Infectious Diseases Watch

March 28, 2022

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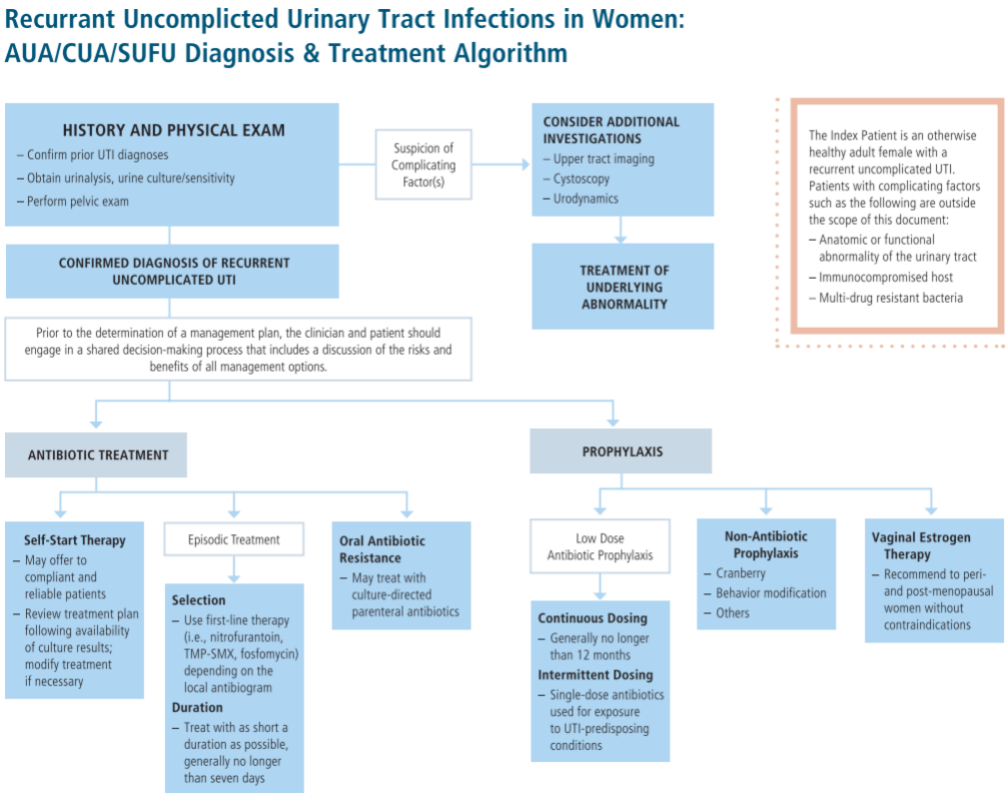
General Infectious Disease

Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial

BMJ 2022;376:e068229

doi: 10.1136/bmj-2021-068229

Recurrent urinary tract infection (UTI) is defined as repeated UTI with a frequency of at least two episodes in the preceding six months or three episodes in the past year. UK and US strongly recommend the use of daily, low dose antibiotics as the standard prophylactic treatment for recurrent UTI. (Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol 2019;202:282-9) see below



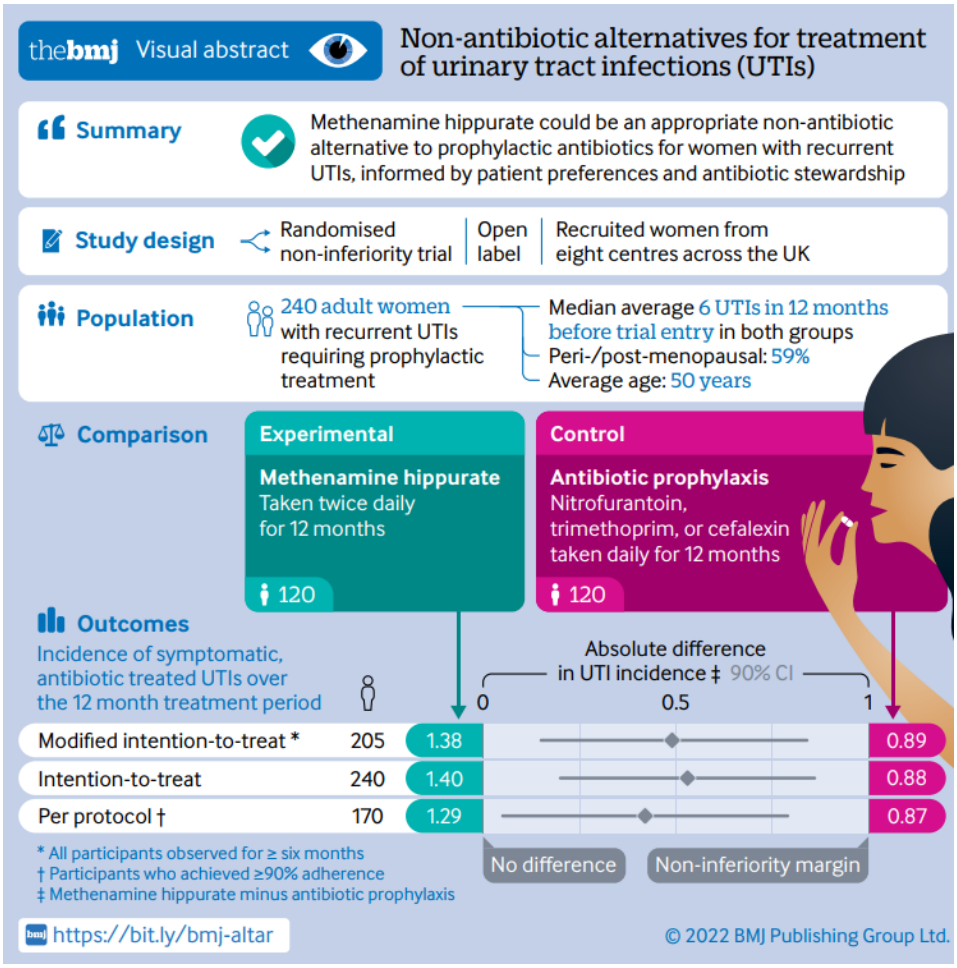
Antibiotic Prophylaxis: Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. (Moderate Recommendation; Evidence Level: Grade B)

