# **BMJ Open** Association between influenza vaccination, all-cause mortality and cardiovascular mortality: a protocol for a living systematic review and prospective meta-analysis

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## **ABSTRACT**

**To cite:** Liu R, Patel A, Du X, *et al.* Association between influenza vaccination, all-cause mortality and cardiovascular mortality: a protocol for a living systematic review and prospective meta-analysis. *BMJ Open* 2022;**12**:e054171. doi:10.1136/ bmjopen-2021-054171

Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/ bmjopen-2021-054171).

Received 07 June 2021 Accepted 28 February 2022

Check for updates

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Dr Gian Luca Di Tanna; GDiTanna@georgeinstitute. org.au increase the risk of cardiovascular events, especially in populations with pre-existing cardiovascular disease (CVD). Considering that influenza is vaccine preventable, international guidelines recommend high-risk populations with CVD receive an influenza vaccine every year. However, there are various classifications of recommendations and levels of evidence. Previous systematic reviews concluded uncertain evidence on influenza vaccine efficacy for preventing cardiovascular events in the general population or in populations with pre-existing CVD. Limited safety data of influenza vaccines were reported for populations with pre-existing CVD. Randomised controlled trials with larger sample sizes relative to previous studies are emerging, the findings of these trials are likely to be highly influential on summary efficacy estimates.

Introduction Influenza virus infection is known to

Methods and analysis We aim to perform a living systematic review and a prospective meta-analysis to evaluate the efficacy and safety of influenza vaccines compared with no vaccines or placebo for preventing mortality or CVD events in the general population and in populations with pre-existing CVD. Any types of randomised controlled trial and observational study meeting the Population, Intervention, Comparator, Outcome and Study design criteria for the research question will be selected for inclusion. The living systematic review status will be maintained for 3 years with an update for every 6 months. Mainstream medical literature databases will be independently searched by two authors with predefined strategies. Two authors will perform the risk of bias assessment with consensus. Narrative synthesis and meta-analyses will be performed to summarise the results.

Ethics and dissemination Formal ethical review is not required as this study does not involve primary data collection. We will publish results of the living systematic review and prospective meta-analysis in a peer-reviewed journal. Findings will also be presented at relevant meetings.

PROSPERO registration number CRD42021222519.

# Strengths and limitations of this study

- The living systematic review will continually incorporate the latest research findings and keep the synthesised information updated.
- A prospective meta-analysis will better address this evolving evidence while minimising the risk of selective reporting and publication biases.
- In particular, the safety of influenza vaccines in populations with pre-existing cardiovascular diseases will be studied to augment the current evidence base.
- The inclusion of observational studies raises the potential limitations of confounding bias; however, we will perform subgroup meta-analysis by study design and present both randomised and nonrandomised results.

#### INTRODUCTION

Influenza virus infection is known to increase the risk of cardiovascular events, especially in populations with pre-existing cardiovascular disease (CVD).<sup>1</sup> The WHO recommends countries aim for 70% influenza vaccine coverage for high-risk groups, including the elderly and individuals with known chronic conditions.<sup>2</sup>

CVD takes approximately 18 million lives each year, which accounts for one-third of all deaths worldwide. In order to achieve the global target of '25 by 25' and '1/3 by 30', reducing a quarter of premature deaths from Noncommunicable Disease (NCD) by 2025 and one-third of them by 2030, effective interventions need to be identified and implemented in the most vulnerable populations.<sup>3</sup> The economic burden of CVD is projected to be more than \$1 trillion in 2030, half of which relates to direct medical costs. Cost-effective interventions are needed to flatten the rising curve of healthcare costs for CVD.<sup>4 5</sup> A modelling study showed a fully funded influenza vaccination programme compared with a self-paid one was cost-effective in a population over 60 years old in China, with vaccination coverage rate being 30% vs 0% respectively. An influenza vaccine coverage of 30% would avert 8800 influenza-associated excess deaths attributable to respiratory causes per year in China, which accounted for 98% of all costs from outpatient consultation, hospitalisation, death and loss of productivity.<sup>6</sup>

