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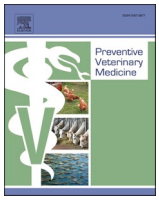

Efficacy of swine Influenza A virus vaccines on transmission, viral shedding and clinical signs: Systematic review and meta-analysis

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ABSTRACT

Swine influenza A viruses (swIAV) are a major cause of respiratory disease in pigs, and vaccination remains the main control strategy. The objective of this systematic review and meta-analysis was to quantify the efficacy of swIAV vaccines in pigs, regarding viral transmission, viral shedding and clinical signs. Data were extracted from experimental studies involving vaccinated pigs subsequently challenged with swIAV. The review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Article selection was performed using two approaches: conventional dual-reviewer screening and ASReview, an artificial intelligence-based tool for systematic reviews. A total of 163 publications met the eligibility criteria, and data were extracted from 146 studies. Meta-analyses were conducted on 11 articles for transmission, 72 for shedding, and 89 for clinical signs. Vaccination, both homologous and heterologous, significantly reduced the median transmission rate (β) and the median reproduction ratio (R) compared to unvaccinated controls. However, the median R-values remained above 1 (4.15 for heterologous and 1.44 for homologous challenges), indicating continued potential for outbreak occurrence. Vaccination also significantly reduced both mean and peak viral shedding, with standardized mean differences of –0.53 and –0.25, respectively. A generalized linear mixed model revealed a strong effect of vaccination under homologous challenge conditions. Meta-regression confirmed the influence of vaccine and challenge type on shedding outcome. No statistically significant difference in body temperature was found between vaccinated and control groups. This review highlights the need for greater harmonization in experimental study design and reporting, to improve the comparability of swIAV vaccine efficacy studies.

1. Introduction

Swine influenza is an important respiratory disease in pigs, caused by Influenza A viruses. Swine Influenza A Viruses (swIAV) subtypes are classified based on the two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). Three primary subtypes (i.e., H1N1, H1N2, and H3N2) co-circulate and are considered enzootic in pigs in most countries. Since 2009, the pandemic H1N1 (pH1N1) virus has been circulating alongside the three primary enzootic strains (European Centre for Disease Prevention and Control, 2023; Vincent et al., 2014). The genetic diversity of pH1N1 - containing gene segments of human, avian, and swine origin – highlights the susceptibility of pigs to both human and avian influenza strains. This susceptibility makes pigs effective mixing vessels (Mancera Gracia et al., 2020; Qiu, 2015),

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enabling genetic reassortment and the emergence of novel variants with potential zoonotic implications (Klivleyeva et al., 2024; Ma, 2020; Salvesen and Whitelaw, 2021).

Transmission of swIAV among swine occurs rapidly and efficiently, resulting in clinical signs including hyperthermia, lethargy, loss of appetite, and respiratory symptoms such as coughing and nasal discharge. These clinical signs often lead to weight loss, which in turn can negatively impact productivity and reproductive performance of breeding sows and growing pigs (Gumbert et al., 2020). Although the disease generally has low mortality, co-infections with other pathogens (i.e. Porcine Reproductive and Respiratory Syndrome virus or Porcine Circovirus) can exacerbate its severity, contributing to the Porcine Respiratory Disease Complex (PRDC) and resulting in economic losses due to reduced productivity and increased mortality (Czyżewska-Dors et al., 2019; Saade et al., 2020). It is estimated that the economic impact can reach up to €45,000 in annual profit losses per farm driven by higher mortality, feed cost, and reduced sales due to lower productivity and slower growth (Calderón Díaz et al., 2020; Salvesen and Whitelaw, 2021).

Vaccines serve as promising means for effective control of swIAV within and between farms. They are mainly administered to sows during gestation to reduce reproductive disorders, and to protect piglets during the suckling period. This strategy enhances the transfer of maternally derived antibodies (MDA), providing higher and long-lasting passive immunity in the offspring (Ghattas et al., 2021). However, the genetic composition, antigenic properties, and epidemiological patterns of swIAV vary regionally, further complicating disease control efforts (Klivleyeva et al., 2024; Ma, 2020).

The vaccine efficacy describes the relative difference in disease attack rates between vaccinated and unvaccinated groups and is quantified in animal experimental challenge studies, most of which measure several indicators: clinical signs, immune responses, histopathology, viral shedding and/or transmission (Halloran et al., 1999; Weinberg and Szilagyi, 2010). For this last indicator, experimental challenge studies involve inclusion of sentinel animals to monitor viral transmission from challenged animals.

Although swIAV vaccine efficacy have been extensively studied, a comprehensive overview of the effects of vaccines is missing. This study aims to quantify the effects of various vaccines on viral transmission between pigs, and viral shedding in nasal swabs and clinical signs of swIAV in pigs under controlled conditions.

2. Methods

2.1. Research question and protocol

The research question of this study was: What is the effect of vaccination against swIAV in pigs on transmission, viral shedding, and clinical signs? To address this question, a systematic review (SR) and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Page et al., 2021) (in the supplementary document Table S1), structured according to the Population, Intervention, Comparator, and Outcome statement (PICO statement) described in Table 1.

Table 1
Detailed PICO statement for this study.

Variable	Description
Population (P)	Swine
Intervention (I)	Vaccine used for the prevention of Swine Influenza
Comparator (C)	Unvaccinated animals challenged with swIAV in experimental studies
Outcomes (O)	Viral transmission, viral shedding in nasal swabs, and clinical signs parameters

2.2. Information sources

This study used seven electronic databases (Scopus, PubMed, Web of Science, Science Direct, Agricola & CAB Abstract, Google Scholar) to identify references.

2.3. Search strategy

The literature search was structured around four main conceptual domains using the terms reported in Table 2. Appropriated filters were applied to avoid articles related to human diseases such as COVID-19, Ebola, Guillain-Barré syndrome, AIDS, etc. Detailed queries used for each database are available in the supplementary document Table S2. The literature search was conducted on 27 July 2023 and updated until 21 January 2025.

2.4. Search strings for identifying articles

In this study, the free online tool CADIMA (https://www.cadima.info/index.php) - a tool facilitating the conduct and assuring the documentation of SR and literature reviews (Kohl et al., 2018) - was used for deduplication, tracking in- and excluded papers and tracking exclusion criteria. Accuracy and completeness of deduplication were manually verified.

2.5. Eligibility criteria

An initial screening of titles and abstracts was used to select relevant references. This screening was based on five eligibility criteria: 1) the study involved pigs (only living animals), 2) the exposure was related to swIAV or swine influenza vaccine, 3) the subjects of the study include vaccines, viral shedding, virus transmission, and/or immunological responses, 4) the study was a field or experimental study (exclusion of review and modelling studies), 5) the publication was written in English, French, or Dutch. Language restrictions were based on author's language proficiency and resource constraints. Publications without abstract but with full text available were included in the second phase.

In the second phase, full-texts were assessed for eligibility based on seven criteria: 1) the full text was available, 2) all criteria of the Title and abstract screening were met, 3) An experimental challenge was performed in pigs, 4) pigs were administered an Influenza A virus vaccine, 5) the challenge virus was a swIAV; and 6) data were reported at least one of the following subjects: virus shedding measured in nasal swabs, clinical signs and/or immune responses, 7) group sizes of two or more animals. Additionally, the following exclusion criteria were applied during the full-text screening: 1) studies involving pigs co-infected with other respiratory pathogens, 2) studies including pigs with prior exposure to swIAV or those accidentally infected by ubiquitous pathogens, unless the data were excluded from the trial 3) studies in which animals were supplemented with immune-boosting compounds, such as iron, zinc, etc.

Table 2
Search strings for identifying articles.

Category	Terms
Virus	"influenza A" OR "influenza A virus*" OR "swine flu" OR "swine influenza" OR "swine influenza virus"
Population	swine OR pig* OR pork OR porcine OR suidae
Vaccination	vaccin* OR "maternally-derived antibodies"
Outcomes	transmissi* OR shedding OR "basic reproduction number" OR dynamic* OR excretion OR immun* OR antibod*

OR: Boolean operator; * : truncation. These categories were combined using the Boolean operator AND within the data base research boxes

2.6. Study selection

The study selection was divided between two reviewers (O.M. & E. G.). To enhance the reliability of the selection process and evaluate the level of agreement between the two reviewers, a subset of ten publications was independently reviewed three times in CADIMA. The level of agreement between the two reviewers' selections was fair, as shown by the kappa value of 0.58, which was automatically calculated via the tool (Kohl et al., 2018).

To ensure that no relevant papers were overlooked, an additional screening was conducted by a third reviewer (B.B.) utilizing an artificial intelligence-based tool ASReview Lab v1.5 (https://asreview.nl/ht), a web-based application designed to enhance screening efficiency based on titles and abstracts. Prior to the screening, B.B. was acquainted with enhancing familiarity and maintaining consistency, in collaboration with O.M. The screening included the same set of articles previously reviewed, focusing on titles and abstracts. Before initiating the screening process, 11 relevant records and 15 irrelevant papers were preselected and used as prior knowledge for the tool (in the supplementary document Table S3). The reviewer labeled papers and ASReview iteratively updated its knowledge based on this selection and presented the likely relevant abstracts. The reviewer ceased the screening process after labelling fifty consecutive abstracts as irrelevant, which is in accordance with the SAFE procedure (Boetje and van de Schoot, 2024). Subsequently, full-text screening of the articles was conducted in CADIMA, applying the same inclusion and exclusion criteria as in the initial screening phase.

2.7. Risk of bias assessment

The risk of bias was assessed for each selected study using SYRCLE's risk of bias (RoB) tool, which is based on the Cochrane RoB tool and adapted for animal intervention studies (Hooijmans et al., 2014). Before the assessment, a prior consultation was conducted among the reviewers to ensure maximum consistency The assessment was performed independently by five reviewers (O.M, E.G, U.H.P.N, C.H, A.A). In case of doubt, the reviewers consulted each other to reach a consensus.

