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Critical Opinion on Cochrane Review of HPV Vaccines

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1 Introduction

In May 2018, Cochrane published the findings of a systematic review of 26 randomised controlled trials to determine the efficacy and harms of human papillomavirus (HPV) vaccines [1]. The aim of a systematic review is to provide highly reliable evidence on efficacy and harms by exhaustively collecting randomised controlled trials on the efficacy of a particular medical intervention, providing a critical appraisal of each trial's methodology, and applying appropriate statistical methodology to synthesise the results of these trials. The Cochrane HPV vaccine review, however, falls far short of an ideal systematic review and contains numerous problems that cannot be ignored. These problems are discussed below.

2 Review of Efficacy

The HPV vaccine review claims to have confirmed a reduction in the risk of developing precancerous cervical lesions (even though the longest follow-up period was 8 years) based on an evaluation of efficacy in 26 randomised controlled trials, 25 of which were industry-funded. The risk of developing precancerous cervical lesions is a surrogate endpoint, but what the review did not confirm was a reduction in cervical cancer itself as a true endpoint of efficacy. Thus, the review does not add anything new to previous claims of efficacy by the pharmaceutical industry.

The age range for HPV vaccination in Japanese clinical practice is primarily 12 to 16 years, whereas the HPV vaccine review evaluated efficacy in females aged 15 and older, and the review authors claim in their conclusion that a prophylactic effect against precancerous lesions was confirmed in females aged 15 to 26. It should therefore be noted that the efficacy claimed in the review does not coincide with the current vaccination age group in Japan. In their discussion, the authors suggest that HPV vaccines may also be effective in girls younger than 15, noting that this age group is assumed to resemble the population of HPV-negative females 15 and older in terms of efficacy, further citing research in which girls 15 and younger showed a similar immune response to females aged 15 to 26 years. However, the review evaluated efficacy only in the population aged 15 years and above and failed to point out that efficacy has not been verified in the primary age group for clinical practice in Japan.

3 Review of Harms

The HPV vaccine review investigated harms based on the number of adverse event reports in 23

of the 26 clinical trials evaluated. It found that the HPV vaccination group had no increased risk of serious adverse events compared to the control groups, and no significant increase in deaths. However, the analysis of harms in this review contained the following problems.

(1) Adjuvanted placebos or other vaccines were used as controls

Of the 23 evaluated trials, one used an unadjuvanted hepatitis A vaccine as the control and the remaining 22 trials used an adjuvanted placebo or other adjuvanted vaccine as the control (See appendix table). Considering that there appear to be risks not only from HPV-derived ingredients (L1 protein) [2] but also from powerful adjuvants, the safety of HPV vaccines should be verified by comparison between an HPV vaccine formulation (designed to maintain a high antibody titer over a long period by adding a powerful adjuvant to L1 protein) and an unadjuvanted placebo.

In fact, study V501-018 was the only study to use a saline placebo control for the quadrivalent vaccine Gardasil. However, this trial was excluded from the HPV vaccine review's evaluation. The review authors justified this exclusion on the grounds that although the trial included both sexes, the paper presenting the trial results did not separate male and female data, and upon inquiry the authors were told that separate data was not available for females. However, considering that study V501-018 was funded and sponsored by Merck and targeted both sexes, it is difficult to imagine that separate data was not maintained for males and females. In fact, an FDA clinical review [3] presents data on adverse reactions in 320 females vaccinated with saline placebo in study V501-018. Although the FDA review only gives data on vaccination site pain, swelling and redness, the incidence of these reactions is two to three times greater in the Gardasil group than in the saline control group, suggesting that adjuvanted HPV vaccine formulations could induce a strong immune response. This exclusion, for inexplicable reasons, of a key trial from the HPV vaccine review's evaluation of efficacy and safety, casts doubt on the reliability of the review.

(2) Post-HPV vaccination symptoms cannot be ascertained from adverse event information in the clinical trials

The characteristics of post-HPV vaccination clinical symptoms are gradually being revealed in numerous physician-reported adverse events, showing both the complexity of these symptoms and their clinical course. There are reports of a wide range of symptoms developing in a multi-layered manner over long periods spanning several months to several years (period of maintenance of high HPV antibody titer), as well as known autoimmune diseases such as complex regional pain syndrome (CRPS), chronic fatigue syndrome (CFS) and postural orthostatic tachycardia syndrome (POTS) or similar symptoms, and even symptoms such as higher cognitive impairment.

