Overview of Ongoing Zoetis Antimicrobial Susceptibility Surveillance of Major Veterinary Pathogens in North America

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Zoetis 2019

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Zoetis Antimicrobial Susceptibility Surveillance Program History

Bovine & Swine Respiratory Pathogens

- Started in 1998
- 2018 – 21 laboratories/~2300 Isolates/yr

Bovine Mastitis Pathogens

- Started in 2001
- 2018 – 16 laboratories/~1100 Isolates/yr

Equine Pathogens

- Started in 2010
- 2018 - 21 laboratories/~800 Isolates/yr

Companion Animal Pathogens

- Started in 2011
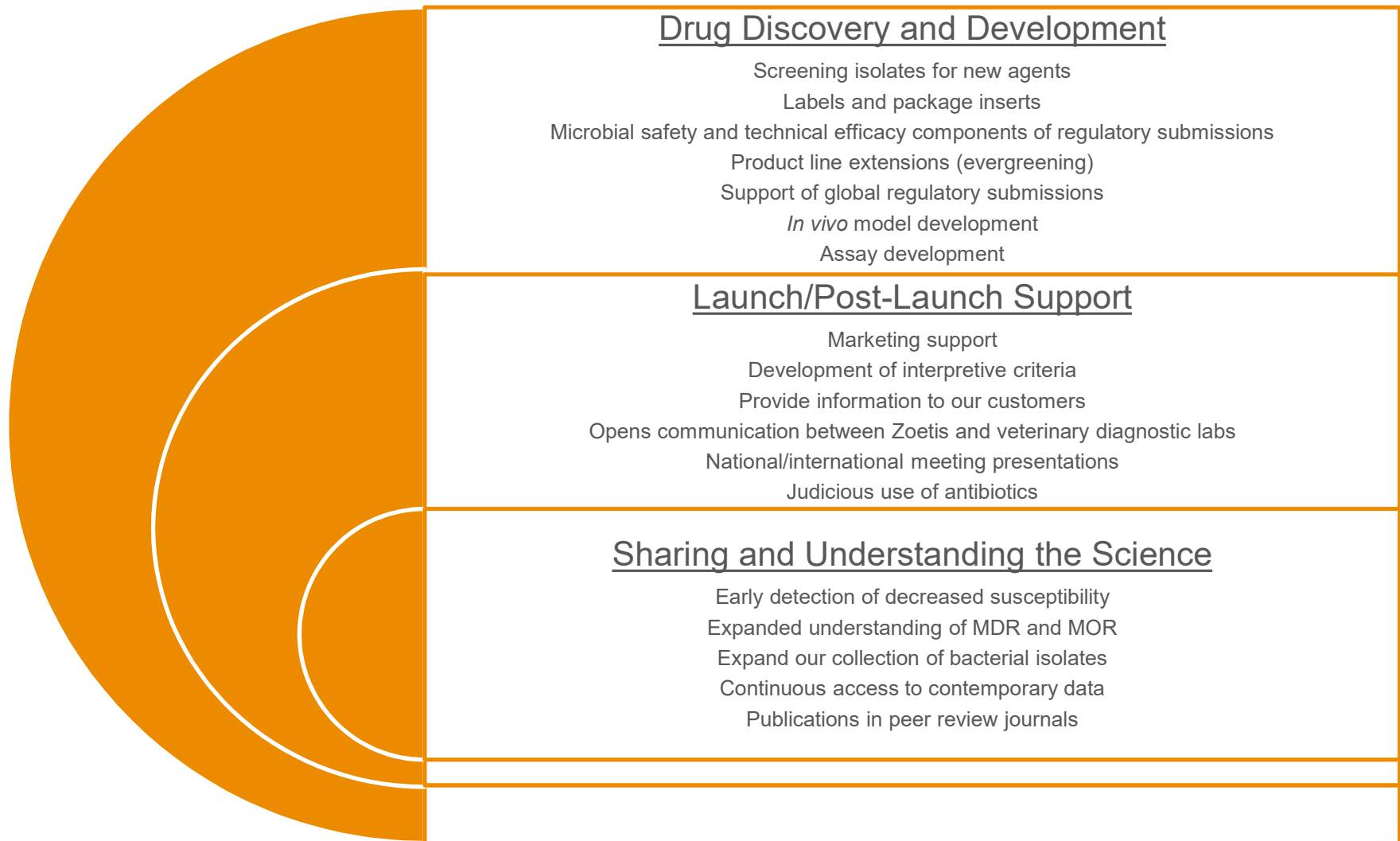- 2018 – 17 laboratories/~3100 Isolates/yr

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Why does Zoetis do surveillance?

✓ Zoetis is the pharmaceutical leader in veterinary antimicrobial agents

✓ The concern over bacterial resistance continues to increase in human and veterinary medicine

✓ As the leader in anti-infectives, Zoetis is committed to supporting responsible use

✓ Without a surveillance program, treatment decisions and understanding of antimicrobial resistance will continue to be based on anecdotal evidence rather than good scientific data

Overview of Zoetis Antimicrobial Susceptibility Surveillance Programs

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Goals of the Programs

✓ Collect bacterial pathogens from across the US and Canada that represent the population of animals in all regions

✓ Monitor the susceptibility to Zoetis antimicrobial agents and comparators

✓ Provide valuable information to veterinarians to help make decisions on rational antimicrobial use

✓ Expand our understanding of mechanisms of resistance and multidrug resistance

✓ Support responsible use

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Use of Zoetis Susceptibility Surveillance Data and Isolates

Drug Discovery and Development

Screening isolates for new agents

Labels and package inserts

Microbial safety and technical efficacy components of regulatory submissions

Product line extensions (evergreening)

Support of global regulatory submissions

In vivo model development

Assay development

Launch/Post-Launch Support

Marketing support

Development of interpretive criteria

Provide information to our customers

Opens communication between Zoetis and veterinary diagnostic labs

National/international meeting presentations

Judicious use of antibiotics

Sharing and Understanding the Science

Early detection of decreased susceptibility

Expanded understanding of MDR and MOR

Expand our collection of bacterial isolates

Continuous access to contemporary data

Publications in peer review journals

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Zoetis Surveillance Publications