2.8. Data collection process

A database associated with a data dictionary developed with Microsoft ® Excel ® (version 2021) was used to collect the data. When the raw data was not available, data concerning experimental results (e.g., body temperature or virus titer) were extracted from the publication's figures using the online tool WebPlotDigitizer (https://apps.automeris.io/wpd4/). Data collection was conducted by four reviewers (O.M., E.G., B.B, & C.H.). Prior to the data extraction, the reviewers conducted a preliminary test of the database to ensure consistency in data collection. In cases where any reviewer encountered uncertainty, a discussion was held until consensus was reached.

2.9. Data items

The extracted data were organized into eleven Excel ® spreadsheets, containing information on the following categories: Paper Details, Experimental Animals, Experimental Setup, Vaccine and Virus Information, Vaccination Protocol, Clinical Signs, Body Temperature and Shedding Excretion (nasal swabs) and Transmission Parameters. Detailed information is available in the supplementary document. Below, we outline the assumptions made during the data extraction process.

2.9.1. Group level

Animals were assigned to one of three groups: vaccinated, control and non-vaccinated/non-challenged groups. The vaccinated group included animals that received either homologous or heterologous vaccines, followed by viral challenge. The control group consisted of non-vaccinated (NV) or placebo-vaccinated (mock) animals, also challenged with the virus. The non-vaccinated/non-challenged groups included animals that neither received a vaccination nor were exposed to the viral challenge. Such groups are generally included to ensure the safety of the experimental setup but were not considered in the current analysis.

Each included study reported data from at least one vaccinated and one control group. For viral shedding and clinical signs parameters, most outcomes were reported at group level; data were extracted accordingly. When outcomes (e.g., mean or standard deviation (SD) were reported at the individual level, they were recalculated to group level.

2.9.2. Vaccine type and category

Vaccine type was collected and classified into one of the following categories (Table 3) (Ghattas et al., 2021).

An overview of the vaccine categories and corresponding descriptions

Globally, various vaccine types and technologies are employed. Current commercially available vaccines are inactivated or adjuvanted whole virus vaccines.

2.9.3. Challenge type (homologous or heterologous)

Categorization between homologous and heterologous challenges was done based on the information in the article. If the information was not available, the challenge was classified as homologous when the vaccine virus and the challenge virus were similar or when the vaccine was partly based (VLP, DNA, etc.) on the same virus strain as the challenge virus. Otherwise, the challenge type was categorized as heterologous.

2.9.4. Transmission

For each group, data about the vaccination status (vaccinated or control) and challenge (homologous or heterologous) was extracted. Additionally, information about the starting- and last day of shedding measured by nasal swabs was extracted to determine the infectious period. For each measurement time point, the number of susceptible, infectious, new infected, recovered, total animals and the time interval, were recorded to estimate the transmission parameters.

2.9.5. Viral Shedding

The mean and SD per group for each day were collected. Standard

Table 3
An overview of the vaccine categories and corresponding descriptions.

Vaccine Category	Description
Inactivated Vaccine	Vaccines made from whole viruses that have been killed (inactivated) to avoid replication or cause disease. Wild types are also included in this category.
Live Attenuated Influenza Vaccine (LAIV)	Vaccines that use a weakened form of the influenza virus to induce immunity. Their use is limited due to concerns about viral reassortment and the potential emergence of more virulent strains.
Subunit Vaccine	Vaccines that use specific components of a pathogen, such as proteins, to trigger an immune response. This category include: - Recombinant protein vaccines - Virus-like particle (VLP) vaccines - Nanoparticle vaccines - Subunit vaccines All variants offer different methods of presenting antigen to the immune system.
Nucleic Acid Vaccine	Vaccines that use mRNA or DNA to deliver genetic instructions to host cells, which then produce antigens to stimulate an immune response.
Viral Vectored Vaccine	Vaccines that use harmless viruses as vectors to deliver the genetic material encoding vaccine antigens into cells. The cells then produce antigens to elicit an immune response.

error (SE) was also recorded and converted to SD. Studies exclusively reporting cycle threshold (Ct) values were excluded from extraction.

2.9.6. Clinical Signs

- Body temperature: The mean (in °Celsius) and SD per group for each day were collected. When the mean temperature was reported in Fahrenheit, it was converted to Celsius.

- Other clinical signs: The presence or absence of nasal discharge, cough, sneezing, anorexia, lethargy, weakness, respiratory issues, pyrexia, and loss of appetite were assessed. These parameters were recorded in a binary value (presence = 1, absence = 0). A symptom score of 1 was attributed when at least one clinical sign was reported and/or any elevation in body temperature, in accordance with the authors' own terminology (e.g., increase in body temperature).

3. Data synthesis and statistical analysis

Analyses of transmission were conducted at the individual level, while viral shedding and clinical signs were assessed at the group level. Table 4 summarizes the key analytical steps undertaken, highlighting the logical flow and resulting outcomes of the study.

3.1. Transmission

Transmission parameters — infectious period (T), transmission rate (β) and the reproduction ratio (R) — were estimated from studies in which sentinels, pigs that were exposed by direct contact to inoculated pigs, were included in an experiment. To estimate the transmission parameters, longitudinal data on absence or presence of viral shedding, measured by RT-PCR or virus isolation from nasal swabs, was extracted for each pig. A pig was considered infected if a nasal swab was positive for the virus genome. Based on this assumption, data were organized for each experimental group in a way that we could record, for each specific time interval of observation ("Δ time in days"), the number of susceptible, infectious, recovered, new cases and total animals in the group. Using this dataset, the mean length of the infectious period — defined as the interval during which an individual can transmit the virus — was calculated for each experiment. When test intervals exceeded one day, generating censoring on the day a pig stopped shedding virus, the midpoint between the last positive test and the first subsequent negative test was used as the estimated end of the infectious period. No additional assumptions were made if pigs remained virus positive on the last day of measurement.

The mean transmission rate β — defined as the average number of infections per infectious individual per unit time — and its SE were estimated using a generalized linear model (GLM), following the approach described by Sitaras et al. (2016). The R and its corresponding 95% confidence intervals (CI) were estimated as the product of T and β as described by Gonzales et al. (2012).

Table 4
Consolidates the various analyses undertaken in the study, allowing for a clear visualisation of the research progression and outcome. T: infectious period. β: transmission rate. R: reproduction ratio. GLM: generalized linear model. GLMM: generalized linear mixed model. SMD: Standardized mean difference. OR= Odds ratios.

Subjects	Outcomes	Methods	Plot
Transmission	T, β, R	GLM	Boxplot (Fig. 3)
Viral shedding	-SMD mean and peak	Effect size	Forest plot (in the supplementary document; mean Figure S2a, peak Figure S2b)
	Mean across time point	GLMM	Line plot (Fig. 4)
Clinical signs	SMD of body temperature (> 40°C) OR of clinical signs (presence/absence)	Effect size	Forest plot (maximum body temperature Fig. 5. In the supplementary document for clinical signs Figure S6)

3.2. Viral shedding

We conducted an effect size analysis, using standardized mean differences (SMD), by differencing the mean of the vaccinated and control groups. Hedge's g was used to adjust for small sample size bias (Borenstein, 2009). We performed two analyses, one assessing mean and the other on peak shedding. To assess the mean shedding, we computed the mean titre across all available timepoints for each group. For peak shedding, within each group, we identified the sampling day with the highest mean titre. The two analyses were performed for the two subgroups based on challenge type (homologous and heterologous). In the same subgroup, when a single control group was used for multiple vaccinated groups, the control group sample size was split by the number of vaccinated groups to avoid double counting in the analysis (Harrer et al., 2021). Heterogeneity across studies was evaluated using I^2 and τ^2. Potential publication bias of the peak and mean viral shedding parameters was assessed using funnel plots. Visual inspection of the funnel plots did not reveal marked asymmetry, suggesting limited evidence of publication bias (in the supplementary document Figure S3–S4).

Model selection and comparison were conducted using both the Akaike Information Criterion (AIC) - to evaluate the overall fit of the final models and the Likelihood Ratio Test (LRT) - to determine whether the inclusion of additional variables significantly improved model fit, with p-values based on chi-square tests. Challenge type and vaccine type were used as moderators. This dual approach allowed us to assess both the overall fit and the relative importance of specific moderators in explaining viral shedding dynamics.

A generalized linear mixed model (GLMM) with a Gamma distribution and log link was used to analyse log-transformed viral shedding. Fixed effects included vaccination status, challenge type, vaccine type, vaccine subtype, virus subtype, age at challenge, immune status, number of vaccine administration, interval time and day post-challenge. To assess the effect of age at challenge, data were stratified into five age groups: < 4 weeks, 5–8 weeks, 9–16 weeks, 17–24 weeks and > 24 weeks. A group-level random effect was included to account for between-group variability within and across studies. To generate clear prediction plots, we initially attempted to compute estimated marginal means (EMMs) from the GLMM, but the model failed to converge due to numerical instability. Consequently, a reduced model retaining vaccine type, challenge type and day post challenge as fixed effects, was fitted using the random-effects structure. The simplified model converged robustly and was used solely to compute EMMs (±95% CI) for plotting purposes.

3.3. Clinical signs

This study assessed the impact of vaccination on clinical outcomes, focusing on maximum body temperature. Groups were classified as febrile if the maximum temperature exceeded 40°C. For each study, SMD was calculated for the maximum temperature between vaccinated and control groups. To adjust for small-sample bias, Hedge's g was used to the SMD (Borenstein, 2009). When a control group was shared among multiple vaccinated groups, the mean of the maximum temperature was calculated across the vaccinated groups (Cuijpers et al., 2017). A random-effect meta-analysis model was fitted using the restricted maximum likelihood (REML) estimator to account for heterogeneity. Between-study heterogeneity was quantified using τ^2, I^2, and Q statistics, and the model provided pooled effect estimates and measures of variability.

