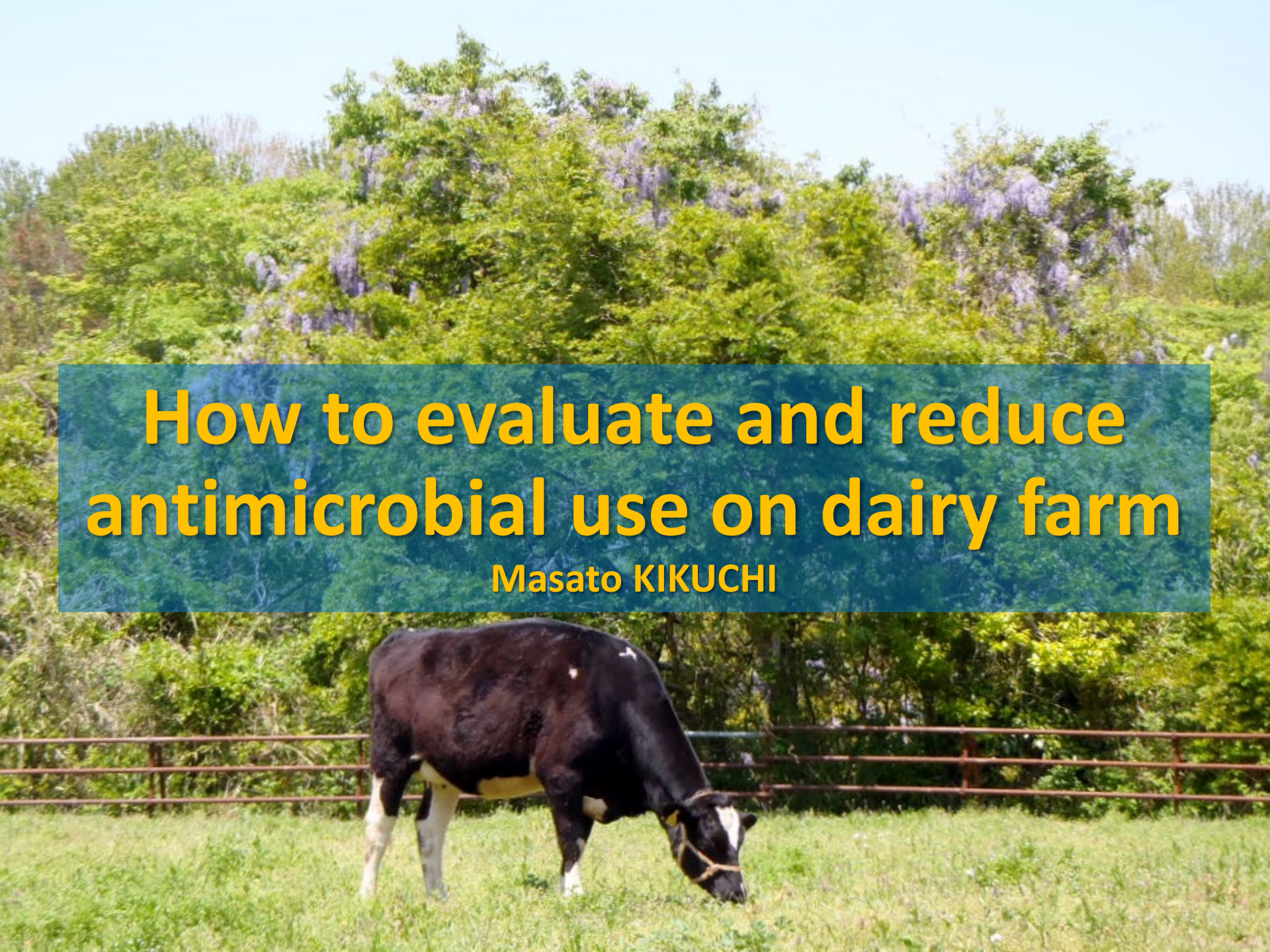


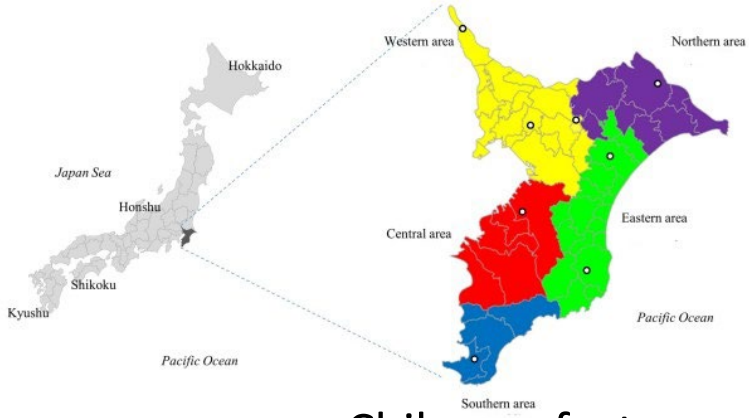
How to evaluate and reduce antimicrobial use on dairy farm

Masato KIKUCHI

Chiba Prefectural Agricultural Mutual Aid Association (NOSAI Chiba), Chiba, Japan

- **NOSAI** is a nationwide agricultural insurance scheme supported by the Japanese government.
- NOSAI provides contracted farmers (of dairy and beef cattle, horse and breeding pigs) with life **insurance** for dead and culled animals as well as **veterinary service** (medical treatment, reproductive management, nutritional management, etc…)

安心のネットワーク NOSAI



Chiba prefecture

≠ Livestock hygiene Service Centre

Investigation of AMU and AMR in NOSAI Chiba

- From 2017, NOSAI Chiba started investigation of the antimicrobial use (AMU) and antimicrobial resistance (AMR) on dairy farms in Chiba following the National action plan established by the government of Japan.

