Outlines

• Introduction:
  – What is simulation modeling?
  – Why simulation modeling is used?
  – What are the types of simulation models?

• A stochastic bio-economic model of Intramammary infections (IMI):
  – Development.
  – Results.
  – Application.

REM EMB E R

All Models are wrong, 
BUT 
some are useful !!

Prof. George Box
Simulation modeling

• A representation of real life systems to gain insight into their functions and to investigate the effects of alternative conditions or actions on the modeled system.

• This representation can be illustrated using:
  – Mathematical equations.
  – Computer code.
  – Both.

• It is frequently referred to as Monte Carlo simulation.

Why simulation modeling is used?

• It is best to use experiments and trials to investigate the effect of alternative conditions or actions on a specific system.

• Experiments and trials are very expensive.

Simulation modeling?

• Cheaper choice.

• As soon as the model is validated, further changes to examine alternative choices and actions can be incorporated quite fast and easy.

• Therefore, models can be a good alternative to experiments and trials, only when sufficient data is available to model a system.
Types of simulation models

- Stochastic vs. deterministic.
  - Deterministic: use one input value to represent the occurrence of an event; for instance the use of average values.
  - Stochastic: use randomness to model chance or events; for instance the use of probability distribution.

- Static vs. dynamic.
  - Dynamic: changes in the modeled system occur as response to changes over the course of time.
  - Static: the course of time is not modeled.

Dynamic simulation models

- Continuous vs. discrete:
  - Continuous: based on continuous solving of differential equations.
  - Discrete: chronological sequence of events occurring at instant points in time and result in a change of state in the modeled system. A discrete time period can be a day, a week, a month or a year... et cetera.

A Stochastic Bio-economic Model of Bovine Intramammary Infections (IMI)
Intramammary infections (IMI) or mastitis

- Intramammary infections (IMI) is “synonym” to mastitis, which is the inflammation of mammary glands.
- It can be caused by different pathogens.
- It leads to:
  - Adverse welfare effect, pain to the infected cow.
  - Economic damage to the farmer: milk production loss, use of antibiotics to treat the infected cow, and higher risk of culling the infected cow.
- It is the costly endemic disease in the developed countries.

A stochastic bio-economic model of bovine intramammary infections (IMI)

- Bio-economics: the integration of economic analysis on the course of a biological system to provide economic sound decisions.
- Stochastic dynamic discrete-event simulation model.
- Each discrete time step is represented by 2-weeks.
- Halasa et al. (2009), Livestock Science 124:295-305.
Objectives

- Simulate a herd of dairy cows to:
  - Obtain insight into the dynamics of pathogen-specific IMI in Dutch bovine dairy herds to better prevent and control IMI.
  - Estimate the costs of IMI in an endemic situation in Dutch bovine dairy herds.
  - Support decision making in relation to IMI prevention and control.

Choice of modeling procedure

- Obtain insight into the dynamics of pathogen-specific IMI over time and determine their effects on the variability of the costs of IMI.
- Investigate alternative actions to prevent and control pathogen-specific IMI.
- Predict economic consequences of future changes of IMI management.

Modeled IMI pathogens

- *Staphylococcus aureus*
- *Streptococcus uberis*
- *Streptococcus dysgalactiae*
- *Escherichia coli*  

Contagious pathogens (Zadoks et al., 2001, 2002)  

Environmental pathogens
Contagious transmission of IMI pathogens

- An IMI cow transmits the infection to healthy herd mates through the milking process, equipments and the farmer.

Modeling contagious IMI pathogens

- Reed-Frost model: explains the infection behavior of a contagious pathogen in a population of susceptible individuals.
- The probability of new infections at a specific discrete point in time is dependent on:
  - The transmission rate parameter (β) of the IMI pathogen, which represent the average probability of new infection per unit of time.
  - The number of infectious animals (I).
  - The total number of lactating animals (N).
- Probability of infection = 1 - EXP( -β * I * ΔT / N). ΔT is the time difference.
- The probability of infection is calculated by the model at each discrete time period. Therefore, it is dynamic.

Environmental IMI

- Infection originates from the environment.
Modeling environmental IMI pathogen (*E. coli*)

- Greenwood model: explains the infection behavior of a pathogen originates from the environment in a population of susceptible individuals.
- The probability of infection at any point in time is independent from the number of infected animals; given that the pathogen exists in the environment permanently.
- The probability of new infections at any point in time is based on:
  - The cumulative incidence of *E. coli* IMI per 14-cow-days at risk.
- The probability of infection is fixed over the discrete time period of the model.