3.4. Software

Data cleaning, data analyses, and computation of the figures were performed using the R programming language (v.4.4.2) (R Core Team, 2024) with RStudio interface (RStudio Team, 2024). Data visualization was performed with 'ggplot2' (Hadley Wickham, 2016), 'tidyverse' (Wickham et al., 2019), 'patchwork' (Pedersen, 2025), 'grid' and 'gridExtra' (Auguie and Antonov, 2017) packages. Effect size analysis was performed using the metacont function from the 'meta' package (Balduzzi et al., 2019). Total effect sizes (95% confidence intervals were calculated, forest and funnel plots were produced. All other inferential analyses involving moderators or repeated measures across days were conducted using GLMMs fitted with 'glmmTMB' package (Brooks et al., 2017; McGillycuddy et al., 2024). The PRISMA flow diagram was created using draw.io (JGraph, 2021).

4. Results

4.1. Study selection

An initial literature search was conducted, covering studies published between January 1936 and July 2023. A total of 4230 records were retrieved from seven electronic databases. Of these, 2191 were identified as duplicates and subsequently removed (Fig. 1). The remaining 2039 records were screened based on their titles and abstracts. Of these, 459 publications were selected for full text screening, resulting in 139 studies that met the predefined eligibility criteria. The screening using ASReview Lab v1.5 identified four additional eligible studies. A subsequent literature update added 20 extra publications published between July 2023 and January 2025.

In total, 163 studies met the inclusion criteria. Following the risk of bias assessment, data from 146 studies were retained. Several studies were excluded from the meta-analysis. The meta-analysis included 11 studies on viral transmission, 72 studies on viral shedding in nasal swabs, and 89 studies of clinical signs. Notably, a single article could report more than one parameter.

4.2. Study characteristics and risk of bias within studies

The characteristics and risk of bias for each study included in this work are presented in the supplementary document S2 (csv file).

4.3. Descriptive analysis

A total of 163 articles met the inclusion criteria; however, data could be extracted from only 146 studies. The other studies reported immune responses in formats too heterogenous to allow data extraction. Among the 146 included studies, the three most frequently used vaccine types were inactivated vaccines (88 studies), LAIV (34), and viral vector vaccines (28) (Fig. 2a). A total of 78 studies used homologous challenge strains, while 104 used heterologous strains (Fig. 2b). The most tested influenza subtype was H1N1(39 studies), followed by H3N2 (32), pH1N1(24), and H1N2 (19) subtypes. Some studies employed multivalent vaccines (in the supplementary document Figure S1). A single study could include several vaccinated groups using different vaccine and challenge types.

Most studies employed a single method to quantify viral shedding, with cell culture expressed as $TCID_{50}$/ml being the most commonly used technique (Fig. 2c).

Different vaccination schedules were implemented across the studies, ranging from one to three doses. For protocols involving a single injection, the median age at vaccination was 28 days (SD = 17.34). In two-dose schedules, the median age at the first and second injections was 28 days (SD = 13.98) and 49 days (SD = 15.94), respectively. In protocols of three-dose schedule, the median age at the first, second, and third injections was 28 days (SD = 15.11), 56 days (SD = 17.07) and 98 days (SD = 25.24), respectively.

-RNA copies/ ml includes: GEC/ml, Genome copy number/ml, M gene copy number per 10^6 copies of β-actin gene, Genome copies/ml, RNA copies/ml, Copies/μL, Viral copy no/ul RNA, Genomic equivalent copies (GEC)/ml, RNA copies log10/ul, Genomic copies/ml, Copies/ml, Copy/ml, RNA copies log 10/μl, RNA copies/100 μl, RNA copies/100 μL, RNA copies log 10/μl. -REU includes: log10 REU RNA and REU. $TCID_{50}$: Tissue Culture Infectious Dose. EID: Egg Infectious Dose. PFU: Plaque Forming Units. REU: Relative Equivalent Units.

4.4. Meta-analysis

4.4.1. Transmission

Data from 11 of the 13 included articles were used to estimate viral transmission parameters; two articles were excluded from analysis. The data from Klingbeil et al. (2015) could not be extracted and Loving et al. (2013) was excluded because it was the only study to investigate indirect virus transmission. Table S4 in the supplementary document provides an overview of the viral transmission parameters for all control and treatment groups. The median transmission parameters T, β, and R of the treatment groups — heterologous or homologous challenged — were compared to those of the control groups (Fig. 3). The median T showed no significant reduction in the treatment groups compared to the control groups (heterologous $p = 0.06$; homologous $p = 0.27$). In contrast, the median β was significantly reduced in both treatment groups compared to the control groups (heterologous $p = 0.01$; homologous $p = 0.02$). Similarly, the median R was significantly reduced in both treatment groups compared to the control groups ($p = 0.02$). Nevertheless, the median R-values remained above 1, at 4.15 for the heterologous challenged and 1.44 for the homologous challenged groups, indicating continued potential for viral transmission despite reductions.

4.4.2. Viral shedding

The viral shedding was quantified using various methods, and values were expressed as $\log_{10}$ transformed, including zero values. Therefore, the ratio of means method was not applicable (Friedrich et al., 2008). To enable comparisons of results across studies, we selected those presenting data in the most common units, i.e. $TCID_{50}$/ml and $TCID_{50}$-equivalent/ml. Data reported in Plaque-Forming Units (PFU) were converted to $TCID_{50}$/ml using the formula $TCID_{50}/ml = 0.7 \times PFU$ (Hierholzer and Killington, 1996; Reed and Muench, 1938). Groups for which the challenge type could not be determined, and those used wild type as vaccines, were excluded from the analysis. In total, 72 articles were included to quantify viral shedding.

4.4.2.1. Effect size. Effect sizes indicated significant reductions in both mean and peak viral shedding among vaccinated groups compared to controls (in the supplementary document Table S5).

Due to incomplete data, mean viral shedding was analyzed using data from 42 studies, comprising a total of 3158 observations (1257 from vaccinated groups and 1901 from controls). The overall SMD was –0.53 (95% CI –0.71 to –0.35; $p < 0.0001$; $I^2 = 72.3\%$). Subgroup analysis showed significant reductions for both heterologous (SMD = –0.46; 95% CI –0.62 to –0.30; $I^2 = 49.3\%$) and homologous challenge groups (SMD = –0.79; 95% CI –1.34 to –0.23; $I^2 = 89.5\%$). The difference between these subgroups was not statistically significant ($p = 0.26$).

Due to missing data, peak viral shedding was analyzed using data from 38 studies with 544 group-level observations (277 vaccinated, 267 controls). The overall SMD was smaller than that for the mean viral shedding but remained statistically significant (SMD = –0.25; 95% CI –0.45 to –0.05; $p = 0.013$; $I^2 = 21.9\%$). In subgroup analyses, a significant effect size was found in the homologous group (SMD = –0.56; 95% CI –1.02 to –0.11), whereas the heterologous challenge group showed a non-significant effect (SMD = –0.16; 95% CI –0.38–0.07). The difference

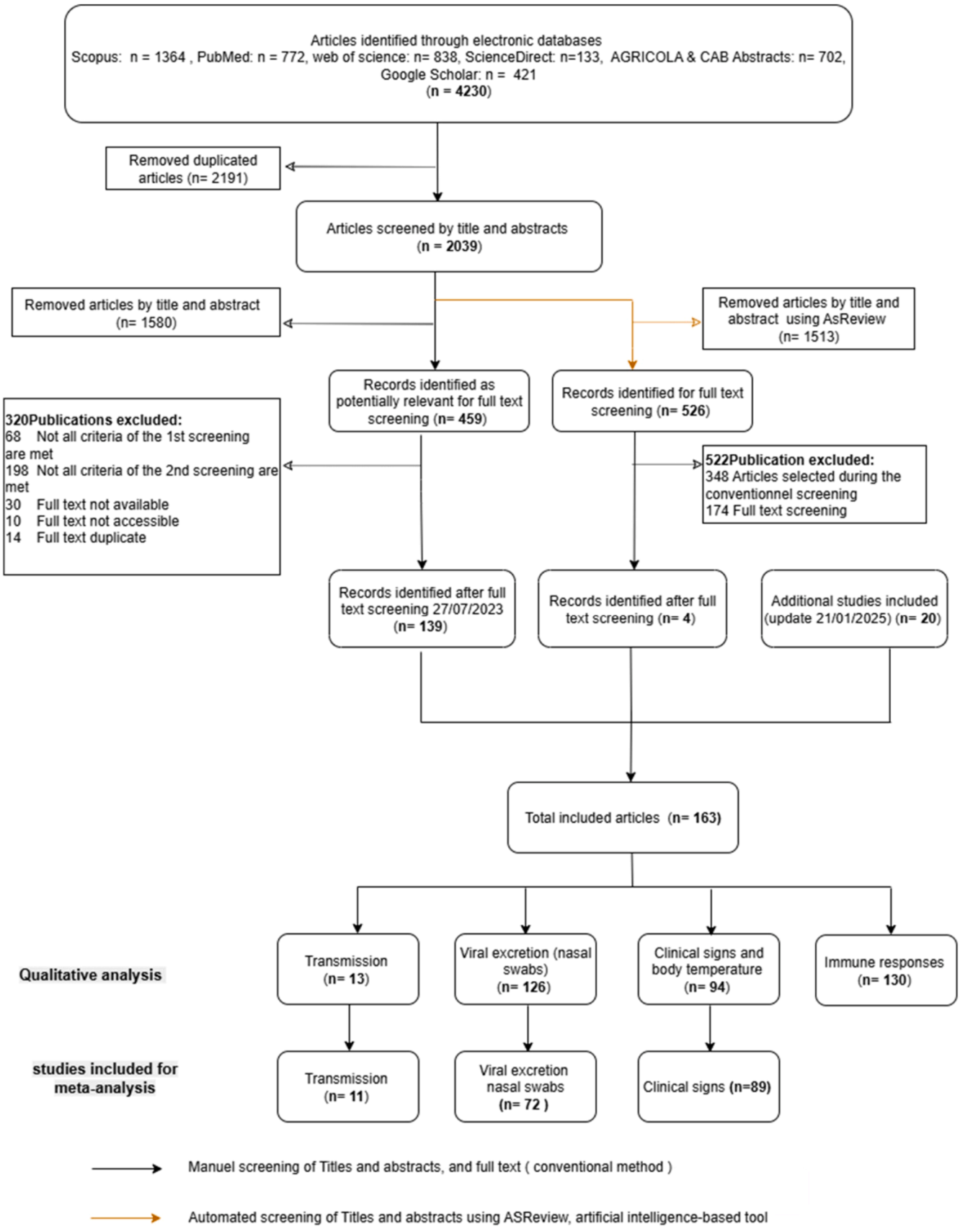

Fig. 1. PRISMA flow diagram illustrating the selection of studies related to vaccine efficacy.

