Passive Immunity and IgG-like antibodies as an alternative to antibiotics

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Bangkok 16-18 December 2019
TOOLS FOR HANDLING INFECTIOUS DISEASES OF LIVESTOCK

modified from van Dijk et al. Vet Res. 49., 2018
Perceived effectiveness, feasibility & ROI of ATAs

Table 2
Statistics of perceived effectiveness, feasibility and return on investment (ROI) for alternatives to antimicrobial usage as expressed by European experts (n = 111).

<table>
<thead>
<tr>
<th>Alternative</th>
<th>Average of the three parameters</th>
<th>Effectiveness</th>
<th>Feasibility</th>
<th>ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Ranking&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SD</td>
<td>Mode</td>
</tr>
<tr>
<td>Internal biosecurity</td>
<td>7.5</td>
<td>1</td>
<td>1.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Increased vaccination</td>
<td>7.2</td>
<td>2</td>
<td>1.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Zinc/metals</td>
<td>7.2</td>
<td>3</td>
<td>1.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Feed quality/optimization</td>
<td>7.2</td>
<td>4</td>
<td>1.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Diagnostics/action plan</td>
<td>7.0</td>
<td>5</td>
<td>1.6</td>
<td>7.0</td>
</tr>
<tr>
<td>External biosecurity</td>
<td>7.0</td>
<td>6</td>
<td>1.5</td>
<td>8.0</td>
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<tr>
<td>Climate/environmental</td>
<td>7.0</td>
<td>7</td>
<td>1.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Communication/unified advice</td>
<td>6.6</td>
<td>8</td>
<td>1.7</td>
<td>7.3</td>
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<tr>
<td>Water quality</td>
<td>6.5</td>
<td>9</td>
<td>1.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Age and transfer management</td>
<td>6.5</td>
<td>10</td>
<td>1.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Strict euthanasia</td>
<td>6.3</td>
<td>11</td>
<td>1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>High health/SFF/eradication</td>
<td>6.3</td>
<td>12</td>
<td>1.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Reduced stocking density</td>
<td>6.3</td>
<td>13</td>
<td>1.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Increased use anti-inflammatory</td>
<td>6.2</td>
<td>14</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Benchmarking farmers/vets</td>
<td>6.2</td>
<td>15</td>
<td>1.6</td>
<td>7.0</td>
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<tr>
<td>Acidification feed/water</td>
<td>6.0</td>
<td>16</td>
<td>1.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Financial/tax</td>
<td>5.3</td>
<td>17</td>
<td>1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Genetics</td>
<td>5.2</td>
<td>18</td>
<td>1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Feed additives</td>
<td>5.1</td>
<td>19</td>
<td>1.8</td>
<td>5.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> The ranking is provided for each measure and presented in bold for the top 5.

M. Postma et al. / Preventive Veterinary Medicine 118 (2015) 457–466
Component loadings and centroids

“Practical” respondents versus “Scientific” respondents

M. Postma et al. / Preventive Veterinary Medicine 118 (2015) 457–466
ATA: vaccination succes: marine aquaculture

http://www.fao.org/3/A0192E09.htm
Salmon Rickettsial Septicemia (SRS)

1987: 50t antibiotics/50kt salmon (1g/kg); 2017: 300kg antibiotics/1,3mill t salmon (0.0002g/kg).

"The estimated impact of PCV-2 vaccination revealed a **highly significant** (P<0.001) decline in total antimicrobial drug use from 1.72 ADDkg/kg/year to 0.56 ADDkg/kg/year on finishing farms"
Antimicrobials with gastro-intestinal indication

Antimicrobials with respiratory indication

Fig. 3 Use of antimicrobials with respiratory indication – measured as Animal Daily Doses (ADD) per 100 weaners per day – in 836 Danish sow herds, divided according to the combined use of vaccination against PCV2, Mycoplasma hyopneumoniae (MYC), and Lawsonia intracellularis (LAW), 2013.
The hard ones....

