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An Epidemiological Exploration of Reduced Vancomycin Susceptibility in *Clostridioides difficile* and Impact on Patient Outcomes

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Clostridioides difficile infection (CDI)

- The most common hospital-acquired infection in the USA and the leading cause of death due to gastroenteritis[1,2]
- Only 2 antibiotics recommended as treatment[3]
  - Oral vancomycin serves as current mainstay of therapy

CDC's *Antibiotic Resistance Threats in the United States, 2019*.

1. Hall et al. *Clin Infect Dis.* 2012; 55:216-223.
2. Lessa et al. *N Engl J Med.* 2015; 372:825-834.
3. Johnson et al. *Clin Infect Dis.* 2021; 73:e1029–e1044.

Vancomycin role in CDI

- Culture and susceptibility testing not routinely conducted for *C. difficile* in clinical practice
- Minimum inhibitory concentration (MIC) of > 2 mg/L considered vancomycin non-susceptible[1,2]

Hypothesis: Increases in vancomycin use applies a selective pressure expediting resistance development

1. CLSI M11: Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria. 9th edition.
2. EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022.
3. Saha et al. *Anaerobe.* 2019; 58:35-46..

Previous surveillance studies

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- Vancomycin non-susceptible isolates: 0% - 39.1%
- Timeframe: 2011 - 2022

J Antimicrob Chemother 2020; **75**: 1824–1832
doi:10.1093/jac/dkaa118 Advance Access publication 15 April 2020

Journal of Antimicrobial Chemotherapy

Antimicrobial susceptibility of *Clostridioides difficile* isolated from diarrhoeal stool specimens of Canadian patients: summary of results from the Canadian *Clostridioides difficile* (CAN-DIFF) surveillance study from 2013 to 2017

James A. Karlowsky[1,2], Heather J. Adam[1,2], Melanie R. Baxter[1], Christopher W. Dutka[1], Kim A. Nichol[2], Nancy M. Laing[1], George R. Golding[1,3] and George G. Zhanel[1]*

J Antimicrob Chemother 2021; **76**: 1815–1821
doi:10.1093/jac/dkab099 Advance Access publication 25 April 2021

Journal of Antimicrobial Chemotherapy

Antimicrobial resistance surveillance of *Clostridioides difficile* in Australia, 2015–18

Papanin Putsathit[1], Stacey Hong[2,3], Narelle George[4], Christine Hemphill[5], Peter G. Huntington[6], Tony M. Korman[7], Despina Kotsanas[7], Monica Lahra[8], Rodney McDougall[9], Andrew McGlinchey[5], Casey V. Moore[10], Graeme R. Nimmo[4], Louise Prendergast[5], Jennifer Robson[9], Lynette Waring[5], Michael C. Wehrhahn[11], Gerhard F. Weldhagen[10], Richard M. Wilson[12], Thomas V. Riley[1,2,3,13] and Daniel R. Knight[2,3]*

IENTIFIC
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High prevalence of *Clostridiodes difficile* PCR ribotypes 001 and 126 in Iran

Clinical Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Reference Susceptibility Testing and Genomic Surveillance of *Clostridioides difficile*, United States, 2012–17

Amy S. Gargis,[1,a,c] Maria Karlsson,[1,2,a,c] Ashley L. Paulick,[1,c] Karen F. Anderson,[1] Michelle Adamczyk,[1] Nicholas Vlachos,[1] Alyssa G. Kent,[1,c] Gillian McAllister,[1] Susannah L. McKay,[1] Alison L. Halpin,[1,d] Valerie Albrecht,[1] Davina Campbell,[1] Lauren C. Korhonen,[1] Christopher A. Elkins,[1,d] J. Kamile Rasheed,[1] Alice Y. Guh,[1] L. Clifford McDonald,[1,d] Joseph D. Lutgring,[1,d] and the Emerging Infections Program *C. difficile* Infection Working Group[b]

[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; and [2]Goldbelt C6, LLC, Chesapeake, Virginia, USA

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hivma hiv medicine association
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Emergence of Clinical *Clostridioides difficile* Isolates With Decreased Susceptibility to Vancomycin

Charles Darkoh,[1,2] Kadiatou Keita,[3] Chioma Odo,[2] Micah Oyaro,[4] Eric L. Brown,[1] Cesar A. Arias,[1,2,5] Blake M. Hanson,[1,5] and Herbert L. DuPont[1,2,6]

