Invasive Group A Streptococcal Infections

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- This material is the result of work supported with resources and the use of facilities at the Whiteriver Service Unit, located in the Phoenix Area of the Indian Health Service.
- Dr. McAuley is employed by HIS and serves as the Chief Medical Officer at WRSU, Whiteriver, AZ
- The contents do not represent the views of the Indian Health Service or the United States Government
- Dr. McAuley reports no conflicts of interest.
- No off-label treatments will be discussed

Gram-Positive *Streptococcus*

- Characteristics of Streptococci
  - Gram positive cocci
  - Size 1µm
  - Chains or pairs
  - Non motile
  - Non spore forming
  - Facultative anaerobes
  - Fastidious
  - Catalase negative

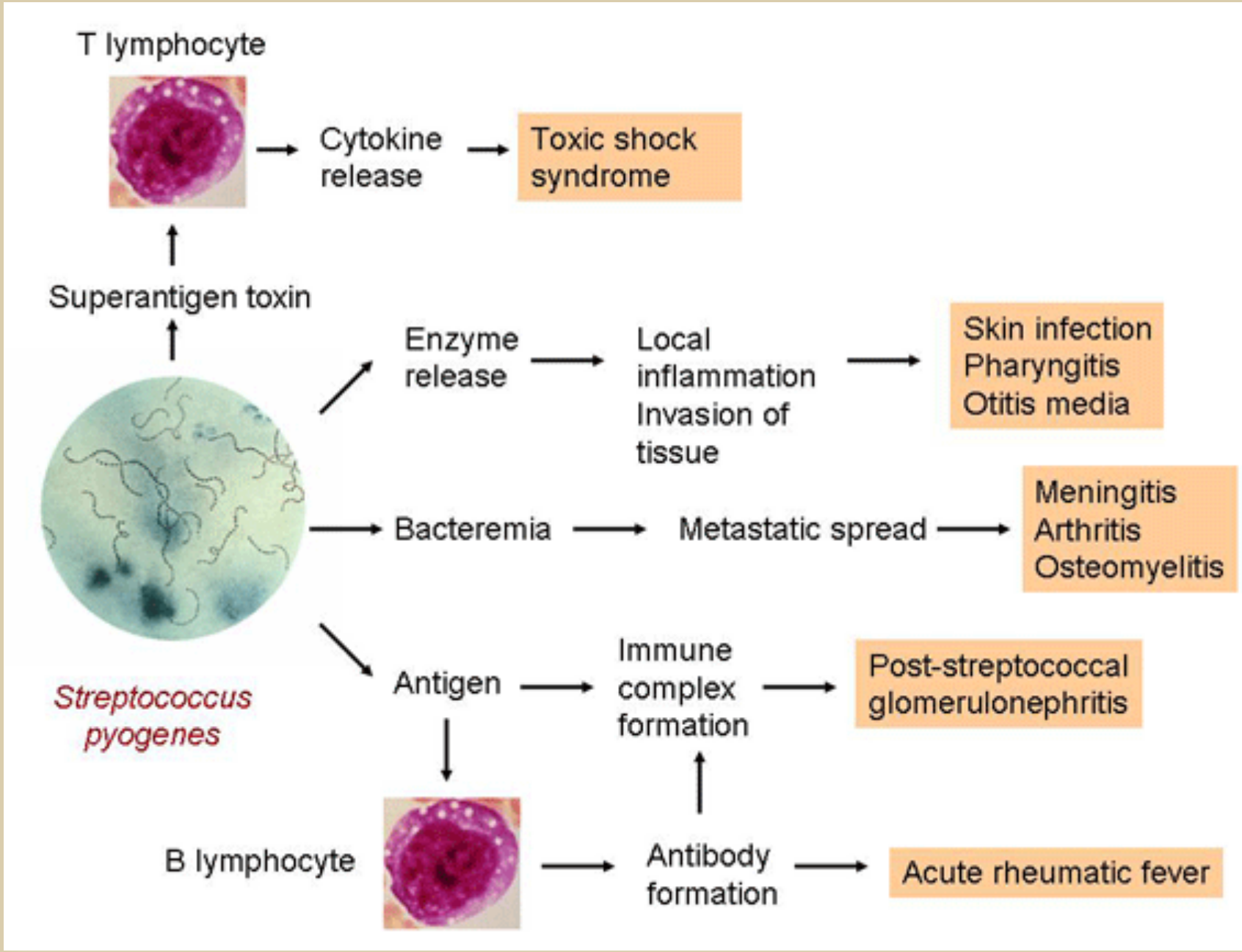
Classification of *Streptococcus*

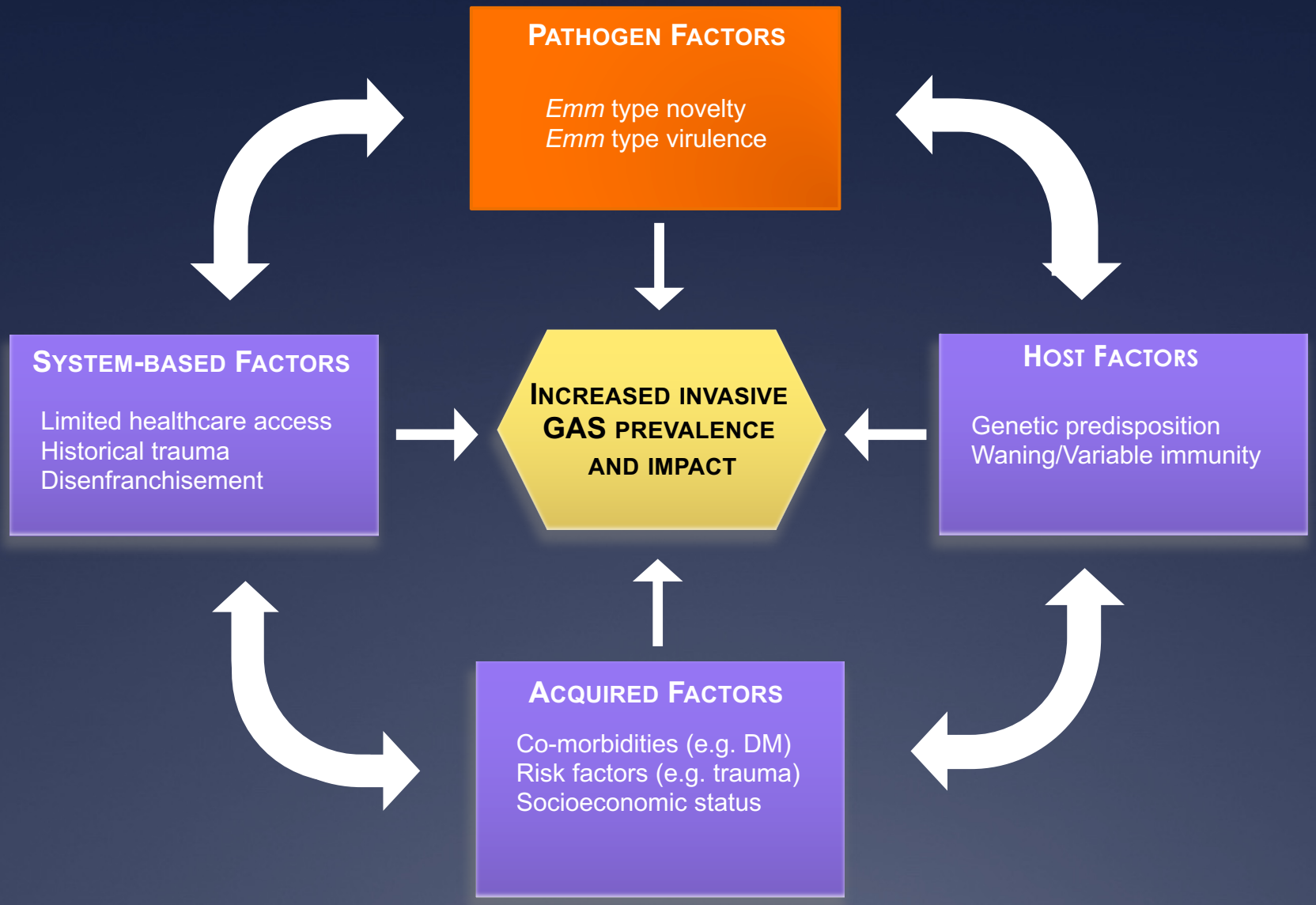
- <u>According to:</u>
  - Oxygen requirement
    - Anaerobic (*Peptostreptococcus*)
    - Aerobic or facultative anaerobic (*Streptococcus*)
  - Hemolysis on Blood Agar- α, β, Y
  - Lancefield classification-
    - for β hemolytic streptococci,

    based on C antigen – 20 groups.

    Group A – further grouped by

    M, T, R proteins (80+ serotypes)


T lymphocyte
Cytokine release
Toxic shock syndrome
Superantigen toxin
Enzyme release
Local inflammation Invasion of tissue
Skin infection Pharyngitis Otitis media
Bacteremia
Metastatic spread
Meningitis Arthritis Osteomyelitis
Streptococcus pyogenes
Antigen
Immune complex formation
Post-streptococcal glomerulonephritis
B lymphocyte
Antibody formation
Acute rheumatic fever


PATHOGEN FACTORS
Emm type novelty
Emm type virulence
SYSTEM-BASED FACTORS
Limited healthcare access
Historical trauma
Disenfranchisement
INCREASED INVASIVE GAS PREVALENCE AND IMPACT
HOST FACTORS
Genetic predisposition
Waning/Variable immunity
ACQUIRED FACTORS
Co-morbidities (e.g. DM)
Risk factors (e.g. trauma)
Socioeconomic status

Major Human Diseases of Beta-Hemolytic Streptococci

Group A *Streptococcus* (*S. pyogenes*):

Diverse group of **acute suppurative** (pus-forming) & nonsuppurative diseases

Suppurative Streptococcal Diseases

Pharyngitis (& **tonsilitis**):

Scarlet fever: Complication of streptococcal pharyngitis when infecting strain is lysogenized; Frequently develop **scarletina** rash on upper chest spreading to extremities, Pastia's lines, circumoral pallor, strawberry tongue. High mortality in pre-antibiotic era.

Cutaneous & Soft Tissue Infections.

Pyoderma (Impetigo: contagious pyoderma with superficial yellow weeping lesions)

Erysipelas: Acute superficial cellulitis of skin with lymphatic involvement; face and lower extremities, skin and subcutaneous tissues

Major Human Diseases of Group A Streptococcus (cont.)

Suppurative Streptococcal Diseases

Cutaneous & Soft Tissue Infections (cont.)