Considering that influenza is vaccine preventable, international guidelines recommend high-risk populations with CVD receive an influenza vaccine every year, but there are various classifications of recommendations and levels of evidence.<sup>7 8</sup> This uncertainty is reflected in the most recent 2015 Cochrane systematic review, which concluded uncertain evidence on influenza vaccine efficacy for preventing cardiovascular events in the general population or in populations with pre-existing CVD.<sup>9</sup> The uncertainty derives from risks of bias in pooled studies and therefore higher quality evidence is needed to confirm the findings.

This Cochrane review included eight randomised controlled trials (RCTs) of influenza vaccine versus placebo or no vaccine with a total of 12029 participants, and searched literature between the starting dates of database archive and October 2013. Their meta-analysis, pooling four of the included trials which assessed the association between influenza vaccination and cardio-vascular mortality, showed a pooled risk ratio (RR) of 0.45 (95% CI 0.26 to 0.76, p=0.003). With more RCTs and a number of large-scale observational studies having been conducted since the Cochrane review, it is useful to update our understanding of the current evidence on influenza vaccines for preventing CVD events in both the general population and high-risk groups.<sup>10–13</sup>

While the safety of influenza vaccines in the general population is well established, there is a paucity of safety data in populations with existing chronic disease. In these populations, current synthesised data on adverse event following immunisation or adverse health events that may be vaccine attributable are sparse.

Perhaps as a consequence of persistent uncertainty relating to both efficacy and safety, influenza vaccine coverage rates (VCR) are variable and often low in populations with pre-existing CVD. For example, recent influenza VCR in patients with heart failure (HF) ranges from nearly 0% in Asia to approximately 80% in Europe.<sup>14</sup> In particular, most low and middle-income countries have not reached the target of 70% VCR set by WHO for high-risk groups. In China, the estimated influenza VCR for the entire population is 2% and is even lower (<1%) among high-risk groups.<sup>14 15</sup> In a limited number of Chinese cities with a policy for free influenza vaccination among seniors, VCR in those older than 65 years is reported to be around 20%.<sup>16</sup>

With the COVID-19 pandemic and mitigation measures such as facial masks, social distancing, lockdowns and

travel restrictions, influenza activity globally was low in 2020. However, the potential for reduced population immunity due to low levels of circulating influenza, combined with countries reopening borders and relaxing mitigation measures in 2021, may lead to potential rebounds in rates of influenza infections.<sup>17</sup>

As evidence from ongoing RCTs is still emerging, it is appropriate to conduct a living systematic review (LSR), which will continually incorporate the latest research findings and keep the synthesised information updated.<sup>18</sup> Along with the LSR design, a prospective meta-analysis (PMA) will better address this evolving evidence. Through a PMA, we will aim to include studies to be published from December 2021 onwards to avoid potential bias.<sup>19</sup>

# **METHODS**

This protocol follows the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRIS-MA-P) statement, along with the elaboration and explanation report, and the checklist.<sup>20 21</sup>

# **Objective**

The overall objective of this LSR is to evaluate the efficacy and safety of influenza vaccines compared with no vaccines or placebo for preventing mortality or CVD events in the general population and in high-risk populations with CVD.

## **Eligibility criteria**

Studies selected for inclusion will meet the following Population, Intervention, Comparator, Outcome and Study design criteria.

## Population

We will include studies focusing on the general population aged 18 years and above, or high-risk population with CVD. CVD is defined to include any diagnosis of hypertension (high blood pressure), coronary heart disease, cerebrovascular disease (stroke), peripheral vascular disease, HF, rheumatic heart disease, congenital heart disease (repaired or unrepaired), cardiomyopathies, valvular heart disease or atrial fibrillation. Studies focused on particular subgroups of the general population (eg, healthcare workers or pregnant women) will not be excluded.

