ID WATCH

by Ed Septimus, MD

Editor's Choice

1

Disinfection of central venous access device needleless connectors: A human factors analysis

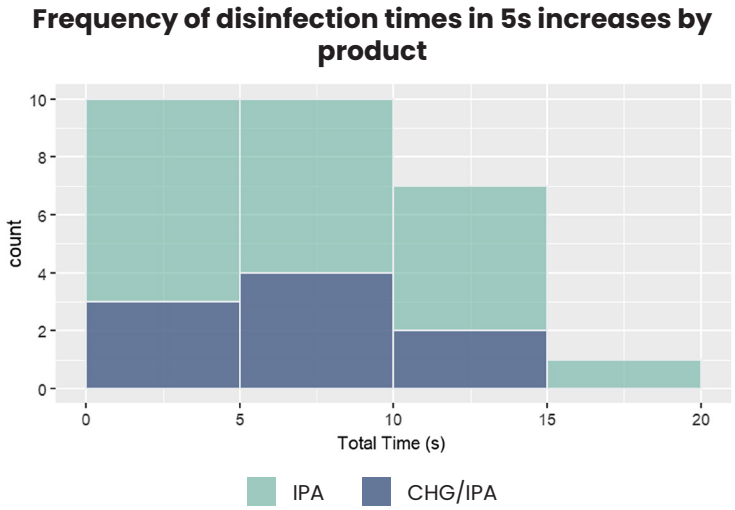
Infect Control Hosp Epidemiol published online February 23, 2024 (*Article suggested by Keith St John*)
doi:10.1017/ice.2024.22

Evidence-based central-line–associated bloodstream infection (CLABSI) prevention guidelines recommend scrubbing the hub before device access. [Infect Control Hosp Epidemiol 2022; 43:553–569] Current recommendations and clinical data suggest that active needleless-connector disinfection should be performed following these steps:

1. Vigorously scrub the threads and septum of the needleless connector with a wipe for at least 15 seconds.
2. Let needleless connector air dry.
3. Every additional access to the needleless connector requires a new 15-s scrub. [Nurs Manag 2010; 41:40–41]

Noncompliance is not uncommon which may render disinfection less effective. The goal of this study was to observe needleless-connector disinfection practices and to identify facilitators and barriers to best practices of needleless-connector access. Participation was voluntary.

A human factors mixed-methods study involving nursing focus groups of perceived barriers and facilitators and clinical observations of compliance with instructions and protocols for use of 3.15% chlorhexidine gluconate/70%



isopropyl alcohol (CHG/IPA) and 70% isopropyl alcohol (IPA) antisepsis products for central venous access device (CVAD) needleless-connector disinfection was conducted in ICUs at 2 academic medical centers.

Access to the antiseptic product and lesser workload were identified as best-practice facilitators. Barriers were the time required per needleless-connector access and knowledge deficits. Of the 48 observed access events, 77% resulted in needleless-connector disinfection. [meaning 23%, no disinfection or inadequate disinfection of the needleless connector occurred before device access] The observed mean needleless connector scrubbing times when using IPA were substantially below the recommended time. Drying time after product use was negligible.

Dr. Septimus's Annotations

Not surprisingly, the results of this study suggest that disinfection time for needleless connectors was less than recommended. Lack of access to the disinfection product, emergency situations, and high workload were barriers to needleless-connector disinfection. Observed scrubbing and drying times were shorter than recommended, especially for IPA wipes. HCWs know about hospital policy; however, when faced with time-challenged and/or high acuity workloads, they may reduce needleless-connector disinfection time. As an alternative the Compendium made antiseptic caps an additional approach, as they are not considered better than traditional manual disinfections if done properly. [Infect Control Hosp Epidemiol 2022; 43:553–569] The relatively small sample size in this study did not allow for a generalizability of these results outside ICU or nonteaching-hospital settings. The direct observations of needleless-connector disinfection were conducted in an inpatient care setting during routine daily care and therefore were not able to be blinded. Nursing staff were aware that the investigator was observing infection prevention practices and behaviors. In addition, participation was voluntary, which may have contributed to a self-selection bias.

Bottom line: Auditing and optimizing both needleless-connector scrubbing and drying times, visual reminders, workload management and bedside supply management are efforts that will promote needleless-connector practice adherence.

Complication Rates of Central Venous Catheters A Systematic Review and Meta-Analysis

JAMA Intern Med published online March 4, 2024
doi:10.1001/jamainternmed.2023.8232

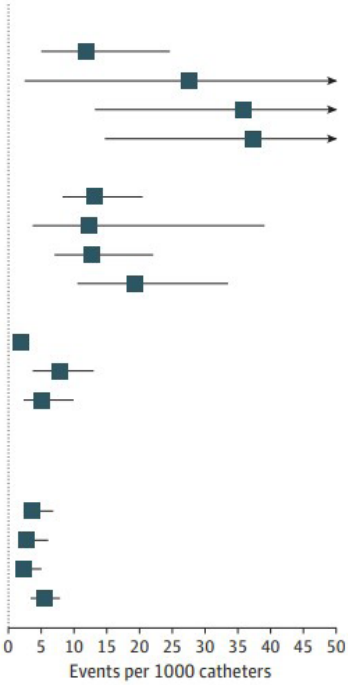
To estimate the complication rate of central venous catheters (CVCs), investigators performed a systematic review and meta-analysis of 130 observational and randomized studies published from 2015 to 2023 in which short term complication rates associated with CVCs were examined in adult inpatients. Peripherally inserted central venous catheters(PICCS), dialysis catheters, long-term tunneled catheters, and catheters placed by radiologists were excluded.

The three most common complications associated with CVC insertions were placement failure (20.4 events/1000 catheters placed), arterial puncture (16.2 events/1000 catheters placed), and pneumothorax (4.4 events/1000 catheters placed). A composite outcome of four serious complications (i.e., arterial cannulation, pneumothorax, infection, and deep venous thrombosis) from a CVC placed for 3 days was estimated to be 30 events per 1000 catheters placed (3%). Use of ultrasonography was associated with a fourfold lower rate of immediate insertion complications (i.e., placement failure, arterial puncture, and pneumothorax) compared with no ultrasonography guidance.

Most common complications associated with CVC insertions

Placement failure	**20.4 events** per 1000 catheters placed
Arterial puncture	**16.2 events** per 1000 catheters placed
Pneumothorax	**4.4 events** per 1000 catheters placed

Catheter type	No. of groups	Events/ catheters	No. of events per 1000 catheters (95% CrI)
Placement failure			
Internal jugular	21	247/8852	11.9 (5.0-24.7)
Femoral	2	58/1200	27.7 (2.5-225.8)
Subclavian	12	401/4253	35.9 (13.2-86.1)
Other	12	128/3102	37.4 (14.7-89.1)
Arterial puncture			
Internal jugular	38	153/10307	13.3 (8.3-20.5)
Femoral	6	14/1678	12.4 (3.7-39.1)
Subclavian	23	101/5690	12.8 (7.1-22.1)
Other	21	120/4621	19.3 (10.5-33.6)
Pneumothorax			
Internal jugular	31	63/19312	1.9 (0.9-3.5)
Subclavian	34	80/7111	7.8 (4.3-13.0)
Other	20	41/4883	5.1 (2.3-10.0)
		Events/ catheter-days	Incidence rate per 1000 catheter–days
Infection			
Internal jugular	12	185/50007.5	3.8 (2.0-6.9)
Femoral	7	58/19094.46	2.7 (1.1-6.1)
Subclavian	10	57/21076.05	2.5 (1.2-5.1)
Other	35	3127/459068.8	5.6 (3.9-7.9)



Dr. Septimus's Annotations

In this systematic review of complications following CVC insertion, the rate of major complications was approximately 3%. Ultrasonography use was associated with fewer immediate insertion-related complications. However, outcome definitions were not uniform across studies. Although efforts were made to standardize estimates and account for dissimilar follow-up whenever feasible, the wide CIs and statistical heterogeneity among estimates can be partially attributed to variation in patient samples, study design, and different definitions of CVC-associated complications. They found that many studies on CVC-associated complications provided suboptimal descriptions of the purpose of catheter use and characteristics of operators inserting catheters. The investigators also could not account for the effect of the experience, type, and skill levels of clinicians in these analyses. The investigators emphasize that it is important to interpret the results obtained from their metaregression models as suggestive associations, not definitive evidence of causality.

"...[A]n overemphasis on hospital-acquired infection reporting could unintentionally shift the focus away from direct infection prevention activities within hospitals, leading to potential negative impacts on patient care and overall hospital quality."

In an invited commentary [JAMA Intern Med published online March 4, 2024] the authors point out new practices call into question the widespread use of CVCs. Studies suggest that peripheral administration of vasopressors for patients with septic or cardiogenic shock, among others, is feasible and safe. [J Clin Med 2023; 12:5734] Advances in parenteral nutrition and chemotherapeutic agent formulations have made peripheral administration more acceptable. Recent developments in medical technology have led to minimally invasive and noninvasive hemodynamic monitoring techniques, reflecting a growing focus on patient safety and comfort in critical care settings. [Anesthesiology 2020;133;921-928] However, we know CVC use remains high. A systematic approach to clinician training and adherence to evidence-based interventions is essential to ensure that these minimally invasive techniques are effectively utilized. They go on to say: "There is growing debate surrounding the reliability of hospital-acquired infection metrics, with infection control experts raising concerns about potential misinterpretations

and susceptibility to manipulation by external factors. Adjustment of CLABSI rates for quality reporting and comparison remains suboptimal and often fails to account for multifactorial influences affecting infection rates; this has been highlighted in the recent literature, emphasizing the need for refined methodologies that accurately reflect a health care facility's quality of care. [Clin Infect Dis 2022; 74:1748-1754] Furthermore, an overemphasis on hospital-acquired infection reporting could unintentionally shift the focus away from direct infection prevention activities within hospitals, leading to potential negative impacts on patient care and overall hospital quality." In addition, studies have questioned CLABSI misclassification using current surveillance definitions. [Crit Care Med 2024 52: 357-361] The consistent implementation of evidence-based practices proven to lower the risk of complications from CVCs, such as ultrasonography-guided placement and insertion and maintenance bundle (e.g. scrub the hub-see above), has been suboptimal. The commentary also recommends ensuring a more balanced assessment of health care quality. They proposed that process measures be incorporated into the quality reporting and reimbursement models in place of outcome measures. They claim an emphasis on process measures offers a proactive approach to infection prevention by promoting the standardization of practices known to reduce infection risk. This would be a reversal of recent trends to move away from process measures to outcomes measures.

Lastly, there is an ongoing discussion on the need for infection prevention programs to expand surveillance beyond CLABSI and institute standardized interventions to prevent BSIs associated with all vascular devices (VDs). Determining infection risk associated with VDs first requires a method for accurately measuring the risk for individual types of VDs used in healthcare. Although data provides some insight into the nationwide prevalence of CLABSI events, the infection risk associated with non-central line VD-associated BSIs is less well described, particularly in the US. Evidence however in selected studies on infection risk with non-central line VDs indicates that such devices as arterial, hemodialysis, midlines, and peripheral intravenous catheters (PIVCs), are associated with substantial numbers of hospital-onset BSIs. In fact, CMS is considering revisions to the Hospital Inpatient Prospective Payment System (IPPS) aimed at expanding BSI surveillance in US hospitals under the Inpatient Quality Reporting (IQR) Program. The Hospital-Onset Bacteremia and Fungemia (HOB) proposal would require hospitals to expand surveillance to all HOB. This measure is now endorsed by Battelle's Partnership for Quality Measurement (PQM). CDC is the measure developer and is validating the measure. CDC will enable volunteer reporting of HOB in this calendar year.

Bottom line: This study is a reminder that clinicians need to weigh risks and benefits prior to inserting CVCs. An excellent tool has been published [Ann Intern Mead 2015;163:S1] called MAGIC (Michigan Appropriateness Guide for Intravenous Catheters) which can assist in the decision-making process.

The **Michigan MAGIC** app is free and available for download for both iOS and Android platforms

3 Identification of carbapenem-resistant organism (CRO) contamination of in-room sinks in intensive care units in a new hospital bed tower

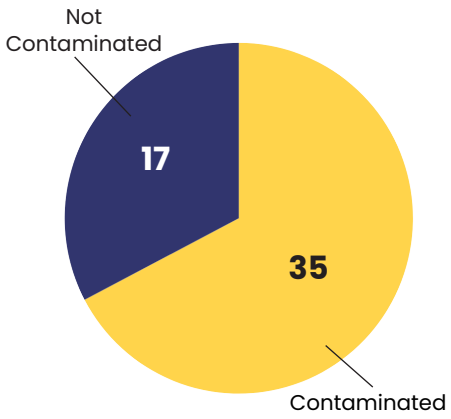
Infect Control Hospital Epidemiol published online January 2024
doi: 10.1017/ ice.2023.289

The investigators performed a prospective observational study to describe the timing, rate, and frequency of CRO contamination of in-room handwashing sinks in 2 ICUs in a newly constructed hospital bed tower. Study units, A and B, were opened to patient care in succession. The patients in unit A were moved to a new unit in the same bed tower, unit B. Each unit was similarly designed with 26 rooms and in-room sinks. Microbiological samples were taken every 4 weeks from 3 locations from each study sink: the top of the bowl, the drain cover, and the p-trap. The primary outcome was sink conversion events (SCEs), defined as CRO contamination of a sink in which CRO had not previously been detected. Routine environmental disinfection was performed in all study rooms according to standard hospital protocols. However, adherence

was not measured. All rooms were single-patient rooms with no shared bathrooms. Routine disinfection was defined as (1) daily disinfection of patient-room surfaces with nonbleach solutions and (2) terminal disinfection of patient-room surfaces with nonbleach solutions and ultraviolet C (UV-C) treatment. Enhanced terminal disinfection was defined as routine terminal disinfection while substituting bleach solutions for nonbleach solutions.

Sink samples were obtained 22 times from September 2020 to June 2022, giving 1,638 total environmental cultures. In total, 2,814 patients were admitted to study units while sink sampling occurred. They observed 35 SCEs (73%) overall; 9 sinks (41%) in unit A became contaminated with CRO by month 10, and all 26 sinks became contaminated in unit B by month 7. Overall, 299 CRO isolates were recovered; the most common species were Enterobacter cloacae and P aeruginosa. Of the 299 CROs recovered, 42 (14%) had at least 1 carbapenemase gene; 9 (28%) of 32 in unit A and 33 (12%) of 267 in unit B. The majority of recovered CROs harboring carbapenemase genes were Enterobacter cloacae complex [22 (52%) of 42]. Additionally, 18 non-EIP species harboring carbapenemase genes were identified, including 10 Pseudomonas spp (not P. aeruginosa) and 7 Delftia acidovorans. [Delftia acidovorans is an aerobic, nonfermenting Gram-negative bacillus. It is usually a nonpathogenic environmental organism and is rarely clinically significant] Among all bacteria with an identifiable carbapenemase gene, the most common gene was KPC (60%), followed by New Delhi metallo-β-lactamase-1 (NDM-1) (28%) and IMP (active against imipenem; imipenemase) (12%).

SCEs Outcomes, Sept 2020 - June 2022



Sink Conversion Events (SCEs)

CRO contamination of a sink in which CRO had not previously been detected.

Routine Disinfection*

1. Daily disinfection of patient-room surfaces with nonbleach solutions
2. Terminal disinfection of patient-room surfaces with nonbleach solutions and ultraviolet C (UV-C) treatment

**adherence to routine evironmental disinfection was not measured*

Dr. Septimus's Annotations

Sinks in healthcare settings often contain pathogenic bacteria, including bacteria harboring genes that confer high-level resistance to multiple antibiotics. These sinks have been identified as the source of in-hospital transmission to patients and outbreaks of infection, leading to the recognition that a sink, often situated less than 1 meter from a patient, can serve as an important reservoir for multidrug-resistant pathogens, such as CROs. [J Hosp Infect 2013; 85:106–111; Infect Control Hosp Epidemiol 2018;39:1307–1315; Antimicrob Resist Infect Control 2017;6:24] These results, paired with growing literature, support in-room hospital sinks as an important reservoir of CRO, and they emphasize the need for infection prevention strategies to mitigate contamination of surfaces from sinks (e.g., splash guards) as well as the development of novel strategies to eliminate CRO from sinks. In February 2024 ID Watch a study was reviewed where the investigators reported the frequency of CPE-contaminated sinks in an acute-care hospital, and they have demonstrated that they are frequently and persistently contaminated with a dominant clone. Most importantly, they showed that CPE contaminated sinks were not only a source of outbreaks in high-risk units, but that sink-traps serve as an important environmental niche of gram-negative MDRO (specifically CPE) that play a major role in CPE transmission in nonoutbreak settings. [Infect Control Hosp Epidemiol published online December 27, 2024]

"...[A]sink, often situated less than 1 meter from a patient, can serve as an important reservoir for multidrug-resistant pathogens, such as CROs."

Bottom line: CRO contamination of sinks in 2 newly constructed ICUs was rapid and cumulative. Their findings support in-room sinks as reservoirs of CRO and emphasize the need for prevention strategies to mitigate contamination of hands and surfaces from CRO-colonized sinks.

4

FDA rejects new drug application for cefepime-taniborbactam

February 27, 2024

FDA issued a Complete Response Letter (CRL) regarding the New Drug Application (NDA) for cefepime-taniborbactam, a beta-lactam/beta-lactamase inhibitor (BL/BLI) combination antibiotic under review as a potential treatment for adult patients with complicated urinary tract infections (cUTI), including acute pyelonephritis caused by susceptible gram-negative microorganisms.

The CRL did not identify clinical safety or efficacy issues in the NDA, and the FDA did not request any new clinical trials to support the approval of cefepime-taniborbactam. The FDA requested additional chemistry, manufacturing, and controls (CMC) and related data about the drug, testing methods, and manufacturing process.

Dr. Septimus's Annotations

Taniborbactam is a beta-lactamase inhibitor (BLI) that, in combination with cefepime, is being studied as a potential treatment option for patients with serious bacterial infections caused by antibiotic resistant gram-negative bacteria, most notably ESBL-expressing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and MDR P aeruginosa (MDR-PA), which can include carbapenem-resistant P. aeruginosa (CRPA).

Cefepime-taniborbactam has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations by the FDA. Fast Track designation is designed to facilitate the development, and to expedite the review of drugs to treat serious conditions that do not have sufficient treatment options. QIDP designation provides certain incentives for the development of new antibiotics, including priority review, as well as a five-year regulatory exclusivity extension. QIDP was authorized under the Generating Antibiotic Incentives Now (GAIN) Act of 2012, as part of the FDA Safety and Innovation Act, to underscore the urgency in development of new antibiotics.