- Conducted research study in collaboration with the University of Tokyo

Today's topic

1. How to evaluate AMU

   "Active ingredient weight-based"

   vs "Dosage-based

2. How to reduce AMU on dairy farm

How to evaluate AMU

1. Active ingredient weight-based（mg）

- ESVAC routinely report the amount of antimicrobials sold for use in food-producing animals as mg of active ingredient, adjusted by animal biomass (population correction unit: PCU)

※ **PCU** ：a theoretical unit of measurement developed by EMA.

Estimated average weight at treatment (e.g. Dairy cow:425kg)

multiplied by animal population over a year

$$\frac{\text{Weight of active ingredient of antimicrobial agent / year / spiecies}}{\text{Estimated average weight} \times \text{total number of animals kept (PCU)}}$$

- Japan, U.S., Canada and other countries use this method

(In Japan, Average weight of dairy cow is set to **635kg** based on livestock improvement association of Japan)

How to evaluate AMU

Disadvantage of active ingredient weight-based method

- Dose of agents are not taken into account
- The use of antimicrobials that are effective in small dose is underestimated

e.g. mastitis treatment with different antimicrobials

Active ingredient weight of product in a treatment

- Ampicillin (injection product)
  5,000mg/cow/day
- Penicillin (injection product)
  6,000,000 IU (3,600mg)/cow/day
- Penicillin (intramammary product)
  300,000 IU (180mg)/teat/day
  (combined with streptomycin)

It is not appropriate to treat these weights equally.

How to evaluate AMU

2. Dosage-based (DDD-based)

・In Denmark, the Netherlands and some other European countries and Canada, dosage-based indicators are used to monitor antimicrobial usage at the farm level

・**Defined Daily Dose (DDD)**

"The assumed average maintenance dose per day for a drug used for its main indication in adults." (WHO)

・**DDD for animals（mg/kg/day）** has been set in many countries.

・DDD for animals were also established in Japan by the University of Tokyo（**DDDjp**） （Fujimoto *et al.* 2021）

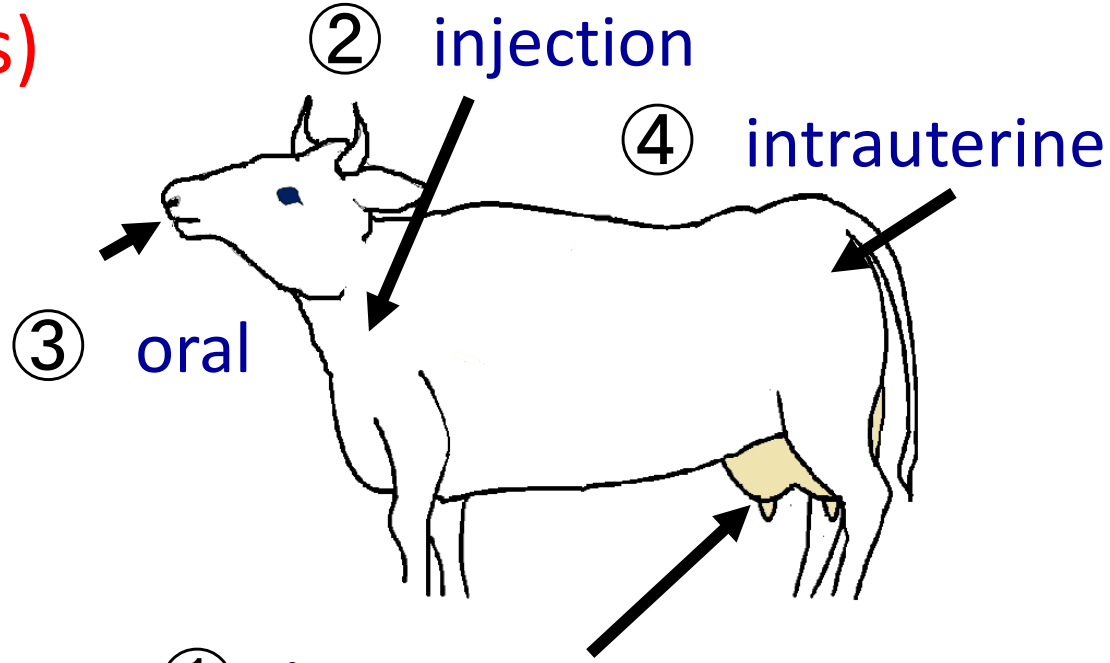
e.g. DDDjp for Cefazolin (injection product): 5 mg/kg/day

DDDjp for Cefazolin (intramammary product): 0.39 mg/kg/day

Class and administration route of antimicrobial agents with DDDjp

9 classes (24 agents)

- Cephalosporins
- Penicillins
- Aminoglycosides
- Tetracyclines
- Macrolides
- Amphenicol
- Sulfonamides
- Trimetoprim
- Quinolones



2. Dosage-based method (ATI)

Usage of antimicrobial agent α (number of DDDs α) in a farm

$$= \frac{\text{Weight of active ingredient of antimicrobial agent } \alpha \text{ in a year (mg)}}{\text{DDDjp value of antimicrobial agent } \alpha}$$

Antimicrobial treatment incidence (ATI) agent α (ATIα) in a farm

$$= \frac{\text{Number of DDDs } \alpha(\text{kg} \cdot \text{day}) \times 1000(\text{animals})}{\text{Average number of cows on the farm (animals)} \times 635(\text{kg}) \times 365(\text{days})}$$