## Intervention

We will include studies that investigate the effects of inactivated influenza vaccine or live attenuated influenza vaccines during any influenza season, regardless of the valency, dose, administration route, boosts and use of concomitant vaccination strategies.

## Comparator

We will include studies of no vaccine or placebo as comparators.

## Outcomes

Outcomes of interest are all-cause mortality, cardiovascular-specific mortality, all-cause hospitalisation and cardiovascular-specific hospitalisation or events. Cardiovascular events include any diagnoses relating to myocardial infarction (MI), HF or stroke.

# Types of studies

We will include any type of RCT (individually randomised, cluster, stepped wedge, other) and observational study (cohort and case-control). We will include published or accepted articles with RCT or observational designs without date limits. Preprints, theses or dissertations without formal peer review will not be included. No language restrictions will be imposed on the search strategies. We will include studies conducted in hospitalbased, community-based or long-term care facility-based settings in both the Northern Hemisphere and Southern Hemisphere.

### Time frame

We will include studies reporting outcomes with the follow-up period lasting an entire year after vaccination. The living status of the systematic review will be maintained for a minimum of 3 years after protocol publication. The baseline LSR and PMA are planned to start from December 2021. An update will be performed every 6 months after the baseline. At 3 months after previous reviews, an updated search will be performed. At 4 months after previous reviews, a reanalysis will be performed. At 5 months after previous reviews, an updated report will be drafted. Depending on the differences from previous reviews, the update will be considered to submit to peerreviewed journals.

# **Information sources**

We will search the following databases:

- ► Cochrane CENTRAL.<sup>2</sup>
- ► ClinicalTrials.gov.<sup>23</sup>
- ▶ Chinese Clinical Trial Registry (ChiCTR).<sup>24</sup>
- ► Medline (PubMed interface).
- ► Embase (Ovid interface).
- ► CNKI.<sup>25</sup>
- ► Wanfang.<sup>26</sup>
- ► Database of Abstracts of Reviews of Effects (DARE).<sup>27</sup>
- ► Economic Evaluation Database (EED).<sup>28</sup>
- ► Health Technology Assessment (HTA).<sup>29</sup>

Each database will be searched separately by two authors with an initial search strategy developed from PubMed and then adapted for other databases. We plan to search the reference lists of eligible articles and contact the corresponding authors of papers for missing information.

## Search strategy

We will use the search strategy of the previous Cochrane review by Clar *et al* (online supplemental appendices 1 and 2).<sup>9</sup> Keywords of 'Influenza Vaccines' and 'Cardiovascular Diseases' will be used to capture observational studies. Auto alerts will be configured to receive monthly updates.

#### **Study records**

## Data management

The search results from all databases will be imported into the reference management software EndNote V.X9. Duplicated reports from the same study will be removed. The unique records will be imported to the study screening and data extraction software Covidence.<sup>30</sup>

#### Selection process

Predefined inclusion and exclusion criteria will be used for screening. After title and abstract screening, full texts will be downloaded for the remaining studies. Study tags will be created to mark predefined eligibility criteria for easier screening and post hoc checks. The entire selection process will be conducted independently by two reviewers. Conflicts or disagreements between the two reviewers will be resolved by a third reviewer. A screening process flow chart will be presented as per PRISMA recommendation.

LSR-specific indicators will also be reported. These will include, for example, LSR version number, time since preceding update, number of citations screened for the LSR update period, number of identified newly published eligible primary study protocols, number of identified newly published eligible primary studies and disposition of newly identified eligible primary studies (ie, incorporated or not). Changes in LSR methodology compared with previous versions will be reported. Any changes in statistical results, certainty of evidence and conclusions from previous iterations will be highlighted in the LSR report. Differences between the protocol and the review will be recorded and justified.

#### Data collection process

Data will be extracted and entered into a predefined data extraction form. Data extraction will be done by two authors independently, with discrepancies resolved by a third author. The data extraction form will be reviewed by the entire review team and piloted for the first three studies before its roll-out.