Resistance to carbapenems among Enterobacterales is primarily achieved by production of carbapenemases, which are enzymes capable of hydrolyzing carbapenem antibiotics and most other beta-lactams and fall into two distinct families: serine beta-lactamases and metallo-beta-lactamases (MBLs). K pneumoniae carbapenemase (KPC), a class-A serine beta-lactamase, is one of the most prevalent carbapenemases, and New Delhi MBL (NDM) and Verona Integron-encoded MBL (VIM) are common variants of MBLs identified in gram-negative infections due to Enterobacterales and P. aeruginosa. According to an IHMA surveillance study in 2018-2019 and a JMI US Surveillance study from 2021, MBLs were the most commonly identified carbapenem resistance mechanism globally among Enterobacterales isolates, with ~16 to 18% of US CRE isolates carrying MBLs. The results of a phase 3 trial was recently reviewed in March 2024 ID Watch which demonstrated the combination antibiotic was superior to meropenem in patients with complicated UTIs. [N Engl J Med 2024; 390:611-22]

5

The FDA approved cefepime/enmetazobactam

February 27, 2024

The FDA approved cefepime/enmetazobactam for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTIs), including pyelonephritis. The approval was based on data from a double-blind, noninferiority phase 3 trial that evaluated the efficacy and safety of cefepime/enmetazobactam in 1041 adults with cUTI, including pyelonephritis. [JAMA. 2022;328(13):1304-1314] Study participants were randomly assigned 1:1 to receive cefepime 2g/enmetazobactam 500mg (n=345) or piperacillin 4g/tazobactam 500mg (n=333) every 8 hours for 7 days, or up to 14

days for patients with concurrent bacteremia. The primary efficacy endpoint was composite response defined as clinical cure (complete resolution of the baseline signs/symptoms of cUTI or pyelonephritis that were present at screening) and microbiological eradication (Gram negative pathogens reduced to <103 colony-forming units/mL in urine culture and a negative blood culture for a Gram-negative pathogen that was identified as the pathogen at the test-of-cure (TOC) visit.

Results showed that 79.1% (273/345) of patients treated with cefepime/enmetazobactam achieved composite response compared with 58.9% (196/333) of the piperacillin/tazobactam group (adjusted stratified difference, 21.2% [95% CI, 14.3-27.9]). Among patients with bacteremia at baseline, 71% (27/38) of patients treated with cefepime/enmetazobactam achieved composite response compared with 50% (14/28) of the piperacillin/tazobactam group.

Among study participants with extended spectrum beta-lactamase (ESBL)-producing bacteria at baseline, composite response was observed at TOC in 74% (56/76) of patients treated with cefepime/enmetazobactam and 52% (34/66) of those treated with piperacillin/tazobactam.

The most common adverse reactions reported with cefepime/enmetazobactam were increased transaminases, increased bilirubin, headache, and phlebitis/infusion site reactions.

Dr. Septimus's Annotations

Cefepime/enmetazobactam is indicated for the treatment of patients 18 years of age and older with cUTI including pyelonephritis, caused by the following susceptible microorganisms: E coli, K pneumoniae, P aeruginosa, Proteus mirabilis, and Enterobacter cloacae complex. In vitro, the novel β-lactamase inhibitor enmetazobactam restored the activity of cefepime against β-lactamase–producing gram-negative pathogens, and was more potent than piperacillin/tazobactam against extended-spectrum β-lactamase producers. [Enmetazobactam restored the activity of cefepime against class A serine β-lactamase–producing Enterobacterales] Enmetazobactam does not exhibit activity against carbapenem-resistant pathogens.

6

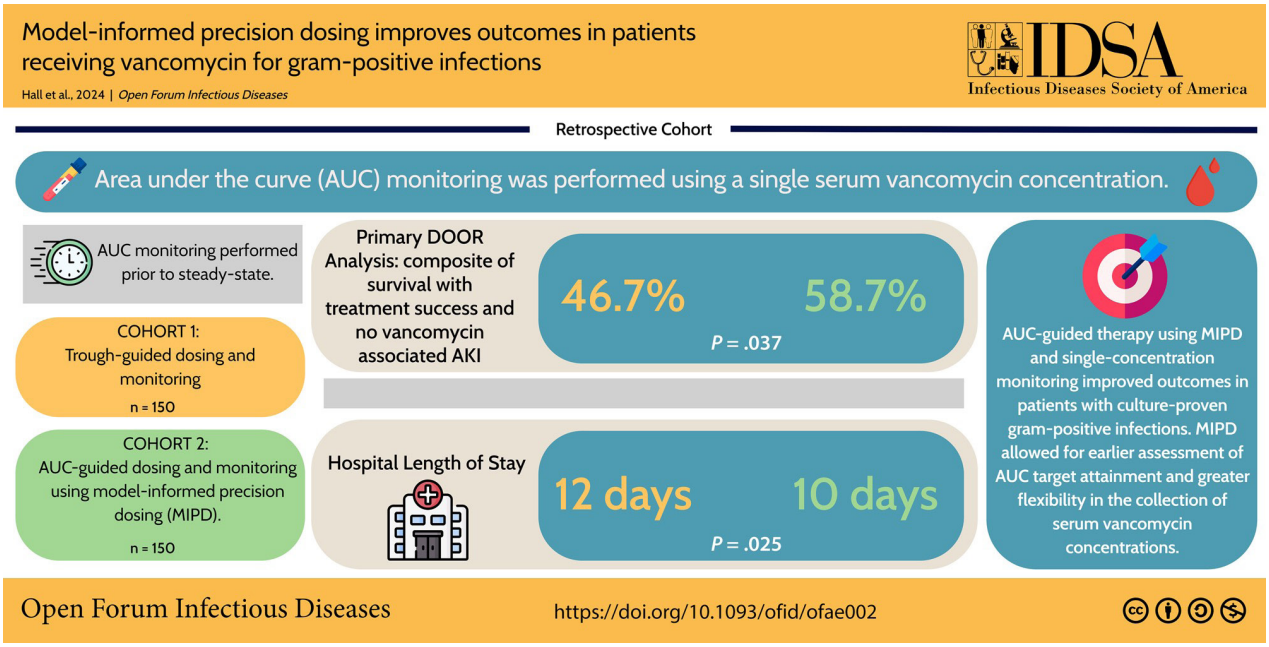
Model-Informed Precision Dosing Improves Outcomes in Patients Receiving Vancomycin for Gram-Positive Infections

OFID published online January 5, 2024
doi.org/10.1093/ofid/ofae002

Consensus guidelines for dosing and monitoring of vancomycin recommend collection of 2 serum concentrations to estimate an area under the curve/minimum inhibitory concentration ratio (AUC/MIC). Use of Bayesian software for AUC estimation and model-informed precision dosing (MIPD) enables pre–steady state therapeutic drug monitoring using a single serum concentration; however, data supporting this approach is limited.

Adult patients with culture-proven gram-positive infections treated with vancomycin for ≥72 hours receiving either trough-guided or AUC-guided therapy were included in this retrospective study. AUC-guided therapy was provided using MIPD and single-concentration monitoring. Treatment success, vancomycin-associated acute kidney injury (VA-AKI), and inpatient mortality were compared using a desirability of outcome ranking analysis. The most desirable outcome was survival with treatment success and no VA-AKI, and the least desirable outcome was death.

The study involved 300 patients. They were equal number of patients receiving AUC-guided or trough guided therapy. More patients experienced the most desirable outcome in the AUC-guided group compared to the trough guided group (58.7% vs 46.7%, P = .037). Rates of VA-AKI were lower (21.3% vs 32.0%, P = .037) and median hospital length of stay was shorter (10 days [interquartile range {IQR}, 8–20] vs 12 days [IQR, 8–25]; P = .025) among patients receiving AUC guided therapy.



Dr. Septimus's Annotations

The updated consensus guidelines for vancomycin dosing and monitoring prefer Bayesian-assisted AUC-guided therapy, preferably based on the collection of 2 serum concentrations due to limited data supporting the use of single-concentration monitoring. Trough concentrations ≥15 µg/mL and area under the curve over minimum inhibitory concentration ratios (AUC/ MIC) as low as 515 mg/L × hour have been associated with an increased risk of VA-AKI. [Antimicrob Agents Chemother 2013; 57:734–44.]. AUC/MIC is the pharmacokinetic parameter best correlated with the antibacterial activity of vancomycin, and AUC-guided dosing and monitoring has been shown to reduce risk of VA-AKI and improve patient outcomes [Antimicrob Agents Chemother 2018; 62: e02042-17]. As a result, consensus guidelines on the dosing and monitoring of vancomycin were updated in 2020 to recommend the use of AUC-guided dosing and monitoring over a trough-guided approach [Am J Health-Syst Pharm 2020; 77:835–64] A Bayesian approach using 2 pharmacokinetic samples is the preferred method for AUC-guided vancomycin dosing. Bayesian software does allow for model-informed precision dosing (MIPD) using a validated pharmacokinetic model in combination with patient-specific characteristics to design dosing regimens intended to achieve the recommended AUC/ MIC target of 400–600 mg/L × hour. Single serum concentrations may be obtained pre–steady state at any time point following vancomycin administration and pharmacokinetic distribution (i.e., during the pharmacokinetic elimination phase which occurs 1–2 hours after the end of the infusion until the next dose is administered). These advantages can allow for earlier dose optimization. Currently there is limited clinical data to support the use of single pre–steady state concentrations or single nontrough concentrations to facilitate AUC-guided vancomycin therapy. The investigators in this study demonstrated overall improved patient outcomes with AUC-guided therapy using Bayesian MIPD single-concentration monitoring compared with trough-guided therapy.

"The investigators in this study demonstrated overall improved patient outcomes with AUC-guided therapy using Bayesian MIPD single-concentration monitoring compared with trough-guided therapy."

Bayesian MIPD allows for vancomycin concentrations to be obtained at nearly any time point following administration and pharmacokinetic distribution. This enables orders for vancomycin concentrations to be obtained at times most

convenient for nursing, phlebotomy staff, and patients, such as during routine blood draws for other laboratory testing. In addition, single concentration monitoring offers additional convenience over 2-concentration monitoring as it avoids the need for extra blood draws and laboratory testing. However, this was a retrospective and single-center study design. Their study also included patients with non–S aureus infections as well as various types of infections (e.g., skin and soft tissue infections and bone and joint infections) where overall data for AUC-guided vancomycin therapy is limited. It should also be pointed out that a high, but similar, percentage of patients in each group received concurrent antimicrobial therapy at the time of vancomycin initiation. The study was not designed to evaluate the impact of concurrent antibiotic therapy on the outcomes assessed. Furthermore, the heterogeneity of clinical diagnoses included made it difficult to definitively assess treatment success or failure for some types of infection. This study did not compare 2-concentration AUC monitoring to single concentration MIPD.

Bottom line: Use of MIPD and single-concentration monitoring improved overall outcomes among patients receiving AUC-guided vancomycin for culture-proven gram-positive infections compared to patients receiving trough-guided therapy.

7

Measuring waning protection from seasonal influenza vaccination during nine influenza seasons, Ontario, Canada, 2010/11 to 2018/19

Eurosurveillance published February 22, 2024

The study objective was to evaluate influenza vaccine protection over time. They examined vaccinations during the 2010/11 to 2018/19 influenza seasons in Ontario, Canada, for all ages and any influenza types/subtypes, and stratified by age group, by age group and influenza type/subtype and by influenza season, in order to confirm and build on findings from previous studies.

They included laboratory results for respiratory specimens tested for influenza by PCR and defined each unique specimen collection day as a testing episode. They defined each influenza season as starting on 1 October and ending on 31 March to ensure consistent observation time. For cases, they included their first testing episode that was positive for influenza after vaccination to emulate the primary outcome of a time-to-event analysis if waning influenza vaccine protection was estimated using a cohort study design. For individuals without any positive testing episodes (i.e. controls), they included their first negative testing episode after vaccination. Both vaccination and the selected testing episode had to be within the same influenza season. They excluded individuals who tested positive for influenza by any method before vaccination within the same season. They ascertained physician- and pharmacist-administered influenza vaccinations from billing claims recorded in the Ontario Health Insurance Plan (OHIP) and the Ontario Drug Benefit (ODB) databases. The claim date was assumed to be the vaccination date. Current season vaccination was defined as a claim after 1 October of the index season, whereas prior season vaccination was a claim between 1 October and 31 August in the season before the index season. Individuals were fully vaccinated against influenza if they met age-based recommendations as of the index date (i.e. one dose for those ≥ 9 years; one dose for children aged 6 months to < 9 years who were vaccinated in any previous season; two doses ≥ 4 weeks apart for children aged 6 months to < 9 years who were first time influenza vaccine recipients). They excluded individuals: (i) who had more than one influenza vaccine in the same season (except first time recipients aged 6 months to < 9 years)

Criteria for individuals to be considered fully vaccinated against influenza

≥ 9 years	One dose
6 months to < 9 years (and vaccinated in any previous season)	One dose
6 months to < 9 years (and first time influenza vaccine recipients)	Two doses (≥ 4 weeks apart)

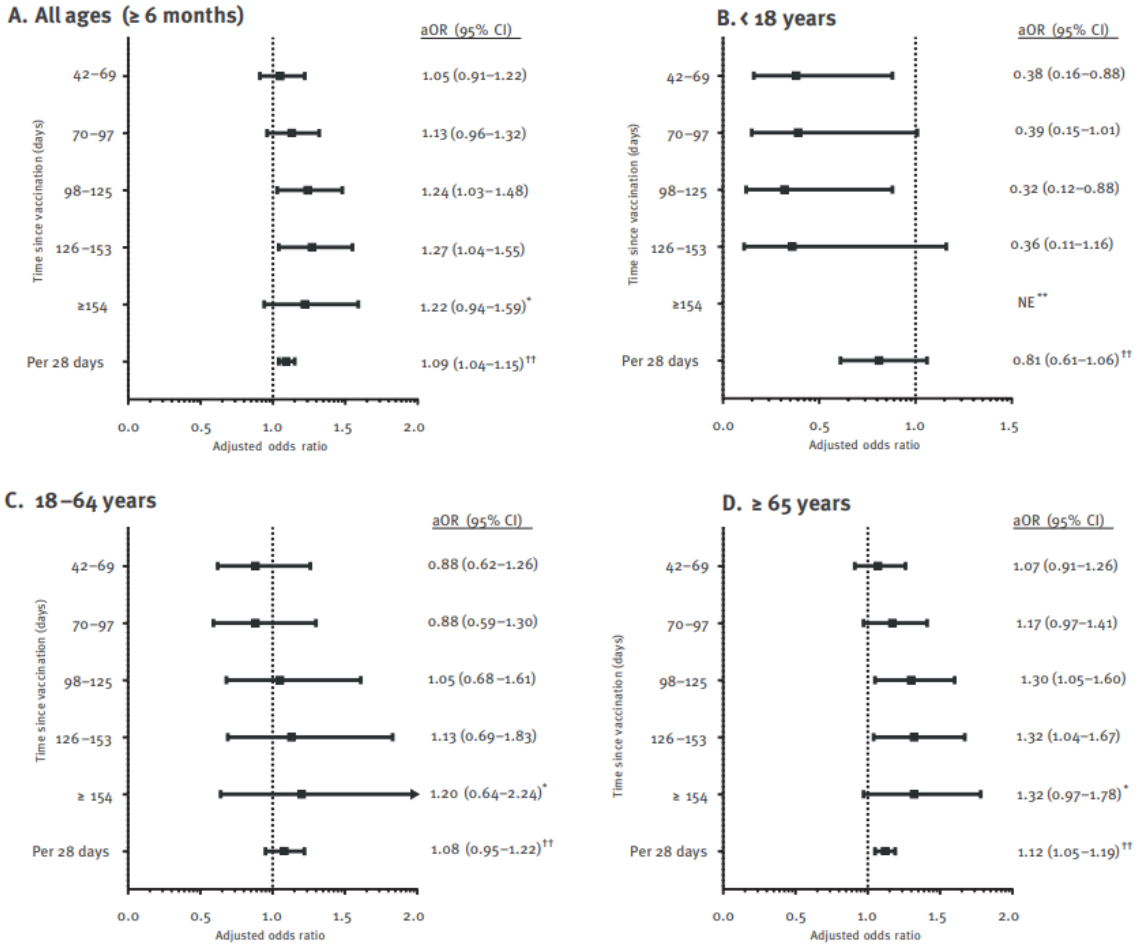
Excluded individuals:

1. who had more than one influenza vaccine in the same season (*except first time recipients aged 6 months to < 9 years*) since additional doses could impact antibody levels
2. who were first time recipients aged 6 months to < 9 years but only received one dose
3. who met the fully vaccinated definition < 14 days before the index date

since additional doses could impact antibody levels; (ii) who were first time recipients aged 6 months to < 9 years but only received one dose; and (iii) who met the fully vaccinated definition < 14 days before the index date. Time since vaccination was calculated as the number of days between the fully vaccinated and index dates, which they divided into intervals (14–41, 42–69, 70–97, 98–125, 126–153 and ≥ 154 days) and used this categorical variable as the main exposure in the analyses. They obtained age (categorized as 6 months to 17 years, 18–49, 50–64, 65–74, 75–84 and ≥ 85 years), sex (male/female), neighborhood income quintile, rurality and Public Health Unit (PHU) region from the Registered Persons Database as of index date. They also determined healthcare utilization (number of hospitalizations in the past 3 years, number of outpatient visits and prescription medications in the past year and receipt of home care services in the past year before index date) using the Canadian Institute for Health Information's Discharge Abstract Database, Home Care Database, OHIP and ODB databases.

Of 53,065 people who were vaccinated before testing, 10,264 (19%) tested positive for flu. The investigators determined that the odds of contracting influenza increased from 1.05 (95% confidence interval [CI], 0.91 to 1.22) at 42 to 69 days after vaccination, and peaked at 1.27 (95% CI, 1.04 to 1.55) at 126 to 153 days compared with the reference interval, which was 14 to 41 days after vaccination. This corresponds to a 5% to 27% drop in VE compared with shortly after vaccination. The investigators also determined that VE dropped 9% every 28 days—or a 1.09-times increased risk of influenza every 28 days (adjusted odds ratio [aOR], 1.09; 95% CI, 1.04 to 1.15). They did not, however, observe any VE waning in children. Adults 18 to 64 years showed the greatest decline in protection against the H1N1 strain (aOR per 28 days, 1.26; 95% CI, 0.97 to 1.64). For people 65 years and older, it was against the H3N2 strain (aOR per 28 days, 1.20; 95% CI, 1.08 to 1.33).

