Controversial Topics in Microbiology

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Richmond, VA

10/11/2022

Conflicts of Interest

Scientific Advisory Board – Quidel, GeneCapture

Scientific Advisory Panels – Cepheid

Son of notable contrarian

Father of future notable contrarians

Public Awareness of Medical Topics

IMPORTANCE OF THE LAY PRESS IN THE TRANSMISSION OF MEDICAL KNOWLEDGE TO THE SCIENTIFIC COMMUNITY

Abstract *Background.* Efficient, undistorted communication of the results of medical research is important to physicians, the scientific community, and the public. Information that first appears in the scientific literature is frequently retransmitted in the popular press. Does popular coverage of medical research in turn amplify the effects of that research on the scientific community?

THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 17, 1991

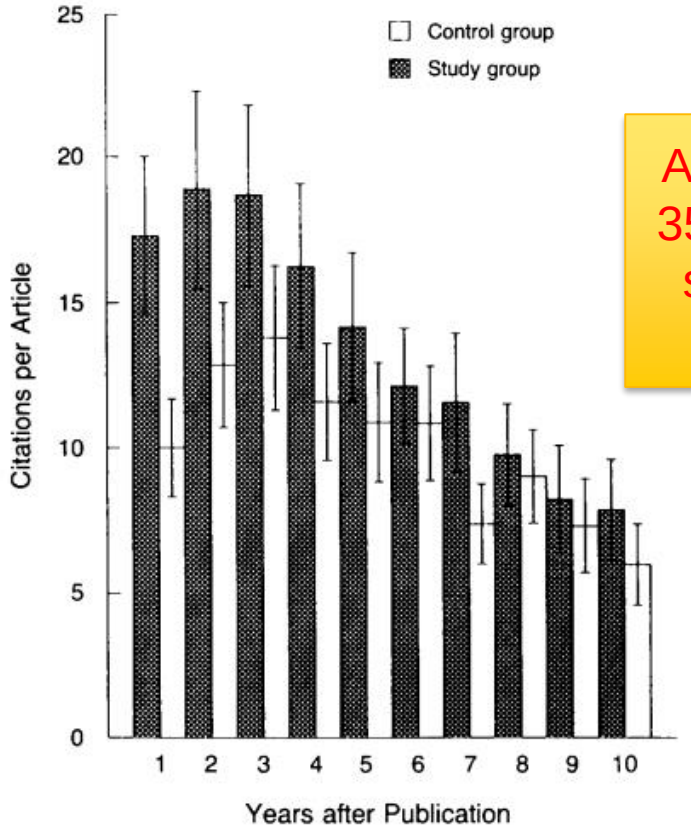


Figure 1. Mean (±SE) Number of Scientific Citations of 25 *Journal* Articles Covered by the *Times* (Study Group) and 33 *Journal* Articles Not Covered by the *Times* (Control Group).
The articles were published in the *Journal* in 1979, and citations were tracked for the 10 years from 1980 to 1989.

Articles featured in the NYT had 35% more citations compared to similar articles not featured by the NYT.

JOURNAL OF MEDICAL INTERNET RESEARCH

Review

Prevalence of Health Misinformation on Social Media: Systematic Review

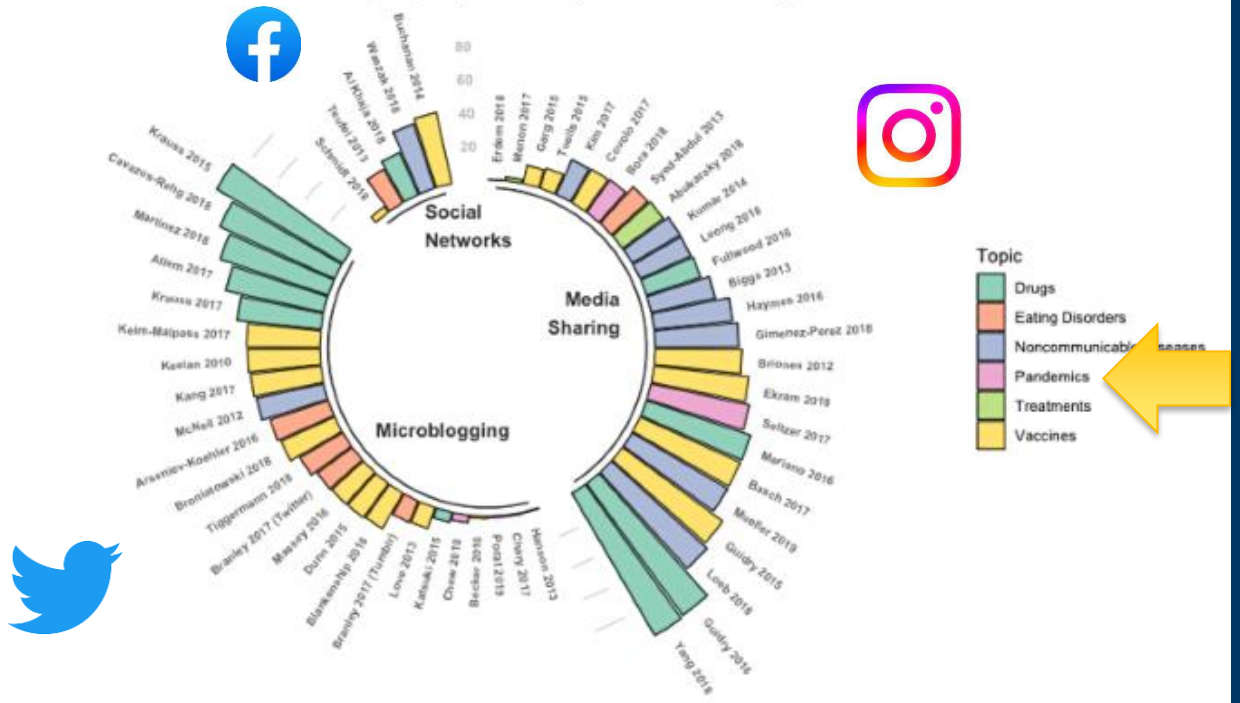
Victor Suarez-Lledo[1,2*], BSc, MSc; Javier Alvarez-Galvez[1,2*], BSc, MSc, PhD

[1]Department of Biomedicine, Biotechnology and Public Health, University of Cadiz, Cadiz, Spain

[2]Computational Social Science DataLab, University Research Institute on Social Sciences, University of Cadiz, Jerez de la Frontera, Cadiz, Spain

*all authors contributed equally

Figure 2. Prevalence of health misinformation grouped by different topics and social media type.



Clinical Infectious Diseases

SUPPLEMENT ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Misinformation and Disinformation: The Potential Disadvantages of Social Media in Infectious Disease and How to Combat Them

Angel N. Desai,[1] Diandra Ruidera,[2] Julie M. Steinbrink,[3] Bruno Granwehr,[4] and Dong Heun Lee[5]

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associa by the parents, with measles, mumps, and rub vaccination in eight of the 12 children, with measl infection in one child, and otitis media in a All 1 children had intestinal abnormalities rangi from lymphoid nodular hyperplasia to a oid u ration. Histology showed patchy chronic inflam tion in 11 children and reactive ileal mpho perplasia in seven, but no granulomas. Be ioural disor s included autism (nine), disintegrativ sis (one), a possible postviral or vaccinal encephalitis o). There were no focal neurological ab malities and and EEG tests were normal. Abno al laboratory results re significantly raised urinary thylmal c acid compared with age-matched contro p=0·003), lo haemoglobin in four children, a low s m IgA in r children.

Inter tation e iden associated gastrointestinal di se and evelopmental regression in a group of previ ly mal chi n, which was generally associated in time o possible environmental triggers.

Lancet 199 **351:** 637–41

Introduction

We saw several children who, after a pe d of apparent normality, lost acquired skills, includ g com ication. They all had gastrointestinal mptoms, luding abdominal pain, diarrhoea, and ating and, some cases, food intolerance. We scribe clinical f dings, and gastrointestinal featur of these chi en.

Patients and meth ds

12 children, cons ctively red to department of paediatric gastr terology a hi y of a pervasive developmental der with loss quired skills and intestinal symptoms arrh abdomina in, bloating and food intolerance), were inv gated. All children were admitted to the ward f week, accomp ed by their parents.

Clinical investigations

took histor including details of immunisations and e sure to infec s diseases, and assessed the children. In 11 cas the histor as obtained by the senior clinician (JW-S). Neure ical and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental s included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known

RETRACTED

VCU Health

Great controversies (and stories) in microbiology history…

Discovery of the Gram stain

Controversial "Pathogens"

Aeromonas

Dientamoeba fragilis

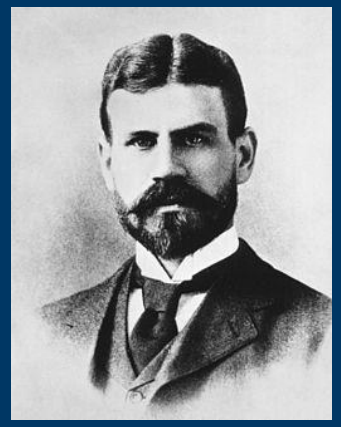
***Fusobacterium* (Respiratory flora?)**

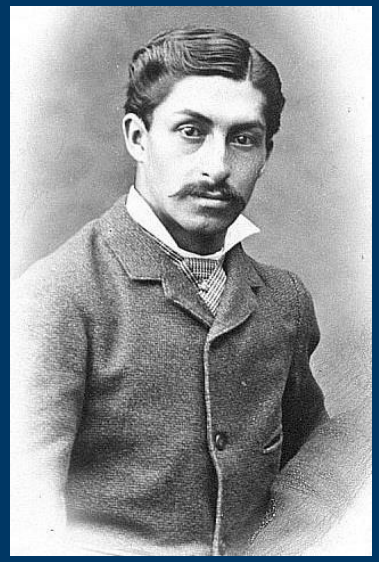
~~***Propionibacterium***~~ **(dammit!!!) *Cutibacterium***

Sooooo many things COVID-19

VCU Health

Self-Experimentation in Science





- 5 Nobel laureates
- Some have died
  - Jesse Lazear – yellow fever
  - Dan Carrion – Bartonella (now known as Carrion's disease)
- Other infectious diseases studied
  - Cholera, HIV, dysentery, *H. pylori*, *Campylobacter*
  - *S. aureus* – (Gail Dack – former president of ASM)
  - Syphillis
  - Schistosomiasis

The Controversial History of the Gram stain

"A defective and imperfect method"
- H. Christian Gram referring to his development of the Gram stain

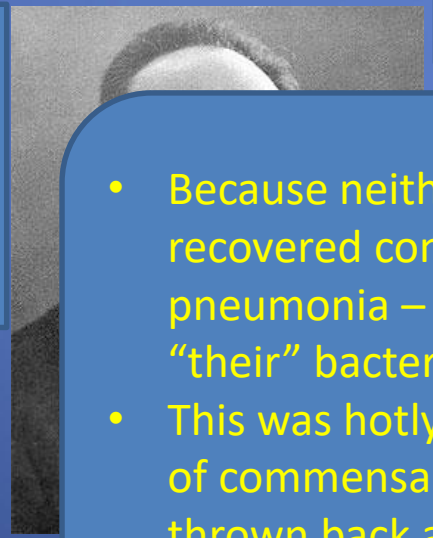
After earning his MD and PhD, Gram joined the laboratory of Karl Friedlander. 1883

Friedlander was investigating the bacterial etiology of pneumonia.