Cellulitis: Involvement of deeper subcutaneous tissues; Deeper invasion with systemic symptoms

Necrotizing fasciitis: (a.k.a., "flesh-eating bacteria"): Infection deep in subcutaneous tissues that spreads along fascial planes, destroying muscle and fat; Initially cellulitis followed by bullae (fluid filled blisters; bulla is singular), gangrene, systemic toxicity, multiorgan failure and mortality in more than 50% of patients

Wound Infections: often rapid onset compared to staphylococcal disease, tender regional nodes common

Suppurative Streptococcal Diseases
Group A *Streptococcus* (cont.)

Other Suppurative Diseases

Puerperal & **neonatal sepsis**

Lymphangitis: Inflammation of lymphatic vessel(s)

Pneumonia

Systemic Disease

Streptococcal Toxic Shock Syndrome (TSS): **Multisystem toxicity** following soft tissue infection progressing to shock and organ failure (not to be confused with Staphylococcal Toxic Shock Syndrome)

Bacteremia

Group A Streptococcal Diseases (cont.)

Nonsuppurative Sequelae

Post-infection complications of Group A streptococcal disease; Serious complications likely related to auto-immune reaction – damage is cumulative

Acute rheumatic fever (ARF):

Inflammation of heart, joints, blood vessels, sub-cutaneous tissues

Rheumatic heart disease (RHD):

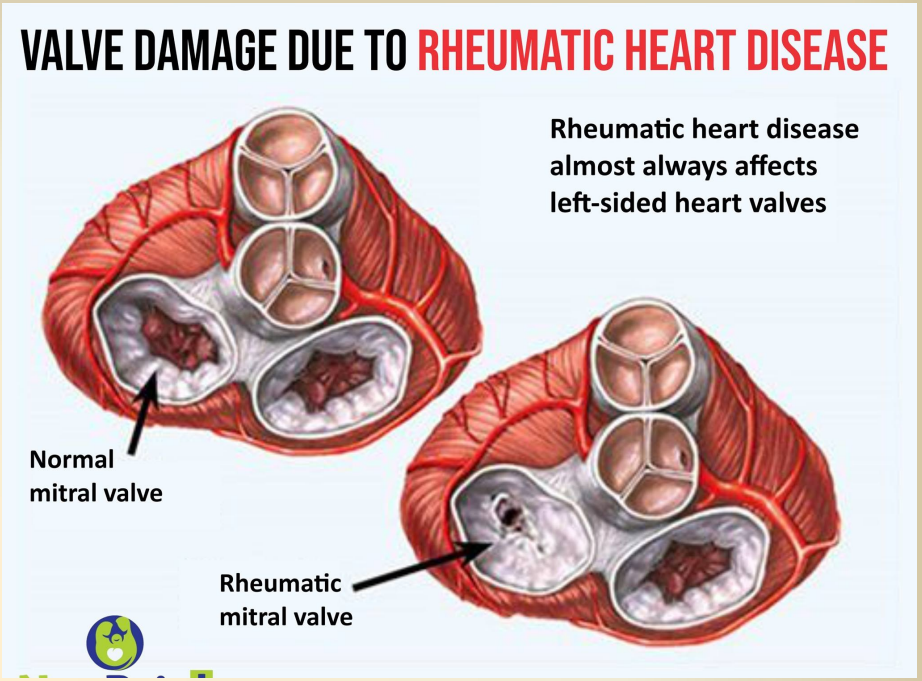
Chronic, progressive heart valve damage

Acute glomerulonephritis (AG):

Acute inflammation of renal (kidney) glomeruli

Erysipelas

Impetigo



Scarlet Fever

Necrotizing Fasciitis

Pharyngitis

Risk Factors for iGAS

* Varicella infection
* Influenza
* Trauma, burns, surgery
* Immunosuppression or immunodeficiency
* Neoplasm
* Age < 1 year
* IDU

GAS – Global Burden of Disease

- 111 million globally develop impetigo each year
- 470,000 new cases of rheumatic fever each year
- 282,000 new cases of rheumatic heart disease
- Estimated 33.4 million prevalent cases of rheumatic heart disease globally

Invasive GAS – US Burden of Disease – 2021 ABCs (10% of US)

	Cases		Deaths	
Age (years)	No.	Rate*	No.	Rate*
<1	9	2.5	0	0.00
1	4	1.1	0	0.00
2-4	6	0.5	0	0.00
5-17	23	0.4	1	0.02
18-34	416	5.2	19	0.24
35-49	489	7.0	25	0.36
50-64	651	9.6	64	0.95
65-74	292	8.6	30	0.88
75-84	204	13.0	37	2.35
≥85	100	17.0	21	3.57
Total	2,194	6.3	197	0.56

Rate per 100,000

Invasive GAS – US Burden of Disease – 2021 ABCs

Syndrome	No.	%
Cellulitis	1,065	48.5
Bacteremia without focus	376	17.1
Pneumonia	230	10.5
Necrotizing fasciitis	99	4.5
Streptococcal toxic shock syndrome	36	1.6

Note: Some cases had more than 1 syndrome.

Increase in Pediatric Invasive Group A Streptococcal Infections

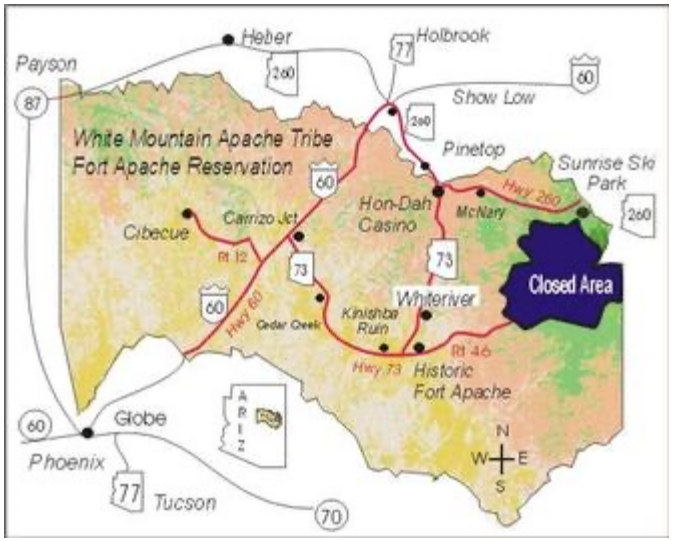
HAN
HEALTH ALERT NETWORK

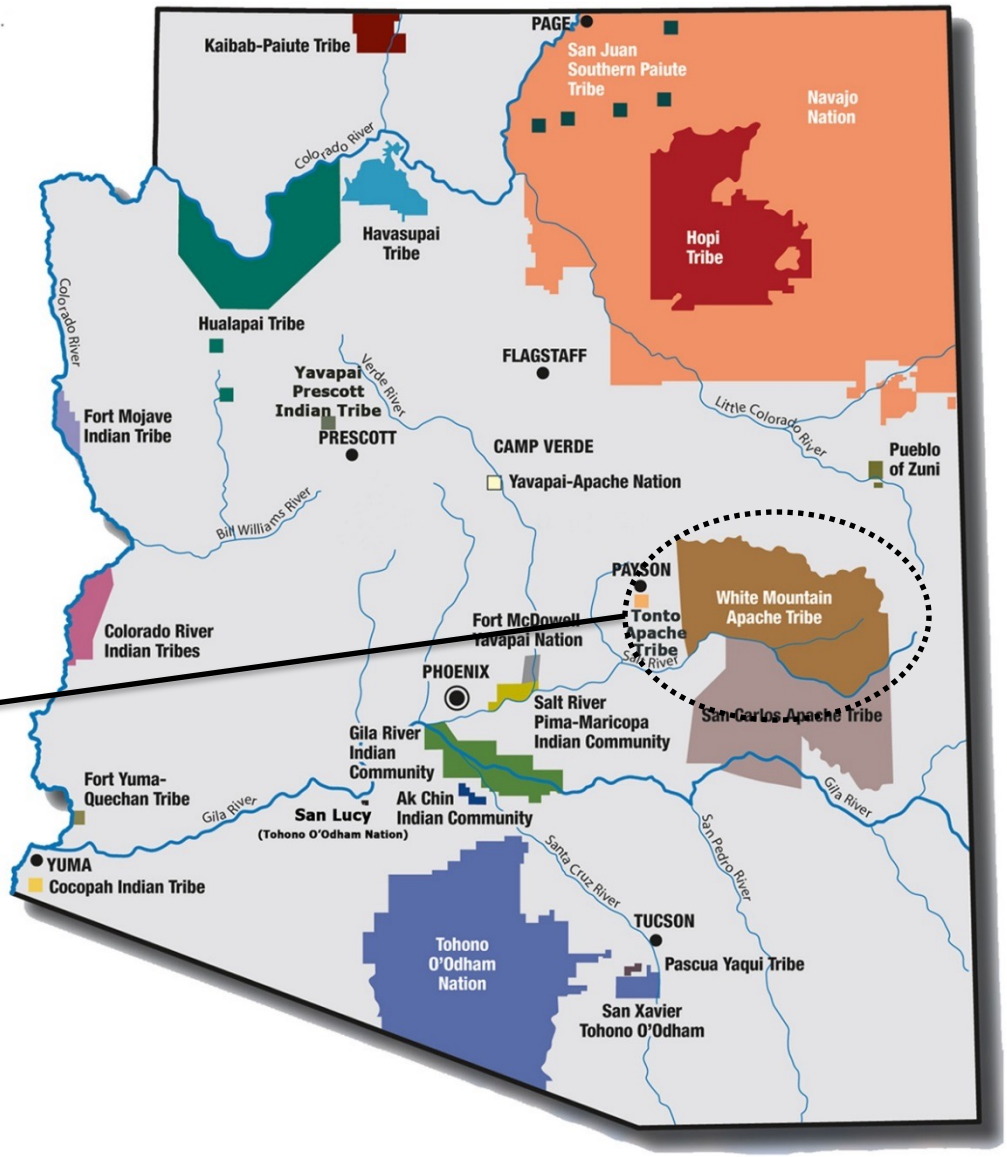
This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
December 22, 2022, 1:45 PM ET
CDCHAN-00484

Arizona – Many Tribal Lands

- White Mountain Apache Reservation ~ 3-4 hour drive from Phoenix, Tucson, Grand Canyon, Albuquerque
- A bit smaller than Delaware
- One of the few reservations that includes the community's traditional lands





2016: Discovering GAS at WRSU

- String of GAS bacteremia (20), 16 with necrotizing fasciitis
- Call to other nearby IHS facilities – "Yes we see this often…"
- 12 month old with acute Rheumatic Carditis (Case)
- Investigations begin

Case

- DG was a previously healthy 12-month-old AI boy who presented to the emergency department in cardiopulmonary arrest
- He was well enough to attend a parade that morning.
- That afternoon, over the source of two-hours, he experienced emesis, diarrhea, increased fussiness, and was refusing fluids.
- He was given ibuprofen for discomfort and eventually “collapsed” on his bed, presumably from exhaustion. Found unresponsive 30 minutes later. Resuscitation efforts started on-scene, and continued at the local emergency department were ultimately unsuccessful

Cause of death as “**acute and ongoing fulminant rheumatic carditis** … sections of the left ventricle and interventricular septum show acute and ongoing rheumatic carditis with patchy areas of confluent **Aschoff nodules** throughout, areas of resolving injury and fibrosis, and foci of granulation

The Pediatric Infectious Disease Journal 40(5):495-7, 2021

Defining the problem

- Do AI/AN have excess GAS pharyngitis?
- Does WRSU actually have more skin and soft tissue infections admitted than expected?
- Are there limitations to our current diagnostic and prevention tools?
- How much Rheumatic Heart Disease do we have among the WMAT?

