**Vaccination of calves against BRD using commercial vaccines: is there a gold standard?**

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**ABSTRACT**

*Keywords:*

Bovine respiratory disease, Vaccination, Calves, Efficacy, Review

*Abbreviations*

BRD: Bovine respiratory disease
BRSV: Bovine respiratory syncytial virus
PI-3: Parainfluenza type 3 virus
BHV-1: Bovine herpesvirus 1
MLV: Modified live
INAC: Inactivated
CMI: Cell-mediated immunity
IFN: Interferon
TNF: Tumor necrosis factor

## 1. Introduction

In Middle Europe, most bull calves of pure dairy breeds (Holstein, Brown Swiss) and F1 cross breedings are marketed at an age of 3-5 wks. They are transported by traders to fattener units to produce either veal calves (120 kg carcass weight within 14-18 wks) or beef cattle (300-400 kg carcass weight within 10-16 months). Predominantly during the first four weeks after purchase by the fattener, bovine respiratory disease (BRD) represents the most important health issue leading to low daily weight gains (typically 600-900 g/d in the first weeks), high expenses for veterinary treatments and drugs (typically CHF 50-100/calf in the first weeks) and losses of severely diseased animals (typically 2-4 %).

To cope this problem, for decades antimicrobials have been used more or less excessively for metaphylaxis and therapy orally and/or parenterally. In the last years, however, the application of antibiotics has been critizised due to it's limited efficiency (Review) and the concomitant risk in respect to the spread of resistant isolates of the most relevant infectious agents (i. e., Pasteurella multocida, Mannheimia haemolytica, Mycoplasma spp.). Thus, prevention is crucial. Most promising approaches focus on a minimization of transport stress, an optimization of the housing management in the fattener unit (i. e., feeding, hygiene and ventilation) and the improvement of the constitution of the calf already on the dairy farm ("preconditioning"). Unfortunately, these strategies cannot solve the problem of commingling many young calves from a variety of dairy farms in the fattener unit due to the small-scale dairy farms at least in Switzerland. Vaccination is considered as a tool to reduce problems caused by BRD in purchased calves. Although hundreds of thousands calves are vaccinated using either inactivated or attenuated vaccines year by year, the effects on morbidity, mortality, proportion of relapses, return on investment (ROI) and protection rate of vaccinated calves varies between the farms tremendously. Generally acknowledged recommendations in respect to the vaccine (inactivated vs. attenuated), route of administration (intranasal vs. parenteral), booster interval, time point of administration (directly after arrival vs. days/weeks thereafter) do not exist. Moreover, in the last years, the immunomodulatory effect of vaccines in addition to the adaptive immune response is a matter of debate – the relevance of this issue for vaccinations against BRD is, however, simply unknown.

Accordingly, it was the objective (a) to put together systematically the results of experimental studies as well as field studies which investigated the vaccination of calves against BRD using commercial vaccines, (b) to compare the efficiency of different vaccination protocols in order to obtain an evidence-based gold standard for an optimized vaccination protocol for young calves, (c) to evaluate whether a view on all peer-reviewed studies allows to assess the efficiency of vaccination protocols, and (d) to investigate the significance of immunomodulatory effects of vaccines.

## 2. Material and methods

The concept of this systematic review was 'a priori' individually created according to the PRISMA statement (Moher et al., 2009). The research question was designed following the PICOS scheme (Liberati et al., 2009): the population are calves (fattening and rearing), the intervention is a vaccination with activated or inactivated vaccines against pathogens of the Bovine Respiratory Disease complex/Enzootic Bronchpneumonia; the comparator is no vaccination or placebo; the outcome is the effectivity of the vaccination (clinical symptoms, pathomorphological parameters, virus shedding, antibody titers, cell-mediated immune responses, daily weight gains and protection rates); the study design includes *in vivo* experimental and field trials, no *in vitro* or *ex vivo* trials.

*2.1. Search strategy*

A bibliographic web-based scientific search was performed derived on the recommendations of the PRISMA statement (Liberati et al., 2009). The bibliographic data bases used were PubMed.gov (National Center for Biotechnology Information) and Web of Science (Thomson Reuters TM), consulted on the 2017-10-23 by one person. The search term used in both databases was: *(calf OR calves OR fattening OR cattle OR beef OR bovine OR veau OR veaux OR broutard OR bovin OR Kalb OR Kaelber) AND (vaccination OR vaccine OR immunisation OR paramunisation OR immunization OR paramunization OR vaccin OR Impfung) AND (BRD OR UDR OR „respiratory disease" OR enzootic OR bronchopneumonia OR pneumonia OR pleuritis OR BRSV OR syncytial OR parainfluenza OR „maladie respiratoire" OR enzootique OR pleurite OR parainfluenca OR Pneumonie OR Bronchopneumonie OR Atemwegserkrankung)*. The results were refined by choosing only peer-reviewed studies written in German, French or English and published between 1987 and 2017. The references matching these criteria were loaded in an EndNote 8.1 data base and duplicates were removed.

*2.2 Study selection*

Of the remaining studies titles and abstracts were screened for their content with help of predefined exclusion and inclusion criteria. All in all, only studies published in peer-reviewed scientific journals were included. They were inspected for the used vaccines (antigen, serotype, inactivated/modified live, parenteral or intranasal application). Only studies using vaccines in calves until an age of 12 months for protection against pathogens associated with the Bovine Respiratory Disease complex were included. Studies dealing with lung worms (e.g. *Dictyocaulus viviparus*), notifiable epizootic diseases (e.g. Infectious Bovine Rhinotracheitis (BHV-1, Tuberculosis, etc.) or other factors associated with lung health (e.g. ventilation, climate, feeding etc.) were excluded. Only *in vivo* experimental or field trials were included, studies reporting on biochemical, *in vitro* or *ex vivo* experiments and reviews were excluded. Further exclusion criteria were: effectivity of the vaccination is not verifiable; the study deals with development of vaccines, molecular methods or the investigation of serotypes; quality deficits e.g. no control or placebo as comparator group. In a following step, full text articles were examined again for meeting predefined selection criteria by one person.

*2.3 Additional considered references*

In addition to the bibliographic search, some studies were included in this review, because they were already known by the authors and meet, in their opinion, the selection criteria.

*2.4 Data selection process*

The remaining studies were assessed by the following characteristics and given information was sampled tabularly: study type (experimental or field study), authors of the study, vaccinal strain, vaccination scheme, study design, number, age, immune status at the beginning of the trial (seronegative or seropositive) and breed of used animals, measured parameters and effects as well as the outcome of study. In some studies more than one trial or experiment (e.g. with different application schemes or on several herds) was documented. They were counted and evaluated as single experiments within studies. To compare the experiments with each other the following definitions were implemented.

