ANTIMICROBIALS IMMUNIZATION

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Definitions

- Bacteriostatic activity is the ability of an anti-infective agent to inhibit the growth of a micro-organism.
- It is a reversible action.
- Bactericidal activity is the ability to kill a micro-organism.
- It is irreversible.
- Autolysins are involved.
- The minimum inhibitory concentration (MIC) is the lowest drug concentration that inhibits growth.
- The minimum bactericidal concentration (MBC) is the lowest concentration that kills 99.9% of the bacterial population (a 3-log kill).
- Only free (non-protein bound) drug is effective.

Delivery

- Five doses are required to achieve a steady state level.
- If a loading dose is given, steady state levels may be maintained from the first dose.
- Alternatively, continuous infusion may be employed to maintain steady state levels.
- For synergism, the agents employed must be bactericidal (penicillins and aminoglycosides, fluoroquinolones or vancomycin and β-lactams).
- Bactericidal agent less effective in slow growth phase.
- Macrolides batericidal in high doses.
- Tetracycline and β-lactams should not be combined.

Delivery

- Time (of exposure) dependent killing is noted with penicillins, cephalosporins, aztreonam, carbapenems, vancomycin, macrolides, clindamycin, oxazolidinones, ketolides, tetracyclines, streptogramins, and azoles.
- There is no effect of the antibiotic when its level falls below the MIC when treating gram negative organisms.
- A limited (1-2 hour) effect is noted with use of carbapenems, vancomycin, macrolides, and clindamycin when treating gram positive organisms.

Delivery

- Concentration dependent killing is seen with fluoroquinolones, aminoglycosides, metronidazole, amphotericin B, flucytosine, nystatin, echinocandins, and daptomycin.
- Rate and extent of bacterial killing is maximized at high drug levels.
- Significant post-antibiotic effect noted when treating gram negative organisms, permitting extended dosing of aminoglycosides, for example.

Antibiotic inhibition of folate biosynthesis

- Folic acid synthesis inhibitors.
- Competition with p-aminobenzoic acid as a substrate for dihydropteric acid synthetase.
- Too little tetrahydrofolic acid results.
- Inhibit nucleotide synthesis.
- Sulfonamides used for Nocardia, Toxoplasma.
- Dapsone (a sulfone) is used for treatment of Mycobacteria.
- Concentrate in macrophages.

Antibiotic inhibition of folate biosynthesis

- Dihydrofolate reductase inhibitors
- Too little tetrahydrofolic acid results. Inhibit nucleotide synthesis.
- Trimethoprim inhibits bacterial dihydrofolate reductase.
- Pyrimethamine inhibits malarial dihydrofolate reductase.
- Concentrate in macrophages.
- Sulfonamides and trimethoprim used together to treat enteric and uroepithelial pathogens, Pneumocystis jiroveci.

Antibiotic inhibition of murein synthesis

- β-lactams irreversibly inhibit dd-transpeptidase (a serine hydrolase), which catalyzes the peptide cross-linkage in murein.
- Stops further cell wall synthesis.
- Release of autolysins.
- Enzymatic destruction of murein.
- Lysis due to high internal osmotic pressure.
- Bactericidal in cell division only.
- Intracellular bacteria not effected.

Antibiotic inhibition of murein synthesis

- Porins serve as barrier to in gram negative organisms.
- Penicillinases, cephalosporinasesin periplasm in many gram negative organisms
- Zinc metalloenzymes attack all β-lactams.

Penicillins

- Penicillin is bound to a penicillin binding protein.
- Activates autolytic enxymes.
- However, is susceptible to penicillinase.
- Drug of choice for Streptococcus, Neisseria meningitidis, Clostridium spp., and Treponemal infections.
- Methicillin, nafcillin, dicloxacillin are resistant to penicillinases (bulkier R group).
- Effective against Staphylococci (Dicloxacillin, against Streptococci as well.)

Penicillins

- Aminopenicillins are sensitive to penicillinase.
- Combined with clavulinic acid (penicillinase inhibitor).
- Also used for Hemophilus, Listeria, Chlamydial infections.
- Piperacillin (more than ticarcillin) is effective against Pseudomonas, Klebsiella, Enterobacter, and multiple drug resistant gram negative bacilli.
- Penicillinase sensitive.
- Combined with tazobactam (penicillinase inhibitor).
- Synergistic with aminoglycosides.

Cephalosporins

- Less susceptible to penicillinases.
- Not as effective as penicillin against Streptococcus.
- 1st and 2nd generations (cefazolin, cephalothin; cefuroxime, cefotetan) used for Hemophilus, Proteus, Klebsiella, Enterobacter, Serratia infections.
- 3rd generation used in meningitis (cefoperazone, ceftriaxone), gonorrhea (ceftriaxone), Pseudomonas (ceftazidime).
- 4th generation active against Pseudomonas and multiple drug resistant bacteria (cefepime). .

Carbapenems and monobactam

- Imipinem is a carbapenem resistant to β-lactamase. Administered with cilastin (inhibitor of renal dihydropeptidase I).
- Meropenem is a carbapenem resistant to β-lactamase and to renal dihydropeptidase I.
- Used in Enterobacter infections.
- Aztreonam is a monobactam resistant to β-lactamase.
- No cross-allergenicity with penicillins.
- No activity against gram positives or anerobes

Antibiotic inhibition of RNA transcription

- Rifamycin
- Blockage of β unit of DNA-dependent RNA polymerase. Bactericidal.
- Rifabutin used in the treatment of Mycobacterium tuberculosis.
- Rifampin prophylaxis for Hemophilus influenzae and Neiseria meningitidis
- Spectinomycin
- Binds to 30S subunit; 70S complex formed is unstable.
- Treat gonorrhea only.

Antibiotic inhibition of RNA transcription

- Aminoglycosides
- Blockage of elongation (30S ribosome) and amino acid-position occupancy by minoacyl-tRNA.
- Bacteriacidal in all stages of cell cycle.
- Require Oxygen for uptake.

Antibiotic inhibition of RNA transcription

- Tetracyclines
- Blockage of elongation and initiation (30S ribosome amine-position occupancy by aminoacyl- tRNA).
- Energy dependent transport mechanism in bacteria.
- Bacteriostatic. (Tigecycline does not induce tetracycline efflux pump.)
- Limited CNS penetration.

Antibiotic inhibition of protein synthesis

- Tetracycline used to treat Ricketssiae, Vibrios, Chlamydia, Francisella, Plasmodium falciparum.
- Second line after penicillin for syphilis (no studies, however, have evaluated its efficacy).
- Interferes with β-lactams
- Chloramphenicol
- Inhibition of peptidyl transferase activity (50S ribosome).
- Bacteriostatic.
- Used in treatment of typhoid fever, meningitis.
- May induce aplastic anemia.

Antibiotic inhibition of protein synthesis

- Macrolides (erythromycin, azithromycin, clarithromycin).
- Inhibition of elongation of the polypeptide chain by blocking the release of t-RNA (bind to the 23S rRNA of the 50S ribosome).
- Bacteriostatic (bactericidal at high doses).
- Methylation of 23S ribosomal RNA causes resistance.
- Efflux pump also extrudes drug.
- Legionella drug of choice.

Antibiotic inhibition of protein synthesis

- Lincosamide (clindamycin), ketolides (telithromycin), streptogramins (quinopristin/dalfopristin) have mechanism of action similar to macrolides.
- Clindamycin useful for anerobes.
- Implicated as causative agent in C. dificile pseudomembranous colitis.

Antibiotic inhibition of protein synthesis

- Telithromycin not affected by methylation nor is it extruded by a drug pump.
- Quinopristin/dalfopristin
- Bactericidal.
- Used against MRSA (methicillin resistant Staph. aureus) and VRE (vancomycin resistant enterococcus).

