Combatting antimicrobial resistance during a pandemic: The Pediatric Perspective

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Pandemic preparedness in pediatric populations: Issues to consider

AMR infections in children occur in both community and healthcare settings

Prioritization of children's needs during a pandemic – kids come in all sizes

Optimizing quality of care and patient safety across EDs and other settings

The importance of social determinants of health among children

Bed shortages and surge capacity when viruses no longer "seasonal"

Taking care of hospitalized families, separate facilities, interconnectivity

Complicated process of pediatric antibiotic development and clinical trials

Drug shortages, formulation availability, education on misuse

Outpatient resources telehealth, stewardship and vaccination

Background

- Multi-drug resistant (MDR) bacterial infections account for 700,000 deaths per year globally, of which ~200,000 are infants.[1,2]
- Bacterial (secondary and co-) infections when occur do so most often in association with viral ear, nose, throat, sinus and respiratory tract pathogens.[3]
- Children receive more antibiotics than any other type of drug.[2]
- Surges in respiratory infections drive antibiotic shortages (children's formulations)[4]
- Common failures to deescalate or discontinue therapy in both inpatient and outpatient pediatric settings increase risk for colonization and infection with antibiotic resistant pathogens.[5]
- Children remain colonized MDR bacteria for prolonged periods (months to years) and may become silent carriers impacting spread of antimicrobial resistance (AMR) and are at risk for subsequent infection.[6]
- Households with children have high MDRO[7] and viral[8] transmission rates

https://www.who.int/health-topics/antimicrobial-resistance; Romandini et al., Antibiotics, 2021.10(4): 393; Ther Clin Risk Manag. 2015; 11: 1265–1271; Hersh et al. JAMA Int Med 2016; 176(12): 1870-1872; Langford et al. Can Pharm J. 2017 Nov-Dec; 150(6): 349–350; Zerr et al. Antimicrob Agents Chemother 2014; 58:3997–4004; Mork et al. Lancet Inf Dis 2020; 20(2): 188-198; Tsang et al. Trends Microbiol. 2016 Feb; 24(2): 123–133.

Community-onset AMR infections increasing among children

Clinical Infectious Diseases
MAJOR ARTICLE
2021 Mar 1
72(5):797-805.

Rising Pneumococcal Antibiotic Resistance in the Post–13-Valent Pneumococcal Conjugate Vaccine Era in Pediatric Isolates From a Primary Care Setting

Ravinder Kaur,[1] Minh Pham,[2] Karl O. A. Yu,[1,a] and Michael E. Pichichero[1]

[1]Center for Infectious Diseases and Immunology, Rochester General Hospital Research Institute, Rochester, New York, USA, and [2]School of Mathematical Sciences, College of Science, Rochester Institute of Technology, Rochester, New York, USA

- Prospective cohort study of 6- to 36-month olds in primary care pediatric practices in New York. (PCV-13 start April, 2010)
- Predominantly non-Hispanic White (78%); 55% Male
- Periodic NP samples at well visits and with AOM (NP or MEF)
- 1201 isolates from 448 children between 2006-2016

Pneumococcal antibiotic nonsusceptible isolates, 2013-2016

	All Common Serotypes (N=490)							
	11A	15B/C	15A	21	23A	23B	35B	35F
	n=59	n-77	n=20	n=39	n=21	n=64	n=103	n=22
penicillin	15(25.4%)	4(5.1%)	7(35%)	-	13(16.9%)	12(18.7%)	72(69.9%)	16(50%)
amoxicillin	-	-	-	-	-	1(1.6%)	19(18.4%)	5(15.6%)
ceftriaxone	-	-	-	-	-	-	9(8.7%)	4(12.5%)
cefotaxime	-	-	2(10%)	-	-	-	42(40.8%)	12(37.5%)
meropenem	1(1.7%)	-	-	-	-	1(1.5%)	66(64.1%)	14(43.8%)
ertapenem	-	-	-	-	-	-	-	-
ofloxacin	-	-	-	-	-	-	-	-
levofloxacin	-	-	-	-	-	-	-	-
moxifloxacin	-	-	-	-	-	-	-	-
erythromycin	14(23.7%)	33(42.8%)	9(45%)	-	5(23.8%)	14(21.8%)	59(57.3%)	12(37.5%)
telithromycin	-	-	-	-	-	-	-	-
vancomycin	1(1.7%)	-	-	-	-	-	-	-
linezolid	-	-	-	-	-	-	-	-
tetracyline	1(1.7%)	2(2.6%)	8(40%)	-	-	1(1.5%)	1(0.9%)	-
chloramphenicol	-	-	-	-	-	-	-	-
TMP/SMX	7(11.8%)	6(7.8%)	3(15%)	-	-	8(12.5%)	11(10.7%)	5(15.6%)
Pen+Ceph+Fluoro	-	-	-	-	-	-	-	-
Pen+Ceph+Carb	-	-	-	-	-	-	42(40.8%)	12(54.5%)
Pen+ Ceph+Carb+other	-	-	-	-	-	-	32(31.1%)	10(45.4%)

Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Group A *Streptococcus*

Year	Cefotaxime	Clindamycin**	Erythromycin	Tetracycline	Penicillin	Vancomycin	Number of isolates
2010	0.0%	3.6%	8.2%	12.6%	0.0%	0.0%	971
2011	0.0%	8.9%	11.5%	11.2%	0.0%	0.0%	1,108
2012	0.0%	11.2%	13.2%	15.7%	0.0%	0.0%	852
2013	0.0%	12.5%	13.9%	16.2%	0.0%	0.0%	940
2014	0.0%	13.1%	14.5%	16.3%	0.0%	0.0%	1,259
2015	0.0%	13.1%	14.9%	17.0%	0.0%	0.0%	1,404
2016	0.0%	14.7%	16.0%	20.1%	0.0%	0.0%	1,737
2017	0.0%	21.3%	22.0%	25.7%	0.0%	0.0%	2,177
2018	0.0%	24.2%	24.8%	27.0%	0.0%	0.0%	2,281
2019	0.0%	23.8%	24.7%	30.5%	0.0%	0.0%	2,235
2020	0.0%	29.2%	29.8%	37.3%	0.0%	0.0%	1,790

Macrolide and Clindamycin Resistance in Group A Streptococci Isolated From Children With Pharyngitis

DeMuri at al. Pediatr Inf Dis J 2017; 36(3):342-344

Madison, WI **2011-2015** **n = 143**

Susceptibility	Erythromycin, %	Clindamycin, %
Susceptible	85	85
Intermediate	1	2
Resistant	14	13
Total non-susceptible	15	15

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

Healthcare-onset AMR infections increasing among children

Infection Control & Hospital Epidemiology (2020), **41**, 19–30
doi:10.1017/ice.2019.297

Original Article

Antimicrobial-resistant pathogens associated with pediatric healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017

Lindsey M. Weiner-Lastinger MPH, Sheila Abner PhD, Andrea L. Benin MD, Jonathan R. Edwards MStat, Alexander J. Kallen MD, MPH, Maria Karlsson PhD, Shelley S. Magill MD, PhD, Daniel Pollock MD, Isaac See MD, Minn M. Soe MBBS, MPH, Maroya S. Walters PhD and Margaret A. Dudeck MPH
Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Percentage of Pathogens Reported from Pediatric Central Line-Associated Bloodstream Infections (CLABSIs) that Tested Nonsusceptible (NS) to Selected Antimicrobial Agents by Location Type, 2015–2017

	NICUs[b]			Pediatric ICUs			Pediatric Oncology Units			Pediatric Wards[b]		
Pathogen, Antimicrobial	No. Reported	% Tested	% NS[a]	No. Reported	% Tested	% NS[a]	No. Reported	% Tested	% NS[a]	No. Reported	% Tested	% NS[a]
Staphylococcus aureus	1,381			420			266			313		
OX/CEFOX/METH (MRSA)		92.8	27.6		90.2	31.1		91.0	23.6		92.7	26.2
Enterococcus faecium	12			92			117			63		
Vancomycin (VRE)		91.7	. . .		91.3	42.9		98.3	54.8*		85.7	33.3
Enterococcus faecalis	483			492			179			264		
Vancomycin (VRE)		92.8	0.2		90.0	0.2		90.5	0.6		90.2	0.0
Selected *Klebsiella* spp	408			368			374			375		
ESCs		85.5	6.6*		88.6	13.2		88.5	22.7*		86.7	12.0
Carbapenems (CRE)		76.2	0.0		82.1	3.3*		80.2	3.0*		73.9	0.7
MDR		90.4	1.6		92.1	6.5		90.6	10.3*		91.2	4.1
Escherichia coli	596			151			429			205		
ESCs		84.6	7.5*		91.4	22.5		93.5	33.7*		82.4	22.5
Carbapenems (CRE)		74.0	0.5		84.1	2.4		87.4	1.1		75.6	0.6
FQs		78.2	22.7		85.4	25.6		87.4	38.1*		84.9	26.4
MDR		90.8	3.3*		92.7	12.1		93.5	20.0*		88.8	9.3
***Enterobacter* spp**	229			278			218			191		
Cefepime		70.7	4.9		85.3	9.3		77.5	14.2		79.1	9.9
Carbapenems (CRE)		82.5	1.6		85.6	3.4		83.0	5.0		77.0	2.7
MDR-2		89.5	0.5*		92.4	2.7		88.5	6.7		92.1	5.1
Pseudomonas aeruginosa	156			167			173			78		
AMINOs		91.7	7.0		94.6	10.8		96.0	4.2*		94.9	12.2
ESCs-2		91.0	7.0*		94.6	22.2		95.4	15.8		91.0	16.9
FQs-2		76.3	1.7*		88.6	11.5		86.1	13.4		91.0	11.3
Carbapenems-2		75.6	5.1		85.0	19.7		90.2	16.7		79.5	11.3
PIP/PIPTAZ		85.9	5.2		83.8	19.3		89.6	15.5		83.3	12.3
MDR-3		91.0	2.8		94.6	12.0		96.0	6.0		93.6	5.5
***Acinetobacter* spp**	47			43			24			29		
Carbapenems-2		72.3	0.0		90.7	2.6		70.8	. . .		72.4	0.0
MDR-4		87.2	4.9		100.0	9.3		95.8	13.0		86.2	8.0