Adjusted odds ratios for any laboratory-confirmed influenza infection by time since seasonal influenza vaccination in community-dwelling individuals aged ≥ 6 months, Ontario, Canada, seasons 2010/11 to 2018/19



Dr. Septimus's Annotations

Intraseasonal declines in vaccine protection could arise from decreasing antibody levels after vaccination, which is impacted by age. Unlike Belongia et al., who found that young children aged 2 years had 1.20 times higher odds of influenza A(H3N2) every 14 days after vaccination [Vaccine. 2015; 33:246-51], this study did not observe that children and adolescents aged< 18 years had increased odds of influenza over time. This result is consistent with immunogenicity studies which found that children have persistent antibody responses after vaccination that last throughout an influenza season. [Vaccine. 2023; 41:4462-71] Like Belongia et al. this study also found that older adults had higher odds of influenza over time.

"Annual influenza vaccination programs need to strike the balance between vaccinating the population too early versus too late, while considering system vaccination capacity and year-to-year variability of influenza season timing."

This study had a few limitations. First the investigators used specimen collection dates instead of symptom onset dates (which were not available in their data) to calculate time since vaccination. Second, specimens used in this study are mostly collected in inpatient settings and the interpretation of the findings might be limited to severe outcomes. Third, they did not have antigenic characterization data to account for intraseasonal antigenic drift. They were also unable to account for vaccine type (TIV/QIV (including LAIV)) since this information is only available for individuals vaccinated in pharmacies (22% of their cohort). This limitation is particularly important for the 2017/18 season, which had a late influenza B Yamagata season while the TIV contained the Victoria lineage component.

Bottom line: Annual influenza vaccination programs need to strike the balance between vaccinating the population too early versus too late, while considering system vaccination capacity and year-to-year variability of influenza season timing. Protection declines during an influenza season may differ between different age groups and different influenza types/subtypes. Optimal timing of annual influenza vaccination may improve protection during epidemic waves.

8

Effect of pneumococcal conjugate vaccines on viral respiratory infections: a systematic literature review

J Infect Dis published online March 11, 2024
DOI: 10.1093/infdis/jiae125

This review was conducted by investigators with Pfizer and Belgian research company P95. They looked at observational and interventional studies published from 2000 through 2022 on the vaccine efficacy (VE) and overall effect of the PCV7, PCV9, PCV10, or PCV13 vaccines against viral RTIs. Given the synergistic interactions between viral and bacterial pathogens and the hypothesis that the effectiveness of PCVs against all-cause pneumonia might be linked to reduction of viral-associated pneumonia episodes, the investigators wanted to evaluate the evidence if PCV has impact against virus-related RTIs in children and adults.

Of the 16 studies that were included in the final analysis, 13 described the effects of PCVs against viral RTIs in children and 3 included data on adults. In children, data from 4 studies showed VE against influenza ranged from 41% to 86%, except for the 2010-2011 flu season, and a randomized controlled trial showed PCV9 demonstrated efficacy against human seasonal coronavirus, parainfluenza, and human metapneumovirus. In adults, PCV13 VE ranged from 4% to 25% against viral lower RTI, 32% to 35% against Covid-19 outcomes, 24% to 51% against human seasonal coronavirus, and 13% to 36% against influenza A lower RTI. They did not find any protection against adenovirus or rhinovirus in children or adults.

Dr. Septimus's Annotations

The study authors say the simplest explanation is that PCVs are preventing pneumococcal-viral coinfections. But they also suggest that the vaccines, by influencing pneumococcal carriage in the upper airway, may modify host susceptibility to viral lower RTIs.

Bottom line: PCVs were associated with protection against some viral RTI, with the strongest evidence for influenza in children. Limited evidence for adults was generally consistent with pediatric data. Further research is needed to confirm the findings and to further explore the clinical benefits and broader public health impacts of PCVs at a population level.

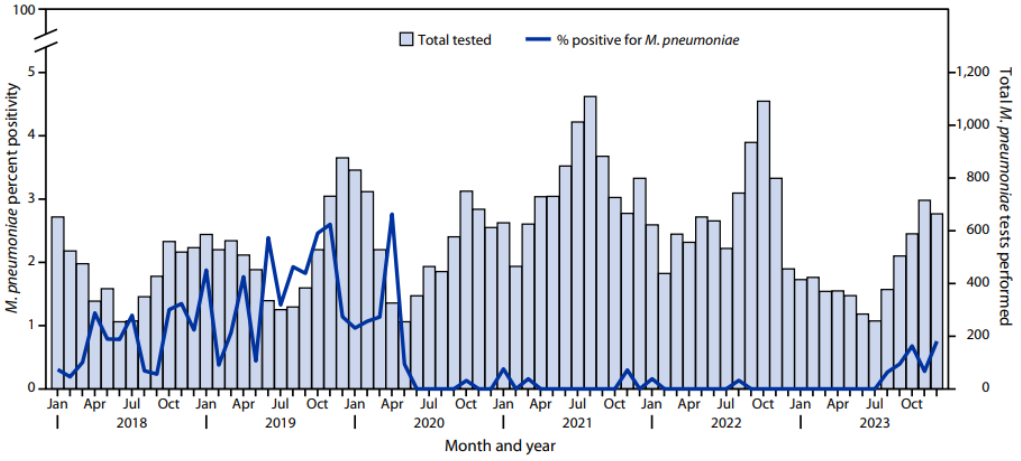
9

Reemergence of Mycoplasma pneumoniae Infections in Children and Adolescents After the COVID-19 Pandemic, United States, 2018–2024

MMWR 2024
73:149-151

Mycoplasma pneumoniae is a common cause of respiratory infections, particularly in school-aged children. After implementation of nonpharmaceutical interventions in response to Covid-19, the frequency of identified M. pneumoniae infections substantially declined beginning in 2020. This pattern was also observed for other respiratory pathogens. Beginning in the fall of 2023, China and other countries identified a reemergence of this bacterium [World J Pediatr 2024;20:1–4); Lancet Microbe. 2024 Nov 23:S2666–5247

Monthly number of Mycoplasma pneumoniae tests performed and percentage of positive test results among children and adolescents with acute respiratory illness, 2018–2023



Using data from CDC's National Syndromic Surveillance Program (NSSP), the percentage of M. pneumoniae–related diagnoses among all pneumonia emergency department visits were compared before, during, and after the Covid-19 pandemic. For this analysis, data from NSSP were restricted to ED visits by children and adolescents. Data from the New Vaccine Surveillance Network (NVSN) were also analyzed to compare the percentage of positive M. pneumoniae laboratory test results in the US during the same periods. During September 2023–January 2024, 14 M. pneumoniae–positive specimens collected at four NVSN sites were sent to CDC for molecular testing to identify common genetic changes that confer macrolide resistance. Three periods were defined and analyzed: January 2018–April 2020 (prepandemic period), May 2020–August 2023 (pandemic period), and September 2023–December 2023 (postpandemic period).

The percentage of M. pneumoniae–related diagnoses among pneumonia ED visits reported in NSSP decreased from 1.15% (4,681 of 407,514) during the prepandemic period to 0.35% (1,233 of 355,508) during the pandemic period and then increased to 0.89% (597 of 66,736) during the postpandemic period. Similarly, the percentage of test results within the NVSN network that were positive for M. pneumoniae decreased from 1.2% (165 of 13,800) during the prepandemic period to 0.04% (10 of 24,256) during the pandemic period and then increased to 0.53% (13 of 2,470) during the postpandemic period. Fourteen M. pneumoniae–positive specimens collected at four NVSN sites during September 2023–January 2024 were sent to CDC for macrolide resistance testing. Among 14 specimens, 13 were determined to be susceptible to macrolides.

Dr. Septimus's Annotations

Data collected by NSSP and NVSN demonstrate that the percentage of M. pneumoniae diagnoses and positive M. pneumoniae test results decreased during the Covid-19 pandemic. The percentage of diagnoses and positive test results have increased since September 2023 but remain below prepandemic levels. Significant cyclical increases in M. pneumoniae infections have been observed every 3–5 years. Among the small number of specimens available for testing, resistance to macrolides was uncommon. However, macrolide resistance varies globally, with the highest resistance prevalence (>90%) in Asia [World J Pediatr 2024;20:1–4].

Bottom line: Providers should consider M. pneumoniae during fall and winter respiratory illness seasons. Macrolides remain the first-line treatment for M. pneumoniae infections in the US, but ongoing surveillance is necessary.

Real-World Implications of Updated Surviving Sepsis Campaign Antibiotic Timing Recommendations

Crit Care Med published online February 23, 2024
DOI: 10.1097/CCM.0000000000006240

This was a retrospective cohort study involving 12 hospitals in the Southeastern US between 2017 and 2021. One hundred sixty-six thousand five hundred fifty-nine adult hospitalized patients treated in the ED for suspected serious infection were included. They determined the number and characteristics of patients affected by updated SSC recommendations for initiation of antibiotics that incorporate a risk- and probability-stratified approach. Using an infection prediction model with a cutoff of 0.5 to classify possible vs. probable infection, they found that 30% of the suspected infection cohort would be classified as shock absent, possible infection and thus eligible for the new 3-hour antibiotic recommendation. In real-world practice, this group had a conservative time to antibiotics (median, 5.5hr; interquartile range [IQR], 3.2–9.8hr) and low mortality (2%). Patients categorized as shock absent, probable infection had a median time to antibiotics of 3.2 hours (IQR, 2.1–5.1hr) and mortality of 3%. Patients categorized as shock present, the probable infection had a median time to antibiotics 2.7 hours (IQR, 1.7–4.6hr) and mortality of 17%, and patients categorized as shock present, the possible infection had a median time to antibiotics 6.9 hours (IQR, 3.5–16.3hr) and mortality of 12%.

2021 Surviving Sepsis Campaign (SSC) Guidelines for Antibiotic Timing

Sepsis is **definite or probable** and shock is **present**	Administer antimicrobials **immediately**, ideally **within 1 hour** of recognition.
Sepsis is **definite or probable** and shock is **absent**	Administer antimicrobials **immediately**, ideally **within 1 hour** of recognition.
Sepsis is **possible** and shock is **present**	Administer antimicrobials **immediately**, ideally **within 1 hour** of recognition.
Sepsis is **possible** and shock is **absent**	• Rapid assessment of infectious vs. noninfectious causesof acute illness. • Administer antimicrobials **within 3 hours** if concern for infection persists.

Source: Society of Critical Care Medicine

Dr. Septimus's Annotations

The 2021 Surviving Sepsis Campaign (SSC) Guidelines for Management of Sepsis and Septic Shock includes updated recommendations for initiation of antibiotics that incorporate a risk- (shock present vs. shock absent) and probability- (high, intermediate, or low likelihood of sepsis) stratified approach to decision making. [Crit Care Med 2021; 49: e1063–e1143] The updated SSC recommends 1-hour

antibiotic timing targets for patients with shock regardless of infection probability and for patients without shock who have high likelihood of sepsis. A 3-hour timing target is suggested for patients without shock who have only possible infection (i.e., intermediate likelihood), and it is recommended to defer antibiotics while continuing close monitoring of patients without shock who have low likelihood of infection. The emphasis of this new recommendation is the goal of preventing antibiotic overuse in patients with low risk of infection not in shock. They applied an internally derived infection probability model to categorize probable vs. possible infection that represents only one of multiple acceptable approaches. They also used the infection criterion of the CDC ASE (adult sepsis event) definition as the outcome definition for infection because of its demonstrated validity and widespread use. [JAMA 2017; 318:1241–1249] There are limitations of evaluating observational data and many suggest that changes to sepsis treatment strategies be guided by randomized controlled trial data where possible. This study supports the IDSA Sepsis Position Paper which recommended removing sepsis without shock from SEP-1 to mitigate the risk of unnecessary antibiotic prescribing for noninfectious syndromes and focus attention on the population most likely to benefit from immediate empiric broad-spectrum antibiotics. [Clin Infect Dis 2021; 72:541–552]

Bottom line: Applying a 3-hour antibiotic target to suspected infection patients without shock and with an intermediate to low likelihood of infection appears to be a safe approach that would impact a substantial number of patients.

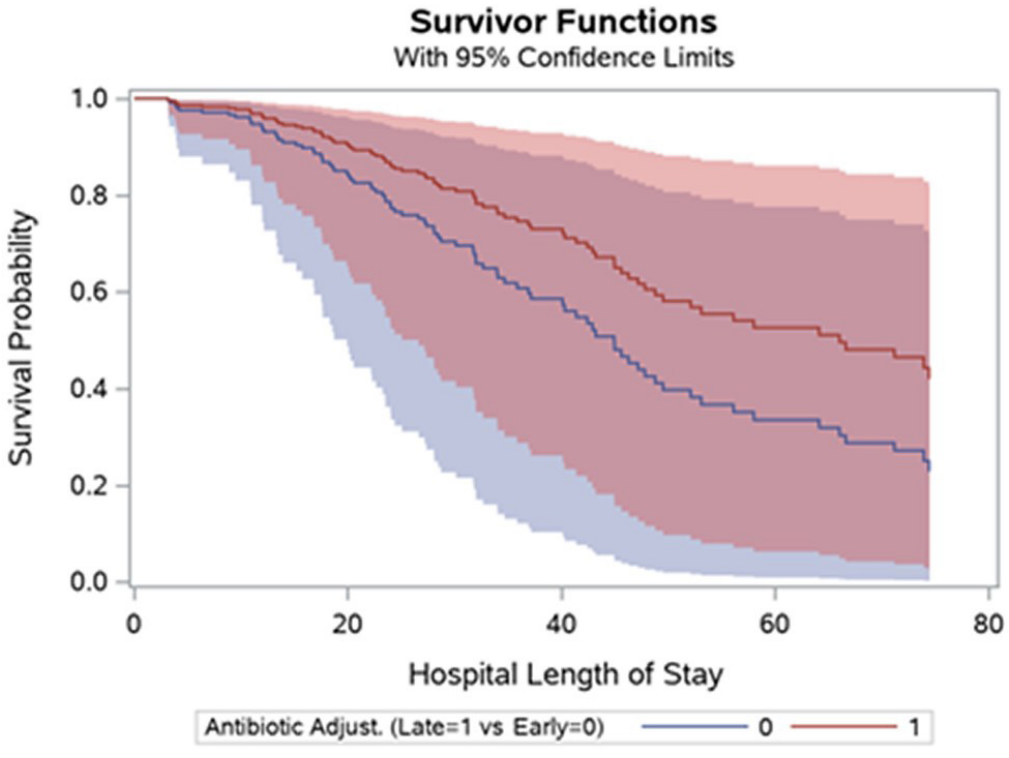
11

Early versus Late Antipseudomonal β-Lactam Antibiotic Dose Adjustment in Critically Ill Sepsis Patients with Acute Kidney Injury: A Prospective Observational Cohort Study

OFID published online February 1, 2024
doi.org/10.1093/ofid/ofae059

Patients with sepsis often present with acute kidney injury that typically resolves over the course of hospitalization, raising a question as to whether initial dosing of antimicrobial therapy should be adjusted to reflect decreased renal function in an otherwise hyperdynamic state. The purpose of this study was to provide insight with regard to outcomes when antipseudomonal β-lactams are dose-adjusted initially versus later in hospitalization.

This was a prospective observational study. Investigators at four hospitals observed whether adult patients with sepsis associated with acute kidney injury (defined as an increase in serum creatinine at least 1.5-fold from baseline) received, after an initial full dose of an antipseudomonal β-lactam, dose reduction to reflect decreased renal function within the first 24 hours of sepsis recognition versus dose reduction after 24 hours.

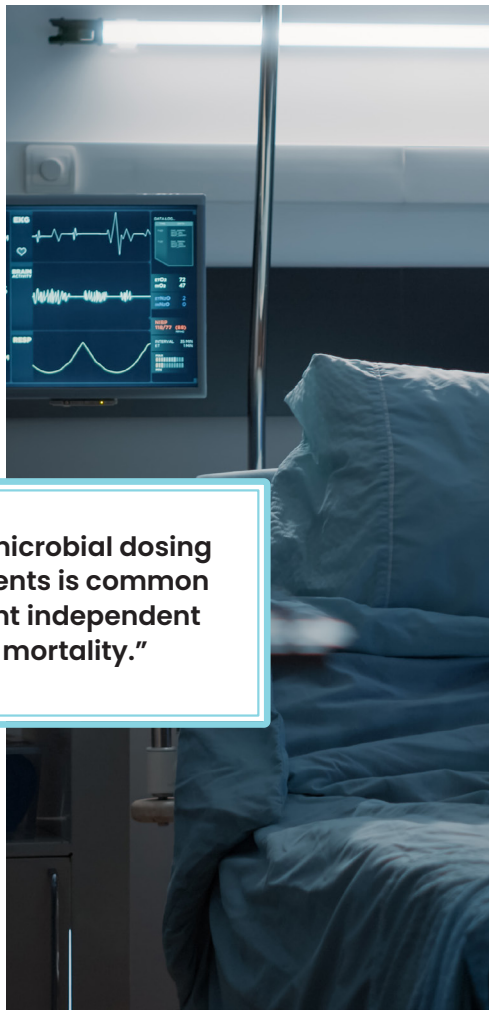


Eighty-four patients were in the early dose adjustment group, and 140 were in the late dose adjustment group; 55% overall received piperacillin-tazobactam as their antipseudomonal β-lactam. Approximately half of the

cohort presented with AKI stage II. Mean age of the cohort was 63 years, 62% were male, and pneumonia was the documented source of infection in 51%. Patients with end-stage renal disease or those who required renal replacement therapy during hospitalization were excluded. In a multivariable model, late adjustment was associated with a significant reduction in in-hospital mortality within 90 days (hazard ratio, 0.588; 95% confidence interval, 0.355-0.974). The late adjustment group also had a higher rate of renal recovery at 48 hours and 7 days (possibly due to lower severity of illness at baseline).