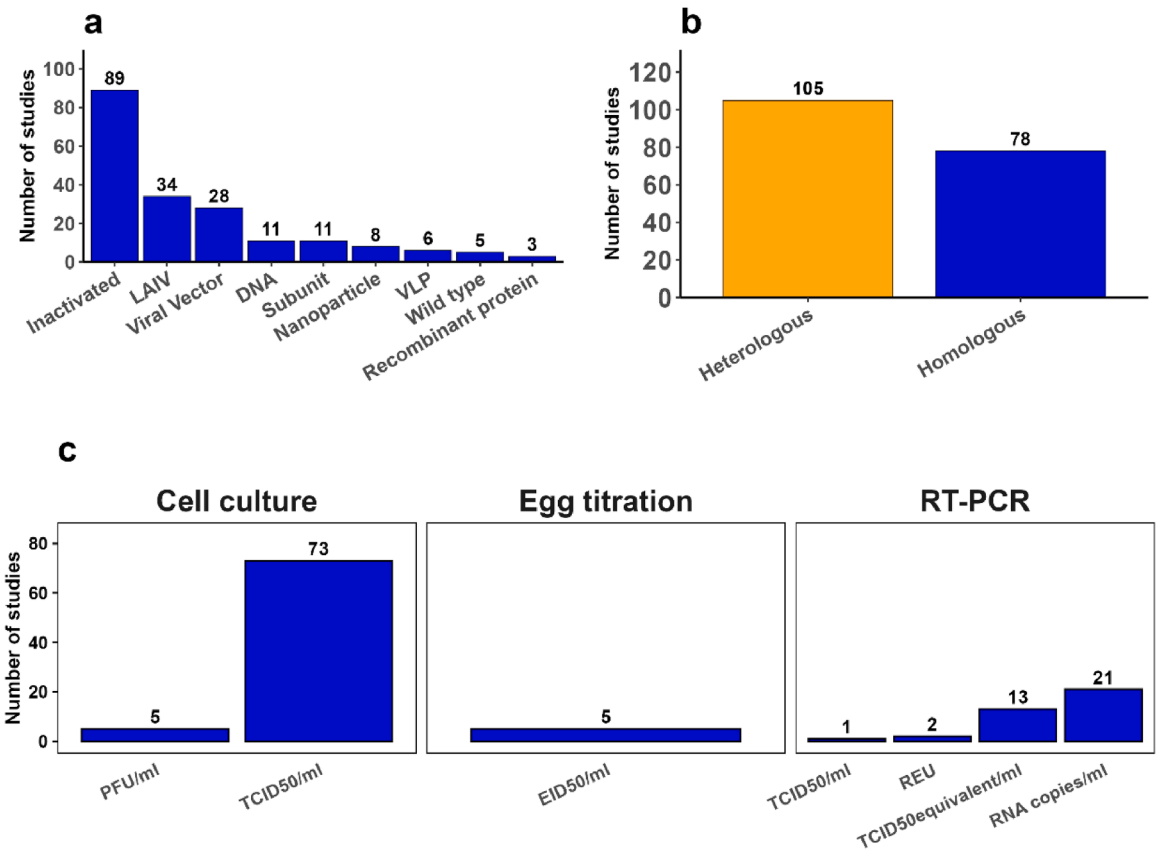

Fig. 2. Descriptive analysis of studies. a: number of studies per vaccine categories. LAIV= Live-Attenuated Influenza Vaccine. DNA= Deoxyribonucleic Acid. VLP=Virus-Like Particle. b: number of studies per virus types. C: unit and methods used to quantify viral shedding in nasal swabs, expressed in log-decimal units. For simplification of the graph some units were regrouped together: - $TCID_{50}$ /ml includes: $TCID_{50}$ ml and $TCID_{50}$ /100 mg nasal secrete.

between these subgroup effect sizes was not statistically significant ($p = 0.11$).

These results indicate that vaccination leads to a moderate effect size in reducing mean shedding, with more consistent effects across challenge types.

4.4.2.2. Heterogeneity source. To explore potential sources of heterogeneity, we performed meta-regression analyses using vaccine type and challenge type as moderators. Including both variables, significantly improved model fit compared to the null model without moderators (LRT = 19.28. $p = 0.01$), explaining approximately 22.85% of the between-study heterogeneity (τ^2 reduced from 0.23 to 0.18) (in the supplementary document Table S6). Vaccine type accounted for most of the explained variability, although substantial residual heterogeneity remained in all models (I^2 ~70%–77%).

4.4.2.3. Generalized linear mixed model analysis. To further partition residual variance and robustly estimate the fixed effects of vaccine type, challenge type and other covariates, while accounting for group-level differences, we fitted a GLMM, weighting each group by its sample size. Full model results and 95% confidence intervals showed that viral shedding kinetics differed significantly by vaccine and challenge type (in the supplementary document Table S7. EMMs; Fig. 4). Time since challenge had a significant effect ($p < 0.001$), with peak viral shedding occurring on Day 4 (Estimate = 10.56) and gradually declining thereafter. This temporal trend was consistent across vaccine types, with homologous challenge groups consistently showing the lowest predicted shedding at all time points. Among vaccine types, LAIV (Estimate = –1.49; $p < 0.001$) showed a statistically significant reduction in viral shedding compared to inactivated vaccines (reference group). This estimate reflects an average across challenge types, as interaction terms were not included due to model simplicity and convergence constraints. Other vaccine types did not show statistically significant effects.

4.4.3. Clinical signs

Among 89 studies, 34 reported body temperature for both vaccinated and control groups, yielding 126 observations. After accounting for missing data, nine studies met the inclusion criteria for the meta-analysis. Temporal patterns of febrile response (in the supplementary document Figure S5) showed that vaccinated groups maintained lower body temperature throughout the observation period. The forest plot for difference maximum body temperature between vaccinated and control groups across studies is showed in Fig. 5. The total effect was not significant: the common-effect model yielded a SMD of −0.283°C (95% CI: −0.886–0.321, z = -0.92, p = 0.359), while the random-effects model resulted in an SMD of −0.338°C (95% CI: −1.007–0.331, z = -0.99, p = 0.322). Heterogeneity across studies was low, with I^2 statistic of 11.5% (95% CI: 0.0–53%) and a heterogeneity variance t^2 of 0.156 (95% CI: 0.016–3.142), with standard deviation of true effect t of 0.395 (95% CI: 0.125–1.773). The H statistics were 1.06 (95% CI: 1.00–1.46), and non-significant Q statistic (Q = 9.04, df = 8, p = 0.339). The effect size for all clinical signs is shown in the supplementary document Figure S6.

5. Discussion

This review aimed to quantify vaccine efficacy (VE) against swIAV in pigs. A total of 146 experimental challenge studies were included to assess VE based on viral transmission, viral shedding (both measured via nasal swabs), and clinical signs following swIAV infection. This study showed that vaccination against swIAV in pigs significantly reduced

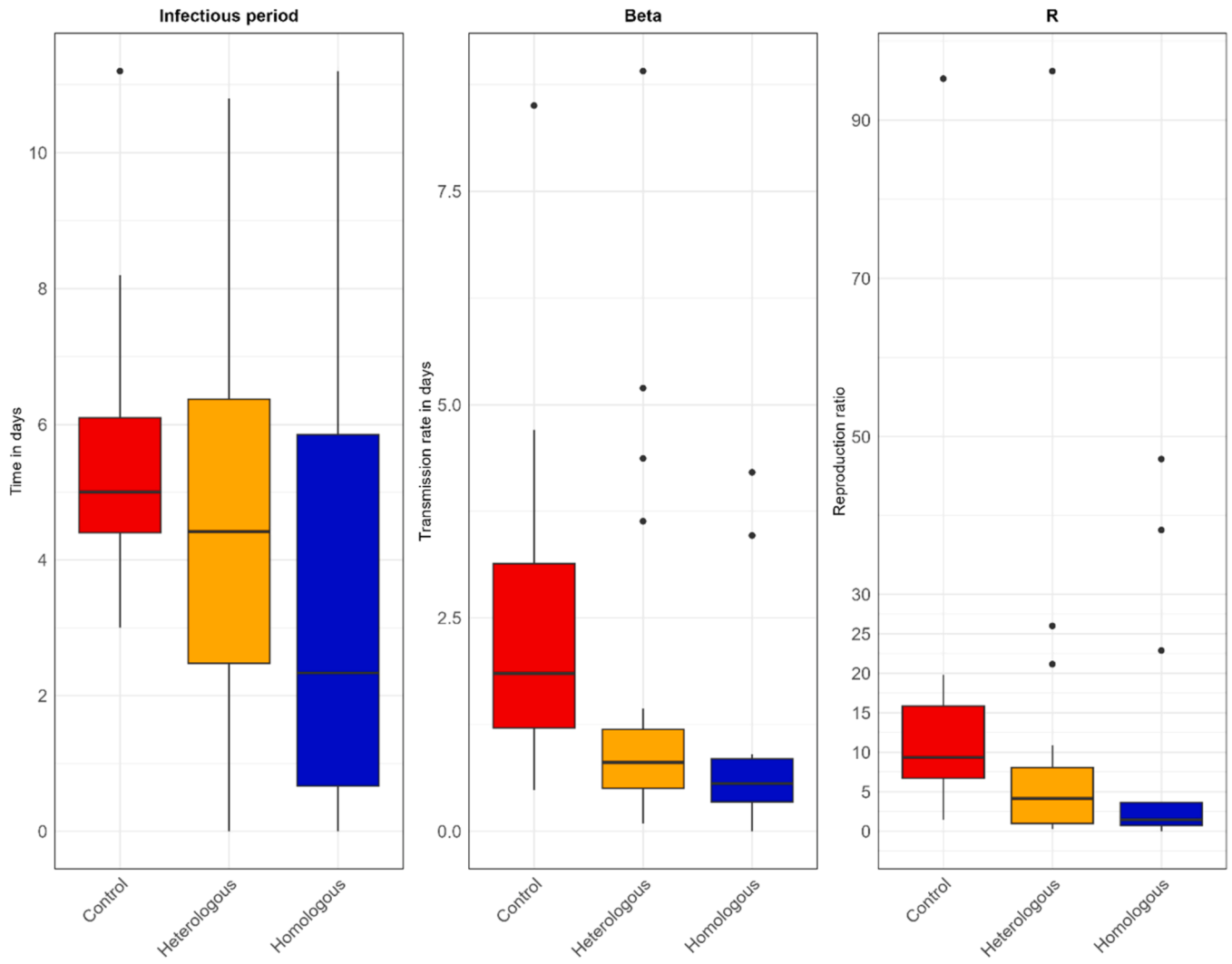

Fig. 3. Distribution of the estimated median values, from each included experiment, of the infectious period (T), transmission rate parameter (β) and reproduction ratio (R) grouped by control and vaccinated groups i.e., heterologous and homologous. The box represents the first quartile, the median, and the third quartile. Individual black dots are outliers.

