Johne's disease.

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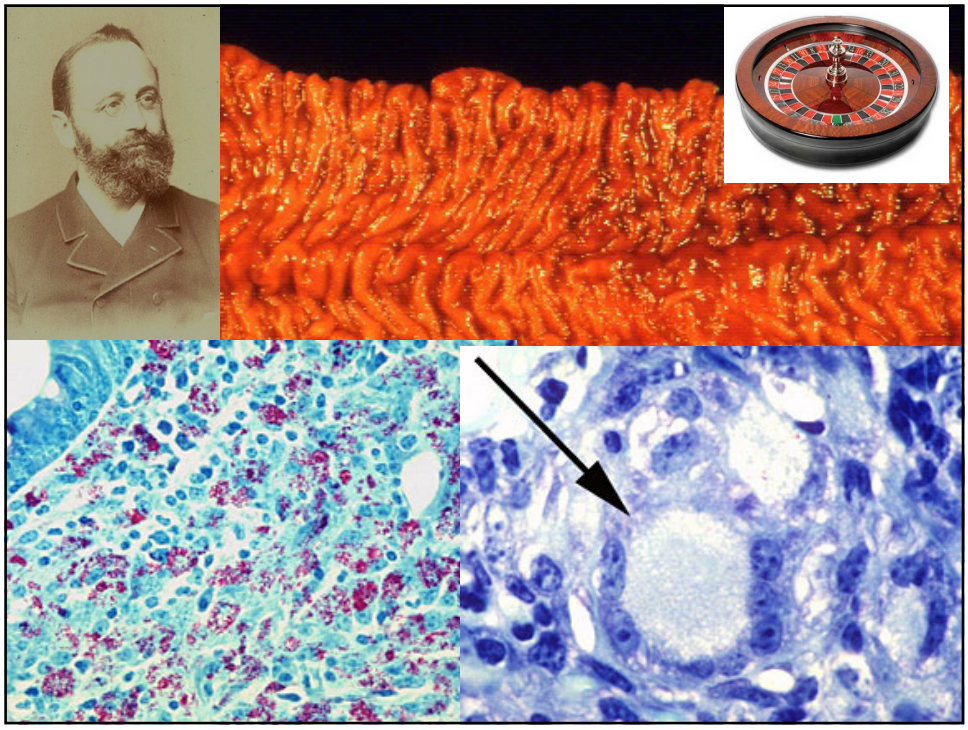
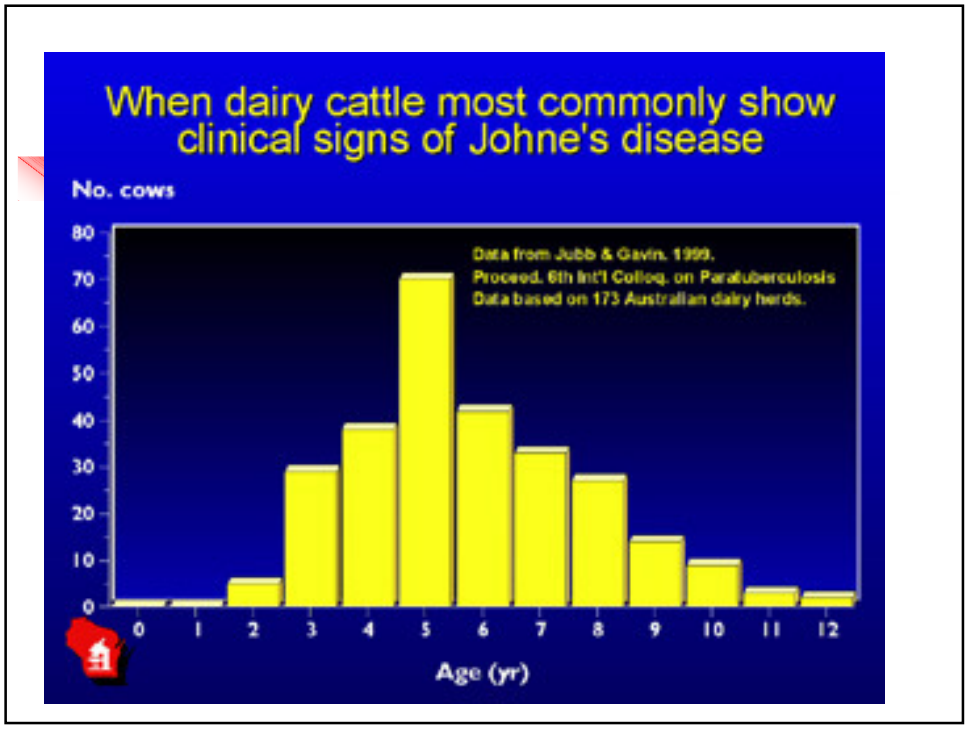


