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Global Academy of
Agriculture and Food Systems

Modelling the AMR jump from farm animals to humans

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INTRODUCTION

1. AMU in humans vs. AMU in animals

- Primary focus is QALYs
- Human health :: welfare

- Goals:
  - Reduce hospital LOS (length of stay)
  - Reduce SD (sick days)

- Control:
  - NHS
  - UK Health Security Agency
  - Department of Health and Social Care

- Primary focus is production
- Animal health :: productivity

- Goals:
  - Reduce financial losses
  - Reduce animal weight loss

- Control:
  - Veterinary Medicines Directorate
  - Department for Environment, Food & Rural Affairs

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Environment

- Primary focus is production
- Animal health :: productivity

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  - Reduce financial losses
  - Reduce animal weight loss

- Control:
  - Veterinary Medicines Directorate
  - Department for Environment, Food & Rural Affairs

2. Not a new a idea

- Goal: connect AMU in farm animals to AMR in humans
- Environment as a reservoir of bacteria (AMR and "Simple")

Lanzas 2011

Research article

Modelling the impact of curtailing antibiotic usage in food animals on antibiotic resistance in humans

B. A. D. van Bunnik and M. E. J. Woolhouse

Van Bunnik 2017

3. What can be improved?

$$\frac{\mathrm{d}R_\mathrm{H}}{\mathrm{d}t} = \Lambda_\mathrm{H}(1-R_\mathrm{H}) + \beta_\mathrm{HH}R_\mathrm{H}(1-R_\mathrm{H}) + \beta_\mathrm{AH}R_\mathrm{A}(1-R_\mathrm{H}) - \mu_\mathrm{H}R_\mathrm{H};$$

$$\frac{\mathrm{d}R_\mathrm{A}}{\mathrm{d}t} = \Lambda_\mathrm{A}(1-R_\mathrm{A}) + \beta_\mathrm{AA}R_\mathrm{A}(1-R_\mathrm{A}) + \beta_\mathrm{HA}R_\mathrm{H}(1-R_\mathrm{A}) - \mu_\mathrm{A}R_\mathrm{A},$$

parameter	high impact
β_{AA}	0.1
β_{HH}	0.1
β_{AH}	0.1
β_{HA}	0.001
Λ_H	0.1
Λ_A	0.1
μ_A	0.1
μ_H	0.1

Van Bunnik 2017

3. What can be improved?

Knight 2019

$$\frac{dR_H}{dt} = \Lambda_H(1 - R_H) + \beta_{HH}R_H(1 - R_H) + \beta_{AH}R_A(1 - R_H) - \mu_H R_H;$$

$$\frac{dR_A}{dt} = \Lambda_A(1 - R_A) + \beta_{AA}R_A(1 - R_A) + \beta_{HA}R_H(1 - R_A) - \mu_A R_A,$$

However, **the current state** of mathematical modelling of ABR **has both conceptual and empirical gaps**, which urgently need to be filled given the importance of having good models. Model results tell us that details matter […]. However, without being able to routinely **inform and calibrate** these **models with** comprehensive **epidemiologic data**, we currently lack confidence in model predictions, most notably at the larger regional and national scale.

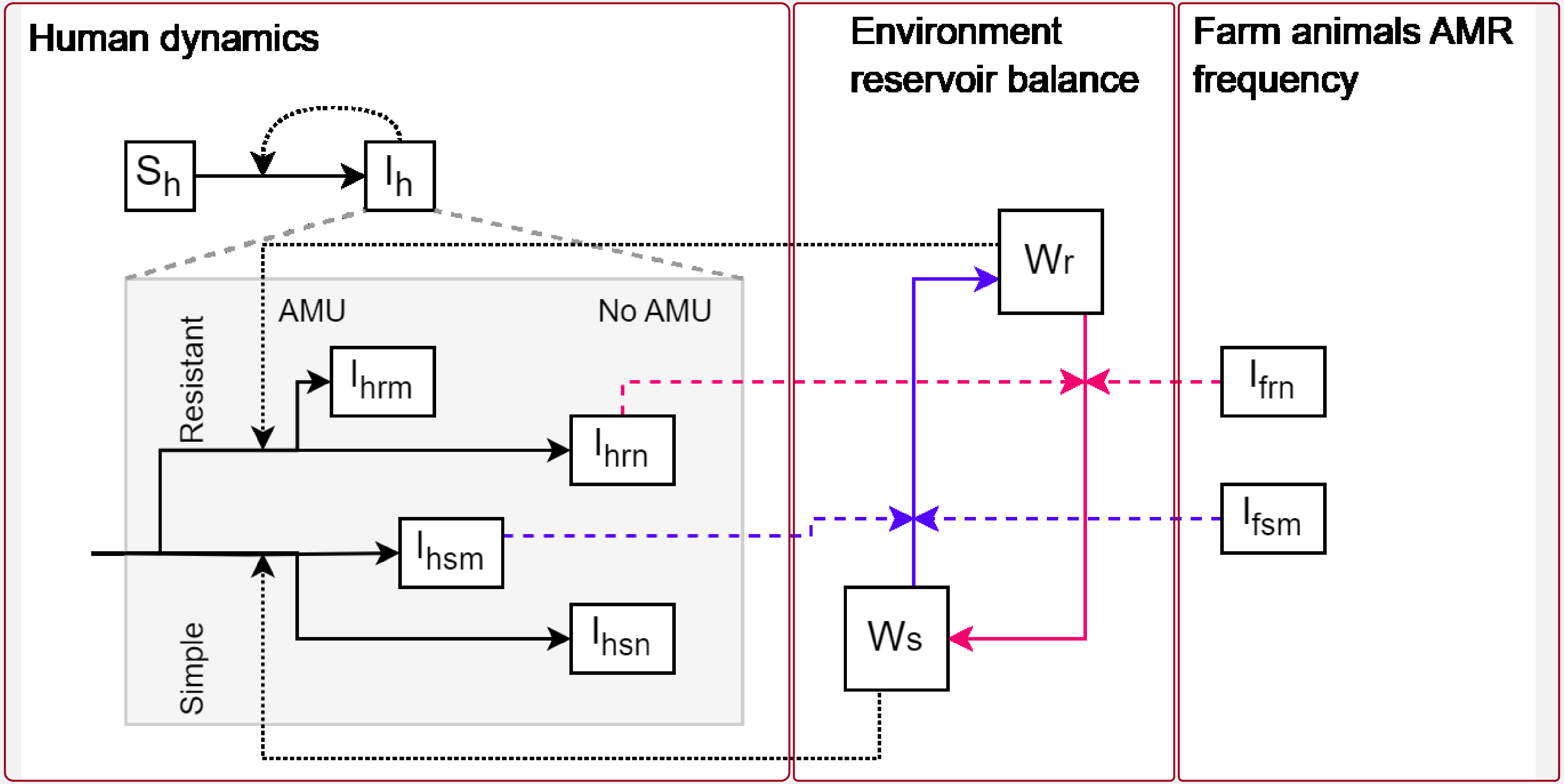
Van Bunnik 2017

4. Narrowing the problem

- E. coli infection in humans
- Generalized AMR prevalence in farm animals
- Proxy by antimicrobials sales
- Indirect effect of farm animal on humans (environment reservoir)
- Environment reservoir "self regulates".

