ANTIMICROBIAL STEWARDSHIP IN VETERINARY MEDICINE: PREVALENCE OF STEWARDSHIP PROGRAMS AND PRELIMINARY ANTIMICROBIAL USE DATA

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4/5/19

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Introduction

Introduction: About Me

- MPH student at Kansas State University
  - Infectious Disease and Zoonoses Emphasis
- Kansas Department of Health and Environment (KDHE) employee

My Applied Practice Experience Site

- Dispensary at the Veterinary Health Center (VHC)
  - Critical role in the VHC daily functions
  - Consistently update their practices to enhance safety for their patients
  - Worked directly with the Director of Pharmacy, Dr. Colvin-Marion, and the College of Veterinary Medicine's Computer and Technical Support Group, Nancy Hawkins and Daniel Cutting

Background

Background: Antimicrobials

One Health Approach

- One Health is a collaborative effort of science professionals attaining optimal health in people, animals and the environment.
- The Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) utilize a One Health approach

Food and Drug Administration, 2018
Presidential Advisory Council on Combating Antibiotic Resistant Bacteria, May 2018
The Centers for Disease Control and Prevention, 2018

Antimicrobial Resistance Goals of One Health:

The goal of One Health approaches for antimicrobial resistance include:

- Ensure the continuation of antimicrobial efficacy in treatment of disease in humans and animals
- Promote judicious use of antimicrobial agents
- Ensure global access to high quality medications

Food and Drug Administration, 2018
Presidential Advisory Council on Combating Antibiotic Resistant Bacteria, May 2018
The Centers for Disease Control and Prevention, 2018

Antimicrobial Stewardship

- Implemented by multidisciplinary teams of health care professionals seeking to optimize antimicrobial prescribing to improve therapeutic success and minimize development of further resistance
- As of 2017, stewardship programs are required in human health care by The Joint Commission
  - No requirement currently exists for veterinary health care

The Joint Commission (2016, July). *Approved: New Antimicrobial Stewardship Standard*[PDF}

KDHE Antimicrobial Resistance Efforts

- KDHE epidemiologists and clinicians team up to guide health care professionals to
  - Enhance prevention and response efforts
  - Promote antimicrobial resistance prevention initiatives

Kansas Department of Health and Environment

Kansas State University

VHC Stewardship Efforts

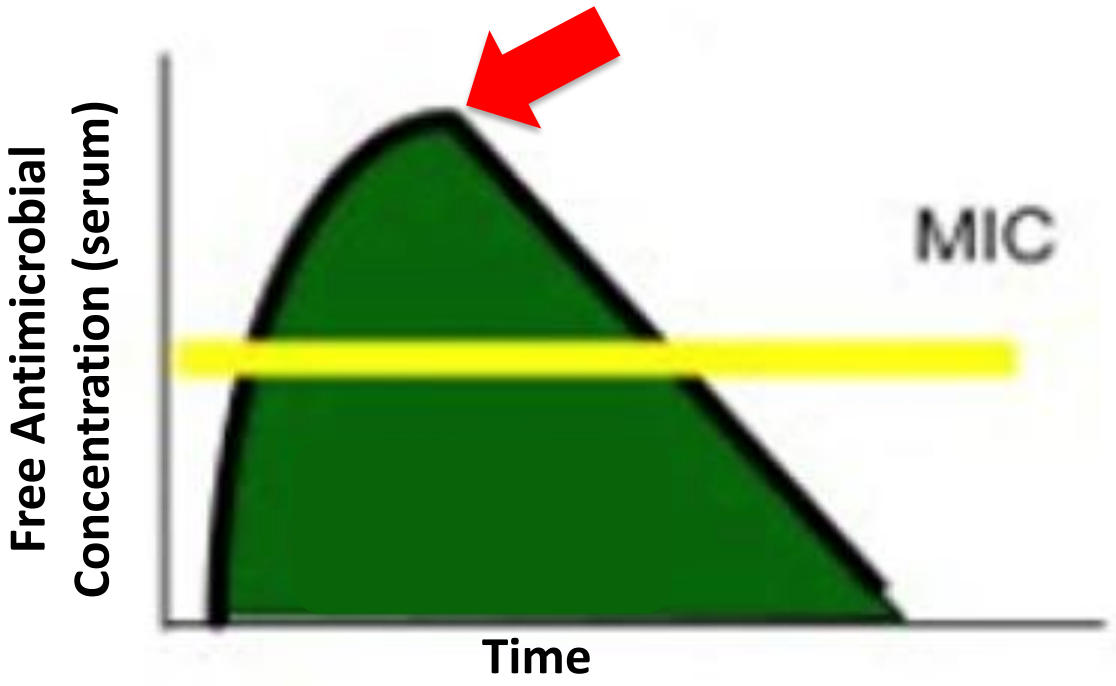
- Organizations such as the AVMA, AABP, AAEP, AAFP are promoting antimicrobial stewardship in veterinary medicine
  - As leaders in veterinary medicine, the VHC is taking an initiative to establish an antimicrobial stewardship program at their facility
  - A core component is to determine baseline data regarding how antimicrobials are being prescribed at the VHC

The American Veterinary Medical Association (2018). Antimicrobial Resistance

Antimicrobials

- Used in veterinary and human medicine to inhibit the growth or kill microorganisms
  - Bacteriostatic
  - Bactericidal
- Can be concentration-or time-dependent
- Can be AUC/MIC -dependent

Concentration-Dependent Antimicrobials



Hayat, K. (2012, August). *What is the Difference Between Time Dependent Antibiotics?*[PDF]. Drug Information Center.

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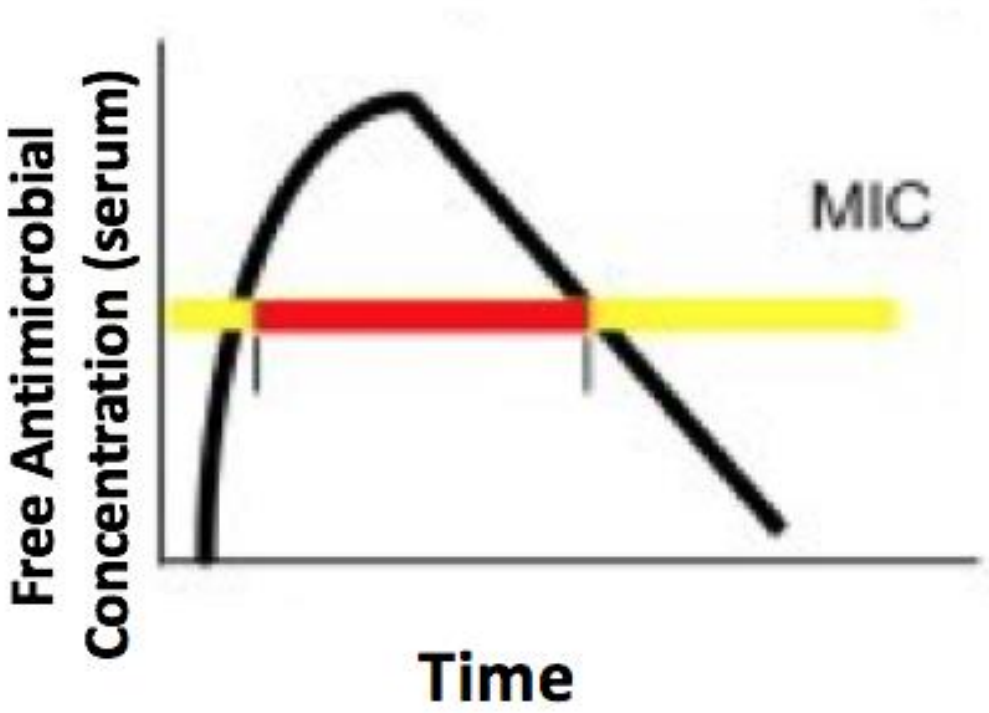
Time-Dependent Antimicrobials