#### **Data items**

The following data elements will be extracted:

- General information: title, authors, author contact details, year of publication, journal, language, type of paper (original research, protocol, review and editorial).
- Population: inclusion and exclusion criteria, sampling and recruitment methods, study population characteristics and comparability between groups at baseline (age, sex, socioeconomic status, country, inpatient or outpatient, comorbidity and concomitant treatment regimen other than vaccination). General population or population with pre-existing CVD, and the disease subtype (MI, HF, stroke, etc) if with pre-existing CVD. COVID-19 status.

- Intervention: vaccine type, valency, dose, administration route, timing of vaccination, number of participants in intervention group, duration of follow-up. Level of the match of influenza vaccines to circulating strains.
- Comparator: placebo, or no vaccine, number of participants in the control group, overall follow-up, duration of follow-up.
- Outcomes: definition, time points measured, number of outcome events in intervention and control groups, incidence rate in intervention and control groups, prevalence in intervention and control groups, unadjusted and adjusted effect measures (OR, RR or HR), covariates used for adjustment, effect size (point estimate, SE or SD or CI), missing data, reason for missingness, approach to handling missing data, statistical methods, randomisation process. Dropout rate, loss to follow-up rate and adverse event rate in intervention and control groups.
- Study design and methods: study type, registration number, country and setting, recruitment time, date of first participant (or cluster) randomised, date of last participant (or cluster) randomised, date of last participant followed up for outcomes in RCTs, date of first participant recruitment, date of last participant followed up for outcomes in observational studies, vaccination date, hemisphere, match of the influenza vaccine strains to those circulating, reporting time, study duration, study objectives.
- ► Study funding and conflict of interest.

Effect sizes will be extracted as reported in the source article, and transformed when appropriate. In case of missing information from an included paper, an attempt of contacting the authors to obtain these data will be made.

## Assessment of risk of bias in individual studies

We will apply version 2 of Cochrane risk-of-bias tool (RoB 2) to included RCTs.<sup>31 32</sup> Through RoB 2, studies will be assessed across a number of domains, including random allocation sequence, allocation sequence concealment, blinding, outcome assessment, missing data and analysis methods, to classify studies into a 'low risk of bias', 'some concerns of risk' or 'high risk of bias' categories.

For observational studies, we will apply the Risk of Bias in Non-randomized Studies–of Interventions (ROBINS-I).<sup>33</sup> ROBINS-I assesses a number of domains, including confounding, selection bias, baseline comparability between groups, intervention fidelity, outcome measurement and selection of reported results. Studies will be classified into categories reflecting risks of 'low', 'moderate' and 'serious' bias. Two authors will perform the RoB assessment with consensus.

# **Data synthesis**

# Narrative synthesis

A narrative summary of the effect of influenza vaccines on outcomes will be provided. Study characteristics (design, participants, intervention, comparator, outcomes, methods, funding and conflict of interest) will be presented in a table.

# Criteria for quantitative data synthesis

We will perform separate meta-analyses pooling results from observational studies and RCTs. We will evaluate differences between the two sets of results, although we expect observational studies to report higher effect sizes compared with RCTs. We plan to carry out a Hartung-Knapp-Sidik-Jonkman random effects meta-analysis whenever it is feasible to do so. If it is not feasible, we will revert to narrative review (for instance, if only one study reported a specific outcome). We will also report pooled effects according to the common (ie, fixed) effect model. To better handle the uncertainty of the various parameters to be estimated (especially the betweenstudy variance) and also considering the prospective nature of this study, we will also perform a Bayesian meta-analysis. This will allow us to calculate the probabilities of the vaccine to be effective. As data accrue, the posterior distribution of the pooled effect will be updated to reflect the information derived until that moment, which will be used as an informative prior distribution of the effect size. Sensitivity analyses will be performed using vague and vaguely informative priors for the effect size and for the between-study heterogeneity.