transmission (median β and R-value) and mean viral shedding, particularly under homologous challenge conditions. However, no significant differences were observed in the mean body temperature, which was used as a proxy for clinical signs. Notably, the median R remained above 1, even in the homologous challenge groups, suggesting continued potential for viral spread. Although viral shedding was the lowest in homologous challenges, the difference compared to heterologous challenges was not statistically significant.

Our meta-analysis demonstrated that vaccination significantly reduced both median β and R either in hetero- and homologous challenges. When vaccination can reduce R< 1, virus transmission within a herd is halted and in case all farms are vaccinated this could also block virus transmission at between-farm level (Van Nes et al., 1998). However, an R value below 1 was observed in only six of eleven experimental groups (Ding et al., 2019; Graaf et al., 2022; Klingbeil et al., 2015; Li et al., 2020; Ma et al., 2014; Rose et al., 2013) involving one viral vector vaccine, three inactivated vaccines, one subunit vaccine and one LAIV. The findings of this study highlight the need to develop improved vaccines capable of consistently reducing R< 1, which is essential for effective control of swIAV transmission within herds. Nevertheless, an effect of size corresponding to an R of 1.44, as observed under homologous challenge conditions, could still offer substantial benefits in the field. For instance, the probability that a virus introduction leads to a major outbreak is equal to (1–1/R) (Diekmann et al., 2012), implying that approximately 70% of virus introductions in vaccinated herds would not result in an outbreak—compared to only 10% in unvaccinated herds. Moreover, in vaccinated pigs where outbreaks do occur, the proportion of pigs affected would be considerably smaller. The combined effect of fewer and smaller outbreaks may also reduce transmission between farms, in particular, if accompanied by good biosecurity practices. This principle is exemplified by the successful eradication of Aujeszky's disease in several European countries through vaccination, even though vaccination in finishing pigs only reduced the transmission rate to an R value of 1.5. To achieve such effects, it is essential to use a vaccine that closely matches circulating field strains. The R value of 4.15 observed under heterologous challenge conditions suggests that, in the absence of such a match, no meaningful reduction in transmission can be expected under field conditions (Stegeman et al., 1997).

Despite the critical role of transmission dynamics, current evidence on transmission dynamics remains limited. Of the 146 studies included, only 13 incorporated sentinel pigs to investigate viral transmission post-challenge, of which just one study studied indirect transmission. The study by Graaf et al. (2022) highlights the value of using sentinels: while inoculated pigs shed virus, no viral shedding was detected in contact animals during 5 dpc. This provides evidence of non-transmission –

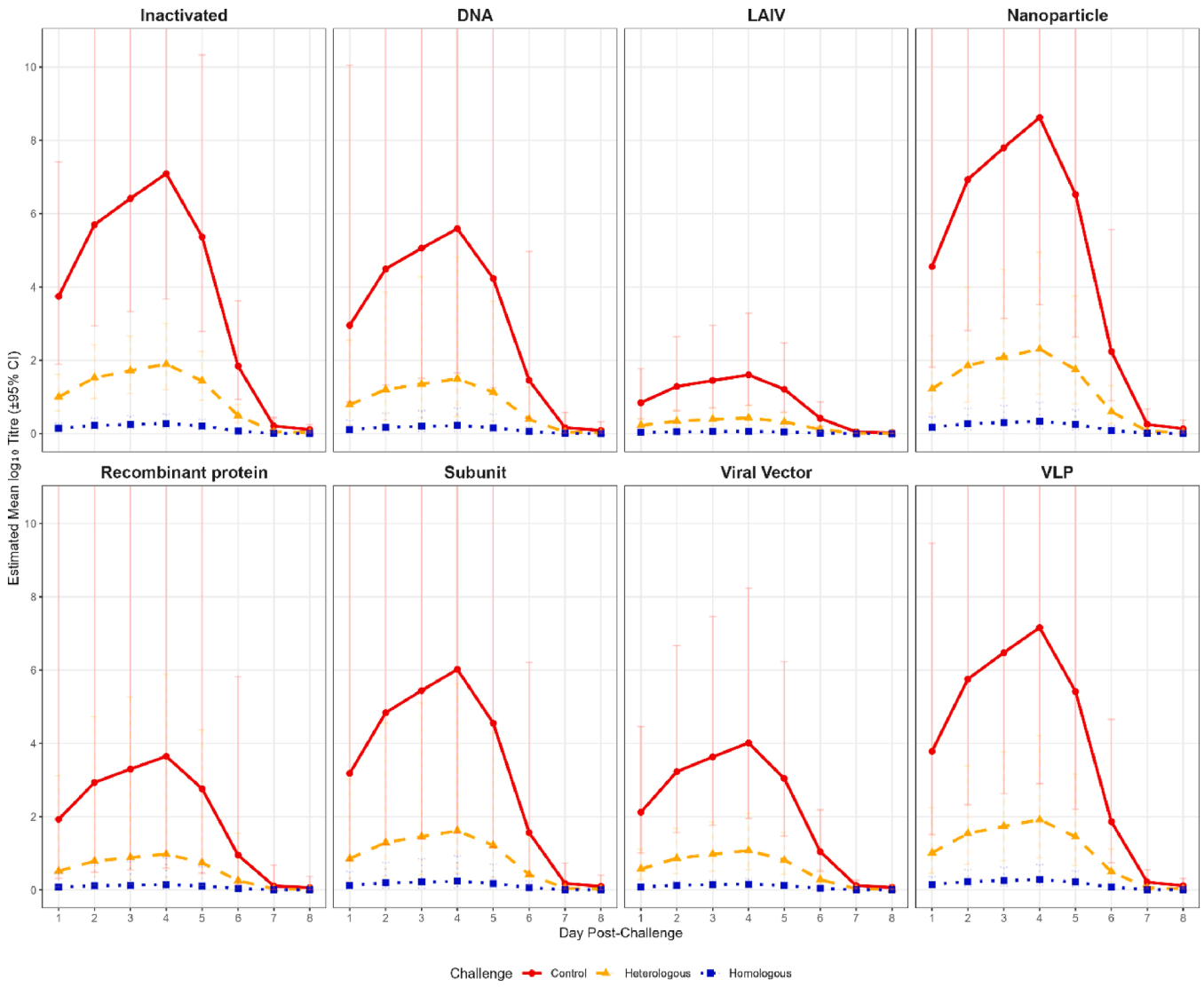

Fig. 4. Estimated marginal means (EMMs) of viral shedding over time by vaccine types and challenge types. EMMs (log_{10} virus titre) was obtained from a generalized linear mixed model (GLMM) with a Gamma distribution and log link, adjusting for group-level stratification. Each panel represents one vaccine type. Lines indicate the adjusted mean viral shedding over time (days post challenge) for homologous challenge (blue), heterologous challenge (orange), or control group (red). Error bars represent 95% confidence intervals. Homologous challenge consistently resulted in the lowest viral shedding across most vaccine type, highlighting the importance of antigenic matching between vaccine and challenge type. LAIV: Live Attenuated Influenza Vaccine. VLP: Virus-like particle.

something that cannot be concluded from shedding data alone. The inclusion of sentinel pigs in future challenge studies, and study both direct and indirect transmission, would provide a more comprehensive assessment of vaccine efficacy.

As previously noted, no significant difference in the mean duration of the infectious period was observed between vaccinated and control groups. This may be due to limitations of RT-PCR, which detects viral RNA, but cannot distinguish between infectious and non-infectious viral particles. Consequently, RT-PCR may overestimate the infectious period, potentially masking the true impact of vaccination on reducing the infectious period.

Our study showed that vaccination significantly reduced both mean and peak viral shedding following homologous challenge, consistent with the observed reduction in transmission. The magnitude of this reduction varied by vaccine categories, with LAIV achieving greater reductions in viral shedding than inactivated vaccines following homologous challenge. Although previous studies have reported that LAIV provides broader heterologous protection than to inactivated vaccines (Ma, 2020; Mancera Gracia et al., 2020), our results did not replicate these findings, as no superior cross-protection was observed with LAIV.

A commonly cited concern with LAIV is the potential risk of genetic reassortment between the vaccine virus and circulating endemic strains (Sharma et al., 2020; WOAH, 2009). Despite this concern, an LAIV vaccine has been commercially available in the US since 2017(Ma, 2020). In contrast to LAIV, inactivated vaccines generally offer strong protection against homologous strains but exhibit limited efficacy against heterologous strains. Moreover, inactivated vaccines may, in rare case, exacerbate disease through Vaccine-Enhanced Respiratory Disease (VAERD), raising concerns about their reliability for broad-spectrum protection (De Vleeschauwer et al., 2015; Kumari, 2022).