The disease – key points

- Chronic, insiduous
- Long time scale
  - Spread within herd
  - Control
- Immunology
  - Cell mediated response
- "tip of the iceberg"
- SiM disease
- Diagnostic tests

Johne's disease – clinical disease.

- Older animals > 3years old.
- Often after calving (stress).
- Profuse diarrhoea (often with bubbles).
- Weight loss.
- Animal remains bright and eating.
- Individual cases.


When dairy cattle most commonly show clinical signs of Johne's disease
No. cows
80
70
60
50
40
30
20
10
0
Data from Jubb & Gavin. 1999.
Proceed. 6th Int'l Colloq. on Paratuberculosis
Data based on 173 Australian dairy herds.
0
1
2
3
4
5
6
7
8
9
10
11
12
Age (yr)

Importance of Johne's disease to the farmer.

- Clinical cases.
- Sub clinical losses: >50% of total losses
  - Reduced milk yield.
  - Increase in other diseases eg mastitis, infertility, lameness, LDA etc etc ……..
  - increased culling rate.

Most losses are sub-clinical !

What's their MAP status ?

Prevalence of Johne's disease.

- USA. 30 –70% of dairy herds infected.
- Holland. 50% of dairy herds infected.
- U.K. – VLA/SAC study: dairy herds
  - 65.4% 95%CI 56.8 - 73.4%: serology
  - 34.7% 95%CI 27.6 - 42.5: all tests
- Beef herds ?
  - Breed associated

Playing the odds

"assume herd is infected unless evidence to the contrary"

What level of confidence ?

What evidence ?

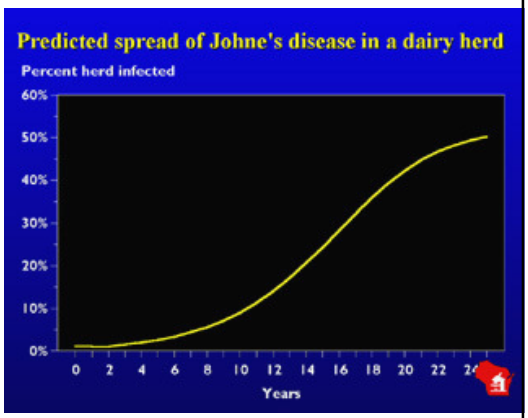
- No disease in the last 20 years ?
  - dairy VS beef
- 5 – 10 years annual testing
- "one clean test" ????

Issues

- insiduous disease
- poor tests ?
- low infectious dose
- long incubation
- Not all infected animals develop disease
- Slow !
  - 3 year research grants
  - 10 – 20 year endpoints

Infectious disease dynamics

- Is an infectious disease
- R_0
  - > 1 – disease will spread
  - = 1 – endemic
  - < 1 - control
- Will spread unless action taken !
  - If no problem now ..... just wait !
- Control is possible



Transmission of Johne's disease

Infection acquired during early life.

Baby calves are at biggest risk.

Calves less than 12 month old are at risk.

Infection of adults is possible but unlikely ?

Routes of transmission

- **Oro-faecal is major route. SiM disease**
- Transmission via colostrum & milk.
  - By 36% of heavy shedders.
  - By 9% of light shedders.
- Uterine infection.
  - In 20-40% of clinical cases.
  - In 9% cows with no clinical signs.
  - "minor route"

Relative importance of transmission routes.

