

# Background

- Our environment is occupied by a wide range of pathogenic microbes and to substances that threaten normal homeostasis.
- **Homeostasis**, any self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival. If homeostasis is successful, life continues; if unsuccessful, disease developed or worse death occurs.
- In the past “some” relied on use of antibiotics as preventive or treatment of certain diseases.
- Today, Antimicrobial Resistance (AMR) poses a significant problem in health care, animal health, and food safety.
- To limit AMR, there is a need for alternatives to antibiotics to enhance disease resistance and minimize antibiotic usage in animals and humans.

# Background

Therefore understanding immunity as a specialized form of host defense mechanism that works particularly in relation to the causes and prevention of diseases becomes relevant.

To achieve resistance against disease, the most important is strengthening the immune system.

If the immune system fails become under or over active it can lead to a variety of adverse consequences. Under-activity lead to loss the defensive mechanism against infections; whereas over-activity can lead to autoimmune diseases.

Nevertheless, immunomodulation is a promising strategy to enhance disease resistance without antibiotics in food animals.

# Understanding Immune System

- **Immune system** is a host defense system.
- It comprises many biological structures as well as many complex biological processes.
- Its main function is to protect the host from pathogens and other causes of disease and able to distinguish the cells of pathogens from the host's own cells including damaged host cells from healthy cells.
- Immune systems are usually classified into two subsystems called the innate immune system and the adaptive immune system.

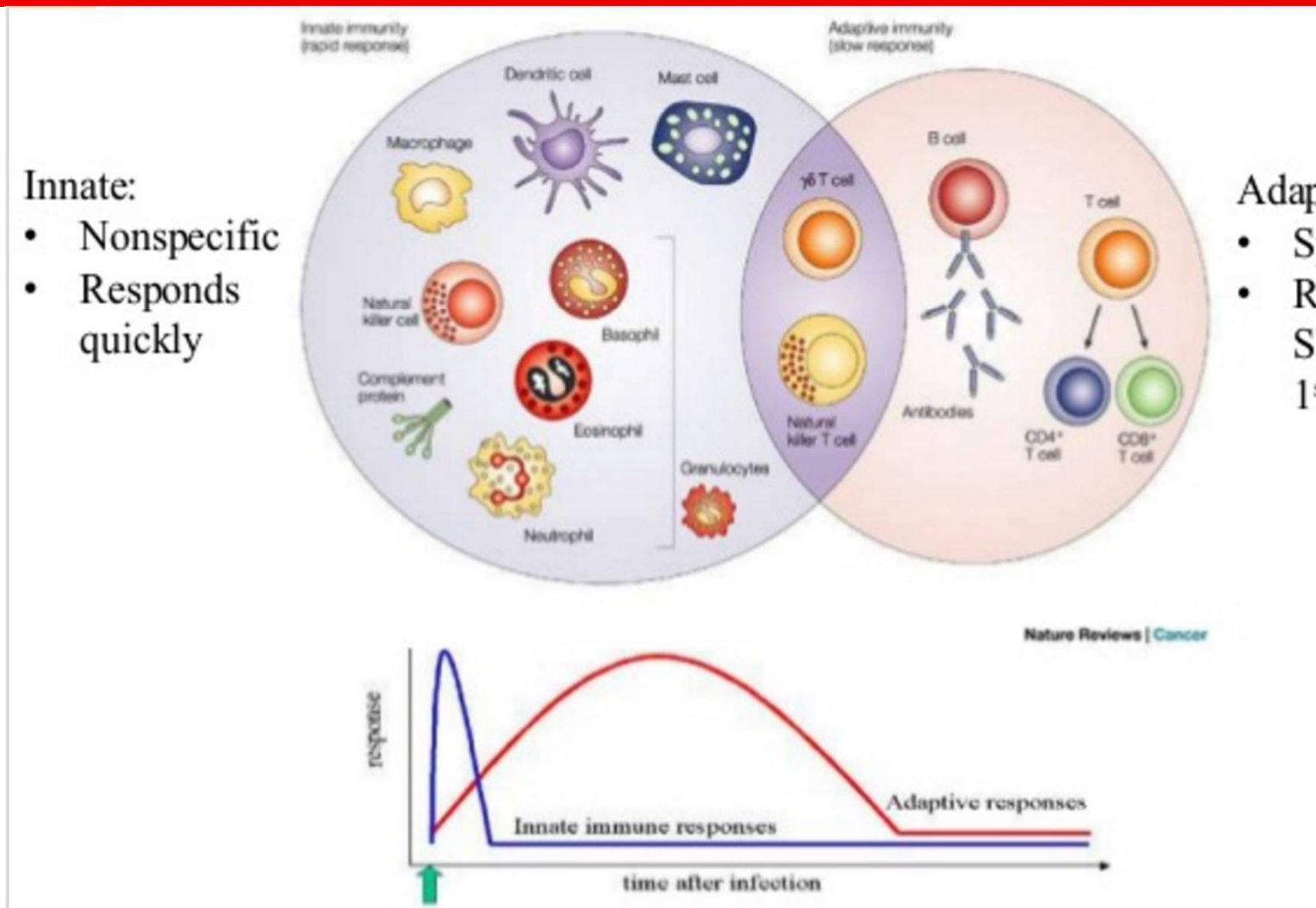
# General classification of Immune System

## Innate Immunity

Non specific,  
which is present  
right from birth

## Adaptive Immunity

Specific acquired,  
which is acquired  
during life



# Innate (Natural) Immunity

Provides the first line of defense against infection.

Usually begins with the physical barriers such as skin including epithelial cells and resident tissue cells.

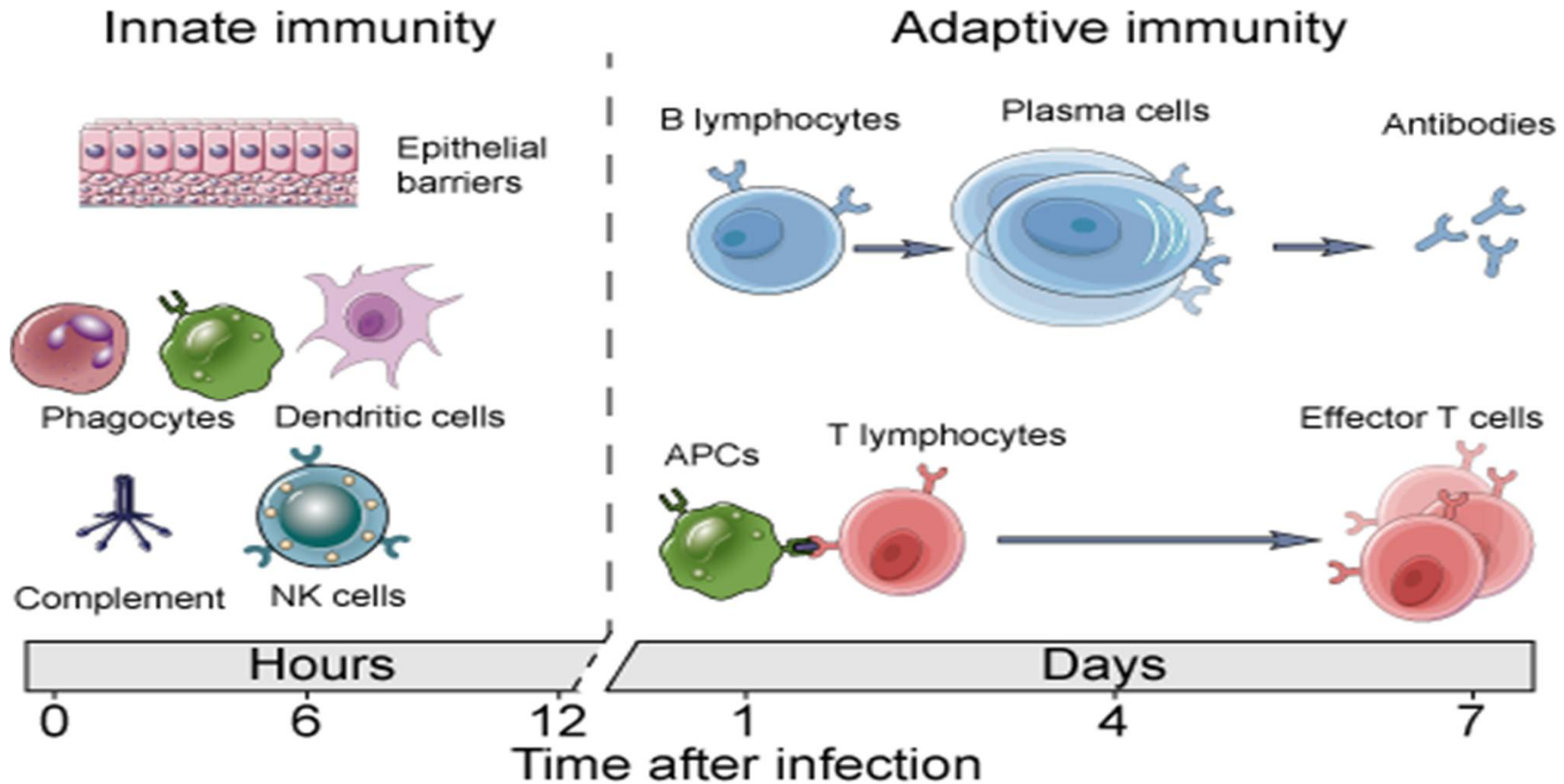
Then production of pro-inflammatory cytokines and phagocytic cells like macrophages, NK cells, dendritic cells, etc..

