Annex to:

EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare), Nielsen SS, Alvarez J, Bicout DJ, Calistri P, Canali E, Drewe JA, Garin-Bastuji B, Gonzales Rojas JL, Gortázar Schmidt C, Herskin M, Michel V, Miranda Chueca MA, Padalino B, Pasquali P, Stahl K, Velarde Calvo A, Viltrop A, Winckler C, De Clercq K, Sjunnesson Y, Gervelmeyer A and Roberts HC, 2022. Assessment of the control measures of the category A diseases of the Animal Health Law: Prohibitions in restricted zones and risk-mitigating treatments for products of animal origin and other materials. EFSA Journal 2022;20(8):7443, doi: 10.2903/j.efsa.2022.7443

Annex A – Extensive literature search on the presence of selected Category A disease pathogens in germinal products

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1 Context

The EFSA has been requested to provide scientific opinions to support the European Commission (EC) in the production of amending and implementing acts related to Regulation 2016/429 (the 'Animal Health Law' (AHL)) which lays down rules for the prevention and control of diseases included in the list of Category A diseases. The Commission has developed and adopted a Delegated Regulation ("the Delegated Regulation") supplementing the rules laid down in AHL. Certain disease control measures proposed in the Annexes of the Delegated Regulation are considered as outdated and need to be updated by reviewing the current scientific literature.

As part of this, and in order to answer ToR 4.1 to assess the effectiveness of the control measures related to oocytes and embryos set out in Annex VI to the Delegated Regulation, the EFSA has asked P95 to carry out an extensive literature search (ELS).

2 Review question

As described in the final protocol (**Appendix 1**), the aim of the ELS was to answer the question whether *in vivo*/*vitro* embryos or oocytes (i.e., "matrices") collected from affected animals of listed species in affected establishments pose a risk to transmit the following diseases:

- Foot and Mouth Disease (FMD)
- Infection with Rinderpest virus (RP)
- Infection with Rift Valley Fever virus (RVF)
- Infection with Lumpy Skin Disease virus (LSD)
- Infection with Mycoplasma mycoides subsp. mycoides (Contagious Bovine Pleuropneumonia) (CBPP)
- Sheep Pox and Goat Pox (SPGP)
- Infection with Peste des Petits Ruminants virus (PPR)
- Contagious Caprine Pleuropneumonia (CCPP)
- Classical Swine Fever (CSF)
- African Swine Fever (ASF)
- African Horse Sickness (AHS)

The diseases and matrices covered by this ELS were the following:

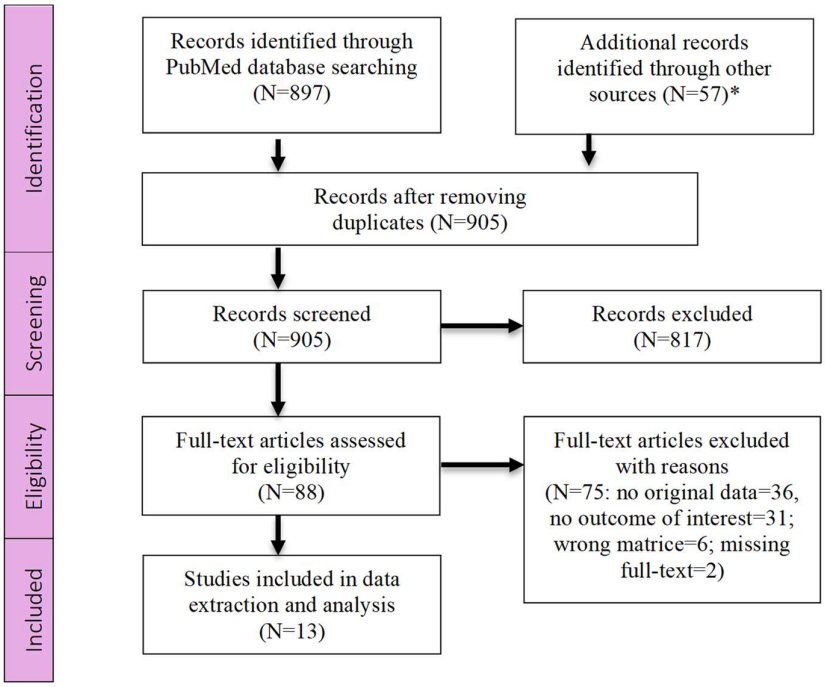
Matrix	FMD	RP	RVF	LSD	CBPP	SPGP	PPR	CCPP	CSF	ASF	AHS
in vivo produced embryo											
in vitro produced embryo											
oocyte											

