'A real mouthful': The **intricacies** and complexities of pharyngitis diagnostics

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November, 2025

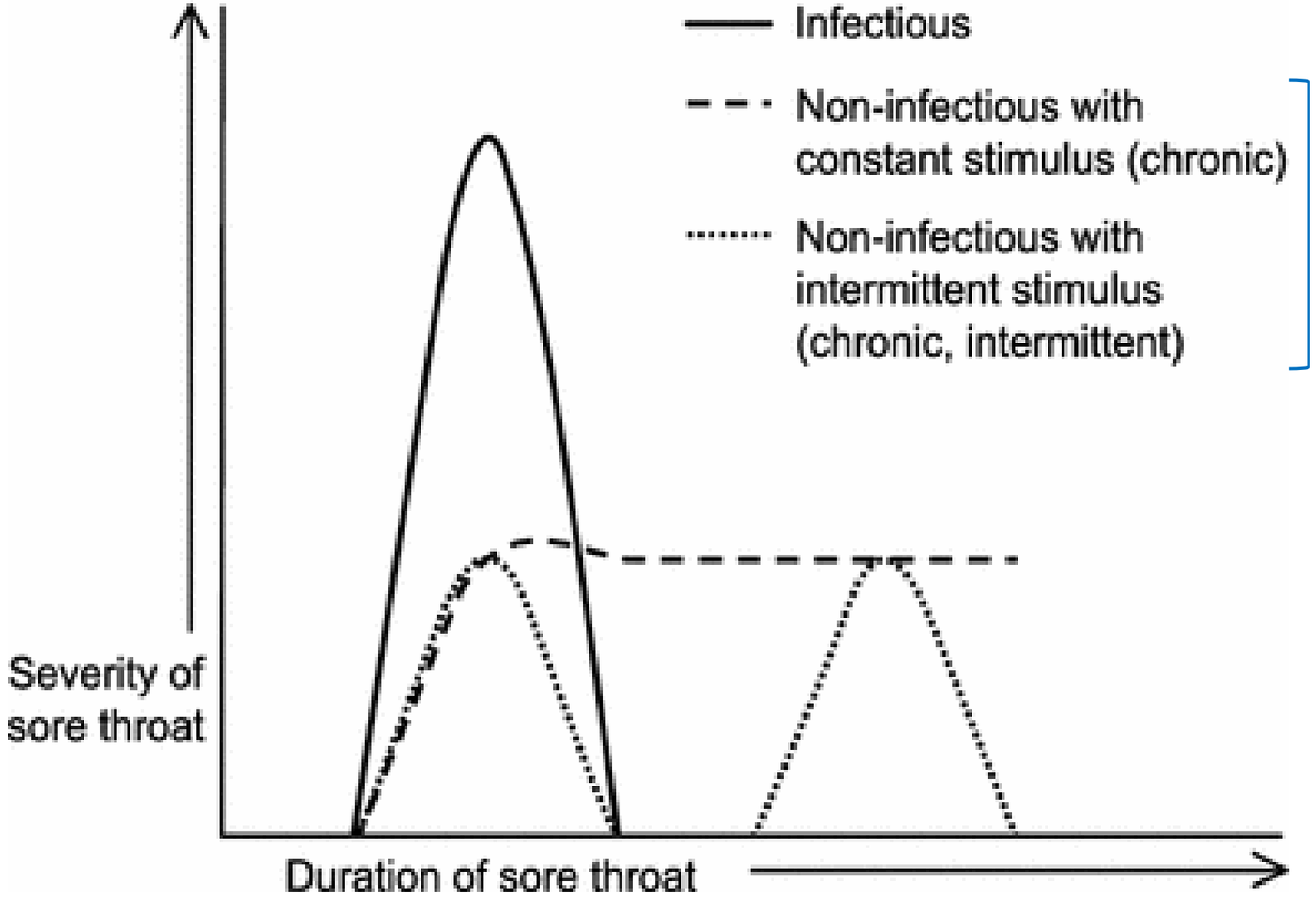
Objectives

- Compare and contrast current practice guidelines recommendations for the diagnosis and treatment pharyngitis
- Understand the limitations of standard diagnostic methods approaches
- Discuss the pros and cons of molecular-based approaches for the diagnosis of pharyngitis

Disclosures

- Abbott: consulting honoraria
- Diasorin: consulting honoraria, research support
- bioMérieux: consulting honoraria
- Shionogi: consulting honoraria

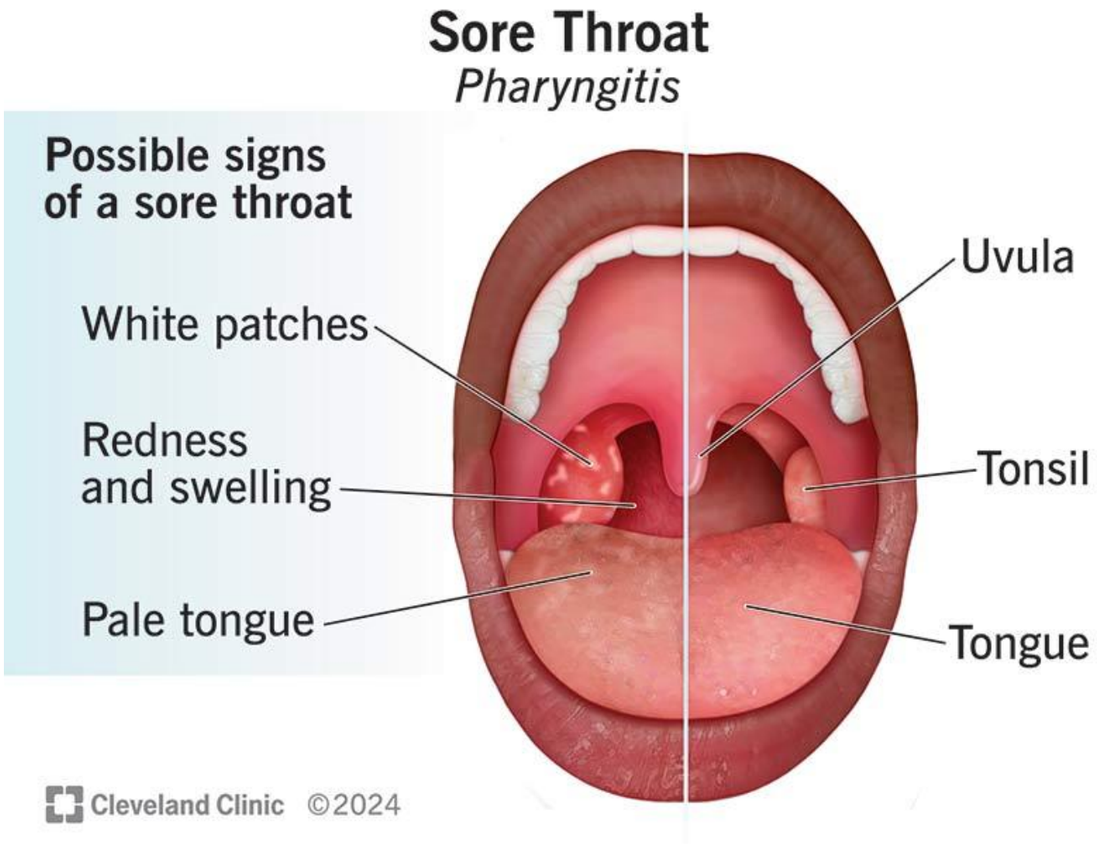
Causes of pharyngitis (AKA sore throat)



- **Physico-chemical factors (e.g. smoking)**
- **Environmental factors (e.g. air pollution)**

Renner et al. *Inflamm. Res*. 2012. 61:1041–1052

Pharyngitis = inflammation of the pharynx



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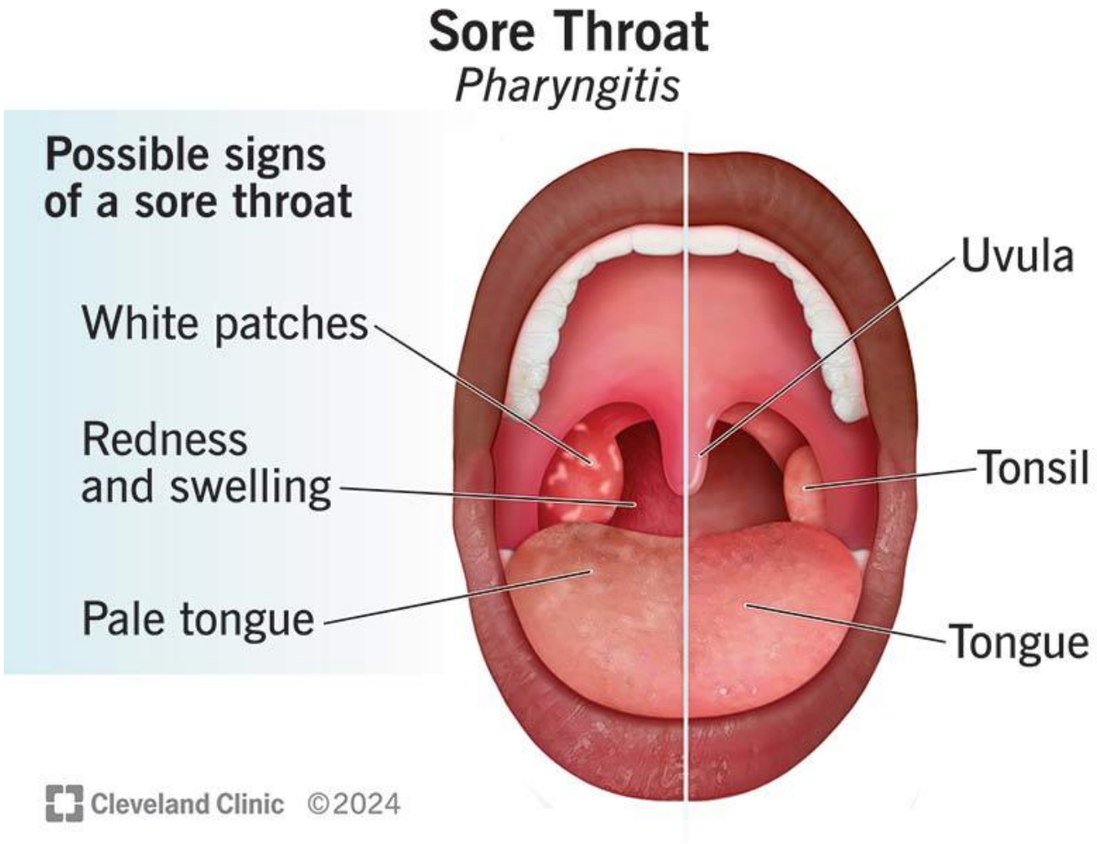

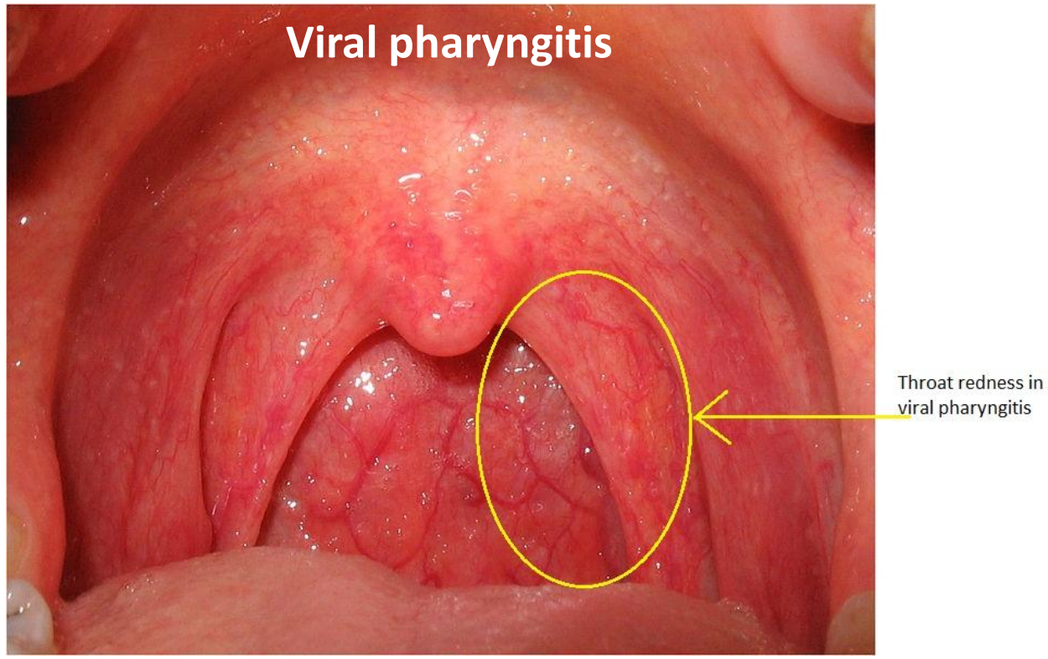

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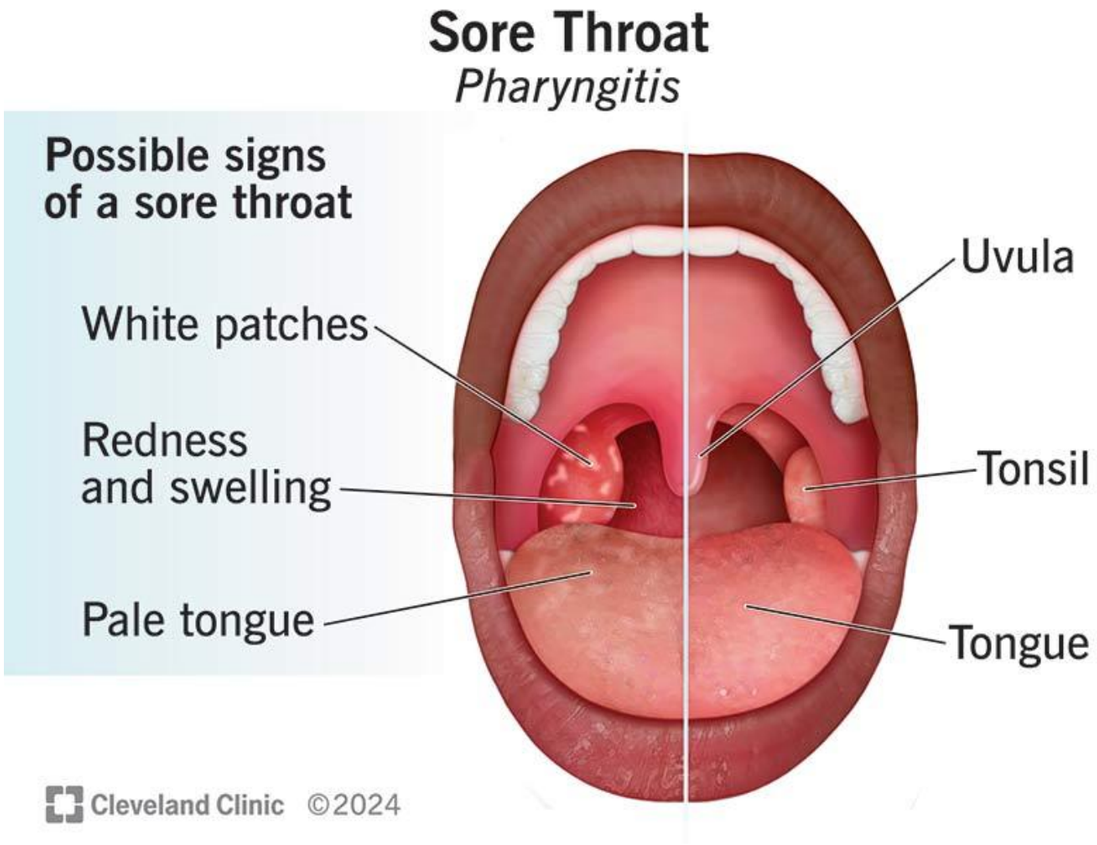

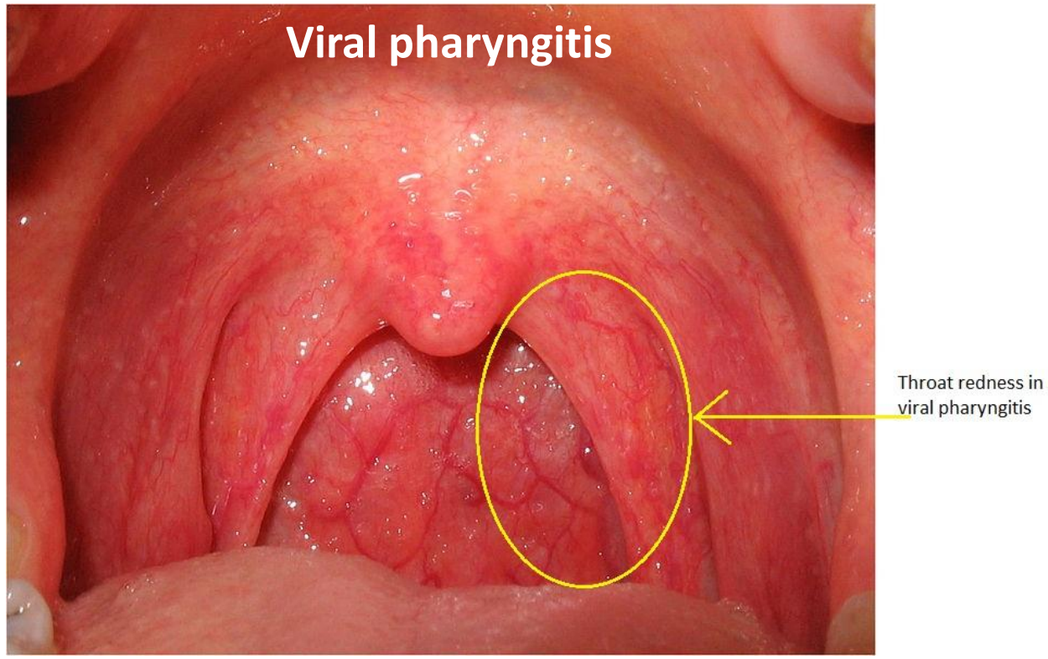

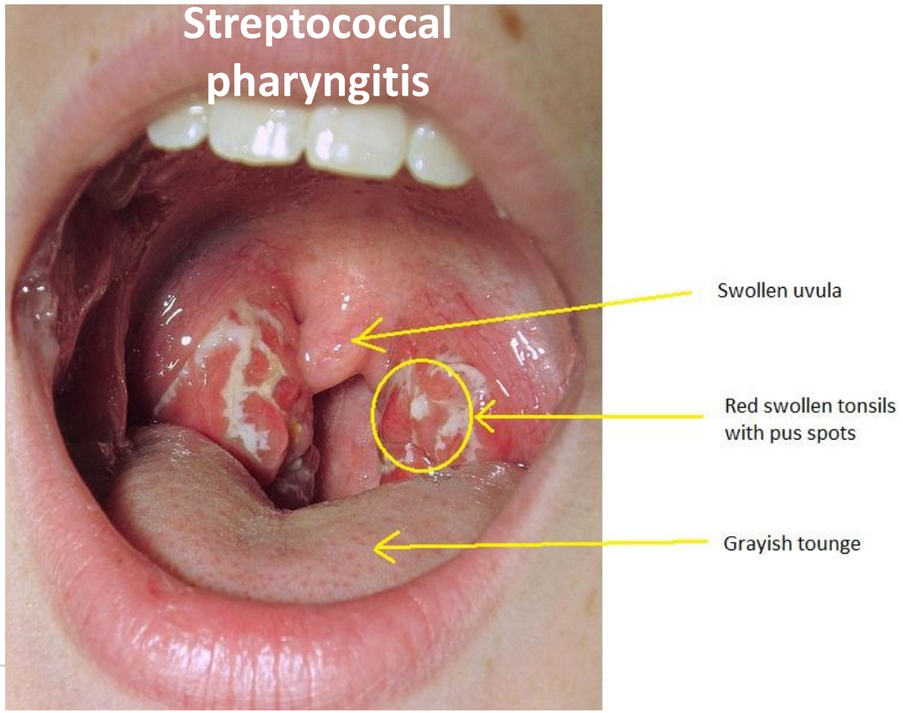

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The majority of pharyngitis is viral

Cause	Proportion of Pharyngitis Cases
Viruses	50 - 80%
Bacteria	5 - 36%
Fungi	Extremely rare (<1%)

- Alternative estimates of viral pharyngitis prevalence = 25-45%
- Rhinovirus, coronavirues, adenovirus account for at least 30% of pharyngitis cases

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Table 3. Microbial Etiology of Acute Pharyngitis

Organisms	Clinical Syndrome(s)
Bacterial	
Group A streptococcus	Pharyngotonsillitis, scarlet fever
Group C and group G streptococcus	Pharyngotonsillitis
Arcanobacterium haemolyticum	Scarlatiniform rash, pharyngitis
Neisseria gonorrhoeae	Tonsillopharyngitis
Corynebacterium diphtheriae	Diphtheria
Mixed anaerobes	Vincent's angina
Fusobacterium necrophorum	Lemierre's syndrome, peritonsillar abscess
Francisella tularensis	Tularemia (oropharyngeal)
Yersinia pestis	Plague
Yersinia enterocolitica	Enterocolitis, pharyngitis
Viral	
Adenovirus	Pharyngoconjunctival fever
Herpes simplex virus 1 and 2	Gingivostomatitis
Coxsackievirus	Herpangina
Rhinovirus	Common cold
Coronavirus	Common cold
Influenza A and B	Influenza
Parainfluenza	Cold, croup
EBV	Infectious mononucleosis
Cytomegalovirus	CMV mononucleosis
HIV	Primary acute HIV Infection
Mycoplasma	
Mycoplasma pneumoniae	Pneumonitis, bronchitis
Chlamydia	
Chlamydophila pneumoniae	Bronchitis, pneumonia
Chlamydophila psittaci	Psittacosis

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

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Impact of pharyngitis on healthcare

- Accounts for approx. 1–2% of all US outpatient visits
  - 15 million visits in 2006

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- 2.8 million antibiotic prescriptions
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- Group A *Streptococcus* accounts for 5.2 million annual outpatient visits in US
  - >1.1 million ED visits

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Image: Giant Microbes

Streptococcus pyogenes (Group A Strep)


Image: CDC


Image: NHS UK


Image: J of Young Investigators

These large, dark, boil-like blisters are a diagnostic symptom of necrotizing fasciitis (also known as flesh-eating disease).
(Source: EMBBS, 1998 http://mdchoice.com/)

- Non-invasive Disease
  - pharyngitis
  - scarlet fever
  - impetigo
  - non-necrotizing skin & soft tissue infection
- Invasive Disease
  - cellulitis
  - necrotizing soft tissue infection
    - necrotizing fasciitis
  - bacteremia; endocarditis
  - toxic shock syndrome (TSS)
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Group A *Streptococcus* is believed to be the fifth most lethal pathogen in the world!

