The Online R-FETPV 1st Module : Basic Epidemiology and Surveillance Data Analysis

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USAID FROM THE AMERICAN PEOPLE

Department of Livestock Development

Food and Agriculture Organization of the United Nations

R-FETPV Regional Field Epidemiology Training Program for Veterinarian

Lesson 3: Causal Association and how it is used to address animal and human health problems

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Content/Outline (Learning Objectives)

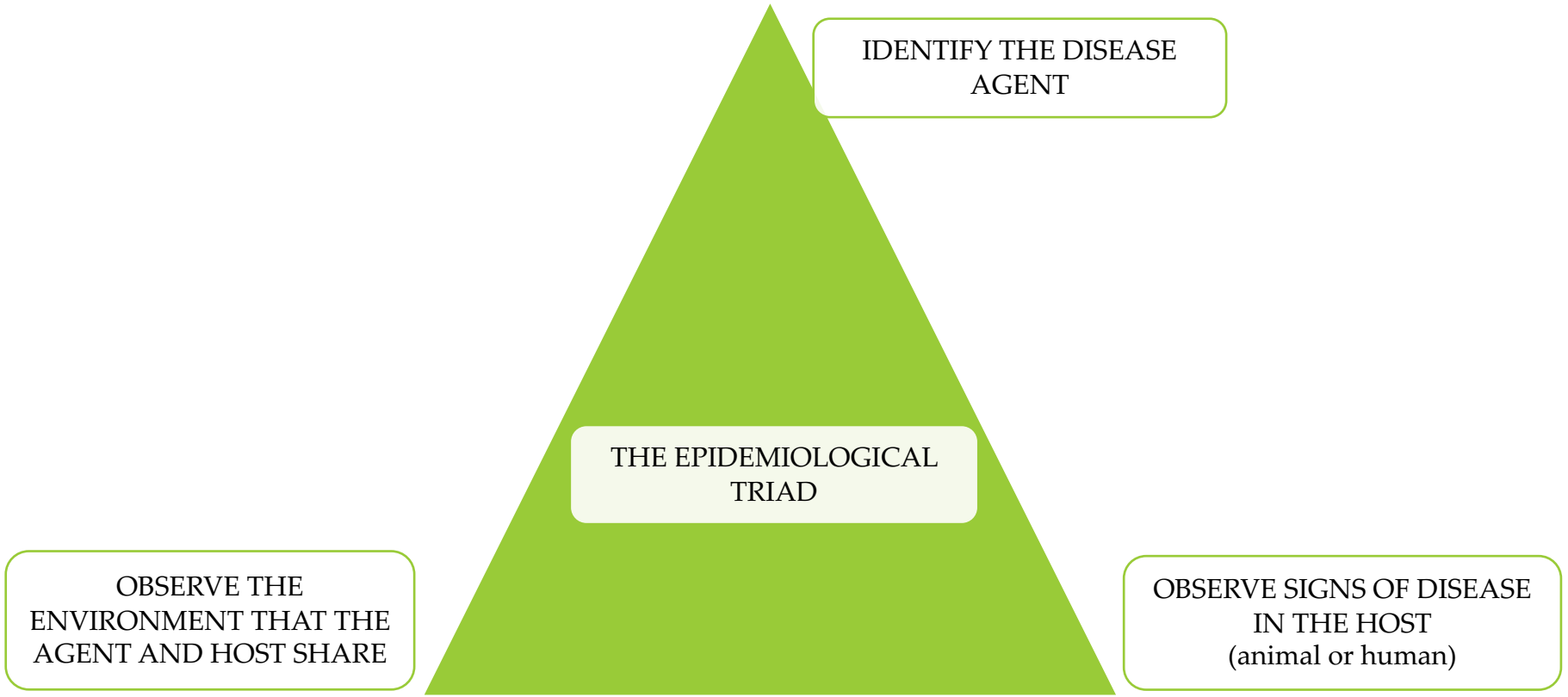
At the end of this lesson, you will be able to:

3.1. Explain and apply the concepts of association and causation (lecture and a short case study)
3.2. Explain Koch's Postulates and Hill's criteria of causation
3.3. Explain and apply the concepts of sufficient cause and necessary cause
3.4. Explain the difference between direct and indirect causation
3.5. Describe multi-factorial causation

Lesson 3: Part 1 of 4

Addressing animal and human health problems

DISEASE IS NOT RANDOM: IT IS EXPLAINED BY THE RELATIONSHIP BETWEEN DISEASE AGENT, HOST AND THE ENVIRONMENT



What is Epidemiology?

Epidemiology…
is a scientific discipline…
that involves the study of…
the frequency…
and distribution…
of health and disease…
in populations…
in order to find risk factors…
for prevention and control.

Risk Factors

Qualitative definition:

- Risk factors are conditions that influence the occurrence of health and disease events

Quantitative definition:

- When we quantify and assess risk factors statistically, we refer to them as **"variables"** to measure their influence the occurrence of health and disease events

Qualitative example:

- Lack of biosecurity on pig farms increases the risk of exposure to African swine fever (ASF)

Quantitative example:

- Pig farms that do not restrict access to their animals are 5.8 times more likely to become infected with African Swine Fever
- *What is the variable?* ***Restricting access***
- *What is the risk associated with not restricting farm access?* ***Farms without restricted access are 5.8 times more at risk for ASF than farms that do restrict access***

Types of Variables

Dependent variables

- health or disease outcome variables that "depend" on the independent variables

Independent variables

- are risk variables that influence health or disease outcomes

Examples:

- *Weight gain (health)*
- *Mastitis in cattle (disease)*

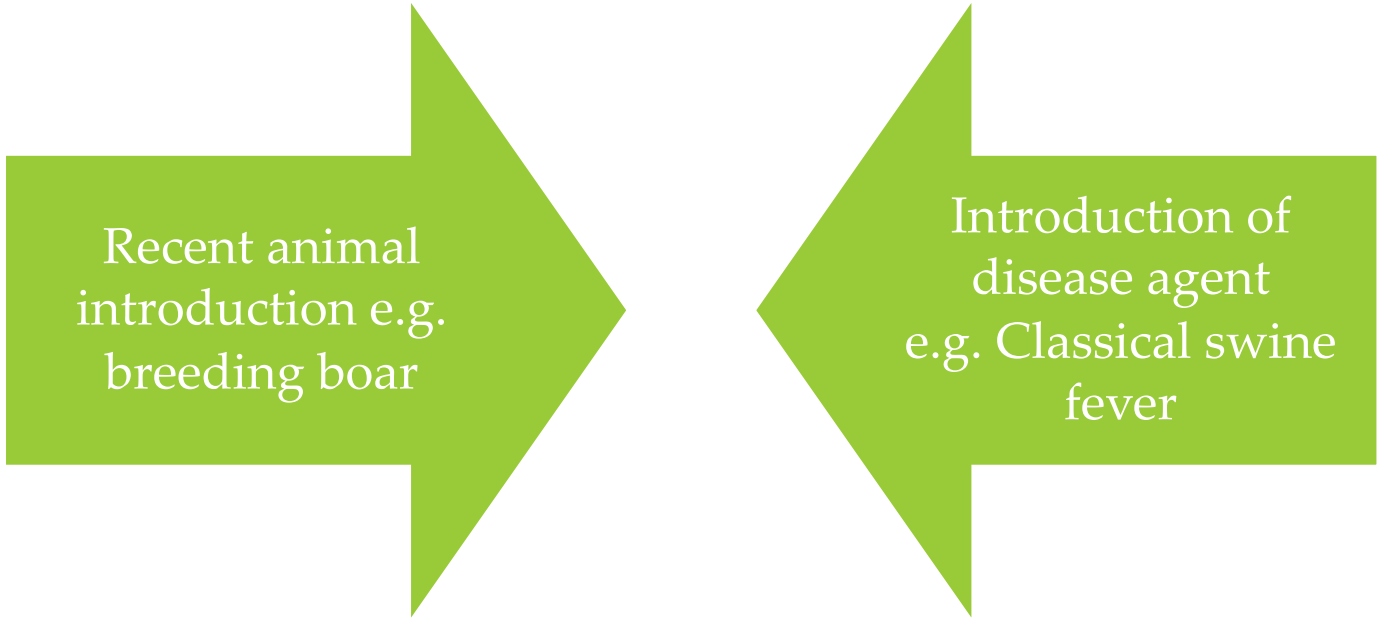
Examples:

- *Feed energy and protein levels provided (health)*
- *Udder wash, use of teat dip (disease)*

What is association?

- Association is a general relationship where one variable provides information about another (Altman and Krzywinski, 2015)

Example:

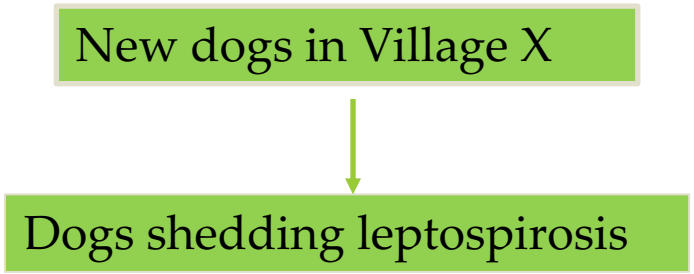


What is causation?