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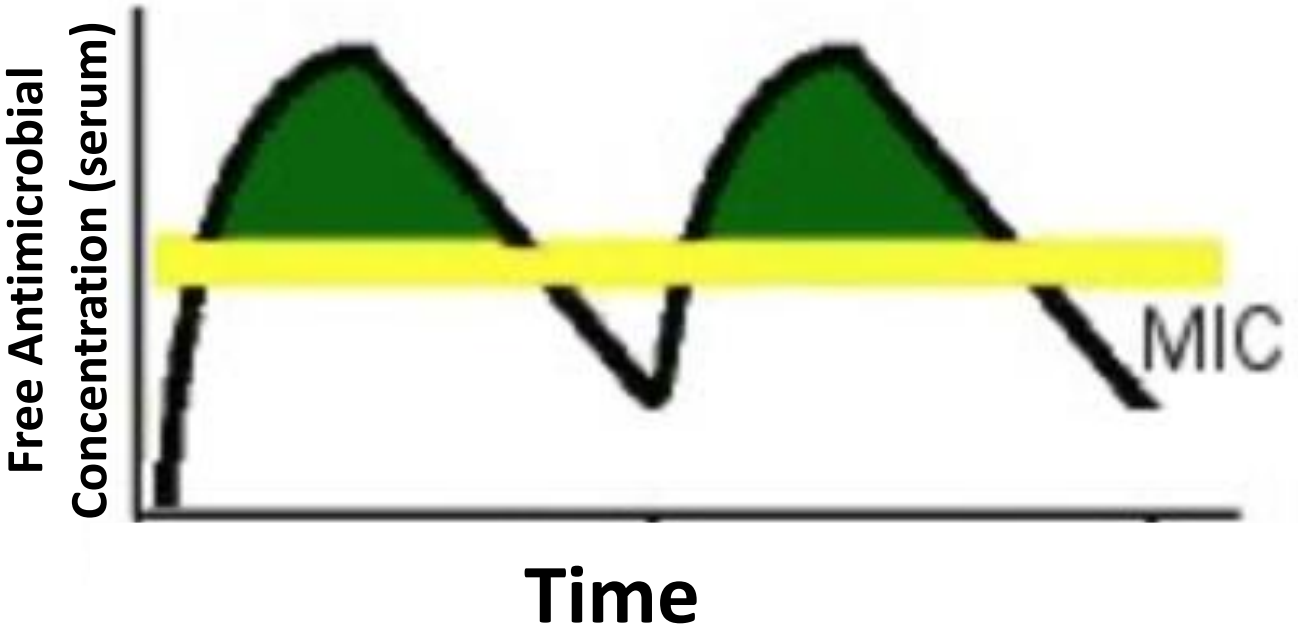
AUC/MIC-Dependent Antimicrobials



Hayat, K. (2012, August). *What is the Difference Between Time Dependent Antibiotics?*[PDF]. Drug Information Center.

Antimicrobials

- Critical in treating infections
- Microorganisms develop resistance mechanisms to evade antimicrobial agents

Consequences of Antimicrobial Resistance

- Prolonged treatment
- Increased diagnostic and therapeutic costs
- Prolonged hospitalization
- Increased morbidity and mortality

Antimicrobial Labeled Dosing and Therapeutic Decisions

	Evidence-based Research for Therapeutic Decisions	Derivations from Labeled Dosing
Human Medicine	**+++**	**Off label drug use**
Veterinary Medicine	**+**	**Extra label drug use** • American Medicinal Drug Use Clarification Act • American College of Veterinary Medicine • Consults with pharmacologists

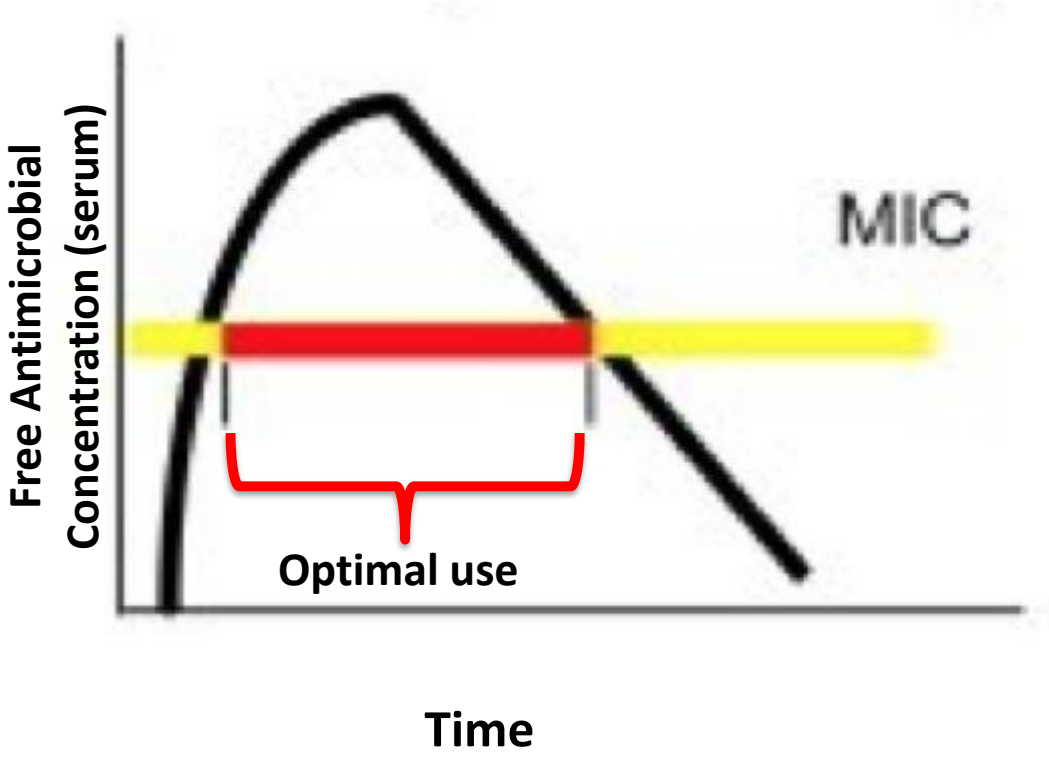
Food and Drug Administration. Animal Medicinal Drug Use Clarification Act 1994

Background:
Amoxicillin-Clavulanic Acid

Amoxicillin-Clavulanic Acid

- Bactericidal aminopenicillin with β-lactamase inhibitor, which expands its spectrum to overcome β-lactamase producing microorganisms
  - *Staphylococcus spp.*
  - *Streptococcus spp.*
  - *Escherichia coli*
  - *Pasteurella spp.*
- Although it is not a bioequivalent, Augmentin use in human medicine is often compared to amoxicillin-clavulanic acid in veterinary medicine

Time-Dependent Activity of Amoxicillin-Clavulanic Acid



Hayat, K. (2012, August). *What is the Difference Between Time Dependent Antibiotics?*[PDF]. Drug Information Center.

