Vaccination against PPR: effectiveness of current vaccines, challenges and future perspectives

Arnaud Bataille

Peste des Petits Ruminants (PPR)

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Vaccination against PPR: effectiveness of current vaccines, challenges and future perspectives

Arnaud Bataille
CIRAD, UMR ASTRE, Montpellier, France
OIE/FAO/EU Reference Laboratory for PPR
arnaud.bataille@cirad.fr
Important requirements for a vaccine in general

- **Efficacy:**
  - Must give strong protection following proper administration
  - Must protect against all strains

- **Safety**
  - No side effect whatever the physiological status of the host (in particular no abortion)

Affordable cost

Available: must be easy to be procured
Important requirements for a vaccine in general

- The attenuated Rinderpest vaccine used during the Global Rinderpest Eradication Campaign (GREP) has all the above attributes
- Same for PPR attenuated vaccines
- Convalescent animal infected by PPRV (and other morbilliviruses) produces a high protective immune response and is never more susceptible to the disease
- Vaccinated (conventional vaccine) animal is also protected for life
Vaccination, main tool for PPR eradication

- PPR target for global eradication (FAO/OIE, 2015)
- Based on massive vaccination campaigns
- 70% immunity needed to stop virus circulation

Progressive step-wise approach for the prevention and control of PPR (FAO/OIE, 2015)
Conventional PPR vaccines

Nigeria 75-1 vaccine strain developed by CIRAD and Pirbright

Origin: Nigeria 75/1 strain (lineage II) attenuated by 74 successive passages on Vero cells (Diallo et coll., 1989).

- Field trials on nearly 100,000 animals,
- Efficacy, innocuity, no residual side effects
- Scalable for mass production
- Safety: 3 back passages in animals with no reversion
- Protective antibodies generated after a single injection in one week and persisting for at least 3 years
Conventional PPR vaccines

Nigeria 75-1 vaccine strain developed by CIRAD and Pirbright

- Confers a clinical protection against all lineages of PPRV, with no transmission of challenge virus to in-contact animals
- Can be used in pregnant animals at any stage of pregnancy
- Passive immunity in young animals for 2-4 months after birth
- Extensively tested since 25 years in Africa, the Middle East and Asia
Mass vaccination: Morocco outbreak in 2008

Large outbreak in June-August 2008

- Perifocal vaccination + full-scale vaccination campaign with vaccine Nigeria 75/1 started in September 2008
- In 3 months time, about 20.6 millions out of the 25 millions sheep and goats of the country were vaccinated
Mass vaccination: Morocco outbreak in 2008

Post vaccination

- Decrease in number of outbreaks

Mass vaccination continued in 2009-2011

Serosurveillance study in young animals (less than 8 months of age) in 2012 revealed no antibody prevalence against PPR virus
Conventional PPR vaccines

Now multiple attenuated PPR vaccine strains are available:

- PPRV Nigeria 75/1 (Nigeria, lineage II, goat origin)
- PPR Sungri 96 (India, Lineage IV; goat origin)
- Arasur 87 (India, lineage IV; sheep origin)
- Coimbatore 97 (India, lineage IV; goat origin).
- Titu (Bangladesh, lineage IV; goat origin)
- 45G37/35-K PPR Vaccine (Kazakhstan, Lineage IV?)
- ...

- Should have same characteristics: protection, thermosensibility, duration of immunity: safety etc..
Conventional PPR vaccines

Available for use for a Global Control Programme:

- Produced by more than 20 vaccine manufacturers
- So need for independent certification of produced vaccines to ensure good quality of vaccines to be used for PPR Control Program
- But PPR vaccine quality not always controlled by independent body
PPR vaccine quality control

AU-PANVAC provides an independent quality control (QC) of veterinary vaccines; it can eventually provide expertise to laboratories outside of Africa. Currently, the AU-PANVAC missions are:

- Promote the availability of safe, effective veterinary vaccines and diagnostic reagents,
- Assist in improved production/formulations or new vaccines into Africa,
- Strengthen Africa’s capacity building Quality Assurance. Provide free QC for AU member states.
PPR vaccine quality control

CIRAD performs vaccine quality control if:

- Certificate from OIE/FAO international reference laboratory is requested by manufacturer or a potential buyer
- Requested by European Commission (as part of activities of EURL-PPR)
PPR vaccine quality control

Tests typically performed:

- Confirmation of the presence of PPR virus in the product (RT-PCR)
- Sequence homology to CIRAD vaccine strain (255bp)
- Titration (dose $\geq 10^{2.5}$ TCID50)
- Fungal/bacterial contamination
- Presence of Mycoplasma
- Presence of pestiviruses (BVDV/BDV)
- Presence of Rinderpest virus
- Presence of Bluetongue virus
- Presence of FMD virus
- Presence of Circovirus
Risk of genetic drift

- Only few passages from master seed recommended
- Live vaccines produced by repeated laboratory sub passages consist of mixed viral populations
- The more passages, the higher the risk of loss of efficacy or reversion to virulence
- Not controlled up to now
- Potential solution: next generation sequencing
- Master seed of PPR strain Nigeria 75-1 sequenced (Genbank reference: KY628761)
NGS quality control

Deep sequencing of Nigeria 75/1 vaccine master seed

- >8 millions reads, min cov 1500x
- Comparison with Nigeria 75/1 wild type:
  - Only 18 mutations across the genome
  - Mutations specific to vaccine strain, not present in wild strain genome
  - Potentially associated with virus attenuation
  - Deep analysis: no back mutation detected in the vaccine population
  - Same could be done with commercial vaccines, or experimental passages of vaccine to evaluate risks of genetic drift
Efficacy and innocuity of vaccines