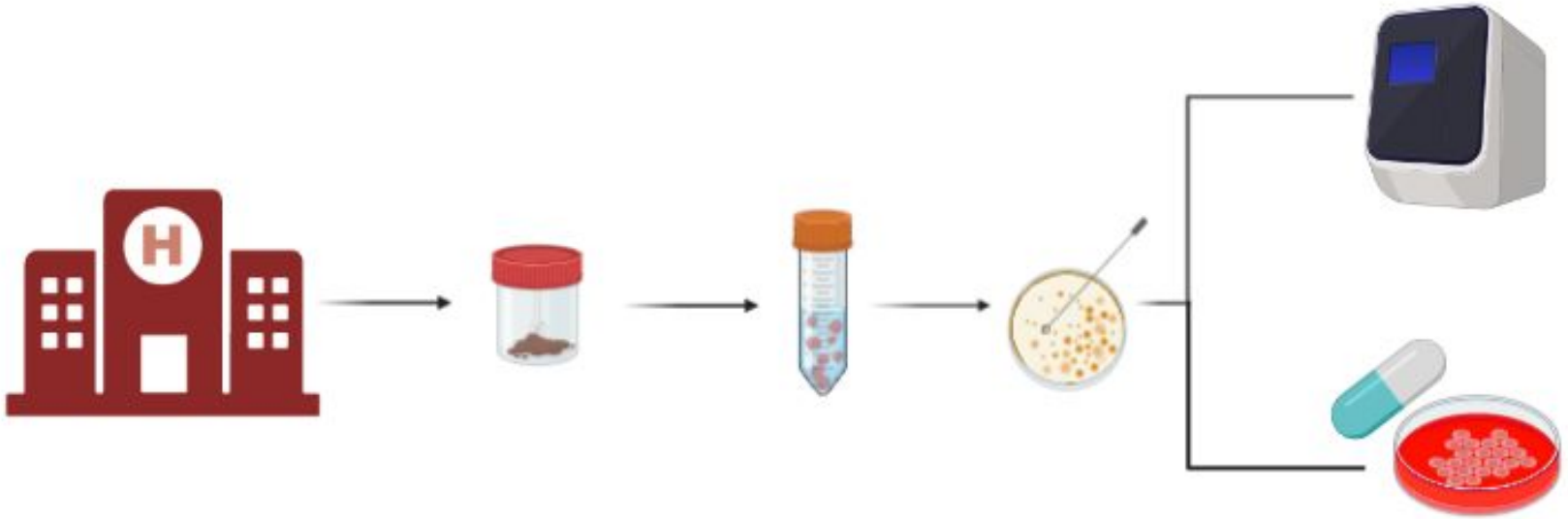
[1]University of Texas Health Science Center, School of Public Health, Department of Epidemiology, Human Genetics, and Environmental Sciences, Center for Infectious Diseases, Houston, Texas, USA; [2]University of Texas MD Anderson Cancer Center, UTHealth Graduate School of Biomedical Sciences, Microbiology and Infectious Diseases Program, Houston, Texas, USA; [3]Alabama A&M University, Huntsville, Alabama, USA; [4]University of Nairobi, School of Medicine, College of Health Sciences, Nairobi, Kenya; [5]Division of Infectious Diseases and Center for Antimicrobial Resistance and Microbial Genomics, UTHealth, McGovern School of Medicine at Houston, Houston, Texas, USA; and [6]Kelsey Research Foundation, Houston, Texas, USA

Specific Aims

- SA1: Epidemiology of vancomycin non-susceptibility
- SA2: Impact of vancomycin non-susceptibility on patient outcomes

Methods: laboratory

- Multicenter cohort study – 2 unique hospital systems within Greater Houston Area
- Adult patients with CDI between 2016 – 2021



