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Adverse events associated with human papillomavirus vaccines: a protocol for systematic review with network meta-analysis incorporating all randomised controlled trials comparing with placebo, adjuvants and other vaccines

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ABSTRACT

Introduction Adverse events following the injection (AEFIs) of human papillomavirus vaccine (HPVv) among female adolescents are still a major public health concern.

Methods According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension statement for systematic reviews incorporating network meta-analyses, all prospective randomised trials will be included. The primary outcome for adverse events is topical pain during the observation period.

We will mainly search 17 electronic databases from January 2000 through September 2019 with suitable Medical Subject Headings and text words for PubMed. Two reviewers will independently check the reports at the title/abstract level and identify potentially applicable studies. Then we will obtain their full texts and decide whether to include them based on the same eligible criteria.

We will compare HPVv with placebo, HPVv with adjuvant and HPVv with other vaccines. Interstudy heterogeneity, publication biases or small study effects will be evaluated using conventional meta-analysis methods. The consistency of the network will be checked using tests for local and global inconsistency and the side-splitting method. To address the heterogeneity of treatment effects among the studies, we will use the multivariable random effect model.

Ethics and dissemination This pairwise or network meta-analysis does not require ethics approval. The data used here are not individual nor private. We will be able to determine which component of the vaccine induces adverse events, especially topical pain. This systematic review with network meta-analysis will provide valid answers regarding AEFIs for HPVv.

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Strengths and limitations of this study

► We will perform network meta-analysis to integrate direct evidence with indirect evidence to compare human papillomavirus vaccine (HPVv) with placebo, HPVv with adjuvant and HPVv with other vaccines.
► We will employ search strategy with 17 electronic databases and 21 clinical trial database or registries, to suppress publication bias as much as possible.
► We will clarify 12 relevant clinical questions with several sensitivity analyses.
► We will not collect real life data, and we try to ascertain only component associated with adverse events limited in clinical trial.

Japan.[1] Persistent pain and motor disorders associated with vaccines are often considered immune abnormalities or psychosomatic disorders. However, some researchers suspect them to be associated with complex regional pain syndrome or postural orthostatic tachycardia syndrome.[2] In 2013, the Ministry of Health, Labour and Welfare of Japan stated that the causes of these adverse events could not be specified merely based on the following epidemiological reports.[3]

First, the US' report in 2009, after the distribution of quadrivalent human papillomavirus (types 6, 11, 16 and 18) recombinant vaccine (qHPVv; Gardasil), described that the incidence of adverse events following immunisation was 53.9 per 100 000 doses, which included 772 (6.2% of total events) serious AEFIs. AEFIs offer more often following vaccination with HPVv than with other vaccines, such as for influenza vaccine, pneumococcal conjugate vaccine, Japanese encephalitis and diphtheria-tetanus-pertussis vaccine.[4] Second, Lu, *et al* reported that no significantly increased

BACKGROUND

Adverse events following injection (AEFIs) of human papillomavirus vaccine (HPVv) in female adolescents have been reported nationwide by various media outlets, and they are still a major public health problem in

risk of severe AEFIs and no vaccine-related serious AEFIs were found (relative risk (95% CI) of 1.00 (0.91 to 1.09) and 1.82 (0.79 to 4.20), respectively) in a meta-analysis of seven randomised control trials (RCTs).[5] HPVv is now unrecommended even though it was once obliged in 2013 because of the social anxiety in Japan. Even in the USA, a leading country in prevention of vaccine-preventable diseases, there was only 49.5% coverage of Human papillomavirus vaccination series among female adolescents in 2016.[6] Considering that the rates of cervical cancer may increase with time,[7] it is urgent to confirm the safety of HPV vaccination.

