Title: Protection of piglets against influenza A viruses from vaccine derived maternal immunity – A systematic review and meta-analysis

Authors:
Sheila Keay[1], Jan M. Sargeant[1], [2], Annette O'Connor[3], Robert Friendship[1], Terri O'Sullivan[1], and Zvonimir Poljak[1]

[1]Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Canada
[2]Centre for Public Health and Zoonoses, Ontario Veterinary College, University of Guelph, Guelph, Canada
[3] Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI, U.S.A.
Corresponding author: S. Keay: Ontario Veterinary College, University of Guelph. 50 Stone Road East. Guelph, Ontario. Canada. NIG 2W1
Email: skeay@uoguelph.ca

Registration:
This protocol will be archived in the University of Guelph's institutional repository (The Atrium; https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046) and published online with Systematic Reviews for Animals and Food (SYREAF) available at: http://www.syreaf.org/. The systematic review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher et al., 2009). This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines (Moher et al., 2015).

Support. Funding support for this systematic review and meta-analysis, including the development of the protocol, was provided by an Ontario Veterinary College Fellowship grant (SK) https://ovc.uoguelph.ca/ and the Ontario Ministry of Food Agriculture and Rural Affairs (OMAFRA) http://www.omafra.gov.on.ca/english/ project# KTT2015-10253 (ZP).

Introduction.
Vaccination of breeding females against IAV-S is a common practice to achieve clinical stability and reduced viral shedding by dams, and to reduce, both pre and post-weaning, clinical signs and shedding by offspring (Rahn et al., 2015; USDA, 2016; Van Reeth and Ma, 2013; Vincent et al., 2017). Questions continue to be raised, however, about the benefits of IAV-S vaccine derived maternally derived immunity (MDI) for protecting piglets (Cador et al., 2016; Khurana et al., 2013; Rose et al., 2013; Ryt-Hansen et al., 2019).

Rationale:

Standards for human influenza vaccine evaluation and approval are globally harmonized, and influenza vaccine performance is systematically reviewed regularly (Demicheli et al., 2020, 2018; ECDPC, 2020; Jefferson et al., 2018; Weir and Gruber, 2016; Wood and Weir, 2018). Veterinary vaccine research has not been similarly harmonized and unlike the requirement for clinical trials to approve human vaccines, challenge trials are sufficiently

pivotal for the approval of veterinary vaccines (CFIA, 2020; Knight-Jones et al., 2014; USDA, 2018).

Here we describe a protocol for a systematic review and meta-analysis of IAV-S vaccine interventions in sows for the protection of offspring.

Two well established factors impact influenza vaccine performance and should be considered in any review:

1. The degree of antigenic matching of the vaccine with circulating (or challenge) virus(es) (Cador et al., 2017; Chamba Pardo et al., 2018; Diaz et al., 2015; Van Reeth and Ma, 2013).
2. 'Original antigenic sin', or the timing and characterization of the first IAV exposure as it antigenically primes all subsequent immunologic responses to influenza (Francis et al., 2019; Lewnard and Cobey, 2018; Yewdell and Santos, 2020).

Poorly defined circulating viruses and unknown influenza exposure history therefore complicates interpretation of findings from research, particularly research conducted in the field or under conditions of natural exposure.

This is the first systematic review and meta-analysis of IAV-S vaccines in swine.

We acknowledge also that a systematic review and meta-analysis of studies conducted under conditions of natural IAV-S exposure, may have been more informative for practitioners but given the above noted considerations, challenge trials only will be the focus of this review.

The primary audience for this review is therefore researchers, research funders, authorities involved in influenza vaccine approval, and systematic reviewers wishing to conduct additional syntheses on IAV-S vaccine interventions in swine.

Objective:
Research question: A systematic review and meta-analysis will be conducted to investigate the question: "Does evidence from challenge trials support vaccination of sows against IAV-S for the protection of offspring?"

Elements of the research question are defined as follows:

P = Swine dams (intervention population) and their offspring (population for measuring outcomes)
I = Vaccination of sows against influenza pre-farrowing.
C = Sows not vaccinated against IAV (or vaccinated with a sham vaccine), or sows vaccinated with an IAV vaccine differing from the intervention vaccine.
O = Outcome (O):

Primary outcomes:

i. Serum hemagglutination inhibition (HAI) titres

ii. Virus detection (incidence)

Secondary outcomes:

i. Duration of virus shedding
ii. Virus titres
iii. Average daily gain (ADG)
iv. Coughing

METHODS

***Eligibility criteria*:**

Populations eligible:

Population (P):

Sow eligibility: All parity sows or gilts of reproductive age.