For binary outcomes, we will use RR with 95% CI (or credible intervals for the Bayesian meta-analysis) to measure the effect of influenza vaccination. For time-to-event data, we will use HR with 95% CI accordingly.

## Unit of analysis issues

Analyses will be done at a study level. For cluster randomised trials (including stepped wedge trials, if any), we will ensure the cluster effect has been taken into account. If not, we will inflate SEs using the design effect (which is a function of the average cluster size and intraclass correlation (ICC) coefficient). If the ICC coefficient is not reported, we could 'borrow' the ICC from one study and apply to another, or run sensitivity analyses by various design effect inflation factors.

# Dealing with missing data

For studies without reported data for an outcome of interest, we will try to obtain this information by contacting the original authors. For studies with a high level of missing outcome data, we will analyse the available data sets and explore the robustness of results by sensitivity analyses for each outcome variable. A high level of missing data is defined as more than 10% data for any variables of interest.

# Assessment of heterogeneity

We plan to assess heterogeneity by formal test of homogeneity and evaluating the proportion of variability attributable to heterogeneity rather than sampling error using the I<sup>2</sup> statistic. As per the Cochrane Handbook, we will consider values of I<sup>2</sup> between 50% and 90% as substantial heterogeneity and above 75% as considerable heterogeneity. Subgroup analyses and meta-regression based on the following variables will be used to explore possible reasons of heterogeneity:

- ► Population type (general population, pre-existing CVD population, COVID-19 population).
- Age groups (if feasible).
- ► Hospitalised versus outpatient.
- ► If disease-specific population, then consider the severity of disease, for example, ejection fraction category for patients with HF.
- Non-pandemic years versus 2009/2010 pandemic year if feasible.
- ▶ Follow-up length in season and out of season if applicable. Influenza season for the Northern Hemisphere is defined from 1 September until 31 May of the following year. Influenza season for the Southern Hemisphere is defined from 1 April until 30 September of the same year.
- Level of the match of influenza vaccines to circulating strains if reported.
- Level of risk of bias.

We plan to investigate the likelihood of selective outcome reporting bias by comparing the study report and its corresponding protocol.<sup>34</sup> If more than 10 studies are finally selected, formal Egger's regression-based test and eyeball assessment of the funnel plots will be explored to evaluate small-study effects.

# Sensitivity analysis

Sensitivity analysis will be applied for excluding studies with high level of missing data or other critical issues identified during the review process. First, we will analyse all the available studies, and then only include studies that are definitely eligible. Results from different scenarios will be compared and reported.

## **Confidence in cumulative evidence**

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to judge the overall quality of all findings.<sup>35</sup> The GRADE system classifies evidence into 'high quality', 'moderate quality', 'low quality' and 'very low quality', based on methodology quality, consistency, directness, precision and the risk of reporting bias. The cumulative quality of evidence will be assessed by all authors.

## Patient and public involvement

No patient was involved.

# DISCUSSION

## Main findings of previous reviews

The 2015 Cochrane review included four RCTs (n=1682) of influenza vaccination compared with placebo or no vaccination for preventing cardiovascular mortality in populations with pre-existing CVD. It presented a wide CI around the pooled RR for preventing cardiovascular mortality associated with influenza vaccines (0.45, 95% CI 0.26 to 0.76, p=0.003). The pooled studies had some risk of bias and were of small sample size, which contributed to the wide CI of estimated efficacy. Not enough evidence was available to establish the role of influenza vaccination in the primary prevention of

cardiovascular events. With ongoing trials aiming to recruit more than 9000 participants, pooling these results together would substantially contribute to the evidence base.

One more recent systematic review and meta-analysis has been conducted, pooling four RCTs (n=1667) and 12 observational studies (n=235391) and indicating a pooled RR of 0.87 (95% CI 0.80 to 0.94, p<0.001) for major adverse cardiovascular events among patients receiving influenza vaccines versus those receiving no vaccine or a placebo.<sup>36</sup> This systematic review focused on the use of influenza vaccine as a secondary prevention measure for patients with established CVD and extracted articles published through to January 2020.