In general, our innate immune system clears most of the microorganisms before they activate the adaptive immune system.

# Adaptive (Acquired) Immunity

- Activated once pathogens successfully enter the body and manage to evade the innate immune system.
- It takes longer to launch a specific attack, but its specificity makes it very effective. It usually leads to immunity by “remembering” the pathogen.
- Generally seen after 5 to 6 days of exposure to a particular antigen.

# Innate and Adaptive Immunity



# Earlier

- In the past “some” relied on use of antibiotics as preventive treatment.
- Today, with the campaign reduction on antimicrobial use, the need for alternatives by early stimulation or modulating immune response.
- Under-activity lead to loss the defensive mechanism against infections.
- Immunomodulation or immune stimulation is a promising strategy to enhance disease resistance without reliance on antibiotics in food animals.



# Immunostimulants

- Are biologically active substances from natural or synthetic sources that increase the ability of the immune system to fight against various infections and disease.
- They interact with specific receptors and cellular components of innate and adaptive immunity to modulate the immune response.
- They do not cure disease. But they stimulate major factors of the immune system including phagocytosis, secretory IgA antibodies,  $\alpha$ - and  $\gamma$ -interferon release, T- and B-lymphocytes, and synthesis of specific antibodies and cytokines.
- Its principle is relatively simple: **TO BOOST IMMUNE SYSTEM.**

# Immunostimulants

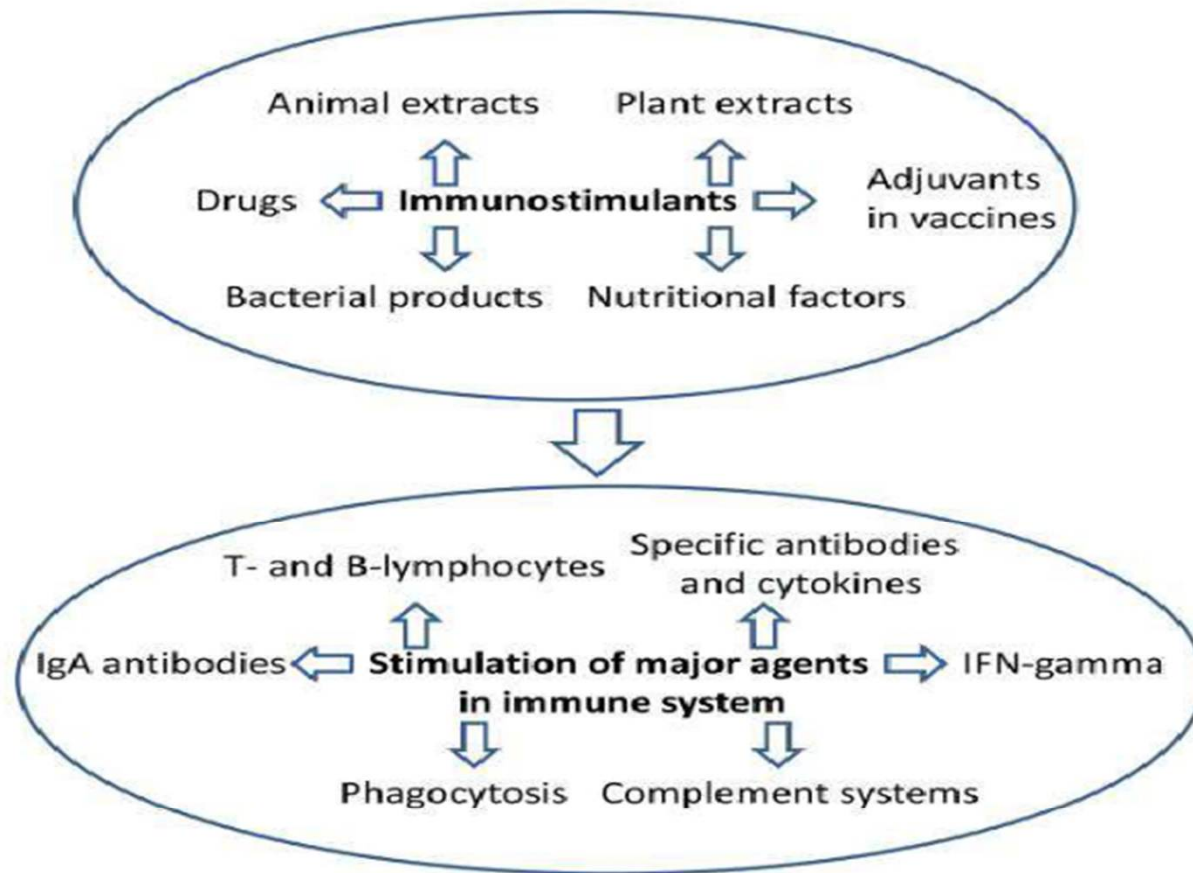


Figure 3: Schematic representation of some types of immunostimulants and their general functions

# Reasons for using the immunostimulants

Antibiotic resistance of the bacteria  
Allergic reactions to antibiotics  
Immunosuppressive effects of certain drugs  
Side effects of the antibiotics in viral infections

*As a therapeutic strategy based on modulation of the immune response provides a number of advantages, without directly affecting the pathogen, immunostimulants do not prevent the development of multidrug resistance among bacteria.*





# Two major groups of immunostimulants

- Specific immunostimulants
  - Provide antigenic specificity in immune response, such as vaccines or any antigen
- Non-specific immunostimulants
  - Act irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immune stimulators.

# NSI + Bacillus

## Active ingredients

- Non-specific Immuno-Stimulator [NSI]
- Bacillus subtilis :  $1.0 \times 10^9$  cfu/kg

Ingredient	Concentration (g/L of water)
Sodium metasilicate ( $\text{Na}_2\text{SiO}_3$ )	600
Potassium carbonate ( $\text{K}_2\text{CO}_3$ )	300
Sodium carbonate ( $\text{Na}_2\text{CO}_3$ )	9
Sodium borate ( $\text{Na}_2\text{B}_4\text{O}_7$ )	9
Sodium thiosulphate ( $\text{Na}_2\text{S}_2\text{O}_3$ )	0.12
Sucrose ( $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ )	q.s.
Silver nitrate ( $\text{AgNO}_3$ )	q.s.
Sodium chloride ( $\text{NaCl}$ )	q.s.

# NSI + Bacillus

... to its Non Specific Immune Stimulators

- It stimulates the innate immune system (non specific defenses of the body) which is activated within hours upon recognition of foreign body that triggers the adaptive immune system or specific immune system.
- This makes the immune system well primed to repulse and eliminate threatening foreign body because it has already an operational cell mediated immune response

# NSI + Bacillus

- Anionic mineral complex
  - Fast dispersion and absorption
- SiO<sub>2</sub> (Silica or Silicon dioxide)
  - Proven as immune-stimulator
- Alkaline Product (pH 13-14)
  - Helps in proliferation and activation of porcine immune cells, particularly CD4<sup>+</sup>CD8<sup>+</sup> double-positive T lymphocytes in peripheral blood and in the secondary lymphoid organ.
  - As an alkaline solution it can aid in better enzymatic digestion.

**IMMUNE ENHANCING EFFECT**



# NSI + Bacillus

- $\text{SiO}_2$  (Silica or Silicon dioxide)
  - Proven as immune-stimulator
  - Silica is recognized as a PAMP (pathogen-associated molecular pattern) by the Receptors of Innate Immunity
  - This causes the stimulation of Innate Immunity (the macrophages)
  - While stimulated, macrophages produce cytokines (IL-1 and TNF)
  - Cytokines produced by silica-activated macrophages induce the maturation of dendritic cells, which are the connecting elements between the Innate and the Adaptive (lymphoid) Immune Systems



# NSI + Bacillus

## *Bacillus subtilis*

- . Gut Health and Digestion
- . Enhanced Nutrient Utilization
- . Immune System Stimulation
- . Reduction of Gastrointestinal Infections
- . Stress Reduction
- . Antibiotic Alternatives

# NSI + Bacillus

Immune System Stimulation:

*Bacillus subtilis* can modulate the immune system of animals, enhancing their immune responses against pathogens.

It stimulates the production of immune cells and immune-modulating substances, such as cytokines.

This immune stimulation can help animals combat infections, reduce disease susceptibility, and improve overall resistance to pathogens.

Additionally, by maintaining a healthy gut microbiota, *Bacillus subtilis* indirectly supports the immune system, as a significant portion of the immune system is located in the gut.

