Quantification of infectious agents transmission in pigs: Mathematical modelling of experimental and field data.

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Outline

Model building

An infectious disease is often characterized by its

- transmission route
- transmission potential
- natural history
  - incubation time
  - latent period
  - infectious period
- acquired immunity
- symptomatic/asymptomatic

Identification of these characteristics is essential for realistic modelling assumptions.

Symboles and notations

Entity	Symbol 1	Symbol 2
Maternal immune	M (number)	m (proportion)
Susceptibles	S (number)	s (proportion)
Infected	I (number)	i (proportion)
Recovered	R (number)	r (proportion)
New cases	C (number)	c (proportion)
Total population size	N (number)	-
Recovery rate	γ (rate)	-
Force of infection	λ (rate)	-
Transmission parameter	β (rate)	-
Basic reproduction number	R_0 (dec. number)	-

Table: *Commonly (and non-exhaustive) notations in epidemiological model*

Model parameters

Once the conceptual model is built, questions remain:

- What are the underlying parameters,their meanings and/or interpretations?
- Is there any information on their values in literature?
- What kind of data could allow for parameter inference?
- How could we use these data whenever they were available?
- Are such data available in the literature?
- Is it possible to generate such data?

Data and parameter inference

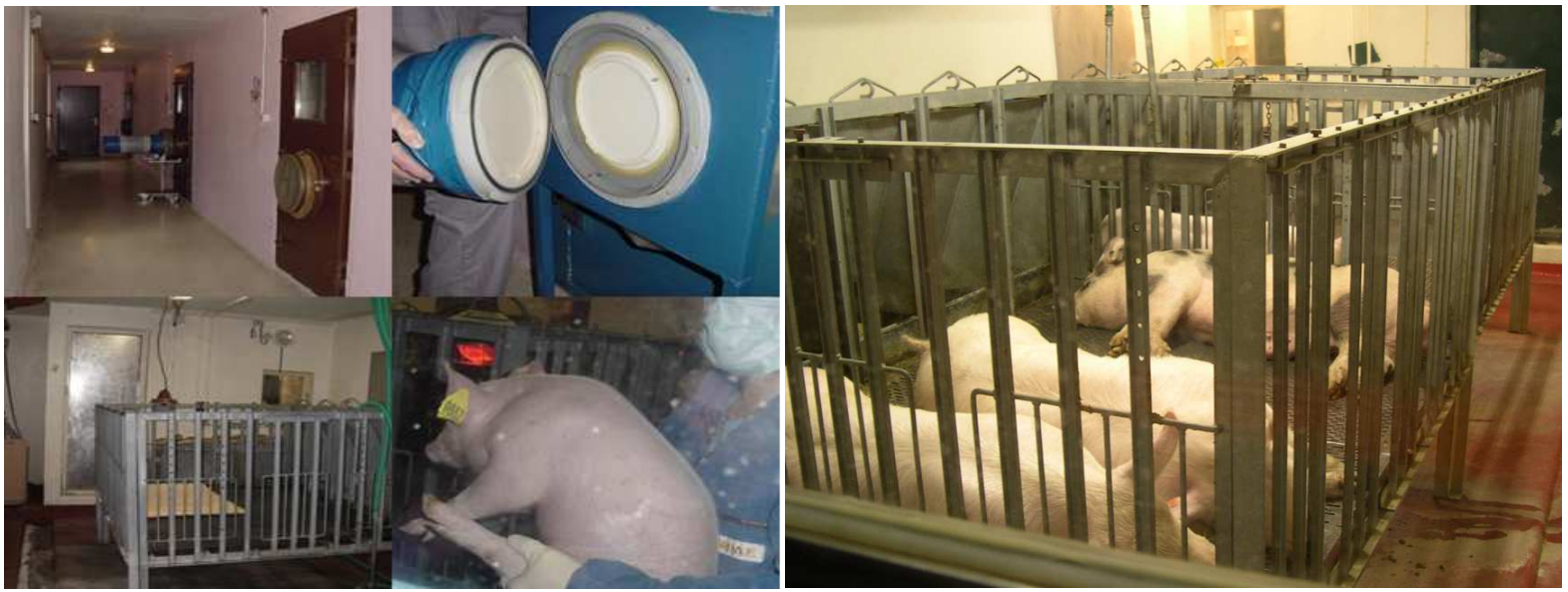
Parameter estimation from available data is often challenging for multiple reasons:

- Data are often sparse.
- Transmission process is partially observed.
- Data are mostly based on case notifications (*i.e.* only symptomatic cases are reported).
- The exact time of infection is unknown.
- External factors can modify the course of infection.

In this context, experimental transmission trials offer the opportunity to study specific aspects of transmission in fully controled environment.

Experimental facilities

- All experiments were carried out in level 3 biosecurity air-filtered facilities.
- Specific Pathogen Free pigs were derived from Anses' confined pig herd.



Parameter estimation from experimental trials

Porcine CircoVirus of type 2

Context

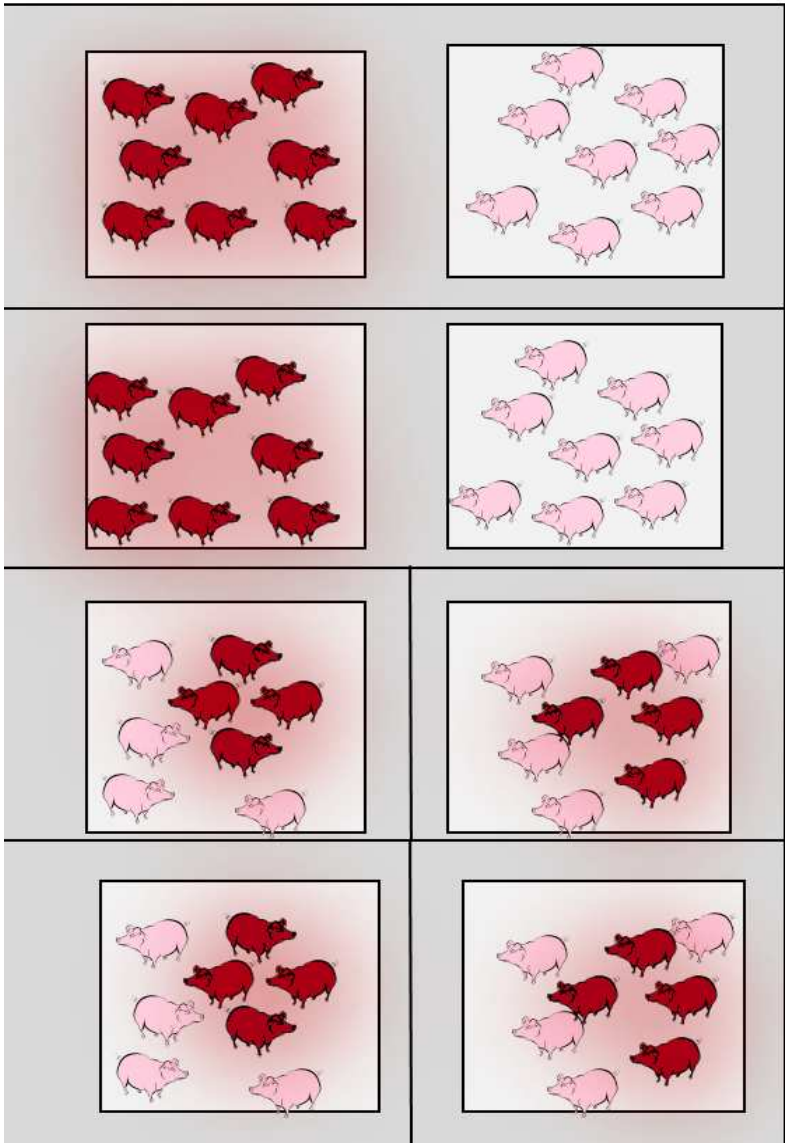
- Small DNA virus widely prevalent in pig herds
- Aetiologic agent of Postweaning Multisystemic Wasting Syndrome (PMWS)
- Vertical and horizontal transmission
- Huge protection confered by maternally derived antibodies