Amoxicillin-Clavulanic Acid (Continued)

Dosage Form	Strength (mg)	Amoxicillin (mg)	Clavulanic Acid (mg)
Tablet 	62.5	50	12.5
	125	100	25
	250	200	50
	375	300	75
Oral Suspension 	62.5/mL	50/mL	12.5/mL

Putney Pharmaceutical Company, 2019. https://www.heartlandvetsupply.com/generic-amoxicillin-clavulanicacid-putney-tablets.aspx. Accessed 3/29/19

Zoetis Pharmaceutical Company, 2019 https://www.zoetisus.com/contact/pages/product_information/amoxicillin-clavulanicacid Accessed 3/12/19

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Amoxicillin-Clavulanic Acid (Continued)

- Per medication package insert, it is recommended to store this medication in a cool and dry place at room temperature
- Moisture sensitive (can affect potency)
  - The tablets are not stable outside of their foil packaging and should remain in the provided foil strip until ready for use
  - The oral suspension powder for reconstitution turns brown when exposed to moisture
- The oral 62.5-mg/mL suspension should be reconstituted with 14-mL of water to the 15-mL bottle
  - Reconstituted suspension has to be discarded after **10 days**
  - Refrigeration of reconstituted suspension is required

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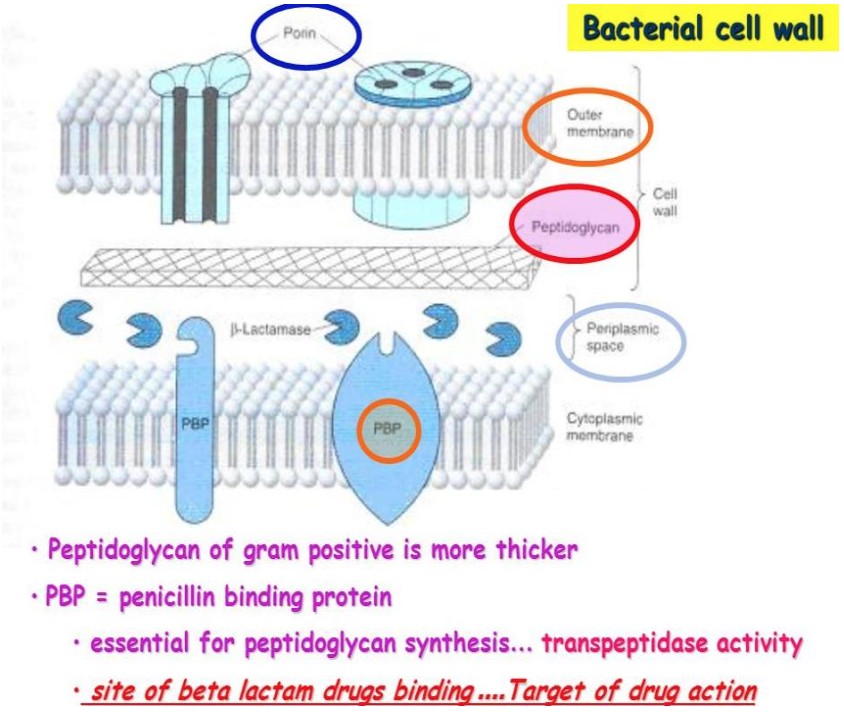
Amoxicillin-Clavulanic Acid (Continued)

- Indications
  - Soft tissue infections
  - Periodontal infections
  - Urinary tract infections
  - Respiratory infections
- Labeled dose:
  - Canine: 6.25 mg/lb (13.75 mg/kg) by mouth twice a day
  - Feline: 62.5 mg **per cat** by mouth twice a day

Amoxicillin-Clavulanic Acid Mechanisms of Action

- **Mechanism of action**
  - **Amoxicillin**
    - Functions in binding to the penicillin-binding proteins on the inner membrane of bacterial cell wall
    - In actively growing cells, the binding of amoxicillin leads to interference with production of cell wall peptidoglycans and subsequent lysis of the cell in an iso-osmotic environment



Elufisian et. Al, 2011, African journal of microbiology research, vol. 6, 4833-4844

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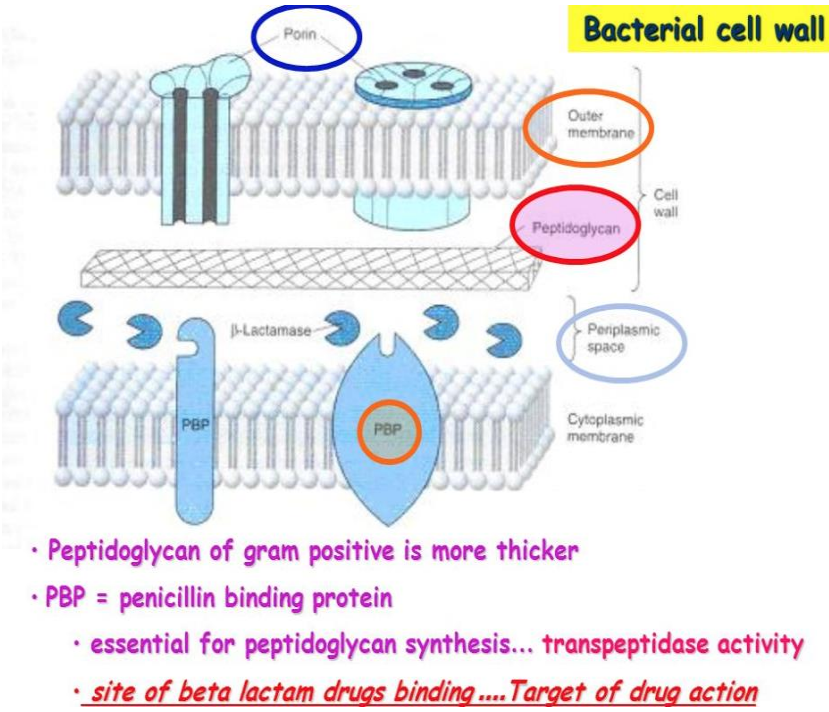
Amoxicillin-Clavulanic Acid Mechanisms of Action (Continued)

- **Mechanism of action**
  - **Clavulanate**
    - Binds irreversibly to susceptible beta-lactamase enzymes, prevents hydrolysis of the amoxicillin beta-lactam ring
    - Upon the clavulanate enzyme binding, a chemical complex is formed, subsequently destroys the clavulanate, and inactivates beta-lactamase



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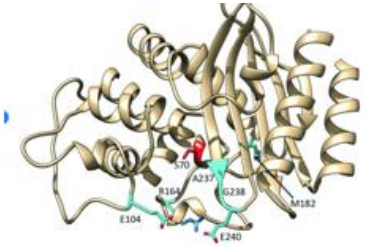
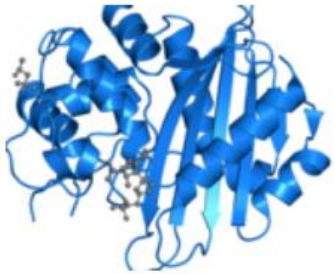
Amoxicillin-Clavulanic Acid (Continued)

- Resistance to amoxicillin-clavulanic acid is due to hyperproduction of beta-lactamase enzymes

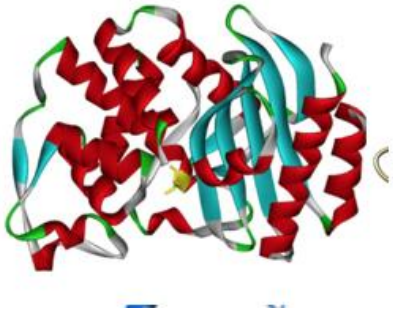
TEM-1



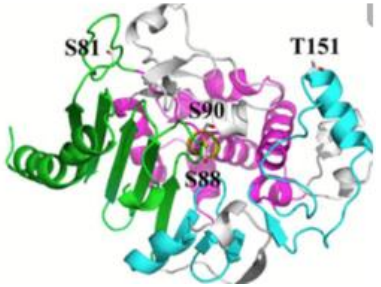
OXA-1



SHV-1



AmpC



Bush (2010). Antibiotic and Chemotherapy *Concentration and* Chemotherapy- Other β-lactam antibiotics. Journal of Expert Opinions on Therapeutic Patents Vol 20 226-244.
United States Pharmacopenial Convention, 2007, PDF
Constanca…et. Al 2002. Journal of Antimicrobial Chemotherapy. Vol 49 77-85

Project Objectives

- Create and analyze a survey inquiring about prevalence of antimicrobial stewardship programs in veterinary teaching hospitals across the United States and Canada
- Create a foundation for the next phase in implementing an antimicrobial stewardship program at the VHC
  - Determine prescribing patterns of one antimicrobial agent at the VHC: amoxicillin-clavulanic acid
  - Determine trends in prescribed dosing, duration, indication, and frequencies

Methods

Methods: Survey

Survey Methodology

- Sampling:
  - Designed survey and sent to veterinary teaching hospitals
  - Utilized convenience sampling
  - All responses were collected and analyzed
- Survey was emailed from 11/14/2018-1/17/2019

Survey

1. Does your teaching hospital have a stewardship program in place that monitors antibiotic use?
2. If so, when was this program implemented?
3. Which antibiotics do you monitor?
4. What data/ information do you collect regarding antibiotic use?
5. Do you share this data with clinicians? If yes, what is the format and does it work well?
6. Has your stewardship program led to changes in antibiotic prescribing behavior?