PHARYNGITIS

Pharyngitis - Very high rates of GAS pharyngitis in adults
IDWeek 2018

- From Jan. 1 to Feb. 28, 2017, there were 251 patients ≥ 18 years for whom RAT, TC, and mCS were performed.
- Median age 32 years (IQR 26-46)
- 71% aged 18-45

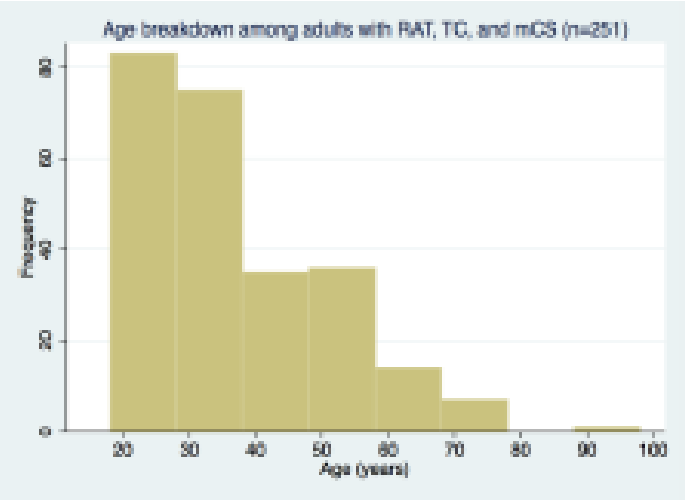


TABLE 1: RAT and GAS Culture positivity relationship to age and compared to general population (n=268)

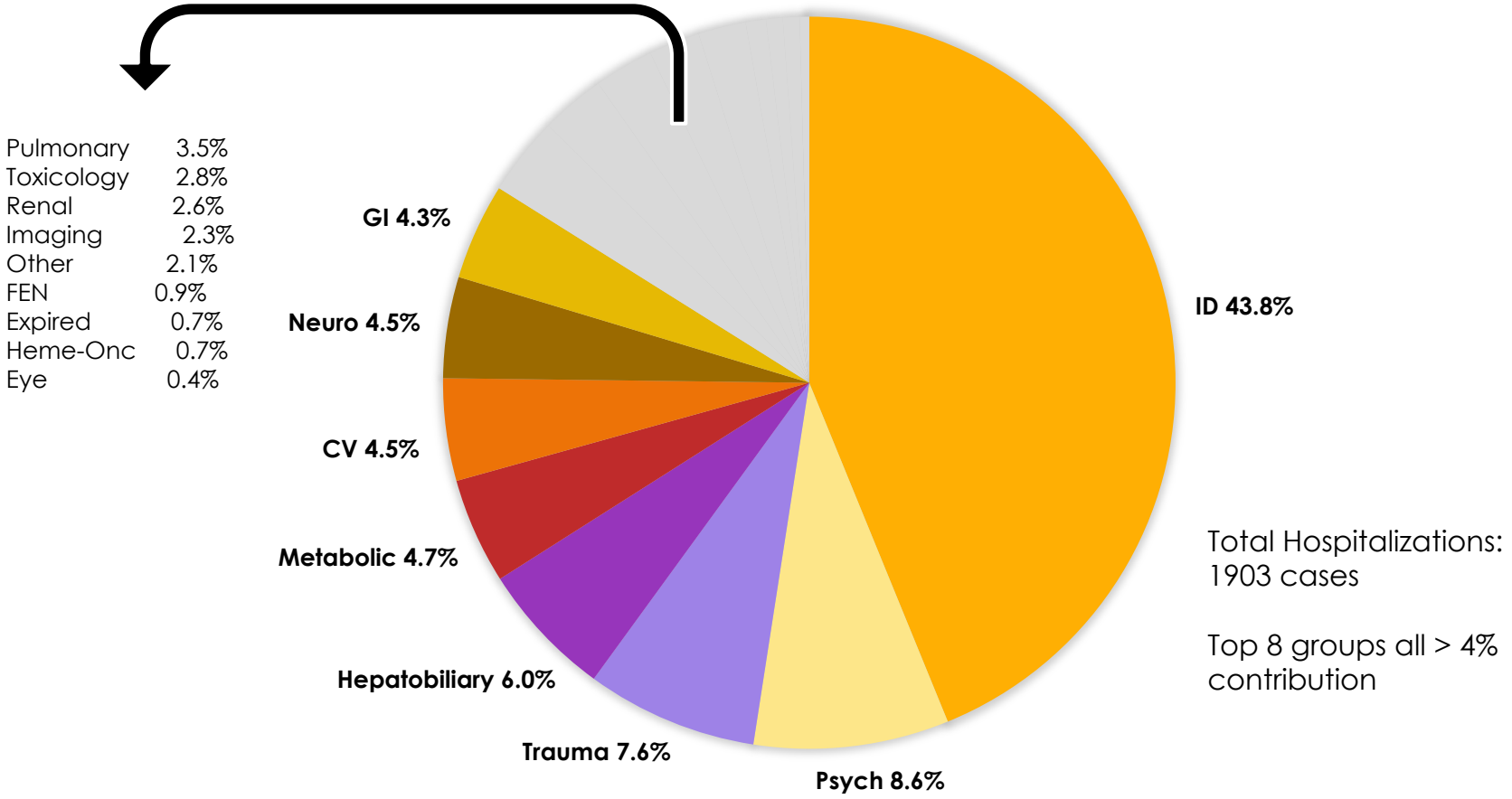
	18-44 yo	≥ 45 yo	All adults
RAT POS n (%)	63 (33.9%)[i]	23 (28.0%)	86 (32.1%)[§]
TC POS n (%)	67 (36.0%)[ii]	18 (22.0%)	85 (31.7%)[§]
	[i] OR 1.3, $p = 0.35$ [ii] OR 2.0, $p = 0.02$ Using age 18-44 yo as exposure		[§] $p < 0.001$ X^2 goodness-of-fit compared to expected prevalence

- GAS pharyngitis 2x greater in WMAT than US General Population
- Centor (mCS) scoring system performed poorly

HOSPITALIZATIONS FOR SKIN & SOFT TISSUE INFECTIONS - 2017

WRSU Morbidity 2017

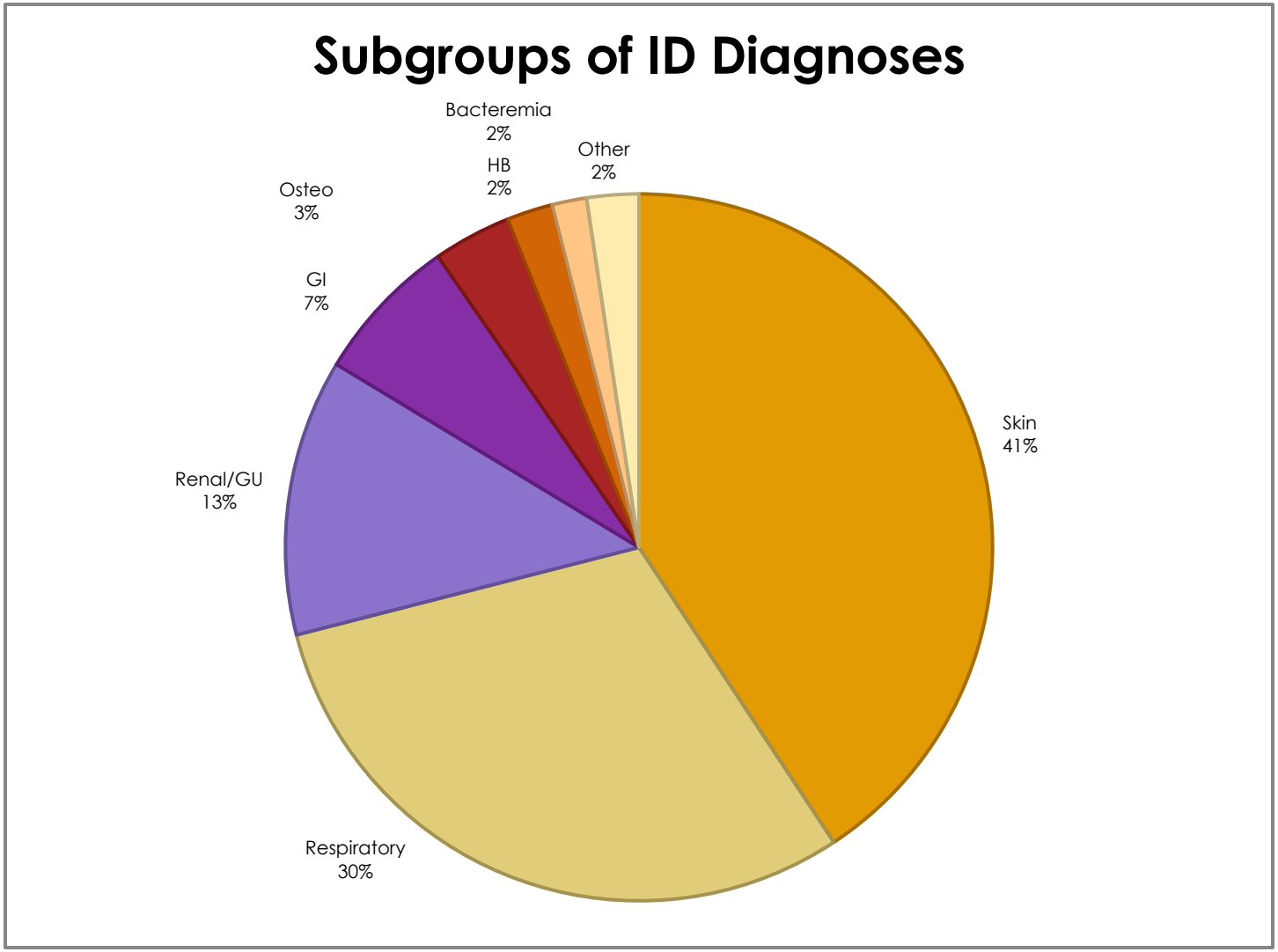
84% of all Hospitalizations due to top 8 Categories