Pattern recognition receptor (PRR)

# NSI + Bacillus

- Hog Cholera (Swine Fever)
- Porcine Epidemic Diarrhea (PED)
- Transmissible Gastroenteritis (TGE)
- Postweaning Multisystemic Wasting Syndrome (PMWS)
- Porcine Reproductive & Respiratory Syndrome (PRRS)
- Foot & Mouth Disease (FMD)
- E. coli infection in piglet



# NSI + Bacillus Immune Enhancing Effect

Objective : Immunostimulatory effects of anionic alkali mineral complex solution NSI+Bacillus in porcine lymphocytes

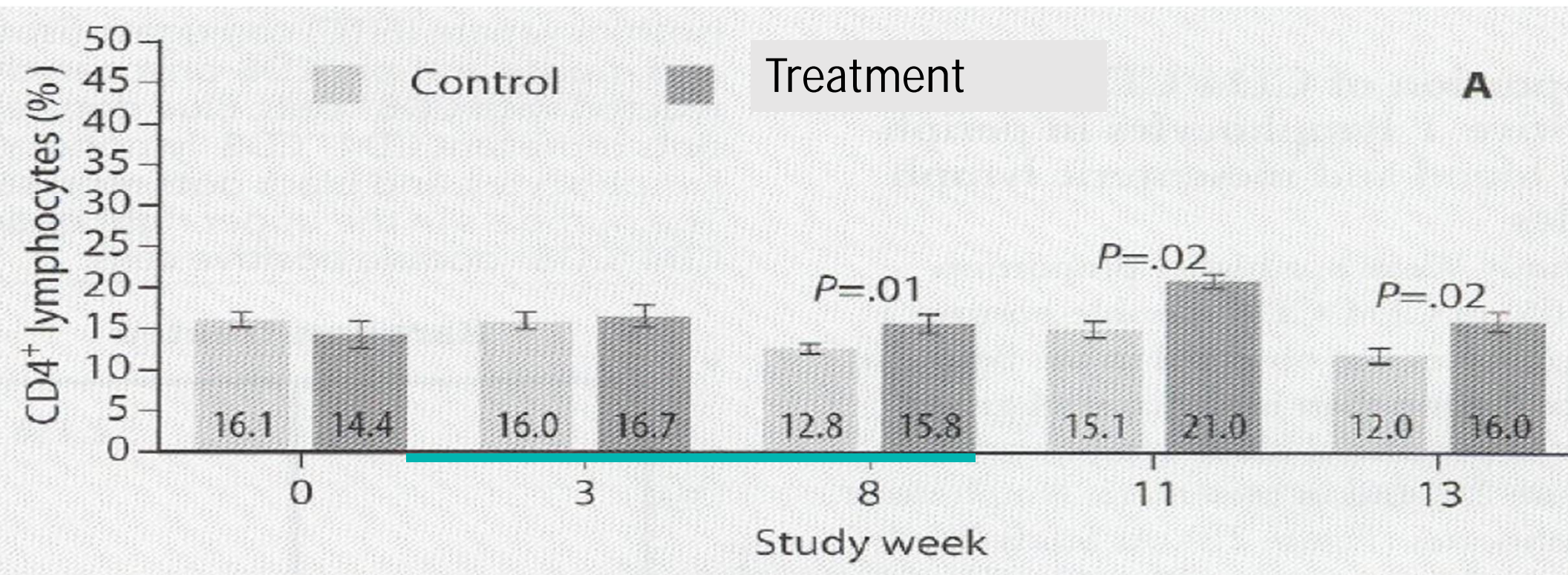
Investigator : Dr. Yoo, B. W., Dr. S. I. Choi, Dr. S. H. Kim, Dr. S. J. Yang, Dr. H. C. Koo, Dr. S. H. Seo, Dr. B. K. Park, Dr. H. S. Yoo, Dr. Y. H. Park (Seoul National University)

J. Vet. Sci., 2(1):15-24, 2001

# NSI + Bacillus Immune Enhancing Effect

Immunostimulatory effects of an anionic alkali mineral complex solution on porcine lymphocytes  
JOURNAL OF SWINE HEALTH AND PRODUCTION

Proportions of CD4<sup>+</sup> in peripheral blood of pigs  
Flow cytometry analysis, performed with P(C) feedmill and 1-9 weeks treatment period.



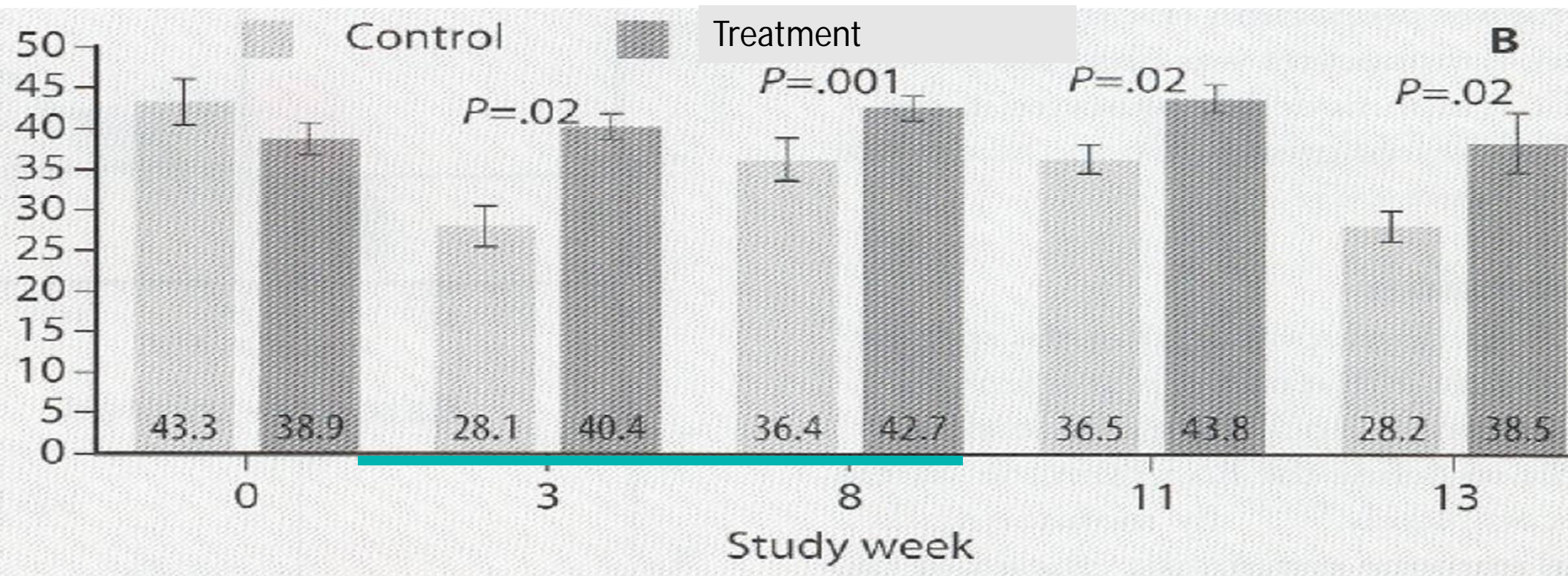


# NSI + Bacillus Immune Enhancing Effect

Immunostimulatory effects of an anionic alkali mineral complex solution on porcine lymphocytes  
JOURNAL OF SWINE HEALTH AND PRODUCTION

## Proportions of CD8+ in peripheral blood of pigs

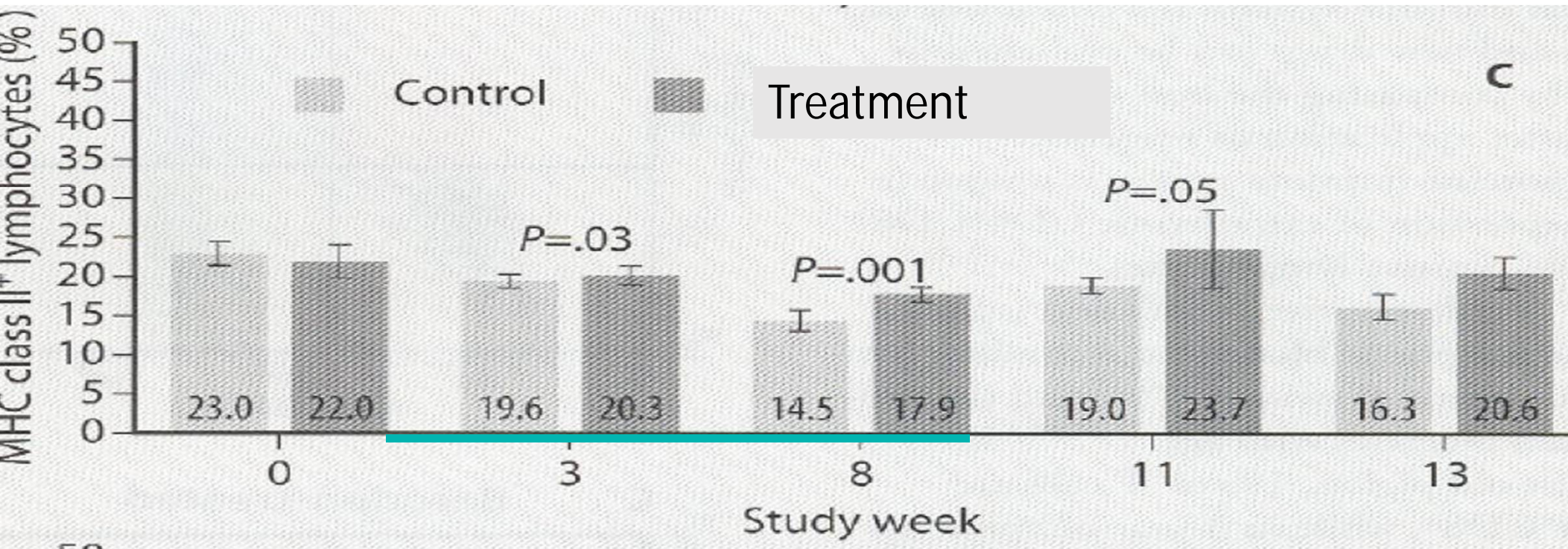
Flow cytometry analysis, performed with P(C) feedmill and 1-9 weeks treatment period.



