# Assessment of genetic recombination and re-assortment of imported veterinary vaccines



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**Cataloguing data**

This publication (and any material sourced from it) should be attributed as: Department of Agriculture and Water Resources 2018, *Assessment of genetic recombination and re-assortment of imported veterinary vaccines*, Canberra. CC BY 3.0.

This publication is available at [agriculture.gov.au/publications](http://agriculture.gov.au/publications).

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**Acknowledgements**

The department thanks Professor Glenn Browning, University of Melbourne, and Dr Andrew Pearce, APVMA, for their considerable input.

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## Introduction

Veterinary vaccines are important medicines for the protection of Australian animals against communicable diseases. However, the importation and use of veterinary vaccines may be associated with several biosecurity risks, including the risk of genetic *recombination* or *re-assortment* between vaccines and other strains already circulating in Australia, potentially generating pathogenic strains of the agent. While the likelihood of this occurring is low, it has been confirmed by published research, which shows that recombination involving live veterinary vaccines has occurred under Australian field conditions. Furthermore, novel vaccines and therapeutics (which include replication deficient but not incompetent nucleic acid), may also pose risks of recombination or re-assortment.

To help facilitate the importation of veterinary vaccines (and master seeds) into Australia, a risk assessment framework and methodology consisting of a series of questions formatted into a decision tree was developed. – the [Decision tree for assessing the risk of hazardous genomic recombination or re-assortment in veterinary vaccines](#_Decision_Tree_for).

The decision tree will help inform the Department of Agriculture and Water Resources in its assessment of an import application for a veterinary vaccine (or master seed) but does not indicate if acceptance for importation and/or distribution will be approved. It can also be used for veterinary therapeutics which contain replication competent nucleic acid that are intended for importation into Australia.

## Decision tree

Applications for import permits for veterinary vaccines will be progressed through the decision tree to determine whether the level of risk associated with specific recombination and assortment events requires a *detailed risk assessment*. The decision tree is comprised of 20 questions, each of which directs the user to further questions, and eventually a conclusion regarding the potential recombination risk.

The questions in the decision tree enable assessment of the two fundamental components of risk relating to recombination and re-assortment in imported live veterinary vaccines:

1. The likelihood of recombination or re-assortment between nucleic acid contained within the vaccines, with other vaccines or with circulating infectious agents in target-animal populations, or the likelihood of distribution of an *autonomous genetic element* from the vaccine into circulating infectious agents in target-animal populations.
2. The magnitude of the consequences if recombination or re-assortment produces a more virulent or transmissible virus or bacterium that could have an adverse impact on animal or human health greater than that already caused by circulating viruses and bacteria already present in Australia.

The decision tree reaches a conclusion at 17 points; three of these result in the application to import a vaccine being refused. Six points conclude that the vaccine poses minimal risk and therefore is suitable for consideration for import into Australia. Eight decision points conclude that a *detailed risk assessment* is required to resolve concerns about the likelihood of recombination and re-assortment and/or the magnitude of the potential hazard posed by the genetic composition of the vaccine.

Also, where the vaccine or master seed contains nucleic acid components derived from infectious species not identical (at the nucleic acid level) to species circulating in Australia, the decision tree directs the applicant to an assessment of the risks posed by any autonomous genetic elements which may be present.

## Detailed risk assessment

When the decision tree process concludes that a *detailed risk assessment* is required, the applicant will need to provide the necessary data and scientific evidence to the department, including formal advice from an independent external expert with relevant expertise. The applicant should contact the department to confirm the suitability of the expert.

Guidance to assist in the preparation of the data package for a *detailed risk assessment* is provided in the appendices. However, the applicant should always seek confirmation of the data required from both the department and the external expert prior to finalisation of the data package.

After assessing all the available information, the department will determine whether the likelihood and consequences of any possible recombination or re-assortment event are sufficiently low to support the application to import the vaccine or master seed into Australia.

## Decision tree for risk assessment

The decision tree is intended to help inform the import risk assessment of veterinary vaccines and master seeds. It can also be used for veterinary therapeutics which contain replication competent nucleic acid and are intended for importation into Australia.

The decision tree considers the possibility of a vaccine genetically recombining, re-assorting or introducing autonomous genetic elements into Australian microbial populations, which could lead to adverse effects for Australian animals and the environment.

An application progresses through the decision tree using all the available evidence, including that provided by the applicant. At several points, the decision tree concludes that there is minimal risk involved and therefore, no further assessment of recombination and re-assortment is required. If the decision tree concludes that the risk is unacceptable, then the importation application will most likely be refused, unless there is sufficient and sound scientific evidence to prove otherwise.