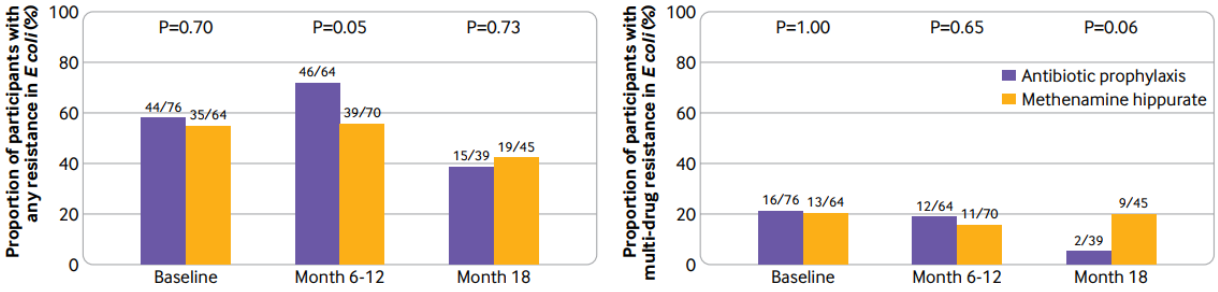
Methenamine has been evaluated in previous Cochrane systematic reviews, which concluded that “methenamine may be effective for preventing UTI” but recognized the “need for further large well-conducted RCTs to clarify.” (Cochrane Database Syst Rev 2012;10:CD003265. doi:10.1002/14651858.CD003265.pub3) Methenamine is a urinary antiseptic (non-antibiotic) which breaks down to ammonia and formaldehyde in acidic urine. It is the formaldehyde that is antibacterial. Methenamine requires a low urinary pH (≤5.5), Cannot be used for CrCl <50 mL/min and cannot be used to treat pyelonephritis. Recommended to avoid co-administration with sulfa which can precipitate in the presence of formaldehyde.

This is a pragmatic noninferiority trial. Investigators in the U.K. randomized 240 women with recurrent symptomatic UTIs (mean, 7 episodes in the past year) to receive either daily low-dose antibiotic prophylaxis (i.e., nitrofurantoin, trimethoprim, or cefalexin, at the discretion of the patient and clinician) or methenamine (100 mg twice daily) for 12 months. Patients could switch between antibiotics or between treatment strategies. Women who experienced UTI symptoms were advised to seek short courses of antibiotics from their usual clinicians. Follow-up assessments took place every three months until month 18. A positive urine culture was defined as on isolate of a potential uropathogen at a concentration of ≥104 colony forming units/mL or two species of uropathogens isolated at ≥105 colony forming units/ mL. Asymptomatic bacteriuria was defined as a positive urine culture from urine samples submitted to the central laboratory in the absence of symptoms. Antibiotic resistance was assessed from urine and perineal swabs with antimicrobial sensitivity tested in triplicate against a panel of antibiotic drugs. Multidrug resistance in *E coli* was defined as resistance to at least one antibiotic drug in at least three antimicrobial categories. The trial was powered to assess non-inferiority of the absolute difference in UTI incidence over the 12-month treatment period. The non-inferiority margin, defined after a series of patient focus group meetings, was a difference of one UTI episode per year.

In a modified intent-to-treat analysis, more symptomatic, antibiotic-treated UTIs (with or without bacteriologic confirmation) occurred in the methenamine group than in the antibiotic group (1.38 vs. 0.89 per patient-year), but the confidence interval around the difference fell within the prespecified, noninferiority limit of 1 UTI per person-year. A similarly small difference was noted in the first 6 months after completion of treatment.

Overall rates of resistance to nitrofurantoin were very low. [should not be used in patients with CrCl<30 and caution in elderly] During the treatment period, a higher proportion of patients allocated to daily prophylactic antibiotics showed resistance to at least one antibiotic in *E coli* isolates from perineal swabs than patients allocated to methenamine. This is similar to findings from a previous randomized controlled trial exploring antibiotic prophylaxis in patients with recurrent complicated UTIs. (Health Technol Assess 2018; 22:1-102. doi:10.3310/hta22240) However, at the end of the follow-up period, the rate of multidrug resistance in *E coli* isolates from perineal swabs was higher in the methenamine arm than in the antibiotics arm. They say this difference could be due to a sustained effect of daily antibiotics on the fecal microbiome or the greater incidence of antibiotic treated acute UTIs in the methenamine group during follow-up.





