Recent history demonstrates that vaccination of children to prevent future disease can induce an often-acrimonious debate.[1] Add into this mix a vaccine aimed at adolescent girls to prevent an infection acquired through sexual contact, to prevent a disease that causes harm in adulthood, and the scene is set for a predictable controversy.

These debates are often presented in the interests of ‘balance’. However, ‘balance’ is both a noun (a situation where elements are equal, or in the correct proportions) and a verb (to offset or compare the value of one thing with another). Synonyms for the verb ‘balance’ include ‘evaluate’, ‘compare’, ‘consider’, and ‘appraise’. Cochrane is founded on the principles of balance (verb), and Cochrane researchers have worked to evaluate, consider, and appraise the evidence about human papillomavirus (HPV) vaccination to prevent cervical cancer.[2]

Cervical cancer is the fourth most common cancer in women worldwide. It is estimated that in 2012, approximately 528,000 women developed cervical cancer and that 266,000 died from the disease.[3] This is a real-world tragedy. It often affects young women, leaving children without their mothers. The peak age of incidence of cervical cancer in the UK is now 25 to 29 years of age, and only two-thirds of women in this age group have regular screening.[4] However, the vast majority of cervical cancer deaths occur in regions of the world where women lack access to cervical screening programmes, which are expensive and labour-intensive to run, requiring high-level co-ordination of care to deliver effectively across a population.

Cervical screening programmes aim to identify and treat women who have the precursor lesion of cervical cancer: cervical intra-epithelial neoplasia (CIN). One in three women who have the most severe grade of CIN (CIN 3) will go on to develop cervical cancer if left untreated for several years.[5] Women with high-grade CIN can be treated by removal of the abnormal tissue from the cervix, a procedure commonly called large loop excision of the transformation zone (LLETZ). Cervical screening has significantly reduced the rate of cervical cancer in the UK since the 1990s,[4] demonstrating what a screening programme can achieve when the natural history of the disease is understood, and where there is an effective screening test for a pre-malignant stage of
disease and a relatively simple treatment to prevent disease progression. However, cervical screening is not completely benign. Women may find screening and treatment of CIN distressing, and LLETZ can affect future pregnancy outcomes by increasing the risk of late miscarriage and premature delivery.[6-8]

The aetiology of cervical cancer and the natural history of its development are well understood.[9] High-risk types of HPV are the main cause of almost all cervical cancers, with HPV types 16 and 18 together responsible for 70% of cervical cancer worldwide.[10] Although almost everyone will be exposed to HPV, most will clear the virus through an immune response within six to 18 months. In a minority of women, the virus infection is not cleared, and they can go on to develop CIN and then cervical cancer over several years.

HPV is a DNA virus, made up of a protein shell (capsid) containing viral DNA. The proteins that make up the capsid, when produced artificially, self-assemble into empty capsids, forming virus-like particles (VLPs).[11] VLPs do not contain viral DNA and so cannot cause an active infection. VLPs stimulate an immune response, producing antibodies that bind to the virus shell, blocking the receptors that mediate infection. By priming the immune system with VLPs, the body is able to mount a more robust response to subsequent natural exposure to HPV, thereby reducing the likelihood of infection and its consequences. Vaccines have been developed based on combinations of VLPs for HPV types 16 and 18, plus types 6 and 11 (which cause genital warts), or newer combinations of up to nine different VLPs.

Cervical cancer can take many years to develop following the initial HPV infection, so waiting to see to what extent HPV vaccines could reduce cancer rates would take several decades and involve trials of millions of women. Reduction of development of high-grade CIN is therefore thought to be a valid, medium-term outcome that will predict whether vaccination can reduce cervical cancer rates.[12] Furthermore, reduction in CIN rates alone could lead to clinically meaningful outcomes, reducing pain, distress, and poor obstetric outcomes.

In their Cochrane Review, Arbyn and his team have combined the results of 26 randomized control trials of HPV vaccination to prevent cervical cancer.[2] These trials included 73,428 women and adolescent girls, across a variety of populations. The authors looked separately at the effects of vaccination in those who at baseline had no evidence of HPV DNA, HPV 16/18 specifically, or participants unselected for baseline DNA status. They also looked at whether the results of studies done in younger women (aged under 26 years of age) differed from those in older women (aged 24 to 45 years).

The results for women known to be negative for HPV16/18 are interesting in a research context and tell us that HPV vaccines reduce high-grade CIN caused specifically by HPV16/18 in younger women from 113 to 6 per 10,000 women. This would mean that we need to vaccinate about 62 young women who are known to be free of HPV16/18 for one to be protected against high-grade cervical lesions. However, in a real-world setting it is unlikely that HPV testing would be performed prior to vaccination. In adolescent girls and young women (15 to 26 years) who were unselected on the basis of HPV exposure, vaccination reduced high-grade CIN caused specifically by HPV16/18 from 341 to 157 per 10,000 women, and any high-grade CIN from 559 to 391 per 10,000 women. The corresponding numbers needed to vaccinate for these outcomes are 54 and 68, respectively.
In women aged over 24 years (the population most likely to have already been exposed to HPV) the vaccines do not confer similar benefits. The risk of any high-grade CIN is similar between unvaccinated and vaccinated older women, although CIN caused specifically by HPV 16/18 is probably slightly lower following HPV vaccination.