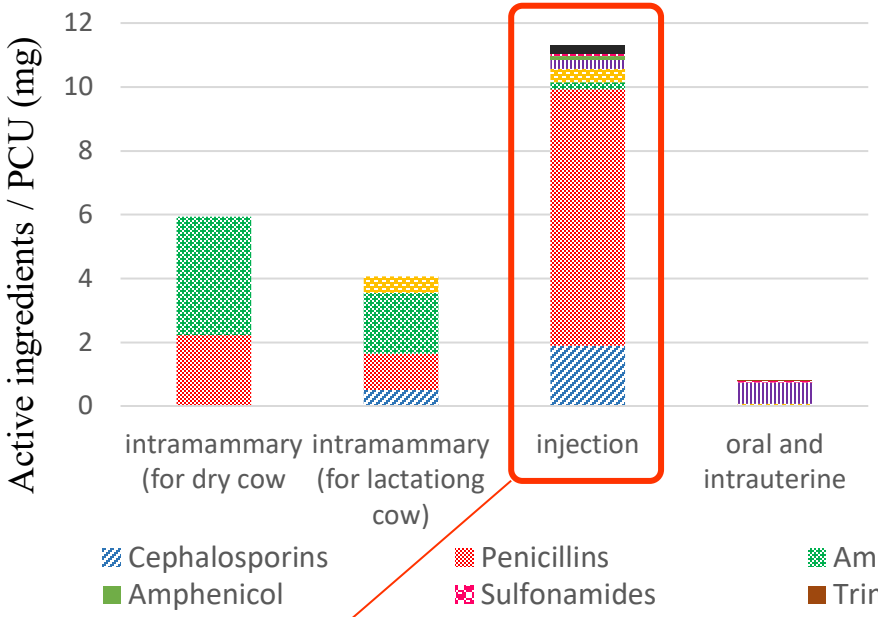
Overall antimicrobial usage of a farm

$$\text{ATI} = \sum_{\alpha=1}^{n} \text{ATI } \alpha$$

Comparison of two methods

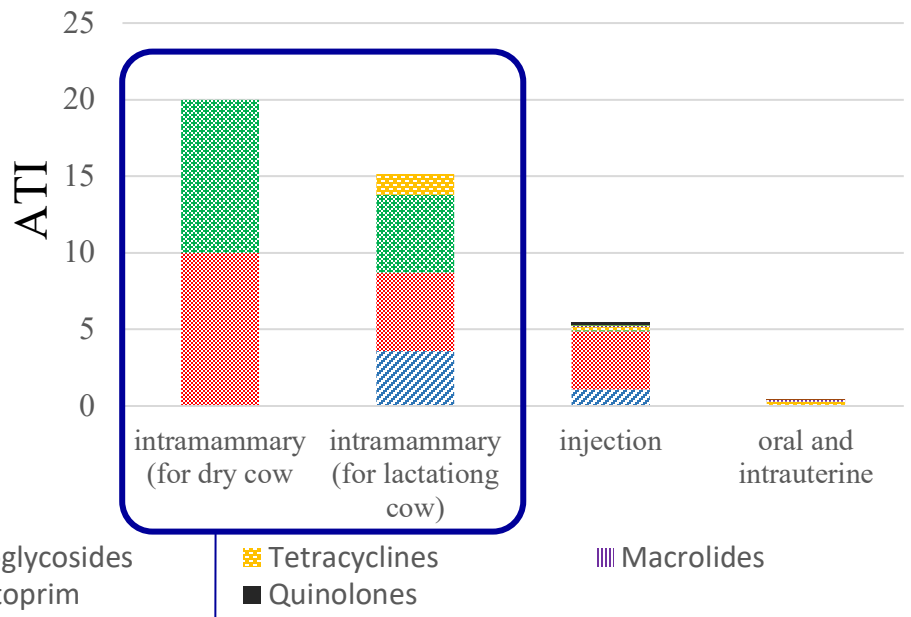
(Average of antimicrobial usage on 442 dairy farms in Chiba, 2017)

1. Active ingredient weight-based（mg/PCU）



Ampicillin (injection) was most used

2. Dosage-based（ATI）



The usage of intramammary products is estimated much higher

Dosage-based method represents the opportunity for one animal to receive antimicrobial treatment in a certain period of time (1,000days)