- 5% - before birth (if dam is clinical).
- **80% - new born calf (0 – 4 weeks).**
- 10% - young heifer.
- 5% - older heifers and cows.

Infection routes in baby calves.

- In utero.
- **Dirty environment.**
  - **Calving area**
- **Dam faeces:**
  - **Teat**
  - **Contamination of environment**
- Dam colostrum.
- Pooled colostrum.
- Waste milk.
- Calf to calf – increasing evidence

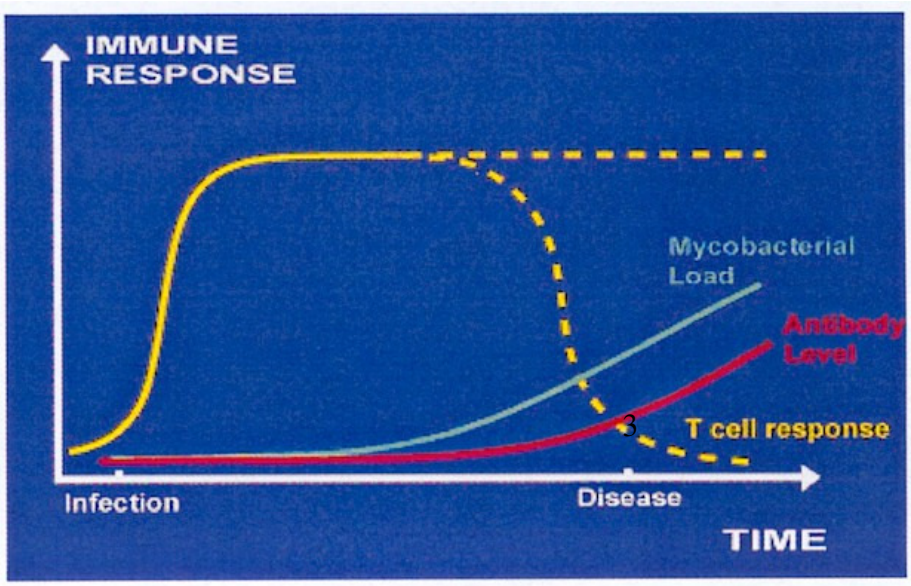
Iceberg effect. (Whitlock *et al*)

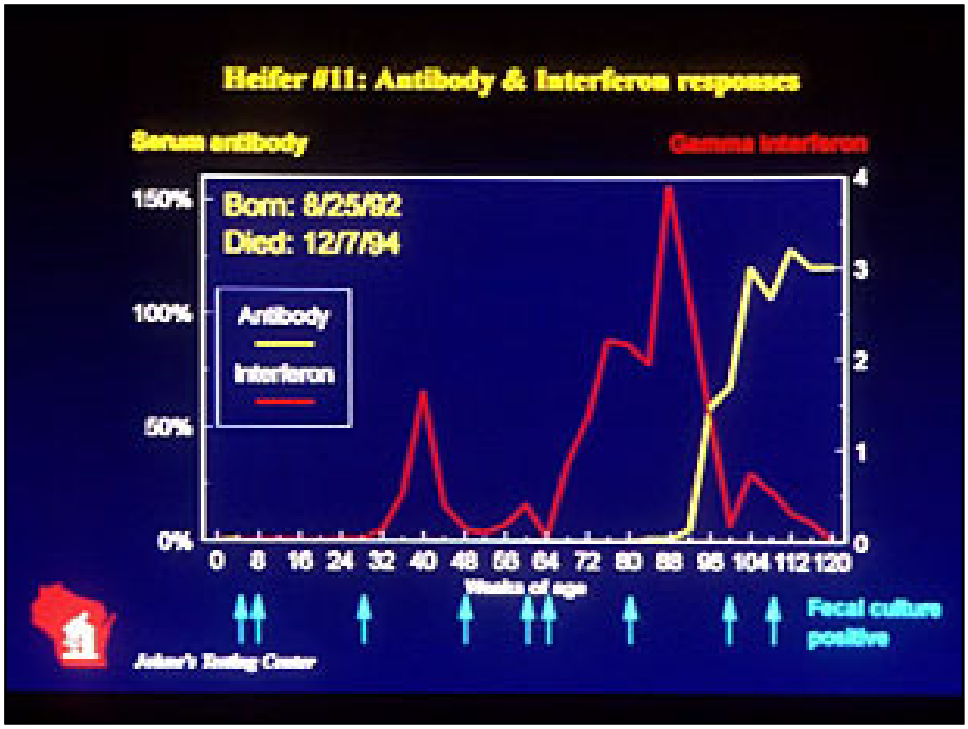
- Clinical case is "tip of the iceberg."
- For each clinical case:
  - 10 – 25 infected animals.
  - Most will never develop the disease.
  - Many will be infectious (at least 30%).