METHODOLOGY

5. Dynamic system



Quick recap 1

- S – susceptible proportion
- I – infected proportion
- 1 = S+I

- X – susceptible (total)
- Y – infected (total)
- N = X+Y

$$\frac{dX}{dt} \times \frac{1}{N} = \frac{dI}{dt}$$

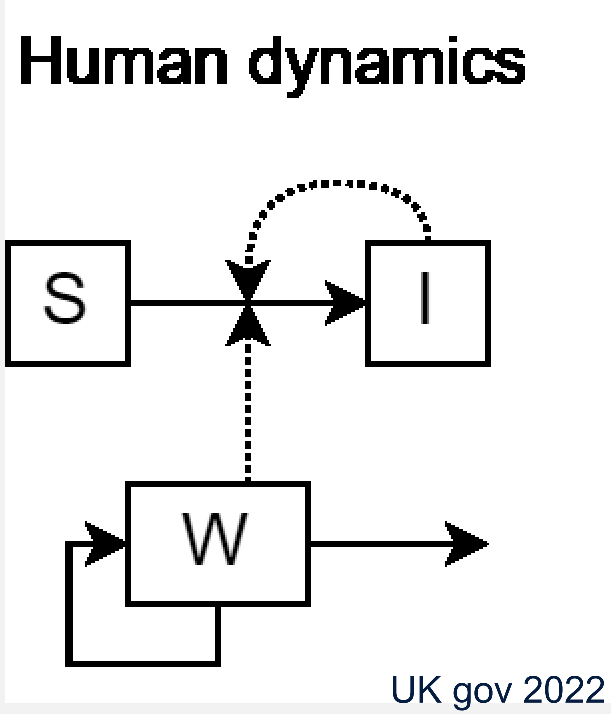
5.1 Modelling AMR humans

- Data for England
- E. coli yearly infections
- Divided by hospital/community
- Sapronotic pathogen

- Estimation of:

$$\frac{dI_h}{dt}, \frac{dS_h}{dt}$$

Lanzas 2019



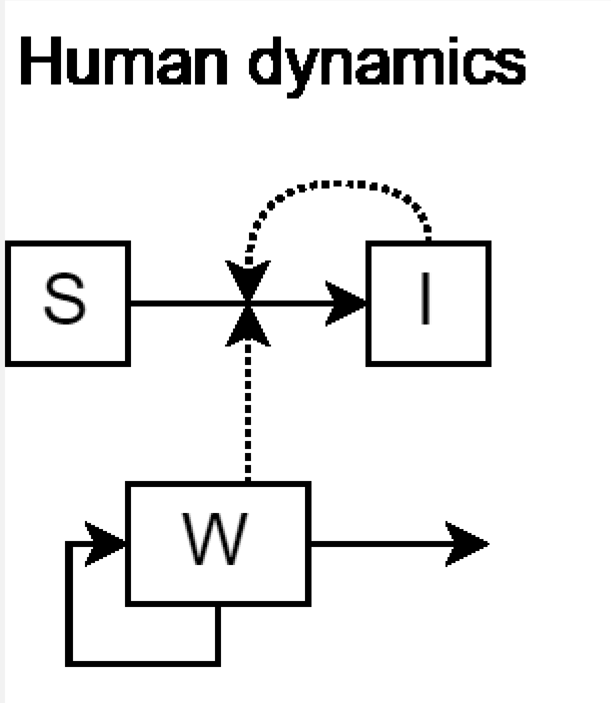
UK gov 2022

5.1 Modelling AMR humans

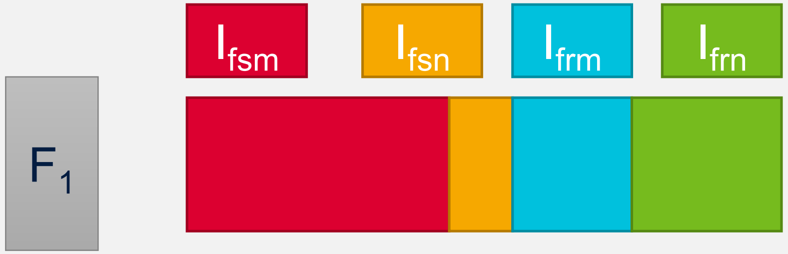
$$\frac{dI_h}{dt} = (1 - \alpha_{hW})\frac{dI_{h\beta}}{dt} + \alpha_{hW}\frac{dI_{hW}}{dt} - \gamma_h I_h$$