*2.5 Definitions*

**young calves:** age of calves at time of the first vaccination ≤ 12 weeks
It is expected that in this period maternal antibodies are present and that they could effect the vaccine antigens.
**older calves:** age of calves at time of the first vaccination > 12 weeks
It is expected that in this period no maternal antibodies are present and that the animals are seropositive (due to contact with antigenes from the enviroment and/or colostrum) or that the influence of the antibodies is negligible.

**seronegative serostatus:** no antibodies against the vaccine antigen could have been documented before the vaccination
**seropositive serostatus:** antibodies against the vaccine antigen could have been documented before the vaccination
**unknown serostatus:** unknown if the animal is seronegative or seropositive against the vaccine antigen

**inactivated vaccine:** contains inactivated pathogens of the enzootic bronchopneumonia
**modified live vaccine:** contains attenuated pathogens of the enzootic bronchopneumonia

**parenteral application:** vaccine application subcutaneous, intramuscularly or intradermally
**local application:** vaccine application intranasally

**experimental studie:** few animals (a maximum of 90 animals per study, a maximum of 20 animals per group), standardized environmental conditions, majority of the groups are challenged
**field studie:** many animals (≥ 20 animals per group), less defined environmental conditions in the field, no challenge

**booster:** repeated vaccine application
**vaccination interval (d):** time period in days between the first and the second vaccine application

**challenge:** specific experimental transmission of disease pathogens and afterwards evaluation of the outcome with determined factors (clinical outcome, pathomorphological alterations, virus shedding, antibody titer, cell-mediated immunity).

**clinics:**
- **„+“:** significant less morbidity and/or significant milder disease progression and/or significant less mortality and/or significant less recurrence rate in vaccinated animals compared to unvaccinated animals
- **„0“:** no significant differences in morbidity and/or disease progression and/or mortality and/or recurrence rate in vaccinated animals compared to unvaccinated animals
- **„-“:** significant higher morbidity and/or significant more serious disease progression and/or significant higher mortality and/or significant higher recurrence rate in vaccinated animals compared to unvaccinated animals

**pathomorphological alterations:** evalution of pathomorphological findings in perished/euthanasied animals within a necropsy
- **„+“:** macroscopical and/or histological signifcant less pathomorphological findings in the respiration tract of vaccinated animals compared to unvaccinated animals
- **„0“:** macroscopical and/or histological no signifcant differences in pathomorphological findings in the respiration tract of vaccinated animals compared to unvaccinated animals
- **„-“:** macroscopical and/or histological signifcant more pathomorphological findings in the respiration tract of vaccinated animals compared to unvaccinated animals

**virus shedding:**

**„+“:** significant less (quantitative) and/or shorter virus shedding in the nasal discharge of vaccinated animals compared to unvaccinated animals

**„0“:** no significant differences in duration and/or amount of virus shedding in the nasal discharge of vaccinated animals compared to unvaccinated animals

**antibody titers:**

**„+“:** significant higher antibody titers against pathogens of the enzootic bronchopneumonia in the blood and/or at the mucosa in vaccinated animals compared to unvaccinated animals

**„0“:** no significant differences in the antibody titers against pathogens of the enzootic bronchopneumonia in the blood and/or at the mucosa in vaccinated animals compared to unvaccinated animals

**„-“:** significant lower antibody titers against pathogens of the enzootic bronchopneumonia in the blood and/or at the mucosa in vaccinated animals compared to unvaccinated animals

**cell-mediated immunity:**

**„+“:** significant stronger cell-mediated immunity in vaccinated animals compared to unvaccinated animals

**„0“:** no significant differences in cell-mediated immunity in vaccinated animals compared to unvaccinated animals

**daily weight gain:**

**„+“:** significant higher daily weight gains in a defined time period in vaccinated animals compared to unvaccinated animals

**„0“:** no significant differences in daily weight gains in a defined time period in vaccinated animals compared to unvaccinated animals

**protection Rate (%):** percentage oft the calves that are protected from respiratory disease because of an vaccination against enzootic bronchopneumonia

## 3. Results

A number of 252 studies were identified through database searching in PubMed.gov and Web of Science (Fig. 1). A number of 6 studies were additionally added through other sources. A sum of 94 duplicates were removed. On basis of title and abstract screening 86 of the remaining 158 studies were excluded. For the remaining 73 studies full text-articles were assessed and a number of 20 studies were excluded due to not fitting scope, aim or content: the effectivity of the vaccination was not verifiable (n=4), the reference dealt with development of vaccines, molecular methods or the investigation of serotypes (n=34), other mammalians than cattle or adult cattle (not calves) were investigated (n=23), other pathogens than one of the Bovine Respiratory Disease complex were used (n=10), no control or placebo comparator group (n=13), study not published or published in a not peer-reviewed journal (n=5), reviews or in vitro studies (n=17). Finally, 52 studies reporting on 131 experiments were included in the following review process.

- Figure 1 near here -

### *3.1 Parenteral vaccination of naïve calves using an inactivated vaccine*

The effects of applying an inactivated vaccine in seronegative calves were studied in 20 experiments published in 10 studies (Tab. 1). None of the studies has been published in the past ten years. Most of the experiments (19/20) were conducted with young calves. A booster vaccination was compulsive. Whenever tested, the VACCinact vaccination induced a reduced virus excretion compared to controls, a cell-mediated immune response and except in 1 out of 15 experiments significant titers of antibodies. The effects of the vaccination on clinical outcome and pathomorphological alterations in the lung were less clear. In only 8 out of 18 experiments, advantageous effects of the vaccination on clinic parameters were found, while in 9 out of 18 experiments the clinical outcome was not significantly affected. In one study even more severe clinical symptoms were reported for vaccinated calves compared to controls (Berghaus et al., 2006). Less severe pathomorphological alterations in the lung were observed in 7 of 14 experiments, but not in the other 7 experiments. Neither a protection rate nor the effects of the vaccination on DWG were evaluated – this may be due to the low number of animals used in these experimental studies.

**Table 1**
Results of experimental studies conducted to evaluate the effect of parenteral administered inactivated vaccines against BRD in naïve calves. Detailed explanations of parameters and effects according to 2.5.