The decision tree may also identify an issue that needs to be resolved before a decision can be made. In these cases, the application will need to undergo a *detailed risk assessment* and the applicant will need to seek advice from an independent external person with appropriate expertise.

Where a *detailed risk assessment* is required the applicant should continue through the decision tree and complete the set of questions. Each question that concludes with a requirement for a *detailed risk assessment* should be noted. This is to ensure that the risks of recombination and re-assortment, as well as those posed by autonomous genetic elements, are individually assessed as appropriate.

### [Decision tree for assessing the risk of hazardous genomic recombination or re-assortment in veterinary vaccines](#_Decision_Tree_for)

1. Is the vaccine inactivated so that the vaccine and all genetic material cannot replicate within target or off-target animals?
   1. Yes – use of the vaccine is unlikely to result in recombination, re-assortment or genetic transfer and therefore, there is no need for further risk assessment of the potential for recombination, re-assortment or transfer of autonomous genetic elements.
   2. No – Proceed to question 2.
2. Does any part of the vaccine nucleic acid replicate in host cells after inoculation?
   1. Yes – There is potential for recombination to occur, even if the vaccine undergoes abortive replication. Proceed to question 3.
   2. No – Use of the vaccine is unlikely to result in recombination, re-assortment or genetic transfer and therefore, there is no need for further risk assessment of the potential for recombination, re-assortment or transfer of autonomous genetic elements.
3. Does the vaccine contain genetic information derived from multiple strains of the same virus or bacterial species?
   1. Yes – The potential for inter-genomic recombination or re-assortment between the components of the vaccine must be assessed. In particular, the potential for multiple strains of the same agent to recombine or re-assort into strains with an increased level of animal biosecurity concern than the *parental strains* in the vaccine, needs to be assessed. A *detailed risk assessment* is required and, in addition, the risks posed by each strain should be assessed independently. Refer to **Appendix A** for relevant decision tree.
   2. No – Proceed to question 4.
4. Does the parental vaccine strain from which the nucleic acid is derived occur in Australia? For *vectored vaccines*, both the host and any donor organism(s) must be considered.
   1. Yes – Proceed to question 6.
   2. No – Proceed to question 5.
5. Are there viral or bacterial species in the Australian environment sufficiently similar to the vaccine strain from which the genetic information was derived such that recombination or re-assortment is likely? For vectored vaccines, both the host and the donor organism must be considered.
   1. Yes – The vaccine may introduce genomic alterations into circulating pathogens that may lead to an increased level of animal biosecurity concern. A *detailed risk assessment* is required. Refer to **Appendix B** for relevant decision tree. Proceed to question 7.
   2. No – The vaccine is unlikely to pose a risk of recombination or re-assortment, but is an exotic infectious agent. Proceed to question 15.
6. Is all the genetic material in the vaccine strain or, for a vectored vaccine, are both the *insert* and the vector, derived entirely from an Australian isolate of the virus or bacterial species?
   1. Yes – Any recombination, re-assortment or acquisition of an autonomous genetic element is unlikely to result in variants of the wild-type agent that cannot already arise in the field. Therefore, the additional risk likely to be contributed by the vaccine is minimal. Proceed to question 20.
   2. No – There is potential for the vaccine to introduce genes or mutations that do not occur in Australia. Proceed to question 7.
7. Is the virus family or bacterial genus (or family) of the vaccine strain, vector or any infectious agent from which the nucleic acid inserted within the vector was derived, known to recombine, re-assort or horizontally transfer autonomous genetic elements in the field or could be expected to contain plasmids, genetic elements, recombine, re-assort or transfer genetic material horizontally in the field?
   1. Yes – Proceed to question 9.
   2. No – Proceed to question 8.
8. Is there specific evidence that the viral or bacterial species of the vaccine strain, vector or nucleic acid insert within the vector, DOES NOT recombine with other vaccines or with the wild type agent or include autonomous genetic elements?
   1. Yes – The vaccine is unlikely to pose an increased risk to animal health in Australia. There is no need for further risk assessment of the potential for recombination, re-assortment or transfer of autonomous genetic elements.
   2. No – Proceed to question 9.
9. Is the parental vaccine strain, or the strain from which any of the nucleic acid in the vaccine was derived, considered to have factors of animal biosecurity concern which represent increased risk over the same species in Australia?