- Over 517,000 people die from severe GAS infection annually


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Group A *Streptococcus* (GAS) Pharyngitis

Images: Microbe Canvas

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- GAS responsible for acute pharyngitis in:
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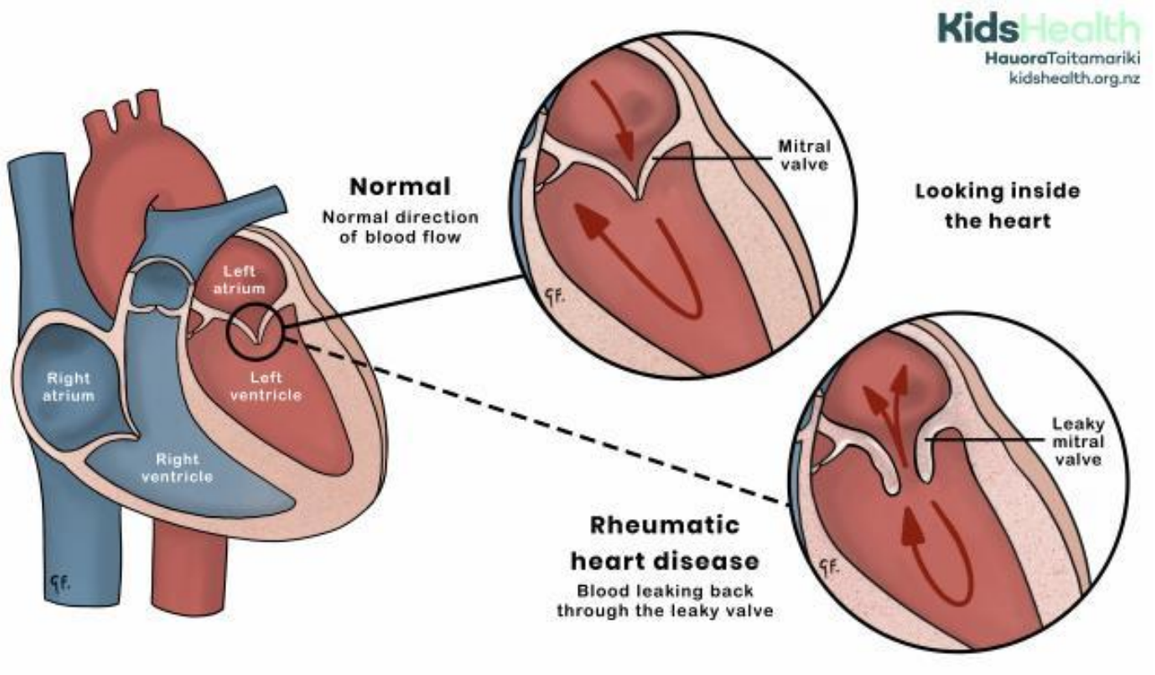
- Though infection is generally <u>self-limiting</u> for many patients, complications can occur, particularly in children aged 3-15 yo
  - <u>Suppurative</u>
    - abscess, mastoiditis, cervical lymphadenitis, otitis media, sinusitis, meningitis, bacteremia
  - <u>Non-suppurative</u> i.e. immune-mediated
    - **acute rheumatic fever**
    - post-streptococcal glomerulonephritis

Acute rheumatic fever (ARF)

- Typically occurs 2-3 weeks <u>after</u> GAS pharyngitis



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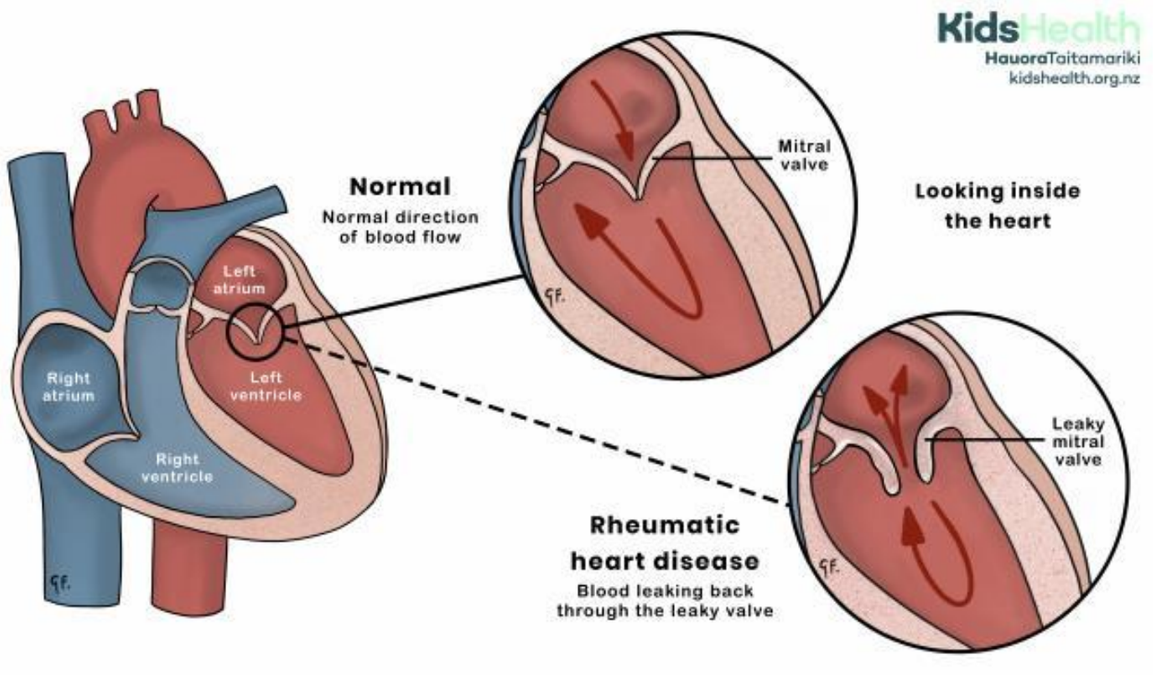

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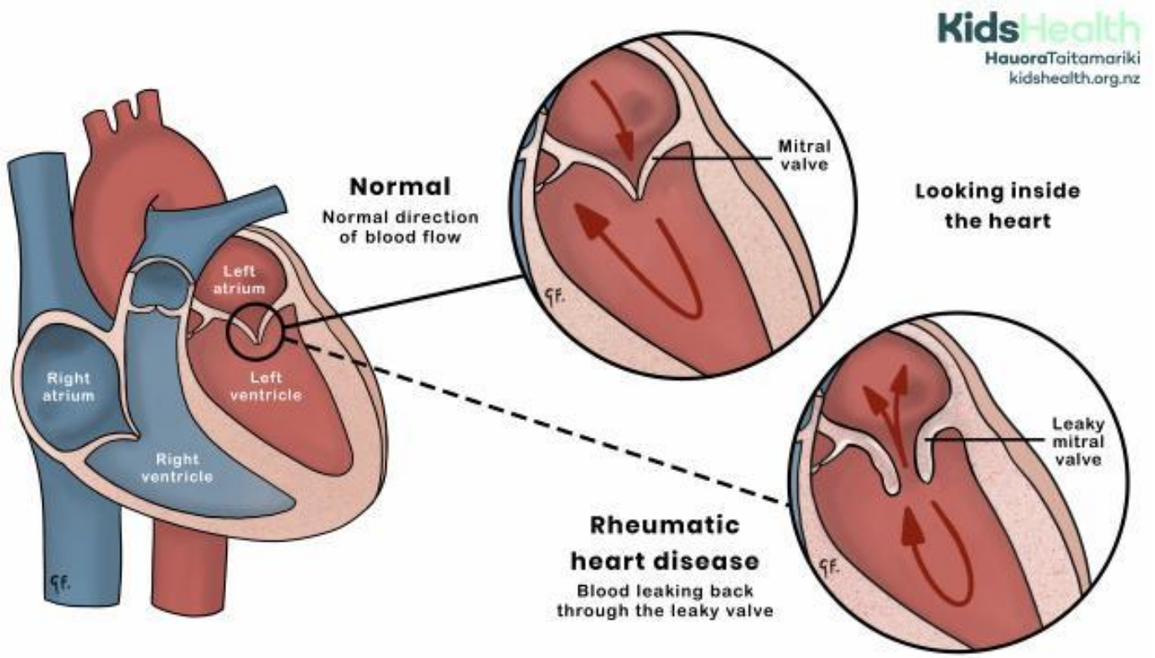

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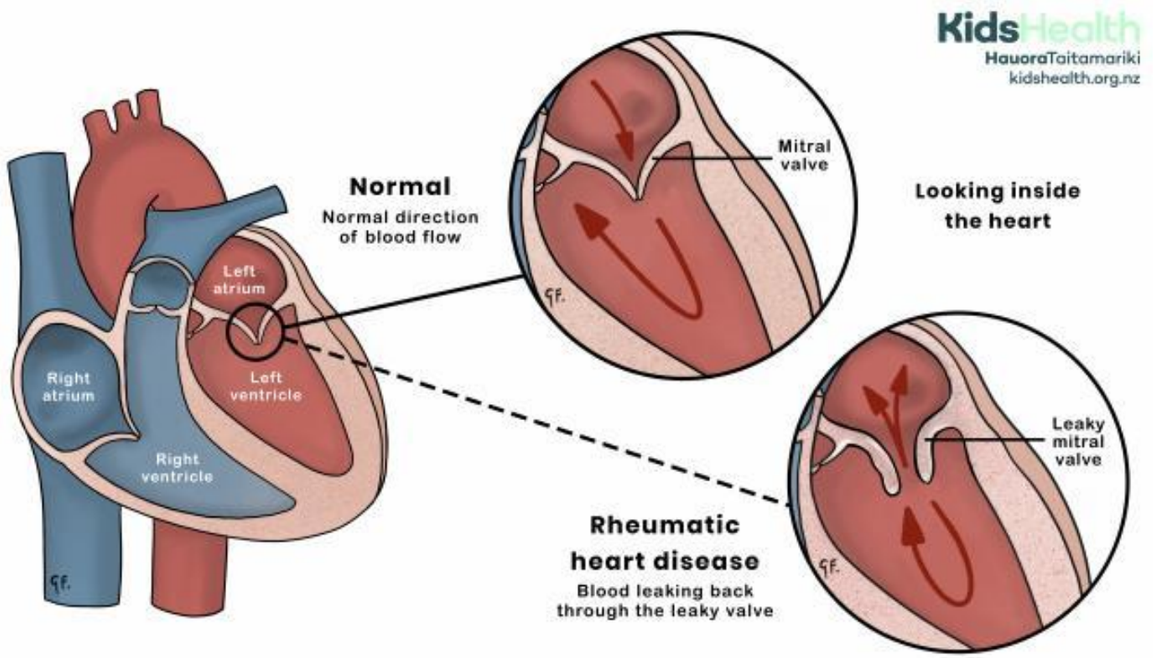

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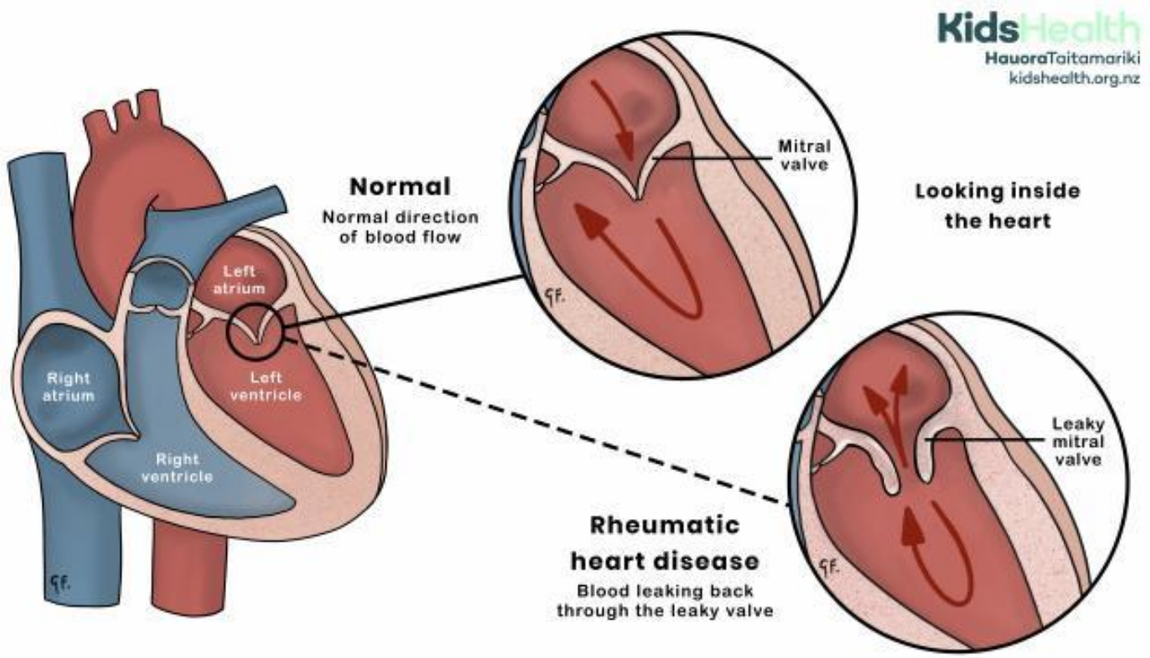

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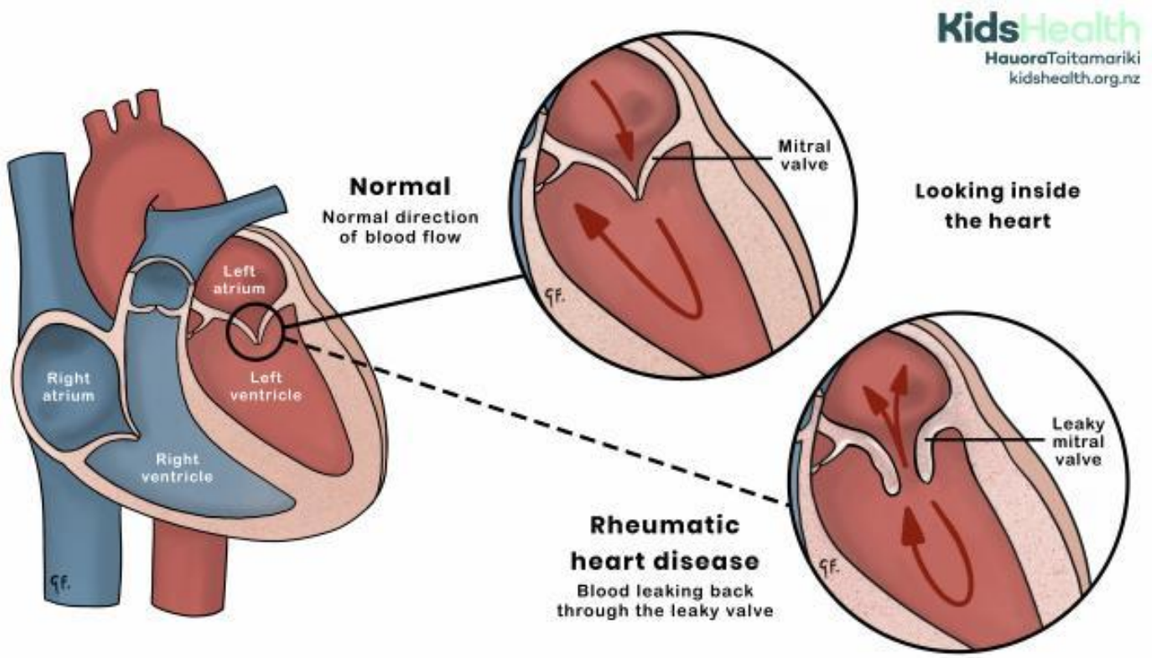

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  - pancarditis = inflammation of pericardium, myocardium & endocardium
- 2-3% of untreated GAS cases will develop ARF vs. <0.3% if treated

Global differences in ARF incidence

WHO Region	Estimated Incidence Rate (per 100,000)	Notes
African Region (AFR)	10–30+	Highest incidence globally; limited healthcare access and surveillance gaps
Region of the Americas (AMR)	<1–2	Low incidence overall; some outbreaks in Indigenous communities
South-East Asia Region (SEAR)	10–20	High burden in countries like India, Nepal, Indonesia
European Region (EUR)	<1	Low incidence; sporadic outbreaks mainly in Eastern and Southeastern Europe
Eastern Mediterranean Region (EMR)	10–20	Moderate to high incidence; endemic in some Middle Eastern and North African countries
Western Pacific Region (WPR)	1–10	Variable incidence; low in high-income countries, higher in rural/Indigenous populations

Source: perplexity.ai

Post-streptococcal glomerulonephritis (PSGN)

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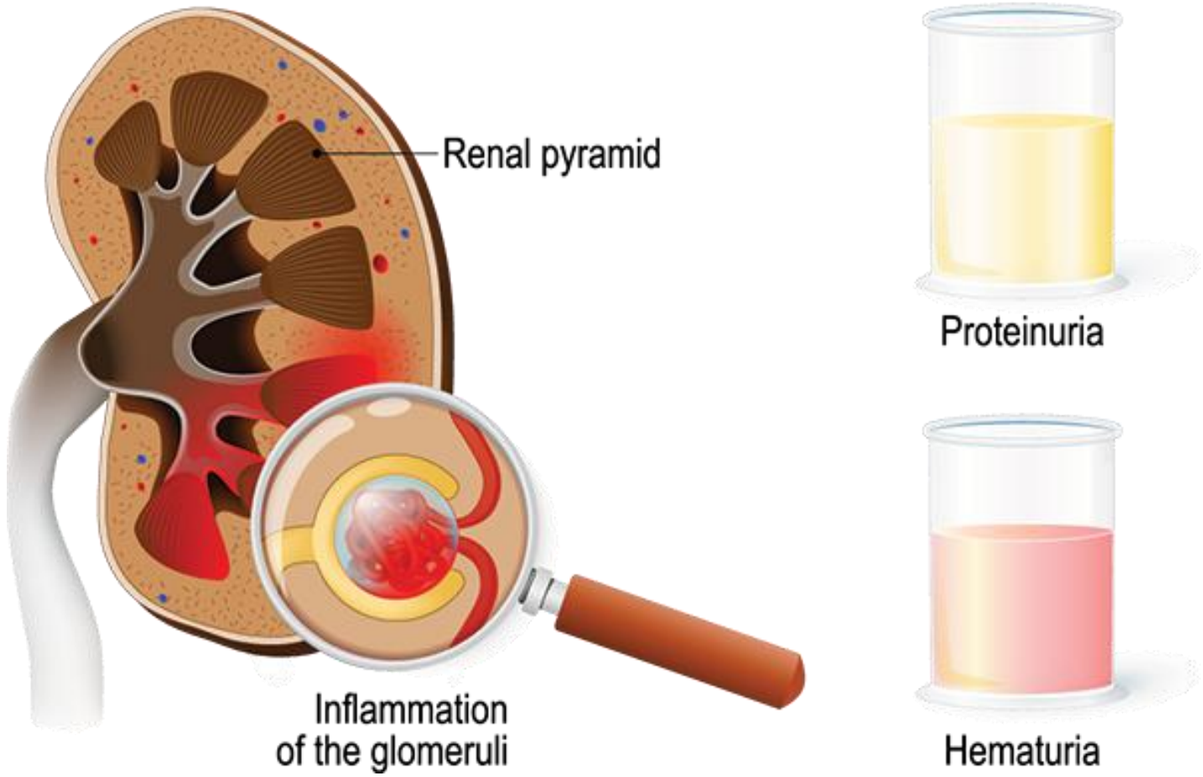
  - **occurs 1-3 weeks after pharyngitis**, 3-6 weeks after skin infection



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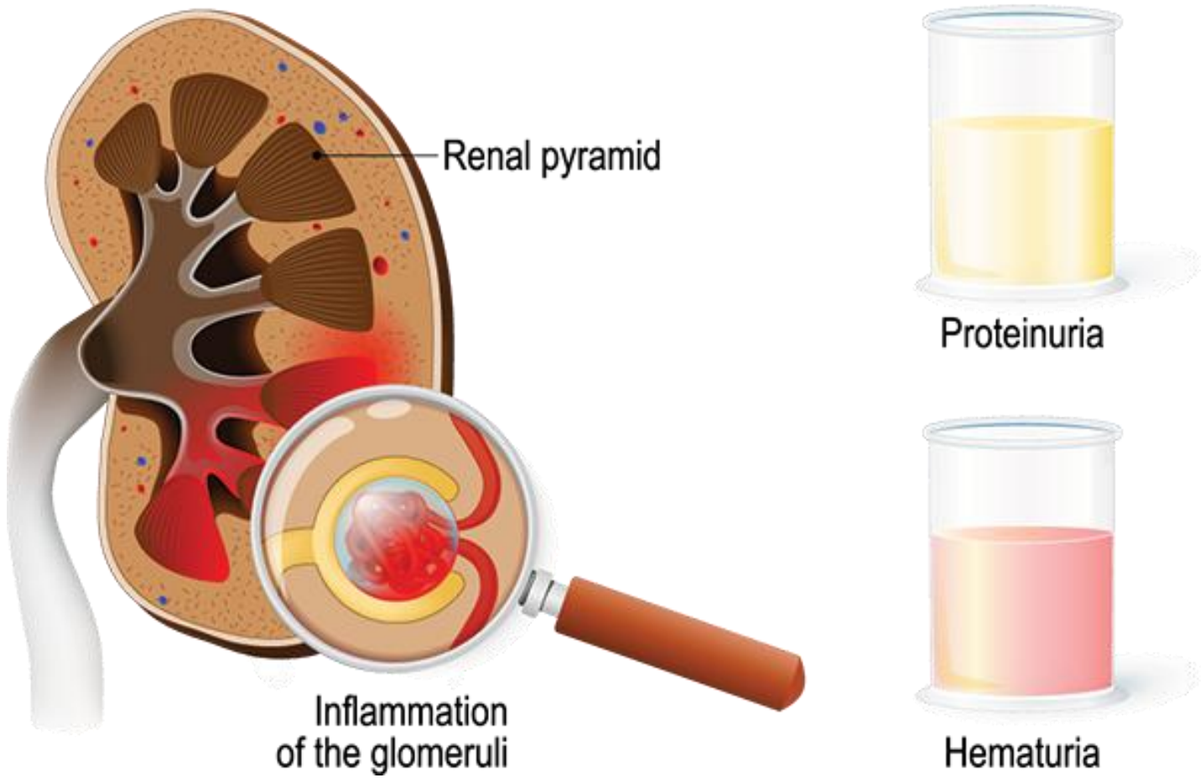

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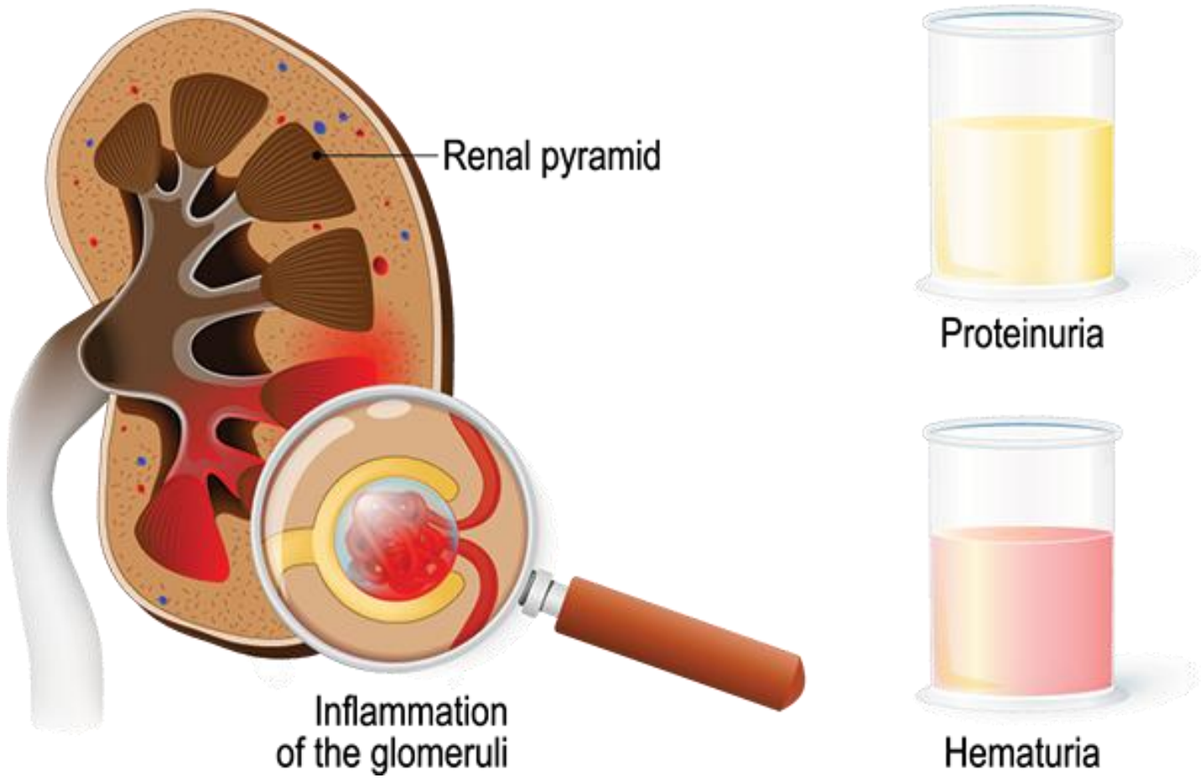

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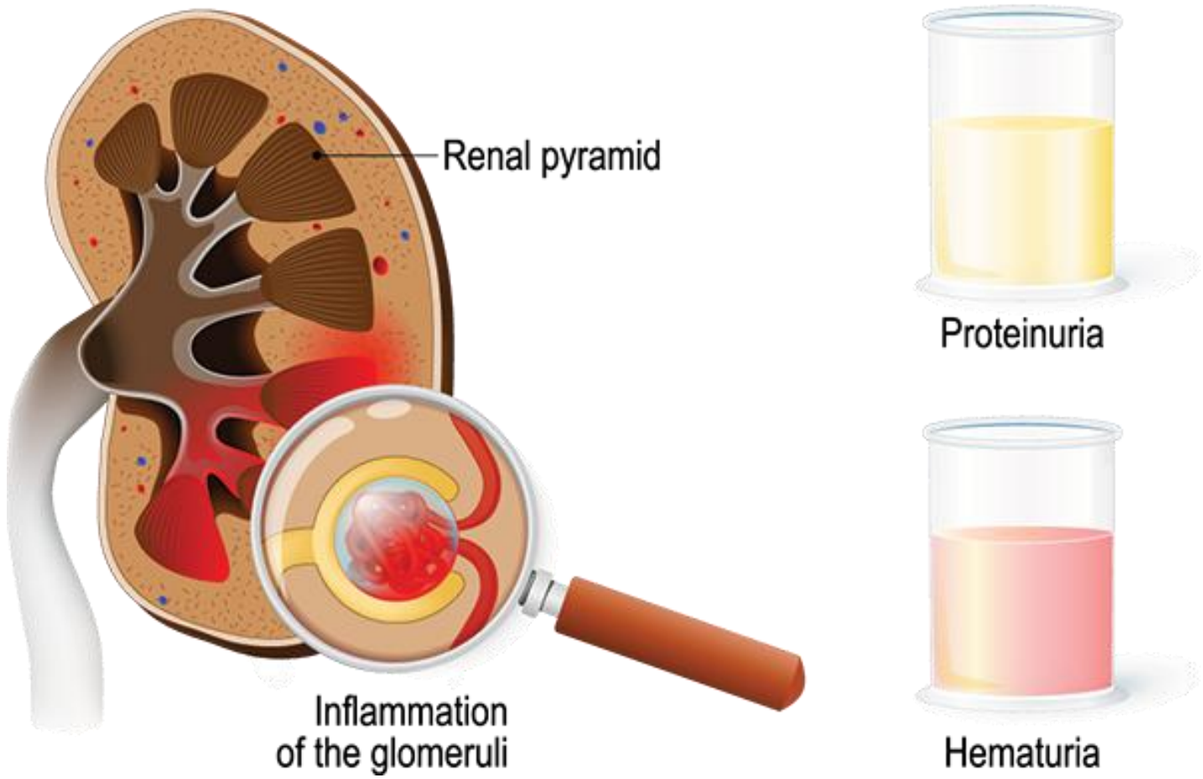