Antibiotic inhibition of protein synthesis

- Linezolid, an oxazolidinone, binds to the interphase of both subunits of the 50S ribosome and inhibits initiation complex formation.
- No cross-resistance with other classes or compounds.
- Effective when vancomycin fails (MRSA, VRE).
- Mupirocin blocks isoleucine-tRNA synthetase. Used topically.

Antibiotic inhibition of nucleic acid synthesis

- 4-Quinolones (parent compound is nalidixic acid)
- Inhibition of the DNA gyrase (topoisomerase II) and topoisomerase IV, prohibiting religation of the chromosome, resulting in the inhibition of DNA replication.
- Gram negative rods.
- Dose levels as a result of oral absorption equivalent to intravenous administration.
- Concentrates in macrophages.
- Good tissue penetration.
- Targets mitochondrial rich tissue (joint laxity may result)

Cell membrane alteration

- Vancomycin is a glycopeptide that binds the d-alanine d-alanine portion of the outer cell wall after glycosylcarrier protein translocated across membrane.
- Steric hindrance prevents precursor binding to synthetase, blocking murein biosynthesis.
- No sensitivity to β-lactamase.
- Bactericidal against gram positive organisms.

Cell membrane alteration

- Vancomycin cannot penetrate outer membrane of gram negative organisms.
- Terminal d-alanine replaced with d-lactone confers resistance to vancomycin.
- Used to treat MRSA, Enterococci.
- Daptomycin is a cyclic lipopeptide that binds to inner bacterial membrane
- Leads to leakage of ions.
- Used with multi-drug resistant gram positive organisms.

Cell membrane alteration

- Bacitractin binds to lipid pyrophosphate of outer cell wall.
- Blocks glycosyl carrier protein dephosphorylation (final step in generation of cell wall).
- No sensitivity to β-lactamase.
- Bactericidal.
- Topical use.

Cell membrane alteration

- Isoniazid is a nicotinamide analogue that blocks NAD, inhibits fatty acid synthetase-2 and mycoloic acid synthesis.
- Is a pro-drug that requires bacterial peroxidase for activation.
- Hepatotoxic.
- Mycobactericidal.
- Depletes vitamin $B_{6.}$

Cell membrane alteration

- Pyrazinamide is a nicotinamide analogue that blocks NAD, inhibits fatty acid synthetase-1 and mycoloic acid synthesis.
- Is a prodrug.
- Hepatotoxic.
- Mycobactericidal.
- Ethambutol inhibits arabinosyl transferase, an enzyme required for synthesis of arabinogalactan, a component of the mycobacterial cell wall.
- Mycobacteriostatic.
- Myelin toxic.

Cell membrane alteration

- Cycloserine competitively inhibits alanine-racemase and alanine-synthetase activity, blocks peptidoglycan synthesis.
- Agonist at the serine site of the NMDA glutamate receptor.
- Used as a second line drug for treatment of tuberculosis.
- Ethionamide inhibits mycolic acid synthesis.
- A second line drug for treatment of tuberculosis.

Other antibiotic mechanisms

- Polymyxins are cationic proteins that disrupt cellular membrane (detergent effect).
- Anti-pseudomonals.
- Fosfomycin binds to pyruval transferase in cytoplasm (PEP structural analog).
- Blocks peptidoglycan synthesis.

Other antibiotic mechanisms

- Metronidazole functions as an electron acceptor.
- Intracellular reduction by nitroreductase.
- Produces nitro radical anion that leads to DNA strand breaks, prevent proper functioning as a template for DNA polymerase.
- Bactericidal.
- Effective against protozoa and anerobes.

Other antibiotic mechanisms

- Alternative drug to metronidazole for treatment of flagellates is nitazoxamide.
- Blocks ferridoxin dependent pyruvate oxidoreductase system, limiting ATP formation.
- Metallic taste with metronidazole (rectally administered form does not have this reaction).
- May precipitate disulfuram reaction if alcohol ingested with medication.
- Discolored dark urine may be present.
- Nitazoxamide is not mutagenic, has lesser toxicity than does metronidazole.

Major anti-fungals

- Polyenes
- Binding at site or ergosterol (only found in fungus). Forms membrane pores.
- Fungicidal.
- Amphotericin B is the drug of choice in serious fungal infections.
- Poor absorption.
- Avidly binds lipoproteins and plasma membranes. 10% excreted daily.
- Nephrotoxic.
- Nystatin used topically.

Major anti-fungals

- Azoles
- Inhibit 14-α demethylase, an enzyme in the lanosterol-ergosterol pathway.
- Membrane function altered.
- Fungistatic.
- Miconazole for topical use.
- Good absorption of other azoles.
- Itraconazole (in cyclodextrin) has poor CSF penetration
- Inhibit P450 metabolism.

Major anti-fungals

- Fluconazole has bioavailability, penetrates CSF.
- Eliminated via the kidney.
- Used to treat Candida, Coccidioides, Cryptococcus.

Major anti-fungals

- Flucytosine
- Converted to fluoruracil, inhibits thymidine synthetase, blocks DNA synthesis.
- Good CSF penetration.
- Use in cryptococcal meningitis.
- Synergistic with amphotericin for systemic mycoses.

Major anti-fungals

- Capsofungin is an echinocandin.
- Inhibits synthesis of β(1,3) D-glucan, a major component of fungal cell walls.
- Poorly absorbed.
- No P450 metabolism.
- Fungicidal.
- Used in the treatment of candidemia, invasive aspergillosis.

Other anti-fungals

- Griseofulvin
- Binds to mitotic spindle, inhibits tubulin. Deposited in keratin containing tissues. Activates P450.
- Dermatophytoses.
- Terbinafine
- Inhibits squalene peroxidase (ergosterol precursor synthesis blocked).
- Dermatophytoses.

Anti-protozoals

- Metronidazole for treatment of intestinal and urogenital protozoa.
- Paromycin may be useful for Cryptosporidium.
- Sulfonamide and pyrimethamine for treatment of Toxoplasma.
- Trimethoprim/Sulfonamide or pentamidine for treatment of Pneumocystis.
- Atovaquine and proguanil may also be used together as are synergistic.

Anti-protozoals

- Dapsone blocks dihydropteroate synthetase.
- Used in treatment of Mycobacterium leprae, Pneumocystis jiroveci.
- Causes hemolysis if G6PD deficiency.

Anti-protozoals

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Anti-protozoals

- Nifurtimox for treatment of Trypanosoma cruzi.
- Reduction in cell leads to formation of toxic metabolites.
- Suramin for treatment of T. gambiense or T. rhodesiense.
- Melarsoprol is used if there is CNS involvement.
- Inactivate pyruvate kinase.
- Stibogluconate is used for treatment of Leishmania.
- Pyrimethamine (dihydrofolate reductase inhibitor) and sulfadiazine (dihydropteroate synthetase inhibitor) used together for Toxoplasma, Plasmodium spp.

Anti-malarials

- Chloroquine kills blood schizonts.
- Chloroquine binds to and inhibits DNA and RNA polymerase.
- May also interfere with nucleoprotein synthesis.
- Is a mannose blocker.
- Inhibits prostaglandin effects as well.
- Retinopathy a concern with long-term use.
- May prolong QT interval

Anti-malarials

- Interferes with metabolism and hemoglobin utilization by parasites.
- Heme polymerization by the parasite is essential to limiting toxic injury.
- Aggregates of ferriprotoporphyrin IX act as chloroquine receptors, blocking further polymerization and causing membrane damage (reactive oxygen species).
- Leads to hemolysis in G6PD deficiency.