Dr. Septimus's Annotations

Early initiation of adequate antimicrobial therapy can reduce sepsis-related mortality. Adequate empirical antimicrobial therapy involves the use of an agent that exhibits in vitro activity against target pathogens and administered at doses capable of reaching pharmacodynamic targets in vivo. It has been observed that patients with septic shock who develop AKI within 24 hours of hypotension onset are more likely to experience longer delays of 1.7 hours in receiving antimicrobial therapy than septic shock patients without AKI. [Intensive Care Med 2009; :871–881] A meta-analysis reported increased odds of mortality associated with inadequate therapy during the first 48 hours of treatment [Antimicrob Agents Chemother 2010; 54:4851–4863] On the other hand, the 2016 and 2021 survival sepsis campaign (SSC) guidelines stated that antimicrobial therapy should always be started with a total high-end-loading dose and recommended optimizing antimicrobial dosage strategies based on accepted PK/PD principles. [Intensive Care Med 2021; 47:1181–1247] Septic patients are initially in a hyperdynamic state, which may lead to increased antibiotic clearance and alterations in volume of distribution following resuscitation. Their hypothesis was in septic patients with AKI, administration of the initial empiric β-lactam in full (not renally adjusted) doses for > 24 hours after sepsis recognition would reduce mortality in comparison with the administration of full doses for less than 24 hours. Critically ill patients admitted with sepsis and AKI are likely to have a higher risk of hospital mortality. Several studies have described the link between inappropriate initial antimicrobial therapy and mortality in sepsis patients admitted to the ICU. [J Intensive Care Med 2016; 31:164–176] Inadequate antimicrobial dosing in critically ill patients is common and is a significant independent risk factor for mortality. They did not evaluate the patients' fluid resuscitation condition and its influence on outcomes such as kidney injury and mortality. Additionally, β-lactam administration in their study was performed by intermittent infusion. Although some benefits of extended and continuous infusion of some β-lactams (piperacillin/tazobactam) have been reported previously. [Antimicrob Agents Chemother 2014; 58:4470–4475] Lastly, patients in the L-BLA group had more transient AKI with a higher length of stay, which could be explained by the less severity of illness of this group at baseline leading to lower mortality and longer ICU and hospital length of stay. Thus, the result of the association between the timing of β-lactam dose adjustment and secondary patient outcome could be affected by the presence of some group differences at baseline.



"Inadequate antimicrobial dosing in critically ill patients is common and is a significant independent risk factor for mortality."

Bottom line: While this study is limited by its observational nature and weaknesses described, it nonetheless underscores the importance of adequate dosing of antipseudomonal β-lactams in patients with potentially severe infections, even in the setting of acute kidney injury that is often transitory.

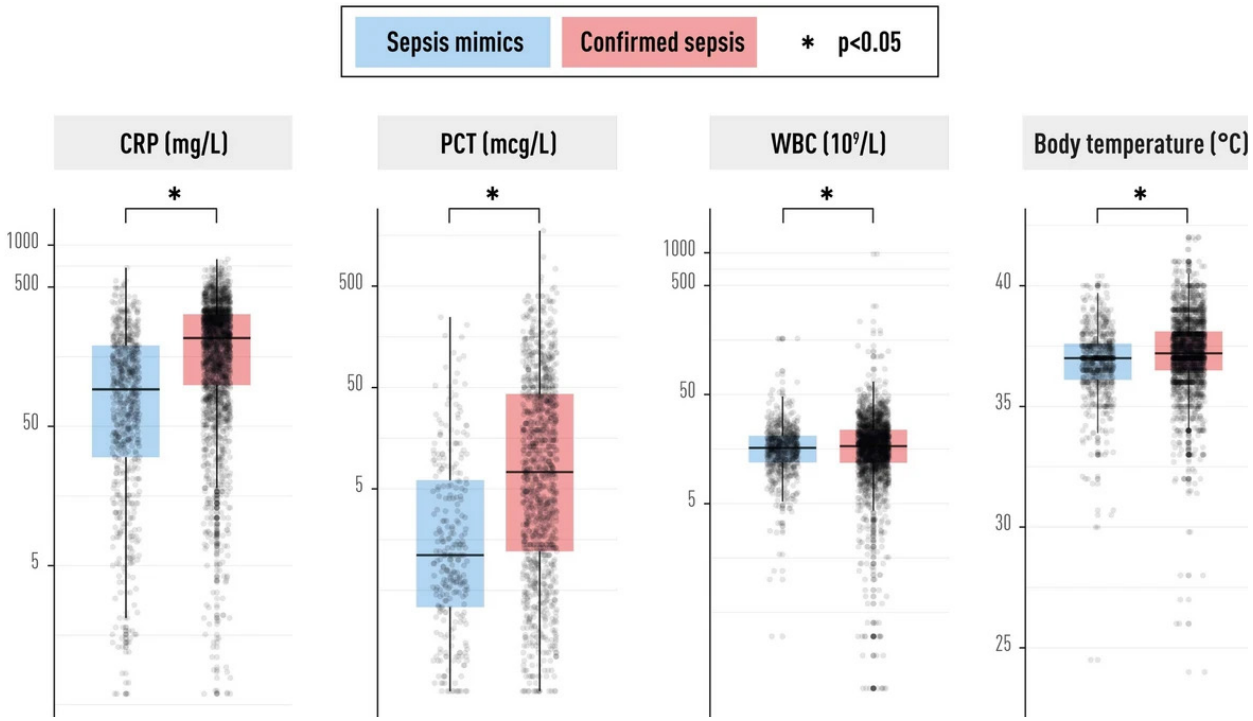
12

Sepsis mimics among presumed sepsis patients at intensive care admission: a retrospective observational study

Infection published online January 27, 2024
doi.org/10.1007/s15010-023-02158-w

Criteria for diagnosing sepsis have been updated several times since first proposed by Bone et al in 1992. The current Sepsis-3 definition is primarily based on criteria for life-threatening organ dysfunction caused by a dysregulated host response to infection, [JAMA 2016; 315:801]; however, criteria for identifying presence of an infection are not included. Because rapid and accurate diagnosis of infection is challenging, misclassification of patients admitted to the ICU with organ dysfunction and presumed sepsis may occur if an initially suspected infectious process is not present (they call "sepsis mimics").

In a retrospective observational study conducted in four general ICUs between 2015 and 2018, investigators sought to estimate the frequency of sepsis mimics. Of 8360 ICU admissions, 2664 met sepsis 3.0 criteria. Applying updated criteria for infection to the 1122 of those that were culture negative, 656 (25%) were eventually labeled as sepsis mimics. Sensitivity analysis using different criteria for infection yielded sepsis mimics rates between 14% and 29%. Mortality did not differ between patients with confirmed sepsis and sepsis mimics, but the former had slightly higher disease severity. Procalcitonin and C-reactive protein levels showed only modest discriminative power between the two groups.



Dr. Septimus's Annotations

One-fourth of a presumed ICU sepsis population identified with the sepsis-3 criteria could be considered sepsis mimics. This was a retrospective analysis which has inherit limitations especially since only culture-negative cases were analyzed. However, this study and others highlight the challenge of identifying true infections. The ability to discriminate between confirmed sepsis and all nonsepsis in the ICU was modest. CRP and PCT had better discriminatory power than

WBC and temperature. Neither had a high sensitivity to be acceptable as decision support to withhold antibiotics. In a study published last year, the investigators compared outcomes in patients with culture-negative serious infection (CNSI) treated with 3 or 4 vs ≥5 days of antibiotics. [OFID published online May 23, 2023] Early discontinuation of antibiotics in CNSI was not associated with significant harm in their primary analysis. Sepsis mimic rate was even higher by culture negative infection at 44% in that study. Patients are frequently hospitalized with CNSI, yet there are few data to inform their duration of antibiotics. There are also limitations in this study too, but it is suggestive that rapid investigations to rule out other diagnoses might represent yet another opportunity to decrease overuse of broad-spectrum antibiotics.

"Early discontinuation of antibiotics in CNSI was not associated with significant harm in their primary analysis."

Bottom line: The weak ability of frequently used clinical tests to identify confirmed sepsis in a presumed sepsis cohort prompts the need for more precise biomarkers or combinations of biomarkers for diagnostic purposes. Antimicrobial stewardship interventions, such as de-escalation and early discontinuation of antibiotics, are important in decreasing unnecessary antimicrobial therapy to decrease selection of resistant organisms and risk of C difficile infections.

13

Outcomes of Ceftriaxone Compared With Cefazolin or Nafcillin/Oxacillin for Outpatient Therapy for Methicillin-Sensitive Staphylococcus aureus Bloodstream Infections: Results From a Large United States Claims Database

OFID published online January 12, 2024
doi.org/10.1093/ofid/ofad662

In this retrospective cohort, a large insurance claims database was queried from 2010 to 2018 for adults with MSSA bloodstream infection (BSI). Patients discharged on OPAT on cefazolin or oxacillin/nafcillin were compared with ceftriaxone with respect to 90-day hospital readmission with the same infection category and 90-day all-cause readmission using logistic regression models.

Of 1895 patients with MSSA BSI, 1435 (75.7%) patients received cefazolin, oxacillin, or nafcillin and 460 (24.3%) cefazolin patients. Readmission due to the same infection category occurred in 366 (19.3%), and all-cause readmission occurred in 535 (28.3%) within 90 days. Risk factors significantly associated with readmission with the same infection category were the oldest sampled age group (61–64 years: adjusted odds ratio [aOR], 1.47 [95% confidence interval {CI}, 1.01–2.14]), intensive care unit stay during index admission (aOR, 2.33 [95% CI, 1.81–3.01]), prosthetic joint infection (aOR, 1.96 [95% CI, 1.18–2.23]), central line–associated BSI (aOR, 1.72 [95% CI, 1.33–2.94]), and endocarditis (aOR, 1.63 [95% CI, 1.18–2.23]). Ceftriaxone was not associated with increased risk of readmission with the same infection category (aOR, 0.89 [95% CI, .67–1.18]), or 90-day all-cause readmission (aOR, 0.86 [95% CI, .66–1.10]) when compared with oxacillin/nafcillin/cefazolin.

Dr. Septimus's Annotations

In this cohort of MSSA BSI patients discharged on OPAT, there were no differences in outcomes of readmission with the same infection and 90-day all-cause readmission in patients treated with ceftriaxone compared to oxacillin/nafcillin or cefazolin. However, patients with complicated BSIs such as endocarditis and epidural abscess were more likely to be prescribed cefazolin or oxacillin/nafcillin. Other studies have demonstrated that ceftriaxone may not be as effective as cefazolin for complex S aureus BSIs.

Bottom line: For patients with complicated S aureus BSIs, I still prefer cefazolin or oxacillin/nafcillin over ceftriaxone.

14

Propensity Score-Weighted Analysis of Postoperative Infection in Patients With and Without Preoperative Urine Culture

JAMA Netw Open 2024; 7(3):e240900
doi:10.1001/jamanetworkopen.2024.0900

This was a cohort study which analyzed surgical procedures performed from January 1, 2017, to December 31, 2019, at any of 112 US Department of Veterans Affairs (VA) medical centers. The cohort comprised VA enrollees who underwent major elective noncardiac, nonurological operations. Machine learning and inverse probability of treatment weighting (IPTW) were used to balance the characteristics between those who did and did not undergo a urine culture. Data analyses were performed between January 2023 and January 2024. The 2 main outcomes were UTI and SSI occurring within 30 days after surgery.

A total of 250,389 VA enrollees who underwent 288,858 surgical procedures were included, with 88.9% (256,753) of surgical procedures received by males and 48.9% (141,340) received by patients 65 years or older. Baseline characteristics were well balanced among treatment groups after applying IPTW weights. Preoperative urine culture was performed for 10.5% of surgical procedures (30,384). The IPTW analysis found that preoperative urine culture was not associated with SSI (adjusted OR [AOR], 0.99; 95% CI, 0.90-1.10) or postoperative UTI (AOR, 1.18; 95% CI, 0.98-1.40). In analyses limited to orthopedic surgery and neurosurgery as a proxy for prosthetic implants, the adjusted risks for UTI and SSI were also not associated with preoperative urine culture performance.

Balanced study population	Independent factor	Postoperative outcome	AOR (95% CI)
All eligible surgical procedures	30-d Preoperative urine culture performed vs not performed	SSI	0.99 (0.90 - 1.10)
		UTI	1.18 (0.98 - 1.40)
Orthopedic and neurosurgery	30-d Preoperative urine culture performed vs not performed	SSI	0.93 (0.76 - 1.12)
		UTI	1.27 (0.97 - 1.65)

Dr. Septimus's Annotations

The 2019 IDSA clinical practice guidelines recommend against testing for and treating ASB in all patients undergoing nonurological surgical procedures. [Clin Infect Dis. 2019;68(10): e83-e110] The untoward outcomes of unnecessary urine culture are well-described in the literature. [Clin Orthop Relat Res. 2013;471 (12):3822-3829] When ASB is identified, almost 75% of patients get antibiotics.[Clin Infect Dis. 2017;65(6):910-917] Clinical trials of antibiotic treatment vs no treatment of ASB primarily in nonsurgical populations have found more harm than benefit. [Cochrane Database Syst Rev. 2015;4(4)] Additionally, previous work focusing on cardiac, vascular, and orthopedic surgical procedures reported that preoperative ASB was not associated with lower postoperative risk of infection, even when accounting for antibiotics. [JAMA Surg. 2019;154(3):241-248] Despite controlling for a multitude of variables in the propensity score estimation, it is possible that residual confounding introduced bias into the regression estimates. The absolute number of females evaluated in the study was small (32 105 [11.1%]) compared with males, making subgroup analysis by sex impossible. In the neurosurgery and orthopedic surgery cohort, patient outcomes were not obtained beyond 30 days although the CDC definitions allows 90 days of follow-up for infections after procedures with implants.

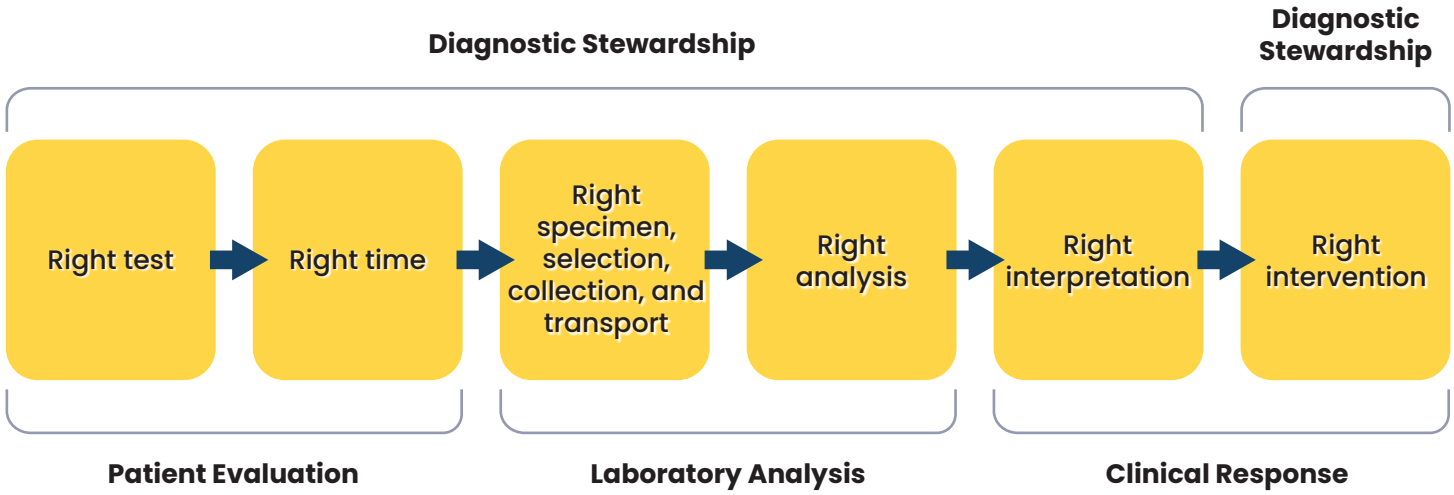
Bottom line: This cohort study found no association between performance of a preoperative urine culture and lower risk of postoperative UTI or SSI. The results support routine screening preoperative urines should not be performed even when using prosthetic implants.

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)

Clin Infect Dis published online March 5, 2024
DOI: 10.1093/cid/ciae104

This publication is an update to the 2013 guide. To provide that level of quality and accurate results, the laboratory requires that all microbiology specimens be properly and carefully selected, collected, and transported to optimize analysis and interpretation. Because accurate result interpretation in microbiology depends entirely on the quality of the specimen submitted for analysis, specimen management is essential to optimize results. Microbiology specimen selection and collection are the responsibility of the medical staff.

Antibiotic stewardship and diagnostic stewardship are interdependent, and the laboratory plays a pivotal role in each of those activities. Diagnostic stewardship leads to the appropriate use of laboratory testing to guide clinical intervention and therapeutics in order to optimize patient outcomes and limit the spread of antimicrobial resistance (which is addressed by antibiotic stewardship). The importance and interdependence of antibiotics and diagnostic stewardship are shown in Figure below



Below are highlights of specimen management and diagnosis of common clinical syndromes.

- Specimens of poor quality must be rejected.
- Full identification of multiple organisms (>3) within a mixed culture is not recommended.
- Commensal microbiota unrelated to the disease process must be avoided where possible during specimen collection- sites such as lower respiratory tract (sputum), nasal sinuses, superficial wounds, fistulae, and others that contain large numbers of normal microbiota require care in collection and interpretation.
- The laboratory needs a specimen, not a swab of a specimen-if a swab is necessary flocked swabs [i.e. E-test] have become a valuable tool for specimen collection and have been shown to be more effective than Dacron, rayon, and cotton wrapped swabs.
- When possible, a specimen should be collected prior to administration of antibiotics.
- Susceptibility testing should be done only on clinically significant isolates, not necessarily on all microorganisms recovered in culture.

- Specimens must be labeled accurately and completely so that interpretation of results will be reliable.
- **Blood cultures**
    i. For adults, 20-30 ml of blood per culture set is recommended and may require inoculation of more than two culture bottles depending on the system. Both aerobic and anaerobic bottles should be inoculated. For children, an age- and weight- appropriate volume of blood should be cultured. Volume of blood collected, not timing, is most critical.
    ii. Should be collected by separate venipunctures.
    iii. Recommend peripheral venipuncture as the preferred technique for obtaining blood for culture based on data showing that blood obtained in this fashion is less likely to be contaminated than blood obtained from an intravascular catheter (see next bullet)
    iv. Diagnosis of catheter-associated BSIs
        – Standard blood cultures (BCs), one from the catheter or port and one from peripheral venipuncture, processed in a continuous-monitoring blood culture system. If both BCs grow the same organism and the BC drawn from the device becomes positive more than 2 h before the BC drawn by venipuncture, there is a high probability of catheter-associated BSI.
- **Diagnosis of SSTIs**
    i. A swab is not the optimal choice for these specimens. Submit tissue, fluid, aspirate when possible.
    ii. The specimen of choice is a firm sample of the advancing margin of the wound/lesion, not just the surface of the wound/lesion.
    iii. When submitting tissue or biopsies for culture, also request histopathology analysis.
    iv. For the common forms of SSTIs, cultures are not indicated for uncomplicated infections (cellulitis, subcutaneous abscesses) treated in the outpatient setting.
- **Lab Diagnosis of lower respiratory infections**
    i. NAATs have largely replaced rapid antigen tests and culture for respiratory virus detection.
    ii. When collecting sputum for bacterial culture, obtaining first morning expectorated sputum is recommended.
    iii. Multiplex molecular pneumonia syndromic panels, when used judiciously, may provide earlier opportunity for therapeutic optimization than traditional cultures.
    iv. In the immunocompromised host, a broad diagnostic approach based upon invasively obtained specimens is suggested.
    v. Culture and Gram stain of good quality samples of expectorated sputum, when available, should be obtained for patients requiring hospitalization. Culture and Gram stain of good quality samples of expectorated sputum, when available, should be obtained for patients requiring hospitalization.
    vi. Urinary antigen tests for S. pneumoniae and L. pneumophila, where available, should be considered for patients with severe CAP.
    vii. Laboratories must have a mechanism in place for screening sputum samples for acceptability (to exclude those that are heavily contaminated with oropharyngeal microbiota and not representative of deeply expectorated samples) prior to setting up routine bacterial culture.
- **Diagnosis of GI Infection**
    I. Fecal testing for causes of infectious gastroenteritis using culture or culture independent methods is indicated for patients with moderate to severe, bloody, febrile, dysenteric, nosocomial, or persistent diarrheal illnesses or immunocompromised patients. Routine testing for other than C. difficile is often restricted to patients who have been hospitalized more than 3 days.
    II. Culture independent multiplex molecular tests are reported to be more sensitive than culture, result in higher rates of detection, and often cost more than culture methods.
    III. Toxin or nucleic acid amplification testing for C. difficile should only be done on diarrheal stool.
- **Urinary Tract Infection**
    i. In the absence of signs and symptoms consistent with urinary tract infection, a urine culture is typically not recommended.
    ii. Urine collected for culture should not be kept at room temperature for more than 30 minutes. Hold at refrigerator temperatures or utilize a preservative tube if not processed by the laboratory within 30 minutes.

iii. Reflexing to culture based on a positive pyuria screen may be considered.

