Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital Cytomegalovirus Infection

May 7-8, 2024

Welcome

Introductory Remarks

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World Health Organization

FDA

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Home / Disease Outbreak News / Item / Enterovirus-Echovirus 11 Infection - the European Region

Disease Outbreak News

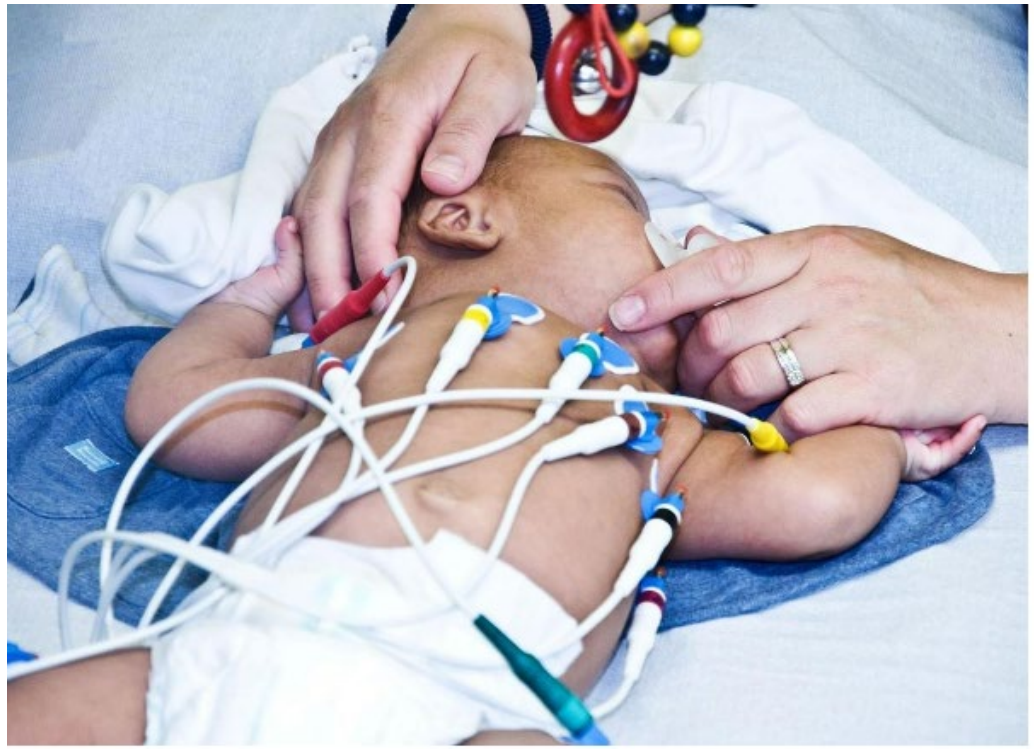
Enterovirus-Echovirus 11 Infection - the European Region

7 July 2023

Situation at a glance

Since the Disease Outbreak News published on 31 May 2023 which reported enterovirus, Echovirus 11 (E-11) infection in France, additional Member States in the European Region have notified WHO of cases of E-11 among newborns. As of 26 June 2023, Croatia, Italy, Spain, Sweden, and the United Kingdom of Great Britain and Northern Ireland have reported cases of E-11 infection confirmed in newborns. Further investigations and public health responses are being implemented in each of these Member States. This Disease Outbreak News provides updates on the event and the public health response implemented in the reporting and non-reporting countries in the European Region. Based on the limited information available, WHO assesses the public health risk for the general population to be low, while we continue to encourage countries to monitor for and report on cases. Health facilities caring for newborns should familiarize themselves with the signs and symptoms of echovirus and maintain vigilance for potential healthcare-associated infections and outbreaks.

Description of the situation



FroggyFrogg / iStock

Spotting CMV

Cytomegalovirus, a common cause of hearing loss in infants, is now part of routine newborn screening in Minnesota, thanks to the work of a U of M professor and parents of affected children.

May 24, 2023
UMN News and Events

By Susan Maas

https://give.umn.edu/stories/spotting-cmv
https://twin-cities.umn.edu/news-events/spotting-cmv

Unmet Need

- Neonatal enteroviral (EV) infection and congenital cytomegalovirus (cCMV) infections can be serious and potentially life-threatening
  - Severe neonatal EV infection and symptomatic cCMV infection
- Rare diseases or conditions
  - Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a rare disease or condition, in part, as a disease or condition that "affects less than 200,000 persons in the United States."
- There are no FDA-approved antiviral products for the treatment of EV or cCMV infection

Evidentiary Requirement for Efficacy Establishment

- Drug approval for pediatric use is held to the same evidentiary standard as adult drug approval
  - Must demonstrate substantial evidence of effectiveness (21CFR 314.50)
- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well-controlled trials on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling

Characteristics of Adequate and Well-Controlled Trials

1	There is a clear statement of the objectives and proposed methods of analysis
2	Permits valid comparison with a control to provide quantitative assessment of drug effect
3	Method of selecting subjects provides assurance they have the disease being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.
4	Method of assignment to study arms minimizes bias and is intended to ensure comparability between groups.
5	Measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.
6	Methods of assessing treatment response are well-defined and reliable.
7	Analysis of the results is adequate to assess the drug effects. Analytic methods used, comparability of test and control groups, effects of any interim analyses should be described.

21 CFR 314.126

Evidentiary Requirement for Efficacy Establishment

- Drug approval for pediatric use is held to the same evidentiary standard as adult drug approval
  - Must demonstrate substantial evidence of effectiveness (21CFR 314.50)
- Evidence of effectiveness [PHS Act, 505(d)]
  - **Pediatric extrapolation**: "…based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients…"

Evidentiary Requirements

- Adequate and well controlled trials are needed to establish the safety and efficacy of drug products for use in neonates and infants to treat
  - Neonatal EV infection
  - cCMV infection

- Challenges
  - Gaps in understanding complex disease pathophysiology/poorly understood natural history
  - Small population, rare disease
  - Limited, if any, animal models
  - Trial design considerations, including endpoint selection

Opportunities

Purpose: Discuss the challenges and identify the needed additional scientific work to advance drug development for the treatment of neonatal EV infection and cCMV infection.

FDA public workshop is intended to facilitate exchange of ideas among stakeholders to identify research gaps and help advance the field to address unmet medical need.

FDA public workshops are not advisory to the Agency, and the Agency will not provide drug development advice.

- Not for regulatory decision-making
- All opinions, recommendations, and proposals are unofficial and nonbinding on FDA or other participants

Overview of Workshop Agenda

Day 1

- ❑ **Session 1 (9:10-11:00 am):** General Principles of Pediatric and Neonatal Drug Development
- ❑ **Break: 11:00-11:20 am** 
- ❑ **Session 2 (11:20-12:20 pm):** Enterovirus Epidemiology and Disease Background
- ❑ **Lunch: 12:20- 1:00 pm** 
- ❑ **Session 3 (1:00-2:00 pm; 2:15-3:30 pm):** Enterovirus Trial Design Challenges
- ❑ **Break: 2:00-2:15 pm** 
- ❑ **Adjourn: 3:30 pm**

Overview of Workshop Agenda

Day 2

- ❑ **Introductory Remark: 9:00-9:10 am**
- ❑ **Session 1 (9:10-10:25 am):** Congenital CMV Infection Epidemiology and Clinical Overview
- ❑ **Break: 10:25-10:40** 
- ❑ **Session 2 (10:40-12:10 pm):** Congenital CMV Infection Drug Development Considerations
- ❑ **Lunch: 12:10-1:00 pm** 
- ❑ **Session 3 (1:00-2:00 pm; 2:15-3:30 pm):** Congenital CMV Infection: Trial Design Challenges
- ❑ **Break: 2:00-2:15 pm** 
- ❑ **Adjourn: 3:30 pm**

Housekeeping

- This meeting is being recorded. Speaker slides, transcripts, and recordings will be available on the meeting's webpage in the coming weeks- please check this page regularly for updates.
- Speaker and panelist affiliations and disclosures are available on the meeting's webpage under "Meeting Materials".

- For the general audience:
  - Your microphone and video are automatically turned off.
  - Submit questions using the "**Q&A**" feature at the bottom center of your screen in Zoom.

- **If you are experiencing technical Zoom difficulties, please reach out to Corey.Farley@fda.hhs.gov or Marcus.Washington@fda.hhs.gov**

Session 1:
General Principles of Pediatric and Neonatal Drug Development

- **Ethical Considerations for Pediatric Clinical Trials**
  - Prabha Viswanathan, MD; FDA
- **Clinical and Regulatory Considerations for Neonatal Antiviral Drug Development**
  - An Massaro, MD; FDA
- **Clinical Pharmacology Considerations for Dose Selection in Pediatric Patients**
  - Kunyi Wu, PharmD; FDA
- **Life of a NICU Parent: Decision-making in Clinical Trial Enrollment**
  - Betsy Pilon; Hope for HIE
- **Facilitating Neonatal and Pediatric Drug Development: Leveraging Pediatric Trial Networks and Global Collaboration**
  - Yeruk Mulugeta, PharmD; FDA
- **Real-world Data and Real-world Evidence in Drug Development**
  - John Concato, MD, MPH; FDA

Ethical Considerations for Pediatric Clinical Trials

Prabha Viswanathan, MD
Deputy Director, Office of Pediatric Therapeutics
Office of the Commissioner | Office of Clinical Policy and Programs
US Food and Drug Administration

Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital Cytomegalovirus Infection

May 7, 2024

Disclosure

- I have no financial conflicts of interest to disclose
- The views shared in this presentation do not necessarily reflect the views of the U.S. Food and Drug Administration

Overview

- Ethical framework for pediatric clinical trials
- Regulations governing inclusion of children in research
  - Prospect of Direct Benefit
  - Assessment of Risk
  - Component Analysis
  - Parent/Guardian Permission
- Impact on drug development for neonatal enteroviral infection and congenital cytomegalovirus infection (cCMV)

Research Involving Children

Department of Health Education and Welfare, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978)

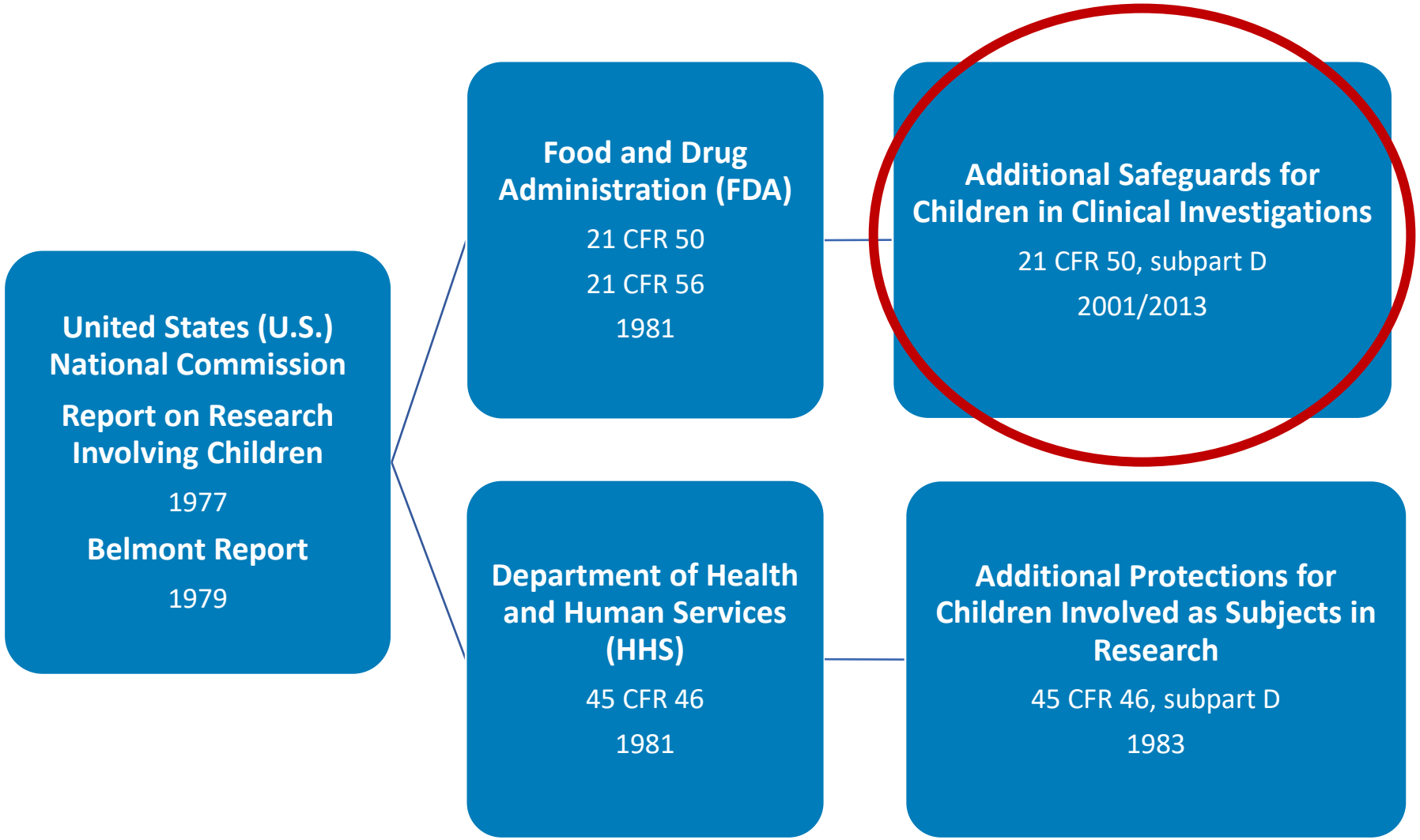
Ethical Framework for Pediatric Research

Ensure Necessity	Limit Risks	Prevent Disadvantage	Obtain Permission
Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally, and the objective(s) are important for the health and welfare of children	Absent a prospect of direct clinical benefit, the risks to which children are exposed must be "low"	Children should not be placed at disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care	Children should have a suitable proxy to provide permission for them to enroll in a clinical trial

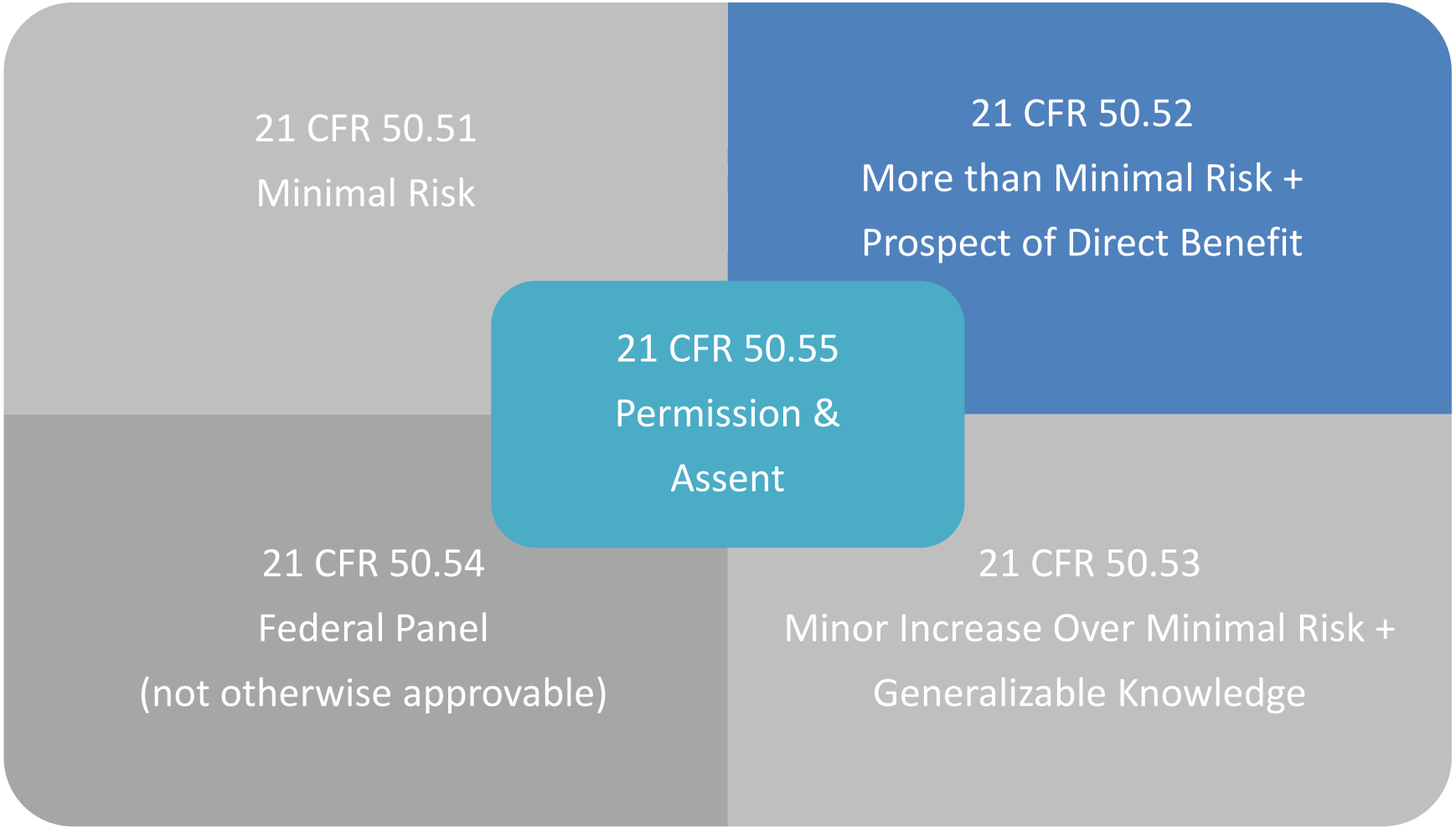
Department of Health Education and Welfare, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977)