# NSI + Bacillus Immune Enhancing Effect

Immunostimulatory effects of an anionic alkali mineral complex solution on porcine lymphocytes  
JOURNAL OF SWINE HEALTH AND PRODUCTION

Proportions of MHC-Class II+ lymphocytes in peripheral blood of pigs  
Flow cytometry analysis, performed with P(C) feedmill and 1-9 weeks treatment period.

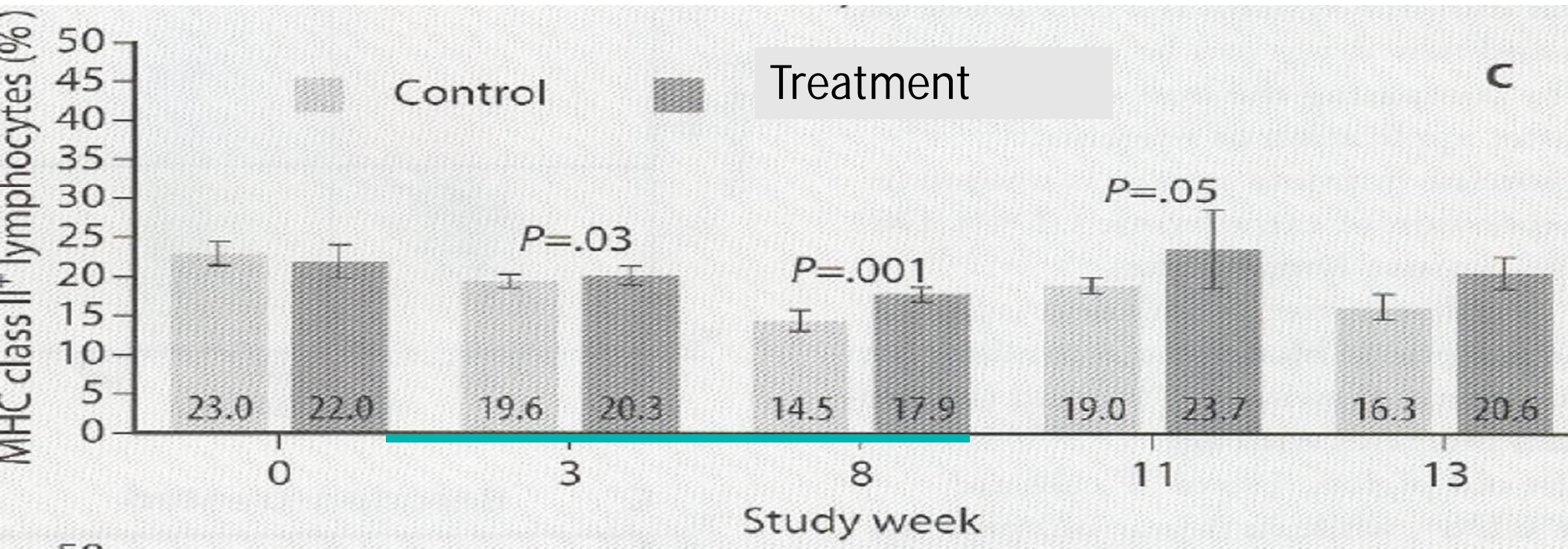




# NSI + Bacillus Immune Enhancing Effect

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# NSI + Bacillus on Hog Cholera

Gyeongsang National University, Veterinary Science Department

Hog cholera challenged

Animal number : Weaned piglet 34 heads

Experimental design

Control : 8 weaned piglets, challenged by hog cholera virus

1 : 8 weaned piglets, challenged by hog cholera virus, then supplement for 20 days

2 : 9 weaned piglets, supplement for 10 days and challenged by hog cholera virus, and then again for 10 days

3 : 9 weaned piglets, supplement for 20 days first and challenged by hog cholera virus

# NSI + Bacillus on Hog Cholera

Group	Clinical sign	Mortality
Control	High fever, depression, anorexia	5/8 (62.5%)
T1	Fever, depression, anorexia	5/8 (62.5%)
T2	Fever, depression	5/9 (55.6%)
T3	No sign	1/9 (11.1%)

# NSI + Bacillus on Hog Cholera

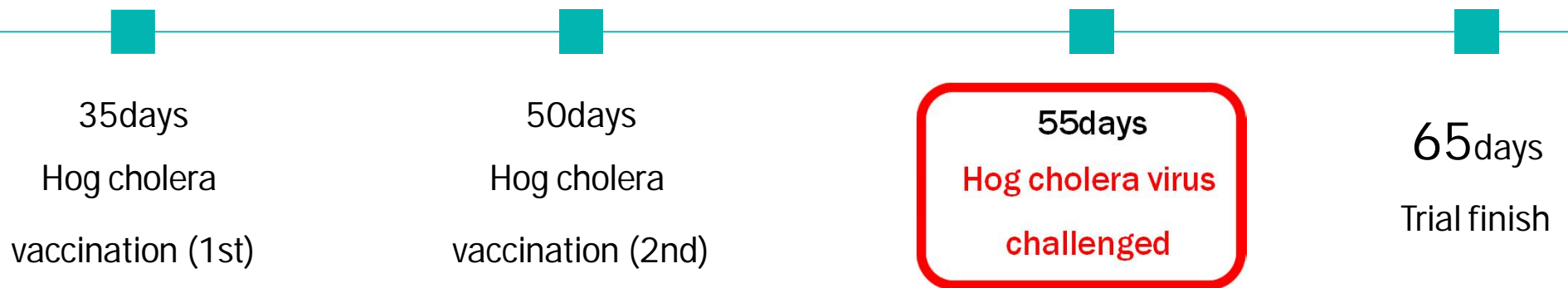
Results (Pathological sign)

Organ	Pathological sign	Control	T1	T2	T3
Brain	Meningitis	6/8	6/8	5/9	1/9
Lymph node	Congestion, Hemorrhage	5/8	5/8	6/9	1/9
Tonsil	Necrotic tonsillitis	5/8	5/8	3/9	1/9
Lung	Congestion, Hemorrhage, Bronchitis	5/8	3/8	6/9	2/9
Heart	Myocardium hemorrhage	2/8	2/8	0/9	1/9
Intestine	Congestion, Hemorrhage, Necrosis	4/8	4/8	6/9	1/9
Kidney	Congestion, Hemorrhage	5/8	4/8	6/9	1/9

# NSI + Bacillus on Hog Cholera

## Trial design (2)

- A, B, C : Treatment group
- D : Control



# NSI + Bacillus on Hog Cholera

## Result

	A (Treatment)	B (Treatment)	C (Treatment)	D (Control)
Head	7	7	7	5
Feeding day	30	30	30	30
Initial weight (total, kg)	60.9	60.4	59.5	41.5
Initial weight (Average, kg)	8.7	8.6	8.5	8.3
Final weight (total, kg)	181.3	173.9	179.8	100.4
Final weight (Average, kg)	25.9	24.8	25.7	20.1
Weight gain (total, kg)	120.4	113.5	120.3	58.9
Weight gain (per head, kg)	18.5	18.0	19.1	11.8
Daily weight gain (per head, kg)	0.573	0.540	0.573	0.393
Feed intake (total, kg)	154.9	154.5	151.4	109.7
FCR	1.29	1.36	1.26	1.86