- **Laboratory diagnosis of bone and joint infections**
  i. Swabs are not recommended for specimen collection, with synovial fluid and/or tissue biopsies being recommended.
  ii. Blood cultures are indicated for detection of some agents of osteomyelitis and native joint infection, but usually not for periprosthetic joint infection diagnosis.
  iii. Joint fluids should ideally be cultured in aerobic and (specimen volume permitting) anaerobic blood culture bottles.
  iv. For periprosthetic joint infection diagnosis, 3-4 separate tissue samples should be submitted for aerobic and anaerobic culture; sonication of explanted prostheses followed by semi-quantitative aerobic and anaerobic culture of the resultant sonicate fluid may be used to detect pathogens.
  v. Some agents of bone and joint infection are non-culturable or poorly culturable and require molecular and/or serologic methods for detection.


Clinical Infectious Diseases

IDSA GUIDELINES

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)

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1

DOI: 10.1093/cid/ciae104

[Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases]

Dr. Septimus's Annotations

This is a terrific reference. It is 244 pages with 496 references. The guideline covers infections including bloodstream/cardiovascular, intraabdominal infections, CNS infections, SSTI, bone and joint infections, ocular infections, arthropod borne infections, genital infections, parasitic infections, infections of the head and neck, and viral syndromes.

Bottom line: Worth reviewing and keeping for future reference. The guidance from this document should form the basis for better diagnostic stewardship.

16

Diagnostic Stewardship in Community-Acquired Pneumonia With Syndromic Molecular Testing A Randomized Clinical Trial

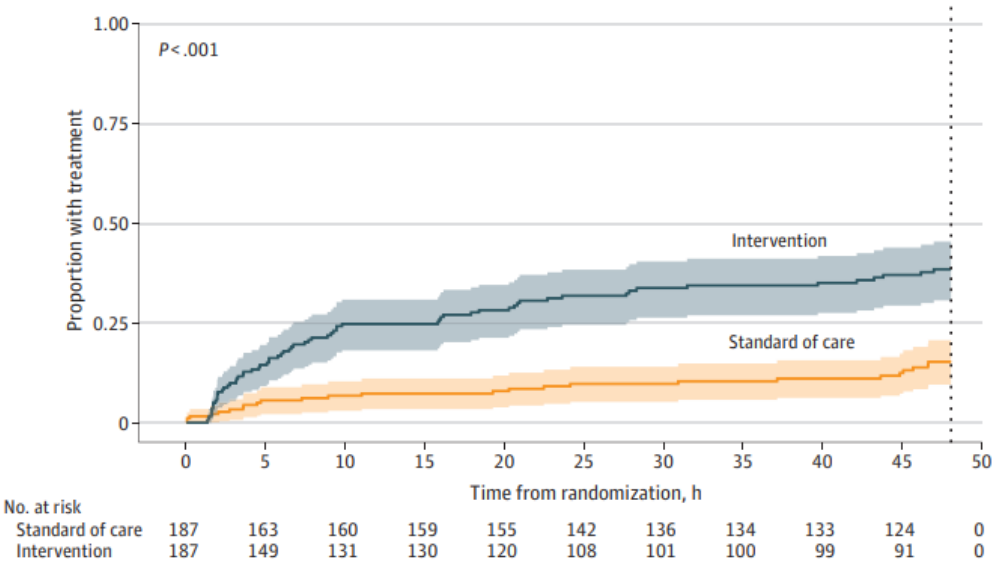
JAMA Network Open. 2024; 7(3):e240830
doi:10.1001/jamanetworkopen.2024.0830

The investigators set out to determine whether the use of a syndromic PCR-based panel for rapid testing of CAP in the ED leads to faster, more accurate microbiological test result–based treatment. To answer this question, they performed a parallel-arm, single-blinded, single-center, randomized clinical superiority trial conducted between September 25, 2020, and June 21, 2022, in the ED in a large tertiary care hospital in Norway. Adult patients who presented to the ED with suspected CAP were recruited. Participants were randomized 1:1 to either the intervention arm or standard-of-care arm. The primary outcomes were analyzed according to the intention-to-treat principle. Patients randomized to the intervention arm received rapid syndromic PCR testing (BioFire FilmArray Pneumonia plus Panel) of LRT samples and standard of care (SOC). Patients randomized to the standard-of-care arm received standard microbiological diagnostics alone. SOC methods included blood cultures, pneumococcal urine test, and an in-house PCR test for oropharyngeal and/or nasopharyngeal swabs targeting respiratory viruses and atypical bacteria (i.e., influenza A and B viruses, human parainfluenza viruses 1-3, respiratory syncytial virus, human metapneumovirus, rhinovirus, coronavirus [229E, OC43, HKU1, NL63], Bordetella pertussis, Bordetella

parapertussis, Mycoplasma pneumoniae, and Chlamydophilia pneumoniae). At admission, all patients were tested for SARS-CoV-2 infection using oropharyngeal or nasopharyngeal swabs tested on the GeneXpert system. The LRT samples were collected in the ED, primarily through sputum induction, using nebulized isotonic (0.9%) or hypertonic (5.8%) saline. Endotracheal aspiration was performed in case of an unsuccessful sputum induction and in patients with SARS-CoV-2 infection. Decisions to continue, switch, or discontinue antimicrobial treatment were at the discretion of the treating physician alone.

There were 374 patients (221 males [59.1%]; median (IQR) age, 72 [60-79] years) included in the trial, with 187 in each treatment arm. Analysis of primary outcomes showed that 66 patients (35.3%) in the intervention arm and 25 (13.4%) in the standard-of-care arm received pathogen directed treatment, corresponding to a reduction in absolute risk of 21.9 (95% CI, 13.5-30.3) percentage points and an odds ratio for the intervention arm of 3.53 (95% CI, 2.13-6.02; P < .001). The median (IQR) time to provision of pathogen-directed treatment within 48 hours was 34.5 (31.6- 37.3) hours in the intervention arm and 43.8 (42.0-45.6) hours in the SOC (mean difference, −9.4 hours; 95% CI, −12.7 to −6.0 hours; P < .001). The corresponding hazard ratio for intervention compared with standard of care was 3.08 (95% CI, 1.95-4.89). Findings remained significant after adjustment for season.

Kaplan-Meier Curve of the Proportion of Patients Receiving Pathogen-Directed Treatment



▪▪▪▪▪ The dotted line at 48 hours indicated the censoring threshold for the primary outcome of time to pathogen-directed treatment.

Patients randomized to the intervention arm received

1. Rapid syndromic PCR testing (BioFire FilmArray Pneumonia plus Panel) of LRT samples
2. Standard-of-care (SOC)

Patients randomized to the standard-of-care arm received

1. Standard microbiological diagnostics alone

Standard-of-care (SOC) includes

- Blood cultures
- Pneumococcal urine test
- In-house PCR test for oropharyngeal and/or nasopharyngeal swabs targeting respiratory viruses and atypical bacteria

The intervention arm compared with SOC arm had a higher number of bacterial detections (175 vs 72) and viral detections (74 vs 63). When considering only the patients with confirmed CAP, the intervention arm maintained a higher total number of bacterial (113 vs 57) and viral (39 vs 34) detections than the standard-of-care arm. The 3 most common bacterial pathogens were H influenzae, S aureus, and S pneumoniae. The 3 most common viral pathogens were SARS-CoV-2, RSV, and rhinovirus.

Dr. Septimus's Annotations

To my knowledge, this trial was the first to examine the effect of a rapid syndromic PCR pneumonia panel applied specifically to patients hospitalized with CAP. Most previous studies did not use a comprehensive syndromic PCR panel or included patients only after admission, potentially limiting the advantages of rapid molecular testing. The intervention

led to a reduction (by 9.4 hours) in the median time without provision of pathogen-directed treatment within the first 48 hours after randomization, compared with standard of care. For patients with CAP, the median turnaround time (from admission to receiving an LRT test result without restriction to 48 hours) was reduced by much more (53.8 hours) for the intervention vs standard-of-care group. A faster microbiological diagnosis allows for directed therapy, which has been shown in previous studies to improve outcomes, limit antibiotic overuse, and prevent antimicrobial resistance. [Eur Respir J. 2016;48(6):1764-1778] Despite crowded conditions at the ED, a FAP plus PCR test result was delivered within 4 hours for patients with CAP. More patients in the intervention arm than in the SOC arm had an escalation from narrow spectrum to broad-spectrum antibiotics. This escalation could raise concerns about antibiotic overuse; however, it is important to emphasize that Norway has a low level of antibiotic resistance, and guidelines recommend using narrow-spectrum antibiotics. Per the guidelines, empirical treatment is benzylpenicillin for mild to moderate CAP and benzylpenicillin and gentamicin for severe CAP. Treatment with narrow-spectrum antibiotics for respiratory tract infections is common practice in Norway, leaving little room for de-escalation, and even change from penicillin G to a more broad-spectrum penicillin (e.g., ampicillin) was considered to be an escalation. This is very different from the ATS/IDSA guidelines. [Am J Respir Crit Care Med 200: e45–e67] This was a single center study. The use of syndromic panels and timely results may not be possible in most facilities, especially with lab consolidations and formation of regional labs. In addition, these panels are expensive and in the average facility without a molecular lab, these panels may not be cost effective with longer turn around times..

"A faster microbiological diagnosis allows for directed therapy, which has been shown in previous studies to improve outcomes, limit antibiotic overuse, and prevent antimicrobial resistance."

Bottom line: Findings from this trial showed that routine deployment of PCR testing for lower respiratory tract pathogens can enable faster and more targeted microbial treatment for patients with suspected CAP, suggesting that this tool could replace selected standard, time-consuming, laboratory-based diagnostics.

17

Clinical Outcomes of Rapid Respiratory Virus Testing in Emergency Departments A Systematic Review and Meta-Analysis

JAMA Intern Med published online March 4, 2024
doi:10.1001/jamainternmed.2024.0037

Since rapid tests for respiratory viruses, including multiplex panels, are increasingly available in EDs, the authors set out to determine the impact on patient outcomes. They developed an electronic search strategy in collaboration with a medical librarian and searched Ovid MEDLINE, Embase (Ovid), Scopus, and Web of Science Core Collection for studies published from 1985 to November 14, 2022. They selected RCTs of patients of any age with acute respiratory illness (ARI) in an ED. The primary intervention was rapid viral testing. Antibiotic use and secondary outcomes were pooled separately as risk ratios (RRs) and risk difference estimates with 95% CIs.

Of 7157 studies identified, 11 (0.2%; n = 6068 patients) were included in pooled analyses. Routine rapid viral testing was not associated with antibiotic use (RR, 0.99; 95% CI, 0.93-1.05; high certainty) but was associated with higher use of influenza antivirals (RR, 1.33; 95% CI, 1.02-1.75; moderate certainty) and lower use of chest radiography (RR, 0.88; 95% CI, 0.79-0.98; moderate certainty) and blood tests (RR, 0.81; 95% CI, 0.69-0.97; moderate certainty). There was no association with urine testing (RR, 0.95; 95% CI, 0.77-1.17; low certainty), ED length of stay (0 hours; 95% CI, -0.17 to 0.16; moderate certainty), return visits (RR, 0.93; 95%, CI 0.79-1.08; moderate certainty) or hospitalization (RR, 1.01; 95% CI, 0.95-1.08; high certainty). Adults represented only 963 participants (16%). There was no association of viral testing with antibiotic use in any prespecified subgroup by age, test method, publication date, number of viral targets, risk of bias, or industry funding.

Dr. Septimus's Annotations

In this systematic review and meta-analysis of 11 RCTs, rapid viral testing was not associated with reduced antibiotic use, ED length of stay, and the rate of ED return visits or of hospitalization. However, rapid viral testing was associated with moderately increased influenza antiviral use (absolute risk difference 1%) and decreased use of chest radiography and blood tests (absolute risk difference, 3%-4% each). It should be noted that all of the studies included in this systematic review and meta-analysis were conducted before the start of Covid-19 pandemic, and only 16% of the population were adults. This study shows that while there is some utility in using rapid monoplex tests to detect influenza virus, however, evidence to use rapid multiplex tests to detect multiple viruses remains unclear. These results align with those from previous systematic reviews which examined the effect of respiratory virus (RV) testing in ambulatory care among studies published to 2017 which also noted no association with antibiotic treatment among RCTs, but more antiviral use and fewer chest radiographs and blood tests. [Clin Infect Dis. 2019; 69:24-33] A 2023 systematic review and meta-analysis focused on the association of multiplex panels in adults, mainly among hospitalized patients. Among RCTs in inpatients, there was no change in antibiotic prescriptions and a nonsignificant trend to shorter antibiotic duration. These RCTs found improved appropriateness of antiviral treatment and improved infection control practices, but no change in hospital length of stay. [J Infect. 2023; 86:462-475]

Bottom line: Overall, the results of this systematic review and meta-analysis suggest that the benefits of routine RV testing in the ED are limited. There is a pressing need to build high-quality evidence to identify at-risk populations for whom these tests are most informative to impact care, and at the same time be cost effective.

Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHA in cooperation with the ASM

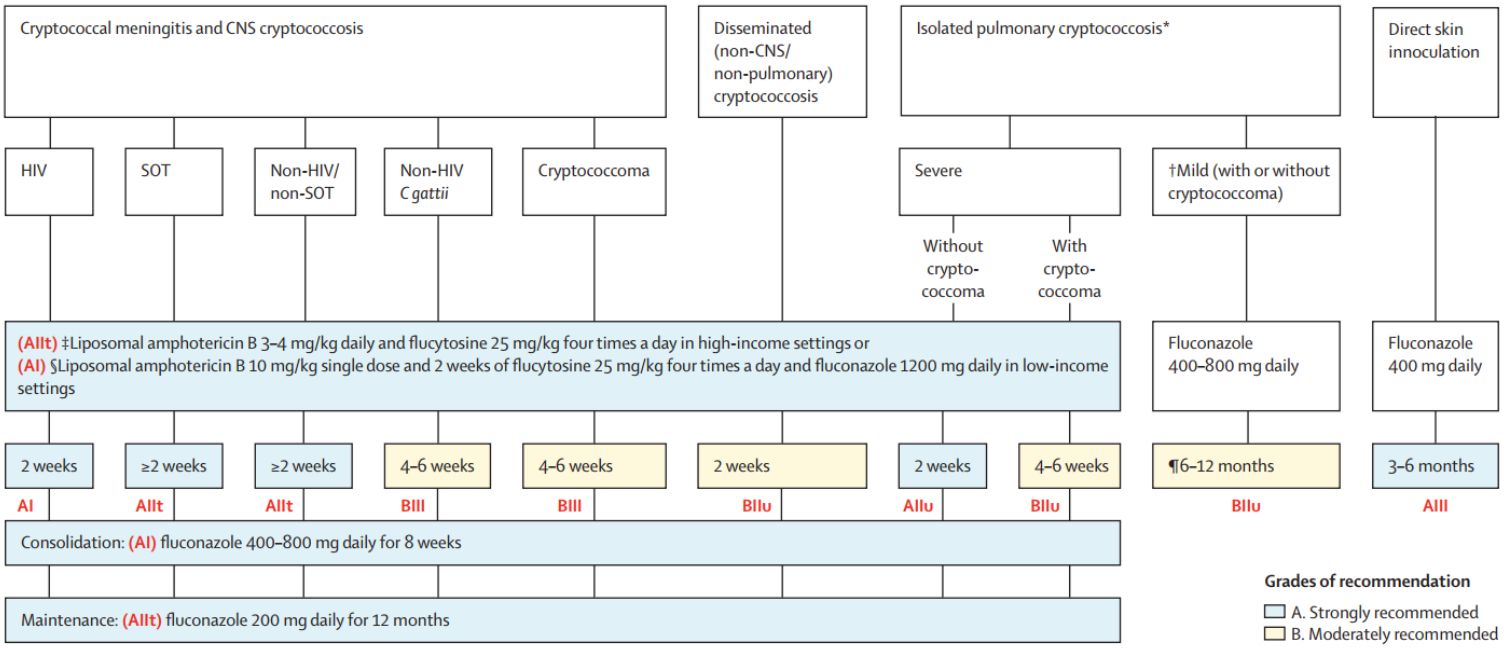
Lancet Infect Dis 2024 Published Online February 9, 2024
doi.org/10.1016/ S1473-3099(23)00731-4

Key Points and Recommendations

- The various phases and anatomical sites of cryptococcal infection affect antifungal therapy differently.
- Liposomal amphotericin B (3–4 mg/kg daily) plus flucytosine (25 mg/kg four times daily) is the best induction regimen for cryptococcal meningitis and other forms of severe disease.
- In resource-limited settings, liposomal amphotericin B (10 mg/kg once) followed by flucytosine and fluconazole is appropriate.
- Regiments should remain optimized and not change needlessly.
- Expect and monitor for clinical relapse and investigate thoroughly for causality; review adherence to antifungal therapy and consider drug–drug interactions; during treatment follow-up, do not escalate antifungal therapy for persistent blood antigenemia (blood cryptococcal antigen), persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry, as they are not necessarily indicators of microbiological failure.
- Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis. Acute symptomatic elevation of the intracranial pressure (≥20 cm of CSF) should be managed by daily therapeutic lumbar punctures (i.e., removal of sufficient CSF, usually around 20–30 mL) to reduce the pressure to 50% of opening pressure or to a normal pressure of ≤20 cm of CSF (documented as closing pressure).

