The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors

Table 1: Our reassessment of the studies we had identified as additionally eligible for the Cochrane HPV vaccine review
[*Key: RCT = randomised clinical trial]

N	Assessment	Funder	Study ID	NCT ID	Type of study	Clinical study report available on trial register	Number of females	Note
1	Eligible for inclusion in the Cochrane review	GSK	HPV-003	Not identified	RCT*	Yes: https://www.gsk-clinicalstudyregister.com/study/580299/003?search=study&#csr	61	HPV-003 is listed in the Cochrane review as "not published"; however, HPV-003's clinical study report can be freely downloaded from GlaxoSmithKline's trial register. The Cochrane review include data from GlaxoSmithKline's trial register, so it could also include HPV-003.
2	Eligible for inclusion in the Cochrane review	GSK	HPV-040	NCT00534638	RCT	Yes: https://www.gsk-clinicalstudyregister.com/files2/gsk-106636-clinical-study-report-redact.pdf	20,515	HPV-040 was excluded from the Cochrane review, as it was considered a "phase IV" study (the Cochrane review only included phase II and III studies). We included HPV-040 in our list, as it is described as a "phase III/IV" study in the freely available clinical study report from GlaxoSmithKline's trial register. HPV-040 includes the bulk of the additional eligible participants: 32,176 of which 20,515 were females.
3	Eligible for inclusion in the Cochrane review	GSK	HPV-073	NCT01627561	RCT	No	148	HPV-073 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
4	Eligible for inclusion in the Cochrane review	Merck	V501-018	NCT00092547	RCT	No	939	V501-018 had been excluded from the Cochrane review, as gender-specific data could not be obtained. However, the gender-specific data are available and can be obtained from EMA. It is unfortunate that these data were not obtained, as V501-018 is the only Gardasil study with a non-aluminium-containing comparator: "carrier solution" (yeast protein, sodium chloride, L-histidine, polysorbate 80 and sodium borate).
5	Eligible for inclusion in the Cochrane review	Merck	V501-028	NCT00411749	RCT	No	107	V501-028 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
6	Eligible for inclusion in the Cochrane review	Merck	V501-030	NCT00496626	RCT	No	400	V501-030 had been excluded from the Cochrane review, as gender-specific data could not be obtained. However, the gender-specific data are available and can be obtained from EMA.
7	Eligible for inclusion in the Cochrane review	Merck	V501-046	NCT01245764	RCT	No	250	V501-046 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
8	Eligible for inclusion in the Cochrane review	Merck	V503-006	NCT01047345	RCT	No	924	V503-006 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1). The Cochrane review stated that it "did not include the nine-valent vaccine [Gardasil 9] … since the randomised trials … did not incorporate an arm with a non-HPV vaccine control" (3), but as we wrote "The only saline

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								placebo trial of approved HPV vaccines is a Gardasil 9 trial (V503-006; NCT01047345) that was published in 2015" (2).
9	Eligible for inclusion in the Cochrane review	Merck	Not identified	NCT01489527	RCT	No	406	We had initially not identified this study as eligible.
10	Eligible for inclusion in the Cochrane review	Xiamen	HPV-PRO-002	NCT01356823	RCT	No	1,600	HPV-PRO-002 was identified and added to the Cochrane review in the Cochrane editors' reassessment (1).
11	Eligible for inclusion in the Cochrane review	None	2010-1090/GaReCo	NCT20101090	RCT	No	200	2010-1090/GaReCo is not included in Cochrane review, but data for safety outcomes are eligible for inclusion: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-004007-13-DE
Total							25,550	
12	Possibly eligible for inclusion in the Cochrane review	GSK	MENACWY-TT-054	NCT01755689	RCT	No	1,300	MENACWY-TT-054 is not included in the Cochrane review. MENACWY-TT-054 is a five-arm trial in which, during a one-month window, exposure to Cervarix was directly compared to another vaccine (Nimenrix), but at study completion all arms may have received Cervarix.
13	Possibly eligible for inclusion in the Cochrane review	Merck	V501-002	Not identified	RCT	No	Numbers not obtained	In our index, V501-002 is a "probably exist" phase 2 trial for which numbers of female participants could not be obtained. We obtained information for V501-002 from an FDA document (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222S-2_files/frame.htm) and obtained additional verification for V501-002 from V501-005's unpublished clinical study report: "...subjects who received HPV 16 LI VLP vaccine (Protocol 002 [i.e., V501-002]) represented the active vaccination group."
14	Possibly eligible for inclusion in the Cochrane review	Merck	V501-004	Not identified	RCT	No	Numbers not obtained	In our index, V501-004 is a "probably exist" study for which numbers of female participants could not be obtained. We obtained information for V501-004 from an FDA document (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222S-2_files/frame.htm) and obtained additional verification for V501-004 from V501-005's unpublished clinical study report: "Protocol 004 [i.e., V501-004] was a Phase lla study designed to determine the tolerability and immunogenicity of a range of doses of pilot manufacturing material HPV 16 LI VLP vaccine (made from the bulk HPV 16 vaccine material used in Protocol 005)."
15	Possibly eligible for inclusion in the Cochrane review	Merck	V503-018	Not identified	RCT	No	615	In our index, V503-018 is a "probably exist" study for which we after our reassessment have obtained numbers of female participants: 615 (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf). V503-018 may be a study that compares females with males that all were vaccinated with Gardasil. Therefore, V503-018 is "possibly eligible."
16	Possibly eligible for inclusion in the Cochrane review	Merck	V503-019	Not identified	RCT	No	Numbers not obtained	In our index, V503-019 is a "probably exist" study for which we have not obtained numbers of female participants (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf).
17	Possibly eligible for inclusion in the Cochrane review	Merck	V505-001	NCT00520598	RCT	No	511	In our initial assessment, we had noted that one of V505-001's five (or six) arms got "unspecified placebo," as stated in V505-001's Study Description: https://clinicaltrials.gov/ct2/show/NCT00520598. On http://inclinicaltrials.com/cervical-cancer/NCT00520598/details/, V505-001 appears to have six arms where one arm receives "placebo." However, it is possible that all non-Gardasil-arms got at least one dose of the V505-formulation, which is a "Multivalent Human Papilloma Virus [HPV] L1 Virus Like Particle [VLP] Vaccine."
Total							27,976	