A ten-year (2000–2009) study of antimicrobial susceptibility of bacteria that cause bovine respiratory disease complex —*Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni*—in the United States and Canada

Ellen Portis, Cynthia Lindeman, Lacie Johansen and Gillian Stoltman

J VET Diagn Invest 2012 24: 932
DOI: 10.1177/1040638712457559

Antimicrobial susceptibility of porcine *Pasteurella multocida,* *Streptococcus suis,* and *Actinobacillus pleuropneumoniae* from the United States and Canada, 2001 to 2010

Ellen Portis, BS; Cynthia Lindeman, BS; Lacie Johansen, BS; Gillian Stoltman, PhD, MPH

Journal of Swine Health and Production — January and February 2013

Antimicrobial susceptibility of *Actinobacillus pleuropneumoniae, Pasteurella multocida,* *Streptococcus suis,* and *Bordetella bronchiseptica* isolated from pigs in the United States and Canada, 2011 to 2015.
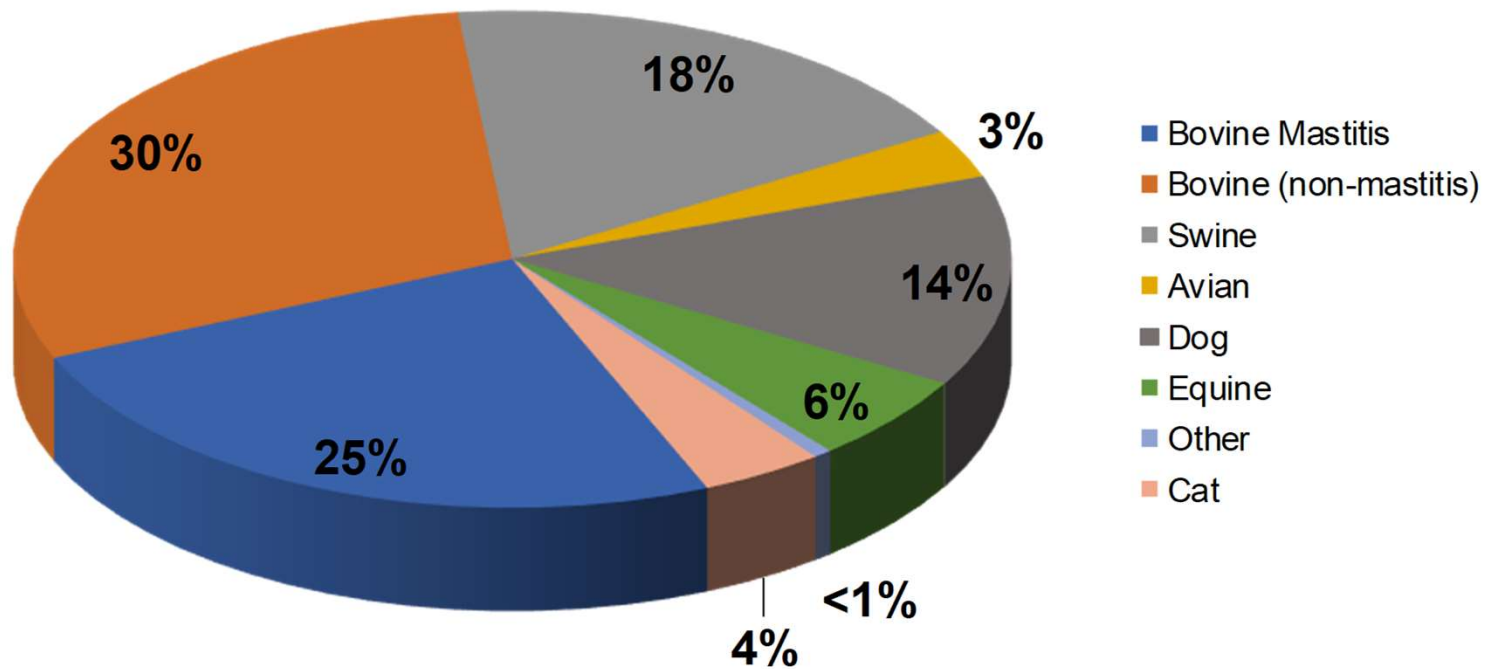
Michael T. Sweeney, et al.   **Journal of Swine Health and Production – May and June 2017**

Susceptibility to antimicrobial agents among bovine mastitis pathogens isolated from North American dairy cattle, 2002 –2010

Cynthia J. Lindeman, Ellen Portis, Lacie Johansen, Lisa M. Mullins and Gillian A. Stoltman

J VET Diagn Invest published online 1 August 2013
DOI: 10.1177/1040638713498085

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Culture Collection Database (>116,000 Isolates 1992-2018)