Offspring eligibility (population sampled for outcomes):

- Offspring from the sow study population up to the end of the nursery period, or age-matched MDI negative piglets (e.g. colostrum deprived piglets, piglets from IAV-S dams from any source)
- Offspring can be vaccinated or unvaccinated against IAV-S.

Interventions eligible:

Intervention (I): Any IAV-S vaccine(s) (commercial, autogenous, or experimental), based on any vaccine platform, and all methods of administration to sows for the purpose of imparting maternally derived immunity (MDI) to offspring.

Comparison groups eligible:

Comparator (C):

- Sows with no prior IAV-S antigenic exposure (as stated by author)

or

- Sows with pre-farrowing IAV-S exposure that is not from the intervention vaccine but may be from vaccination against IAV-S with a vaccine that is different from the intervention vaccine, or due to wild-type IAV-S virus exposure.

Outcomes eligible:

Outcomes must be measured in the eligible offspring up to the end of the nursery stage of production, may be measured at the group or at the individual level, and can be made using any instrumentation, assay type, or using any sample type, except as noted below.

- Virus detection, duration of shedding, or of quantification of shed virus will be measures **from oropharyngeal or nasal swab samples only** as isolated in eggs or

tissue culture (e.g. Log TCID50 titres), or as detected nucleic acids (e.g. RTqPCR methods and RTqPCR cycle threshold (CT) measures). Oropharyngeal or nasal swabs are non-invasive sampling, can be collected repeatedly anti-mortem, and are practical in the field(Garrido-Mantilla et al., 2019).

- Coughing as measured at the group level.

Study designs/settings eligible:

Challenge trials using randomized controlled trials (RCTs) and non-randomized study designs (NRS) will be included only.

Other eligibility criteria:

Timing (T): Samples collected from farrowing to the end of the nursery production stage will be included.

In addition to the PICOTS elements, eligibility will include primary research literature published since 1990, from any geographic location, and available as English language full text. Publications without digitally formatted metadata (RIS standardized tag format to enable citation programs to exchange data) will be excluded.

Information sources:
Previously, a scoping review was conducted current to May 2018 identifying 376 unique primary research publications on IAV-S vaccines in pigs of any age (Keay et al., 2020). The prior search for publications will be updated to current using the following sources:

Table 1. Bibliographic databases and vendor interfaces (platforms) to be searched.

Platform	Database
CAB Direct	CAB Abstracts and Global Health-1973-current and others
PubMed	MEDLINE
Web of Science	The Science Publication Index, Clarivate Analytics, 1864-current-multiple databases
ProQuest	Agricola (USDA National Agricultural Library1970-Current)
ProQuest	Dissertations & Theses A&I: Health & Medicine Full Text (1998-2018)

Grey Literature Sources to be searched:
Conference Proceedings/Abstracts

American Association of Swine Veterinarians (AASV) Swine Information Library - A searchable digital catalogue available to members on the Association website of the following swine conference proceedings: http://www.aasv.org/library/swineinfo/

1. AASV Annual Meeting: 2018-2020
2. AASV Pre-Conference Seminars: 2018-2020

3. International Pig Veterinary Society Congress (IPVS):2018-2020
4. Allen D. Leman Swine Conference: 2018-2020
5. ISU Swine Disease Conference for Swine Practitioners: 2018-2020

Search strategy:
The prior scoping review search strategy and search strings was developed with support from University of Guelph librarians with expertise in systematic review methods and will be amended for the updated using vaccine related search terms to narrow the scope to vaccine studies only. Search start date will be January 2018 to current with no language barriers. Previously identified relevant publications (376 from the scoping review) will be merged in Distiller to be included in the full text screening to exclude studies that do not measure MDI in piglet offspring. Search strings are detailed in Protocol Appendix 1.

Study records:

Data management:
Citations will be deduplicated using EndNote reference management software (© 2018 Clarivate Analytics) and Distiller-SR software (© 2018 Systematic Review and Literature Review Software by Evidence Partners). Eligibility screening, and data extraction will be done using Distiller-SR.

Selection process:

Eligibility screening will be done at two levels by a single reviewer using forms pre-constructed and pre-tested in Distiller SR. The Level 1 form will be pre-tested in duplicate by two reviewers on a sample of 100 citations and the Level 2 form on 10 journal articles. Disagreement on inclusion and exclusion decisions will be reviewed and the screening forms amended. If, in either reviewer's judgement the amendments are substantial, then an additional 100 citations will be screened in duplicate for level 1, and an additional 10 journal articles on level 2 to repeat the form pre-testing. Thereafter all screening will be completed by a single reviewer.