HUMAN SUBJECTS PROTECTION REGULATIONS

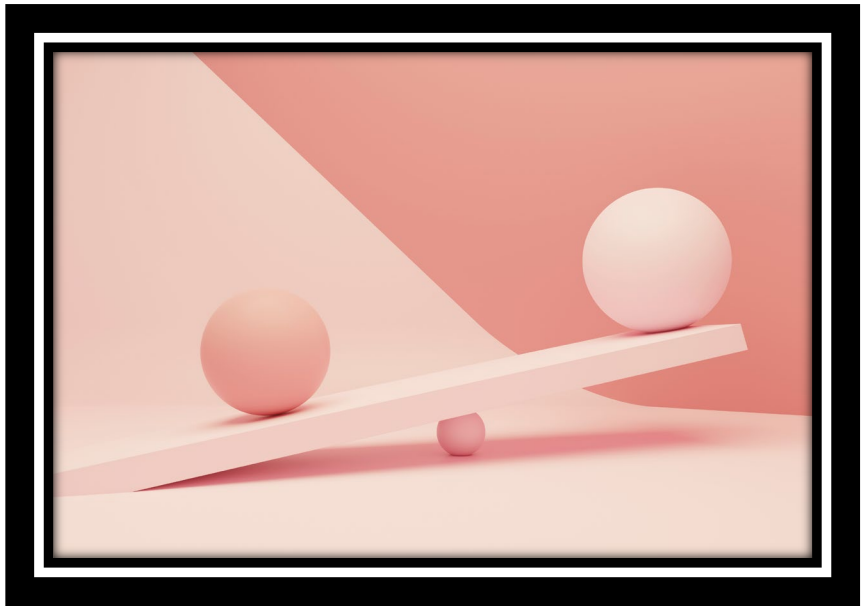
Human Subjects Protection Regulations



Additional Safeguards for Children in Clinical Investigations: 21 CFR 50, subpart D



§ 50.52: Balancing Benefit and Risk



- Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects **and** the risks are justified by the anticipated benefit to the subject
- The anticipated benefit/risk balance is at least as favorable as any available alternatives

Prospect of Direct Benefit (PDB)

- Definition of “direct” benefit:
  - Accrues to individual subject enrolled in the clinical trial
  - Results from the research intervention(s) being studied - not from other clinical interventions included in the protocol
- Based on evidence to support proof of concept and on the “structure” of the intervention as specified in the protocol
  - Proof of Concept can come from adult human data or nonclinical data
  - A minimally effective dose must be tested at a duration long enough to impact a clinically relevant outcome

Categorizing Risk

- Minimal risk: risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children”
- Minor increase over minimal risk: “refers to a risk which, while it goes [slightly] beyond the narrow boundaries of minimal risk […], poses no significant threat to the child's health or well-being” and must contribute to generalizable knowledge about the child’s disorder or condition

National Commission Report on Research Involving Children (1977)

Component Analysis of Risk

- "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively."
- Each intervention must be evaluated separately to determine whether it does or does not hold out the prospect of direct benefit to the enrolled child
  - If the intervention or procedure does not hold out the prospect of direct benefit, it should be restricted to no more than a minor increase over minimal risk (§50.53)
  - If the intervention or procedure does hold out the prospect of direct benefit, the risk should be justified by the potential benefit and the benefit/risk balance should be comparable to any available alternatives (§50.52)

National Commission Report on Research Involving Children (1977)

Examples: Interventions Requiring Special Consideration

Biopsies: Some exceed a minor increase over minimal risk

Diagnostic imaging: Consider radiation and risk of contrast

Nontherapeutic procedural sedation: Inherent risks, may be allowable in certain circumstances

Placebo

- Consider the risk of placebo itself
  - Route of administration and study duration are important considerations
- Consider the risk of withholding an established effective treatment
  - Participants in the control arm of a clinical investigation should receive an established effective intervention*
- However, placebo may be used:
  - When there is no established effective intervention, **OR**
  - When use of an established effective intervention as comparator would not yield scientifically reliable results **AND**
  - When withholding an established effective intervention would expose participants to no more than a minor increase over minimal risk and risks are minimized, including use of mitigation procedures**

*Council for International Organizations of Medical Sciences (CIOMS), 2016
**Declaration of Helsinki, 2013
Also consistent with ICH E10, Choice of Control Groups, 2001

Parent/Guardian Permission

- Informed consent is a process that should:
  - Provide an opportunity for parents/guardians to ask questions and consider their child's participation
  - Continue to provide information as the study progresses and situation requires*
- The parental permission form must contain adequate information to allow the parent or guardian to make an informed decision*
- Permission must be obtained in compliance with 21 CFR 50, subpart B, Informed Consent of Human Subjects [21 CFR 50.20-27] and 21 CFR 50.55

*Informed Consent Information Sheet

DRUG DEVELOPMENT FOR ENTEROVIRUS INFECTION IN NEONATES AND CONGENITAL CYTOMEGALOVIRUS INFECTION

Ethical Framework: EV and cCMV Infection

Ensure Necessity	Limit Risks	Prevent Disadvantage	Obtain Permission
Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally, and the objective(s) are important for the health and welfare of children	Absent a prospect of direct clinical benefit, the risks to which children are exposed must be “low”	Children should not be placed at disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care	Children should have a suitable proxy to provide permission for them to enroll in a clinical trial

Ethical Framework: EV and cCMV Infection

Ensure Necessity

Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally, and the objective(s) are important for the health and welfare of children

- cCMV infection and enteroviral infections in neonates and young children are conditions unique to these populations
  - Unmet medical need for therapeutics for these conditions
  - Efficacy cannot be extrapolated from adults or other pediatric populations because there is no equivalent disease
  - Scientific/public health objectives cannot be met without enrolling neonates/young children in adequate and well controlled clinical trials

Ethical Framework: EV and cCMV Infection

Limit Risks

Absent a prospect of direct clinical benefit, the risks to which children are exposed must be “low”

- Clinical trials evaluating most candidate antiviral treatments will need to fulfill the conditions of 21 CFR 50.52
  - Clinical and nonclinical data can be used to
    - Support prospect of direct benefit
    - Assess the risk of the investigational product, which is generally expected to be more than a minor increase over minimal risk
  - Study design is important (e.g., patient selection, risk mitigation strategies)
- Component analysis: assess risk/benefit of every intervention described in the protocol (e.g., lumbar puncture, laboratory studies, diagnostic imaging, audiology and neurodevelopmental assessments)

Ethical Framework: EV and cCMV EV Infection

Prevent Disadvantage

Children should not be placed at disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care

- Placebo controlled trials are acceptable if criteria are met
  - No established effective intervention
  - Active control would preclude data interpretability AND withholding treatment would confer no more than a minor increase over minimal risk
- Adjunctive evidence-based standard of care should be provided to all participants
  - Examples: supportive care, physical/occupational therapy, early intervention services

Ethical Framework: EV and cCMV EV Infection

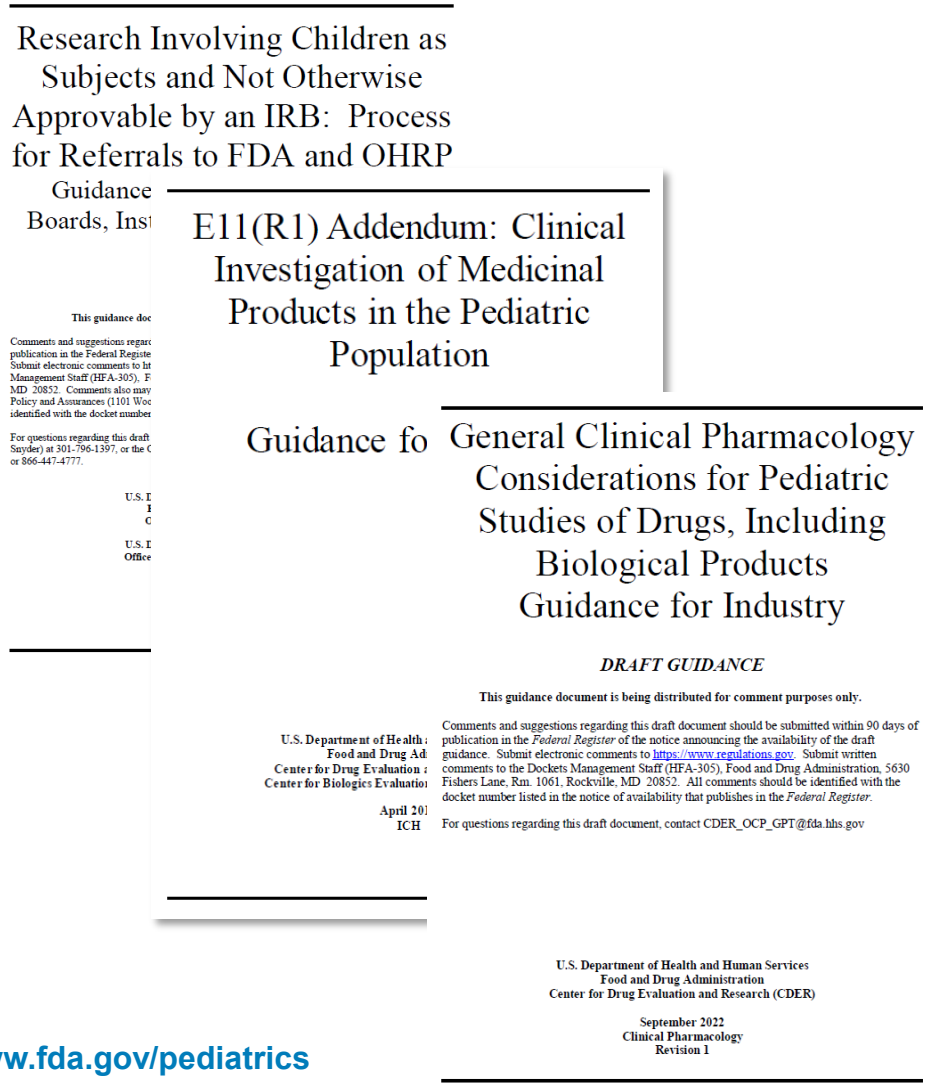
Obtain Permission

Children should have a suitable proxy to provide permission for them to enroll in a clinical trial

- Informed consent is a **process**, not a document
  - Should be differentiated from consent provided for clinical care
  - Consider strategies to ensure that consenting parties understand the full picture
  - Although the focus is currently on neonates and young infants, if interventions are developed for older children, assent may be required

Ethical Considerations for Pediatric Clinical Trials

Resources


Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP

Guidance

Boards, Inst

E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population

Guidance fo

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

DRAFT GUIDANCE

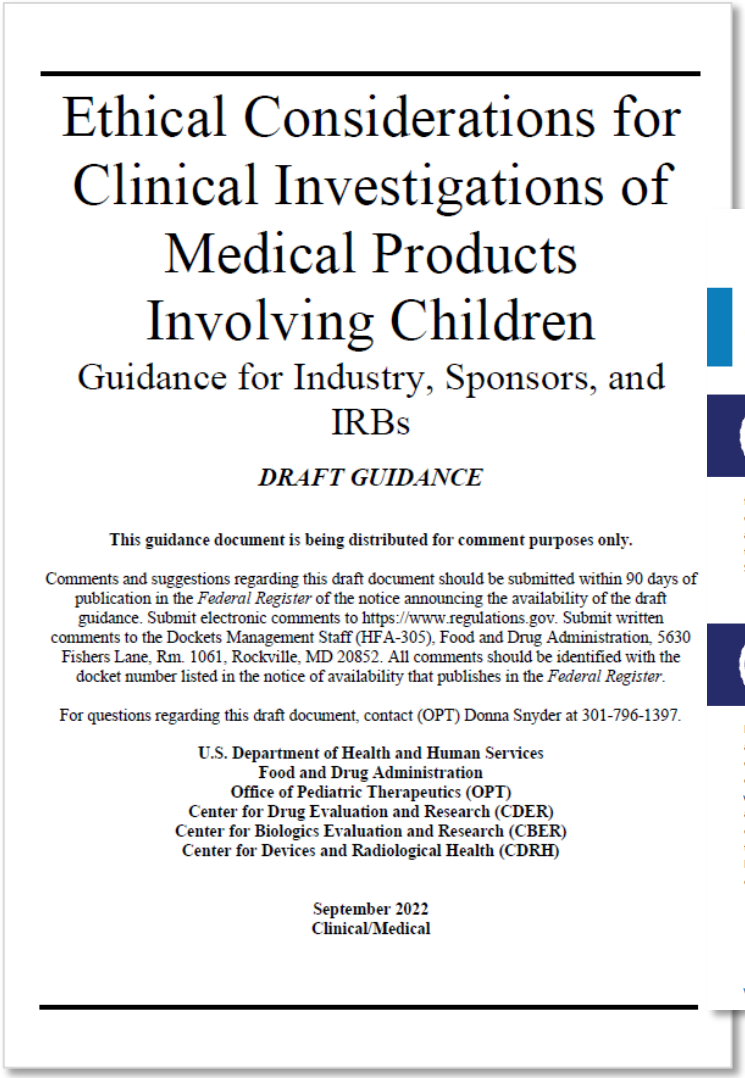
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact CDER_OCP_GPT@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2022
Clinical Pharmacology
Revision 1


Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Guidance for Industry, Sponsors, and IRBs

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For questions regarding this draft document, contact (OPT) Donna Snyder at 301-796-1397.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2022
Clinical/Medical


FDA U.S. FOOD & DRUG ADMINISTRATION

Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Draft Guidance for Industry, Sponsors, and IRBs

What is covered in this guidance?

This draft guidance describes the FDA's current thinking regarding ethical considerations for clinical investigations of medical products in children and provides a detailed description of the additional human subject protection regulations that are included in 21 CFR 50, subpart D (Additional Safeguards for Children in Clinical Investigations).

Why is this guidance important?

Clinical investigations in children are essential for obtaining data on the safety and effectiveness of drugs, biological products, and medical devices in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective. Children are a vulnerable population who cannot consent for themselves and therefore are afforded additional safeguards when participating in a clinical investigation. This draft guidance is intended to assist industry, sponsors, and institutional review boards (IRBs) when considering the enrollment of children in clinical investigations of medical products.

How is this snapshot helpful?