Legend:
- Bovine Mastitis
- Bovine (non-mastitis)
- Swine
- Avian
- Dog
- Equine
- Other
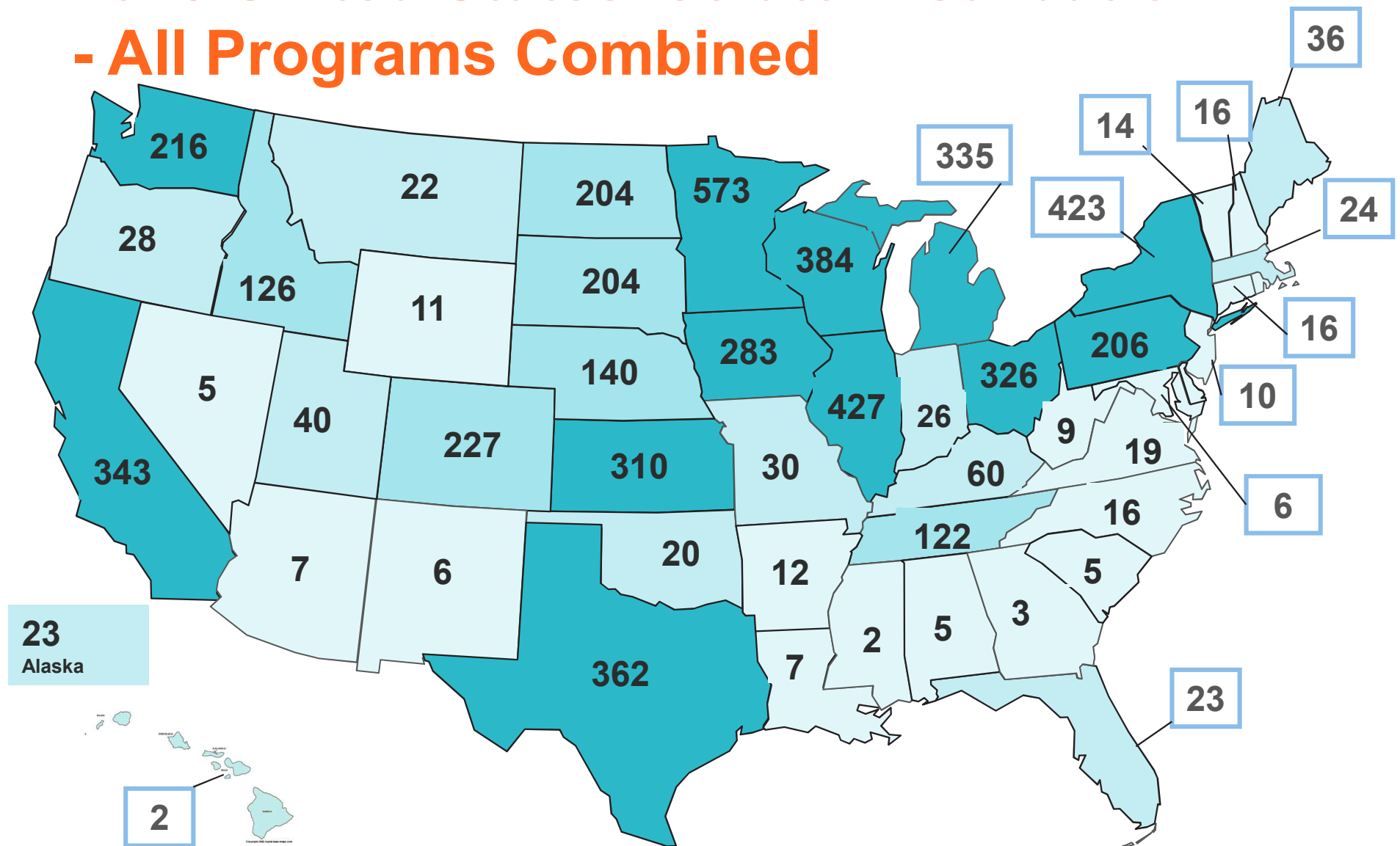- Cat

Values: 30%, 18%, 3%, 14%, 25%, 6%, 4%, <1%

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Zoetis Susceptibility Surveillance Program Design

