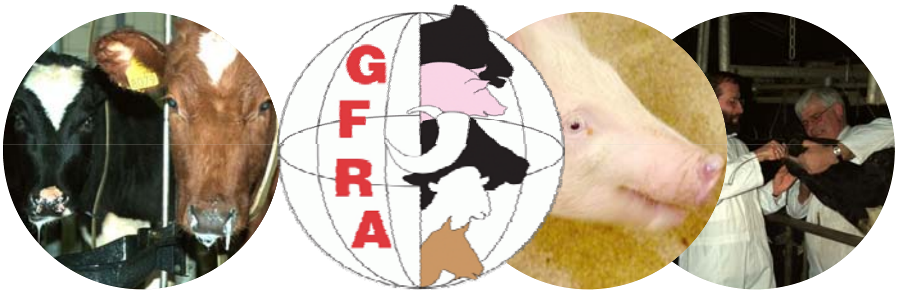
Foot and Mouth Disease vaccination is effective:

Quantification of FMD transmission with and without vaccination

Aldo Dekker



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SEVENTH FRAMEWORK PROGRAMME

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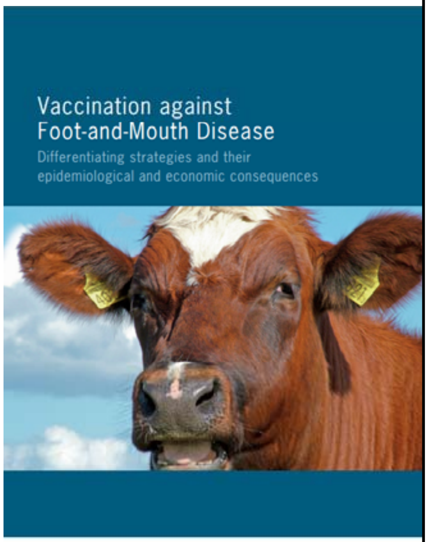
Mathematical modelling

- Basis for the contingency plan
- After 2001 vaccination to live



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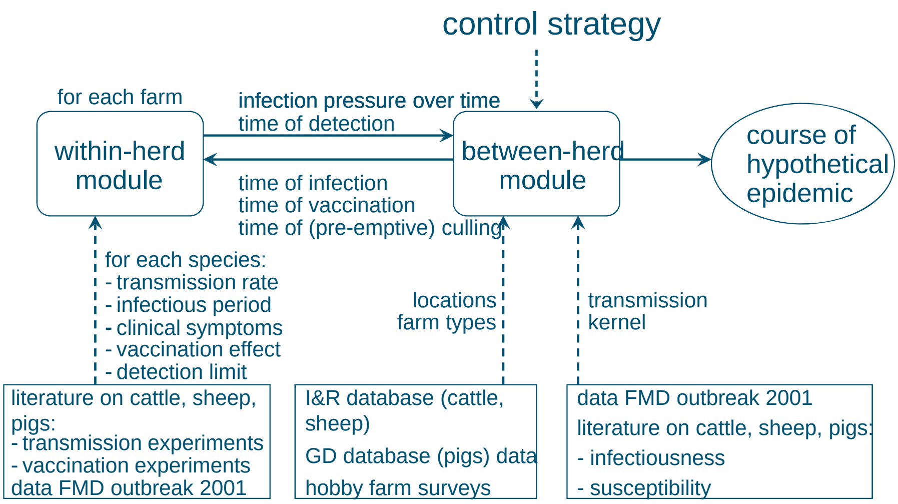
Mathematical model