He had discovered two different bacteria - one bacillus and one coccus

Friedlander declared the bacillus the cause of pneumonia.
"Friedlander's Bacillus"

Meanwhile – Albert Fraenkel – Friedlander's scientific rival – declared the coccus as the cause of pneumonia.
"pneumococcus"



- Because neither organism could be recovered consistently from patients with pneumonia – both scientists advanced "their" bacteria as the true cause.
- This was hotly contested with accusations of commensal and contaminant being thrown back and forth.

Cantey et al. Pediatric Infectious Disease Journal. 2015. 34(8)

The Controversial History of the Gram stain

"(My stain) is very defective and imperfect, but it is to be hoped that…it will turn out to be useful."

- H. Christian Gram in his publication describing the development of the Gram stain

Gram developed the Gram stain - 1884

1. Dry fluid with burner flame onto a slide
2. Poured Gentian violet over it
3. Wash away with water
4. Potassium triiodide solution
5. Wash with ethanol – Purple were positive and colorless were negative

A few years later pathologist Carl Weigert added the final step of safranine.

Ultimately, it was the Gram stain that settled the debate.
Both were causes of pneumonia.
Pneumococcus would turn out to be *S. pneumoniae*
Friedlander's Bacillus would turn out to be *Klebsiella pneumoniae.*

While working late one night Gram spilled iodine on some lung sections that had been stained with methyl violet. He tried to wash this off with ethanol and noticed that those with cocci retained the stain and those with bacillus did not.

Cantey et al. Pediatric Infectious Disease Journal. 2015. 34(8)

As for the dispute....

- Friedlander ended it saying…

"That pneumonia should be produced by different causes is analogous to the multiple causes of acute suppuration….the attacks, let them cease."

Controversial Topics in Microbiology

Objectives

- Provide context to these controversial issues
- Present both sides of the issue
- Provide some education on the issue to enable respectful dialogue (debate)

Topics we'll discuss this morning

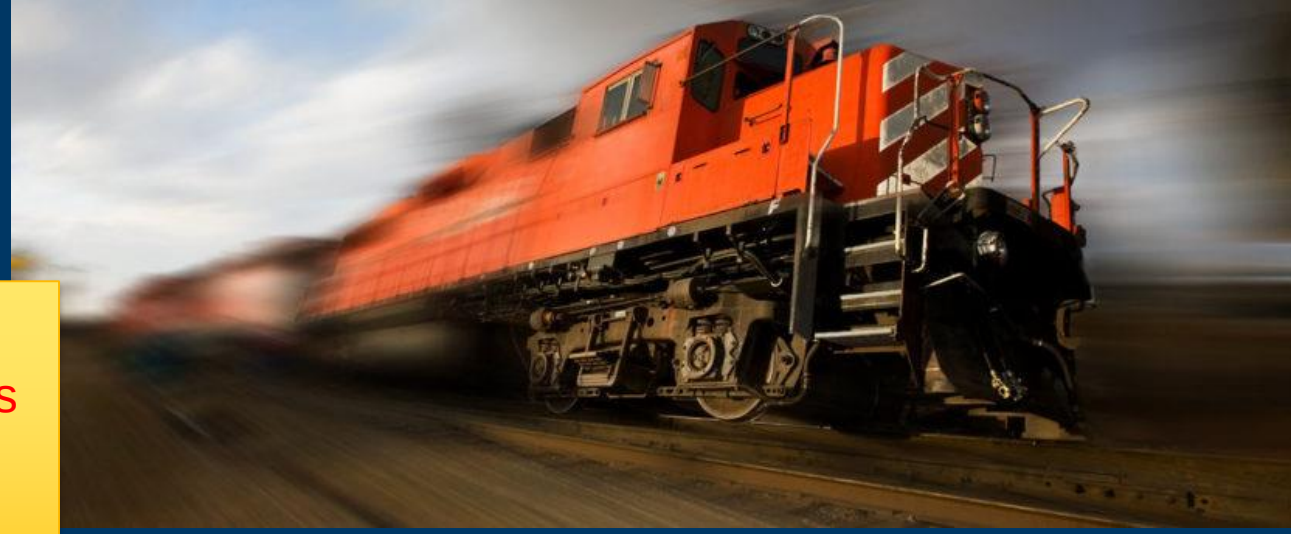
KARIUS
clarity at speed®

Reporting of Vancomycin MICs

What is the utility of COVID-19 antigen testing?

KARIUS

clarity at speed®



Intended Use

- Diagnosis of infection in immunocompromised patients
  - Pneumonia
  - Invasive fungal infection
  - Endocarditis
  - Neutropenic fever

Karius claims

- Avoid >60% of invasive diagnostic procedures from a single blood draw (liquid biopsy)
- <1 day TAT
- Detect >1000 pathogens

Costs

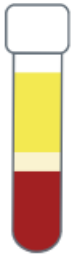
- ~$2,000

Charge to patient

- >$4,000

How it works

** >85% of specimens received by 8:30 AM (PT) Monday through Saturday are reported the next day.*



Step 1
Specimen Collection

5-mL standard blood draw in plasma preparation tube

Step 2
Specimen Processing

DNA extraction and library preparation

Step 3
Sequencing

Microbial cell–free DNA sequencing

Step 4
Analysis

Curated clinical-grade pathogen database

Step 5
Reporting

Quantitative amounts of clinically relevant pathogens

Sample test report >

Consultations are available with Karius infectious disease physicians and clinical microbiologists.

Oops

Order the Karius Test

KARIUS TEST REPORT

Karius ID: KA-XXXXXX

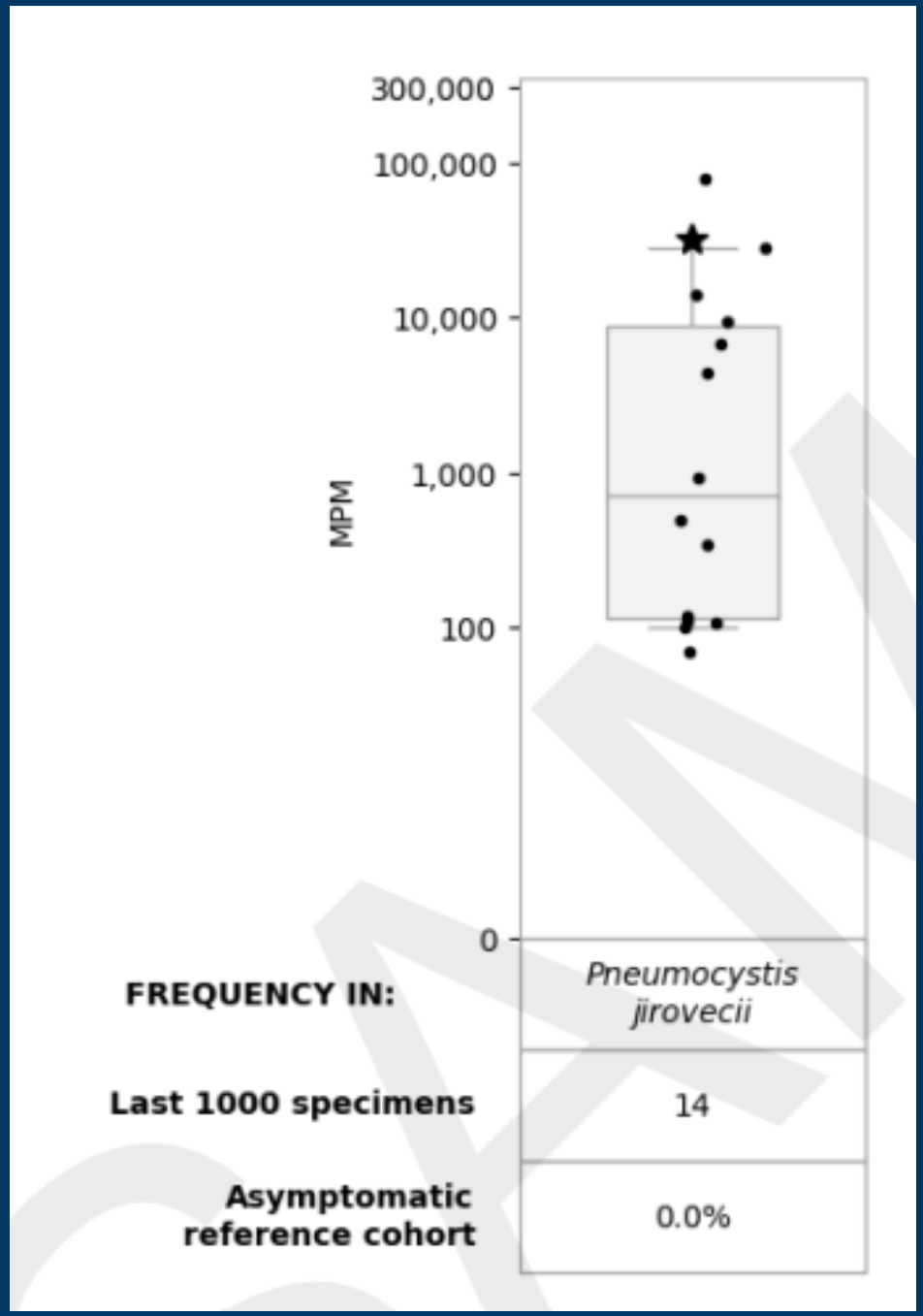
KARIUS® clarity at speed™ | TEST

SPECIMEN TYPE: PLASMA

SPECIMEN INFORMATION	**Collected**	**Received**	**Reported**	**Specimen ID**
PATIENT INFORMATION	**MRN#**	**Last Name**	**First Name**	**Date of Birth**
INSTITUTION INFORMATION	**Ordering Physician**		**Address**	