• Hard to target complex infections (multiple pathogens, including virus/bacteria combinations)
• Hard to target management/infection combinations
• Hard to target infections: unknown/many pathogen variants/ and/or unknown mechanisms
• Chronic disease states increasing susceptibility to infection/decreasing vaccine response
• Mucosal infections
• Neonatal/young animal vaccination: reduced vaccination responses
Challenges for the use of veterinary vaccines in animal production

- Inexpensive (sustainable cost/benefit balance)
- Ease of use/large populations
- Safe (pathogen transmission/reversion)
- Shelf life/non-demanding storage
- No interference with serological monitoring of infection status
- Minimal off-target negative effects
- Measurable positive effect on production parameters
- Consumer concerns
NEW IMMUNE BASED STRATEGIES SHOULD:

• Inexpensive (sustainable cost/benefit balance)
• Ease of use/large populations
• Safe (pathogen transmission/reversion)
• Shelf life/non-demanding storage
• No interference with serological monitoring of infection status
• Minimal off-target negative effects
• Measurable positive effect on production parameters
• Consumer concerns
Non-antibiotic non-vaccine immunization approaches
PASSIVE IMMUNIZATION: IMMUNOGLOBULIN EFFECTORS

Immunoglobulin G (IgG)

Foreign particle binding site

Foreign particle binding site
doi: 10.1111/brv.12325

https://www.researchgate.net/figure/The-canonical-structures-of-IgG-and-IgY

Truncated IgY (IgYΔFc): anseriform birds (duck, goose)
Passive immunization in Nature: Transfer of maternal immunity perinatally

**Fetal stage – mother to embryo immunoglobulin transport**

- **FISH & BIRDS**
  - Active transport
  - Yolk sac

- **PRIMATES & RODENTS**
  - Active transport
  - Hemochorial placenta

- **DOG, CAT, MINK**
  - Limited transport
  - Endotheliochorial placenta

- **RUMINANTS, PIGS, HORSES**
  - No transport
  - Epitheliochorial placenta

**Neonatal stage – circulating immunoglobulins**

- **IgM** (fish)
- **IgY** (birds)
- **IgG**
  - **IgG** (low levels)
  - No circulating Ig’s

- **Gut uptake: (open gut)**
  - No
  - No
  - Yes (< 36 h after birth)
  - Yes (< 24 h after birth)

IgG uptake after birth: Mink example

Mink pre-weaning diarrhea: association with decreased IgG concentration at day 13-15 of age

Rainbow trout IgM immunization

Chettri, JK., et al., 2019, Fish and Shellfish Immunology
Key factors affecting passive immunity in beef-suckler calves


- Dam Vaccination
- Cow perinatal health
- Environmental Conditions
  - Birth site
- Calf vigour
- Cow-Calf Bond
- GENOTYPE – PARITY – NUTRITION
- COLOSTROGENESIS
- PARTURITION
  - Dystocia
  - Prematurity
- TIME OF SUCKLING
  - Maternal behaviour
  - Calf behaviour
    - Stand
    - Walk
    - Teat seeking
- COLOSTRUM INGESTION
  - Yield
  - Ig mass consumed
- Ig ABSORPTION
  - Time of ingestion
- Artificial feeding of colostrum
- Ig Mass
- IMMUNITY
Bovine rotavirus, exp. infection: effect of IgY (hyperimmune egg yolk supplementation)

Vega et al., Vet Immunol Immunopathol. 2011 August 15; 142(3-4): 156–169

3. januar 2020 3rd International Symposium on Alternatives to Antibiotics (ATA) - Bangkok 16-18 December 2019
Bovine IgG supplementation: natural IgG from whey

Final IgG concentrations

<table>
<thead>
<tr>
<th>Treatment group, 26: CTRL, 28: +IgG product</th>
</tr>
</thead>
</table>

- P=0.0013

Weight gain, g

Age, days

Pneumonia in IgG group!
Plant produced immunoglobulin A and G for prevention of experimental E.coli infection in piglets (F4 specific)

Arabidopsis thaliana seeds


IgG: FcNR interaction? Less stable than IgA?
Plant and yeast produced monomeric IgA for prevention of experimental E. coli infection in piglets (F4 specific)

Plant and yeast produced monomeric IgA for prevention of experimental E. coli infection in piglets (F4 specific)

Virdi, V., et al., 2019
Zinc and pplgG compared, *E.coli* O149:F4 challenge model. Faecal bacterial counts