➔ Actual degree of exposure of bacteria to antimicrobials

The Journal of Veterinary Medical Science

FULL PAPER

Epidemiology

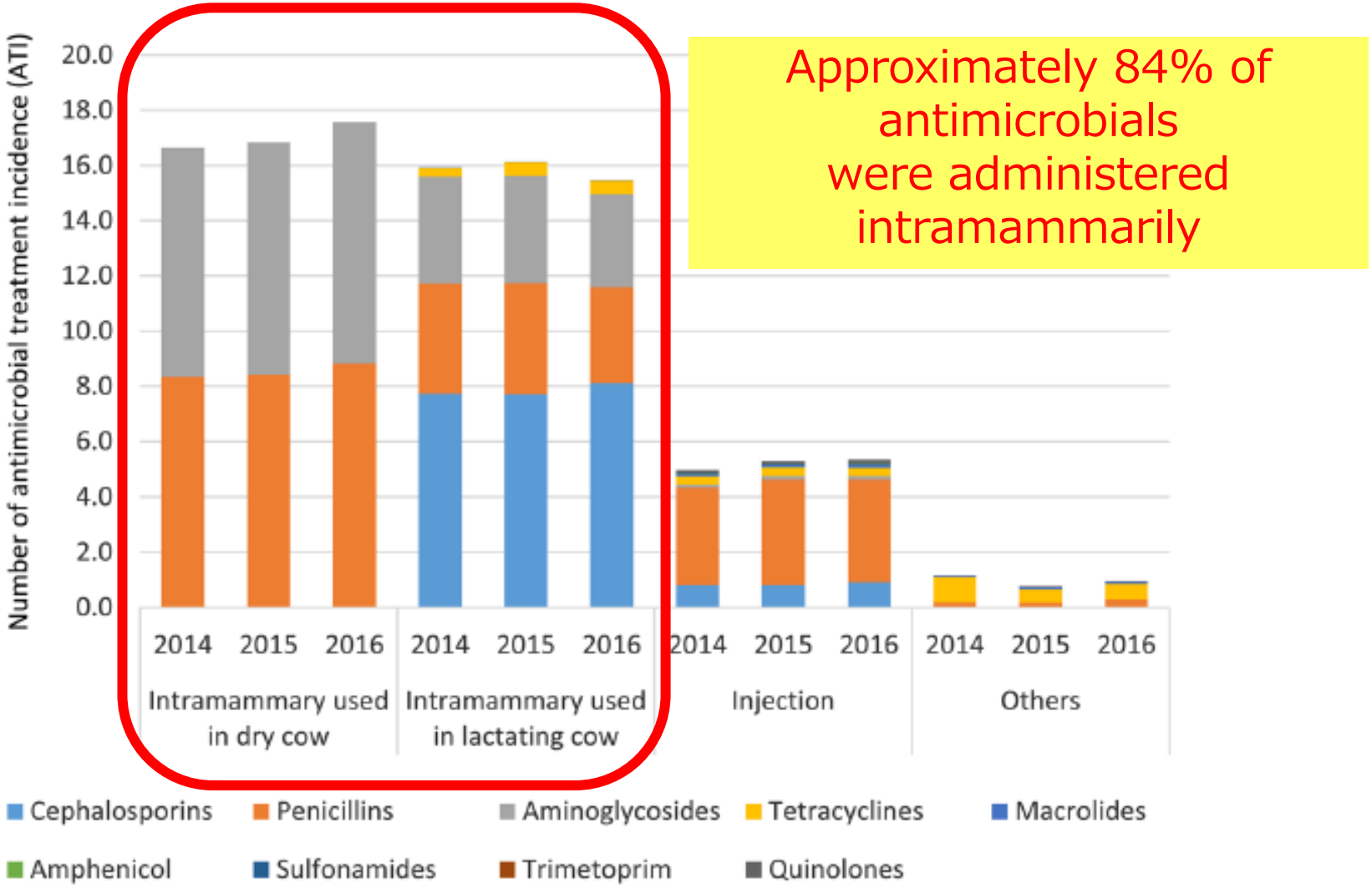
Evaluating the antimicrobial use on dairy farms in Chiba Prefecture in Japan using the antimicrobial treatment incidence, an indicator based on Japanese defined daily doses from 2014–2016

Masato KIKUCHI[1,2], Takuma OKABE[1], Hideshige SHIMIZU[1], Takashi MATSUI[1], Fuko MATSUDA[2], Takeshi HAGA[2], Kyoko FUJIMOTO[3], Yuko ENDO[3], Katsuaki SUGIURA[3,4]*

- Data were collected from 442 dairy farms in Chiba (2014～2016)
- ATI（antimicrobial treatment incidence）was used as dosage-based indicator for AMU

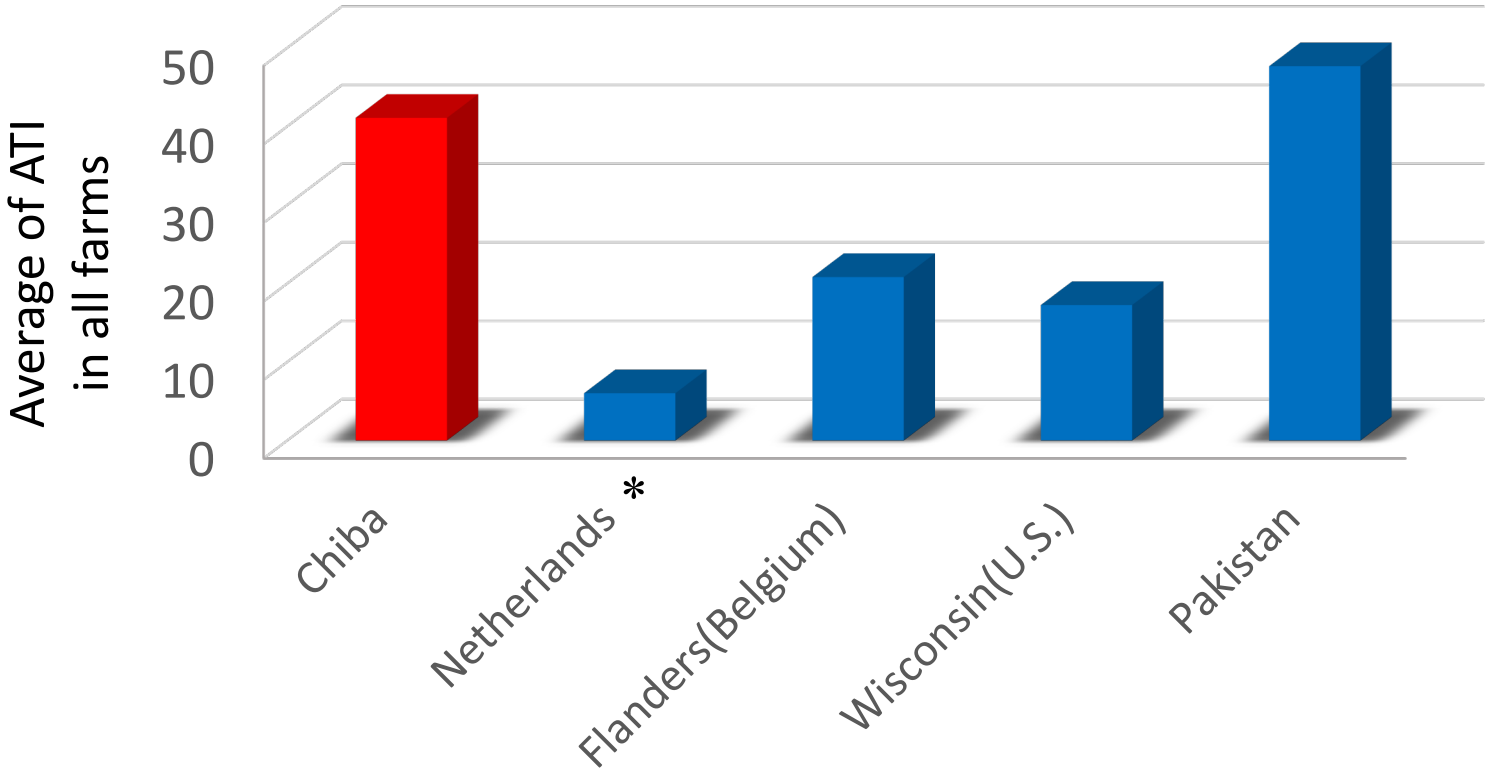
Average antimicrobial use (ATI) on dairy farms in Chiba