Shaded cells represent the disease/matrix combination to be included in the ELS

3 Results

Screening and selection of references

We carried out the PubMed search on 27 January 2022. Adding records retrieved through reference list checking and hand searching via Google Scholar, a total of 905 unique references were identified. From these references, 13 were finally selected for data extraction. The full selection process is displayed in **Figure 1**.



* Records identified through reference list checking and hand searching in Google Scholar

Figure 1. Prisma diagram for the extensive literature search

Overview extracted data

Table 1 provides an overview of the 13 references from which data has been extracted.

Table 1. Overview of extracted references by disease

Disease	#Hits	References
FMD	6	(McVicar et al. 1986; Mebus 1987; Mebus and Singh 1991; Caamano et al. 1993; Thibier and Guérin 2000; Jooste 2005)
RP	2	(Mebus 1987; Bielanski 2014)
RVF	0	
LSD	1	(Annandale et al. 2019)
CBPP	2	(Sylla et al. 2005; Wrathall, Ayling, and Simmons 2007)
SPGP	0	
PPR	0	
CCPP	2	(Thibier 1990; Wrathall, Ayling, and Simmons 2007)
CSF	0	
ASF	0	
AHS	2	(Aznar, McAteer, and Gaynor 2011; Sabirovic, López, and Patel 2008)

4 Disease-specific data extracted

Foot-and-mouth disease

We identified six studies in relation to the association between FMD virus (FMDV) and oocytes (McVicar et al. 1986; Mebus 1987; Mebus and Singh 1991; Caamano et al. 1993; Thibier and Guérin 2000; Jooste 2005).

McVicar et al. (McVicar et al. 1986) failed to detect FMDV (type O subtype 1 strain Brugge) from 48 washed zona pellucida-intact (ZPI) bovine embryos collected 4-5 days post-inoculation (DPI) ('acute study') from donor cattle inoculated intranasally with approximately 10^7 pfu of virus. On the other hand, substantial amounts of infectivity were observed in the ovarian tissue (range: $10^{<2.2}$ to $10^{7.1}$pfu/g) and the follicular fluid (range: $10^{1.2}$ to $10^{4.4}$ pfu/ml) of FMDV viraemic cows, thereby suggesting that the virus might multiply in ovarian tissue. In order to determine if the high amounts of viral infectivity in the ovaries might lead to persistence of FMDV until the next oestrus, two additional experiments were performed. The first experiment found no viral infectivity in ovarian tissues collected from two heifers killed at 2, 4 and 6 weeks post FMDV inoculation. The second experiment also failed to detect FMDV from 42 ZP embryos or wash solutions collected 21 DPI ('convalescent study') from donors that had been inoculated 14 days before artificial insemination. In addition, none of the 28 examined ovaries originating from the recovered cows were positive, suggesting that FMDV does not persist in the ovaries of infected cows.

Mebus et al. (Mebus 1987) described two experiments involving porcine embryos. In the first experiment, 62 embryos and 8 ova were exposed *in vitro* to FMDV. The virus was recovered only from 2 embryos. In the second experiment, no FMDV was detected among 267 embryos collected from 14 viremic donors. The authors concluded that the recovery of FMDV from the in *vitro* exposed embryos was likely to be due to the exposure of the embryos to high titer FMDV.