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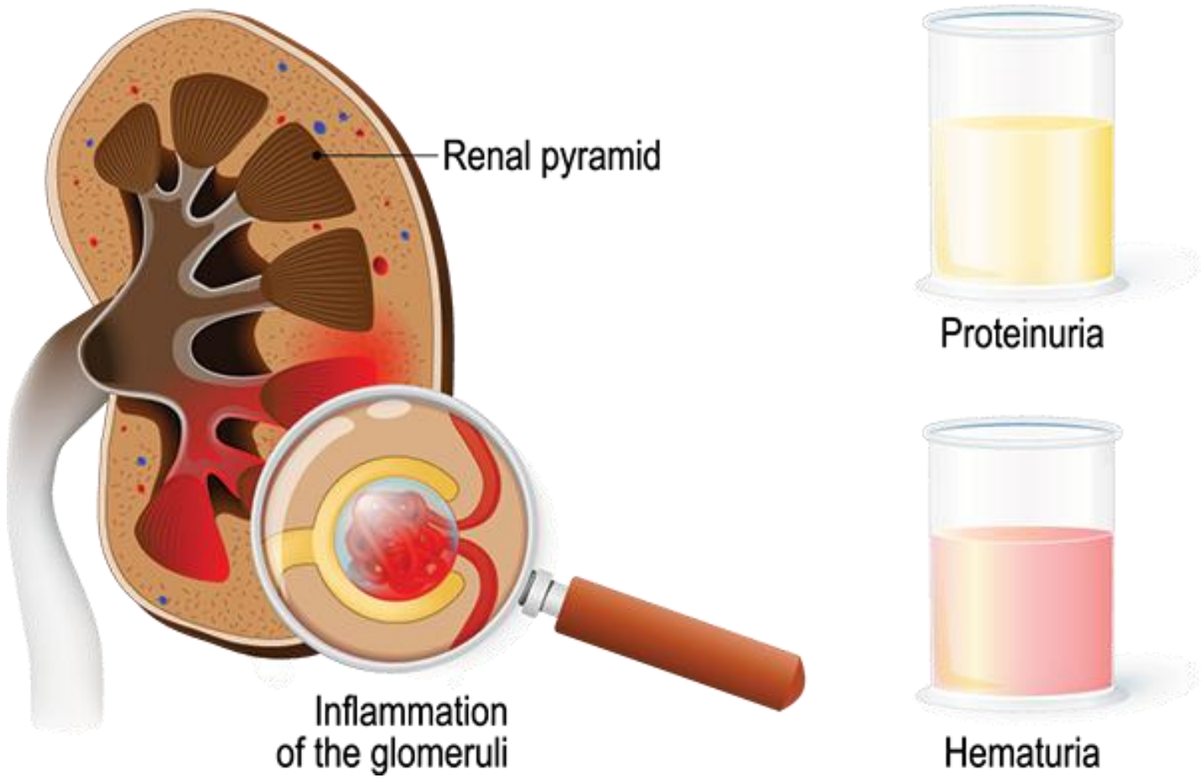

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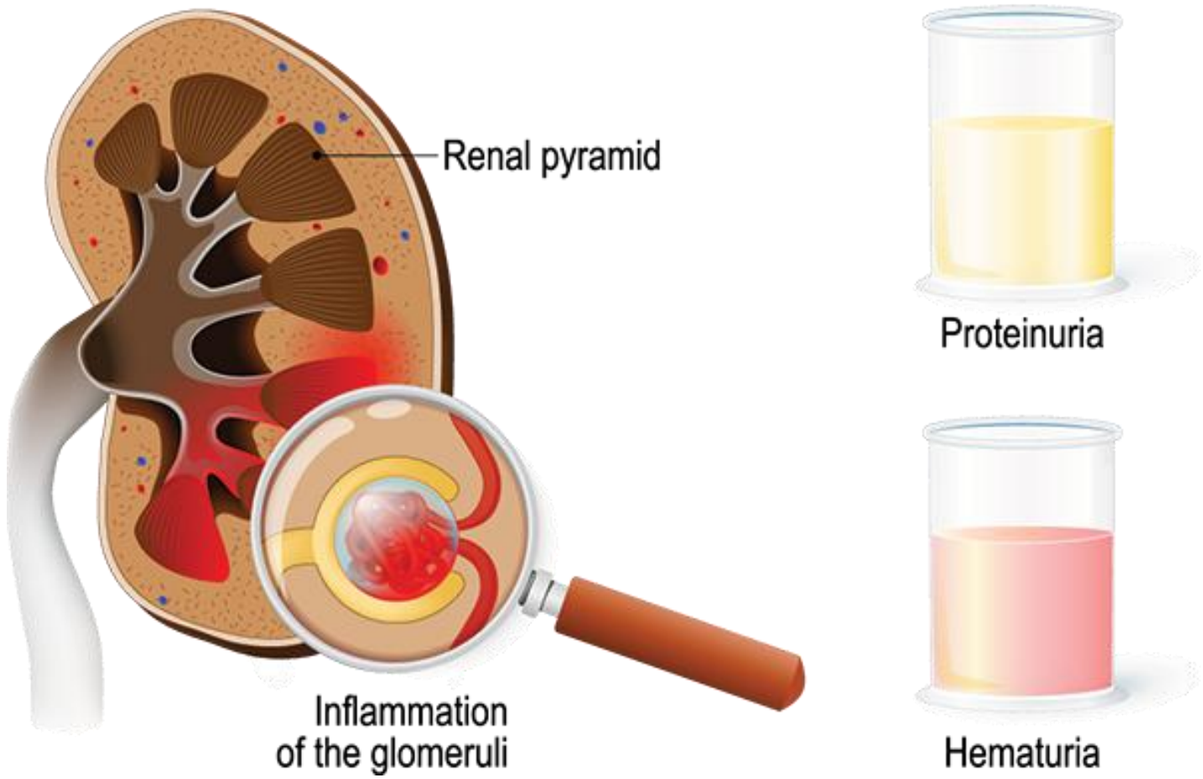

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The colonization conundrum…

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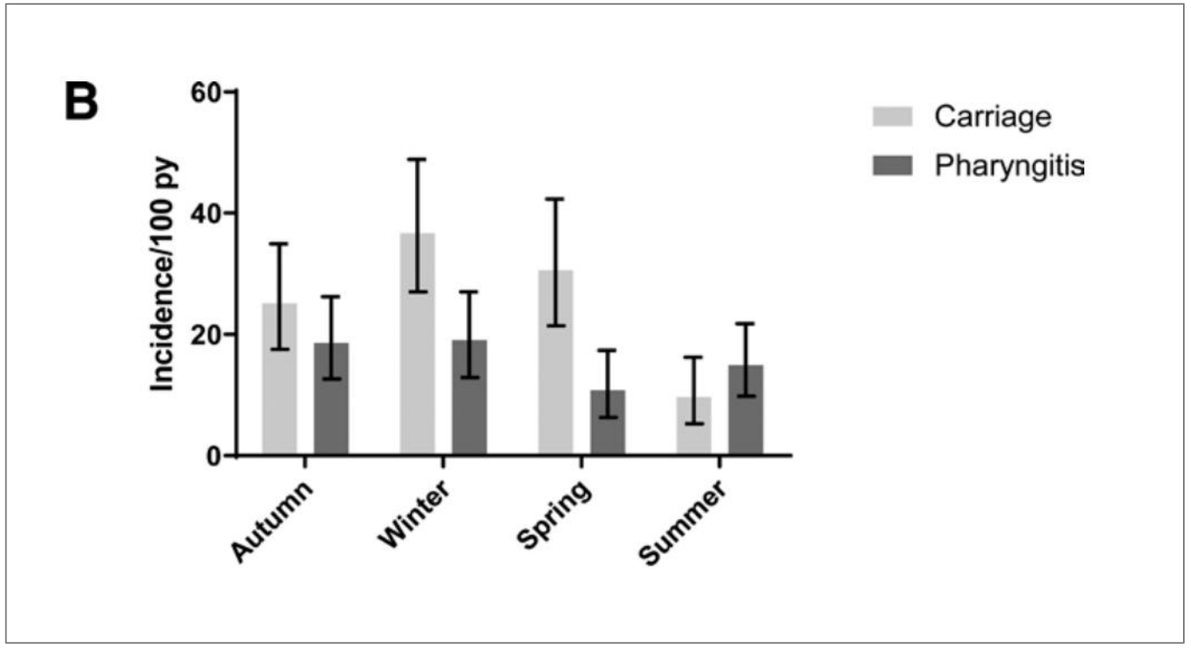

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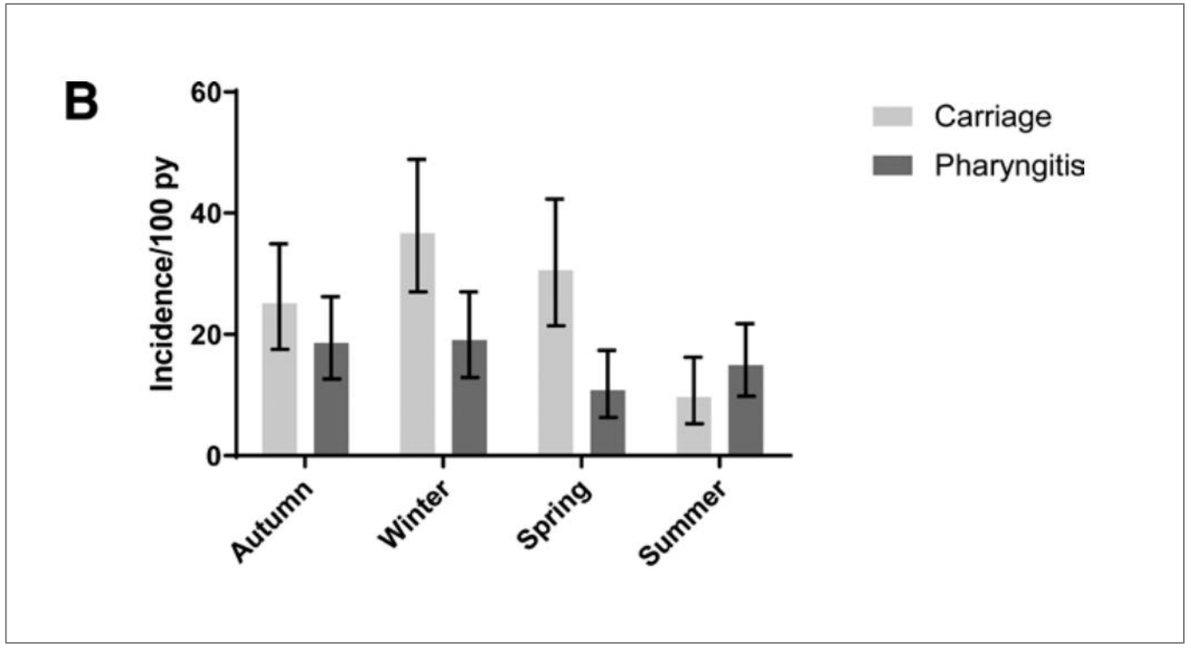

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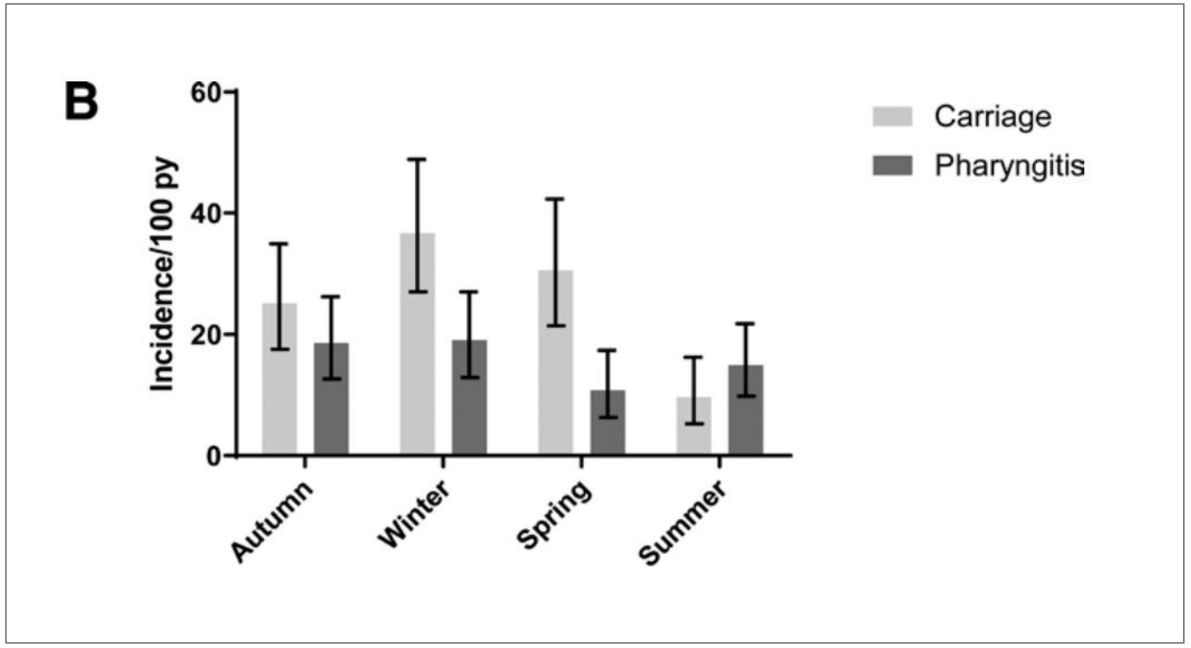

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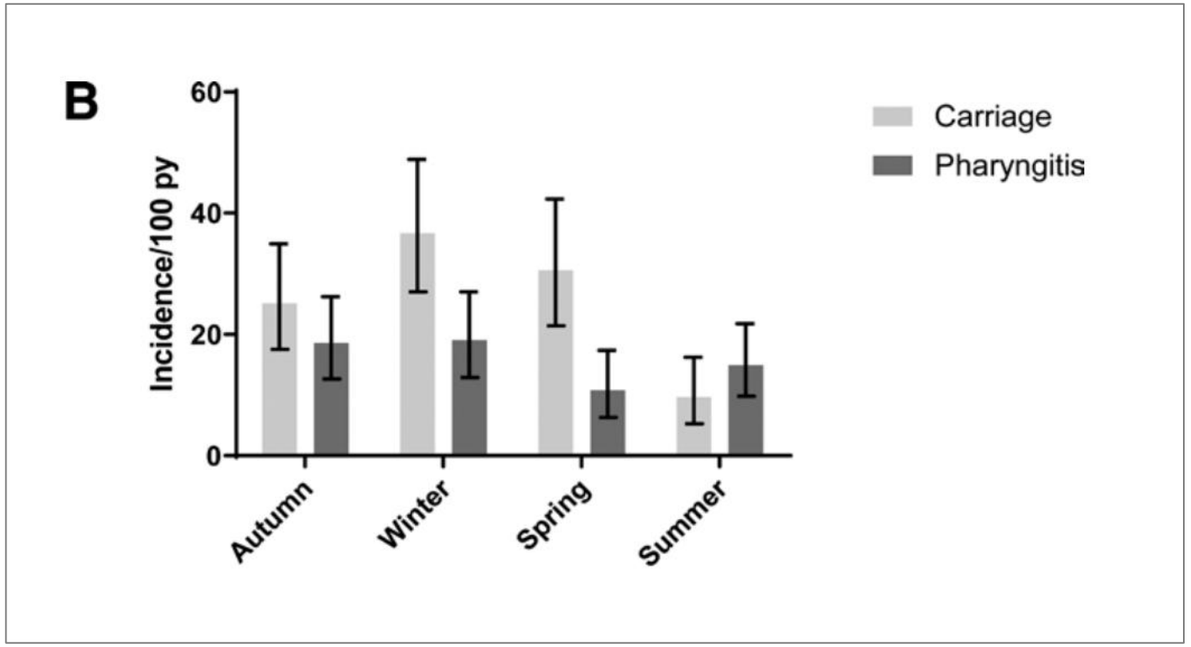

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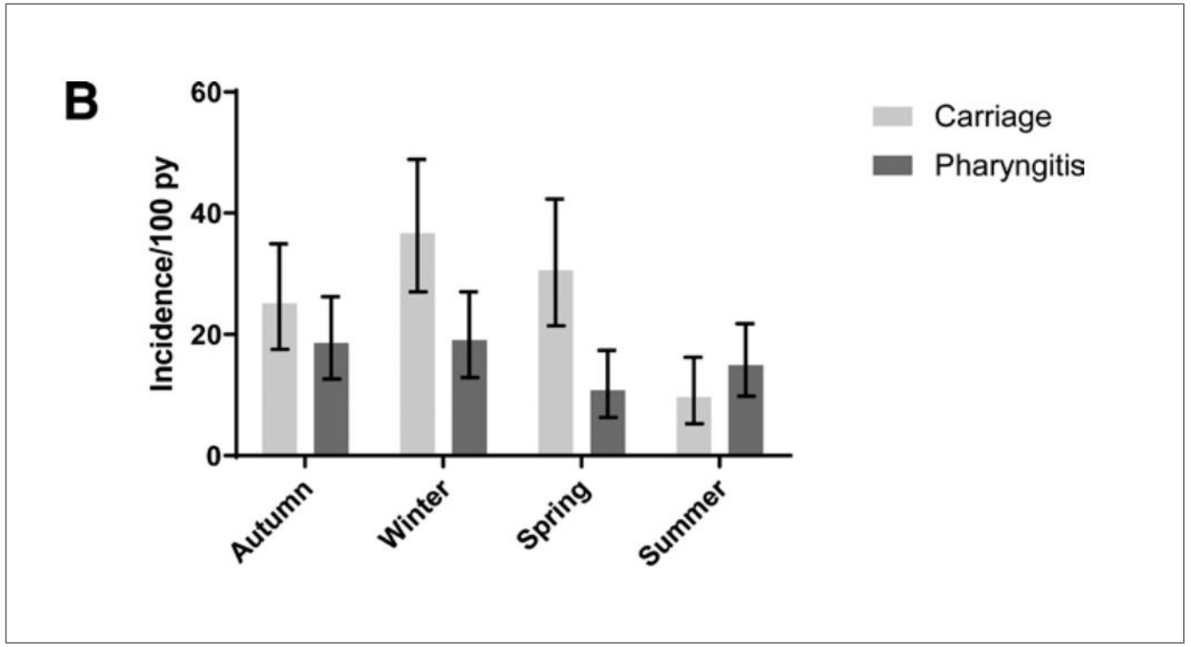

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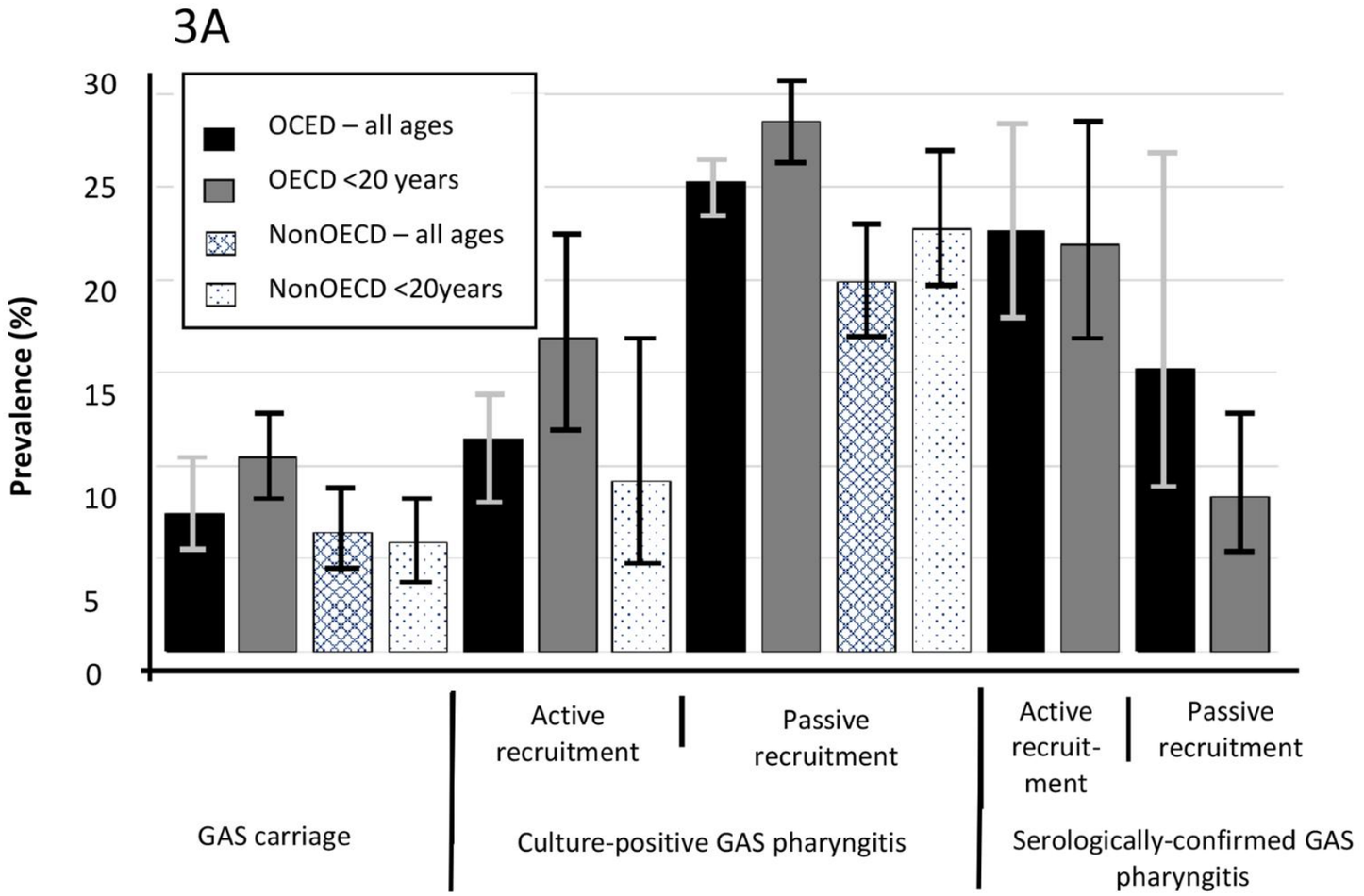
- **Adults: only ≤2% colonization & without seasonal variation**

What about outside the US?