Survey (Continued)

7. Do you restrict the use of certain antibiotics in your hospital?
8. If you do not monitor antibiotic use, have you considered it?
9. What hurdles do you face or have prevented you from starting one?
10. Any additional details that you would like to share about your stewardship efforts?

Methods:
Prescribing Pattern Identification

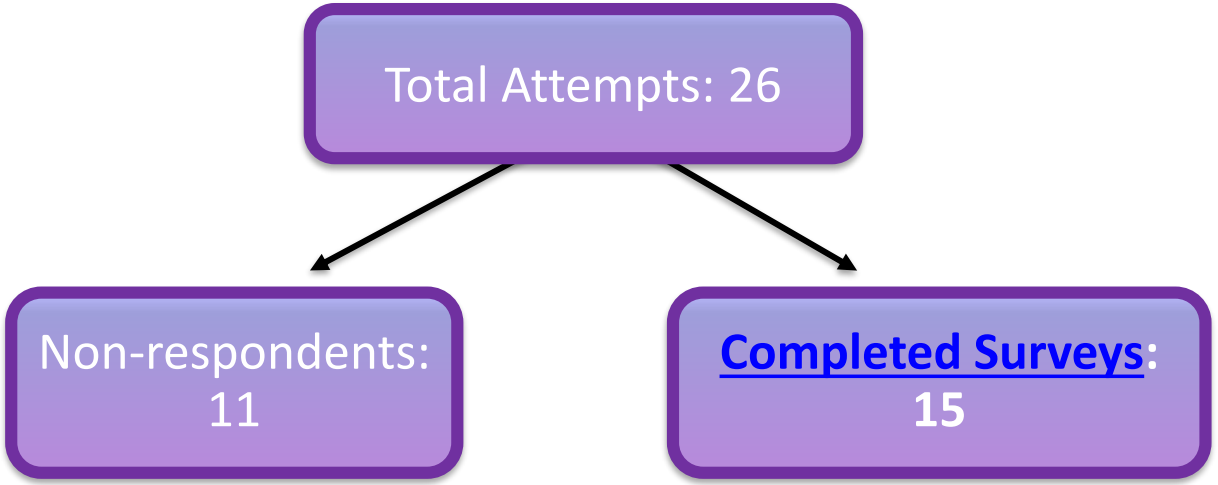
Prescribing Pattern Identification Methodology

- College of Veterinary Medicine's Computer and Technical Support exported a list of all canine and feline patients prescribed amoxicillin-clavulanic acid at the VHC over a seven-month period from the hospital information system system
- All five amoxicillin-clavulanic acid products were collected
- Utilized hospital information system to collect data on dose prescribed, frequency, duration, indication, and prescribing clinician

Results

Results: Survey

Survey Results



Geographic Location of Survey Respondents

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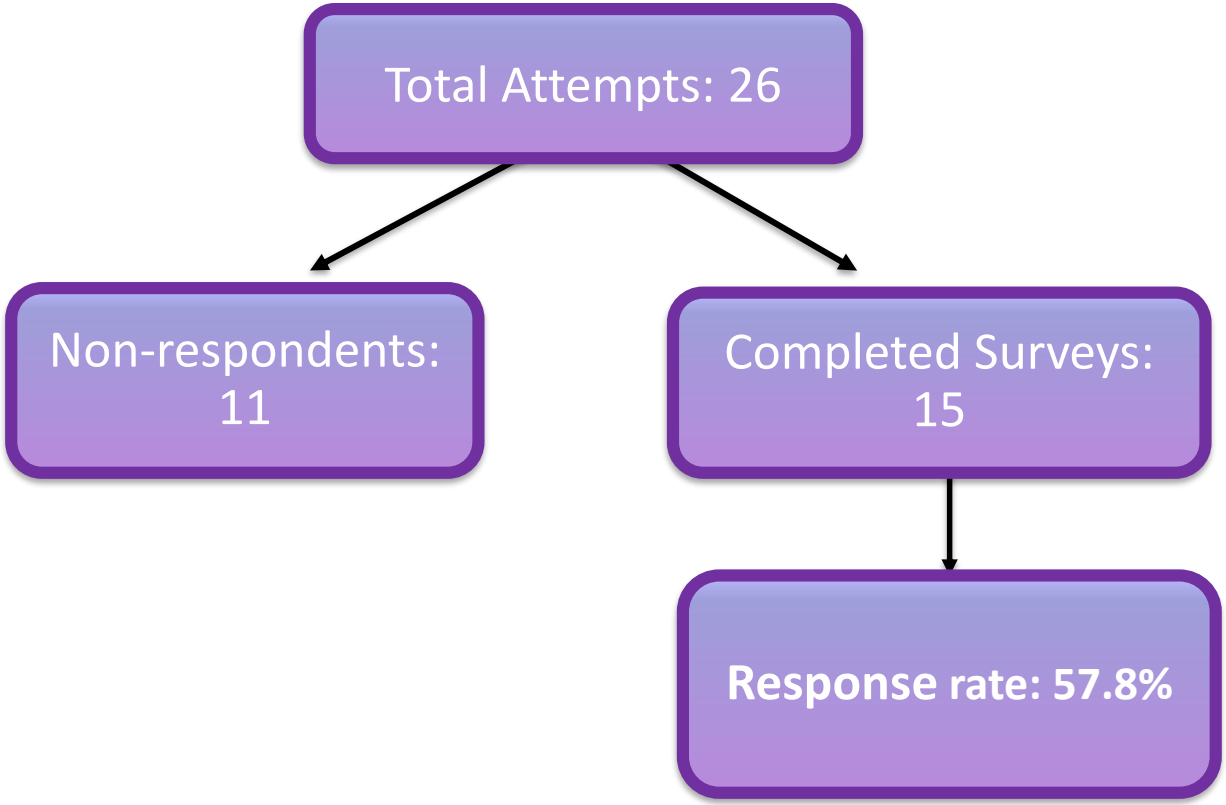
Survey Results



Survey Results (Continued)

- As of 2019, 5/15 (33%) of responding veterinary teaching hospitals reported having an established antimicrobial stewardship program implemented between 2004-2016
- Of the remaining hospitals, 6 considered implementing a program in their hospital