$$\frac{dI_{h\beta}}{dt} = \beta IS \qquad \frac{dI_{hW}}{dt} = \omega WS$$

$$\frac{dS_h}{dt} = \gamma_h I_h$$

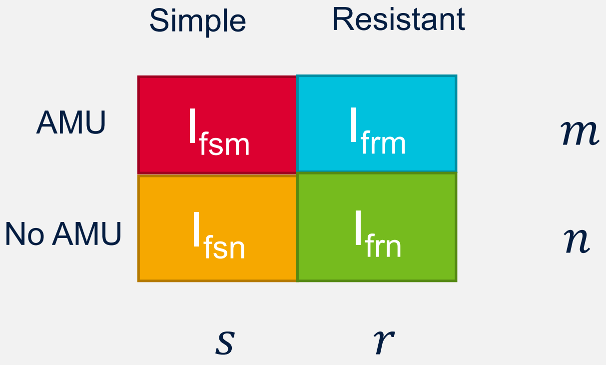


5.2 Modelling AMU on animals



$$I_{fsm} = \frac{Y_{fsm}}{Y_f}$$

$$Y_f = N_f \sum_j I_j$$

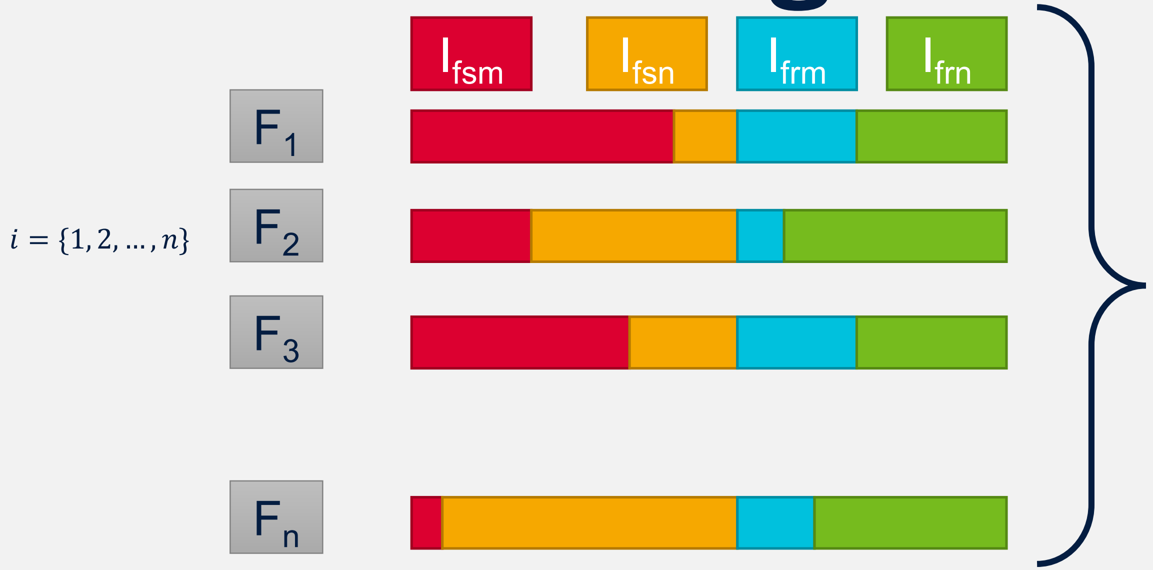


$$j = \{fsm, fsn, frm, frn\}$$

$$I_f = \frac{Y_f}{S_f}$$

- Typically density dependent model

5.2 Modelling AMU on animals



$$I_{i,fsm} = \frac{Y_{i,fsm}}{Y_i}$$

$$Y_i = N_i \sum_j I_{f,j}$$

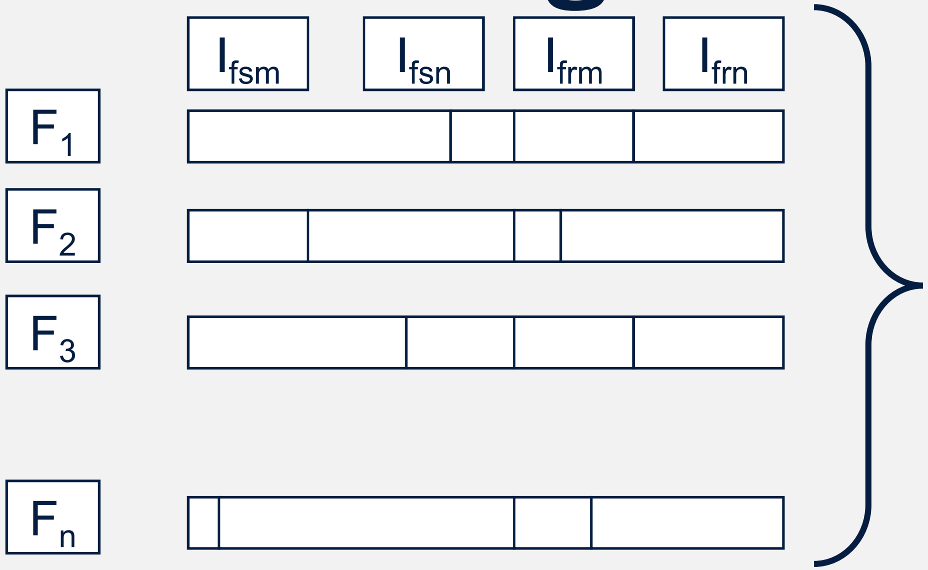
$$Y_f = \sum_i Y_i$$

$$I_f = \frac{Y_f}{S_f}$$

	Simple	Resistant	
AMU	I_{fsm}	I_{frm}	m
No AMU	I_{fsn}	I_{frn}	n
	s	r	

- Frequency dependent model

5.2 Modelling AMU on animals



$$I_{i,fsm} = \frac{Y_{i,fsm}}{Y_i}$$

$$Y_i = N_i \sum_j I_{f,j}$$

$$Y_f = \sum_i Y_i$$

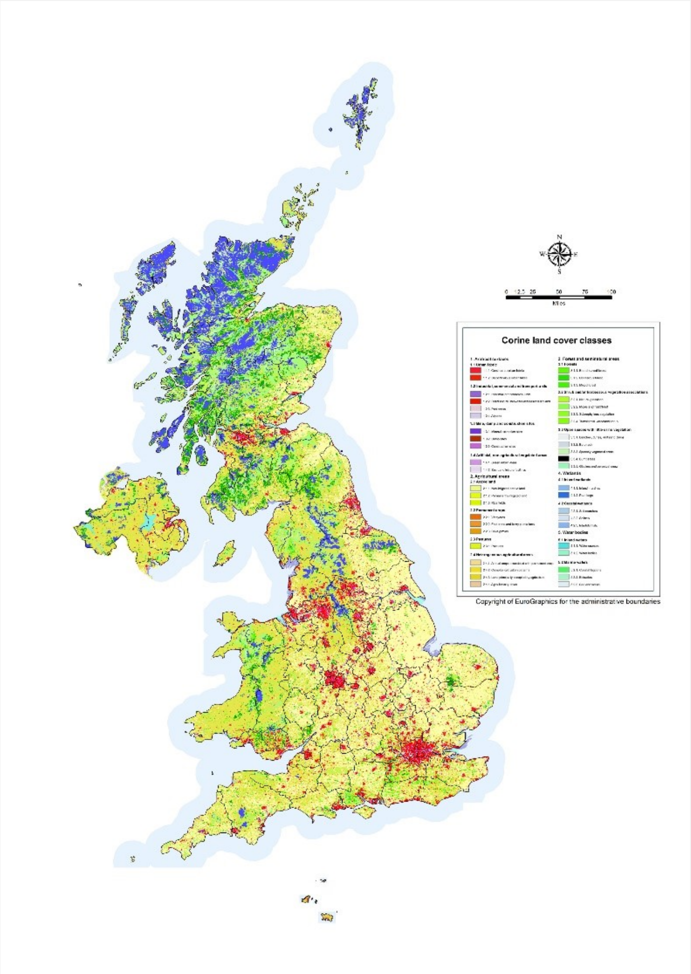
$$I_f = \frac{Y_f}{S_f}$$

- Frequency dependent model

$$\overline{I_{fsm}},\ \overline{I_{fsn}} \rightarrow \overline{I_{fs}}$$

$$\overline{I_{frm}},\ \overline{I_{fsn}} \rightarrow \overline{I_{fr}}$$

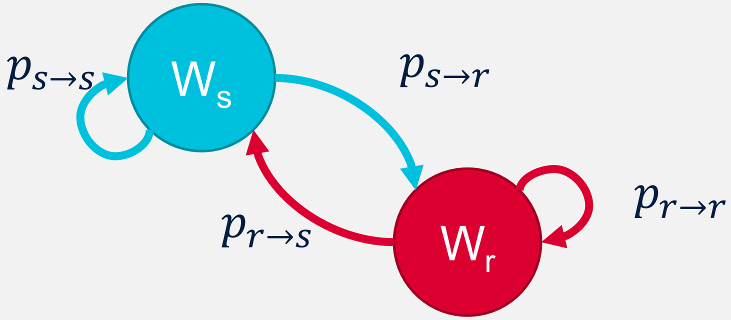
$$\overline{I_{fs}},\ \overline{I_{fr}} \rightarrow \overline{I_f}$$