Effect of COVID-19 pandemic on AMR in pediatric populations

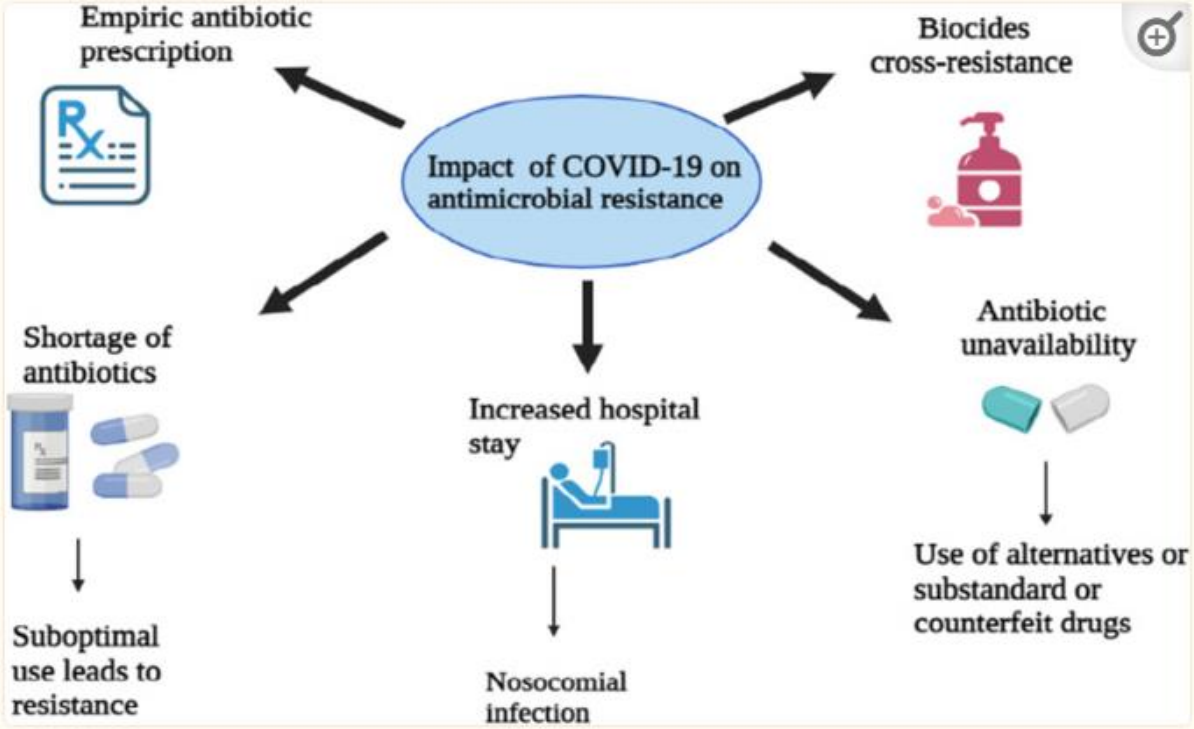


Fig. 1

Impact of COVID-19 on antimicrobial resistance in paediatric population

Karun et al. Curr Pharmacol Rep. 2022; 8(5): 365–375

Social determinants of health significantly impact children during a pandemic

ADVERSE SOCIAL DETERMINANTS

AND THEIR IMPACT ON THE PEDIATRIC POPULATION DURING THE COVID-19 PANDEMIC

Abrams et al. Ann AAI 2022; 128(1): 19-25

01 INCREASED HOMELESSNESS AND HOUSING INSECURITY
Increased viral transmission, reduced access to healthcare and screening facilities, higher risk of COVID-19 mortality, long-term impacts on physical and psychological development.

02 INCREASED FOOD INSECURITY
Risk of developmental delay, behavioral issues, reduced immune function, increased risk of hospitalization. Longer-term associated with many chronic diseases of adulthood.

03 REDUCED FAMILIAL INCOME
Increased risk of COVID-19 infection and outcomes. Longer-term impact includes reduced educational attainment, lower IQ, higher risk of childhood infection and poorer mental health outcomes.

04 IMPACT ON SCHOOL PERFORMANCE
Poorer long-term educational outcomes such as dropout rates, higher learning losses, deeper losses in lifetime earnings.