Comment: Investigators in this report included women presenting with recurrent, uncomplicated UTIs who were then randomized to receive methenamine or low dose antibiotics for 12 months. Over 12 months, the incidence of antibiotic treated UTI was 0.89 and 1.38 episodes per person year in the antibiotic group and methenamine groups, respectively (absolute difference 0.49 episodes (90% confidence interval 0.15 to 0.84)). Because this study was a non-inferiority trial with a difference between treatments less than the prespecified non-inferiority margin of one

episode per person year, the investigators reported that methenamine was no worse than antibiotics at preventing UTIs. The decision was to use a clinical definition rather than a microbiological definition for UTIs for the primary outcome. Results were consistent across other secondary analyses, including sensitivity analyses that exclude days taking therapeutic antibiotics for UTI during the 12-month follow-up time; important because 43% of participants in the antibiotic group and 56% in the methenamine group received therapeutic antibiotics. Regardless of the prophylactic intervention taken, about half the women had a recurrent infection during the 12 months. This highlights the challenge in this population. ADE were very low in both groups. The investigators also monitored for resistance in *E coli* isolated from perineal swabs as a secondary outcome. However, it was optional for participants to provide swabs every six months, with more missing data as the trial progressed. Only about half of participants provided an 18-month swab. At six and 12 months, resistance rates to at least one antibiotic were higher in the antibiotic prophylaxis group than the methenamine group (72% *v* 56%, P=0.05), but at 18 months, the rate of multidrug resistance was higher in the methenamine group (20% *v* 5%, P=0.06). Given only half of participants submitted 18-month swabs, this result is very difficult to interpret. Lastly, whether the non-inferiority margin (one episode of urinary tract infection) used in this trial is correct and/or clinically is a matter of debate. Although the investigators made a valent attempt to study this challenging topic, the results leave me unsatisfied. The guideline (J Urol) discusses the recent interest in another non antibiotic cranberry(non-antibiotic) which has been the subject to an increasing number of randomized clinical trials. The proposed mechanism of action is thought to be related to proanthocyanidins (PACs) present in cranberries and the ability of PACs to prevent the adhesion of bacteria to the urothelium They point out that PACs are found in varying concentrations dependent on the formulation used, and many of the cranberry products used in scientific study are explicitly formulated for research purposes. The availability of such products to the public is a severe limitation to the use of cranberries for rUTI prophylaxis outside the research setting. In the end decisions on preventive treatment for recurrent UTIs should be a shared decision between the physician and the patient weighing benefits and harms of each option. Although methenamine may be a reasonable alternative additional study may be needed.

The Efficacy of Using Combination Therapy against Multi-Drug and Extensively Drug-Resistant *Pseudomonas aeruginosa* in Clinical Settings Antibiotics 2022, 11: 323

doi.org/10.3390/antibiotics11030323

The authors conducted a systematic search with screening criteria using the Ovid search engine and the Embase, Ovid Medline, and APA PsycInfo databases.

To review as background, the most common form of resistance to carbapenems comes from the control of cell permeability through the porins, more specifically the control of the permeability to antibiotics entering the cell. With regards to carbapenems, this is due to the alteration or decreased expression of the outer membrane porin OprD. Beta-lactamase-producing *Pseudomonas* strains are also seen, which cause β-lactamase resistance. Carbapenemase

production is a rare cause of carbapenem resistance in *P. aeruginosa* in the United States but is identified in upwards of 20% of carbapenem-resistant *P. aeruginosa* in other regions of the world. Efflux pumps also play a key part in the antibiotic resistance that is found in *P. aeruginosa.* The overuse of some drugs will even cause the upregulation of multidrug efflux pumps, such as the MexXY-OprM efflux pump, which when overexpressed leads to reduced susceptibility to aminoglycosides, β-lactams, and fluoroquinolones. Below is a slide I made in 2020 for ID Week presentation. There is a new β-lactamase inhibitor taniborbactam (combined with cefepime) which inhibits KPCs, NDMs, Oxa 48, and AmpC now in phase 3 trials which looks promising in treating many of the CRPA.

Drug Name	ESBL activity	KPC activity	NDM activity	OXA activity	*Pseudomonas*	*Acinetobacter*	*Stenotrophomonas*
Ceftazidime-avibactam	Yes	Yes	No	Yes	Yes	No	No
Ceftolozane-tazobactam	Yes	No	No	No	Yes	No	No
Imipenem-relebactam	Yes	Yes	No	No	Yes	No	No
Eravacycline	Yes	Yes	Yes	Yes	No	Yes	Yes
Plazomicin	Yes	Yes	Yes	Yes	Variable	No	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840.
Stewart A, et al. *Antimicrob Agents Chemother.* 2018;62:e01195.
Otsuka Y. *Chem Pharm Bull.* 2020;68:182-190.