Hedegaard et al. 2017
Unstabilized

Heavy chain

Light chain

Pepsin
- +

Activity
+++ +

Activity after digestion / Activity after stabilization

Optimal stabilization range

Extent of stabilization

Chettri and Heegaard, unpublished
Cecal CFU *C. jejuni* (inoculation strain)

Passive immunization, 2x100 mg oral goose immunoglobulin

Mean of group compared to mean of CTRL group:

***: <0.001; **: 0.001 - 0.01; *: 0.01-0.05

Day 7 after inoculation
### Table 2. Effect of hyperimmune egg-yolk IgY on bacterial infections of poultry

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Donor hens immunized with</th>
<th>Experiment</th>
<th>Prevention/therapeutic</th>
<th>In vitro</th>
<th>Mode of IgY treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>Live or killed <em>E. coli</em>, lipopolysaccharide (LPS), FimH, PgpG, lta</td>
<td>Prevention</td>
<td>In vivo</td>
<td>IgY 100 mg iM</td>
<td>Protection from homologous challenge</td>
<td>Kariyawasam et al. (2004)</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td><em>E. coli</em> and Freund’s complete adjuvant (FCA)</td>
<td>Prevention</td>
<td>In vivo</td>
<td>IgY 3 ml orally</td>
<td>Reduced symptoms, lesions</td>
<td>Tamilzarasan et al. (2009)</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> O78K80</td>
<td><em>E. coli</em> O78K80</td>
<td>Prevention</td>
<td>In vivo</td>
<td>IgY powder 50-150 mg ml⁻¹</td>
<td>Reduced growth</td>
<td>Mahdavi et al. (2010a)</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> O78K80</td>
<td><em>E. coli</em> O78K80</td>
<td>Prevention</td>
<td>In vivo</td>
<td>Lyophilized IgY powder in diet (0.1-0.4%)</td>
<td>Reduced growth rate</td>
<td>Mahdavi et al. (2010b)</td>
<td></td>
</tr>
<tr>
<td>C. jejuni, S. enterica</td>
<td>C. jejuni and Campylobacter coli</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>IgY preparation oral</td>
<td>Local bacterial counts</td>
<td>Diraviyam et al. (2011a)</td>
<td></td>
</tr>
<tr>
<td>C. jejuni</td>
<td>C. jejuni and FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>IgY 3 ml orally</td>
<td>Immobility, mortality</td>
<td>Tsubokura et al. (1997)</td>
<td></td>
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<tr>
<td>C. jejuni</td>
<td>C. jejuni colonization-associated proteins</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Lyophilized egg yolk powder</td>
<td>Adherence to cells</td>
<td>Tamilzarasan et al. (2009)</td>
<td></td>
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<tr>
<td>C. jejuni</td>
<td>C. jejuni whole cell lysate or hydrophobic fraction</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Egg yolk 5% (W/V) in feed</td>
<td>Local c. jejuni counts binding to mucus</td>
<td>Hermans et al. (2014)</td>
<td></td>
</tr>
<tr>
<td>C. perfringens</td>
<td>C. perfringens bacterium</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>IgY solution sprayed onto feed (0.05%, 0.069% W/V)</td>
<td>No effect on colonization</td>
<td>Wilkie et al. (2006)</td>
<td></td>
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<tr>
<td>C. perfringens</td>
<td>C. perfringens and FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>IgY 3 ml orally</td>
<td>Immobility, mortality</td>
<td>Tamilzarasan et al. (2009)</td>
<td></td>
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<tr>
<td>S. pullorum</td>
<td>S. pullorum killed antigen with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Reconstituted freeze-dried IgY powder</td>
<td>Generated antibodies specific to <em>S. pullorum</em> Ag</td>
<td>Diraviyam et al. (2011a)</td>
<td></td>
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<tr>
<td>S. pullorum</td>
<td>S. pullorum with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>IgY 3 ml orally</td>
<td>Immobility, mortality</td>
<td>Tamilzarasan et al. (2009)</td>
<td></td>
</tr>
<tr>
<td>S. enteritidis or <em>S. typhimurium</em></td>
<td>Formalin-inactivated <em>S. enteritidis</em> or <em>S. typhimurium</em> with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Reconstituted freeze-dried IgY powder</td>
<td>Growth</td>
<td>Lee et al. (2002a)</td>
<td></td>
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<tr>
<td>S. enteritidis</td>
<td>Formalin-inactivated whole-cell Ag of <em>S. enteritidis</em></td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Whole egg powder in feed (3 g day⁻¹ bird⁻¹)</td>
<td>Rate of contamination of eggs</td>
<td>Gürtler et al. (2004)</td>
<td></td>
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<tr>
<td>S. enteritidis</td>
<td><em>S. enteritidis</em> whole-cell Ag with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>15 ml of antibody in drinking water</td>
<td>Reduced fecal shedding of <em>c. colonizant</em> IgY solution from liver, spleen, ileum</td>
<td>Rahimi et al. (2007a)</td>
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<tr>
<td>S. enteritidis and <em>S. typhimurium</em></td>
<td>Outer membrane proteins (OMP) of <em>S. enteritidis</em> and <em>S. typhimurium</em> with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Reconstituted freeze-dried IgY powder</td>
<td>No effect on cecal colonization</td>
<td>Chalghouni et al. (2006b)</td>
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<tr>
<td>S. enteritidis and <em>S. typhimurium</em></td>
<td>OMP of <em>S. enteritidis</em> and <em>S. typhimurium</em> with FCA</td>
<td>Prevention and therapeutic Prevention</td>
<td>In vivo</td>
<td>Egg yolk powder in feed (5%)</td>
<td>No effect on cecal colonization</td>
<td>Chalghouni et al. (2006c)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Effect of hyperimmune egg-yolk IgY on viral infections of poultry