Level 1 form (Protocol Appendix 2) will include questions for screening titles and abstracts for relevance to IAV-S vaccine primary research involving vaccination of dams.

Each of the 376 citations identified in the scoping review will be included and advanced to the second level full text screening.

Level 2 relevance screening form will include questions to screen full text to confirm studies measure eligible protective outcomes of MDI in offspring. Citations will be advanced to data extraction if responses are affirmative.

Conference proceedings will be excluded if they are less than 500 words, thereafter, conference proceedings will be excluded if the reported data are published elsewhere in a more complete form such as a dissertation or journal article. Likewise, studies reported in dissertations or theses will be excluded if published also as journal articles.

Data collection process:

Data will be extracted using forms pre-constructed in Distiller-SR and pre-tested in duplicate by two reviewers working independently on the first 10 journal articles and refined by reviewer consensus until agreement on extracted data is consistent. Thereafter all data will be extracted by a single reviewer.

Study authors will not be contacted for additional clarification or data.

Data items:

For this study the following terminology for outcomes will be used:
Effect = results for specific intervention group (e.g. proportion positive in a treatment group)
Treatment effect, effect measure, or effect size = the results from an individual study or comparison within a study (e.g. OR for infection in treated versus control group)
Summary treatment effect, summary effect measure, or summary effect size = results from a meta-analysis (e.g. summary OR across multiple studies)

Study level data:
(Other general bibliometric meta-data will be automatically captured by Distiller or reference management software and will not therefore be extracted)
Date published
Number of trials reported in study

Trial level data:
Year and month study initiated
Year and months study concluded
Country where study conducted
Number of trial arms
Cross-fostering restrictions observed/not observed

Arm level data:
Dam data:
The author's definition of eligibility criteria
Unit of allocation (individual/ farrowing crate, or group (pens, room))
Number of individual sows or groups of sows enrolled.
IAV-S exposure history of dams (no prior exposure, prior exposure defined, prior exposure and not defined)
Method of confirmation of dam exposure history
Parity of enrolled dams (median and range per treatment group, or mean and SD per treatment group)
Co-morbidity reported (list pathogens)
Other non-IAV-S vaccines administered during trial (yes/no)

Offspring data:
Author's definition of piglet inclusion criteria

Number of offspring enrolled in each group
Method of confirming piglet MDI status (either overserved colostrum intake within 24 hours of birth, or direct serum measurement of suckling post-partum, or not confirmed)
Weaning age of piglets
Any additional concurrent IAV-S vaccine treatments given to the offspring of the intervention group (vaccine type, antigenic characterization, dose, timing)
Any additional concurrent IAV-S vaccine treatments given to the offspring of the comparator group (vaccine type, antigenic characterization, dose, timing)
Piglet IAV-S infection status confirmed prior to challenge (yes/no)

Intervention details (Sow IAV-S vaccination):
IAV-S vaccine program details as described by authors (for all IAV-S vaccines used) including:
Vaccine platform
Trade name/ experimental identifier
Antigenic/genetic description provided by authors
Dose or antigenic quantity per dose
Vaccine adjuvant described by authors
Route
Timing of administration
Method of assessing post-vaccination immunologic response of dam
Antigenic matching of influenza vaccine and exposure virus (s) (as homologous, heterosubtypic, or as not stated, or antigenically unmatched as defined by researchers)

Comparator details (Comparison Sows):
Description of sow comparison group (no treatment, sham vaccine, an IAV-S vaccine differing from the intervention vaccine)
If applicable, details as above on non-intervention IAV-S vaccine treatment of comparison sows (e.g. program, platform, name, dose, timing, etc.)

IAV-S offspring challenge information:
Age of piglets at time of challenge
Challenge dose
Challenge virus characterization
Method of challenge (intranasal, intratracheal, contact with infected seeder pigs (if seeder pigs, also collect information as above on how seeder pigs were infected and confirmed shedding))

Outcomes:
Details on methods for collection of outcomes, and outcome results data will be collected for six outcomes; serum hemagglutination inhibition (HAI) titres (as titre endpoints or as geometric mean titres (GMT)), virus detection (incidence), duration of virus shedding, virus titres, ADG (grams per day), coughing index at the group level (frequency or count)).