This snapshot provides an overview of the draft guidance to:

- Summarize the steps for considering enrollment of children in a clinical investigation using the ethical framework in 21 CFR 50, subpart D
- Present a high-level perspective of the draft guidance contents
- Consolidate information in the draft guidance into a brief and easy-to-read resource

Who are *children*? For the purposes of this draft guidance, *children* include neonates, infants, children, and adolescents who have not reached the legal age of consent in their local jurisdiction.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about ethical considerations for clinical investigations of medical products involving children, read the guidance.

www.fda.gov

1

www.fda.gov/pediatrics

Search for FDA Guidance Documents | FDA Guidance Snapshot Pilot | FDA

Summary

- Because children are a vulnerable population, additional regulatory protections exist for children involved in research
- Children should not be enrolled in a trial unless necessary to answer an important scientific and/or public health question related to the health and welfare of children
- Research involving children must be either “low” risk (defined as “minimal” or a “minor increase over minimal” risk) OR, if the risks are “higher,” then they need to be balanced by the prospect of direct benefit (unless reviewed by a federal panel)
- Permission by parents or guardians and assent by children (if required by the IRB) need to be solicited

Acknowledgements

- Office of Pediatric Therapeutics
  - Melanie Bhatnagar, MD
  - Dionna Green, MD
  - Pediatric Ethics Program Staff, past and present

Clinical and Regulatory Considerations for Neonatal Antiviral Drug Development

An N. Massaro, M.D.
Supervisory Medical Officer
Neonatology and Rare Pediatric Disease Teams
Office of Pediatric Therapeutics (OPT) | Office of the Commissioner (OC) | US FDA

Drug Development for the Treatment of Congenital Cytomegalovirus Infection and Neonatal Enterovirus Infection – May 7-8, 2024

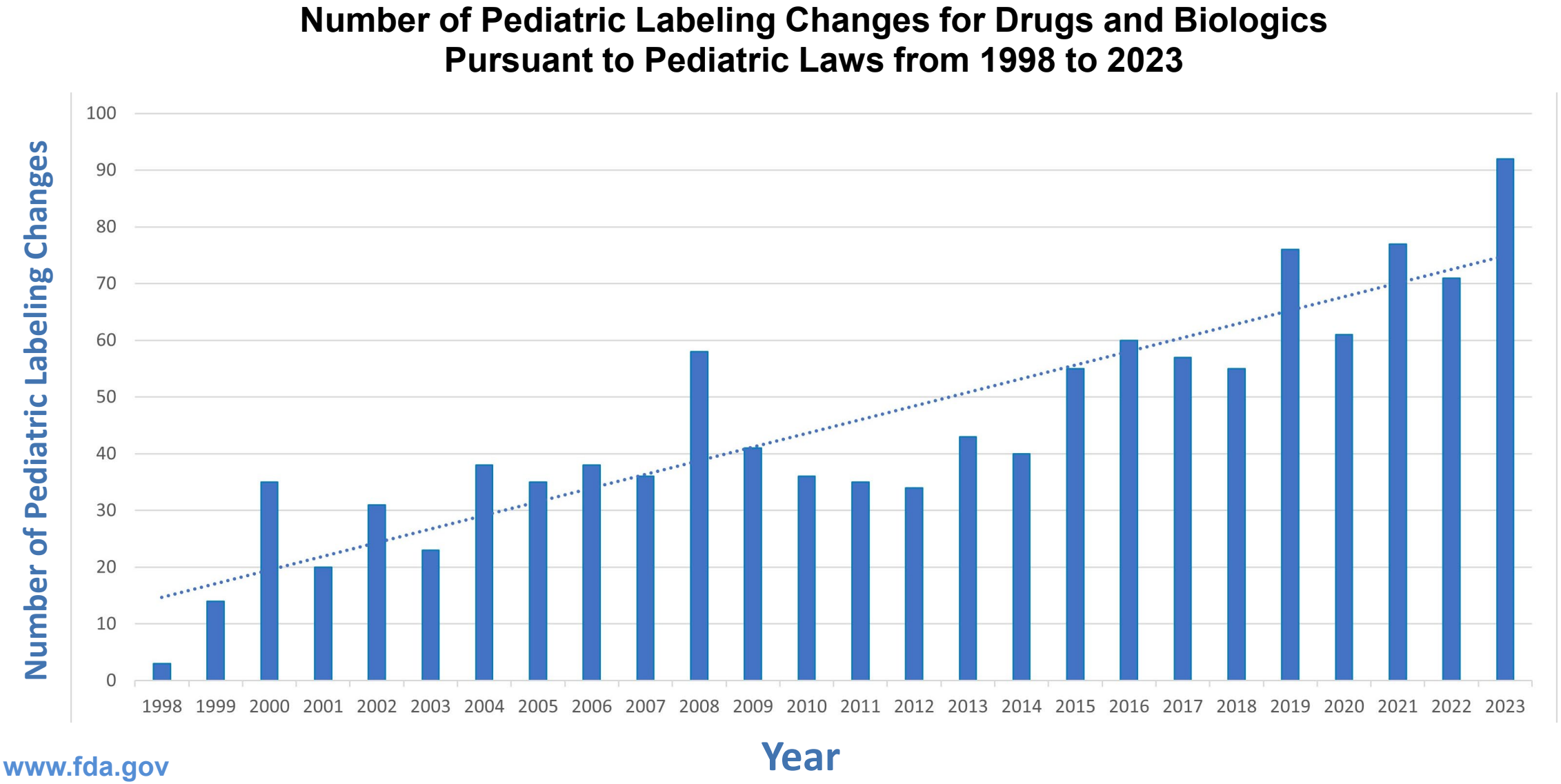
Conflict of Interest and Disclaimer Statement

- The views presented here are personal and do not necessarily reflect the views of the FDA
- All specific product development questions should be discussed with the relevant review center and division
- I have no financial conflicts of interest to disclose
- Off-label or unapproved medical product use may be discussed, as it is common practice in pediatrics (especially neonatology)

Overview

- Discuss special considerations (and challenges) for conducting clinical studies in neonates
- Summarize regulatory considerations for developing antiviral products for treatment of congenital/neonatal infections
- Review available resources and incentives to promote medical product development in neonates and rare pediatric diseases

Pediatric Labeling Changes



Pediatric Labeling Changes Milestone

AAP News

Historic milestone: 1,000 drugs, biologics have new pediatric use information in labeling

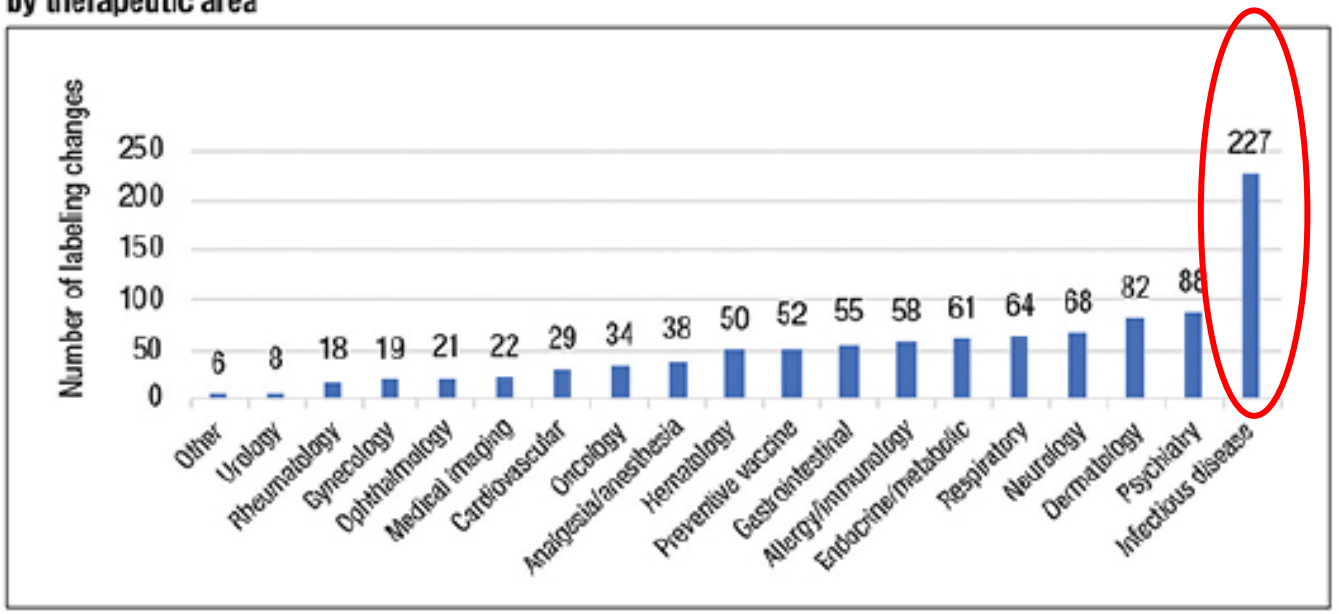
September 1, 2022

from the Food and Drug Administration

Article type: FDA Update

Topics: Pharmacology, Therapeutics

Figure 2. First 1,000 pediatric labeling changes pursuant to PREA, BPCA and the Pediatric Rule by therapeutic area



Neonatal Studies are Needed

- Majority of drugs used in neonates are "off label"[1]

- Scientific (& legislative) mandate to address gaps
  - Marketed products approved for other populations
  - New products for treatment of neonatal conditions

[1]*Laughon et. Al., JAMA Pediatr 2014*

Neonatal Studies are Challenging

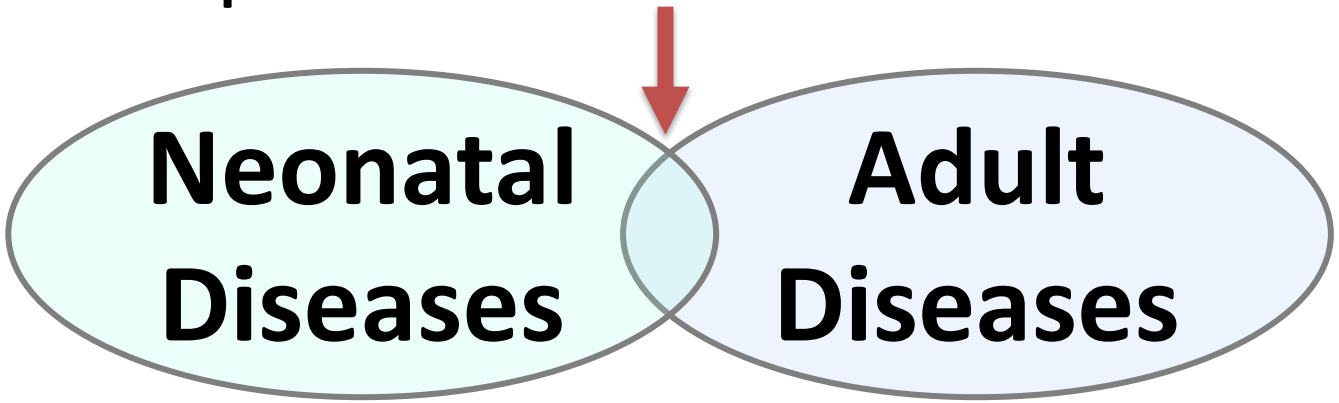
- Rapid development of organs and tissues
- Ontogeny of enzymes, receptors, transporters, neurotransmitters
- Complex transitional physiology
- Comorbidities

Establishing Substantial Evidence of Effectiveness

- Adequate and well-controlled studies evaluating reliable, well-defined, *clinically meaningful endpoints**

Direct measures of how a patient **feels, functions, or survives*

- Pediatric extrapolation[1]



[1]*ICH Harmonised Guideline on Pediatric Extrapolation E11a, Draft guidance April 2022*

Measuring Clinical Benefit is Not Straightforward in Neonates (an incomplete list)

- Not everyone values the same outcomes similarly
- Short term benefit may not be durable and may be counterbalanced by long-term tradeoffs
- Assessment of longer-term endpoints is complicated by attrition and intercurrent experiences
- While surrogate endpoints are attractive, efficiency may come with uncertainty

Challenges with Clinical Endpoints in Neonates

- Rare events → large studies
- May manifest late → longitudinal studies
- Lack of precision in measurement
- Lack of validated tools for the population
- Assessment of “feels” challenging in pediatrics (especially neonates)

** Ideal endpoints are common, assessed in a short time frame and precisely measured

PLOS | MEDICINE

GUIDELINES AND GUIDANCE

Core Outcome Set-STAndards for Development: The COS-STAD recommendations

Jamie J. Kirkham[1], Katherine Davis[1], Douglas G. Altman[2], Jane M. Blazeby[3], Mike Clarke[4], Sean Tunis[5], Paula R. Williamson[1]*

PLOS | MEDICINE

GUIDELINES AND GUIDANCE

Core Outcome Set–STAndards for Reporting: The COS-STAR Statement

Jamie J. Kirkham[1], Sarah Gorst[1], Douglas G. Altman[2], Jane M. Blazeby[3], Mike Clarke[4], Declan Devane[5], Elizabeth Gargon[1], David Moher[6], Jochen Schmitt[7], Peter Tugwell[8], Sean Tunis[9], Paula R. Williamson[1]*

Original research

OPEN ACCESS

Core outcomes in neonatology: development of a core outcome set for neonatal research

James William Harrison Webbe [1], James M N Duffy,[2] Elsa Afonso,[3] Iyad Al-Muzaffar,[4] Ginny Brunton,[5] Anne Greenough [6], Nigel J Hall [7], Marian Knight [8], Jos M Latour,[9,10] Caroline Lee-Davey,[11] Neil Marlow [12], Laura Noakes,[13] Julie Nycyk,[14] Angela Richard-Löndt,[13] Ben Wills-Eve,[15] Neena Modi [16], Chris Gale [1]

Critical Care Medicine

Society of Critical Care Medicine

Wolters Kluwer

A Core Outcome Set for *Pediatric Critical Care*

Multi-national, multi-stakeholder survey

Objective: Develop an evidence-informed, stake-holder recommended pediatric ICU core outcomes set

Performed 2 rounds of a modified Delphi survey

PICU COS features Global Outcome Domains of

Cognitive Function | Emotional Function | Physical Function | Overall Health

PICU COS-Extended includes 14 Specific Outcomes from the Global Domains that met inclusion by > 90% of Family Stakeholders

PICU Core Outcome Set and PICU COS-Extended are recommended resources for clinical and research programs to assess and improve outcomes for critically ill children and their families.