OCED – Organization for Economic Cooperation & Development



- GAS pharyngitis is more prevalent in high income countries vs. low/middle-income countries (24.3% vs. 17.6%)
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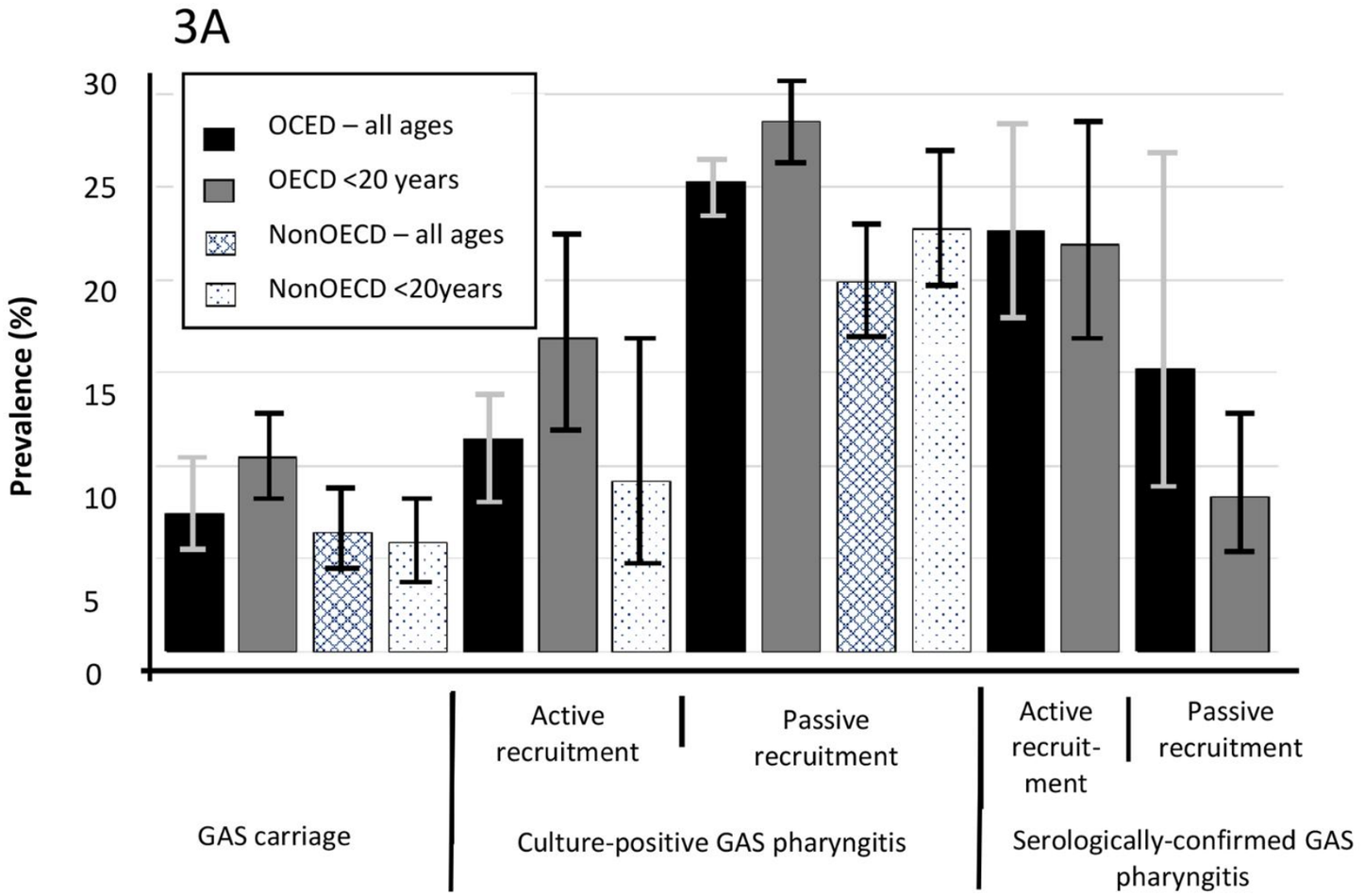
Oliver J. PLOS Negl Trop Dis. 2018. 12(3):e0006335

What about outside the US?

OCED – Organization for Economic Cooperation & Development



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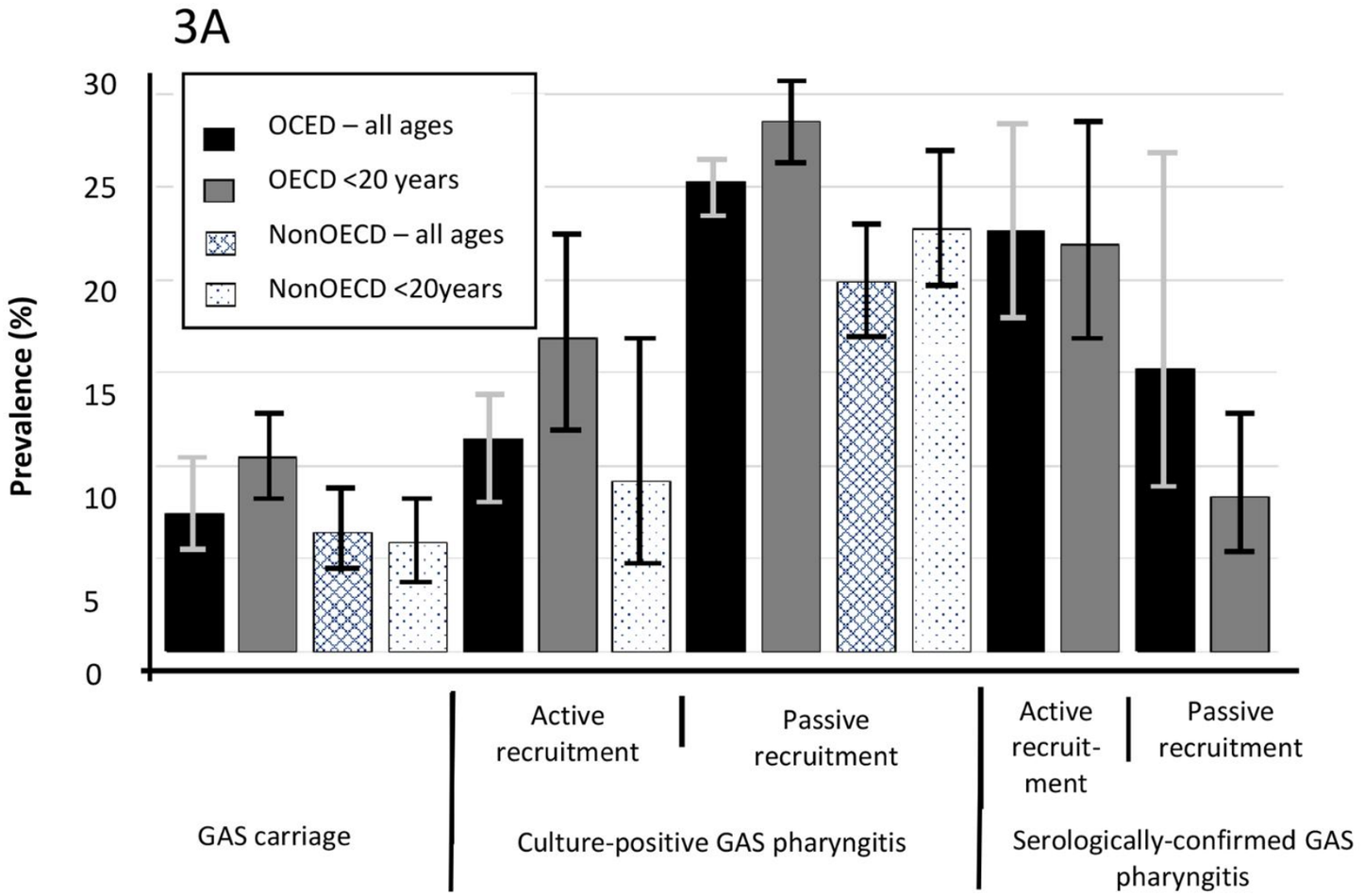

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- In high income countries, only 1 in 10 kids with pharyngitis symptoms are likely to have serologically-confirmed infection

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Colonization is not just limited to GAS…

Table 4. Recent studies reporting asymptomatic carriage of GAS, SDSE, and *F. necrophorum*

	Centor et al. 2015 [3]	Hedin et al. 2015 [6]	Nygren et al. 2021 [11]	Agerhäll et al. (present)	
Number of asymptomatic individuals	180	128	100[a]	217	
Age range in years	15–30 (Mean, 24)	16–46 (Median, 31)	15–25 (Median, 22)	16–25 (Median, 19)	
Included population	University students, USA	Primary healthca re patients, Sweden	Health education students, acute orthopedic patients, Sweden	Secondary school and university students, routine oral health screening, Sweden	
Exclusion	Ongoing sore throat, ongoing antibiotic treatment	Visiting primary health care for infection	Sign of throat infection, antibiotic treatment last 4 weeks, previous tonsillectomy	Ongoing sore throat, antibiotic treatment last 2 weeks, previous tonsillar surgery	
Diagnostic method	PCR	Culture	PCR	Culture and PCR	PCR
GAS	1.1% (2/180)	2.3% (3/128)	N/A	10.1% (22/217)	9.2% (20/217)
SDSE	3.9% (7/180)	7.8% (10/128)	N/A	7.8% (17/217)	6.5% (14/217)
FN	9.4% (17/180)	3.1% (4/128)	21.0% (21/100)	10.1% (22/217)	9.2% (20/217)
Any above	14.4% (25/180)	13.3%[a] (17/128)	N/A	24.4% (53/217)	23.5% (51/217)

FN, Fusobacterium necrophorum; GAS, Group A streptococci; Streptococcus pyogenes; SDSE, Streptococcus dysgalactiae subsp. equisimilis; Group C/G streptococci.

[a]The study of Nygren et al. 2021 [11] has two arms with participants in Sweden and Zambia respectively, with the sampling performed in different periods in the two countries. We have only included the part performed in Sweden.

SDSE = *Streptococcus dysgalactiae* subsp. *equisimilis* (i.e. Group C/G Strep)

- estimated 3% colonization rate for children in multiple studies

Agerhall M et al. *APMIS*. 2021. 129(12):711-716

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Putting it all together…

Table 1. Probability that a potentially pathogenic bacteria detected in someone with a sore throat is linked to the symptoms.

	Children[a]	Adults[a]
Group A *Streptococcus*	65% (42–80%) [19]	92% (87–95%) [19]
Group C *Streptococcus*	9.2% (0.0–41%) [14]	53% (36–67%) [14]
Streptococcus dysgalactiae subspecies equisimilis[b]	68% (0.0–100%) [14]	53% (0.0–92%) [14]
Fusobacterium necrophorum	(No data for children) [20]	64% (33–83%) [21]

[a] Children are defined as being below 15–18 years of age (cut-off varies between studies). Percentages provided are etiologic predictive value, with 95% confidence intervals within parenthesis, indicating the probability for a link between the bacterial finding and symptoms while considering the presence of symptomatic carriers ill from something else like a virus [22].
[b]*Streptococcus dysgalactiae subspecies equisimilis* is a new definition of strains including those groups C and G Streptococci now considered to be potential pathogens in humans. Some strains of group C Streptococci that were previously considered potential pathogens in humans are not included in *Streptococcus dysgalactiae subspecies equisimilis* since their pathogenicity in humans has been reconsidered [14].

- Detection of GAS in adults is more likely to be associated with a sore throat than when detected in children
- Though Group C & G streptococci can cause pharyngitis, guidelines do not currently recommend testing for these bacteria unless specifically indicated (e.g. school-based outbreak)

Gunnarsson RK et al. *Inf. Dis*. 2023. 55(6): 384–395

Image: https://medium.com/@kev.flanco/finding-inner-wisdom-the-place-where-three-roads-meet-f56bcf98f0a1

TEST?

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TEST? **TREAT?**

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TEST? **TREAT?** **NEITHER?**

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The case for treatment beyond just preventing ARF…

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with antibiotics				
Sore throat: day 3	660	462 (396 to 528)	RR 0.70 (0.60 to 0.80)	3730 (16 studies)	⊕⊕⊕⊖ Moderate[a]	
Sore throat: 1 week	190	95 (65 to 143)	RR 0.50 (0.34 to 0.75)	3083 (14 studies)	⊕⊕⊕⊖ Moderate[a]	
Fever: day 3	197	148 (104 to 211)	RR 0.75 (0.53 to 1.07)	1443 (8 studies)	⊕⊕⊕⊕ High	
Headache: day 3	421	206 (143 to 295)	RR 0.49 (0.34 to 0.70)	1020 (4 studies)	⊕⊕⊕⊕ High	
Rheumatic fever (within 2 months, clinical diagnosis)	190	61 (34 to 110)	Peto OR 0.32 (0.18 to 0.58)	12,132 (17 studies)	⊕⊕⊕⊖ Moderate[a]	Based largely on risk in pre-1960 trials
Glomerulonephritis (within 1 month, clinical diagnosis)	1	0 (0 to 2)	Peto OR 0.07 (0.00 to 1.32)	5147 (10 studies)	⊕⊖⊖⊖ Low[b]	Sparse data: 2 cases only in the placebo group
Quinsy (within 2 months, clinical diagnosis)	23	3 (1 to 11)	Peto OR 0.16 (0.07 to 0.35)	2367 (7 studies)	⊕⊕⊕⊕ High	
Otitis media (within 14 days, clinical diagnosis)	20	5 (3 to 11)	Peto OR 0.21 (0.11 to 0.40)	3646 (10 studies)	⊕⊕⊕⊕ High	

Data are from children AND adults

Spinks A et al. *Cochrane Database of Systematic Reviews.* 2021. Issue 12. Art. No.: CD000023

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The case against treating everyone with pharyngitis with antibiotics…

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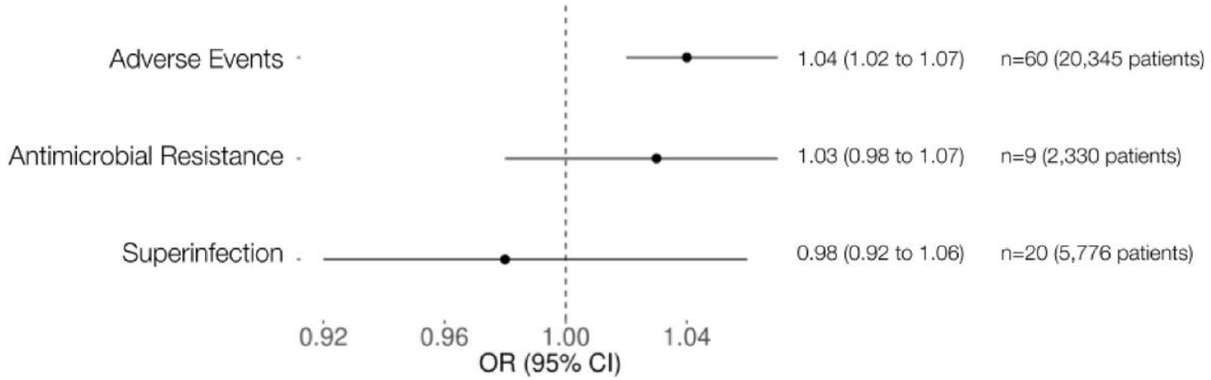

Fig. 2. Forest plots of odds ratios for primary outcomes.

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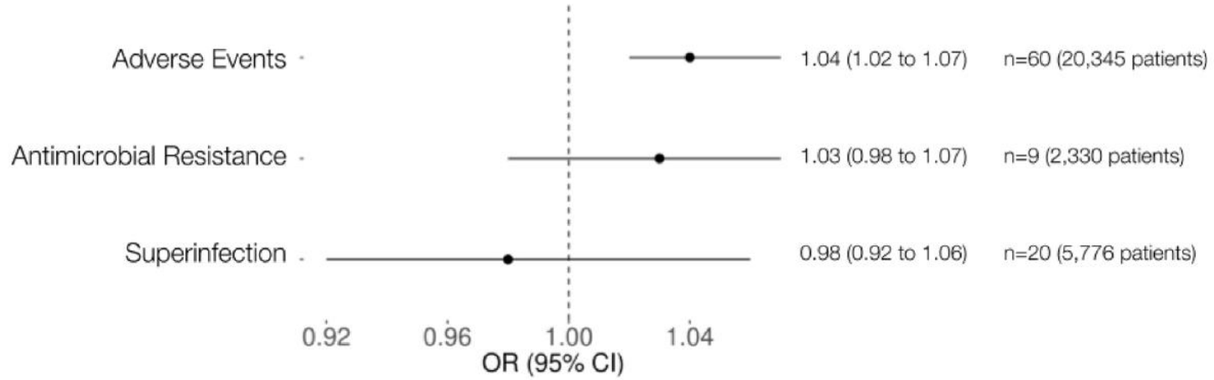

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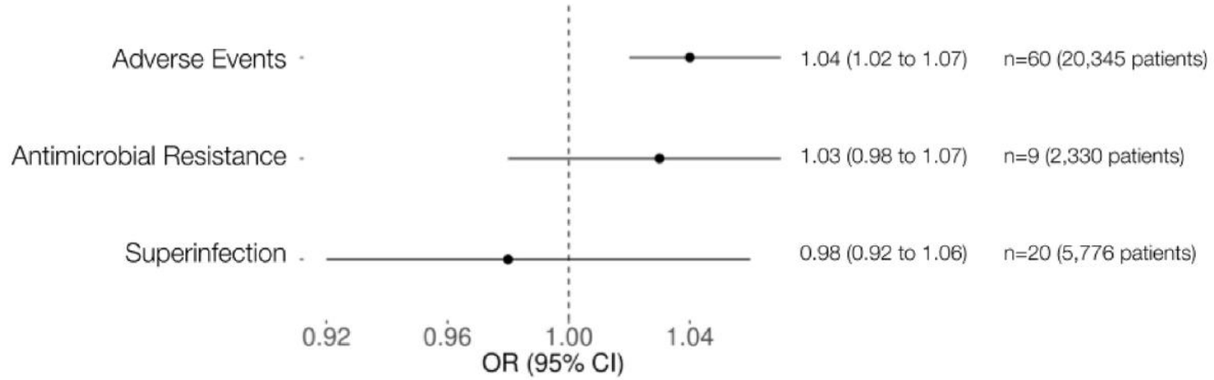

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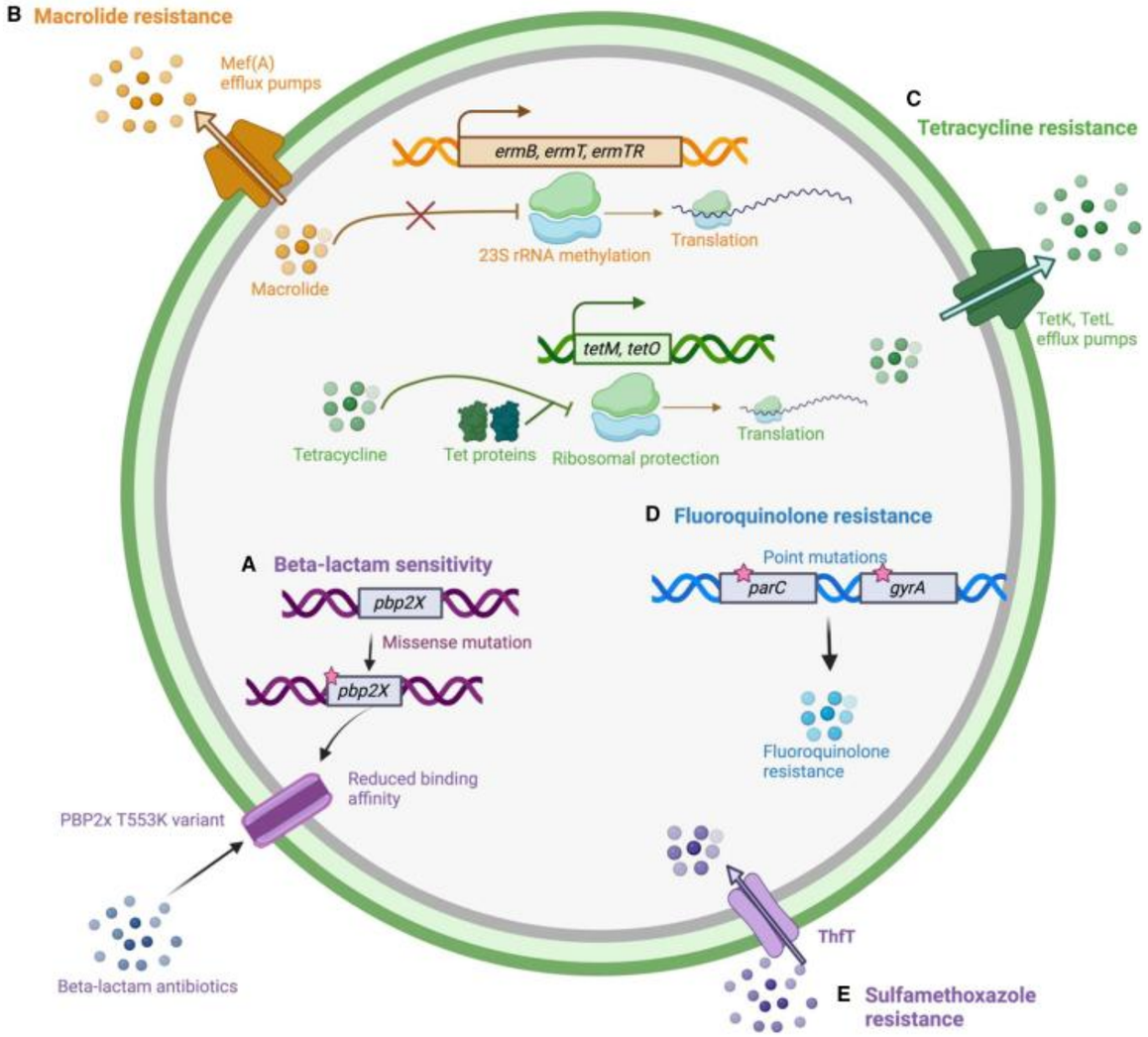
- **Antibiotics are <u>not</u> benign substances!**
- Of the 20,345 patients evaluated, 4039 patients (19.9%) experienced an adverse drug event
- Each day of antibiotic therapy was associated with a 4% increased odds of experiencing an adverse event
  - OR 1.04 (95% CI 1.02e1.07)

The changing landscape of antimicrobial susceptibility in GAS



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Thacharodi et al. *iScience*. 2024. 28(1):111677

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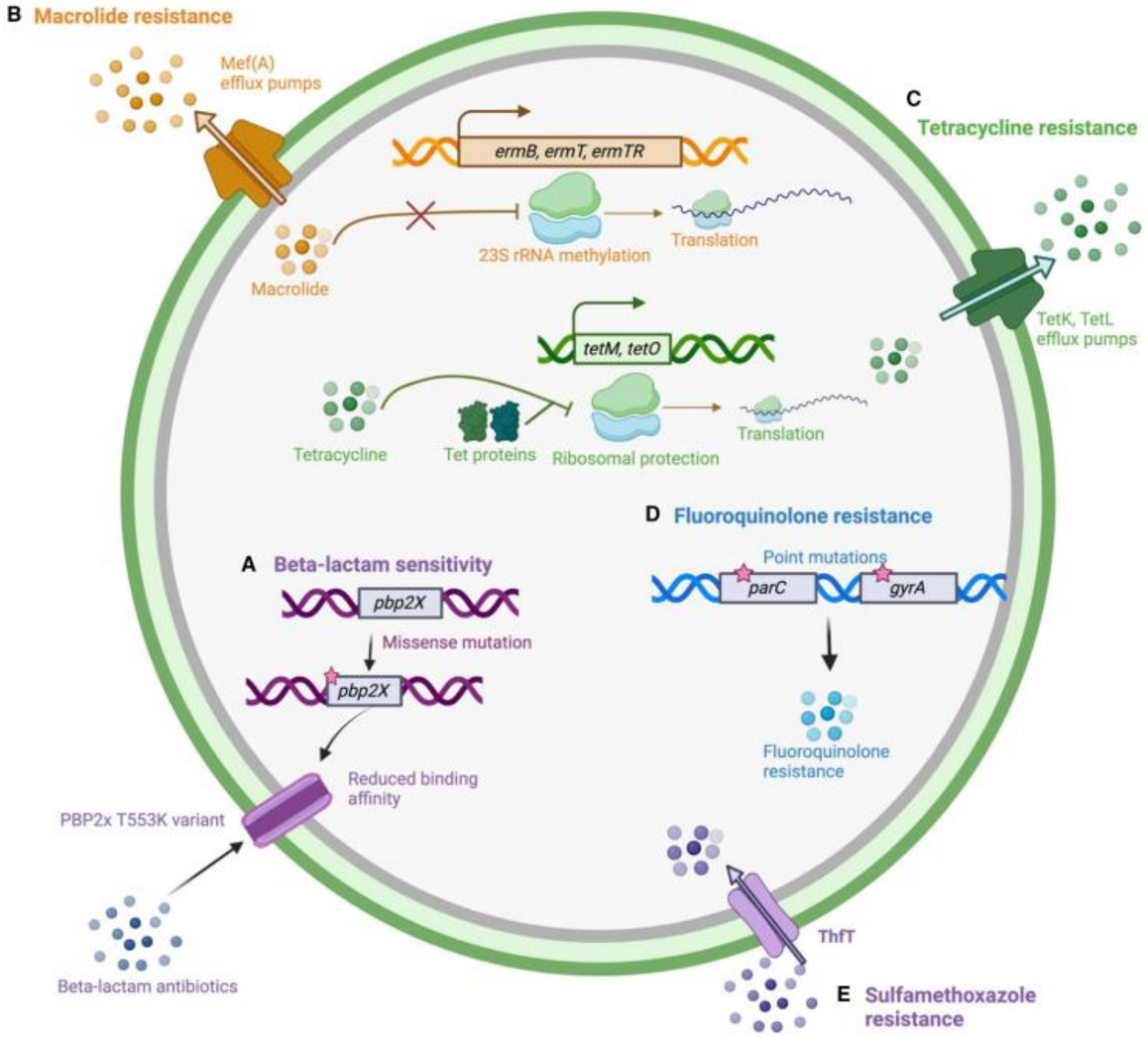