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Cardella et al. 1987 | 1 | MH, PM | 20 | MH | 0 | 0 | | | | | |
| Cardella et al. 1987 | 1 | MH, PM | 21 | MH | 0 | 0 | | | | | |
| Cardella et al. 1987 | 1 | MH, PM | 21 | MH | + | + | | | | | |
| Cardella et al. 1987 | 1 | PM | 16 | PM | 0 | 0 | | | | | |
| Ellis et al. 2001 | 1 | BRSV | 21 | BRSV | + | + | + | + | | | |
| Ellis et al. 2001 | 1 | BRSV | 21 | BRSV | + | + | + | + | | | |
| Antonis et al. 2003 | 1 | BRSV | 21 | BRSV | 0 | 0 | + | + | | | |
| Patel 2004 | 1 | BRSV, PI3 | 28 | BRSV, PI3 | 0 | | + | + | | | |
| Patel 2004 | 1 | BRSV, PI3 | 28 | BRSV, PI3 | 0 | | + | + | | | |
| Ellis et al. 2005 | 1 | BRSV | 19 | BRSV | + | + | + | + | | | |
| Antonis et al. 2006 | 1 | BRSV | 21 | BRSV | | 0 | + | | + | | |
| Berghaus et al. 2006 | 1 | BRSV, HS | 10 | BRSV, HS | 0 | | + | 0 | + | | |
| Berghaus et al. 2006 | 1 | BRSV, HS | 10 | BRSV | - | | + | + | + | | |
| Berghaus et al. 2006 | 1 | BRSV, HS | 10 | HS | + | | + | + | + | | |
| Makoschey et al. 2006 | 1 | BRSV, PI3, MH | 28 | BRSV | 0 | 0 | + | + | | | |
| Makoschey et al. 2006 | 1 | BRSV, PI3, MH | 28 | PI3 | 0 | 0 | + | + | | | |
| Makoschey et al. 2006 | 1 | BRSV, PI3, MH | 28 | MH | + | + | + | + | | | |
| Makoschey et al. 2006 | 1 | BRSV, PI3, MH | 28 | MH | + | + | + | + | | | |
| Makoschey et al. 2006 | 1 | BRSV, PI3, MH | 28 | MH | + | + | + | + | | | |
| Sandbulte and Roth 2003 | 2 | BRSV | 28 | | | | | + | + | | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* HS: *Histophilus somni*
[c]MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* HS: *Histophilus somni*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate

## 3.2 *Pareneral vaccination of calves with unknown or seropositive serostatus using an inactivated vaccine*

Young calves were used in 13 experiments published in 8 studies (Tab. 2). Clearly, vaccinated calves excreted less virus in three experimental studies after a challenge infection. Antibody titers were increased in 7 out of 11 experiments while no effects were

observed in 4 out of 11 experiments. CMI was significantly increased in calves studied in two out of three experiments. In 8 out of 13 experiments, the clinical course was less severe in vaccinated calves while no differences in clinical parameters were obvious in 5 of 13 experiments. In three experiments, the vaccine was applied only once. In all of these experiments, there was no evidence for advantages of the vaccination on the clinical outcome. Pathomorphological changes were checked in 6 experiments. Significantly less alterations were found in 3 out of 6 experiments in vaccinated calves, while in the remaining three experiments no differences were found. The proportion of protected calves was reported to vary between 38 and 77 % in experiments where vaccination induced positive clinical effects. No evidence for positive effects of a vaccination on DWG has been reported.

Older calves were used in 10 predominantly older studies (Tab. 2). Positive effects of the vaccination on the parameters tested were prevailing. Positive effects of the vaccination on the clinical outcome were reported in 7 out of 16 experiments. Interestingly, in one study even more severe clinical symptoms and more excessive pathomorphological alterations were reported for vaccinated calves compared to controls (Schreiber et al., 2000).

**Table 2**
Results of experimental and field studies conducted to evaluate the effect of parenteral administered inactivated vaccines against BRD in calves with unknown or seropositive serostatus. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Howard et al. 1987 | 1 | BRSV, PI3, MB, MD | 21 | | + | | | + | 0 | | 77% |
| Howard et al. 1987 | 1 | BRSV | 21 | | + | | | + | + | | 68% |
| Stott et al. 1987 | 1 | BRSV, PI3, MB, MD | 21 | | + | 0 | | + | | | 69% |
| Stott et al. 1987 | 1 | BRSV, PI3, MB, MD | 21 | | + | + | | + | | | 69% |
| Stott et al. 1987 | 1 | BRSV, PI2, MB, MD | 21 | | 0 | 0 | | 0 | | | |
| Groom and Little 1988 | 1 | HS | | HS | 0 | + | | + | | | |
| Groom and Little 1988 | 1 | HS | 14 | HS | + | + | | + | | | |
| Van Donkersgoed et al. 1994 | 1 | MH, HS | 14 | | 0 | | | 0 | | 0 | |
| Patel and Didlick 2004 | 1 | BRSV | 28 | BRSV | + | | + | 0 | | | |
| Mawhinney and Burrows 2005 | 1 | BRSV, PI3, MH | | BRSV | 0 | | + | + | | | |
| Makoschey et al. 2008 | 1 | BRSV, PI3, MH | 28 | | + | | | | | | 71% |
| Makoschey et al. 2008 | 1 | BRSV, PI3, MH | 28 | | + | | | | | | 38% |
| Van der Sluijs et al. 2010 | 1 | BRSV, PI3, MH | | BRSV | 0 | 0 | + | 0 | + | | |
| Bateman 1988 | 2 | MH | | | + | | | | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3 | 21 | | | | | + | | | |
| Ellis et al. 1992a | 2 | BRSV | 14 | | | | | | + | | |
| Ellis et al. 1992b | 2 | BRSV | 14 | | | | | + | | | |
| Wright et al. 1994 | 2 | BRSV, PI3, MH | 21 | | 0 | | | | | + | |
| Ellis et al. 1995 | 2 | BRSV, PI3 | 14 | | + | | | + | + | | |
| Ellis et al. 1995 | 2 | BRSV, PI3 | 14 | | + | | | + | + | | |
| Ellis et al. 1995 | 2 | BRSV, PI3 | 14 | | + | | | + | + | | |
| Ellis et al. 1995 | 2 | BRSV, PI3 | 14 | | + | | | + | + | | |
| Fulton et al. 1995 | 2 | BRSV, PI3 | 28 | | | | | + | | | |
| Fulton et al. 1995 | 2 | BRSV, PI3 | 28 | | | | | + | | | |
| Schreiber et al. 2000 | 2 | BRSV | 21 | | - | - | | - | | | 21% |
| Fulton et al. 2004 | 2 | BRSV, PI3 | 95 | | | | | + | | | |
| Fulton et al. 2004 | 2 | BRSV, PI3, MH, PM | 95** | | | | | + | | | |
| Patel and Didlick 2004 | 2 | BRSV | 28 | BRSV | + | | + | 0 | | | |
| Patel and Didlick 2004 | 2 | BRSV | 28 | BRSV | + | | + | 0 | | | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* MB: *Mycoplasma bovis,* MD: *Mycoplasma dispar,* HS: *Histophilus somni,* MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida*
[c] HS: *Histophilus somni,* BRSV: *Bovine syncytial virus*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate

grey background: field studies
**special booster procedure: first vaccinated with an inactivated BRSV/PI3 vaccine, 95 days later boostered with an modified live MH/PM vaccine