Data from Fink EL, et al: *Crit Care Med*, 2020

ccmjournal.org
#CritCareMed

Establishing an Adequate Safety Database

- Experience in other populations
- Seriousness of adverse reactions
- Rarity of condition
- Unique vulnerabilities of the neonate

Study Design Considerations

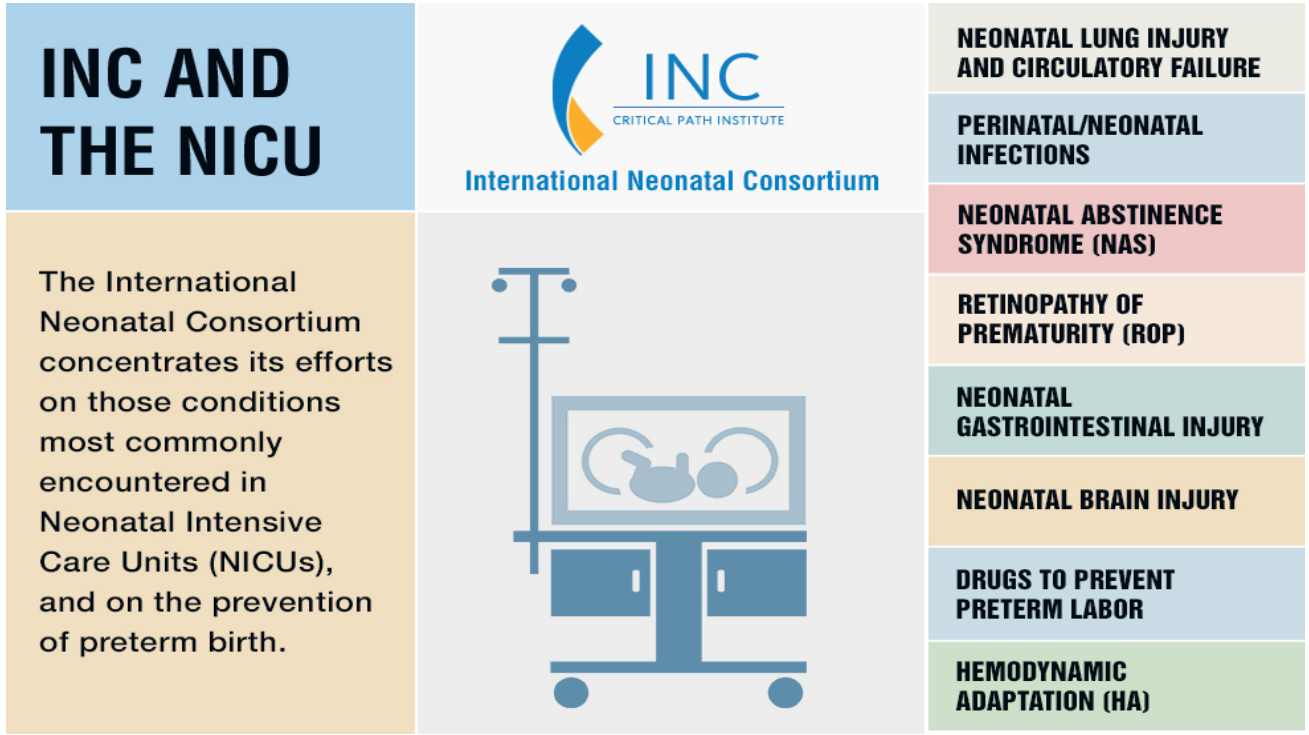
- Clinical variability in the study population
- Limitations of neonatal blood sampling
- Multi-stakeholder input (clinicians, nurses, parents, patients) to inform study design and feasibility
- Safety data should be collected with consideration of neonatal-specific AE definitions/classifications[1]

[1]*Salaets et. al., Arch Dis Child 2019*

Importance of Neonatal Subgroup Classifications

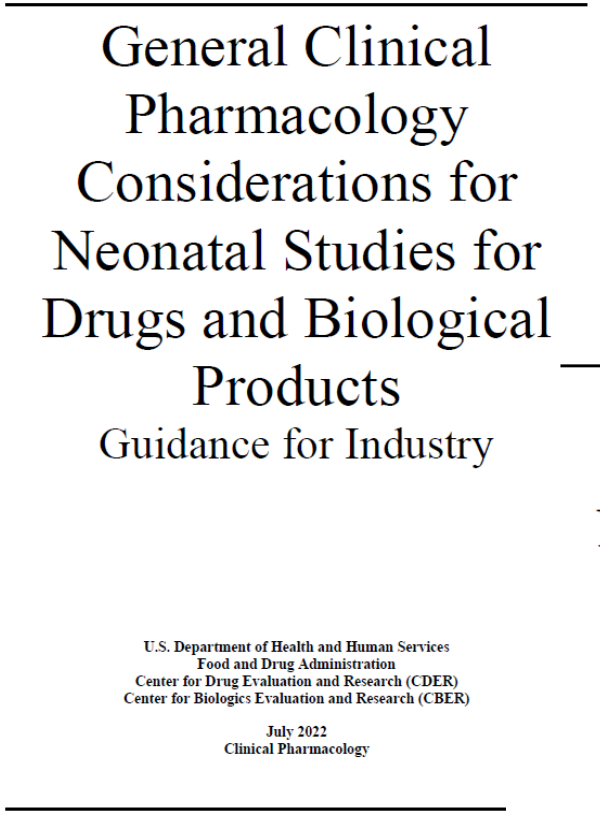
- Use for stratification to address heterogeneity
- Characteristics are not interchangeable
  - Gestational age (GA)/Postmenstrual age (PMA) reflect developmental maturity
  - Postnatal age reflects transitional physiology which changes rapidly after birth
  - Birthweight (BW) impacts allometric scaling
  - Growth disturbances (e.g., small [SGA] or large [LGA] for gestational age) impact developmental physiology & pharmacology

Resources for Neonatal Product Development



[International Neonatal Consortium (c-path.org)]

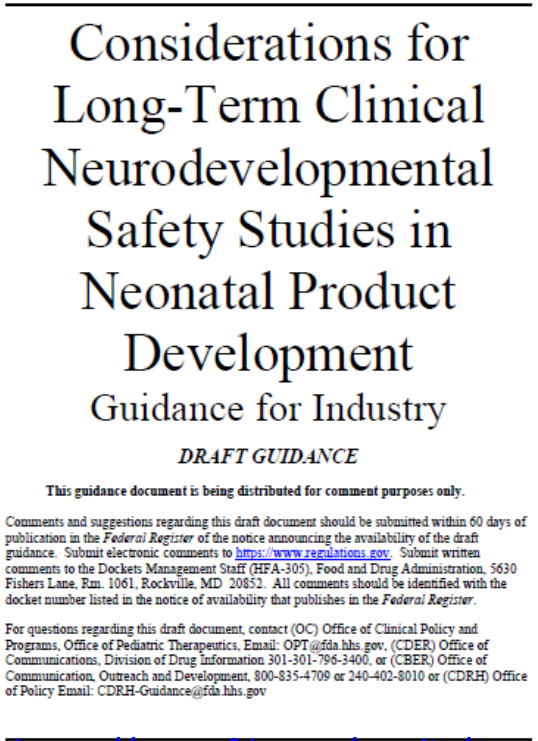
[Measuring Clinical Benefit in Neonatal Randomized Clinical Trials: Challenges and Opportunities (duke.edu)]


General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2022
Clinical Pharmacology

[https://www.fda.gov/media/129532/download]


Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OC) Office of Clinical Policy and Programs, Office of Pediatric Therapeutics, Email: OPT@fda.hhs.gov, (CDER) Office of Communications, Division of Drug Information 301-301-796-3400, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010 or (CDRH) Office of Policy Email: CDRH-Guidance@fda.hhs.gov

[https://www.fda.gov/media/165239/download]

Rare Pediatric Disease Drug Development: FDA Incentive Programs

Legislation

- 1983- Orphan Drug Act
- 2002- Best Pharmaceuticals for Children Act (BPCA)

Expedited Programs

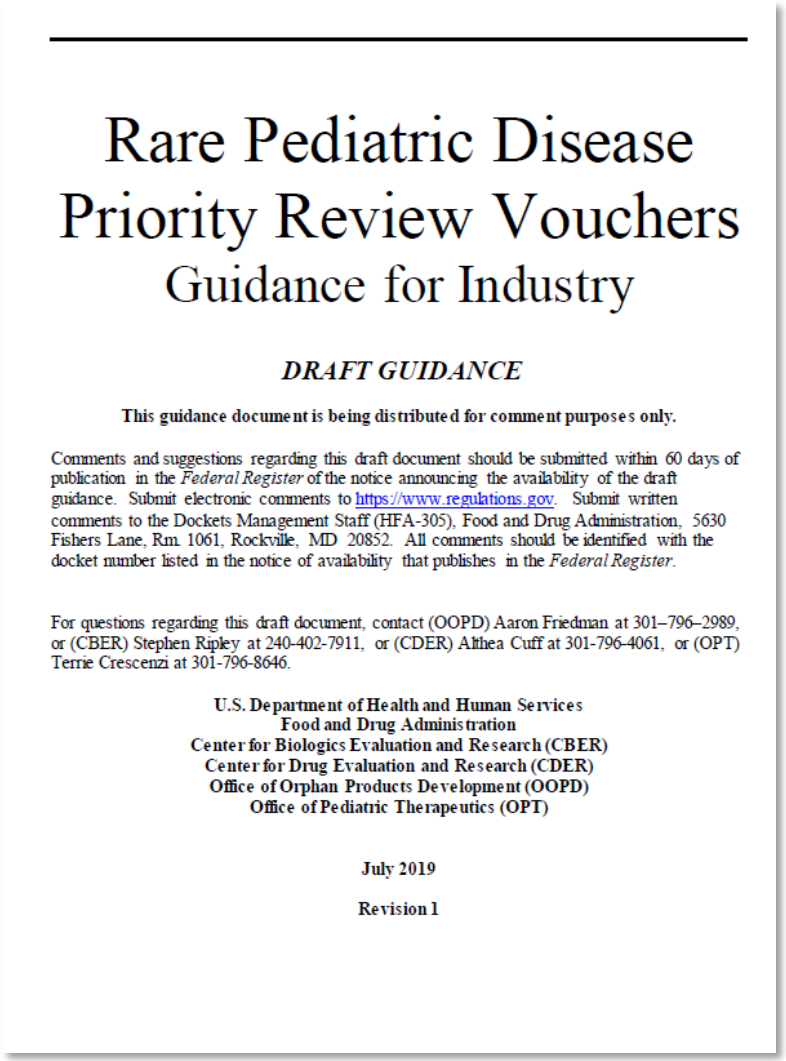
- Approval Pathway
  - accelerated approval
- Designation pathways
  - priority review
  - orphan drug
  - fast track
  - breakthrough therapy
  - regenerative medicine advanced therapy

Voucher Programs

- Rare Pediatric Disease
- Tropical Disease
- Material Threat Medical Countermeasure

Slide courtesy of Dr. Carla Epps

Rare Pediatric Disease



Rare Pediatric Disease
Priority Review Vouchers
Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OOPD) Aaron Friedman at 301–796–2989, or (CBER) Stephen Ripley at 240-402-7911, or (CDER) Althea Cuff at 301-796-4061, or (OPT) Terrie Crescenzi at 301-796-8646.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Office of Orphan Products Development (OOPD)
Office of Pediatric Therapeutics (OPT)

July 2019

Revision 1

Q1. What is a "rare pediatric disease"?

Section 529(a)(3) defines a "*rare pediatric disease*" as a disease that meets each of the following criteria:

> (A) The disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents [; ***and***]
> (B) The disease is a rare disease or condition, within the meaning of section 526 [of the FD&C Act].

https://www.fda.gov/media/90014/download

Neonatal enterovirus and cCMV infections may be considered rare diseases

- A **rare disease** is defined in the **Orphan Drug Act** as a disease/condition that affects <200,000 people in the US*
  - cCMV 1 per 200 live births in US (0.5%)
  - Non-polio enteroviruses cause about 10 to 15 million infections in US; lower incidence of severe disease (tens of thousands of hospitalizations per year); severe neonatal infection rare
- Orphan Drug Designations have been granted in the past:
  - Prevention of cCMV
  - Treatment of symptomatic enteroviral infection in the neonate
- Sponsors seeking orphan drug or rare pediatric disease designation should refer to the applicable guidance documents/FDA resources for more information

**note: prevalence can be >200,000 people if "no reasonable expectation" of recovering development & marketing costs*

Rare Pediatric Disease Resources

Mease et al.
Orphanet Journal of Rare Diseases (2024) 19:86
https://doi.org/10.1186/s13023-024-03097-x

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development

Catherine Mease[1*], Kathleen L. Miller[1], Lewis J. Fermaglich[1], Jeanine Best[2], Gumei Liu[3] and Erika Torjusen[1]

Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development | Orphanet Journal of Rare Diseases | Full Text (biomedcentral.com)

- Rare Pediatric (RPD) Designation and Voucher Programs
https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs
- Rare Pediatric Disease Priority Review Vouchers Draft Guidance
http://www.fda.gov/RegulatoryInformation/Guidances/ucm423313.htm
- Orphan Drug Designation
http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm

Summary

- Drug development in neonates faces unique challenges due to rapid developmental changes and vulnerabilities characteristic of the neonatal period
- FDA has resources and incentives to promote drug development for neonates and for rare pediatric diseases

Clinical Pharmacology Considerations for Dose Selection in Pediatric Patients

Kunyi Wu, Pharm.D.
Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

May 7, 2024

The opinions contained in this presentation are my own and do not represent the views of the FDA.

Outline

- Three broad approaches to pediatric drug development
- The role of modeling and simulation in pediatric drug development
- General clinical pharmacology considerations for dose selection in pediatric patients
- Initial dose selection based on animal data
- Challenges and opportunities

Three Broad Approaches to Pediatric Drug Development

- PK, Safety, and Efficacy Approach
  - The disease or disease progression is unique to pediatric patients
- PK, Safety, and PD/Efficacy Approach
  - The disease or disease progression is similar in pediatric patients and adults, but the exposure – response (E-R) in pediatric patients may be different from adults
- PK and Safety Approach
  - Adults and pediatrics share a sufficiently similar disease course and response to intervention

Draft FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products, September 2022

Valganciclovir – PK and Safety Approach

- Indication: prevention of CMV disease in kidney and heart transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])
- Population: adult and children 1 months and older
- Dosage form: tablet and powder for oral solution
- Pediatric approval approach: based on PK and safety study in children
  - Similar ganciclovir exposure in pediatric patients following proposed dose compared to adults receiving 900 mg dose

Clinical pharmacology review 2009: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022257Original-1_021304s007clinpharmr.pdf
Valganciclovir label assessed on 4/4/2024: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021304.s17_22257s12lbl.pdf

Modeling and Simulation Plays Important Role in Pediatric Drug Development

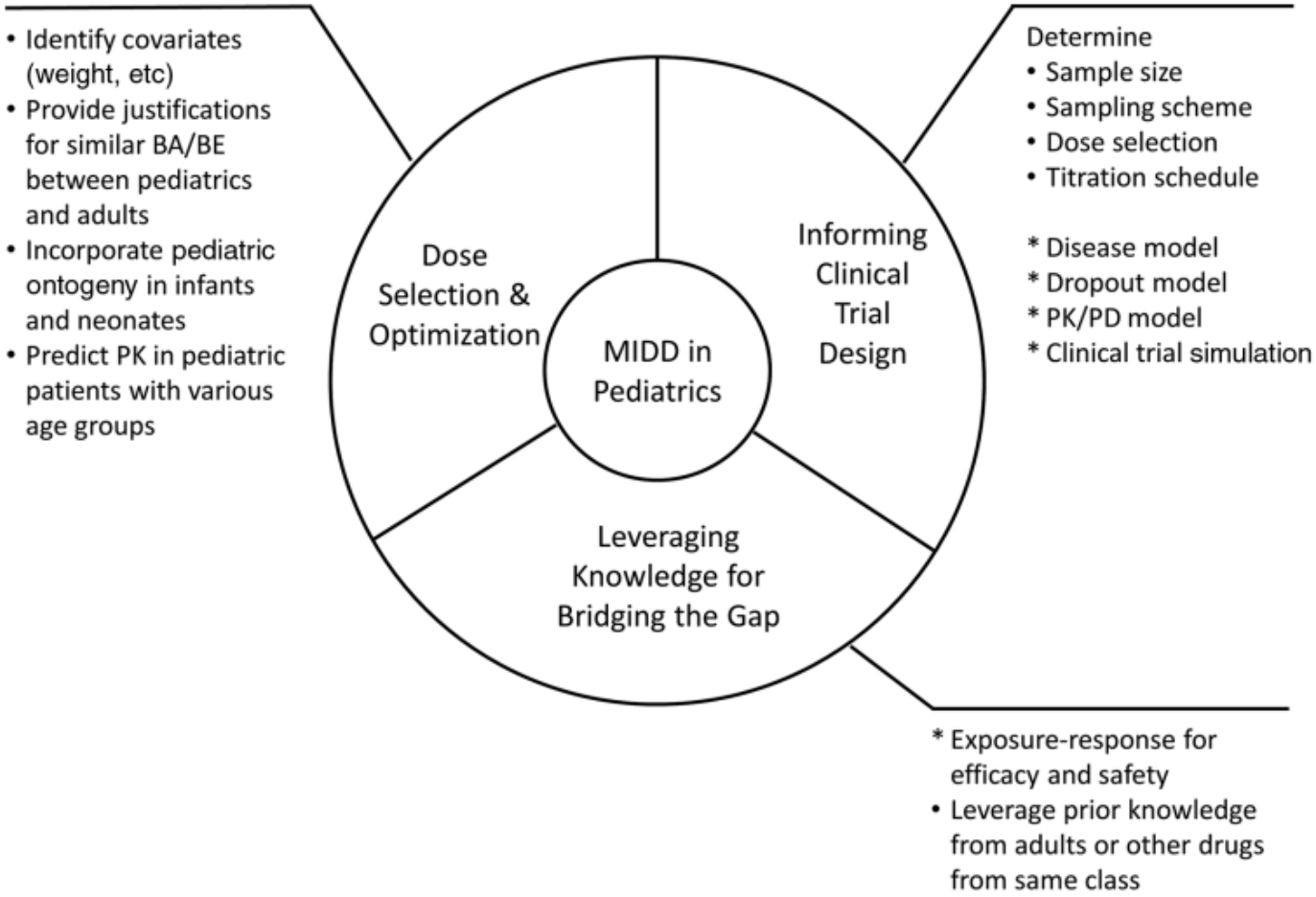


Figure 1. Application of model-informed drug development in pediatric drug development. This figure illustrates the 3 main areas of MIDD application in pediatric drug development. The bullets discuss the typical types (*) or common uses (•) of MIDD in each area. BA, bioavailability; BE, bioequivalence; MIDD, model-informed drug development; PD, pharmacodynamic; PK, pharmacokinetic.