Mebus et al. (Mebus and Singh 1991) observed that no FMDV (type A subtype 5) was recovered from the 436 washed embryos/unfertilized ova collected from 30 cattle that had been inoculated

intravenously with 10^6 pfu/ml FMDV. Mebus et al (1987) reported the collection of 260 bovine embryos from FMD viremic donors. Presence of infectious virus was assessed using 143 of those embryos and no virus was recovered. Of the remaining embryos, 125 were transferred into 95 seronegative recipients. No infections were observed in the recipient caws.

Similarly, Caamano et al. (Caamano et al. 1993) found no viral infectivity in 94 ZPI bovine embryos/unfertilized ova that had been exposed during 16h to high titres of FMDV ($10^{7.5}$ TCID 50/ml) and subsequently washed according to IETS standards. FMDV was only isolated in the first fluid of the embryo washes. Moreover, exposure to FMDV had no effect on the ulterior embryonic development.

Thibier and Guérin (Thibier and Guérin 2000) reported unpublished results from Argentina (personal communication, 1991) indicating that no virus was recovered from 75 washed embryos collected from 31 ewes naturally infected by FMDV (type O1). Thibier and Guérin reported also similar results from Singh and Mebus (1991), detecting no virus in 185 washed embryos collected from 19 FMDV (type A5) infected ewes.

Lastly, Jooste (Jooste 2005) carried out an experiment which showed that bovine oocytes exposed to FMDV during *in vitro* maturation (to mimic a situation where oocytes would be collected from a viremic cow with contaminated follicular fluid) can retain FMDV even after washing according to International Embryo Technology Society (IETS) standards.

Based on several of the results of several of the studies abovementioned, Asseged et al. (Asseged et al., 2012) estimated the probability that cumulus oocyte complexes could be contaminated in the reproductive tract of females (persistently) infected with FMDV to range from 0 to 0.27, and the probability that *in vitro* cultured, denuded, washed, and treated oocytes would carry FMDV from 0 to 0.05.

In Chapter 4.9 of the Terrestrial Animal Health Code (OIE 2021) (last updated in 2018), it is mentioned that donor animals of oocytes should not originate from herds or flocks that are subject to veterinary restrictions for FMD, and neither should the removal of any tissue or aspiration of oocytes take place in an infected zone, or one that is subject to veterinary restrictions for FMD.

Rinderpest

Two studies were retrieved pertaining to the risk of RP virus (RPV) transmission related to oocytes (Mebus 1987; Bielanski 2014).

Mebus et al. (Mebus 1987) described that no RPV was recovered from 107 bovine eggs/embryos that had been collected from ten RP viremic donors and assayed in cell culture and in steers. No RPV was recovered in culture and the test animals remained seronegative.

Bielanski (Bielanski 2014) based on data from Stringfellow and Seidel (Stringfellow and Seidel 1998), reported a positive risk of RPV transmission related to washed *Bos Taurus* embryos, but a negative risk in relation to the presence of RPV in the ovary, oviduct or uterus.

There is no mention of this specific disease/matrix combination in the OIE Terrestrial Animal Health Code.

Rift valley fever

No study was available from the literature with reference to the risk related to RVF virus (RVFV) transmission via the three matrices of interest.

In Article 8.15.10. of the Terrestrial Animal Health Code (OIE 2021) (last updated in 2016), the OIE recommends for the importation of *in vivo* derived embryos of ruminants from countries or zones not free from RVF that Veterinary Authorities should require the presentation of an international veterinary certificate attesting that the donor animals showed no sign of RVF within the period from 14 days prior to and 14 days following collection of the semen or embryos; and either were vaccinated against RVF at least 14 days prior to collection; or were demonstrated to be seropositive on the day of collection; or

testing of paired samples has demonstrated that seroconversion did not occur between semen or embryo collection and 14 days after.

Lumpy skin disease

We identified a single study in relation to the association between LSD virus (LSDV) and oocytes (Annandale et al. 2019).