05 INCREASED ABUSE AND CHILD MALTREATMENT
Variety of long-term adverse health outcomes including psychological disorders, high risk behaviors, and overall lower health status.

06 RACE/ETHNICITY AND SYSTEMIC RACISM
RACISM
Increased risk of COVID-19 infection and morbidity, increased risk of other adverse social determinants of health.

Racial differences in antibiotic prescribing in Peds Primary care[1], EDs[2], Hospitals[3]

Racial Differences in Antibiotic Prescribing by Primary Care Pediatricians

TABLE 3 Within-Clinician Diagnosis Rate of Common Pediatric Conditions, by Patient Race

Diagnosis[a]	OR, Black versus Nonblack (95% CI)[b]	*P* Value	Standardized Probability, % (95% CI)[c]	
			Black	Nonblack
AOM	0.79 (0.75–0.82)	<.001	8.7 (8.2–9.2)	10.7 (10.3–11.2)
Sinusitis	0.79 (0.73–0.86)	<.001	3.6 (3.1–4.0)	4.4 (4.1–4.8)
GAS pharyngitis	0.60 (0.55–0.66)	<.001	2.3 (2.1–2.5)	3.7 (3.5–3.8)
Pneumonia	1.0 (0.89–1.1)	.808	1.3 (1.1–1.4)	1.3 (1.1–1.4)
UTI	1.0 (0.93–1.1)	.725	1.7 (1.7–1.8)	1.7 (1.6–1.8)

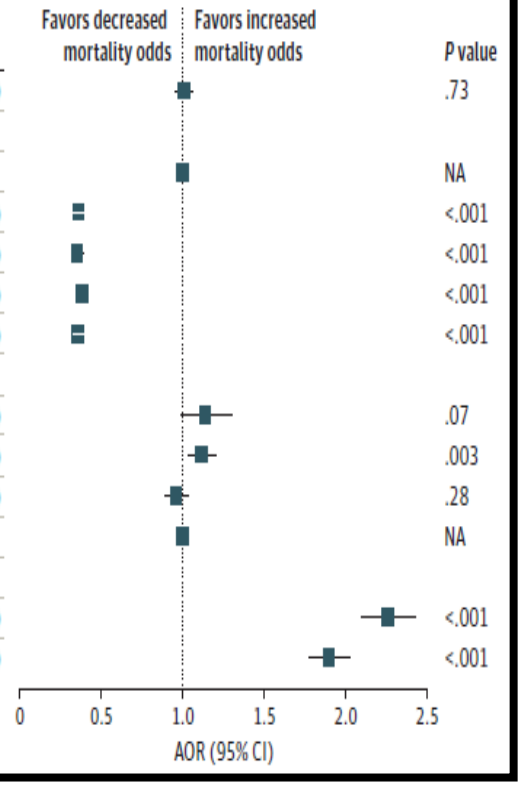
"Improper diagnosis leads to empiric antibiotic prescribing that may include the prescribing of broad-spectrum antibiotics or commonly used narrow-spectrum antibiotics which further leads to increased risk of mortality because of inappropriate therapy." Karun et al. Curr Pharm Rep 2022; 8(5): 365–375.

Racial differences in peds sepsis recognition[4] and sepsis outcomes[5]

Assessment of Racial and Ethnic Disparities in Outcomes of Pediatric Hospitalizations for Sepsis Across the United States

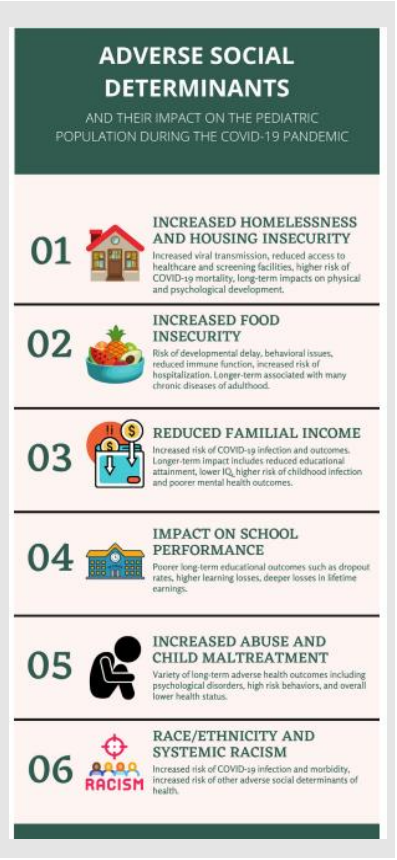
ure 1. Patient Characteristics Associated With In-Hospital Mortality