In this review the authors found that in many cases the combination therapies were able to match or outperform the monotherapies and none performed noticeably worse than the monotherapies. Combination therapy often contained one of the following: polymyxin B, colistin,or AG with a carbapenem, polymyxin B with a carbapenem and rifampin, beta-lactams (including piperacillin/tazobactam, ceftolozane/tazobactam, ceftrazidime/avibactam). However, the clinical studies were mostly small, only a few were prospective randomized clinical trials and statistical significance was lacking. Polymyxin/Colistin is no longer listed as a preferred drug alone due to poorer outcomes and toxicity. See comments below

Comment: It has been known for decades that P. *aeruginosa* can rapidly develop resistance, through its many resistance mechanisms. CRPA is on the rise. The review here concluded that combination therapies have a place in the treatment of these highly resistant bacteria, and, in some cases, there is some evidence to suggest that they provide a more effective therapy leading to better outcomes compared to monotherapies. The review has several tables worth reviewing summarizing current literature. See IDSA guidance next.

The updated IDSA guidelines(https://www.idsociety.org/practice-guideline/amrguidance) recommend traditional non-carbapenem β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), over carbapenem therapy treatment of MDR-PA state when *P. aeruginosa* isolates are susceptible. For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agents [generally due to lack of or limited production of OprD, which normally facilitates entry of carbapenem agents into bacteria] but susceptible to traditional

β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, after antibiotic susceptibility testing results are confirmed. For patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems [most carbapenem-resistant strains are also resistant to traditional β-lactam agents] but susceptible to traditional β-lactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment option. Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy, are preferred options for the treatment of infections outside of the urinary tract, based on *in vitro* activity, observational studies, and clinical trial data. Cefiderocol is recommended as an alternative treatment option for DTR-*P. aeruginosa.* Combination antibiotic therapy is not routinely recommended for infections caused by DTR-*P. aeruginosa* if *in vitro* susceptibility to a first-line antibiotic (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed. Based on existing outcomes data, clinical experience, and known toxicities associated with aminoglycosides and polymyxins, the panel did not recommend that combination therapy be routinely administered for DTR-*P. aeruginosa* infections when susceptibility to a preferred β- lactam agent has been demonstrated. The panel went on to state that if no preferred agent demonstrates activity against DTR-*P. aeruginosa*, an aminoglycoside (if susceptibility is demonstrated) can be considered in combination with either ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam, preferentially selecting the β-lactam-β-lactamase inhibitor agent for which the MIC is closest to its susceptibility breakpoint. If no aminoglycoside demonstrates *in vitro* activity, polymyxin B can be considered in combination with the β-lactam-β-lactamase inhibitor. Polymyxin B is preferred over colistin for non-urinary tract infections because it is not administered as a prodrug and therefore can achieve more reliable plasma concentrations than colistin, and it has a reduced risk of nephrotoxicity; however, colistin, but not polymyxin B, is an alternate consideration for treating DTR-*P. aeruginosa* cystitis as it converts to its active form in the urinary tract. Regardless of the antibiotic agent administered, patients infected with *P. aeruginosa* should be closely monitored to ensure clinical improvement as *P. aeruginosa* has the capacity to acquire additional resistance mechanisms while on therapy. Combination therapy has not been shown to prevent development of resistance compared to effective monotherapy.

Bottom line, if *P. aeruginosa* is susceptible to a beta-lactam, there is no evidence that combination therapy improves outcomes. There may be a role for combination therapy for a patient suspected to have a serious infection due to *P. aeruginosa* pending susceptibilities based on local epidemiology. Lastly combination therapy may improve outcomes if MICs to beta-lactams are around the susceptibility breakpoint or just above.

COVID-19

COVID-19 News

Moderna says its low-dose COVID shots work for kids under 6

Moderna said in the coming weeks it would ask regulators in the U.S. and Europe to authorize two small-dose shots for youngsters under 6. The company also is seeking to have larger-dose shots cleared for older children and teens in the U.S. (25-microgram dose) The trial enrolled about 4,200 children aged 2 to under 6, and 2,500 children 6 months to under 2. Moderna reported that same trend in the trial of children under 6, conducted during the omicron surge. While there were no severe illnesses, the vaccine proved just under 44% effective at preventing any infection in babies up to age 2, and nearly 38% effective in the preschoolers.

Pfizer is testing even smaller doses for children under 5 but had to add a third shot to its study when two didn't prove strong enough. Those results are expected by early April.

Comment: It now appears we may now have a vaccine for children < age 5 in the next 1-2 months. The challenge will be acceptance since the last Kaiser survey indicates only ~25% parents will vaccinate their children when vaccine is available.

FDA to Consider Second Booster

The FDA may take up this recommendation as early as this next week. Unlike prior recommendations the FDA may stop short of a full endorsement and recommendation this as an option for adults older than 50.

Comment: This potential recommendation comes at a time where Covid-19 vaccinations have dropped off. 65.4% of Americans are fully vaccinated, but only 44% have received a booster. The initial rollout has been plagued by conflicted guidance, politics, and the failure to integrate natural immunity in guidance. [See the last ID Watch review on the efficacy of a fourth dose (NEJM March 16 ,2022) and the MMWR article reviewed below]. Once again, if the FDA approves a second booster, but only as an option will this increase confidence in the FDA/CDC or leave Americans confused?