   1. Yes – There is potential for the vaccine to introduce genes or mutations that do not occur in Australia. Proceed to question 10.
   2. No – Proceed to question 12.
10. Is the basis for the increased biosecurity risks of the parental strain understood?
    1. Yes – Proceed to question 11.
    2. No – The vaccine has the potential to recombine, re-assort or donate an autonomous genetic element, which may produce more virulent variants of the virus or bacterial species than currently exist in Australia. A *detailed risk assessment* is required. Refer to **Appendix C** for relevant decision tree. Proceed to question 15.
11. Are all the genes known to be responsible for biosecurity concern in any parental strains deleted from the vaccine strain, or the vector and the insert?
    1. Yes – Proceed to question 20.
    2. No – The vaccine has the potential to recombine, re-assort or donate an autonomous genetic element that may result in variants of the wild-type agent that are more virulent, transmissible or have a broader host range than strains that currently exist in Australia. A *detailed risk assessment* isrequired. Refer to **Appendix C** for relevant decision tree. Proceed to question 15.
12. Are there any genes or mutations that are known to increase *factors of biosecurity concern* in this virus or bacterial species?
    1. Yes – Proceed to question 13.
    2. No – Proceed to question 15.
13. Are these factors of biosecurity concern present within the vaccine strain, vector or insert within the vector?
    1. Yes – Proceed to question 14.
    2. No – There is no evidence to suggest that the genome of the vaccine strain will pose an increased risk to animal health in Australia. Proceed to question 15.
14. Do these genes or mutations occur in circulating viruses, bacteria, or live attenuated vaccines already in use in Australia?
    1. Yes – Any recombination, re-assortment or acquisition of an autonomous genetic element is unlikely to result in variants of the circulating agent that cannot already arise in the field. Proceed to question 15.
    2. No – The vaccine represents an unacceptable risk to animal health in Australia and is unable to be considered further for importation into Australia.
15. Does the vaccine formulation contain any known autonomous genetic elements (including plasmids, viral (sub-) genomes, or segmented viral elements)?
    1. Yes – Proceed to question 16 if the autonomous genetic element is bacterial in origin and to question 19 if it is viral.
    2. No – There is no evidence that the vaccine is likely to pose any additional risk associated with transfer of autonomous genetic elements. Proceed to question 20.
16. Are the autonomous genetic elements transmissible to other bacteria or to the host?
    1. Yes – proceed to question 17.
    2. No – proceed to question 20.
17. Is the host range of the autonomous genetic element restricted to the same bacterial species as the vaccine?
    1. Yes – The vaccine may represent a risk for transfer of autonomous genetic elements, and these may facilitate non-homologous recombination within one species of bacteria or the transfer of autonomous genetic element(s) containing factors of biosecurity concern. A *detailed risk assessment* is required. Refer to **Appendix D** for relevant decision tree. Proceed to question 20.
    2. No – The vaccine may represent a significant risk to animal health in Australia. Proceed to question 18.
18. Does the autonomous genetic element contain genes or mutations known to influence factors of biosecurity concern in this pathogen or other pathogens that do not occur in Australian pathogens?
    1. Yes – The vaccine represents an unacceptable risk to animal health in Australia and is unable to be considered further for importation into Australia.
    2. No – The vaccine may represent a risk for transfer of autonomous genetic elements, and these may facilitate non-homologous recombination, across multiple species of bacteria. A *detailed risk assessment* is required. Refer to **Appendix D** for relevant decision tree.Proceed to question 20.
19. Is the viral nucleic acid that has been introduced into the vaccine able to generate infectious virus?
    1. Yes – The vaccine represents an unacceptable risk to animal health in Australia and is unable to be considered further for importation into Australia.
    2. No – The vaccine may still represent a risk for homologous recombination. A *detailed risk assessment* is required. Refer to **Appendix E** for relevant decision tree**.** Proceed to question 20.
20. Does the vaccine strain contain any known antimicrobial or disinfectant resistance genes?
    1. Yes – The vaccine may contribute to dissemination of antimicrobial or disinfectant resistance genes. A *detailed risk assessment* is required. Refer to **Appendix****F** for relevant decision tree.
    2. No – Any recombination, re-assortment or acquisition of an autonomous genetic element is unlikely to result in variants of the wild-type agent that cannot already arise in the field. Therefore the additional risk likely to be contributed by the vaccine is minimal. There is no need for further assessment of the risks associated with recombination, re-assortment or transfer of autonomous genetic elements.