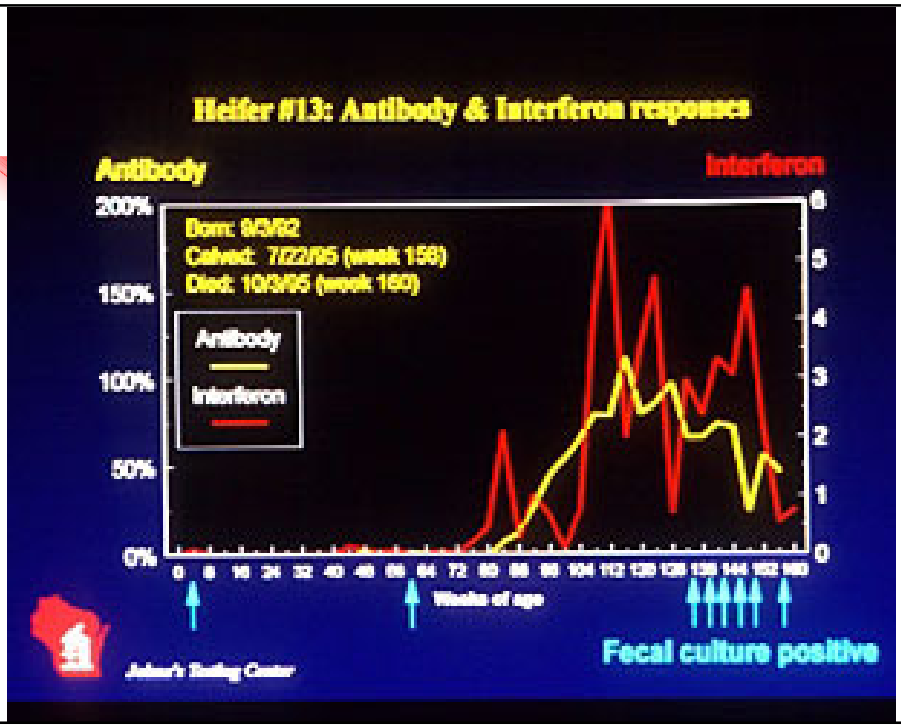
Tip of the iceberg.

- Stage 4. Advanced clinical disease **1**
- Stage 3. Early clinical disease. **1 – 2**
- Stage 2. Sub-clinical disease. Shedders. **4 – 8**
- Stage 1.Silent infection. Calves, youngstock. **10 – 14**
- **TOTAL** **15 - 25**

Immunology


IMMUNE
RESPONSE
Mycobacterial
Load
Antibody
Level
T cell response
Infection
Disease
TIME


Heifer #11: Antibody & Interferon responses
Serum antibody
Gamma interferon
150%
100%
50%
0%
Born: 8/25/92
Died: 12/7/94
Antibody
Interferon
4
3
2
1
0
0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120
Weeks of age
Fecal culture
positive



Immunology

- Infection as calf - infected
- CMI protective
  - Halts disease progression
- If disease progresses
  - Antibody response
  - Which further suppresses CMI
  - Animal likely to be **infectious**

in a herd we have .....