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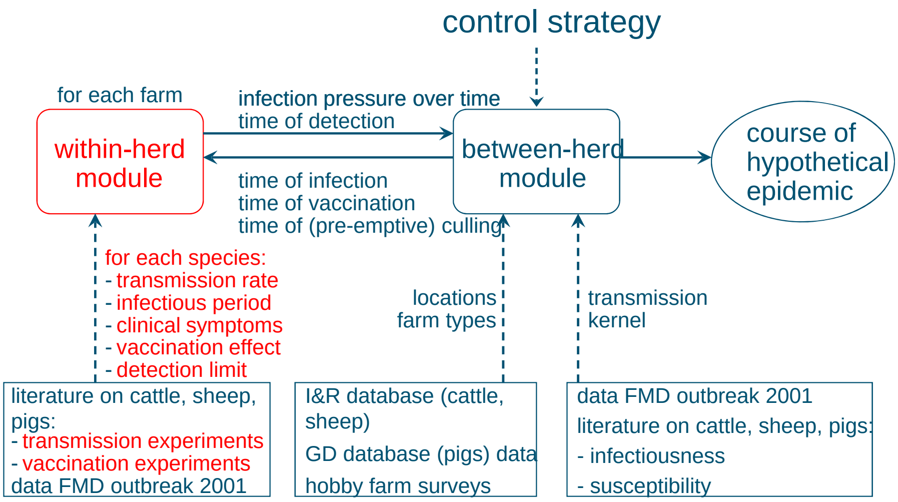

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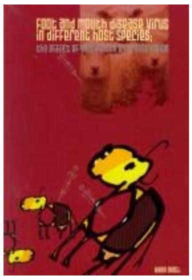
Published studies

- Direct contact transmission of FMDV
  - With and without vaccination
  - Between pigs: O Taiwan, O Netherlands
  - Between cattle: O Netherlands, Asia 1 Turkey
  - Between sheep: O Netherlands, Asia 1 Turkey
  - Between sheep and cattle: Asia 1 Turkey
- Transmission over separations
  - Between groups of pigs: O Taiwan, O Netherlands
  - Between calves



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How to determine the vaccine efficacy

- Classic experiments:
  Vaccination - challenge experiments

  - Protection against clinical signs (e.g. PD_{50})
  - Antibody titre post vaccination

  →Immunity of individual animals

- Essential:
  - Transmission of the pathogen in a group

Basic design transmission experiments

- Groups of animals
- Homogeneously treated (non-vaccinated or vaccinated)
- Start of infection chain: challenge (I_0)
- Contacts introduced after 8 or 24h (S_0)
- Experiments ended at 14 – 28 dpi

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Parameters to detect (contact) infections

- Clinical signs of FMDV (fever, vesicles)
- Virus excretion in OPF (swabs)
  - VI
  - PCR
- Neutralising Antibodies (booster)
- Ab's against non-structural proteins (NS-ELISA)

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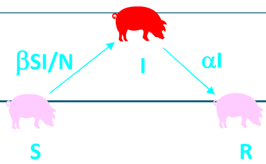
Mathematical Methods



- SIR model (susceptible, infectious, removed)
- Reproduction ratio *R*
  - average number of secondary infections caused by one typical infectious animal during its entire infectious period.
  - $R < 1$: minor outbreak; $R > 1$: major outbreak
- Transmission rate β
  - average number of secondary infections caused by one typical infectious animal *per unit of time*
- Final Size method → *R*
  - The number of contact animals that is infected when the infection chain has ended
- Generalized Linear Modelling → β, *T and R*
  - $E(C) = S\,(1-e^{[-\beta.I.\Delta t/N]})$
  - use of longitudinal (e.g. daily) data
  - $R = \beta.T$ (T=infectious period)

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Example daily data virus isolation OPF swabs:

Titers VI OPF (non-vaccinated group)

	0 dpi	1 dpi	2 dpi	3 dpi	4 dpi	5 dpi	6 dpi	7 dpi	8 dpi	9 dpi	10-14 dpi
S	0	0	2.59	4.24	4.19	1.76	1.3	0	0	0	0
S	0	0	3.17	3.83*							
S	0	0	3.06	4.24	3.06	0.4	1.99	1.18*			
S	0	0	1.83	5.3	3.1	1.91	0.4	0	0	1.35*	
S	0	0	1.95	4.95	2.66	0.7	1.6	0*			
I	0	0	2.7	3.24	2.1	1.3	0.7	0	0	0	0
I	0	1.54	2.94	1.51	1.35*						
I	0	1.8	3.23	3.24*							
I	0	0	1.18	4.11*							
I	0	0	1.48	3.29	2.1*						

* euthanasia pig

- Final size: all 5 contact animals infected
- GLM: per time-period Δt: count number of S, I, C and N