Findings related to clinical signs suggest that the total effect from meta-analysis was not significant, while some studies reported significant differences in body temperature between vaccinated and control groups in some studies. This is unexpected given the effects shown on transmission and virus shedding. Due to small number of papers reporting relevant data (n = 9), subgroup analyses could not be performed. The heterogeneity between the data was moderate, which

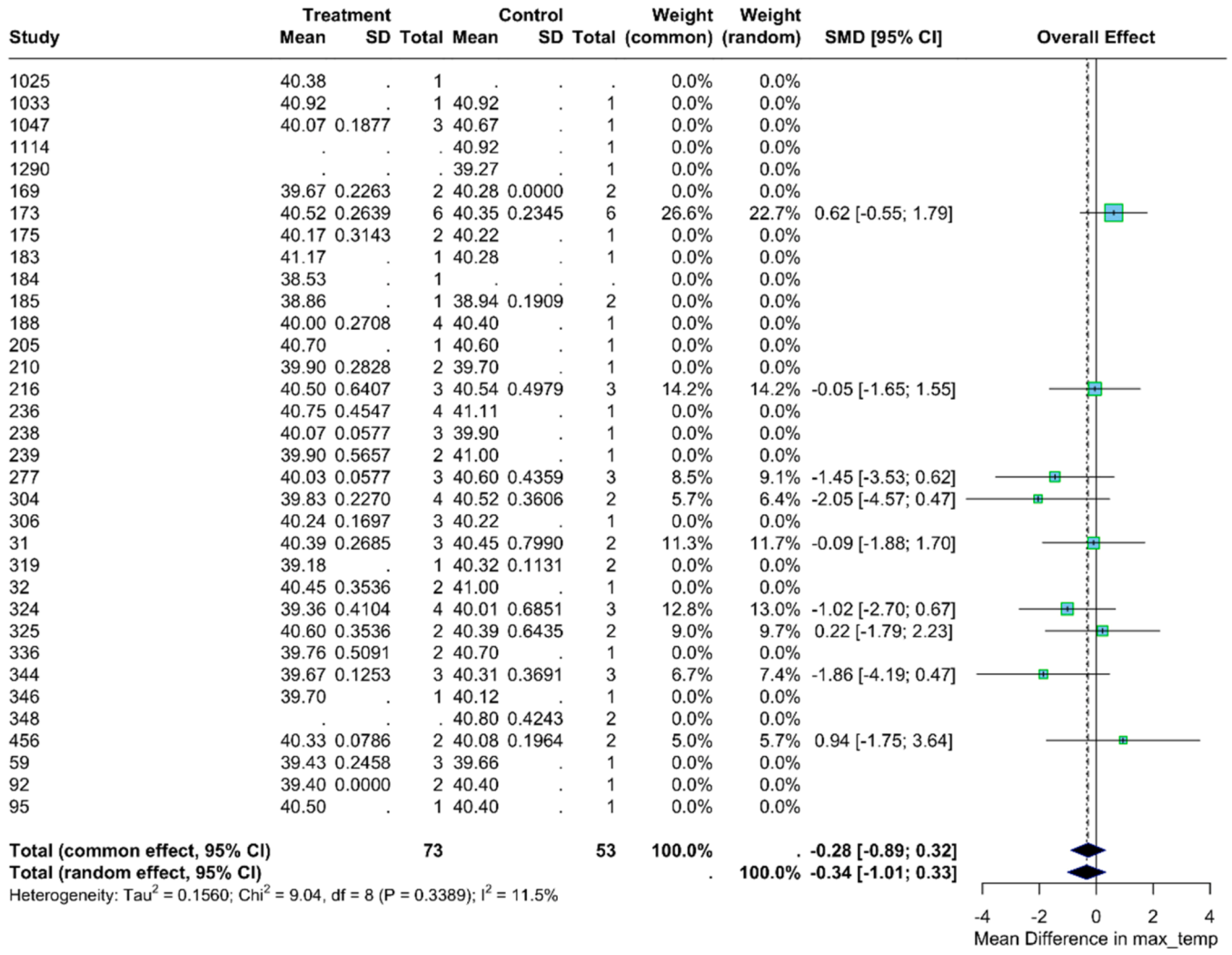

Fig. 5. Forest plot showing the standardized mean difference (SMD) with Hedges' g correction in sample size for difference maximum body temperature between vaccinated and control groups across studies. Each horizontal line represents the 95% confidence interval (CI) for the mean difference within a study, with squares indicating the study-specific SMD and square sizes proportional to study weight. The diamond at the bottom represents the overall pooled effect from the random-effects model.

indicates that body temperature alone may not be a reliable proxy for clinical signs. The variability in body temperature responses may be partly attributed to stress induced during temperature measurement, particularly when using restraint-dependent methods such as rectal thermometry (Zhang et al., 2019). However, emerging technologies such as subcutaneous implants and infrared thermography offer non-invasive alternatives that minimize handling stress (Bowman et al., 2016; Süli et al., 2017). These methods may allow more accurate detection of temperature changes associated with infection.

Clinical signs were reported inconsistently across studies. While some authors reported them using clinical scores, the scoring systems varied widely, resulting in substantial heterogeneity and making direct comparisons difficult. To enable data aggregation and analysis, clinical signs were therefore categorized as a binary outcome (presence or absence). Due to missing data, the meta-analysis included nine studies for body temperature and eight studies for clinical signs.

To ensure comprehensive literature coverage, this review was conducted in accordance with PRISMA guidelines and builds on the recommendation of Keay et al. (2020), who advocated for using systematic reviews to assess protection against swIAV in vaccinated weaned pigs following challenge. The papers included in this review were selected based on author's language proficiency and resource constraints, which may have led to the exclusion of relevant studies.

To assess VE, we evaluated viral transmission, viral shedding, and clinical signs based on experimental challenge studies, because of their availability and the consistency of outcome measures. However, VE estimated under controlled laboratory conditions may not fully reflect VE in field settings. This discrepancy may be attributed to several factors. First, in experimental challenge studies, the virus is administrated directly via the respiratory route, whereas under field conditions, transmission typically occurs through direct nose-to-nose contact, indirect contact via contaminated fomites (e.g., transport vehicles, equipment) and/or short-distance airborne transmission via aerosolized droplets (Allerson et al., 2013; Ma et al., 2023; Torremorell et al., 2012). Second, experimental studies differ from field conditions in several risk factors, including environmental stressors, population size, management strategies, age, and genetics. Moreover, co-infections – common in the field – are typically excluded in experimental settings. Third, swIAV is considered endemic in European pig populations (Mancera Gracia et al., 2020; Richard et al., 2025), so populations are rarely naive. However, studies involving pigs with prior swIAV exposure were excluded in this systematic review to make data comparable. Fourth, while recent European commercial vaccines are used in sows to prevent miscarriage and provide MDA protection to piglets, most challenge studies focus on evaluating vaccine efficacy in piglets. The median age of the first vaccination in pigs in the included studies was approximately 28

days. Although this aligns with European Pharmacopoeia guidelines (European Pharmacopoeia 8 0 8 0 2017) - which call for testing in each minimum age category - piglet immunity is influenced by MDAs. We did not assess the impact of MDAs, as this has been comprehensively addressed by Keay et al., (2023). Moreover, only four studies have investigated the effect of vaccination in the presence of Maternally derived antibodies (MDA) (Bosworth et al., 2010; Kitikoon et al., 2013, 2006; Wesley and Lager, 2006), which is insufficient to fully understand the impact of MDA on vaccination.

Although the funnel plots did not suggest major distortions in the available evidence, the assessment of publication bias remains constrained by the limited number of studies for some outcomes. Consequently, while this meta-analysis provides a structured synthesis of existing data, several assumptions and standardizations were necessary in this study. Thus, the findings should be interpreted with caution, particularly when applying them to field conditions.

In this study, an artificial intelligence-based tool, ASReview, was used to perform a semi-automated search for relevant papers and to minimize the risk of missing relevant studies. ASReview identified four relevant articles that were missed during conventional screening, demonstrating its potential to enhance literature selection at title and abstract level. While ASReview offers a time-efficient alternative to conventional methods, its performance still relies on the expertise of human reviewers. The overall efficacy of ASReview can be improved by applying the SAFE procedure (Boetje and van de Schoot, 2024), which advice stopping the screening after encountering 50 consecutive irrelevant records. Following this rule, we conducted screening after reviewing 1277 of 2039 records. We recommend the use of artificial intelligence assisted tools in future systematic reviews to improve efficiency, whether by reducing time or improving accuracy of article selection.

Another recommendation from this review is the need to address substantial heterogeneity in experimental design and outcome reporting across studies. This includes variations in sample types, measurement units for RT-PCR, and inconsistent methods for recording and evaluating clinical signs. Due to this heterogeneity, we were unable to assess the impact of vaccination against swIAV in pigs on immune responses. Heterogeneity across studies was substantial ($I^2 \approx 70–77\%$) highlighting the limited comparability of the studies included. While we recognize that study protocols are often tailored to specific research questions, we encourage researchers to adopt standardized experimental methods whenever possible. Implementing standardized protocols, like those outlined in the European Pharmacopoeia (European Pharmacopoeia 8 0 8 0 2017), could improve the consistency of study results. In addition, following reporting guidelines like ARRIVE (Animal Research: Reporting of In Vivo Experiments) (Sert et al., 2020) or REFLECT (O'Connor et al., 2010) would improve the quality and transparency in reporting the results of animal experiments. For instance, several studies failed to specify whether the challenge was homologous or heterologous, or details about the vaccine strain were missing. For greater transparency, reporting NCBI or GISAID accession numbers of virus strain would be highly beneficial. Transparency and complete data reporting enable the reuse of scientific data in accordance with the FAIR data principles (Wilkinson et al., 2016).

Together, this systematic review and meta-analysis assessed the efficacy of commercial and experimental vaccines against swIAV in pigs. Vaccination significantly reduced viral transmission parameters and viral shedding. However, most vaccines did not provide full protection against swIAV infection in challenge experiment settings. The development of improved vaccines would enhance the control of swIAV in pig populations.