Objectives

- Evaluation of transmission according to contact structure between animals
- Estimation of the duration of the infectious period
- Estimation of the basic reproduction number (R_0) for PCV-2

Experimental settings

- 72 SPF pigs aged 4 weeks
  - 8 negative control
  - 32 inoculated pigs
  - 32 Sentinel pigs
- Inoculation with 6mL of suspension titrating 10^5 $TCID_{50}$
- Blood samples twice-a-week until 42 DPI
  - Virology: Real-time PCR
  - Serology: Elisa test



Modeling Hypotheses

- SEIR model $\Longrightarrow$ $R_0 = \beta/\gamma$
- Animals with positive PCR results are considered infectious.
- Latent period fixed to 6 days for contact pigs.
- Three assumptions for individual duration of infectious periods:
  - H1: Seroconversion
  - H2: Seroconversion + decline of virological titers
  - H3: Constant infectiousness throughout the trial

Parameter estimation

- Survival analysis for the duration of infectious period
- Transmission Rate: Maximum likelihood method
  - Individual probability to escape infection on time-interval $[t_j; t_{j+1}]$:

$$p_j = exp(-(\beta_w \ I_j^w/N_j^w + \beta_b \ I_j^b/N_j^b) \ \Delta_j)$$

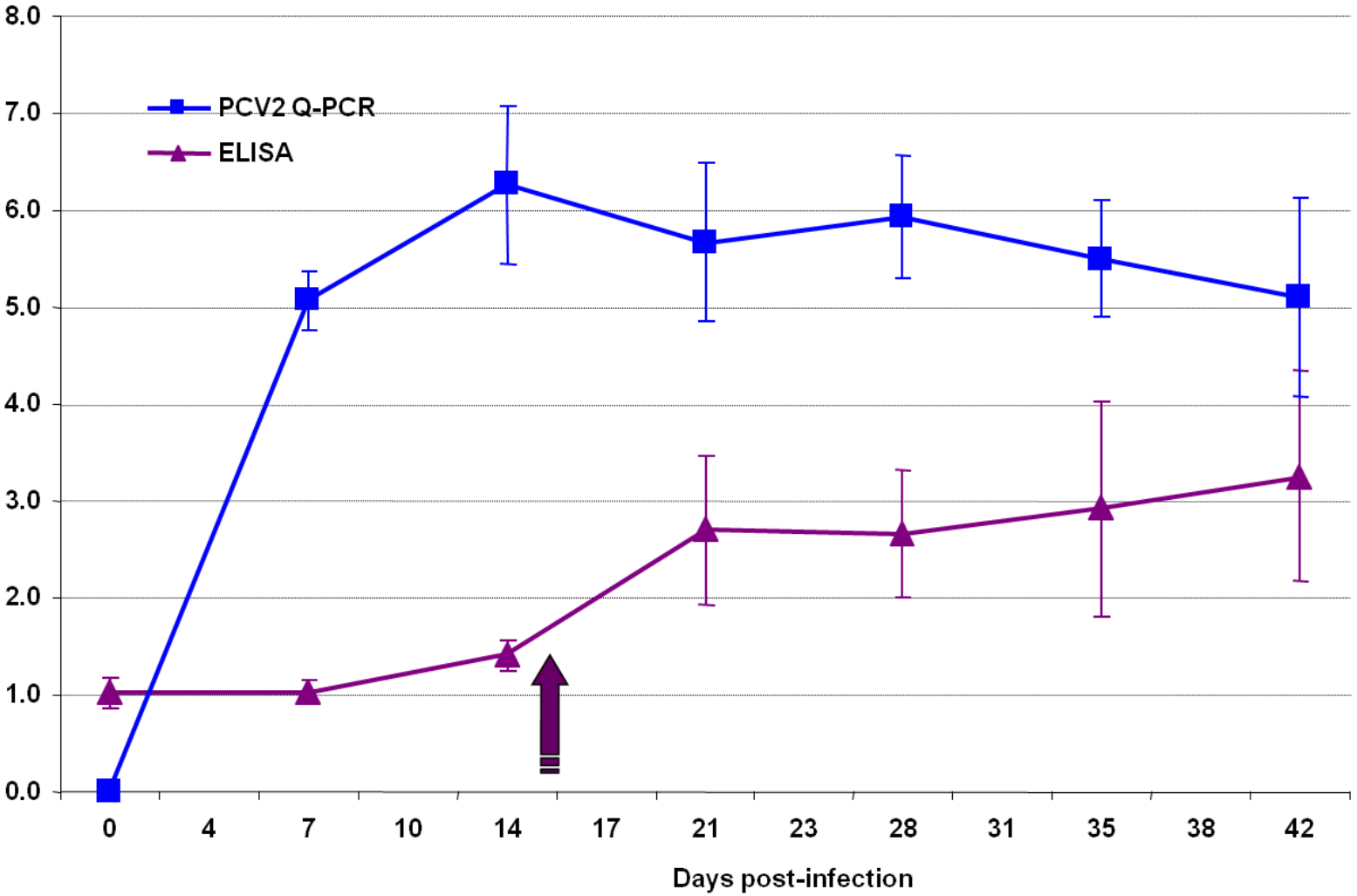
  - Number of **new cases** follows a binomial distribution