For each outcome the following data will be extracted:
The author definition of the outcome
Sample type, frequency (timing) of sampling, method of sampling (e.g. repeated sampling of same animals, or different animals each time), individual or pooled sampling.

Instrumentation or assay used for measurement of outcome.
Number of animals analyzed enrolled in each treatment group

Outcomes and prioritization:

For each of the selected outcomes for meta-analysis we will extract the possible metrics in the following order:

1st priority: Adjusted effect size (adjusted risk ratio or adjusted odds ratio, mean differences for continuous outcomes), variables included in adjustments, and corresponding precision estimate.

2nd Priority: Unadjusted effect size

3rd Priority: Arm level risk of the outcome, or arm level mean of the outcome (continuous outcomes). For dichotomous outcomes, we will extract the number of events and number of total study units analyzed in each study arm. Outcomes reported as HAI titre endpoints will be converted to geometric mean titres (GMT) using the formula:

$$GM = e^{\left(\frac{\ln(a)+\ln(b)+\ln(c)+\cdots}{n}\right)}$$

Where *ln* is the natural logarithm and *e* is the base of the natural logarithm and *n* is the number of observations (Reverberi, 2008).

For continuous outcomes, we will extract means, standard deviations (SDs) and number of total study units analyzed per study arm. When SDs are not available but standard errors (SE), or P values are reported, we will extract these and transform to SDs when possible.

Variance components: If variance estimates are not reported we will calculate them using standard formulas if the necessary data are provided.

Risk of bias in individual studies:
Risk of bias will be assessed at the outcome level for the primary outcomes of HAI titres and virus detection (prevalence or incidence) using a Risk of Bias tool ROB-2.0 (Higgins et al., 2016) previously modified for use in swine trials (Sargeant et al., 2019).

Studies will be evaluated in five domains: bias from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, or in the selection of reported results(Higgins et al., 2016)

Risk of bias assessments will be done in Distiller. The form will be pre-tested on 10 studies in duplicate by two reviewers working independently and refined through consensus. Thereafter, risk of bias assessment will be conducted by a single researcher.

Data synthesis:

The analysis will be conducted using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Meta-analysis:

Based on an *a priori* assumption that the treatment effect size varies between studies, random effects meta-analysis will be performed for each primary and secondary outcome where two or more studies have reported the outcome. Using the method of DerSimonian and Laird (DerSimonian and Laird, 1986), a summary effect estimate will be calculated based on a weighted average of the estimated vaccination effects where the true vaccination effect is assumed randomly and normally distributed between studies with variance τ^2 ("tau-squared") as follows:.

Random-effects estimate will be derived as follows:
Log $OR_R = \sum w_i$ log $OR_i / \sum w_i$

Where $w_i = \frac{1}{v_{i+\tau^2}}$
And v_i is the variance of the log odds ration of the study *i*.

Testing for heterogeneity(Higgins et al., 2003)**:**

Cochrane's *Q* statistic (heterogeneity statistic) will be used to test the null hypothesis that the true vaccination effect is the same in all studies.
Where $Q = \sum w_{i\langle logOR_i - logOR_R \rangle}{}^2$

And the P-value will be calculated in comparison to the χ^2 distribution on (k-1) degrees of freedom (df), (k is the number of studies).

The amount of heterogeneity between studies will be measured using the I^2 test statistic(Higgins et al., 2003) where I^2 = (*Q*-df) / *Q* X 100%

Heterogeneity will be considered substantial if I^2 is greater than 60%.

Subgroup analysis will be considered where studies can meaningfully be grouped into two or more studies.

Although co-morbidity data will be collected and reported descriptively, it will not be considered in further analysis.

Planned sub-groups include:

1) Vaccine platform where platform type will be assigned to one of six different groups;

i. Viral antigen based (WIV, split virus vaccine, virus like-particles (no genomic content), sub-unit)

ii. Recombinant viral vector - both replicating and replication-defective (e.g. Alphavirus-like replicon particles, replication-defective adenovirus recombinants -vector genome is replicated for expression by host machinery)
iii. Live attenuated influenza virus vaccine (LAIV)
iv. Plasmid DNA vaccines
v. RNA vaccines

2) Antigenic matching between vaccine components and the exposure virus or viruses where matching will grouped as:

i. unknown antigenic matching (vaccine components and/or challenge virus not defined)
ii. matched*
iii. unmatched *

*Matched (and unmatched) will be based on sub-type matching of HA and NA, or in the case where the researchers have defined distinct antigenic lineage or strain differences within the sub-type, matched or unmatched will be as defined by the researchers.