ATI



Approximately 84% of antimicrobials were administered intramammarily

Comparison with ATI in other countries



*: dosage-based indicator DDDAF was converted to ATI

(Sda (2018) ; Stevens et al. (2016); de Campos et al.(2021); Umair et al. (2020))

Dry cow terapy (DCT)

Blanket dry cow therapy（BDCT）

- a prophylactic method for drying-off cows by administering intramammary antimicrobials to all cows kept on the farm

- EU countries banned BDCT from beginning of 2022 as a part of strategy against AMR

- Commonly practiced in Japan, contributing to the increased use of antimicrobials on dairy farms.

Heliyon 8 (2022) e12381

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

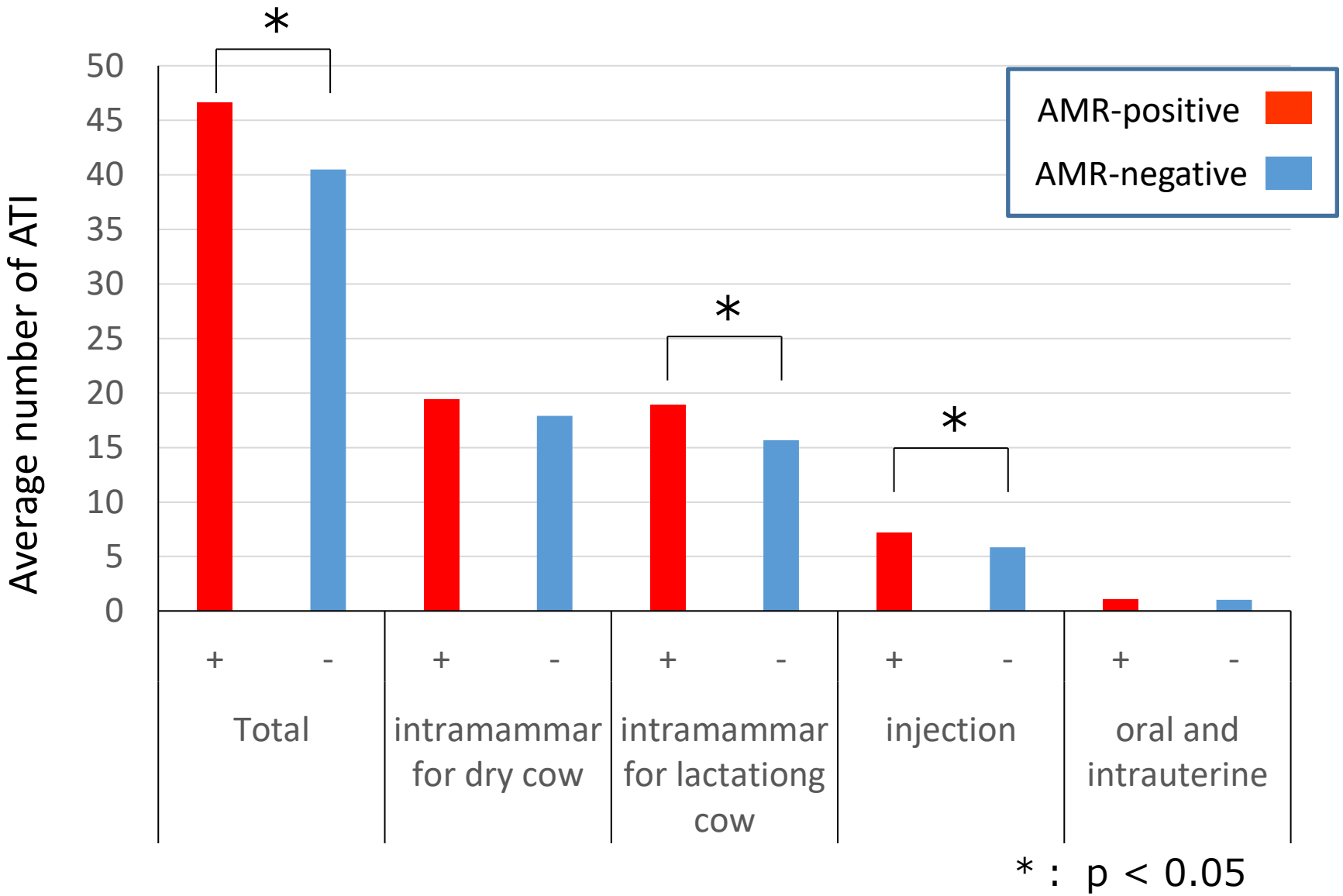
Research article

Antimicrobial use and its association with the presence of methicillin-resistant staphylococci (MRS) and extended-spectrum beta-lactamases (ESBL)-producing coliforms in mastitic milk on dairy farms in the Chiba Prefecture, Japan

Masato Kikuchi [a,b], Takuma Okabe [a], Hideshige Shimizu [a], Takashi Matsui [a], Fuko Matsuda [b], Takeshi Haga [b], Kyoko Fujimoto [c], Yuko Endo [c], Katsuaki Sugiura [c,d,*]