$$C_j \sim Bin(S_j, 1 - p_j)$$

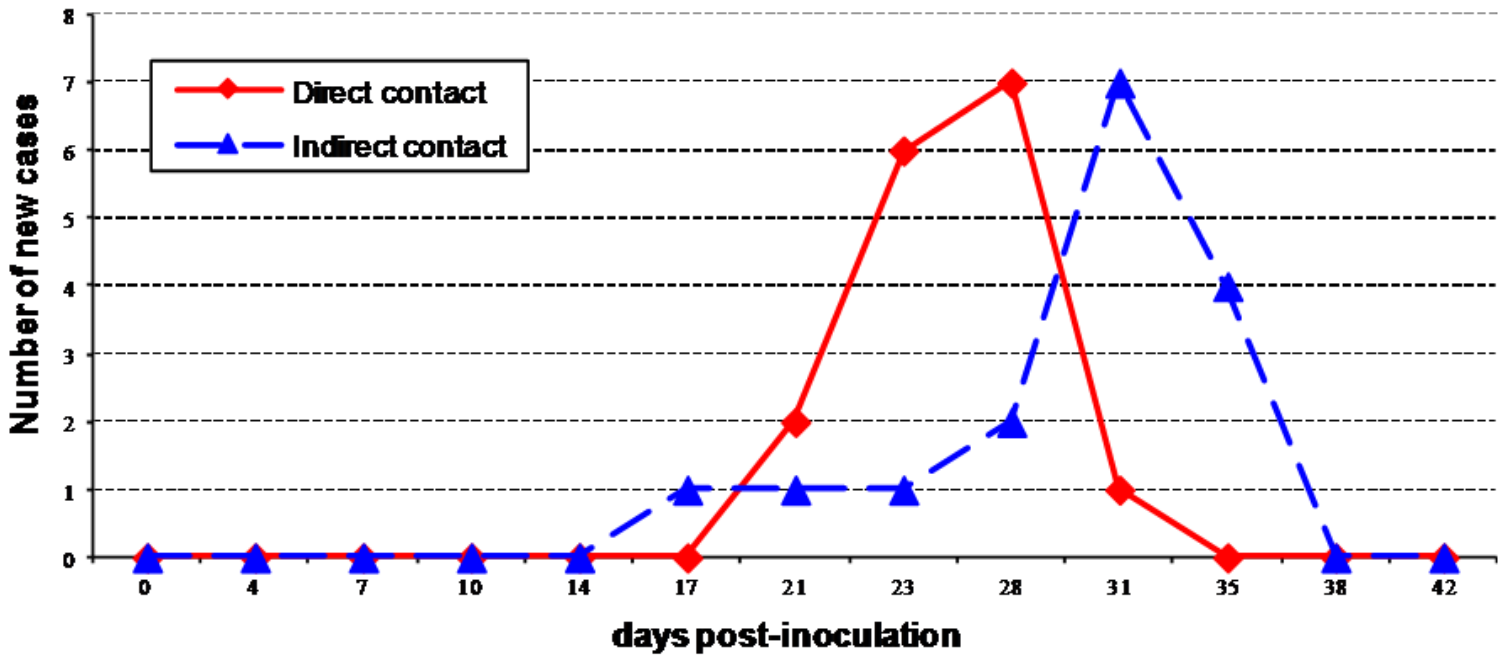
  - Likelihood expression:

$$L = \prod_{g=1}^{nGroups} \prod_{j=1}^{nObs} dBin(S_j^g, 1 - p_j^g)$$

Virological and Serological results



Incidence in contact groups



- Surprisingly the first case was in indirect contact group.
- Peak of incidence was ealier in direct contact group.

Quantification of transmission

Parameter	Hypothesis		
	H1	H2	H3
β_w	0.26 [0.18-0.38]	0.22 [0.14-0.34]	0.19 [0.12-0.30]
β_b	0.03 [0.01-0.06]	0.03 [0.02-0.08]	0.04 [0.02-0.08]
γ	0.06 [0.04-0.08]	0.03 [0.02-0.04]	-
$1/\gamma$	17.9 [12.5-25]	34.6 [23.9-50.2]	-
R_{0w}	4.7 [2.9-7.6]	7.7 [4.3-13.5]	-
R_{0b}	0.47 [0.19-1.17]	1.2 [0.5-2.9]	-

Conclusions

- R_{0b} relatively low but further cause of within-group transmission

$$\Longrightarrow R_{0b} \textbf{ not negligible}$$

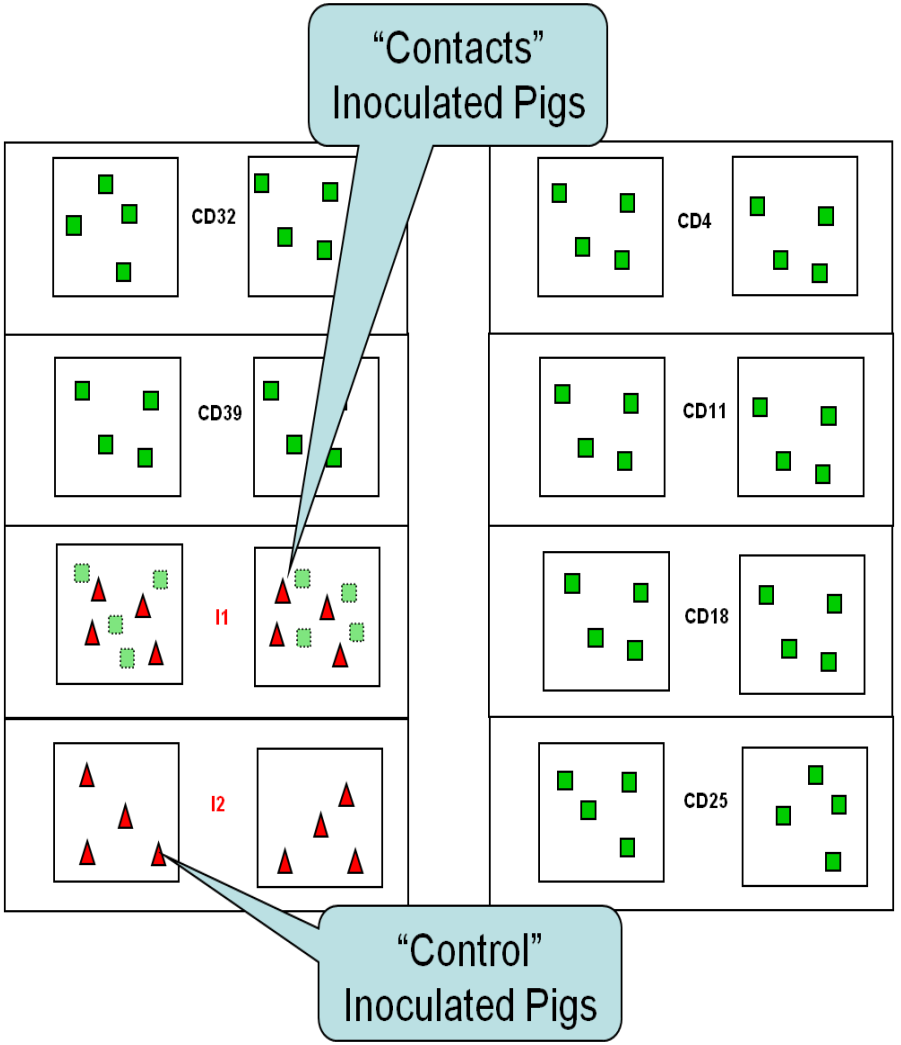
- Huge impact of the assumption on the duration of infectious period on R_0 estimates.
- H2 biologically likely:
  - appearance of neutralizing antibodies
  - decrease of viral load.