# NSI + Bacillus on PRRS

Dr. HAN, Jeong-Hee (Professor) of Kangwon National University

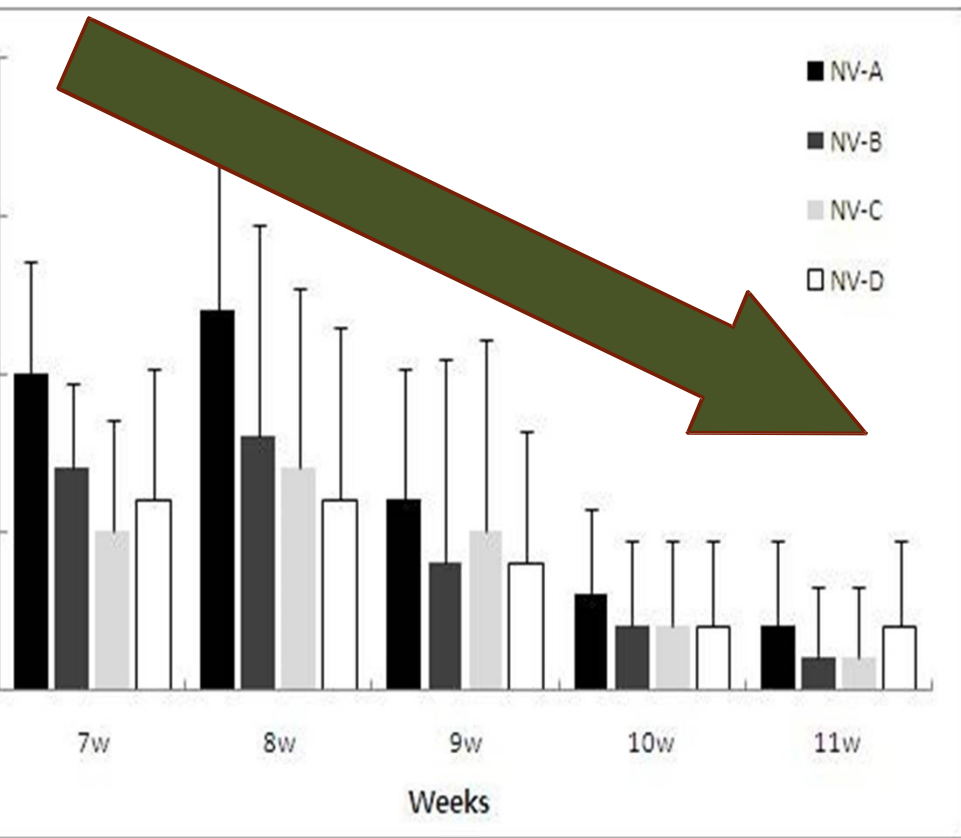
Groups of Vaccinated and Non Vaccinated

- A : Control
- B : Treatment 0.025%
- C : Treatment 0.050%
- D : Treatment 0.100%