CRediT authorship contribution statement

Arjan Stegeman: Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Andrea Apolloni:** Writing – review & editing, Visualization, Validation, Supervision. **Claire Hautefeuille:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Gavrila Amadea Puspitarani:** Writing – review & editing, Visualization, Software, Formal analysis. **Bastien Bayle:** Data curation. **Uyen H.P. Nguyen:** Writing – review & editing, Software, Formal analysis. **Marina Meester:** Writing – review & editing, Visualization, Validation, Supervision. **Oumaima Mtaallah:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Evelien A. Germeraad:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2026.106877.

References

Allerson, M.W., Cardona, C.J., Torremorell, M., 2013. Indirect Transmission of Influenza A Virus between Pig Populations under Two Different Biosecurity Settings. PLOS ONE 8, e67293. https://doi.org/10.1371/journal.pone.0067293.

Auguie, B., Antonov, A., 2017. gridExtra: Miscellaneous Functions for "Grid" Graphics.

Balduzzi, S., Rücker, G., Schwarzer, G., 2019. How to perform a meta-analysis with R: a practical tutorial. BMJ Ment. Health 22. https://doi.org/10.1136/ebmental-2019-300117.

Boetje, J., van de Schoot, R., 2024. The SAFE procedure: a practical stopping heuristic for active learning-based screening in systematic reviews and meta-analyses. Syst. Rev. 13, 81. https://doi.org/10.1186/s13643-024-02502-7.

Borenstein, M. (Ed.), 2009. Introduction to meta-analysis. John Wiley & Sons, Chichester, U.K.

Bosworth, B., Erdman, M.M., Stine, D.L., Harris, I., Irwin, C., Jens, M., Loynachan, A., Kamrud, K., Harris, D.L., 2010. Replicon particle vaccine protects swine against influenza. Comp. Immunol. Microbiol Infect. Dis. 33, e99–e103. https://doi.org/10.1016/j.cimid.2010.05.002.

Bowman, A.S., Nolting, J.M., Workman, J.D., Cooper, M., Fisher, A.E., Marsh, B., Forshey, T., 2016. The Inability to Screen Exhibition Swine for Influenza A Virus Using Body Temperature. Zoonoses Public Health 63, 34–39. https://doi.org/10.1111/zph.12201.

Brooks, M., Kristensen, K., van, Benthem, K., Magnusson, A., Berg, C., Nielsen, A., Skaug, H., Mächler, M., Bolker, B., 2017. glmmTMB balances speed and flexibility among packages for zero-inflated generalized linear mixed modeling. R. J. 9, 378–400. https://doi.org/10.32614/RJ-2017-066.

Calderón Díaz, J.A., Fitzgerald, R.M., Shalloo, L., Rodrigues da Costa, M., Niemi, J., Leonard, F.C., Kyriazakis, I., García Manzanilla, E., 2020. Financial Analysis of Herd Status and Vaccination Practices for Porcine Reproductive and Respiratory Syndrome Virus, Swine Influenza Virus, and Mycoplasma hyopneumoniae in Farrow-to-Finish Pig Farms Using a Bio-Economic Simulation Model. Front. Vet. Sci. 7. https://doi.org/10.3389/fvets.2020.556674.

Cuijpers, P., Weitz, E., Cristea, I.A., Twisk, J., 2017. Pre-post effect sizes should be avoided in meta-analyses. Epidemiol. Psychiatr. Sci. 26, 364–368. https://doi.org/10.1017/S2045796016000809.

Czyżewska-Dors, E., Pomorska-Mól, M., Dors, A., Pluta, A., Podgórska, K., Kwit, K., Stasiak, E., Łukomska, A., 2019. Proinflammatory Cytokine Changes in Bronchoalveolar Lavage Fluid Cells Isolated from Pigs Infected Solely with Porcine Reproductive and Respiratory Syndrome Virus or Co-infected with Swine Influenza Virus. J. Vet. Res 63, 489–495. https://doi.org/10.2478/jvetres-2019-0063.

De Vleeschauwer, A., Qiu, Y., Van Reeth, K., 2015. Vaccination-challenge studies with a Port Chalmers/73 (H3N2)-based swine influenza virus vaccine: Reflections on vaccine strain updates and on the vaccine potency test. Vaccine 33, 2360–2366. https://doi.org/10.1016/j.vaccine.2015.03.031.

Diekmann, O., Heesterbeek, H., Britton, T., 2012. Mathematical Tools for Understanding Infectious Disease Dynamics. Princeton University Press. https://doi.org/10.23943/princeton/9780691155395.001.0001.

Ding, P., Jin, Q., Zhou, W., Chai, Y., Liu, X., Wang, Y., Chen, X., Guo, J., Deng, R., Gao, G. F., Zhang, G., 2019. A universal influenza nanovaccine for "Mixing Vessel" hosts confers potential ability to block cross-species transmission. Adv. Healthc. Mater. 8, 1900456. https://doi.org/10.1002/adhm.201900456.

European Centre for Disease Prevention and Control, 2023. Factsheet on swine influenza in humans and pigs [WWW Document]. URL ⟨https://www.ecdc.europa.eu/en/swine-influenza/factsheet⟩ (accessed 3.4.25).

European Pharmacopoeia 8 0, 2017.

Friedrich, J.O., Adhikari, N.K., Beyene, J., 2008. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: A simulation study. BMC Med. Res. Methodol. 8, 32. https://doi.org/10.1186/1471-2288-8-32.

Ghattas, M., Dwivedi, G., Lavertu, M., Alameh, M.-G., 2021. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccin. (Basel) 9, 1490. https://doi.org/10.3390/vaccines9121490.

Gonzales, J.L., Elbers, A.R.W., Bouma, A., Koch, G., de Wit, J.J., Stegeman, J.A., 2012. Transmission characteristics of low pathogenic avian influenza virus of H7N7 and H5N7 subtypes in layer chickens. Vet. Microbiol 155, 207–213. https://doi.org/10.1016/j.vetmic.2011.09.016.

Graaf, A., Petric, P.P., Sehl-Ewert, J., Henritzi, D., Breithaupt, A., King, J., Pohlmann, A., Deutskens, F., Beer, M., Schwemmle, M., Harder, T., 2022. Cold-passaged isolates and bat-swine influenza a chimeric viruses as modified live-attenuated vaccines against influenza a viruses in pigs. Vaccine 40, 6255–6270. https://doi.org/10.1016/j.vaccine.2022.09.013.

Gumbert, S., Froehlich, S., Rieger, A., Stadler, J., Ritzmann, M., Zoels, S., 2020. Reproductive performance of pandemic influenza A virus infected sow herds before and after implementation of a vaccine against the influenza A (H1N1)pdm09 virus. Porc. Health Manag. 6, 4. https://doi.org/10.1186/s40813-019-0141-x.

Halloran, M.E., Longini, I.M., Struchiner, C.J., 1999. Design and interpretation of vaccine field studies. Epidemiol. Rev. 21, 73–88. https://doi.org/10.1093/oxfordjournals.epirev.a017990.

Harrer, M., Cuijpers, P., Furukawa, T.A., Ebert, D.D., 2021. Doing Meta-Analysis with R: A Hands-On Guide, Boca Raton, FL and London: Chapmann & Hall/CRC Press.

Hierholzer, J.C., Killington, R.A., 1996. Virus isolation and quantitation. In: Mahy, B.W., Kangro, H.O. (Eds.), Virology Methods Manual. Academic Press, London, pp. 25–46. https://doi.org/10.1016/B978-012465330-6/50003-8.

Hooijmans, C.R., Rovers, M.M., De Vries, R.B., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. BMC Med Res. Method. 14, 43. https://doi.org/10.1186/1471-2288-14-43.

JGraph, 2021. draw.io.

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.

Keay, S., Poljak, Z., Alberts, F., O'Connor, A., Friendship, R., O'Sullivan, T.L., Sargeant, J. M., 2023. Does Vaccine-Induced Maternally-Derived Immunity Protect Swine Offspring against Influenza a Viruses? A Systematic Review and Meta-Analysis of Challenge Trials from 1990 to May 2021. Animals 13, 3085. https://doi.org/10.3390/ani13193085.

Kitikoon, P., Nilubol, D., Erickson, B.J., Janke, B.H., Hoover, T.C., Sornsen, S.A., Thacker, E.L., 2006. The immune response and maternal antibody interference to a heterologous H1N1 swine influenza virus infection following vaccination. Vet. Immunol. Immunopathol. 112, 117–128. https://doi.org/10.1016/j.vetimm.2006.02.008.

Kitikoon, P., Gauger, P.C., Anderson, T.K., Culhane, M.R., Swenson, S., Loving, C.L., Perez, D.R., Vincent, A.L., 2013. Swine influenza virus vaccine serologic cross-reactivity to contemporary US swine H3N2 and efficacy in pigs infected with an H3N2 similar to 2011–2012 H3N2v. Influenza Other Respir. Virus 7, 32–41. https://doi.org/10.1111/irv.12189.

Klingbeil, K., Lange, E., Blohm, U., Teifke, J.P., Mettenleiter, T.C., Fuchs, W., 2015. Protection of pigs against pandemic swine origin H1N1 influenza A virus infection by hemagglutinin- or neuraminidase-expressing attenuated pseudorabies virus recombinants. Virus Res. 199, 20–30. https://doi.org/10.1016/j.virusres.2015.01.009.

Klivleyeva, N., Saktaganov, N., Glebova, T., Lukmanova, G., Ongarbayeva, N., Webby, R., 2024. Influenza A viruses in the swine population: ecology and geographical distribution. Viruses 16, 1728. https://doi.org/10.3390/v16111728.

Kohl, C., McIntosh, E.J., Unger, S., Haddaway, N.R., Kecke, S., Schiemann, J., Wilhelm, R., 2018. Online tools supporting the conduct and reporting of systematic reviews and systematic maps: a case study on CADIMA and review of existing tools. Environ. Evid. 7, 8. https://doi.org/10.1186/s13750-018-0115-5.

Kumari, S., 2022. Evaluation of Protective Efficacy of Viral Vector Based Swine Influenza Vaccine and a Method for B Cell Culture for Monoclonal Antibody Generation. University of Nebraska-Lincoln.