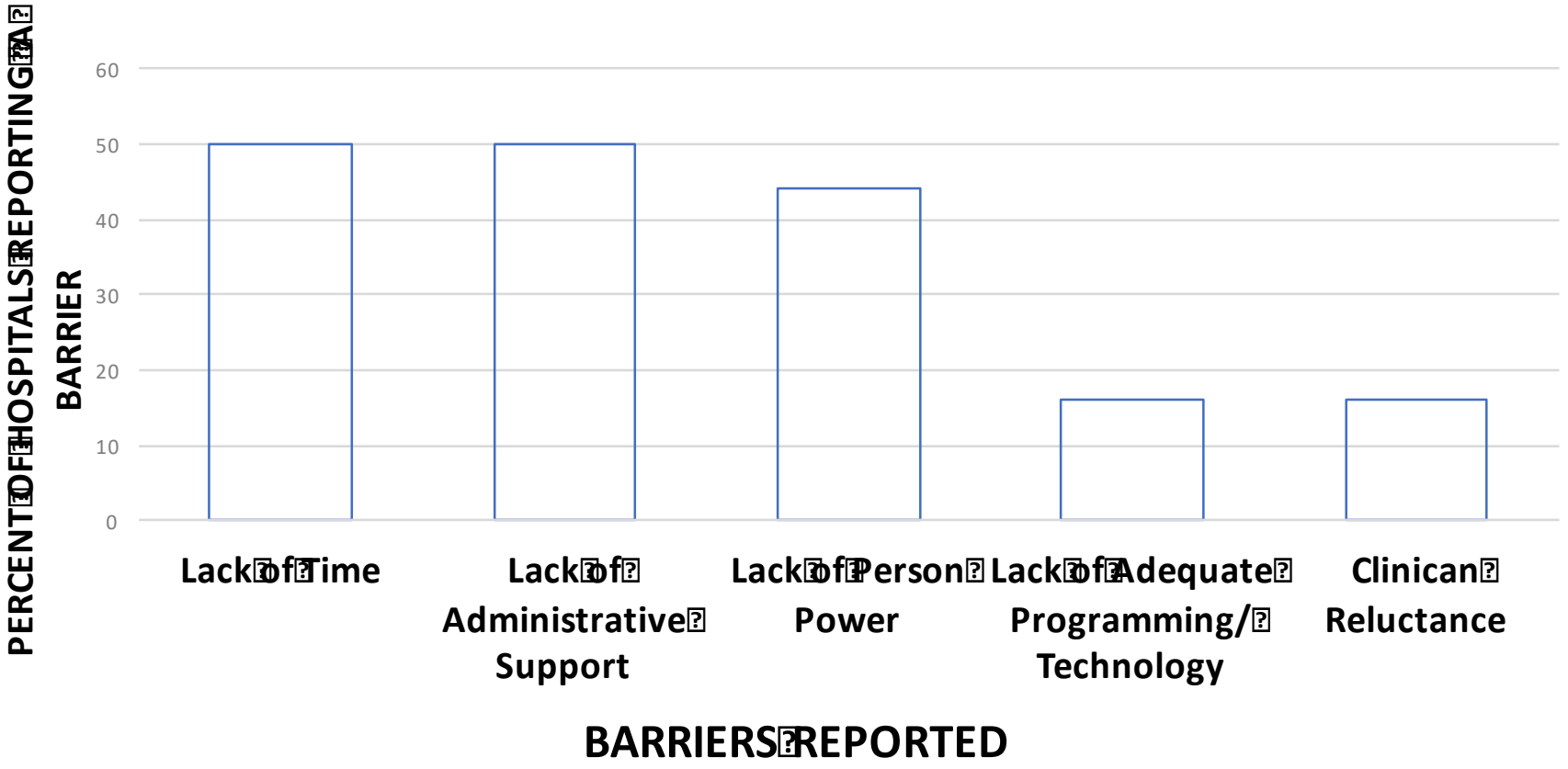
Survey Results (Continued)

- Five responding veterinary teaching hospitals reported monitoring antimicrobial use
  - Antimicrobials on standard MIC panel
  - Carbapenems
  - Vancomycin
  - Chloramphenicol
- Five veterinary teaching hospitals reported sharing antimicrobial use data with clinicians

Survey Results (Continued)

- Five hospitals (including two without an established antimicrobial stewardship program) reported restriction of antimicrobials
  - Vancomycin
  - Carbapenems
  - Imipenem
  - Third-generation cephalosporins

Barriers to Antimicrobial Stewardship Program Implementation in Veterinary Teaching Hospitals



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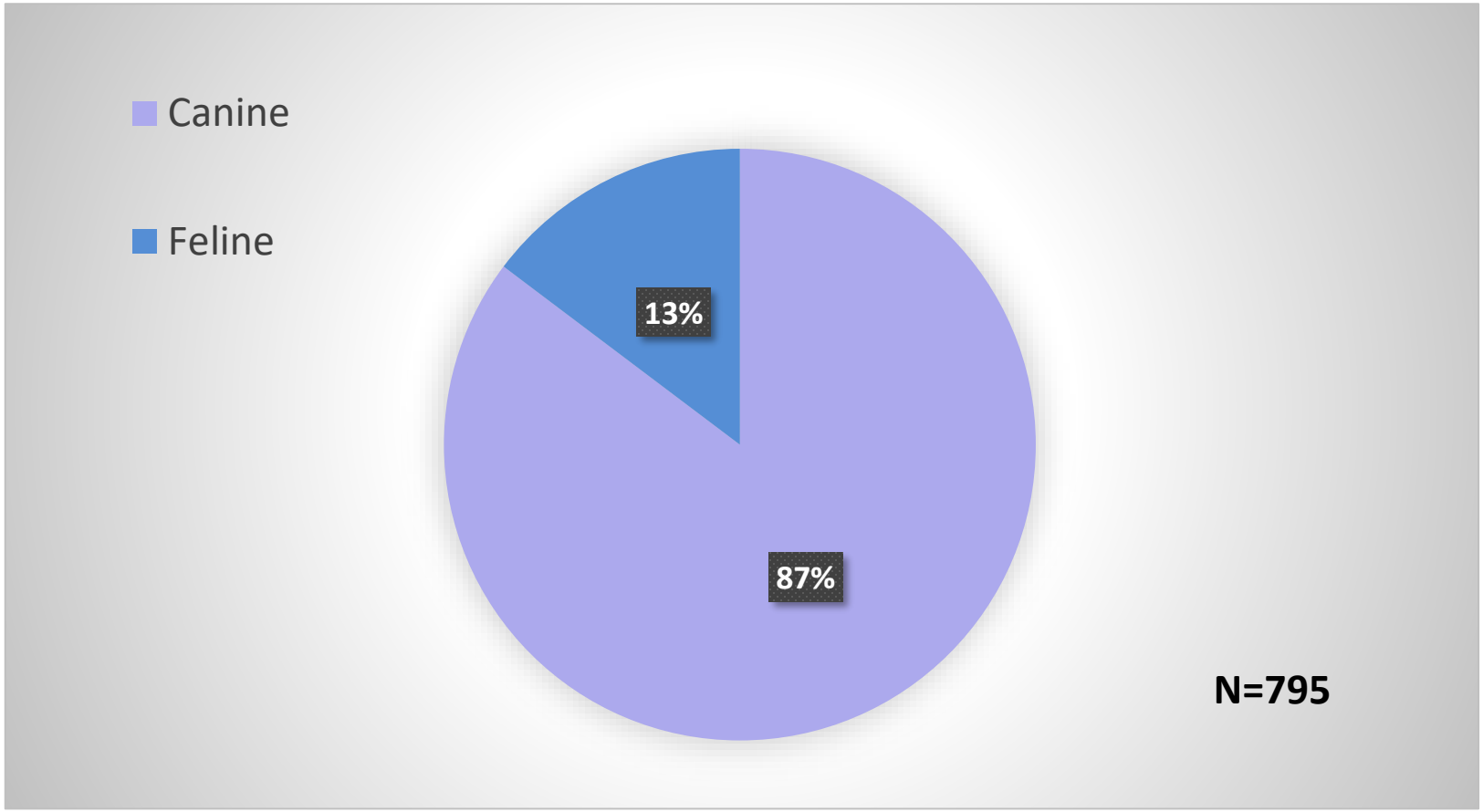
Results:
Amoxicillin-Clavulanic Acid Prescribing Patterns