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Hens immunized with</th>
<th>Experiment</th>
<th>In vitro/ in vivo</th>
<th>Mode of IgY treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBDV</td>
<td>Oil-based IBDV vaccine</td>
<td>Therapeutic</td>
<td>In vivo</td>
<td>Diluted yolk with antibodies</td>
<td>Birds recovered</td>
<td>Muhammad et al. (2001)</td>
</tr>
<tr>
<td>IBDV</td>
<td>Inactivated oil-based vaccine</td>
<td>Therapeutic</td>
<td>In vivo</td>
<td>Hyperimmune yolk solution in drinking water 1 l day⁻¹</td>
<td>↓mortality Shift in morbidity to a milder syndrome</td>
<td>Yousef et al. (2006)</td>
</tr>
<tr>
<td>IBDV</td>
<td>Oil-based vaccine</td>
<td>Therapeutic</td>
<td>In vivo</td>
<td>IgY solution injected I/P</td>
<td>↑recovery rate</td>
<td>Malik et al. (2006)</td>
</tr>
<tr>
<td>IBDV</td>
<td>Live intermediate strain IBDV vaccine and Inactivated IBDV vaccine</td>
<td>Prevention</td>
<td>In vivo</td>
<td>IgY solution orally 0.5 ml bird⁻¹</td>
<td>↓morbidity, mortality, lesions</td>
<td>Abd El-Ghany (2011)</td>
</tr>
<tr>
<td>NDV</td>
<td></td>
<td>Prevention and therapeutic</td>
<td>In vivo</td>
<td>Egg yolk I/M</td>
<td>Prevented ND and protected from challenge</td>
<td>Phillips (1956)</td>
</tr>
<tr>
<td>NDV</td>
<td>Commercial wing-web NDV vaccine</td>
<td>Prevention</td>
<td>In vivo</td>
<td>Egg yolk S/C</td>
<td>Protected 80% of birds</td>
<td>Wills and Lugmibuhl (1963)</td>
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<tr>
<td>NDV</td>
<td>Natural infection</td>
<td>Prevention</td>
<td>In vivo</td>
<td>Egg yolk I/M 1 mL</td>
<td>Conferred passive immunity</td>
<td>Box et al. (1969)</td>
</tr>
</tbody>
</table>

IBDV, infectious bursal disease virus; NDV, Newcastle disease virus.

Conclusions

• LOTS OF EXAMPLES – HOW TO ENABLE USE?

• CHALLENGES REMAINING/oral immunoglobulins:
  • Formulation issues for ease of administration and optimal gut stability
  • Sourcing: Sustainable ‘natural’ sources (slaughter blood, whey, etc.) and securing absence of unwanted agents
  • Dosing (stabilized/non-stabilized)?
  • Non-enteric infections?
Thank you for your attention