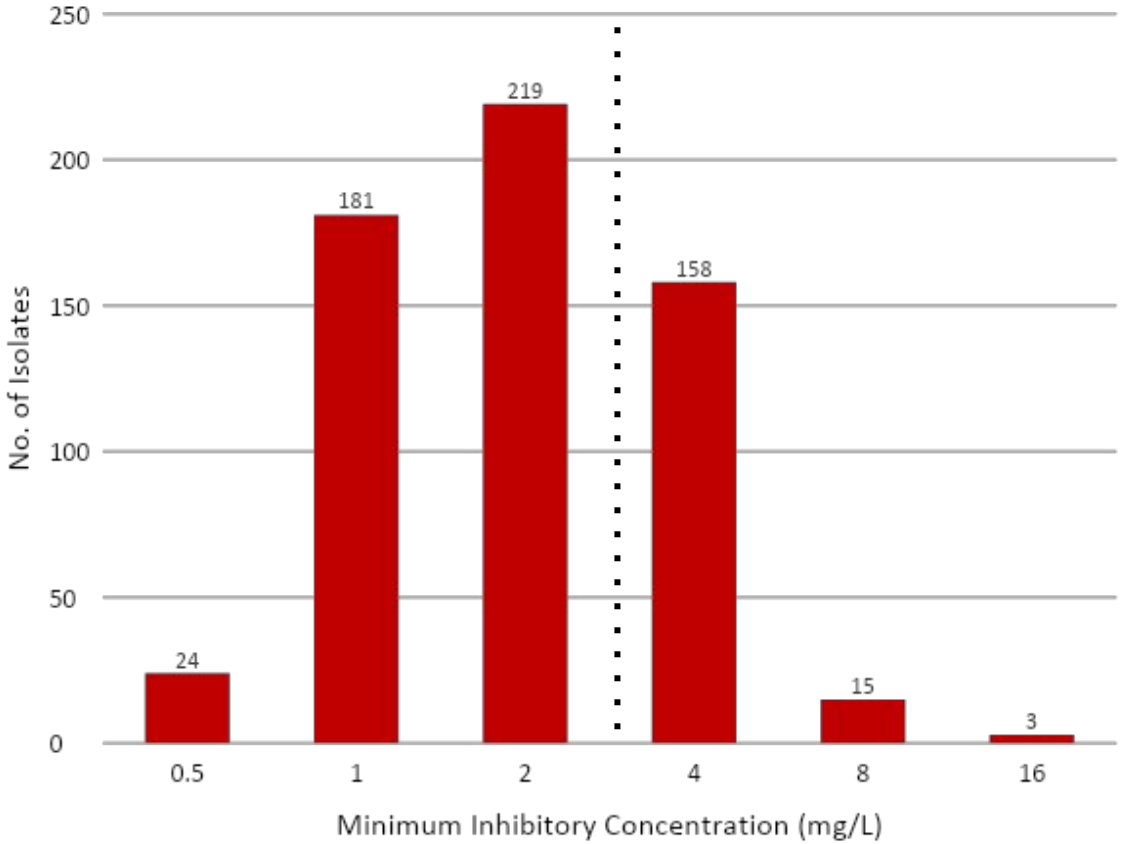
Methods: cohort selection

- **Epidemiology cohort**: 600 isolates from biobank repository
- **Patient outcome cohort:** 300 isolates screened for vancomycin monotherapy
  - Monotherapy defined as definitive vancomycin therapy initiated within 48H of positive CDI test
  - Primary outcome: 30-Day sustained clinical response (no diarrhea by day 14, no recurrence by day 30, alive at day 30)

Specific Aims

- **SA1: Epidemiology of vancomycin non-susceptibility**
- SA2: Impact of vancomycin non-susceptibility on patient outcomes

Epidemiology of vancomycin non-susceptibility



Ribotype	No. isolates	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	% NS
All	600	2	4	0.5 - 16	29.3%
F014-020	111	2	2	0.5 - 8	9.9%
F027	95	4	8	1 - 8	78.9%
F106	69	2	4	0.5 - 16	21.7%
F002	48	2	4	1 - 8	27.1%
F255	32	2	4	0.5 - 4	50%
Other	245	2	4	0.5 - 16	19.6%