Anti-malarials

- Chloroquine concentrates within parasite acid vesicles and raises internal pH resulting in inhibition of parasite growth.
- Mefloquine is schizonticidal as well.
- Primaquine is hypnozoticidal (exo-erythrocytic form of malaria in the liver).
- Binds DNA, inhibits mitochondria.
- Atavaquone inhibits pyrimidine synthesis and blocks mitochondrial electron transport (cytochrome bc1).
- Used with proguanil (metabolized to cyloguanil), a potent dihydrofolate reductase inhibitor.

Anti-malarials

- Chloroquine plus primaquine for treatment of Plasmodium vivax or ovale.
- Chloroquine (with or without doxycycline) for treatment of P. falciparum.
- If chloroquine resistant P. falciparum, mefloquine plus doxycycline.
- (Atovaquine and proguanil may also be used together for treatment of resistant P. falciparum as are synergistic.)
- Quinine plus clinadmycin in pregnant woman.
- Quinidine intravenously if high-risk.

Anti-helminthics

- Praziquantel for treatment of intestinal infestation of cestodes and trematodes.
- Blocks voltage-gated Calcium channels.
- Albendazole for treatment of organ infestation.
- May require surgical resection of cysts.
- Inhibits polymerization of parasitic microtubules.
- Mebendazole (thiobendazole, albendazole) inhibits microtubule assembly.
- Drug of choice for cystericosis.
- Use to treatment infestation of adult worm of Trichinella, Dracunculus, and Ancylostoma larvae.

Anti-helminthics

- Pyrantel pamoate causes neuromuscular blockade and spastic paralysis of parasites.
- For treatment of intestinal infestation of nematodes.
- Blocks glucose absorption.

Anti-helminthics

- Ivermectin is an agonist of glutamate-gated Cl^- channels
- Leads to hyperpolarization of nerve and muscle cells, leading to paralysis of parasites.
- For treatment of Strongylodies and Onchocerca (paralyzes offspring).
- Effective against filaria.
- Inflammatory response because of rapid killing.
- Diethylcarbamazine for treatment of Wucheria and Loa.
- Effective against Covid

Anti-virals

- Acyclovir used in treatment of Herpes simplex viral infections (types 1,2, as well as Varicella-Zoster)
- It inhibits DNA polymerase.
- Acyclovir must be activated within the cell by a virus-encoded thymidine kinase that phosphorylates the drug.
- As it lacks a 3'hydorxyl group, and, thus, a ribose ring, DNA replication is terminated as there is no site to which the next triphosphated nucleoside can be added.
- It does not affect viral latency.
- Weak EBV blocker.

Anti-virals

- Fair oral absorption.
- Penetrates CSF.
- Eliminated by glomerular filtration and tubular secretion.
- Famciclovir is well absorbed.

Anti-virals

- Ganciclovir is used in treatment of severe Cytomegalovirus infections.
- Inhibits DNA polymerase (chain termination).
- Phosphorylation by viral kinase activates drug.
- Foscarnet inhibits the DNA polymerase of all Herpes viruses as well as the DNA polymerase of the retrovirus, Human Immunodeficiency Virus
- It is a pyrophosphate analogue that inhibits cleavage of pyrophosphate from nucleoside triphosphate, terminating DNA replication.
- Does not require activation by viral kinase.
- Virustatic.

Nucleoside reverse transcriptase inhibitors

- Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain
- Lack a 3’-OH group
- Require phosphorylation to be active
- Tenovir is a nucleotide reverse transcriptase inhibitor and does not require phosphorylation to be active
- Adverse effects include bone marrow suppression and peripheral neuropathy
- Lactic acidosis (nucleosides only)

Nucleoside reverse transcriptase inhibitors

- Emtricitabine has few adverse effects
- Selects for the M184V resistance mutation which confers high-level resistance
- Improves susceptibility to tenofovir.
- 5-8% of patients who begin abacavir have hypersensitivity reactions (HSRs).
- Risk highly associated with the presence of the HLA-B*5701 allele.
- Triple NRTI regimens are biologically inferior for treatment of HIV infections.

Non-nucleoside reverse transcriptase inhibitors

- Bind to reverse transcriptase at a site that differs from NRTIs.
- Do not require phosphorylation to be active
- Do not compete with nucleotides
- Rash and hepatotoxicity as common adverse events
- CNS symptoms common with efavirenz
- Not for use in pregnancy either
- Resistance mutations affect all NNRTIs

Integrase strand inhibitors

- INSTI-based regimens have quickly become the recommended regimens because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile.
- Prevent viral integration into host genome
- BIC and DTG, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs RAL and EVG and may have more activity against non-B subtypes of HIV
- TDF has higher renal and bone adverse effects than does TAF
- Hypercholesterolemia may be seen

Protease inhibitors

- Advantages include excellent virologic potency and a high barrier to drug resistance (since multiple mutations are required for a patient to develop resistance).
- Because PIs are metabolized via hepatic enzymes, these drugs have the potential for multiple drug interactions.
- They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance.
- CYP34A inhibitors

Drug names

- Nucleoside reverse transcriptase inhibitors (NRTI)
- ABC abacavir
- 3TC lamivudine
- FTC emtricitabine
- TAF tenofovir alafenamide
- TDF tenovir disoproxil fumarate
- CCR5 antagonists
- MVC maraviroc
- Entry Inhibitors (EI)
- IBA ibalizumab

Drug names

- Protease Inhibitors (PI)
- DRV/c darunavir with cobicistat
- DRV/r darunavir with ritonavir
- Integrase strand inhibitors (INSTI)
- BIC bictegravir
- DTG dolutegravir
- RAL raltegravir
- EVG/c elvitegravir with cobicistat
- Non-nucleoside reverse transcriptase inhitibots (NNRTI)
- NVP nevarapine

Other inhibitors

- CCR5 antagonists
- Maraviroc binds to CCR5, preventing an interaction with gp120.
- CD4 post-attachment inhibitors
- Ibaluzimab is a monoclonal antibody that binds to domain 2 of CD4 and interferes with post-attachment steps required for the entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion.

Anti-virals

- Interferon-α blocks production of viral proteins by inducing the synthesis of a ribonuclease that degrades viral mRNA. (Produced in leukocytes. IFN-β produced in fibroblasts.)
- Ribavirin is a guanosine analogue.
- Blocks nucleic acid synthesis.
- Used in treating respiratory syncytial virus and chronic hepatitis C (with interferon-α).
- Avoid in thalassemia major.

Anti-virals

- Amantadine (and ramantidine) inhibits the uncoating of Influenza A virus by blocking the H^+ channel activity of the viral matrix protein (M2).
- Inhibits endosome acidification and entry of viral genome into the cell nucleus.
- Influenza B, C do not have a H^+ channel
- Viral resistance common
- Zanamir and oseltamivir inhibit the neuraminidase of both Influenza A and B viruses, limiting the release of progeny virus.
- Baloxavir inhibits cap-dependent endonuclease

Anti-virals

- Fomivirsen is an antisense DNA that binds to the mRNA of Cytomegalovirus, blocking protein synthesis.
- Gancyclovir is preferred
- Vitamin C enhances cAMP and cGMP production in monocytes.

Commonly used antibiotics

- Penicillin: Streptococcus species except Enterococcus; oral anerobes
- Ampicillin: Streptococcus species; oral anerobes (moderately active with Hemophilus influenzae, Enterococcus)
- Second or third generation cephalosporins; amoxicillin-clavulanate or ampicillin-sulbactam are preferred for suspected Streptococcus pneumoniae or Hemophilus influenzae.
- Trimethoprim-sulfamethoxazole: Streptococcus species except Enterococcus; Staphylococcus aureus of skin (including MRSA); Escherichia coli.