TEST RESULTS

MICROORGANISM DETECTED	DNA MOLECULES PER MICROLITER (MPM)*	REFERENCE INTERVAL (MPM)**
Pneumocystis jirovecii	**32,023**	**< 10**

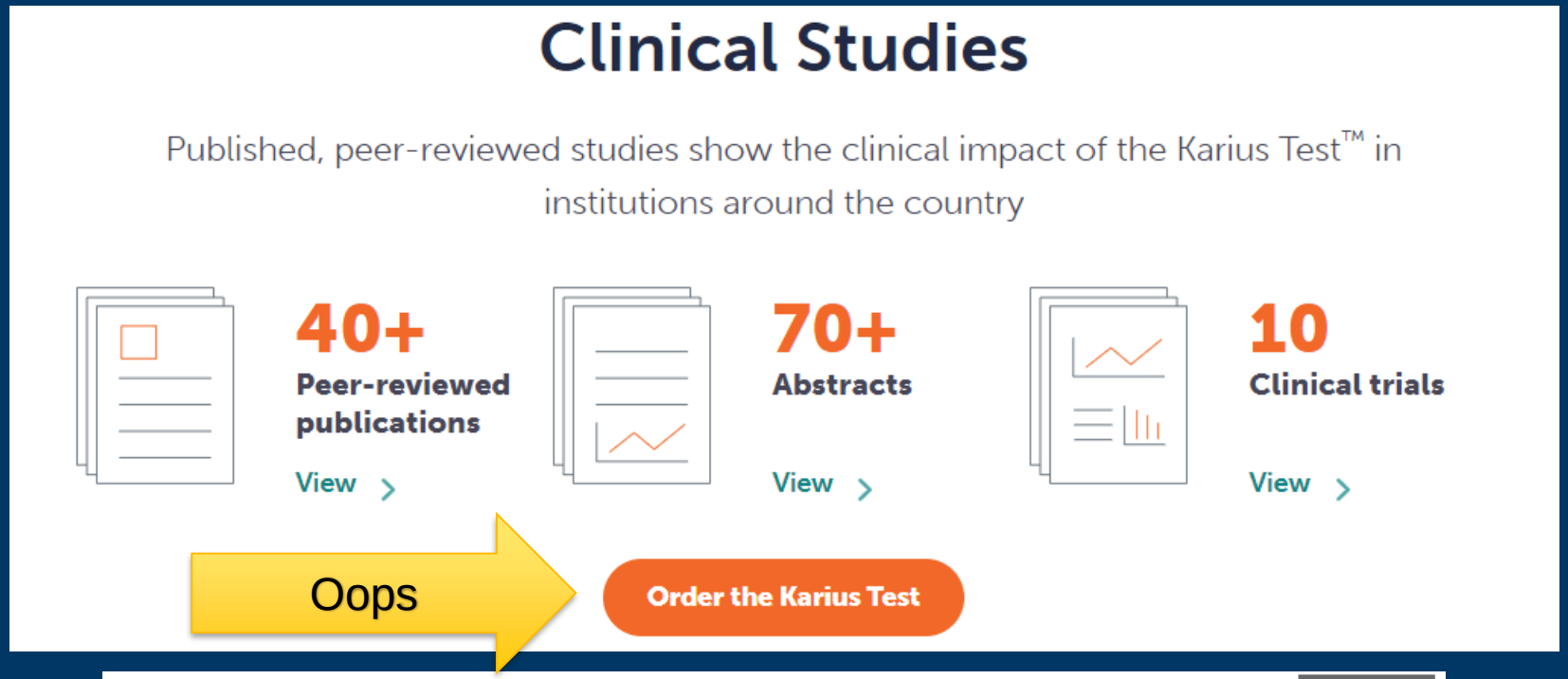

300,000
100,000
10,000
1,000
100
0
MPM
FREQUENCY IN:
Pneumocystis jirovecii
Last 1000 specimens
14
Asymptomatic reference cohort
0.0%

Repeat Testing?

HISTORY OF KARIUS TEST RESULTS ON THIS PATIENT (MPM VALUES BY DATE COLLECTED)

MICROORGANISM NAME	R.I.	02/07/2021	01/31/2021	01/14/2021	12/12/2020	11/05/2020
Pneumocystis jirovecii	< 10	**32,023**	**7,989**	**4,953**	**4,251**	**41,192**

What does the data say?



What did they find?

- 90% positive agreement with culture
  - 61% were polymicrobial
- 31% negative agreement with culture
- 87% Karius results available before culture
- 27.3% of patients had antibiotics narrowed

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Plasma Microbial Cell-free DNA Next-generation Sequencing in the Diagnosis and Management of Febrile Neutropenia

Esther Benamu,[1] Kiran Gajurel,[2,©] Jill N. Anderson,[3] Tullia Lieb,[4] Carlos A. Gomez,[5] Hon Seng,[6] Romielle Aquino,[7] Desiree Hollemon,[7] David K. Hong,[8] Timothy A. Blauwkamp,[7] Mickey Kertesz,[7] Lily Blair,[7] Paul L. Bollyky,[3] Bruno C. Medeiros,[9] Steven Coutre,[9] Simona Zompi,[10] Jose G. Montoya,[11] and Stan Deresinski[3]

Why this test is controversial/troubles many microbiologists (me).

Cost

VCU spent >$225,000 last year on Karius testing

****Our most expensive send out test by more than double.**
*****Second – Beta D Glucan**
******Third - Galactomannan**

Confusing results

Metagenomics picking up environmental contamination…..
61% polymicrobic infection?

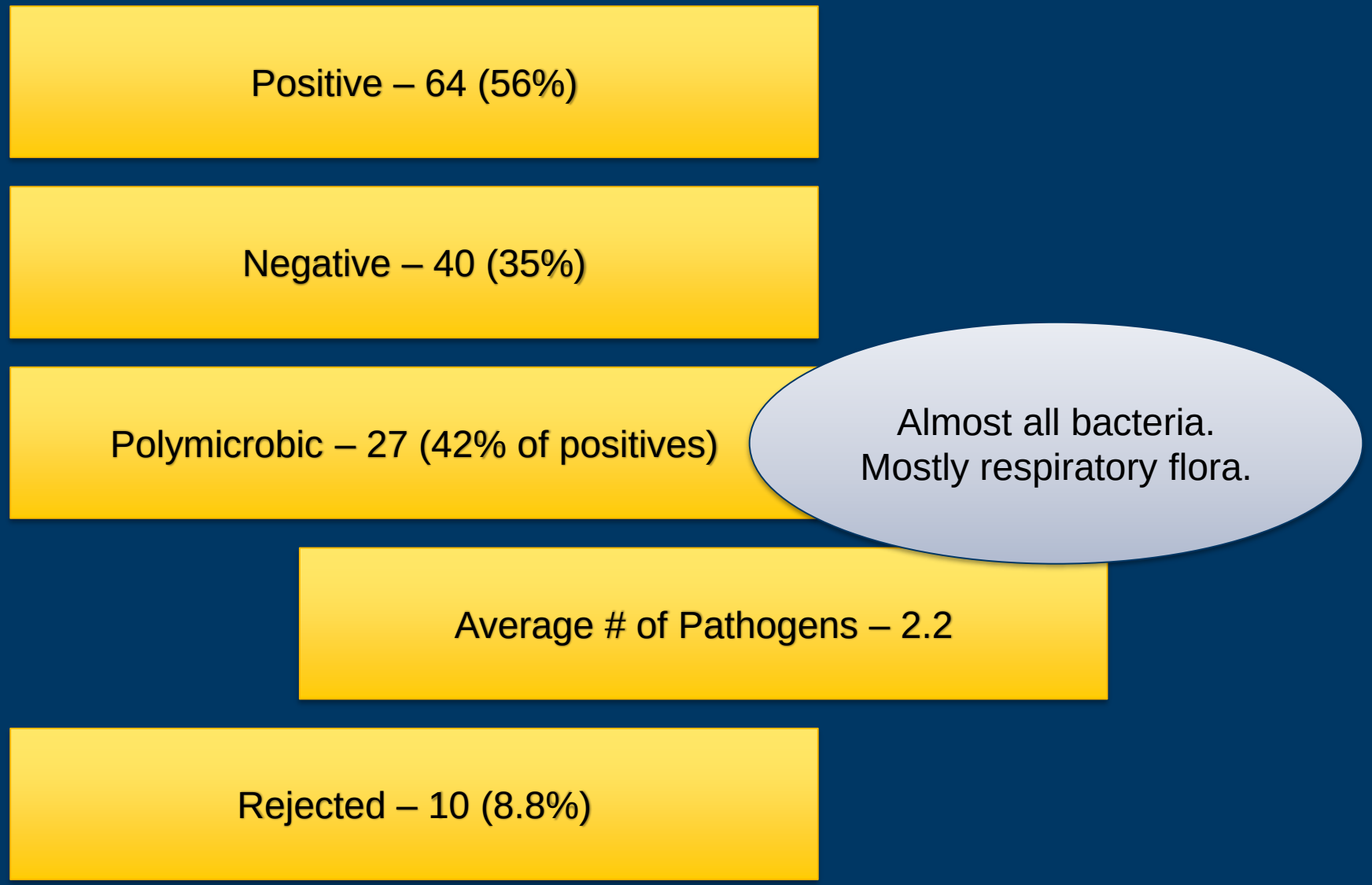
The VCUHS experience

VCU Health

10/11/2022

Utilization Analysis – April 2020 – December 2021

- 114 Tests performed
- ~$228,000 spent
- Average TAT – 33 hours



VCU Health

Some of our positive results

Polymicrobials (N= 27)

- Most mixed respiratory flora
- Some mixed respiratory flora with a real pathogen that was detected by culture

Example 1

Pseudomonas aeruginosa	31927	<10
Klebsiella aerogenes (Enterobacter aerogenes)	9633	<10
Staphylococcus epidermidis (coagulase-negative	4682	<13
staphylococcus)	3356	<10
Lactobacillus rhamnosus	1026	<85
Stenotrophomonas maltophilia		

Patient had *Pseudomonas* BSI
S. maltophilia in respiratory cultures
No indication of other organisms.