### *3.3 Parenteral vaccination of naïve calves using a modified live vaccine*

A total of 15 experiments published in 8 studies has been conducted; predominantly young calves were used (Tab. 3). In 9 experiments, clinical parameters were significantly better in vaccinated compared to non-vaccinated calves, while no effect was seen in 6 of these experiments. Almost consistently, positive effects of the vaccination could be demonstrated in respect to the extent of pathomorphological alterations, virus shedding and cell-mediated immune responses. Moreover, Horne et al. (2007) reported positive effects of the vaccination on DWG (Diana: hier genauer: wie gross war der Effekt? In welchem Zeitraum gemessen? Sollte hier exakter beschrieben werden, weil wir ja ansonsten praktisch nie positive Effekte fanden!). An increase of antibody titers could be found in 5 out of 5 experiments, while there was no increase of antibody titers in the remaining 5 experiments (?). In six studies, positive effects were reported even without a booster vaccination. In none of the experiments, effects of the vaccination on PR were checked.

**Table 3**
Results of experimental and field studies conducted to evaluate the effect of parenteral administered modified live vaccines against BRD in naïve calves. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Cardella et al. 1987 | 1 | MH | | MH | 0 | 0 | | | | | |
| Cardella et al. 1987 | 1 | MH | | MH | + | + | | | | | |
| Cardella et al. 1987 | 1 | PM | 14 | PM | + | + | | | | | |
| Cardella et al. 1987 | 1 | PM | | PM | + | + | | | | | |
| West et al. 1999 | 1 | BRSV, PI3 | 21 | BRSV | + | + | + | 0 | + | | |
| West et al. 1999 | 1 | BRSV, PI3 | | BRSV | + | + | + | 0 | + | | |
| West et al. 1999 | 1 | BRSV, PI3 | | BRSV | + | + | + | 0 | + | | |
| Antonis et al. 2003 | 1 | BRSV | 21 | BRSV | + | + | + | + | | | |
| Peters et al. 2004 | 1 | BRSV, PI3 | 21 | PI3 | 0 | | 0 | + | | | |
| Antonis et al. 2006 | 1 | BRSV | 21 | BRSV | | + | + | | + | | |
| Ellis et al. 2010 | 1 | BRSV, PI3, MH, PM | | BRSV | 0 | + | + | 0 | | | |
| Sandbulte and Roth 2003 | 2 | BRSV | 28 | | | | | + | + | | |
| Peters et al. 2004 | 2 | BRSV, PI3 | 21 | BRSV | 0 | | + | + | | | |
| Horne et. al 2007 | 2 | BRSV, PI3 | | | + | | | | | + | |
| Horne et. al 2007 | 2 | BRSV, PI3 | | | 0 | | | | | + | |
| Salt et al. 2007 | 2 | BRSV, PI3 | 21 | BRSV | 0 | | + | + | | | |
| Salt et al. 2007 | 2 | BRSV, PI3 | 21 | PI3 | + | | + | 0 | | | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus*
[c]MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate
grey background: field studies

*3.4 Parenteral vaccination of calves with a seropositive or unknown serostatus using a modified live vaccine*

This setup was investigated in comparatively many studies, i. e. 16 experiments depicted in 10 studies in young calves and 25 experiments reported in 12 papers in older calves (Tab. 4). When live vaccines were applied parenterally to seropositive young calves, most experiments did not reveal any significantly positive results on the parameters tested. An effect of the vaccination on the development of the calves reflected by DWG could not be found in any of 5 experiments.

In older calves, however, predominantly positive effects on clinical outcome (8 out of 11), antibody titers (15 out of 16) and cell-mediated immune response (3 out of 3) were reported. Kimman et al. (1989), however, described negative effects of the vaccination on clinical and pathomorphological alterations. No positive effects of a vaccination on DWG has been reported (?).

