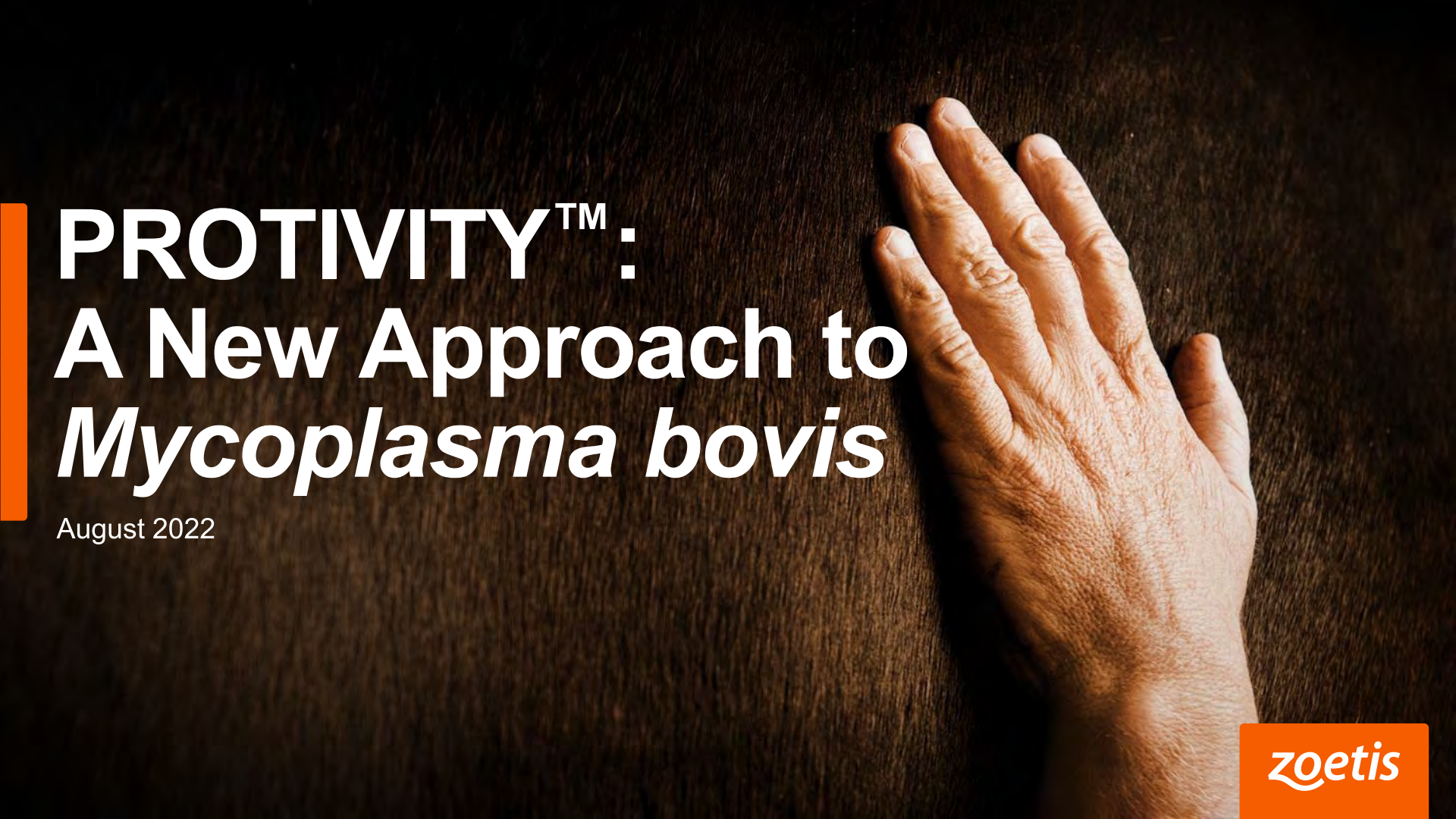

PROTIVITY™: A New Approach to *Mycoplasma bovis*

August 2022

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Agenda

01 Basics of *Mycoplasma bovis* and Its Role in BRD

02 How is PROTIVITY™ Different

03 Efficacy and Safety of PROTIVITY™

04 Adding PROTIVITY™ to Health Programs

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01.
Basics of *Mycoplasma bovis* and Its Role in BRD