Complementary experimental trial to study in depth:

- The **duration of the infectious period**, *i.e* the time during wich an infected animal effectively transmit the virus to susceptible host.
- the evolution of **infectiousness according to time since infection**.

Experimental design

- 72 SPF pigs aged 3 weeks
  - 8 negative control
  - 16 inoculated pigs
  - 48 Sentinel pigs
- Inoculation as in the previous study
- Weekly blood sampling
  - Virology: Real-time PCR
  - Serology: Elisa test



Parameter Estimation

Definition

- τ: time since infection
- $\beta(\tau)$: average number of new cases produced by an individual infected since τ units of time.

Consequences

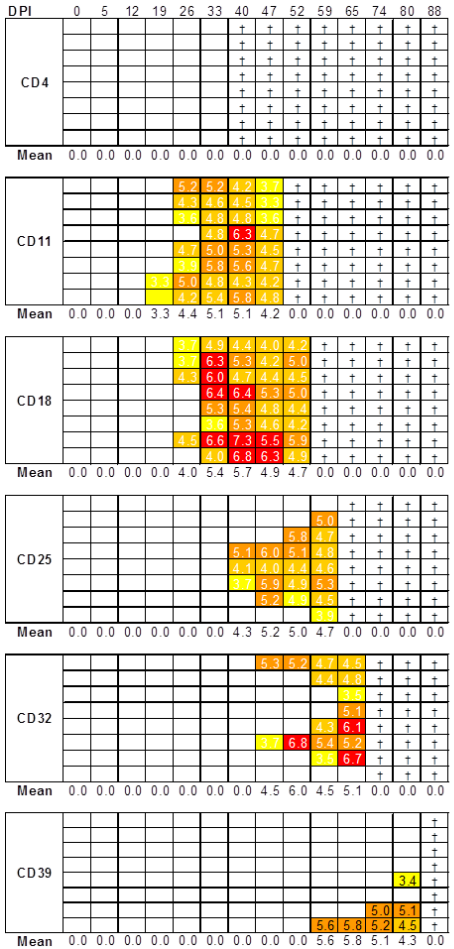
- $\int_0^\infty \beta(\tau)d\tau$: average number of cases produced by an individual during its entire infectious period.
- Individual probability to escape infection on time-interval $[t_j; t_{j+1}]$:

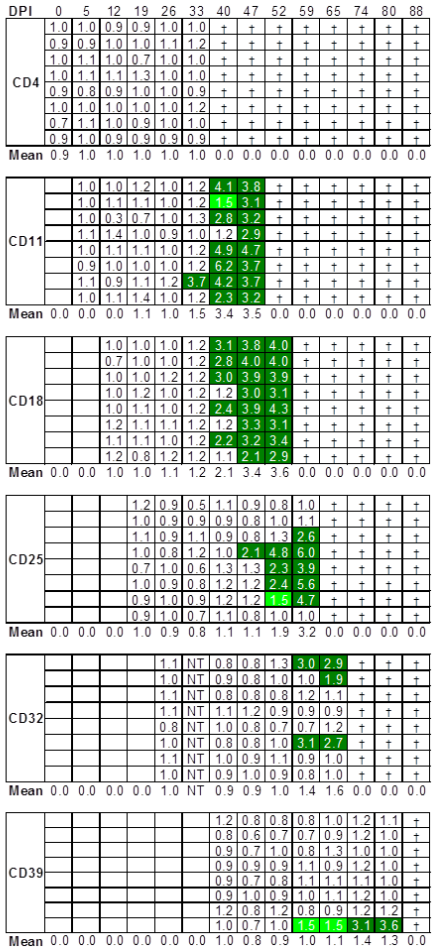
$$p_j = exp(-I_j \int_{t_j}^{t_{j+1}} \beta(\tau)d\tau)$$

- Likelihood expression:

$$L = \prod_{g=1}^{nGroups} \prod_{j=1}^{nObs} dBin(S_j^g, 1 - p_j^g)$$

Virological and serological results

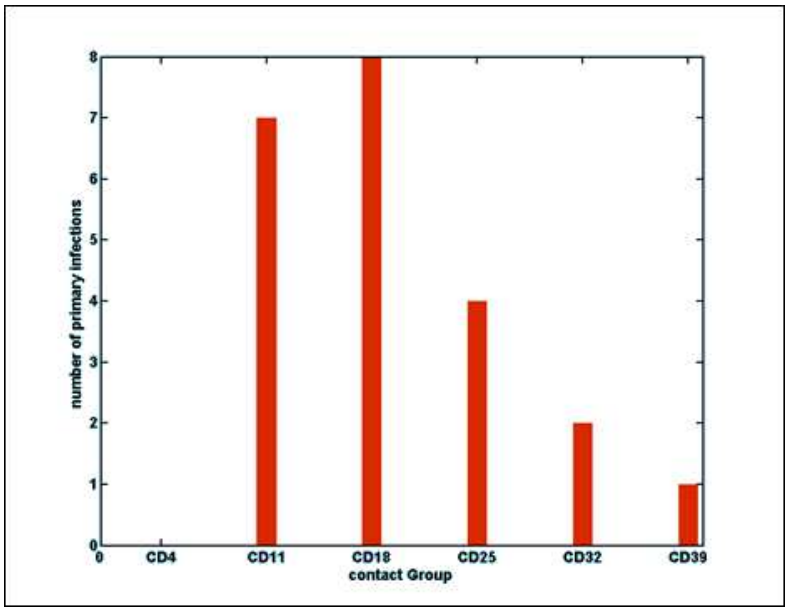




Primary cases: Due to contact with Inoculated pigs
Secondary cases: Within-group transmission process
Discrimination: 14 day-delay between first and next infections