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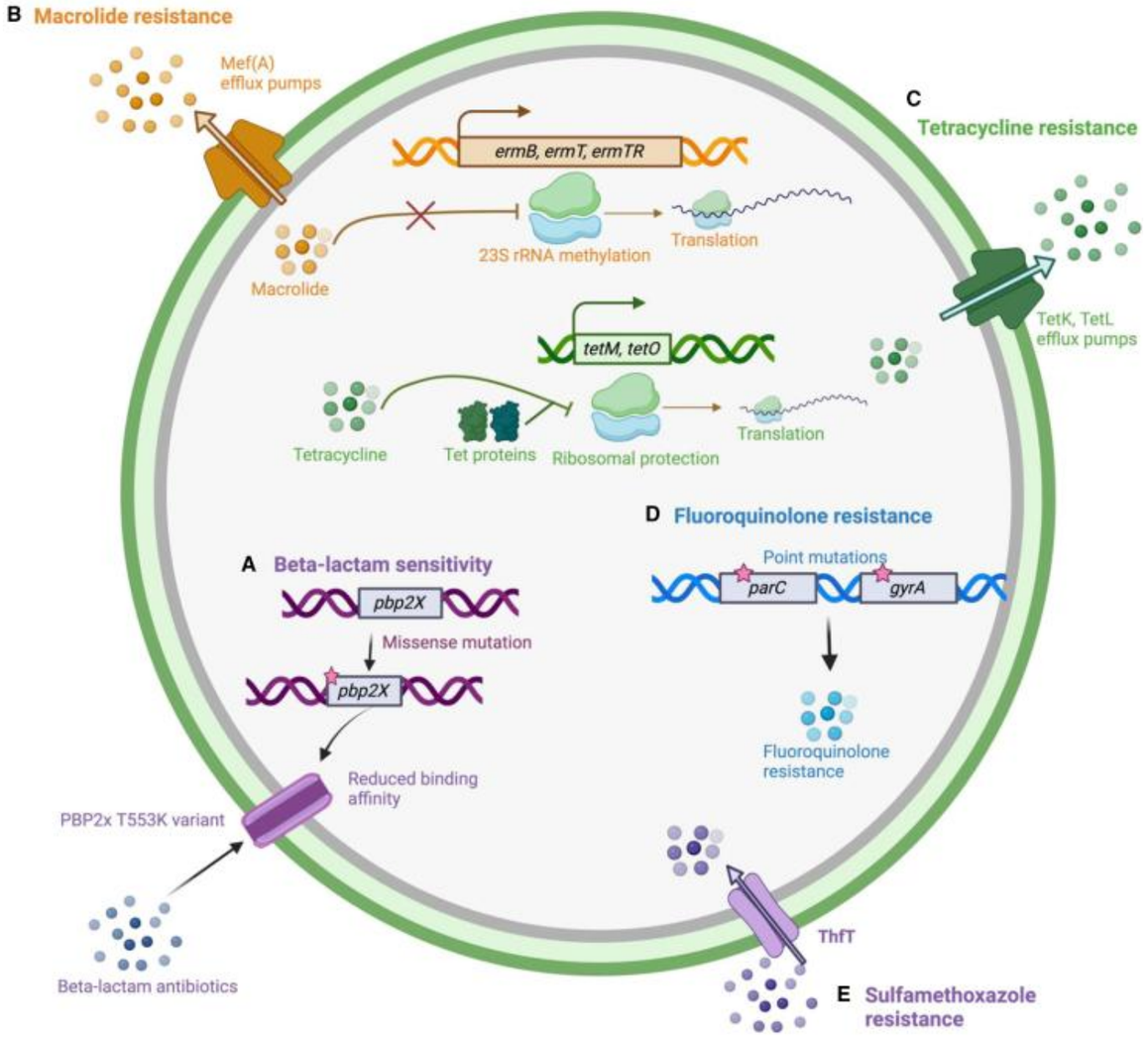

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- Increased rates of resistance to non-β-lactam antibiotics

Thacharodi et al. *iScience*. 2024. 28(1):111677

Table 4. Epidemiologic and Clinical Features Suggestive of Group A Streptococcal and Viral Pharyngitis

Feature, by Suspected Etiologic Agent
GROUP A STREPTOCOCCAL
• Sudden onset of sore throat • Age 5–15 years • Fever • Headache • Nausea, vomiting, abdominal pain • Tonsillopharyngeal inflammation • Patchy tonsillopharyngeal exudates • Palatal petechiae • Anterior cervical adenitis (tender nodes) • Winter and early spring presentation • History of exposure to strep pharyngitis • Scarlatiniform rash
VIRAL
• Conjunctivitis • Coryza • Cough • Diarrhea • Hoarseness • Discrete ulcerative stomatitis • Viral exanthema

Shulman ST et al. *Clin. Inf. Dis*. 2012. 55(10): e86-102

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Table 1
Clinical decision tools substantiated specifically for streptococcal pharyngitis

Criteria	Centor	McIsaac/ Modified Centor	Fever-PAIN
Lack of cough	+1	+1	+1
Tonsillar exudate or swelling	+1	+1	Not applicable
Fever (≥100.4°F)	+1	+1	+1
Swollen, tender anterior cervical chain lymphadenopathy	+1	+1	Not applicable
Age	Not applicable	3–14 y = +1 15–44 y = 0 ≥45 y = −1	Not applicable
Purulent tonsils	Not applicable	Not applicable	+1
Intensely inflamed tonsils	Not applicable	Not applicable	+1
Presentation within 3 d of symptom onset	Not applicable	Not applicable	+1
Risk score	1–1, low risk; 2–3, intermediate risk; 4–5, high risk		

Holley A. *Prim Care Clin Office Pract.* 2025. 52. 99–109

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IDSA PRACTICE GUIDELINES CURRENT

Clinical Practice Guideline Update by the Infectious Diseases Society of America on Group A Streptococcal (GAS) Pharyngitis

Published October 14, 2025

Endorsed by ASM + SIDP

"First part of an update to the clinical practice guideline on the diagnosis and management of… GAS pharyngitis, developed by the Infectious Diseases Society of America (IDSA)"

Clinical scoring has lower sensitivity but higher specificity for GAS in adults vs. children

Table 1. Summary of Findings per Outcome for Studies Comparing Use of Clinical Scoring System vs. No Scoring System in Evaluation of Patients with Suspected GAS Pharyngitis

Outcome	No. of Studies, no. of patients*	Scoring tools evaluated	Scoring system	No scoring system
CHILDREN				
Sensitivity	3 studies [McIsaac 1998, Breese 1977, Attia 2001] 1309 patients	McIsaac, Breese and Attia	Range: 0.83 – 0.97 [Supplementary figure 4]	Range: 0.71 – 0.87 [Supplementary figure 4]
Specificity	3 studies [McIsaac 1998, Breese 1977, Attia 2001] 1309 patients	McIsaac, Breese and Attia	Range: 0.60 – 0.72 [Supplementary figure 4]	Range: 0.60 - 0.92 [Supplementary figure 4]
PPV[i]	1 [Funamura 1983] 892 patients	Breese	40%	44%
NPV[ii]	1 [Funamura 1983] 892 patients	Breese	80%	75%
Correct diagnosis[iii]	1 [Funamura 1983] 892 patients	Breese	70%	69%
Tentative diagnosis	1 [Fujikawa 1985] 271 patients	Fujikawa	54-93%	53.5%
False positive rate[iv]	1 [Funamura 1983] 892 patients	Breese	20%	25%

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Outcome	No. of Studies, no. of patients*	Scoring tools evaluated	Scoring system	No scoring system
ADULTS				
Sensitivity	1 [McIsaac 1998] 423 patients	McIsaac score	0.70 (95%CI 0.51 - 0.84) [Supplementary figure 4]	0.68 (95% CI: 0.51–0.82) [Supplementary figure 4]
Specificity	1 [McIsaac 1998] 423 patients	McIsaac score	0.98 (95% CI: 0.97–0.99) [Supplementary figure 4]	0.97 (95% CI: 0.95–0.99) [Supplementary figure 4]
			2.5% - 55.7%	
			15% with 2 variables, 32% with 3 variables, & 55.7% with 4 variables)	

Wessels MR et al. *Clinical Practice*. 2025

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Wessels MR et al. *Clinical Practice*. 2025

Clinical scoring for predicting GAS Pharyngitis

Risk Stratification	Points	% Strep	Points	% Strep	Points	% Strep
Low Risk	0-1	7-12%	0-1	7.6-13.1%	0-1	1-10%
Intermediate Risk	2-3	21-38%	2-3	20.8-33.6%	2-3	11-35%
High Risk	4	57%	4-5	50.7-69.3%	4-5	51%-53%

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Specificity	1 [McIsaac 1998] 517 patients	McIsaac score	0.94 (95% CI: 0.92 to 0.96) [Supplementary figure 4]	0.97 (95% CI: 0.95 to 0.98) [Supplementary figure 4]

Score	Action
0-1	No testing or antibiotics
2-3	Perform testing for GAS
≥4	Acceptable to empirically treat; can consider testing

Wessels MR et al. *Clinical Practice*. 2025

Putting it all together: What do clinical practice guidelines say?

Received: 16 June 2020 | Accepted: 18 November 2020
DOI: 10.1111/ijcp.13879

SYSTEMATIC REVIEW
GENERAL/SURGERY/INTERNAL

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Worldwide comparison of treatment guidelines for sore throat

Graça Coutinho[1] | Martin Duerden[2] | Aurelio Sessa[3] | Sergio Caretta-Barradas[4] | Attila Altiner[5]

Summarizes 36 guidelines from 26 countries!

- Varying global practices re: testing vs. treatment
  - e.g. China & much of Africa: treat based on clinical signs and symptoms only – no testing
- International variation on performing RADT with Centor scores ≥2 vs. ≥3
- N. America & European guidelines recommend triage for RADT testing based on clinical scoring (except: Netherlands, UK, Mexico)

USA	American Academy of Family Physicians[35]	Treatment if modified Centor score[13,14] ≥ 4; RADT if score 1-3	not specified	not specified
USA	American Heart Association[36]	RADT or culture if symptoms suggest GAS; no test if symptoms suggest viral infection	Penicillin V, amoxicillin or benzathine penicillin G 10 days; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin	not specified
USA	Infectious Diseases Society of America[105,37]	RADT, in children and adolescents culture if RADT negative, for acute pharyngitis except if viral features are present (e.g. like rhinorrhea, cough, oral ulcers, and/or hoarseness	Penicillin V, amoxicillin or benzathine penicillin G 10 days; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin	Paracetamol or NSAIDs; aspirin to be avoided in children

RADT = Rapid Antigen Detection Tests

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USA	Infectious Diseases Society of America[105,37] **No back-up culture in ADULTS**	RADT, in children and adolescents culture if RADT negative, for acute pharyngitis except if viral features are present (e.g. like rhinorrhea, cough, oral ulcers, and/or hoarseness	Penicillin V, amoxicillin or benzathine penicillin G 10 days; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin	Paracetamol or NSAIDs; aspirin to be avoided in children

RADT = Rapid Antigen Detection Tests

How to test?

Clinical Infectious Diseases

IDSA GUIDELINES

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2024 Update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)*

J. Michael Miller,[1] Matthew J. Binnicker,[2] Sheldon Campbell,[3] Karen C. Carroll,[4] Kimberle C. Chapin,[5] Mark D. Gonzalez,[6] Amanda Harrington,[7] Robert C. Jerris,[6] Sue C. Kehl,[8] Sixto M. Leal Jr,[9] Robin Patel,[2] Bobbi S. Pritt,[2,10] Sandra S. Richter,[11] Barbara Robinson-Dunn,[12] James W. Snyder,[13] Sam Telford III,[14] Elitza S. Theel,[2] Richard B. Thomson Jr,[15] Melvin P. Weinstein,[16] and Joseph D. Yao[2]

Table 24. Laboratory Diagnosis of Pharyngitis

Etiological Agents	Diagnostic Procedures	Optimum Specimens	Transport Issues
Bacterial			
Streptococcus pyogenes	Rapid direct antigen test (followed by a secondary test if negative)[a]	Dual pharyngeal swab	Swab transport device, RT, <2 h
	Direct NAAT[b] Nucleic acid probe tests[b]	Pharyngeal swab Pharyngeal swab	Swab transport device, RT, stability as specified by lab/manufacturer. Specific swabs/transport media may be required for each different NAAT in some cases.
Groups C and G beta-hemolytic streptococci[c] *(S. dysgalactiae, S. canis, or S. equi)*	Throat culture and antigen tests on isolates for Groups C and G streptococci	Pharyngeal swab	Swab transport device, RT, <2 h
Arcanobacterium haemolyticum[d]	Throat culture for *A. haemolyticum*	Pharyngeal swab	Swab transport device, RT, <2 h
Neisseria gonorrhoeae[d]	Throat culture for *N. gonorrhoeae*	Pharyngeal swab	Swab transport device, RT, <2 h
	Direct NAAT	Pharyngeal swab	Swab transport device, RT, stability as specified by lab/manufacturer. Specific swabs/transport media may be required for each different NAAT in some cases.
Corynebacterium diphtheriae[d]	Methylene blue stain *C. diphtheriae* culture	Pseudomembrane	Sterile container, RT, <2 h
Fusobacterium necrophorum	Anaerobic incubation. A selective medium is available	Pharyngeal swab	Anaerobic swab transport, RT, <2 h
Viral			
EBV	Monospot test[e] EBV serology	5 mL serum	Clot tube, RT, <2 h or refrigerated <24 h
HSV [usually Type 1]	Direct detection test (DFA/NAAT) or Culture[f,g]	Swab of pharyngeal lesion	Swab transport device, RT, <2 h
HIV	(see XIV Viral Syndrome)		
Screening for STI[h]			
Neisseria gonorrhoeae and *Chlamydia trachomatis*	Direct NAAT	Pharyngeal swab	Swab transport device, RT, stability as specified by lab/manufacturer. Specific swabs/transport media may be required for each different NAAT in some cases.

Miller JM et al. *Clin. Inf. Dis*. 2024:ciae104

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Pre-analytical variables

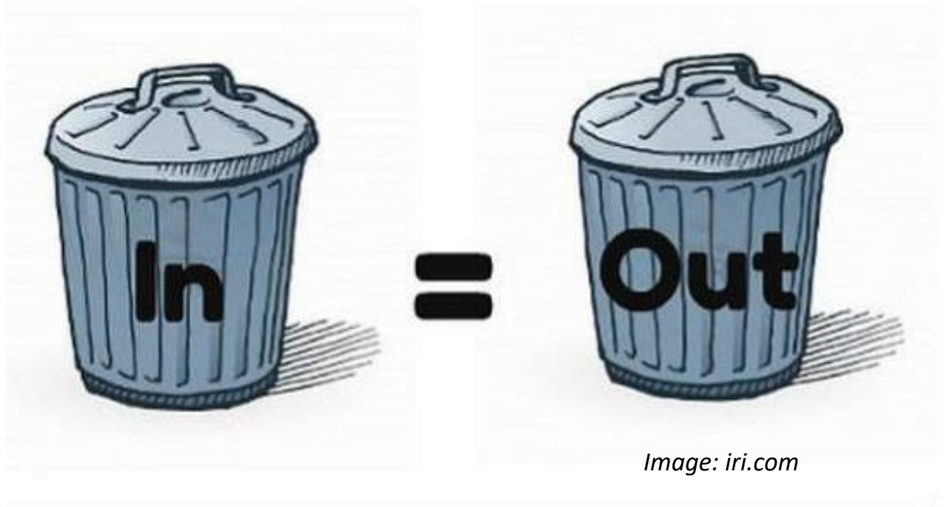

Image: iri.com

- Swab between tonsillar pillars and behind uvula, avoiding contact with tongue & buccal mucosa
- For antigen testing, one swab missed 9-12% of true positive (TP) cases due to suboptimal collection technique and/or operator error during lab testing[1]
- Challenge with Group A *Streptococcus* colonization!

[1]Patel AB et al. *Clin. Microbiol. Inf.* 2021. 27: 1718-1720

Boyanton BL Jr et al. *J. Inf. Dis*. 2024. 230(S3):S182–9

Pre-analytical variables

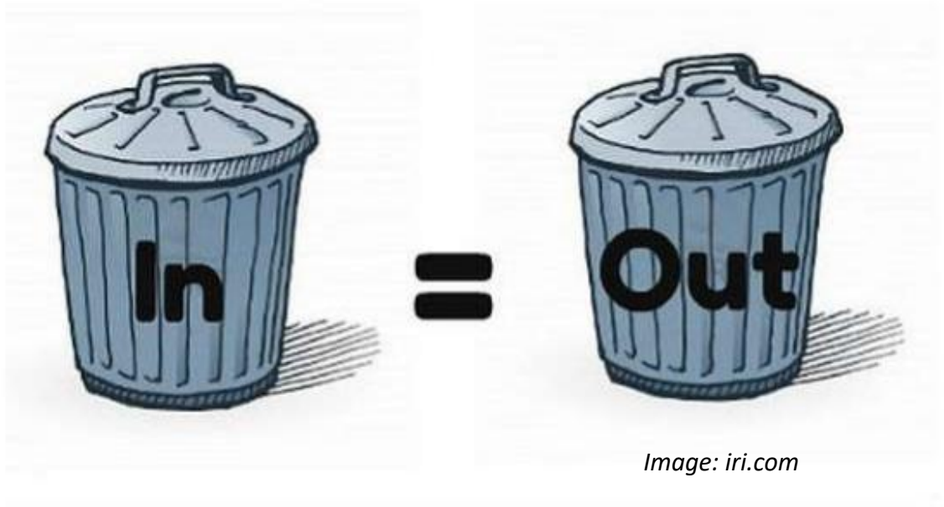

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Table 3. Variables Affecting the Performance of Diagnostic Tests for Acute Pharyngitis

Category	Culture	RADT	NAAT
Preanalytical			
Patient			
Symptom duration prior to sample collection	+	+	+
Disease severity	+	+	+
Organism prevalence in patient population	+	+	+
Seasonality of organism	+	+	+
Administration of antibiotics prior to sample collection	+	+	+/–
Specimen collection			
Anatomic location where clinical sample was obtained	+	+	+
Expertise of individual collecting the sample	+	+	+
Placing swab in liquid transport media (1 mL vs 3 mL)	+/–	+	+/–
Improper specimen labeling	+	+	+
Use expired collection supplies (swab, transport media)	+	+	+
Use incorrect collection system(s) for downstream testing	+	+	+
Specimen transportation and temperature			
Delays ≥ 24 h	+	+	+/–
Temperature extremes	+	+	+/–

[1]Patel AB et al. *Clin. Microbiol. Inf.* 2021. 27: 1718-1720

Boyanton BL Jr et al. *J. Inf. Dis*. 2024. 230(S3):S182–9

Rapid Antigen Direct Tests (RADTs)

Image: Abdington Health

Cochrane Library

Cochrane Database of Systematic Reviews

Rapid antigen detection test for group A streptococcus in children with pharyngitis (Review)

Cohen JF, Bertille N, Cohen R, Chalumeau M

- Looked at both enzyme immunoassays (EIA) and optical immunoassays (OIA) for GAS in children
- Reference standard = throat culture with sheep blood agar plate

	Quantity of evidence		Average diagnostic accuracy		Consequences in a cohort of 1000 patients…		
	Studies (n)	Participants (n)	Sensitivity (95% CI)	Specificity (95% CI)	…given 20% prevalence of GAS cases?	…given 30% prevalence of GAS cases?	…given 40% prevalence of GAS cases?
RADT for the diagnosis of GAS pharyngitis in children (EIA and OIA tests)	105	58,244	85.6% (83.3 to 87.6)	95.4% (94.5 to 96.2)	200 children will have a positive culture for GAS. Of these, 171 will be identified (TP); 29 will be missed (FN). Of the 800 children without GAS, 763 will not be treated (TN); 37 may receive unnecessary antibiotics (FP)	300 children will have a positive culture for GAS. Of these, 257 will be identified (TP); 43 will be missed (FN). Of the 700 children without GAS, 668 will not be treated (TN); 32 may receive unnecessary antibiotics (FP)	400 children will have a positive culture for GAS. Of these, 342 will be identified (TP); 58 will be missed (FN). Of the 600 children without GAS, 572 will not be treated (TN); 28 may receive unnecessary antibiotics (FP)

Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010502

Cochrane Library

Cochrane Database of Systematic Reviews

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	Quantity of evidence		Average diagnostic accuracy		Consequences in a cohort of 1000 patients…		
	Studies (n)	Participants (n)	Sensitivity (95% CI)	Specificity (95% CI)	…given 20% prevalence of GAS cases?	…given 30% prevalence of GAS cases?	…given 40% prevalence of GAS cases?
RADT for the diagnosis of GAS pharyngitis in children (EIA and OIA tests)	105	58,244	85.6% (83.3 to 87.6)	95.4% (94.5 to 96.2)	200 children will have a positive culture for GAS. Of these, 171 will be identified (TP); 29 will be missed (FN). Of the 800 children without GAS, 763 will not be treated (TN); 37 may receive unnecessary antibiotics (FP)	300 children will have a positive culture for GAS. Of these, 257 will be identified (TP); 43 will be missed (FN). Of the 700 children without GAS, 668 will not be treated (TN); 32 may receive unnecessary antibiotics (FP)	400 children will have a positive culture for GAS. Of these, 342 will be identified (TP); 58 will be missed (FN). Of the 600 children without GAS, 572 will not be treated (TN); 28 may receive unnecessary antibiotics (FP)

Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010502

The ‘nitty-gritty’ on RADTs for GAS pharyngitis

- Target antigen = Lancefield group A carbohydrate for majority of assays
- FAST! <15 mins
- Sensitivity can range from 50-90%, depending on study
- False-positive results reported in approx. 5% of children and up to 15% of adults with acute pharyngitis
- Use of RADTs led to 41% reduction in antibiotics prescriptions based on 5 RCTs (randomized control trials)

Mägdefrau AS et al. *OFID*. 2025. 12(7):ofaf407

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Table 3. Diagnostic Accuracy of Antigen Point-of-Care Test for Group A *Streptococcus*

Study	Prevalence of Group A *Streptococcus* in Pharyngitis	Sensitivity	Specificity	PPV	NPV
Wächtler, 2023 [21]	17%	65%	85%	46%	92%
Llor, 2011 [25]	18%	90%	94%	76%	98%
Maltezou, 2008 [26]	32%	83%	93%	82%	94%

In all studies, standard laboratory culture of pharyngeal swabs for group A *Streptococcus* was the gold standard.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Mägdefrau AS et al. *OFID*. 2025. 12(7):ofaf407

Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010502
Johnson DR et al. J Inf. Dis. 2001. 183:1135-2237

‘One & Done’? Not so fast…

- IDSA guidelines only require reflexive culture on RADT-negative specimens for pediatric patients
- Some international clinical guidelines do not require back-up (i.e. reflex) culture with negative RADT results on any patients (pediatric or adult)

POC.04575 Group A Streptococcus Direct Antigen Detection **Phase I**

If group A Streptococcus direct antigen testing is performed on pediatric patients, confirmatory testing is performed on negative samples.

NOTE: Cultures or other confirmatory tests must be performed on pediatric specimens that test negative when using antigen detection methods or if the manufacturer's guidelines include recommendations for culture follow-up. The laboratory policy must take into account the sensitivity of the assay in use, the age and clinical presentation of the patient, and other factors.

REFERENCES

1) Shulman S, Bisno A, Clegg H, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55(10). doi: 10.1093/cid/cis629.