✓ Designed as an ongoing surveillance program

✓ Program 'enrolls' veterinary diagnostic laboratories

✓ Laboratories send specific bacterial pathogens to Zoetis

✓ Zoetis chooses and controls what drugs are tested

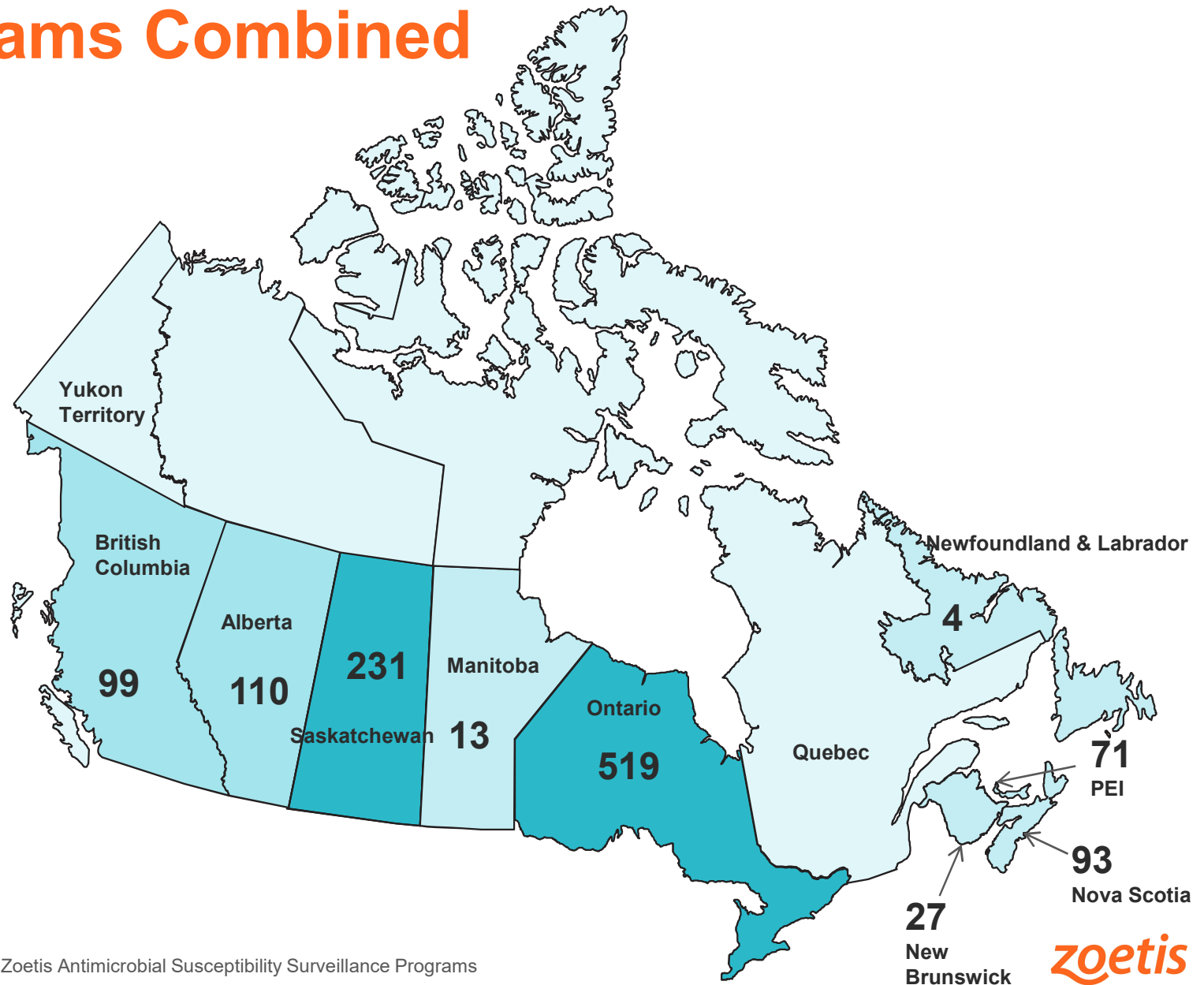✓ Testing is done using CLSI methods

✓ Zoetis analyzes annually

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Laboratory Partners

✓ US and Canada diagnostic laboratories

✓ Enrolled annually at the beginning of each year

✓ Chosen by the type of samples they typically process

✓ Chosen for maximum geographic distribution

✓ Expenses are covered by Zoetis

✓ Periodic meetings with laboratory partners

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2018 United States Isolate Distribution - All Programs Combined

Overview of Zoetis Antimicrobial Susceptibility Surveillance Programs

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2018 Canada Isolate Distribution – All Programs Combined

Yukon Territory

British Columbia
99

Alberta
110

Saskatchewan
231

Manitoba
13

Ontario
519

Quebec

Newfoundland & Labrador
4

1
PEI

93
Nova Scotia

27
New Brunswick

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Bacterial Strains

✓ Naturally occurring infections

✓ Collected from sick or dead animals

✓ Geographically diverse collection

✓ No more than a single isolate from each animal

✓ No more than one isolate of each bacterial species from each household/dairy/farm/year

✓ Treatment status is collected when available

✓ Laboratories are allowed to submit isolates from states other than their own

✓ Maximum number of isolates from each lab; no minimum number required

✓ Strains are identified by the submitting laboratory

✓ Strains are retained by Zoetis for future *in vitro* testing

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Bacterial Strains

Swine Respiratory Pathogens

- *Pasteurella multocida*
- *Actinobacillus pleuropneumoniae*
- *Bordetella bronchiseptica*
- *Streptococcus suis*
- *Escherichia coli*
- *Salmonella species*

Cattle Respiratory Pathogens

- *Pasteurella multocida*
- *Mannheimia haemolytica*
- *Histophilus somni*
- *Escherichia coli*
- *Salmonella* species

Bovine Mastitis Pathogens

- *Escherichia coli*
- *Klebsiella species*
- *Coagulase Negative Staphylococcus* species
- *Staphylococcus aureus*
- *Streptococcus dysgalactiae*
- *Streptococcus uberis*

Equine Pathogens

- *Streptococcus equi* subspecies zooepidemicus
- *Streptococcus equi* subspecies *equi*
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*

Companion Animal SSTI Pathogens

- *Pasteurella multocida* (cats only)
- *Staphylococcus pseudintermedius*
- *Staphylococcus aureus*
- *Streptococcus* species (beta-haemolytic)

Companion Animal UTI Pathogens

- *Escherichia coli*
- *Proteus mirabilis* (dogs only)
- *Staphylococcus* species (Coagulase Positive and Negative)
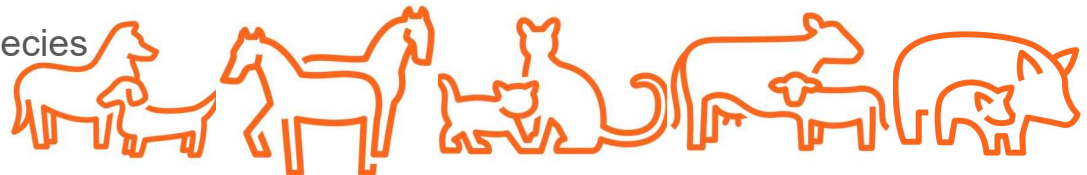
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Minimal Inhibitory Concentration Testing

✓ Zoetis determines drugs tested

✓ Primary testing is done in one laboratory

✓ Quality control reference strains are tested daily

✓ Strict adherence to Clinical and Laboratory Standards Institute (CLSI) standardized methods

✓ Tested drug concentration ranges are set to include breakpoints and quality control ranges and to enable detection of MIC shifts

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Antimicrobial Agents Tested in 2018

Antimicrobial Drug	Bovine & Swine Respiratory	Bovine Mastitis	Equine	Companion Animal UTI	Companion Animal SSTI
Amikacin			✔		
Amoxicillin/Clavulanic Acid				✔	✔
Ampicillin	✔	✔		✔	
Ceftiofur	✔	✔	✔	✔	
Cefovecin				✔	✔
Cefoperazone & Cephalothin		✔			
Cefpodoxime				✔	✔
Cephalexin				✔	✔
Chloramphenicol					✔
Clindamycin					✔
Danofloxacin	✔		✔		
Doxycycline			✔		
Enrofloxacin	✔		✔	✔	✔

Antimicrobial Drug	Bovine & Swine Respiratory	Bovine Mastitis	Equine	Companion Animal UTI	Companion Animal SSTI
Erythromycin		✔	✔		
Florfenicol	✔				
Gentamicin			✔		
Marbofloxacin				✔	✔
Orbifloxacin				✔	
Oxacillin		✔	✔		✔
Penicillin	✔		✔		
Penicillin/Novobiocin		✔			
Pirlimycin		✔			
Tetracycline	✔				
Tilmicosin	✔				
Trimethoprim/ Sulfamethoxazole	✔		✔	✔	✔
Tulathromycin	✔				