HPVv is composed of virus-like particles (VLPs) and an adjuvant, stabiliser and buffer. Among these components, both amorphous aluminium hydroxyphosphate sulfate (AAHS) and aluminium hydroxide ($Al(OH)_3$) are known to increase the risk of AEFIs. Monophosphoryl lipid A (MPL) combined with $Al(OH)_3$ is used as an adjuvant in Cervalix (GlaxoSmithKline plc).[8 9] Cervalix, which contains MPL, boosts serum antibody titre to a greater extent than Gardasil (Merck & Co.) or Gardasil9 (Merck & Co.), both of which contain only $Al(OH)_3$ as an adjuvant. Therefore, it is important to determine whether the components of the vaccines, including vaccine adjuvants and VPLs, are harmful, even if the adverse events were caused by the HPVv itself. However, ongoing studies have yet to answer these questions.

Owing to the above-mentioned reasons, we will conduct a network meta-analysis that allows simultaneous comparison of various types of vaccinations, adjuvants and placebos while preserving the merits of randomisation within a single analysis.[10] Using this method, we will integrate direct evidence (from direct comparison) and indirect evidence (from common comparator evaluation) to observe the whole picture across all vaccinations.[11]

Objective

We inspect AEFI among the participants of RCTs, including those vaccinated with HPVv and those vaccinated with other vaccinations, adjuvants or placebos. The aspects to be addressed in this systematic review are as follows: participants, participants of RCTs; intervention, vaccination with HPVvs; control, vaccinated with other HPVvs or other vaccinations, adjuvants or placebos; and outcomes, AEFI (PICO).

METHODS

Our meta-analysis will be conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 as a guide of systematic review and meta-analysis protocol.[12] Similarly, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension statement, the methods of this systematic review have been explicated to report systematic reviews incorporating network meta-analyses of healthcare interventions (online supplementary file).[13]

This protocol was registered in the International Prospective Register of Systematic Reviews.[14]

Criteria for included studies

Study design

All prospective RCTs, including those with crossover design and cluster randomisation trials, will be included. However, quasi-randomised trials (eg, those allocating participants to the intervention arms alternately) will be excluded. Trials with a small sample size will be included to avoid publication bias.

Participants

We will include all trials which look at AEFI, including those with participants diagnosed with comorbid immune deficiency disorders, such as HIV infection. These participants will also be included in a separate subgroup analysis. However, we will exclude trials that did not examine adverse events in the control participants, who did not receive any injection. We will also exclude vaccine recipients who had previously been vaccinated with HPVv or placebo-containing adjuvants.

Interventions

HPVv injection in children and adults will be included as an intervention and compared with another vaccine, adjuvant or placebo. Trials comparing HPV vaccination with vaccines of the same virus type but with different brand name or different adjuvant will be treated as another node in the network meta-analysis. We will include novel trials implementing the two-dose schedule,[15 16] and nine or other valent HPVvs.[17] We will exclude trials involving combined vaccination. Next, we will also exclude phase II studies that did not mention the vaccine components. For trials that did not describe the vaccine type, we will contact the author of the published paper to obtain information on the vaccine type. If the vaccine type remains unknown, we will reconsider its dealing.

Patient and public involvement

There is not any patient and public involvement (PPI) in the included studies.[18]

Outcome measures

We will report, in a concise manner, adverse events that occur following HPV vaccination.[1] We define three primary outcomes: persistent pain, motor disorders and fatigue, all of which cause social anxiety. Next, we inspect all adverse events, hard outcome (severe adverse event or death) immune abnormalities and discontinuation of injections. We also define five the secondary outcomes, which are less associated with social anxiety, compared with the primary outcomes. Immune abnormalities are suspected as the causes of all other outcomes.

In this study, the acute phase is defined as the period from 0 to 4 weeks after injection with a vaccine, whereas the chronic phase is defined as the period thereafter. We do not limit the length of the observation period beyond 4 weeks.