Update [3/25/2022] FDA limits use of Sotrovimab to treat COVID-19 in some U.S. regions due to the BA.2 Omicron sub-variant

Considering the most recent data available (sotrovimab is less effective against the BA.2 variant), FDA is announcing that sotrovimab is no longer authorized for use at this time in the following states and territories with high BA.2 cases):

- Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Health and Human Services [HHS] Region 1)

- New Jersey, New York, Puerto Rico, and the Virgin Islands (HHS Region 2)

Comment: This will complicate choices in areas with the BA.2 variant. Paxlovid, remdesivir, bebtelovimab, and molnupiravir are expected to be effective against the BA.2 sub-variant and are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease.

CDC Updates

1. The seven-day average number of vaccines administered daily was 181,945 as of March 23, a 27.1 percent decrease from the previous week.
2. As of March 23, about 255 million people — 76.8 percent of the total U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 217.2 million people, or 65.4 percent of the population, have received both doses.
3. About 96.9 million additional or booster doses in fully vaccinated people have been reported. However, 49.8 percent of people eligible for a booster dose have not yet gotten one. See above
4. Based on projections for the week ending March 19, the CDC estimated that the omicron variant accounts for 100 percent of new COVID-19 cases in the U.S.
5. CDC estimates that BA.1.1 accounts for 57.3 percent of cases, while the BA.2 subvariant accounts for 34.9 percent of cases. This is increasing every week.
6. As of March 23, the nation's seven-day case average was 27,134, a 5.4 percent decrease from the previous week's average.
7. The current seven-day death average is 749, down 29.5 percent from the previous week's average. This marks the seventh consecutive week deaths have fallen.
8. The seven-day hospitalization average for March 16-21 was 1,827, a 21 percent decrease from the previous week's average.

Comment: Not everyone is experiencing a spike in BA.2 at present (see above), but trends do show a steady increase over time. As reported in ID Week BA.2 is more transmissible than BA.1, but vaccines work equally well against both. Sotrovimab does not work against BA.2-see above

Journal Review

Perinatal Complications in Individuals in California With or Without SARS-CoV-2 Infection During Pregnancy JAMA Intern Med published online March 21, 2022

doi:10.1001/jamainternmed.2022.0330

Kaiser Permanente Northern California investigators analyzed the electronic medical records of 43,886 pregnant women who delivered from March 1, 2020, to March 16, 2021. Average patient age was 30.7 years, 33.8% were White, 28.4% were Hispanic, 25.9% were Asian or Pacific Islander, 6.5% Black, 0.3% American Indian or Alaska Native, and 5% were multiracial or of another race.

Among these women, 1,332 (3.0%) tested positive for COVID-19 from 30 days before conception to 7 days after delivery. Infected women were more likely than their uninfected peers

to be younger and Hispanic and to have had multiple babies, a higher neighborhood deprivation index, and obesity or chronic high blood pressure. Before universal COVID-19 testing of pregnant women admitted for delivery was implemented in the healthcare system in December 2020, the positivity rate was 1.3%, compared with 7.8% after.

After adjustment for demographic characteristics, underlying medical conditions, and smoking status, infected women were at double to triple the risk for severe illness such as acute respiratory distress syndrome and sepsis (hazard ratio [HR], 2.45), birth at less than 37 weeks gestation (HR, 2.08), and venous thromboembolism (blood clots) (HR, 3.08).

COVID-19 infection was also tied to an elevated risk of medically indicated preterm birth (e.g., for a life-threatening maternal condition such as preeclampsia) (HR, 2.56), spontaneous preterm birth (HR, 1.61), and early (HR, 2.52), moderate (HR, 2.18), and late (HR, 1.95) preterm birth.

Among infected women, 5.7% were hospitalized for COVID-19. A diagnosis of pregestational diabetes (HR, 7.03), as well as Asian/ Pacific Islander (HR, 2.33) and Black (HR, 3.14) race, were linked to an increased risk of hospitalization. Of the 307 women diagnosed as having COVID-19 during or 3 weeks before hospitalization, 24.8% (5.7% of the 1,332 total infected women) required respiratory support, 1.3% of them received mechanical ventilation, and 1 died. In contrast with a recent study (MMWR 2021;70(47):1640-1645), they did not find an association between SARS-CoV-2 infection and stillbirth.

Comment: This study confirms that SARS-CoV-2 infection is associated with an increased risk of perinatal complications. They were not able to rule out the possibility of detection bias owing to increased testing in patients at risk of perinatal complications. They could not exclude the possibility that the association between SARS-CoV-2 and preterm birth was partially attributable to medical intervention, such as purposeful earlier delivery in individuals with SARS-CoV-2 infection. This study supports prior studies and should inform clinicians and patients about the risk of perinatal complications associated with SARS-CoV-2 infection in pregnancy and support vaccination of pregnant individuals and those planning conception. Coupled with the evidence that the COVID-19 vaccines are safe during pregnancy, these findings should aid patients in understanding the risks of perinatal complications and the need for vaccination. See next article

COVID-19 Cases and Disease Severity in Pregnancy and Neonatal Positivity Associated With Delta (B.1.617.2) and Omicron (B.1.1.529) Variant Predominance