- **Non-infected – no risk**
- **Infected but non-shedding – no risk yet**
- **Infectious – shedding – risk**
  - Low shedders
  - High shedders
  - "super shedders"
    - Colostrum & milk risk most likely in High & super-shedders

"super-shedders"

- Whitlock *et al*
- > 1 million cfu/g faeces
  - 50 Kg faeces per day
  - 50 billion cfu per day (50 X 10^9)
  - Infective dose 100,000 cfu (1 X 10^5)
  - theoretically infect 50,000 calves !
  - Also transient infection of adults

Diagnostic tools

- Faecal culture and/or PCR
  - Detects shedders (above a threshold ?)
  - Time & cost
- ELISA
  - Detects antibody
  - High probability of being a shedder

Test characteristics.

- Sensitivity.
  - Ability to detect true positives.
- Specificity.
  - Ability to detect true negatives.
- Predictive value. (+ & -).
  - Depends on prevalence.
  - "how much can I believe this test result"

SENS & SPEC

- "trade-off"
- for ELISA – depends on cut-off used
- So ……..
  - can "manipulate Sens and Spec"
  - optimum SENS or optimum SPEC

How do we validate tests ?

- **Sensitivity.**
- Compare to "gold standard".
- **Specificity.**
- Use in a "clean population."

"Gold standard" = best test we have

Faecal culture

- "gold standard" in live animal
- SENS 50%-60% against PME
  - detects shedders
  - overgrowth in culture – reduces sens
- Expensive
  - +ve result in 10 days
  - -ve result in 3 months

ELISA

- Detects antibody
  - Animal "losing the fight"
  - Likely to be shedding
- Sensitivity – depends on
  - age distribution of population
    - Older animals more likely to be ELISA positive
  - Stage of disease process
    - 85% sensitive in clinical case

ELISA SENS & SPEC

- ~ 30 – 40% in adult animals over 2 yo
- ~ 10% in young
  - against faecal culture - **shedders**
  - true sensitivity – infected
    - 10 – 20% e.g. 0.40*0.50 = 0.20
- SPEC 97% - 99%

want to detect INFECTIOUS not INFECTED for control

Manipulation of Sens and Spec

- CHECS – ELISA as per maker
  - Sens ~ 40%
  - Spec ~ 98%
  - one +ve test – true positive
- Milk test – "traffic light" NMR Nielsen
  - Have increased SENS at expense of SPEC
  - so …. two or more +ve test results to say she is truly positive and to be culled

Future tests.

- Faeces PCR.
- Gamma interferon – detects CMI.
  - Specificity poor.
  - Sensitivity should be good for early infection.

Why are we testing?

- To demonstrate existence of disease
  - identify infected herds
- To identify INFECTIOUS animals
  - or animals likely to become infectious

Identification of infected herds. (1)

*30% – 50% of dairy herds are infected

- History of disease – clinical cases
  - Is this a reliable indicator
  - Beef V Dairy
    - Age profile of herd
    - How far back does history go

Identification of infected herds. (2)

*30% – 50% of dairy herds are infected

- Risk assessment for introduction
  - Purchase policy
  - Biosecurity
  - Don't forget bulls (purchased & hired)!
  - MHH

Identification of infected herds. (3) *30% – 50% of dairy herds are infected

- Identification of MAP
  - ELISA
  - Environmental sampling (faecal culture)
  - Bulk milk ELISA

Identification of infected herds. ELISA *30% – 50% of dairy herds are infected

- Sens is low
  - 45% overall in adults over 2 years old
- Whole herd test
  - Blood or milk
- Targeted sampling
  - 30 animal screen

30 cow screen (1)

- Pick animals carefully
  - Older
  - "suggestive signs"
  - Fresh calved after poor lactation
  - Will increase
    - Prevalence of infected animals within the 30 cow herd
    - Sensitivity of ELISA
      - more likely to be at a "later stage of infection"

NON RANDOM selection

30 cow screen (2)

- If one animal positive = MAP positive
- If negative
  - What does it mean ?
  - Is herd truly negative ?
    - Repeat test in 6 months ?