Follow-up periods in the studies in the review ranged between 1 and 8.5 years, with most around 3 to 5 years. Over time, the vaccine may have even more of an effect in those not exposed prior to vaccination, since high-grade CIN can take several years to develop following initial HPV exposure.

While we can be confident that rates of serious adverse events and miscarriage are similar between vaccinated and unvaccinated women, other rare harms are difficult to determine in randomized controlled trials, even those that have recruited tens of thousands of participants. We now need to look to follow-up of registry data involving millions of women to assess any relationship between vaccination and autoimmune conditions.

The data indicate that HPV vaccination is most effective in those not already exposed to HPV, supporting the widespread introduction of vaccination programmes aimed at young adolescent girls. Catch-up vaccination programmes in older girls and young women will have less of a benefit, based on these data. Importantly, some harms of vaccination are likely to be detected over a relatively short period, compared with harms from other medicines, and all but very rare harms would be captured during large randomized controlled trials. A more complete picture of the beneficial effects on CIN and pregnancy outcomes is only likely to be realized over the course of many years. In the case of cervical cancer, the true effects will probably not be evident for one to two decades.

This Cochrane Review answers some important questions with high certainty of evidence. Some questions cannot be answered by this review, including effects on very rare side effects, vaccination of boys, and other, longer-term HPV-related cancer outcomes. HPV is known to increase the risk of other cancers, such as vulval and penile cancers, and some head and neck cancers. Such cancers are rarer and take longer to develop. Ascertaining effects of vaccination on these rarer outcomes may require the evaluation of non-randomized, population-level evidence over many years.

Cochrane aims to evaluate and present the evidence to decision-makers, be they governments, healthcare policy makers, parents, or young women. We hope that this review will be used to support policy or personal decision-making about HPV vaccination that is informed by the best current evidence, balancing facts rather than opinions.

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**How to cite**
References


**Declarations of interest**

The authors have completed the ICMJE form for disclosure of potential conflicts of interest. JM is a gynaecological oncologist and lead colposcopist, responsible for delivering part of the UK National Health Service (NHS) cervical screening programme in her region of the UK. JM treats patients with CIN and cervical cancer but is not involved in vaccination for HPV and does no private work, working full time for the NHS. TL is a paid employee of Cochrane. The authors report no other conflicts of interest.

**Provenance and peer review**

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**Related Cochrane Reviews**

*Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors*

Marc Arbyn, Lan Xu, Cindy Simoens, Pierre PL Martin-Hirsch

**Feedback**

To comment on this editorial or to propose ideas for future editorials please contact the Cochrane Editorial Unit (ceu@cochrane.org).
The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias

Lars Jørgensen,1 Peter C Gøtzsche,1 Tom Jefferson2

Key findings
- The Cochrane human papillomavirus (HPV) vaccine review missed nearly half of the eligible trials.
- The review was influenced by reporting bias and biased trial designs.
- Authors of Cochrane reviews should make every effort to identify all trials and the trials’ limitations.

In May 2018, the Cochrane Collaboration published its review of the human papillomavirus (HPV) vaccines.1 The review primarily assessed the vaccines’ effect on precursors to cervical cancer. Cochrane has high standards for its reviews3; however, there were important limitations in its HPV vaccine review, which we address in this paper.

No included trial in the Cochrane review used a placebo comparator
All 26 trials included in the Cochrane review used active comparators: adjuvants (aluminium hydroxide [Al(OH)3] or amorphous aluminium hydroxyphosphate sulfate [AAHS]) or hepatitis vaccines.

Adjuvants are not regulated separately from vaccine antigens. According to the Food and Drug Administration (FDA), adjuvants are unreliable comparators.7 One HPV vaccine manufacturer (GlaxoSmithKline that produces Cervarix) states that its aluminium-based comparator induces harms: ‘higher incidences of myalgia might namely be attributable to the higher content of aluminium in the HPV vaccine (450 µg Al(OH)3) than the content of aluminium in the HAV [hepatitis A] vaccine (225 µg Al(OH)3).’8 The comparator hepatitis vaccines also used the HPV vaccines’ aluminium-based adjuvant.

The Cochrane authors mistakenly used the term placebo to describe the active comparators. They acknowledged that ‘The comparison of the risks of adverse events was compromised by the use of different products (adjuvants and hepatitis vaccines) administered to participants in the control group.’ Nevertheless, this statement can easily be overlooked, as it comes after 7500 words about other issues in the discussion and under the heading ‘Potential biases in the review process’. Active comparators was not a bias in the review process but a bias in the design of the HPV vaccine trials.