Example 3

Rhizomucor pusillus	10607	<10
BK polyomavirus	1126	<10
Lactobacillus rhamnosus	82	<10
Human polyomavirus 6	66	<10

1 colony of a zygomycete isolated from liver biopsy

Example 2

Pichia kudriavzevii	3345	<10
Rothia mucilaginosa	427	<10
Prevotella oris	209	<10
Schaalia odontolytica	135	<10
Prevotella buccae	126	<10
Tannerella forsythia	110	<10

The other side of the coin…

- Low level Tuberculosis (probably real)
- *Nocardia*
- *Legionella pneumophila*
- Numerous low level *P. aeruginosa* (unclear significance)
- *Rhizopus* spp. (repeatedly positive)

The TAT is excellent

- We've had instances where Karius helped us identify organisms from positive blood cultures.

Why this test is controversial/troubles many microbiologists.

Cost

VCU spent >$225,000 last year on Karius testing

****Our most expensive send out test by more than double.**
*****Second – Beta D Glucan**
****** Third - Galactomannan**

Confusing results

Metagenomics picking up environmental contamination…..
61% polymicrobic infection?

Inappropriate uses

Narrowing therapy - Is this a rule-out test?

Repeat testing for “trending”?

Of the 114 tests over this time – 16 (14%) were repeated
Apparently to adjudicate possible contamination

VCU Health

Observed trends to watch out for in use

Repeat testing

Karius as a rule out

- It is not a rule out and **negative** results should be interpreted very cautiously.

Claims that things will not be done according to Karius test results -

- “Saves a patient a BAL”

Karius in actively bacteremic patients

What to do with this test?

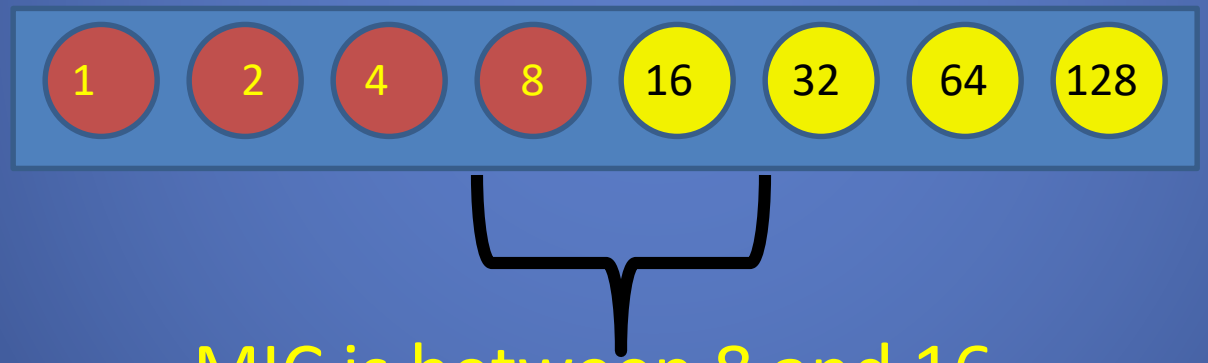
1. Implement an approval process.
2. Restrict repeat testing
3. Reserve for difficult cases where standard of care methods have failed to yield a diagnosis.
4. Collaborate with Infectious Diseases and Transplant Services

Next topic…

Reporting of Vancomycin MICs

But First: What is the value of the MIC?

- **The MIC does not represent an absolute value!**
- The “true” MIC is somewhere between the lowest test concentration that inhibits growth and the next lower concentration.



MIC is between 8 and 16

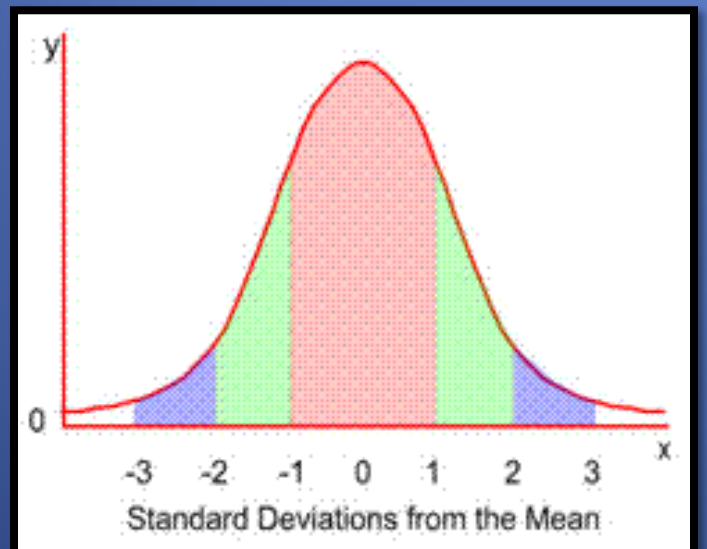
Shouldn’t we be more precise?

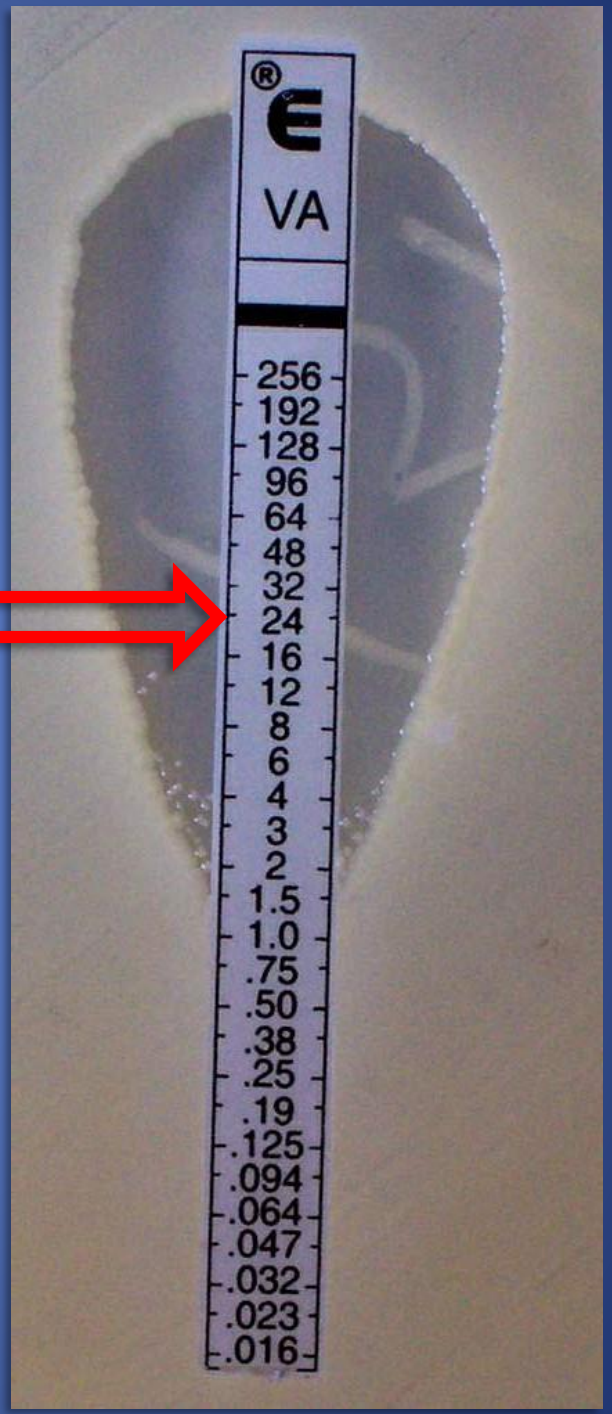
The value of an MIC…

What about the E-test?

Remember….

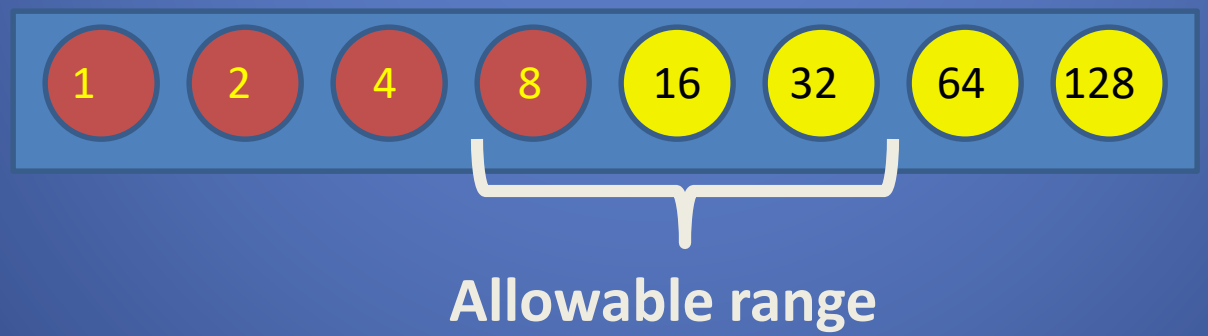
- The acceptable reproducibility of the test is within **ONE** twofold dilution of the actual end point.





The value of an MIC…

- In this example the MIC was read as 16.
- If this isolate were to be retested some percentage of the time the value would be 8 or 32.