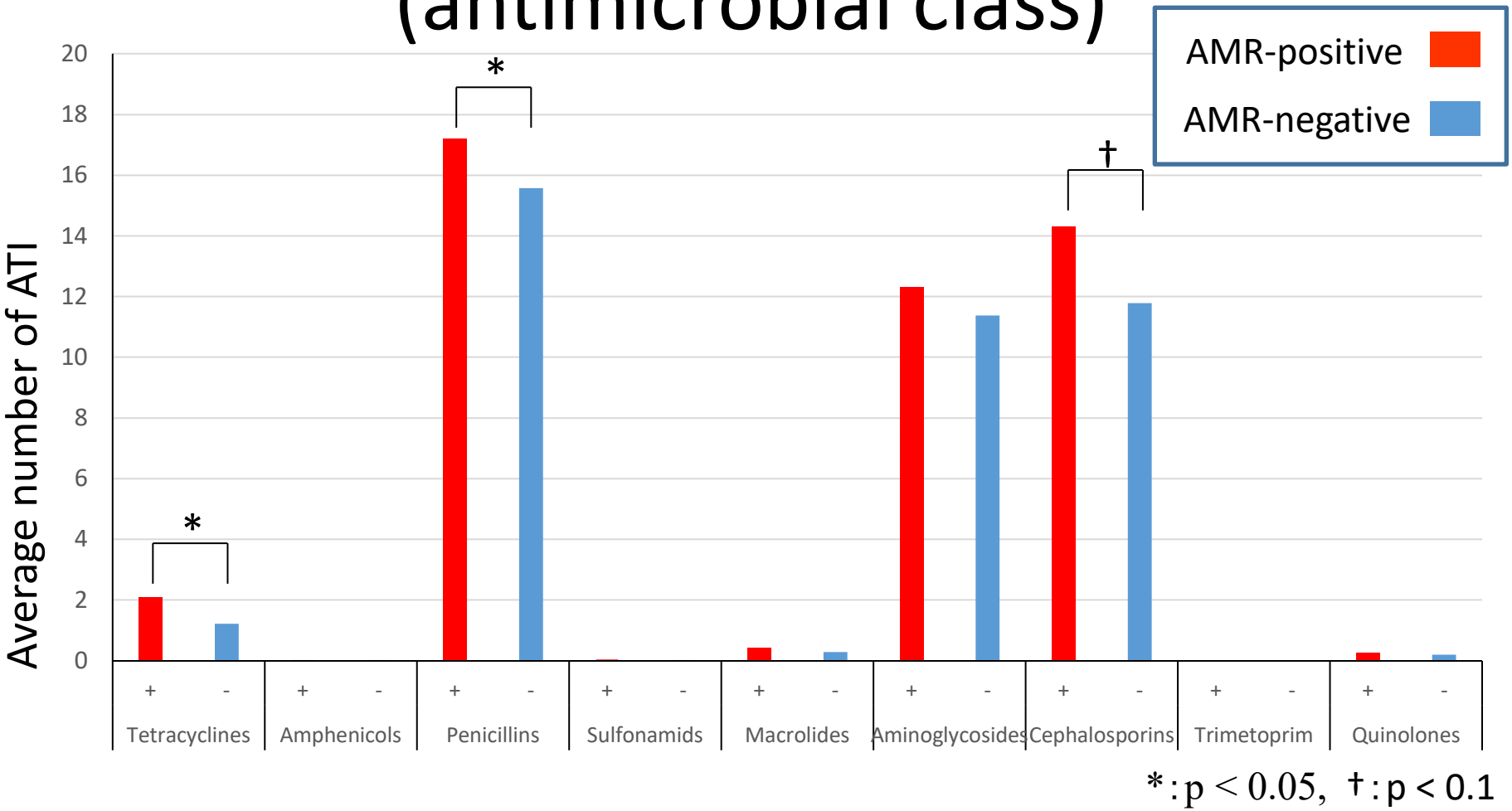
- Data were collected from 134 dairy farms in Chiba (2016)
- The farms in which **methicillin-resistant staphylococci (MRS)** or **extended-spectrum beta-lactamases (ESBL)-producing coliforms** were isolated from at least one mastitic milk sample in a year were classified as AMR-positive (n = 47), and those in which neither MRS nor ESBL-producing coliforms were isolated were classified as AMR-negative farm (n = 87).
- Antimicrobial use (ATI) was investigated in the two groups.

Comparison of ATI between groups (administration route)



* : $p < 0.05$

Comparison of ATI between groups (antimicrobial class)



*: $p < 0.05$, †: $p < 0.1$

ATI of Penicillins, Tetracyclines were significantly high,
ATI of Cephalosporins was high in AMR (+) farms.

Summary

- Dosage-based evaluation of AMU revealed intramammary antimicrobial products, in particular intramammary products for dry cow therapy account for a large proportion of the total AMU in dairy cattle in Chiba Pref.

- The results indicate that high usage of some antimicrobial agents is associated with AMR in staphylococci and coliforms isolated from mastitic milk on dairy farms in Chiba Pref.

→ How to reduce antimicrobial use?