Overview of Zoetis Antimicrobial Susceptibility Surveillance Programs

Summaries of Zoetis Antimicrobial Susceptibility Data

✓ Population distribution of bacteria according to MIC

✓ MIC_{50} and MIC_{90} values

✓ Clinical Breakpoints

✓ Epidemiological cut-off values

✓ Modes, ranges, geometric means, many other statistical or stratification methods

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Limitations of Zoetis Surveillance

✓ Passive surveillance has inherent sampling biases

✓ No globally standardized Epidemiological Cut-Off Values or Clinical Breakpoints

✓ Information on sampling/treatment history is not always available

✓ These programs do not provide prevalence information

✓ Zoetis surveillance does not provide information on the source of the resistance or how resistance is disseminated

✓ Study design variations make direct comparisons to other programs difficult

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Definitions

Minimal Inhibitory Concentration (MIC) - The lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism in an agar or broth dilution susceptibility test - (CLSI)

Interpretive Criteria (IC) or Breakpoint (BP) - MIC or zone diameter value used to indicate susceptible, intermediate, or resistant – (CLSI)

Susceptible – a category that implies that an infection due to the isolate may be appropriately treated with the dosage regimen of an antimicrobial agent recommended for that type of infection and infecting species, unless otherwise indicated.

Resistant – resistant isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy has not been reliable in treatment studies.

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SWINE PATHOGEN SUSCEPTIBILITY RESULTS

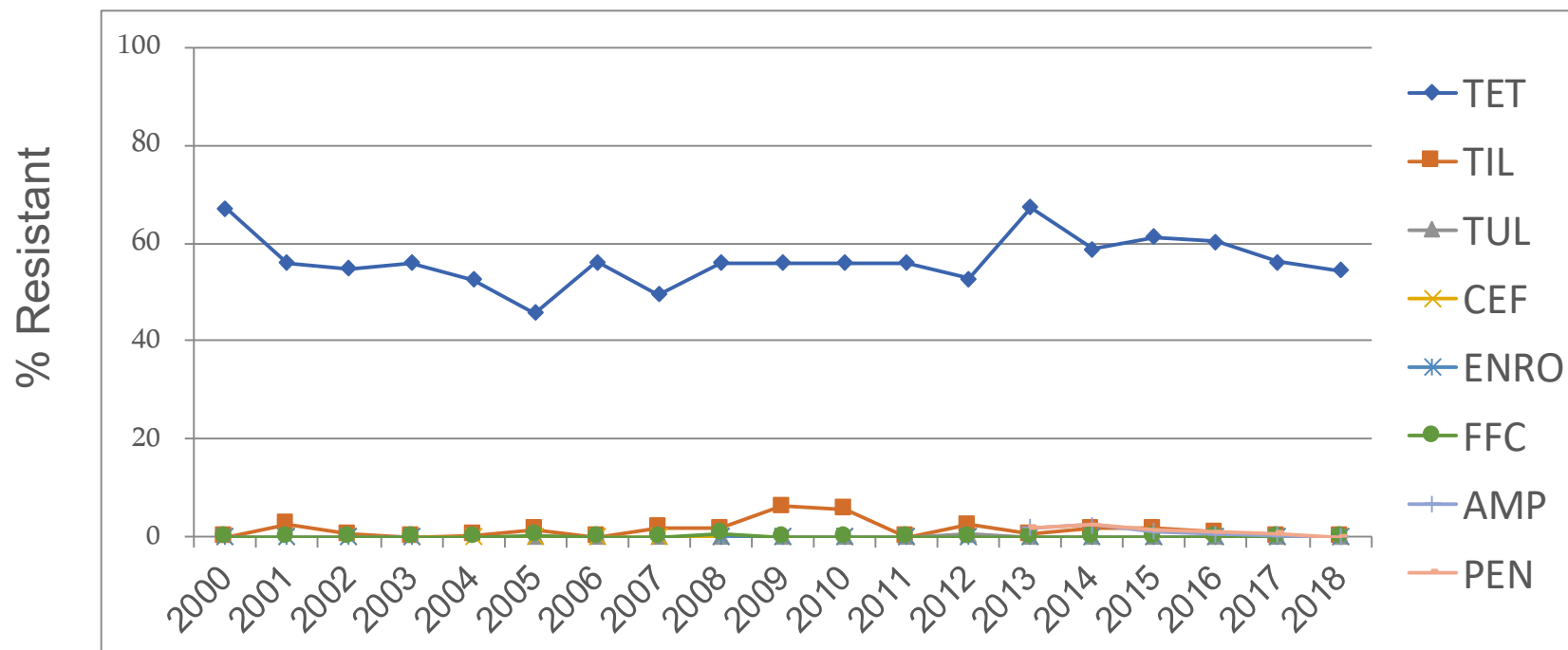**Antimicrobial Agents with CLSI breakpoints:**
Ampicillin, Penicillin, Ceftiofur, Enrofloxacin, Florfenicol, Tetracycline, Tilmicosin, Tulathromycin

Swine Pasteurella multocida
% Resistant 2000-2018

Surveillance Year & Isolate Number	Tetracycline (TET)	Tilmicosin (TIL)	Ampicillin (AMP)	Penicillin (PEN)	Tulathromycin (TUL)	Ceftiofur (CEF)	Enrofloxacin (ENRO)	Florfenicol (FFC)
2018 (n=147)	**54.4%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
2017 (n=262)	56.1%	0%	0.4%	0.8%	0%	0%	0%	0%

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CATTLE PATHOGEN SUSCEPTIBILITY RESULTS

Antimicrobial Agents with CLSI breakpoints:
Ceftiofur, Enrofloxacin, Florfenicol, Penicillin, Tetracycline, Tilmicosin, Tulathromycin