Is the MIC…

16 ug/ml

Or

8 – 32 ug/ml

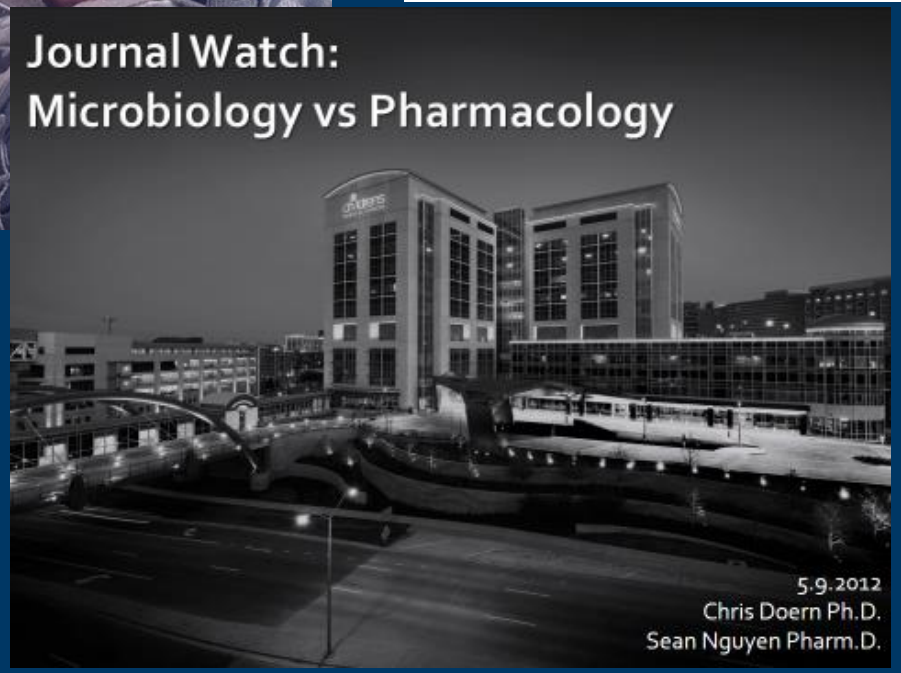
What about Vancomycin MICs????

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

POINT-COUNTERPOINT

Point-Counterpoint: Should Clinical Microbiology Laboratories Report Vancomycin MICs?

Sara L. Revolinski,[a] Christopher D. Doern[b]



Who is reporting Vancomycin MICs?

Institution	Method	MIC Reporting (Y/N
UTSW	Microscan	Yes
VCU	Vitek	Yes
Ontario	Vitek (confirm 2's with ETEST)	Yes
Cook Childrens, TX	Vitek	Yes
Tristar, TN	Microscan	Yes
U of Tennessee	Microscan	Yes
CHOP	Vitek	Yes
Mayo AZ	BD Phoenix	Yes
Northwestern	Vitek	Yes
Wash U	Vanc Screen Agar	No
CMC Charlotte	Microscan	Yes
Augusta	Vitek	Yes
Oklahoma	Microscan	Yes
Columbia	Microscan	Yes
Altru Health, ND	Vitek	Yes
SSM, STL	Vitek	Yes
ARUP	BD Phoenix	Yes
Prisma Health	Vitek	No
UCLA	ref BMD	Yes
Parkland	Microscan	Yes
ACL Laboratories	Microscan	Yes
VA Boston	Microscan	Yes
SUNY	Vitek	Yes
Miami	Vitek	Yes (only 2's)
Arizona	Vitek	Yes
MSK	Microscan	Yes
Penn State	Microscan	Yes
U of Maryland	Vitek	Yes
Military Med Hosp, Hanoi	Etest	Yes
Mayo, Rochester	Agar Dilution	Yes
CHOLA	BD Phoenix	Yes
Dartmouth	Microscan	No
Seattle Childrens	Etest	Yes
Bach Mai Hosp, Hanoi	Etest	Yes
UPMC Childrens	Vitek	Yes
UPMC Core	Microscan	Yes
Childrens National	Microscan	Yes (ID only view)
Case Western	Microscan	No
Johns Hopkins	BD Phoenix	Yes
UTHSA	Vitek	Yes
Emory	Vitek	No
Childrens Milwaukee	BD Phoenix	Yes
WVU	Vitek	Yes

Why do we do this?

Outcomes of Vancomycin Therapy in 92 Patients with MRSA Bacteremia (2005-2007)

Outcome	VAN MIC ≥1.5 (66 patients)	VAN MIC <1.5 (26 patients)	*P* value
Overall failure	24 (36.4)*	4 (15.4)	0.049
Hospital length of stay	21 (9.0-43.0)	10.5 (9.0-16.5)	0.02

* No. (%) of patients

MIC testing performed by Etest

Lodise et al. 2008. Antimicrob Agents Chemother. 52:3315.

See also…

Soriano et al. 2008. Clin Infect Dis. 46:193.

Kollef et. al. 2007. Clin Infect Dis. 45 (Suppl 3): S191.

Slide courtesy of Janet Hindler

Conclusion

MRSA infections caused by organisms with vancomycin MIC =2 have worse outcomes than…

MRSA infections with vancomycin MIC <2.

Patients are more likely to die and have longer lengths of stay with vancomycin MICs of 2.

Why the controversy?

- Limitations of the MIC in general
- Vancomycin testing method dependent
- This conclusion isn’t what it seems (microbiology cliffhanger) ☺

Method Matters: Vancomycin MIC (N=101 MRSA)

Etest MICs > Reference Broth Microdilution and Agar Dilution MICs

TABLE 1. Comparison of vancomycin MICs determined by broth microdilution, agar dilution, and Etest[a]

Vancomycin MIC (μg/ml)	No. of isolates (%) with MIC (μg/ml) determined by:			
	Broth microdilution	Agar dilution	Etest (Remel agar)	Etest (BBL agar)
0.5	21 (20.8)	1 (1)	0 (0)	0 (0)
0.75			1 (1)	1 (1)
1	77 (76.2)	88 (87)	11 (10.9)	1 (1)
1.5			69 (68.3)	62 (61.4)
2	3 (2.97)	12 (11.9)	20 (19.8)	37 (36.6)
Modal MIC (μg/ml)	1	1	2	2

[a] MICs were determined for 101 MRSA blood isolates obtained between 2002 and 2006.

Prakash et al. 2008. Antimicrob Agents Chemother. 52:4528.
See also…Hsu et al. 2008. Intl J Antimicrob Agents. 32:378.
Sader et al. 2009. Antimicrob Agents Chemother. 53:3162.

Method dependence: Multicenter QC Data

					QC MIC Result (%)		
Lab #	**Organism**	**Method**	**QC Range**	**Total Tests**	**≤0.5 ug/ml**	**1 ug/ml**	**2 ug/ml**
1	*S. aureus* 29213	Vitek 2	≤0.5 - 2 ug/ml	20	10 (50%)	10 (50%)	0
2	*S. aureus* 29213	Vitek 2		18	13 (82%)	5 (18%)	0
3	*S. aureus* 29213	Vitek 2		47	13 (28%)	34 (72%)	0
6	*S. aureus* 29213	Vitek 2		20	0	20 (100%)	0
3	*S. aureus* 29213	Etest		4	0	0	4 (100%)
4	*S. aureus* 29213	Etest		50	0	6(12%)	44(88%)
5	*S. aureus* 29213	Etest		21	0	0	21 (100%)
6	*S. aureus* 29213	Etest		20		1 (5%)	19 (95%)
5	*S. aureus* 29213	Microscan	0.5-2 ug/ml	20	0	20 (100%)	0
5	*S. aureus* BAA-977	Microscan	None	20	13 (65%)	7 (35%)	0

What IDSA says…

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

crodilution testing [341]. Because current susceptibility testing methods are unable to reliably distinguish MICs of 1 μg/mL from MICs of 2 μg/mL, the Panel recommends evaluation of the patient's clinical and microbiologic response along with MIC results when making decisions regarding therapy.

Liu et al. 2011. CID. 52:285

What is the question being asked by these studies?

- Does an MIC of 2 for *S. aureus* infection mean that the patient is more likely to have a poor outcome?
- Data from the meta analysis suggests yes!

But……

- Comparison of MRSA isolates in BSI with various vancomycin MIC's treated with vancomycin.
- When we report an MIC of 2 what does a physician do? Change therapy.
- When we report an MIC of 1 what does a physician do? Continue vancomycin.
- What the data doesn't show….

That **alternative therapies** are superior to vancomycin at MIC's of 2, but NOT at lower MIC's.

The real question…

Are other antibiotics superior to vancomycin when MIC's are 2
BUT…
Equivalent at lower MICs?

Because if other therapies are superior at lower MIC's as well, then those therapies ought to be considered based on a patient's clinical response…NOT the MIC.

IDSA GUIDELINES

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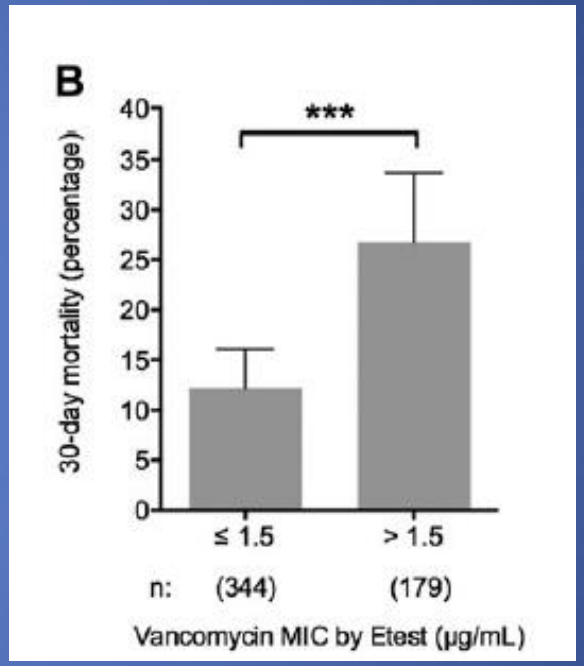
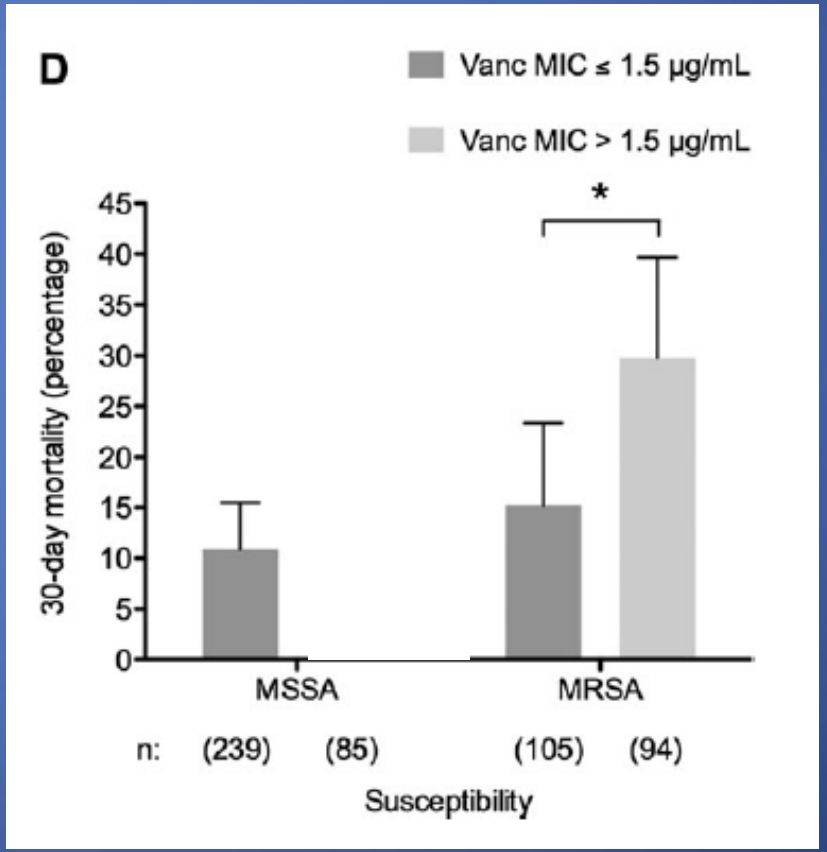
Alternative therapies to vancomycin