Bulk milk ELISA

- when 5% of herd are antibody +ve
  - will have already seen clinical cases ?
  - Think of "iceberg"
    - 5% ELISA +ve in 100 cow herd
    - Prevalence of infection is 40% - 80% !

Environmental sampling

- 2 samples taken from
  - Cow alleyways
  - manure / slurry
- ~ 70% sensitive for +ve herds

Options in infected herds

- Do nothing – will get worse
  - $R_0 > 1$
- Eradicate
  - CHECS
  - Can it actually be achieved ?
- Control

Control of Johne's disease.

- Not a quick fix
- Farmer motivation
  - How long before we know it is working?
  - Disease can appear to get worse during control scheme!
    - Identifying "backlog of infected animals"
- Improved Farm Management (IFM)
  - KEY

Testing schemes

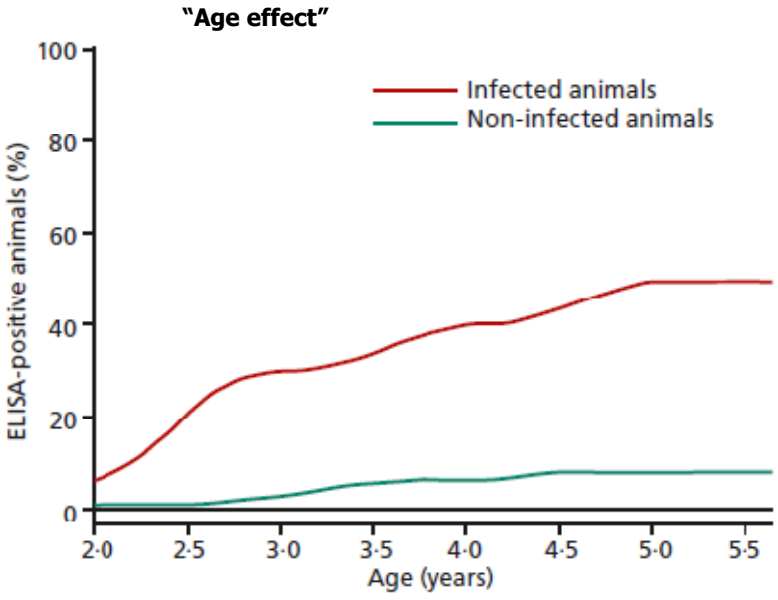
- Who do we want to detect
  - Infected *versus* Infectious
    - Ideally
  - detect BEFORE becomes INFECTIOUS
- Why
  - Eradication
  - Control
    - 2 very different objectives

Aim should be …….

- detect infectious animals
- detect animals likely to become infectious
- No interest in "infected non-infectious?"

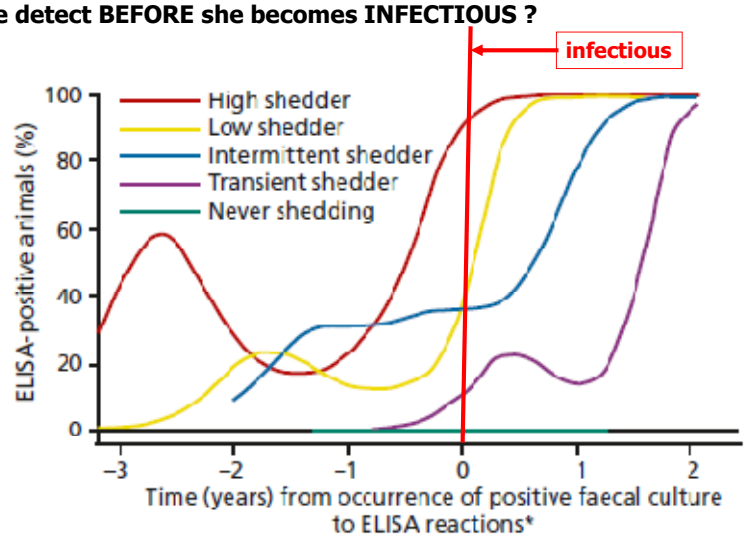
ELISA test

- Detects antibody
  - High probability of being infectious
- Repeat testing
  - Increases sensitivity
    - Get more positives
  - Decreases specificity
    - greater probability of being False-positive
- Age effect – increased sensitivity



Probability of animals testing positive using a Danish milk ELISA for infected and non-infected cows

Can we detect BEFORE she becomes INFECTIOUS ?