Interpretation

Number of primary cases according to contact groups

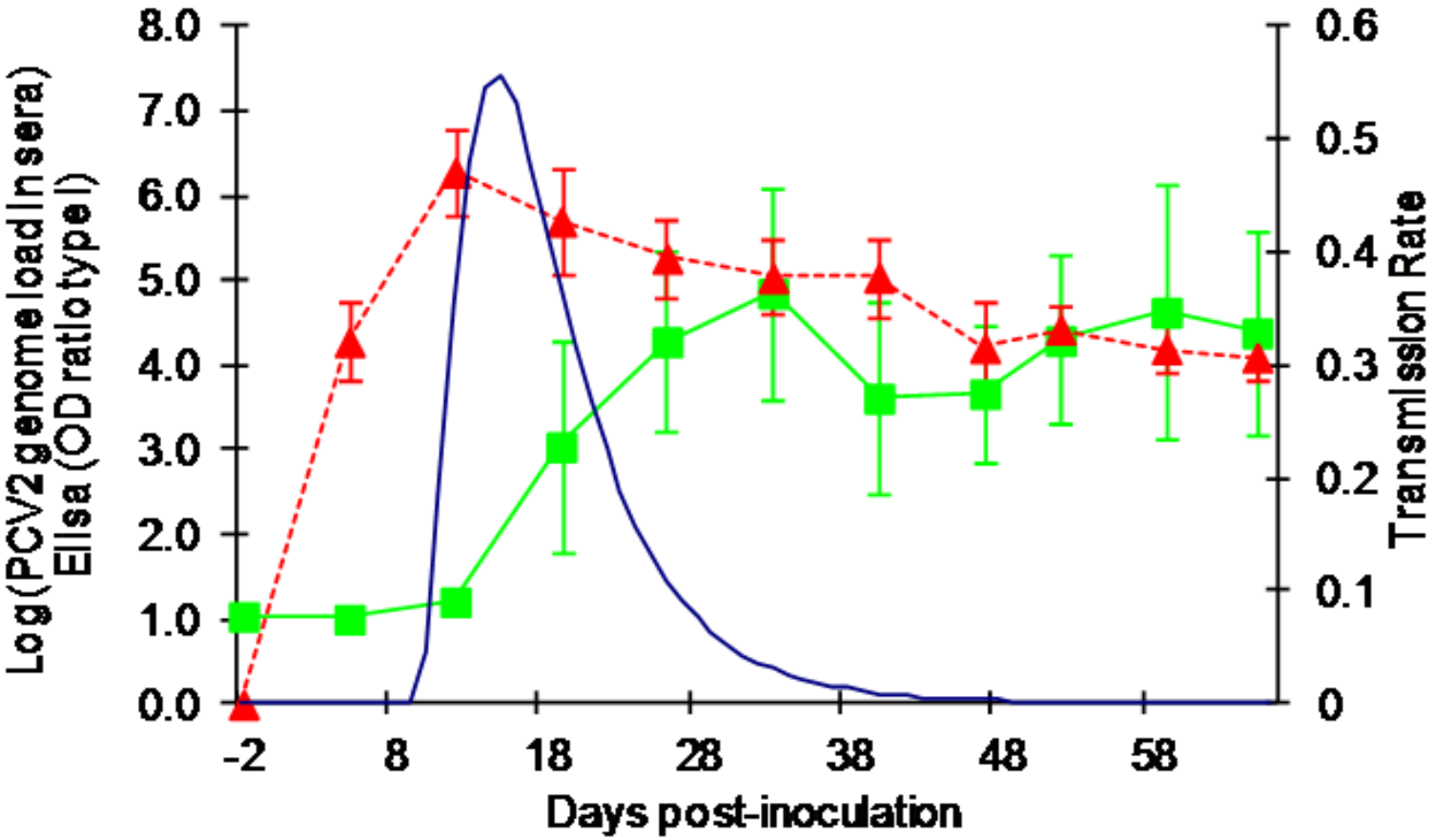


- Skewed distribution
- Mode: 11 - 18 DPI
- Left bounded (latency)
- Three functions tested:
  - Gamma-like,
  - Log-Normal-like,
  - Weibull-like,

  defined as the product of R_0 with the related **probability density function**.

For each function three parameters were estimated:
R_0 and two parameters defining the probability density function.

Time-dependent transmission



Conclusions

- Evidence of time-varying transmission.
- Basic reproduction number for PCV-2 estimated to 5.9 (1.8;10.1).
- Transmission rate vanishes (< 0.001) 56 days post-infection.
- Qualitative relationship between transmission, viremia and serology.

Could we relate quantitative laboratory analysis to transmission?

Fluoroquinolone-Resitant E. coli

Context

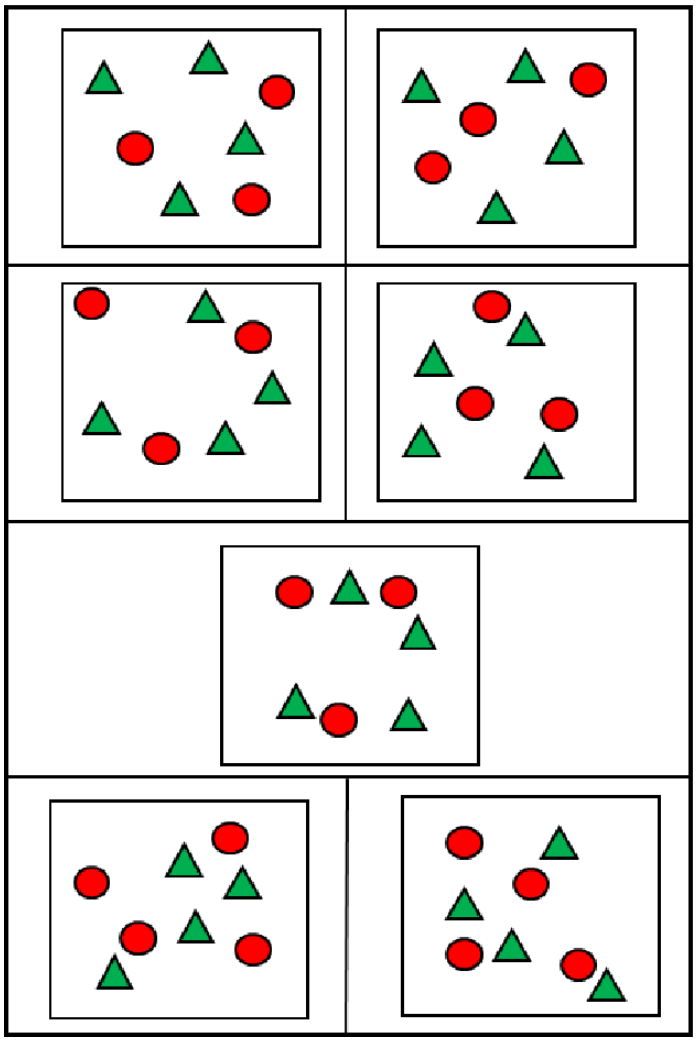
- Antimicrobial resistance: public health issue.
- Persistence and spread of resistant bacteria $\Longrightarrow$ treatment failures
- Quinolones widely used in pig production $\Longrightarrow$ selective pressure.