The use of active comparators probably increased the occurrence of harms in the comparator groups and thereby masked harms caused by the HPV vaccines. It is noteworthy that many women were excluded from the trials if they had received the adjuvants before or had a history of immunological or nervous system disorders; for example, in the PATRICIA trial with 18,644 women9 and the FUTURE II trial with 12,167 women.10 These exclusion criteria lowered the external validity of the trials and suggest that the vaccine manufacturers were worried about harms caused by the adjuvants. The criteria are not listed as warnings on the package inserts of the HPV vaccines.
vaccines, which may have led to more vaccine-related harms in clinical practice than in the trials.

The included HPV vaccine trials used composite surrogate outcomes for cervical cancer

In line with World Health Organization (WHO) recommendations, the Cochrane review was based on composite surrogate outcomes: ‘cervical intraepithelial neoplasia grade 2 and above [CIN2+]’, CIN grade 3 and above [CIN3+] and adenocarcinoma in situ (AIS). The use of such outcomes seemed reasonable for a preliminary assessment of HPV vaccine benefits, but the outcomes can be difficult to interpret. If there were clinically important differences in the severity of the cervical lesions in the two compared groups, they may not have been apparent in the composite outcomes of CIN2+ and CIN3+. The Cochrane authors did not describe any cervical cancers in the 26 trials, although cancers did occur in the trials; for example, in the ClinicalTrials.gov entry for the VIVIANE trial, one case of ‘Adenocarcinoma of the cervix’ and one case of ‘Cervix cancer metastatic’ are listed in the HPV vaccine group (see ‘Results: Serious Adverse Events’). Furthermore, the relationship between CIN2 and cervical cancer is not clear-cut. Most CIN2 lesions in women below age 30 regress spontaneously; an active surveillance approach has therefore been recommended for this group. The Cochrane review’s 26 trials mainly included women below age 30 and used frequent cervical screening (often every six months) that did not reflect real-life practice (often every three to five years).

The Cochrane review incompletely assessed serious and systemic adverse events

The Cochrane authors reported that they made a ‘Particular effort’ to assess serious adverse events and performed a sensitivity analysis that gave them ‘confidence that published and registry or website-sourced data are similar for the same study’. This seems unlikely. As an example, the PATRICIA trial publication only included two thirds (1400/2028) of the serious adverse events listed on ClinicalTrials.gov. The Cochrane authors included 701 vs 699 serious adverse events (1400) from the PATRICIA trial publication (see the Cochrane reviews’ ‘Figure 10, Analysis 7.6.2’) and 815 vs 829 serious adverse events from its ClinicalTrials.gov entry (see ‘Comparison 7, Analysis 6: 7.6.2’; both analyses were called ‘7.6.2’). We found 1046 vs 982 serious adverse events (2028) when we summarised the data from ClinicalTrials.gov (see ‘Results: Serious Adverse Events’).

The Cochrane authors concluded with ‘high certainty’ that the risk of serious adverse events was similar in the HPV vaccine groups and the comparator groups. However, the authors failed to mention that several of the included trials did not report serious adverse events for the whole trial period. For example, FUTURE I, FUTURE II and FUTURE III, which in total included 21 441 women with up to four years follow-up, only reported serious adverse events occurring within 14 days postvaccination. Furthermore, the Cochrane authors did not explain what the serious adverse events consisted of or whether some of them were more common in the HPV vaccine groups.

The Cochrane authors found more deaths in the HPV vaccine groups than in the comparator groups. The death rate was significantly increased in women above age 25 (risk ratio [RR] 2.16, 95% confidence interval [CI] 1.10 to 5.03; no absolute numbers were provided for this subgroup analysis, but the total numbers of deaths were 51 in the HPV vaccine groups and 19 in the comparator groups). The Cochrane authors suggested that this was a chance occurrence since there was no pattern in the causes of death or in the time between vaccine administration and date of death. However, as the Cochrane review only included randomised trials, the authors cannot rule out that the increase could be caused by the HPV vaccines. A death may be coded in a way that does not raise suspicion that the vaccine caused it; for example, a ‘traumatic head injury’ or ‘drowning’ could have been caused by a ‘syncpe’, which is a recognised harm. As of May 2018, WHO’s pharmacovigilance database—VigiBase, managed by the Uppsala Monitoring Centre (UMC)—contained 499 deaths reported as related to HPV vaccination.

The Cochrane authors concluded that, ‘Systemic events with general mild symptoms were similarly frequent in vaccinated recipients and placebo or control vaccine recipients’. Their Analysis 7.5 showed a non-significant increase in systemic events: RR 1.02 (95% CI 0.98 to 1.07) with a total of 9137 vs 9054 events. The Cochrane authors did not include all of their trials that were eligible for systemic events in Analysis 7.5; for example, the PATRICIA trial was not included. On ClinicalTrials.gov, PATRICIA has 7129 vs 6557 systemic events listed under ‘Results: Other Adverse Events (General disorders)’, which in itself is a significantly increased risk: RR 1.09 (95% CI 1.07 to 1.11).