Total Hospitalizations: 1903 cases

Top 8 groups all > 4% contribution

Skin, Respiratory, Renal/GU contributed majority of ID Cases



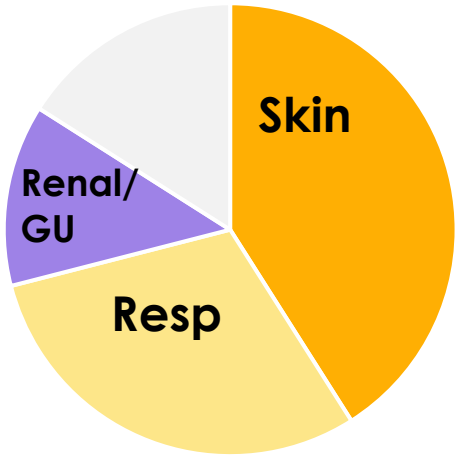
SKIN infections are the main driver of increased ID-related Hospitalizations at WR

Top 3 Causes of ID Diagnoses in AI/AN population - US (Holman et al 2011):

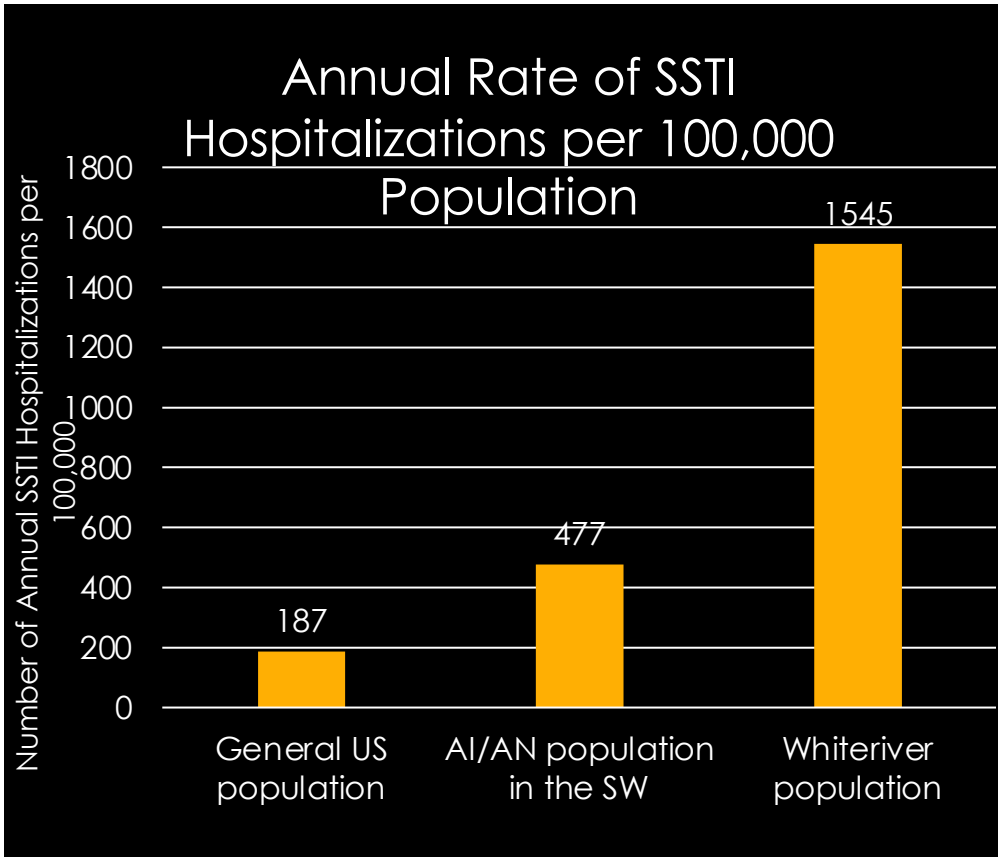
35% Lower-respiratory-tract infections
19% SSTI infection
11% Renal / GU

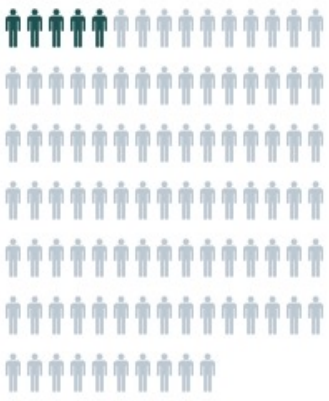
Top 3 Causes of ID Diagnoses at Whiteriver:

41% Skin infection
30% Respiratory
13% Renal/GU

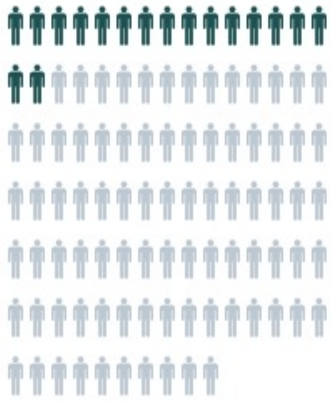


WR has higher Rate of SSTI hospitalization than General US (8.3x) and AI/NA populations (3.2x)





5% of annual hospital admissions are SSTI in AI/AN
(Holman et al., 2011; Trends in Indian Health 2014)



17% of annual hospital admissions are SSTI at Whiteriver

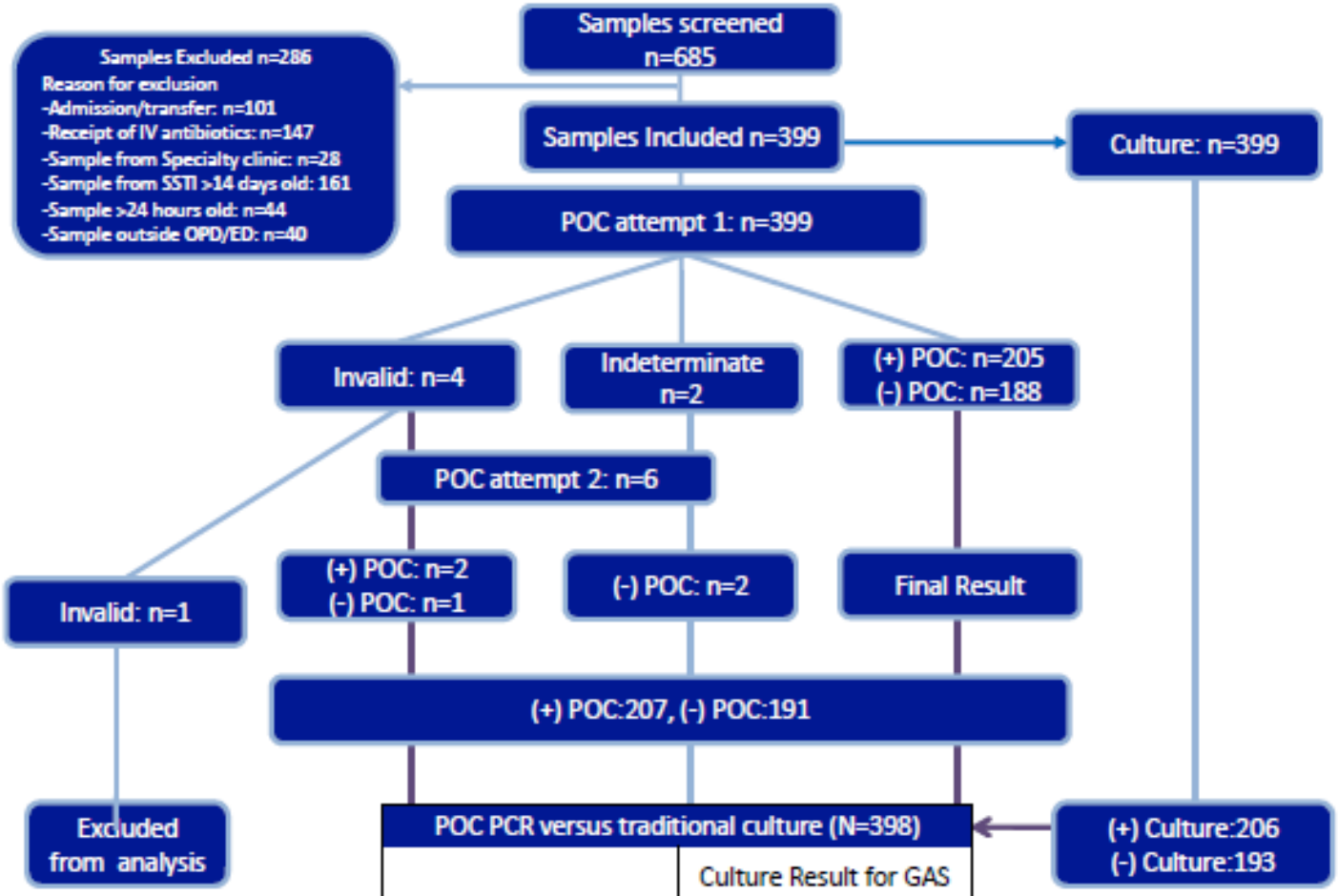
SKIN & SOFT TISSUE INFECTIONS – GAS OR MRSA/MSSA

Are these skin and soft tissue infections GAS?

* Culturing wounds or cellulitis can be slow and results too late to guide decisions.
* Point of Care PCR tests for GAS and Staph (MSSA/MRSA) have been developed but not yet validated in clinical settings 2018).
* Clinicians often treat for GAS/MSSA/MRSA – which potentially over uses antibiotics.