Commonly used antibiotics

- Clindamycin: Streptococcus species except Enterococcus; Staphylococcus aureus; anerobes
- Ciprofloxacin: Aerobic gram negative rods
- Other quinolones: Streptoccous species; Staphyloccus aureus
- Azithromycin, clarithromycin: Streptococcus species except Enterococcus; Hemophilus influenzae; Chlamydia; Mycoplasma pneumoniae; Helicobacter pylori; Mycoobacterium avium complex
- Intravenous therapy with high dose erythromycin or azithromycin if documented Legionella infection.

Commonly used antibiotics

- Tetracycline should be used empirically if Psittacosis, Chlamydia, or Q fever suspected.
- The aminoglycosides and aztreonam are the most effective drugs for gram negative organisms.
- Imipinem and meropenem have the widest spectrum of activity and are effective against gram positive organisms as well as gram negative organisms.

Antibiotic therapy

- Abscesses should be incised and drained.
- Staphyloccus aureus not resistant to methicillin is best treated with dicloxacillin or cephalexin. Dicloxacillin also provides excellent coverage of Streptococcus species (impetigo is often a mixed Staph. and Strep. infection)
- Skin infections (usually community acquired MRSA) respond to trimethoprim-sulfisoxazole, doxycycline, clindamycin, or linezolid. A beta-lactam may be added to the coverage if β-hemolytic streptococus spp. is suspected.

Antibiotic therapy

- Mupirocin should be applied to pustular lesions in children.
- For serious MRSA infections, intravenous vancomycin is begun. With improvement, it is possible to transition to oral clindamycin or linezolid.
- Daptomycin and teravancin are other agents available for MRSA.

Antibiotic therapy

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Anerobic infections

- Anerobes found in the mouth are generally sensitive to penicillin or ampicillin.
- Anerobes in the gastrointestinal tract (particularly Bacteroides fragilis) usually manufacture beta-lactamase. Ciprofloxacin is often the drug of choice.
- Clindamycin, metronidazole, amoxicillin-clavulanate or ampicillin-sulbactam, cefotetan, cefoxitin, imipinem, or meropenem are the best drugs for anerobic organisms from the gastrointestinal tract.
- Metronidazole is used with ciprofloxacin in the treatment of diverticulitis. Metronidazole or oral vancomycin is used in the treatment of Clostirdium difiicle infections.

Empirical IV antibiotic therapy

- Gram positive cocci
- Vancomycin (1.5mg/kg q6h to a maximum of 4g).
- Substitute rifampin (600mg/day) for adults receiving dexamethasone
- plus
- Cefotaxime (50mg/kg q6h in neonates)
- or
- Ceftriaxone (50-100mg/kg q12h in children, 2g q12h in adults)

Sepsis

- 200mg Thiamine q12h and 1500mg Vitamin C infusions q6h with 50mg hydrocortisone q6h for 48 hours is associated with greatly reduced mortality in both adult and pediatric patients.

Empirical IV antibiotic therapy

- Gram negative cocci
- Penicillin G (300,000 units/kg/d to maximum 24 million units)
- Gram positive bacilli
- Ampicillin (100mg/kg q8h in children, 2g q4h in adults)
- Or
- Penicillin G (300,000 units/kg/d to maximum 24 million units)

Empirical IV antibiotic therapy

- Gram negative bacilli
- Cefotaxime (50mg/kg q6h in neonates)
- or
- Ceftriaxone (50-100mg/kg q12h in children, 2g q12h in adults)
- or
- Ceftazidime (50-100mg/kg q8h to maximum 2g)
- plus
- Gentamicin (1.5kg/mg loading dose followed by 1-2mg/kg q8h)

Empirical IV antibiotic therapy

- Pseudomonas aeruginosa, gram negative enteric bacilli, Staphylococcus and Streptococcus spp. likely agents in septic shock.
- Vancomycin plus Gentamicin
- plus either
- Piperacillin/ tazobactam **or** Cefepime
- Activated drotrecogin alfa may be used in those septic patients whose APACHE II score is >25 and/or have multi-organ failure.

Empirical IV antibiotic therapy

- Septic shock post-splenectomy
- Streptococcus pneumoniae, Neisseria meningitidis, Hemophilus influenzae likely agents.
- Ceftriaxone plus Gentamicin
- Activated drotrecogin alfa may be used in those septic patients whose APACHE II score is >25 and/or have multi-organ failure.

Empirical IV antibiotic therapy

- Septic shock with rash
- Purpura fulminans (Streptococcus pneumoniae, Neisseria meningitidis, Hemophilus influenzae likely agents.)
- Ceftriaxone plus vancomycin
- If a lactam sensitive strain is identified, vancomycin may be discontinued

Empirical IV antibiotic therapy

- Septic shock with rash
- N. meningitidis
- Penicillin or ceftriaxone
- Consider Protein C replacement in fulminant meningococcemia.
- Rocky Mountain Spotted fever (Rickettsia rickettsi)
- Doxycycline

Empirical IV antibiotic therapy

- If both meningococcemia and RMSF are being considered:
- Chloramphenicol or ceftriaxone plus doxycycline.
- If RMSF is diagnosed, doxycycline is the proven superior agent.

Empirical IV antibiotic therapy

- Toxic shock syndrome
- Vancomycin plus clindamycin
- If penicillin or oxacillin sensitive strain is identified, either drug is superior to vancomycin.
- The site should be debrided.
- IV immunoglobulin may be employed in severe cases.

Empirical IV antibiotic therapy

- Septic shock with soft tissue findings
- If myonecrosis, Clostridial perfringens likely agent.
- If necrotizing fasciitis, Group A Streptococcus, or mixed aerobic/anerobic infection is likely.
- Penicillin **plus** clindamycin
- If methicillin resistant Staphylococcus aureus is suspected (MRSA),
- Vancomycin can be substituted for penicillin pending culture results.
- Immediate surgical evaluation is critical.

Empirical IV antibiotic therapy

- Bacterial meningitis
- If Streptococcus pneumoniae is suspected:
- Vancomycin plus ceftriaxone or cefotaxime (if neonate)
- Rifampin may be substituted for vancomycin in adults receiving dexamethasone.
- Dexamethasone improves outcomes in older adult patients with CSF leukocyte counts >1000/ml.
- If the patient is >50 years old, add ampicillin for coverage of Listeria monocytogenes.
- If a lactam sensitive strain is identified, vancomycin may be discontinued.
- 10-14 days therapy

Empirical IV antibiotic therapy

- If Hemophilus influenzae is suspected:
- Ceftriaxone
- If Neisseria meningitidis is suspected,
- Penicillin
- 7 days therapy
- If Group B Streptococcus (algalactiae) is suspected,
- Penicillin
- If Listeria monocytogenes is suspected,
- Ampicillin plus gentamicin
- 14-21 days therapy

Empirical IV antibiotic therapy

- If Enterobacteraciae are suspected,
- Gentamicin plus ceftriaxone (adults) or cefotaxime (neonates)
- If Pseudomonas aeruginosa, Acinetobacter suspected,
- Ceftazidime plus gentamicin
- 21 days therapy

Empirical IV antibiotic therapy

- Brain abscess, suppurative brain infection
- Staphylococcus spp., Streptococcus spp., anerobes, gram negative bacteria likely agents.
- Vancomycin plus metronidazole plus ceftriaxone
- **Spinal epidural abscess**
- Staphylococcus spp., gram negative bacteria likely agents.
- Vancomycin plus ceftriaxone
- If penicillin or oxacillin sensitive strain is identified, either drug is superior to vancomycin.
- Immediate surgical evaluation is critical.

Empirical IV antibiotic therapy

- Acute bacterial endocarditis
- Staphylococcus aureus, Streptococcus spp., HACEK group, Neisseria spp., Streptococcus pneumoniae are likely agents.
- Ceftriaxone plus vancomycin
- Immediate surgical evaluation is critical.