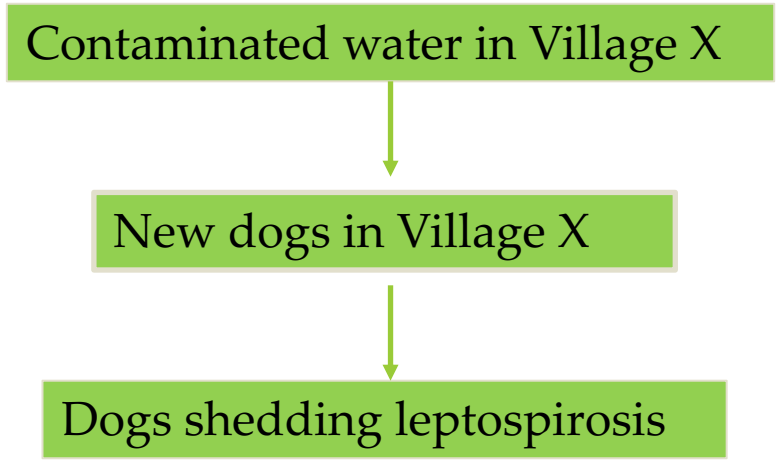
- **Given: It is not possible to demonstrate with 100% certainty that an independent variable causes a health or disease outcome**
- **Strategy:** The best we can do is to support a causal hypothesis based on valid, statistical associations among variables
- Association should not be confused with causality but association is necessary to support a causal hypothesis (Altman and Krzywinski, 2015)
- We will consider two theories of Causation:
  - Koch's Postulates, and
  - Hill's Criteria

Challenges of Causation

- *Scenario 1: if newly introduced dogs in village X are shedding leptospirosis, then the two variables, 1) new dogs in village X and 2) presence of leptospirosis may be associated (dependency exists).*



- *Scenario 2: However, associations can arise between variables in the absence of a causal relationship (i.e., they have a common cause).*



Koch's Postulates of Causation

- **The agent**
  - Is present when the disease exists and is absent when the disease does not exist
  - The agent can be isolated in pure culture and results in disease when given to susceptible animals
- **Exposure**
  - Occurs before the disease occurs
- **Consistency**
  - The disease is reproducible in different populations at different times
- **Strength of statistical association**
  - The results are not due to chance
- **Dose-response**
  - Increase in exposure leads to increase in disease
- **Removal or change in the factor**
  - Decrease in exposure leads to less disease
- **Consistent with current knowledge**
- **Results agree with other studies or knowledge**

Hill's Criteria of Causation

- **Strength of association –** The stronger the association, between a risk factor and outcome, the more likely the relationship is thought to be causal.
- **Consistency –** The same findings observed among: different populations; different study designs; and at different times.
- **Specificity –** There is a one-to-one relationship between the exposure and outcome.
- **Temporal sequence –** The exposure must precede outcome
- **Biological gradient –** Dose-response relationship - as dose increases, so does severity response.
- **Biological plausibility –** Biological plausibility
- **Coherence –** The relationship found agrees with the current knowledge of the disease.
- **Experiment –** Removal of the exposure alters the frequency of the outcome.
- **Analogy –** The relationship is consistent with other established cause-effect relationships.

Comparison: Koch and Hill Theories

CRITERIA	KOCH	HILL
Agent is present with disease; absent without disease; isolated in pure culture	✓	
Temporal sequence of exposure and disease	✓	✓
Consistency and reproducibility	✓	✓
Strength of statistical association	✓	✓
Dose-response; biological gradient	✓	✓
Removal or addition; experiment changes response	✓	✓
Consistent with current knowledge and different situations	✓	✓
Agreement and coherence with other studies	✓	✓
Specificity of exposure leading to specific outcome		✓
Analogous and comparable cause-effect relationships with similar diseases		✓

Both theories are similar but have different explanations and logic for each criteria

Lesson 3: Part 2 of 4

Comparison: Koch and Hill Theories

CRITERIA	*Examples*
Agent is present with disease; absent without disease; isolated in pure culture	*Mycobacterium bovis is the agent of tuberculosis in animals and humans*
Temporal sequence of exposure and disease	*Clinical signs of avian influenza occur 2-14 days after exposure*
Consistency and reproducibility	*Colibacillosis due to E. coli is most common is young, juvenile livestock and poultry*
Strength of statistical association	*Obesity is dependent on eating a high fat diet*
Dose-response; biological gradient	*100 bacteria may not kill;1 million bacteria will*
Removal or addition; experiment changes response	*Antisera react differently to FMD serotypes*
Consistent with current knowledge and different situations	*Same results in different populations and areas*
Agreement and coherence with other studies	*10 different studies identify same risk factor*
Specificity of exposure leading to specific outcome*	*Slaughter of pigs leads to death*
Analogous and comparable cause-effect relationships	*High dose vaccines are effective for AI and ND>*

Exercise: Provide one example for each criteria

CRITERIA	*Examples*
Agent is present with disease; absent without disease; isolated in pure culture	
Temporal sequence of exposure and disease	
Consistency and reproducibility	
Strength of statistical association	
Dose-response; biological gradient	
Removal or addition; experiment changes response	
Consistent with current knowledge and different situations	
Agreement and coherence with other studies	
Specificity of exposure leading to specific outcome*	
Analogous and comparable cause-effect relationships	

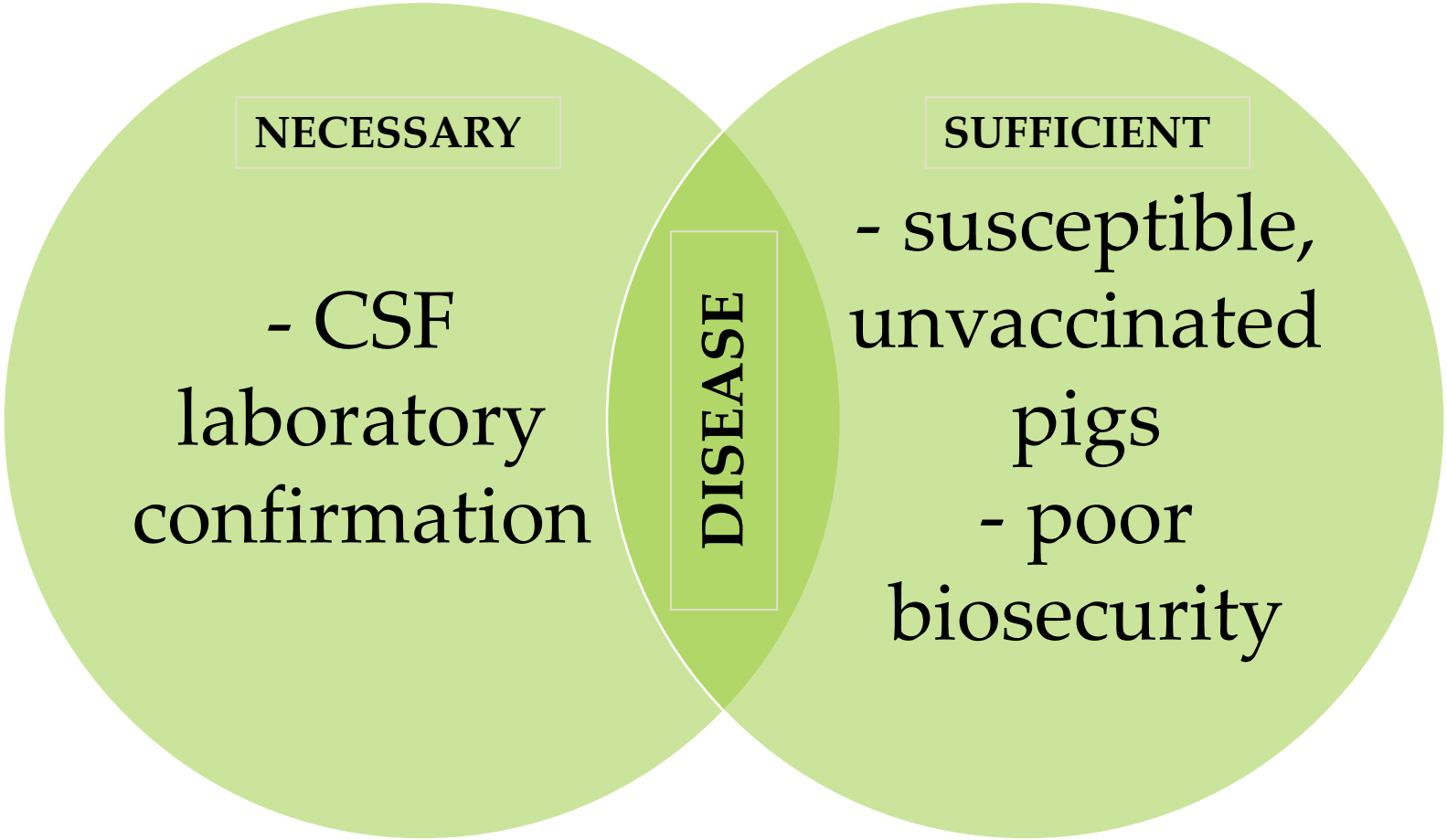
Necessary and Sufficient Causes

1. A **necessary** cause is a condition that must be present for an outcome to occur.

2. A **sufficient** cause is a condition or set of conditions that may OR may not produce the outcome when present.

3. A **necessary** cause must exist for the outcome to occur… but it alone does not provide **sufficient cause** for the occurrence of the event. Other conditions also need to be present.