Percent of Amoxicillin-Clavulanic Acid Prescriptions by Species at the VHC



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Amoxicillin-Clavulanic Acid Results

- Prescribed frequency results
  - The most commonly prescribed frequency at the VHC was twice a day (99.8%)
  - One patient chart was found to have one time administration

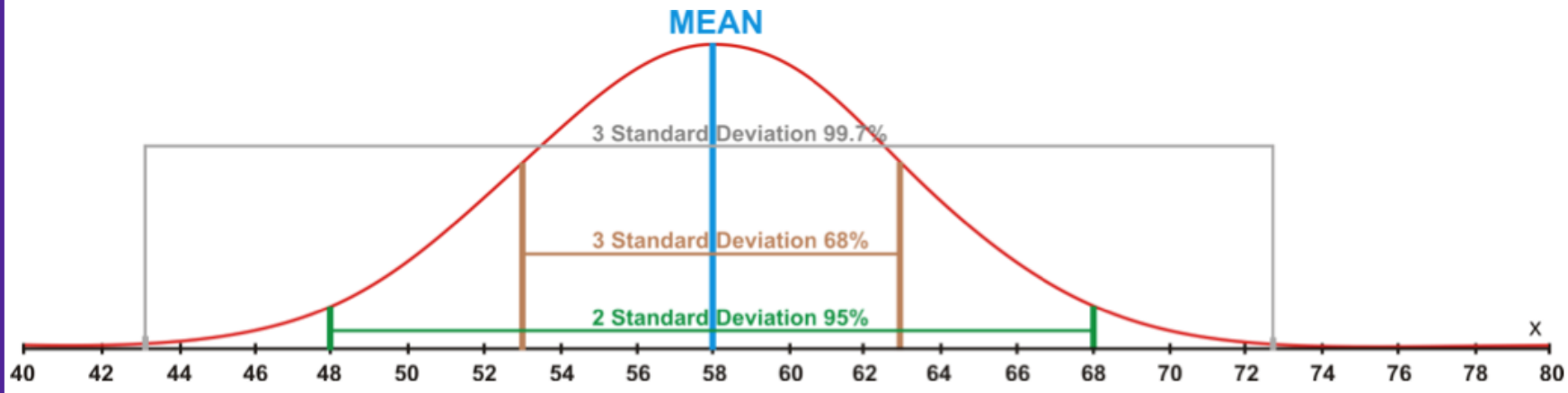
Statistical Parameters of Amoxicillin-Clavulanic Acid Dosing at the VHC

Canine:

- **Labeled:** 13.75mg/kg
- **Mean:** 14.43 mg/kg
- **Range:** 5.97 mg/kg-49.86 mg/kg
- **Standard Deviation:** 5.64

Feline

- **Labeled:** 62.5mg
- **Mean**: 14.48 mg/kg
- **Range:** 6.43 mg/kg-24.47 mg/kg
- **Standard Deviation:** 4.37



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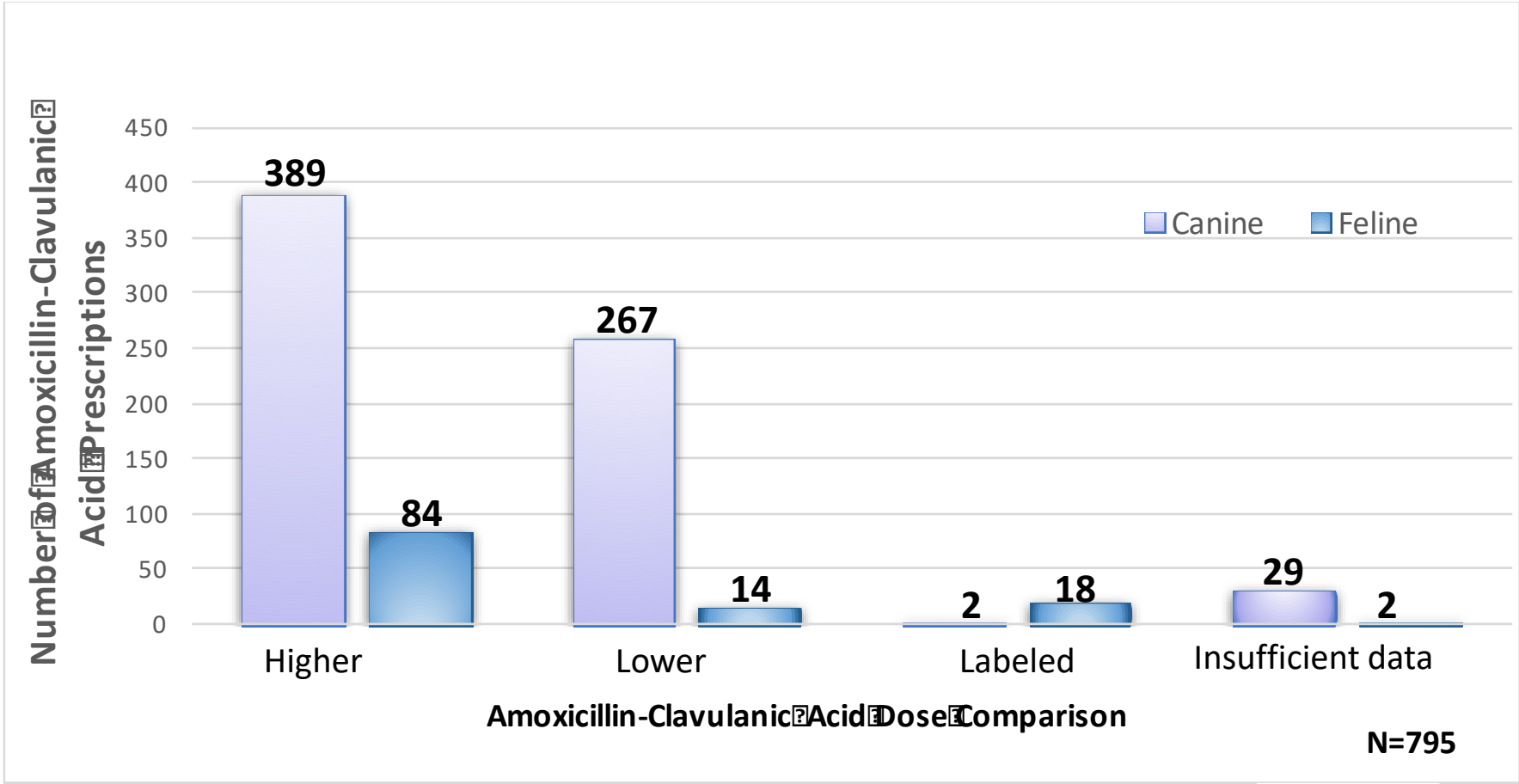
Actual VS. Labeled Dose of Amoxicillin-Clavulanic Acid Prescribed at the VHC