**Table 4**
Results of experimental and field studies conducted to evaluate the effect of parenteral administered modified live vaccines against BRD in calves with unknown or seropositive serostatus. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Frankena et al. 1994 | 1 | BRSV | 21 | | + | + | | | | 0 | 57% |
| Van Donkersgoed et al. 1994* | 1 | BRSV | 14 | | 0 | | | 0 | | 0 | |
| Aubry et al. 2001 | 1 | MH, PM | 14 | | | | | + | | 0 | |
| Mawhinney and Burrows 2005 | 1 | BRSV | | BRSV | 0 | | + | + | | | |
| Harmeyer et al. 2006 | 1 | BRSV, PI3 | 20 | BRSV | + | | + | + | | | |
| Makoschey et al. 2008 | 1 | BRSV, PI3 | 28 | | 0 | | | | | | 38% |
| Makoschey et al. 2008 | 1 | BRSV, PI3 | 28 | | 0 | | | | | | 8% |
| Windeyer et al. 2012 | 1 | BRSV, PI3 | | | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | BRSV, PI3 | | | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | BRSV, PI3 | 21 | | 0 | | | | | 0 | |
| Woolums et al. 2013 | 1 | BRSV, PI3, MH, PM | 215 | | | | | 0 | 0 | | |
| Woolums et al. 2013 | 1 | BRSV, PI3, MH, PM | 147 | | | | | 0 | 0 | | |
| Ellis et al. 2014 | 1 | BRSV, PI3 | | BRSV | 0 | 0 | 0 | 0 | 0 | | |
| Windeyer et al. 2015 | 1 | BRSV, PI3 | | | | | | 0 | | | |
| Windeyer et al. 2015 | 1 | BRSV, PI3 | | | | | | 0 | | | |
| Windeyer et al. 2015 | 1 | BRSV, PI3 | 21 | | | | | 0 | | | |
| Kimman et al. 1989* | 2 | BRSV | | | - | - | | | | | -50% |
| Ellis et al. 1990 | 2 | BRSV | 14 | | + | | | + | + | | |
| Van Donkersgoed et al. 1990 | 2 | BRSV, PI3, HS | 21 | | + | | | + | | | |
| Van Donkersgoed et al. 1990 | 2 | BRSV, PI3 HS | 14 | | 0 | | | 0 | | | |
| Van Donkersgoed et al. 1990 | 2 | BRSV, PI3, HS | 21 | | 0 | | | + | | 0 | |
| Van Donkersgoed et al. 1990 | 2 | BRSV, PI3, HS | | | 0 | | | | | | |
| Van Donkersgoed et al. 1990 | 2 | BRSV, PI3, HS | | | + | | | | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3 | 21 | | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3 | 21 | | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3 | 21 | | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | BRSV | 21 | | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3, BRSV | 21 | | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | PI3, BRSV | 21 | | | | | + | | | |
| Ellis et al. 1992a | 2 | BRSV, PI3 | 14 | | | | | | + | | |
| Ellis et al. 1992b | 2 | BRSV | 14 | | | | | + | | | |
| Ellis et al. 1992b | 2 | BRSV, PI3 | 14 | | | | | + | | | |
| Ellis et al. 1995 | 2 | BRSV, PI3 | 14 | | + | | | + | + | | |
| Fulton et al. 1995 | 2 | BRSV, PI3 | 28 | | | | | + | | | |
| Fulton et al. 1995 | 2 | PI3 | 140 | | | | | + | | | |
| Bechtol and Jones 1996* | 2 | MH, PM | | | + | | | | | | |
| Fulton et al. 2004 | 2 | MH, PM | | | | | | + | | | |
| Stilwell et al. 2008 | 2 | BRSV, PI3 | 15-28 | | + | | | | | | |
| Macek et al. 2010 | 2 | BRSV, PI3 | | | + | | | | | 0 | |
| Macek et al. 2010 | 2 | BRSV, PI3 | 14 | | + | | | | | 0 | |
| Macek et al. 2010 | 2 | BRSV, PI3 | 14 | | + | | | | | 0 | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]BRSV: *Bovine syncytial virus,* MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* PI3: *Parainfluenza type 3 virus,* HS: *Histophilus somni*
[c]BRSV: *Bovine syncytial virus*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate
grey background: field studies
*Application not clearly defined

### *3.5 Intranasal vaccination of naïve calves using a modified live vaccine*

A vaccine was applied intranasally in 11 experiments published in 7 papers; exclusively young calves were used (Tab. 5). In 8 out of 11 experiments, clinical parameters were improved in vaccinated calves while positive effects could not be found in three experiments. Also for the other parameters used to assess the efficiency of the immune response, more significantly positive effects were reported than missing effects of the vaccine. No positive effects could only been found in the CMI (3 out of 3 experiments). Interestingly, in this setup even a single application of the vaccine induced frequently positive effects.

**Table 5**
Results of experimental studies conducted to evaluate the effect of intranasal administered modified live vaccines against BRD in naïve calves. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Bryson et al. 1999 | 1 | PI3 | 49 | PI3 | + | + | + | + | | | |
| Ellis et al. 2007 | 1 | BRSV | 21 | BRSV | + | | + | + | 0 | | |
| Ellis et al. 2007 | 1 | BRSV | | BRSV | + | | + | 0 | 0 | | |
| Ellis et al. 2007 | 1 | BRSV, PI3 | | BRSV | + | + | + | 0 | 0 | | |
| Vangeel et al. 2007 | 1 | BRSV, PI3 | | BRSV | + | | 0 | + | | | |
| Vangeel et al. 2009 | 1 | BRSV, PI3 | | PI3 | 0 | | + | + | | | |
| Ellis et al. 2010 | 1 | BRSV, PI3, MH, PM | | BRSV | 0 | 0 | + | + | | | |
| Ellis et al. 2010 | 1 | BRSV, PI3, MH, PM | | BRSV | 0 | + | + | 0 | | | |
| Xue et al. 2010 | 1 | BRSV, PI3, MH, PM | | BRSV | + | 0 | + | + | | | |
| Xue et al. 2010 | 1 | BRSV, PI3, MH, PM | | PI3 | + | | + | + | | | |
| Ellis et al. 2013 | 1 | BRSV | | BRSV | + | + | + | + | | | |

[a]1: ≤ 12 weeks
[b]PI3: *Parainfluenza type 3 virus,* BRSV: *Bovine syncytial virus,* MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,*
[c]PI3: *Parainfluenza type 3 virus,* BRSV: *Bovine syncytial virus*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate

### *3.6 Intranasal vaccination of calves with a seropositive or unknown serostatus using a modified live vaccine*

This setup was tested again predominantly in young calves resulting in a total of 11 experiments published in 9 papers. This setup was accompanied by less significantly positive effects and a higher number of insignificant effects on clinical outcome as well as additional parameters indicative for a successful immune response compared to seronegative calves treated with a modified live vaccine.

**Table 6**
Results of experimental and field studies conducted to evaluate the effect of intranasal administered modified live vaccines against BRD in calves with unknown or seropositive serostatus. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigens[b] | Vaccination interval (d) | Challenge[c] | C[d] | PM[e] | VS[f] | AB[g] | CMI[h] | DWG[i] | PR[k] |
| Bryson et al. 1999 | 1 | PI3 | 28 | PI3 | + | + | + | 0 | | | |
| Miao et al. 2004 | 1 | BRSV | | BRSV | + | + | | | 0 | | |
| Woolums et al. 2004 | 1 | BRSV | | BRSV | + | + | | 0 | + | | |
| Vangeel et al. 2007 | 1 | BRSV, PI3 | | BRSV | + | | + | + | | | |
| Vangeel et al. 2009 | 1 | BRSV, PI3 | | PI3 | 0 | | + | 0 | | | |
| Ellis et al. 2010 | 1 | BRSV, PI3, MH, PM | | BRSV | 0 | 0 | + | 0 | | | |
| Ellis et al. 2013 | 1 | BRSV | | BRSV | + | + | + | + | | | |
| Ellis et al. 2013 | 1 | BRSV | | BRSV | 0 | 0 | + | + | | | |
| Woolums et al. 2013 | 1 | BRSV, PI3, MH, PM | 215 | | | | | 0 | 0 | | |
| Woolums et al. 2013 | 1 | BRSV, PI3, MH, PM | 147 | | | | | 0 | 0 | | |
| Van Donkersgoed et al. 1991 | 2 | PI3 | 21 | | | | | + | | | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]PI3: *Parainfluenza type 3 virus,* BRSV: *Bovine syncytial virus,* MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,*
[c]PI3: *Parainfluenza type 3 virus,* BRSV: *Bovine syncytial virus*
[d]C: clinical outcome
[e]PM: pathomorphological alterations
[f]VS: virus shedding
[g]AB: antibody titer
[h]CM: cell-mediated immunity
[i]DWG: daily weight gain
[k]PR: protection rate
grey background: field studies