In contrast, adverse events collected in clinical trials are reported according to predetermined reporting criteria that presuppose the occurrence of known diseases and individual symptoms. Such a reporting system cannot capture post-HPV vaccination symptoms that follow a complex course characterized by multi-layered emergence of various symptoms over a long period, and it therefore follows that the true harms of HPV vaccines cannot be detected by simply comparing

the incidence of individual adverse events reported in trials.

The HPV vaccine review analysed serious adverse events through a meta-analysis based on the number of reports of individual symptoms collected during each trial's follow-up period of several months to several years. The analysis found no difference in the incidence of adverse events between the HPV vaccine and control groups, and the review seems to conclude from this result that a certain level of safety has been demonstrated. However, as already discussed, this result is only based on the number of reports of known diseases and individual symptoms, and does not capture the multi-layered occurrence of various symptoms in the long-term after HPV vaccination in individual adolescent girls. This is a point that demands further attention.

In an analysis of adverse event reports using Vigibase, Chandler and colleagues at the WHO Uppsala Monitoring Center noted that when symptoms such as headache, dizziness and syncope, or headache, dizziness and fatigue were analyzed as symptom clusters, the result was a significantly higher proportion of adverse event reports associated with HPV vaccines than with other vaccines, and the authors point out the limitations in the conventional analytical method of only extracting individual adverse events [4, 5].

(3) Much of the literature showing evidence of harms is excluded from the Discussion

As discussed above, there are some basic limitations in the evaluation of harms associated with HPV vaccines in the systematic review of 23 trials. In addition to the paper by Chandler et al, Japanese researchers alone have published many papers providing evidence of the harms of HPV vaccines. These include case reports [6, 7, 8, 9, 10, 11] by physicians who have observed in their own patients the characteristic adverse reactions described above, papers describing objective test findings of changes in the cerebrospinal fluid, brain and nervous system that can explain patients' symptoms [12, 13, 14, 15], an animal experiment [16], and a paper reporting a temporal relationship between HPV vaccination and onset of HPV vaccine-related symptoms in vaccinated patients [17]. At the very least, the results of these studies should have been discussed in relation to the review findings in the Discussion section, but these articles were entirely ignored and excluded from the Discussion.

(4) Critical discussion of epidemiology studies or reviews by international organisations and regulatory authorities is absent

The only results considered in the Discussion section are those that deny any evidence of harm due to HPV vaccines, such as certain epidemiology studies and reviews by the CDC, EMA and other national regulatory authorities, the WHO Global Advisory Committee on Vaccine Safety (GACVS) and other international organisations. Moreover, these conclusions are accepted without any critical scrutiny.

However, the cited epidemiology studies were designed to target predefined known conditions and specific autoimmune diseases, and did not capture the characteristic post-HPV vaccination adverse reactions described above. Furthermore, even if patients with adverse reactions to an HPV vaccine were examined by a medical facility after developing a condition or autoimmune disease

defined in the research, these are fundamentally difficult diseases to diagnose, and it is easy to imagine patients being given an inaccurate diagnosis. In fact, the paper by Chandler et al reports that despite POTS, CRPS and CFS being included in 20–58% of reported adverse reactions to HPV vaccines, the disease diagnosis only included these terms in 15% of 694 cases analysed using symptom cluster analysis. The opinions of the EMA and other national regulatory authorities and the statement from GACVS also rely on this kind of limited epidemiological research as their main evidence [18, 19].

Notable bias was also apparent on the part of GACVS. Vaccine makers were in constant attendance as external experts at the regular meetings of GACVS, and a Freedom of Information request brought to light improper interference by the GACVS chairperson at a meeting of the Japanese Ministry of Health, Labour and Welfare in 2014 in order to quash concerns over HPV vaccines [20]. It is therefore inadvisable to unquestioningly accept these opinions.

4 Lessons from Review of Oseltamivir (Tamiflu)

The conclusions of a Cochrane review published in 2000 claiming the efficacy and safety of zanamivir (Relenza) and oseltamivir (Tamiflu) for the prevention and treatment of influenza [21] were revised in 2009 to acknowledge that zanamivir and oseltamivir have a small effect in reducing the time needed for alleviation of influenza symptoms, and that their use for both prevention and treatment must be decided after weighing the benefits against the risks of adverse reactions. This revision process started when the Japanese physician Keiji Hayashi requested a reappraisal of the review, pointing out that the Kaiser Study in 2000 supporting the review conclusions had used data primarily from unpublished clinical trials for its evaluation. The Kaiser Study was a meta-analysis of 10 industry-funded clinical trials conducted in the latter half of the 1990s, but while two of these trials had been published in peer-reviewed journals, the other eight were unpublished or only published as abstracts. The Cochrane review team then asked the Kaiser Study authors for the data, but because the data was not forthcoming, the meta-analysis was repeated without the Kaiser Study, resulting in a very different conclusion [22, 23]. This episode demonstrates that even Cochrane Systematic Reviews are at risk of reaching the wrong conclusion if the appropriate selection and critical examination of evaluated trials are neglected.

