# Taking Vaccine Research to the Field

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#### Vaccines



## All products designed to stimulate active immunization of animals against disease







### Vaccine efficacy/effectiveness

- Ability of a vaccine to protect animals from disease or infection
- Efficacy ≠ Immunogenicity
- Vaccine efficacy –ideal circumstances and 100% vaccine uptake.
- Vaccine effectiveness routine circumstances in the community





#### Calculation of vaccine efficacy

- Efficacy = (R0 R1)/ R0
- Efficacy = 1 RR
- The vaccine efficacy is the percentage of morbidity prevented by vaccination

Δ\_

R1 = risk in vaccinated group = A/N1

R0 = risk in non-vaccinated group = B/N0



Vaccine



Placebo



### Field Effectiveness/Efficacy studies - Pros

- Large sample size: safety and effectiveness
- Natural challenge
- Natural conditions
- Good for measuring other vaccine characteristics:
  - Duration of immunity
  - Interference by other vaccines
  - Adverse effects influencing production
  - Equivalence studies
  - With certain design can calculate direct and indirect protection
  - Un expected situations
- Can be performed where no special facilities are in place





### Effectiveness/Efficacy studies - Cons

- Need circulating disease
- Need good surveillance system
- Might be expensive
- Ethical challenge
- Exposure to the pathogen is not necessarily equal among study groups



## EMA CVMP/852/99 - note for guidance



- Council directive 81/852/EEC Unless justified, results from field trials should be added.
- When efficacy cannot be demonstrated in the laboratory, data from field trials is sufficient!
- However...

If the disease is exotic or rare, data from laboratory trials may be sufficient. In such circumstances the need for extensive laboratory trials may be increased.

 Data from field trials conducted outside the EU, if done in GCP may be considered in support of application fur such vaccines.



## Data gained by post-marketing efficacy and effectiveness studies

- Lumpy skin disease (LSD)
  - Comparison of two vaccines
  - Rare adverse events
  - Time from vaccination to protective immunity
  - Quantitative data for mathematical modelling
- Bovine ephemeral fever (BEF)
  - Comparing various vaccine administration schedules
- Brucella melitnesis and Brucella abortus
  - Vaccine effectiveness for another disease analysis of unexpected results

### Lumpy skin disease

- Capripox lumpy skin disease virus (LSDV)
- Arthropod borne
- Unique to Cattle
- Variable morbidity and case fatality
- Incubation period usually not longer than 2 weeks
- 3 types of clinical appearances:
  - Generalized disease
  - Localized disease
  - Subclinical infection











#### Lumpy Skin Disease Outbreak 2012







Photos by Lior Zamir



#### Immediate control measures

#### Beef Herds

- Vaccination Sheep Pox JOVAC (10<sup>3</sup> TCID/ml s.c.)
- Zoning & Movements restrictions
- Insect control

#### Dairy Herds & Feedlots

- All the above
- + Euthanasia of moderate & severe cases



#### **Epidemic spreads despite vaccination**





#### **Two Choices**



#### SHEEP POX RM65

#### NEETHLING VACCINE



#### JOVIVAC<sup>®</sup>

Freeze dried live attenuated Sheep Pox Virus strain RM-65 Vaccine.



...But no data on efficacy

## Comparison of the efficacy of two LSD vaccines



- Fifteen dairy herds enrolled.
- 4694 cows in 15 herds were randomized to one of the two vaccines



Ben-Gera J et al. Vaccine. 2015 Sep 11;33(38):4837-42.

#### Case definitions and surveillance



- Suspected LSD case: ≥5 typical lesions typical to LSD
- Suspected LSD severe case: Fever (>39.5°C) or/and a 20% reduction in milk production
- Confirmed LSD case wild type LSD virus by PCR (Menasherow et al. 2014).
- All cows were monitored daily by the herdsmen and twice weekly by the herd veterinarians



#### Data collection and summary

Farm	cow #	Group/age	vacc date	vacc type	sick (y/n)	date sick	severe (y/n)

#### Crude efficacy



1:400.000

76 cows were affected by LSD in 8 herds with an incidence of 0.3–5.7%



#### Time of morbidity occurrence

First two weeks - Higher incidence in the Neethling

After two weeks - Higher morbidity in the 10XRM65 group





#### Relative efficacy (cows)

Case definition	Morbidity 10XRM65 (n=1540)	Morbidity Neethling (n=1537)	Vaccine efficacy (Cl <sub>95%)</sub>
LSD case	42 (2.7%)	13 (0.84%)	62% (31-79)
Severe LSD case	20 (1.3%)	1 (0.06%)	91% (57-98)
Confirmed case	22 (1.4%)	6 (0.4%)	77% (37-91)