BRD Isolates Analyzed 2001-2018 - All

	Mannheimia haemolytica	Pasteurella multocida	Histophilus somni
2001	189	259	129
2002	225	235	137
2003	228	223	180
2004	330	364	201
2005	333	377	235
2006	352	392	254
2007	438	508	236
2008	369	397	221
2009	304	328	174
2010	360	359	240
2011	351	355	223
2012	333	298	223
2013	302	334	183
2014	351	342	255
2015	364	374	272
2016	395	394	266
2017	400	406	269
2018	439	411	249

Overview of Zoetis Antimicrobial Susceptibility Surveillance Programs
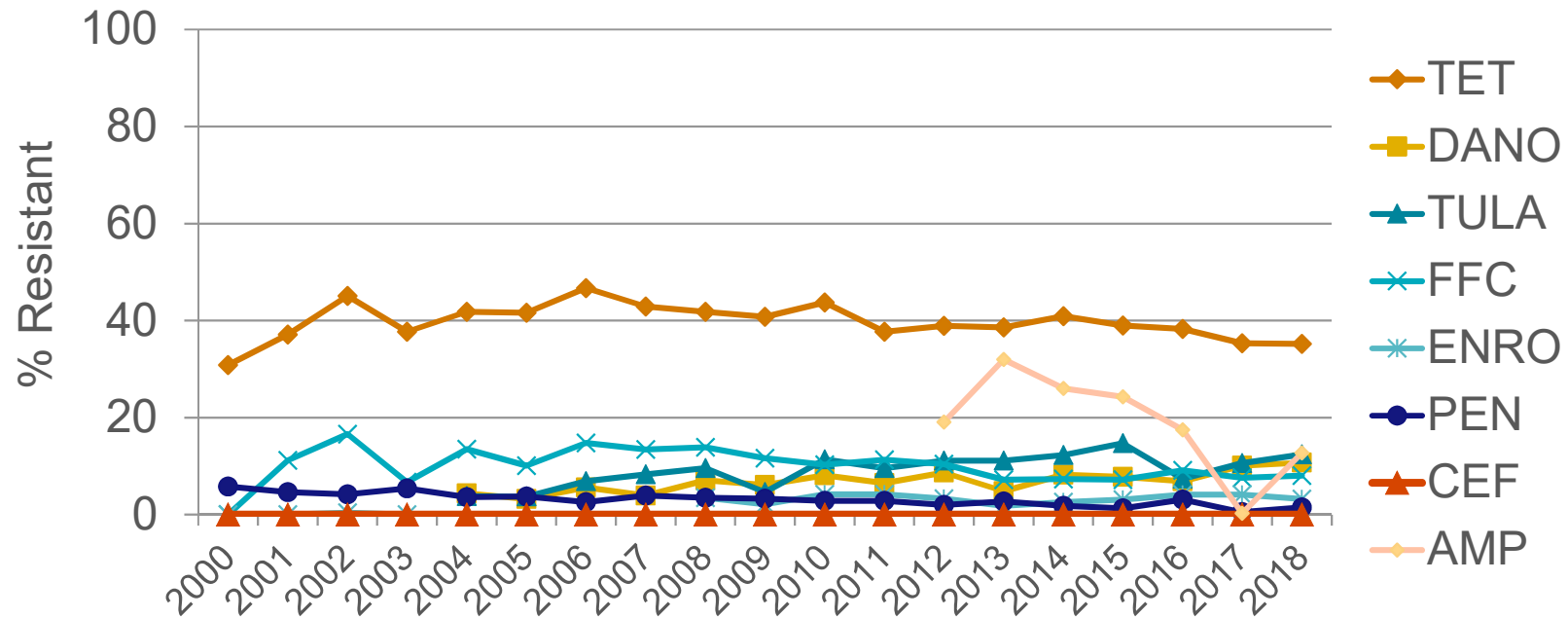
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Mannheimia haemolytica
% Resistant 2000-2018
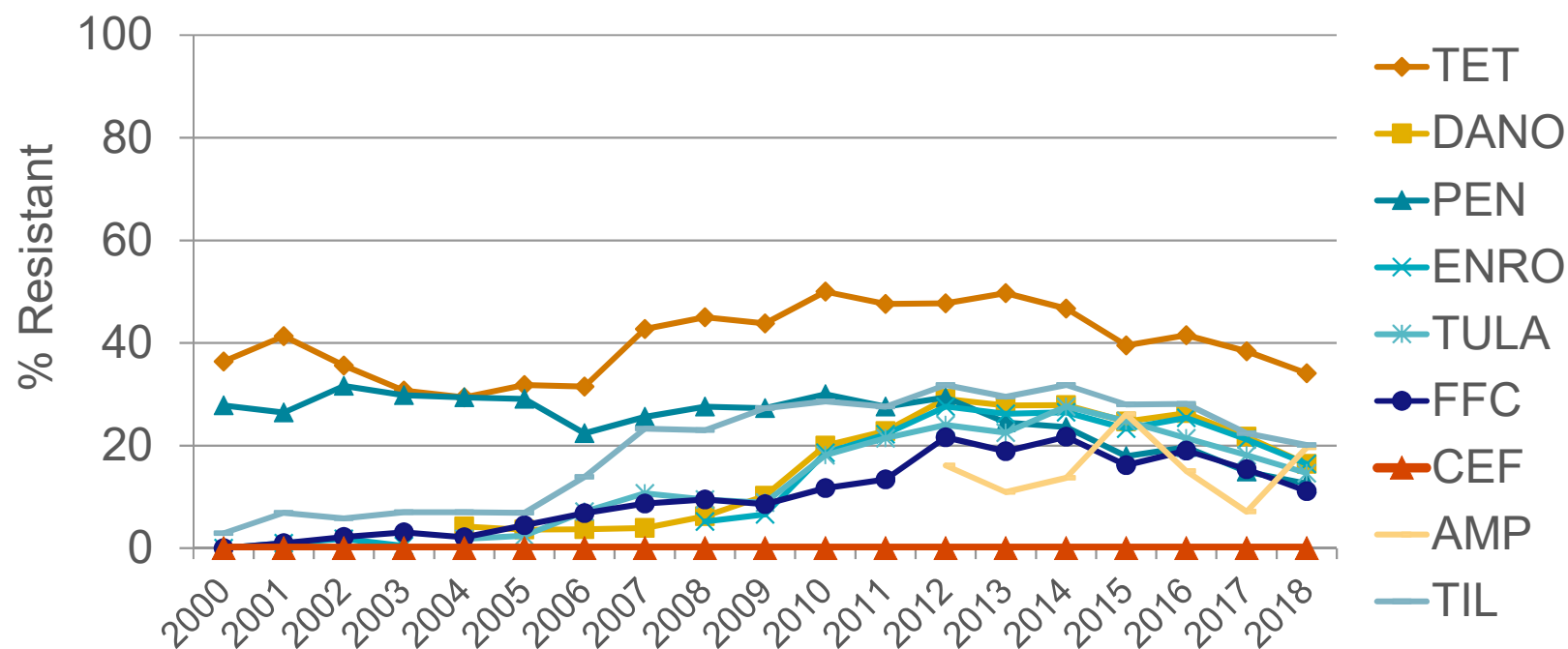
Surveillance Year & Isolate Number	Tetracycline (TET)	Penicillin (PEN)	Danofloxacin (DANO)	Enrofloxacin (ENRO)	Tulathromycin (TUL)	Florfenicol (FFC)	Ceftiofur (CEF)	Ampicillin (AMP)	Tilmicosin (TIL)
2018 (n=439)	**34.1%**	**12.6%**	**16.4%**	**16.4%**	**14.6%**	**11.1%**	**0%**	**19.6%**	**20.1%**
2017 (n=400)	38.4%	14.9%	21.7%	21.2%	18.1%	15.4%	0%	7.1%	22.4%
2016 (n=395)	41.5%	19.7%	26.4%	25.4%	21.4%	19%	0%	15.0%	28.1%
2015 (n=364)	39.5%	17.9%	24%	23.3%	24.8%	16.2%	0%	26.1%	28%