The primary outcomes are

1. Topical pain: (1–1) headache, migraine, musculoskeletal pain or pain in other regions excluding the local/injection site, (1–2) pain in the local/injection site and (1–3) unclassified topical pain.
2. Motor disorders.
3. Fatigue, weariness and hypoactivity during the observation period, which recent reports stated as adverse events during the observation period.[19 20] The secondary outcomes include the following:
4. All adverse events.
5. Severe adverse events causing disabilities in daily life.
6. Death.
7. Immune abnormalities, such as autoantibody at laboratory findings and new-onset immune or autoimmune diseases.
8. Discontinuation of injections.

Confidence in certainty of evidence

We will perform quality assessment of study design or measurement instrument, risk of bias, inconsistency, indirectness and imprecision and will estimate the importance of outcomes with range of point estimates, pooled mean, 95% CI and certainty rating with four grades (high, moderate, low and very low). The body of evidence consists of RCTs based on the Grading of Recommendations, Assessment, Development and Evaluation approach.[21 22]

Data sources and search strategy

We will search 17 electronic databases, namely AMED Allied and Complementary Medicine, BIOSIS Previews, CINAHL, the Cochrane Library, Derwent Drug File, EMBASE, Global Health, Google scholar, Ichu-shi (Japanese), JDreamIII (Japanese), Joanna Briggs Institute EBP Database, National Library of Medicine, Nursing@Ovid, PubMed, Scopus, TRIP and Web of Science, from January 2000 through September 2019 (updated through December 2019). The Medical Subject Headings (MeSH) and text words for PubMed used is as follows: '(human papillomavirus vaccine [tiab] OR papillomavirus vaccine [tiab] OR hpv vaccine [tiab] OR cervarix OR gardasil OR silgard) AND (clinical [tiab] AND trial [tiab] OR clinical trials [MeSH Terms] OR clinical trial [publication type] OR random* [tiab] OR random allocation [MeSH Terms] OR therapeutic use [MeSH subheading]) AND (adverse event* [tiab] OR adverse effect* [tiab]) AND (2000/01 : 2019/09[DP])'.

We will additionally search the following international databases and domestic trial registries of individual nations or regions to reduce publication bias: WHO International Clinical Trials Registry Platform,[23] in alphabetical order:

Australian New Zealand Clinical Trials Registry,[24] Australia and New Zealand; Brazilian Clinical Trials Registry (ReBec),[25] Brazil; Chinese Clinical Trial Register,[26] China; Cuban Public Registry of Clinical Trials,[27] Cuba; EU Clinical Trials Register,[28] European Union; The German Clinical Trials Register,[29] German; Clinical Trials Registry-India,[30] India; Iranian Registry of Clinical Trials,[31] Iran; Japan Primary Registries Network,[32] University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR),[33] Japan Pharmaceutical Information Center,[34] and The Japan Medical Association Center for Clinical Trials,[35] Japan; Pan African Clinical Trial Registry,[36] Pan African Nations; Peruvian Clinical Trial Registry,[37] Peru; Clinical Research Information Service,[38] Republic of Korea; Sri Lanka Clinical Trials Registry,[39] Sri Lanka; Thai Clinical Trials Register,[40] Thailand; The Netherlands National Trial Register,[41] The Netherlands; ISRCTN.org,[42] UK; and The National Institute of Health Clinical Trials Register, ClinicalTrials.gov,[43] USA.

We will also refer to the website of Pharmaceuticals and Medicines Devices Agency,[44] and reports of the US Food and Drug Administration.[45]

Different search systems might require different search strategies in each electronic database or clinical trial registry. In this case, we will employ new search term each time to maintain absolute sensitivity of none of missing collections.

Language and publication type will not be limited. We will search for additional studies from the reference lists of all identified reports, including applicable meta-analyses and systematic reviews. If necessary, we will contact the authors of individual reports via email, to acquire additional data.