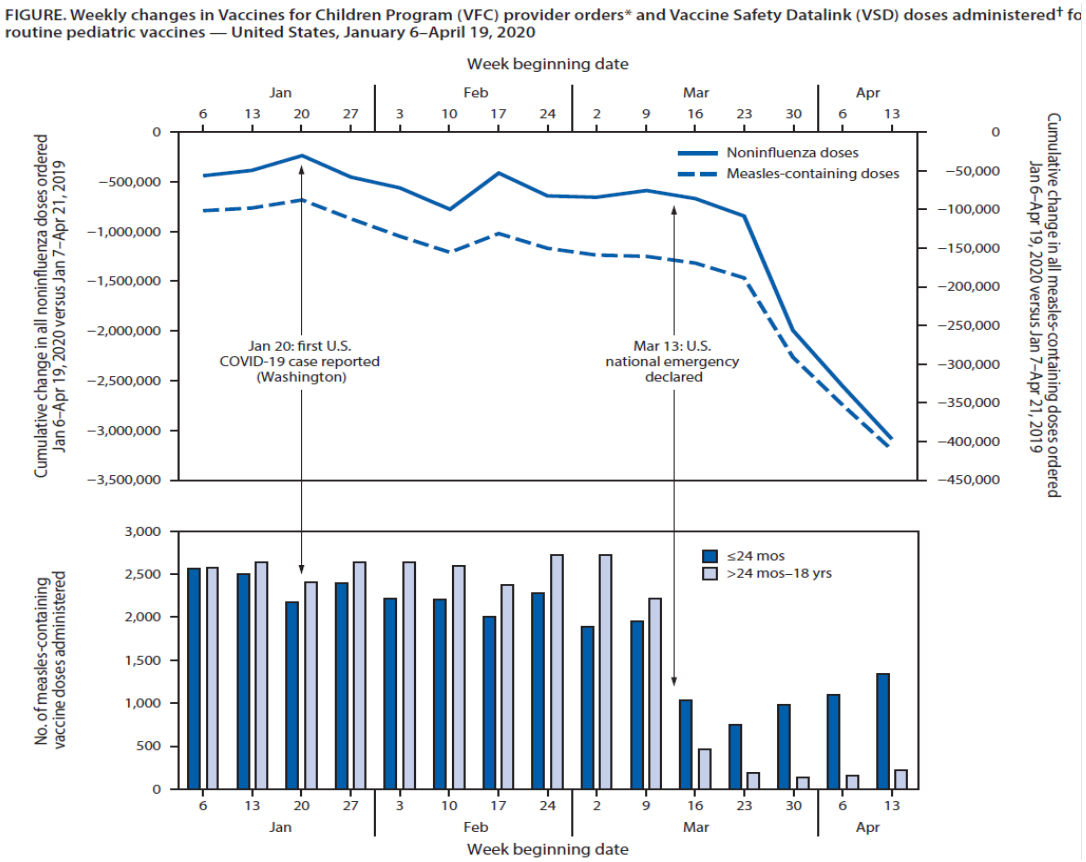
Variable	AOR (95% CI)	*P* value
Female sex[a]	1.00 (0.96-1.06)	.73
Age, y		
<1	1 [Reference]	NA
1-5	0.36 (0.33-0.39)	<.001
6-10	0.35 (0.32-0.39)	<.001
11-14	0.38 (0.34-0.42)	<.001
15-18	0.35 (0.32-0.39)	<.001
Race and ethnicity		
Asian	1.14 (0.99-1.30)	.07
Black	1.12 (1.04-1.20)	.003
Hispanic	0.96 (0.89-1.03)	.28
White	1 [Reference]	NA
CCC		
Neuromuscular disease	2.26 (2.10-2.43)	<.001
Cardiac disease	1.89 (1.77-2.02)	<.001



Gerber et al. Pediatrics 2013; 131(4): 677-684; Goyal et al. Pediatrics 2017 Oct;140(4):eJ; Wercel et al. JAMA Netw

Social determinants of health significantly impact children during a pandemic





Decreased access to care disproportionately affects underserved and marginalized populations during pandemics

Indirect effect of pandemic is increase in vaccine preventable illnesses:

- Increase in antibiotic usage
- Increase in bacterial 2nd/co-infections
- Increase in AMR infections
- Increased hospitalization and use of healthcare resources
- Longer lengths of stay
- Increased risk of nosocomial infections