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# Bovine *Pasteurella multocida*
% Resistant 2000-2018

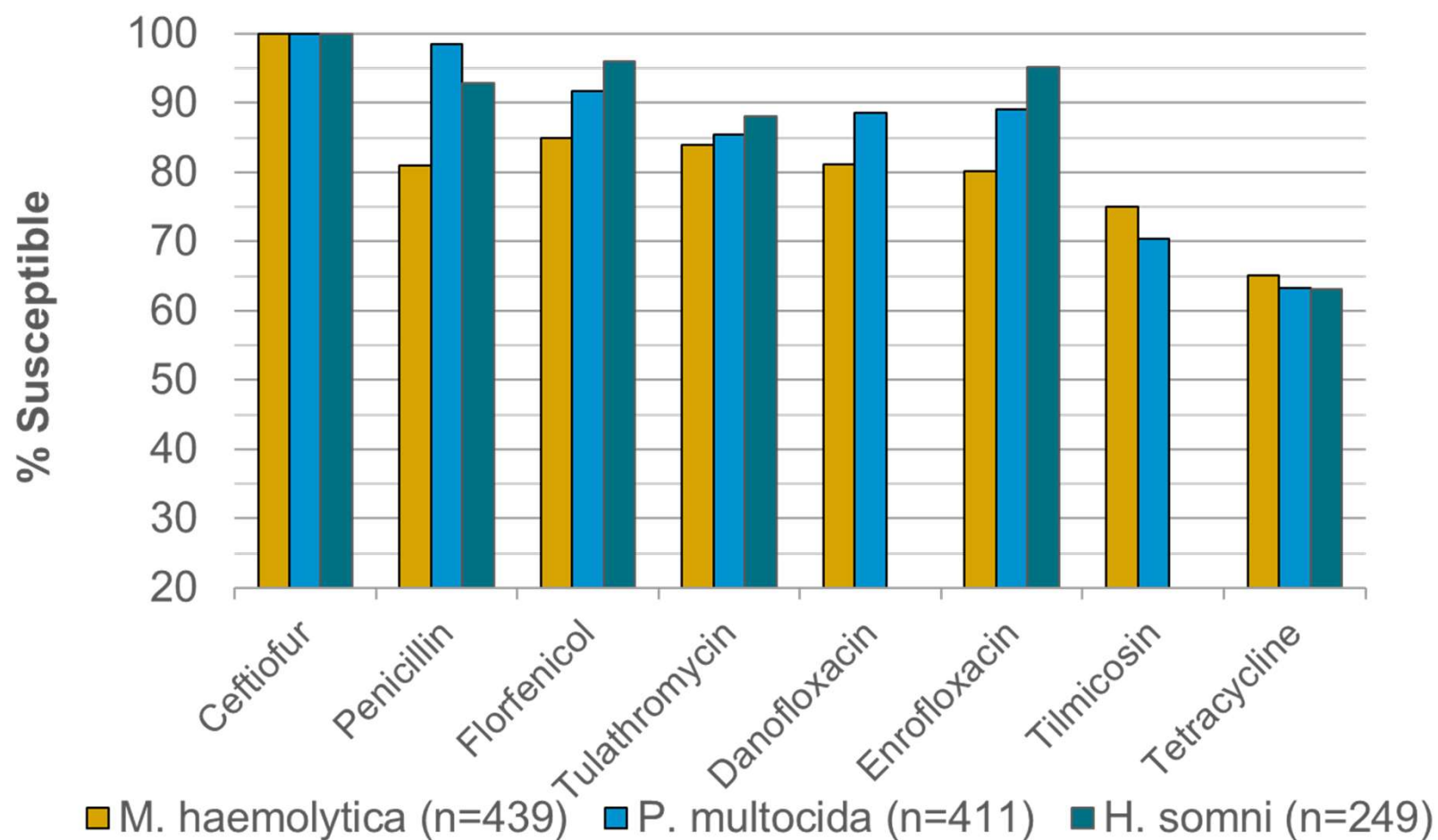| Surveillance Year & Isolate Number	Tetracycline (TET)	Tulathromycin (TUL)	Florfenicol (FFC)	Danofloxacin (DANO)	Enrofloxacin (ENRO)	Penicillin (PEN)	Ceftiofur (CEF)	Ampicillin (AMP)
2018 (n=411)	**35.2%**	**12.4%**	**8.0%**	**10.7%**	**3.2%**	**1.5%**	**0%**	**12.7%**
2017 (n=406)	35.3%	10.6%	7.6%	10.1%	4.9%	0.5%	0%	28.3%
2016 (n=394)	38.3%	7.4%	9.1%	6.9%	4.1%	3.1%	0%	17.5%
2015 (n=383)	39%	14.7%	7.2%	7.8%	3.1%	1.3%	0%	24.3%

