specialist referral of cases harbouring precancerous lesions, especially those related to HPV genotypes other than 16/18 (90).

Are HPV vaccines cost-effective?

The currently licensed HPV vaccines are among the most expensive vaccines on the market (i.e. Gardasil currently costs US $400 for the three required doses) (87), making it unlikely that those countries with the heaviest burden of cervical cancer mortality (i.e. Uganda, Nigeria, and Ghana) would ever benefit from them. That is under the assumption that the long-term benefits from HPV vaccination (i.e. cancer prevention) were proven. For example, preadolescent HPV vaccination in Thailand is cost-effective only when assuming lifelong efficacy and a cost of 10 international dollars (I$, a currency that provides a means of translating and comparing costs among countries) per vaccinated girl (approximately I$2/dose) or less (91). The cost-effectiveness analysis of HPV vaccination for Eastern Africa shows a similar outcome (25). In countries where pricing is less of an issue, such as the US, HPV vaccination is only cost-effective based on the assumption of complete and lifelong vaccine efficacy and 75% coverage of the targeted preadolescent population (92,93). In the Netherlands, HPV vaccination is not cost-effective under similar assumptions (e.g. that the HPV vaccine provides lifelong protection against 70% of all cervical cancers, has no side-effects, and is administered to all women regardless of their risk of cervical cancer) (94). Note that the reason why high coverage is needed for a vaccine to be cost-effective in the developed countrysetting is the very low incidence of cervical cancer (due to effectiveness of Pap screening programmes). For example, to prevent a single out of 5.7/100,000 cervical cancer cases (or one out of 1.7/100,000 cervical cancer deaths) in the US, nearly every girl would need to be vaccinated for the HPV vaccine programme to be cost-effective.

The increased pressure to make the HPV vaccines mandatory for all preadolescent girls makes the cost of the HPV vaccination programme a significant issue. For example, according to a 2006 report in *The New York Times* (95), to make Gardasil mandatory would probably double the cost of the US vaccination programme: 'North Carolina, for instance, spends $11 million annually to provide every child with seven vaccines. Gardasil alone would probably cost at least another $10 million.' Under the assumption that the HPV vaccine offers full protection against HPV infection for 5 years, an 11-year-old girl would need 13 booster shots if she were to live to the age of 75. At a current cost of US $120 per dose, the total cost for vaccinating one girl would thus exceed US $1500. According to some estimates, to vaccinate every 11- and 12-year-old girl in the US would cost US $1.5 billion and to

Table V. Key cervical cancer statistics according to the 2010 World Health Organization (WHO)/Institut Catala d'Oncologia (ICO) report on HPV and related cancers (107).

	World	Developing countries (% total)	Developed countries (% total)
Women at risk for cervical cancer (aged ≥ 15 y)	2,336,986	1,811,867 (77.5)	525,120 (22.5)
Annual number of new cases of cervical cancer	529,828	453,321 (85.6)	76,507 (14.4)
Annual number of cervical cancer deaths	275,128	241,969 (87.9)	33,159 (12.1)
Prevalence (%) of HPV-16 and/or HPV-18 among women with cervical cancer	70.9	71.0	70.8

protect only these girls for a lifetime would cost US $7.7 billion (96). If we were to estimate just the cost of initial vaccination excluding the booster shots for 11- and 12-year-old girls, in ten years the US would spend at least 15 billion of limited health care dollars on Gardasil alone (96). Who then reaps the benefit at no risk from making the HPV vaccine mandatory? The customer or the manufacturer?

Altogether the above observations do not support the claim made by the US CDC and the FDA, that is, 'This [Gardasil] vaccine is an important cervical cancer prevention tool that will potentially benefit the health of millions of women' (6) and, instead, appear to suggest that current worldwide immunization campaigns (Table I) with either of the two HPV vaccines are neither justified by long-term health benefits nor economically viable.

How does HPV vaccine marketing and promotion line up with international ethical guidelines for informed consent?