Identification and selection of studies

First, we will identify eligible studies through electronic and manual searches, list the titles and abstracts in Endnote (Clarivate Analytics) and then exclude duplicates using the Endnote function 'remove duplicates'. Second, we will also identify eligible studies excluding duplicates of the same study by referring to study programme ID, manufacturer specific ID, national clinical trial ID and other identification ID.[46] Third, two reviewers (JT and YS) will independently check the reports at the title/abstract level and identify potential applicable studies. Third, we will assess their full texts and decide whether or not to include them based on the same eligibility criteria. Additionally, the two reviewers will also check the reference papers for relevant reviews. The reasons for exclusion will be indicated in a table. Any disagreements will be resolved by an additional reviewer (TK).

Data extraction and risk of bias assessment

After completing the Endnote list, two reviewers (JT and YS) will independently extract the essential trial parameters using a standardised data abstraction form and assess the risk of bias. The standardised data extraction forms will include the trial characteristics (eg, first listed author, publication year, journal, country, institution and sponsor), participant characteristics (eg, number, sex, age and comorbidities), intervention elements (eg, control type, dose of vaccine and follow-up duration) and

outcomes. We will assess the risk of bias in the trials with the Cochrane tool.[47] We will regard trials with high risk of bias in one or more domains as 'high risk', those with low risk of bias in all domains as 'low risk' and those with unclear risk of bias in one or more domain as 'unclear risk'.[48] Moreover, an additional review author (TK) will resolve any disagreements. We will also assess the inter-rater reliability of the two reviewers.

Data items and management
The following data will be collected from each included study:

1. Characteristics of study: study ID in our own study, author(s)' name, protocol, citation or publication, year(s) of study, year of publication, study programme ID/manufacturer specific ID/national clinical trial ID/any identification ID, location, setting, number of centres, type of RCT, sample size, observation period, recruitment, with or without PPI, information for participants, contributor-ship statement/acknowledgements for participants and funding/sponsor.
2. Characteristics of study participants: gender distribution, mean (or median) and range of age, presence and type of comorbidity, number allocated into each group, number of dropouts and any medication at baseline.
3. Characteristics of interventions: number of vaccine doses, type of vaccine or placebo and add-on interventions (if any) and force-optimised treatment.
4. Outcome measures: time(s) of outcome measurement, whether the outcome was based on intention-to-treat or per protocol, methods of imputation and number of each measured outcome.

One reviewer (JT) will input the above data as variables into a data set in excel. This data set will be independently cross-checked by another reviewer (YS). They will consult with an additional reviewer (TK) regarding the variables with missing information. Nevertheless, if we cannot solve this problem, we will employ expert opinion.

Data synthesis and analysis
First, in conventional analyses, we will compare HPVv with placebo, that is, saline, to detect differences between the vaccine itself and any harmful substance. Second, we will compare HPVv with an adjuvant, that is, AAHS or Al (OH)$_3$, to detect difference between the vaccine and the adjuvant. Finally, we will compare HPVv with other vaccines to detect difference between vaccines. In these steps, we will identify the hazardous components.

In network meta-analyses, we will first provide a summary information on the eligible trials and summarise the geometry of the network of evidence using network plots. Second, we will conduct standard pairwise meta-analyses for all direct comparison to provide basic information on the trials using the ordinary DerSimonian-Laird-type random effect model. To measure treatment effects (efficacy and safety), we will use OR, risk ratio or risk difference, where appropriate. Interstudy heterogeneity,

publication biases or small study effects will be evaluated using conventional meta-analysis methods (eg, Q and I^2 statistics, tests of publication biases on funnel plots).