Non-invasive skin and soft tissue infections

Figure 4. Determination of sample eligibility and flowchart to final result



		Culture Result for GAS	
		(+)	(-)
POC Result for GAS	(+)	206	1
	(-)	0	191

Table 2. Clinical characterization among eligible samples (N=399)

Lesion	n (%)	Lesion	n (%)
Impetigo	81 (20.3)	Wound	38 (9.5)
Abscess	153 (38.4)	Folliculitis	5 (1.3)
Cellulitis	151 (37.8)	Furuncle	5 (1.3)
Erysipelas	3 (0.8)	Hydradenitis	3 (0.8)
Paronychia	10 (2.5)	Ingrown toenail	6 (1.5)
Superinfected eczema	4 (1.0)	Blister	7 (1.8)
Animal bite	3 (0.8)	Diabetic foot ulcer	3 (0.8)
Insect bite	3 (0.8)	Other	44 (11.0)
Human/Fight bite	1 (0.3)		

Microbiology

Figure 5. Contribution of GAS, MRSA, and MSSA mono- and co-infections (N=399

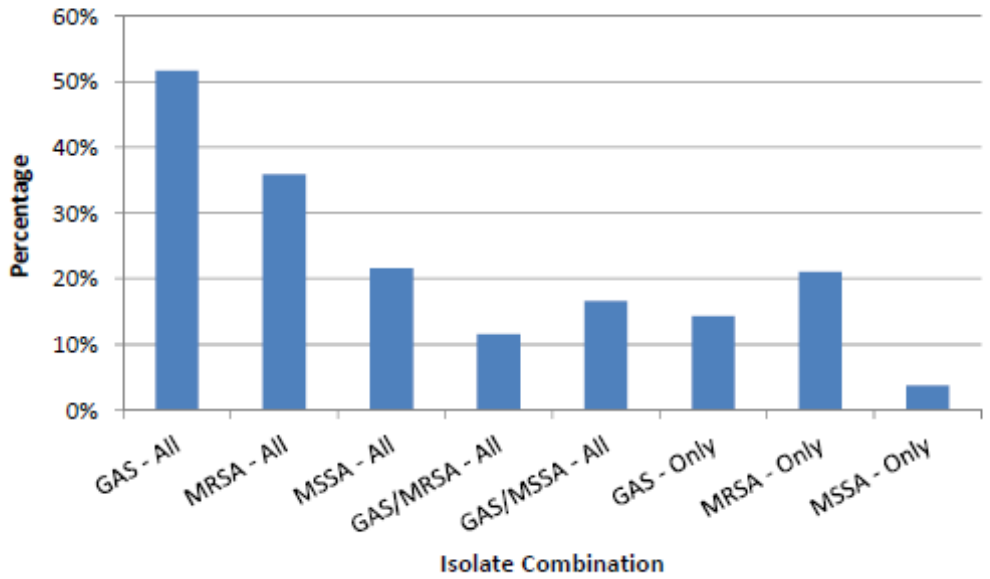


Table 5. Co-infections with GAS

Co-infection	GAS Positive (N=206)	GAS Negative (N=193)	P-value
Any pathogen	149 (72.3)	173 (89.6)	<0.0001
S. aureus	112 (54.4)	117 (60.6)	0.21
MRSA	46 (22.3)	97 (50.3)	< 0.001
MSSA	66 (32.0)	20 (10.4)	< 0.001
CoNS	34 (16.5)	47 (24.4)	0.05

MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; CoNS: Coagulase-negative Staphylococci

Close RM, Sutcliffe CG, Galdun P, et al. Point-of-care molecular diagnostics for the detection of group A *Streptococcus* in non-invasive skin and soft tissue infections: a validation study. Diagnostic Microbiology and Infectious Disease. 2022;103(4):1-6. https://doi.org/10.1016/j.diagmicrobio.2022.115729

SEVERE & INVASIVE GAS SURVEILLANCE - WRSU

Methods

Describe burden and characteristics of invasive and severe GAS

Active, laboratory-based surveillance for severe and invasive GAS

- March 2017 - February 2019
- Case definition
  - Native American individual living on or near the WMA Tribal lands
  - Invasive: *S. pyogenes* isolated from a normally sterile site OR wound with diagnosis of necrotizing soft tissue infection or STSS
  - Severe: *S. pyogenes* isolated from a wound requiring hospitalization

Methods & Analysis

Describe burden and characteristics of invasive and severe GAS

Characteristics of cases were determined

Overall and annual incidence rates were calculated

- Denominators: 2017 & 2018 Indian Health Service User Population

Incidence rates were compared by age and year

Age-adjusted incidence rates of invasive GAS were calculated for comparison with the general US population

- Adjusted to the US population in 2015

Methods

Evaluate distribution of *emm*-types

1. Active, laboratory-based surveillance for invasive and severe GAS
   - March 2017 to February 2019
   - N=127

2. Convenience sample of GAS positive cultures
   - Aug to Oct 2016
   - Limited demographic and clinical data collected
   - N=19

3. Active, laboratory-based surveillance for GAS pharyngitis
   - May 2017 to April 2018
   - Case definition: Clinical symptoms of pharyngitis and RDT negative
   - Limited demographic data collected
   - N=135

Results:

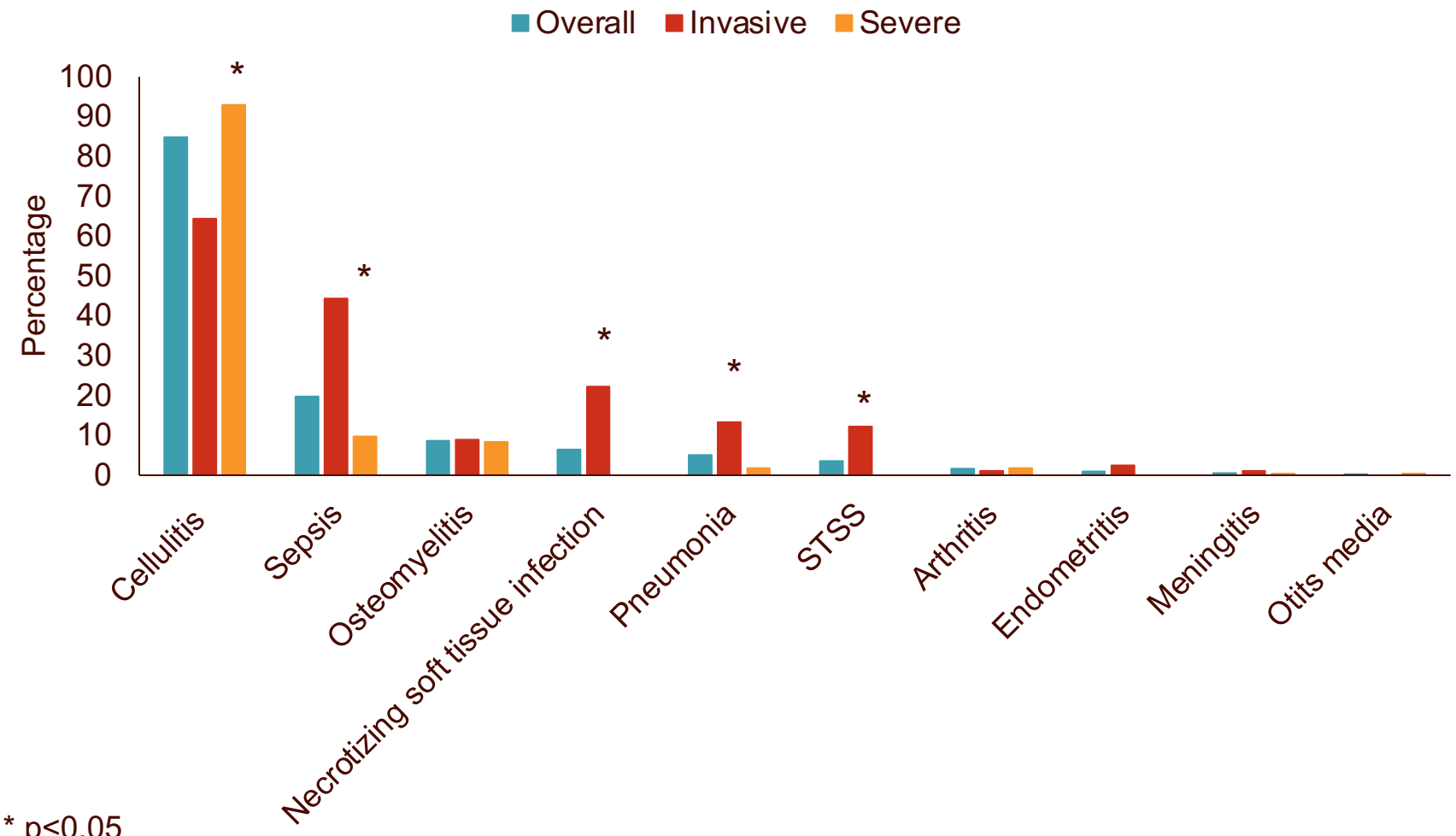
Characteristics of cases of invasive and severe GAS disease

Characteristics of invasive & severe cases

		Total (N=315)	Invasive (N=90)	Severe (N=225)
Female, %		34.6	46.7	29.8*
Age, %	<1 year	2.5	2.2	2.7*
	1-17 years	7.0	3.3	8.4
	18-49 years	52.7	36.7	59.1
	50-64 years	23.2	25.6	22.2
	≥65 years	14.6	32.2	7.6
BMI ≥30, %		43.5	49.4	41.0*
Prior GAS infection, %		14.6	19.2	12.6
Co-infection with *S. aureus*		40.0	15.6	49.8*