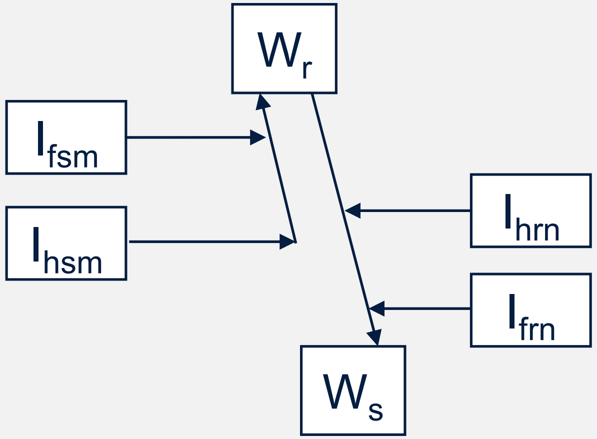


5.3 Modelling AMR environment

- Markov chain ≡ dynamic system

	From Ws	From Wr
To Ws	$p_{s\to s}$	$p_{r\to s}$
To Wr	$p_{s\to r}$	$p_{r\to r}$





$$\frac{dW_r}{dt} = \alpha_{Wh}(\lambda_{hsm}I_{hsm} - \lambda_{hrn}I_{hrn}) + \alpha_{Wf}(\lambda_{fsm}I_{fsm} - \lambda_{frn}I_{frn}) - \tau W_r$$

$$\frac{dW_s}{dt} = \alpha_h(-\lambda_{hsm}I_{hsm} + \lambda_{hrn}I_{hrn}) + \alpha_f(-\lambda_{fsm}I_{fsm} + \lambda_{frn}I_{frn}) + \tau W_r$$

5.3 Modelling AMR environment

- Markov chain ≡ dynamic system

	From Ws	From Wr
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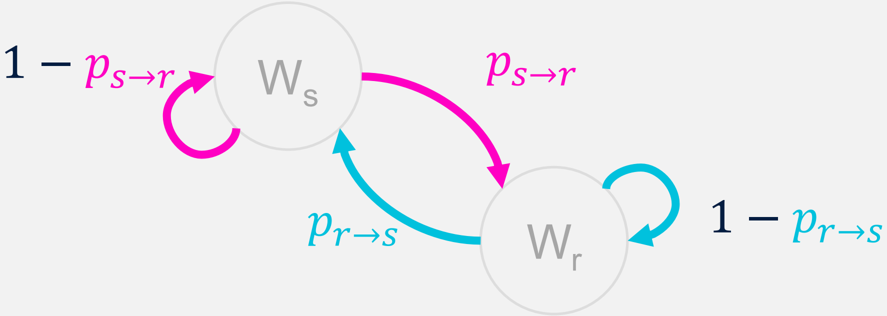


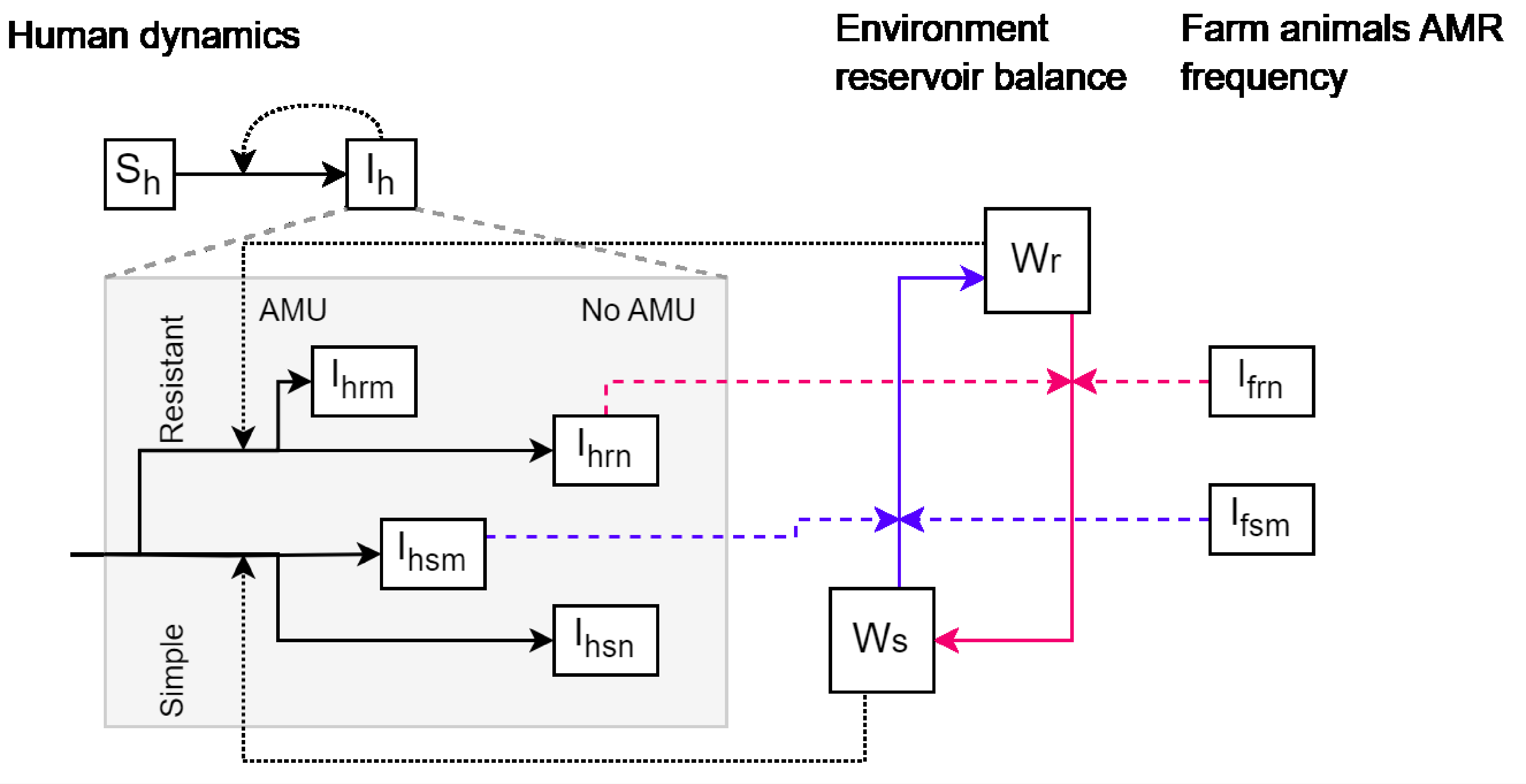
$$\frac{dW_r}{dt} = \alpha_{Wh}(\lambda_{hsm}I_{hsm} - \lambda_{hrn}I_{hrn}) + \alpha_{Wf}(\lambda_{fsm}I_{fsm} - \lambda_{frn}I_{frn}) - \tau W_r$$

$$p_{r\to s} = \frac{\alpha_{Wh}\lambda_{hrn}I_{hrn} + \alpha_{Wf}\lambda_{frn}I_{frn} + \tau W_r}{W_r}$$