Necessary and sufficient causes of Classical Swine Fever (CSF)

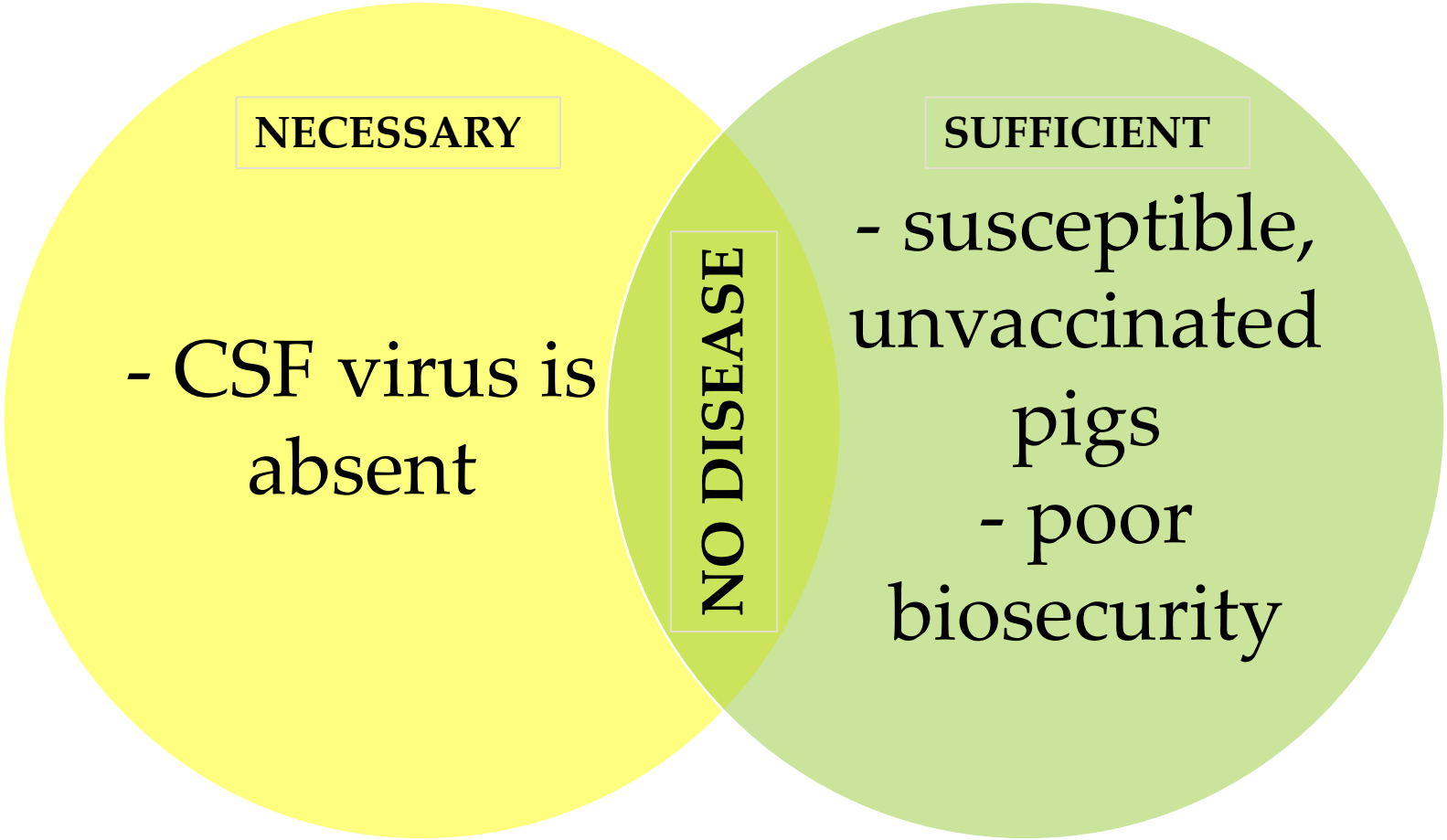


Necessary and Sufficient Causal Associations

1. A **necessary** cause is a condition that must be present for an event to occur.

2. A **sufficient** cause is a condition or set of conditions that will produce the event.

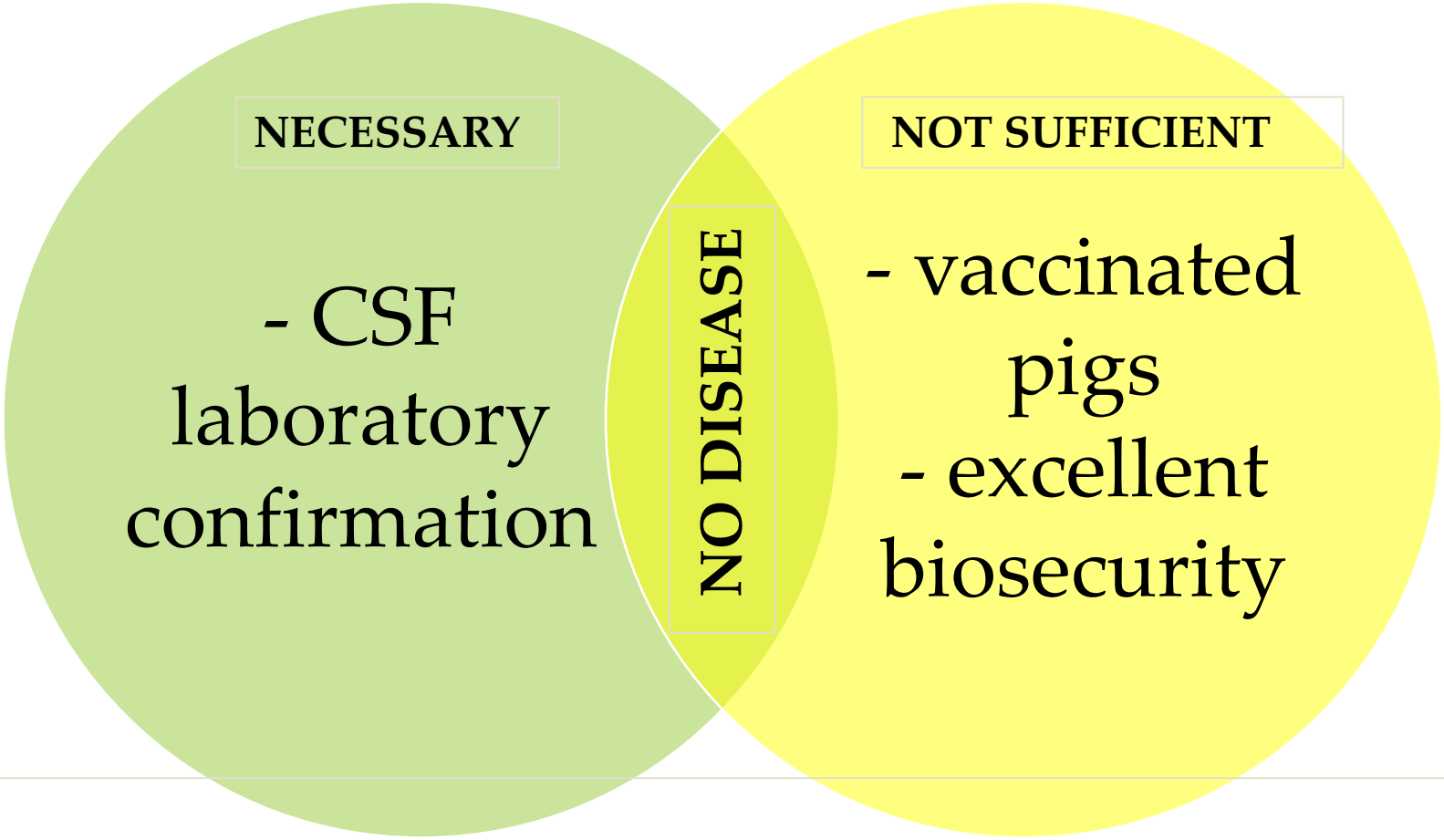
Necessary and sufficient causes of Classical Swine Fever (CSF)