- Immediate or very early commencement of ART is not recommended. Wait at least 4-6 weeks.
- These recommendations should be adapted to local practices.

Figures summarize all recommended first-line therapies for cryptococcosis, present an algorithm for management of cryptococcal meningitis, and show antifungal options for induction therapy for meningitis as well as therapy for those with HIV infection. They also indicate populations at risk, diagnostic methods, recommendations for screening, prophylactic and preemptive therapy, the 10 principles of meningitis management, and recommendations for managing cryptococcomas and nonmeningeal disease. See figure below



Dr. Septimus's Annotations

This is a thoughtful and comprehensive review regarding the diagnosis and treatment of cryptococcal disease. This publication combines other guidelines and is an excellent reference. The figures are very useful.

Bottom line: Cryptococcosis and its management can be complex and challenging. Adherence to clinical practice guidelines can improve outcomes. Although there has been substantial development of evidence over the past 20 years, there are considerable unmet needs.

19

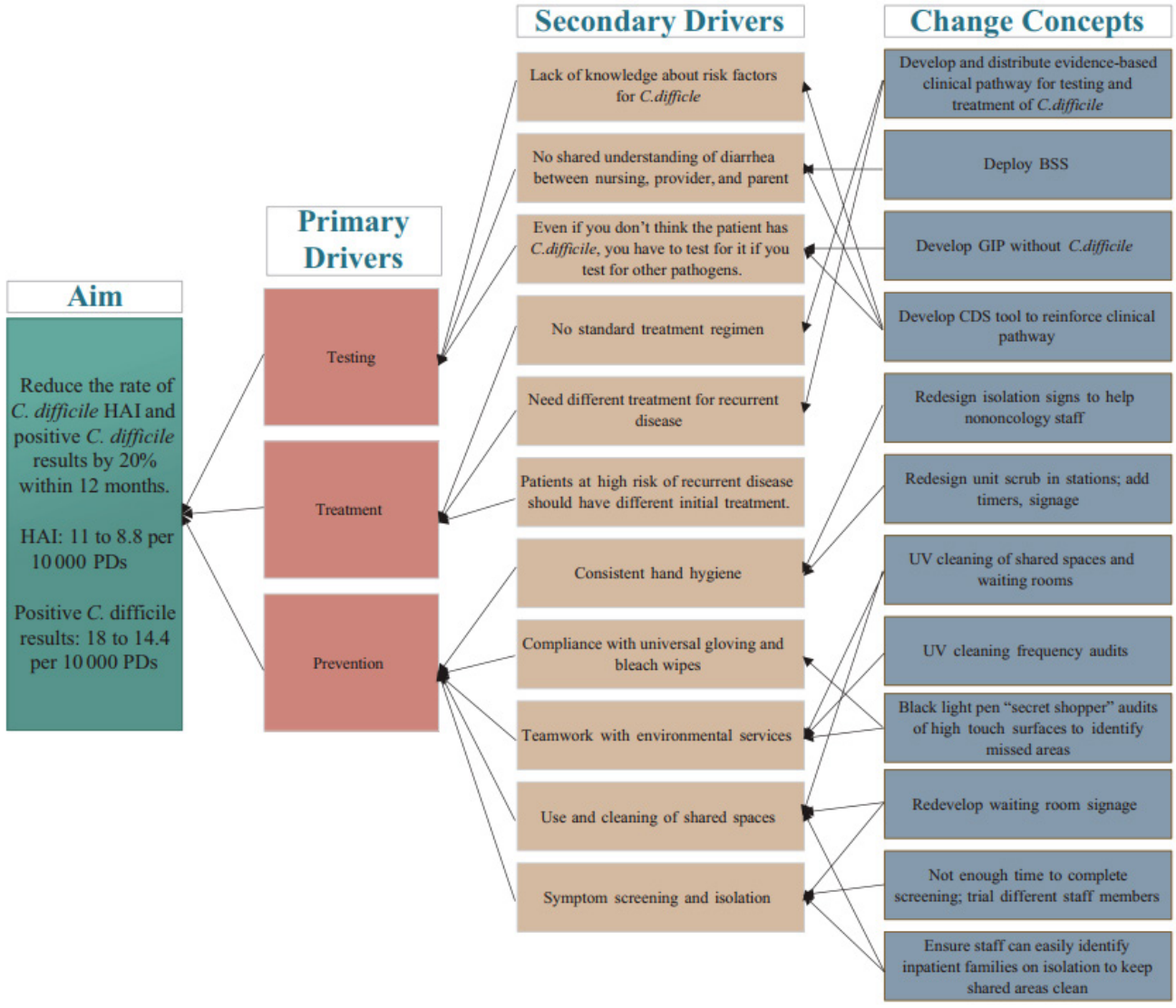
A Multimodal Intervention to Reduce C. difficile Infections and Stool Testing

Pediatrics 2024; 153(3):e2023061981
doi:10.1001/jamainternmed.2024.0037

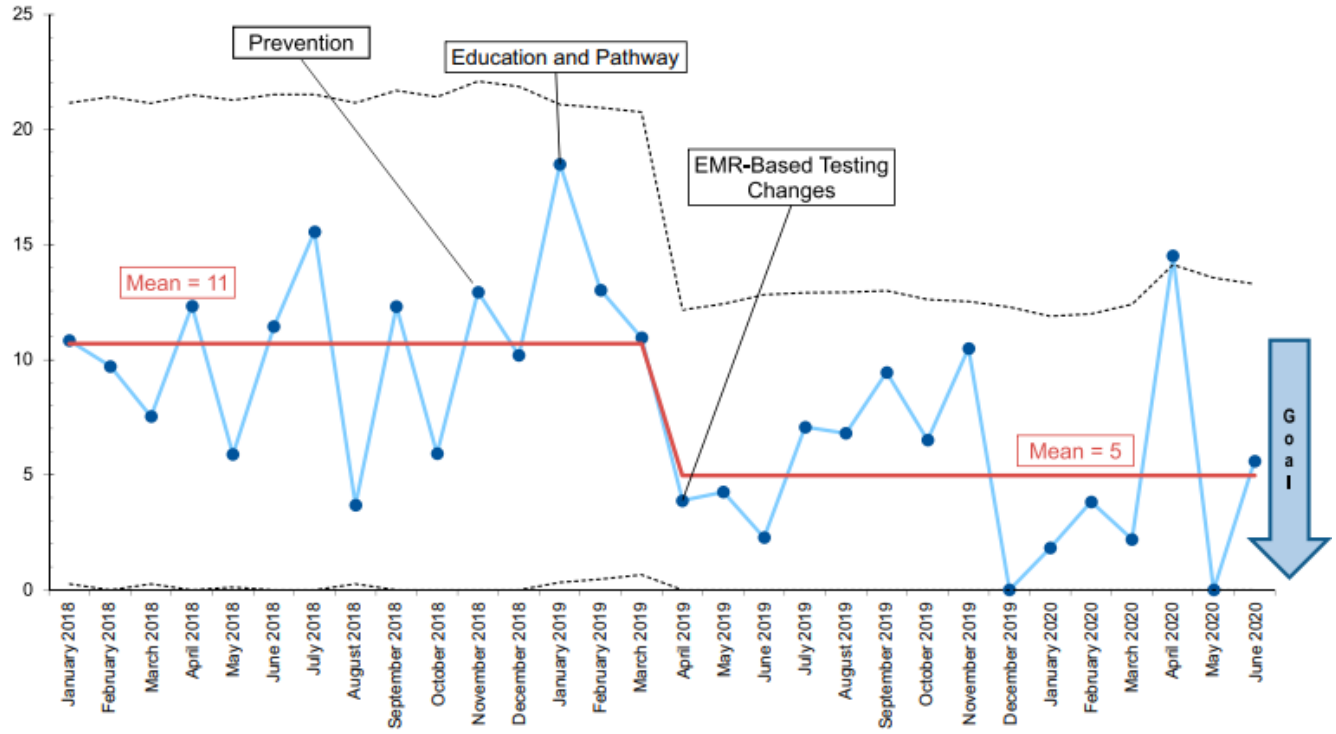
The investigators conducted a quality improvement project from 2018 to 2020 at a large children's hospital. Interventions included development of a C. difficile testing and treatment clinical care pathway, new options for GI panel testing with or without C. difficile, clinical decision support tool to restrict testing, and targeted prevention efforts. Outcomes included the rate of HO-CDI (primary), C. difficile detection, and overall stool testing. All measures were evaluated monthly among hospitalized children per 10 000 patient-days (PDs) using statistical process-control charts. For balancing measures, they

tracked suppressed C. difficile results that were released during real-time monitoring because of concern for true infection and C. difficile-related adverse events.

The authors observed a rising rates of CDI at their institution around the same time, in part, because of increased testing with GI panels resulting in increased C. difficile detection and misclassification of colonization as CDI. Testing options for C. difficile included a singleplex PCR assay (Xpert C. difficile, Cepheid, and a GI syndromic panel. (FilmArray, BioFire). To address inappropriate testing related to inappropriate identification of diarrhea, we disseminated an objective definition of diarrhea using a pediatric version of the Bristol stool scale(BSS). Diarrhea was defined as >3 occurrences of Bristol 6 or 7 stool in 24 hours. Nurses began documenting BSS for each stool occurrence in the EMR. They also developed a new test: GI panel without C. difficile, where the laboratory ran the full panel but did not report C. difficile results. Four restricted testing of any kind for children with: (1) no diarrhea defined using the BSS, (2) recent laxative use in previous 24 hours, (3) positive GI panel in preceding 14 days, or (4) negative GIP panel in preceding 7 days. Two rules restricted certain types of testing: (a) no GI panel testing for children hospitalized for >96 hours (recommend C. difficile PCR), and (b) no testing for C. difficile in infants <1 year old. They also increased prevention efforts especially on the oncology unit. See figure below.



HO-CDI decreased by 55%, from 11 to 5 per 10 000 PDs. C. difficile detection decreased by 44%, from 18 to 10 per 10 000 PDs, and overall test utilization decreased by 29%, from 99 to 70 per 10 000 PDs. The decrease in stool tests resulted in annual savings of $55 649. Only 2.3% of initially suppressed positive C. difficile results were released, and no patients had adverse events.



Dr. Septimus's Annotations

Diagnosing CDI, which requires symptoms and a positive test, is challenging in children because of high rates of asymptomatic colonization and the inability of tests to distinguish colonization from infection.[Pediatr Infect Dis J. 2009;28:145–146] Because GI panels test for C. difficile simultaneously with other, more common causes of gastroenteritis, there is a increased risk of detecting colonization, particularly if pretest probability for CDI is low. In this study the combination of a clinical decision support (CDS) tool, clinical pathway, and focused prevention efforts resulted in meaningful decreases in HO-CDI. CDS tools have been used to improve guideline implementation by presenting clinicians with information instantaneously, improving accuracy, and optimizing order efficiency. An important feature of their tool was the optional human override with specialist approval, which allowed for individual patient variation and improves cultural acceptance. They were unable to quantify orders abandoned after clinicians saw restriction alerts; thus, they likely underestimated the impact of their interventions. Restrictions may have resulted in missed cases of CDI.

Bottom line: Diagnostic stewardship strategies, coupled with an evidence-based clinical care pathway, can be used to decrease C. difficile and improve overall test utilization.

20

FDA advisers recommend trivalent flu vaccines for upcoming season

The FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) in a recent meeting noted that the Yamagata influenza B lineage hasn't been detected since March 2020, and evidence suggests it no longer poses a public health threat. The vote was to on a return to trivalent (three-strain) vaccines follows its discussions in October 2023 about whether quadrivalent (four-strain) vaccines were still needed. In September 2023, the WHO flu vaccine advisers recommended a switch back to trivalent flu vaccines.

Bottom line: This decision is supported by the evidence.

21

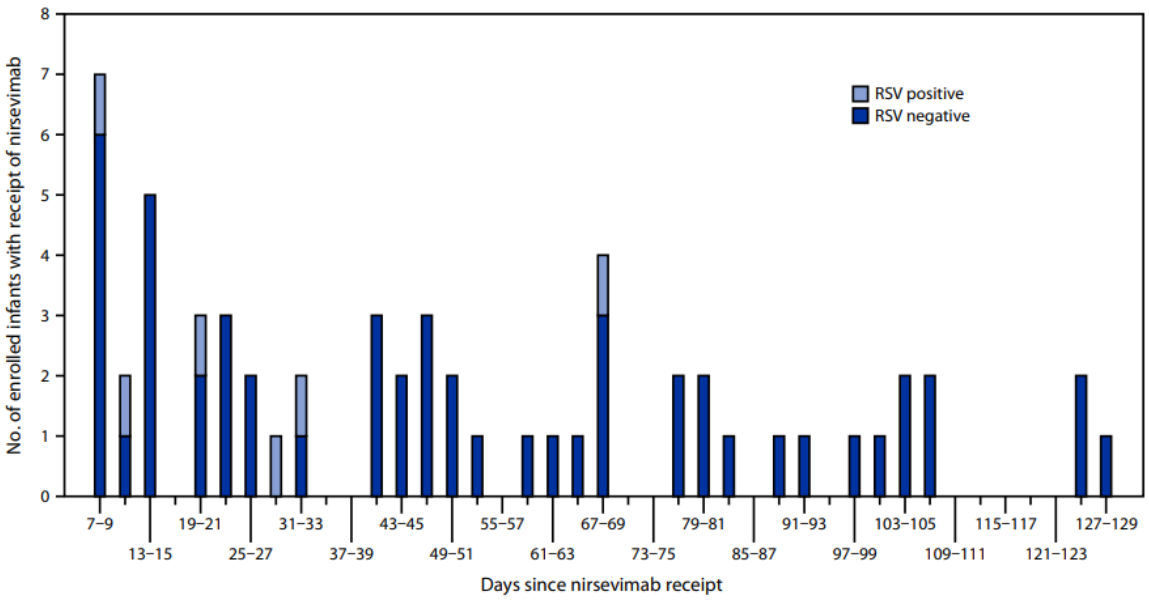
Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus–Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season — New Vaccine Surveillance Network, October 2023–February 2024

MMWR; 73:209-214

The investigators, who monitor pediatric respiratory viruses at seven US pediatric medical centers, collected demographic, clinical, and immunization data on infants hospitalized for RSV from parent interviews, medical records, and state immunization records and obtained respiratory samples for testing from October 2023 to February 2024. The study used a test-negative, case-control design. Pooled data from prelicensure RCTs showed that one dose of nirsevimab (a long-acting monoclonal antibody) given before 8 months of age was 79% effective against medically attended RSV infection and 81% effective against related hospitalization for 150 days after receipt.

Among the 699 infants hospitalized for respiratory disease at one of four sites, 407 (58%) were diagnosed as having RSV, and 292 (42%) were control patients. A total of 6 (1%) RSV patients and 53 (18%) controls were given nirsevimab 7 or more days before symptom onset. Nirsevimab was 90% effective (95% confidence interval, 75% to 96%) against RSV-related hospitalization, with a median time from receipt to symptom onset of 45 days.

Time from receipt of nirsevimab to symptom onset among infants born during or entering their first respiratory syncytial virus season who were hospitalized with acute respiratory illness, by respiratory syncytial virus test result, Oct 2023 - Feb 2024



Dr. Septimus's Annotations

In August 2023, the CDC recommended nirsevimab to protect infants younger than 8 months and children up to 19 months at increased risk for severe RSV, the leading cause of hospitalization of US infants. A maternal RSV vaccine, RSVpreF (Abrysvo) also became available to help protect infants. Owing to nirsevimab shortages this past RSV season, the number of infants given the drug was too low to stratify by protection over the entire season. The investigators cautioned that the

results may not be fully generalizable to all infants eligible for nirsevimab because infants with high-risk medical conditions were more likely than their healthy counterparts to receive the drug.

Bottom line: Nirsevimab was highly effective against RSV-associated hospitalization in infants entering their first RSV season. This finding supports current CDC recommendations that all infants should be protected by maternal RSV vaccination or infant receipt of nirsevimab, to reduce the risk for RSV-associated hospitalization.

22

CDC limits ordering of tetanus-diphtheria vaccine as it braces for shortage

The tetanus and diphtheria (Td) vaccine is expected to be in short supply throughout the year after one of the two suppliers to the US discontinued production leaving only Sanofi's Tenivac on the market.

To conserve available supplies of Tenivac, the CDC has implemented temporary ordering limits. While supplies of the diphtheria, tetanus, and pertussis (Tdap) vaccines (Sanofi's Adacel and GSK's Boostrix) aren't limited, they are more expensive, and a very small fraction of patients can develop encephalopathy from the pertussis component.

The CDC recommends that healthcare providers use Tdap vaccine rather than Td vaccine in patients without a pertussis vaccine contraindication. CDC said that Tdap can also be substituted when a tetanus booster is needed for wound management. Td and Tdap vaccines are given during childhood and then every 10 years or when needed for tetanus prevention after severe or contaminated wounds or burns.

Dr. Septimus's Annotations

The Td vaccine shortage comes on the heels of a recent and ongoing US shortage of the new respiratory syncytial virus (RSV) monoclonal antibody injection for infants. These shortages emphasize the importance of assuring multiple sources for key vaccines and antibiotics.

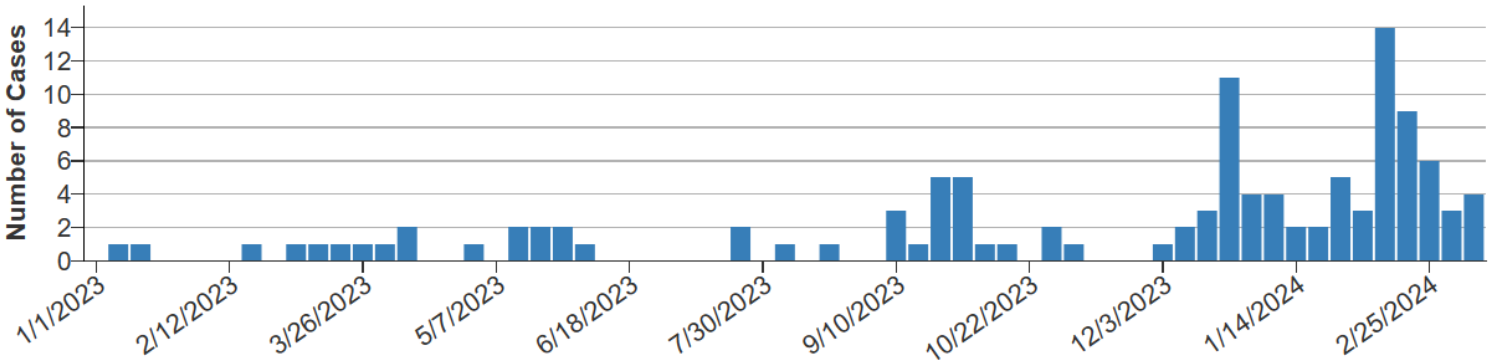
23

CDC Measles Cases and Outbreaks in 2024

March 14, 2024

As of March 14, 2024, a total of 58 measles cases were reported by 17 jurisdictions:

- Arizona
- California
- Florida
- Georgia
- Illinois
- Indiana
- Louisiana
- Maryland
- Michigan
- Minnesota
- Missouri
- New Jersey
- New York City
- Ohio
- Pennsylvania
- Virginia
- Washington



Dr. Septimus's Annotations

Fifty-eight cases of measles have been reported in the first quarter of 2024, the same number of total cases in 2023. This is probably the result of two factors: (1) increase in the number of travelers who get measles abroad and bring it into the US[migrant shelters] and (2) further spread of measles in U.S. communities with pockets of unvaccinated people.