The Journal of Clinical Pharmacology 2019, 59(S1) S104–S111

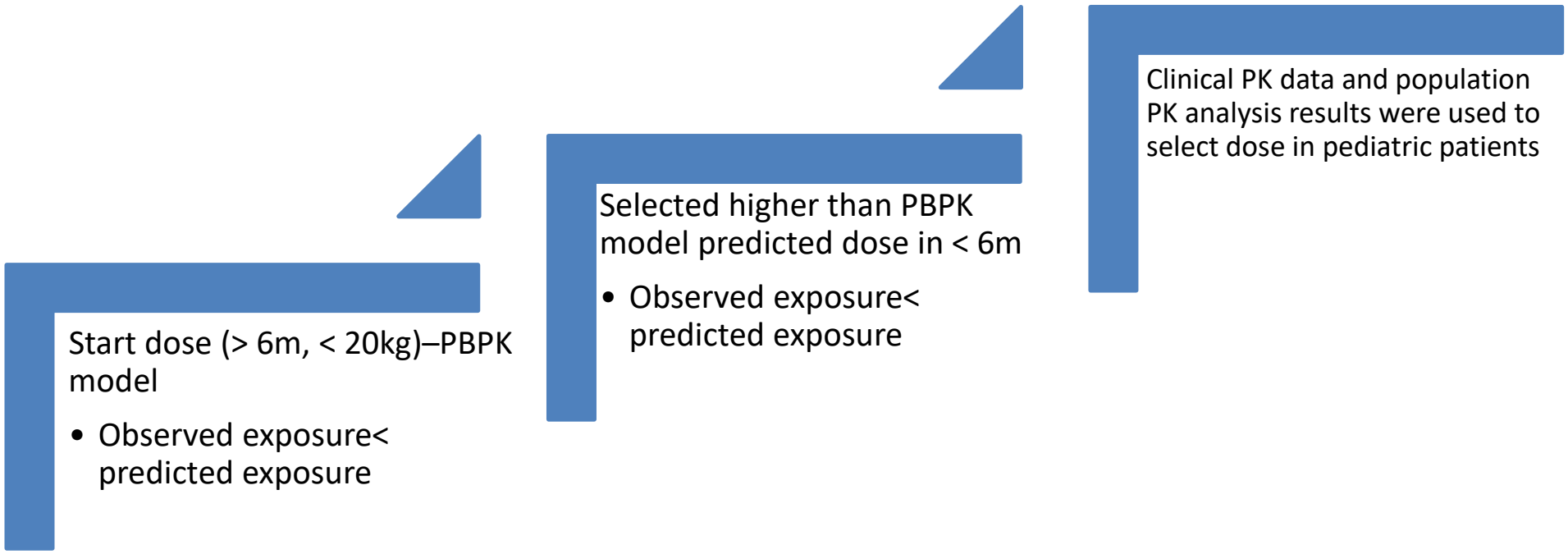
Pediatric Dose Selection for Maribavir

- No subjects <18 years of age, and no PK data were available for subjects 12 to 18 years of age in the completed or ongoing clinical trials at the time of the review
- The dose in adolescents was selected based on population PK modeling and simulation
  - Efficacy in adolescents (12 years of age and older weighing at least 35 kg) was extrapolated from efficacy in adults in the Phase 3 trial and predicted similar maribavir exposures in adults and adolescents based on modeling and simulation

Maribavir review 2021: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215596Orig1s000IntegratedR.pdf

“Learn and confirm”– Rivaroxaban Case Study

- Rivaroxaban: an anti-coagulant
- Rivaroxaban pediatric dosing strategy: to achieve similar drug exposure in pediatric patients compared to exposures observed in adults at the approved dose(s)



US Food Drug Administration Office of Clinical Pharmacology Review—Xarelto assessed on 4/11/2024: https://www.fda.gov/media/158802/download

Clinical Pharmacology Considerations for Dose Selection in Pediatric Patients

- Route of administration: oral (age-appropriate formulation) vs. parenteral
- Rapid change in body size, especially in neonates and infants
- Local drug concentration: e.g., CNS (drug concentration in CSF), inner ear penetration
- Drug elimination: organ maturation, age related changes in expression and activity of DMET (drug metabolizing enzymes and transporters)

Draft FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products, September 2022

One Example of Using Animal Studies to Select Dose in Neonates – Lucinactant Case

- Lucinactant: For the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS
- Initial dose to be evaluated in neonates was directly selected based on premature monkey and premature rabbit model study results
- Three clinical studies were conducted in premature neonates in the lucinactant drug development program

Approaches to Dose Finding in Neonates, Illustrating the Variability between Neonatal Drug Development Programs, Pharmaceutics 2020, 12(7), 685

Challenges and Opportunities

- Less intensive PK samples are collected in pediatric patients → population PK model is important and frequently used
- Heterogenicity: age, weight, development stages → PBPK approach has been used in organ and enzyme ontogeny
- Local drug exposure: animal model and PBPK model are helpful
- More…..data are needed especially in very young children

Acknowledgements

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- Yodit Belew
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- Colleagues in FDA/OND/DAV


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Drug Development Considerations for the Treatment of Congenital Cytomegalovirus Infection and Neonatal Enterovirus Infection

MAY 7 - 8, 2024

Life of a NICU Parent: Decision-making in Clinical Trial Enrollment

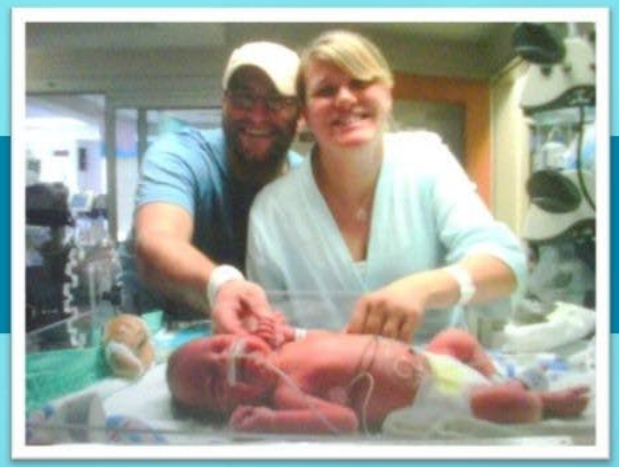
Betsy Pilon
Executive Director, Hope for HIE

WHAT DID YOU WALK IN THE ROOM WITH TODAY?

WHAT DID YOU WALK IN THE ROOM WITH TODAY?

FAMILIES COME INTO THE NICU WITH SOMETHING TRAUMATIC HAPPENING AT BIRTH.

PLUS, their other potential baggage!



THE NICU IN 2012

- Max, born April 2012
- First pregnancy, all normal, until it wasn't at 37 weeks.
- Born in a community hospital setting, transferred to "the mothership" in Downtown Detroit for therapeutic hypothermia.
- But the NICU is just for preemies, right? Or transient full term babies who need observation?

- **Prognosis:** MRI Day showed "moderate" damage to the occipital, parietal and frontal lobes… the dreaded HIE "wait and see".
- No mention of HIE, until non-family-centered rounds and overheard "encephalopathy"
- Left the NICU without connection to any support, feeling isolated and frustrated.

BIRTH

NICU ARRIVAL

COOLING PROCESS

MRI DAY

FIRST HOLDS

NICU DURATION

NICU DISCHARGE

POST-NICU SUPPORT

HIE NEONATAL CLINICAL TRIALS

Lots of variables working against researchers & families

- Time-sensitive (cooling initiated within 6 hours)
- Resource variability
- Mother/baby health and separation
- Overwhelming consent insisted by IRBs
- Quick health literacy lessons to consent
- Mistrust of medical system
- Era of medical misinformation
- Trauma
- Bias/Gatekeeping/Misperceptions of Families
- Systemic inequity

WE MUST ACCEPT
FINITE DISAPPOINTMENT,
BUT NEVER LOSE
Infinite Hope

- MARTIN LUTHER KING, JR.

HIE NEONATAL CLINICAL TRIALS

Lots of exciting work with researchers & families

- 30+ years of research with HIE
- Cooling: head cooling vs. whole body
  - Longer, quicker, colder, gestation modifiers
  - COOL PRIME, HEAL (powerful secondary analyses)
- Gates Foundation preclinical pipeline:
  - Various small and large animal models, human organoid model
  - Equity for LMIC
- Novel and repurposed medication possibilities:
  - Stem cells
  - Peptides
  - Biologic: Coral derived?
  - Melatonin

HOPE IS THAT THING INSIDE US THAT INSISTS, DESPITE ALL THE EVIDENCE TO THE CONTRARY, THAT SOMETHING BETTER AWAITS US IF WE HAVE THE COURAGE TO REACH FOR IT AND TO WORK FOR IT AND TO FIGHT FOR IT.

BARACK OBAMA

NEONATAL GAP AREAS TO CONSIDER

Silos, Bias & Impact to Enrollment

- Center the community you're studying & avoid tokenization for funding
- Early multidisciplinary stakeholder involvement - think outside neonatology - early in the trial design process
- Site training on communcation is ***essential*** to enrollment success

Measures

- Develop measures that matter - composite vs. lumping death & disability
- Help patient-family stakeholders understand biomarkers

Longitudinal Engagement & Support

- Proactive communication planning should be formalized, using best practices, patient-family engagement with considerations to build health literacy, and include longitudinal support resources for enrolled families.

MAX'S JOURNEY: BIRTH TO 12 YEARS OLD

- Middle School: Grade 6
- Loves basketball & video games & annoying his little sister
- Favorite food: Seafood
- Favorite band: Metallica

THREE MONTHS: Vision concerns *permanent vision impairment*

THREE MONTHS: Parents pushed to wean off phenobarbital

NINE MONTHS: Spastic cerebral palsy diagnosis *spastic diplegia*

TWO YEARS: Corrective Vision Surgery

MOST CLINICAL TRIALS END HERE WITH OUTCOME DATA (AND FUNDING)

THREE YEARS: Begins walking independently with AFOs

FIVE YEARS: Delayed toilet training, enters kindergarten, suspected ADHD

EIGHT YEARS: Confirmed inattentive ADHD

8.5 YEARS: Epilepsy onset at the sleep/wake cycle

10 YEARS: Anxiety Diagnosis

11 YEARS: CVI Diagnosis SDR Surgery

From six months old onward:

- Physical & Occupational Therapy (never speech)
- Pediatrics, neurology, epileptology, PMR, ophthalmology, optometry, vision consultant & resource support at school.

Medications:

- Trileptal for epilepsy maintenance, Nayzilam for seizure rescue
- Adderal XR for ADHD

THANK YOU!

betsy@hopeforhie.org

Follow across social media:
@HopeforHIE

Facilitating Pediatric Drug Development

Leveraging Pediatric Trial Networks and Global Collaboration

Lily Mulugeta, PharmD

Associate Director, Policy and Research
Division of Pediatric and Maternal Health
ORPURM/OND/CDER

Disclosures and Disclaimers

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Pediatric Drug Development: General Principles

Pediatric patients should have access to products that have been appropriately evaluated

Product development programs should include pediatric studies when pediatric use is anticipated

Incorporation of regulatory standards into pediatric clinical research strengthens the quality of the research

FDA guidance to industry E11(R1)- Clinical Investigation of Medicinal Products in the Pediatric Population, 2017

Pediatric Drug Development: Challenges

- Persistent lag from adult approval to pediatric labeling (typically averaging 7 years)
- Patient accrual difficulties account for nearly 40% of study discontinuations*
  - Population affected by the condition is often small
  - Willingness of clinicians to use therapeutics off-label
  - Inefficiencies in conducting pediatric clinical trials*
- These challenges, especially in neonates and infants, may lead to insufficient evidence to support the labeling of a product for pediatric use

*: Greenberg, Rachel G., et al. *Therapeutic Innovation & Regulatory Science* (2022)

Evolution in Pediatric Drug Development

- Children are protected THROUGH research, not from it
- Recognition that evaluation of new and existing drugs in pediatric patients requires collaboration:
  - Patients and patient organizations
  - Academic researchers and community practitioners
  - FDA committed to working with external stakeholders to improve efficiency of pediatric clinical trials
  - Collaboration initiatives

Opportunities for Collaboration in Pediatric Drug Development

Precompetitive Collaborations

Sharing preclinical data, tools, and resources among stakeholders.

Consortia and Partnerships

Collaborative efforts between academia, industry, and regulators

Innovative Trial Designs

Adaptive designs/novel methodologies to overcome limits related to small sample size and acceptability of the trial

Pediatric Research Networks

Facilitate setup and execution of pediatric clinical trials

Roles of Pediatric Research Networks

Networks have been identified as one way to overcome inefficiencies in clinical research

Innovation

May allow for innovative trial designs (e.g., registries, modeling, platform trials)

Multicenter Trials

Enabling larger and more diverse trial populations

Facilitating Collaboration

Networks bring together researchers, clinicians, and industry stakeholders

Resource Pooling

Shared data and resources accelerate research and development in pediatric patients

Pediatric Research Networks

- A wide variety of structures and levels of activity

- Different organizational and funding models based around:
  - **Clinical specialties**
    - Optimize patient outcomes: Bring patients and families, data on endpoints and biomarkers, disease natural history and stratification, establish standard of care, extrapolation of data
  - **Geographical location** with multiple specialties
    - Address barriers and inefficiencies in the conduct of clinical research including regulatory, ethics, data management, site function, training, etc.