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Understanding the Pathogen

What is *Mycoplasma bovis*

- *Mycoplasma bovis* (*M. bovis*) is a bacteria that can cause mastitis, arthritis and bovine respiratory disease (BRD).
- Respiratory disease caused by *M. bovis* targets beef and dairy calves and can be chronic, leading to irreversible lung damage, mortality, and high costs.[1]

How *M. bovis* Spreads

- *M. bovis* enters the upper respiratory tract, where the pathogen can reside without showing clinical disease.
- Stress from weaning, transportation and commingling can trigger disease from *M. bovis.*
- Disease associated with *M. bovis* in young calves usually presents as pneumonia, otitis media, arthritis, or any combination.[1]
  - The age of onset is typically between 2 and 6 weeks, but has been reported as early as 4 days of age.

[1] Maunsell FP, Woolums AR, et al. Mycoplasma bovis Infections in Cattle. *J Vet Intern Med*. 2011;25:772–783.

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Challenges of *Mycoplasma bovis*

Cell Structure Presents Issues

- *Mycoplasma* bacteria are characterized by their small size and the lack of a cell wall.
- Due to the lack of a rigid cell wall, mycoplasmas are pleomorphic (assume many forms) and not classified as either rods or cocci, nor Gram-negative or Gram-positive.
- Lack of cell wall also affects which antibiotics are selected for treatment of disease caused by *M. bovis,* because antibiotics that act on the cell wall like penicillin or ceftiofurs will not be effective against mycoplasma.
- *M. bovis* can be the sole cause of BRD in calves, but the disease is more often multifactorial involving secondary infections with other bacteria or respiratory viruses.

Challenges in treating

- The unique ability of *M. bovis* to avoid the host's immune response and insidious nature of *M. bovis* leads to slow development of clinical signs which can delay disease detection.
- Late detection of *M. bovis* infections with delayed treatment, can lead to poor treatment response. Therefore, prolonged antibiotic therapy of weeks duration can be necessary to treat *M. bovis* infections..
- Despite the availability of commercial vaccines, respiratory disease caused by *M. bovis* continues to be a problem.[1]

[1] Maunsell FP, Woolums AR, et al. Mycoplasma bovis Infections in Cattle. *J Vet Intern Med*. 2011;25:772–783.

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02. How is PROTIVITY™ Different

What is PROTIVITY™?

First Modified-Live Vaccine for *Mycoplasma bovis*

- PROTIVITY consists of two parts:
  - A freeze-dried (lyophilized) modified live preparation containing a particular avirulent (not disease-causing) strain of *M. bovis.*
  - A sterile diluent used to rehydrate the freeze-dried fraction when ready to inject cattle.
- The avirulent live culture of *M. bovis* used in PROTIVITY makes the product different from other *M. bovis* vaccines available, all of which are killed vaccines.

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Key Benefits of PROTIVITY™

First Modified Live Vaccine for *Mycoplasma bovis*

Early Administration

- PROTIVITY has the youngest administration age of any commercial *M. bovis* vaccine on the market with a label indication of one week of age.[1]
- The young administration age allows flexibility in the timing and convenience of vaccination while providing calves protection from *M. bovis* pneumonia at a younger age.

Two-Dose Regimen

- PROTIVITY requires two 2-mL doses, with 21 days between doses
- There is flexibility in when PROTIVITY can be added to an on-arrival program or calf vaccination program.