The Cochrane authors ‘planned requesting data from data owners, to fill in gaps with available unpublished data’, but ‘due to constraints in time and other resources’ they were unable to do so. Considering that seven years passed from the publication of the Cochrane protocol in 2011 to the Cochrane review in 2018, lack of time seems a poor excuse for not trying to obtain unpublished trial documents and data. More importantly, harms cannot be assessed reliably in published trial documents—especially in journal publications of industry-funded trials where even serious harms often are missing. One reason may be the space restrictions that most medical journals have. As an example, the journal publication for the PATRICIA trial is 14 pages long while its publicly available corresponding clinical study report is over 7000 pages long, although it is an interim report that has been shortened. Clinical study reports are usually confidential documents, but they can be requested from the European Medicines Agency (EMA) and ClinicalStudyDataRequest.com (CSDR).

Despite the mentioned examples of reporting bias, the Cochrane authors judged all trials at low risk of reporting bias (see the Cochrane review’s ‘Figure 4: Risk of bias’ summary).

The Cochrane review did not assess HPV vaccine-related safety signals

The Cochrane authors referred to many observational studies in their discussion that found no safety signals of harms associated with the HPV vaccines. They cited WHO’s Global Advisory Committee on Vaccine Safety (GACVS) that expressed ‘concerns about unjustified claims of harms’. The Cochrane authors did not mention a study from 2017 by the WHO UMC that found serious harms following HPV vaccination overlapping with two syndromes: postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS). The WHO UMC provided part of the rationale for EMA’s investigation of POTS and CRPS in 2016. As of May 2018, the WHO UMC VigiBase contained 526 cases of POTS and 168 cases of CRPS reported related to HPV vaccination.

The Cochrane authors did not investigate whether the included trial data reported cases of POTS, CRPS or other safety signals. Instead, the authors cited EMA, which concluded that ‘No causal relation could be established’ between POTS or CRPS and the
HPV vaccines. EMA’s conclusion was based on the HPV vaccine manufacturers’ own unverified assessments that only included half of the eligible trials. Furthermore, the HPV vaccine manufacturers search strategies for POTs and CRPs were inadequate and led to cases being overlooked. As an example, in 2014, the Danish Medicines Agency (DMA) asked the HPV vaccine co-manufacturer Sanofi-Pasteur-MSD to search for specific POTs-related symptoms in its database (including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting). The manufacturer only searched for ‘postural dizziness’, ‘orthostatic intolerance’ and ‘palpitations and dizziness’. The Danish Medicines Agency discovered this because only three of 26 Danish reports of POTs showed up in Sanofi’s searches. As another example, EMA identified six possible cases of POTs and CRPs related to Gardasil 9 that Merck had not identified.

Industry trial funding and other conflicts of interest
The Cochrane authors assessed the impact of industry funding by meta-regression. No significant effects were observed. They stated that, ‘All but one of the trials was funded by the vaccine manufacturers’, which is not correct. According to ClinicalTrials.gov, this particular trial (‘CVT’ or ‘Costa Rica trial’) was sponsored by GlaxoSmithKline. Therefore, all included trials were funded by the HPV vaccine manufacturers and the meta-regression was meaningless.

The Cochrane Collaboration aims to be free from conflicts of interest related to the manufacturers of the reviewed products. Most of the 14 Cochrane authors on the first published protocol for the Cochrane review had major conflicts of interest related to the HPV vaccine manufacturers. The Cochrane review only has four authors; three of whom had such conflicts of interest a decade ago. The review’s first author currently leads EMA’s ‘post-marketing surveillance of HPV vaccination effects in non-Nordic member states of the European Union’, which is funded by Sanofi-Pasteur-MSD that was the co-manufacturer of Gardasil.

Cochrane’s public relations of the review were uncritical
The announcement of the Cochrane review on Cochrane.org under ‘News’ included a ‘Science Media Centre round-up of third-party expert reaction to this review’. Six experts were cited—all from the UK, although the Cochrane Collaboration is an international organisation. Two of the experts had financial conflicts of interest with the HPV vaccine manufacturers. A third expert was responsible for vaccinations in Public Health England (PHE) that promotes the HPV vaccines. The experts highlighted the ‘intensive and rigorous Cochrane analysis’, ‘that the HPV vaccine is the most effective way for young girls to protect themselves against cervical cancer’ and that ‘the vaccine causes no serious side-effects’. No expert criticised the review. In our view, this is not balanced and people with conflicts of interest in relation to the manufacturers should not be quoted in relation to a Cochrane review. Richard Smith—the former editor of the British Medical Journal (BMJ)—described medical journals as an extension of the marketing arm of the drug industry. We are concerned that some observers may see Cochrane reviews in the same light when Cochrane publishes such public relation messages.