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- This is not a pediatric vs. adult issue – it is a manufacturer labelling issue!
- Laboratories (& clinics) must follow the manufacturers’ instructions
- **If negative result is considered “presumptive”, requires validation to perform without back-up culture**

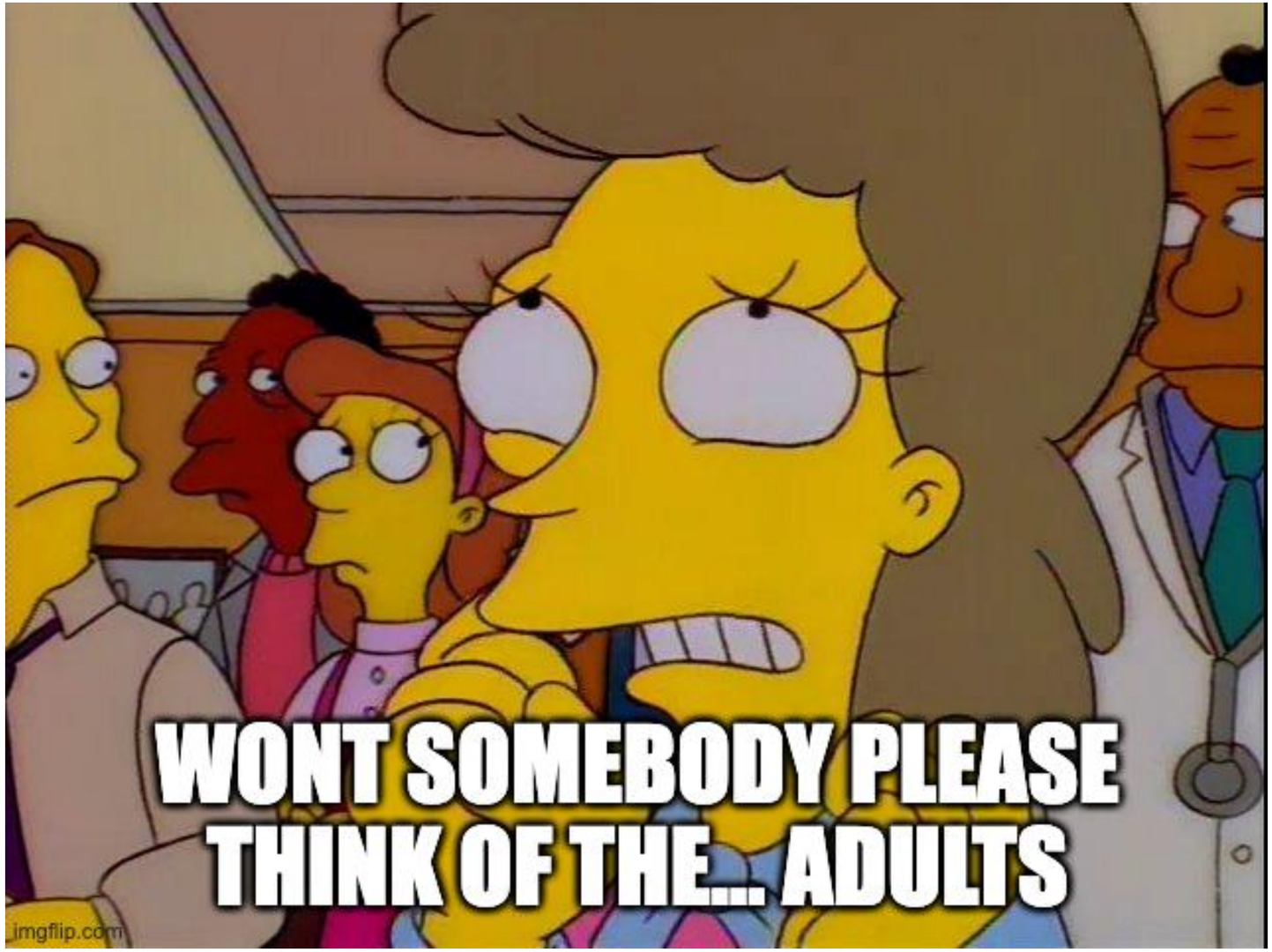
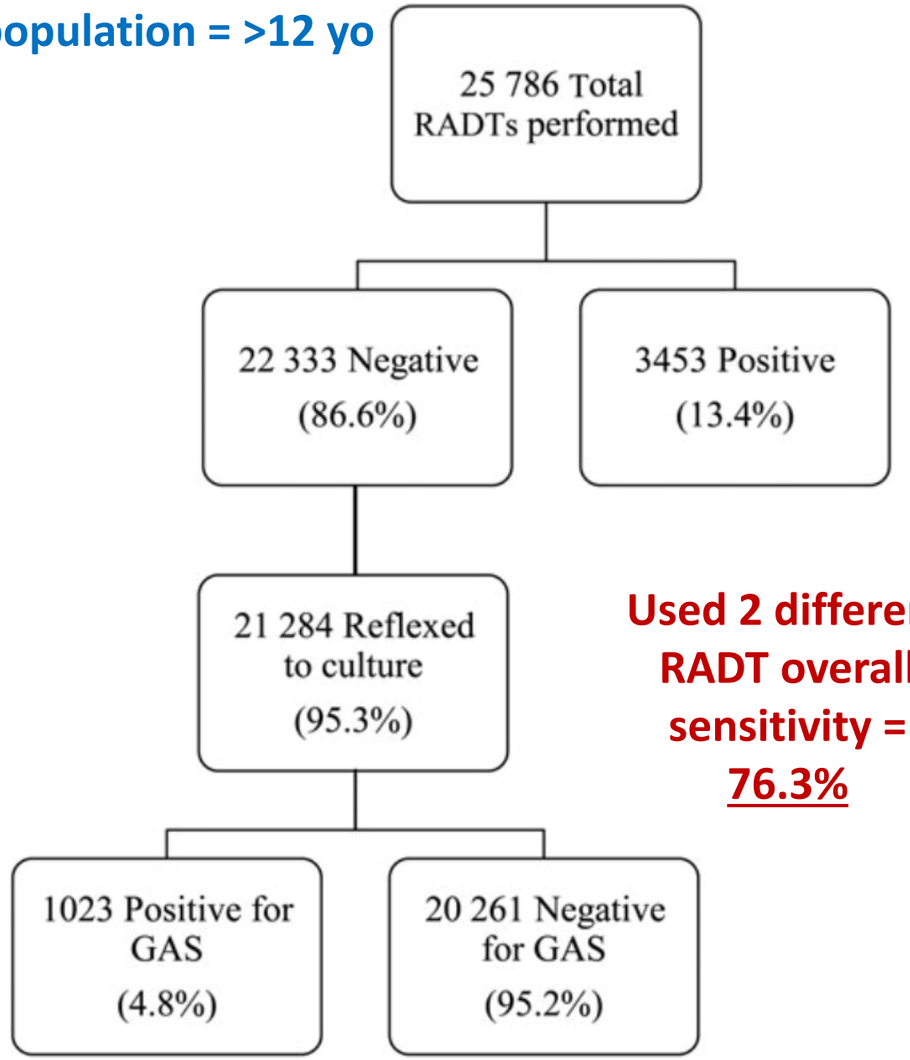


Image: img flp, meme generator

Study period = 11 years
Study population = >12 yo



Used 2 different RADT overall sensitivity = 76.3%

Figure 1. Number and results of rapid antigen detection tests and throat cultures performed on patients aged >12 years during the study period. Abbreviations: GAS, group A streptococci; RADT, rapid antigen detection test.

Dingle TC et al. Clin Inf Dis.2014. 59(5):643–50

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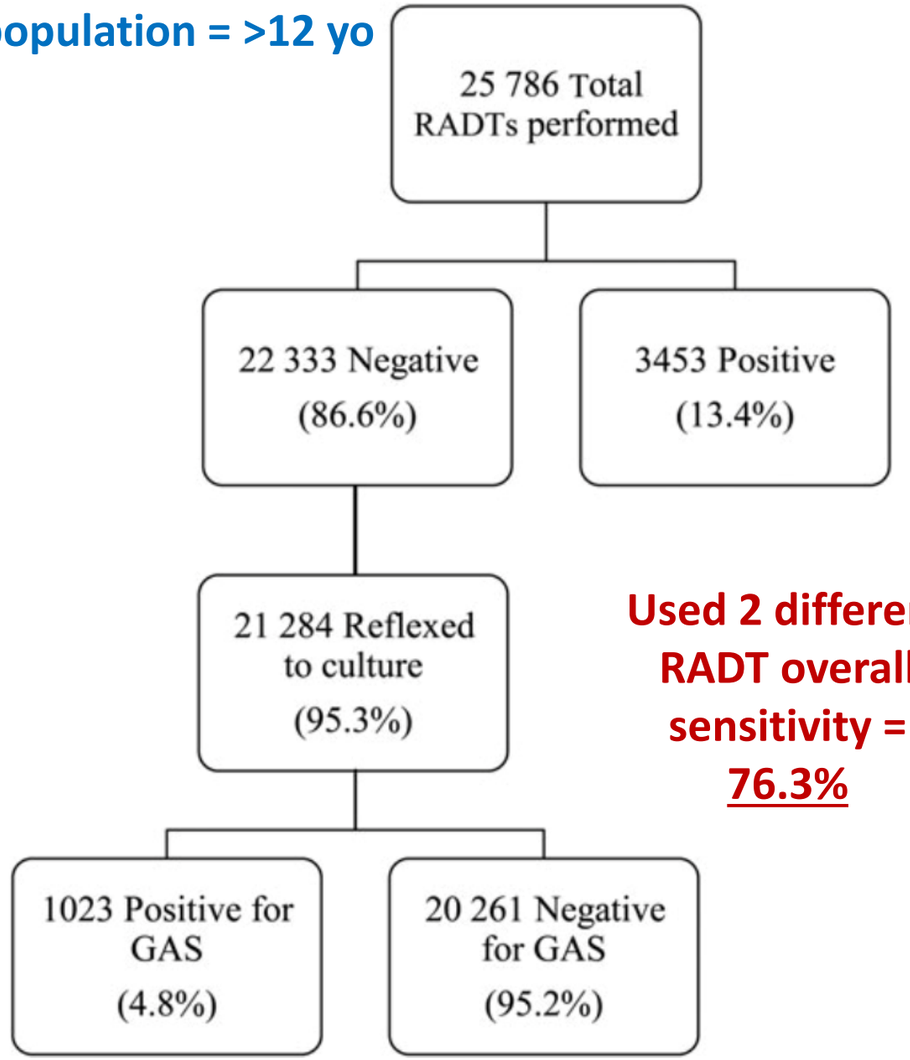

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Table 1. Study Parameters and Results for All Patients With a Negative Rapid Antigen Detection Test and Positive Group A Streptococci Throat Culture

Parameter	All Patients, No. (%) (n = 726)
Sex	
Male	363 (50.0)
Female	363 (50.0)
Age, y, mean (range)	32 (13–78)
Symptoms	
Sore throat	696 (95.9)
Absence of cough	491 (67.6)
Anterior cervical lymphadenopathy	373 (51.3)
Trismus	22 (3.0)
Odynophagia	260 (35.8)
Signs	
Tonsillar swelling or exudate	341 (47.0)
Peritonsillar abscess	29 (4.0)
Rheumatic fever	2 (0.28)
Laboratory results	
Leukocytosis (>10 000 cells/uL)	122 (16.8)
Fever (>38°C [>100.4°F])	100 (13.8)
Treatment	
Patient treated	499 (68.7)
Patient treated based on culture results	217 of 499 (43.5)
Surgical drainage	28 (3.9)

Dingle TC et al. Clin Inf Dis.2014. 59(5):643–50

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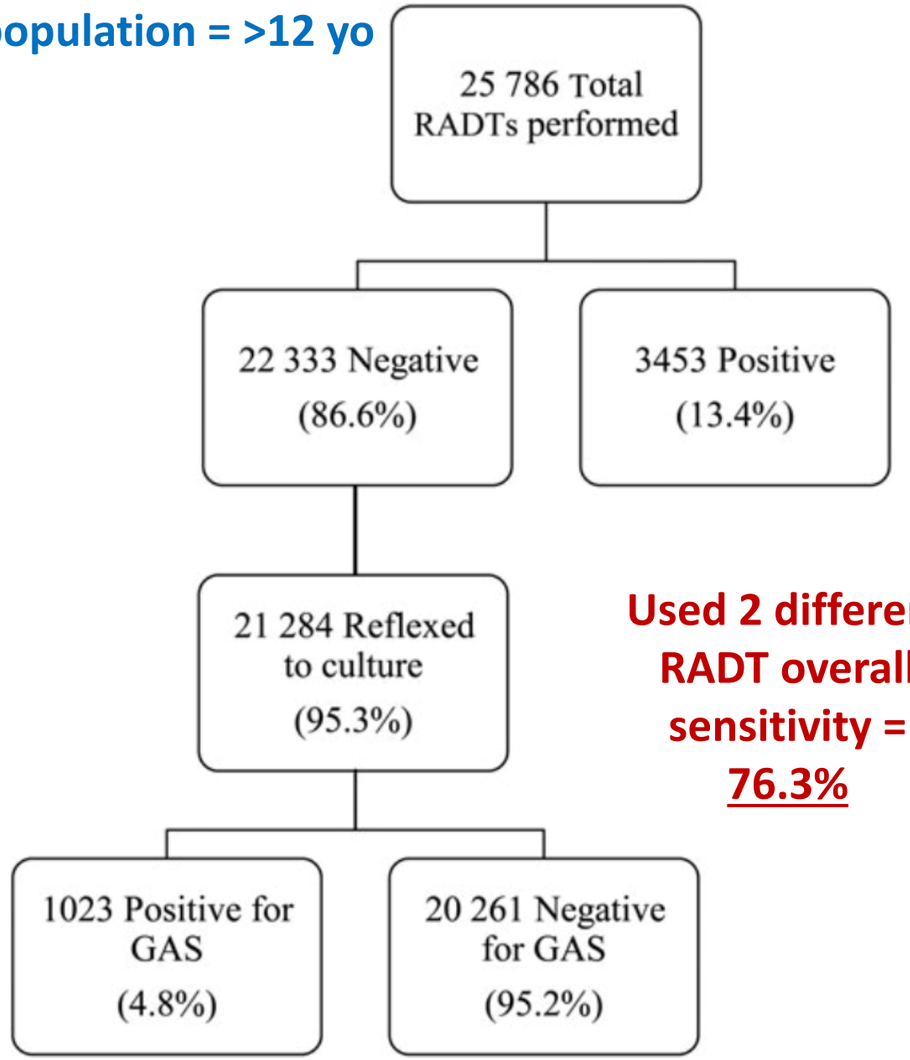

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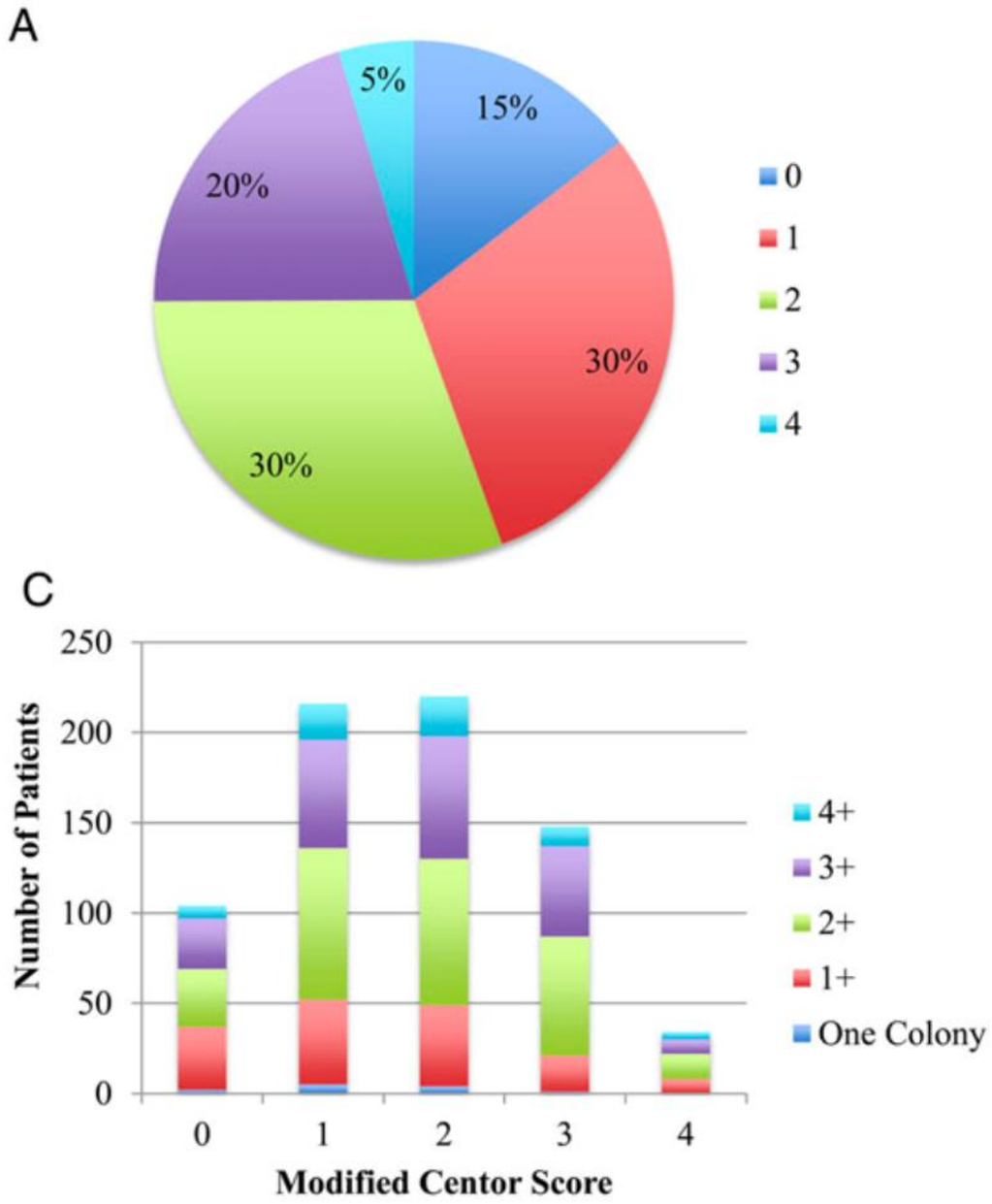
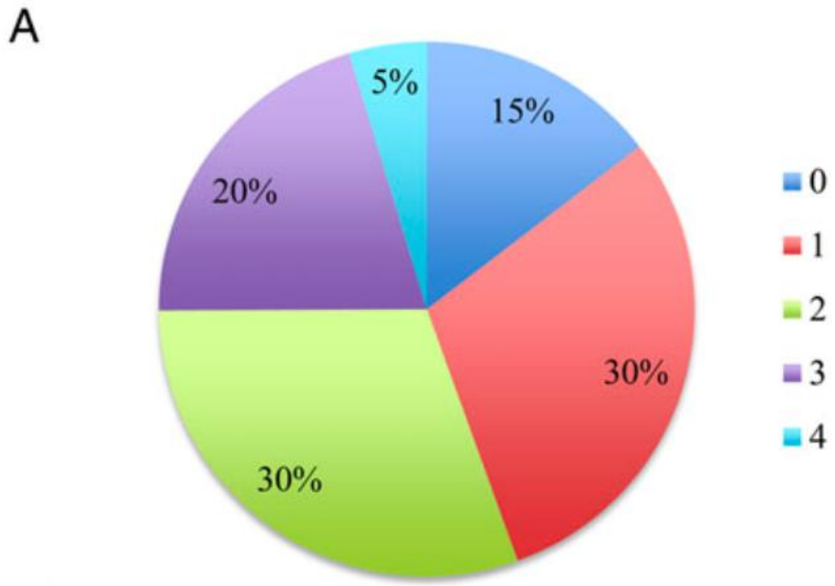
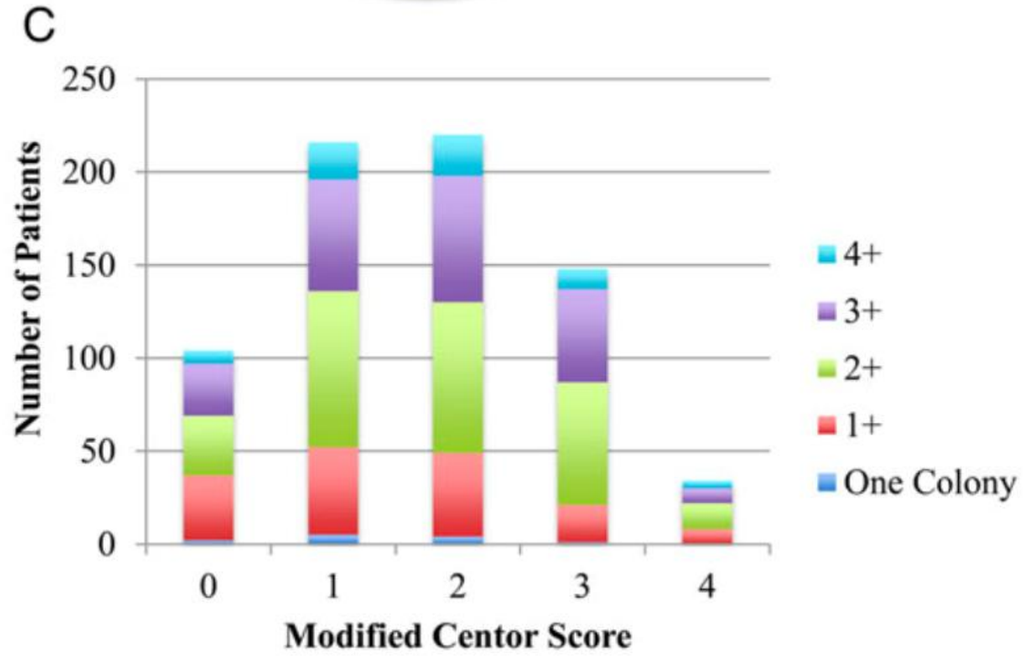


- RADT sensitivity did not correlate with either disease severity (as assessed by modified Centor score) or bacterial burden
- Modified Centor score did not correlate with with bacterial burden
- 55% of patients with negative RADT & positive culture had Centor scores ≥2
  - per IDSA guidelines would not necessarily be cultured
- 72% of patients that were RADT-negative, culture-positive had ≥2+ organism growth

Dingle TC et al. Clin Inf Dis.2014. 59(5):643–50





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Risk vs. benefit of treating these patients???

Dingle TC et al. Clin Inf Dis.2014. 59(5):643–50

Throat Culture

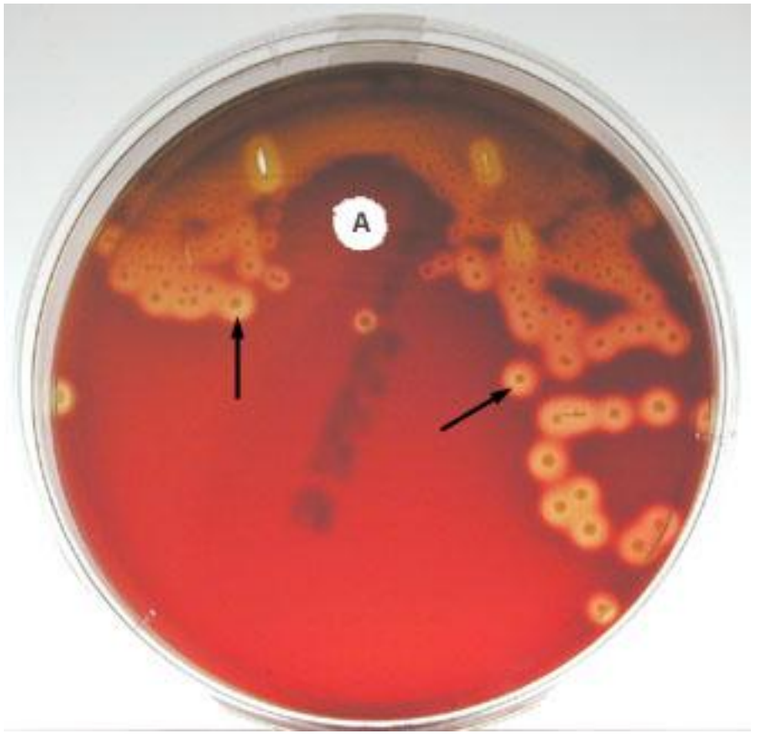

Image: https://bio.libretexts.org/

Culture

- Considered the ‘gold standard’ for the diagnosis of GAS pharyngitis
  - pooled sensitivity ranges 90–95%, pooled specificity ranges 95–99% with ROC AUC 0.92 to 0.97.
- BUT test sensitivity impacted by:
  - duration of incubation
  - culture medium used
  - method of agar inoculation (agar stabs)
  - incubation atmosphere
  - number of plates inoculated
- Group A Strep throat culture vs. comprehensive throat culture
- Labs should only identify LARGE β-hemolytic colonies only
  - Anginosus group streptococci can be positive for Lancefield Groups A, C, F or G
- **Takes 24-48 hours to result**

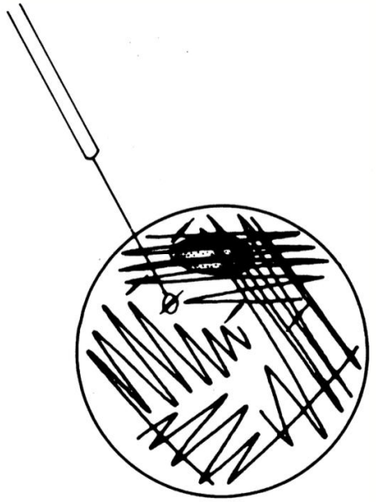

Figure 3.11.8–1 Method of streaking plate for throat culture with stabs in agar.

Wolford RW et al. “Pharyngitis”. *StatPearls*. 2025.