- Holmes *et al*. 2011. JID
- Australia and NZ
- 532 matched patients treated with vancomycin and flucloxacillin



Do MSSA isolates with Vancomycin MICs of 2 ug/ml which are treated with Vancomycin do worse than isolates with MICs < 2 ug/ml?

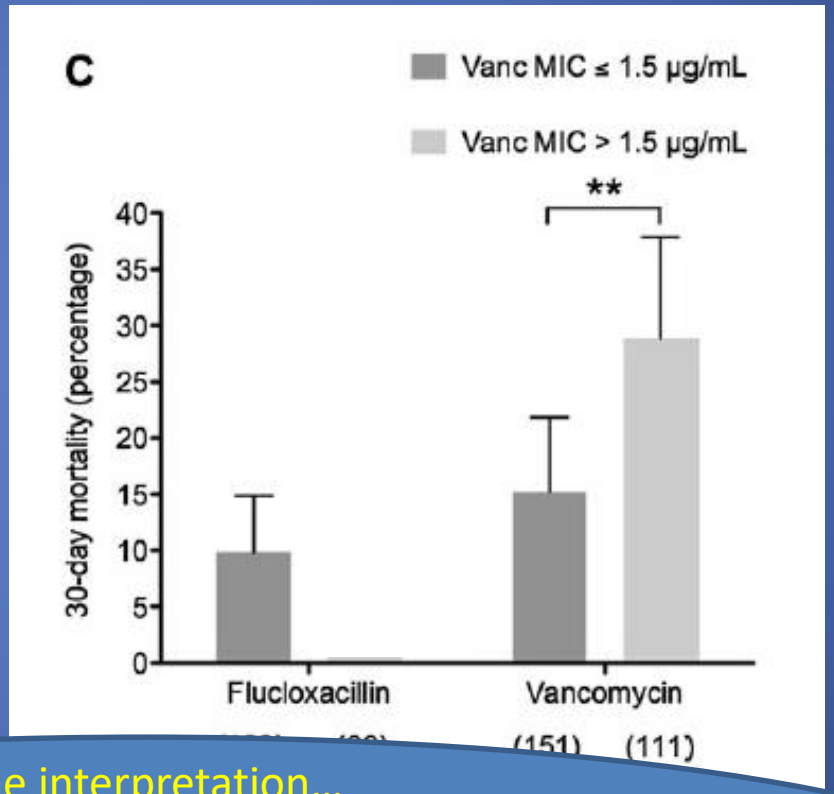
Yes!!



What drug would you want to compare to vancomycin for the treatment of BSI?

Do MSSA isolates with Vancomycin MICs of 2 ug/ml which are treated with **Flucoxacillin** do worse than isolates with MICs < 2 ug/ml?

Yes!!



One interpretation…
Elevated vancomycin MIC's are surrogate markers of poor outcomes in general.

But this is about treating MRSA

Is daptomycin superior to vancomycin for the treatment of MRSA BSI?

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections

Kimberly C. Claeys,[a,b*] Evan J. Zasowski,[a,b] Anthony M. Casapao,[a,b*] Abdalhamid M. Lagnf,[a,b] Jerod L. Nagel,[e] Cynthia T. Nguyen,[e*] Jessica A. Hallesy,[a] Mathew T. Compton,[a] Keith S. Kaye,[d] Donald P. Levine,[d] Susan L. Davis,[b,c] Michael J. Rybak[a,b,d]

Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA[a]; Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA[b]; Department of Pharmacy, Henry Ford Health-System, Detroit, Michigan, USA[c]; Department of Internal Medicine, Division of Infectious Diseases, Wayne State University School of Medicine, Detroit, Michigan, USA[d]; Department of Pharmacy, University of Michigan Hospital and Health Centers, Ann Arbor, Michigan, USA[e]

Claeys et al. 2016. AAC. 60: 5441-5448	Composite Failure	45%	29% (p=0.007) ✓	BSI
	30 day mortality	15.30%	6.1% (p=0.01) ✓	

Why this matters…

- New vancomycin dosing recommendations all but require the reporting of Vancomycin MIC's
  - Don't say what method to use
  - Don't address changes in MIC over time
  - Solution – treat all vanc susceptible isolates as MIC's of 1

TABLE 5 Activity of antimicrobial agents tested against *Staphylococcus aureus*, *Enterobacteriaceae*, and *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex submitted to the SENTRY Program, 1997–2016

Organism/antimicrobial agent (no. tested)	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
Staphylococcus aureus (56,579)								
Ceftaroline (16,658)	0.25	1	96.2	3.7	0.1	96.2	3.7	0.1
Ceftobiprole (23,214)	0.5	2				99.4		0.6
Dalbavancin (36,161)	0.06	0.06	>99.9[b]			99.7		0.3
Daptomycin (37,814)	0.25	0.5	99.9			99.9		0.1
Linezolid (53,595)	2	2	>99.9		<0.1	>99.9		<0.1
Teicoplanin (56,570)	≤2	≤2	>99.9[c]			98.8		1.2
Tigecycline (37,085)	≤0.12	0.25	99.8[b]			99.8		0.2
Vancomycin (56,575)	1	1	99.9	0.1	0.0	99.9		0.1

Diekema et al. AAC. 2019. 63(7)

So should we report vancomycin MICs?

- I don’t think it is an accurate data point.
- I don’t think the data used to justify its reporting is being interpreted in the right context.
- It does serve the purpose of pushing more patients to alternative therapies.
- In the end, it probably does more good than harm but in principle I don’t like the practice.

Up Next:
How to use COVID-19 Antigen Testing…Now?

So many questions…

1. Has home use antigen testing helped control the pandemic?
2. Do rapid results, that are more readily accessible, compensate for inferior performance?
3. What is the performance of antigen testing in asymptomatic infection?
4. Do antigen tests identify those who are infectious?

What is the performance of antigen testing?

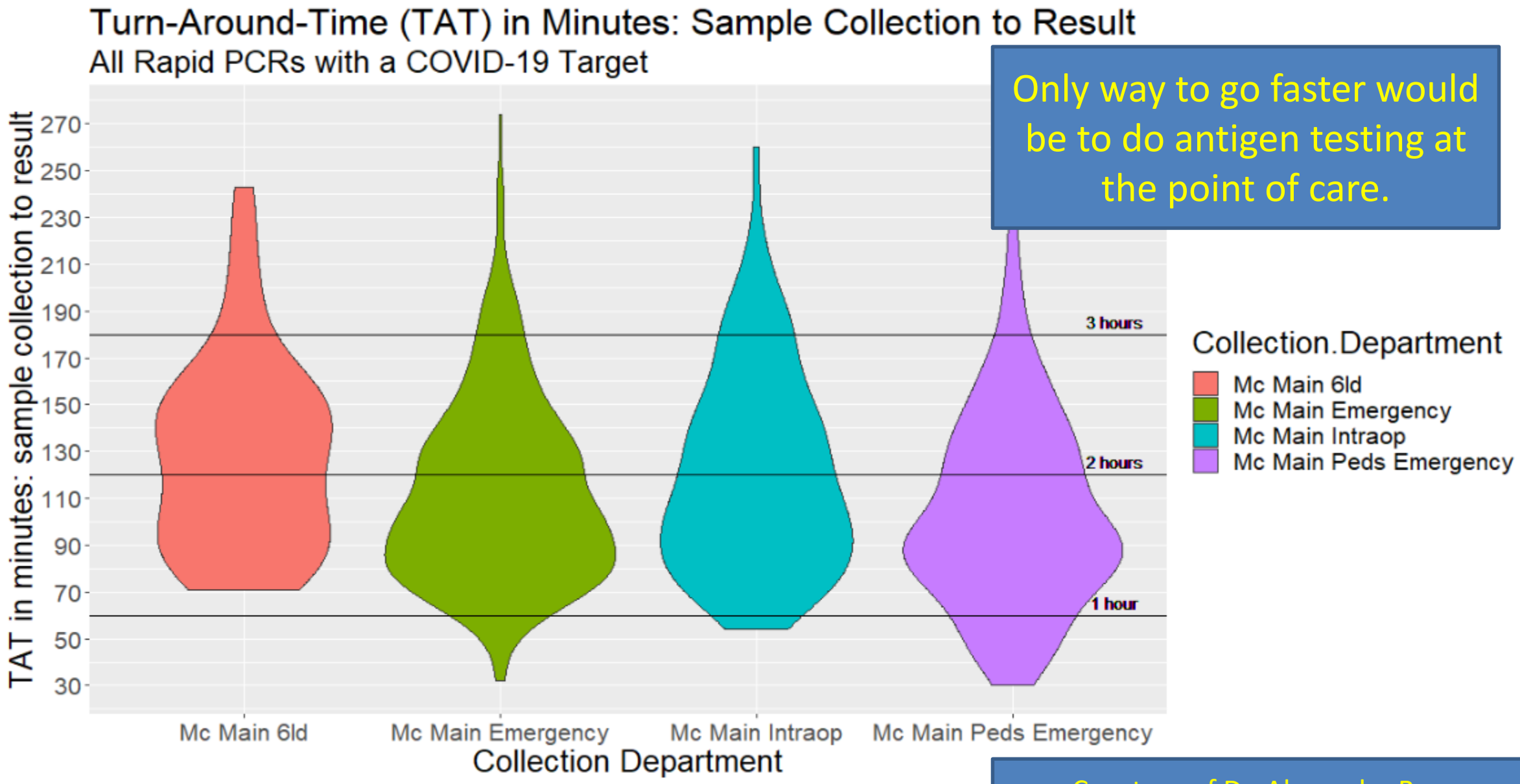
	Evaluations (studies)	Samples (SARS-CoV-2 cases)	Sensitivity (95% CI) [Range]	Specificity (95% CI) [Range]
Symptomatic	37 (27)	15,530 (4410)	72.0 (63.7 to 79.0) [0% to 100%]	99.5 (98.5 to 99.8) [8% to 100%]
Symptomatic (up to 7 days from onset of symptoms)[a]	26 (21)	2320 (2320)	78.3 (71.1 to 84.1) [15% to 95%]	-
Asymptomatic	12 (10)	1581 (295)	58.1 (40.2 to 74.1) [29% to 85%]	98.9 (93.6 to 99.8) [14% to 100%]