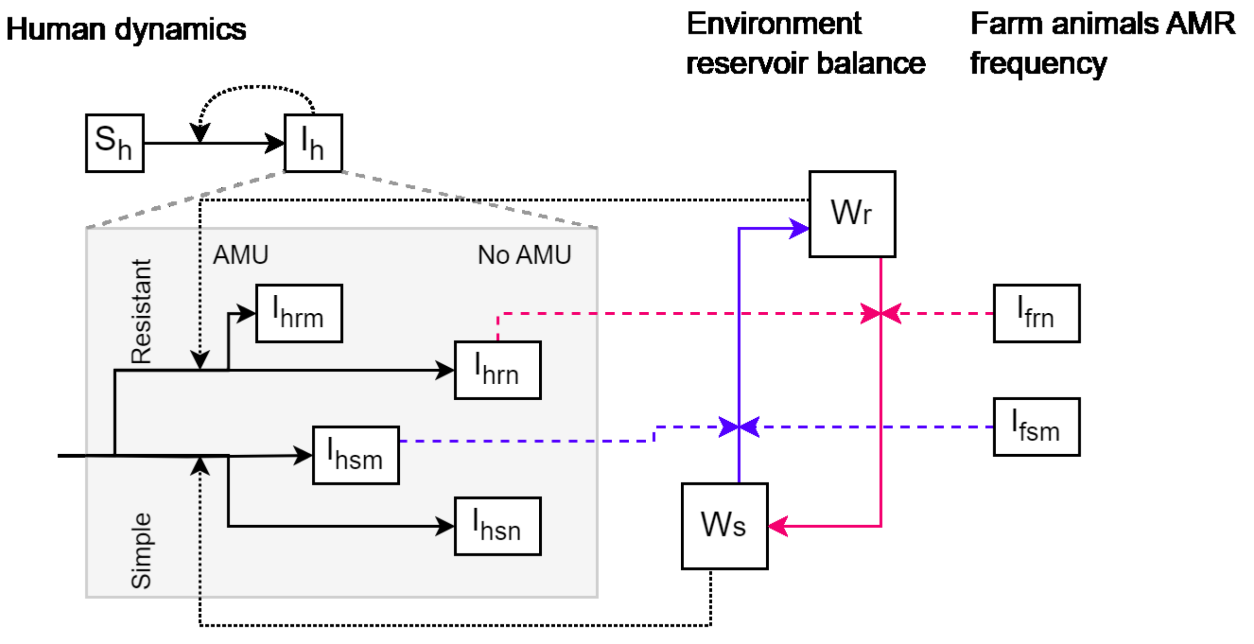
$$p_{s\to r} = \frac{\alpha_{Wh}\lambda_{hrn}I_{hrn} + \alpha_{Wf}\lambda_{frn}I_{frn} + \tau W_r}{W_s}$$

$$\frac{dW_s}{dt} = \alpha_h(-\lambda_{hsm}I_{hsm} + \lambda_{hrn}I_{hrn}) + \alpha_f(-\lambda_{fsm}I_{fsm} + \lambda_{frn}I_{frn}) + \tau W_r$$

6. Dynamic system



6. Dynamic system



Data values / calibrated equilibrium:

- Human: S_h, I_h, β, ω

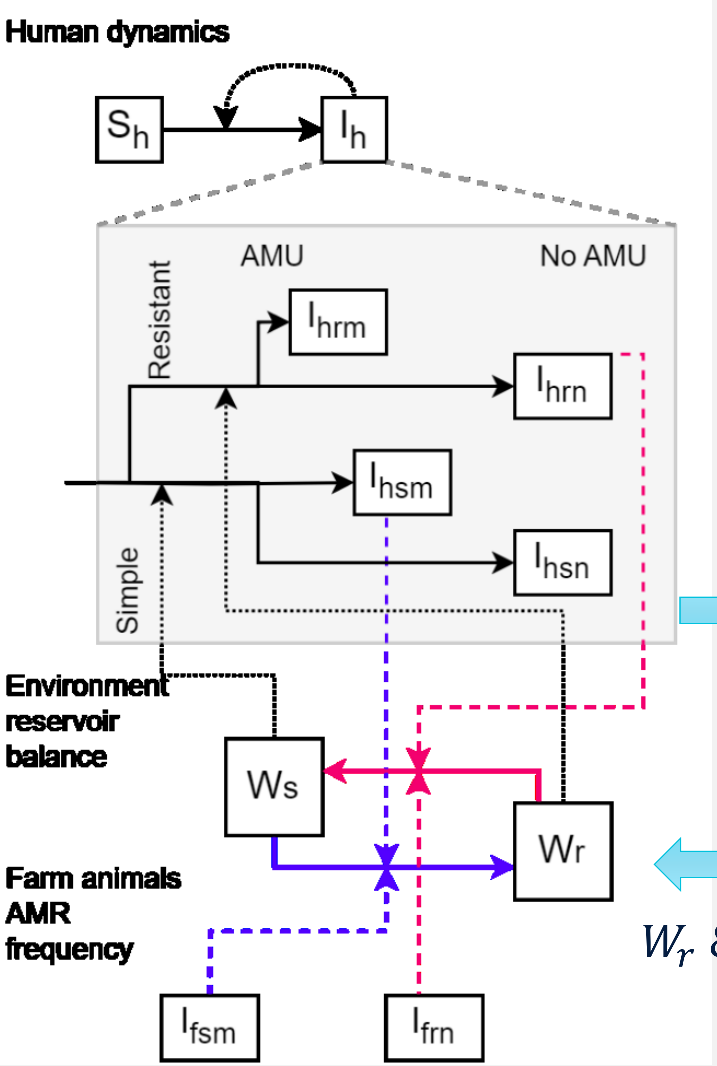
Estimated:

- Environment: $W_s, W_r, \alpha_{Wh}, \alpha_{Wf}, \lambda$
- Human: α_w
- Farm: $I_f, I_{frm}, \ldots$

Output:

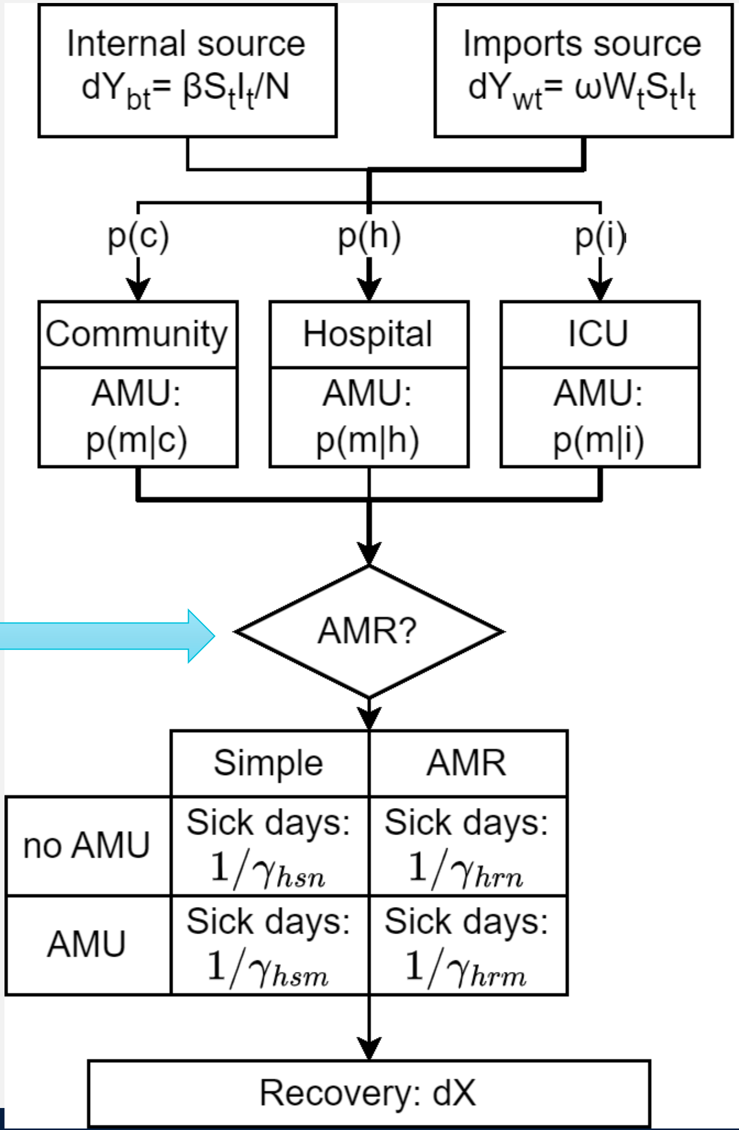
- Environment: W_s, W_r
- Human: S_h, I_h

7. Discrete event simulation



p_r dynamic

W_r & W_s dynamic



Exponential arrival:
$t_X = dY^{-1} e^{-dY^{-1}x}$

Bernoulli decision (based on data)

Bernoulli decision (estimated)

Bernoulli decision (based on data)

Deterministic decision

PRELIMINARY RESULTS

Quick recap 2

- DALY and QALY:

$$D = 1 - Q$$

- QALYs gained:

$$Q_g = Q_i \frac{1 - e^{-rL_i}}{r} - \mathrm{Q}\frac{1 - e^{-rL}}{r}$$

L: duration of the disease (i : with treatment)

Q: health-related quality of life weights predicted (or observed)

r: discount rate

Sassi 2006

- DALYs from infection:

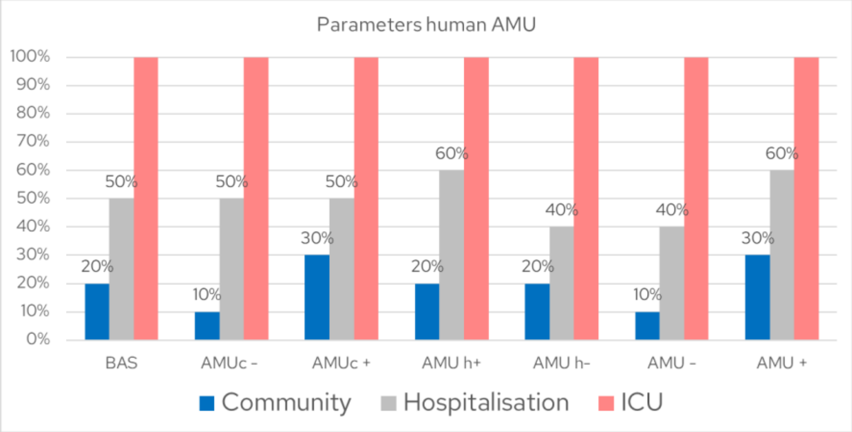
$$D_g = \frac{D}{r}(1 - e^{-rL_i})$$

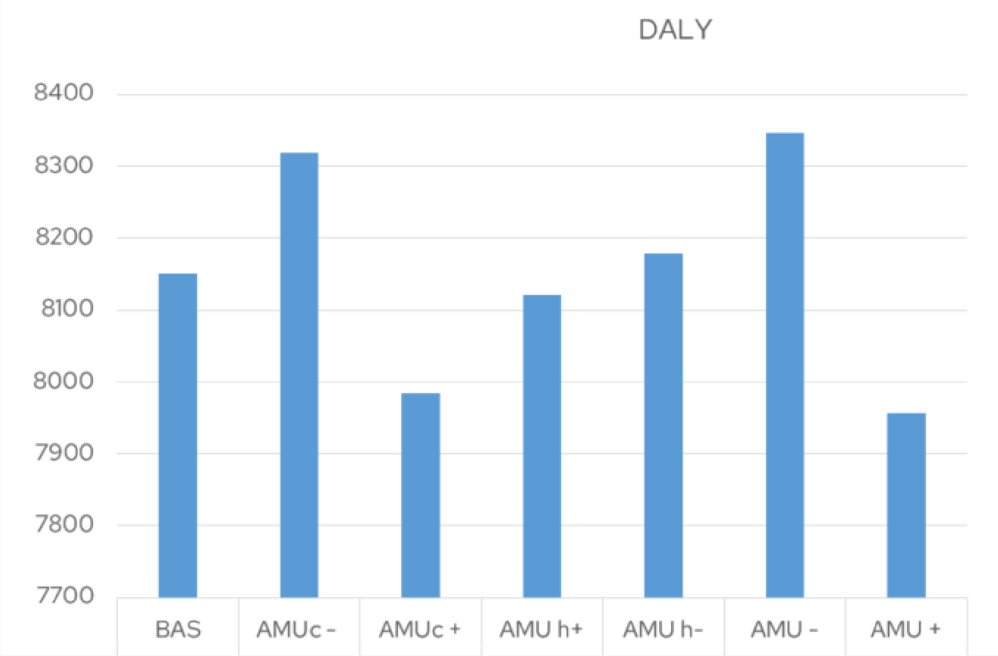
- Infectious disease, acute episode moderate D = 0.051
- r = 3%