Image: Clinical Microbiology Procedures Handbook

Majority of studies on culture optimization are '*vintage*'…

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 1991, p. 2084–2085 Vol. 29, No. 9
0095-1137/91/092084-02$02.00/0

Selective Streptococcal Agar versus Blood Agar for Detection of Group A Beta-Hemolytic Streptococci in Patients with Acute Pharyngitis

JAN BELLON,[1]* BARBARA WEISE,[1] GERDA VERSCHRAEGEN,[1] AND MARC DE MEYERE[2]
Department of Bacteriology[1] and Department of General Practice,[2] University Hospital, Ghent, Belgium

Received 22 February 1991/Accepted 24 June 1991

TABLE 1. Effects of duration of incubation and type of medium on the recovery of GABHS from 721 throat cultures

Medium	Duration of incubation (h)	No. of GABHS isolates recovered	% Detected
SBA	24	167	90.3
	48	181[a]	91.9
ssA	24	183[b]	98.9
	48	196[a,b]	99.5
Both	24	185	
	48	197	

[a] $P < 0.001$ for the difference in recovery of GABHS after 24 and 48 h of incubation.
[b] $P < 0.001$ for the difference in recovery of GABHS on SBA and recovery on ssA after 24 and 48 h of incubation, respectively.

SBA= sheep blood agar
ssA = streptococcal selective agar

JOURNAL OF CLINICAL MICROBIOLOGY, May 1981, p. 891–894 Vol. 13, No. 5
0095-1137/81/050891-04$02.00/0

Evaluation of Techniques for Isolation of Group A Streptococci from Throat Cultures

TERRENCE A. KURZYNSKI* AND CHERI MEISE VAN HOLTEN
General Bacteriology Laboratory, State Laboratory of Hygiene, Madison, Wisconsin 53706

Received 28 November 1980/Accepted 30 January 1981

TABLE 1. *Comparison of four methods in detecting group A streptococci in throat cultures*

Method	Total no. of cultures positive for beta-hemolytic streptococci	Group A streptococcal cultures		False-negative cultures	
		Total no. (%)[a]	% Detected[b]	Total no.	Rate (%)[b]
SXT-BA (CO_2)	108	100 (92.6)	98	2	2
BA (CO_2)	107	78 (72.9)	76.5	24	23.5
SXT-BA (An)	127	102 (80.3)	100	0	0
BA (An)	159	91 (57.2)	89.2	11	10.8

[a] Percentages are based on total number of cultures positive for beta-hemolytic streptococci by each method.
[b] Percentages are based on the total of 102 cultures positive for group A streptococci as determined by all four methods.

Can we do culture, but *better*?

- Relying on the detection of β-hemolysis on BAP from throat specimen is problematic, even when using a bacitracin disk
- Automation of microbiology culture reading can improve detection of microbiological growth and potentially shorten incubation times

FIG 1 Example of Colorex Strep A agar growing GAS.

le of orange colonies growing on Colorex Strep A agar that were not confirmed as GAS

TABLE 1 Sensitivity and specificity, compared to true-positive specimens, for the five methods studied

Method	Sensitivity (%) (no. positive/total no.)	Specificity (%) (no. positive/total no.)	Positive predictive value (%)	Negative predictive value (%)
Lyra molecular assay	96.9 (93/96)	100 (384/384)	100	99.2
Manual reading of Colorex Strep A agar images	87.5 (84/96)	97.7 (375/384)	90.3	96.9
PhenoMATRIX reading of Colorex Strep A agar images	90.6 (87/96)	94.0 (361/384)	79.1	97.6
Manual detection of β-hemolytic colonies on BAP images	83.3 (80/96)	69.3 (224/384)	44.7	93.3
Manual detection of β-hemolytic colonies on BAP images with any zone of inhibition with bacitracin disk	39.5 (38/96)	83.1 (319/384)	36.9	84.6

November 2019 Volume 57 Issue 11 e00811-19 jcm.asm.org 3

NOTE: Study only looked at 24h incubation time point

Van TT et al. *J. Clin. Micro.* 2019. 57(11): 11 e00811-19

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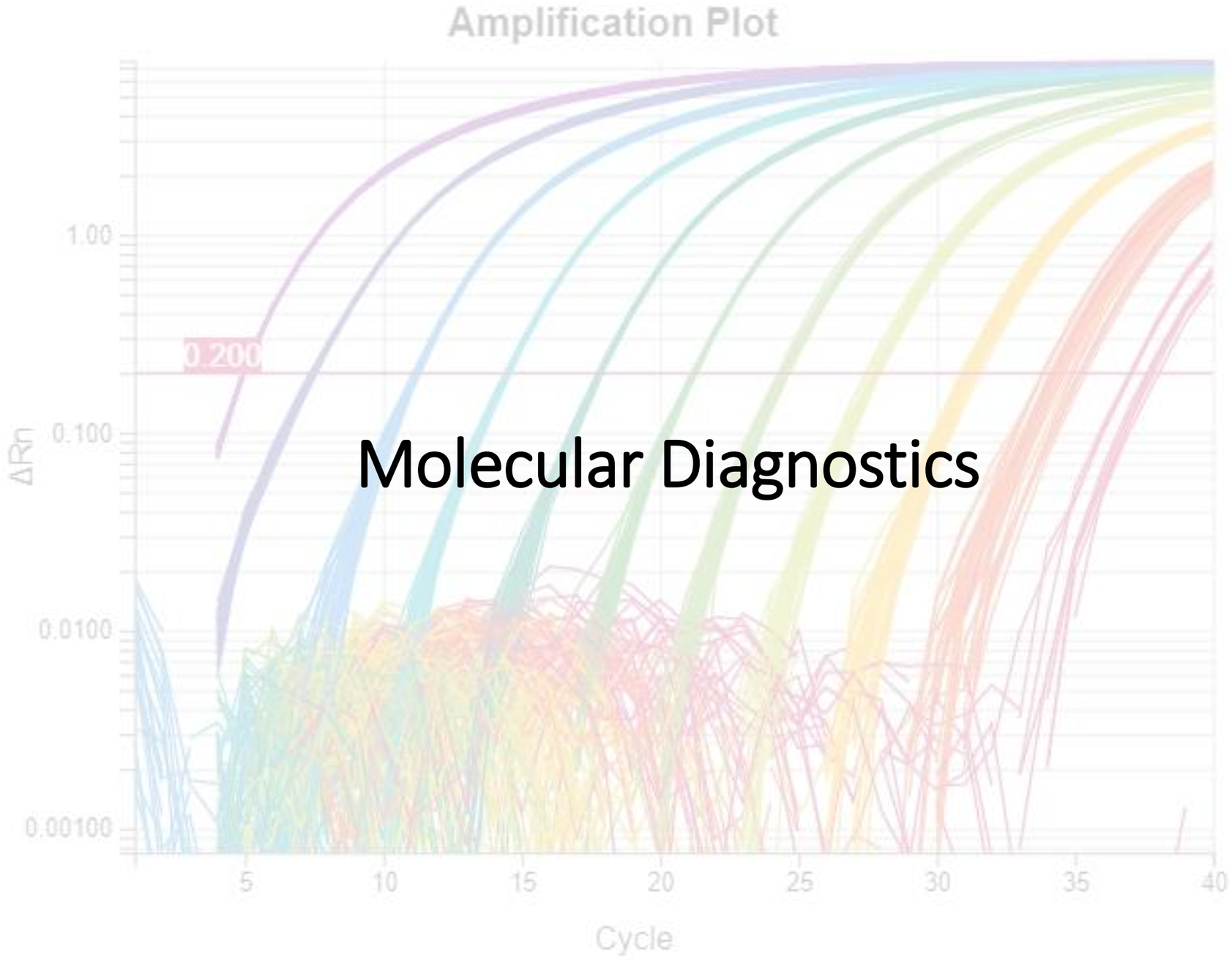

Molecular Diagnostics

Image: ThermoFisher Scientific

What’s in a name?

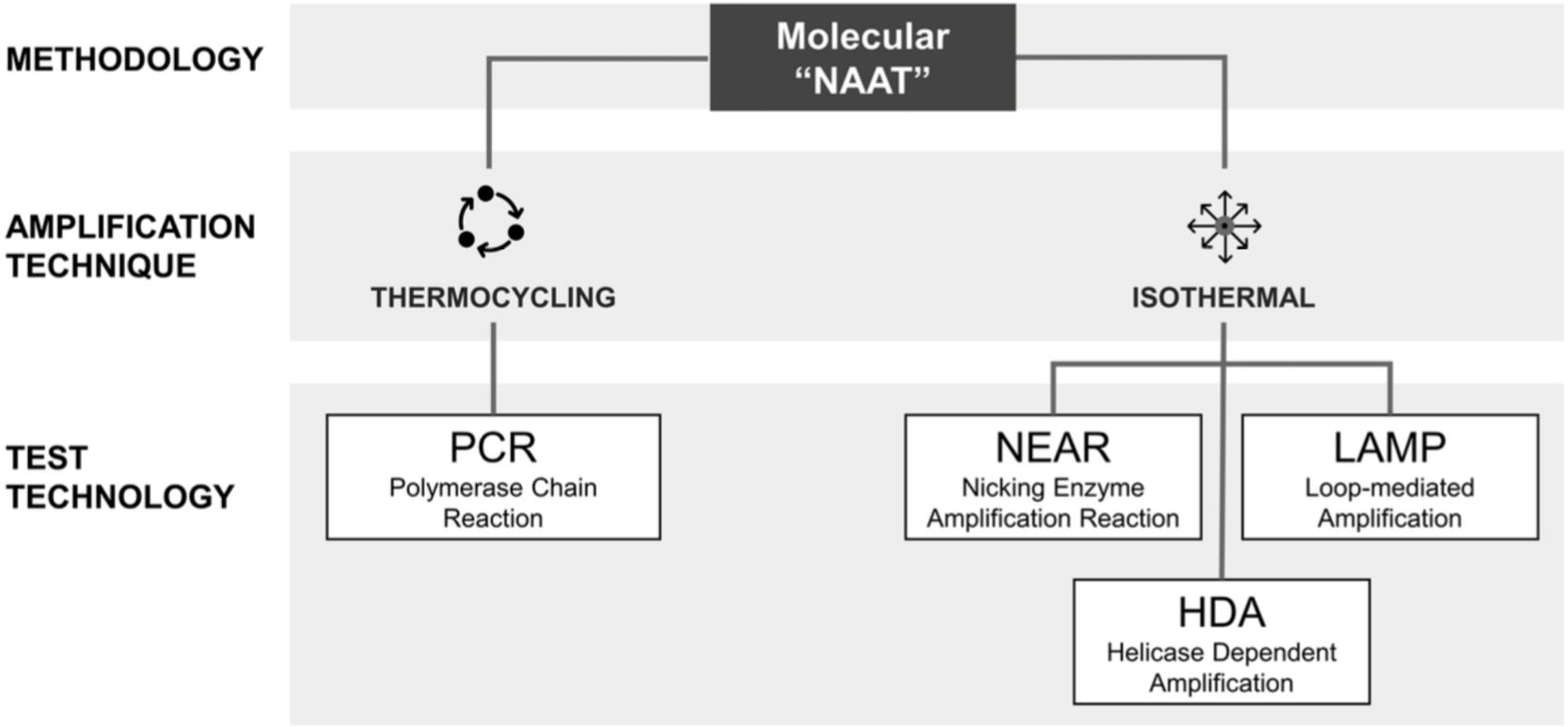

Figure 1. Different types of nucleic acid amplification tests (NAATs) for Group A Strep.

Cohen JF et al. *J. Ped. Inf. Dis. Soc*. 2024. 13(4):250–256

Table 2
Main meta-analysis, subgroup analyses with meta-regression, sensitivity analyses and comparison of rapid nucleic acid test (RNATs) versus rapid antigen detection tests (RADTs)

Analysis	Evaluations (*n*)	Test results (*n*)	Sensitivity, % (95% CI)	p	Specificity, % (95% CI)	p
Main meta-analysis	46	17 411	97.5 (96.2–98.3)		95.1 (93.6–96.3)	
Subgroup analysis: Test type						
qPCR	21	6312	98.3 (97.2–99.0)	<0.001	94.2 (91.7–96.0)	0.038
ssDNA	7	4043	90.5 (84.7–94.3)		98.2 (96.5–99.1)	
LAMP	6	2595	95.6 (90.5–98.1)		95.3 (91.1–97.6)	
HDA	7	3393	97.5 (95.1–98.7)		92.7 (87.4–95.9)	
NEAR	5	1068	98.4 (95.4–99.5)		94.8 (88.9–97.6)	
Subgroup analysis: GAS prevalence[a]						
Below the median	23	12 824	95.9 (93.5–97.4)	0.007	95.6 (93.7–97.0)	0.448
Above the median	23	4587	98.5 (97.3–99.2)		94.6 (91.9–96.4)	
Subgroup analysis: Study setting						
Emergency room	5	670	95.1 (86.6–98.3)	0.047	95.6 (89.5–98.2)	0.136
Walk-in clinic and physician's office	12	6282	96.3 (93.2–98.0)		95.1 (92.3–97.0)	
Hospital	7	1746	98.5 (96.1–99.4)		90.0 (82.5–94.5)	
Mixed setting (including schools)	12	5064	96.1 (92.5–98.0)		96.6 (94.3–98.0)	
Not reported	10	3649	99.0 (97.5–99.6)		95.6 (92.4–97.5)	
Sensitivity analyses						
With ≥2 QUADAS-2 domains with low risk of bias	6	2531	96.5 (93.0–98.3)	–	93.4 (82.7–97.7)	–
With ≥2 QUADAS-2 domains with low applicability concerns	13	6592	96.5 (94.1–97.9)	–	96.9 (94.5–98.3)	–
RNATs with amplification (i.e. not ssDNA)	39	13 368	98.2 (97.1–98.8)	–	94.2 (92.5–95.6)	–
Low complexity RNATs	25	6996	98.2 (97.1–98.8)	–	94.2 (91.4–96.1)	–
Direct comparison: RNATs versus RADTs						
RNATs	13	4224	96.8 (94.6–98.1)	0.004	97.0 (94.3–98.5)	0.92
RADTs	13	3936	82.3 (65.0–92.1)		97.2 (94.3–98.6)	

Abbreviations: GAS, group A streptococcus; HDA, helicase-dependent amplification; LAMP, loop-mediated isothermal amplification; NEAR, nicking enzyme amplification reaction; qPCR, quantitative (real-time) polymerase chain reaction; RNAT, rapid nucleic acid test; RADT, rapid antigen detection test; ssDNA, single-stranded DNA.
[a] Median GAS prevalence 27%.

- **In this meta-analysis, NAAT's had improved sensitivity compared to RADTs but with similar specificities**
- **Apparent potential differences in analytical test performance between NAAT methods**

Dubois C et al. *Clin. Microbiol. Inf.* 2021. 27: 1736e1745

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Direct comparison: RNATs versus RADTs						
RNATs	13	4224	96.8 (94.6–98.1)	0.004	97.0 (94.3–98.5)	0.92
RADTs	13	3936	82.3 (65.0–92.1)		97.2 (94.3–98.6)	

Abbreviations: GAS, group A streptococcus; HDA, helicase-dependent amplification; LAMP, loop-mediated isothermal amplification; NEAR, nicking enzyme amplification reaction; qPCR, quantitative (real-time) polymerase chain reaction; RNAT, rapid nucleic acid test; RADT, rapid antigen detection test; ssDNA, single-stranded DNA.
[a] Median GAS prevalence 27%.

- **In this meta-analysis, NAAT's had improved sensitivity compared to RADTs but with similar specificities**
- **Apparent potential differences in analytical test performance between NAAT methods**

Dubois C et al. *Clin. Microbiol. Inf.* 2021. 27: 1736e1745

Table 2
Main meta-analysis, subgroup analyses with meta-regression, sensitivity analyses and comparison of rapid nucleic acid test (RNATs) versus rapid antigen detection tests (RADTs)

Analysis	Evaluations (*n*)	Test results (*n*)	Sensitivity, % (95% CI)	p	Specificity, % (95% CI)	p
Main meta-analysis	46	17 411	97.5 (96.2–98.3)		95.1 (93.6–96.3)	
Subgroup analysis: Test type						
qPCR	21	6312	98.3 (97.2–99.0)	<0.001	94.2 (91.7–96.0)	0.038
ssDNA	7	4043	90.5 (84.7–94.3)		98.2 (96.5–99.1)	
LAMP	6	2595	95.6 (90.5–98.1)		95.3 (91.1–97.6)	
HDA	7	3393	97.5 (95.1–98.7)		92.7 (87.4–95.9)	
NEAR	5	1068	98.4 (95.4–99.5)		94.8 (88.9–97.6)	
Subgroup analysis: GAS prevalence[a]						
Below the median	23	12 824	95.9 (93.5–97.4)	0.007	95.6 (93.7–97.0)	0.448
Above the median	23	4587	98.5 (97.3–99.2)		94.6 (91.9–96.4)	
Subgroup analysis: Study setting						
Emergency room	5	670	95.1 (86.6–98.3)	0.047	95.6 (89.5–98.2)	0.136
Walk-in clinic and physician's office	12	6282	96.3 (93.2–98.0)		95.1 (92.3–97.0)	
Hospital	7	1746	98.5 (96.1–99.4)		90.0 (82.5–94.5)	
Mixed setting (including schools)	12	5064	96.1 (92.5–98.0)		96.6 (94.3–98.0)	
Not reported	10	3649	99.0 (97.5–99.6)		95.6 (92.4–97.5)	
Sensitivity analyses						
With ≥2 QUADAS-2 domains with low risk of bias	6	2531	96.5 (93.0–98.3)	–	93.4 (82.7–97.7)	–
With ≥2 QUADAS-2 domains with low applicability concerns	13	6592	96.5 (94.1–97.9)	–	96.9 (94.5–98.3)	–
RNATs with amplification (i.e. not ssDNA)	39	13 368	98.2 (97.1–98.8)	–	94.2 (92.5–95.6)	–
Low complexity RNATs	25	6996	98.2 (97.1–98.8)	–	94.2 (91.4–96.1)	–
Direct comparison: RNATs versus RADTs						
RNATs	13	4224	96.8 (94.6–98.1)	0.004	97.0 (94.3–98.5)	0.92
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Dubois C et al. *Clin. Microbiol. Inf.* 2021. 27: 1736e1745

Snap-shot of commercially available GAS NAAT assays in the U.S.

Table 1. Currently Available Food and Drug Administration-Approved Nucleic Acid Amplification Tests for Acute Pharyngitis

Manufacturer	Abbott	Cepheid	Roche	Cepheid	DiaSorin	Meridian Bioscience		QuidelOrtho		
Instrument	ID NOW	Xpert Xpress	LIAT	Xpert/Xpert Infinity	Liaison MDX	Alethia	RevoGene	Solana		ABI 7500
Test name	ID NOW Strep A 2	Xpert Xpress Strep A	cobas Strep A	Xpert Xpress Strep A	Simplexa Group A Strep Direct	Alethia Group A Streptococcus	Revogene Strep A	Solana GAS	Solana Strep Complete	Lyra Direct Strep
Technology	iNAAT (NEAR)	qPCR	qPCR	qPCR	qPCR	iNAA (LAMP)	qPCR	iNAA (HDA)	iNAA (HDA)	qPCR
Assay run time, min	8–10	18–24	15	18–24	60	45–60	42–70	30	30	90
Number of samples per instrument	1	1–4	1	1–80	1–8	1–10	1–8	1–12	1–12	1–94
CLIA status	Waived	Waived	Waived	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	High
Throat swab testing, direct	Yes	No	No	No	No	No	No	No	No	No
Throat swab testing, transport media[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Instrument size, inches, H × W × D	12 ×8 × 12	12 × 18 × 16	8 × 5 × 10	12 × 18 × 16 79 × 108 × 35	tel:25-147%209-18%205-20%209-18		13 × 16 × 10	6 × 9 × 9	6 × 9 × 9	19 × 14 × 18
Instrument weight, lbs	10	25	8	25–2100	17	13	22	9	9	75
Limit of detection, CFU/mL										
Group A *Streptococcus*	25–147	9–18	5–20	9–18	682–2350	400–430	333–1333	24 400–68 100	85 000	600–1500
Streptococcus dysgalactiae	…	…	…	…	…	…	…	…	710 000	16 000–18 000

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; HDA, helicase dependent amplification; iNAAT, isothermal nucleic acid amplification; LAMP, loop-mediated isothermal amplification; NEAR, nicking enzyme amplification reaction; qPCR, real-time polymerase chain reaction.

[a]See package insert for specific assay transport media requirements.

Boyanton BL Jr et al. *J. Inf. Dis.* 2024. 230(S3):S182–9

Table 2. Performance Characteristics of Food and Drug Administration-Approved Nucleic Acid Amplification Tests for Acute Pharyngitis

Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Group A *Streptococcus*				
ID NOW Strep A 2				
Package insert	98.5	93.4	78.9	99.6
References [13–15]	95.5–100	91.3–100	73.6–100	91.3–99
cobas Strep A				
Package insert	98.3	94.2	88.1	99.2
References [6, 12, 16]	95.5–100	93.3–99.3	86.3–99.1	96.6–100
Xpert Xpress Strep A				
Package insert	100	96.4	87.8	100
References [11, 12, 17, 18]	100	79.3–97.4	48.8–96.7	100
Simplexa Group A Strep Direct				
Package insert	97.4	95.2	72.7	99.7
References [19–22]	91–100	86–100	67–100	97–100
Alethia Group A *Streptococcus*				
Package insert	98.0	97.7	86.2	99.7
References [23–29]	81.5–100	87–97	60.3–96.3	95.9–100
Revogene Strep A				
Package insert	98.1	94.7	86.3	99.3
Reference [30][a]	…	…	…	…
Solana GAS				
Package insert	98.2	97.2	90.1	99.5
References [18, 21, 31, 32]	91.4–100	84.4–98.7	78–98.5	94.8–100
Solana Strep Complete				
Package insert	98.8	98.9	95.0	97.7
Lyra Direct Strep				
Package insert	96.5	98.0	81.9	99.7
References [33, 34]	100	89.4–100	58.7–100	100
***Streptococcus dysgalactiae* (β-hemolytic group C/G streptococci)**				
Solana Strep Complete				
Package insert	100	99.5	84.7	100
Lyra Direct Strep				
Package insert	95.7	98.3	76.1	99.8
References [33, 34]	50–100	99.5–100	66.7–100	99.1–100

[a]Reference [30] is a peer-reviewed publication that led to the data in the package insert.

- Package inserts for FDA-cleared NAAT assay report similar sensitivities, with minor differences in specificities
- There are a variable number of independently published studies evaluating individual assay performance or comparing performance between NAAT assays

Boyanton BL Jr et al. *J. Inf. Dis.* 2024. 230(S3):S182–9

Table 2. Sensitives, specificities, and positive and negative predictive values for 3 NAATs and Quidel QuickVue In-Line strep A assay compared to the results of culture for the detection of group A Streptococci from throat swabs.

Type of assay	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Roche cobas Liat	100 (88.06–100)	97.4 (86.5–99.9)	96.7 (82.8–99.9)	100 (90.75–100)
Cepheid Xpert	100 (88.06–100)	97.4 (86.5–99.9)	96.7 (82.8–99.9)	100 (90.75–100)
Luminex Aries	95.2 (76.2–99.9)	100 (83.9–100)	100 (83.2–100)	95.5 (77.2–99.9)
Quidel QuickVue	5.3 (0.1–26.0)	96.9 (83.8–99.9)	50 (1.3–98.7)	63.3 (48.3–76.6)

Table 1 Clinical performance of POC PCR, laboratory PCR, bacterial culture, and POC RADT when compared with final results by sequencing for group A *Streptococcus* ($n = 255$)

	Cobas Liat POC PCR[a]			Quidel QuickVue POC RADT			Bacterial culture		
Final result[b]	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Positive	105	1	106	94	9	103	79	0	79
Negative	5	144	149	16	136	152	31	144	175
Total	110	145	255	110	145	255	110	144	254
Sensitivity n/N (%, 95 CI)	105/110 (95.5%, 89.7–98.5)			94/110 (85.5%, 77.5–91.5)			79/110 (71.8%, 62.4–80.0)		
Specificity n/N (%, 95 CI)	144/145 (99.3%, 96.2–99.9)			136/145 (93.7%, 88.5–97.1)			144/144 (100.0%, 97.5–100.0)		
PPV n/N (%, 95 CI)	105/106 (99.1%, 94.9–99.9)			94/103 (91.3%, 84.1–95.9)			79/79 (100.0%, 95.4–100.0)		
NPV n/N (%, 95 CI)	144/149 (96.6%, 92.3–98.9)			136/152 (89.5%, 83.5–93.9)			144/175 (82.3%, 75.8–87.6)		
OPA n/N (%, 95 CI)	249/255 (97.6%, 94.9–99.1)			230/255 (90.2%, 85.9–93.6)			223/254 (87.8%, 83.1–91.6)		

NPV negative predictive value, *OPA* overall percentage agreement, *PPV* positive predictive value
[a]cobas Liat Strep A (POC) and Solana GAS NAAT (laboratory based). PCR via Clopper–Pearson (exact)
[b]Results based on concordant test results or bidirectional DNA sequencing when results were discordant

- **NAAT assays emerging as new "gold standard" for the detection of GAS in throat swab specimens**
- **Appear to be *more* specific than RADTs in some studies, but *less* specific than culture in others**

Parker KG et al. *J. Appl. Lab. Med*. 2019. 4(2): 164-169
Rao A et al. *BMC Pediatrics.* 2019. 19:24

Improved assay sensitivity due to lower limit of detection (LoD)

Table 2. LoD determination with ATCC 19615.