Dinnes et al. Cochrane Data System Rev. 2021. 3(3)

Get ready for the conversation…

- COVID-19 testing impacting hospital throughput
  - Testing of admissions → clogs the ED waiting for results
    - Ask is for faster results

How long are results taking?



Only way to go faster would be to do antigen testing at the point of care.

Courtesy of Dr. Alexandra Bryson

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-22-25-CLIA

DATE: September 26th, 2022

TO: State Survey Agency Directors

FROM: Director, Quality, Safety & Oversight Group (QSOG)

SUBJECT: CMS Rescinds December 7, 2020, Enforcement Discretion for the Use of SARS-CoV-2 Tests on Asymptomatic Individuals Outside of the Test's Instructions for Use

Implications:

- Testing must be indicated for asymptomatic testing.
- IF NOT – LDT for asymptomatic is allowed.
- POC asymptomatic testing no longer allowed if asymptomatic not in IFU.
- Laboratory developed antigen testing for asymptomatic is allowed.
  - No longer waived

Conclusion

- Asymptomatic testing outside the IFU is no longer allowed.
- POCT for asymptomatic testing no longer allowed.
- Asymptomatic testing in general is now discouraged.

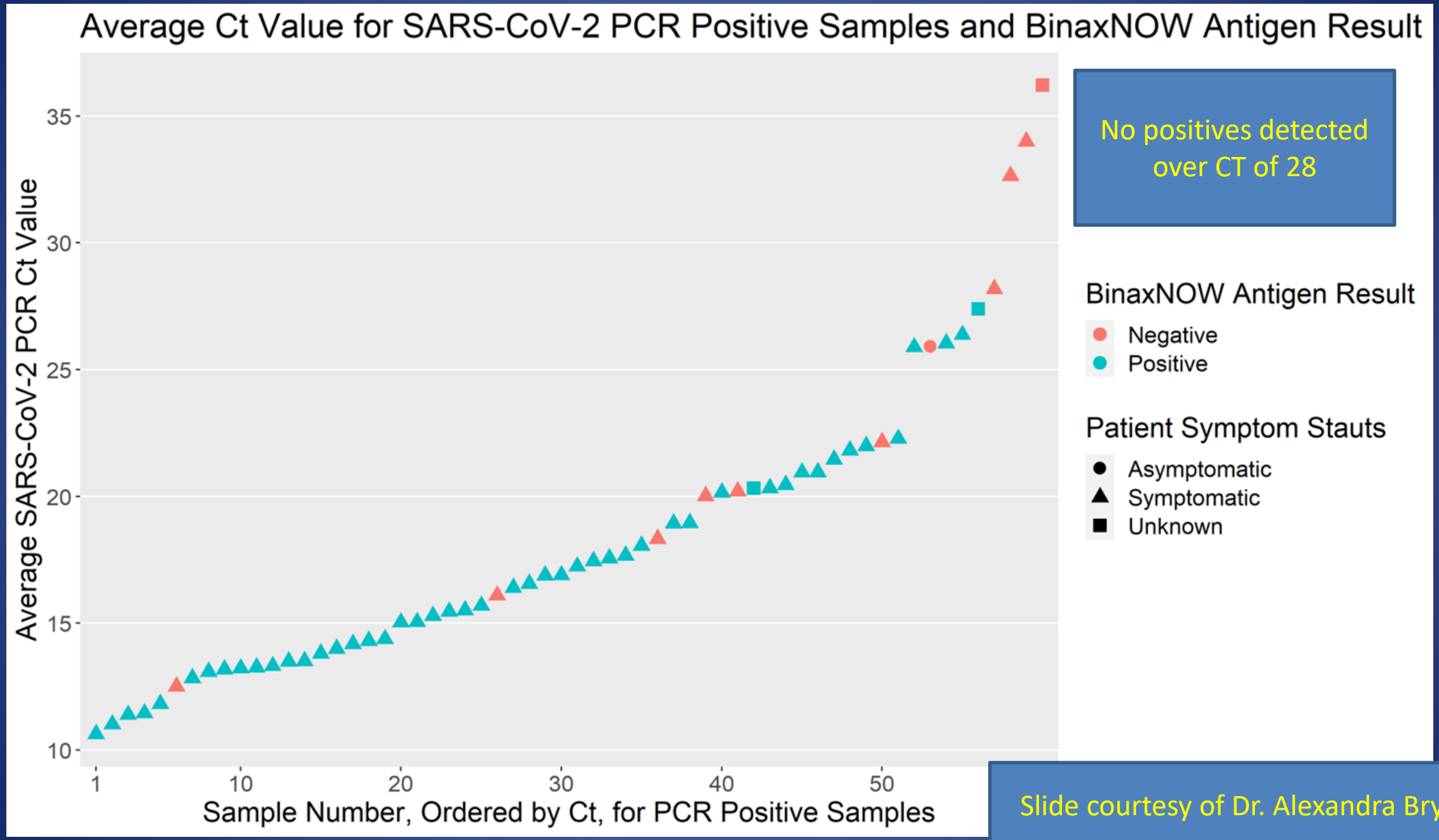
https://www.cms.gov/files/document/qso-22-25-clia.pdf

Get ready for the conversation…

- COVID-19 testing impacting hospital throughput
  - Testing of admissions → clogs the ED waiting for results
    - Ask is for faster results
  - **Discharge testing → clogs the floor waiting for discharge disposition**
    - **Too many "false positive" PCR results.**
    - **In other words – too many positives we don't want to know about.**

Antigen Testing and Infectivity

- What do we know?
  - PCR is more sensitive than antigen.
  - PCR can be positive in patients long after a resolved infection
    - i.e. after patients are no longer infectious.
  - Antigen testing roughly correlates with PCR CT value



Slide courtesy of Dr. Alexandra Bryson

Now what do we know?

- Antigen testing will fail to detect CT values >25-30.

What does that mean?

- Lower CT values = higher viral burden
- Higher viral burden = higher infectivity (probably)

Does a CT Value of 25-30 differentiate those who are infectious from those who are not?

What do we know about infectivity and viral burden?

Postmortem Antigen-Detecting Rapid Diagnostic Tests to Predict Infectivity of SARS-CoV-2–Associated Deaths

Fabian Heinrich, Ann Sophie Schröder, Anna-Lina Gerberding, Moritz Gerling, Felicia Langenwalder, Philine Lange, Axel Heinemann, Eric Bibiza-Freiwald, Dominik Sebastian Nörz, Martin Aepfelbacher, Susanne Pfefferle,[1] Benjamin Ondruschka,[1] Marc Lütgehetmann[1]

Author affiliation: University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 28, No. 1, January 2022

- 128 COVID-19 positive corpses
  - Culture
    - +ve = infectious
    - -ve = non-infectious
  - Quantitative PCR
  - Antigen Testing

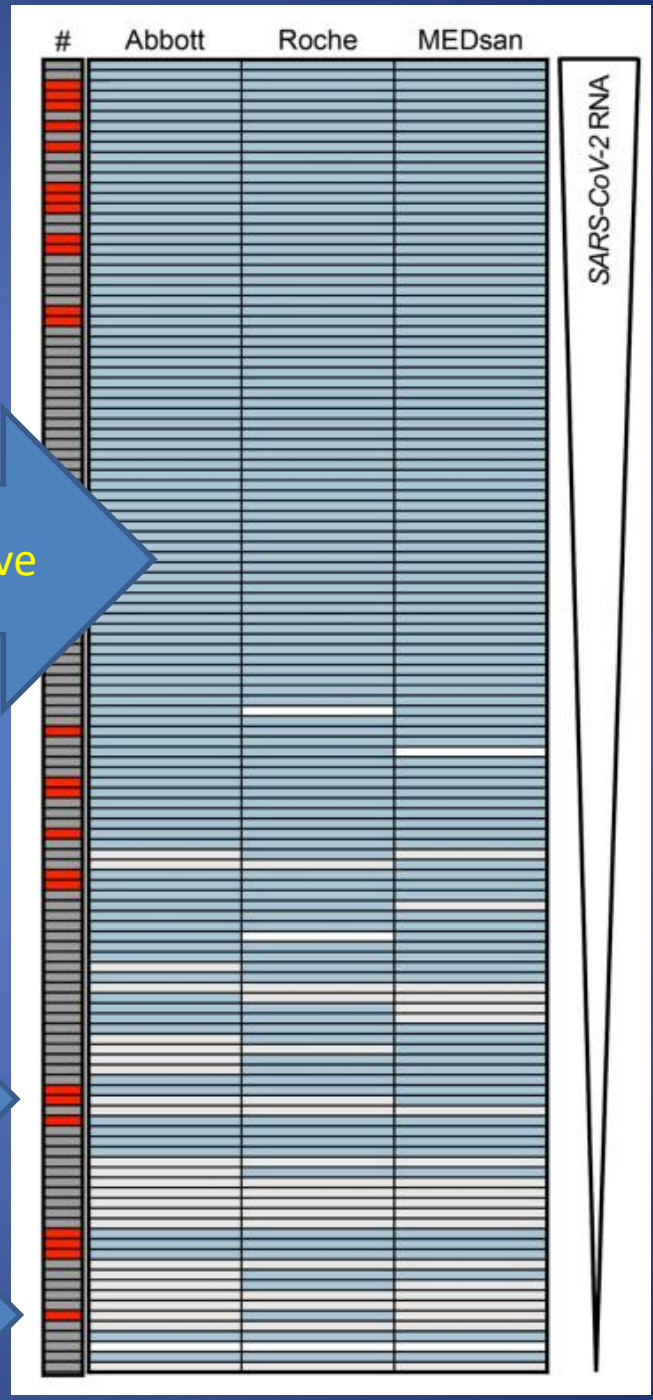
Antigen tests roughly 95% sensitive for culture positive specimens