The influenza review was redone by Tom Jefferson of the Nordic Cochrane Centre in response to criticism of the review's findings. Also based at the Nordic Cochrane Centre, a research group led by Peter C. Gøtzsche conducted a detailed review of the EMA evaluation of HPV vaccines, and identified failings in the basic evaluation materials and review methodology, including a lack of critical scrutiny and independent re-analysis of data provided by the vaccine makers, and omission of some clinical trials in a less-than-exhaustive review [24]. It is therefore inexplicable that the HPV vaccine review should uncritically accept the EMA evaluation without mentioning these findings from the Nordic Cochrane Centre.

5 Bias in Press Release

The way in which the HPV vaccine review was announced raises questions about bias. Cochrane's

press release introduced the first author M. Arbyn as citing the GACVS statement, "...the risk-benefit profile of prophylactic HPV vaccines remains favourable and unjustified claims of harm that lack biological and epidemiological evidence may affect the confidence of the public". The HPV vaccine review has numerous limitations, as discussed above, but characterising expressions of doubt over the risk-benefit profile of HPV vaccines as "unjustified claims of harm" is more than enough to raise questions about the neutrality of this review.

Research on capturing the actual situation and identifying causes needs to progress in order to ascertain the true harms of pharmaceuticals, and the history of pharmaceutical scandals demonstrates that this process takes time. Therefore, the approach required when reviewing harms should be one that seeks detection of risk signals rather than evidence of safety defined as the absence of any increased risk from an intervention. However, this basic approach is completely absent in the HPV vaccine review and press release.

In addition to the press release, the Cochrane website also presents feedback from the medical community in the form of comments from physicians welcoming the review findings, but it seems inappropriate to publish comments from physicians acting as consultants for GlaxoSmithKline and Merck (known as MSD in the US and Japan).

6 Conflict of Interest

(1) Authors' conflict of interest

At publication of the final version of the protocol, conflicts of interest had already been identified for two of the review's six authors. When the review results were subsequently published there were four authors (one of the two protocol authors with conflicts of interest remained as the lead author of the review). In addition, three of the remaining four authors (M. Arbyn, C. Simoons and PPL. Martin-Hirsch) had received travel grants from HPV vaccine manufacturers, which in and of itself raises questions about conflict of interest.

In particular, the lead author of the review, M. Arbyn, has continued to publish papers emphasizing the efficacy of HPV vaccines as lead author or co-author of papers on HPV vaccine trials. For example, 'Prophylactic human papillomavirus vaccines: the beginning of the end of cervical cancer' [25], published in the International Journal of Gynecological Cancer in 2004, was co-authored by M. Arbyn with J. Paavonen, who has written papers on clinical trials of Cervarix and Gardasil. Also, 'Review of current knowledge on HPV vaccination' [26], published in the Journal of Clinical Virology in 2008 was co-authored by M. Arbyn with J. Dillner, who has written papers on clinical trials of Gardasil.

M. Arbyn is also closely connected with EUROGIN, an international organisation of which MSD is the Platinum sponsor [27], and he has been selected as a program committee member for EUROGIN 2018, together with the likes of X. Bosch, J. Paavonen and J. Dillner, who have all written papers on vaccine clinical trials [28]. In 2012, M. Arbyn also wrote a review in EUROGIN 2011 which expressed an optimistic view about HPV vaccines [29].

It is notable that a 2015 Cochrane review on type 2 diabetes was withdrawn when a conflict

of interest emerged between the review's authors and the pharmaceutical industry [30]. As this withdrawal demonstrates, rather than unquestioningly accepting a review by a particular research group, Cochrane has, in the past, openly debated each review's validity and made the necessary corrections and changes, even after publication of the review plan and review findings. Thus, it is difficult to understand Cochrane Review's inaction in the face of these obvious and documented instances of conflict of interest.

(2) Donation of 130 million yen from the Bill & Melinda Gates Foundation

In 2016, Cochrane received roughly 130 million yen from the Bill & Melinda Gates Foundation [31], which promotes vaccination. Half of this amount was spent in the same year [32]. In 2016, Cochrane reported income of 6.8 million pounds (about one billion yen) and expenditures of 8.1 million pounds (about 1.2 billion yen). This donation constitutes more than 10% of Cochrane's income for 2016, a significant fact that cannot be ignored.