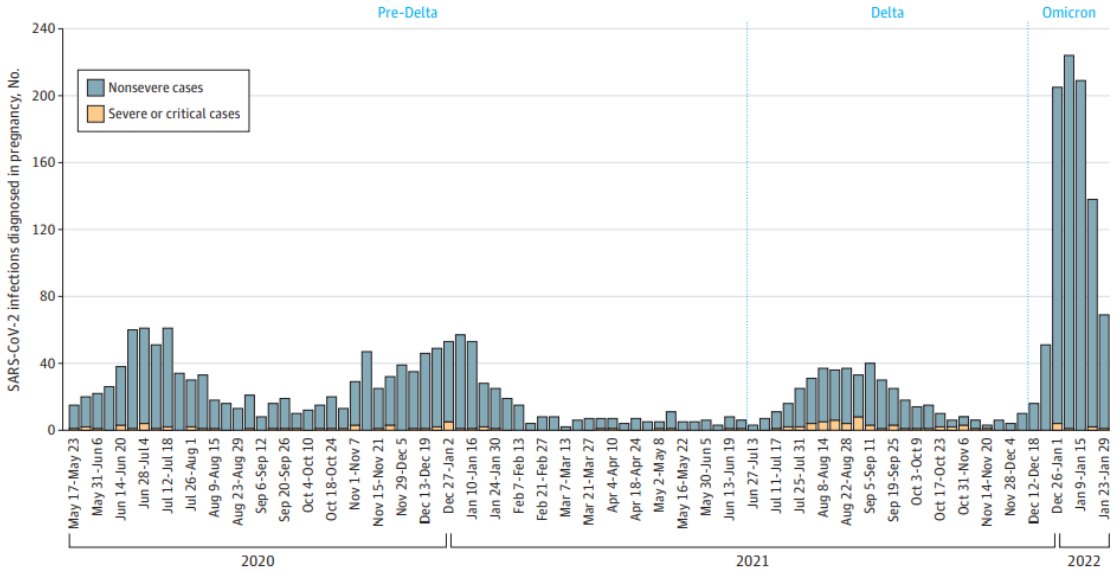
JAMA published online March 24, 2022

doi:10.1001/jama.2022.4356

The investigators prospectively studied pregnant patients diagnosed with SARS-CoV-2 infection in an urban health system. Positive tests were grouped by week of diagnosis. Severe or critical illness was defined as requiring supplemental oxygen, high flow nasal cannula, mechanical ventilation, or extracorporeal membrane oxygenation. COVID-19 vaccines were offered beginning December 2020. Following delivery, neonatal nasal PCR was performed at 24 and 48 hours for infants born within 4 weeks of maternal diagnosis or when clinically indicated until late 2021, when 1-time testing was permitted. Local SARS-CoV-2 variant surveillance was conducted beginning in early 2021. Covariates included dominant variant, week (to account for differing lengths of the 3 periods), and complete vaccination status. Dominant variant was

assigned based on 50% or more of surveillance samples having Delta or Omicron predominance (pre-Delta epoch, May 17, 2020, through June 26, 2021; Delta epoch, June 27 through December 11, 2021; and Omicron epoch, December 12, 2021, through January 29, 2022).

As in nonpregnant people, Delta and Omicron variant predominance were associated with increased SARS-CoV-2 infections in pregnancy, with the majority occurring in unvaccinated individuals. Delta variant predominance was associated with increased illness severity and Omicron with decreased illness severity after adjusting for prior vaccination. The majority of early neonatal SARS-CoV-2 infections occurred among unvaccinated mothers with nonsevere COVID-19.



Comment: Whether the decreased illness severity during Omicron is related to greater numbers of pregnant people previously infected and/or vaccinated or to intrinsic virological properties could not be determined. There were missing data on vaccination or positive results of tests conducted outside the health care system. Rates of SARS-CoV-2 exposure and vaccinations among uninfected individuals were also not available. Long-term risks of early neonatal SARS-CoV-2 infection are unknown, but maternal vaccination has been shown to be protective.

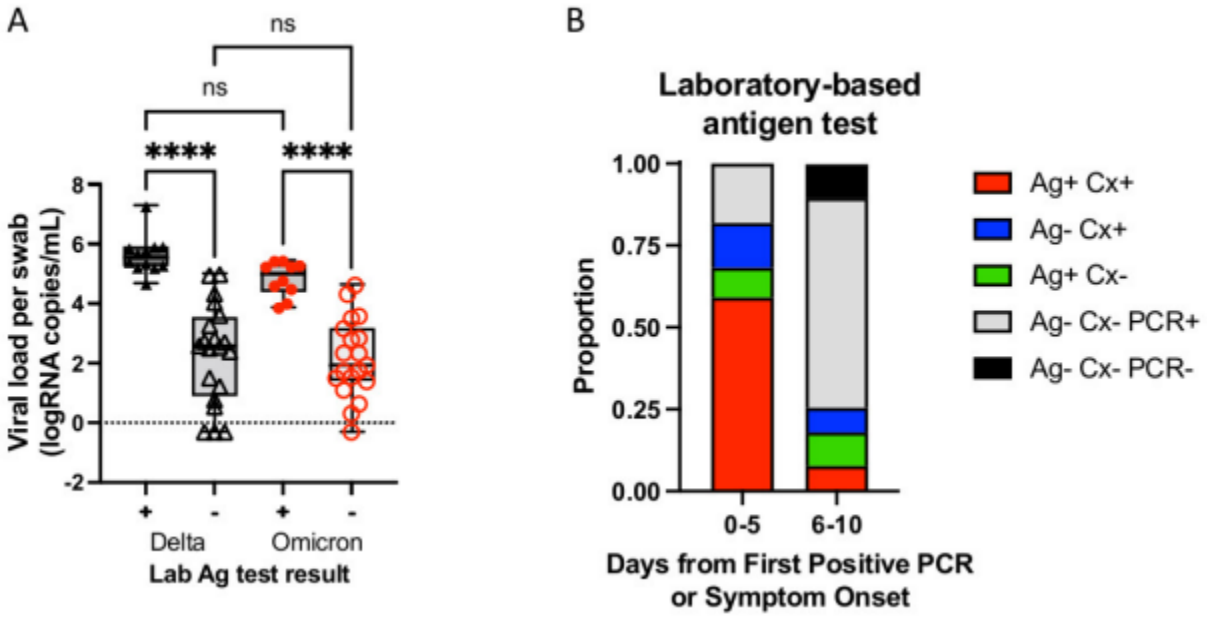
Duration of viable virus shedding in SARS-CoV-2 omicron variant infection medRxiv March 2, 2022

