Challenging Current Control Strategies of Livestock Diseases

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Safe Harbor Statement

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Antivirals = Proven concept in human medicine
No antivirals for animals?

Drug development in human medicine

- In vitro discovery
- Pre-clinical
- Phase I
- Phase II
- Phase III
- Animal models

HIV / AIDS
Hepatitis B/C
Herpes: HSV/VZV/CMV
Why antivirals for livestock?

- Prevent spread of the virus
  - Rapid response
    - Rapid response stockpile: no stability issues
  - Ease of application
    - Mix in feed
  - Rapid containment
    - Acts directly on the virus: freeze, reduce and prevent infection
- Minimise impact on export
  - Not depending on immune system
    - Differentiation with infected animals
  - Residues
    - Optimise compound for short withdrawal time
- Epidemiological and cost-effective strategy
FMD control measures

- Ban on prophylactic vaccination
- Pre-emptive culling
- Emergency vaccination (DIVA)

Prophylactic vaccination (conventional vaccines)
2001
FMD Hits UK
4.9 million sheep culled
0.7 million cattle culled
Summary of 2001 FMD outbreak in the UK

- **Total cost**: £8 billion
- **First case**: 19 Feb 2001
- **Last case**: 30 Sep 2001
- **Total # cases**: 2030
- **Last cull**: 01 Jan 2002
- **80,000 – 93,000 culls/week**
- **6 million culls for disease control**
  - 1.3 million on infected premises
  - 1.5 million on dangerous contacts
  - 1.2 million on neighbouring premises
  - 2.0 million welfare culls
- **~4 million extra culls “at foot” of young animals**
- **10 million animals were culled**
- **£2.5 billion in compensations**
FMDV hit screening – Unique collaboration

[Willems et al., 2011]
From hit to lead compound

**Hit compound**

- only Eurasian
- 4.5 µM
- ±
- ✓

**Compound profile**

- Active against 7 FMDV serotypes
- Active in low nM range
- Stable and soluble compound
- Easy synthesis

**Combination compound**

- ✓
- 45 nM
- ✓
- ✓
What a difference a factor 100(0) makes...

Economic viability of FMD antiviral containment approach will be key
Proof-of-concept with antivirals and FMDV

- SCID mice FMDV A_{22} Iraq 24/64 inoculation i.p.
  - 2’-CMC administration s.c.
    - 5 consecutive days from day 0 → day 4 p.i.
    - 2 x 50 mg/kg per day

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<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>100%</td>
<td>0%</td>
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<tr>
<td><strong>Mean day of death p.i.</strong></td>
<td>4.0 ± 1.3</td>
<td>&gt;14</td>
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<tr>
<td><strong>Weight loss</strong></td>
<td>&gt;20%</td>
<td>healthy</td>
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<tr>
<td><strong>Respiratory distress</strong></td>
<td>severe</td>
<td>healthy</td>
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<tr>
<td><strong>Viraemia serum 2 d.p.i.</strong></td>
<td>100%</td>
<td>~2000-fold decrease</td>
</tr>
<tr>
<td><strong>Viraemia serum 14 d.p.i.</strong></td>
<td>†</td>
<td>negative (13/15)</td>
</tr>
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SCID mice have crippled immune system (lacking T-cell and B-cell responses)
13 of 15 mice completely protected by 2’-CMC
Protection is solely due to 2’-CMC

[Lefebvre et al., 2010; 2013]
Classical swine fever
CSF control measures

- Prophylactic vaccination (conventional vaccines)
- Ban on prophylactic vaccination
- Pre-emptive culling
- Emergency vaccination (DIVA)
Classical Swine Fever  
Benelux 1997-1998

12,000,000 Pigs killed  
Damage above €3 billion

United Kingdom 2000

75,000 Pigs killed  
Compensation £4.4 million
Proof-of-concept with antivirals and CSFV

- Experimental efficacy studies in pigs
  - BPIP treatment of CSFV-infected piglets reduces
    - Viral load by 1000-fold
    - Viraemic period by 74%
    - Transmission rate to untreated sentinels by 85%
  → Input parameters used in epidemiological disease modelling studies

- BPIP = early hit compound; not optimised; not highly potent

Vrancken et al., 2008; 2009a; 2009b.
Model impact of different CSF control measures

Dense pig population in The Netherlands

- Starting situation
  (e.g. simulation 74 of 1000)

- Control strategies (selection)
  - 1 km pre-emptive culling (all animals)
  - 2 km vaccination (except sows)
  - 2 km antiviral treatment (all animals)
  - 2 km vaccination (except sows) + 2 km antiviral treatment (sows)

CSF outbreak in De Peel, a DPLA in the Netherlands with intensive pig reearing
Source farm and 10 others farms infected before detection of CSFV

Model impact of different CSF control measures

Application of pre-emptive culling in 1-km radius around detected farms

Model impact of different CSF control measures

Application of E2-subunit emergency vaccination in 2-km radius around detected farms

Dutch CSF contingency plan preferred method for densely populated pig areas
Sows are left unvaccinated

Model impact of different CSF control measures

Application of antiviral treatment in 2-km radius around detected farms

Model impact of different CSF control measures

Application of antiviral treatment combined with E2-subunit emergency vaccination in 2-km radius around detected farms

Model impact of different CSF control measures

Simulating CSF outbreaks in The Netherlands
Economic aspects

Dense pig population in The Netherlands

**Direct costs of CSF outbreak**

- Costs to authorities (not reimbursed by EU Veterinary Fund)
- Costs to farmers
- Costs to authorities (reimbursed by EU Veterinary Fund)

**Indirect costs of CSF outbreak**

- Costs of trade restrictions
- Costs of ripple effects
- Costs of spill-over effects

Only this small fraction of total costs were considered in model
Simulating CSF outbreaks in The Netherlands

Economic aspects

Benchmark:

Pre-emptive culling (1km)
Difference: 132 M€
Doses: 13 million
Price tolerance: 10 €/dose

Emergency vaccination (2km)
Difference: 7 M€
Doses: 1 million
Price tolerance: 7 €/dose

* Cost of antiviral drug not included
Concluding remarks

• Antiviral drugs are a viable alternative for conventional control measures
• Innovative and conventional methods not mutually exclusive
• Additional weapon in disease control arsenal
Relevant Literature

- **General concept – Containment of livestock diseases using antiviral drugs**

- **FMD and antiviral drugs**

- **CSF and antiviral drugs**