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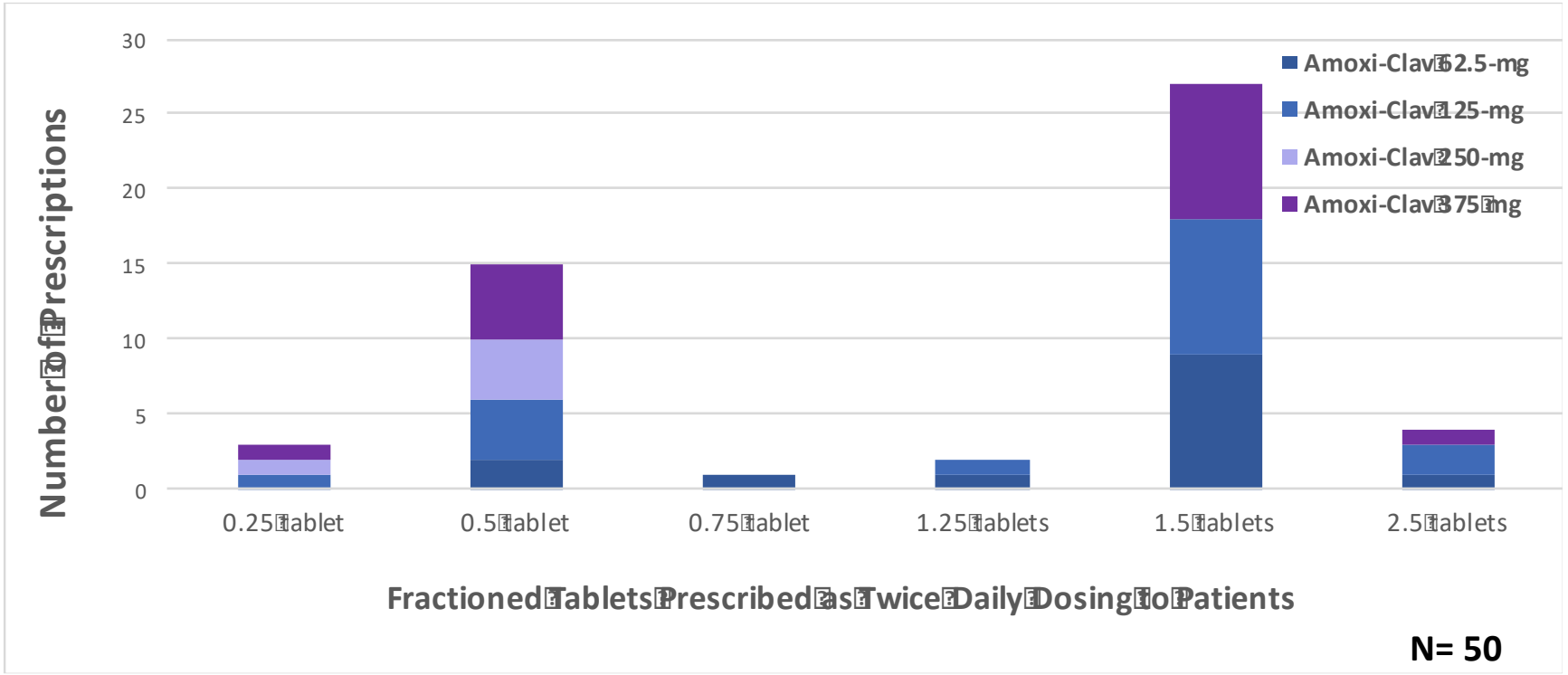
Frequency of Fractioned Amoxicillin-Clavulanic Acid Tablets Prescribed



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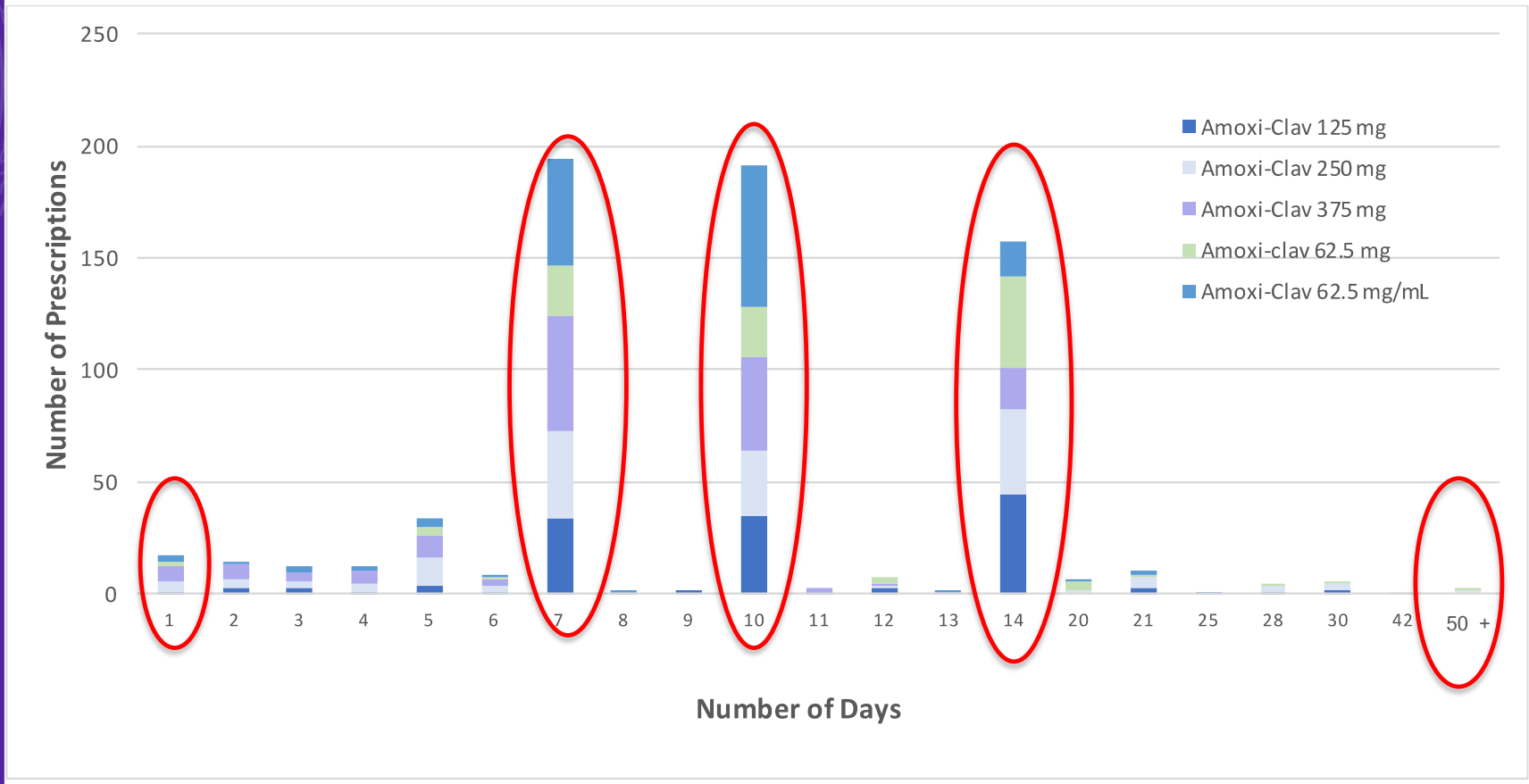
Range of Prescribed Amoxicillin-Clavulanic Acid Durations at the VHC