How to reduce AMU in dairy farm

1. Selective dry cow therapy (SDCT)

2. Control of clinical mastitis by mastitis vaccine

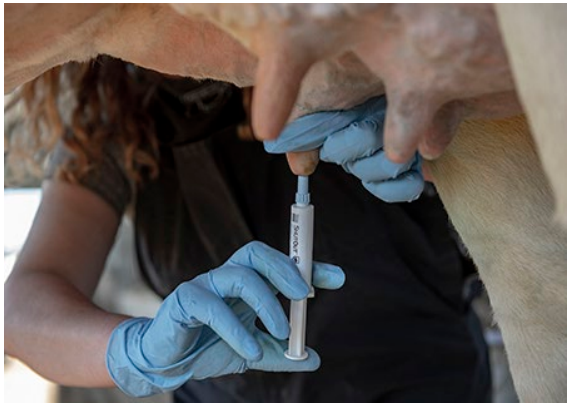
1. Selective dry cow therapy (SDCT)

A method of injecting antibacterial agents for only in udder with mastitis or at high risk (high SCC)

Switch from BDCT to SDCT can significantly reduce the amount of antimicrobial use

Precautions

- hygiene management of dry cow
- Using internal teat sealant at drying off is recommended (Not approved in Japan)

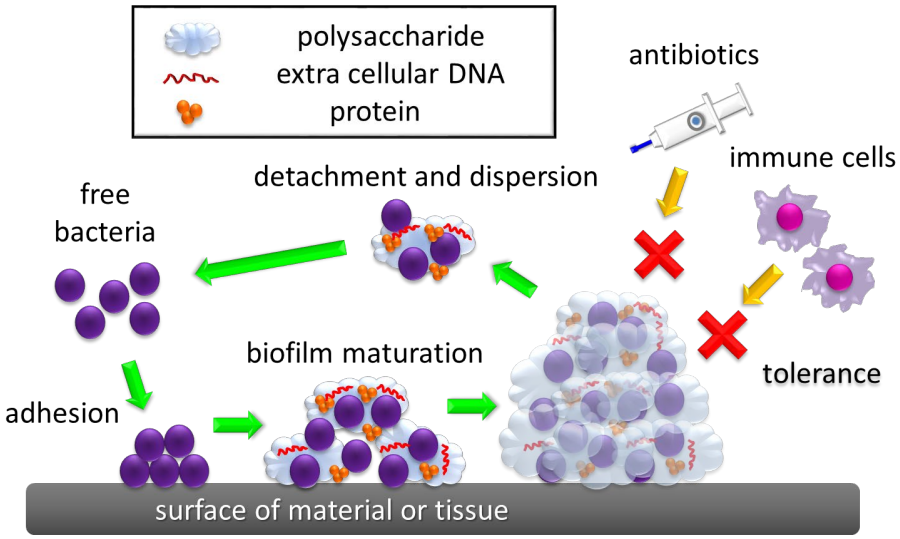


Internal teat sealant
（Merck animal health HP）

2. Control of clinical mastitis by mastitis vaccine

Mastitis pathogens

Streptococcus uberis
Staphylococcus aureus
Escherichia coli
Klebsiella spp.
Enterococcus spp.
Pseudomonas aeruginosa
etc…



Biofilm formation and tolerance
（schematic diagram）

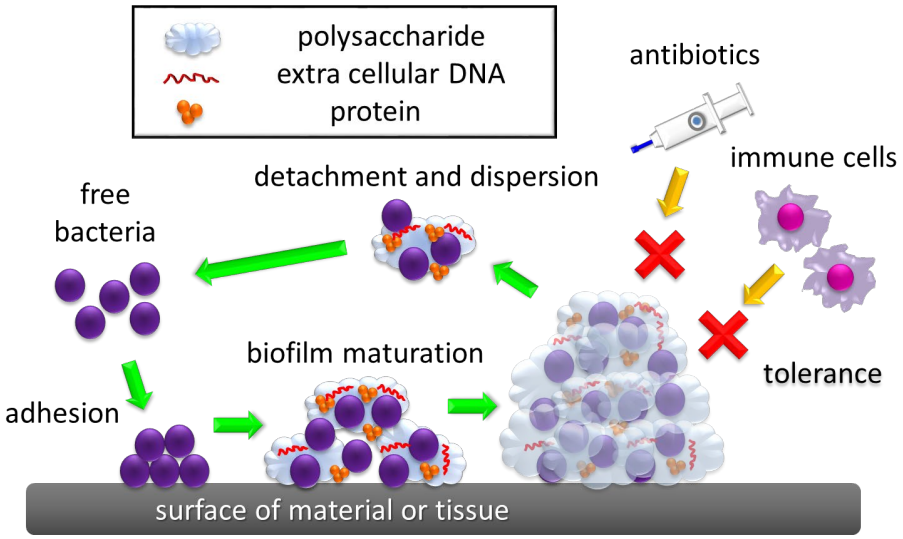
- Biofilm formation thought to be a possible cause of chronic or recurrent mastitis


Severe coliform mastitis

2. Control of clinical mastitis by mastitis vaccine

Mastitis pathogens

Streptococcus uberis
Staphylococcus aureus
Esherichia coli
Klebsiella spp.
Enterococcus spp.
Pseudomonas aeruginosa
etc…



Biofilm formation and tolerance
（schematic diagram）

- Biofilm formation thought to be a possible cause of chronic or recurrent mastitis
- Chronic mastitis and severe mastitis are difficult to treat
- **Prevention** is better than treatment

2. Control of clinical mastitis by mastitis vaccine

- **“5-point plan” for mastitis management**

  i) identify and treat clinical cases
  ii) post milking teat disinfection
  iii) Dry cow therapy
  iv) cull chronic cases
  v) routine maintenance of milking machine

- **Vaccination**

(Cheng and Han 2020)

2. Control of clinical mastitis by mastitis vaccine

Mastitis vaccine

vaccine against *E.coli, Klebsiella spp.*, *Staphylococcus aureus*, coagulase-negative staphylococci and *Streptococcus uberis* are on sale

- **STARTVAC®** is an only mastitis vaccine approved in Japan(from 2016)

  vaccine against *Staphylococcus aureus*, coliforms and coagulase-negative staphylococci

Vaccination schedule:

45 days and 10 days before the expected date of delivery , and 52 days after the expected date of delivery , a total of 3 doses.