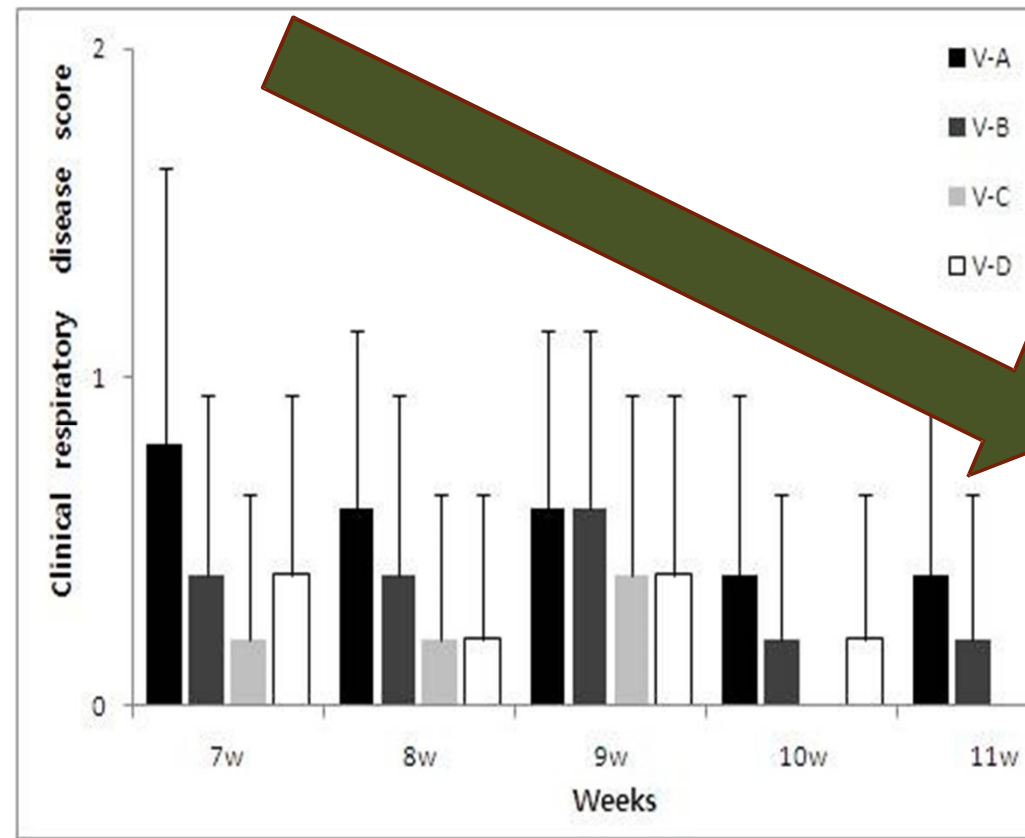
At 4 weeks : Vaccination

At 7 weeks : PRRS virus challenged

# NSI + Bacillus on PRRS



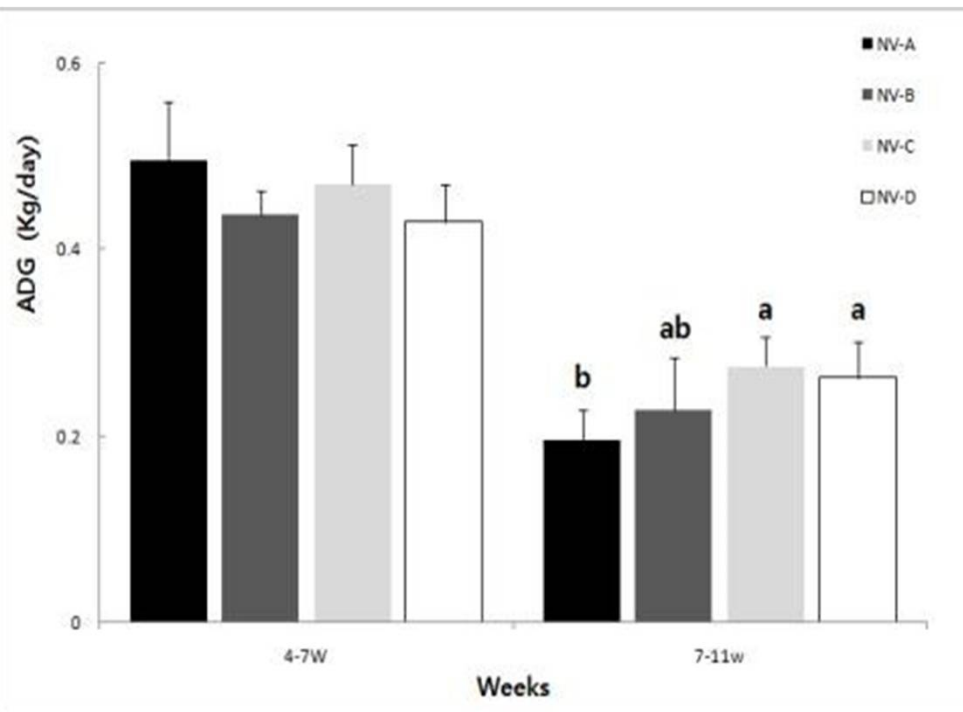
Non-vaccinated groups



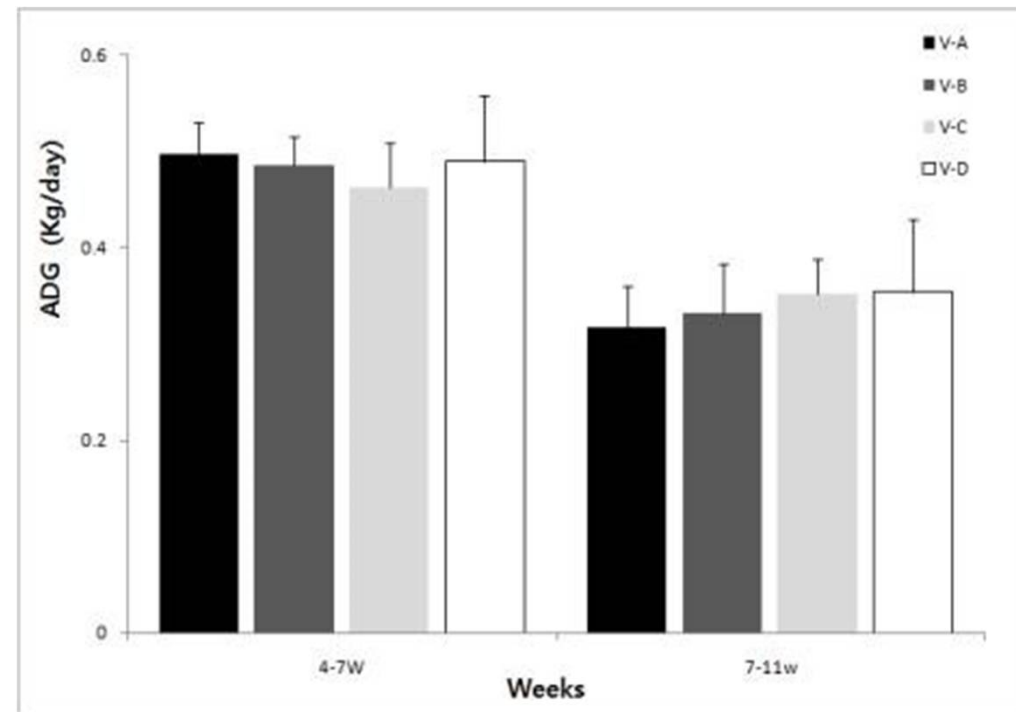
Vaccinated groups

Respiratory Clinical Sign

# NSI + Bacillus on PRRS



Non-vaccinated groups

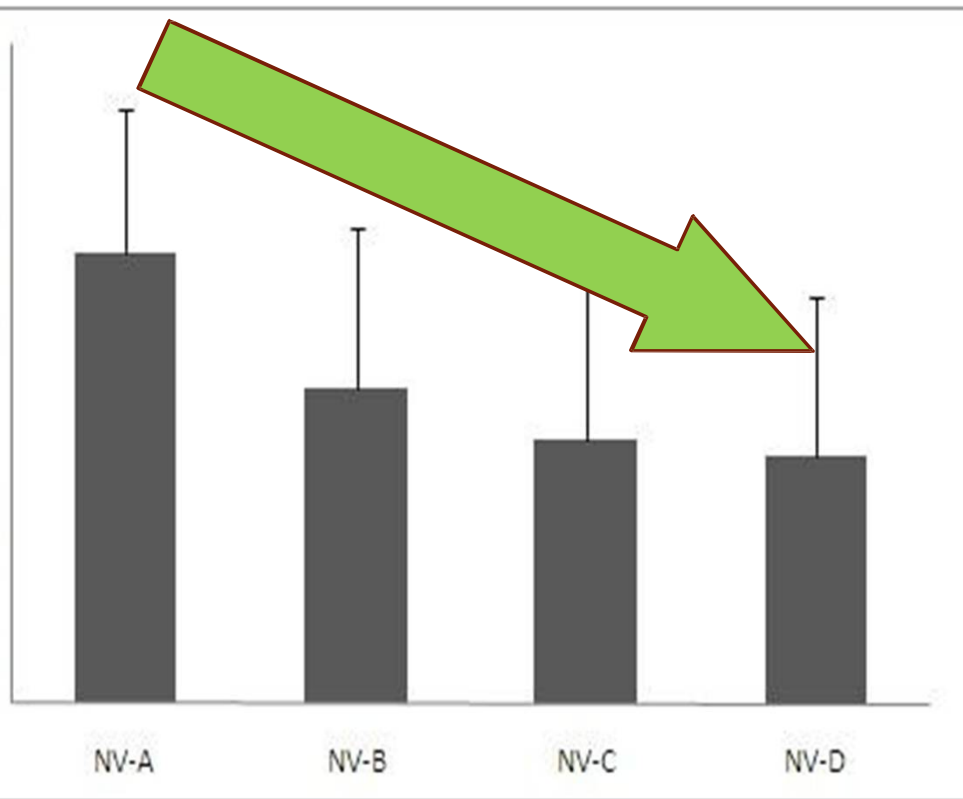


Vaccinated groups

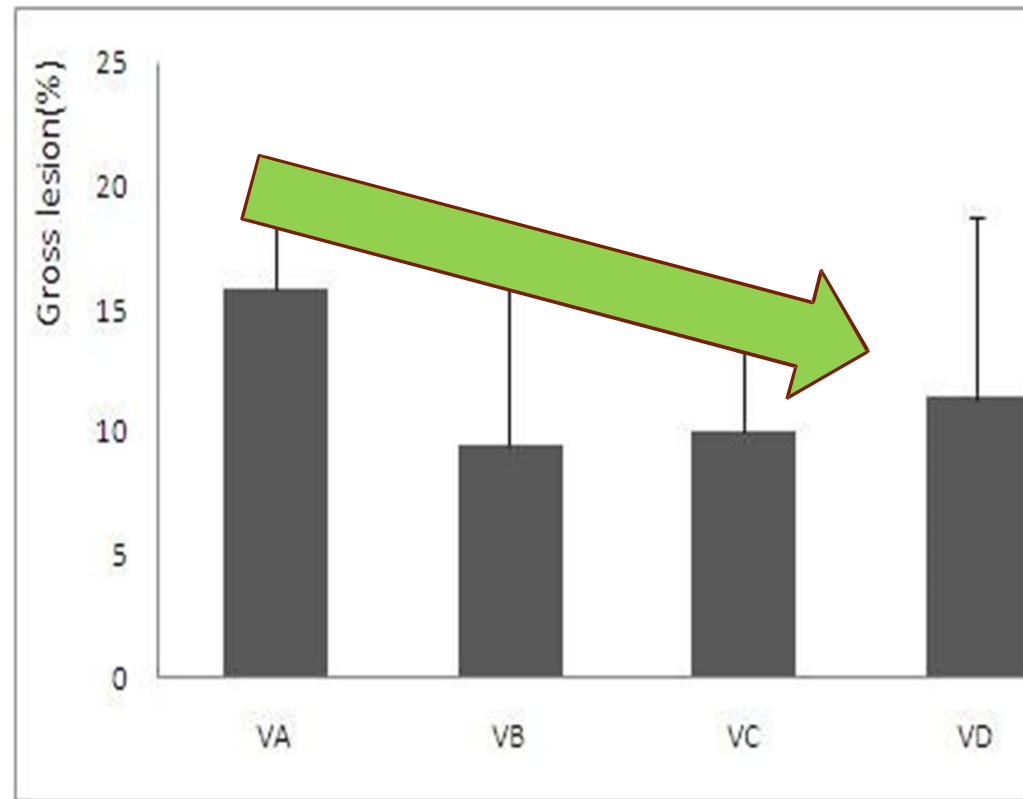
## Growth Performance



# NSI + Bacillus on PRRS



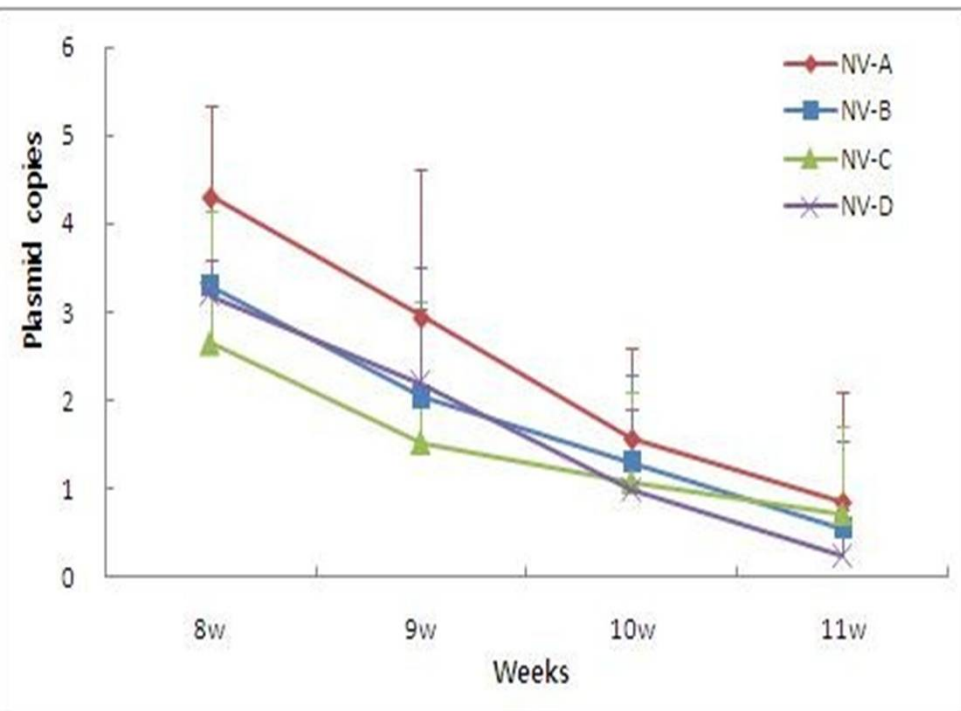
Non-vaccinated groups



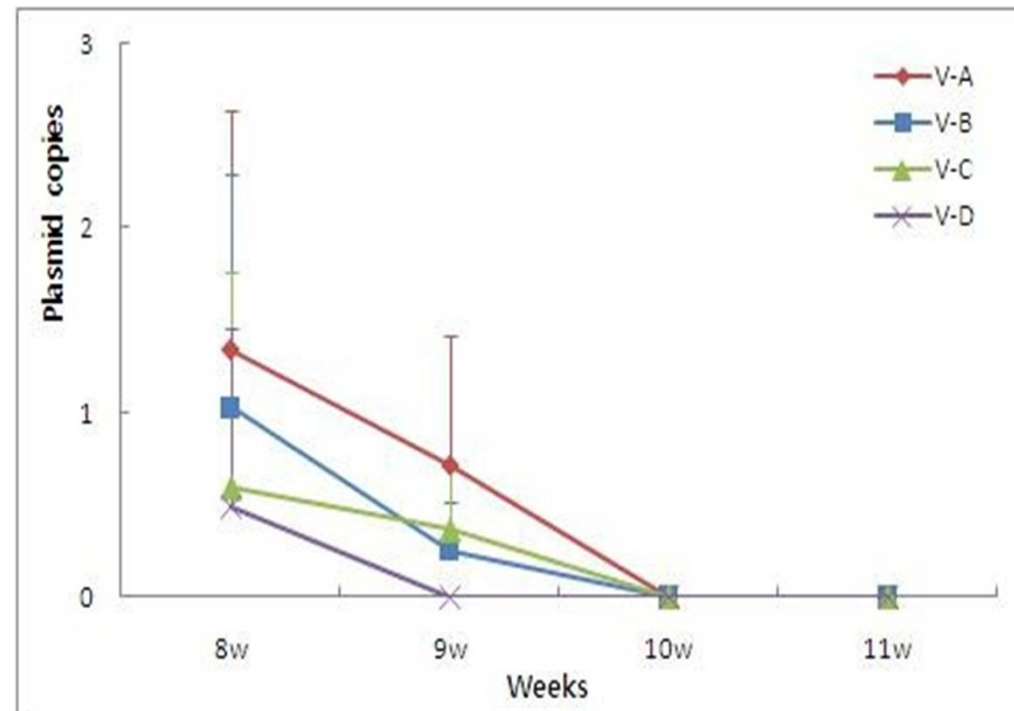
Vaccinated groups

Lung Lesion

# NSI + Bacillus on PRRS



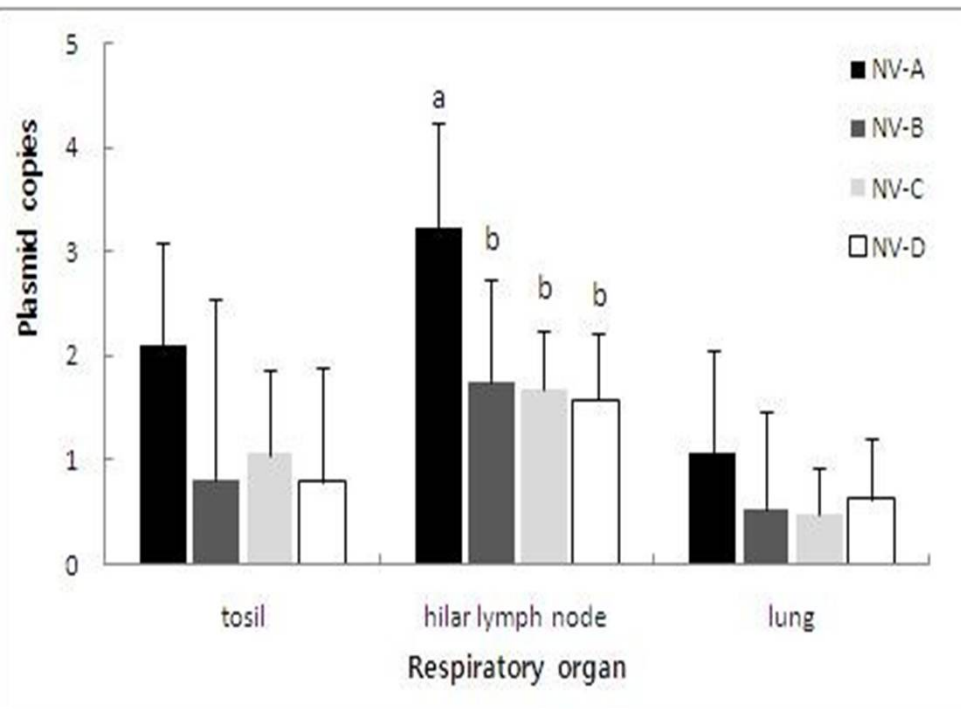
Non-vaccinated groups



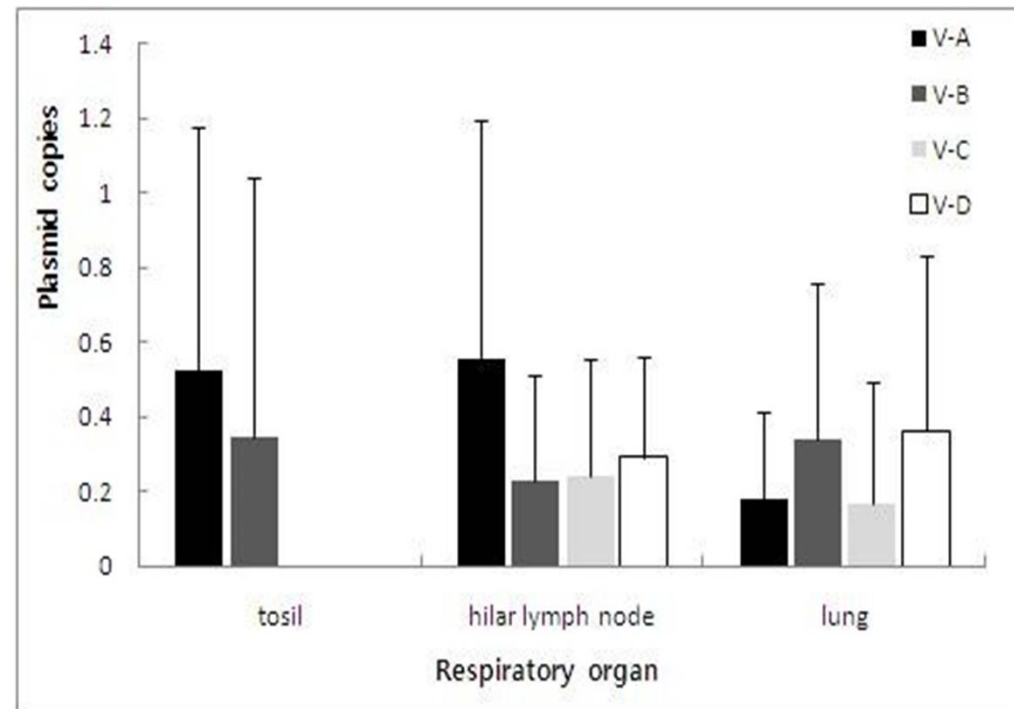
Vaccinated groups

PRRSV detection at nasal cavity

# NSI + Bacillus on PRRS



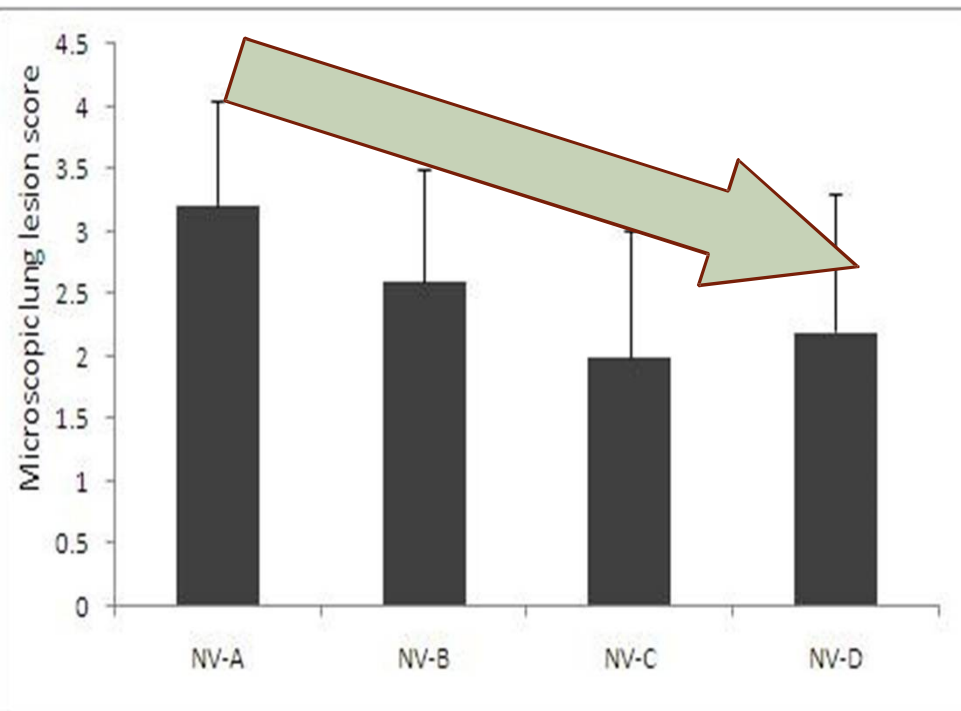
Non-vaccinated groups



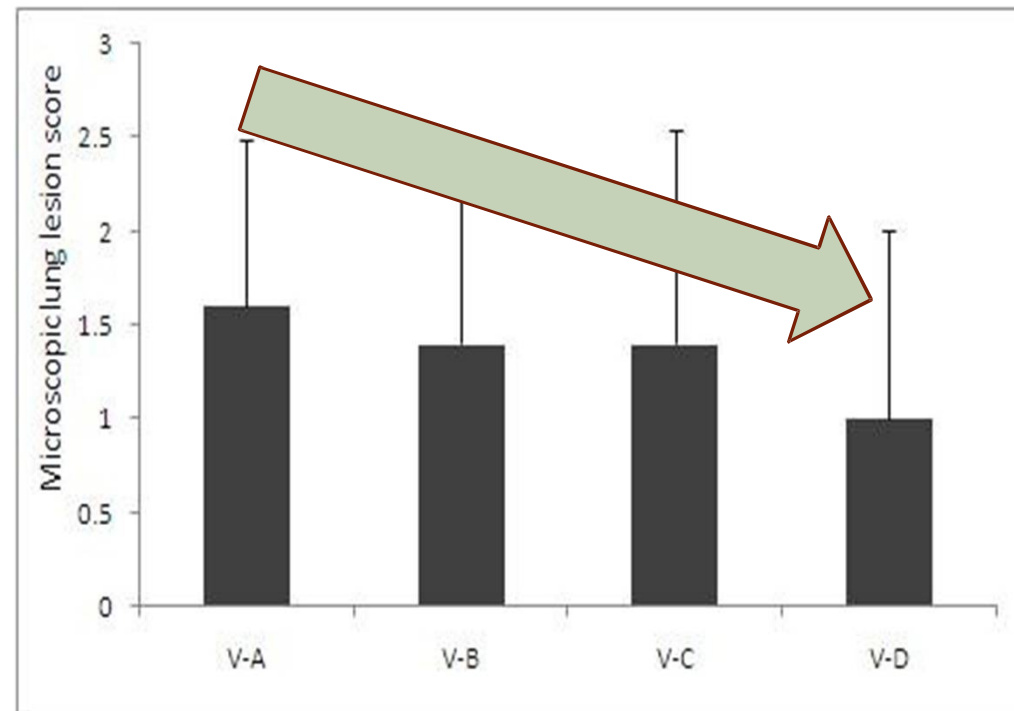
Vaccinated groups

## PRRSV detection at tissue

# NSI + Bacillus on PRRS



Non-vaccinated groups



Vaccinated groups

Histopathological finding