Next, we will compare the efficacy and safety using multivariate meta-analysis methods from the frequentists' perspective.[49] To address the heterogeneity of treatment effects among the studies, we will use the multivariable random effect model. Quantitative evaluation of the comparative efficacy or safety, and the interstudy heterogeneity will be conducted using the multivariable meta-analysis methodology. We will conduct an inference for HPVv safety using the restricted maximum likelihood methods. Furthermore, we will estimate the probabilities of ranks by using the surface under the cumulative ranking curve of treatments based on the estimated models.[50 51] In addition, the consistency of the network will be examined using tests of local and global inconsistency and the side-splitting method. The local inconsistency tests will be used to evaluate loop inconsistency by (pseudo-) Wald tests of all the triangle loops on the network. Moreover, the global inconsistency test is the goodness-of-fit test, which uses Higgins's design-by-treatment interaction model. In addition, we will evaluate concordance between direct and indirect evidence on the network for certain pairs of treatments by the side-splitting method. If any relevant sources of biases are found, we will further investigate the sources of evidence. Finally, sensitivity analyses will be performed to assess how these factors affect the overall results.

Subsequently, we will perform a direct comparison using a traditional pairwise meta-analysis method for cases where indirect comparison network is not performed or where there is a risk for a high level of inconsistency or heterogeneity. In such case, all types of HPV vaccination will be compared in one node with all placebos or adjuvants. This method will also be applicable to assess heterogeneity using the I^2 statistic, χ^2 test and visual inspection of the forest plots network meta-analysis.

Sensitivity analysis
The following sources of possible clinical heterogeneity will be evaluated as effect modifiers in meta-regression or subgroup analyses as necessary. Systematic subgroup analysis is important to inspect each variation in all sensitivity analyses[52] : (1) sex (only female vs only male); (2) age group (>20 vs ≤20 years); (3) follow-up duration (chronic phase >30 days vs acute phase ≤30 days); (4) nation (Asian vs non-Asian); (5) comorbid immune deficiency disorders (eg, HIV+) (with vs without comorbidities); (6) dose (2 doses vs 3 doses); (7) VLPs (other vaccines including a same adjuvant vs other vaccines including each adjuvant); (8) risk of bias ('high risk' literature vs 'unclear and low risk' literature); (9) sample size (>300 vs ≤300); (10) sponsor (with vs without sponsors); (11) publication (published vs unpublished literature); and (12) marketing (pre vs post). In cases of limited small-sized comparison of potential modifiers in accomplishment of subgroup

analyses on these variables, we will conduct sensitivity analyses by omitting specific trials from the overall analysis.

Analyses will be performed using the Stata V.15 software.

ETHICS AND DISSEMINATION

This pairwise network meta-analysis does not require ethics approval. The data used here are not individual nor private.

We have presented a study protocol consisting of an objective, rationale and methodology. This network meta-analysis will synthesise all the available direct and indirect evidence, incorporating comparison studies with placebos, adjuvants and other vaccines. We will provide the final results regarding the safety of HPVvs with the following logistics.

RCTs allow high comparability between intervention and control groups. However, there should be a minimum sample size in each RCT to illustrate the effectiveness of an intervention because the sample size is sometimes too small to allow evaluation of adverse effects, which generally occur less frequently than the favourable effects. Furthermore, intension-to-treat analysis will underestimate the nature of effects, either positive or negative, whereas observational studies may include some inherent biases for causal inference. Thus, a meta-analysis is a suitable resolution to overcome such problems. Previous meta-analyses did not support the specified AEFIs with the use of HPVv.[53–55] Although another research group recently suggested a high risk of topical reactions at the injection site,[19 20] we must assess whether an adjuvant evokes such topical reactions.

There may be several methodological limitations in these analyses including heterogeneity of vaccines. To overcome this limitation, we will launch a network meta-analysis—a more comprehensive research method—focusing on vaccine components to avoid vaccine heterogeneity due to structural theory. However, this method has an essential problem of enclosing risk of failure, resulting in a triangle loop. We can avoid this risk by conducting a thorough literature search. In addition, a recently suggested two-dose policy and nine-valent HPVvs can be used to construct a network triangle. Furthermore, if any adverse event occurs in any arm, we will know which component of the vaccine induces these adverse events. This systematic review with network meta-analysis will provide valid answers to the clinical and social anxiety regarding AEFIs caused by HPVv.

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