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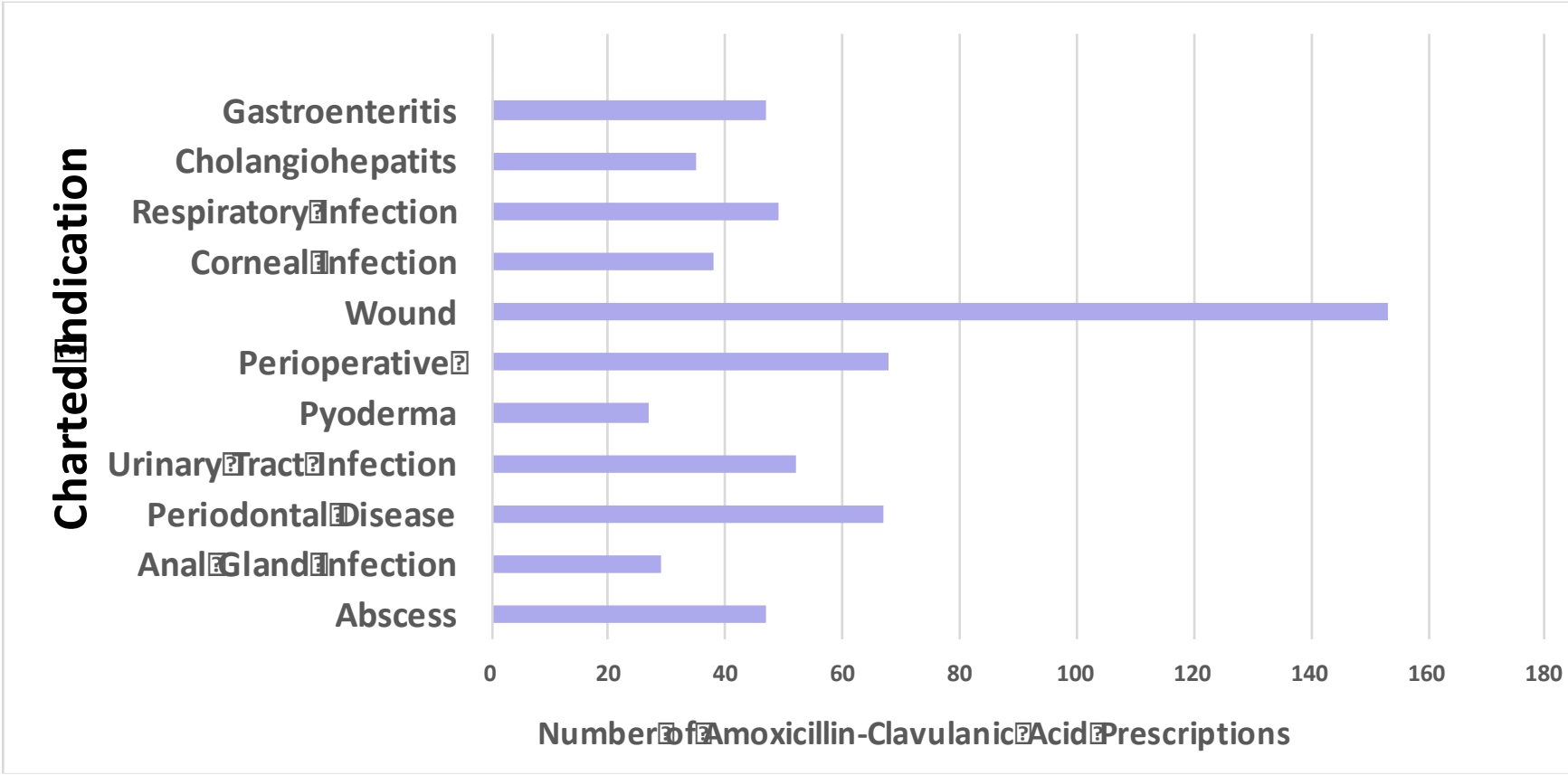
Common Indications for Amoxicillin-Clavulanic Acid Prescriptions at the VHC



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Discussion

Discussion

- Despite encouragement from the AVMA for veterinarians to take action towards antimicrobial stewardship, few veterinary schools reported having an existing antimicrobial stewardship program in their teaching hospitals
- Where programs have been established in veterinary teaching hospitals, monitoring and reviewing antimicrobial use has been well received and has resulted in positive change for antimicrobial use within those hospitals

Discussion (Continued)

- Most veterinary drugs are dosed on mg/kg basis, whereas many human prescriptions are dosed per person
  - Body-weight dosing results in rounding to the nearest dosage form size for the pet, thus it is rare to have the exact labeled dose
    - 15 kg beagle needing amoxicillin-clavulanate for UTI example

Discussion (Continued)

- VHC clinicians use a range in dosing durations, most commonly 7, 10, or 14 days
- Research is needed to determine optimal treatment duration for many veterinary infections

Jessen…et al., 2014, The Veterinary Journal, Vol 203, 270-277

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Limitations

- Data were analyzed over a 7-month period
- Limitations in data collection and analysis:
  - Data for one antimicrobial were monitored due to limited export function of the electronic health record system
  - Some records for patients required paper charts to complete analysis

Limitations (Continued)

- Veterinary Diagnostic Laboratory system is a separate system from the VHC hospital information system
  - Susceptibility cultures determine which antimicrobial to use in addition to providing minimum inhibitory concentration, these were not analyzed in this phase due to limited time

Next Steps…

- It would be beneficial to learn more about clinician attitudes towards altering prescribing patterns
- Work with information technology at the VHC to determine an easier or more efficient method of exporting patient information
  - Move towards completely electronic health record
- The VHC is interested in repeating this project with the antimicrobial: Enrofloxacin
- Recommend looking at data over a year period rather than 7-months in order to have a broader range of data and view trends over a full year

Conclusions

Conclusions

- Amoxicillin-clavulanic acid is a commonly prescribed antimicrobial agent at the VHC for cats and dogs
- Although trends show the dose prescribed does not always match the labeled dose, the current consensus statements, weight based dosing, and pharmacology guidelines advise clinicians to use higher doses for many indications and therefore, is often appropriate
- Further research is warranted to determine appropriate duration in veterinary infections and analyze susceptibility information to determine appropriateness of antimicrobial therapy

Conclusions (Continued)

- The AVMA promotes initiatives that prompt veterinary health professionals to practice judicious use of antimicrobials
- This has led to veterinary teaching hospitals leading the way by creating antimicrobial stewardship programs
  - Creating a multi-disciplinary team to implement a stewardship program is essential for success

Conclusions (Continued)

- Collaborative committees that are state-wide or nation-wide are necessary to improve stewardship

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Core Area Competencies

Core Area Competencies

Number	Competency	Description
3	**Analyze quantitative and qualitative data using bioinformatics, computer-based programming and software**	Utilized VHC's information system to collect prescribing information for each patient. Although there were a lot of data to analyze, I learned how to efficiently present trends in data in a concise and simple format.

Core Area Competencies

Number	Competency	Description
7	**Assess population needs, assets and capacities that affect communities' health**	By creating a survey that was sent to 26 veterinary teaching hospitals and collecting respective responses regarding barriers hindering implementation, current dilemmas in established antimicrobial stewardship programs I was able to understand a range of needs and capacities that affect veterinary health

Core Area Competencies

Number	Competency	Description
19	**Communicate audience-appropriate public health content, both in writing and through oral presentation**	Presenting to University of Kansas Veterinary Pharmacy Club students to understand the initial stages of developing an antimicrobial stewardship program. Developing a poster for presentation to the the patrons of the Phi-Zeta Research Day at KSU, enabled me to share the results of the poster to a wide ranged audience. The creation of a flyer for KDHE distribution was created with a general public audience in mind, therefore the terms were altered for public understanding while conveying an appropriate message.

Core Area Competencies

Number	Competency	Description
21	**Perform effectively on interprofessional teams**	Working on a multidisciplinary team has given me an insight to professional relationships and how to utilize resources available in implementing an antimicrobial stewardship program at the VHC. This experience has provided me many interdisciplinary interactions and made me realize how many people it takes to have a successful experience and the numerous collaborators that have an interest in public health issues.

Core Area Competencies

Number	Competency	Description
22	**Apply systems thinking tools to a public health issue**	There are various unintended consequences that have to be accounted for when developing a program such as an ASP for a veterinary hospital. Working with various health professionals involved in veterinary health allowed me to focus on applying systems thinking approaches and models toward the overall outcomes.

Thank you! Questions?

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Director of Pharmacy

Dr. Ellyn Mulcahy PhD, MPH
Director, Master of Public Health Program

Dr. Michael Apley, DVM, PhD, DACVCP
Professor, Production Medicine/Clinical Pharmacology Frick Professorship

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