Annandale et al. (Annandale et al. 2019) examined the presence of LSDV in unfertilized oocytes which had been exposed to frozen-thawed semen spiked with a higher (4 log TCID50) dose ('HD group') and a lower (10^3 dilution) dose ('LD group') of LSDV (Mireil isolate (Neethling strain) (V103/91). While no sign of LSDV was found in any of the samples of the LD group, viable LSDV and viral DNA was found in some unfertilized oocytes belonging to the HD group (exact proportion not reported).

There is no mention of this specific disease/matrix combination in the OIE Terrestrial Animal Health Code.

Contagious bovine pleuropneumonia

We retrieved two studies in relation to the risk of transmission of *Mycoplasma mycoides ssp. mycoides* via embryos or oocytes (Sylla et al. 2005; Wrathall, Ayling, and Simmons 2007).

Sylla et al. (Sylla et al. 2005) observed that day-7 contaminated bovine *in vitro* embryos showed *Mycoplasma mycoides ssp. Mycoides* large-colony (LC) particles adhering and infiltrating the outer layer of the ZP.

Wrathall, Ayling, and Simmons (Wrathall, Ayling, and Simmons 2007) described unpublished work from Kate Brown and Robin Nicholas (1993) involving *in vitro*-produced bovine embryos that had been cultured with *Mycoplasma mycoides subsp. mycoides* small-colony (SC) for 16 h seven days after fertilization, and subsequently washed. The results of the assays showed that *Mycoplasma mycoides subsp. mycoides* SC could not be detected by culture from embryos that had been washed more than four times. However, the authors pinpoint that these results are not in line with other studies involving different types of mycoplasmas that generally indicate that if the oocytes, semen, media or the cells used for co-culture in the embryo production system are contaminated with mycoplasmas, then it is likely that the *in vitro* embryos that are produced will be also infected.

In addition, Wrathall, Ayling, and Simmons summarized their review on the risk of transmitting mycoplasmas by semen or embryo transfer, by stating that if mycoplasmas are present in the genital tracts of donors, there is a significant risk that they will be transmitted by embryo transfer. Indeed, mycoplasmas appear to have a much stronger propensity to adhere to the ZP than other pathogens and are particularly difficult to remove or inactivate by washing, including the additional washings with trypsin advocated by the IETS for resistant pathogens, and the inclusion of antibiotics in media to inactivate bacteria.

Based on the last conclusions of the IETS for *in vivo* derived embryo transfer (last updated in 2015), *Mycoplasma* spp in cattle has been assessed as a Category 4 disease in Article 4.8.14 of the Terrestrial Animal Health Code (OIE 2021): no conclusions are yet possible with regard to the level of transmission risk, and the risk of transmission via embryo transfer might not be negligible even if the embryos are properly handled in accordance with the Manual of the IETS between collection and transfer.

Also, in Article 11.5.11.of the Terrestrial Animal Health Code (last updated 2014), it is recommended for the importation of *in vivo* derived or in *vitro* produced oocytes or embryos of domestic bovids and water buffaloes from infected countries that: 1. the donor animals showed no clinical sign of CBPP on the day of collection of the oocytes or embryos, were subjected to the complement fixation test for CBPP with negative results, on two occasions, with an interval of not less than 21 days and not more than 30 days between each test, the second test being performed within 14 days prior to collection,

were isolated from other domestic bovids and water buffaloes from the day of the first complement fixation test until collection, were kept since birth, or for the past six months, in an establishment where no case of CBPP was reported during that period, and that the establishment was not situated in a CBPP infected zone, and either have not been vaccinated against CBPP, or were vaccinated using a vaccine complying with the standards described in the Terrestrial Manual not more than four months prior to collection; 2. the oocytes were fertilized with semen meeting the conditions of Article 11.5.10.; 3. the oocytes or embryos were collected, processed and stored in accordance with Chapters 4.8., 4.9. and 4.10., as relevant.

Sheep pox and goat pox

No study was available from the literature concerning the risk related to SPGP virus (SPGPV) transmission via the three matrices of interest.