A contemporary trial Influenza Vaccination After Myocardial Infarction (IAMI, NCT02831608) has even more recently published findings.<sup>13 37</sup> This trial specifically focused on patients with recent MI (n=2571). Compared with placebo, participants receiving influenza vaccines had a 28% lower risk of all-cause death, MI or stent thrombosis (0.72, 95% CI 0.52 to 0.99). Another trial, Influenza Vaccine to Prevent Adverse Vascular Events (RCT-IVVE, NCT02762851), comparing inactivated influenza vaccine to placebo in patients with HF is ongoing.<sup>12</sup> This trial is expected to report results in 2022.<sup>38</sup> The large sample size of these two more recent trials, relative to previous studies, suggests that their findings are likely to be highly influential on pooled efficacy estimates.

# Impact and significance of the review

Although current guidelines recommend populations with pre-existing CVD receive annual influenza vaccinations, there is inconclusive evidence regarding the efficacy and safety of influenza vaccines for preventing death or hospitalisation from CVD.<sup>7 8</sup> Previous systematic reviews reached uncertain conclusions with a lack of high-quality studies. As large ongoing trials are investigating influenza vaccination for preventing cardiovascular events, new evidence is accumulating and may substantially add to the evidence base. This provides an important opportunity to update current literature on the efficacy of influenza vaccination on cardiovascular mortality and hospitalisation.

The LSR will continuously synthesise the latest research findings so as to inform the public and healthcare professionals. With the most updated evidence regarding the efficacy of influenza vaccination in preventing CVD morbidity and mortality especially in high-risk populations, healthcare providers may be able to make recommendations to individual patients with more certainty. From a public health point of view, the findings may influence vaccine policies in relation to the general and high-risk populations.

This review will also provide important pooled parameters estimates that can also inform subsequent economic evaluations of various vaccines and vaccination strategies.

## Registration

This LSR protocol was registered with the International Prospective Register of Systematic Reviews.<sup>39</sup>

## Editorial and publication process consideration

LSR versions will be submitted to a peer-reviewed journal accommodating iterative versions of the same systematic review.

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**Contributors** All authors have contributed to the final submitted manuscript. GLDT is the lead supervisor of the first author. AP, XD and HL are cosupervisors. BL gave significant input regarding the epidemiology of influenza virus circulation. RL drafted the initial manuscript and received guidance regarding the content area and methodology from all authors. CW is the second reviewer. All authors have read and agreed to the final manuscript.

**Funding** This research is being funded by an Australian Government Research Training Program (RTP) Scholarship.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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#### REFERENCES

- 1 Madjid M, Naghavi M, Litovsky S, et al. Influenza and cardiovascular disease. Circulation 2003;108:2730–6.
- 2 Teresa Aguado M, Barratt J, Beard JR, et al. Report on who meeting on immunization in older adults: Geneva, Switzerland, 22-23 March 2017. Vaccine 2018;36:921–31.
- 3 Bennett JE, Kontis V, Mathers CD, *et al.* NCD countdown 2030: pathways to achieving sustainable development goal target 3.4. *The Lancet* 2020;396:918–34.
- 4 Ghebreyesus TA. Acting on NCDs: counting the cost. *Lancet* 2018;391:1973–4.
- 5 Bloom DE, Cafiero E, Jané-Llopis E. *The global economic burden of noncommunicable diseases*. Geneva: World Economic Forum, 2012.