- Ideally, these two models are highly integrated

Turner, Mark A., et al. *Clinical Therapeutics* (2017)

Potential Role of Research Networks in Drug Development

Networks can impact decisions spanning the product development and life cycle

Trial design

Population; **inclusion/exclusion criteria**; Duration of Treatment; effect size for powering trial; **historical control**; **supplementary safety data**; **Extrapolation assumptions/Bayesian prior**

Trial conduct

Potential trial candidates; sites/investigators

Discovery

Disease prevalence; **Treatment patterns/standard of care**; Patient heterogeneity: **Biomarkers**

Early Phase Trials

Late Phase Trials

Post Approval Studies

Expanding labeling to other populations; new regimens; Supplementary safety data or **long- term safety data** unknown at the time of new drug approval

Examples of Pediatric Research Networks

- Critical Path launched 2 pediatric network initiatives in 2014
  - International Neonatal Consortium (INC)
  - Institute for Advanced Clinical Trials for Children (I-ACT for Children)

- The Pediatric Trials Network (PTN) was established in 2010
  - Contract awarded by NICHD (to fulfill mandate under BPCA); renewed in 2018
  - Leadership at Duke clinical Research Institute (Clinical Coordinating Center), with Emmes as the Data Coordinating Center
  - Collaborates with academic institutions, industry sponsors, and regulatory agencies
  - Provides infrastructure for designing and conducting pediatric clinical trials
  - Data submitted to FDA to update product labeling for off-patent drugs

- Collaborative Antiviral Study Group
  - Multi-center clinical trials group
  - Funded by NIH
  - Collaborates with pharmaceutical companies to evaluate new antiviral therapies

Other Examples of Pediatric Research Networks

	International Alliance for Clinical Trials in Children (iACT)	International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT)	Pediatric European Network for Treatment of AIDS (PENTA)	European Network of Paediatric Research at the European Medicines Agency (ENpr-EMA)	Global Research in Paediatrics (GriP)	Innovative Therapies for Children with Cancer (ITCC)	Connect4Children (C4C)
Collaborators	Global stakeholders, healthcare, industry, professionals, patient advocates	Global investigators, institutions, community representatives, (funded by NIH)	Pediatric hospitals, healthcare systems, academia, industry, global health organizations	Regulatory bodies, researchers, healthcare providers, industry sponsors	Global stakeholders, academia, industry, patient advocacy groups	Oncologists, researchers, industry partners, healthcare providers	Academic centers, industry partners, patient organizations across Europe
Collaborative Efforts	From protocol development to labeling, novel therapy development, trial sites, network of experts	Evaluation of novel treatments and interventions for HIV and TB	Guidelines, training programs, research, network building, patient engagement	Network of investigators within and outside EU, facilitates studies	Training program, structured pediatric research capacity, electronic infrastructures	Evaluation of novel agents, collaborative clinical trials, early clinical trials, preclinical models	Multinational trials; large patient advocacy, educational and training programs

Networks increasingly broadening to a global and patient-centered approach

Examples of Neonatal Networks: INC

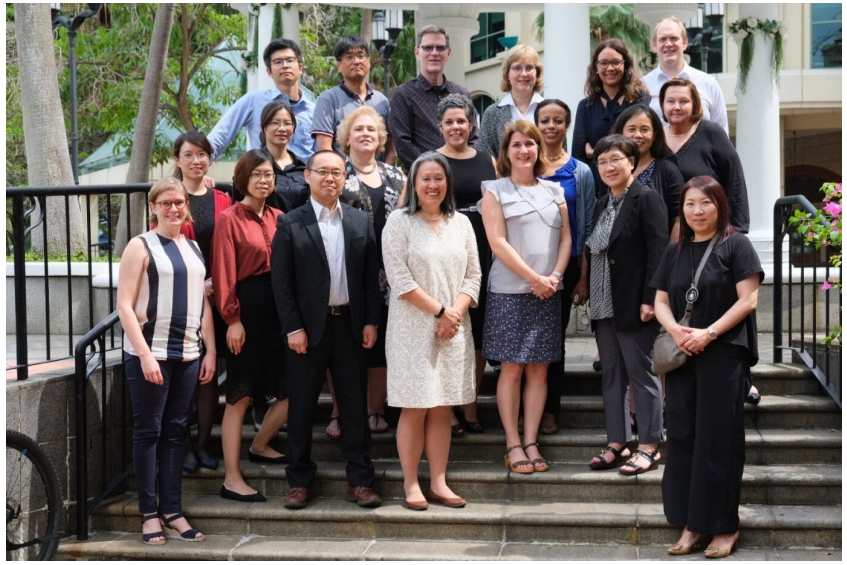
International Neonatal Consortium (INC):

- Global collaboration of stakeholders
- Goal: Advance neonatal drug development and research
- Hospitals, drug developers, patient advocacy groups, regulatory agencies, and other organizations
- Generate consensus and develop tools to accelerate medical innovation and regulatory science for neonates

Example: Consensus recommendations developed/published to facilitate neonatal seizure clinical trials including alternative designs, inclusion and exclusion criteria, safety monitoring, appropriate outcome measures, etc.

Global Collaborations: International Council for Harmonisation (ICH)

- **Focus:** Global organization that develops guidelines and standards for pharmaceuticals development
- **Collaborative Efforts:** Brings together regulatory authorities and industry experts to harmonize regulatory requirements and promote global cooperation



Recent publication: ICH E11A Guideline: Harmonized global guideline on extrapolation of data in pediatric drug development programs

International Regulatory Collaborations

- **Monthly Pediatric Cluster Conference**
  - Established in 2007
  - European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada (HC); Australia Therapeutic Goods Administration (TGA)

- **WHO Pediatric Regulators Network**
  - Reactivated in 2019
  - Support the availability of quality medicines for children through facilitation of communication, collaboration, training, and regulatory harmonization across the development, registration and pharmacovigilance of pediatric medicines

- **Quarterly Pharmacometrics Cluster meeting**
  - FDA and other regulatory agencies
  - Exchange of scientific information, sharing of experiences, and discussion of review and policy issues (including pediatric issues)

Summary

- Significant achievements in advancing pediatric drug development through collaborative efforts and multidisciplinary approaches
- Collaborative networks will continue to extend globally for broader impact
- Growing emphasis on inclusion of patient outcomes and experiences in research to drive meaningful results
- Continued development of policies to support efficient and practical pediatric drug development

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U.S. FOOD & DRUG ADMINISTRATION

FDA Workshop

Real-World Data and Real-World Evidence in Drug Development

7 May 2024

John Concato, MD, MS, MPH

- **Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration**
- **Adjunct Professor of Medicine, Yale University School of Medicine**

Disclaimer

- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**
- **No conflicts of interest exist related to this presentation**
- **Mention of a commercial product should not be construed as actual or implied endorsement**

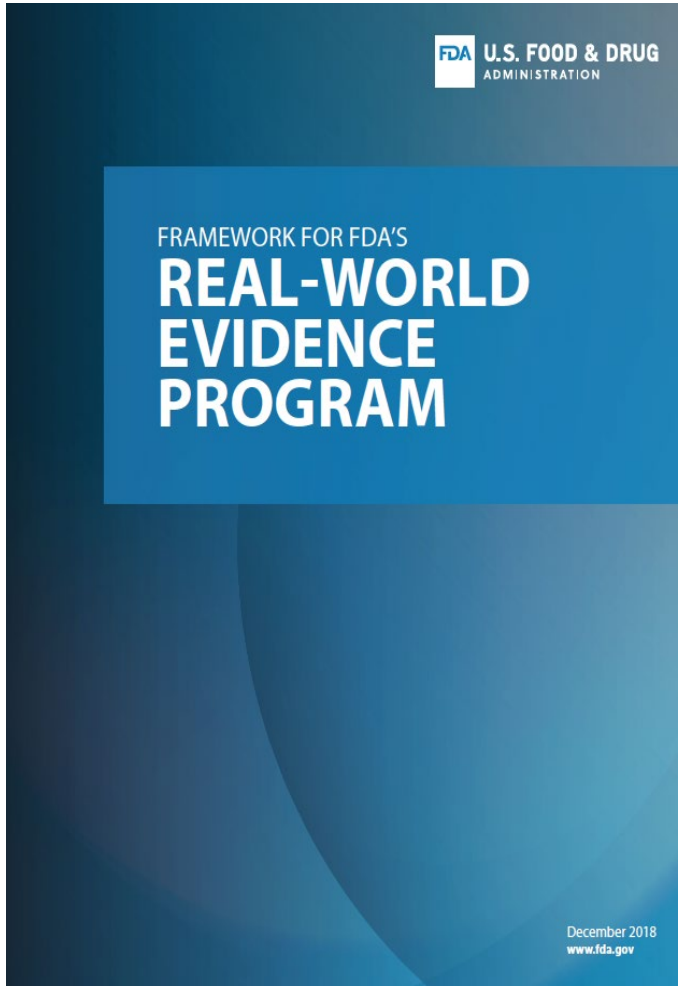
Outline of Presentation

- **Background on “real-world evidence” (RWE)**
- **Selected aspects of FDA’s RWE Program, including guidance development and demonstration (research) projects**
- **Real-world data (RWD) and RWE activities related to neonatal healthcare**

21st Century Cures of 2016 – 'Mandates Met'

- **FDA established a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework issued in 2018:**
  - **Describe sources of data, challenges, opportunities, etc.**
- **Draft guidance for industry issued 2021-2024**
- ***Note: Standard for substantial evidence to approve drug & biologics unchanged***

FDA's RWE Framework For Drugs & Biologics (2018)



- **Applies to Center for Drug Evaluation & Research (CDER), Center for Biologics Evaluation & Research (CBER), and Oncology Center of Excellence (OCE);** ***Center for Devices & Radiological Health (CDRH) has separate regulations and RWE program***

- **Multifaceted program to implement RWE:**
  - **internal agency processes**
  - **external stakeholder engagement**
  - **demonstration (research) projects**
  - **guidance development**

https://www.fda.gov/media/120060/download

‘Real-World’ Definitions (from 2018 FDA Framework)

Real-World Data (RWD) are data relating to patient health status and/or delivery of health care **routinely collected from a variety of sources**

- electronic health records (EHRs)
- medical claims data
- product and disease registries
- data from digital health technologies in non-research setting
- other data sources that can inform on health status, such as questionnaires

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product **derived from analysis of RWD**

Generated using various study designs—including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, and observational studies

https://www.fda.gov/media/120060/download

Emergence of Real-World Evidence

Interest in real-world evidence (RWE) can be attributed to:

- **Improved access to, and rapid analysis of, information in the era of big data**
- **Research showing observational studies can generate valid results**
- **21st Century Cures Act mandating U.S. Food and Drug Administration (FDA) evaluate the potential use of RWE for medical product approvals**
- **Popularity of "real-world" as a term; other factors, including COVID-19**

Note: With or without invoking the terms "RWD" and "RWE," types of data sources and study designs aren't entirely new

Current Status of RWE

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Issue being addressed: More than five years after passage of the 21st Century Cures Act, the terms RWD and RWE are being used inconsistently and interchangeably

Content of article:

- **addressed two common misconceptions**
- **provided conceptual overview of study design**
- **described FDA guidance and demonstration projects**
- **highlighted regulatory approvals**
- **offered path forward**

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

Misconceptions Regarding RWD & RWE

Frequent instances of:

- ***Misconception #1 – RWD & RWE are new concepts***: **"In reality, sources of data and types of study design haven't fundamentally changed, but electronic access to more detailed clinical data is evolving & the data are becoming more relevant and reliable"**

- ***Misconception #2 – A simple dichotomy of randomized trials vs. observational studies exists***: **"In reality, clinical trials are defined by assignment of treatment according to an investigational protocol, and single-arm trials face challenges similar to those in observational studies in determining whether difference in clinical outcomes (compared to an external control group) represent actual treatment effects"**

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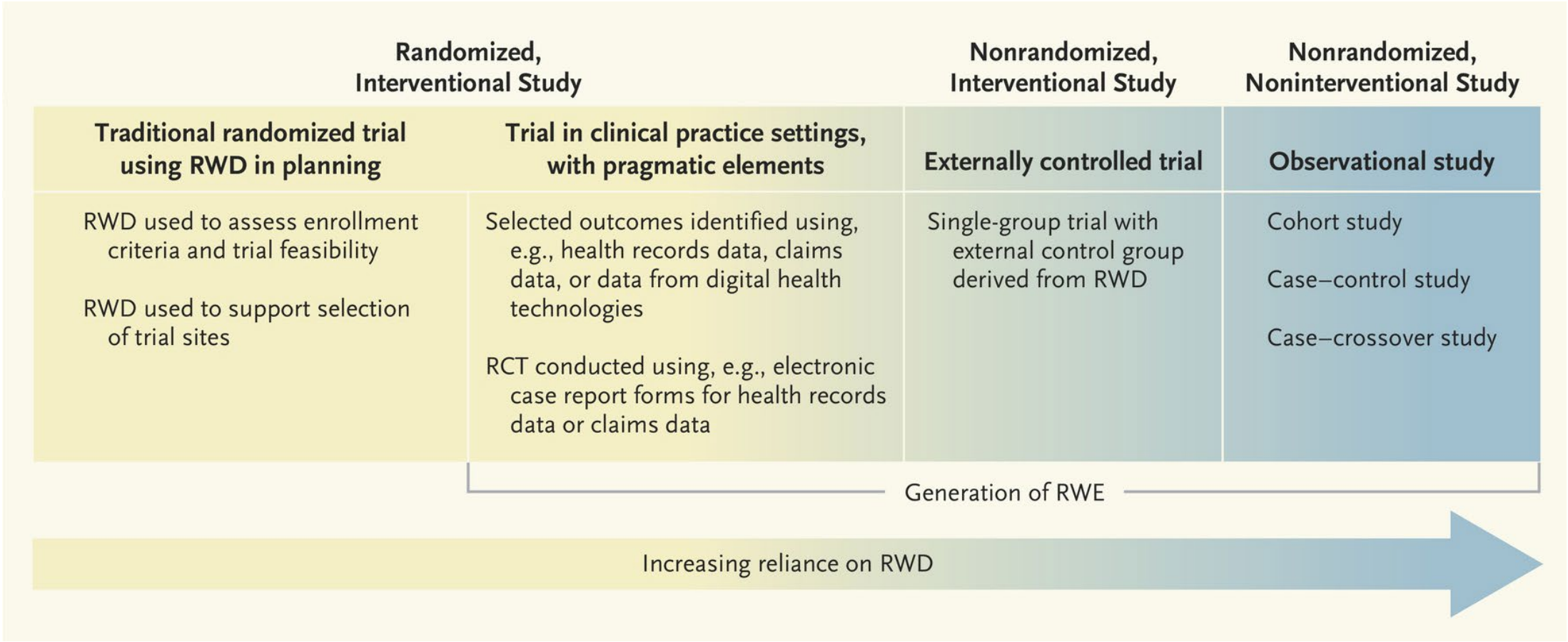
When Does RWD Generate RWE?

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

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FDA RWE Guidance (2021-2024)

Topic	Category	Status
EHRs and claims data	Data considerations	draft issued
Registry data	Data considerations	final issued
Data standards	Submission of data	final issued
Regulatory considerations	Applicability of regulations	final issued
Externally controlled trials	Design considerations	draft issued
Non-interventional studies	Design considerations	draft issued
RCTs in clinical practice settings	*Design considerations*	*in development*
Submitting RWE	Procedural	final issued

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

‘EHR/Claims Data’ Guidance

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

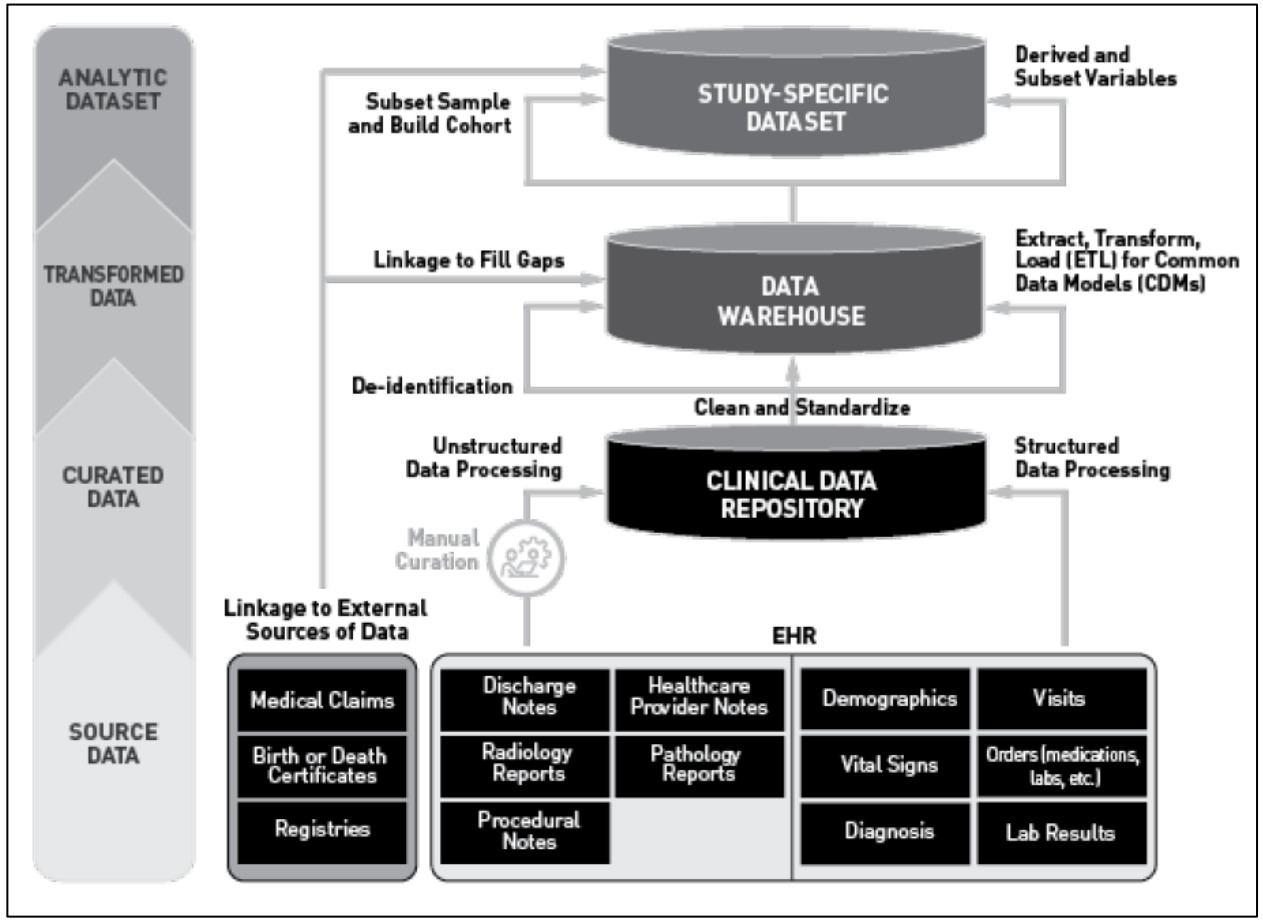
DRAFT GUIDANCE

September 2021
Real World Data/Real World Evidence (RWD/RWE)