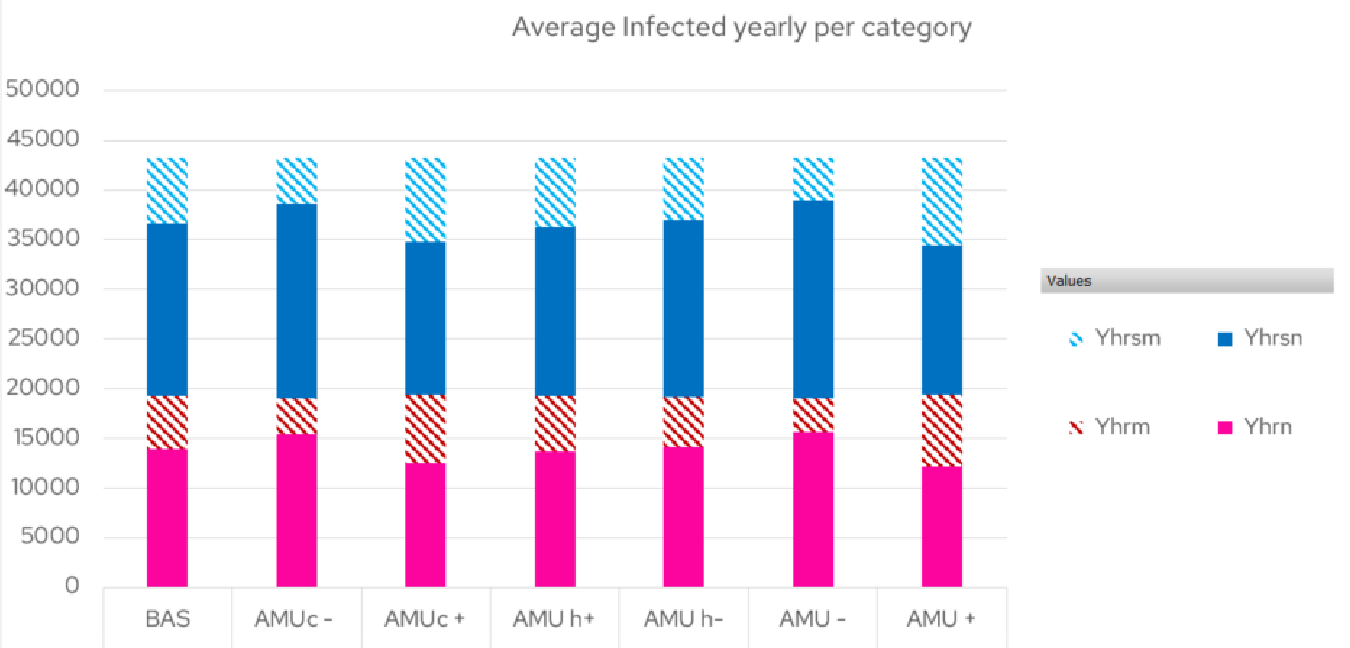
Haagsma 2015

8.1 Scenarios Human

- Changing AMU prescription policy

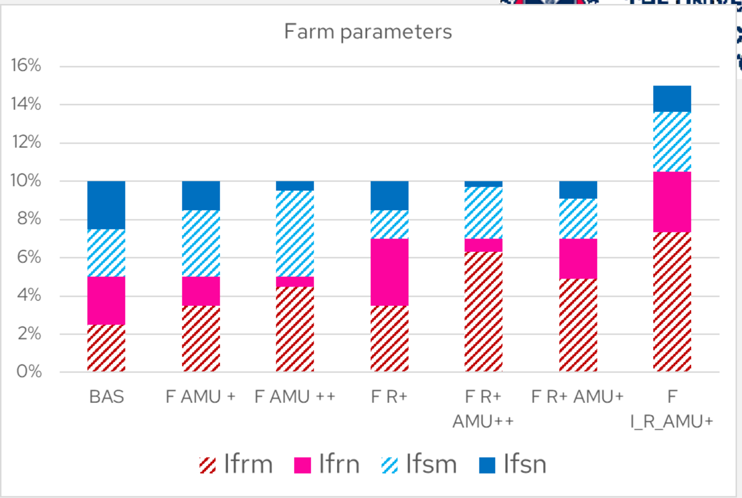


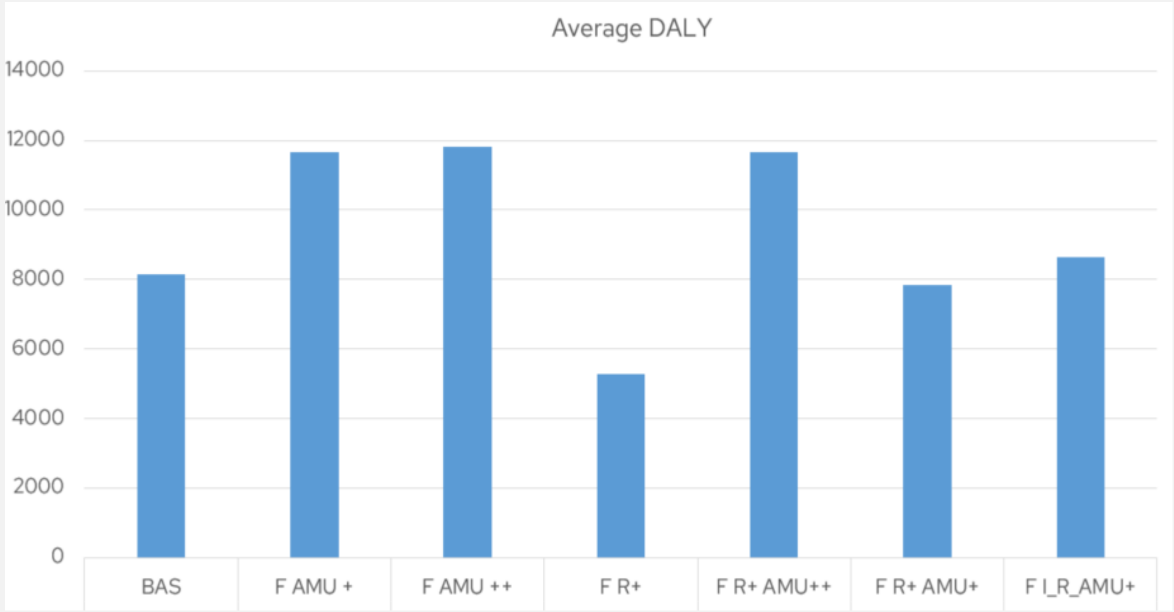


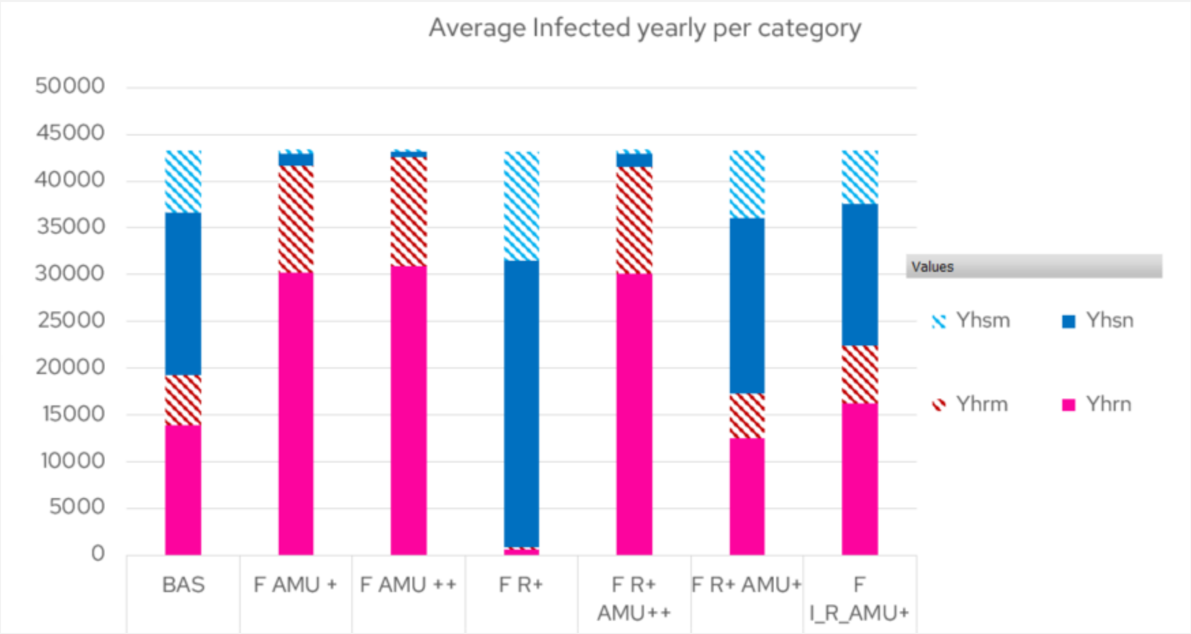


8.2 Scenarios Farm

- Farm parameters analysis

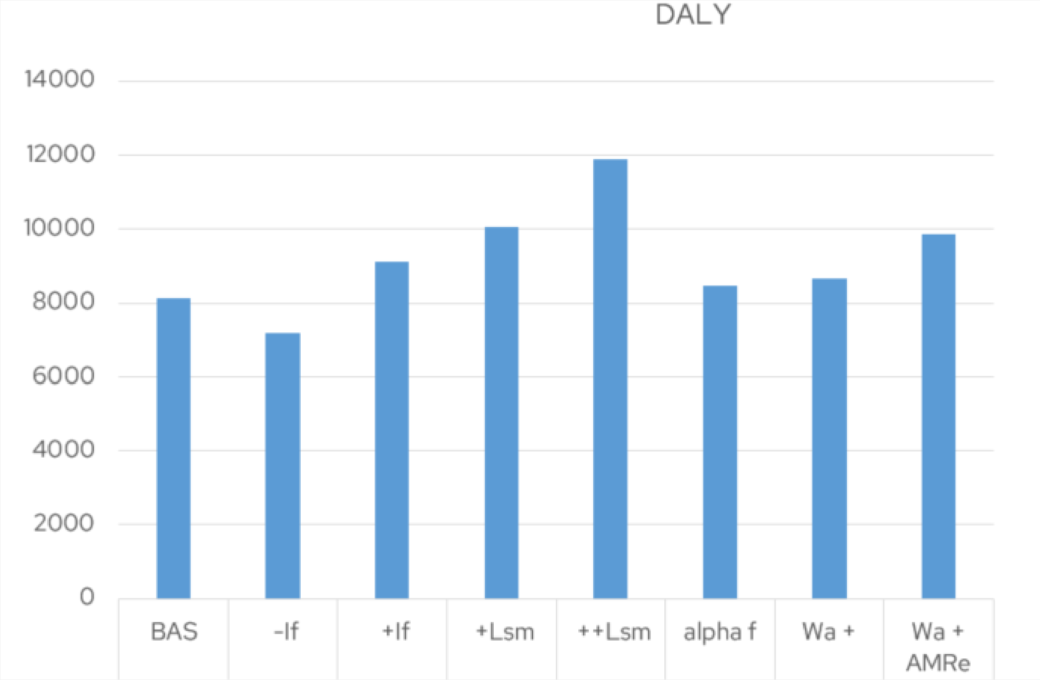


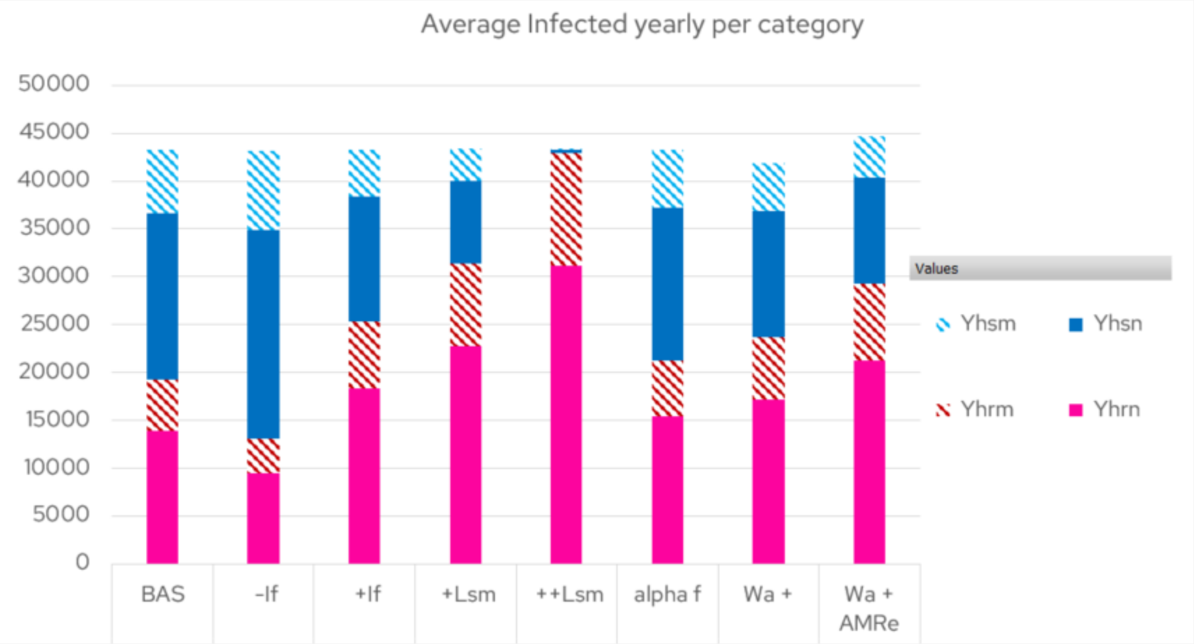




8.3 Scenarios Meta

Scenario Name	If	Lhsm	Lfsm	alphaW	Wa0	Ws0	alpha_fw	alpha_hw
BAS	0.1	0.6	0.6	0.4	0.4	0.6	0.01	0.99
-If	0.05	0.6	0.6	0.4	0.4	0.6	0.01	0.99
+If	0.15	0.6	0.6	0.4	0.4	0.6	0.01	0.99
+Lsm	0.1	0.7	0.7	0.4	0.4	0.6	0.01	0.99
++Lsm	0.1	0.9	0.9	0.4	0.4	0.6	0.05	0.95
alpha f	0.1	0.6	0.6	0.4	0.4	0.6	0.05	0.95
Wa +	0.1	0.6	0.6	0.4	0.45	0.55	0.01	0.99
Wa + AMRe	0.1	0.6	0.6	0.5	0.45	0.55	0.01	0.99





9. Next steps

- Calibrate different years will produce information on
  - W_s and W_r dynamics
  - α_{Wh} and α_{Wf}: effects of human and farm animals in the environmental equilibrium
  - λ: effect of each infected proportion in the environmental equilibrium
  - α_{hW}: proportion of human infections coming from the environment

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Thank you!

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