Empirical IV antibiotic therapy

- Cerebral malaria (Plasmodium falciparum)
- Quinine plus tetracycline
- Do not use steroids
- Babesiosis
- Either clindamycin plus quinine
- Or atovaquone plus azithromycin
- Atovaquone and azithromycin are as effective as clindamycin and quinine and are associated with fewer side effects.
- Treatment with doxycycline for potential coinfection with Borrelia burgdorferi or Ehrlichia spp. may be prudent.

HAART therapy

- The fixed-dose combinations of the nucleoside reverse transcription inhibitors tenofovir/ emtricitabine with the non-nucleoside reverse transcriptase inhibitor efavirenz which can be given once a day is the preferred initial choice. These drugs also have activity against Hepatitis B virus.
- Neurotoxicity is a problem with efavirenz.

HAART therapy

- Protease inhibitors are potent inhibitors of viral replication.
- If nelfinavir or atazanavir are not employed, current guidelines recommend ritonavir boosting of the other protease inhibitors if possible.
- Lipodystrophy is a problem with protease inhibitor use.

Active immunization

- Immune response stimulated by presentation of protein antigen to T cells.
- Memory B and T cells produced.
- Immune response stimulated by presentation of polysaccharide.
- Conjugated to hapten for presentation to cells.
- Memory B cells produced.
- Effective response to vaccine requires repeat immunizations to boost memory cells.

Vaccine types

- Killed, whole-cell vaccines involve the inactivation of viruses and bacteria with heat or chemicals.
- Induces predominantly a humoral immune response. Requires repeated booster immunizations.
- Risk of inducing response to cell vehicle (mitigated if acellular vaccine used).
- Live-attenuated, whole-cell vaccines involve the use of weakened strains of the micro-organism.
- Can reproduce in the host.
- Produces both a humoral and a cellular response.
- May not require booster immunization.
- May revert to virulent form.

Vaccine types

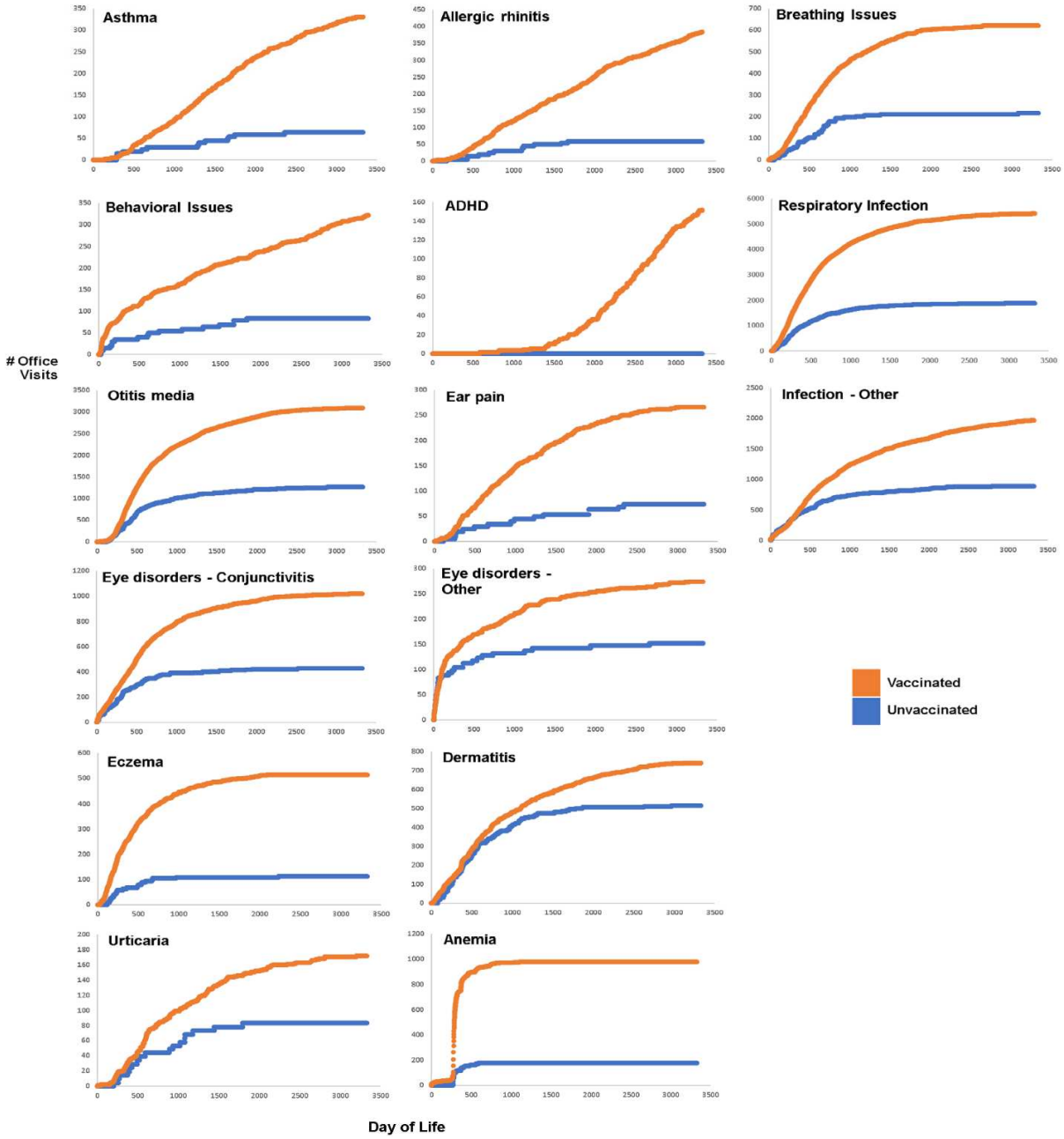
- Toxoids are exotoxins inactivated by formalin.
- Administration leads to humoral response (in animal from which anti-serum is obtained).
- In recent years, exotoxin genes as well as molecular antigens have been cloned in yeast or bacteria. (recombinant vaccines)
- Capsular polysaccharide may be attached to protein carrier to induce T-cell response as well (e.g., Hemophilus influenzae 1b vaccine links polysaccharide to tetanus toxoid).
- May see serum sickness as non-human cell lines employed.

Vaccine types

- mRNA “vaccines”
- Engineered against specific gene
- Taken up by T cells; immune response generated
- In animal experiments, later challenge with wild type virus has led to death of immunized animals
- Exposure to free nucleic acid is associated with later development of autoimmune disease (and is thought to be a major reason for the 8:1 prevalence of autoimmune disease in women).

Passive immunization

- Transfer of preformed immunoglobulin between mother and fetus (transplacental), in colostrum, (or by injection).
- Does not activate immune response.
- No memory cells produced.



Lyons-Weiler J, Thomas P. Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination. International Journal of Environmental Research and Public Health. 2020; 17(22):8674. https://doi.org/10.3390/ijerph17228674

Table 1 Recommended Adult Immunization Schedule by Age Group, United States, 2024

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
COVID-19	1 or more doses of updated (2023–2024 Formula) vaccine (See Notes)			
Influenza inactivated (IIV4) or **Influenza recombinant** (RIV4)	1 dose annually			
or	or			
Influenza live, attenuated (LAIV4)	1 dose annually			
Respiratory Syncytial Virus (RSV)	Seasonal administration during pregnancy. See Notes.			≥60 years
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For healthcare personnel, see notes
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)				See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication			
Mpox				

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of immunity

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

No recommendation/ Not applicable

Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2024

Always use this table in conjunction with Table 1 and the Notes that follow. Medical conditions or indications are often not mutually exclusive. If multiple medical conditions or indications are present, refer to guidance in all relevant columns. See Notes for medical conditions or indications not listed.