- Not always tested
- When done, not always with same model systems (hard to do comparative studies)
- Need robust challenge models
  - Mimicking natural infections
  - With highly infectious strains
  - With breeds of regional relevance
  - Using adapted methods to follow virus excretion kinetics
PPR challenge model

Tests of virulence of strains and inoculation routes (in collaboration with Merial) on Saanen goats

Maroc 2008

<table>
<thead>
<tr>
<th>Maroc 2008</th>
<th>IV</th>
<th>CIV 1989</th>
<th>IV</th>
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<tr>
<td>IN</td>
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IV = intra-venous
IN = intra-nasal
**PPR challenge model**

- MA08 more virulent to Saanen goats
- Symptoms and excretion differ with inoculation route
- Intra-nasal inoculation more natural
- Ocular swabs better than blood samples to follow virus excretion
- Strong seropositivity in all cases
PPR challenge model

Vaccination trial (PPR-VAC® , BVI, Botswana) with MA08, intra-nasal route
  ▪ 2 groups (20 goats vaccinated, 20 goats not vaccinated)
  ▪ Vaccination at day 0
  ▪ Challenge with MA08 at day 21
**PPR challenge model**

Vaccinated group:
- No virus shedding
- No clinical signs
- Seroconversion within 9 days post vaccination

Good protection of commercial vaccines against virulent PPRV strains threatening european ruminants

**Antibody detection**

**Virus shedding (ocular swabs)**

**Clinical score**
Need for new generation of vaccine

Disadvantages of conventional vaccines

Problems with vaccine delivery - thermostability

- PPRV is heat sensitive requiring an effective cold chain under hot climate
- PPR vaccines lyophilized with lactalbumin hydrolysate–sucrose (LS) or trehalose dehydrate (=Xerovac),
- Shelf life is 2051 days at 4°C, 19 days at 25°C
- Efficacy drops within few hours after resuspension: all doses to be used quickly
- Animals dispersed, difficulty to reach
- Vials of 100 doses – not used in time of certified efficacy
Need for new generation of vaccine

Disadvantages of conventional vaccines

Problems with vaccine delivery - thermostability

- On-going work on improvement of thermostability of live attenuated vaccines (better lyophilization, better resuspension diluent)
- Regionally-adapted logistics needed, taking into account reality of field (close collaboration with field veterinarians, livestock owners)
- Countries ask for vials of 50 doses, but same price as vials of 100 doses (production costs)
Need for new generation of vaccine

Disadvantages of conventional vaccines
No differentiation of vaccinated and infected animals (DIVA vaccine)
Need for new generation of vaccine

Advantages of DIVA vaccines

- Follow-up of vaccination success
- Identification of remaining outbreaks
- Allow to get faster to OIE PPR-free status
- Important at last stages of eradication campaign
- Several DIVA prototypes under development
PPR Capripox recombinant vaccine

Capripox viruses:

- Large DNA virus
- Host specific
- High thermostability
- Ideal virus for the development of multivalent recombinant vaccines and thermostable
- Overlapping geographic distribution of Capripox and PPR viruses
PPR Capripox recombinant vaccine

- KS1 vaccine strain + haemagglutinin (H) and/or the fusion (F) proteins of Nigeria 75/1 attenuated PPR strain = PPR Capripox (sheep and goat pox virus) recombinant vaccines
- Decreasing the cost of campaigns
- Thermal stability
- Single subcutaneous shot
- DIVA vaccines
- Ongoing trials for immunity duration
PPR Capripox recombinant vaccine

- KS1 expressing either H- or F- PPRV
- Single subcutaneous shot
  - Doses as low as 0.1 PFU
  - Protect against challenges
    ✓ With virulent PPRV
    ✓ With virulent CapV
- Preimmunity to PPRV has no effect on vaccination with PPR-capripoxvirus vaccine
- Pre-immunity to CapV lowers the PPR protection
**DIVA vaccine**

Modification of Nigeria 75/1 using reverse genetics

- Patented markers, molecules, and technologies ready to be used to produce prototypes of DIVA vaccines
- Developed a PPRV Nigeria 75/1 vaccine strain that expresses the Green Fluorescent Protein (eGFP)
DIVA vaccine

Modification of Nigeria 75/1 using reverse genetics

- Adopted strategy: immunogenic and specific epitope swap
- Antibody detected, using indirect peptides based ELISAs/cELISA

Pep E = PPRV 75/1
Pep F = Non PPR
Conclusions

We have good vaccines to get to global PPR eradication, but efficiency of campaign could be increased with:

- Strict vaccine quality control
  - Not always sure what is inside vaccine sold
  - Buyers may go for price not quality
  - Impact vaccination campaigns and risks of emergence

- New generation of vaccines (thermotolerant, recombinant, DIVA)
- Regionally adapted vaccination strategies
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**OPERA**

Viale Parioli 96, 00197 Roma - Italy  
Tel +39 06 96042652- / +39 06 8080111  
Fax +39 06 89280678  
info@opera-Italy.it;  www.btsftraining.com;  www.opera-Italy.it

**Better Training for Safer Food**  
**BTSF**

European Commission  
Consumers, Health and Food Executive Agency  
DRB A3/042  
L-2920 Luxembourg