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18	Eligible in serious adverse event analyses: "Figure 10" and "Analysis 7.6"	GSK	HPV-023	NCT00518336	Follow-up to HPV-001	Yes: https://www.gsk-clinicalstudyregister.com/files2/gsk-109616-clinical-study-report-redact.pdf	433	HPV-023 was a follow-up study to HPV-001. HPV-023's journal publication is listed in "References to studies included in this review": https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896780/. HPV-023 is not included in the serious adverse events meta-analyses: "Figure 10" and "Analysis 7.6" (i.e., no data from HPV-023's journal publication: 20 serious adverse events in 224 participants vs. 11 serious adverse events in 213 participants, or its clinicaltrials.gov entry: https://clinicaltrials.gov/ct2/show/results/NCT00518336?sect=X30156#evnt, similarly 20/224 vs. 11/213).
19	Eligible in serious adverse event analyses: "Figure 10" and "Analysis 7.6"	GSK	HPV-029	NCT00578227	RCT	Yes: https://www.gsk-clinicalstudyregister.com/files2/gsk-110886-clinical-study-report-redact.pdf	541	HPV-029's journal publication is listed in "References to studies included in this review": http://www.jahonline.org/article/S1054-139X(11)00353-3/pdf. HPV-029 is not included in the serious adverse events meta-analyses: "Figure 10" and "Analysis 7.6" (i.e., no data from HPV-029's journal publication: "HPV: ankle fracture, anal abscess, anorexia, and syncope; HAB: head injury, gastritis, injury to posterior tibial vein [in a 9-year-old girl], depression, and tibia fracture"; or its clinicaltrials.gov entry: https://clinicaltrials.gov/ct2/show/results/NCT00578227?sect=Xr0156#outcome21: 4/270 vs. 5 or 4/271—"5 or 4" depending on whether one counts participants with serious adverse events or number of serious adverse events).
20	Eligible in serious adverse event analyses: "Figure 10" and "Analysis 7.6"	GSK	HPV-030	NCT00652938	RCT	Yes: https://www.gsk-clinicalstudyregister.com/files2/gsk-110886-clinical-study-report-redact.pdf	493	HPV-030's journal publication is listed in "References to studies included in this review": http://www.sciencedirect.com/science/article/pii/S0264410X11012680. HPV-030 is not included in the serious adverse events meta-analyses: "Figure 10" and "Analysis 7.6" (i.e., no data from either HPV-030's journal publication or its clinicaltrials.gov entry: https://clinicaltrials.gov/ct2/show/results/NCT00652938?sect=X30156#evnt, 2/247 vs. 1/247).
Total							29,443	
21	Possibly eligible in serious adverse event analysis: "Analysis 7.6"	GSK	HPV-063	NCT00929526	Follow-up to HPV-032	Yes: https://www.gsk-clinicalstudyregister.com/files2/gsk-112949-clinical-study-report-redact.pdf	752	HPV-063 was a follow-up study to HPV-032. HPV-063's journal publication is listed in "References to studies included in this review": https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4186043/. The journal publication that HPV-063 is reported in only reported the serious adverse events for HPV-032, which is included in meta-analysis "Figure 10" of serious adverse events: 26/519 vs. 34/521. But in "Analysis 7.6" of serious adverse events, we could not find data from HPV-063's clinicaltrials.gov entry: https://clinicaltrials.gov/ct2/show/results/NCT00929526?sect=X30156#evnt, 11/375 vs. 16/377.
Total							30,195	