VACCINE	Pregnancy	Immunocompromised (excluding HIV infection)	HIV infection CD4 percentage and count		Men who have sex with men	Asplenia, complement deficiency	Heart or lung disease	Kidney failure, End-stage renal disease or on dialysis	Chronic liver disease; alcoholism[a]	Diabetes	Healthcare Personnel[b]
			<15% or <200mm³	≥15% and ≥200mm³							
COVID-19		See Notes									
IIV4 or RIV4	1 dose annually										
LAIV4					1 dose annually if age 19–49 years		1 dose annually if age 19–49 years				
RSV	Seasonal administration. See Notes	See Notes				See Notes					
Tdap or Td	Tdap: 1 dose each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	*										
VAR	*			See Notes							
RZV		See Notes									
HPV	*	3 dose series if indicated									
Pneumococcal											
HepA											
Hep B	See Notes									Age ≥ 60 years	
MenACWY											
MenB											
Hib		HSCT: 3 doses[c]				Asplenia: 1 dose					
Mpox	See Notes				See Notes						See Notes

- Recommended for all adults who lack documentation of vaccination, **OR** lack evidence of immunity
- Not recommended for all adults, but recommended for some adults based on either age **OR** increased risk for or severe outcomes from disease
- Recommended based on shared clinical decision-making
- Recommended for all adults, and additional doses may be necessary based on medical condition or other indications. See Notes.
- Precaution: Might be indicated if benefit of protection outweighs risk of adverse reaction
- Contraindicated or not recommended *Vaccinate after pregnancy, if indicated
- No Guidance/ Not Applicable

Table 1 Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars.
To determine minimum intervals between doses, see the catch-up schedule (Table 2).

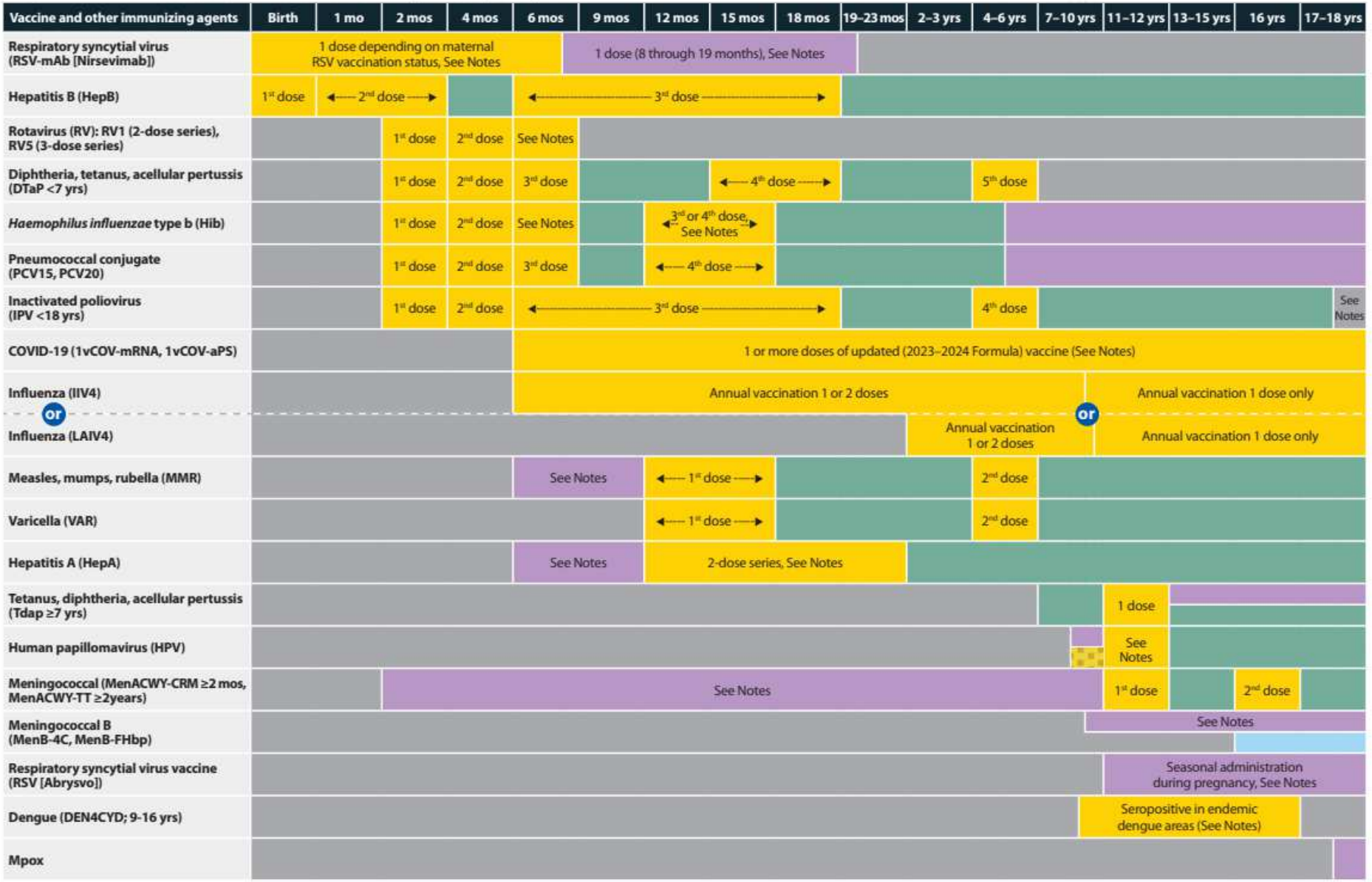


Table 3 Recommended Child and Adolescent Immunization Schedule by Medical Indication, United States, 2024

Always use this table in conjunction with Table 1 and the Notes that follow. Medical conditions are often not mutually exclusive. If multiple conditions are present, refer to guidance in all relevant columns. See Notes for medical conditions not listed.

Vaccine and other immunizing agents	Pregnancy	Immunocompromised (excluding HIV infection)	HIV infection CD4 percentage and count[a]		CSF leak or cochlear implant	Asplenia or persistent complement component deficiencies	Heart disease or chronic lung disease	Kidney failure, End-stage renal disease or on Dialysis	Chronic liver disease	Diabetes
			<15% or <200mm	≥15% and ≥200mm						
RSV-mAb (nirsevimab)		2nd RSV season		1 dose depending on maternal RSV vaccination status, See Notes			2nd RSV season for chronic lung disease (See Notes)	1 dose depending on maternal RSV vaccination status, See Notes		
Hepatitis B										
Rotavirus		SCID[b]								
DTaP/Tdap	DTaP Tdap: 1 dose each pregnancy									
Hib		HSCT: 3 doses	See Notes			See Notes				
Pneumococcal										
IPV										
COVID-19		See Notes								
IIV4										
LAIV4							Asthma, wheezing: 2–4 years[c]			
MMR	*									
VAR	*									
Hepatitis A										
HPV	*	3 dose series. See Notes								
MenACWY										
MenB										
RSV (Abrysvo)	Seasonal administration, See Notes									
Dengue										
Mpox	See Notes									

Recommended for all age-eligible children who lack documentation of a complete vaccination series

Not recommended for all children, but is recommended for some children based on increased risk for or severe outcomes from disease

Recommended for all age-eligible children, and additional doses may be necessary based on medical condition or other indications. See Notes.