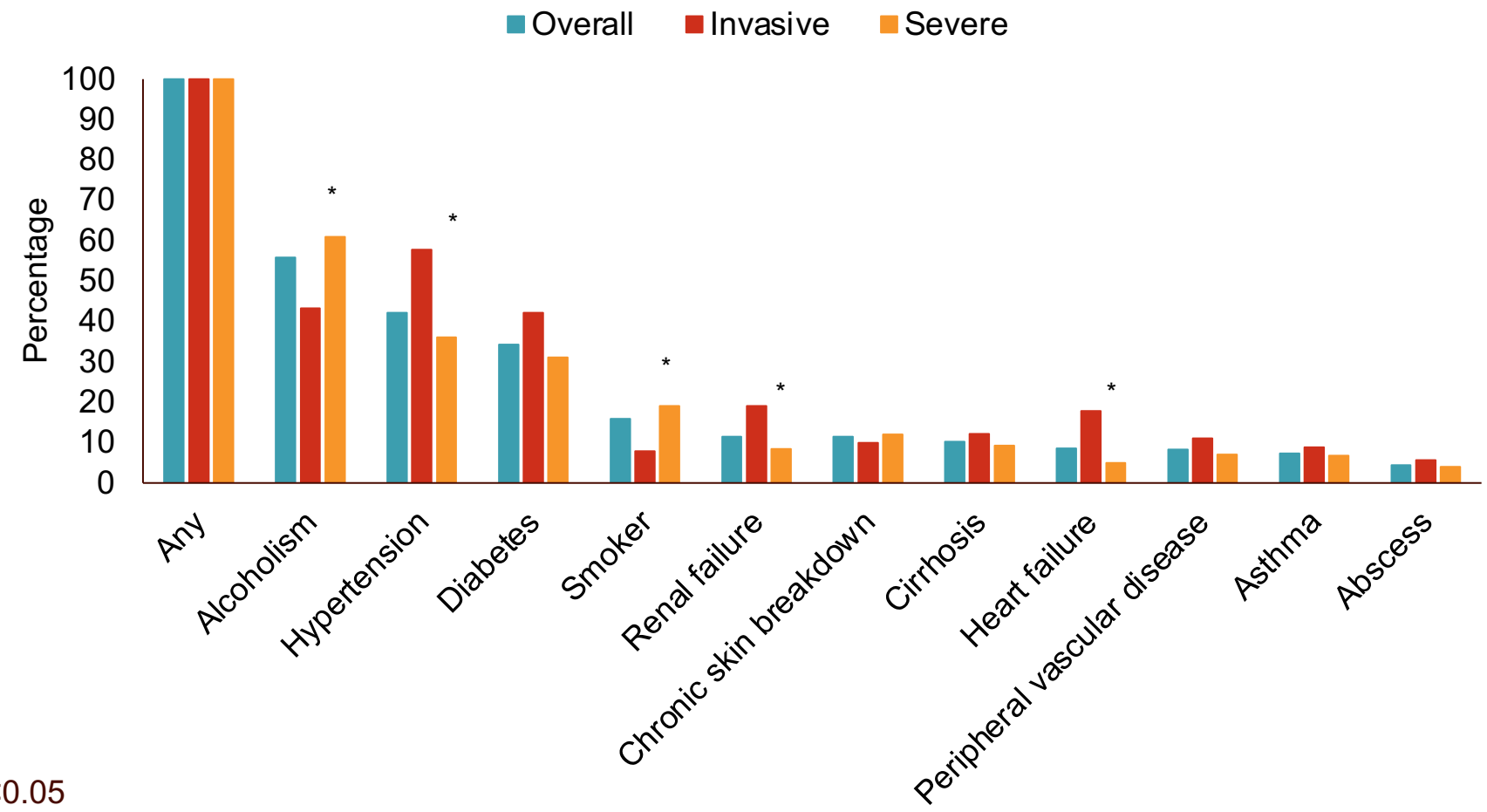
* $p<0.05$

Disease syndromes of invasive & severe GAS



* p<0.05

Underlying conditions of invasive & severe GAS



* $p<0.05$

Note: Top 10 underlying conditions shown

Outcomes of invasive & severe GAS cases

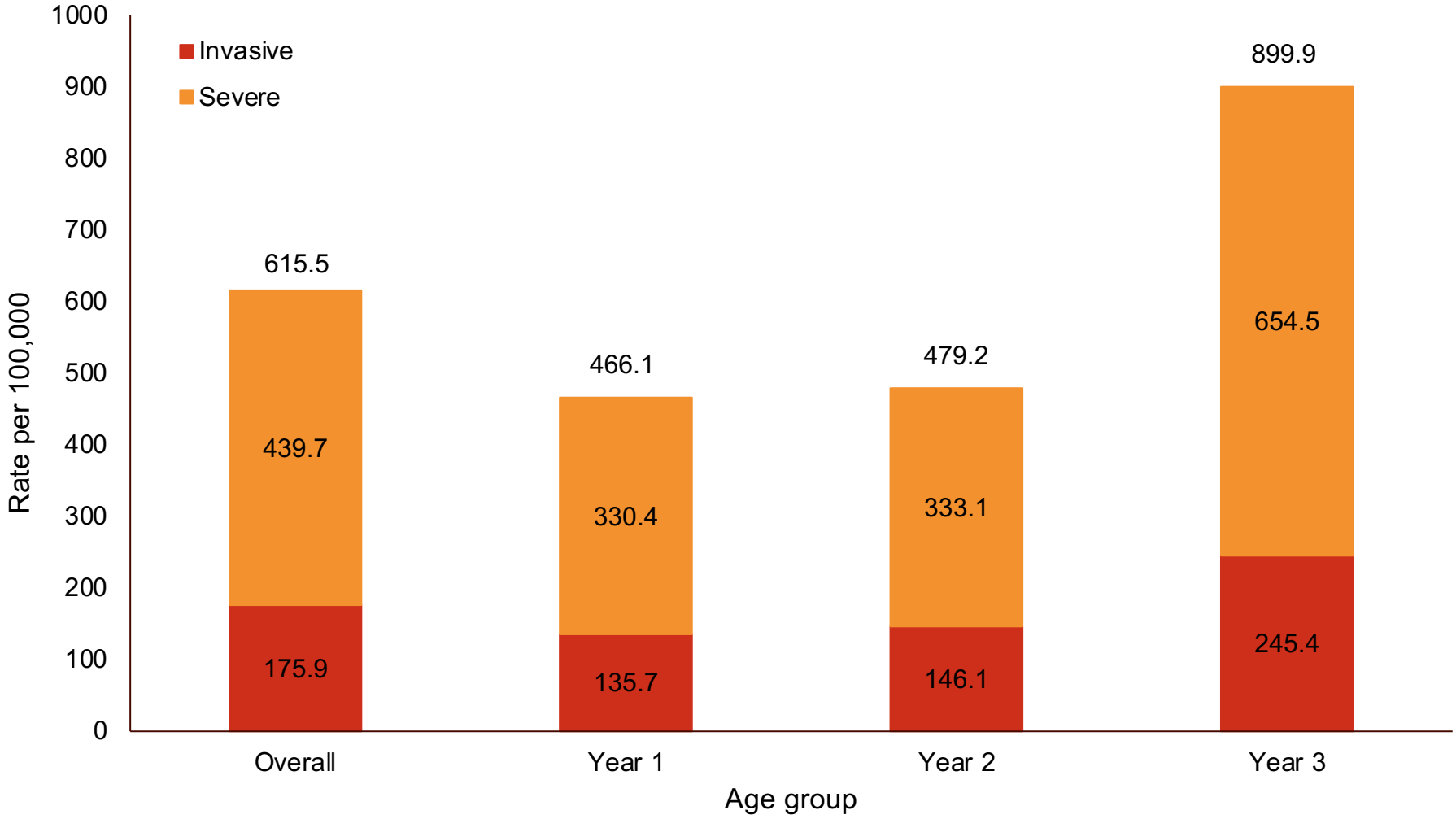
	Total (N=315)	Invasive (N=90)	Severe (N=225)
Hospitalized, %	98.1	94.4	99.6*
Length of hospitalization, median (IQR)	4 (3, 6)	5 (3, 11)	4 (3, 6)*
Amputation, %	4.4	4.4	4.4
Died, %	1.3	4.4	0.0*

* $p<0.05$

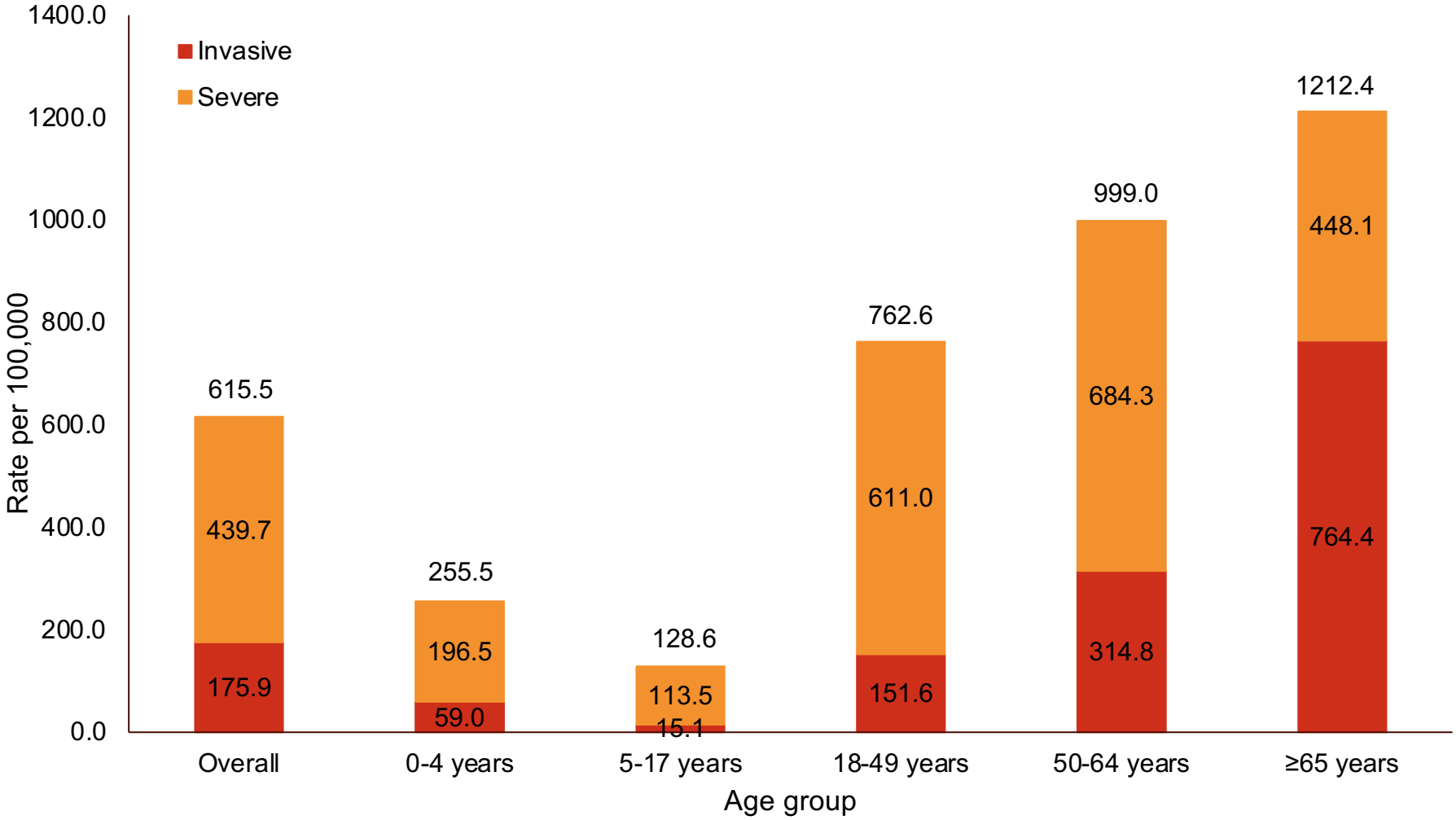
Results:

Burden of invasive and severe GAS disease

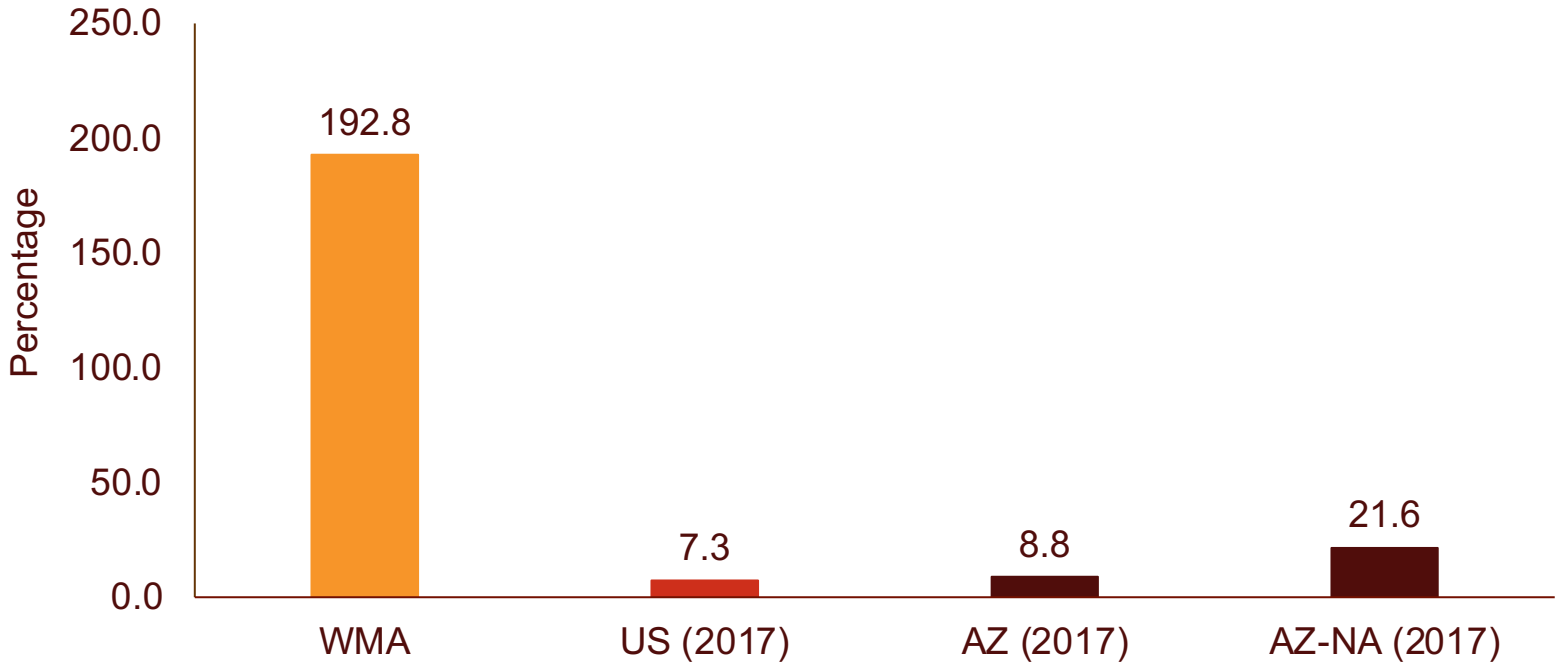
Incidence rates, overall and by year



Incidence rates, overall and by age



Comparison of invasive GAS disease on the WMA Tribal lands with the general US population



Sources: ABCs Report EIP Network Group A *Streptococcus* – 2017
Arizona Department of Health infectious disease report 2017

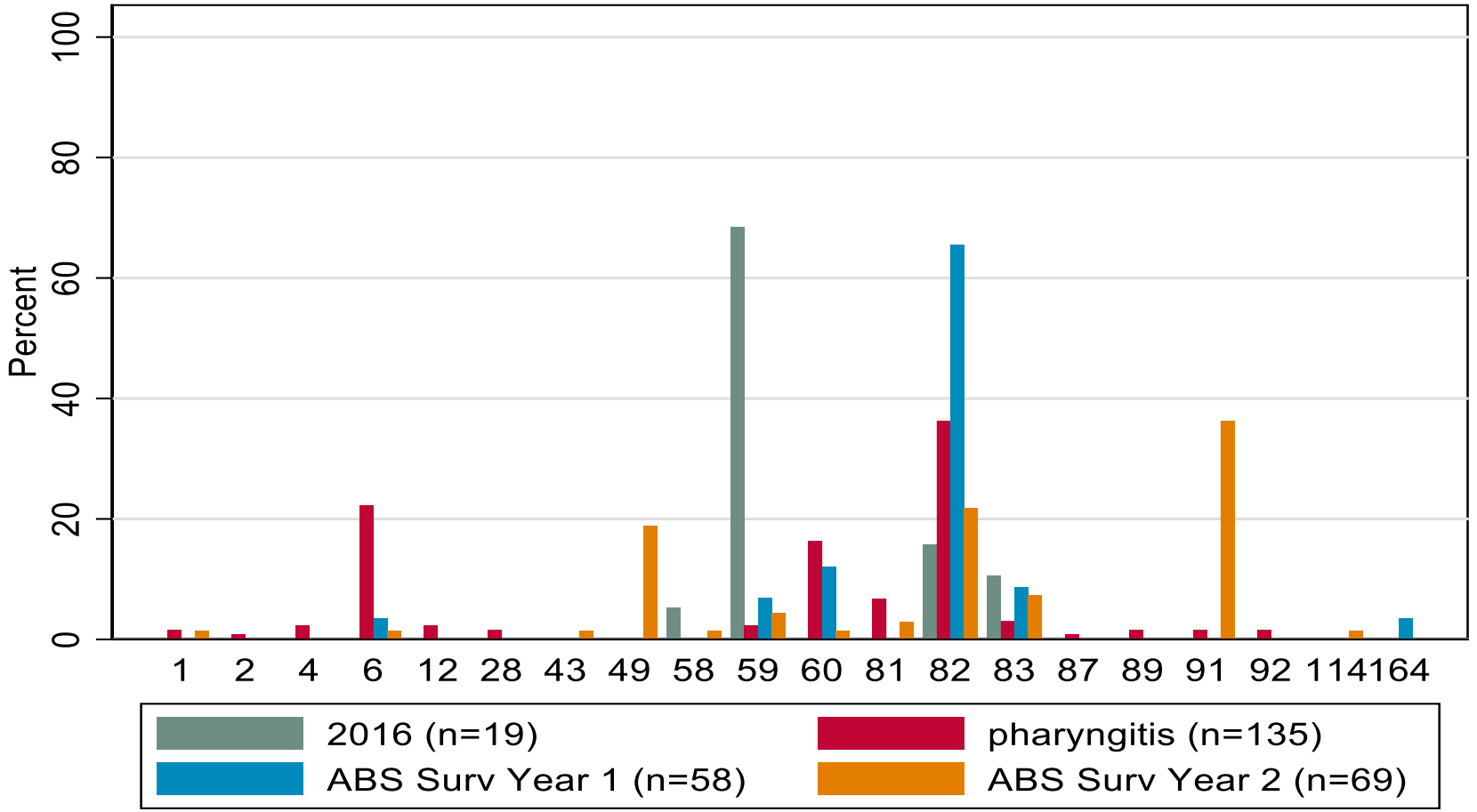
Results:

Distribution of *emm*-types among non-severe and severe GAS disease

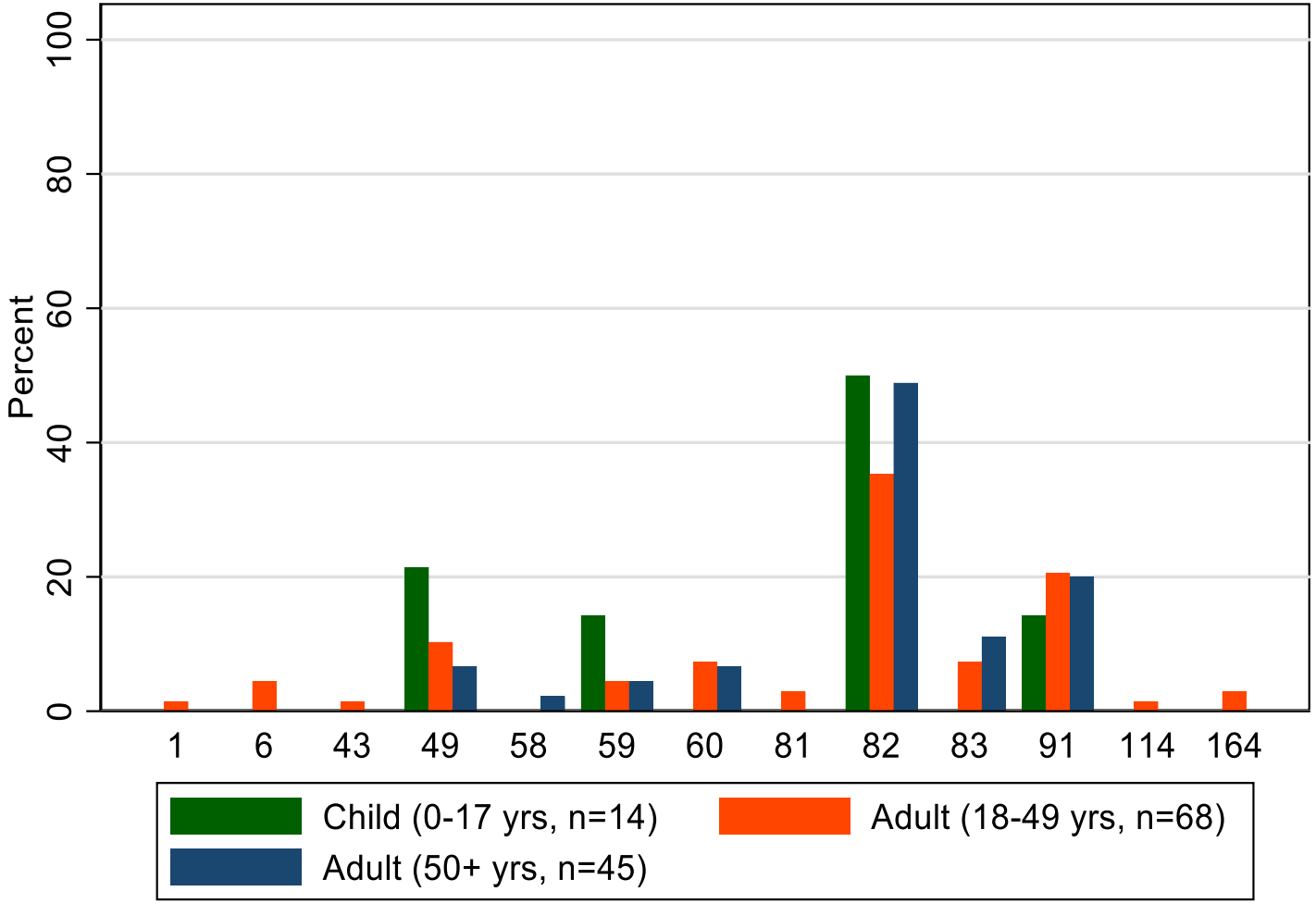
Characteristics of isolates

	2016 isolates (n=19)	Pharyngitis isolates (n=135)	Invasive and severe isolates (n=127)
Age (years), %			
0-4	31.6	1.5	4.7
5-17	26.3	48.9	6.3
18-49	36.8	36.3	53.5
≥50	5.3	13.3	35.4
Female, %	26.3	n/a	37.0
Clinical disease, %			
Invasive	10.5	0	29.1
Severe wound	26.3	0	70.9
Non-severe wound	63.2	0	0
Pharyngitis	0	100.0	0