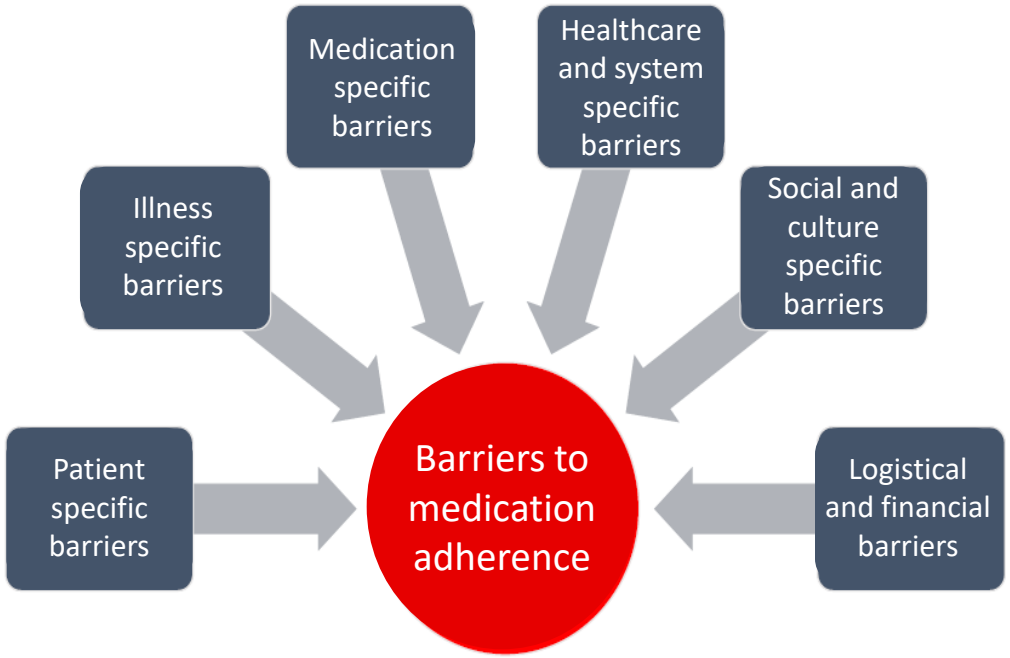
Access to outpatient preventive and therapeutic treatments limited in children during pandemic

- Parental antibiotics
- Biologic therapies
- Vaccines
- Home health

Abrams et al. Ann AAI 2022; 128(1): 19-25; Santoli et al. MMWR 2020 / 69(19);591–593

Barriers to adherence in children with chronic conditions exacerbated by pandemic

- Underserved and marginalized communities disproportionally affected with chronic conditions
- Resource shifting and/or closures of maternal-child and pediatric facilities, especially in lower socioeconomic areas
- Job losses, transportation and technology issues
- Results in even greater health disparities



- **Patient-specific barriers**
  - Lack of knowledge
  - Lack of routines or changes in routines
  - Stress of helplessness
  - Poor health literacy
- **Illness-specific barriers**
  - Poor understanding of disease
  - Disease not a priority
  - Lack of symptoms
  - Illness fatigue
  - Something out of one's own control
- **Medication-specific barriers**
  - Lack of medication information
  - Side effects or their fear
  - Polypharmacy
  - Complexity of medication: administration, dosage form or cumbersome medicine package
  - Lack of trust: Generic, substitution, new medicines
  - Previous experiences
- **Health care and system-specific barriers**
  - Lack of communication with health professionals
  - Distrust or paternalism
  - Lack of time or support
  - Multiple prescribers
  - Poor access to care or pharmacy
- **Social and culture-specific barriers**
  - Stigma
  - Lack of support from significant others
  - Religious restrictions
  - Alternative medicines
  - Difficult to reconciliate work and illness
  - Poverty
- **Logical and financial barriers**
  - Cost of medicines
  - Medicine shortage
  - Logistical problems
  - Renewal of medicines
  - Lack of resources

Kvarnström et al. Pharmaceutics 2021, 13, 1100; Plevinsky et al. J Pediatr Psychol. 2020 Oct; 45(9): 977–982.

Emergency and outpatient facilities readiness highly variable for children: Issues of Equity, Safety and Access