The medical profession's ethical duty is to provide a full and accurate explanation of the benefits as well as the risks associated with a particular drug so that a patient is able to make an informed decision regarding a treatment. If a physician fails to do so and/or if financial interests take precedence over public health, breaches of informed consent guidelines may occur. For instance, presenting information in a way which promotes fear of a disease while undervaluing potential vaccine risks is likely to encourage patients to give consent to the treatment, even when the latter has no proven significant health benefit.

Both Gardasil and Cervarix were approved by the US FDA, which in 2006 was found to be '...not positioned to meet current or emerging regulatory responsibilities', because 'its scientific base has eroded and its scientific organizational structure is weak' (97). According to the Science and Mission at Risk Report prepared by the FDA Science Board in 2006 (97), the risks of an 'under-performing' FDA are far-reaching for two main reasons. First, 'The FDA's inability to keep up with scientific advances means that American lives are at risk', and second,' The world looks to the FDA as a leader in medicine and science. Not only can the agency not lead, it can't even keep up with the advances in science' (97).

If the FDA's decisions to approve certain drugs could by its own admission be unreliable, then the only other gate-keeper for consumer safety is the expert advice provided by other health

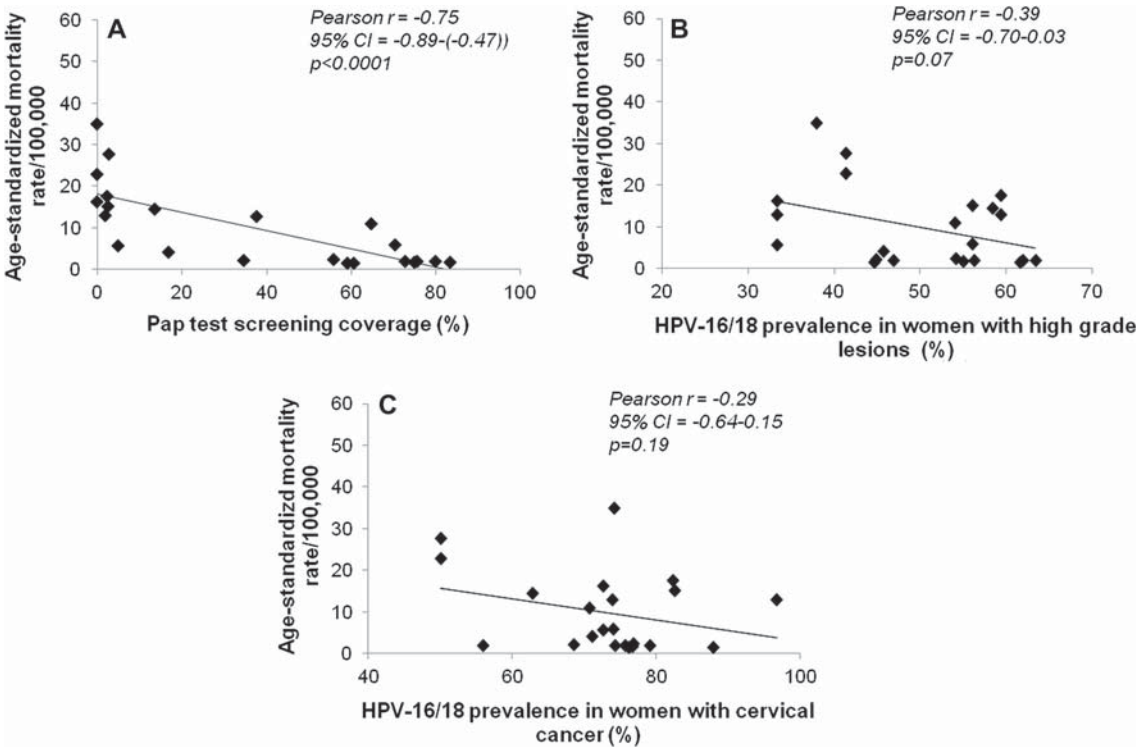

Figure 4. Correlation between cervical cancer mortality rates and A: Pap test screening coverage; B:HPV-16/18 prevalence in women with high-grade lesions (CIN 2/3, carcinoma *in situ* (CIS), and high-grade cervical squamous intraepithelial lesions (HSIL)); C: HPV-16/18 prevalence in women with cervical cancer. Data were sourced for 22 countries from World Health Organization (WHO)/Institut Catala d'Oncologia (ICO) Information Centre on HPV and cervical cancer (Table I). The correlation analysis was carried out using GraphPad Prism statistical software to derive Pearson correlation coefficients (r). The level of significance was determined using a two-tailed test. The correlation was considered statistically significant at $P < 0.05$.