## *3.8 Field studies conducted to evaluate the effect of a polyvalent vaccine*

**Table 8**
Results of field studies conducted to evaluate the effect of a polyvalent vaccine. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | | | | Experimental design | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | | Antigen[b] | Application[c] | Vaccination Interval (d) | Challenge | Immunstatus[d] | | C[e] | PM[f] | VS[g] | AB[h] | CMI[i] | DWG[k] | PR[l] |
| Howard et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | quadrivalenter Impfsoff | + | | | + | 0 | | 77% |
| Stott et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | 12 Wo alt | + | 0 | | + | | | 69% |
| Stott et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | 7 Wo alt | + | + | | + | | | 69% |
| Stott et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | 3 Wo alt | 0 | 0 | | 0 | | | |
| Van Donkersgoed et al. 1994 | 1 | 1 | MH, HS | 1 | 14 | | 1 | | 0 | | | 0 | | 0 | |
| Van Donkersgoed et al. 1994 | 1 | 3 | BRSV, MH, HS | 1* | 14 | | 1 | | 0 | | | 0 | | 0 | |
| Aubry et al. 2001 | 1 | 2 | MH, PM | 1 | 14 | | 1 | | | | | + | | 0 | |
| Makoschey et al. 2008 | 1 | 1 | BRSV, PI3, MH | 1 | 28 | | 1 | Studie 1, Bovilis Bovipast RSP | + | | | | | | 71% |
| Makoschey et al. 2008 | 1 | 2 | BRSV, PI3 | 1 | 28 | | 1 | Studie 1, Rispoval 3 | 0 | | | | | | 38% |
| Makoschey et al. 2008 | 1 | 1 | BRSV, PI3, MH | 1 | 28 | | 1 | Studie 2, Bovilis Bovipast RSP | + | | | | | | 38% |
| Makoschey et al. 2008 | 1 | 2 | BRSV, PI3 | 1 | 28 | | 1 | Studie 2, Cattlemaster 4 | 0 | | | | | | 8% |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 2Wo | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 5Wo | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | 21 | | 1 | geimpft mit 2 und 5 Wochen | 0 | | | | | 0 | |
| Woolums et al. 2013 | 1 | 2 | BRSV, PI3, MH, PM | 2 | 215 | | 1 | geimpft mit 2d | | | | 0 | 0 | | |
| Woolums et al. 2013 | 1 | 2 | BRSV, PI3, MH, PM | 2 | 147 | | 1 | geimpft mit 70d | | | | 0 | 0 | | |
| Woolums et al. 2013 | 1 | 2 | BRSV, PI3, MH, PM | 1 | 215 | | 1 | geimpft mit 2d | | | | 0 | 0 | | |
| Woolums et al. 2013 | 1 | 2 | BRSV, PI3, MH, PM | 1 | 147 | | 1 | geimpft mit 70d | | | | 0 | 0 | | |
| Windeyer et al. 2015 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 2Wo | | | | 0 | | | |
| Windeyer et al. 2015 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 5Wo | | | | 0 | | | |
| Windeyer et al. 2015 | 1 | 2 | BRSV, PI3 | 1 | 21 | | 1 | geimpft mit 2 und 5 Wochen | | | | 0 | | | |
| Bateman 1988 | 2 | 3 | PI3, MH | 1 | | | 1 | | - | | | | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 21 | | 1 | Studie 1 (ranch calves) | + | | | + | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 14 | | 1 | Studie 2 (bull test station) | 0 | | | 0 | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 21 | | 1 | udie 3 (research station calve | 0 | | | + | | 0 | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | | | 1 | Studie 4 (feedlot yearlings) | 0 | | | | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | | | 1 | Studie 5 (feedlot yearlings) | + | | | | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3, BRSV | 1 | 21 | | 1 | Cattlemaster 4 | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3, BRSV | 1 | 21 | | 1 | Horizon 4 | | | | + | | | |
| Wright et al. 1994 | 2 | 1 | BRSV, PI3, MH | 1 | 21 | | | | 0 | | | | | + | |
| Bechtol and Jones 1996 | 2 | 2 | MH, PM | 1* | | | 1 | | + | | | | | | |
| Fulton et al. 2004 | 2 | 1 | BRSV, PI3 | 1 | 95 | | 1 | | | | | + | | | |
| Fulton et al. 2004 | 2 | 2 | MH, PM | 1 | | | 1 | | | | | + | | | |
| Fulton et al. 2004 | 2 | 3** | BRSV, PI3, MH, PM | 1 | 95** | | 1 | | | | | + | | | |
| Horne et. al 2007 | 2 | 2 | BRSV, PI3 | 1 | | | 0 | Impfstoff A | + | | | | | + | |
| Horne et. al 2007 | 2 | 2 | BRSV, PI3 | 1 | | | 0 | Impfstoff B | 0 | | | | | + | |
| Stilwell et al. 2008 | 2 | 2 | BRSV, PI3 | 1 | 15-28 | | | | + | | | | | | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | | | | | + | | | | | 0 | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | 14 | | | 2x geimpft | + | | | | | 0 | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | 14 | | | 3x geimpft | + | | | | | 0 | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]1: inactivated Vaccine, 2: modified live vaccine, BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* MB: *Mycoplasma bovis*, MD: *Mycoplasma dispar*, MH: *Mannheimia haemolytica,* PM: *Pasteurella multocida,* HS: *Histophilus somni*
[c]1: parenteral
[d]0: seronegative, 1: seropositive

[e]C: clinical outcome
[f]PM: pathomorphological alterations
[g]VS: virus shedding
[h]AB: antibody titer
[i]CM: cell-mediated immunity
[k]DWG: daily weight gain
[l]PR: protection rate