NS = non-susceptibility

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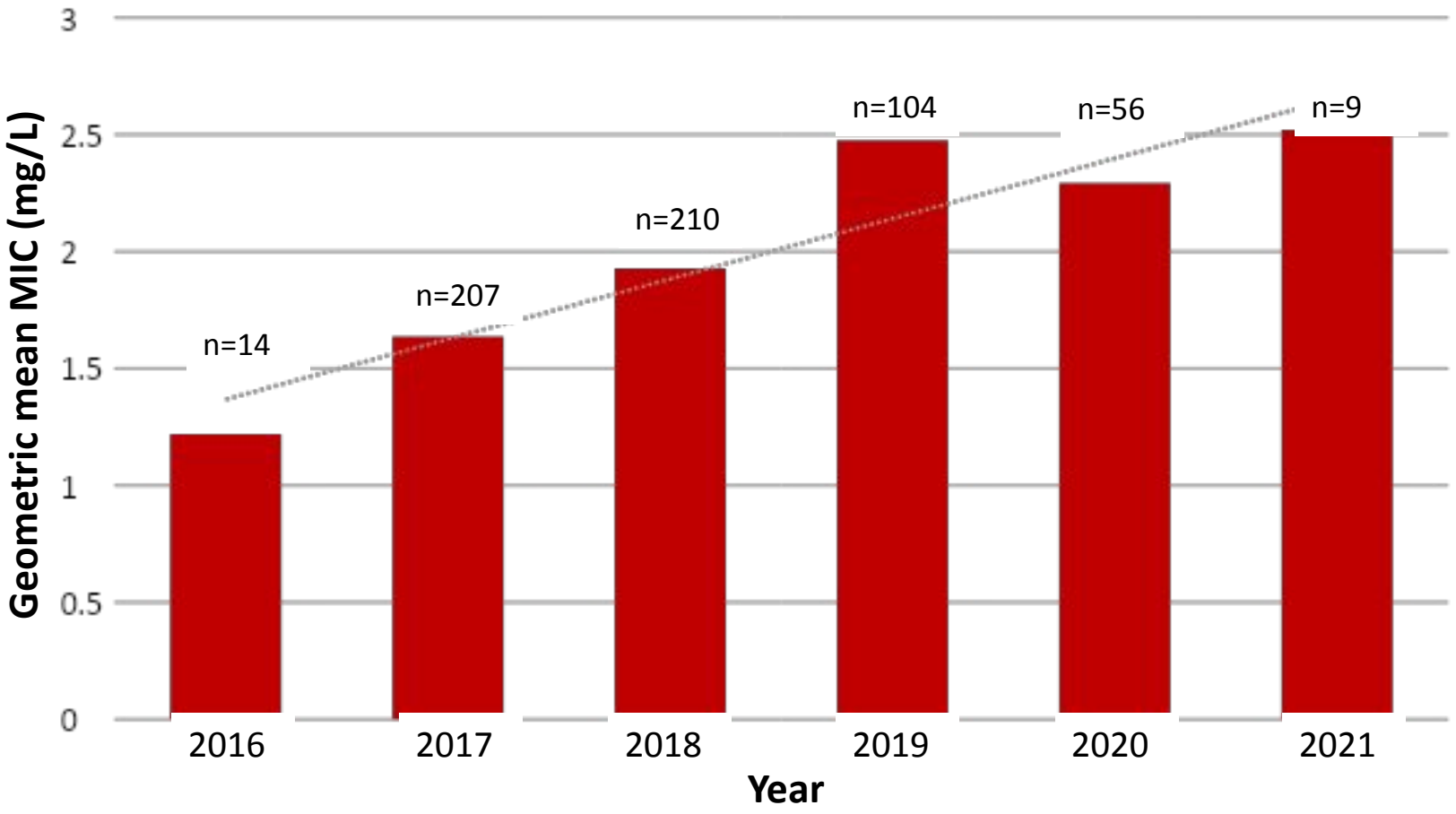
Geometric mean MICs are increasing over time