Objective

Quantifying the transmission of FQ-resistant E. coli in pig population

Fluoroquinolone-Resitant E. coli

- 65 SPF pigs (3 weeks post-weaning)
  - 6 negative control
  - 8 inoculated control
  - 23 inoculated (contact) pigs
  - 28 Sentinel pigs
- Inoculation: 10 mL suspension (10^9 CFU/mL)
- Fecal sampling:
  - daily from 0 to 4 DPI
  - every 2 days until 10 DPI
- Bacterial counts(BC).



Model hypotheses

- Susceptible-Infectious-Susceptible (SIS)
- Susceptible: $BC < 5\ 10^3$ (CFU/g of feces)
- Infectious individual distributed according to three assumption
  - H1: All individuals have equal transmission potential (I_L)
  - H2: Two infectious states:

$$I_L \text{ if } 5 \cdot 10^3 < BC < 10^6$$
$$I_H \text{ if } BC > 10^6$$

  - H3: Three infectious states:

$$I_L \text{ if } 5 \cdot 10^3 < BC < 10^5$$
$$I_M \text{ if } 10^5 < BC < 10^6$$
$$I_H \text{ if } BC > 10^6$$

Parameter estimation

- Survival analysis for the duration of infectious period
- Transmission Rate: Maximum likelihood method
  - Individual probability to escape infection on time-interval $[t_j; t_{j+1}]$:

$$p_j = exp(-(\beta_L \ I_{L\,j}/N + \beta_M \ I_{M\,j}/N + \beta_H \ I_{H\,j}/N) \ \Delta_j)$$

  - Number of **new cases** follows a binomial distribution

$$C_j \sim Bin(S_j, 1 - p_j)$$

  - Likelihood expression:

$$L = \prod_{g=1}^{nGroups} \prod_{j=1}^{nObs} dBin(S_j^g, 1 - p_j^g)$$

Results

Hypothesis	Parameters			AIC
	β_L	β_M	β_H	
H1	0.55 (0.40; 0.74)	-	-	121.00
H2	0.41 (0.27; 0.62)	-	0.98 (0.59; 1.62)	117.85
H3	0.41 (0.23; 0.71)	0.42 (0.15;1.19)	0.98 (0.59; 1.62)	119.85

Conclusions

- Transmission dependent on the quantity of bacteria shed in feces
- No appearent role of the intermediate level:
  - Transient state
  - low number of animal simultaneously in this compartment
- the basic reproduction number was not estimated:
  - the dose-dependent transmission
  - the variability in individual shedding
  - the evidence of host reinfection
- Only **horizontal transmission** was considered when **oro-fecal** transmission is more likely.

In this particular case, **environmental reservoir** should play a non-negligible role in transmission.

Hepatitis E virus transmission

Context

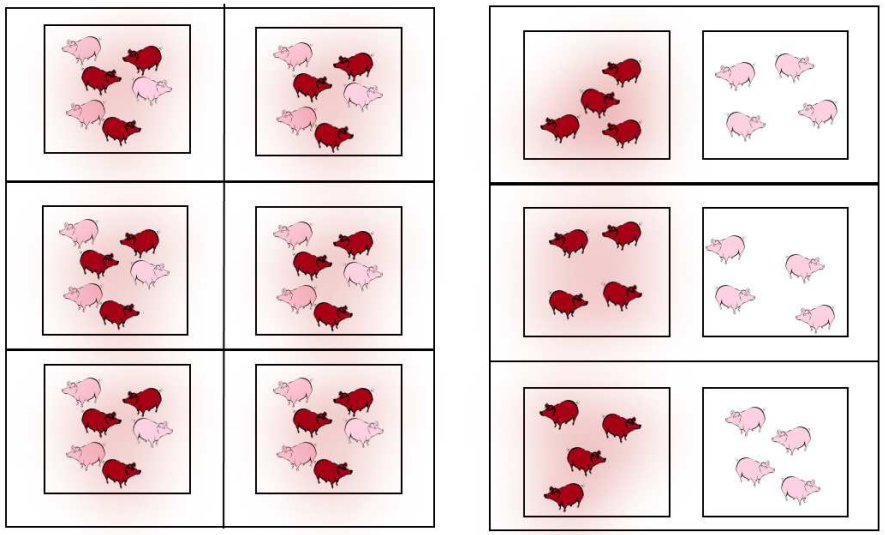
- Hepatitis E is a zoonotic disease.
- Clinical expression similar to hepatitis A in humans.
- Possible chronic infections in immunocompromised humans.
- Pigs are considered as the main reservoir.
- Totally asymptomatic in pigs.
- Oro-fecal transmission is predominant.

Objective

- Estimating HEV transmission in pigs.
- Disentangling the different transmission routes: horizontal (direct contacts) and environmental transmission.

Experimental design

- 68 SPF pigs (5 weeks)
  - 8 negative control
  - 30 inoculated (contact) pigs
  - 30 Sentinel pigs
- Oral inoculation: 10 mL suspension (10^8 ge/mL)
- Fecal sampling:
  3-times a week for 39 days.
- Virology: Quantitative RT-PCR.
- Serology: Elisa test.



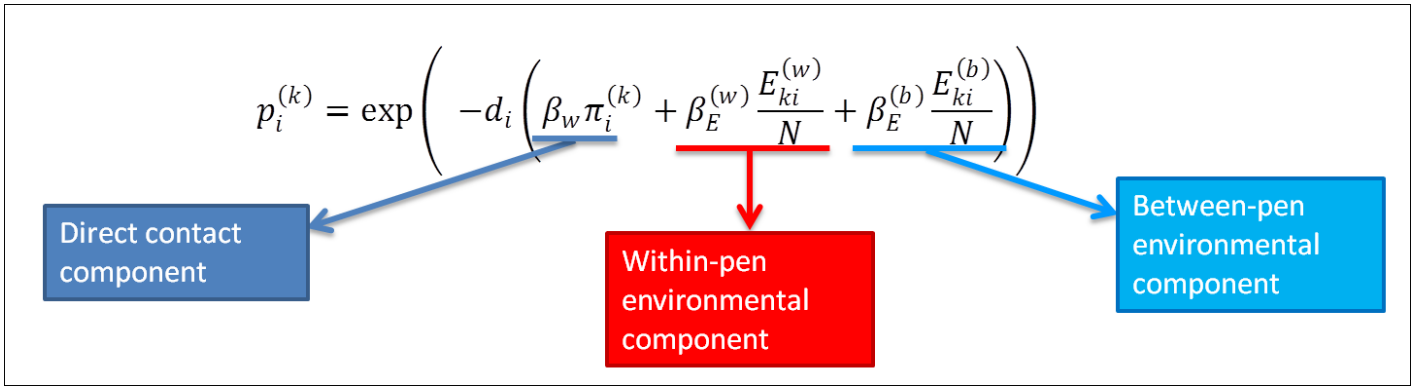
Modeling framework

Environmental Component

- Average quantity of virus shed within a specific pen
- Accounting for a daily clearance rate (δ)

$$E_{ki} = E_k(t_{i+1}) = (E_k(t_i) + \int_0^{\Delta_t} V_k(t_i + u)e^{\delta u}du)e^{-\delta \Delta t}$$

Probability to escape from infection



Likelihood expression

- Assumption: A pig is infectious when fecal samples are positive for HEV.
- Date of infection: Any time prior to the first positive sample.
- This time has to be wheighted by the duration of latency period.