# NSI + Bacillus on APP

## Bacterial Disease - Prophylactic effect of APP (*Actinobacillus pleuropneumoniae*) of Swine

- Objective : To investigate the effect of Acemmune on prophylaxis of APP that is the popular swine pneumonia which has high mortality
- Animal : 4 weeks old piglets vaccinated and non-vaccinated
- Investigator : Dr. JH Han (Pathologist at Kangwon National University)
- Findings :
  - Non-vaccinated : Less lung lesion of pneumonia (17.3%, 18.4%) compared to non-Acemmune group (22.3%)
  - Vaccinated : Less lung lesion of pneumonia (11.8%, 11.4%) compared to non-Acemmune group (15.2%)

# Paper Summaries Conclusion

## Immune Enhancing Effect

The anionic alkali mineral complex solution increased the level of CD 4+, CD 8+ and MHC-C II+ lymphocytes in blood of pig.

## Non-Specific Immuno-stimulation (NSI)

The SiO<sub>2</sub> (Silica or Silicon dioxide) as an immune stimulant increased immune response of both non vaccinated and vaccinated pigs.

The immune systems is well primed and already has an operational cell mediated can quickly repulse and eliminate threatening foreign body helping pigs recover faster.

Being NSI, the immunity stimulation is not specific to any bacterial and viral infection.