3) Vaccination status of population sampled (offspring)

i. offspring were not vaccinated against IAV-S
ii. offspring were vaccinated also against IAV-S

Meta-bias(es):

Publication bias will be assessed for each meta-analysis including 10 or more studies using funnel plots (Sterne and Egger, 2001), an estimation of missing studies will be made using the trim and fill method (Duval and Tweedie, 2000), and funnel plot asymmetry will be investigated via methods of Begg (Begg and Mazumdar, 1994) and of Egger(Egger, M. et al., 1997).

Confidence in cumulative evidence:

The quality of evidence will be assessed for each primary outcome overall from the results of meta-analysis using the approach proposed by GRADE (Schünemann et al., 2021) and presented as a 'Summary of findings' table (Schünemann et al., 2021).

Discussion:

Differences in sub-groups outcomes will be discussed within the context of vaccine platforms, and of the strengths and weaknesses of the various measures used as the study endpoint, heterogeneity of methods employed, and of repeatability of findings. The limitations and advantages of challenge trials versus trials with natural exposure will be discussed within the context of antigenic priming, timing of exposures, and of identifying IAV-S antigenic differences of immunologic importance.

References:

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Cador, C., Andraud, M., Willem, L., Rose, N., 2017. Control of endemic swine flu persistence

in farrow - to - finish pig farms : a stochastic metapopulation modeling assessment 1–14. https://doi.org/10.1186/s13567-017-0462-1
Cador, C., Rose, N., Willem, L., Andraud, M., 2016. Maternally derived immunity extends swine influenza A virus persistence within farrow-to-finish pig farms: Insights from a stochastic event-driven metapopulation model. PLoS One 11, 1–16. https://doi.org/10.1371/journal.pone.0163672
CFIA, 2020. Veterinary Biologics Guideline 3.13E - Guideline for Autogenous Veterinary Biologics [WWW Document]. Guid. Doc. Repos. URL https://www.inspection.gc.ca/animal-health/veterinary-biologics/guidelines-forms/3-13e/eng/1328594554673/1328594626360 (accessed 12.22.20).
Chamba Pardo, F.O., Schelkopf, A., Allerson, M., Morrison, R., Culhane, M., Perez, A., Torremorell, M., 2018. Breed-to-wean farm factors associated with influenza A virus infection in piglets at weaning. Prev. Vet. Med. 161, 33–40. https://doi.org/10.1016/j.prevetmed.2018.10.008
Demicheli, V., Jefferson, T., Ferroni, E., Rivetti, A., C, D.P., 2018. Vaccines for preventing influenza in healthy adults (Review) - Summary of findings for the main comparison. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD001269.pub6.www.cochranelibrary.com
Demicheli, V., Jefferson, T., Ferroni, E., Rivetti, A., Di Pietrantonj, C., 2020. Vaccines for preventing influenza in the elderly: A Cochrane review summary. Int. J. Nurs. Stud. 109. https://doi.org/10.1016/j.ijnurstu.2019.06.003
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188. https://doi.org/10.1016/0197-2456(86)90046-2
Diaz, A., Perez, A., Sreevatsan, S., Davies, P., Culhane, M., Torremorell, M., 2015. Association between influenza A virus infection and pigs subpopulations in endemically infected breeding herds. PLoS One 10, 1–11. https://doi.org/10.1371/journal.pone.0129213
Duval, S., Tweedie, R., 2000. Trim and Fill: A simple funnel-plot-based method. Biometrics 56, 455–463.
ECDPC, 2020. Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over. Stockholm. https://doi.org/10.2900/751620
Egger, M., Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634. https://doi.org/https://doi.org/10.1136/bmj.315.7109.629
Francis, M.E., King, M.L., Kelvin, A.A., 2019. Back to the future for influenza preimmunity—Looking back at influenza virus history to infer the outcome of future infections. Viruses 11. https://doi.org/10.3390/v11020122
Garrido-Mantilla, J., Alvarez, J., Culhane, M., Nirmala, J., Cano, J.P., Torremorell, M., 2019. Comparison of individual, group and environmental sampling strategies to conduct influenza surveillance in pigs. BMC Vet. Res. 15. https://doi.org/10.1186/s12917-019-1805-0
Higgins, J.P., Savović, J., Page, M.J., Sterne, J.A., 2016. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [WWW Document]. riskofbias.info. URL https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/archive-rob-2-0-2016 (accessed 3.14.21).
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in