## Guidance for supporting information

### Detailed risk assessment

The decision tree will direct applicants to a *detailed risk assessment* if it is required for the potential import application in order to address specific risks associated with genetic recombination or re-assessment. The information on the following pages provides guidance on the requisite data and evidence that needs to be provided with the import application.

### Categories of information required

The decision tree concludes that a *detailed risk assessment* is required at eight decision points. Each decision point identifies a technical concern that requires clarification to determine if the concern is relevant and, if so, the magnitude of the concern. Six categories of required data covering the eight decision-tree decision-points are listed below. Each category highlights the specific concern raised by the decision-tree process and recommends data and other evidence to assess the potential biosecurity risks.

### Data requirements

Peer-reviewed scientific journal publications or data generated by the applicant should be submitted as evidence in support of an import permit application.[[1]](#footnote-1)

Any information to support an argument for why the vaccine will not pose the risk identified by the decision tree analysis should be provided. Copies of all papers referenced need to be provided. If unpublished data which is available only to the applicant is referenced, then the data, a full explanation of the methods and any software used for genetic analysis must be provided if requested. All nucleotide or amino acid sequence data used for analysis needs to be provided in a standard format suitable for bioinformatics analysis.

Examples of information that would support the assessment of the level of risk associated with genetic recombination/re-assortment at each point throughout the decision tree are:

* genomic information annotated appropriately and included in appropriate formats for bioinformatics analysis
* annotated genomic sequences of the vaccine, of target pathogens and closely related species
* genomic sequences of circulating virus populations post-vaccination of infected target animals
* an established vaccine safety record derived from surveillance data
* genomic sequences of parental species populations and closely related species circulating in Australia and internationally
* calculated recombination rates within parental species of virus or bacterium and within any closely related Australian species of virus or bacterium. Peer reviewed publications supporting the methods used to calculate the recombination rates
* evidence that demonstrates the host species range of the virus or bacterium
* evidence that demonstrates the host cell range of the virus or bacterium
* evidence that demonstrates that a vectored viral vaccine does not generate nucleic acid capable of inter-genomic recombination or re-assortment with circulating viruses homologous to the insert within the vector or to the vector itself
* international and Australian field studies characterising disease outbreaks associated with the pathogen from which the vaccine strain(s) are derived
* annotation and characterisation of autonomous genetic elements within the vaccine strain
* mutations or genetic variations affecting virulence, transmissibility, host range or tropism within the vaccine strain
* distribution of any known disinfectant or antimicrobial resistance genes in the vaccine strain in Australian pathogens
* any other relevant evidence in support of a scientific argument that could alleviate any concerns regarding the risk/s raised by the decision tree risk assessment process.

## Appendix A: Decision tree question 3a

When a vaccine contains multiple strains of the same virus or bacterial species, there is the potential for recombination or re-assortment between components of the vaccine. The recombination or re-assortment may result in strains which present increased risks compared to any of the parental strains. The risks of recombination between components of the vaccine exist when any genetic information from multiple genetic or serological lineages are present in the vaccine. Such risks are greatest when there are multiple complete viral or bacterial genomes present within the vaccine formulation.

1. The tendency for inter-genomic recombination or re-assortment in the viral species, bacterial species or closely related species during natural infections under field conditions can be assessed using:
   1. Complete genomic sequences of the viruses or bacteria that make up the vaccine population
   2. Complete genomic sequences of circulating viral or bacterial populations post-vaccination of infected target animals
   3. Complete genomic sequences of representative parental species and closely related species circulating in Australia
   4. Calculated recombination or re-assortment rates of the vaccine or parental species.
2. The degree of variation in factors of biosecurity concern in the parental vaccine species and thus the risk that recombination or re-assortment between the stains in the vaccine could lead to the generation of new strains with greater factors of biosecurity concern can be assessed using:
   1. International and Australian field studies characterising disease outbreaks caused by this virus or bacterial species that assess similarities in:
      1. Tropism
      2. Virulence
      3. Transmissibility
      4. Host range
      5. Arthropod vector competence (if relevant)
      6. Any other factors of biosecurity concern.
   2. An established safety record derived from surveillance survey data.