Red = culture positive

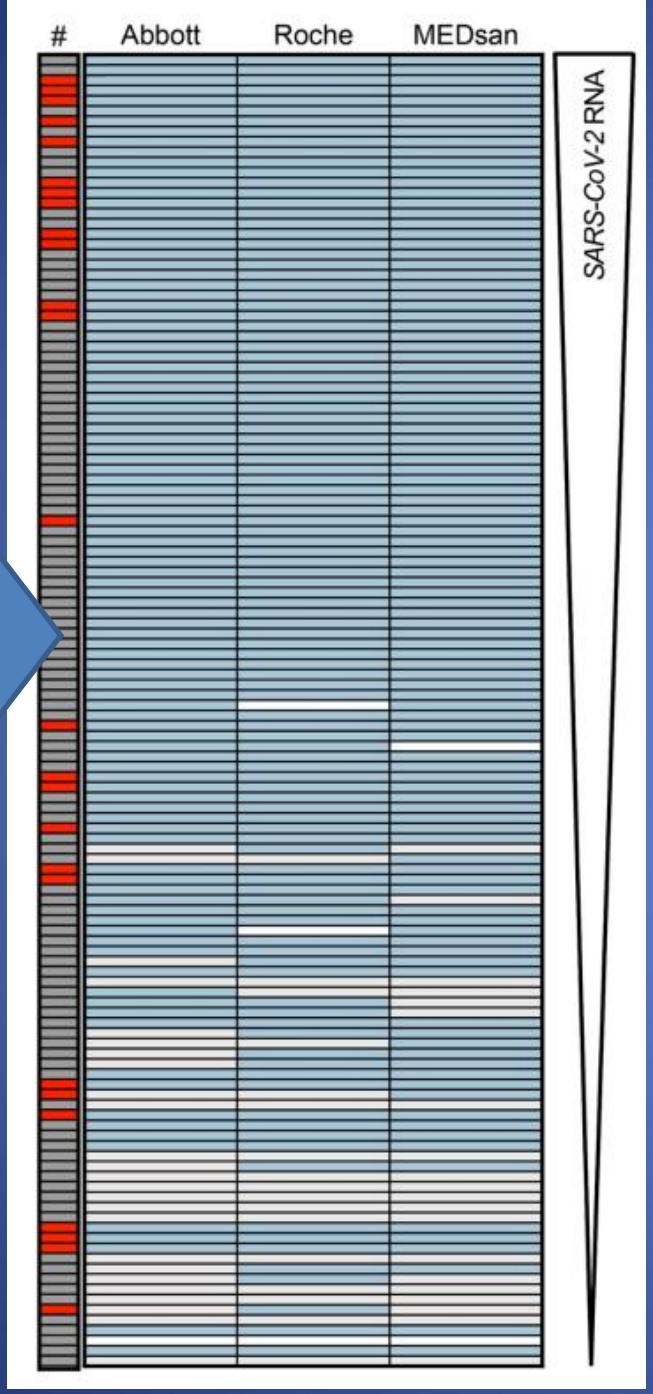
Blue = antigen positive

Miss

Miss



What about all of these culture –ve but antigen +ve?



Journal of *Clinical Medicine*

MDPI

Article

The Comparative Clinical Performance of Four SARS-CoV-2 Rapid Antigen Tests and Their Correlation to Infectivity In Vitro

Niko Kohmer [1,†], Tuna Toptan [1,†], Christiane Pallas [1], Onur Karaca [1], Annika Pfeiffer [1], Sandra Westhaus [1], Marek Widera [1], Annemarie Berger [1], Sebastian Hoehl [1], Martin Kammel [2,3], Sandra Ciesek [1,4,5,*,‡] and Holger F. Rabenau [1,*,‡]

Antigen missed between 18 and 50% of culture positives.

Antigen positive in 4 – 23% of culture negatives.

Table 3. Sensitivity and specificity of the examined SARS-CoV-2 Ag-RDTs. (1) Sensitivity % (cell culture-positive samples), (2) specificity % (cell culture-negative samples).

Cell Culture		RIDA®QUICK SARS-CoV-2 Antigen (R-Biopharm)	SARS-CoV-2 Rapid Antigen Test (Roche)	NADAL® COVID-19 Ag Test (Nal von Minden)	SARS-CoV-2 Ag Test (LumiraDx)
(1) Sensitivity	$n = 34$	61.8% (21/34) (43.6–77.8% 95% CI)	70.6% (24/34) (52.5–84.9% 95% CI)	50% (17/34) (32.4–67.6% 95% CI)	82.4% (28/34) (65.5–93.2% 95% CI)
(2) Specificity	$n = 31$	93.6% (29/31) (78.6–99.2% 95% CI)	77.4% (24/31) (58.9–90.4% 95% CI)	96.8% (30/31) (83.3–99.9% 95% CI)	77.4% (24/31) (58.9–90.4% 95% CI)

J. Clin. Med. **2021**, *10*, 328. https://doi.org/10.3390/jcm10020328

So is antigen testing indicative of infectivity?

- If positive – Yes a patient is probably infectious
  - Specificity is very good, perhaps better than PCR.
- If negative – I don't know
  - Is culture a good marker of infectivity?
  - Are all of those antigen positive but culture negative patients infectious?

I don't think we've proven that antigen testing truly correlates with infectivity.

How would we really prove that?

PCR +VE Antigen +VE

Transmission to others

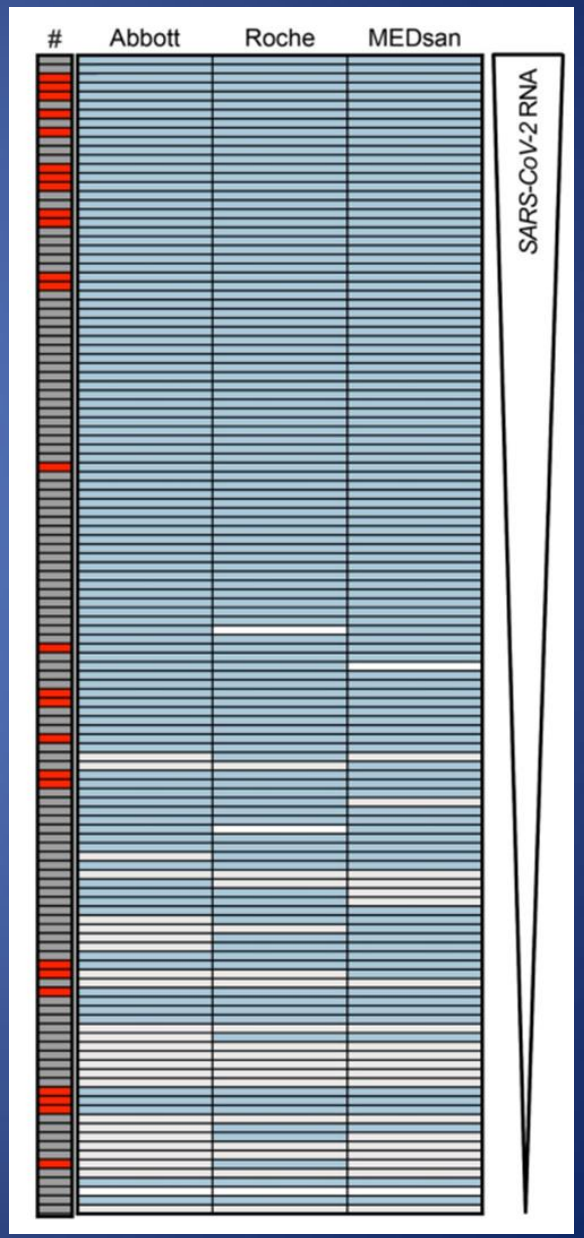
Is there a difference?

PCR +VE Antigen -VE

Transmission to others

So does antigen tell us something about infectivity of a patient?

- Antigen positive patients are <u>probably</u> more infectious than antigen negative patients.
- Antigen negative (but infected) patients almost certainly are infectious.
- Careful when using absolute language around this.
  - Antigen negative does not equal not infectious
  - Antigen negative probably equals less infectious



Summary

- Always capitalize Gram stain ☺
- Implement laboratory stewardship for Karius before it is too late
- The MIC is an inherently inaccurate value
  - The vancomycin MIC is particular so given method dependence
  - Daptomycin, and probably ceftaroline, are superior antibiotics regardless of vancomycin MIC
- COVID-19 antigen testing is not a perfect surrogate for infectivity

Do me a favor

If I'm even in your hospital with a MRSA BSI, please make sure I get daptomycin.

Some other great topics…

Does urine culture susceptibility testing predict outcome?

C. difficile Diagnosis – PCR vs. Toxin testing?

Are taxonomists the worst people on earth?

Is pediatric bacteremia different than that of adults?

What are the origins of COVID-19?

What is a Lyme literate doctor?

Thank you for very much for your attention.

Questions?

VCUHealth

christopher.doern@vcuhealth.org