Precaution: Might be indicated if benefit of protection outweighs risk of adverse reaction

Contraindicated or not recommended
*Vaccinate after pregnancy, if indicated

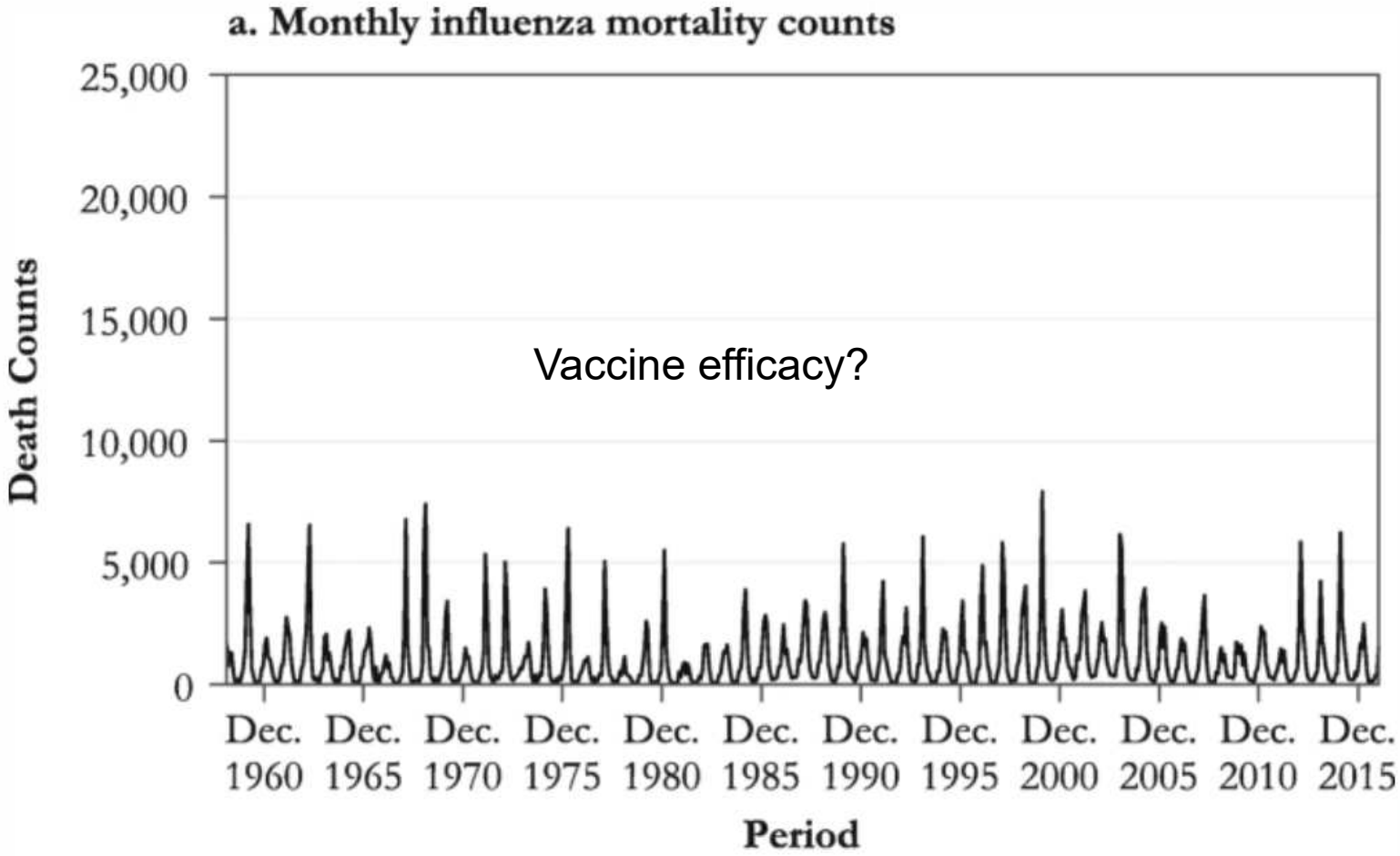
No Guidance/ Not Applicable

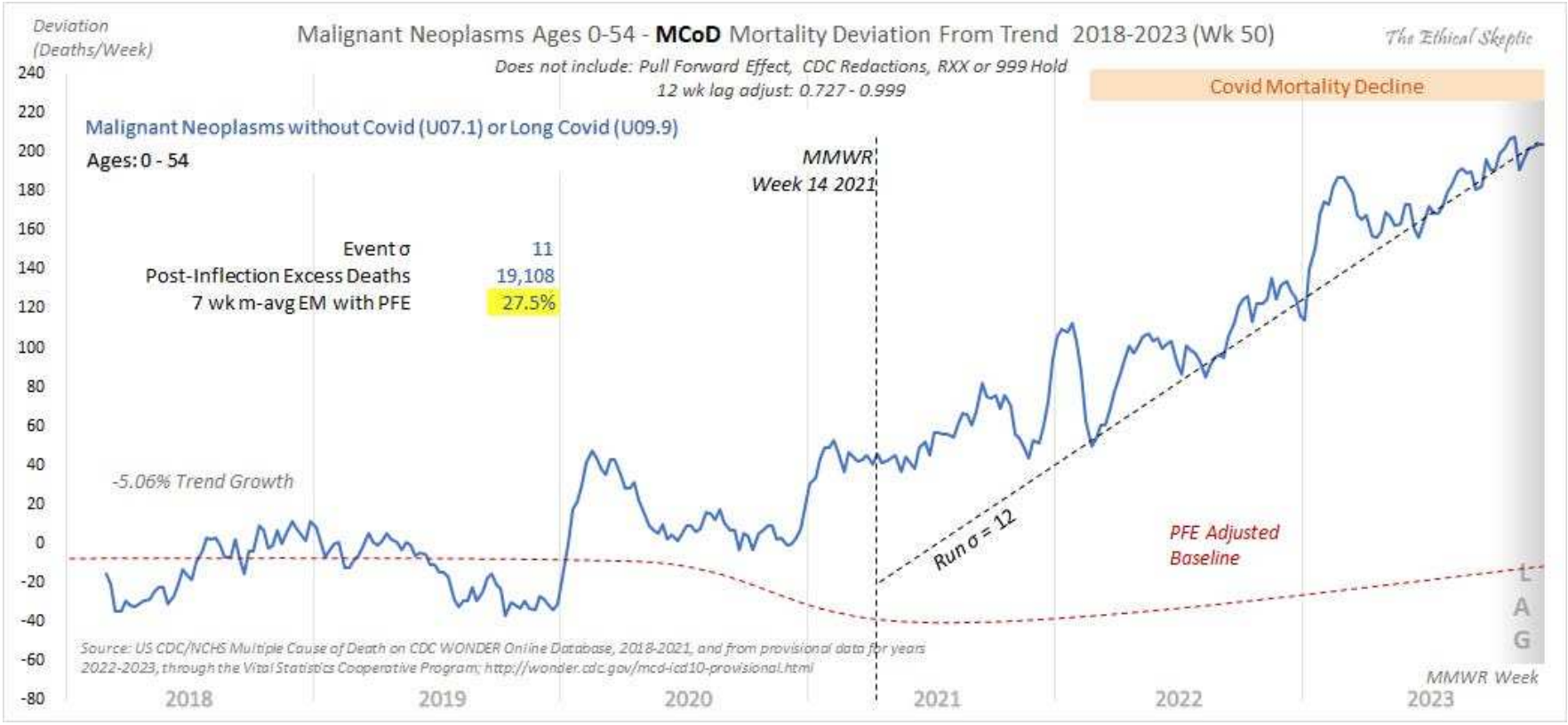
a. For additional information regarding HIV laboratory parameters and use of live vaccines, see the General Best Practice Guidelines for Immunization, "Altered Immunocompetence," at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html and Table 4-1 (footnote J) at