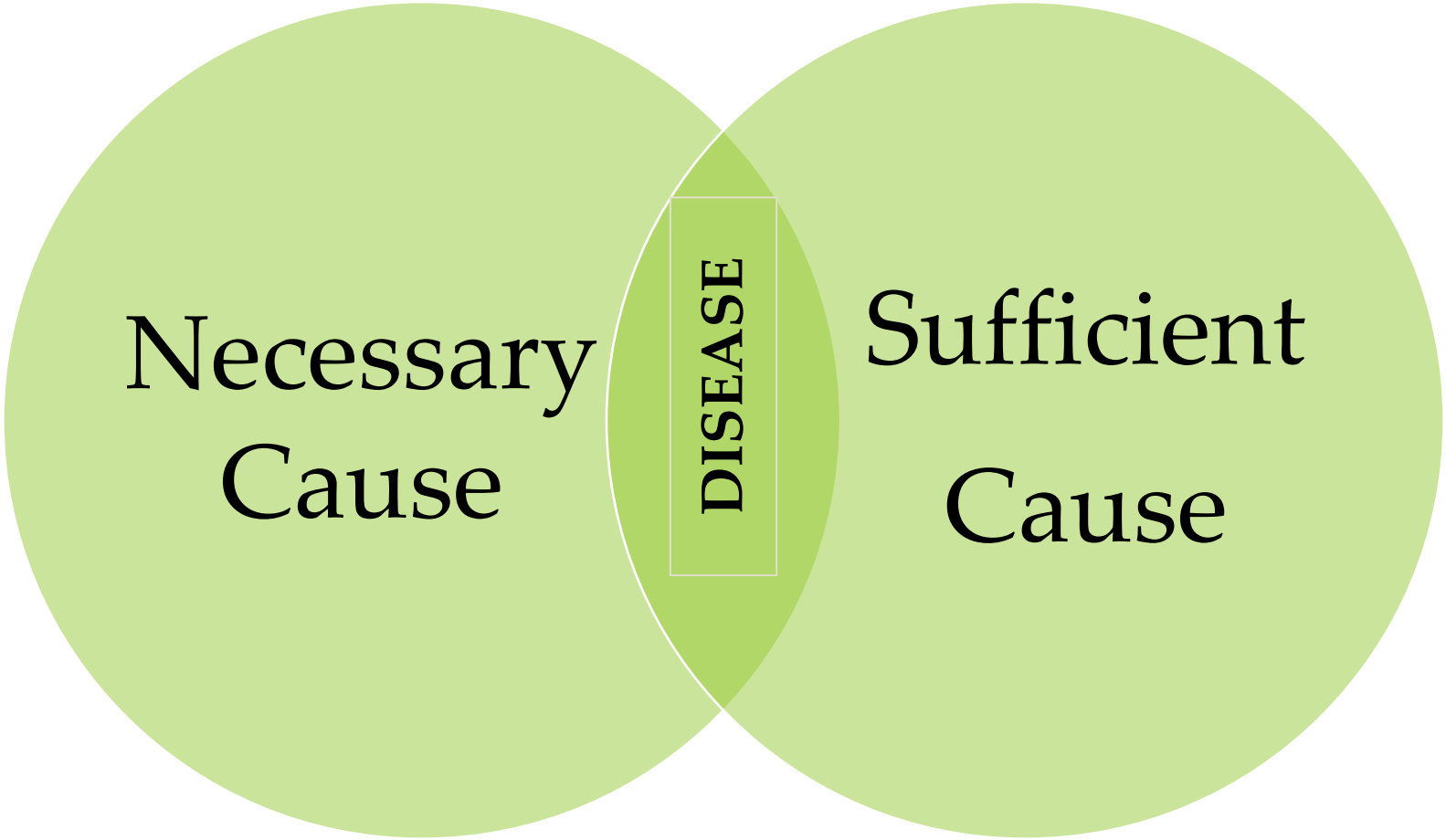
Necessary and Sufficient Causes

3. A **necessary cause** must exist for disease to occur, but it alone does not provide **sufficient cause** for the occurrence of the event.

Necessary and sufficient causes of Classical Swine Fever (CSF)



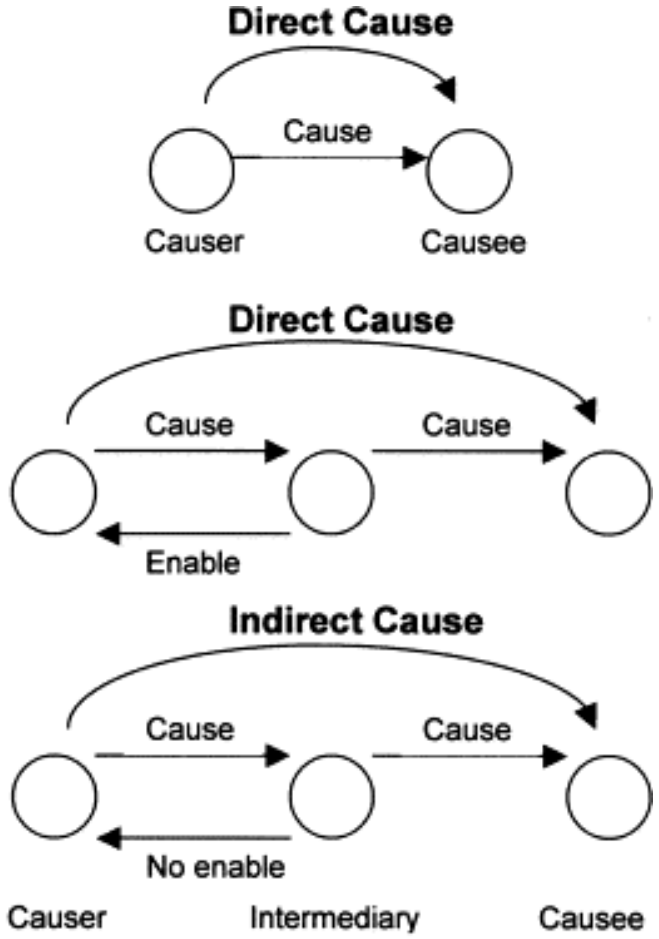
Summary: Both necessary and sufficient causal associations required to produce disease…



Lesson 3: Part 3 of 4

Direct and Indirect Causal Associations

- How do multiple causal interact to produce disease?
- Directly: causal association can occur in two ways
  - One step
  - Multiple steps – biologically amplified and mediated
- Indirectly:
  - Multiple steps without biological mediation



Let's consider Foot and Mouth Disease (FMD)

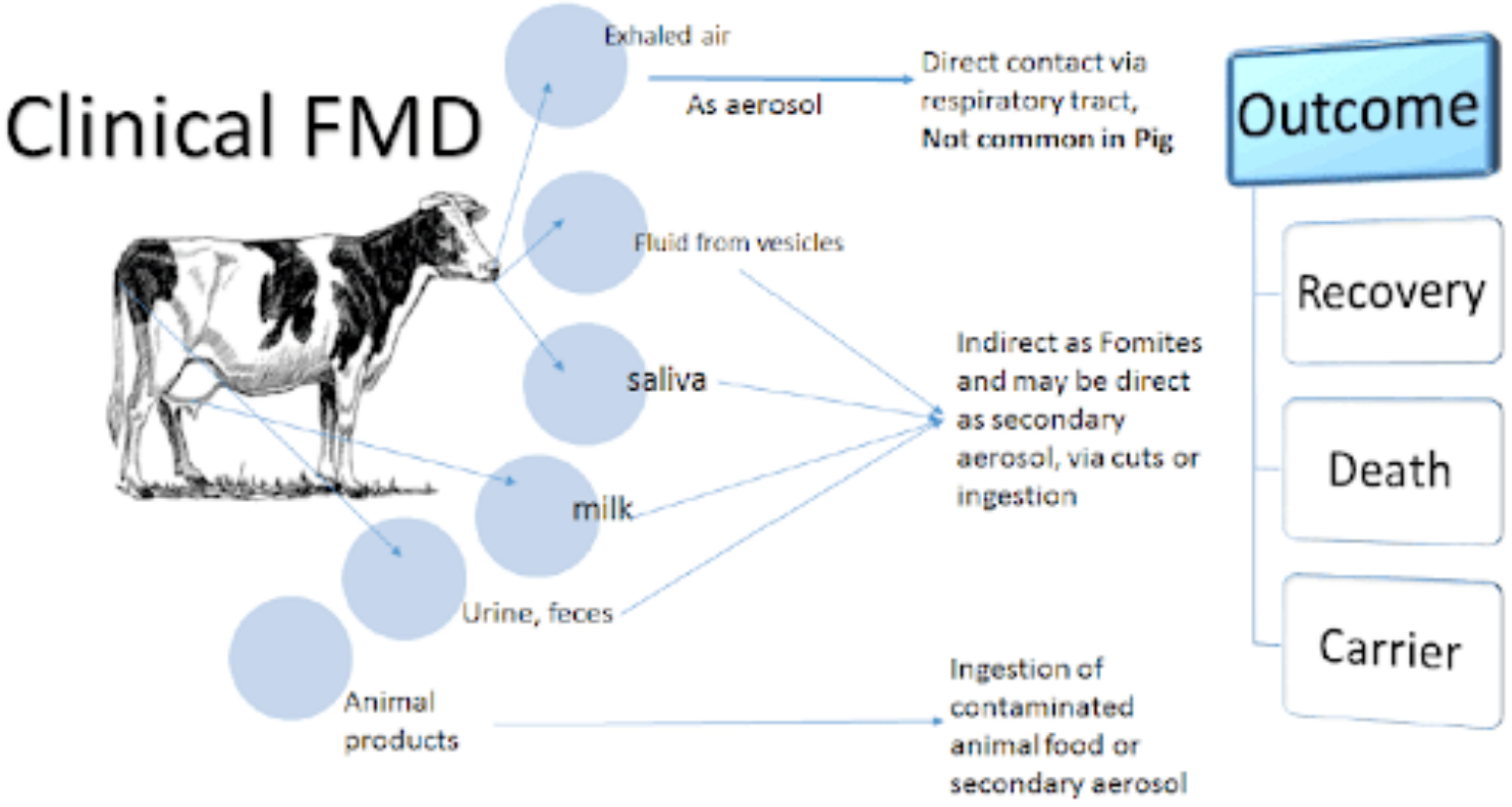


Figure 1. Virus transmission in FMD from clinically infected animal and outcome.