Demonstrated Efficacy

- In a challenge study, PROTIVITY vaccination generated 74% ($p < 0.0001$) reduction of total lung lesions (mean percentage), relative to controls.[2,*]
- The study demonstrated an onset of immunity as soon as 11 days after administration of the second dose.[2]

* (mean percentage of total lung lesion) Mitigated fraction estimate for median percentage of total lung with lesion for treatment group T02 was 0.66 (95% CL: 0.37, 0.90).

[1] Based on approved labels of Protivity™, Mycoplaz®, Myco-B One Dose™, Myco-Bac® B and MpB Guard.

[2] Data on file. Study Report No. B832R-US-17-665, Zoetis Inc.

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03. Efficacy and Safety of PROTIVITY™

The PROTIVITY™ Advantage

Benefits of modified-live vaccines

- A strong, long-lasting immune response that is achieved with fewer doses.
- No need for adjuvants
  - Less chance for allergic reactions
- Replication of a modified live mycoplasma vaccine provides stimulation of cell mediated immunity which is critical with *M. bovis* because of its ability to cause intracellular infection.
- Challenge study evidence validating the ability to help prevent irreversible lung damage, distinguishes PROTIVITY from unproven killed autogenous vaccines.[1]

[1] Data on file. Study Report No. B832R-US-17-665, Zoetis Inc.

Born of the Bond

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The PROTIVITY™ Advantage

Adding PROTIVITY to Vaccine Programs

- When used with vaccines for other respiratory viruses and bacteria, PROTIVITY offers a proactive approach to a widespread problem (*M. bovis*).
  - It provides another tool for more comprehensive BRD prevention and innovative BRD management.
- PROTIVITY can be used with ceftiofur antibiotics like Excede® (*ceftiofur crystalline free acid*) Sterile Suspension / Excenel® RTU EZ (*ceftiofur hydrochloride*) Sterile Suspension / Naxcel® (*ceftiofur sodium*) Sterile Powder if antimicrobial therapy is needed during the immune-response phase after vaccination.
  - Ceftiofur antibiotics have the benefit of proven efficacy against other BRD bacterial pathogens, but will not affect the replication of PROTIVITY mycoplasma microbes.[1]

Born of the Bond

[1] Rosenbusch RF, Kinyon JM, Apley M, Funk ND, Smith S, Hoffman LJ. In Vitro Antimicrobial Inhibition Profiles of *Mycoplasma Bovis* Isolates Recovered from Various Regions of the United States from 2002 to 2003. *J of Vet. Diagnostic Investigation*. 2005;17(5):436-441.

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Field Studies for Safety

- Two field studies evaluated the safety of PROTIVITY™ in young calves reared under commercial production conditions
- Another study evaluated nasal shedding and/or spread of vaccine microbes following vaccination of young calves with PROTIVITY.
- A final study evaluated young calves for the reversion to virulence of the modified-live *M. bovis* strain used in PROTIVITY.

Safety Study #1

Evaluation of injection site or adverse responses

01

Three locations

- The study had 1,069 young, healthy calves maintained under typical commercial production conditions at sites in California (n=357), Idaho (n=359), and Kansas (n=353)
- Two age groups represented
  - week-old (1-8 days of age);
  - month-old (25-43 days of age)

02.

Two treatment groups

- Calves in the respective treatment groups were vaccinated on study days 0 and 21:
  - Control, unvaccinated (n=355)
  - Protivity, 2 mL SC (n=714).
- Day-0 injections were given in the left neck region, and day-21 in the right neck.

03.

Results

- Total of 310 abnormal health events were observed during the study, with the incidence, types, and proportions of the events distributed similarly among controls and vaccinates.
- This 8-week, multi-site field study demonstrated the safety of Protivity™ in young calves.

Data on file, Study Report No. B931R-US-18-745, Zoetis Inc.