EHR/Claims Guidance – 'Life Cycle of EHR Data'

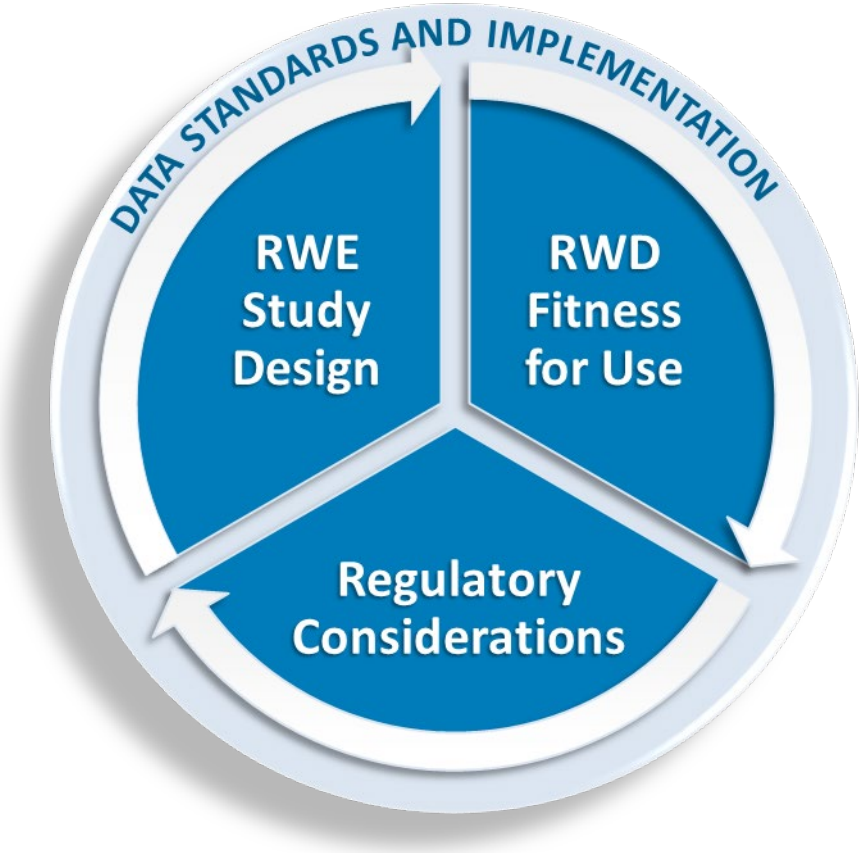
Excerpts from *Real-World Data: Assessing Electronic Health Records and Medical Claims […]* (Sep 2021)

- "[…] the process for examining the quality of the data […] is not a one-time assessment"
- "[…] rather, it is an ongoing process […] in multiple phases of the [life cycle of HER data]"



See https://www.fda.gov/media/152503/download

FDA Approach to Evaluating RWE



Key considerations:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

New Indication for Prograf® Based on RWE

- **Prograf® (tacrolimus) approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 (later for kidney & heart) based on RCT evidence, and the drug is used widely in clinical care**
- **RCTs not done for lung transplant, but sponsor (Astellas Pharma US) submitted supplemental New Drug Application to FDA with observational 'RWE' study**
- **Study data and design were evaluated according to FDA standards**
- **Approval for preventing rejection/death in lung transplant granted 16 Jul 2021**

https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

Representative Challenges with Use of RWE

Real-world data sources:

- data reliability and clinical relevance
- missing or "mistimed" data
- suitable capture of endpoint data
- need for linkage with other data sources

Design and interpretation of non-randomized studies:

- residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

Conduct of non-randomized studies:

- protocol and analysis plan not *pre-specified*
- access to patient-level data and ability to inspect RWD sources

FDA U01 Award – 'RWD on Neonates'

Advancing standards and methodologies to generate real-world evidence from real-world data through a neonatal pilot project

This project, led by Klaus Romero, M.D., chief science officer at the Critical Path Institute (C-Path), and Jonathan Davis, M.D., professor of pediatrics at Tufts Medical Center and U.S. academic director of the International Neonatal Consortium (INC), will support the collection of neonatal intensive care unit (NICU) data from many key stakeholders worldwide. The data will then be deposited into a Real-World Data and Analytics Platform (RW-DAP).

[...]

The electronic medical records data collected in this project will facilitate the design and conduct of clinical trials in neonates. This collaborative effort with C-Path and INC partners will help address the fact that neonates have relatively few FDA-approved therapeutic options for various medical problems.

https://www.fda.gov/drugs/science-and-research-drugs/fda-grant-awards-projects-supporting-use-real-world-data-generate-real-world-evidence-regulatory#2020%20Grant%20Awards

FDA U01 Award (cont'd)

Real-World Evidence for Neonatal Drug Development: Challenges and Opportunities

Kanwaljit Singh, MD, MPH[1], John Concato, MD, MS, MPH[2,3], and Jonathan M. Davis, MD[4,5]

The challenges surrounding the use of RWD are substantial but not insurmountable

[…]

RWE-driven drug development represents an evolution in scientific methodology as well as a renewed commitment to advancing neonatal health on a global scale

THE JOURNAL OF PEDIATRICS
https://doi.org/10.1016/j.jpeds.2023.113806

Looking Forward

Closing paragraph from 2022 NEJM article:

- **"The FDA remains committed to robust policy development aligned with the 21st Century Cures Act while maintaining evidentiary standards in honoring our obligation to protect and promote public health. Focusing on the distinction between interventional studies and noninterventional studies can help researchers, sponsors, and regulators better understand and describe relevant methodologic issues. Gaining more experience, including conduct of rigorous noninterventional studies, will help to advance drug development."**

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Summary

- In addition to the randomized trial paradigm, availability of “big data” and passage of 21st Century Cures Act reflect & contributed to emergence of “real-world evidence”
- FDA’s RWE Program is advancing as outlined in the 2018 *Framework for FDA’s Real-World Evidence Program*, including guidance and demonstration projects
- CDER approves drugs and biological products based on existing evidentiary standards when evaluating real-world evidence
- Appropriate use of RWD/RWE can advance neonatal drug development


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ADMINISTRATION

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Clarifying Questions and Answers

U.S. FOOD & DRUG ADMINISTRATION

Break

Session 2:
Enterovirus Epidemiology and Disease Background

- **Picornaviruses and Neonatal Sepsis**
  - Amy Rosenfeld, PhD; FDA
- **National Surveillance Data on Neonatal Enterovirus Infections in the United States**
  - Miranda Delahoy, PhD; FDA
- **Neonatal Enterovirus Infections: Challenges and Opportunities**
  - Mark Abzug, MD; University of Colorado

Picornaviruses and neonatal sepsis

Amy B Rosenfeld, PhD
Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Review
Food and Drug Administration
May 7, 2024

Picornaviridae

U.S. FOOD & DRUG ADMINISTRATION

- Genus: *Aalivirus*
- Genus: *Ampivirus*
- Genus: *Aphthovirus*
- Genus: *Aquamavirus*
- Genus: *Avihepatovirus*
- Genus: *Avisivirus*
- Genus: *Bopivirus*
- Genus: *Cardiovirus*
- Genus: *Cosavirus*
- Genus: *Crohivirus*
- Genus: *Dicipivirus*
- Genus: *Enterovirus*
- Genus: *Erbovirus*
- Genus: *Gallivirus*
- Genus: *Harkavirus*
- Genus: *Hepatovirus*
- Genus: *Hunnivirus*
- Genus: *Kobuvirus*
- Genus: *Kunsagivirus*
- Genus: *Limnipivirus*
- Genus: *Megrivirus*
- Genus: *Mischivirus*
- Genus: *Mosavirus*
- Genus: *Orivirus*
- Genus: *Oscivirus*
- Genus: *Parechovirus* → **Parechovirus 1, 3A, 6**
- Genus: *Pasivirus*
- Genus: *Passerivirus*
- Genus: *Potamipivirus*
- Genus: *Rabovirus*
- Genus: *Rosavirus*
- Genus: *Sakobuvirus*
- Genus: *Salivirus*
- Genus: *Sapelovirus*
- Genus: *Senecavirus*
- Genus: *Shanbavirus*
- Genus: *Sicinivirus*
- Genus: *Teschovirus*
- Genus: *Torchivirus*
- Genus: *Tremovirus*

40 genera

- Species: *Enterovirus A* → **Enterovirus A71, A16, A6**
- Species: *Enterovirus B* → **Echovirus 11, echovirus 30, Coxsackievirus A9**
- Species: *Enterovirus C* → **Poliovirus 1, 2, 3, enterovirus C99**
- Species: *Enterovirus D*
- Species: *Enterovirus E*
- Species: *Enterovirus F*
- Species: *Enterovirus G*
- Species: *Enterovirus H*
- Species: *Enterovirus I*
- Species: *Enterovirus J*
- Species: *Enterovirus K*
- Species: *Enterovirus L*
- Species: *Rhinovirus A*
- Species: *Rhinovirus B*
- Species: *Rhinovirus C*