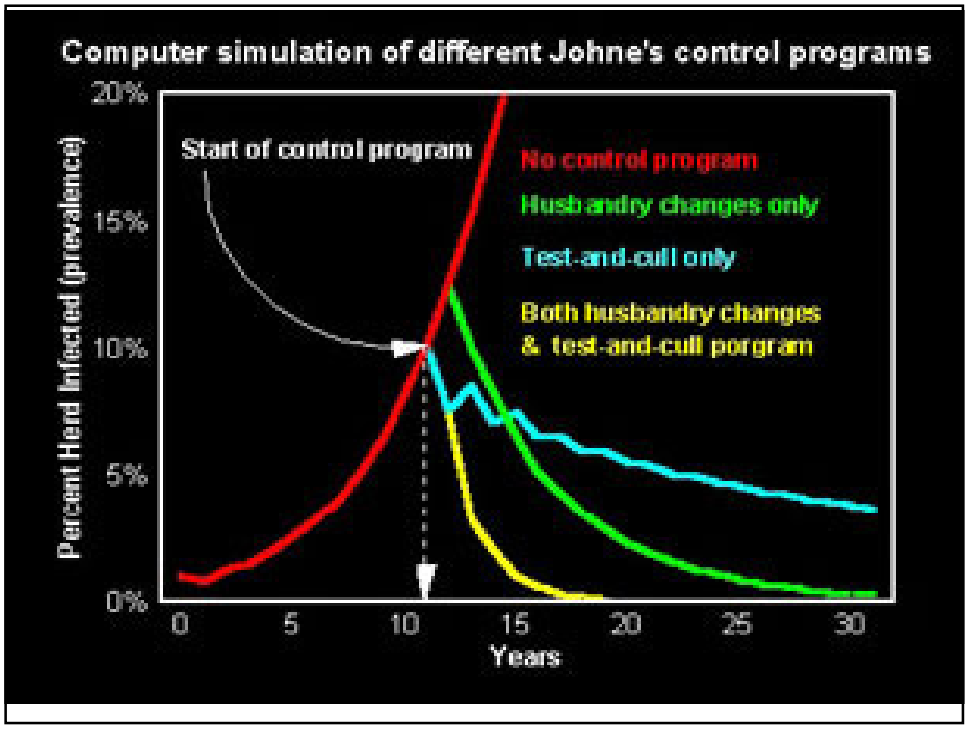
Percentage of cows testing positive using the Pourquier ELISA relative to when they started shedding high, low, intermittent or transient levels of MAP. The cut-off sample to positive ratio is 30 per cent. *For cows not shedding MAP, the median time in a test period was zero

Control of Johne's disease.

- **Reduce transmission to young stock**

Control of Johne's disease

- "uniform risk approach"
  - Assumes every adult cow is a risk
- "animal-based risk approach"
  - Assumes some cows are a greater risk than others
    - Test & Cull
    - Test & Manage



What does the model tell us ?