One out of 714 (0.14%) vaccinated calves developed arthritis. The vaccine strain was isolated from the affected joint. Causation was not determined due to ceftiofur antibiotic treatment prior to culture of the joint.

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Safety Study #2

Evaluate long-term safety impacts

01
Study set-up

- Evaluate longer-term safety impacts of vaccination with Protivity when administered to week-old, conventionally raised calves maintained under typical commercial production conditions over a 4-month period.
- 148 healthy Holstein or Holstein-cross neonatal calves

02.
Treatment groups

- Calves in the respective treatment groups were vaccinated on study days 0 and 21:
  - Control (inert diluent), 2 mL SC (n=51);
  - Protivity, 2 mL SC (n=97)
- Day-0 injections were administered in the left neck region, and day-21 in the right neck.

03.
Results

- No abnormal events of unexpected type or frequency were detected during 4 months of post-vaccination clinical observation.
- All abnormal health events noted in vaccinated animals resolved and were unrelated to the product.

Data on file, Study Report No. B930R-US-19-770, Zoetis Inc.

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Shedding Study

Evaluate potential spread of *M. bovis*

01
Study set-up

- A study was designed to confirm the absence of nasal shedding and/or spread of vaccine *M. bovis* microbes following PROTIVITY vaccination of young calves.
- The study involved 16 healthy, Holstein neonatal calves

02.
Treatment groups

- Calves in the respective treatment groups were vaccinated on study day-0:
  - Control, not treated (n=8);
  - PROTIVITY, 2 mL SC (n=8)
- Mycoplasmal shedding and spread were the primary interests of the study.

03.
Results

- The study demonstrated the lack of *M. bovis* transmission by young PROTIVITY vaccinates, thus allowing confident use without concern of shedding or spread of vaccine microbes by vaccinated cattle.

Data on file, Study Report No. B933N-US-16-614, Zoetis Inc.

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Virulence Study

Evaluation strain reversion

01
Study set-up

- A study was designed to demonstrate that the *M. bovis* strain used in the PROTIVITY modified-live formulation does not revert to virulence after inhabiting cattle populations.
- The study comprised five 'passages' of the *M. bovis* strain found in PROTIVITY through separate groups of healthy, week-old Holstein calves.

02.
Handling of each passage

- Calves on day-0 were inoculated intranasally in one nostril with 2 mL of the *M. bovis* 'master seed' strain used in PROTIVITY, while 3 non-inoculated calves served as controls.
- Animals observed for adverse events within 4 hours post-inoculation, rectal temperatures and clinical observations were performed daily through study end.
- Nasopharyngeal samples were collected daily beginning at day-5.

03.
Results

- Assessment of reversion to virulence for each passage was based on *M. bovis* isolation data from nasopharyngeal secretions, and the severity of clinical signs of acute *M. bovis* disease
- No signs of clinical disease related to *M. bovis* were observed during 5 separate passages of the vaccine microbes, indicating PROTIVITY poses no threat of disease to vaccinated animals.

Data on file, Study Report No. B932N-US-13-254, Zoetis Inc.