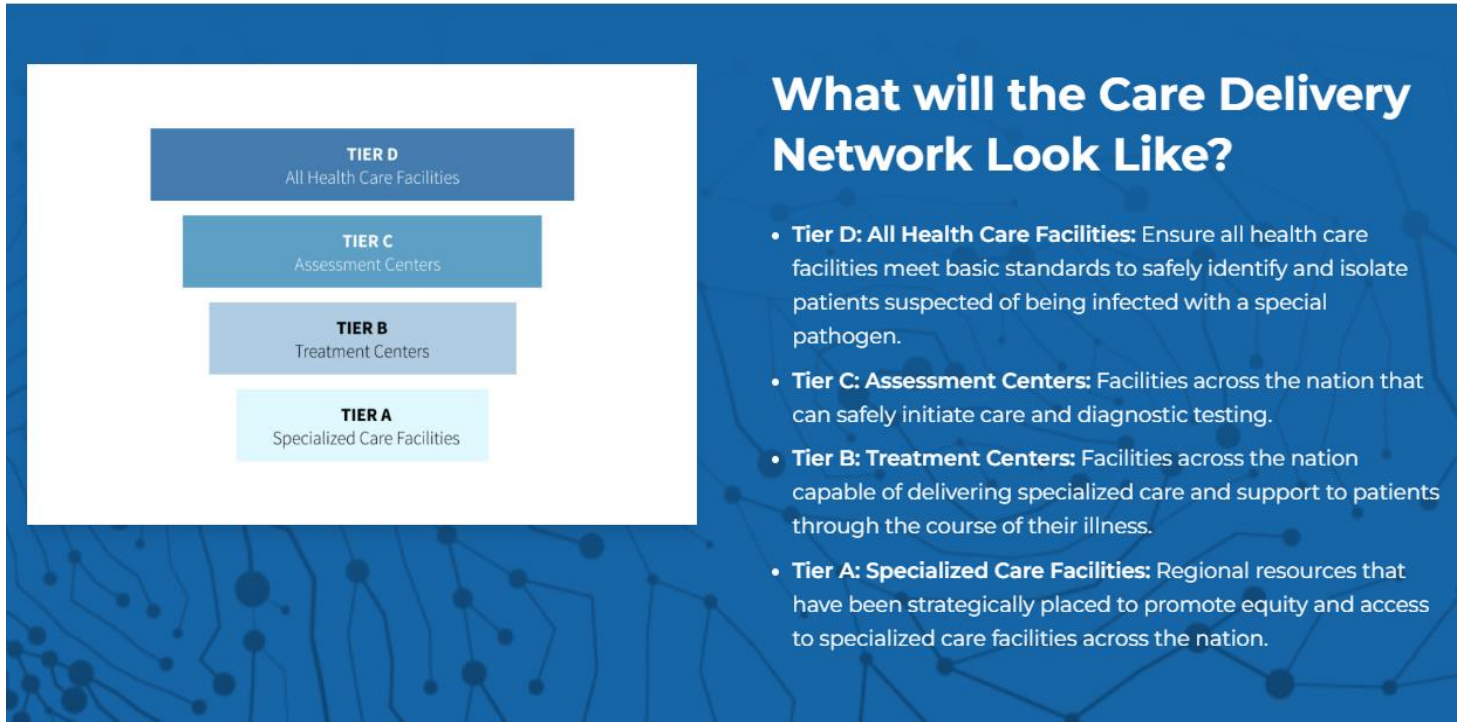
Children comprise 27% of the U.S. population and account for approximately 20% of all hospital ED visits. Data validate that 90% of these emergency pediatric visits take place in a local general hospital rather than a facility with pediatric specialization or expertise.

Hospitals with high ED readiness scores demonstrate a 4-fold lower rate of mortality for children with critical illness than those with lower readiness scores; thus, improving pediatric readiness improves outcomes for children and their families.

https://emscimprovement.center/domains/pediatric-readiness-project/

Problem of national shortage of pediatric beds during pandemic surge of infections

- Byproduct of financial decisions over last decade –
  Pediatrics -- “not profitable”
- Staff shortages
- Supply and equipment shortages
- “Seasonality” destroyed by pandemic
- Secondary bacterial infections
  - → increase in length of stay
  - → increase nosocomial infections
  - → increase AMR infections



https://netec.org/

The complicated process of pediatric antibiotic development needs to be less complicated