authorities. The history of how HPV vaccines came to market, however, indicates that such advice was not always given from the basis of the best available evidence. A 2009 Special Communication from *JAMA* by Rothman and Rothman (98) provides compelling evidence that Gardasil manufacturer Merck funded educational programmes by professional medical associations (PMAs) as a marketing strategy to promote the use of their vaccine. The marketing campaign proceeded 'flawlessly', according to Merck's chief executive officer, and in 2006 Gardasil was named the pharmaceutical 'brand of the year' for building 'a market out of thin air' (98). The reason why the marketing campaign for Gardasil was so successful was that 'By making this vaccine's target disease cervical cancer, the sexual transmission of HPV was minimized, the threat of cervical cancer to all adolescents maximized, and the subpopulations most at risk [women in developing countries] practically ignored' (98).That these arguments were delivered by the PMAs is cause for concern, since PMAs are obligated to provide members with evidence-based data so that they in turn are able to present relevant risks and benefits to their patients (98).

India's medical authorities have also been publicly condemned after a civil society-led investigation revealed that trials for HPV vaccines in the states of Andhra Pradesh and Gujarat violated established national and international ethical guidelines on clinical research as well as children's rights (99). These events apparently occurred as a result of 'aggressive' promotional practices of the drug companies and their uncritical endorsement by India's medical associations (99). Although proclaimed as a post-licensure observational study of HPV vaccination against cervical cancer, the project was in fact a clinical trial and, as such, should have adhered to protocols mandated by the Drugs and Cosmetics Act (DCA) and the Indian Council for Medical Research (ICMR) (100). Instead, the trial was found in serious breach of both the DCA's and the ICMR's guidelines for informed consent and was terminated in April 2010, following six post-HPV vaccination deaths (99). The report in the 2011 issue of *Lancet Infectious Diseases* further reveals that both ICMR and DCA subsequently denied information on the study protocols as a 'trade secret and commercial confidence of third party' (100). According to the authors, 'It remains unclear how information from a study done in collaboration with government health organisations can be regarded as a trade secret' (100). It is worth emphasizing that the termination of HPV vaccine trials in India occurred despite an annual cervical cancer mortality rate of 15.2/100,000 women, which is over 7–10 times greater than that in the developed world (Table I). Such an outcome indicates that even situations of unmet medical needs cannot be resolved at the expense of abandoning ethical requirements for informed consent.

Questionable HPV vaccine marketing strategies were also seen in France and were eventually stopped by the action of government health authorities who found the sponsorship of several Gardasil advertisements to be in direct violation of French public health codes (101). These violations included, but were not limited to: 1) Claiming longer efficacy than was actually proven (8.5 versus 4.5 years) and 2) Making false claims (the ads in question replaced the officially approved use of Gardasil for 'the prevention of low-grade lesions' with statements indicating Gardasil should be used for 'the prevention of pre-malignant genital lesions, cancers of the cervix and external genital warts').

In the US, Merck has been heavily criticized for the fact that it spent vast sums in lobbying to make the vaccine mandatory (12,98). According to an editorial from *The American Journal of Bioethics*, even those who strongly favoured the vaccine were 'stunned at the degree to which Merck has pushed its $400 vaccine as a mandatory measure'(102). Nonetheless, what is more disconcerting than the aggressive marketing strategies employed by the vaccine manufacturers is the practice by which the medical profession has presented partial information to the public, namely, in a way that generates fear, thus likely promoting vaccine uptake. For example, the US CDC and the FDA state that 'Worldwide, cervical cancer is the second most common cancer in women, causing an estimated 470,000 new cases and 233,000 deaths per year' (6). The Telethon Institute for Child Health Research in Australia made a similar statement in 2006 while recruiting volunteers for a HPV vaccine study. In the opening paragraph the point was also made that cervical cancer was one of the most common causes of cancer-related deaths in women worldwide (103). A crucial fact was omitted in both instances which is that while it is certainly true that approximately a quarter of a million of women die of cervical cancer each year, 88% of these deaths occur in the developing countries and certainly not in the US nor Australia (Table V), where cervical cancer is the 15th and 17th cause of cancer-related deaths, respectively, and where mortality rates from this disease are the lowest on the planet (1.4–1.7/100,000) (Table I). Finally, contrary to the information provided by the CDC and the FDA, there is no evidence that Gardasil is 'an important cervical cancer prevention tool' (6).