- Prevalence will increase if no action taken
- Control takes a long time
- Husbandry is key control method (IFM)
- Test & Cull is add on

Uniform risk approach

- Reduce all transmission pathways to calves
- Avoid / reduce oro-faecal transmission from adults to calves
- …….hygiene

IFM

- johnes.org
  - up to date research
  - Specific Risk assessment Guides
    - dairy
    - beef

IFM

- Whole herd – best
- Targeted – at Red and Yellow cows

Reducing risk factors - IFM

- Avoid faeces.
- Calving area – **snatch calving at birth.**
- Clean calving pens.
  - Separate area for high risk cows ?
- Calf pens / hutches – individual (?) clean.
- Keep young stock separate from adults.
- Colostrum – only feed dam's colostrum.
- **No pooled colostrum feeding.**
- **No waste milk feeding – throw it !**

What to do with the pregnant high risk cow – red tag

- Cull her !
- Calve down
  - separate to main herd – "leper colony"
  - snatch calve if Holstein
  - Back to milking herd
  - At end of lactation
    - cull
    - back to leper colony

Colostrum and milk.

- Frozen colostrum.
  - From heifers
  - From test negative cows.
- Do not feed pooled colostrum.
- Pasteurise waste milk and colostrum ?

Other risk factors.

- Slurry & manure on grazing.
- Watercourses – esp stagnant ponds.
- Contamination of feeds.
- Other hosts:
  - Sheep ?
  - Wildlife – rabbits ?

Animal based risk approaches

- Test & Cull
  - Annual ELISA test – all adults > 2 year old
  - Cull all positives
  - Cull daughters

T & C

- Sensitivity for infectious 30-40%
- Likely to fail if done alone
- Should be "add on"
- CHECS

Issues with T & C

- ELISA sensitivity
- Duration between tests
- "false sense of security"
- Holland – abandoned as ineffective
  - Must have IFM
- Add-on
- Minimum of 5-7 years before can evaluate ?

Test & Manage

- Use ELISA to assess probable risk an individual may represent
- Manage accordingly
- 2 methods
  - blood test ELISA – interpret %OD rather than a cut-off – Mike Collins Wisconsin
  - repeat Milk ELISA's –
    - NMR Herdwise 3X/year

Test & Manage

- Traffic Light system
  - Green – currently non-infectious
  - Yellow – medium/high risk
  - Red – very high risk
- Test results updated with recent results

Traffic light system

- Frequent testing
  - Increased sensitivity
  - Less time between tests for infectious animals to shed
  - Reduced specificity – more false+ves
- **Must be as well as IFM etc**

Beef Suckler herd

- Only applicable if rear replacements
- Pedigree sales £££ (must be in CHECS)
- Breed problem
  - Welsh Blacks – but we have a scheme !
  - Limousin
- CHECS
- IFM

IFM in beef suckler herd

- Outdoor calving
  - Or move outside immediately calved
- Cull daughters
- Clip and clean teats before calving
- Bull purchase ?
  - Ensure is clean
    - How ?

Biosecurity.

- Purchased stock is chief risk factor for introduction.
- Holland – 42 % of "clean herds" were infected !!
- Wisconsin – 10% risk of introduction with each purchase from a mart or dealer.

Biosecurity.

- **Know your own disease status first ?**

Options when purchasing.

- **From clean herds** –
  - No history of disease.
  - Test negative on at least three occasions.
- **ELISA test whole herd** e.g for bull purchase
- **ELISA test individual animal** ???
  - "false confidence" ?
- **Faecal culture individual animal**
  - "False confidence" (better than ELISA) ?

Vaccination

- Does it work ?
  - Lack of good evidence but
    - Anecdotal evidence
    - Holland – prevention of clinical cases
    - Wilesmith 1988 – prevention of clinical cases
    - Use in sheep in Australia
  - As much (or as little) evidence as for T&C !

Vaccination.

- Does not prevent infection.
- Reduces incidence of clinical disease.
- Reduces shedding.
- Interference with TB testing.
- Administer in 2nd week of life.

Odds & sods

- The future – PCR on faeces ?
  - Vaccine & faecal PCR ???
- Improve welfare – stressors
  - Reduce probability of infected animal "breaking down"
    - Reduce clinical cases
    - Reduce shedding
- How long does MAP live for in soil ?
  - amoebae

Human health.

- Crohne's disease – 500,000 + cases in USA.
- Evidence for link is increasing.
- FSA – "precautionary principle."
- Pasteurising does not kill it always.
- Meat, water ?
- "immune dysregulation"