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FMD: Direct causal association (1-step)

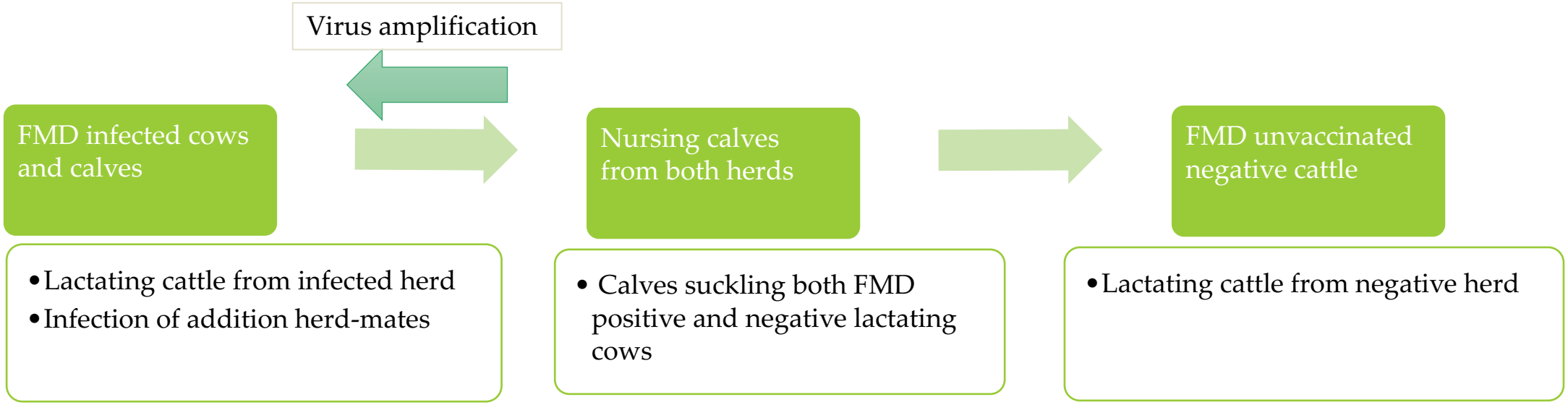
FMD infected cattle

- Nose to nose contact occurs

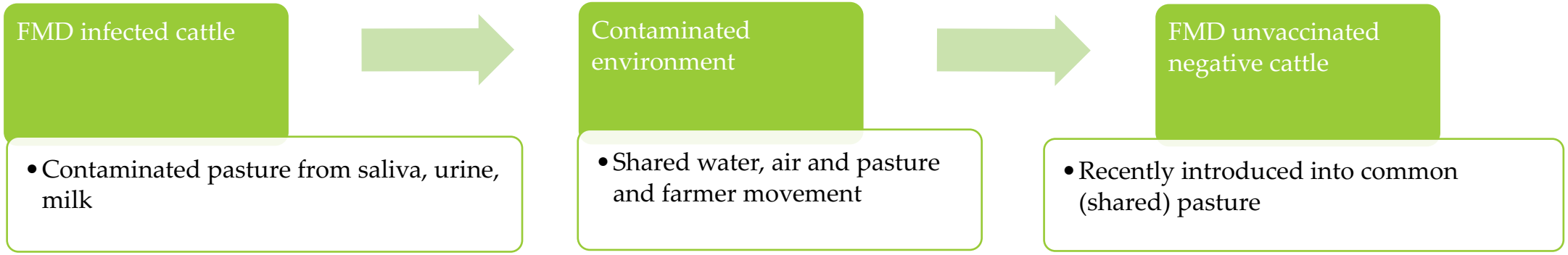
FMD unvaccinated negative cattle

- Recently introduced into common (shared) pasture

FMD: Direct causal association (2-step)

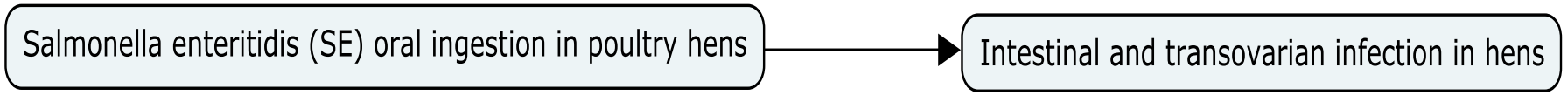


FMD: Indirect causal association



Simple Causal Pathway: Salmonella enteritidis (SE) in poultry hens

- Disease causality is seldom simple
- A simple pathway can be created to depict the pathogenesis of SE

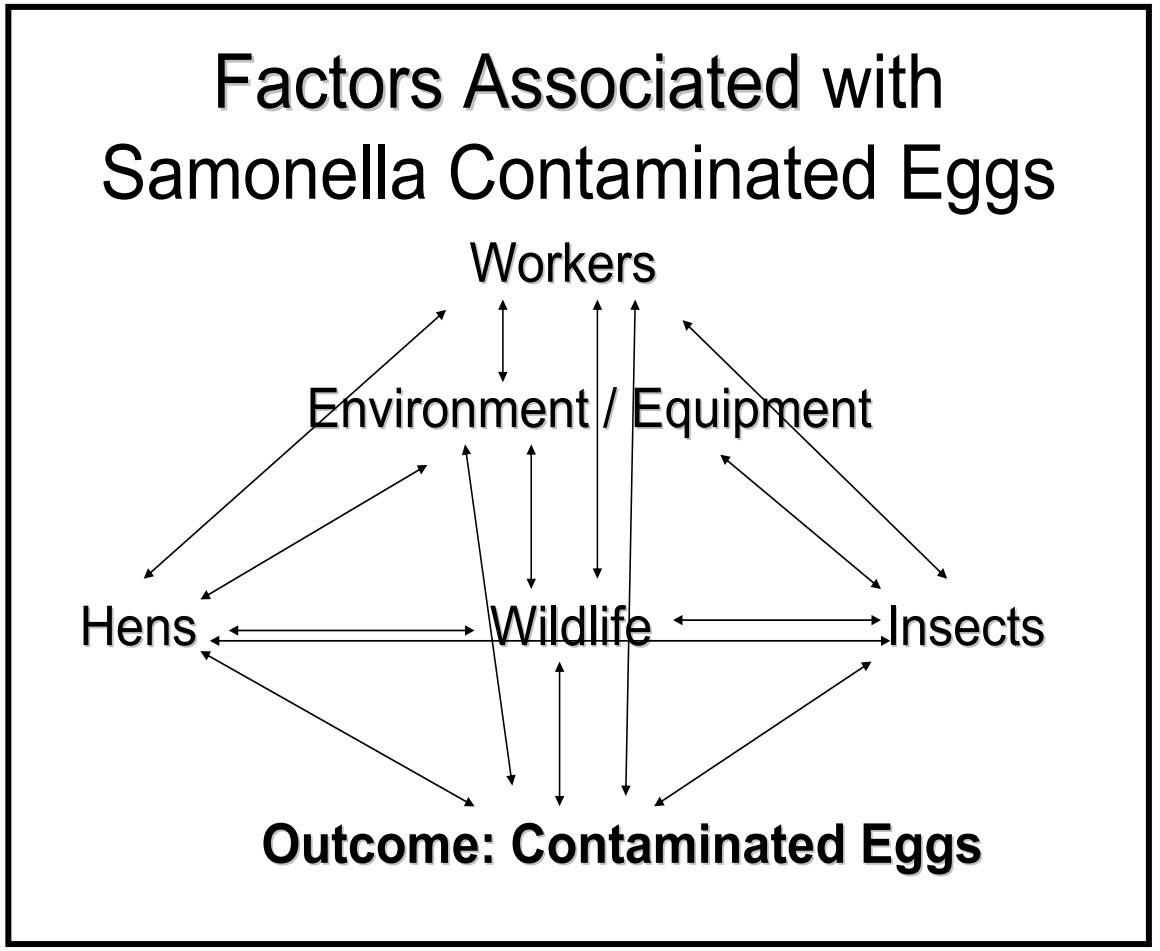


Example: Salmonella enteritidis from infected poultry is an important zoonotic food safety pathogen causing human illness and death and is reportable in many countries