Probability of infection in:
- Contagious transmission = \( 1 - \exp(-\beta \times I \times \Delta T / N) \).
- Environmental transmission = fixed value / 14-cow days.

Modeling the dynamics of IMI during the lactation
Modeling the dynamics of IMI during the lactation

Healthy (No IMI)

2 weeks

The lactation

Clinical IMI (CIMI)
Subclinical IMI (SCIMI)
Modeling the dynamics of IMI during the lactation: State transition probabilities

- State changing is based on probabilities:
  - Become a new IMI case.
  - Cure from IMI.
  - Be culled.
  - Change the IMI status.

- These transitional probabilities are used in different random distributions to determine the state of each cow at each discrete time period.

Input parameters for the dynamics of IMI

- Pathogen-specific transmission parameters obtained from field studies (Zadoks et al., 2001; 2002).
- Other parameters obtained from field studies and experiments and were pathogen-specific.
- All rates and probabilities were recalculated per 14 cow-days, because each discrete time period in the model was 14 days.
- Replacement (α) was based on the quota situation.
Modeling the herd

- The model simulates a herd of 100 dairy cattle within 1 quota-year.
- The herd demography was based on Dutch data from the national recording system and from field studies.
  - Distribution of age in the herd (parity numbers).
  - Lactation stage and length
  - Milk production per cow.
- Several random distributions were used to determine the herd demographical characteristics.

Modeling cow level production

- Milk production per cow was calculated based on the lactation curve of Wood (Wood et al., 1976).
Effects of IMI on milk production

- Mastitis or IMI results in decreased milk production.
  - Clinical mastitis causes a persistent loss of milk production (Grohn et al., 2004).
  - Subclinical mastitis causes milk production loss (Halasa et al., 2009).

Modeling cow level production

- Milk production loss due to clinical and subclinical IMI.

![Graph showing milk production loss over time due to IMI](image-url)
Modeling the herd level milk production and milk quota

- Herd level milk production at time period \( t \) = \( \sum \) (milk production of all cows at time period \( t \)).
- Cumulative herd level milk production at time period \( t \) = \( \sum \) (herd level milk production at time period \( t \times t-1 \)).
- Milk quota was defined as the total milk that should be produced within 1 year.
- IMI reduce milk production. So the quota might not be reached.
- What should the farmer do????

Modeling milk quota

- Cumulative herd level milk production was calculated at each time period twice:
  - Including the effects of IMI (milk production loss) and culling.
  - Excluding the effects of IMI and culling (the total milk that should be produced to reach the quota by the end of the year).
- Milk quota deficiency = cumulative herd level milk production excluding effects of IMI and culling - cumulative herd level milk production including effects of IMI and culling.
- When the milk quota deficiency \( \geq \) a production of an average cow, a new cow was included (replacement (\( \alpha \))).

Economic effects
Economic effects of IMI

- Costs of clinical IMI
- Costs of subclinical IMI

Economic effects of clinical IMI

- Costs of milk production loss = the cost of the replacement heifer to produce the milk production lost due to clinical IMI. This include:
  - Price of the heifer.
  - Cost of feed.

- Costs of culling due to clinical IMI = the retention pay-off of the culled cow (RPO), which is the future expected value of keeping the cow in production (Houben et al., 1994).

Economic effects of clinical IMI

- Costs of antibiotic treatment:
  - Costs of the antibiotics.
  - Costs of veterinary service.
  - Costs of labour time to treat the infected cows.

- Saved costs: IMI cows are given less concentrates, because they produce less milk.
  - Amount of concentrate to produce the lost milk.
  - Price of concentrate.

- Total net cost of clinical IMI per pathogen = Σ (all costs of clinical IMI per pathogen).
Economic effects of subclinical IMI

- Costs of milk production loss due to subclinical IMI.
- Costs of culling due to subclinical IMI.
- Costs of high bulk tank somatic cell count (penalty).
- Saved costs due to lower milk production.
- Total net cost of subclinical IMI per pathogen = Σ (all costs of subclinical IMI per pathogen).

Economic effects of IMI

- Prices of materials and labor time were based on previous studies and commercial products from the market.

Sensitivity analysis

- Sensitivity analysis to investigate the effects of parameters’ value changing on the outcome of the model.
- Sensitivity analysis was conducted on most model parameters.
Model validation

• To make sure that the model is credible and the predictions are useful and applicable to the field.
  • Internal validation: Does the model do what we actually think it should be doing?
    – Rationalism method: change the input values and compare outcomes.
    – Tracing back: follow individual cows in the model to verify the consistency of the outcome
    – Face validity: expert consultancy.
  • External validation: compare the model prediction to real life (e.g. field data).