Conclusion
Part of the Cochrane Collaboration’s motto is ‘Trusted evidence’. We do not find the Cochrane HPV vaccine review to be ‘Trusted evidence’, as it was influenced by reporting bias and biased trial designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make ‘Informed decisions’, which also is part of Cochrane’s motto. We recommend that authors of Cochrane reviews make every effort to identify all trials and their limitations and conduct reviews accordingly.

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Contributors
LJ: wrote the first draft. LJ, PCG and TJ: contributed to the conception, drafting, critical revision for important intellectual content and the final approval of the article.

Competing interests
LJ and PCG have no conflicts of interest to declare. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011–2013, TJ acted as an expert witness in a litigation case related to the antiviral oseltamivir, in two litigation cases on potential vaccine related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997–1999), GSK (2001–2002), Sanofi-Synthelabo (2003), and IMS Health (2013) and in 2014 was retained as a scientific advisor to a legal team acting on oseltamivir. TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017–2020) and Jean Monnet Network Grant, 2017–2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018–2023).

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References
EBM Analysis: Primary care


Dear Mark and David, I am writing to formally complain about the content and the tone of the editorial (1) following the publication of the Arbyn et al (2) review of HPV vaccines. The editorial is signed by Jo Morrison and Toby Lasserson.

The editorial is factually wrong. The editorial states “This Cochrane Review answers some important questions with high certainty of evidence”. No such certainty exists for the main questions of the review. There are numerous reasons for this. Perhaps the most important is the omission of many eligible trials. The Arbyn et al review (2) conducted trial searches up until June 2017 and included 26 randomised trials with 73,428 females. In January 2018, we published an index of the study programmes of the HPV vaccines that included 206 comparative studies (3). As of June 2017, about one third of the 206 studies were not published and half of the completed studies listed on ClinicalTrials.gov had no results posted (3). Although we sent our index to the Cochrane group handling the Cochrane review, the review stated that, “nearly all end-of-study reports have been published in the peer-reviewed literature.” When we applied the Cochrane review’s inclusion criteria to the 206 studies, we identified 46 completed and eligible trials. We could calculate the number of randomised participants for 42 of the 46 trials: 121,704 people. With nearly half of the trials and half of the participants missing, the Cochrane authors’ conclusion, “that the risk of reporting bias may be small,” is unwarranted and potentially misleading. It is clearly and unequivocally counter to the evidence available at the time of its publication.

You should note that our index was sent on 19 January to Tracey Harrison (for onward transmission to the authors) to David Tovey, Toby Lasserson and to the Scientific Committee - on 14 March. An informal preliminary warning was sent by me to CEU in early November 2016. At that time we were aware of 113 HPV studies.

There are other major biases and mistakes in the review which we have described elsewhere (4) and have addressed in other submitted publications, but for the purpose of this complaint it is sufficient for you to note that the presence of a sizeable number of trials that the authors did not include was flagged up many months prior to publication and ignored by authors, review group and Editorial Unit.

The editorial may breach the spokesperson policy. The editorial states “We hope that this review [Arbyn] will be used to support policy or personal decision-making about HPV vaccination that is informed by the best current evidence, balancing facts rather than opinions.” Ever since I have been involved in Cochrane we specifically avoid making any statements on policy. That is not our job. Here we have statements on both personal and general policies. Given the visibility and the role of the authors this seems to infringe the spokesperson policy statement “we can protect against this by clarifying when we are speaking on Cochrane’s behalf or in a personal capacity”. The policy suggests two ways of doing this. By saying (or writing) “in my opinion…” or adding a statement such as “The views expressed are my opinions and not the expressed views of any organization to which I am affiliated.” No such disclaimers or qualifiers were visible in the editorial, leaving readers to assume the statements represented the views of Cochrane.

The editorial states that “all but very rare harms would be captured during large randomized controlled trials.” This is misleading, as not a single trial included in the Arbyn review had a control group where participants were treated with a placebo. They all received a hepatitis vaccine or the adjuvant, and if these cause similar harms as the HPV vaccines, such harms would be overlooked in the trials.

It is unclear to me on what basis editorials are commissioned, by whom, whether they are peer reviewed or not and what is the criterion for preferring an editorial to a humble blog and how the degree of press releasing is decided.

Finally it would be good to know how the six “experts” interviewed in the press release were selected (5). Their gushing statements and the content of the Arbyn et al review are not based on any serious effort to assess the evidence. Collectively, the Review, Editorial, and the press release create the impression that there was an overarching strategy behind their publication to send a political message. This would be counter to the fundamental purposes of the Cochrane Collaboration.
I look forward to hearing from you and would be grateful for an acknowledgment of this letter.