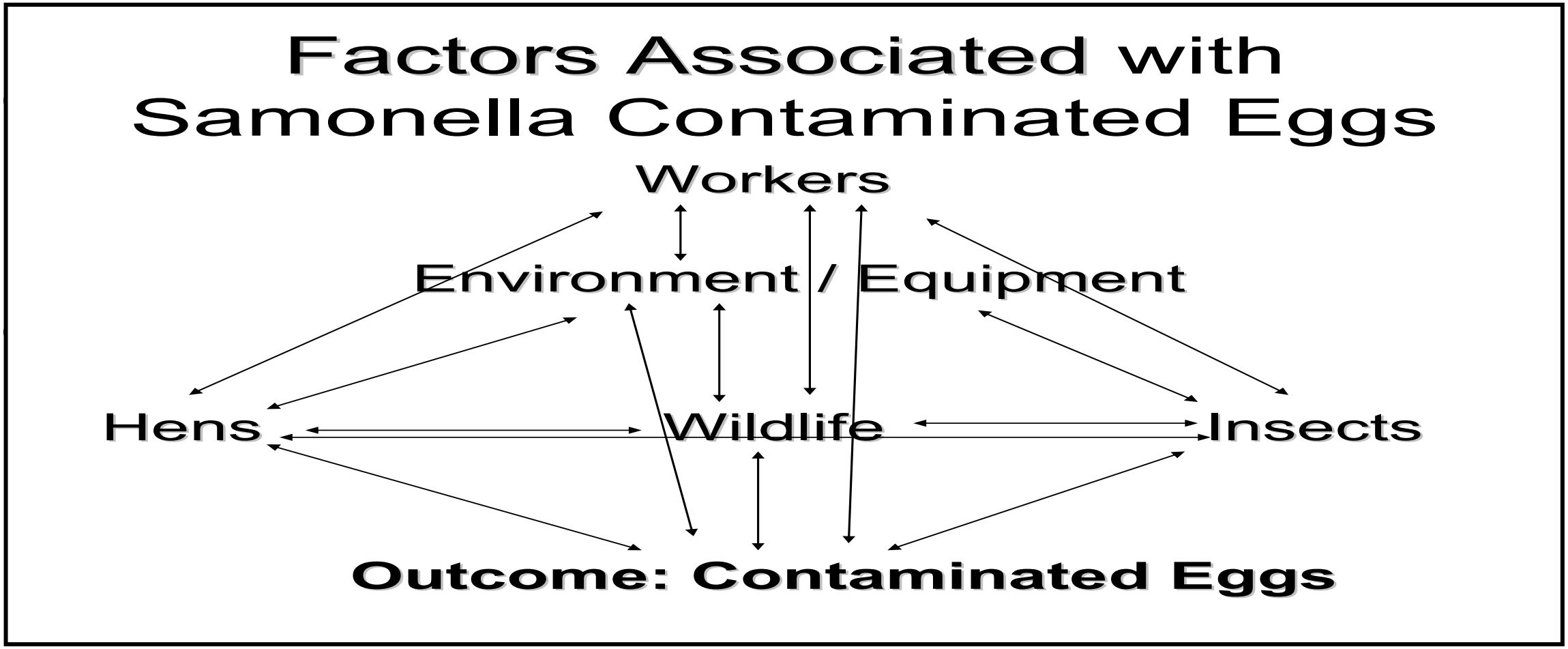
- *Transmission includes*
  - *fecal-oral among poultry*
  - *Transovarian to infertile eggs or developing embryos*

Multifactorial Causal Pathway: Salmonella enteritidis in poultry hens

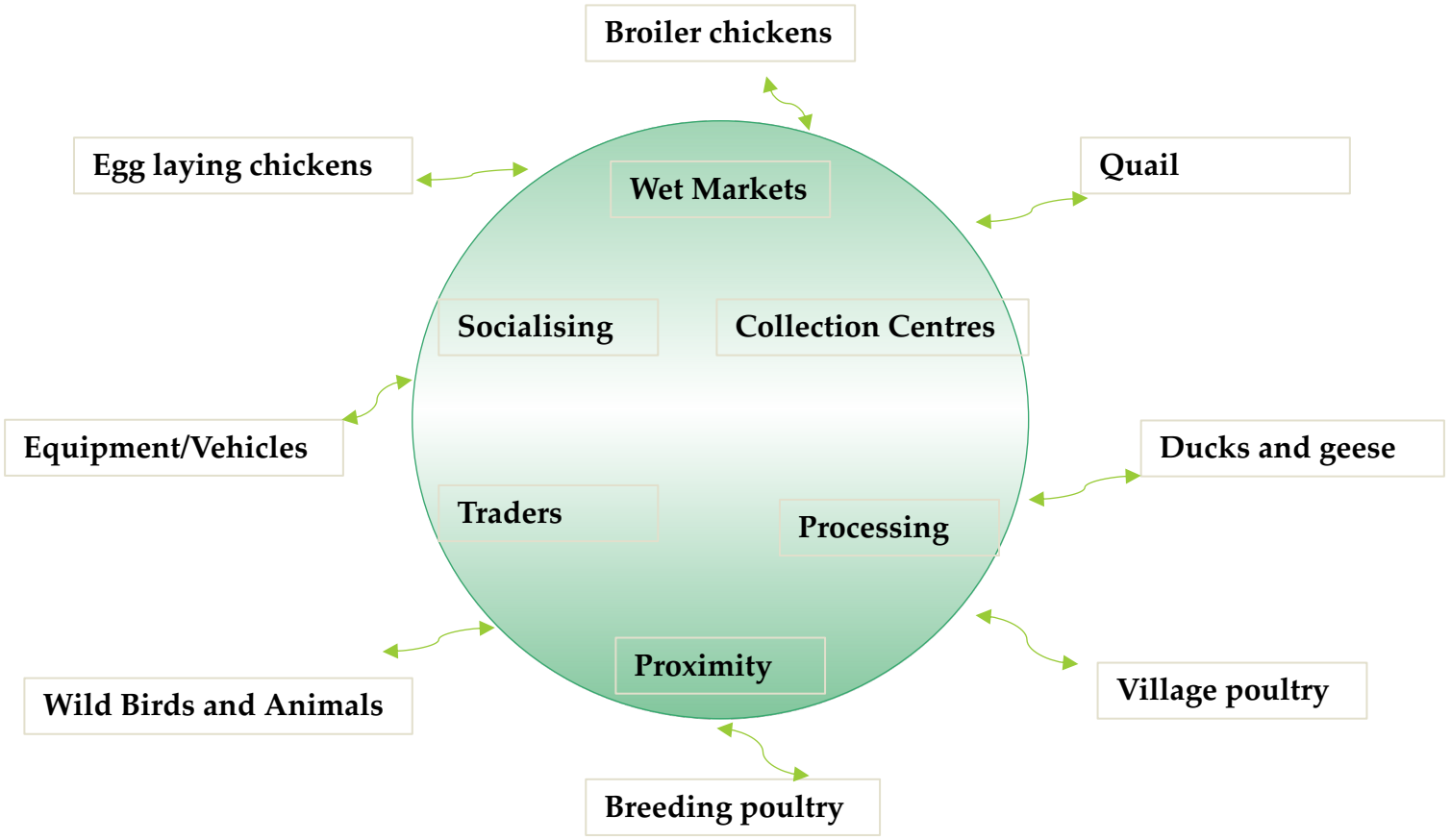
- Necessary Causes
  - Salmonella enteritidis positive
  - Susceptible hens
- Sufficient Causes
  - Environmental contamination
  - Management of farm environment and equipment
  - Workers
  - Wildlife – rodents, birds, cats, dogs
  - Flies, darkling beetles, lice



Farm Level: Multifactorial Causal Pathway for Salmonella enteritidis in Poultry Hens



System Level: Multifactorial Causal Pathway for Avian Influenza Virus Transmission in Myanmar