Results - Descriptive data on herd demography

• Primiparous cows were 30% and producing on average 23 kg per day and varied from 18 to 27 kg per day.
• Multiparous cows produced on average 27 kg per day and varied from 22 to 34 kg per day.
• On average the length of lactation was 339 days and the calving interval was 399 days.
• The culling rate was on average 29% and replacement rate was on average 32%.
• The annual herd level milk production was 832,000 kg milk and varied from 821,000 to 849,000.
Dynamics of pathogen-specific IMI

Median incidence of new pathogen-specific IMI per year as produced by the model together with the 5th and 95th percentiles

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clinical IMI</th>
<th>Subclinical IMI</th>
<th>Flare ups</th>
<th>Remission</th>
<th>Culling due to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (0-36)</td>
<td>7 (0-52)</td>
<td>3 (0-16)</td>
<td>4 (0-25)</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td></td>
<td>2 (0-14)</td>
<td>2 (0-17)</td>
<td>1 (0-7)</td>
<td>0 (0-3)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td></td>
<td>5 (2-10)</td>
<td>1 (0-9)</td>
<td>1 (0-5)</td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
</tr>
</tbody>
</table>

Clinical IMI: E. coli, Strep. dysgalactiae, Strep. uberis, Staph. aureus

Results-costs

Pathogen-specific average total annual net cost and cost factors (€) of clinical IMI (CIMI) and subclinical IMI (ScIMI)

<table>
<thead>
<tr>
<th>Cost factors</th>
<th>CIMI</th>
<th>ScIMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vet. service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saved cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|          | 2594 (0-8,595) | 790 (0-3,281) | 574 (0-2,268) | 446 (0-1,599) | 446 (0-1,599) | 858 (206-1,713) |
| Milk loss | 275 (0-1,013)  | 75 (0-318)    | 74 (0-319)    | 74 (0-319)    | 74 (0-319)    | 147 (50-262)    |
| Medication| 399 (0-1,440)  | 142 (0-506)   | 138 (0-520)   | 138 (0-520)   | 138 (0-520)   | 227 (80-400)   |
| Vet. service| 75 (0-251)    | 20 (0-101)    | 20 (0-99)     | 20 (0-99)     | 20 (0-99)     | 45 (15-75)     |
| Labor      | 359 (0-1,298)  | 128 (0-494)   | 124 (0-494)   | 124 (0-494)   | 124 (0-494)   | 204 (72-760)   |
| Culling    | 529 (0-2,000)  | 175 (0-1,013) | 175 (0-1,013) | 175 (0-1,013) | 175 (0-1,013) | 330 (130-2,300) |
| Saved cost | 260 (0-998)    | 72 (0-309)    | 71 (0-309)    | 71 (0-309)    | 71 (0-309)    | 120 (42-247)   |
| Cost of CIMI| 1219 (0-4,430) | 365 (0-1,510) | 288 (0-710)   | 288 (0-710)   | 288 (0-710)   | 27 (0-48)      |
| Milk loss  | 69 (0-242)     | 23 (0-103)    | 17 (0-82)     | 17 (0-82)     | 17 (0-82)     | 5 (0-4)        |
| Culling    | 1215 (0-4,112) | 383 (0-1,595) | 206 (0-641)   | 206 (0-641)   | 206 (0-641)   | 29 (0-49)      |
| Saved cost | 67 (0-230)     | 20 (0-99)     | 15 (0-89)     | 15 (0-89)     | 15 (0-89)     | 1 (0-2)        |

Total cost of IMI

Combined annual net cost of IMI (×1000 €/herd)
Total cost of IMI

- Total costs are approximately 5000 €, is that important?
- What about the uncertainty?
- The effect could be extreme > 25,000 €, is that important?

Sensitivity analysis on the transmission rate ($\beta$)

$\beta$ represent the average probability of a new infection per unit of time.

Sensitivity analysis on the cure from clinical and subclinical IMI

- Using a high probability of cure from clinical IMI, the costs decreased to approximately 3000 €, while using low cure probability the costs increased to approximately 6200 € per year.
- Using a high probability of cure from subclinical IMI, the costs decreased to approximately 2000 €, while using low cure probability the costs increased to approximately 8100 € per year.
Validation of the output

- Internal validation methods were followed.
- A field study was used to validate the output by comparing the model predictions to field study (Barkema et al., 1998).
- Economic output was compared to previous studies.
- The model prediction was deemed valid.