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Specific Aims

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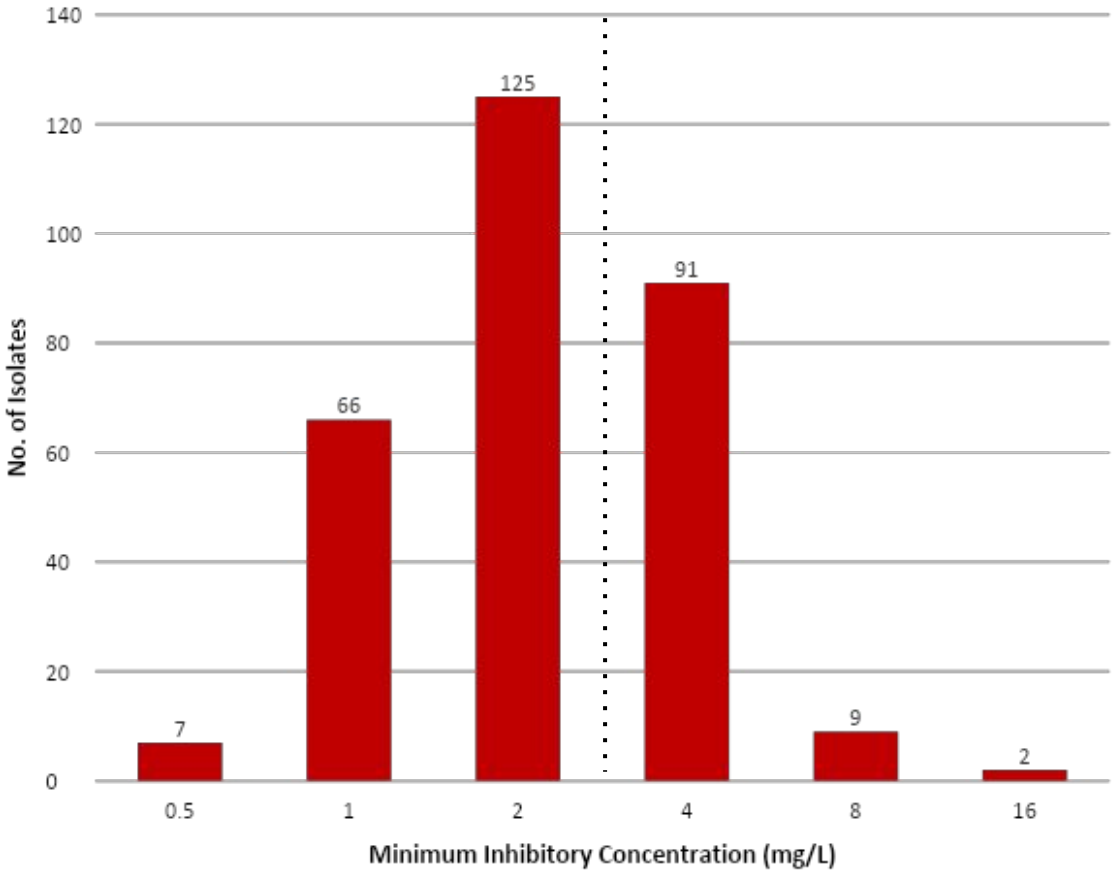
Patient outcome cohort demographics (n=300)

- Male: 71.6% (215/300)
- Mean age: 67 years (18 – 95)
- Race: White 67.6% (203/300)
- Initial Episode: 72.3% (217/300)



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Patient Characteristics	Vancomycin Susceptible (n=198)	Vancomycin Non-susceptible (n= 102)	P value
Male	89 (45%)	42 (41%)	0.533
Age, years (median, IQR)	67 (47 - 87)	70 (50 - 89)	0.100
Charlson Comorbidity Index (median, IQR)	5 (2 – 8)	5 (2 – 8)	0.365
Comorbidities			
Chronic heart failure	33 (16.7%)	29 (28.4%)	**0.017**
Chronic pulmonary disease	46 (23.2%)	29 (28.4%)	0.288
Chronic liver disease	48 (24.2%)	28 (27.5%)	0.545
Chronic kidney disease	68 (34.3%)	34 (33.3%)	0.861
Diabetes mellitus	79 (39.9%)	33 (32.4%)	0.201
Hx of cerebrovascular accident	38 (19.2%)	12 (11.8%)	0.102
Hx of solid organ transplant	20 (10.1%)	8 (7.8%)	0.524
Hx of hematopoetic stem-cell transplant	4 (2.0%)	2 (2.0%)	0.972
GERD	42 (21.2%)	18 (17.6%)	0.465
Other chronic diarrheal diseases	27 (13.6%)	10 (9.8%)	0.339
Community Hospital	85 (42.9%)	52 (51.0%)	0.185
Hospital system 1	136 (68.7%)	78 (76.5%)	0.158
Hospital system 2	62 (31.3%)	24 (23.5%)	0.158