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References
1. Jo Morrison, Toby Lasserson. HPV vaccination: balancing facts. Available from 
against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database
of Systematic Reviews. 2013. DOI: 10.1002/14651858.CD009069.pub2
3. Jørgensen L, Gøtzsche PC, Jefferson T. Index of the human papillomavirus (HPV) vaccine industry
clinical study programmes and non-industry funded studies: a necessary basis to address reporting
4. Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and
ignored important evidence of biasBMJ Evidence-Based Medicine Epub ahead of print: 27 July
2018. doi:10.1136/bmjebm-2018-111012
5. Scientific expert reaction to new Cochrane Review on HPV vaccine for cervical cancer prevention in
girls and women. Available from https://www.cochrane.org/news/scientific-expert-reaction-new-
cochrane-review-hpv-vaccine-cervical-cancer-prevention-girls-and
DATA SHARING IN MEDICAL RESEARCH

Why Cochrane should prioritise sharing data

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Packer1 says that the one who submits a research for public good should be ready to receive a request for data sharing for examination and re-analysis and that tax payers assume that a national agency is checking such data and analysis. Here we discuss Cochrane’s practice on data sharing.

Open science, as endorsed by the G7,2 includes sharing data, computer code, and materials. It is essential for reproducibility, collaboration, and innovation. We support the work of Cochrane, but are concerned that Cochrane is not sharing all its reviews’ data. These data should be fully accessible for reuse by third parties.

Cochrane, a non-profit private company3 and registered charity, produces and maintains systematic reviews in health and social care. Its work is undertaken by a global network of thousands of people,4 and its support largely comes from public funding.5 Most people producing Cochrane reviews are volunteers not specifically funded for this work,6 and Cochrane encourages “crowdsourcing” of work.6,9

Cochrane editorial bases help volunteers obtain study reports and manually extract the wealth of data needed to generate systematic reviews.10,11 Cochrane teams use RevMan software12 to produce files in standard format (XML), storing information on the studies, their methods, and results for publication in the Cochrane Library.

Benefits of sharing extracted data from trials and systematic reviews are well known, as are the costs of not sharing.13,14 Sharing maximises transparency, reliability of data extraction, and syntheses. It improves access to data—saving time and money—and opens new avenues of inquiry.14 Sharing is associated with increased citations,14 more publications,15 and reuse for new purposes.15

Structured data from Cochrane should be fully accessible for download, reuse, and review (box 1). Currently, they are not. Although Cochrane supports transparency initiatives such as AllTrials16 and is explicit about this in its policy,17 it has no similar clear principles on opening full access to the data in Cochrane reviews. Cochrane does provide access to results data from reviews but, crucially, these cannot be readily reused, and the available information is an incomplete set of the data generating these reviews, comes in a technically problematic
Small amounts of Cochrane data have been released with bespoke arrangements for specific individuals. This sharing is welcome, but organisational culture, policy, and process regarding data release are lacking; there is no appeals process. For example, OpenTrials aggregates all accessible documents on all trials in an open database and makes it free for public reuse.\textsuperscript{24,27} Thus far, OpenTrials has been unable to persuade Cochrane to share data for reuse. The Trip Database\textsuperscript{39} is a searchable library of evidence that asked if it could re-present structured data from Cochrane and also encountered barriers to access.\textsuperscript{39} Open sharing could foster collaborative ecosystems of digital innovation going beyond academic publications, with outputs that might include live, interactive presentations of summaries and results of trials produced by teams around the world, interactive decision support tools, and many more.

Cochrane’s non-release of data is unlikely to reflect the preferences of funders, publishers, the thousands of Cochrane volunteers, participants in trials, or patients. When asked, 83\% of the members of the Cochrane Individual Participant Data Meta-analysis Methods Group supported sharing systematic review data through a central repository (recognising that these data might require some form of moderated access).\textsuperscript{38} Many funders now require that data arising from their grants are shared.\textsuperscript{38,40} Cochrane volunteer authors give tacit consent for use of their work in reviews but may not be aware of the restrictions placed on access to the data they worked so hard to prepare.\textsuperscript{3} This is morally and ethically questionable, potentially eroding public trust.\textsuperscript{35,36}

This issue of open science is now pressing; after recent moves by Cochrane to create more information and become a hub for systematic review data. This has the potential to improve evidence and patient care, but although the Cochrane Linked Data Project aims to share reusable data in some form,\textsuperscript{36,37} there is not yet any information on how or when this will happen.\textsuperscript{36,38} Furthermore, Cochrane is working towards “living” systematic reviews, with updates from data in real time.\textsuperscript{38} This is important work, but progress is slow. Opening up this work with shared data resources and in collaboration with the open source software community—where all can contribute—would accelerate progress and best reflect the culture of collaboration in science.