Individual contribution to Likelihood

$$L^{(j)}\left(\mathbf{D_I}, \pi_{\mathbf{w}}, \mathbf{E}, \beta_w, \beta_E^{(w)}, \beta_E^{(b)}, A, B, \delta\right) = \sum_{i=1}^{I_j} \left\{ \prod_{l=1}^{i} p_{l-1}^{(k)} (1-p_i^{(k)}) f_{Lat}(t_{I_j} - t_i, A, B) \right\}$$

Likelihood

$$L\left(\mathbf{D_I}, \pi_{\mathbf{w}}, \mathbf{E}, \beta_w, \beta_E^{(w)}, \beta_E^{(b)}, A, B, \delta\right) = \prod_{j=1}^{nC} L^{(j)}\left(\mathbf{D_I}, \pi_{\mathbf{w}}, \mathbf{E}, \beta_w, \beta_E^{(w)}, \beta_E^{(b)}, A, B, \delta\right)$$

Bayesian inference using Metropolis-Hasting Algorithm.

Results

Virology direct contact groups

HEV ge/g of feces

	DPI	1	3	6	8	10	13	15	17	20	22	24	28	31	34	36	38	44
Room1. Group 1	Inoculated	0	0	0	0	0	$3.58\,10^{4}$	$2.07\,10^{5}$	$8.72\,10^{4}$	$1.27\,10^{4}$	0	0	0	0	0	0	0	0
	Inoculated	0	0	$4.39\,10^{4}$	$7.89\,10^{4}$	$5.54\,10^{5}$	$2.75\,10^{5}$	$5.40\,10^{4}$	$2.45\,10^{4}$	$2.14\,10^{4}$	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	0	0	$2.39\,10^{4}$	$3.37\,10^{4}$	$2.98\,10^{4}$	$1.70\,10^{4}$	$1.10\,10^{4}$	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	$3.09\,10^{4}$	$1.20\,10^{5}$	$5.12\,10^{4}$	$6.55\,10^{4}$	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	$8.82\,10^{3}$	$4.47\,10^{4}$	$3.66\,10^{4}$	$7.80\,10^{3}$	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	$1.08\,10^{4}$	$1.25\,10^{4}$	$3.56\,10^{4}$	0	0	0	0	0
Room1. Group 2	Inoculated	0	0	0	0	$1.33\,10^{4}$	$9.52\,10^{4}$	$1.27\,10^{5}$	$8.37\,10^{4}$	$7.41\,10^{3}$	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	0	$9.78\,10^{4}$	$2.99\,10^{5}$	$9.90\,10^{4}$	$2.56\,10^{4}$	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	$1.06\,10^{4}$	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	$1.53\,10^{4}$	$1.30\,10^{4}$	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Room2. Group 3	Inoculated	0	0	0	0	$3.03\,10^{4}$	0	0	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	$6.63\,10^{3}$	$3.86\,10^{4}$	$2.28\,10^{5}$	$9.77\,10^{4}$	$2.74\,10^{5}$	$1.43\,10^{6}$	$2.69\,10^{4}$	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	$2.23\,10^{4}$	0	$3.65\,10^{4}$	$4.17\,10^{4}$	$2.58\,10^{5}$	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	$9.03\,10^{4}$	$1.99\,10^{5}$	$3.03\,10^{5}$	$2.86\,10^{5}$	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	$2.16\,10^{4}$	$2.73\,10^{5}$	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Room2. Group 4	Inoculated	0	0	0	0	0	0						0	0	0	0	0	0
	Inoculated	0	0	0	$6.05\,10^{4}$	$5.51\,10^{4}$	$2.58\,10^{4}$						0	0	0	0	0	0
	Inoculated	0	0	0	$1.79\,10^{4}$	$1.21\,10^{4}$	$1.83\,10^{4}$						0	0	0	0	0	0
	Contact	0	0	0	0	0	0						0	0	0	0	0	0
	Contact	0	0	0	0	0	0						$1.15\,10^{4}$	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	$9.05\,10^{4}$	$3.38\,10^{4}$	0	0	0
Room3. Group 5	Inoculated	0	0	0	0	$1.97\,10^{4}$	$2.24\,10^{5}$	$3.68\,10^{5}$	$4.06\,10^{4}$	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	$5.27\,10^{4}$	$3.34\,10^{4}$	$1.24\,10^{5}$	$2.59\,10^{5}$	$5.03\,10^{5}$	$1.57\,10^{5}$	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	$7.16\,10^{4}$	$1.20\,10^{5}$	$7.47\,10^{5}$	$1.06\,10^{6}$	$4.51\,10^{5}$	$1.57\,10^{5}$	$2.72\,10^{4}$	$8.24\,10^{3}$	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	$1.78\,10^{4}$	0	$2.88\,10^{4}$	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	$1.75\,10^{4}$	$2.65\,10^{4}$	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	$9.60\,10^{3}$	0	$1.07\,10^{4}$	$5.39\,10^{4}$	0	0
Room3. Group 6	Inoculated	0	0	0	0	0	$7.20\,10^{5}$	$2.23\,10^{4}$	$4.01\,10^{4}$	$7.12\,10^{4}$	$1.66\,10^{5}$	$2.67\,10^{4}$	0	0	0	0	0	0
	Inoculated	0	0	0	0	$2.36\,10^{3}$	$7.73\,10^{4}$	$9.68\,10^{4}$	$3.06\,10^{5}$	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	$8.82\,10^{3}$	$1.34\,10^{5}$	$3.71\,10^{5}$	$2.38\,10^{5}$	$1.94\,10^{5}$	$2.41\,10^{4}$	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	$1.03\,10^{4}$	$1.47\,10^{5}$	$6.08\,10^{5}$	$1.38\,10^{6}$	$1.17\,10^{6}$	$7.76\,10^{4}$	0	0
	Contact	0	0	0	0	0	0	0	0	0	$1.12\,10^{5}$	$4.58\,10^{4}$	$1.15\,10^{5}$	$2.14\,10^{5}$	$4.65\,10^{5}$	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