doi.org/10.1101/2022.03.01.22271582

Investigators took blood samples from 56 newly diagnosed patients, including 37 with Delta infections and 19 with Omicron infections. All were mildly ill, such as with flu-like symptoms, but none were hospitalized. To characterize how variant and vaccination status impact shedding of

viable virus, we serially sampled symptomatic outpatients newly diagnosed with COVID-19. Anterior nasal swabs were tested for viral load, sequencing, and viral culture.

Time to PCR conversion was similar between individuals infected with the Delta and the Omicron variant. Time to culture conversion was also similar, with a median time to culture conversion of 6 days (interquartile range 4-8 days) in both groups. There were also no differences in time to PCR or culture conversion by vaccination status.



Comment: Although it is unknown exactly how much live virus is needed to spread the disease to others, the data presented suggest that people with mild COVID-19 infection may be contagious on average for 6 days, and sometimes longer. Unlike other papers which did show increased clearance in vaccinated versus unvaccinated, this paper did not see a difference. The duration of live viral shedding does match other studies which demonstrated that live viral shedding maybe longer than the 5 days. The antigen test seemed to corelate with live virus. Decisions about isolation and masking should take such information into account, regardless of variant or prior vaccination status.

Real-world incidence of breakthrough COVID-19 hospitalization after vaccination versus natural infection in a large, local, empaneled primary care population using time-to-event analysis

Clin Infect Dis published online March 6, 2022

doi/10.1093/cid/ciac186/6542971

The investigators compared the incidence of breakthrough hospitalization after natural infection versus vaccination using time-to-event analysis in a real-world setting among empaneled primary care patients at a large academic healthcare institution in the US Midwest.

Patients contributed person-time in the following immune statuses:

- vaccine immunity, beginning 14 days after the second dose of mRNA vaccine or first dose of Johnson & Johnson vaccine
- natural immunity, beginning 90 days after the initial positive PCR/antigen test
- vaccine and natural immunity, beginning 14 days after the second dose of mRNA vaccine or first dose of Johnson & Johnson vaccine and 90 days after the initial positive PCR/antigen test.

During a follow-up time of 21 calendar months, out of 106,349 primary care patients (mean age, 52.3 years; 56.6% were female), there were 69 breakthrough COVID-19 hospitalizations. Of these, 65 (0.06%) occurred among 102,613 patients with vaccine immunity, 3 (0.03%) occurred among 11,047 patients with natural immunity, while the remaining 1 (0.01%) patient was among 7,313 patients with both natural and vaccine immunity.

The incidence rate ratio (IRR) comparing natural immunity to vaccine immunity was 0.60 (95% confidence interval [CI] 0.12,1.83; *P* = 0.55) and the IRR comparing the combination of vaccine immunity and natural immunity to vaccine immunity was 0.25 (95% CI 0.01,1.43; *P* = 0.19). In sensitivity analyses restricting to patients aged above 50 years and above 65 years, results were consistent with the main analysis indicating the highest incidence rate in the vaccine immunity group and lowest incidence for the combination of vaccine immunity and natural immunity.

Most of the patients with natural and vaccine immunity (57%) and vaccine immunity only (63%) received the Pfizer-BioNTech vaccine, followed by the Moderna vaccine (36% and 32%, respectively).