## *3.9 Field studies conducted to evaluate the effect of a monovalent vaccine*

**Table 9**
Results of field studies conducted to evaluate the effect of a monovalent vaccine. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | | | | Experimental design | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | | Antigen[b] | Application[c] | Vaccination Interval (d) | Challenge | Immunstatus[d] | | C[e] | PM[f] | VS[g] | AB[h] | CMI[i] | DWG[k] | PR[l] |
| Howard et al. 1987 | 1 | 1 | BRSV | 1 | 21 | | | monovalenter Impfstoff | + | | | + | + | | 68% |
| Frankena et al. 1994 | 1 | 2 | BRSV | 1 | 21 | | 1 | Rispoval 3 | + | + | | | | 0 | 57% |
| Van Donkersgoed et al. 1994 | 1 | 2 | BRSV | 1* | 14 | | 1 | | 0 | | | 0 | | 0 | |
| Bateman 1988 | 2 | 1 | MH | 1 | | | 1 | | + | | | | | | |
| Kimman et al. 1989 | 2 | 2 | BRSV | 1* | | | | | - | - | | | | | -50% |
| Van Donkersgoed et al. 1991 | 2 | 1 | PI3 | 1 | 21 | | 1 | Triangle 3 | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3 | 1 | 21 | | 1 | Resbo IBR/PI3 | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3 | 1 | 21 | | 1 | Cattlemaster 3 | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3 | 1 | 21 | | 1 | Sentry 1 + IBR/PI3/Somnugen | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | PI3 | 2 | 21 | | 1 | TSV-2 | | | | + | | | |
| Van Donkersgoed et al. 1991 | 2 | 2 | BRSV | 1 | 21 | | 1 | BRSV Vac + Horizon II | | | | + | | | |
| Schreiber et al. 2000 | 2 | 1 | BRSV | 1 | 21 | | 1 | | - | - | | - | | | 21% |

[a]1: ≤ 12 weeks, 2: > 12 weeks

[b]1: inactivated Vaccine, 2: modified live vaccine, BRSV: *Bovine syncytial virus,* MH: *Mannheimia haemolytica,* PI3: *Parainfluenza type 3 virus*
[c]1: parenteral
[d]1: seropositive
[e]C: clinical outcome
[f]PM: pathomorphological alterations
[g]VS: virus shedding
[h]AB: antibody titer
[i]CM: cell-mediated immunity
[k]DWG: daily weight gain
[l]PR: protection rate
*Application not clearly defined

## *3.10 Field studies with positive clinical outcome*

**Table 10**
Field studies with positive clinical outcome. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | | | | Experimental design | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigen[b] | | Application[c] | Vaccination Interval (d) | Challenge | Immunstatus[d] | | C[e] | PM[f] | VS[g] | AB[h] | CMI[i] | DWG[k] | PR[l] |
| Howard et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | quadrivalenter Impfsoff | + | | | + | 0 | | 77% |
| Howard et al. 1987 | 1 | 1 | BRSV | 1 | 21 | | | monovalenter Impfstoff | + | | | + | + | | 68% |
| Stott et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | 12 Wo alt | + | 0 | | + | | | 69% |
| Stott et al. 1987 | 1 | 1 | BRSV, PI3, MB, MD | 1 | 21 | | | 7 Wo alt | + | + | | + | | | 69% |
| Frankena et al. 1994 | 1 | 2 | BRSV | 1 | 21 | | 1 | Rispoval 3 | + | + | | | | 0 | 57% |
| Makoschey et al. 2008 | 1 | 1 | BRSV, PI3, MH | 1 | 28 | | 1 | Studie 1, Bovilis Bovipast RSP | + | | | | | | 71% |
| Makoschey et al. 2008 | 1 | 1 | BRSV, PI3, MH | 1 | 28 | | 1 | Studie 2, Bovilis Bovipast RSP | + | | | | | | 38% |
| Bateman 1988 | 2 | 1 | MH | 1 | | | 1 | | + | | | | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 21 | | 1 | Studie 1 (ranch calves) | + | | | + | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | | | 1 | Studie 5 (feedlot yearlings) | + | | | | | | |
| Bechtol and Jones 1996 | 2 | 2 | MH, PM | 1* | | | 1 | | + | | | | | | |
| Horne et. al 2007 | 2 | 2 | BRSV, PI3 | 1 | | | 0 | Impfstoff A | + | | | | | + | |
| Stilwell et al. 2008 | 2 | 2 | BRSV, PI3 | 1 | 15-28 | | | | + | | | | | | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | | | | | + | | | | | 0 | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | 14 | | | 2x geimpft | + | | | | | 0 | |
| Macek et al. 2010 | 2 | 2 | BRSV, PI3 | 1 | 14 | | | 3x geimpft | + | | | | | 0 | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]1: inactivated Vaccine, 2: modified live vaccine, BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* MB: *Mycoplasma bovis*, MD: *Mycoplasma dispar*, MH: *Mannheimia haemolytica,* HS: *Histophilus somni,* PM: *Pasteurella multocida*
[c]1: parenteral
[d]0: seronegative, 1: seropositive
[e]C: clinical outcome
[f]PM: pathomorphological alterations
[g]VS: virus shedding
[h]AB: antibody titer
[i]CM: cell-mediated immunity
[k]DWG: daily weight gain
[l]PR: protection rate
*Application not clearly defined

## *3.11 Field studies with no effect on the clinical outcome*

**Table 11**
Field studies with no effect on the clinical outcome. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | | | | Experimental design | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigen[b] | | Application[c] | Vaccination Interval (d) | Challenge | Immunstatus[d] | | C[e] | PM[f] | VS[g] | AB[h] | CMI[i] | DWG[k] | PR[l] |
| Van Donkersgoed et al. 1994 | 1 | 2 | BRSV | 1* | 14 | | 1 | | 0 | | | 0 | | 0 | |
| Makoschey et al. 2008 | 1 | 2 | BRSV, PI3 | 1 | 28 | | 1 | Studie 1, Rispoval 3 | 0 | | | | | | 38% |
| Makoschey et al. 2008 | 1 | 2 | BRSV, PI3 | 1 | 28 | | 1 | Studie 2, Cattlemaster 4 | 0 | | | | | | 8% |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 2Wo | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | | | 1 | geimpft mit 5Wo | 0 | | | | | 0 | |
| Windeyer et al. 2012 | 1 | 2 | BRSV, PI3 | 1 | 21 | | 1 | geimpft mit 2 und 5 Wochen | 0 | | | | | 0 | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 14 | | 1 | Studie 2 (bull test station) | 0 | | | 0 | | | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | 21 | | 1 | udie 3 (research station calve | 0 | | | + | | 0 | |
| Van Donkersgoed et al. 1990 | 2 | 2 | BRSV, PI3, HS | 1 | | | 1 | Studie 4 (feedlot yearlings) | 0 | | | | | | |
| Wright et al. 1994 | 2 | 1 | BRSV, PI3, MH | 1 | 21 | | | | 0 | | | | | + | |
| Horne et. al 2007 | 2 | 2 | BRSV, PI3 | 1 | | | 0 | Impfstoff B | 0 | | | | | + | |

