Will genomics spell the end of vaccines?

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Why vaccines feed the world?
Traditional health management approaches

PAST / PRESENT
- Antimicrobials
- Vaccines
- Herd elimination
- Regional control
- Biosecurity

CURRENT THREATS
- Antimicrobial usage / resistance
- Cost / time of vaccine development
- Elimination / regional re-breaks
- Biosecurity: implementation & lack of scientific assessment
Traditional vaccine strategies (pork industry)

PAST / PRESENT
- Whole cell killed
- Attenuated
- Multivalent
- Subunits
- Autogenous

STRATEGIES
- Identify risk / reward
- Identify target population
- Delivery parenteral, oral, transdermal
- Follow up / monitoring (clinical, diagnostic)
Need for improved health management strategies?

- New diseases
- Pathogen evolution
- Reduced antimicrobials
- Intensified production
- Zoonotic threats
- Animal welfare
- Public scrutiny

WILL VACCINES BE ENOUGH?

- Identify risk / reward
- Identify target population
- Delivery parenteral, oral, transdermal
- Follow up / monitoring (clinical, diagnostic)
23andMe

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Inherited Conditions
- Cystic fibrosis
- Sickle cell anemia
- Tay-Sach’s Disease
- 41 more...

Genetic risk factors
- Alzheimer’s
- Caeliac disease
- Parkinson’s
- Hereditary breast & ovarian cancers
- 8 others...

Traits
- Alcohol flush reaction
- Asparagus metabolic detection
- Breast morphology
- Caffeine metabolism
- Earwax type
- Pain sensitivity
- Male baldness
- 37 others...

Drug response
- Hep C treatment response
- Warfarin sensitivity
- Proton pump inhibitor metab
- 8 others...

www.23andme.com
Animals Tested: 22

Sire: HOUSA000062253367
Dam: HOUSA000072390933

Viewing: Key Traits Compared To All Herds

Key Traits

Compare To My Herd Only

Health Yield Fertility

Genetic Conditions
Genomics: opportunity for swine health management?

Litter size
- Estrogen receptor
- Erythropoeitin receptor

Growth, feed intake & efficiency

Fat content

Meat quality
- Porcine stress syndrome (HAL)
- Rendement Napole (RN)

Disease
- *E. coli* resistance (F4 ab/ac)
- PRRSV resilience
- PCV2
Use of “functional genomics” to improve swine health

- Genome
- Epigenome
- Transcriptome
- Proteome
- Metabolome
- Phenome
Genomic application for improved health phenotypes

a) Single markers

- **FUT1**
  - Miejerink et al., 2000

- **HAL 1843**
  - Fujii et al., 1991

- **RN**
  - de Vries et al., 1997
Genomic application for improved health phenotypes

b) Polygenic traits

Annotation of genome wide association analysis of PCV2 viral load (McKinte et al., 2014)
Genomic application for improved health phenotypes

c) Gene editing (CRISPR/Cas9)

Lung histopathology

PRRSV RNA concentration

Days after inoculation

Whitworth et al., 2016
Will genomics be sufficient to control all diseases?

Doubtful

- Cost
- Polygenic traits
- Interaction with other valuable traits
- Involvement with MHC genes (SSC 7)
- Resistance versus tolerance versus resilience
- Complex logistics from discovery to application
- Consumer and regulatory acceptance (editing)
Application of genomics to improve vaccines / strategies

**Vaccine development / manufacturing**

1. “Reverse vaccinology” – development of protein-based vaccines by using sequence data without bacterial propagation

**“Vaccinomics” (genetics + epidemiology + genomics)**

1. Selection of animals with improved vaccine response
2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring
3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes
1. Selection of animals with improved vaccine response

**M. hyopneumoniae** IgG levels in serum following vaccination (n=100)

**M. hyopneumoniae** IFNγ secreting cells in blood following vaccination (n=66)

Harding et al., unpublished
Mechanisms of genetically-mediated vaccinal responses (human)

- HLA (MHC) class I and II polymorphisms
  - Measles, mumps, rubella
  - Antibody & cellular immune responses
  - IFN-gamma responses following vaccination

- Cytokine genes
  - IL-2, IL-4, IL-10, IL-12 responses (measles, mumps, hep B)

- Innate immunity
  - TLR2, TLR3, TLR4 responses (measles, rubella)

Reviewed by: Castiblanco & Anaya, Current Genomics, 2015
1. Selection of animals with improved vaccine response

- Relevant “test” of immune response following vaccination
- Could be antigen-specific response or generic immune response
- Test has moderate to high heritability and genetic correlation
  
  Humans: 40-70% heritability; high genetic correlation
  
  (40-90% of variability related to genetic factors)

- Initially – best to eliminate “low or non”-responders, versus selection of “high” responders?
- Feasibility: at laboratory and use in seedstock (nucleus) farms
2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring

Genetic diversity within a heterogeneous population

Low risk population

Differential vaccine strategies based on predicted phenotypic responses (health phenotype)

high risk population
Phenotypic variation following type 2 PRRSV challenge in pregnant gilts

Ladinig et al., 2014
2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring

- Requires accurate assessment of phenotypes
  - Identification of extreme populations
- Requires a modified vaccination or intensive monitoring strategy
  - Superior product
  - 2 versus 1 dose strategy
  - Vaccination response monitoring
- Easily implemented at farm if functional genomic testing available to identify high risk populations
3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes

Bertolini & Rothschild, unpublished
Given vast genomic heterogeneity, should vaccines be better targeted towards homogeneous populations or genetic lines with defined immune responses?
3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes

✓ Requires understanding of global genotypic variability and its potential impact on vaccine response and disease susceptibility
✓ Could be streamlined by understanding variability amongst major genetics companies
✓ Requires large enough market to stimulate novel products specific to anticipated genotypic responses (global / niche)

Antigen, antigen load, novel adjuvants, formulation?
Development costs?
Critical evaluation of efficacy across many genetic populations and regions
Swine health dashboard

Predicted herd responses

- E coli resistance
- HAL 1843 frequency
- RN frequency
- PCV2 resistance
- PRRSV resistance
- CMI responses
- AMI responses
- Vx A responses
- Vx B responses
- Vx C responses
Conclusions

1. Excellent products available today; some of the most effective vaccines ever produced; excellent technical support

2. Swine health management founded on 20th century technology

3. Exponential advance of genomic technologies advancing will revolutionize health care over next 20 years

4. Solving the complex swine health issues of the 21st century will require more than vaccines
Conclusions

5. Application of “vaccinomics” (merger of functional genomics with innovative vaccine design) offer great potential to improve swine health in next 2 decades

6. Moving towards an era of “personlized and predictive vaccinology instead of a one-size fits all approach”

*Personalized medicine for pig populations*