Open data offers a transformative, collaborative future for the systematic review community. Cochrane has enabled a vast workforce to painstakingly extract information for great benefit. It could act as a hub, harmonising data collected across groups and sharing these widely, reflecting the collective funding and volunteer workforce that produces them. This could include converting the morass of free text trial reports into machine readable curated data, in archived, citable, accessible, interoperable and reusable formats, as set out in the FAIR principles.\textsuperscript{41,42} Cochrane could show leadership in supporting innovation and open science for clinical trials with full credit to all data extractors before\textsuperscript{43} and after review publication\textsuperscript{44} and, in this way, harness the greatest broadest impact. This reflects the exciting current move towards better use of data to produce digital tools of direct value to clinicians, rather than academic publications alone.

We have raised these issues with Cochrane and understand that the organisation is considering whether to start reviewing its approach to sharing data (D Tovey, personal communication, 2017). We hope that our setting out the benefits of open data is a helpful contribution to open that discussion.

We appreciate that Cochrane must focus on making itself sustainable and that open data sharing may be commercially sensitive.\textsuperscript{45} But making Cochrane a champion for openness, transparency, and sharing can only be beneficial for the organisation’s reputation—and finances. We encourage Cochrane leadership to create a policy that allows open data sharing and to make explicit any concerns they have on open data sharing so that these can be resolved.

Key messages

- Cochrane could lead and set standards for open data sharing from systematic reviews
- Availability of data from Cochrane reviews would give opportunities for collaboration, innovation, scientific replication, novel research, and clinical decision making
- It would also reduce the considerable waste of the current duplication of effort in systematic reviewing

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Competing interests. FS is the information specialist of Cochrane Schizophrenia and has voluntarily extracted data for 13 Cochrane groups. CEA promotes Cochrane extensively to the public and policy makers; trains hundreds of reviewers per year, is coordinating editor of Cochrane Schizophrenia, is principal investigator on randomised trials testing the effects of disseminating Cochrane reviews in different forms and on the National Institute for Health Research infrastructure grant for Cochrane Schizophrenia. MC promotes Cochrane to the public, practitioners, and policy makers; provides training in the conduct of randomised trials and systematic reviews, is coordinating editor of the Cochrane Methodology Review Group, and seeks funding and conducts research into the methods using in systematic reviews and other evaluations of health and social care. BOG has promoted Cochrane extensively to the public and policy makers; is principal investigator on OpenTrials.net, which has had a data sharing request rejected by Cochrane; has received research funding from the Laura and John Arnold Foundation, the Wellcome Trust, the NHS NIHR School of Primary Care, the Health Foundation,
on the misuse of science; and has a longstanding commitment to open science. LA promotes Cochran on the public and policy makers; is coordinating editor of Cochrane Drugs and Alcohol Group; has received grant funding from WHO, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the Italian National Institute of Health, and AIFA (Italian Medicines Agency). HB has received access to Cochran data for projects and services. JB is director and shareholder in the Trip Database, a limited company, and is actively involved in evidence synthesis, Trip has the potential to benefit from better access to the data Cochran currently restricts. RB promotes Cochran extensively to the public, clinicians, and policy makers; trains several reviewers a year, is joint coordinating editor of Cochran Musculoskeletal, is principal investigator on grants developing two living Cochran reviews and on National Health and Medical Research Council (NHMRC) editorial base funding for Cochran Musculoskeletal, and has received research funding from the NHMRC, Cabrini Foundation, Medical Research Council, and Patient Centered Outcomes Research Institute. She is funded by an NHMRC Senior Principal Research Fellowship. GDM has received consultancy fees/honorariums from National Prescribing Service MedicineWise, the Royal Australian College of General Practitioners’ “red book” preventive guidelines committee, Therapeutic Guidelines (eTG), Remote Primary Health Care Manuals Editorial Committee for expert advice; editorial work (deputy editor of the Medical Journal of Australia; American College of Physicians’ journal club: The BMJ); Consultation work for Bupa (UK) on shared decision making: Australian Medicine Handbook; royalties for three books (Wiley and BMJ Books) on evidence based medicine and clinical thinking; grants from NHMRC (Australia) two centres for research excellence; NHIR (UK); Human Tissue Authority (UK); from a private donor (for the Cochran Collaboration Acute Respiratory Infections Group); Australian Commission on Safety and Quality in Health Care. MD is coordinating editor of Cochran Drugs and Alcohol Group; has received grant funding from WHO, EMCDDA, the Italian National Institute of Health and AIFA, and disseminates Cochran review results to the public and policy makers, PG is a member of editorial group of the Cochran Acute Respiratory Infections Group. CH has received grant funding from WHO, NHIR and the NIHR School of Primary Care, MJ is an editor at Cochran Schizophrenia Group, DM is on Cochran Oversight Committee, RSS is joint coordinating editor of the Cochran Schizophrenia group. LV holds an NIH systematic reviews grant for the Cochran Incontinence. He holds grants from: EU2020, Wellcome, Economic and Social Research Council. MRC, Health Foundation, NHIR for research using systematic review methods. EB, CG, TH, JPAI, JK, and EO have declared no conflict of interests.