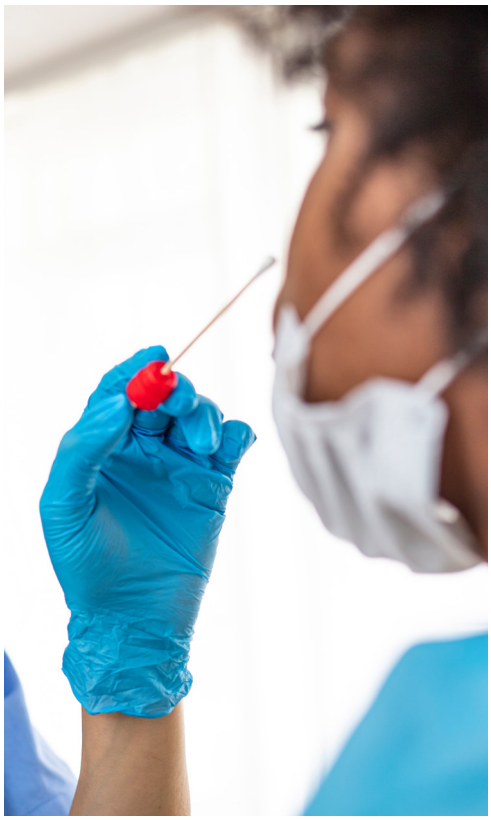
Bottom line: We are seeing a significant increase in measles cases. The best prevention is vaccination.

24

Persistence in risk and effect of COVID-19 vaccination on long-term health consequences after SARS-CoV-2 infection

Nat Comm published online February 26, 2024
doi.org/10.1038/s41467-024-45953-1

The investigators conducted symptom follow-up surveillance on 1,175,277 patients with a confirmed SARS-CoV-2 test. Of those, 124,443, 101,379, 457,896, and 491,559 patients were unvaccinated, had 1, 2, and 3 or more doses of Covid-19 vaccine prior to infection, respectively. All participants tested positive from April 1, 2020, to October 31, 2022, and were matched to uninfected controls without a positive SARS- CoV-2 test record throughout the study period. All study participants were followed for up to 1 year after infection, and clinical symptoms were noted.



Completely vaccinated and patients with booster dose of vaccines did not see significantly higher risk of health consequences from 271 and 91 days of infection onwards, respectively. Unvaccinated and incompletely vaccinated patients, however, continued to have a greater risk of clinical symptoms (sequelae) for up to a year following SARS-CoV-2 infection.

Unvaccinated participants with SARS-CoV-2 infections had the greatest risk of all observed clinical sequelae, including major cardiovascular diseases (hazard ratio [HR], 4.64, 95% confidence interval, 4.00 to 5.38). Participants with 1 dose had an HR of cardiovascular disease of 3.13, those receiving 2 doses had a 2.53 HR, and 3 or more doses were associated with an HR of 1.99. The risk of all-cause mortality was most significant between the unvaccinated and vaccinated,

with almost a fivefold reduction in risk of all-cause mortality between unvaccinated patients (HR, 18.89) and patients with complete vaccination (HR, 3.95) during the acute phase of infection. The risk of all-cause mortality dropped even further among patients with a booster dose of vaccine (HR, 1.74).

After the first 30 days following infection, risk of death continued to be significantly lower for those fully vaccinated and boosted against Covid-19, with participants who received three or more doses of vaccines not incurring any significant risk of clinical sequelae from 91 days onward from their initial infection.

Dr. Septimus's Annotations

This study examined the risk of long-term health consequences of SARS-CoV-2 infection involving multiple organ systems between patients with a history of SARS-CoV-2 infection and non-infected controls over the course of a year. The findings of this study showed a reduction in the risk of most clinical sequelae over the course of the observation window suggesting the gradual reduction of the risk of long-term health consequences over a year. The uptake of the booster dose was found to have additional effect in reducing the risk of health consequences. Patients who received three or more doses of vaccines did not have any significant risk increased in clinical sequelae from 91 days onwards from their initial infection. On the other hand, unvaccinated patients were at a greater risk of several clinical sequelae including all-cause mortality up to one year following infection.

Bottom line: The findings of this study demonstrated a gradual reduction in the risk of long-term health consequences associated with SARS-CoV-2 over one year, indicating a lesser disease burden compared to that reported in earlier studies as well as the effect of Covid-19 vaccination in reducing the risk of clinical sequelae beyond the acute phase of SARS-CoV-2 infection. See next review.

"The findings of this study showed a reduction in the risk of most clinical sequelae over the course of the observation window suggesting the gradual reduction of the risk of long-term health consequences over a year."

25

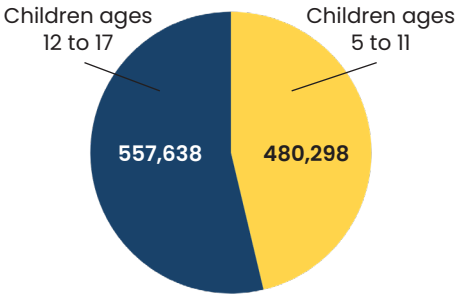
Vaccine Effectiveness Against Long COVID in Children

Pediatrics published online March 8, 2024 (*Pediatrics e2023064446*)
doi.org/10.1542/peds.2023-064446

This was a retrospective cohort study which used data from 17 health systems in the RECOVER PCORnet electronic health record program for visits after vaccine availability. They examined both probable (symptom-based) and diagnosed long Covid after vaccination. The study included two groups: 480,298 children ages 5 to 11, and 557,638 children ages 12 to 17. Overall, 67% received at least 1 SARS-CoV-2 vaccine, and 88% of vaccinated children received 2 or more doses. [much higher than most studies-see next review]

The vaccination rate was 67% in the cohort of 1,037,936 children. Girls, increasing age, and being Asian were associated with Covid-19 vaccination. The incidence of probable long Covid was 4.5% among patients with Covid-19, whereas diagnosed long Covid was 0.8%. Adjusted vaccine effectiveness within 12 months was 35.4% (95 CI 24.5–44.7) against probable long Covid and 41.7% (15.0–60.0) against diagnosed long Covid. VE was higher for adolescents (50.3% [36.6–61.0])

The study included two groups:



- **67%** of children received at least **1 SARS-CoV-2 vaccine**
- **88%** of vaccinated children received **2 or more doses**

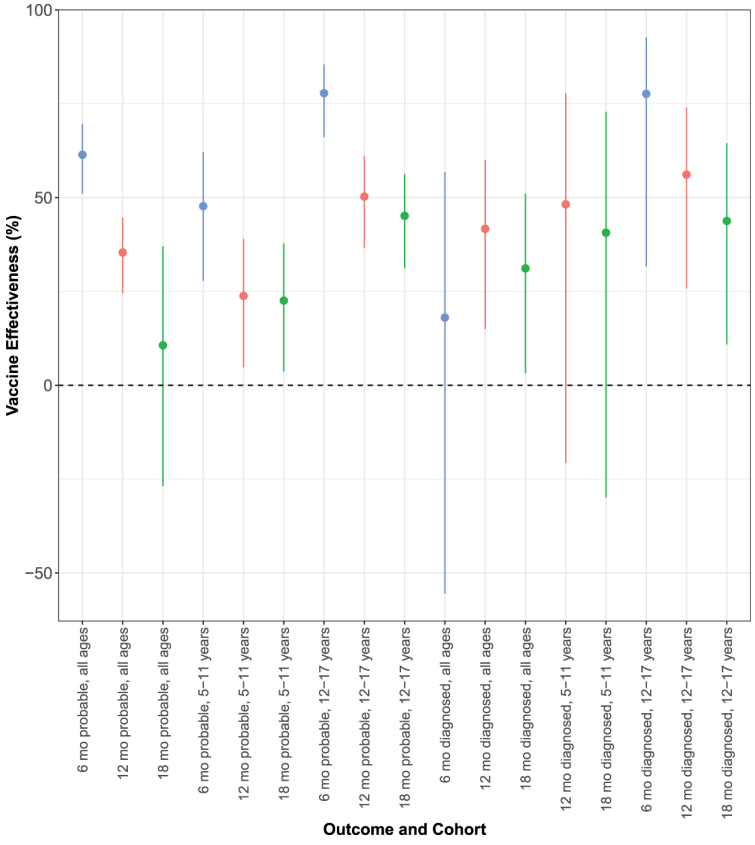
than children aged 5 to 11 (23.8% [4.9–39.0]). VE was higher at 6 months (61.4% [51.0–69.6]) but decreased to 10.6% (−26.8% to 37.0%) at 18-months.

Dr. Septimus's Annotations

This is the first known study to investigate if vaccination protects children from long Covid. Their findings of a protective effect against long Covid in children are consistent with those observed in adults. It was difficult to establish how much this results from differential reporting of symptoms at different ages, greater difficulty distinguishing long Covid from other childhood illnesses or effects of the pandemic (e.g., disruption of seasonal viral patterns, or of school progress, mental illness etc.). Waning effects of vaccine against long Covid are to be expected, similar to studies against acute infection. [N Engl J Med 2022; 386:1899-1909]

Bottom line: This large retrospective study shows moderate protective effect of SARS-CoV-2 vaccination against long Covid. The effect is stronger in adolescents, who have a higher risk of long Covid, and wanes over time.

Durability of vaccine effectiveness of SARS-CoV-2 vaccine against long COVID



Cognition and Memory after Covid-19 in a Large Community Sample

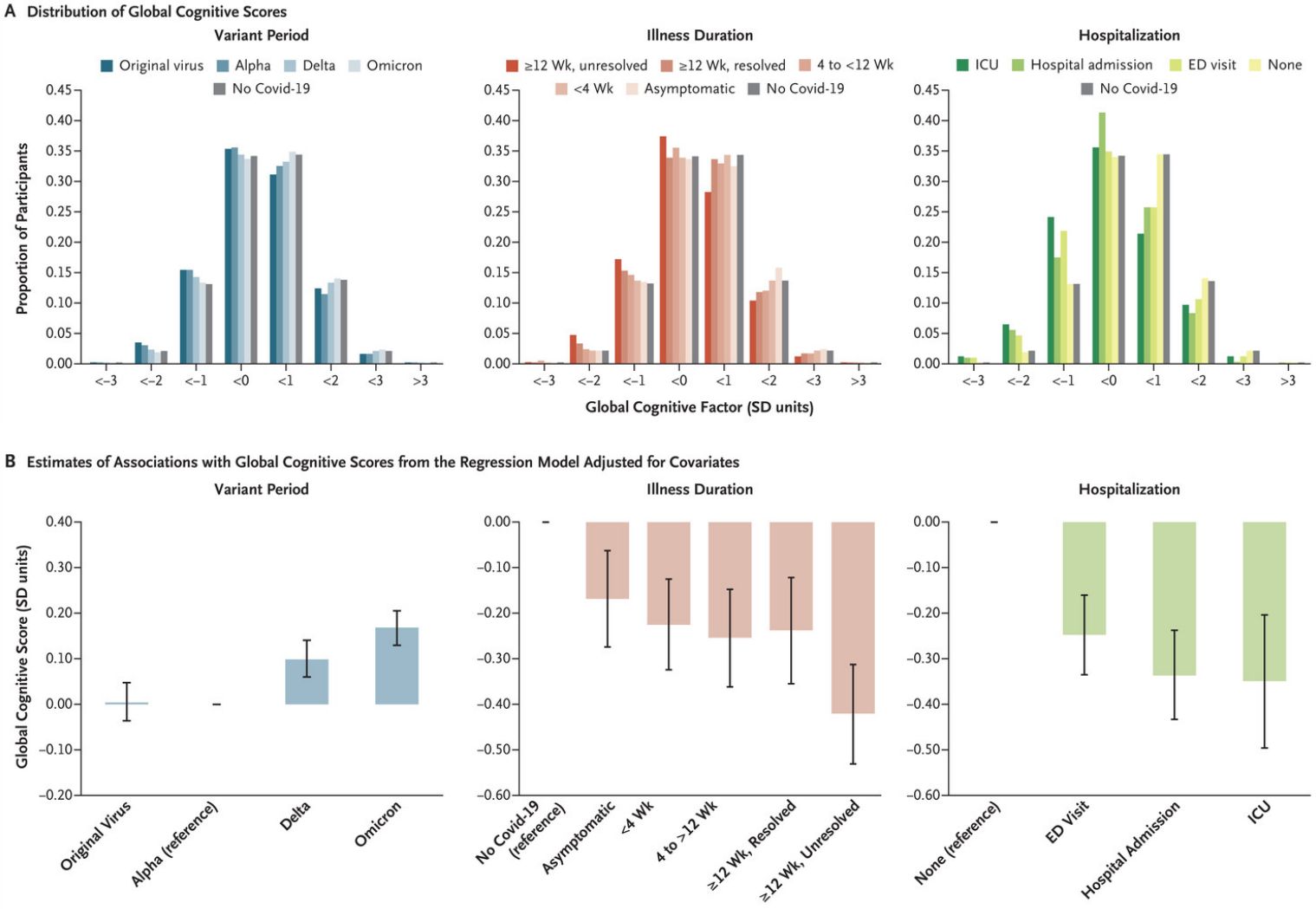
N Engl J Med 2024; 390:806-18
DOI: 10.1056/NEJMoa2311330

The investigators calculated a global cognitive score across eight tasks using online self-reports of cognitive function among 112,964 adults participating in a study in England. They compared the results of Covid-19 survivors with those of their uninfected counterparts.

A multiple regression analysis showed that Covid-19 survivors whose symptoms had resolved in less than 4 weeks or at least 12 weeks had comparable small deficits in cognitive function—or the ability to think—compared with uninfected participants (−0.23 and −0.24 standard deviations [SD], respectively). Covid-19 survivors demonstrated greater deficits than uninfected controls (−0.42 SD). Mild cognitive decline was noted after infection with the wild-type virus and with each variant, including B.1.1.529 (Omicron). Relative to uninfected participants, cognitive deficit (3-point loss in IQ) was seen even in participants who had had completely recovered from mild Covid-19. Participants with persistent symptoms had the equivalent of a 6-point loss in IQ, while those who had been admitted to an intensive care unit (ICU) experienced the equivalent of a 9-point loss in IQ.

Participants who contracted Covid-19 during the periods of wild-type and Alpha variant predominance exhibited larger deficits than those infected with later variants (e.g., −0.17 SD for B.1.1.7 vs B.1.1.529). Similar findings were observed in hospitalized versus unhospitalized participants (e.g., ICU admission, −0.35 SD) and in those with longer periods of acute illness and hospital stays. A comparison of the group with unresolved persistent symptoms with the uninfected group revealed that memory, reasoning, and executive function tasks were associated with the greatest cognitive deficits (−0.33 to −0.20 SD). These tasks had a weak correlation with recent symptoms, including impaired memory and brain fog. Covid-19 vaccination provided a small cognitive benefit, while reinfection was tied to an IQ loss of nearly 2 points, compared with no reinfection. Longer-term persistence of cognitive deficits and any clinical implications remain uncertain.

In an analysis that matched vaccinated groups with unvaccinated groups with regard to demographic characteristics, number of preexisting conditions, and variant period, they observed a small cognitive advantage among participants who had received multiple vaccinations (one dose, 0.08 SD; and at least two doses, 0.15 SD).



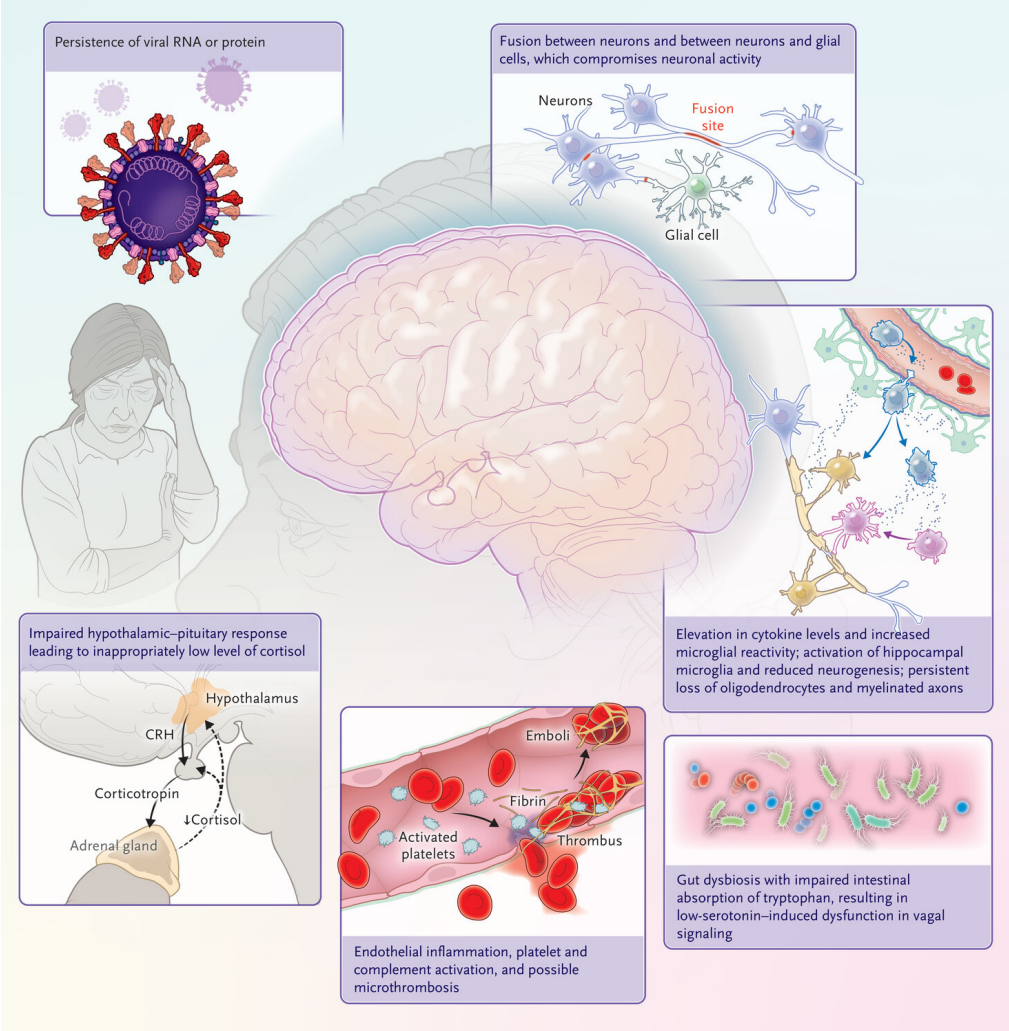
Dr. Septimus's Annotations

Studies involving humans have shown prolonged neuroinflammatory responses, structural abnormalities, and accelerated aging in the brains of persons with mild¬ to ¬moderate SARS-CoV¬-2 infection. Virus was present in brain tissue samples obtained during autopsy from persons who had had severe Covid¬19. [Neuron 2022;110:3484¬96.] Infection with SARS-CoV-2 can produce microvascular damage and neuroinflammation. Longitudinal studies of cognition and brain gray matter volume — some of which included measurements taken before and after the pandemic — have shown that even people with mild acute Covid-19 experience some loss of cognitive capacity and of gray matter compared with those who did not have Covid-19 (Nature 2022; 604:697). See figure on next page from the editorial [N Engl J Med 2024; 390:858-860]

What are the functional implications of a 3-point loss in IQ? Whether these cognitive deficits persist or resolve along with predictors and trajectory of recovery should be investigated. The study was based on an engagement survey; hence, there may be an ascertainment bias, such that either more persons with long Covid may have opted to enroll and that persons who were sick and had disability would not participate in the surveys. Also, there was a lack of racial diversity, which will lead to uncertainty regarding the

effects of long Covid on cognition in underrepresented populations. The relationship of their results to the literature about long Covid is complicated owing to a lack of established, standard criteria for post–Covid-19 syndromes.