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Example daily data virus isolation OPF swabs:

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I	0	1.8	3.23	3.24*							
I	0	0	1.18	4.11*							
I	0	0	1.48	3.29	2.1*						

* euthanasia pig

- S=5; I=2; C=5; N=10; Δt=1

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Infectious period T

Titers VI OPF (non-vaccinated group)

	0 dpi	1 dpi	2 dpi	3 dpi	4 dpi	5 dpi	6 dpi	7 dpi	8 dpi	9 dpi	10-14 dpi
S	0	0	2.59	4.24	4.19	1.76	1.3	0	0	0	0
S	0	0	3.17	3.83*							
S	0	0	3.06	4.24	3.06	0.4	1.99	1.18*			
S	0	0	1.83	5.3	3.1	1.91	0.4	0	0	1.35*	
S	0	0	1.95	4.95	2.66	0.7	1.6	0*			
I	0	0	2.7	3.24	2.1	1.3	0.7	0	0	0	0
I	0	1.54	2.94	1.51	1.35*						
I	0	1.8	3.23	3.24*							
I	0	0	1.18	4.11*							
I	0	0	1.48	3.29	2.1*						

* euthanasia pig

Duration of virus shedding
Count, survival analysis

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Results direct contact transmission

Species	Strain	vaccinated	R (final size)	R (GLM)
pigs	O Taiwan	no	∞ (2.1-∞)	33 (16-65)
pigs	O NET/2001	no	∞ (1.3-∞)	ND
Calves	O NET/2001	no	2.5	ND
Cattle	Asia 1	no	∞ (1.4-∞)	ND
Cattle	O NET/2001	no	∞ (1.3-∞)	ND
Sheep	O NET/2001	no	1.1 (0.3-3.4)	ND
Sheep	Asia 1	no	1.1 (0.3-3.4)	ND
pigs	O Taiwan	- 7 DPI	∞ (1.3-∞)	11 (5-24)
Cattle	Asia 1	- 7DPI het	0	ND
pigs	O Taiwan	- 7DPI 4 x	1.2 (0.2-5.4)	1.1 (0.2-7.5)
pigs	O Taiwan	- 14 DPI	0 (0-0.9)	0
pigs	O Taiwan	-14 DPI het	0 (0-2.2)	0
pigs	O NET/2001	-14 DPI het	2.4 (0.9-6.9)*	ND
Calves	O NET/2001	-14 DPI het	0.2	ND
Cattle	O NET/2001	-14 DPI het	0 (0-3.4)	ND
Cattle	Asia 1	-14 DPI het	0	ND
Sheep	O NET/2001	-14 DPI het	0.22 (0-1.8)	ND
Sheep	Asia 1	-14 DPI het	0 (0-0.8)	ND

Summary results direct contact

No vaccination

- In cattle and pigs very extensive spread within a stable
- In calves with O Netherlands and in sheep limited spread

Vaccination

- Cattle, calves and sheep are very well protected
- Pigs are protected against a limited dose of virus (no infection)
- Pigs can spread if exposed to a massive amount of virus

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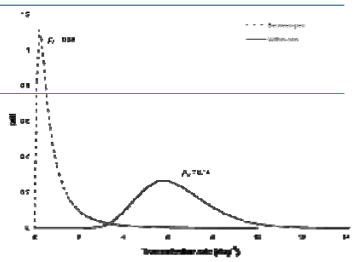
Between pen transmission



- Pigs O TAW:
  - Within-pen: β = 6.14
  - Between-pen: β = 0.6
- Pigs O NET:
  - Indirect contact 0 cm:
    R=1.1
  - Indirect contact 70 cm:
    R=0
  - Indirect contact 0 cm and vaccination at -14dpi
    R=0

→ Combination of limited contact structure and vaccination reduces transmission in pigs sufficiently

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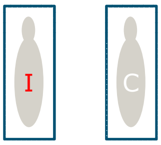
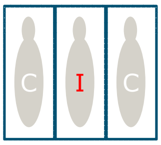
Between pen transmission calves O NET

- No transmission



- No transmission



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Conclusions between pen transmission