meta-analyses. Br. Med. J. 327, 557–560. https://doi.org/10.1136/bmj.327.7414.557
Jefferson, T., Rivetti, A., Di Pietrantonj, C., Demicheli, V., 2018. Vaccines for preventing influenza in healthy children. Cochrane Database Syst. Rev. 2018. https://doi.org/10.1002/14651858.CD004879.pub5
Keay, S., Poljak, Z., Klapwyk, M., O'Connor, A., Friendship, R.M., O'Sullivan, T.L., Sargeant, J.M., 2020. Influenza A virus vaccine research conducted in swine from 1990 to May 2018: A scoping review. PLoS One 15, e0236062. https://doi.org/10.1371/journal.pone.0236062
Khurana, S., Loving, C.L., Manischewitz, J., King, L.R., Gauger, P.C., Henningson, J., Vincent, A.L., Golding, H., 2013. Vaccine-Induced Anti-HA2 antibodies promote vvirus fusion and enhance influenza virus respiratory disease. Sci. Transl. Med. 5. https://doi.org/10.1126/scitranslmed.3006366
Knight-Jones, T.J.D., Edmond, K., Gubbins, S., Paton, D.J., 2014. Veterinary and human vaccine evaluation methods. Proc. R. Soc. B Biol. Sci. 281. https://doi.org/10.1098/rspb.2013.2839
Lewnard, J.A., Cobey, S., 2018. Immune history and influenza vaccine effectiveness. Vaccines 6, 1–14. https://doi.org/10.3390/vaccines6020028
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 339, 332–336. https://doi.org/10.1136/bmj.b2535
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Alessandro, L., Petticrew, M., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 9.
Rahn, J., Hoffmann, D., Harder, T.C., Beer, M., 2015. Vaccines against influenza A viruses in poultry and swine: Status and future developments. Vaccine 33, 2414–2424. https://doi.org/10.1016/j.vaccine.2015.03.052
Reverberi, R., 2008. The statistical analysis of immunohaematological data. Blood Transfus. 6, 37–45. https://doi.org/10.2450/2008.0001-08
Rose, N., Herve, S., Eveno, E., Barbier, N., Eono, F., Dorenlor, V., Andraud, M., Camsusou, C., Madec, F., Simon, G., 2013. Dynamics of influenza a virus infections in permanently infected pig farms: Evidence of recurrent infections, circulation of several swine influenza viruses and reassortment events. Vet. Res. 44, 1–14. https://doi.org/10.1186/1297-9716-44-72
Ryt-Hansen, P., Larsen, I., Kristensen, C.S., Krog, J.S., Wacheck, S., Larsen, L.E., 2019. Longitudinal field studies reveal early infection and persistence of influenza A virus in piglets despite the presence of maternally derived antibodies. Vet. Res. 50, 1–10. https://doi.org/10.1186/s13567-019-0655-x
Sargeant, J.M., Deb, B., Bergevin, M.D., Churchill, K., Dawkins, K., Dunn, J., Hu, D., Moody, C., O'Connor, A.M., O'Sullivan, T.L., Reist, M., Wang, C., Wilhelm, B., Winder, C.B., 2019. Efficacy of bacterial vaccines to prevent respiratory disease in swine: A systematic review and network meta-analysis. Anim. Heal. Res. Rev. 20, 274–290. https://doi.org/10.1017/S1466252319000173
Schünemann, H.J., Higgins, J.P., Vist, G.E., Glasziou, P., Akl, E.A., Skoetz, N., Guyatt, G.H., 2021. Completing 'Summary of findings' tables and grading the certainty of the evidence, in: Higgins, J., Thomas, J., Chandle, J., Cumpston, M., Li, T., Page, M., Welch, V. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021). Cochrane, Available from