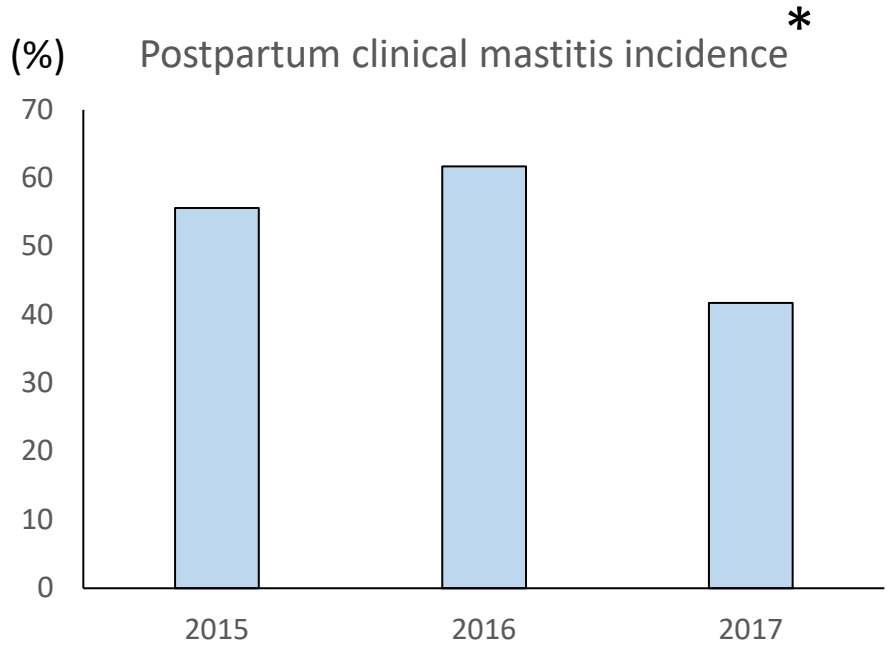
STARTVAC® (Kyoritsu HP)

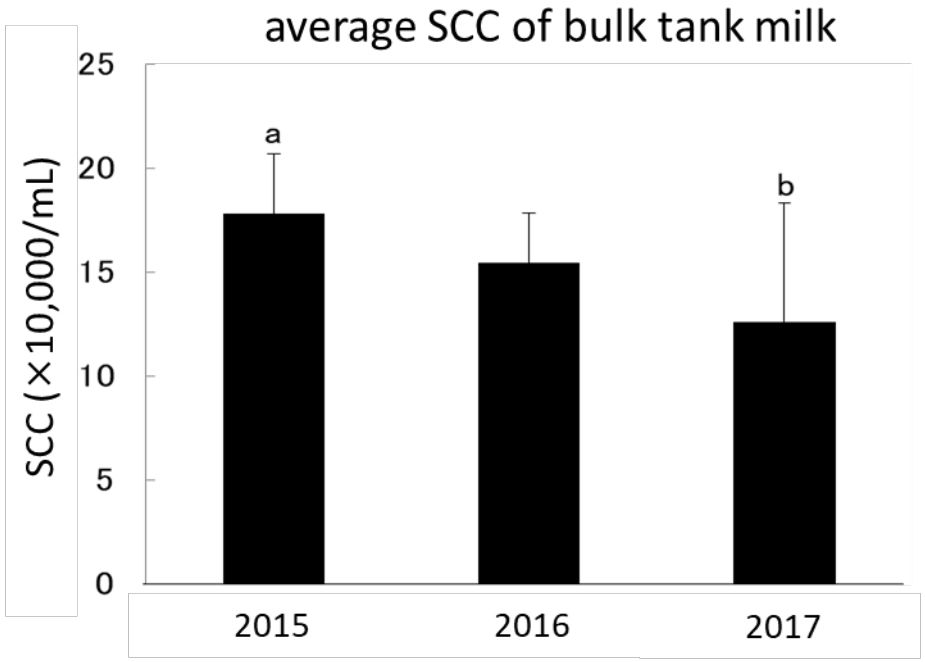
Vaccination and antimicrobial use (Case of a dairy farm in Chiba)

- A dairy farm (with 65 dairy cows) with high incidence of **coliforms** and ***S.aureus*** mastitis started using STARTVAC from early 2017
- Incidence of postpartum (up to 60days after delivery) clinical mastitis, bulk tank somatic cell count (SCC) (2015-2017) and AMU (2014-2018) were investigated
- **ATI**（antimicrobial treatment incidence） was used as dosage-based indicator for AMU

(Unpublished data)

Vaccination and antimicrobial use (Case of a dairy farm in Chiba)





*: number of affected animals / calving animals

a-b: $p<0.05$

- Decrease in postpartum clinical mastitis and subclinical mastitis in 2017 were suggested

(Unpublished data)

Vaccination and antimicrobial use (Case of a dairy farm in Chiba)

Start using STARTVAC®

Antimicrobial use (ATI)	2014	2015	2016	2017	2018
Total	81.1	87.7	77.3	54.0	35.6
Administration route		AMU decreased			
Injection	9.6	10.1	11.0	6.3	2.5
Intramammary	69.6	77.3	64.4	47.1	32.9
Oral	0.0	0.1	1.6	0.5	0.0
Intrauterine	1.9	0.3	0.3	0.0	0.0

(Unpublished data)

Vaccination and antimicrobial use (Case of a dairy farm in Chiba)

- Vaccination was effective in reducing clinical mastitis and AMU in this farm
- Efficacy of vaccination on mastitis control depends on various factors (main causative pathogens, hygiene level, nutrition status, etc..)
- We will continue to promote mastitis vaccine with other mastitis control procedure
- AMU monitoring by dosage-base method is useful in evaluating effectiveness of mastitis control

The number of dairy cow kept in large scale farms (with 100 or more adult dairy cows) in japan is on the rise

423,000 cows (2008) → 601,000 cows (2020)

（MAFF　livestock statistics）

Reducing AMU through disease control is more important than ever


Thank you for your attention