#### Neethling vaccine adverse reactions

- 9 confirmed cases out of 2356 vaccinated cows (incidence= 0.4%). Of these one severe case
- All occurring within 14 days from vaccination
- No Isolation of Neethling strain from a non-Neethling vaccinated cow





EFSA Journal 2017;15(4):4773

#### An effectiveness study

EFSA urgent advice on lumpy skin disease (EFSA journal, 2016)

- Analysis of the outbreak in Serres, Greece, where the disease occurred in April 2016
- Part of the herds vaccinated after April
- Effectiveness in the herd level





#### Data collection and summary

ID farm	vaccine	Date of Vaccination	LSD	Suspicion date
EL6202166	1	16/11/2015	0	
EL6201836	1	18/11/2015	0	
EL6201848	0		1	02/05/2016

#### Data analysis



- Analysis of the Greek data
  - Follow up period:



## Vaccine effectiveness - time from vaccination

Time from vaccination to protection			0 DAYS
Incidence rate - vaccinated (# cases/days of follow-up)	31/38927		
Incidence rate – <b>non-vaccir</b> (# cases/days of follow-up)	39 / 34724		
IRR (Cl <sub>95%</sub> )			1.41 (0.88-2.26)
Vaccine effectiveness			29.1%
	Proportion of herds infected	0.08 0.06 0.04 0.02 0.00	10 20 30 40 50 Days of follow-up



#### **Conclusions - LSD**



- Both efficacy and effectiveness studies show that the homologous Neethling vaccine is about 80% effective for protection against clinical LSD infection
- An adverse event which looks like a natural infection occurs in about 0.5% of the vaccinated cows
- It takes about 30 days for the vaccine to reach its full effectiveness
- The results enables the formation of more accurate models

#### **Bovine Ephemeral Fever**

- Caused by a vector borne *Rhabdovirus*.
- Causes transient fever, milk loss and recumbency
- Epidemics almost every other year
- Large economical losses
- Vector borne viral disease



## Immunogenicity of an inactivated BEF vaccine (MONTANIDE™ adjuvant)



Aziz Boaron *et al.* Plos-One, 2014



#### Efficacy of an inactivated BEF vaccine



Vaccine is effective only if administered in two consecutive years

Aziz Boaron et al. Vet Microbiol, 2014



A. Milk production: Affected vs. non-affected



- -175.9 kg/sick cow (Cl<sub>95%</sub> = 127.9–223.9)
- B. Milk production: Vaccinated vs. non-Vaccinated

37 kg/vaccinated cow (
$$CI_{95\%}$$
 = -3.6 - 77.7)

C. Epidemic curve

Aziz Boaron et al. Vet Microbiol, 2014

#### **Conclusions - BEF**

- Two vaccination with an inactivated BEF vaccine are not effective for protection against infection
- Three vaccination are 50% effective for preventing clinical disease

• Protection from milk-loss provided by the vaccine is low

#### Does Brucella abortus S19 vaccine protects from B. melitensis

 Brucellosis – a zoonotic disease Cattle Swine Vaccination accident causes by a gram negative or laboratory accident with cultures Slaughter or coccobacilli bacteria veterinary care B suis B abortus • Eight species typical for certain reservoirs Goats and sheep Milk Dogs Veterinary care Slaughter Veterinary care B canis B melitensis

#### B. melitensis and B. abortus

- Vaccines:
  - *B. melitneis* (sheep)– REV-1
  - *B. abortus* S-19
- In Israel:
  - B. abortus
    - was eradicated in the 80's
  - B. melitensis
    - Highly endemic in sheep with some outbreaks in dairy cattle herds
    - High morbidity among Bedouin population in Israel



### Vaccination against B. abortus in Israel



To continue or not to

continue!?

- Risk for incursion of *B. abortus* from neighboring countries negligible
- Expert opinion S19 is not effective against *B. melitensis*

As of September 2013 compulsory vaccination with the S19 vaccine was ceased!

# B. melitensis in a diary herd in the south of Israel



Curtsey of Aniela Gilboa, Israeli veterinary services

### Brucellosis in a dairy herd in the Negev



- November 2015 Diagnosis of *Brucella melitensis* in a cow after abortion
- Outbreak investigation traced the probable index case as an abortion which occurred on May 2015.
- At initial serological sampling 200 / 1700 cows positive and culled
- Since then 420 animals were destroyed.



Van-Straten et al. Vaccine. 2016

# S19 effectiveness against infection and abortion by *B. melitensis*



#### Conclusions – S19 and B. melitensis



• S19 vaccine is 87.2% (95% CI 69.5–94.6%) effective for protecting against infection by *B. melitensis* 

• S19 vaccine is 100%\* effective for protecting against abortions caused by *B. melitensis* (p=0.011)



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