38. Data Citation Synthesis Group, Joint Declaration of Data Citation Principles, 2014, https://www.force11.org/datadiscitationprinciples.
Should we screen women for abdominal aortic aneurysm?

In The Lancet, Michael Sweeting and colleagues' report their estimate of the benefits, harms, and cost-effectiveness of screening women for abdominal aortic aneurysm (AAA) based upon their modelling study. A discrete event simulation model was set up and women-specific parameters were obtained from systematic literature reviews, national registry or administrative databases, major AAA surgery trials, and UK National Health Service reference costs. By use of the same screening strategy as used for men (age 65 years; 3.0 cm cutoff for diagnosis; 5.5 cm cutoff for surgery), there were three fewer AAA-related deaths, ten women overdiagnosed with AAA, and one woman overtreated for AAA per 10,000 invited over a 30-year period. For every four women who avoided an AAA-related death, one died because of additional elective repair as an outcome of screening. The authors conclude that this screening is not cost-effective. In the authors' best-alternative strategy (including women aged 70 years; 2.5 cm cutoff for diagnosis; 5.0 cm cutoff for surgery), screening resulted in six fewer AAA-related deaths, 67 women overdiagnosed with AAA, and five women overtreated for AAA for every 10,000 women invited over a 30-year period. For every seven women who avoided an AAA-related death, two died because of additional elective repair as an outcome of screening. It is unusual for cost-effectiveness analyses of screening to include overdiagnosis and overtreatment. This study is therefore an important step forward. However, there was considerable uncertainty regarding the cost-effectiveness (incremental cost-effectiveness ratio of £23,000 per quality-adjusted life-year [QALY] for the best-alternative strategy; 95% CI 9500–71,000), mainly because of assumptions about AAA prevalence, distribution of aortic size at different ages, and effects on quality of life. Sensitivity analyses showed that a negative effect on quality of life as a result of diagnosis, including overdiagnosis, would substantially reduce cost-effectiveness. This association has been poorly investigated for most screening programmes. Therefore, this finding could challenge the continued justification of screening for many other diseases, making the effects of screening on quality of life a high-priority research area.

Assumptions about future reductions in disease prevalence also substantially reduced cost-effectiveness.

Previous studies have shown decreasing AAA-related mortality in women from the mid-1990s to 2009. In 1974, 41% of UK women smoked compared with 17% in 2014, and since the correlation between smoking and AAA is stronger in women than in men, AAA-related mortality is likely to continue to decrease for women, reducing the need for screening.

Apart from concerns about cost-effectiveness, there are ethical dilemmas associated with the use of AAA screening. That the health-care system causes the death of healthy citizens by inviting them to an intervention that they have not asked for is ethically problematic. It is not as simple as a matter of net benefit in terms of mortality because it is not clear that a death saved by screening equals out a death caused by screening—such strict utilitarianism is hardly acceptable.

Furthermore, there are other important harms. The best-alternative strategy in the study by Sweeting and colleagues resulted in a 55% increase in women who fulfilled criteria for elective surgery for AAA but had contraindications. They were told that they have a condition that could cause death at any minute but that nothing can be done for them since any elective procedure would be too risky.

Elective surgery for AAA has serious complications such as myocardial infarction, stroke, amputation, respiratory failure, renal failure, ischaemic colitis, spinal cord ischaemia, and prosthetic graft infections. Screening results in a large increase in elective surgeries during the...
first 10 years after screening, but much of the benefit occurs 10–30 years later. Unfortunately, complications to surgery were not included in the present analysis. A recent study on endovascular repair for thoracic aneurysms showed that cerebral embolisms occur with 80% of surgeries, affecting cognitive function. There has been no similar study for AAA surgery. Clearly, repair of thoracic aneurysms is likely to infer a substantially higher risk for cerebral embolism than AAA surgery; however, future studies should explore how AAA surgery affects cognition and how many patients return to an independent life.

The authors suggest a lower threshold for diagnosis and for elective surgery in women on the basis of biological features. However, there is no evidence for this claim and there are potential harms. Actually, the study by Sweeting and colleagues suggests that lower thresholds for the diagnosis and for elective surgery in women might result in a less favourable benefit–harm balance because of substantial increases in overdiagnosis and overtreatment.

Screening requires skilled human resources and occupies operation theatres and hospital beds. These opportunity costs might, for example, increase waiting time for other types of surgery, such as for cancer surgery. Indeed, considering the small estimated average benefit from screening women for AAA (0·00112 QALYs, equivalent to 9·8 h per invited woman), the net effect may be negative from a public health perspective.

This study indicates that screening women for AAA is not economically acceptable. The benefit–harm balance might also be ethnically questionable, but this remains a value judgment. Furthermore, this study points to an urgent need for cost-effectiveness analyses for current AAA screening programmes for men that take into account both the large declines in AAA-related mortality and harms of screening such as overdiagnosis, overtreatment, and effects on quality of life.10

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We declare no competing interests.

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