It thus appears that to this date, medical and regulatory entities worldwide continue to provide inaccurate information regarding cervical cancer risk and the usefulness of HPV vaccines, thereby making informed consent regarding vaccination impossible to achieve.

Concluding remarks

Regulatory authorities are responsible for ensuring that new vaccines go through proper scientific evaluation before they are approved. An equal fiduciary responsibility rests with the medical profession to only promote vaccinations with those vaccines whose safety and efficacy have been thoroughly demonstrated. The available evidence, however, indicates that health authorities in various countries may have failed to provide an evidence-based rationale for immunization with HPV vaccines and, in doing so, may have breached international ethical guidelines for informed consent. Contrary to the information from the US CDC, Health Canada, Australian TGA, and the UK MHRA, the efficacy of Gardasil and Cervarix in preventing cervical cancer has not been demonstrated, and the long-term risks of the vaccines remain to be fully evaluated.

Current worldwide HPV immunization practices with either of the two HPV vaccines appear to be neither justified by long-term health benefits nor economically viable, nor is there any evidence that HPV vaccination would reduce the rate of cervical cancer beyond what Pap screening has already achieved. Furthermore, the frequency, the severity, as well as the consistency of the patterns of ADRs reported to various governmental vaccine surveillance programmes for both Gardasil and Cervarix (Figures 2 and 3) raise significant concerns about the overall safety of HPV vaccination programmes. Because these programmes have global coverage (Table I), the long-term health of many women may be unnecessarily at risk against still unknown vaccine benefits. Altogether these observations suggest that a reduction in the burden of cervical cancer globally might be best achieved by targeting other risk factors for this disease (i.e. smoking, use of oral contraceptives, chronic inflammation) (85) in conjunction with regular Pap test screening. The latter strategy has already been proven successful in developed nations where the incidence of cervical cancer is very low (Table I).

According to the Helsinki Declaration and the International Code of Medical Ethics (104), the well-being of the individual must be a physician's top priority, taking precedence over all other interests. Although the Declaration is addressed primarily to physicians, the World Medical Association encourages other participants in medical research involving human subjects to adopt these same principles (104). Greater efforts should thus be made to minimize the undue commercial influences on academic institutions and medical research, given that these may impede unbiased scientific inquiry into important questions about vaccine science and policy.

The almost exclusive reliance on manufacturers' sponsored studies, often of questionable quality, as a base for vaccine policy-making should be discontinued. So should be the dismissal of serious ADRs as coincidental or 'psychogenic' in spite of independent research suggesting otherwise. It can hardly be disputed in view of all the evidence (i.e. case reports and vaccineADR surveillance in various countries) that HPV vaccines do trigger serious ADRs. What does remain debatable, however, is the true frequency of these events because all systems of monitoring for vaccineADRs currently in place rely on passive reporting.Passive ADR surveillance should thus be replaced by active surveillance to better our understanding of true risks associated with particular vaccines (especially new vaccines). The presentation of partial and non-factual information regarding cervical cancer risks and the usefulness of HPV vaccines, as cited above, is, in our view, neither scientific nor ethical. None of these practices serve public health interests, nor are they likely to reduce the levels of cervical cancer. Independent evaluation of HPV vaccine safety is urgently needed and should be a priority for government-sponsored research programmes. Any future vaccination policies should adhere more rigorously to evidence-based medicine as well as strictly follow ethical guidelines for informed consent.

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