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Clinical Characteristics	Vancomycin Susceptible (n=198)	Vancomycin Non-susceptible (n= 102)	P value
Initial Episode	146 (73.7%)	70 (68.65)	0.449
≥2 Episode			
Prior episode within 30d	11 (5.6%)	11 (10.8%)	0.099
Prior episode within 30 – 90d	13 (6.6%)	6 (5.9%)	0.818
CDI classification			
Community onset	60 (30.3%)	23 (22.5%)	0.155
Healthcare-associated community onset	49 (24.7%)	30 (29.4%)	0.385
Healthcare onset	89 (44.9%)	49 (48.0%)	0.611
2018 IDSA severity index			
Non-severe	98 (49.5%)	57 (55.9%)	0.294
Severe	90 (45.5%)	40 (39.2%)	0.302
Fulminant	10 (5.1%)	5 (4.9%)	0.955
ICU within 48h of diagnosis	43 (21.7%)	26 (25.5%)	0.462
Previous oral vancomycin use[¥]	16 (8.1%)	17 (16.7%)	**0.024**
Days of oral vancomycin therapy (median)	14	14	0.809
Recommended oral vancomycin dose[€]	153 (77.3%)	69 (67.6%)	0.071

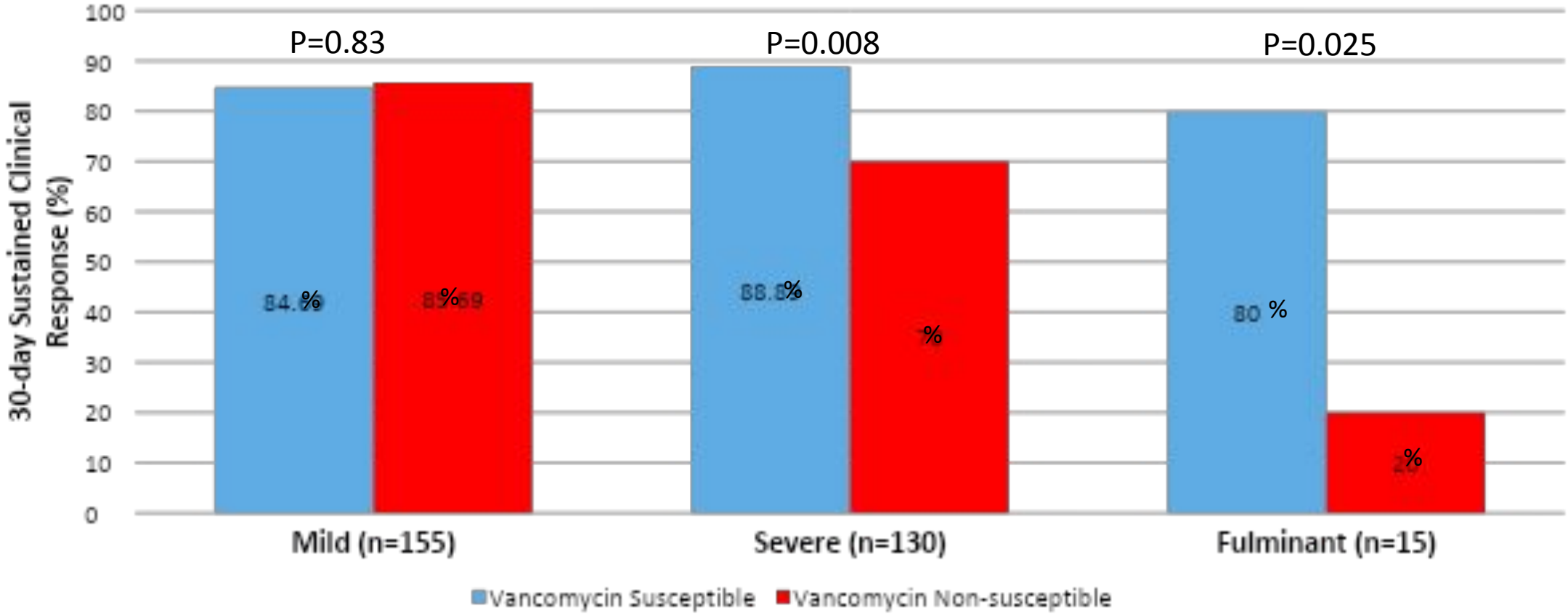
[¥]90 days prior to current CDI diagnosis; [€]125 mg four times daily

Vancomycin non-susceptibility was present in most of the common circulating ribotypes