					ID-Now results			BD Veritor results			Quidel Sofia results			Sekisui OSOM results		
Dilution	CFU/mL	Volume of stock/dilution	Volume of PBS	Total Volume	Replicate-1	Replicate-2	Replicate-3	Replicate-1	Replicate-2	Replicate-3	Replicate-1	Replicate-2	Replicate-3	Replicate-1	Replicate-2	Replicate-3
Stock	3.7 × 10^7	NA	NA	NA		Not tested		Pos	Pos	Pos		Not tested			Not tested	
Additional dilution for BD	1.5 × 10^7	415 ul of stock	585 ul	1000 uL		Not tested		**Pos**	**Pos**	**Pos**		Not tested			Not tested	
Dil-1	1 × 10^7	555 ul of stock	1445 ul	2000 ul	Pos	Pos	Pos	Pos	Neg	Neg	**Pos**	**Pos**	**Pos**	**Pos**	**Pos**	**Pos**
Dil-2	1 × 10^6	200 ul of dil-1	1800 ul	2000 ul	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Pos	Neg	Neg	Neg
Dil-3	1 × 10^5	200 ul of dil-2	1800 ul	2000 ul	Pos	Pos	Pos				Neg	Neg	Neg			
Dil-4	5 × 10^4	900 ul of dil-3	900 ul	1800 ul	Pos	Pos	Pos									
Dil-5	2.5 × 10^4	900 ul of dil-4	900 ul	1800 ul	Pos	Pos	Pos									
Dil-6	1.25 × 10^4	900 ul of dil-5	900 ul	1800 ul	Pos	Pos	Pos									
Dil-7	6.25 × 10^3	900 ul of dil-6	900 ul	1800 ul	Pos	Pos	Pos									
Dil-8	3.125 × 10^3	900 ul of dil-7	900 ul	1800 ul	**Pos**	**Pos**	**Pos**									
Dil-9	1.562 × 10^3	900 ul of dil-8	900 ul	1800 ul	Neg	Neg	Neg									

Bold indicates the lowest dilution where all 3 replicates were detected.

Chandrasekaran A et al. *J. Appl. Lab. Med.* 2025. 10(04):901–910

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Dil-3	1 × 10^5	200 ul of dil-2	1800 ul	2000 ul	Pos	Pos	Pos				Neg	Neg	Neg			
Dil-4	5 × 10^4	900 ul of dil-3	900 ul	1800 ul	Pos	Pos	Pos									
Dil-5	2.5 × 10^4	900 ul of dil-4	900 ul	1800 ul	Pos	Pos	Pos									
Dil-6	1.25 × 10^4	900 ul of dil-5	900 ul	1800 ul	Pos	Pos	Pos									
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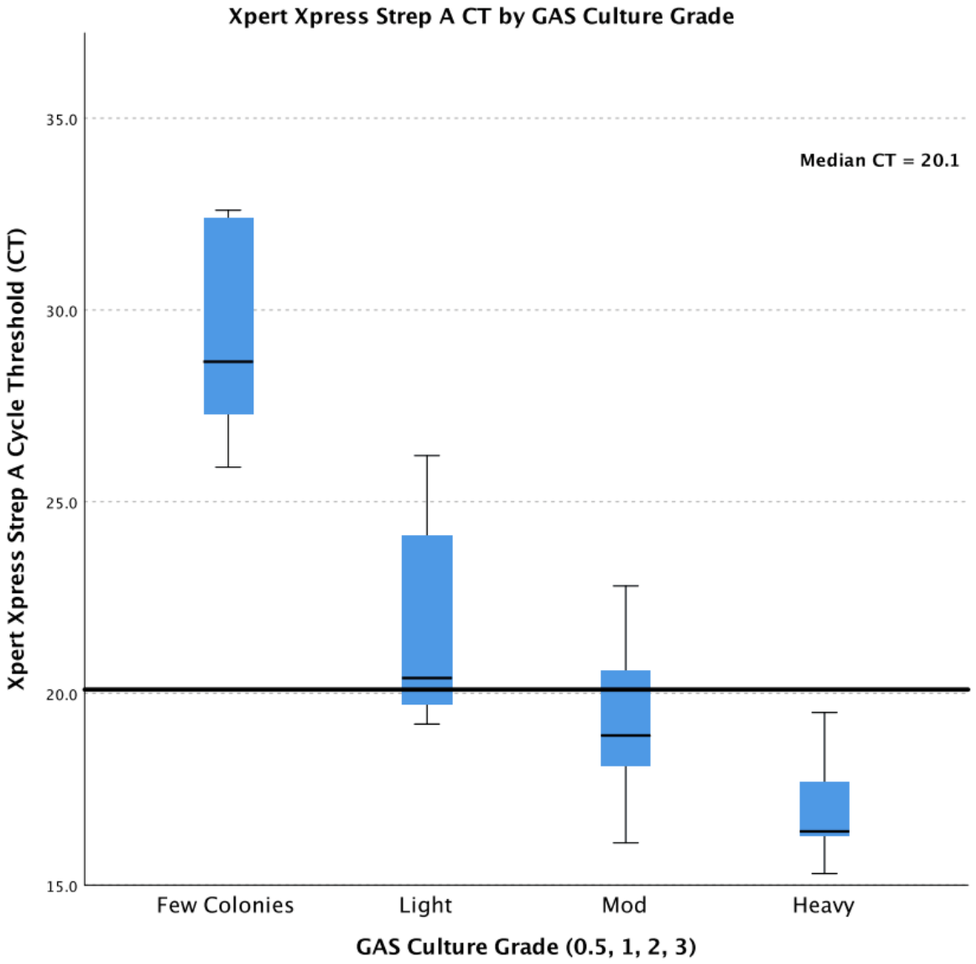
Chandrasekaran A et al. *J. Appl. Lab. Med.* 2025. 10(04):901–910

Potential NAAT caveats?

- As with all diagnostics tests, results are impacted by specimen quality
- Improved performance over culture has potential to lead to increased rates of detection of colonized individuals
  - ***'right test, right patient, right time'***
- Detects both viable & non-viable bacteria
  - NAATs can remain positive for 2-6 weeks post-infection
- Prevent contamination by proper specimen collection & handling
- **No such thing as a 'closed system'!** Potential for amplicon contamination in the lab
- All molecular assays (even CLIA-waived!) require monitoring for reliability and a robust quality management program



Taylor A et al. *J. Clin. Microbiol*. 2021. 59(12):e00978-21

The importance of looking for environmental contamination

Donato LJ et al. *J. Clin. Microbiol*. 2019. 57(2): e01629-18

The importance of looking for environmental contamination

- Study with two Cobas Liat instruments at two distinct clinical sites testing for GAS (i.e. point of case testing, POCT)

Donato LJ et al. *J. Clin. Microbiol*. 2019. 57(2): e01629-18

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- Study with two Cobas Liat instruments at two distinct clinical sites testing for GAS (i.e. point of case testing, POCT)
- Performed weekly environmental testing at each site (i.e. wipe testing)
  - no special cleaning performed prior to collection of the environmental swabs

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Donato LJ et al. *J. Clin. Microbiol*. 2019. 57(2): e01629-18

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Donato LJ et al. *J. Clin. Microbiol*. 2019. 57(2): e01629-18

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- Total of 26 environmental swabs (13 swabs from site A, 13 swabs from site B) were collected – all swabs were negative with both POCT and lab-based tests

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- **Wipe-testing is an important part of both lab-based and POCT-based NAAT testing program**

Donato LJ et al. *J. Clin. Microbiol*. 2019. 57(2): e01629-18

The potential promise of NAAT assays for GAS diagnosis

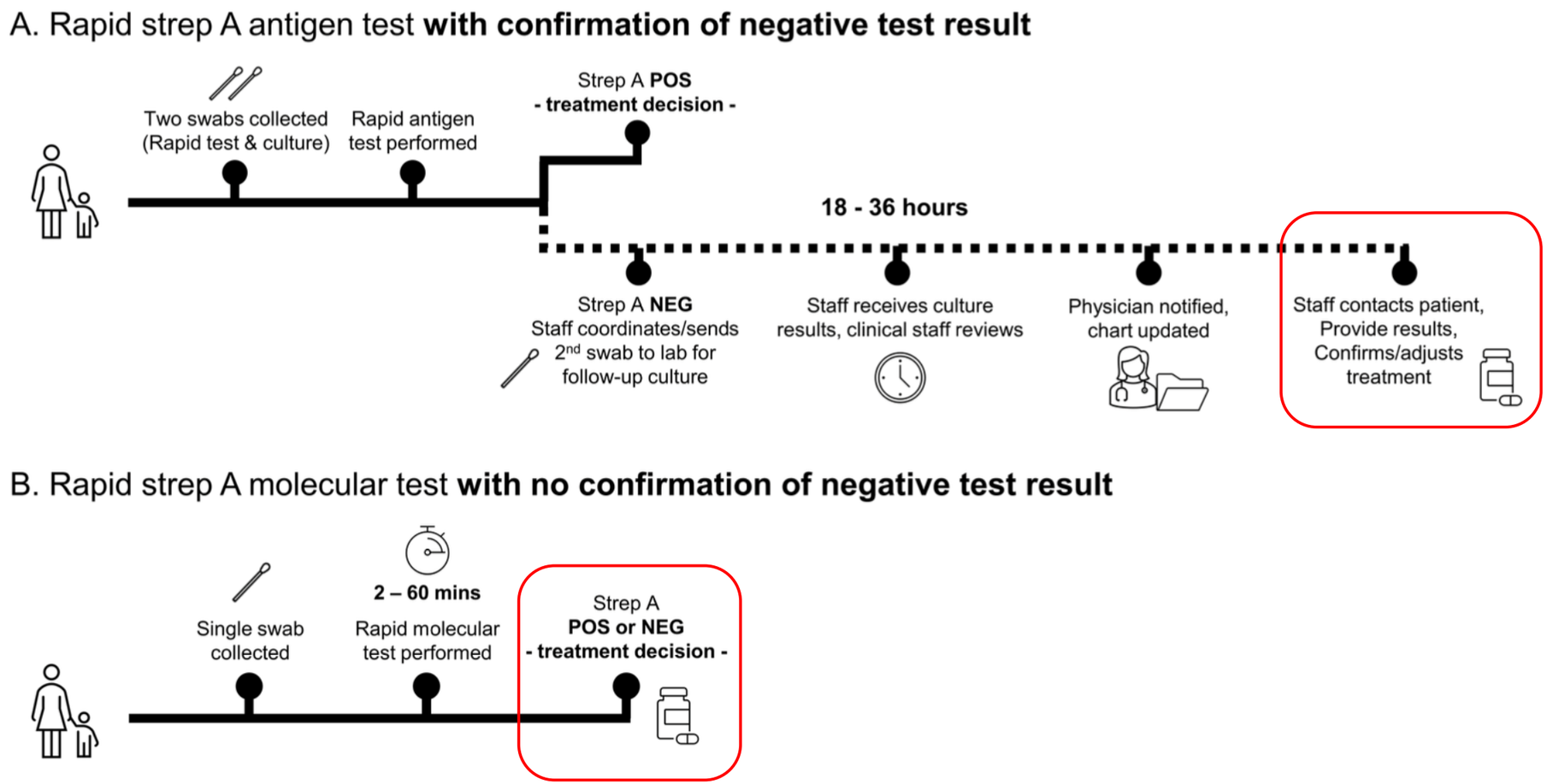

Figure 2. Workflow comparison: (A) Rapid antigen detection tests (RADTs); (B) Nucleic acid amplification tests (NAATs).

Cohen JF et al. *J. Ped. Inf. Dis. Soc*. 2024. 13(4):250–256

Is a more rapid test result just a theoretical benefit?

Table 2 Appropriate antibiotic prescribing in relation to group A Streptococcal testing results

Antibiotic use		Final result*			
		SOC[a] ($n = 152$)		Liat[b] ($n = 103$)	
		Positive	Negative	Positive	Negative
Antibiotic	Yes	61	10	38	1
	No	9	72	2	62
Appropriate antibiotic use, % (n/N)[c]		87.5 (133/152)		97.1 (100/103)	

*Final result by bidirectional DNA sequencing; $P = .0065$

[a]RADT plus culture

[b]cobas Liat Strep A POC PCR assay

[c]Appropriate antibiotic use defined as follows: final result positive plus antibiotics = yes or final result negative plus antibiotics = no. SOC % = (61 + 72)/(61 + 10 + 9 + 72); Liat% = (38 + 62)/(38 + 1 + 2 + 6 + 62)

Rao A et al. *BMC Pediatrics.* 2019. 19:24
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Appropriate antibiotic use, % (n/N)[c]		87.5 (133/152)		97.1 (100/103)	

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Table 3. Anti-infective Prescriptions for Strep A, Within 0 Days and 14 Days of Clinic Visit

Characteristic	Control Period (POC RADT)		Intervention Period (POC PCR)	
	Within 0 Days	Within 14 Days	Within 0 Days	Within 14 Days
Patients[a], No.	5307	5307	4774	4774
Anti-infective prescriptions[b]				
Antibiotics only	1381 (26.0)	1390 (26.2)	1194 (25.0)	1200 (25.1)
Antivirals only	40 (0.8)	41 (0.8)	25 (0.5)	25 (0.5)
Antivirals and antibiotics together	9 (0.2)	9 (0.2)	7 (0.2)	7 (0.2)
POC tests performed, No.[c]	3368	3368	2412	2412
POC test positive, No.	646	646	604	604
Antibiotic prescription	494 (76.5)	494 (76.5)	460 (76.2)	460 (76.2)
Antiviral prescription	0 (0.0)	0 (0.0)	6 (1.0)	6 (1.0)
POC test negative, No.	2714	2714	1757	1757
Antibiotic prescription	489 (18.0)	494 (18.2)	177 (10.1)	179 (10.2)
Antiviral prescription	33 (1.2)	34 (1.3)	18 (1.0)	18 (1.0)
No POC test, No.	1939	1939	2362	2362
Antibiotic prescription	406 (20.9)	410 (21.1)	552 (23.4)	556 (23.5)
Antiviral prescription	16 (0.8)	16 (0.8)	8 (0.3)	8 (0.3)

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- >10,000 eligible patient records
- **44.1% reduction in abx prescriptions with a negative POC PCR test result (10.1% PCR vs 18.0% RADT; P < .0001)**
- No impact on prescription rates in patients with positive POCT result (76.2% PCR vs 76.5% RADT)
- >99% of antibiotics were prescribed during the initial primary care encounter

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Diagnosis and Management of Group a Streptococcal Pharyngitis in the United States, 2011–2015

Robert Luo[1], Joanna Sickler[1*], Farnaz Vahidnia[2], Yuan-Chi Lee[2], Bianca Frogner[3] and Matthew Thompson[3*]

- Retrospective analysis of MarketScan commercial/Medicare databases between 2011-2015
- **18.8 million acute pharyngitis events were identified in 11.6 million patients**
- Evaluated patient & provider characteristics for patients with: RADT, RADT + culture, other tests, NAAT, & no test
- 43% patients diagnosed by RADT, 20% diagnosed by RADT + culture
- Proportion of cases diagnosed by NAAT increased 3.5-fold from 2011 to 2015 (0.06% vs 0. 27%)
- **Reduced antibiotic use in patients with RADT + culture (31.2%) or NAAT alone (34.5%) vs. RADT alone (53.4%) or no test (57.1%)**

Table 3 Factors associated with antibiotic use among sore throat/pharyngitis visits[c]

	Events (n)	ABX %	Adjusted HR[b]	95% Confidence Limits	
A. 17 years and younger					
Diagnostic test (ref. NAAT)					
RADT only	4,682,423	52.49	2.23	2.16	2.31
RADT and culture	2,751,575	26.56	0.91	0.88	0.94
No test	1,834,351	55.73	2.30	2.22	2.38
Other test combinations	950,367	40.68	1.57	1.52	1.62
Place of service (ref. office)					
ED	262,364	50.15	1.01	1.00	1.01
Urgent care[a]	483,304	55.71	1.15	1.15	1.16
Laboratory/other	554,423	34.45	0.76	0.76	0.77
Provider type (ref. pediatrician)					
Family medicine	1,577,559	56.53	1.40	1.40	1.41
Internal medicine	235,431	55.6	1.40	1.39	1.41
Other	3,309,058	46.52	1.20	1.20	1.21
B. 18 years and older					
Diagnostic test (ref. NAAT)					
RADT only	3,400,327	54.66	1.49	1.44	1.54
RADT and culture	967,958	44.58	1.16	1.13	1.20
No test	3,397,174	57.88	1.59	1.54	1.64
Other test combinations	773,114	50.57	1.41	1.36	1.45
Place of service (ref. office)					
ED	411,369	51.01	0.92	0.91	0.92
Urgent care	824,376	57.39	1.10	1.10	1.11
Laboratory/other	537,543	41.82	0.73	0.72	0.73
Provider type (ref. family medicine)					
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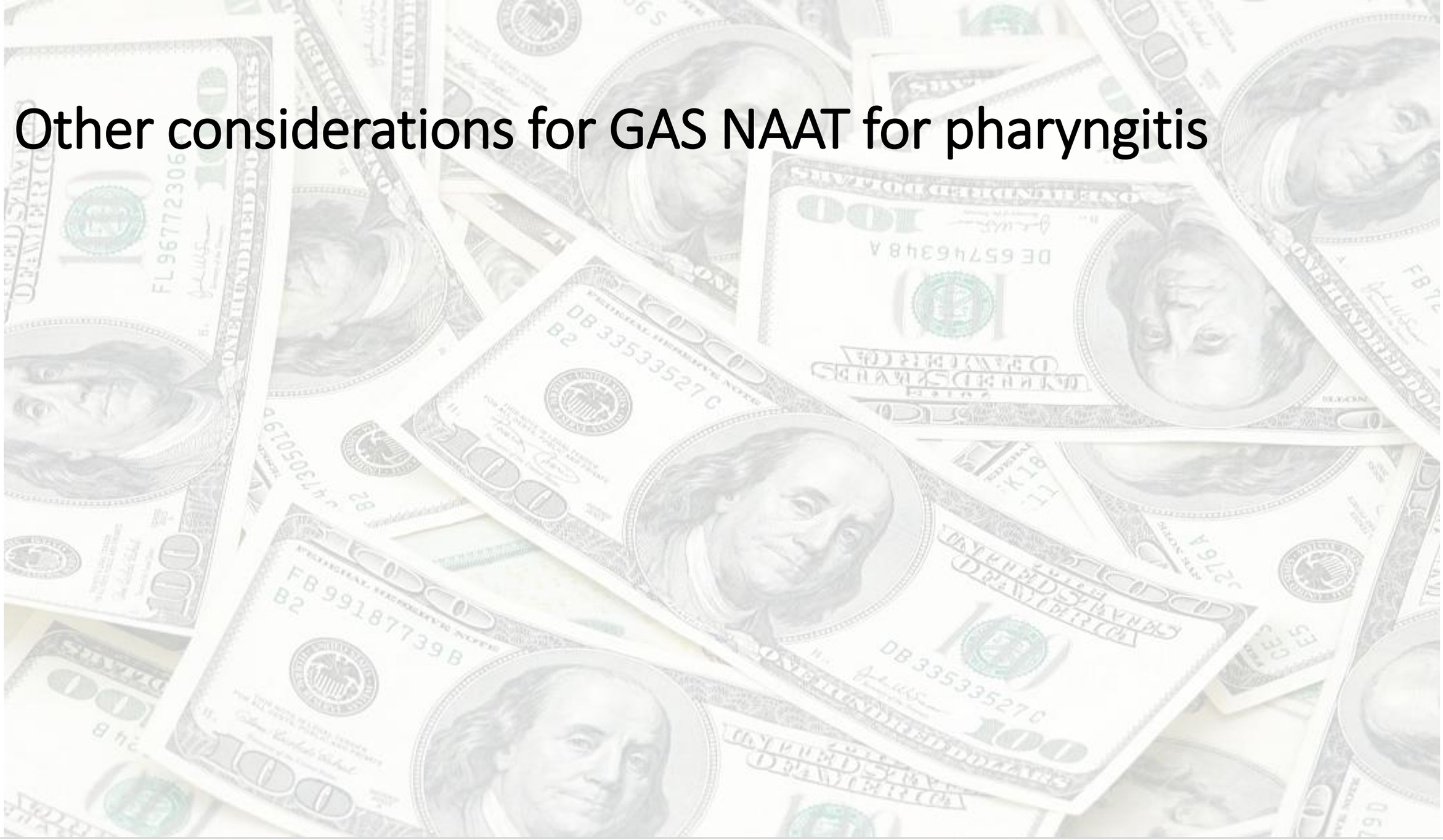

Weinzierl EP and Gonzalez MD. *Clin. Micro. Newletter*. 2020. 42(13): 105-110

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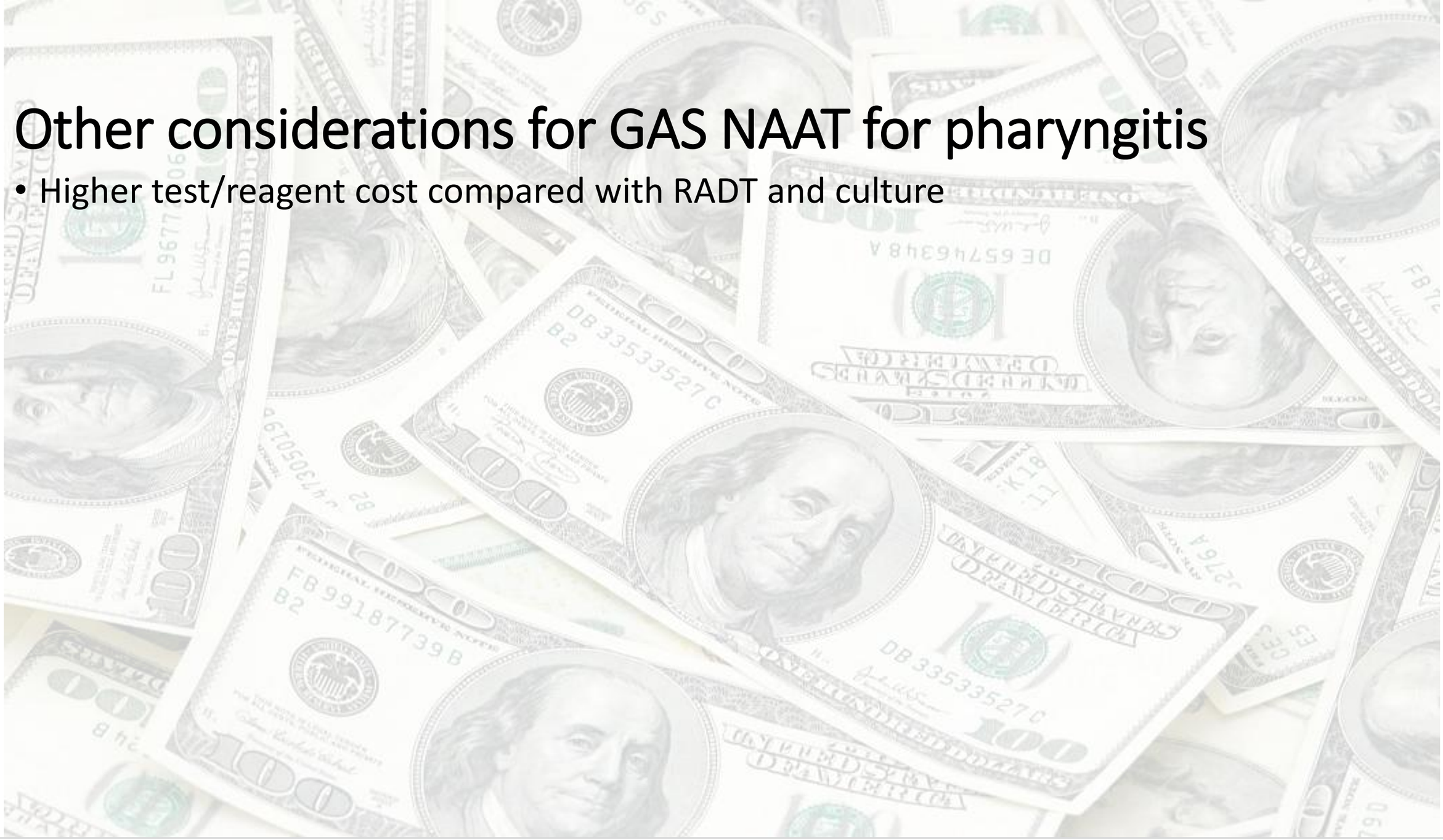

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- 2012 IDSA guidelines are from before increased adoption of NAAT for GAS – practice guideline recommendations have the potential to change payor reimbursement rates
  - guideline update is in progress

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- Despite their higher cost, NAAT assays for GAS pharyngitis have the potential to improve antibiotic prescribing habits due to their generally improved test performance and reduced turnaround time
- Never forget: Right test, right patient, right time! ☺