Li, C., Culhane, M.R., Cheeran, M., Galina Pantoja, L., Jansen, M.L., Amodie, D., Mellencamp, M.A., Torremorell, M., 2020. Exploring heterologous prime-boost vaccination approaches to enhance influenza control in pigs. Vet. Res. 51, 89. https://doi.org/10.1186/s13567-020-00810-z.

Loving, C.L., Lager, K.M., Vincent, A.L., Brockmeier, S.L., Gauger, P.C., Anderson, T.K., Kitikoon, P., Perez, D.R., Kehrli, M.E., 2013. Efficacy in Pigs of Inactivated and Live Attenuated Influenza Virus Vaccines against Infection and Transmission of an Emerging H3N2 Similar to the 2011-2012 H3N2v. J. Virol. 87, 9895–9903. https://doi.org/10.1128/JVI.01038-13.

Ma, W., 2020. Swine influenza virus: Current status and challenge. Virus Res. 288, 198118. https://doi.org/10.1016/j.virusres.2020.198118.

Ma, W., Liu, Q., Qiao, C., del Real, G., García-Sastre, A., Webby, R.J., Richt, J.A., 2014. North American Triple Reassortant and Eurasian H1N1 Swine Influenza Viruses Do Not Readily Reassort to Generate a 2009 Pandemic H1N1-Like Virus, 10.1128/mbio.00919-13 mBio 5. https://doi.org/10.1128/mbio.00919-13.

Ma, W., Loving, C.L., Driver, J.P., 2023. From Snoot to Tail: A Brief Review of Influenza Virus Infection and Immunity in Pigs. J. Immunol. 211, 1187–1194. https://doi.org/10.4049/jimmunol.2300385.

Mancera Gracia, J.C., Pearce, D.S., Masic, A., Balasch, M., 2020. Influenza A Virus in Swine: Epidemiology, Challenges and Vaccination Strategies. Front. Vet. Sci. 7. https://doi.org/10.3389/fvets.2020.00647.

McGillycuddy, M., Popovic, G., Bolker, B., Warton, D., 2024. Parsimoniously Fitting Large Multivariate Random Effects in glmmTMB. https://doi.org/10.48550/arXiv.2411.04411.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group, 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med. 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097.

O'Connor, A.M., Sargeant, J.M., Gardner, I.A., Dickson, J.S., Torrence, M.E., Participants, C.M., Dewey, C.E., Dohoo, I.R., Evans, R.B., Gray, J.T., Greiner, M., Keefe, G., Lefebvre, S.L., Morley, P.S., Ramirez, A., Sischo, W., Smith, D.R., Snedeker, K., Sofos, J., Ward, M.P., Wills, R., 2010. The REFLECT Statement: Methods and Processes of Creating Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety by Modifying the CONSORT Statement. Zoonoses Public Health 57, 95–104. https://doi.org/10.1111/j.1863-2378.2009.01311.x.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLOS Med. 18, e1003583. https://doi.org/10.1371/journal.pmed.1003583.

Pedersen, T.L., 2025. patchwork: The Composer of Plots.

Qiu Y., 2015. Cross-protection studies with swine influenza viruses in pigs and public health aspects (PhD thesis).

R Core Team, 2024. R: A Language and Environment for Statistical Computing.

RStudio Team, 2024. RStudio: Integrated Development Environment for R. Posit Software. PBC, Boston, MA.

Reed, L.J., Muench, H., 1938. Simple method of estimating fifty per cent endpoints. Am. J. Epidemiol. 27, 493–497. https://doi.org/10.1093/oxfordjournals.aje.a118408.

Richard, G., Ryt-Hansen, P., Byrne, A., Network, E.S.I., 2025. European Swine Influenza Network Report #2 on Swine Influenza A Viruses Evolution and Diversity in Europe from October 2022 to September 2024. Zenodo.

Rose, N., Hervé, 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, 72. https://doi.org/10.1186/1297-9716-44-72.

Saade, G., Deblanc, C., Bougon, J., Marois-Créhan, C., Fablet, C., Auray, G., Belloc, C., Leblanc-Maridor, M., Gagnon, C.A., Zhu, J., Gottschalk, M., Summerfield, A., Simon, G., Bertho, N., Meurens, F., 2020. Coinfections and their molecular consequences in the porcine respiratory tract. Vet. Res. 51, 80. https://doi.org/10.1186/s13567-020-00807-8.

Salvesen, H.A., Whitelaw, C.B.A., 2021. Current and prospective control strategies of influenza A virus in swine. Porc. Health Manag. 7, 23. https://doi.org/10.1186/s40813-021-00196-0.

Sert, N.P. du, Hurst, V., Ahluwalia, A., Alam, S., Avey, M.T., Baker, M., Browne, W.J., Clark, A., Cuthill, I.C., Dirnagl, U., Emerson, M., Garner, P., Holgate, S.T., Howells, D.W., Karp, N.A., Lazic, S.E., Lidster, K., MacCallum, C.J., Macleod, M., Pearl, E.J., Petersen, O.H., Rawle, F., Reynolds, P., Rooney, K., Sena, E.S., Silberberg, S.D., Steckler, T., Würbel, H., 2020. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLOS Biol. 18, e3000410. https://doi.org/10.1371/journal.pbio.3000410.

Sharma, A., Zeller, M.A., Li, G., Harmon, K.M., Zhang, J., Hoang, H., Anderson, T.K., Vincent, A.L., Gauger, P.C., 2020. Detection of live attenuated influenza vaccine

virus and evidence of reassortment in the U.S. swine population. J. VET Diagn. Invest 32, 301–311. https://doi.org/10.1177/1040638720907918.
Sitaras, I., Rousou, X., Peeters, B., de Jong, M.C.M., 2016. Mutations in the haemagglutinin protein and their effect in transmission of highly pathogenic avian influenza (HPAI) H5N1 virus in sub-optimally vaccinated chickens. Vaccine 34, 5512–5518. https://doi.org/10.1016/j.vaccine.2016.10.002.
Stegeman, A., de Jong, M.C., van Nes, A., Bouma, A., 1997. Dynamics of pseudorabies virus infections in vaccinated pig populations: a review. Vet. Q 19, 117–122. https://doi.org/10.1080/01652176.1997.9694754.
Süli, T., Halas, M., Benyeda, Z., Boda, R., Belák, S., Martínez-Avilés, M., Fernández-Carrión, E., Sánchez-Vizcaíno, J.M., 2017. Body temperature and motion: Evaluation of an online monitoring system in pigs challenged with Porcine Reproductive & Respiratory Syndrome Virus. Res. Vet. Sci. 114, 482–488. https://doi.org/10.1016/j.rvsc.2017.09.021.
Torremorell, M., Allerson, M., Corzo, C., Diaz, A., Gramer, M., 2012. Transmission of Influenza A Virus in Pigs. Transbound. Emerg. Dis. 59, 68–84. https://doi.org/10.1111/j.1865-1682.2011.01300.x.
Van Nes, A., De Jong, M.C.M., Buijtels, J.A.A.M., Verheijden, J.H.M., 1998. Implications derived from a mathematical model for eradication of pseudorabies virus. Prev. Vet. Med. 33, 39–58. https://doi.org/10.1016/S0167-5877(97)00058-5.
Vincent, A., Awada, L., Brown, I., Chen, H., Claes, F., Dauphin, G., Donis, R., Culhane, M., Hamilton, K., Lewis, N., Mumford, E., Nguyen, T., Parchariyanon, S., Pasick, J., Pavade, G., Pereda, A., Peiris, M., Saito, T., Swenson, S., Van Reeth, K., Webby, R., Wong, F., Ciacci-Zanella, J., 2014. Review of influenza A virus in swine worldwide: a call for increased surveillance and research. Zoonoses Public Health 61, 4–17. https://doi.org/10.1111/zph.12049.
Weinberg, G.A., Szilagyi, P.G., 2010. Vaccine Epidemiology: Efficacy, Effectiveness, and the Translational Research Roadmap. J. INFECT DIS 201, 1607–1610. https://doi.org/10.1086/652404.
Wesley, R.D., Lager, K.M., 2006. Overcoming maternal antibody interference by vaccination with human adenovirus 5 recombinant viruses expressing the hemagglutinin and the nucleoprotein of swine influenza virus. Vet. Microbiol 118, 67–75. https://doi.org/10.1016/j.vetmic.2006.07.014.
Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L.D., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T.L., Miller, E., Bache, S.M., Müller, K., Ooms, J., Robinson, D., Seidel, D.P., Spinu, V., Takahashi, K., Vaughan, D., Wilke, C., Woo, K., Yutani, H., 2019. Welcome to the Tidyverse. J. Open Source Softw. 4, 1686. https://doi.org/10.21105/joss.01686.
Wickham, Hadley, 2016. ggplot2: Elegant Graphics for Data Analysis (3e). Springer-Verlag New York.
Wilkinson, M.D., Dumontier, M., Aalbersberg, Ij.J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.-W., da Silva Santos, L.B., Bourne, P.E., Bouwman, J., Brookes, A.J., Clark, T., Crosas, M., Dillo, I., Dumon, O., Edmunds, S., Evelo, C.T., Finkers, R., Gonzalez-Beltran, A., Gray, A.J.G., Groth, P., Goble, C., Grethe, J.S., Heringa, J., 't Hoen, P.A.C., Hooft, R., Kuhn, T., Kok, R., Kok, J., Lusher, S.J., Martone, M.E., Mons, A., Packer, A.L., Persson, B., Rocca-Serra, P., Roos, M., van Schaik, R., Sansone, S.-A., Schultes, E., Sengstag, T., Slater, T., Strawn, G., Swertz, M. A., Thompson, M., van der Lei, J., van Mulligen, E., Velterop, J., Waagmeester, A., Wittenburg, P., Wolstencroft, K., Zhao, J., Mons, B., 2016. The FAIR Guiding Principles for scientific data management and stewardship. Sci. Data 3 160018. https://doi.org/10.1038/sdata.2016.18.
WOAH, 2009. Swine influenza.
Zhang, Z., Zhang, H., Liu, T., 2019. Study on body temperature detection of pig based on infrared technology: A review. Artif. Intell. Agric. 1, 14–26. https://doi.org/10.1016/j.aiia.2019.02.002.