There is also no mention of any of these specific disease/matrix combinations in the OIE Terrestrial Animal Health Code.

Peste des petits ruminants

No study was available in relation to the risk related to PPR virus (PPRV) transmission via the three matrices of interest.

In Chapter 4.9 of the Terrestrial Animal Health Code (OIE 2021) (last updated in 2018), it is recommended that donor animals of *in vitro* embryos and oocytes should not originate from flocks that are subject to veterinary restrictions for PPR, and neither should the removal of any tissue or aspiration of oocytes take place in an infected zone, or one that is subject to veterinary restrictions for PPR.

In Article 14.7.15 (last updated in 2021), it is recommended for the importation of embryos of domestic sheep and goats from countries or zones considered infected with PPR that the Veterinary Authorities should require the presentation of an international veterinary certificate attesting that the donor animals and all other animals in the establishment showed no clinical sign suggestive of PPRV infection at the time of collection and during the following 21 days; were kept, for at least the 21 days prior to collection, in an establishment where no case of PPR was reported during that period, and to which no susceptible animals had been added during the 21 days prior to collection; were not vaccinated against PPR and were subjected to a diagnostic test for PPRV infection with negative results at least 21 days prior to collection; or were vaccinated against PPR with live attenuated PPRV vaccines at least 21 days prior to embryo collection; the embryos were collected, processed and stored in accordance with Chapters 4.8., 4.9. and 4.10., as relevant; semen of domestic sheep and goats used to fertilise the oocytes complies at least with the requirements in Article 14.7.12. or Article 14.7.13.

Contagious caprine pleuropneumonia

Although, we did not retrieve any study from the literature focusing on the risk posed by *Mycoplasma capricolum subsp. Capripneumoniae* itself, a study by Guerin (reported by Thibier (Thibier 1990)) investigated the risk of transmission of *Mycoplasma mycoides ssp. Mycoides LC* via caprine *in vivo* embryos. Embryos collected from goats 7 days after insemination were exposed for 12 h to Mycoplasma suspensions and washed ten times as recommended in the IETS Manual. The culture results showed that the mycoplasmas adhered to the embryos and were also detected in many of the wash fluids.

The abovementioned conclusions that mycoplasmas most likely can be transmitted via embryos and oocytes (Wrathall, Ayling, and Simmons 2007) (section 3.3.5. Contagious bovine pleuropneumonia), also apply to goats Mycoplasmas. Moreover, Wrathall, Ayling, and Simmons also refered to *Mycoplasma capricolum subsp. capricolum* (closely related to *Mycoplasma capricolum subsp. Capripneumoniae*) and *Mycoplasm*. mycoides subsp. mycoides LC occurring in the genital organs of female goats.

Based on the last conclusions of the IETS for *in vivo* derived embryo transfer, *Mycoplasma* spp in goats has been assessed as a Category 4 disease in Article 4.8.14 of the Terrestrial Animal Health Code (OIE 2021) (last updated in 2015): no conclusions are yet possible with regard to the level of transmission risk and the risk of transmission via embryo transfer might not be negligible even if the embryos are properly handled in accordance with the Manual of the IETS between collection and transfer.

Also, in Article 14.3.11 of the Terrestrial Animal Health Code (last updated in 2021), it is recommended for the importation of *in vivo* derived or in *vitro* produced oocytes or embryos of goats from infected countries that the donor animals that: 1. the donor animals showed no clinical sign of CCPP on the day of collection, and were isolated from other domestic goats from the day of the test until collection, were kept since birth, or for at least the 45 days prior to collection, in an establishment where no case of CCPP was officially reported during that period, and that the establishment of origin was not situated in a CCPP infected zone; 2. the collection fluids and/or degenerated and unfertilised oocytes were subjected to a validated culture or PCR test for CCPP with negative results; 3. the oocytes or embryos were collected in accordance with Chapters 4.8., 4.9. and 4.10., as relevant.