- Contact structure has huge influence on the outcome

Remaining questions (for now)

- What will happen in mixed populations
- What is the contribution of infected environment

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Mathematical model mixed populations

- SIR = Susceptible Infectious Removed
- R_0 = average number of new infections by a typically infectious individual in a completely susceptible population
- R_0 = sus x inf x C x T
- Matrix based on separable mixing

			From	
			$inf_c \times C \times T_c$	$inf_s \times C \times T_s$
			cattle	sheep
$F_c \times sus_c$	To	cattle		
$F_s \times sus_s$		Sheep		

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Next generation matrix

- Inf = infectivity
- sus = susceptibility
- C = contact rate
- T = time of infectious contact
- F = fraction
- $R_{s,c} = inf_s \times sus_c \times C \times T_s$

			From	
			$inf_c \times C \times T_c$	$inf_s \times C \times T_s$
			cattle	sheep
$F_c \times sus_c$	To	cattle	$F_c \times inf_c \times sus_c \times C \times T_c$	$F_c \times inf_s \times sus_c \times C \times T_s$
$F_s \times sus_s$		Sheep	$F_s \times inf_c \times sus_s \times C \times T_c$	$F_s \times inf_s \times sus_s \times C \times T_s$

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Next generation matrix

- Inf = infectivity
- sus = susceptibility
- C = contact rate
- T = time of infectious contact
- F = fraction (sheep or cattle)
- $R_{s,c}$ = inf_s x sus_c x C x T_s

			inf_c x C x T_c	inf_s x C x T_s
			From	
			cattle	sheep
F_c x sus_c	To	cattle	F_c x inf_c x sus_c x C x T_c	F_c x inf_s x sus_c x C x T_s
F_s x sus_s		Sheep	F_s x inf_c x sus_s x C x T_c	F_s x inf_s x sus_s x C x T_s

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Results mixed non-vaccinated populations

			inf_c x C x T_c	inf_s x C x T_s
			From	
			cattle	sheep
F_c x sus_c	To	cattle	F_c x inf_c x sus_c x C x T_c	F_c x inf_s x sus_c x C x T_s
F_s x sus_s		Sheep	F_s x inf_c x sus_s x C x T_c	F_s x inf_s x sus_s x C x T_s

			inf_c x C x T_c	inf_s x C x T_s
			From	
			cattle	sheep
½ x sus_c	To	cattle	**7**	**1**
½ x sus_s		Sheep	½ x inf_c x sus_s x C x T_c	**0.57**

- Infectivity sheep is 1/7 = 0.14 infectivity of cattle
- Susceptibility of sheep is 0.57/1 = 0.57 susc. of cattle
- Extension to vaccinated cattle and sheep

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Contribution of environment

- Transmission study with direct and indirect exposure
  - Indirect exposed cattle become infected
- 50 – 66% of infectivity can be contributed to contaminated environment on the days following the day that virus excretion was measured
- Assumption all infectivity is picked up from environment

- Remaining question:
  - What is the natural route of infection

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Experimental data used for models

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Vaccination against foot-and-mouth disease I: Epidemiological consequences

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Vaccination against foot-and-mouth disease II: Regaining FMD-free status

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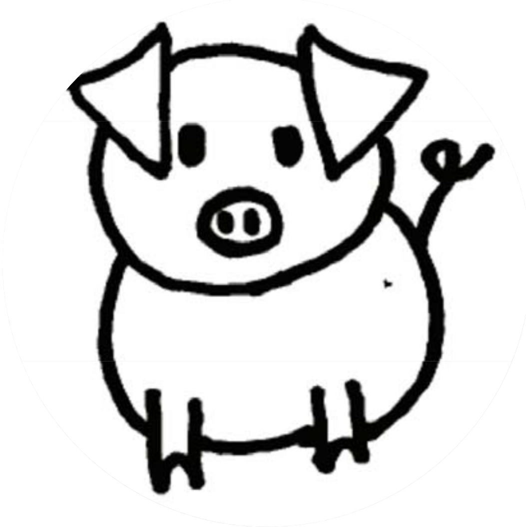
Thank you for listening

Take home message:

Emergency vaccination blocks transmission.



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