[a]1: ≤ 12 weeks, 2: > 12 weeks
[b]1: inactivated Vaccine, 2: modified live vaccine, BRSV: *Bovine syncytial virus,* PI3: *Parainfluenza type 3 virus,* HS: *Histophilus somni,* MB: *Mycoplasma bovis*, MH: *Mannheimia haemolytica*
[c]1: parenteral
[d]0: seronegative, 1: seropositive
[e]C: clinical outcome
[f]PM: pathomorphological alterations
[g]VS: virus shedding
[h]AB: antibody titer
[i]CM: cell-mediated immunity
[k]DWG: daily weight gain
[l]PR: protection rate
*Application not clearly defined

## *3.11 Field studies with a negative clinical outcome*

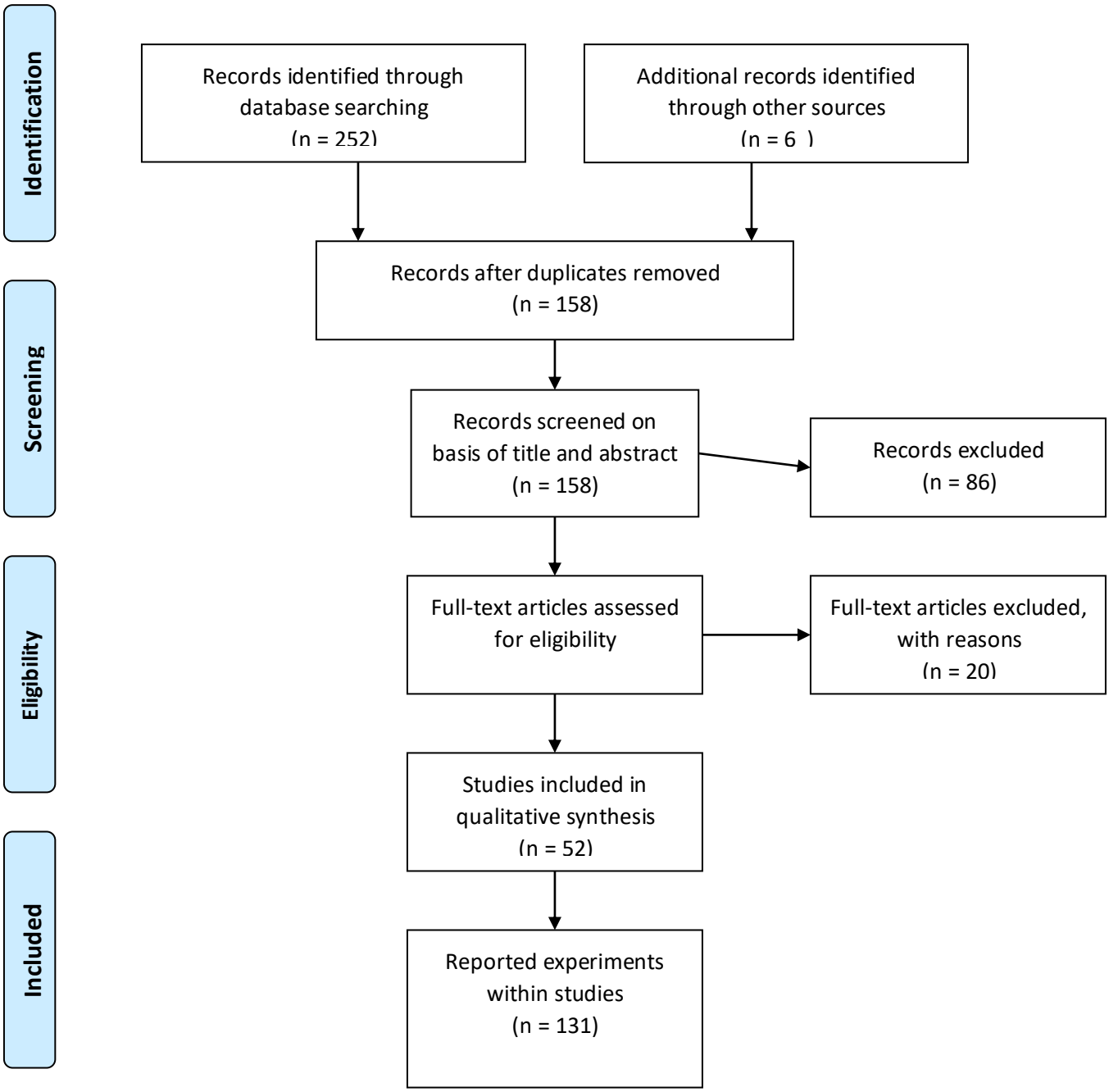
Negative effects on the clinical outcome in field studies occur only in older calves (>12 weeks).

**Table 11**
Field studies with a negative clinical outcome. Detailed explanations of parameters and effects according to 2.5..

| Author | Intervention | | | | | | | Experimental design | Effects | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age[a] | Antigen[b] | | Application[c] | Vaccination Interval (d) | Challenge | Immunstatus[d] | | C[e] | PM[f] | VS[g] | AB[h] | CMI[i] | DWG[k] | PR[l] |
| Bateman 1988 | 2 | 3 | PI3, MH | 1 | | | 1 | | - | | | | | | |
| Kimman et al. 1989 | 2 | 2 | BRSV | 1* | | | | | - | - | | | | | -50% |
| Schreiber et al. 2000 | 2 | 1 | BRSV | 1 | 21 | | 1 | | - | - | | - | | | 21% |

[a]2: > 12 weeks
[b]1: inactivated Vaccine, 2: modified live vaccine, 3: inactivated and modified live vaccine, PI3: *Parainfluenza type 3 virus*, MH: *Mannheimia haemolytica,* BRSV: *Bovine syncytial virus,*
[c]1: parenteral
[d]1: seropositive
[e]C: clinical outcome
[f]PM: pathomorphological alterations
[g]VS: virus shedding
[h]AB: antibody titer
[i]CM: cell-mediated immunity
[k]DWG: daily weight gain
[l]PR: protection rate
*Application not clearly defined

**Figure 1** Decision tree



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