## Digestion performance

The Bacillus and as an alkaline solution aids in better enzymatic digestion thereby better ADG and overall performance.

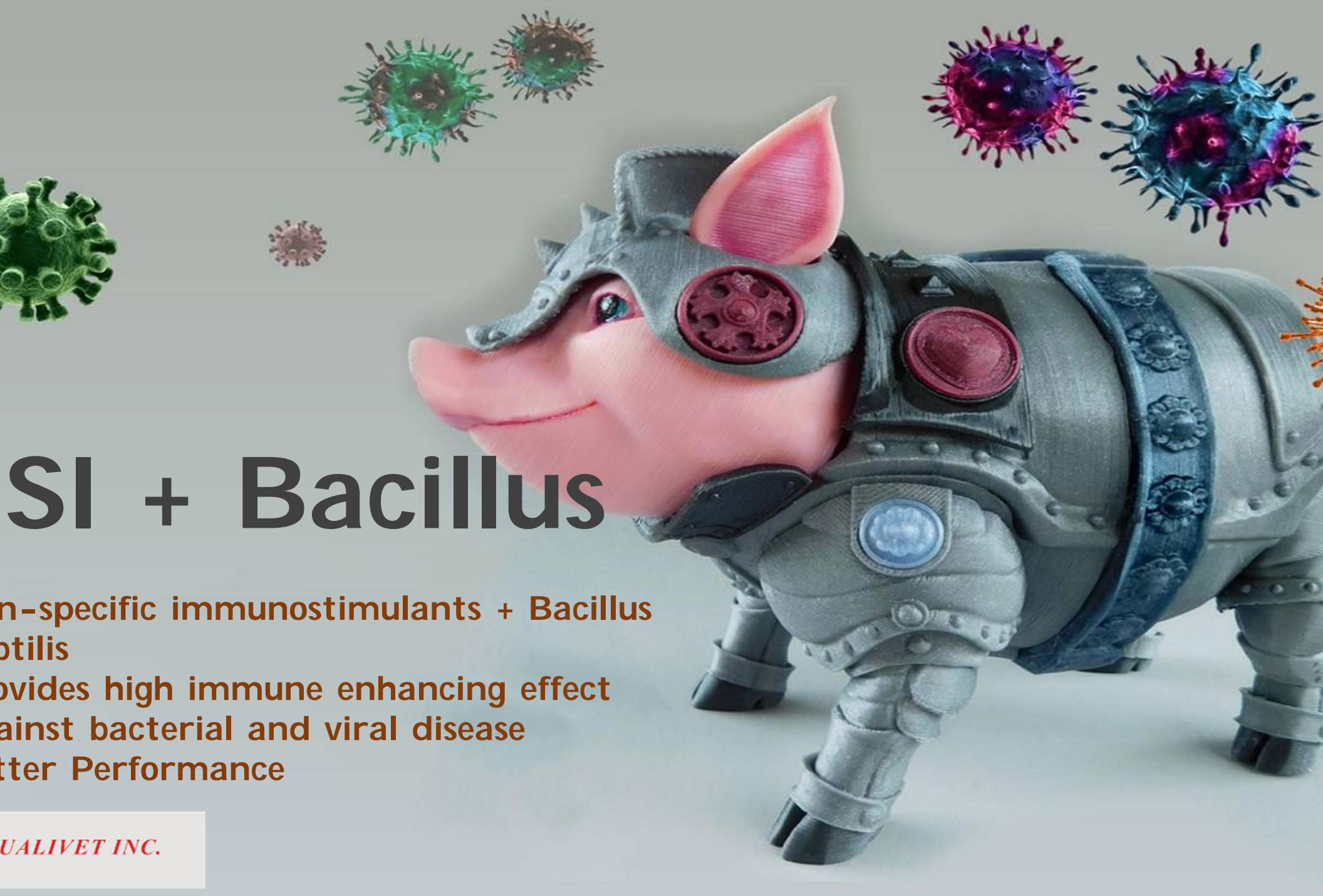
## Disease control spread of infection

Trial shows there is faster reduction of viral detection on specific organs.

# SI + Bacillus

n-specific immunostimulants + Bacillus  
otilis  
Provides high immune enhancing effect  
against bacterial and viral disease  
Better Performance

UALIVET INC.





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Effects of Dietary Supplementation of Barodon, an Anionic Alkali Mineral Complex, on Growth Performance, Feed Utilization, Innate Immunity, Goblet Cell and Digestibility in Olive Flounder (*Paralichthys olivaceus*) [Chang-Hoon Shin](#),<sup>1</sup> [Ji-Hoon](#)  
[Samad Rahimnejad](#),<sup>2</sup> [Joon-Bum Jeong](#),<sup>3</sup> [Byung-Woo Yoo](#),<sup>4</sup> [Bo-Kyeun Lee](#),<sup>4</sup> [Hyung-Jin Ahn](#),<sup>4</sup> [Soo-Il Choi](#),<sup>5</sup> [Yun-Jeong](#)  
[Yong-Ho Park](#),<sup>6</sup> [Jeong-Dae Kim](#),<sup>1</sup> and [Kyeong-Jun Lee](#)<sup>2,7,\*</sup>

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