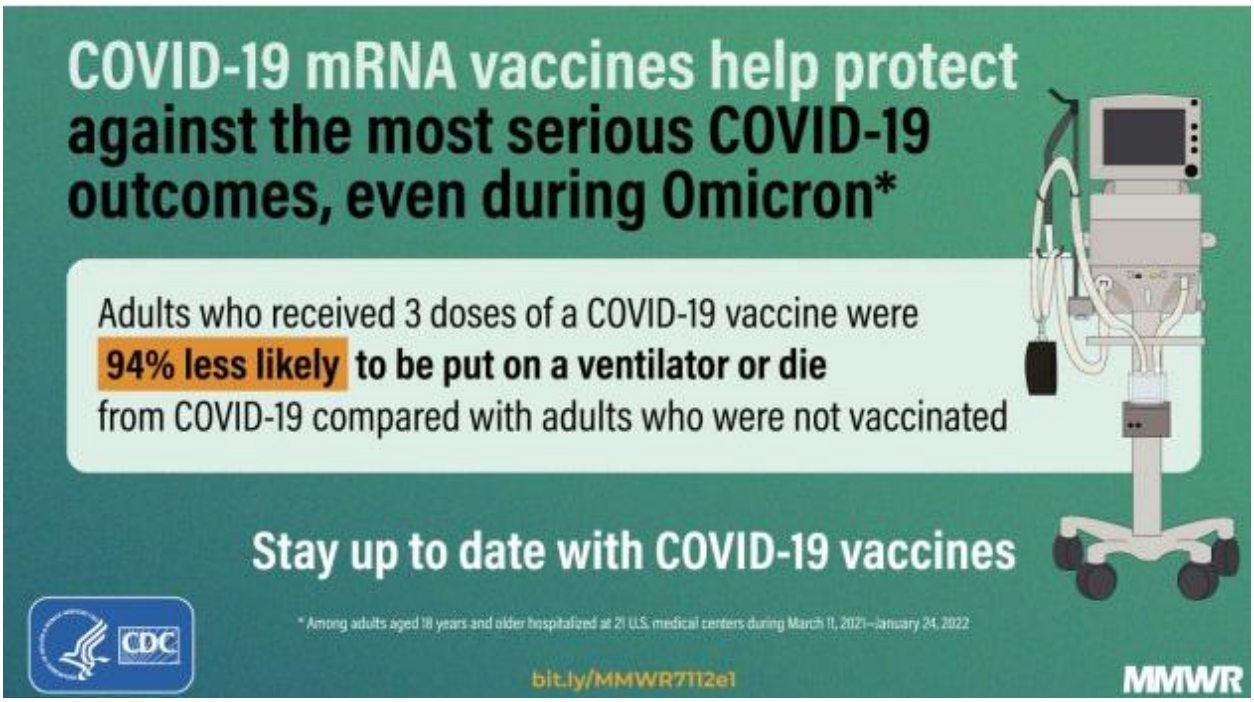
Comment: This analysis found that both natural infection and vaccination led to low incidence rates of breakthrough COVID-19 hospitalization, with natural immunity providing slightly better (but not statistically insignificant) protection than vaccine immunity alone. Double immunity (both prior natural infection plus vaccination) led to lower incidence rates than either natural immunity or vaccine immunity alone, though again this did not reach statistical significance. Despite the results in this study additional studies may still needed to determine the comparative effectiveness of natural immunity versus vaccination in preventing COVID-19 hospitalization, but it is time to consider natural immunity in vaccine recommendations.

Effectiveness of mRNA Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death — United States, March 2021–January 2022

MMWR March 25, 2022

Using a case-control design, mRNA vaccine effectiveness (VE) against COVID-19–associated IMV and in-hospital death was evaluated among adults aged ≥18 years hospitalized at 21 U.S. medical centers during March 11, 2021–January 24, 2022. During this period, the most commonly circulating variants of SARS-CoV-2, the virus that causes COVID-19, were Alpha, Delta, and Omicron. Previous vaccination (2 or 3 versus 0 vaccine doses before illness onset) in prospectively enrolled COVID-19 case-patients who received MV or died within 28 days of hospitalization were compared with that among hospitalized control patients without COVID-19.

Among 1,440 COVID-19 case-patients who received MV or died, 307 (21%) had received 2 or 3 vaccine doses before illness onset. Among 6,104 control-patients, 4,020 (66%) had received 2 or 3 vaccine doses. Among the 1,440 case-patients who received MV or died, those who were vaccinated were older (median age = 69 years), more likely to be immunocompromised (40%), and had more chronic medical conditions compared with unvaccinated case patients (median age = 55 years; immunocompromised = 10%; $p<0.001$ for both). VE against MV or in-hospital death was 90% (95% CI = 88%–91%) overall, including 88% (95% CI = 86%–90%) for 2 doses and 94% (95% CI = 91%– 96%) for 3 doses, and 94% (95% CI = 88%–97%) for 3 doses during the Omicron-predominant period.



Comment: Analysis of data on severe COVID-19 outcomes from this multistate hospital network found that receipt of 2 or 3 doses of a COVID-19 mRNA vaccine conferred 90% protection against COVID-19–associated MV or in-hospital death among adults. Most vaccinated patients who experienced COVID-19–associated MV or who died in hospital were older or had complex underlying conditions, commonly immunosuppression. Protection against MV or death was consistent throughout the Delta and Omicron periods and was higher in adults who received a third vaccine dose, including 94% during the Omicron period. Although receipt of 3 mRNA vaccine doses was associated with better protection against critical COVID-19 outcomes than was receipt of 2 doses, understanding the durability of protection over time or against emerging SARS-CoV-2 variants will require continued surveillance. In addition, although adjustments were made for calendar time, age, and race/ethnicity, among other potential confounders, unmeasured or residual confounders are always possible. Bottom line: COVID-19 mRNA vaccines are highly effective in preventing the most severe forms of COVID-19.