Ribotype	Non-susceptible (no.)	Total (no.)	% NS
F027	41	53	77.4
FP310	5	7	71.4
F255	9	14	64.3
F106	11	31	35.5
F002	8	24	33.3
F087	2	7	28.6
FP502	2	9	22.2
F014-020	5	45	11.1
F001	1	10	10.0
F054	0	7	0.0
All others	12	78	15.4

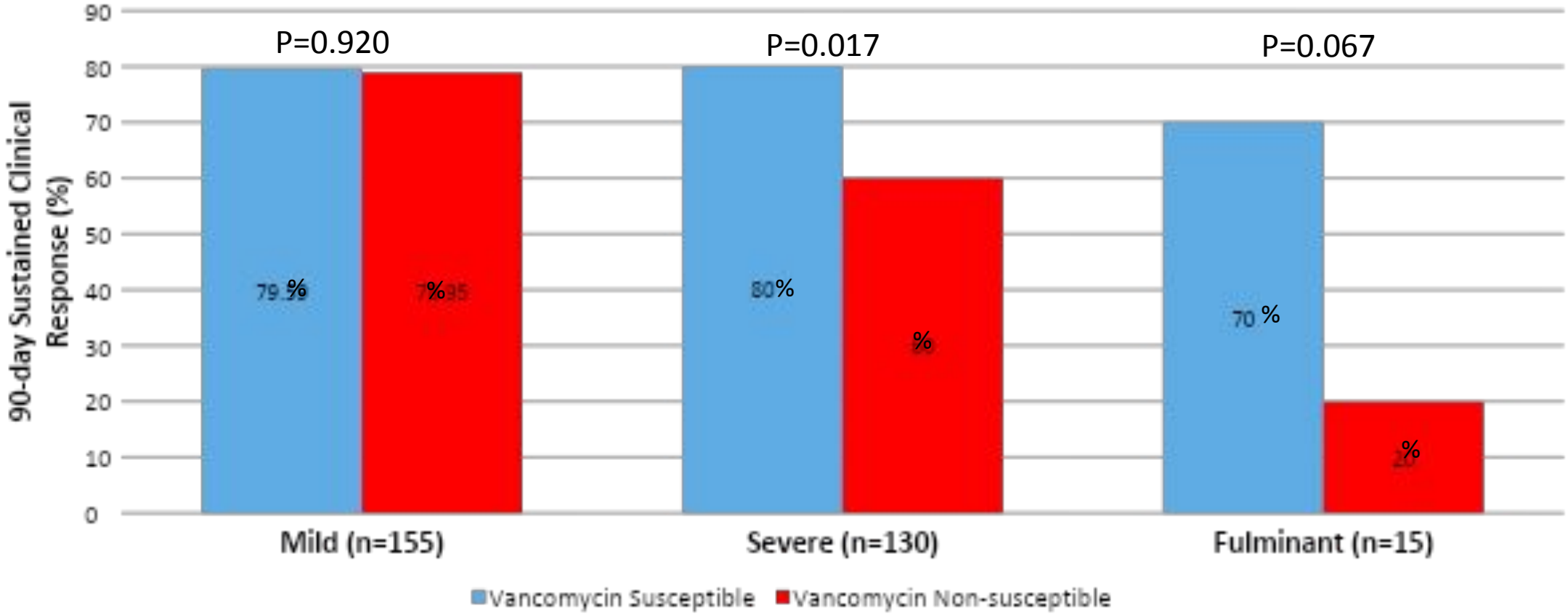
NS = non-susceptibility

In patients with severe/fulminant disease, 30-day sustained clinical response decreased significantly in patients with non-susceptible strains



Results were confirmed with multivariable regression analysis controlling for patient co-morbid conditions

In patients with severe/fulminant disease, 90-day sustained clinical response decreased significantly in patients with non-susceptible strains



Results were confirmed with multivariable regression analysis controlling for patient co-morbid conditions

Conclusions

- Vancomycin non-susceptible strains are common (29.3%, 176/600)
  - Non-susceptibility is most common within ribotype F027 (78.9%, 75/95)
- There is an observed increase in vancomycin MIC over time
- In patients with severe and fulminant disease, 30- and 90-day sustained clinical response is significantly lower in patients with non-susceptible strains

Next steps & future directions

- Identify risk factors driving vancomycin non-susceptibility
- Characterize mutations within the *vanG* operon
- Describe *vanG* expression via qPCR
- Investigate clinical outcomes associated with *vanG* expression

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