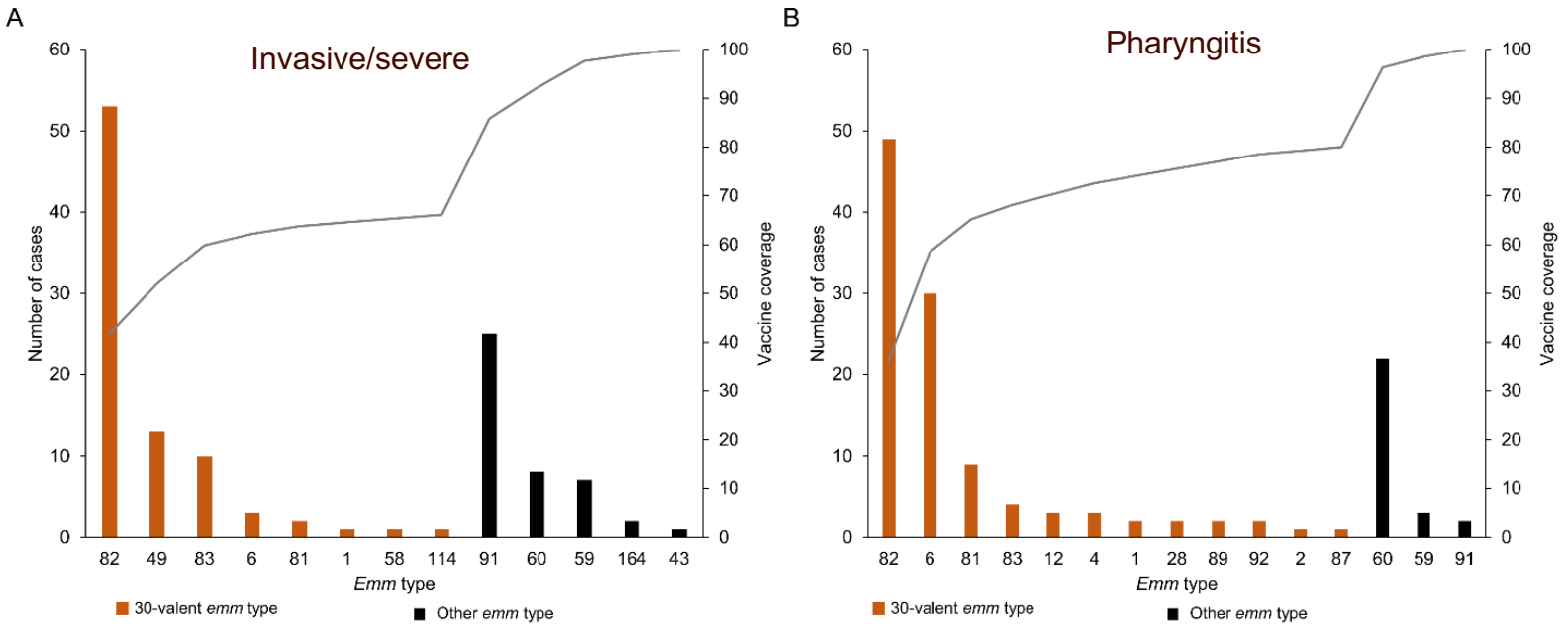
Emm-types by group



Emm type for invasive & severe cases by age



Vaccine coverage – Invasive/severe, and pharyngitis

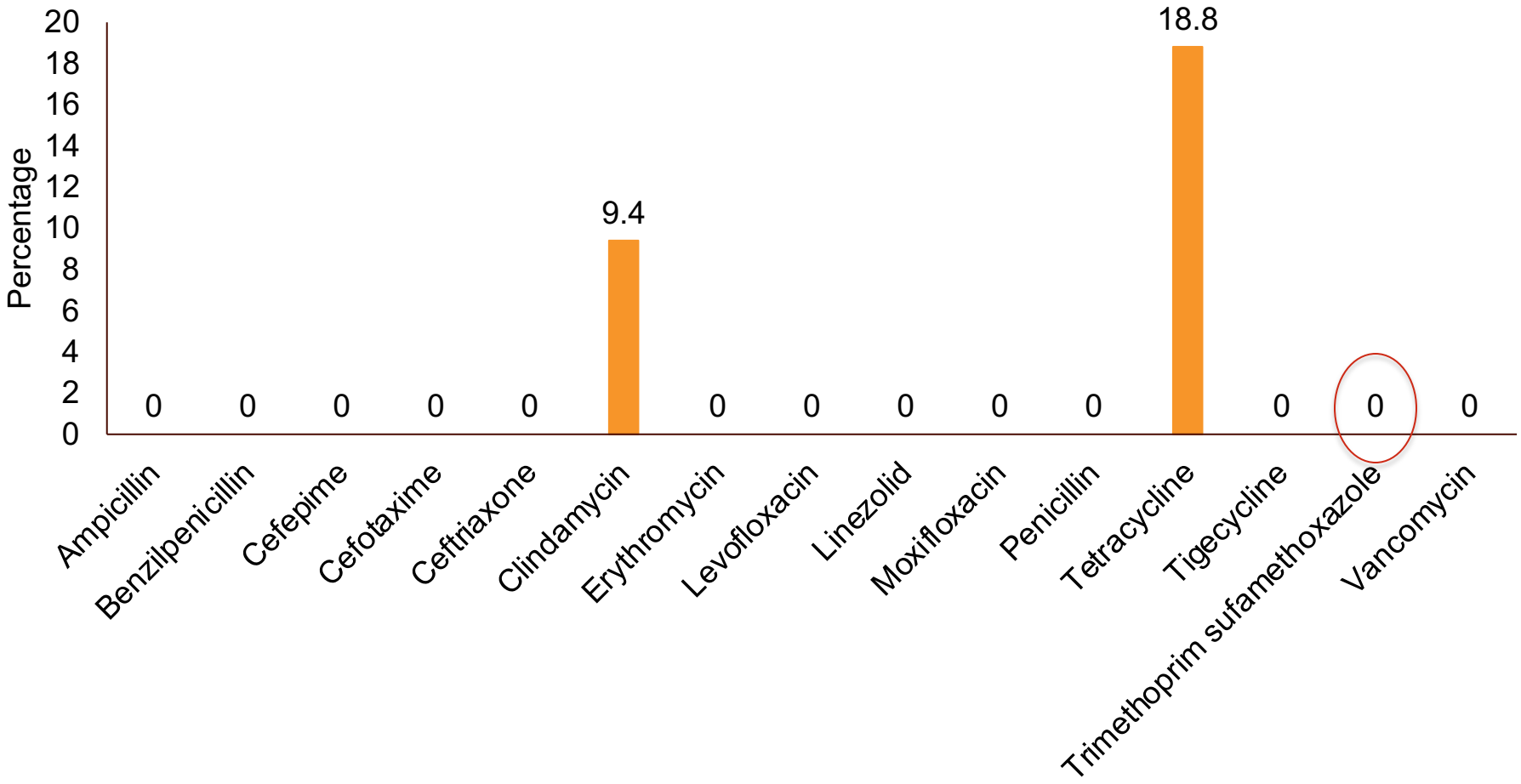


* Reference: Pastural E, McNeil SA, MacKinnon-Cameron D, et al. Safety and immunogenicity of a 30-valent M protein-based group a streptococcal vaccine in healthy adult volunteers: A randomized, controlled phase I study. *Vaccine*. 2020;38(6):1384-1392.

Possible Future Activities

1. Continued surveillance for invasive and severe GAS
2. Surveillance for non-severe GAS
3. Colonization studies
4. Assess interventions to reduce morbidity
    a. Health promotion among healthcare providers and high risk groups (e.g. diabetics)
    b. GAS eradication protocols

Antimicrobial resistance testing (invasive only)



Summary - Studies to date

- Compared utility of Centor score, Rapid Antigen Testing, and Throat Culture from July-December 2017 in adults ≥ 18: n=251, 30% with GAS pharyngitis, Centor score poorly predictive. (IDWeek 2018)
- 12 month old with fatal rheumatic carditis (Ped Infect Dis J, 2023)
- POC GAS PCR – validated for skin/soft tissue infections (Diagnostic Microbiology and Infectious Disease, 2022) – very high correlation.
- Disparate Impact of Invasive GAS on Native Americans (Emerging Infectious Dis, 2020)

GAS as a Health Disparities Disease

- Significant disparities in iGAS rates between indigenous and non-indigenous populations of Australia, New Zealand, and Canada, but much less is understood regarding iGAS among AI/AN in the United States.
- 46% of iGAS in Alaska is among AI/AN (20% of population)
- Post-strep sequelae (RF, PSGN) without recent data.
- Role of SES needs to be defined, role of historical trauma not yet understood (ACEs and chronic disease).
- Need to further define possible risk factors, signs and symptoms to alert clinicians to high risk patients.
- Clinicians can reconsider role of TMP/SMX.

Author(s)*	Years	Location	Indigenous community	Indigenous rate†	Non-Indigenous rate†
Hoge et. al.	1985 – 1990	Southwest, US	American Indians	36.5	2.7
Benjamin et. al.	1982 – 1991	New Mexico, US	American Indians	13.3	1.7‡
Rudolph et. al.	2001 – 2013	Alaska, US	Alaskan Natives	13.7	3.9
Degani et. al.	2000 – 2005	Yukon, CA	Inuit, Métis, and First Nations Canadians	11.0	1.9
Athey et. al.	2007 – 2013	Ontario, CA	First Nations Canadians	9.6 - 18.0	3.6 - 5.0
Bocking et. al.	2009 – 2014	Ontario, CA	First Nations Canadians	56.2	4.0‡
Carapetis et. al.	1991 – 1996	N. Territory, AU	Aboriginal Australians	23.8	4.7
Norton et. al.	1996 – 2001	Queensland, AU	Aboriginal Australians	82.5	10.3
Whitehead et. al.	2007 – 2009	Queensland, AU	Aboriginal Australian children	9.9 - 13.2	2.2 - 3.0
Gear et. al.	1998 – 2009	N. Territory, AU	Aboriginal Australians	40.6	15.8
Boyd et. al.	2011 – 2013	N. Territory, AU	Aboriginal Australians	69.7	8.8
Safar et. al.	2005 – 2006	Auckland, NZ	Indigenous Maori	21.6	5.3
Steer et. al.	2004 – 2005	Fiji	Indigenous Fijians	19.8	13.9
Steer et. al.	2005 – 2007	Fiji	Indigenous Fijians	13.1	2.5