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Histophilus somni
% Resistant 2000-2018
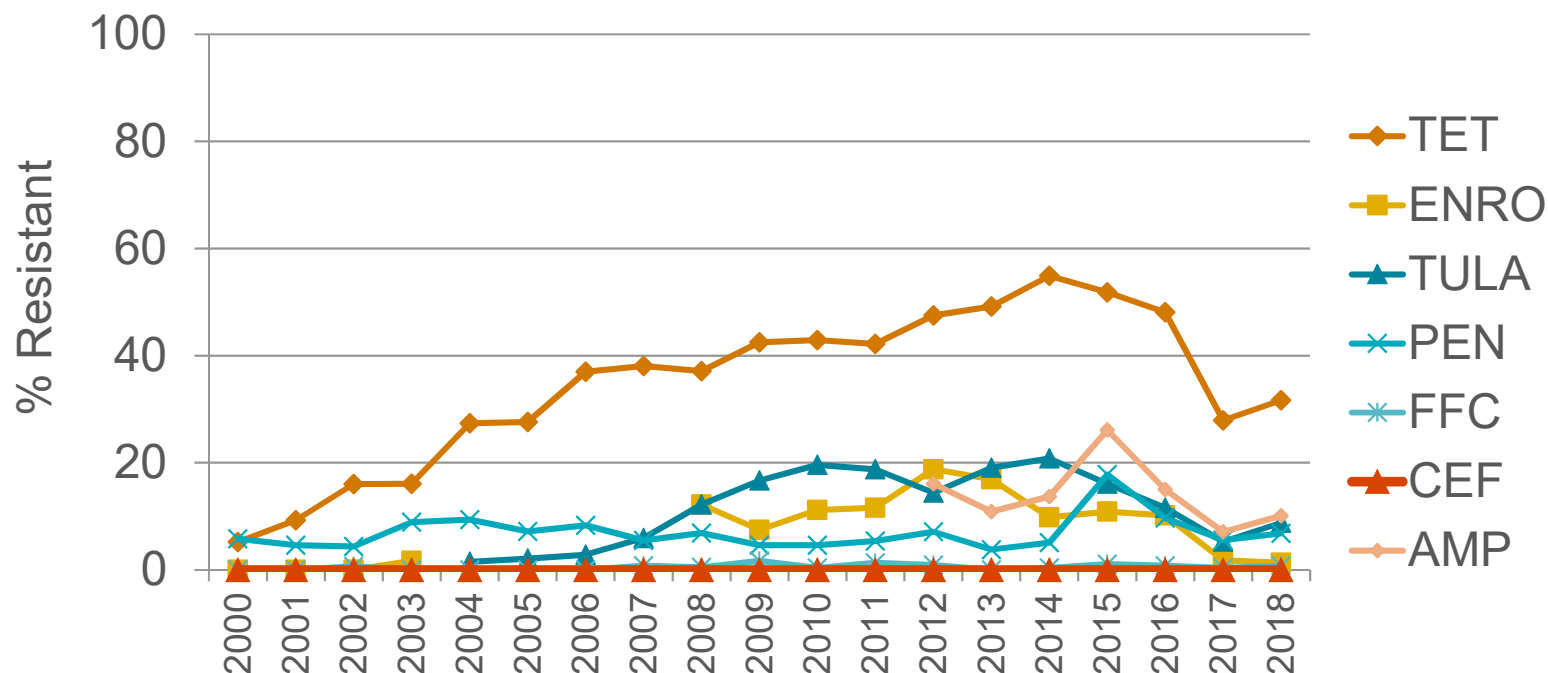
Surveillance Year & Isolate Number	Tetracycline (TET)	Enrofloxacin (ENRO)	Tulathromycin (TUL)	Penicillin (PEN)	Florfenicol (FFC)	Ceftiofur (CEF)	Ampicillin (AMP)
2018 (n=249)	**31.7%**	**1.3%**	**8.8%**	**6.8%**	**0.8%**	**0%**	**10.1%**
2017 (n=269)	27.9%	1.8%	5.3%	5.6%	0.4%	0%	7.1%
2016 (n=266)	46.3%	10.2%	11.6%	9.7%	0.8%	0%	15.0%
2015 (n=274)	51.8%	10.9%	16.1%	17.8%	1.1%	0%	26.1%

Overview of Zoetis Antimicrobial Susceptibility Surveillance Programs

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Summary of 2018 Cattle Pathogens % Susceptible

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Cattle Summary

- Variable susceptibility between drugs

- <u>All</u> *M. haemolytica, P. multocida,* & *H. somni* isolates in the past 20 years of the surveillance program have tested **100% susceptible to ceftiofur** and are **84%, 85.4%, and 88% susceptible to tulathromycin**

- 2018 **Multi-drug Resistance**: 26.1% of *M. haemolytica,* 23.3% of *P. multocida,* and 5.6% *H. somni*

- Resistance rates ≥10% among BRD isolates **drives the need** for new AIF products

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CONCLUSIONS

Zoetis is committed to:

- ✓ Ongoing susceptibility surveillance
- ✓ Replacing anecdotal evidence with good science
- ✓ Expanding the understanding of mechanisms of resistance and multidrug resistance
- ✓ Supporting responsible use

Contact information

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QUESTIONS?