Putative Mechanisms of Cognitive Dysfunction in Long Covid



Bottom line: This large study shows residual objective cognitive deficits post SARS-CoV-2 infection. Studies are ongoing to better understand the biology of cognitive dysfunction after SARS-CoV-2 infection and how best to prevent and treat it are critical for addressing the needs of affected persons and preserving the cognitive health of populations.

27

CDC advisers recommend spring COVID booster

February 27, 2024

CDC(ACIP) recommended that people ages 65 and older receive an additional dose of the current monovalent Covid -19 vaccine this spring. ACIP made similar spring booster recommendations in 2022 and 2023. Like previous recommendations, the next dose would be given at least 4 months after the last dose. People with conditions that compromise their immune system could get their next dose at least 2 months after the last dose. Seniors may get another dose of the vaccine was strengthened should receive.

Following ACIP's action, CDC Director Mandy Cohen, MD endorsed the group's recommendation and noted that the CDC's earlier recommendations say immunocompromised groups are already eligible for an additional dose of Covid-19 vaccine.

Dr. Septimus's Annotations

Predicting what lies ahead with SARS-CoV-2 is more challenging and more nuanced than flu, because SARS-CoV-2 variants change more often, and Covid-19 peaks have been tied to the emergence of a new variants. In addition, Covid-19 activity has not followed a seasonal pattern to date.

Bottom line: High-risk individuals should be offered a spring booster.

28

Covid-19 by the Numbers

COVID-19 Update for the United States

Early Indicators

Test Positivity

% Test Positivity

5.2%

(March 3 to March 9, 2024)

Trend in % Test Positivity

-1.5% in most recent week

Jan 20, 2024 Mar 9, 2024

Emergency Department Visits

% Diagnosed as COVID-19

1.0%

(March 3 to March 9, 2024)

Trend in % Emergency Department Visits

-24.8% in most recent week

Jan 20, 2024 Mar 9, 2024

Severity Indicators

Hospitalizations

Hospital Admissions

13,391

(March 3 to March 9, 2024)

Trend in Hospital Admissions

-13.5% in most recent week

Jan 20, 2024 Mar 9, 2024

Deaths

% of All Deaths in U.S. Due to COVID-19

2.0%

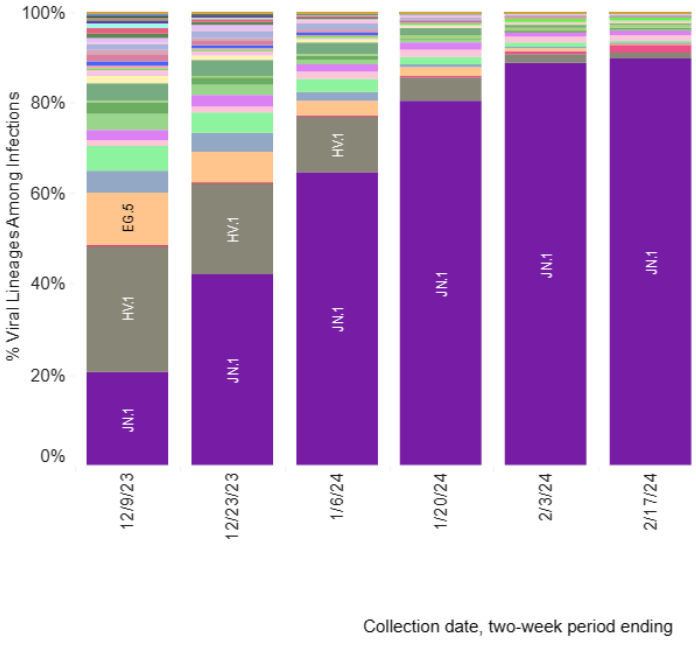
(March 3 to March 9, 2024)

Trend in % COVID-19 Deaths

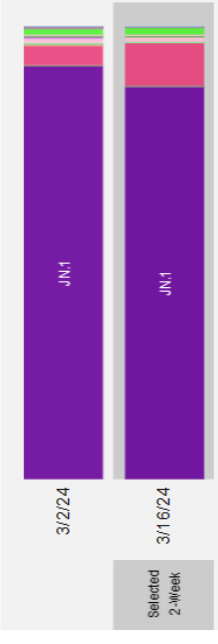
-4.8% in most recent week

Jan 20, 2024 Mar 9, 2024

Weighted Estimates: Variant proportions based on reported genomic sequencing results



Nowcast: Model-based projected estimates of variant proportions



USA

WHO label	Lineage #	%Total	95%PI
Omicron	JN.1	86.5%	81.4-90.5%
	JN.1.13	9.5%	5.5-15.7%
	JN.1.18	1.8%	1.2-2.7%
	BA.2	0.2%	0.0-1.4%
	BA.2.86	0.2%	0.1-0.3%
	GE.1	0.2%	0.1-0.4%
	HV.1	0.1%	0.1-0.2%
	JG.3	0.1%	0.1-0.1%
	JD.1.1	0.1%	0.0-0.1%
	HK.3	0.0%	0.0-0.0%
	XBB	0.0%	0.0-0.0%
	EG.5	0.0%	0.0-0.0%
	XBB.1.9.1	0.0%	0.0-0.0%
	EG.5.1.8	0.0%	0.0-0.0%
	JF.1	0.0%	0.0-0.0%
	XBB.1.16.15	0.0%	0.0-0.0%
	XBB.2.3	0.0%	0.0-0.0%
	FL.1.5.1	0.0%	0.0-0.0%
	XBB.1.5.70	0.0%	0.0-0.0%
	XBB.1.16.6	0.0%	0.0-0.0%
	XBB.1.16.11	0.0%	0.0-0.0%
	GK.1.1	0.0%	0.0-0.0%
	HF.1	0.0%	0.0-0.0%
	XBB.1.16	0.0%	0.0-0.0%
	GK.2	0.0%	0.0-0.0%
	XBB.1.5	0.0%	0.0-0.0%
	XBB.1.16.1	0.0%	0.0-0.0%
Other	Other*	1.2%	0.7-2.0%

Dr. Septimus's Annotations

All the indicators show decreased activity across the US. JN lineage makes up over 95% of variants.

Bottom line: The risk of Covid-19 has declined, but we need to continue to protect the most vulnerable and monitor for any new emerging variants which may predict another wave.

29

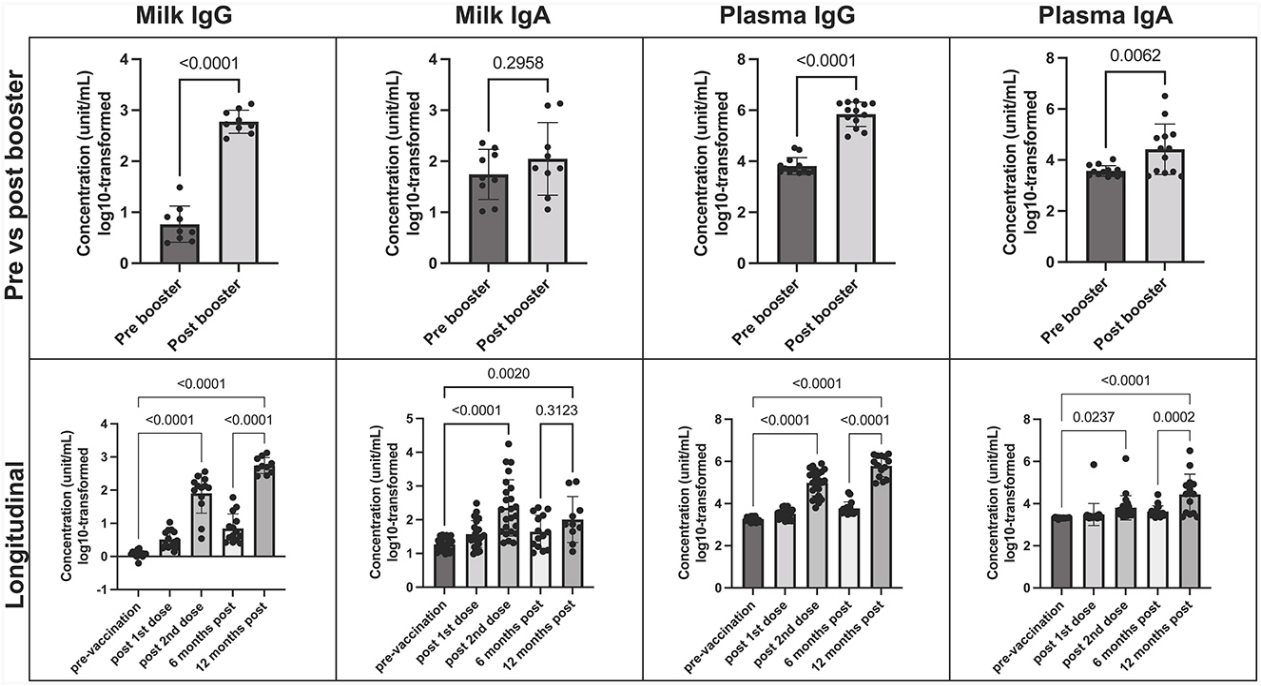
COVID-19 booster enhances IgG mediated viral neutralization by human milk in vitro

Front Nut published online February 9, 2024
doi:10.3389/fnut.2024.1289413

Vaccinated lactating mothers produce specific SARS-CoV-2 antibodies in their milk, capable of neutralizing the virus in vitro. The objective for this study was to assess the effect of Covid-19 booster dose on SARS-CoV-2 antibody concentration and viral neutralization in milk, plasma, and infant stool. Thirty-nine mothers and 25 infants were enrolled from December 2020 to May 2022. Milk, maternal plasma, and infants' stool were collected at various time-points up to 12 months following mRNA COVID-19 vaccination. A subgroup of 14 mothers received a booster dose. SARS-CoV-2 antibody levels and their neutralization capacities were assessed.

Booster vaccination led to significantly higher IgG levels within human milk and breastfed infants' stool. In vitro neutralization of VSV-gfp-SARS-CoV- 2-S-gp, a laboratory safe SARS-CoV-2 like pseudovirus, improved following the booster, with a 90% increase in plasma neutralization and a 60% increase in milk neutralization. They found that post-booster neutralization by human milk was highly correlated to SARS-CoV-2 IgG level. In support of their correlation result, Protein G column depletion of IgG in milk yielded a significant reduction in viral neutralization ($p = 0.04$).

Concentration of SARS-CoV-2 IgA and IgG in milk and plasma post booster dose (top), and over 12-month vaccination course following initial COVID-19 vaccination (bottom)



Dr. Septimus's Annotations

The substantial increase in neutralizing IgG levels in milk and breastfed infants' stool post-booster, coupled with the decrease in milk neutralization capabilities upon IgG depletion, underscores the efficacy of booster doses in augmenting the immune response against SARS-CoV-2 in human milk. Maternal vaccination during breastfeeding has been shown to effectively confer their infant's protection against several viral diseases. The CDC is recommending this intervention against pertussis, RSV, influenza, and most recently, Covid-19. Previous work by the present research group established the presence of SARS-CoV-2 IgG and IgA antibodies in human breastmilk and infant fecal matter, with Halasa and colleagues validating the benefits of maternal Covid-19 vaccination in infant immunity shortly after in 2022. [MMWR. 2022; 71:264–70] Unfortunately, subsequent studies revealed this immunity to be short-lived, with evidence suggesting substantial antibody concentration declines six months following vaccination. This was a small sample size and limited diversity in this cohort of mothers. Furthermore, whether infants or mothers might have had a previously undiagnosed Covid infection, and how this may have interfered with results, cannot be known. They did not test the IgA secretory component, rather they assumed that IgA found in milk is the majority secretory IgA. They did not explore other immune factors in milk (i.e., cell mediated immunity, cytokines, lactoferrin) that might be increased after maternal vaccination and contribute to milk neutralization.

"...Halasa and colleagues validat[ed] the benefits of maternal Covid-19 vaccination in infant immunity... Unfortunately, subsequent studies revealed this immunity to be short-lived..."

Bottom line: Substantial increase in neutralizing IgG levels in milk and breastfed infants' stool post-booster, underscores the efficacy of booster doses increasing the immune response against SARS-CoV-2 in human milk and increasing infant immunity.

30

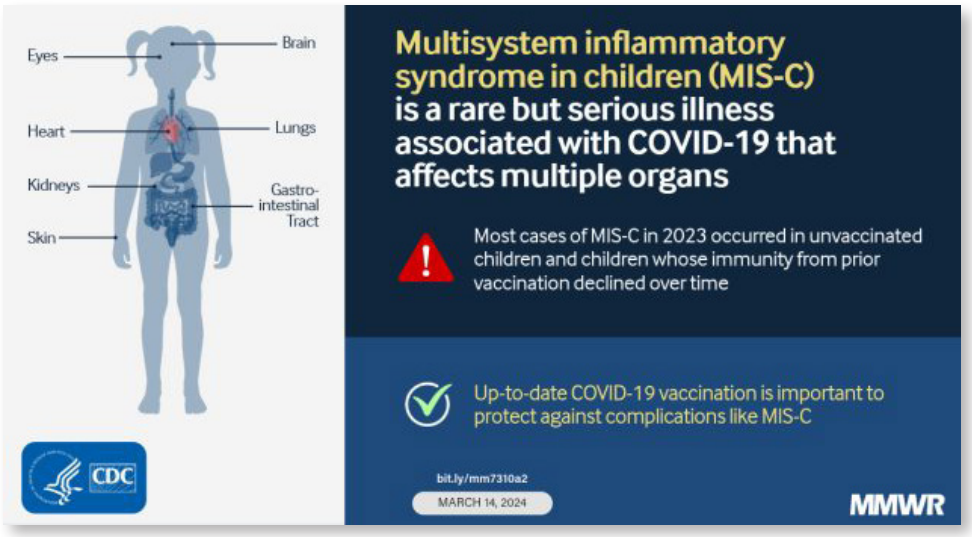
Surveillance for Multisystem Inflammatory Syndrome in Children — United States, 2023

MMWR 2024; 73:225-228

This report describes 2023 MIS-C cases and compares them with cases reported earlier in the Covid-19 pandemic. All MIS-C cases reported to CDC national surveillance as of February 26, 2024, with illness onset during 2023 were included, and patient characteristics were analyzed. Incidence (cases per 1,000,000 person-months) was estimated using bridged-race 2020 population estimates from U.S. Census Bureau data. Covid-19 vaccination status was reported for children who were age-eligible for vaccination at the time of MIS-C illness onset.

Among 117 MIS-C patients with illness onset in 2023, 31 (26%) had onset during August–October, after an increase in Covid-19 activity earlier in the summer; this finding represented a two-thirds increase in case counts compared with the 19 (16%) cases reported with onset during the preceding 3 months. Overall MIS-C incidence in 2023 was 0.11 cases per million person-months (95% CI = 0.10–0.14), representing an 80% decline in incidence compared with that during April–December 2022 (0.56 cases per million person-months; 95% CI = 0.51–0.62), and a 98% decrease from the peak of 6.79 (95% CI = 6.56–7.03) early in the Covid-19 pandemic (October 2020–April 2021). The median age of MIS-C patients with illness onset in 2023 was 7 years, whereas the median age during February 2020–January 2022 was 9 years, and during April– December 2022 was 5 years. Among the 117 MIS-C patients with illness onset in 2023, 68 (58%) had no underlying medical conditions; 58 (50%) required intensive care unit (ICU)-level care, 40 (34%) experienced shock,

and 31 (27%) experienced cardiac dysfunction. These prevalences are similar to published national MIS-C surveillance data for 2,116 cases reported during July 9, 2021– January 31, 2022. More than 80% (92 of 112) of MIS-C cases were in vaccine-eligible but unvaccinated children, and among the 20 vaccinated children, 60% likely had waned immunity at the time of MIS-C illness. Three (3%) patients with MIS-C died in 2023.



Dr. Septimus's Annotations

MIS-C continues to occur, but at lower rates compared with those observed early in the Covid-19 pandemic. MIS-C incidence has declined, but a recent shift to cases in younger children has occurred, and clinical characteristics have evolved. A similar decline in MIS-C incidence and shift to a younger age group in 2022 was reported in England. [J Infect 2022; 85:702–69]

Bottom line: Even though MIS-C incidence has declined MIS-C continues to occur. Vaccination rates remain very low in children. CDC continues to recommend that children aged ≥6 months stay up to date with Covid-19 vaccination to protect against serious Covid-19 illness and complications, including MIS-C.