Conclusions

- The economic impact of the modeled IMI pathogens was determined, and found to be considerable.
- The dynamics of IMI caused by the 4 modeled pathogens influenced the costs largely.
- The costs can be limited by implementing specific control procedures, that could be cost-effective, such as:
  - Long duration treatment of clinical IMI (high cure).
  - Antibiotic treatment of subclinical IMI (high cure).
Costs and benefits of the dry period (DP) interventions

- The model focused only on the dynamics of IMI during the lactation.
- The dry period (DP) is the period before calving in which the cow seizure milk production. It is an important stage of the cows’ life contributing to a higher risk of new IMI.
- Several interventions are applied to limit the risk of IMI during the DP. However, the economic efficiency of these interventions is unknown.

Objectives

- Incorporate the dynamics of IMI during the DP.
- Assess the impact of modeling the dynamics of IMI during the DP on the total net costs of IMI.
- Estimate the cost effectiveness of different DP interventions to control and prevent IMI.

Modeling the DP

- The DP is usually 7-8 weeks, therefore it was modeled in 4 time periods in the model.
- Cows during the DP are usually separated from the lactating herd.
Intervention scenarios

• Blanket dry cow therapy (BDCT): every cow is treated with antibiotics at start of the DP.

• Selective dry cow therapy (SDCT) or teat sealant (TS): cows with history of clinical or subclinical IMI are treated with antibiotics at start of the DP, while TS is applied to the other cows.

• SDCT and TS: cows with history of clinical or subclinical IMI are treated with antibiotics at start of the DP, and TS is applied to all cows.

Modeling the dynamics of pathogen-specific IMI during the DP using BDCT

The DP, 8 weeks
Modeling the dynamics of pathogen-specific IMI during the DP using BDCT
Modeling the dynamics of pathogen-specific IMI during the DP using BDCT

The DP, 8 weeks

Start of new lactation

Infect other cows

Cure rate

Healthy

IMI

2 weeks
Modeling the dynamics of pathogen-specific IMI during the DP using DCT or TS

The DP, 8 weeks

2 weeks

Modeling the dynamics of pathogen-specific IMI during the DP using DCT and TS

The DP, 8 weeks

2 weeks

Modeling IMI during the DP

Only during the first and the last 2 weeks of the DP
Effects of Interventions

- The rate of new IMI changed based on the applied intervention.
- Cure of IMI cows was highest when they obtained DCT.

Parameterization

- Based on meta-analysis studies on field data (Halasa et al., 2009a,b).
- Based on field studies (Green et al., 2002; Bradley and Green, 2004).

Economic effects

- Costs of clinical IMI:
  - Milk production loss.
  - Antibiotics.
  - Labour time.
  - Veterinary service
  - Culling of clinical IMI cows
  - Saved costs.
- Costs of subclinical IMI:
  - Milk production loss.
  - Culling of subclinical IMI cows.
  - Saved costs.
Economic effects

- Costs of intervention, that were based on the intervention scenario:
  - Scenario 1 (BDCT):
    - Costs of antibiotics.
    - Costs of labour to apply the antibiotics.
    - Cost of clinical IMI during the DP.
  - Scenario 2 (SDCT or TS):
    - Costs of antibiotics or TS.
    - Costs of labour to apply the antibiotics or TS.
    - Cost of clinical IMI during the DP.
  - Scenario 2 (SDCT + TS):
    - Costs of antibiotics and/or TS.
    - Costs of labour to apply the antibiotics and/or TS.
    - Cost of clinical IMI during the DP.

RESULTS

New IMI cows during the DP

1: BDCT
2: SDCT or TS
3: SDCT and TS
IMI cows at calving

1. BDCT
2. SDCT or TS
3. SDCT and TS

Scenario of dry off intervention

Costs of the intervention scenarios per year (Primary results)

<table>
<thead>
<tr>
<th>Cost factors</th>
<th>BDCT</th>
<th>SDCT or TS</th>
<th>SDCT + TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed annual fixed costs</td>
<td>8,932(2,216-18,649)</td>
<td>4,384 (677-9,764)</td>
<td>3,054 (0-8,052)</td>
</tr>
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<td>3,054 (0-8,052)</td>
</tr>
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</table>

A scenario where no DP intervention application was also run. It resulted in a total annual net cost of IMI on average 11,000 € and varied from 2000 € to 21,000 € per year.

Conclusions of DP interventions challenge

- Application of DP interventions is necessary to reduce the total net cost of IMI.
- The costs of the different interventions are very close, though, application of BDCT seems to provide the lowest total net costs of IMI per year.
Simulation modeling

- By investigating the model output, we obtained insights into the dynamics of IMI during the lactation and the DP.
- The economic outcome is helpful to:
  - Determine the economic impact of IMI on dairy herds, to further investigate possibilities to optimize production.
  - Support decision making in relation to the application of interventions during the DP to prevent and control IMI.