www.training.cochrane.org/handbook.
Sterne, J.A.C., Egger, M., 2001. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. J. Clin. Epidemiol. 54, 1046–1055. https://doi.org/10.1016/S0895-4356(01)00377-8
USDA, 2018. Code of Federal Regulations . Title 9 - Animals and Animal Products Chapter I - Animal and Plant Health inspection Service, Department of Agriculture Subchapter E - viruses,serums, toxins, and analogous products; organisms and vectors [WWW Document]. URL https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_cfr (accessed 5.15.19).
USDA, 2016. National Animal Health Monitoring System (NAHMS) Swine 2012 study. Part II: Reference of Swine Health and Health Management in the United States, 2012. Fort Collins.
Van Reeth, K., Ma, W., 2013. Swine influenza virus vaccines: To change or not to change-Than's the question, in: Richt, J.A., Richards, W. (Eds.), Current Topics in Microbiology and Immumology. Berlin , Heidelburg, p. 370. https://doi.org/10.1007/82_2012_266
Vincent, A.L., Rajao, D., Anderson, T.K., Abente, E.J., Walia, R.R., Perez, D.R., Lewis, N.S., 2017. Influenza A virus vaccines for swine. Vet. Microbiol. 206, 35–44. https://doi.org/10.1016/j.vetmic.2016.11.026
Weir, J.P., Gruber, M.F., 2016. An overview of the regulation of influenza vaccines in the United States. Influenza Other Respi. Viruses 10, 354–360. https://doi.org/10.1111/irv.12383
Wood, J.M., Weir, J.P., 2018. Standardisation of inactivated influenza vaccines—Learning from history. Influenza Other Respi. Viruses 12, 195–201. https://doi.org/10.1111/irv.12543
Yewdell, J.W., Santos, J.J.S., 2020. Original antigenic sin: How original? How sinful? Cold Spring Harb. Perspect. Med. a038786. https://doi.org/10.1101/cshperspect.a038786

Protocol Appendix 1. Formatted search strings*

For Web of Science:

((TS=(pork OR swine OR "Sus scrofa" OR pig OR pigs OR piglet OR piglets OR gilt OR gilts OR boar OR boars OR sow OR sows OR hog OR hogs OR "weaner pig" OR "weaned pig$" OR "feeder pig$" OR feeder OR feeders OR "finisher pig$" OR "finisher hog$" OR porcine OR "market-weight" NOT "guinea pig$") AND TS=(influenza OR IAV OR IAV$ OR flu OR SIV OR "H3N2" OR "H1N1" OR "H1N2" OR "H3N1" OR "H2N3") AND TS=(immunize OR immuniz$ OR immunise OR immunis$ OR immunoprophylaxis OR intervention$ OR vaccinate OR vaccinat$ OR vaccine$ OR vaccine))) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018-2020

For CAB Direct:

((((pork OR swine OR "Sus scrofa" OR pig OR pigs OR piglet OR piglets OR gilt OR gilts OR boar OR boars OR sow OR sows OR hog OR hogs OR "weaner pig" OR "weaned pig*" OR "feeder pig*" OR feeder OR feeders OR "finisher pig*" OR "finisher hog*" OR porcine NOT "guinea pig*") AND (influenza OR IAV OR IAV* OR flu OR SIV OR "H3N2" OR "H1N1" OR

“H1N2” OR “H3N1” OR “H2N3”))) AND ((immunize OR immuniz* OR immunise OR immunis* OR immunoprophylaxis OR intervention* OR vaccinate OR vaccinat* OR vaccine OR vaccine*)) AND yr:[2018 TO 2020])
For PubMed: (((pork[All Fields] OR ("swine"[MeSH Terms] OR "swine"[All Fields]) OR "Sus scrofa"[All Fields] OR ("swine"[MeSH Terms] OR "swine"[All Fields] OR "pig"[All Fields]) OR ("swine"[MeSH Terms] OR "swine"[All Fields] OR "pigs"[All Fields]) OR piglet[All Fields] OR piglets[All Fields] OR gilt[All Fields] OR gilts[All Fields] OR ("swine"[MeSH Terms] OR "swine"[All Fields] OR "boar"[All Fields]) OR ("swine"[MeSH Terms] OR "swine"[All Fields] OR "boars"[All Fields]) OR sow[All Fields] OR sows[All Fields] OR hog[All Fields] OR hogs[All Fields] OR "weaner pig"[All Fields] OR "weaned pigs"[All Fields] OR "feeder pig"[All Fields] OR feeder[All Fields] OR feeders[All Fields] OR "finisher pig"[All Fields] OR (finisher[All Fields] AND hog[All Fields]) OR ("swine"[MeSH Terms] OR "swine"[All Fields] OR "porcine"[All Fields]) NOT "guinea pig"[All Fields]) AND (("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) OR IAV[All Fields] OR IAV_S[All Fields] OR ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "flu"[All Fields]) OR SIV[All Fields] OR "H3N2"[All Fields] OR "H1N1"[All Fields] OR "H1N2"[All Fields] OR "H3N1"[All Fields] OR "H2N3"[All Fields])) AND (("immunisation"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] OR "immunization"[MeSH Terms]) OR immunized[All Fields] OR immunized[All Fields] OR ("immunization"[MeSH Terms] OR "immunization"[All Fields] OR "immunoprophylaxis"[All Fields]) OR ("methods"[MeSH Terms] OR "methods"[All Fields] OR "intervention"[All Fields]) OR interventions[All Fields] OR vaccinated[All Fields] OR vaccinated[All Fields] OR ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]) OR ("vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinations"[All Fields]) OR ("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]) OR ("vaccines"[MeSH Terms] OR "vaccines"[All Fields]))) AND ("2018/01/01"[CRDAT] : "3000"[CRDAT])
Dissertations and theses: noft(pork OR swine OR "Sus scrofa" OR pig OR pigs OR piglet OR piglets OR gilt OR gilts OR boar OR boars OR sow OR sows OR hog OR hogs OR "weaner pig" OR "weaned pigs" OR "feeder pig" OR feeder OR feeders OR "finisher pig" OR "finisher hog" OR porcine OR "market-weight" NOT "guinea pig") AND noft(influenza OR IAV OR IAV-S OR flu OR SIV OR "H3N2" OR "H1N1" OR "H1N2" OR "H3N1" OR "H2N3") AND (immunize OR immunization OR immunise OR immunisation OR immunoprophylaxis OR vaccinate OR vaccination OR vaccines OR vaccine)Limits applied Databases:32 databases searched View list These databases are searched for part of your query. Limited by:Date: From 2018 January 01 to 2020 Source type:Dissertations & Theses Document type:Dissertation/Thesis