7 Conclusion

On 24 March 2018, YAKUGI Ombudsperson 'Medwatcher Japan' held a symposium which had invited representatives of patient groups for victims of adverse reactions to HPV vaccines from the UK, Spain, Ireland, Colombia and Japan. It became clear from this meeting that each country had witnessed the same clinical characteristics of diverse and multi-layered adverse reactions to HPV vaccines and the same dramatically high number of postmarketing adverse event reports compared to other vaccines. It also emerged that some adverse reaction victims were told that they had 'psychological problems' by medical professionals and were thus unable to receive appropriate medical care. Moreover, not only has industry and government failed to put any relief measures in place due to lack of recognition of any causal relationship between HPV vaccines and adverse reactions, but some victims have been labelled 'anti-vaccine' and falsely accused of lying about symptoms by physicians and journalists promoting the vaccine, even though these patients had chosen to have the HPV vaccination because they believed it to be safe and effective [33].

Until these problems are recognized and understood, we are concerned that Cochrane's HPV vaccine review, which is fundamentally flawed, will be used by people and organisations seeking to promote HPV vaccines. We urge Cochrane to live up to its stated mission of being "the benchmark for high-quality information about the effectiveness of health care."

(English translation of the original Japanese document, 'Critical Opinion on Cochrane Review of HPV Vaccines'; released on 7 June, 2018; revised on 8 June, 2018.
<http://www.yakugai.gr.jp/topics/topic.php?id=956>)

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Appendix Table Trials in Analysis 7.6 (Comparison 7 Adverse events, Outcome 6 Serious adverse events)							
No.	Trial	valency	Control	Serious adverse events			
				HPV vaccine		Control	
				n/N	(%)	n/N	(%)
1	Phase 2 trial (ph2, 1v)	1	Aluminum adjuvant	19/1191	1.73	20/1196	1.67
2	African 2 country trial	2	Aluminum hydroxide adjuvant	17/450	3.78	14/226	6.19
3	Chinese trial, adolescent	2	Aluminum hydroxide adjuvant	5/374	1.34	2/376	0.53
4	Chinese trial, mid-adult	2	Hepatitis B vaccine formulated with adjuvant	3/606	0.50	3/606	0.50
5	Chinese trial, young	2	AS04 adjuvant	56/3026	1.85	81/3025	2.68
6	CVT	2	Hepatitis A vaccine formulated with adjuvant	912/3727	24.47	891/3739	23.83
7	Hong Kong trial	2	Aluminum hydroxide adjuvant	3/148	2.03	1/146	0.68
8	Immunobridging	2	Hepatitis A vaccine formulated with adjuvant	24/1035	2.32	23/1032	2.23
9	Indian trial	2	Aluminum hydroxide adjuvant	2/176	1.14	4/178	2.25
10	Japanese trial (ph2, 2v)	2	Hepatitis A vaccine formulated without adjuvant	26/519	5.01	34/521	6.53
11	Korean trial (ph3, 2v)	2	Hepatitis A vaccine formulated with adjuvant	0/160	0.00	1/161	0.62
12	Korean trial (ph3b, 2v)	2	Aluminum hydroxide adjuvant	2/149	1.34	1/76	1.32
13	Malaysian trial	2	Aluminum hydroxide adjuvant	5/135	3.70	3/136	2.21
14	PATRICIA trial (ph3, 2v)	2	Hepatitis A vaccine formulated with adjuvant	835/9319	8.96	829/9325	8.89
15	Phase 2 trial (ph2, 2v)	2	Aluminum hydroxide adjuvant	22/560	3.93	19/553	3.44
16	VIVIANE trial	2	Aluminum hydroxide adjuvant	291/2877	10.11	269/2870	9.37
17	African 3 country trial	4	Aluminum adjuvant	0/79	0.00	0/19	0.00
18	FUTURE I	4	Aluminum adjuvant	50/2673	1.87	45/2672	1.68
19	FUTURE II	4	Aluminum adjuvant	46/6021	0.76	56/6033	0.93
20	FUTURE III	4	Aluminum adjuvant	15/1890	0.79	17/1888	0.90
21	Japanese trial (ph2, 4v)	4	The same adjuvant as HPV vaccine	39/480	8.13	65/468	13.89
22	Korean trial (ph2,4v)	4	The same adjuvant as HPV vaccine	1/117	0.85	1/59	1.69
23	Phase 2 trial (ph2, 4v)	4	Aluminum adjuvant	3/288	1.04	3/292	1.03
Total				2376/36000	6.60	2382/35597	6.69