14 days

Results

Virology indirect contact groups

HEV ge/g of feces

	DPI	1	3	6	8	10	13	15	17	20	22	24	28	31	34	36	38	44
Room 4, Group a	Inoculated	0	0	$3.34\ 10^{4}$	0	$2.63\ 10^{4}$	$2.86\ 10^{4}$	0	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	$1.77\ 10^{4}$	$2.57\ 10^{4}$	$1.58\ 10^{4}$	$1.01\ 10^{5}$	$4.52\ 10^{4}$	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	$4.90\ 10^{3}$	$4.72\ 10^{4}$	$8.69\ 10^{4}$	$2.09\ 10^{5}$	$9.25\ 10^{5}$	$1.75\ 10^{5}$	$2.13\ 10^{4}$	$5.46\ 10^{4}$	0	0	0	0	0	0	0	0
	Inoculated	0	$3.86\ 10^{3}$	$1.15\ 10^{5}$	$2.18\ 10^{5}$	$1.37\ 10^{5}$	$5.98\ 10^{5}$	$2.39\ 10^{6}$	$6.44\ 10^{5}$	$1.70\ 10^{5}$	$1.23\ 10^{5}$	$4.81\ 10^{4}$	0	0	0	0	0	0
Room 4, Group b	Contact	0	0	0	0	0	0	0	0	0	0	0	0	$1.16\ 10^{4}$	$2.75\ 10^{4}$	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$8.77\ 10^{3}$
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$1.90\ 10^{4}$
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$9.50\ 10^{3}$
Room 5, Group a	Inoculated	0	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	$1.30\ 10^{4}$	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	0	$7.60\ 10^{4}$	$6.34\ 10^{5}$	$3.55\ 10^{5}$	$3.27\ 10^{4}$	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	$7.25\ 10^{4}$	$2.40\ 10^{4}$	$2.47\ 10^{5}$	$1.08\ 10^{6}$	$4.87\ 10^{5}$	$1.47\ 10^{4}$	$1.10\ 10^{4}$	0	$3.48\ 10^{4}$	0	0	0	0	0	0
	Inoculated	0	0	$8.41\ 10^{4}$	$2.70\ 10^{5}$	$6.63\ 10^{5}$	$4.09\ 10^{5}$	$4.10\ 10^{5}$	$1.05\ 10^{5}$	$1.46\ 10^{4}$	0	0	0	0	0	0	0	0
Room 5, Group b	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Room 6, Group a	Inoculated	0	0	0	0	$1.14\ 10^{5}$	$5.64\ 10^{5}$	$2.54\ 10^{6}$	$7.22\ 10^{5}$	$7.33\ 10^{4}$	$1.40\ 10^{5}$	$9.96\ 10^{4}$	$5.19\ 10^{4}$	$4.39\ 10^{4}$	0	0	0	0
	Inoculated	0	0	0	0	$1.37\ 10^{5}$	$1.69\ 10^{4}$	$4.46\ 10^{4}$	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	0	0	7.70 10+02	$9.08\ 10^{5}$	$1.64\ 10^{5}$	0	0	0	0	0	0	0	0	0	0
	Inoculated	0	0	$1.10\ 10^{5}$	$1.61\ 10^{5}$	$4.85\ 10^{6}$	$2.04\ 10^{6}$	$4.74\ 10^{4}$	0	0	0	0	0	0	0	0	0	0
Room 6, Group b	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Results

Parameter	Estimates	
	Median	95% CI
β_w	0.15	$(0.03; 0.31)$
$\beta_E^{(w)}$	$2 \cdot 10^{-6}$	$(1 \cdot 10^{-7}; 7 \cdot 10^{-6})$
$\beta_E^{(b)}$	$7 \cdot 10^{-8}$	$(5 \cdot 10^{-9}; 3 \cdot 10^{-7})$
A	5.3	$(3.2; 8.7)$
B	0.76	$(0.48; 1.25)$
δ	0.33	$(0.19; 0.46)$

Conclusions

Remark

$\beta_E^{(w)}$:Average number of new cases produced by a one ge/g of feces in the environment.

$\Longrightarrow \varepsilon = {\beta_E^{(w)}}^{-1}$ corresponds the the average quantity of virus per gram of feces necessary to infect one individual.

$$\varepsilon = 5.62 \cdot 10^5 \text{ge/g} (1.45 \cdot 10^5; 9.34 \cdot 10^6).$$

- Direct contacts:
  - Sufficient to explain the maintenance of virus in infected pig herds
  - not enough to explain the high prevalences recorded in field conditions
- First clear evidence of environmental transmission:
  - Sustained increase of the force of infection
- indirect transmission *via* the environment
  - Rare events
  - Not negligible since inducing further within-pen transmission.

Analysis of experimental transmission trials...

...presents several advantages:

- Controlled environment
- Investigations on specific aspects
  - Contact structure
  - Vaccination
  - Passive immunity
  - Role of environmental factors

But...

Analysis of experimental transmission trials...

... have to be considered with care because far from field conditions

- Pigs are SPF
- Environment is fully controlled
- No external risk factors (co-infections)

Analysis of experimental transmission trials...

Moreover practical issues have to be considered

- Ethics
- Biosafety
- Heavy and expensive experimental designs
- Specific mathematical model and estimation methods
- Long process to be thought in advance

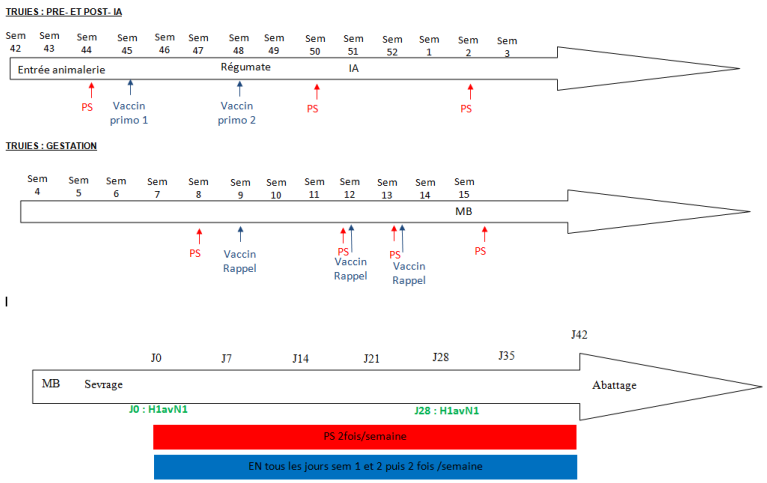


Figure: *Time-scale for a SIV experiment with maternally derived immunity*

Aknowledgements

- Pig Epidemiology and Welfare Unit
- Pig SPF Production and Experimental Unit
- Viral Genetics and Biosafety Unit
- Mycoplasmology-Bacteriology Unit
- Pig Immunology and Virology Unit
- UMR 1161 Virology/ ANSES/ ENVA/ INRA/ UPMC

Aknowledgements

Thanks for your attention