## Appendix B: Decision tree question 5a

If the parental species of a vectored vaccine or insert are sufficiently similar to Australian circulating virus or bacterial species such that interspecies recombination or re-assortment is possible, then the following should be provided:

1. Evidence to demonstrate that inter-genomic recombination or re-assortment does not occur in this species or in closely related species during natural infections under field conditions:
   1. Complete genomic sequences of the target pathogen and closely related species
   2. Complete genomic sequence of the vaccine strain
   3. Calculated recombination or re-assortment rates of parental vaccine strains and closely related Australian species
   4. The mechanisms used to incorporate the insert into the vector have not introduced mechanisms which have introduced autonomous transposable elements.
2. Evidence to support a conclusion that the vaccine strain and the circulating closely related Australian species of the virus or bacterium do not replicate in the same:
   1. Host species
   2. Host cells.
3. For viral vectored vaccines, evidence to demonstrate that the vector does not generate a class of nucleic acid capable of inter-genomic recombination or re-assortment with circulating viruses.

For example*,* an RNA virus vector, except if it is a retrovirus, is unlikely to generate nucleic acid species that could recombine with a circulating virus with a DNA genome. A single stranded RNA virus vector is unlikely to generate RNA that could re-assort with a circulating double-stranded RNA genome virus.

1. The degree of variation in virulence, transmissibility or host range in the parental vaccine strains and thus the potential that recombination or re-assortment could lead to the generation of new strains with increased factors of biosecurity concern can be assessed using:
   1. International (especially in the country of origin of the parental strains) and Australian field studies characterising disease outbreaks caused by this virus or bacterial species to assess similarities in:
      1. Tropism
      2. Virulence
      3. Transmissibility
      4. Host range
      5. Arthropod vector competence (if relevant)
      6. Any other factors of biosecurity concern.
   2. An established safety record derived from surveillance survey data.

## Appendix C: Decision tree questions 10b and 11b

If the parental strain from which the vaccine, the vector or the insert in the vector was derived is more virulent, more transmissible or has a different host range than isolates of the same or very similar virus or bacterial species in Australia, then the following evidence should be provided:

1. An assessment of the amount of inter-genomic recombination or re-assortment across populations of the parental virus or bacterial species or closely related species to determine whether recombination is detectable under field conditions using:
   1. Genomic sequences of the viruses or bacteria that make up the vaccine population
   2. Genomic sequences of parental species populations and closely related species circulating internationally and in Australia.
2. Evidence to support a conclusion that the parental vaccine species and the circulating closely-related Australian species of the virus or bacterium do not replicate in the same:
   1. Host species
   2. Host cells.
3. For a viral vectored vaccine, evidence that the vector does not generate a class of nucleic acid capable of inter-genomic recombination or re-assortment with circulating viruses.

For example an RNA virus vector, except if it is a retrovirus, is unlikely to generate nucleic acid species that could recombine with a circulating virus with a DNA genome. A single stranded RNA virus vector is unlikely to generate RNA that could re-assort with a circulating double-stranded RNA genome virus.

1. The degree of variation in virulence, transmissibility or host range in the parental virus or bacterial species and thus the potential that recombination or re-assortment could lead to the generation of new strains with increased factors of biosecurity concern can be assessed using:
   1. International (especially in the country of origin of the parental strain) and Australian field studies characterising disease outbreaks caused by this virus or bacterial species that assess similarities in:
      1. tropism
      2. virulence
      3. transmissibility
      4. host range
      5. arthropod vector competence (if relevant)
      6. any other factors of biosecurity concern.
   2. An established safety record derived from surveillance survey data.
2. Data showing the basis for the attenuation of the vaccine strain. Such evidence should demonstrate that this mutation eliminates the risk of introduction of the genes contributing to the increased factors of biosecurity concern of the parental vaccine strain, into circulating strains of the pathogen. The mutation(s) have reduced the capacity of the vaccine to recombine, or disrupted any genes known to contribute to the greater virulence of the parental strain.
3. Data showing that the genes or mutations responsible for increased factors of biosecurity concern within parental strain(s), have been deleted or modified in the vaccine strain. These deletions must prevent the transfer of factors of biosecurity concern if regions of the genome are horizontally transferred to another strain.

## Appendix D: Decision tree questions 17a and 18b

If the parental vaccine strain contains one or more autonomous genetic elements, then evidence that the element will not create a risk of non-homologous recombination across one or multiple species of bacteria or viruses should be provided. The following should be addressed:

1. Data that proves the autonomous genetic element(s) already occurs in strains of this bacterium, or closely related species, circulating in Australian populations of animals
2. Data that proves the autonomous genetic element does not contain genes known to influence factors of biosecurity concern
3. If autonomous genetic element genes are known to influence the virulence, tropism, transmissibility and/or host range of bacteria, then documented evidence needs to be provided. This data should demonstrate that these genes are widespread in bacteria and are found in Australian populations of animals likely to be exposed to this vaccine.