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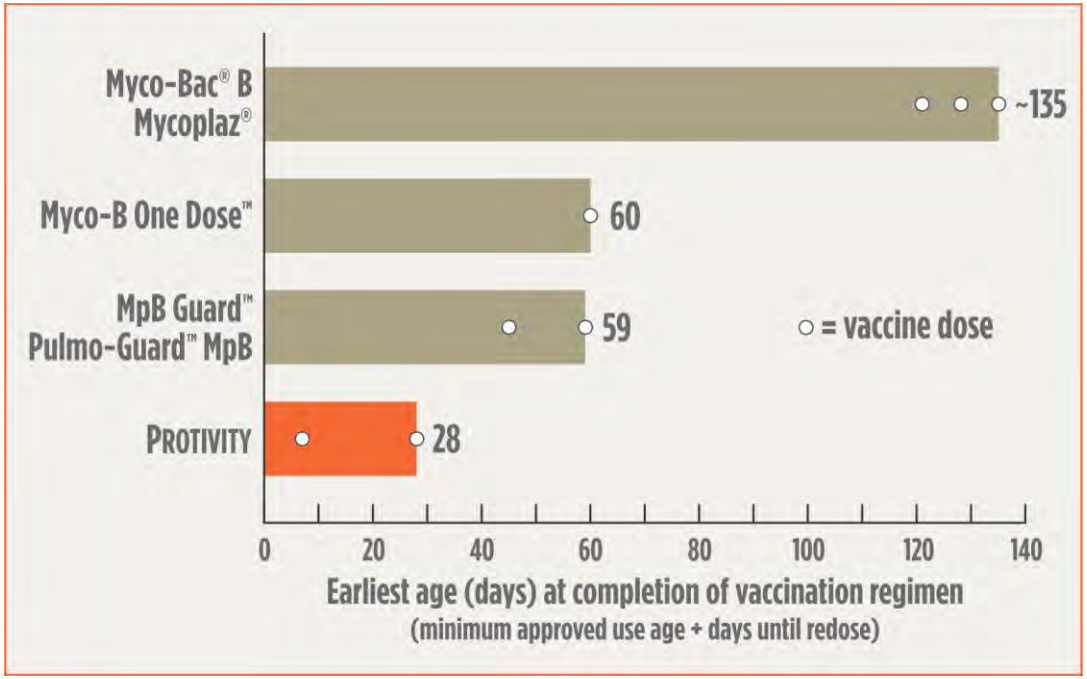
04.
Adding PROTIVITY™ to Health Programs

How does PROTIVITY™ compare?

Calves vaccinated with PROTIVITY can complete their vaccination regimens and receive *M. bovis* protection earlier in their lives than animals vaccinated with other products.

Administration and Timing of PROTIVITY vs competitive vaccines



Based on approved labels of Protivity™, Mycoplaz®, Myco-B One Dose®, Myco-Bac® B, Pulmo-Guard® MpB and MpB Guard.

PROTIVITY™: On arrival programs

Dairy Calf Arrival Programs

- Young administration age of one week allows for use when calves are vulnerable following transportation.
- Could use with Inforce 3® to cover the major virals of BRSV, IBR and PI_3, along with *Mycoplasma bovis*.
- If antibiotic treatment is needed, select one that is not effective against the *Mycoplasma* bacteria
  - Excede® (*ceftiofur crystalline free acid*) Sterile Suspension and Excenel® RTU EZ (*ceftiofur hydrochloride*) Sterile Suspension are solid options.

Stocker/Backgrounder/Feedlot

- *Mycoplasma bovis* takes advantage when calves are stressed at weaning or following transportation.
- Ideally, the first dose would be given before the animal is stressed, but can also be given on arrival, followed by a second dose 21 days later.
- If antibiotic treatment is needed, select one that is not effective against the *Mycoplasma* bacteria
  - Excede® is a good option.

Questions?

Visit Protivity.com to learn more

IMPORTANT SAFETY INFORMATION: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to Excede. Excede is contraindicated in animals with known allergy to ceftiofur or to the β-lactam group (penicillins and cephalosporins) of antimicrobials. Inadvertent intra-arterial injection is possible and fatal. Do not use in calves to be processed for veal. Pre-slaughter withdrawal time is 13 days following the last dose. See full Prescribing Information.

IMPORTANT SAFETY INFORMATION: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to Excenel RTU EZ. Do not use in animals found to be hypersensitive to the product. Do not slaughter cattle for 4 days following last treatment. Do not use in calves to be processed for veal. See full Prescribing Information.

IMPORTANT SAFETY INFORMATION: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to Naxcel. Naxcel has a pre-slaughter withdrawal time of four days. Do not use in animals found to be hypersensitive to the product. See full Prescribing Information.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