- 6 Yang J, Atkins KE, Feng L, *et al.* Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China: a modelling analysis. *BMC Med* 2020;18:90.
- 7 Smith SC, Benjamin EJ, Bonow RO, *et al.* AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. *Circulation* 2011;124:2458–73.
- 8 Piepoli MF, Hoes AW, Agewall S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 20162016;37:2315–81.
- 9 Clar C, Oseni Z, Flowers N, et al. Influenza vaccines for preventing cardiovascular disease. The Cochrane database of systematic reviews 2015;5:Cd005050.
- Modin D, Jørgensen ME, Gislason G, et al. Influenza vaccine in heart failure. Circulation 2019;139:575–86.
- 11 Panhwar MS, Kalra A, Gupta T, et al. Effect of influenza on outcomes in patients with heart failure. JACC Heart Fail 2019;7:112–7.
- 12 Loeb M, Dokainish H, Dans A, et al. Randomized controlled trial of influenza vaccine in patients with heart failure to reduce adverse vascular events (IVVE): rationale and design. Am Heart J 2019;212:36–44.
- 13 Fröbert O, Götberg M, Angerås O, et al. Design and rationale for the influenza vaccination after myocardial infarction (IAMI) trial. A registry-based randomized clinical trial. Am Heart J 2017;189:94–102.
- 14 Vardeny O, Claggett B, Udell JA, et al. Influenza vaccination in patients with chronic heart failure: the PARADIGM-HF trial. JACC Heart Fail 2016;4:152–8.
- 15 Yang J, Atkins KE, Feng L, et al. Seasonal influenza vaccination in China: landscape of diverse regional reimbursement policy, and budget impact analysis. *Vaccine* 2016;34:5724–35.
- 16 Liu R, Liu X, Yang P, et al. Influenza-associated cardiovascular mortality in older adults in Beijing, China: a population-based timeseries study. *BMJ Open* 2020;10:e042487.
- 17 Jones N. Why easing COVID restrictions could prompt a fierce flu rebound. *Nature* 2021;598:395.
- 18 Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol 2017;91:23–30.
- Seidler AL, Hunter KE, Cheyne S, et al. A guide to prospective metaanalysis. BMJ 2019;367:I5342.
- 20 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
- 21 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- 22 Cochrane central register of controlled trials. Available: https://www. cochranelibrary.com/central
- 23 ClinicalTrials.gov. U.S. National library of medicine. Available: https:// clinicaltrials.gov/
- 24 The Chinese clinical trial registry. Available: http://www.chictr.org.cn/ enIndex.aspx
- 25 China National Knowledge InfrastructureN (CNKI). China academic journals (CD edition) electronic publishing house Co., LTD. Available: https://oversea.cnki.net/index/
- 26 Wanfang Data. Available: https://www.wanfangdata.com.cn/index. html
- 27 The Database of Abstracts of Reviews of Effects (DARE). Centre for reviews and dissemination, University of York. Available: https:// www.crd.york.ac.uk/CRDWeb/
- 28 The Economic Evaluation Database (EED). Centre for reviews and dissemination, University of York. Available: https://www.crd.york.ac. uk/CRDWeb/
- 29 Health Technology Assessment (HTA). Centre for reviews and dissemination, University of York. Available: https://www.crd.york.ac. uk/CRDWeb/
- 30 Covidence [computer program].
- 31 Higgins J, Thomas J, Chandler J. Cochrane Handbook for systematic reviews of interventions. 2 edn. Chichester (UK: John Wiley & Sons, 2019.
- Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB
  Available: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

6

- 33 Risk Of Bias In Non-Randomized Studies of Interventions. Available: https://methods.cochrane.org/bias/risk-bias-nonrandomized-studies-interventions
- Kirkham JJ, Dwan KM, Altman DG, *et al*. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;340:c365.
   Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging
- 35 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- 36 Yedlapati SH, Khan SU, Talluri S, *et al.* Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with

cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10:e019636.

- 37 Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebocontrolled, multicenter trial. *Circulation*. In Press 2021;144:1476–84.
- 38 Behrouzi B, Araujo Campoverde MV, Liang K, et al. Influenza vaccination to reduce cardiovascular morbidity and mortality in patients with COVID-19. J Am Coll Cardiol 2020;76:1777–94.
- 39 International prospective register of systematic reviews (PROSPERO). Centre for reviews and dissemination, University of York. Available: https://www.crd.york.ac.uk/prospero/