Classical swine fever

No study was retrieved in relation to the risk of CSF virus (CSFV) transmission related to oocytes.

There is no mention of this specific disease/matrix combination in the OIE Terrestrial Animal Health Code.

African swine fever

No study was retrieved for the risk of ASF virus (ASFV) transmission related to oocytes.

There is no mention of this specific disease/matrix combination in the OIE Terrestrial Animal Health Code.

African horse sickness

Although we did not retrieve any experimental study from the literature focusing on the risk of AHS virus (AHSV) transmission via embryos or oocytes, two risk assessment studies involving these specific risks were identified (Sabirovic, López, and Patel 2008; Aznar, McAteer, and Gaynor 2011).

Sabirovic, Lopez and Patel (Sabirovic, López, and Patel 2008) concluded that the likelihood of the introduction of AHSV to Great Britain via the legal trade of equine semen, ova and embryos, meat and other specified biological products can be considered to be negligible.

Similarly, Aznar, McAteer and Gaynor assessed the risk of introduction of AHS virus (AHSV) into the Republic of Ireland (Aznar, McAteer, and Gaynor) and reported that, as of 2011, there had been no known outbreaks of AHS due to the use of infected semen, ova or embryos.

In Article 12.1.9 of the Terrestrial Animal Health Code (OIE 2021) (last updated in 2014), for the importation of in vivo derived equine oocytes or embryos that Veterinary Authorities of importing countries should require the presentation of an international veterinary certificate attesting that: the donor animals showed no clinical sign of AHS on the day of collection of the oocytes or embryos and for the following 40 days, had not been immunised against AHS with a live attenuated vaccine within 40 days prior to the day of collection, were either kept in an AHS free country or zone for at least 40 days before commencement of, and during collection of the oocytes or embryos, or kept in an AHS free vector-protected collection centre throughout the collection period, and subjected to either a serological test to detect antibodies against the AHSV group carried out with a negative result on a blood sample collected at least 28 days and not more than 90 days after the last collection of oocytes or embryos; or agent identification tests carried out with negative results on blood samples collected at commencement and conclusion of, and at least every seven days during oocytes or embryos collection for this

consignment; the embryos were collected, processed and stored in accordance with Chapters 4.8. and 4.10., as relevant; the semen used to fertilise the oocytes complies at least with the requirements in Article 12.1.8

5 Overall conclusions

The findings of the ELS can be summarized in the following table:

Matrix	FMD	RP	RVF	LSD	CBPP	SPGP	PPR	CCPP	CSF	ASF	AHS
in vivo produced embryo			+-		++	+-	+-	++			+-
in vitro produced embryo			+-		++	+-	+-	++			+-
oocyte	++ [1] +- [2]	+-	+-	++	++	+-	+-	++	+-	+-	+-

++: evidence of risk +-: no data or no clear evidence of risk -: evidence of low risk
[1] for cattle [2] for other susceptible species

6 References

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7 List of abbreviations

AHS(V) African horse sickness (virus)

ASF(V) African swine fever (virus)

CBPP Contagious bovine pleuropneumonia

CCPP Contagious caprine pleuropneumonia

CSF(V) Classical swine fever (virus)

DPI Days post-inoculation

ELS Extensive literature search

FMD(V) Foot-and-mouth disease (virus)

IETS International Embryo Technology Society

LSD(V) Lumpy skin disease (virus)

PFU Plaque forming unit

PPR(V) Peste des petits ruminants (virus)

RP(V) Rinderpest (virus)

RVF(V) Rift valley fever (virus)

SPGP(V) Sheep pox goat pox (virus)

ZP(I) zona pellucida (-intact)

Appendix A – Extensive literature search protocol

Review question

The ELS should allow answering the question whether oocytes or in vivo/vitro embryos (matrices) collected from affected animals of listed species in affected establishments pose a risk to transmit the disease agent. The diseases agents and matrices to be covered by this ELS are the following:

Matrix	FMD	RP	RVFV	LSD	CBPP	SPGP	PPR	CCPP	CSF	ASF	AHS
in vivo produced embryo											
in vitro produced embryo											
oocyte											

Shaded cells represent the disease agent/matrix combination to be included in the ELS

Inclusion criteria

The following criteria for inclusion will be used to select studies to be included in the ELS:

i. Studies on FMD, RP, RVFV, LSD, CBPP, SPGP, PPR, CCPP, CSF, ASF, or AHS.

ii. Studies evaluating the risk of transmission of the disease agent from a matrix (in vivo/vitro embryos or oocytes) collected from affected animals of listed species.

iii. Studies are eligible regardless of study region, study design and publication date.

Exclusion criteria

The references will be excluded from the ELS if they meet one or more of following criteria:

i. Studies concerning only placental and/or foetal transmission of the disease agent

ii. Studies published in another language than English, French, Spanish, German, Dutch, Italian, or Portuguese.

iii. Review papers will be excluded. However, original studies included in the review papers complying with the inclusion/exclusion criteria will be included.

Information sources

Electronic databases

The literature search will be conducted in MEDLINE (via PubMed) to obtain peer-reviewed, scientific publications related to the ELS.

Reference checking and hand searching

The reference list of relevant studies retrieved from the electronic database search will be hand searched to identify additional studies.

Search strategy

The following search strategy will be used in PubMed:

#	Search string	# of hits
1	((((((((((((((((((((((((((((((foot and mouth disease) OR (foot-and-mouth disease)) OR (hoof and mouth disease)) OR (hoof-and-mouth disease)) OR (rinderpest)) OR (cattle plague)) OR (steppe murrain)) OR (Rift Valley fever)) OR (phlebovirus)) OR (lumpy skin disease)) OR (Neethling virus)) OR (contagious bovine pleuropneumonia)) OR (lung plague)) OR (mycoplasma mycoides)) OR (sheep pox)) OR (sheeppox)) OR (goat pox)) OR (goatpox)) OR (variola ovina)) OR (variola caprina)) OR (peste des petits ruminants)) OR (sheep and goat plague)) OR (contagious caprine pleuropneumonia)) OR (mycoplasma capricolum)) OR (classical swine fever)) OR (hog cholera)) OR (pig plague)) OR (african swine fever)) OR (african horse sickness)) OR (asfivirus)) OR (pestivirus)) OR (carpripox)) OR (capripoxvirus)) OR (orbivirus)	30,852
2	((((((((((((embryo) OR (oocyte)) OR (germinal product)) OR (germ cell)) OR (ovocyte)) OR (donor)) OR (recipient)) OR (cumulus oocyte complex)) OR (blastocyst)) OR (ovum)) OR (oophorus)) OR (Zona Pellucida))	856
3	((((((((((((transmission) OR (transmits)) OR (transmitted)) OR (infection)) OR (infects)) OR (infected)) OR (survival)) OR (survives)) OR (survived)) OR (presence)) OR (present)) OR (detection)) OR (detects)) OR (detected)	756

Review methods

Selection of studies

In the first review phase, the resulting list of references will be exported to EndNote to proceed with the title, abstract and key words screening and study selection. To decrease the risk of selection bias, two P95 reviewers will independently review the list of references obtained by screening the titles/abstracts to identify studies that fulfil the abovementioned inclusion/exclusion criteria. Discrepancies will be discussed, and if not resolved, a third reviewer will make the final decision. The complete selection process will be documented in the Endnote library file, containing folders that reflect the selection criteria.

Data extraction

In the second review phase, full-texts for all selected studies will be assessed for eligibility. Data from the eligible full-text papers identified will then be extracted by a reviewer using a standardized extraction form in MS Excel (see Annex) to ensure that all relevant data are extracted systematically. In addition, the sections of the full texts from where data are collected will be highlighted.

Analysis and reporting

The extracted data will be described in a report in a tabular format and a short text summarising the findings per disease agent-matrix. In addition, a flowchart of the studies selected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be prepared for use in the report.