Lesson 3: Part 4 of 4

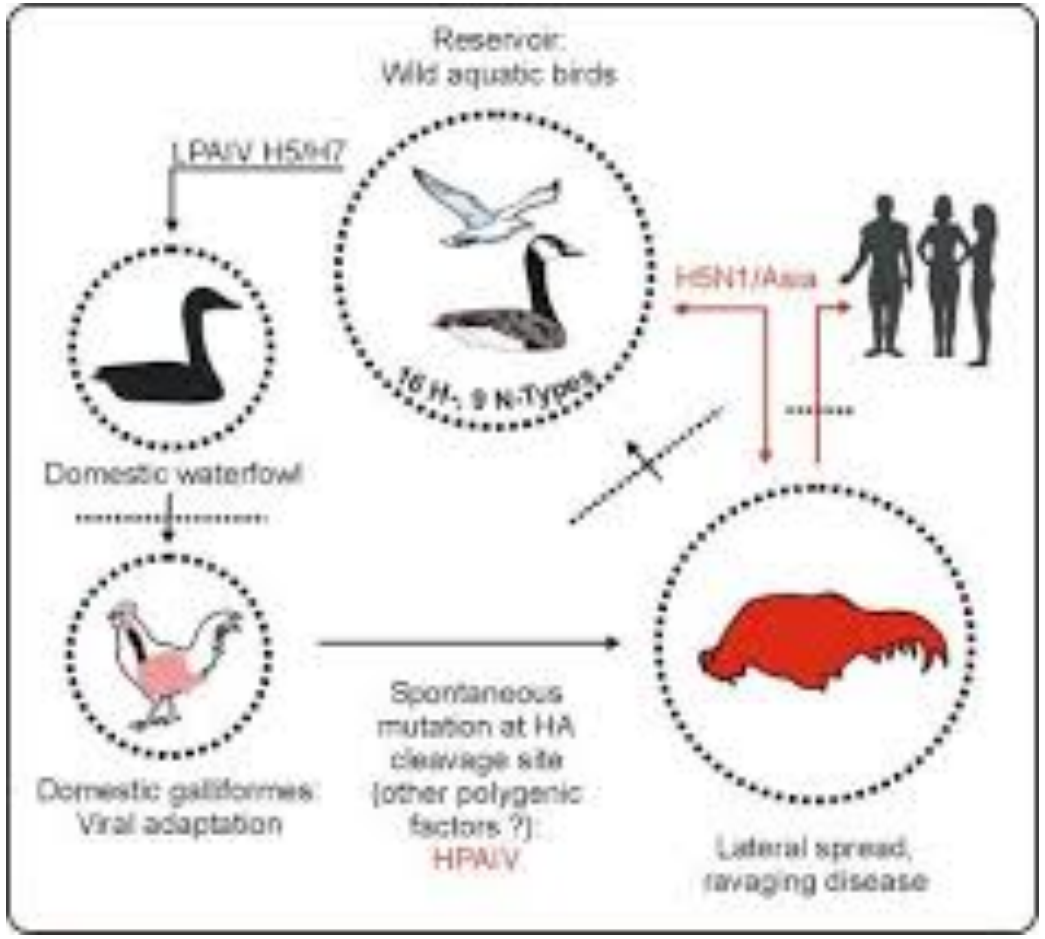
Case Study: Highly Pathogenic Avian Influenza (HPAI)

1. **Understand the disease agent**	A zoonotic orthomyxovirus found in wild birds that are low and high pathogenicity to poultry
	The virus mutates and re-assorts rapidly and constantly with 16 H and 9 N subtypes (Examples: H5N1; H5N8; H7N9, H9N2)
2. Understand transmission risk	Direct: Contact with wild birds (reservoir) and among poultry at farms, households and markets
	Indirect: Movement of people, equipment, vehicles, cages, egg cartons among farms and markets along the value chain
3. Manage risk	Get annual influenza vaccine if you work with poultry
	Reduce exposure: Wear clean PPE at every location and shower
	Post-exposure anti-viral treatment
4.Communicate the risk	Although handling infected birds can result in human infection, cooking destroys the virus in meat and eggs
	Develop and share messages on how to prevent and control avian influenza in poultry and in humans

Background: Zoonotic Avian Influenza Subtypes

Subtype	Pathogenicity	Scope	Case Fatality
H5N1	HPAI	Asia, Europe, Africa 1996-present	53% (WHO)
H7N9	LPAI mutated to HPAI	China 2013-Present	30% (WHO)
H9N2	LPAI – Progenitor Virus of H5N1, H7N9 and H5Nx causing production loss	Asia – Hong Kong, China, Pakistan (sporadic)	Not reported

Virus-Host Adaptation of Avian Influenza (AI) Virus



- Wild birds are the reservoir of AI
- AI virus mutation and reassortment in wild birds and poultry
- Spillover hosts: Poultry and humans

Scenario: Highly Pathogenic Avian Influenza (HPAI)

- Village farmers begin experiencing a high number of deaths in poultry in small poultry holdings 5 days after traders came to buy poultry from the farmers
- Dead birds are submitted for testing
- The laboratory confirms a diagnosis of HPAI H5N1 subtype

Criteria of Causality (Koch, Hill)

- Based on the given scenario:

RESPONSES

1. What is the outcome (dependent) variable?

Poultry Deaths associated with HPAI H5N1 PCR Positive Diagnosis

2. What is a possible risk factor (independent) variable?

Association with movement of traders in village 5 days prior to poultry deaths

3. Which criteria of causality has been fulfilled so far?

Koch: The disease agent has been isolated: HPAI H5N1

Hill: Temporal sequence – The exposure occurred 5 days before poultry deaths

Necessary and Sufficient Cause

- Based on the given scenario:

RESPONSES

1. What is the <u>necessary cause</u> for this disease outcome to occur?

HPAI H5N1 Virus is confirmed PCR positive by laboratory diagnosis

2. What is the <u>sufficient cause</u> for this disease outcome to occur?

Association with movement of traders in village 5 days prior to poultry deaths

Direct and Indirect Cause

- Based on the given scenario:

1. What is a possible direct causal association for this disease outcome to occur?

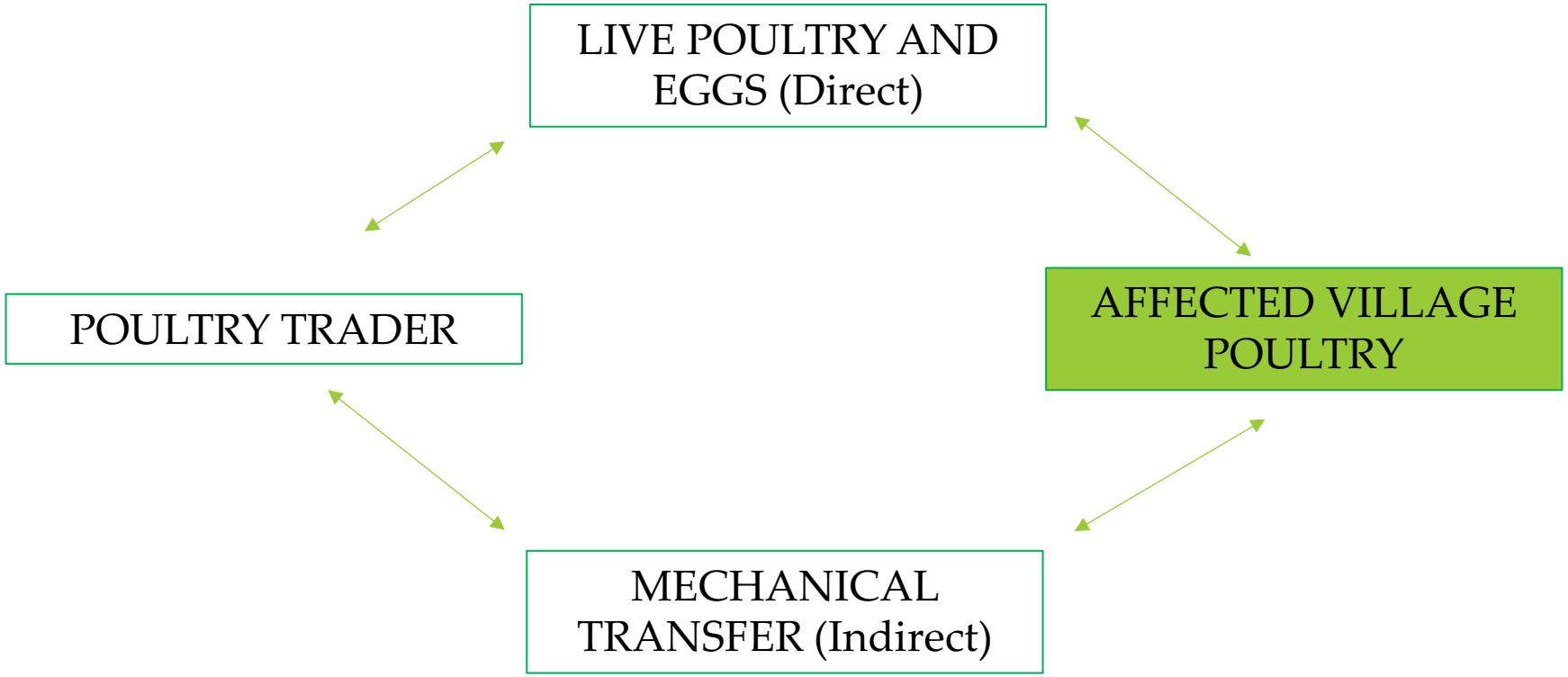
2. What is a possible indirect causal association for this disease outcome to occur?