b. Severe Combined Immunodeficiency

c. LAIV4 contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months

Fig. 3

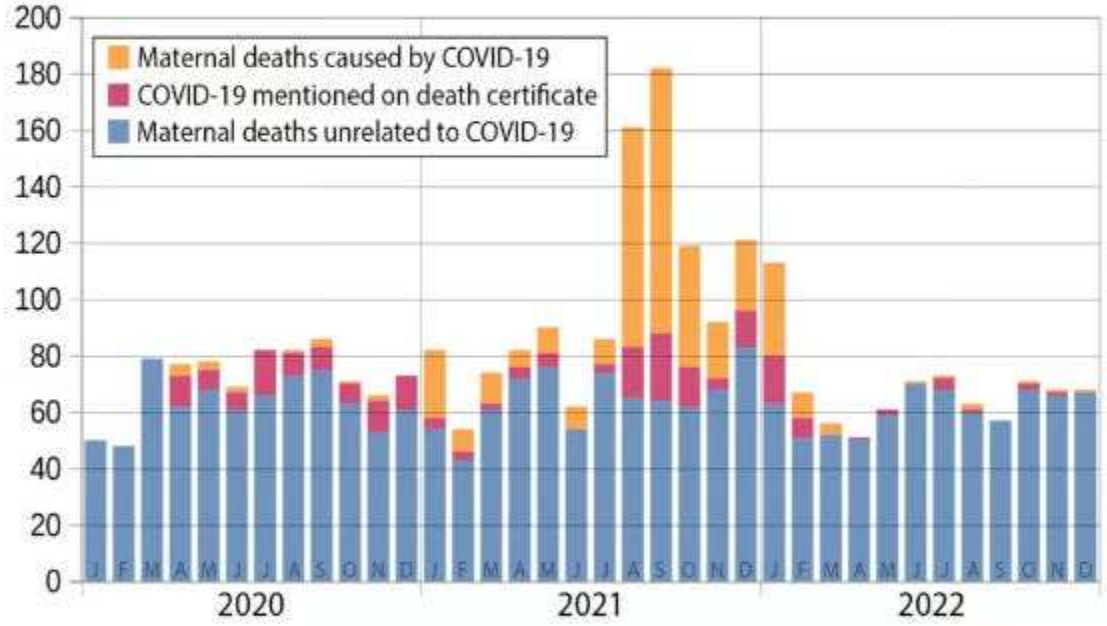

a. Monthly influenza mortality counts
Death Counts
25,000
20,000
15,000
10,000
5,000
0
Vaccine efficacy?
Dec. 1960
Dec. 1965
Dec. 1970
Dec. 1975
Dec. 1980
Dec. 1985
Dec. 1990
Dec. 1995
Dec. 2000
Dec. 2005
Dec. 2010
Dec. 2015
Period



Post roll-out of mRNA vaccine for Covid 19

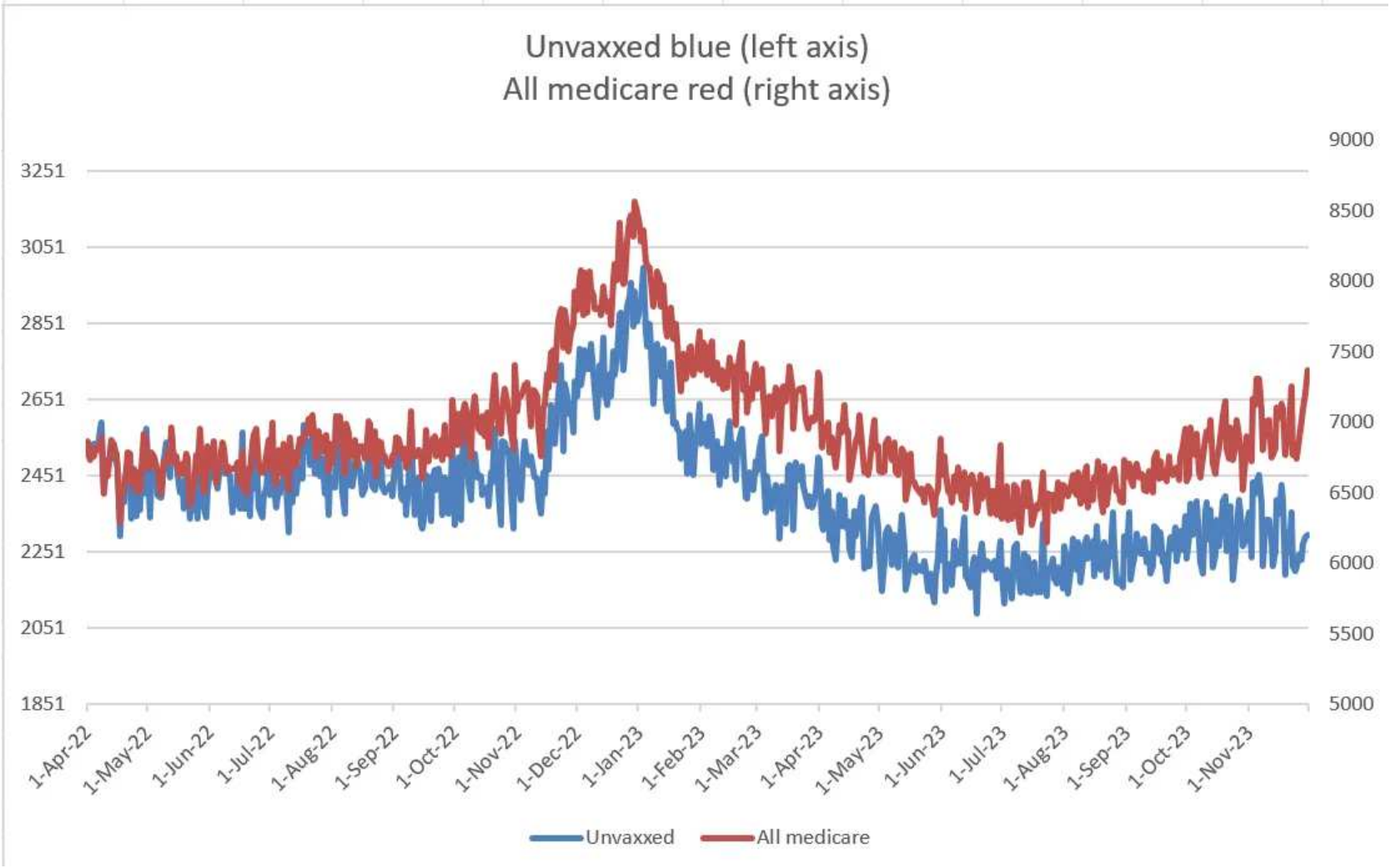
Covid Deaths in Pregnancy Rose 300 Percent During Delta. Blame The Toxic Combination of Covid Plus Vaccines.

PIERRE KORY, MD, MPA AND MARY BETH PFEIFFER



Source: CDC WONDER (data as of January 4, 2024) - Chart and research by Fabian Spieker

Maternal Deaths Across the USA: Pregnancy-related deaths rose sharply in 2021, driven by Covid-19 as the underlying cause (orange) and as a contributing factor (red). Half of the Covid deaths occurred in August and September, coinciding with the Delta wave and advisories for pregnant women to get vaccinated. Maternal Covid Deaths rose 321 percent from 2020 to 2021 while all Covid deaths rose 20 percent.



All cause death rates

Table 1. Pharmacological Therapy for COVID-19 by Stage of Illness: What has worked and what has failed

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Corticosteroids	n/a	Trend to harm	BENEFIT
Anti-androgen Rx	? Benefit	Benefit	BENEFIT
LMWH	n/a	n/a	BENEFIT
Paxlovid/Molnupiravir	n/a	No Benefit	n/a
Monoclonal Abs	No Benefit	No benefit	HARM
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

Source: FLCCC

Covid

- No benefit from vaccination against influenza or Covid (hospitalization or death) demonstrated in review of 9 million VA patient encounter records 2022-2023.
- Xie, Choi, Al-Aly, JAMA (2023) 329:1697-1699
- Vaccination deaths increased following introduction of vaccination; higher risk in those receiving multiple boosters.
- Alessandria, M, Malatesta, GM, Berrino, F, Donzelli, A, Microorganisms (2024) 12:1343