## Appendix E: Decision tree question 19b

If the vaccine strain contains part of a viral genome then the following should be addressed:

1. Inter-genomic recombination in the parental-virus species or closely related species during natural infections to determine if recombination is detectable under field conditions and can be examined using:
   1. Genomic sequences of the viruses or bacteria that make up the vaccine population
   2. Genomic sequences of circulating virus populations post vaccination of infected target-animals
   3. Genomic sequences of parental-species virus populations circulating in Australia
   4. Calculated recombination rates of vaccine and parental species.
2. Evidence to support a conclusion that the parental vaccine species and the circulating closely-related Australian species of the virus or bacterium do not replicate in the same:
   1. Host species
   2. Host cells.

Data that proves the vector does not generate nucleic acid capable of inter-genomic recombination or re-assortment with circulating viruses. For example*,* whether the mutation has reduced the capacity of the vaccine to recombine, or disrupted any genes known to contribute to factors of biosecurity concern in the parental strain.

1. Data showing the extent of any sequence differences between the viral genome found in the vaccine and a representative panel of circulating Australian strains of the virus, and data demonstrating the extent of differences, if any, in factors of biosecurity concern in this virus species in other countries.
2. If there is evidence of variation in factors of biosecurity concern in the viral species, data to show that the extent of this variation is unlikely to have significant consequences if variants were introduced into Australia. Any evidence that proves strains occurring in other countries - particularly those from the country of origin of the parental strain of the vaccine - do not cause factors of biosecurity concern (including vectors for arboviruses) than Australian strains should be provided.
3. If relevant, data demonstrating that a mutation in the region of the viral genome included in the vaccine has disrupted the infectivity of the viral genome, and data that these mutations will remain present following likely recombination and assortment events.
4. Data showing that the genes or mutations responsible for the greater virulence, different tropism, greater transmissibility or broader host range of the parental strain, have been deleted or modified in the vaccine strain so that they can no longer confer greater factors of biosecurity concern if horizontally transferred to another strain.

## Appendix F: Decision tree question 20a

If the vaccine contains genes for resistance to disinfectants or antimicrobial drugs:

1. Data that proves these resistance genes already occur in strains of this bacterium, or closely related species, circulating in Australian populations of animals.

## Glossary

| Term | Definition |
| --- | --- |
| autonomous genetic element | Nucleic acid sequences that are capable of being donated from the vaccine to competent microorganisms. This includes plasmids, transposons and bacteriophages, as well as viral genomes, segments of viral genomes and sub-genomic regions of viral and bacterial genomes. |
| factors of biosecurity concern | The properties of the parental organism(s) from which the nucleic acid in the vaccine are derived, which may influence the pathogenesis or virulence of related or similar organisms. For example, arthropod vector competence, environmental stability, host range, latency, transmissibility, tropism and virulence. |
| insert | Nucleic acid which has been incorporated into a vector from a virus, bacterium or animal to influence the efficacy of the vaccine. |
| re-assortment | The replacement of one genomic segment of a virus with a genomic segment derived from a different virus. |
| recombination | The incorporation of nucleic acid from an exogenous source into the genome of a virus or bacterium. |
| vectored vaccine | A vaccine in which nucleic acid from another virus, bacterium or organism is carried within a host bacterium or virus (the vector). |
| parental vaccine strain | The virus or bacterial strain from which the vaccine strain was derived. For vectored vaccines this includes both the host and the donor organisms. |

1. These peer-reviewed papers contain examples of relevant data concerning recombination:

   Vaz, PK, Job, N, Horsington, J, Ficorilli, N, Studdert, MJ, Hartley, CA, Gilkerson, JR, Browning, GF & Devlin, JM 2016, ‘[Low genetic diversity among historical and contemporary clinical isolates of felid herpesvirus 1](https://doi.org/10.1186/s12864-016-3050-2)’ BMC Genomics, vol. 17, no. 1, pp. 704.

   Vaz, PK, Horsington, J, Hartley, CA, Browning, GF, Ficorilli, NP, Studdert, MJ, Gilkerson, JR & Devlin, JM 2016, ‘[Evidence of widespread natural recombination among field isolates of equine herpesvirus 4 but not among field isolates of equine herpesvirus 1](https://dx.doi.org/10.1099/jgv.0.000378)’, Journal of General Virology, vol. 97, no. 3, pp. 747-55. [↑](#footnote-ref-1)