Language:English

* Search strategy and search strings were developed and formatted for selected bibliometric platforms with support from University of Guelph librarians with systematic review methods expertise.

Protocol Appendix 2

Title/Abstract:
Level 1 relevance screening questions: (1= Advance†, 0 = Exclude)
†Advance to next question or if last question to next level of screening.

1. Is this report/study/document about Influenza A virus in/from swine (IAV-S) where swine or direct applicability to swine is the focus (i.e. excludes studies of IAV-S in humans with variant IAV-S, or IAV-S in other species)?

   Yes 1, No 0, Unclear 1
2. Is the citation primary research?

   Yes 1
   No, it is an editorial or commentary. 0
   No, it is a white paper, working report, policy paper, issue paper, or guidelines 0
   *****No, it is a review.
   No, it is another type of publication. 0
   Unclear 1

   ***3a)** What is the review type as indicated by the authors in the title/abstract?

   A traditional or narrative review. 0
   A systematic review without a meta-analysis 0
   A meta-analysis. 0
   A systematic review and meta-analysis. 0

   * This is a conditional question applied only to citations identified as reviews.
3. Does this study involve vaccine research in swine where the unit of study is higher than the sub-animal level (e.g. not at the tissue, cellular, molecular, etc. level)?

   Yes 1, No 0, Unclear 1

4. Are sows (or first parity gilts) the study population vaccinated?

   Yes 1, No 0, Unclear 1
5. Is the full text available in English?

   Yes 1, No 0, Unclear 1

Protocol Appendix 3.

Full text:
Level 2 relevance screening questions: (1= Advance†, 0 = Exclude)

†Advance to next question or if last question to next level of screening.

1. Is this report/study/document about Influenza A virus in/from swine (IAV-S) where swine or direct applicability to swine is the focus (i.e. excludes studies of IAV-S in humans with variant IAV-S, or IAV-S in other species)?
   Yes 1, No 0

2. Is the citation primary research?
   Yes 1
   No, it is an editorial or commentary. 0
   No, it is a white paper, working report, policy paper, issue paper, or guidelines 0
   No, it is a review*****. 1
   No, it is another type of publication. 0
   ***3a)** What is the review type as indicated by the authors in the title/abstract? (This is a conditional question and applied only to citations identified as reviews.)
   A traditional or narrative review. 0
   A systematic review without a meta-analysis 0
   A meta-analysis. 0
   A systematic review and meta-analysis. 0

3. Does this study involve vaccine research in swine where the unit of study is higher than the sub-animal level (e.g. not at the tissue, cellular, molecular, etc. level)?
   Yes 1, No 0

4. Are sows (or first parity gilts) the study population vaccinated?
   Yes 1, No 0

5. Are outcomes measured in offspring of vaccinated dams?
   Yes 1, No 0

6. Is there an offspring comparison group?
   Yes 1, No 0

7. Is the study a challenge trial?
   Yes 1 No 1

8. Was at least one of the following offspring outcomes reported?
   - serum hemagglutination inhibition (HAI) titres
   - virus detection, duration of virus, or virus titres sampled from oropharyngeal or nasal swab
   - Average daily gain (ADG)
   - Coughing (measured at the group level)

   Yes 1 No 1