RESPONSES

The trader arrived with infected poultry in his truck and several escaped and sold eggs to allow direct contact among transported and village poultry

The trader carried contaminated fecal materials mechanically into the village on his footwear or clothing

Simple Causal Pathway for HPAI

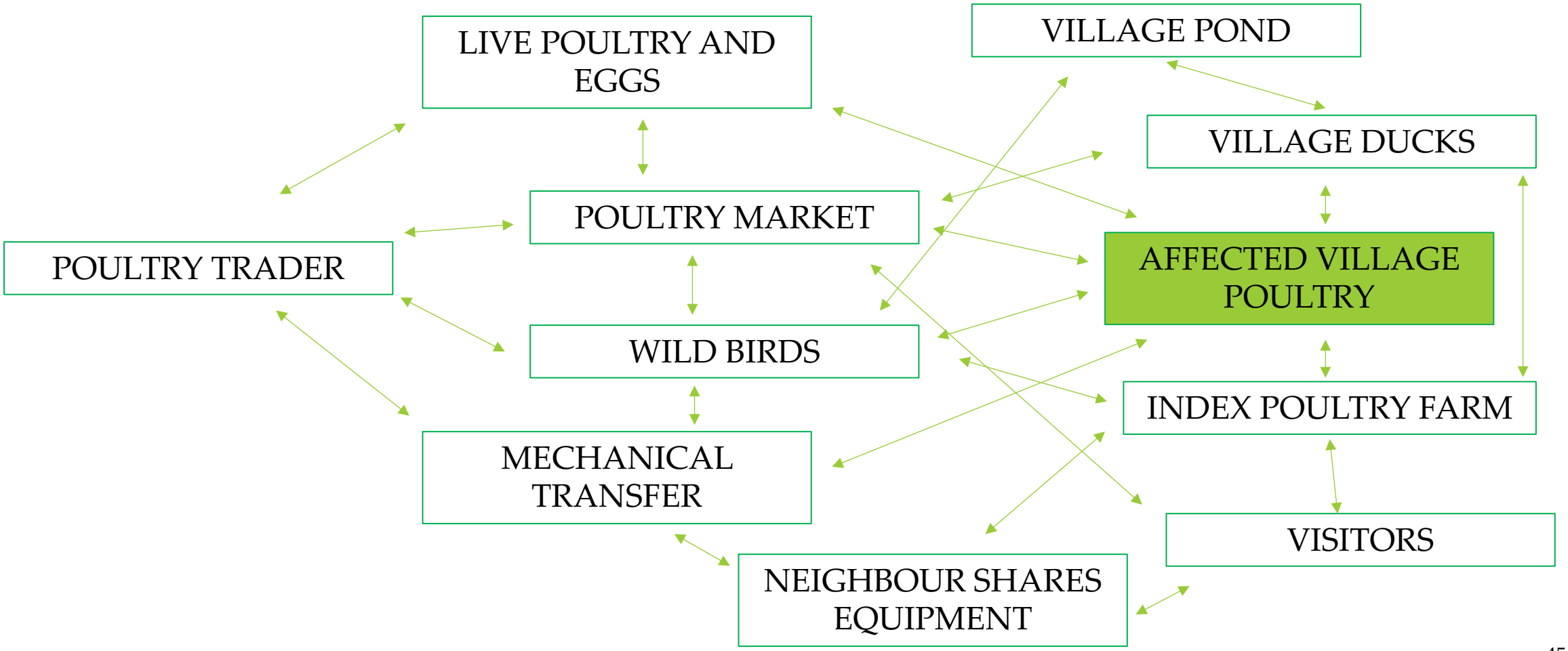


What other factors may have contributed to the HPAI deaths in this village?

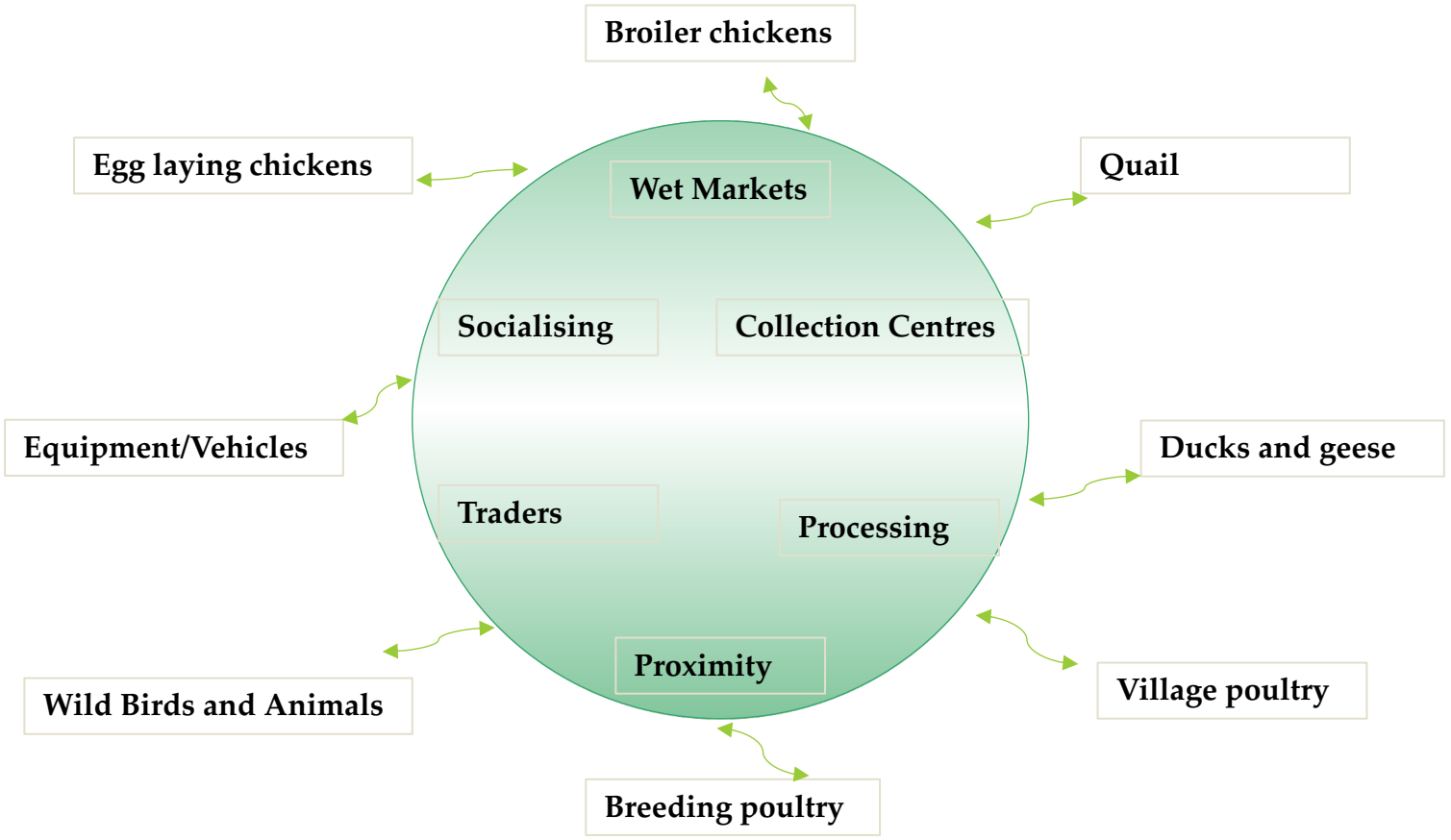
- An outbreak investigation was conducted at the time of the initial laboratory confirmation. Here are some of the findings:

  - Resident and migratory birds observed in poultry houses
  - Farmers visit friends and loan vaccination equipment to other farmers
  - Some farmers transport their own poultry to the live poultry market
  - Some farmers purchase poultry and bring them back to the village
  - Several ponds in the village have ducks and other waterfowl in them

Multifactorial Causal Pathways for HPAI



System Level: Multifactorial Causal Pathway for Avian Influenza Virus Transmission



Summary of Key Points: Lesson 3

- It is not possible to demonstrate with 100% certainty that an independent variable causes a health or disease outcome in humans and animals
- Causal associations can be:
  - Necessary or Sufficient
  - Direct or Indirect
  - Seldom simple, mostly complex
- The best we can do is to support a causal hypothesis based on valid, statistical associations among dependent and independent variables
- Mapping out causal pathways is important so that you can visualise possible associations among variables for your analysis

References

Altman, N. and M. Krzywinski. 2015. Association, correlation and causation. NATURE METHODS. VOL.12 NO.10

Dohoo, I. R., Martin, W., and H. E. Stryhn. 2003). Veterinary epidemiologic research. Charlottetown, P.E.I.: University of Prince Edward Island.

Martin S.W., Meek A.H. and P. Willeberg. 1987. Veterinary Epidemiology. Ames Iowa. Iowa State Press.

Thrusfield M. 2007. Veterinary Epidemiology, (3rd Ed.). Ames, Iowa. Blackwell Science Ltd.