The NEW ENGLAND JOURNAL of MEDICINE

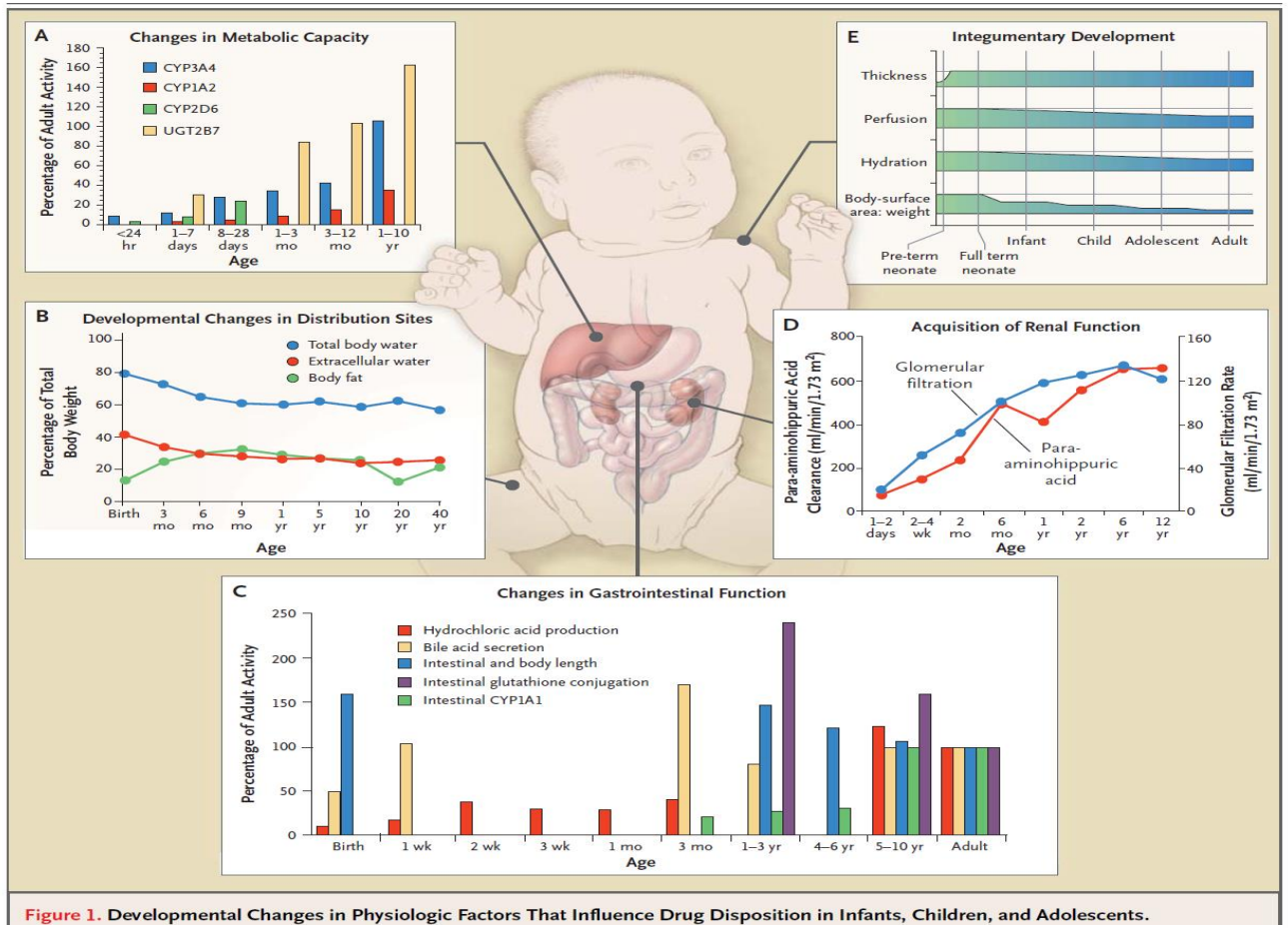


Figure 1. Developmental Changes in Physiologic Factors That Influence Drug Disposition in Infants, Children, and Adolescents.

THE LANCET
Child & Adolescent Health

Harmonising regulatory approval for antibiotics in children

Panel: **Recommendations to achieve harmonised and expedited regulatory approvals for new antibiotics for use in children**

1. There should be recognition that for well established classes of antibiotics such as β-lactam and β-lactam inhibitor combinations, single-dose and multidose pharmacokinetic and safety studies can provide the basis for licensure.
2. Randomised trials with standard of care comparator arms should not be required for licencing well established classes of antibiotics with a well established safety profile.
3. Recruitment of children into pharmacokinetic and safety studies should allow for inclusion of patients with any relevant bacterial infection, rather than restricting enrolment only to those with the adult licensed indication for the antibiotic under investigation. This will enable investigation of a more generalisable patient population and facilitate recruitment, ensuring appropriate sample sizes with adequacy to detect safety signals and accurately predict pharmacokinetic parameters are enrolled.
4. Wherever possible, the goal should be for the US Food and Drug Administration and European Medicines Agency to agree to the development of a single study master protocol for new antibiotics, based on single-dose and multi-dose pharmacokinetics, that requires only one global trial for recruitment and registration across all licensing authorities.
5. A clear focus on reducing the time between new antibiotics being licensed for use in adults and children is necessary. An achievable goal of paediatric licences being issued within 5 years of the adult licence should be established.

Kearns et al. N Engl J Med 2003;349:1157-67; Williams et al. Lancet Child Health 2021; 5:96-98; Gilsen et al. Antibiotics 2021, 10(10), 1182

Summary of considerations for combatting antimicrobial resistance addressed through a pediatric pandemic preparedness lens

Addressing social determinants of health, disparities worsen during pandemics	Improving hospital ED readiness scores to improve pediatric outcomes in all facilities	Investing resources in something that may infrequently happen	Use of modeling to determine viral surges when seasonality no longer predictable	Public-private partnerships (donation of pediatric supplies, time, space, equipment)
Less focus on return on investment for healthcare facilities caring for children	Improving inpatient and outpatient antibiotic stewardship in children	Improving the capacity of telehealth to address unique and specialized needs of children and pts with chronic conditions	Accounting for staffing shortages a/w pandemic exercises, illnesses, education, resignation	Improving strategies for family centered care, interconnectivity when family members apart
Kids come in all sizes: specialized training needs for developmental stages, different sized resources	Improving home health, outpatient infusion center options and resources for kids	Increasing vaccination resources (mobile, school, community, low SES neighborhoods, providing education)	Developing reciprocal arrangements between facilities, decreasing regulatory burden, i.e., credentialing, EMR	Improving the processes of pediatric antibiotic development and regulatory approval

Thank you

- PACCARB and HHS/OASH for the invitation
- Andrea Shane, MD, MPH, MSc for valuable input