Neonatal sepsis

Picornavirus structure

- 3 capsid proteins VP1-3

  VP1-3 exterior

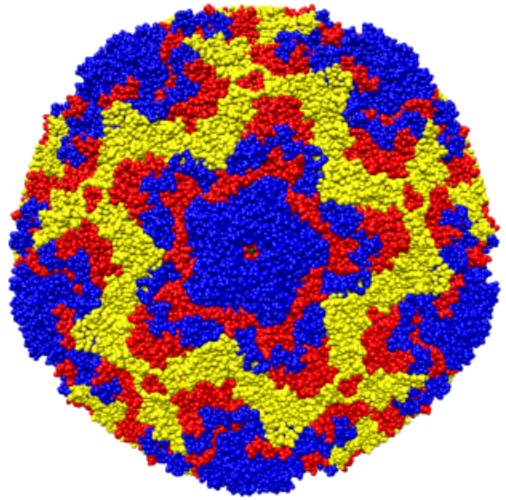
  VP0/4 interior

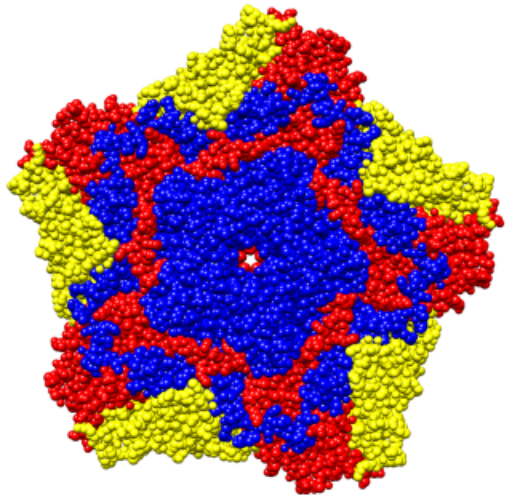
- 60 copies of each protein

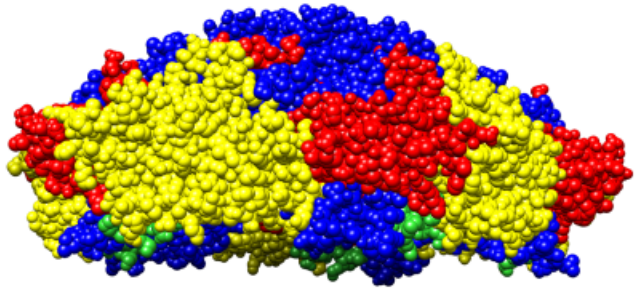
- Icosahedral symmetry

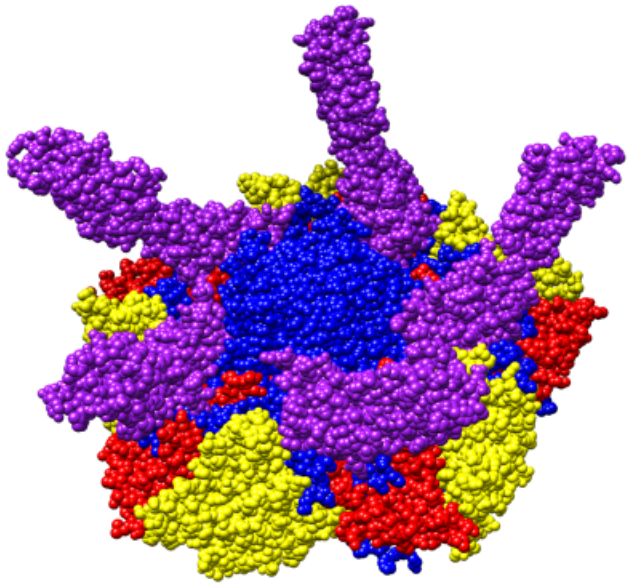
- 5-fold, 3-fold, 2-fold axis

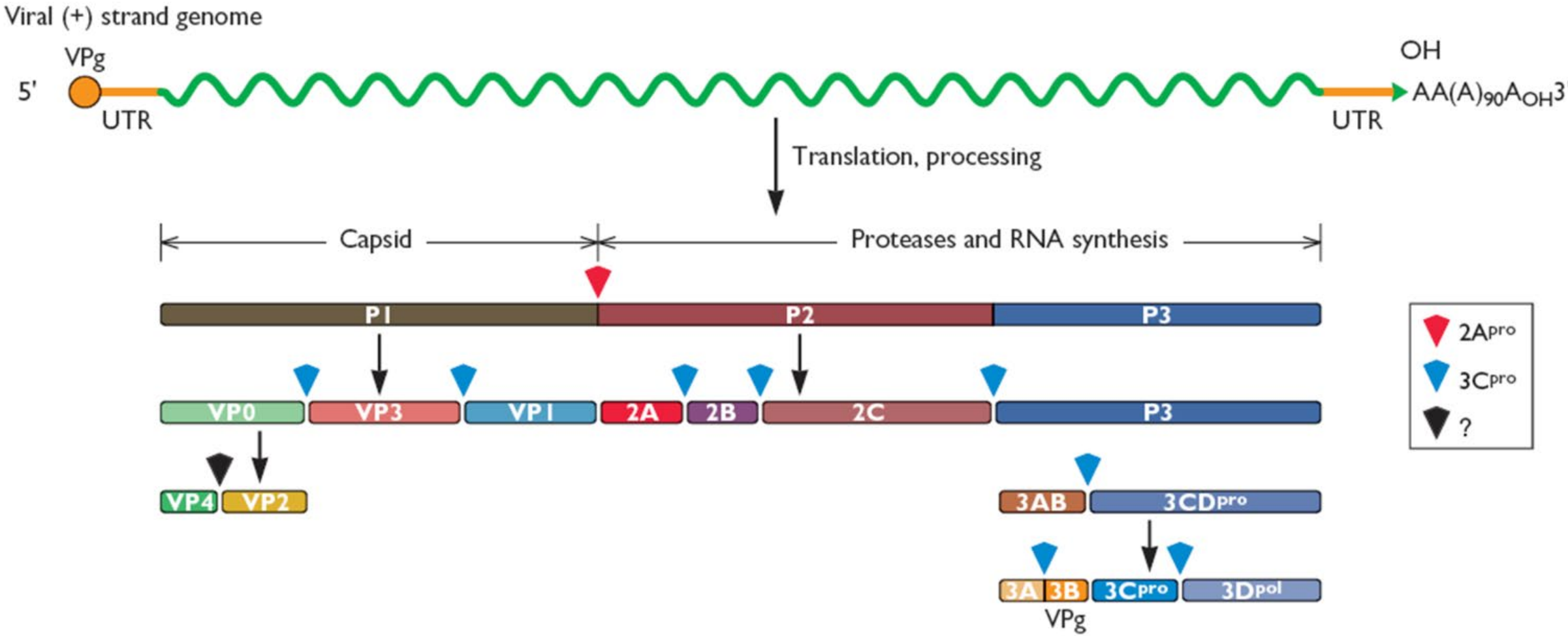
- Not all particles possess a canyon

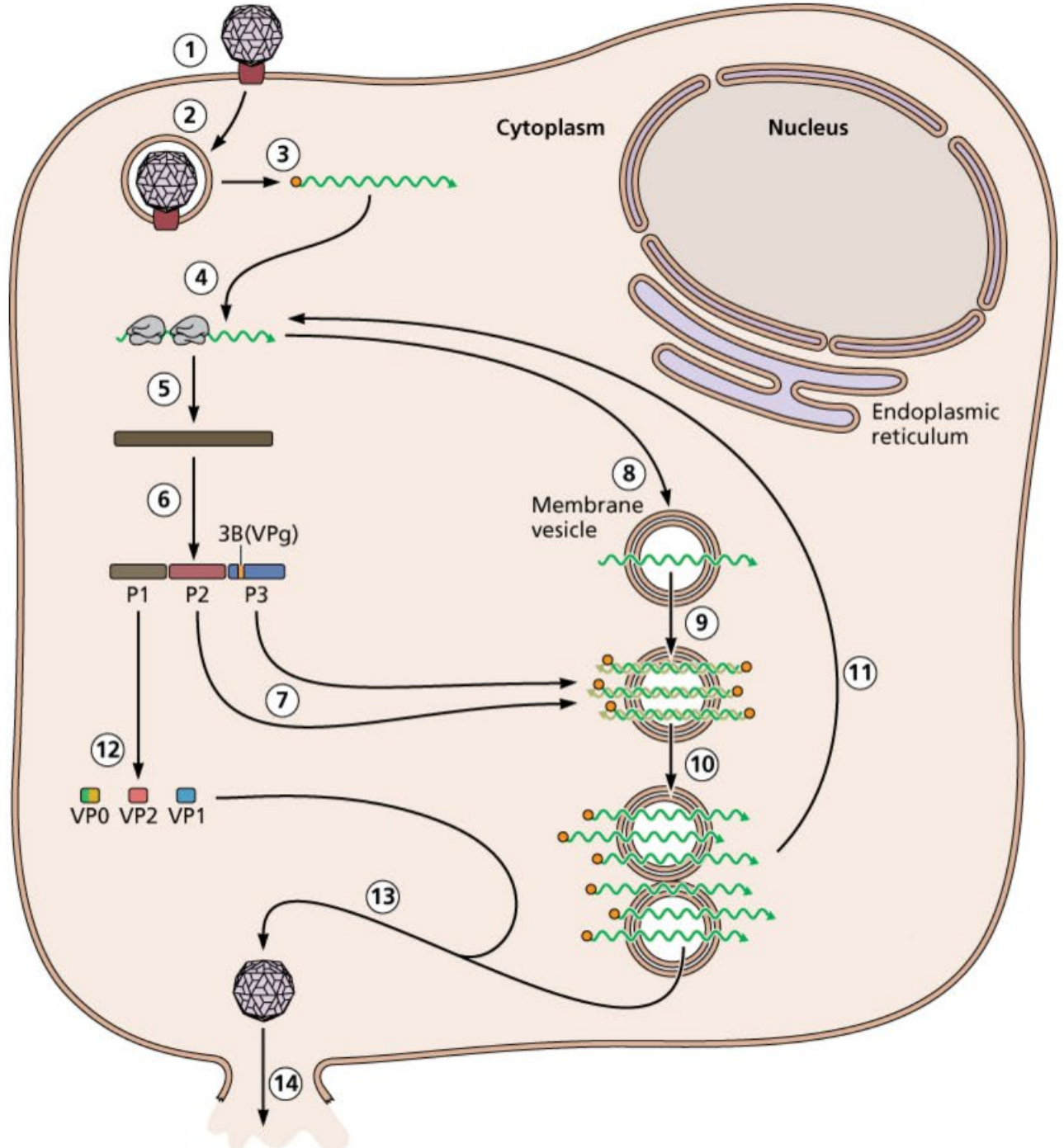






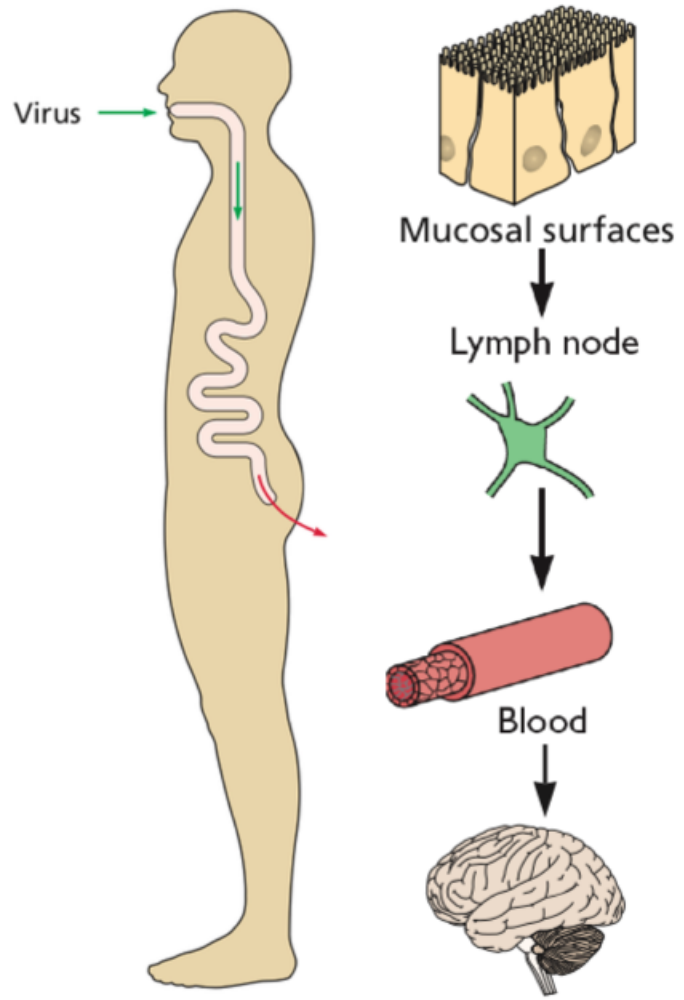






Pathogenesis of picornaviruses

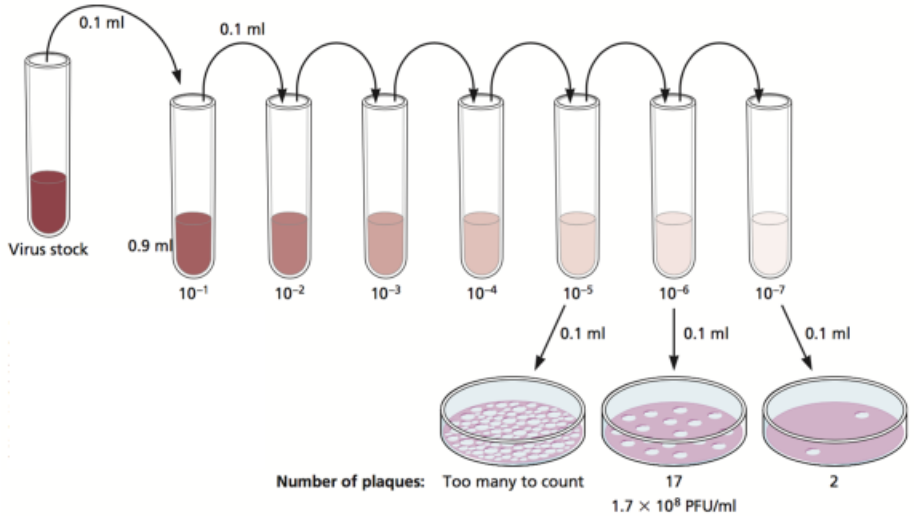
- Species specific
- Spread by fecal-oral or respiratory transmission
- Severe disease occurs at the secondary sites of infection
- Presence of neutralizing antibodies are the best biomarker for protection against the development of severe disease

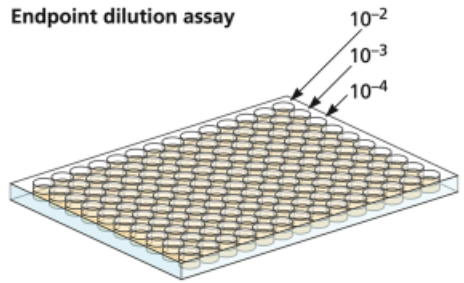


~1% of infections

Measuring infectious virus

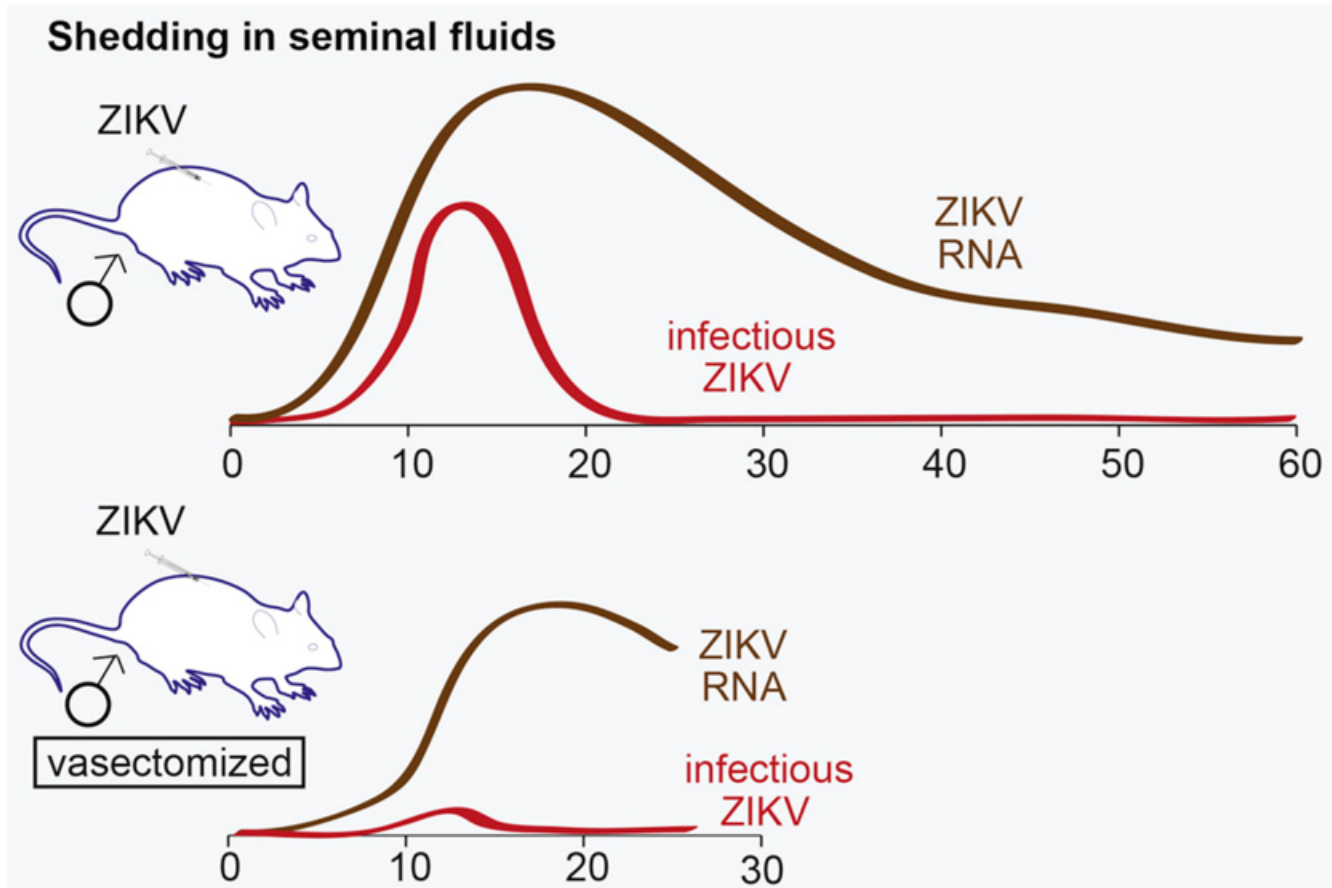
- Plaque assay
- Endpoint/terminal dilution





Virus dilution	Cytopathic effect									
10^{-2}	+	+	+	+	+	+	+	+	+	+
10^{-3}	+	+	+	+	+	+	+	+	+	+
10^{-4}	+	+	−	+	+	+	+	+	+	+
10^{-5}	−	+	+	−	+	−	−	+	−	+
10^{-6}	−	−	−	−	−	−	+	−	−	−
10^{-7}	−	−	−	−	−	−	−	−	−	−

Presence of viral RNA is **NOT** the same as presence of infectious virus



For many RNA viruses, RNA can be detected long after disappearance of infectious virus

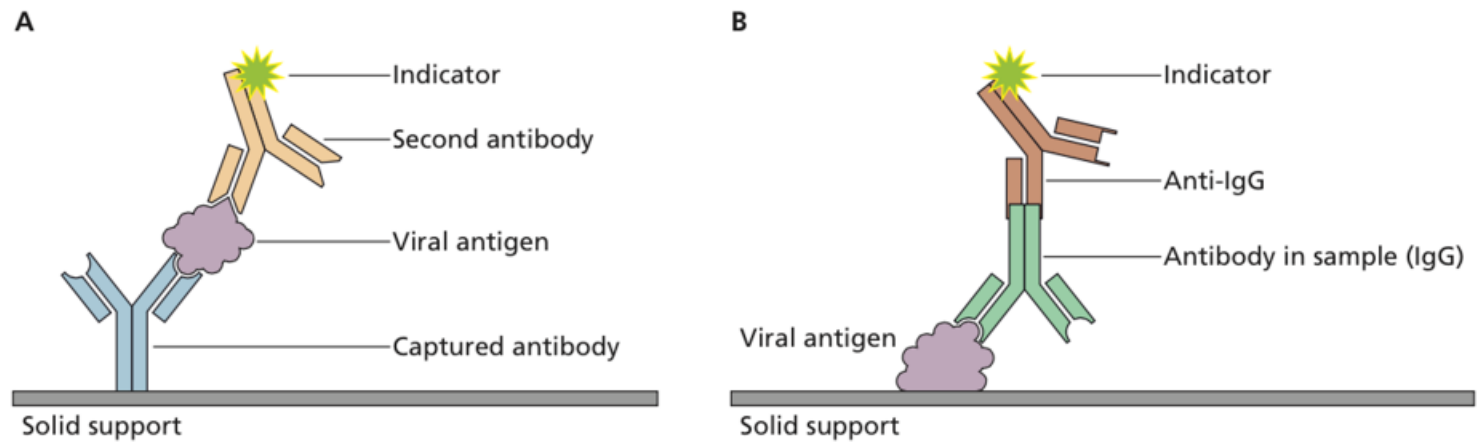
Assessing prior infections or immunity

- ELISA binding assays

  Viral antigen

  Anti-pathogen antibody

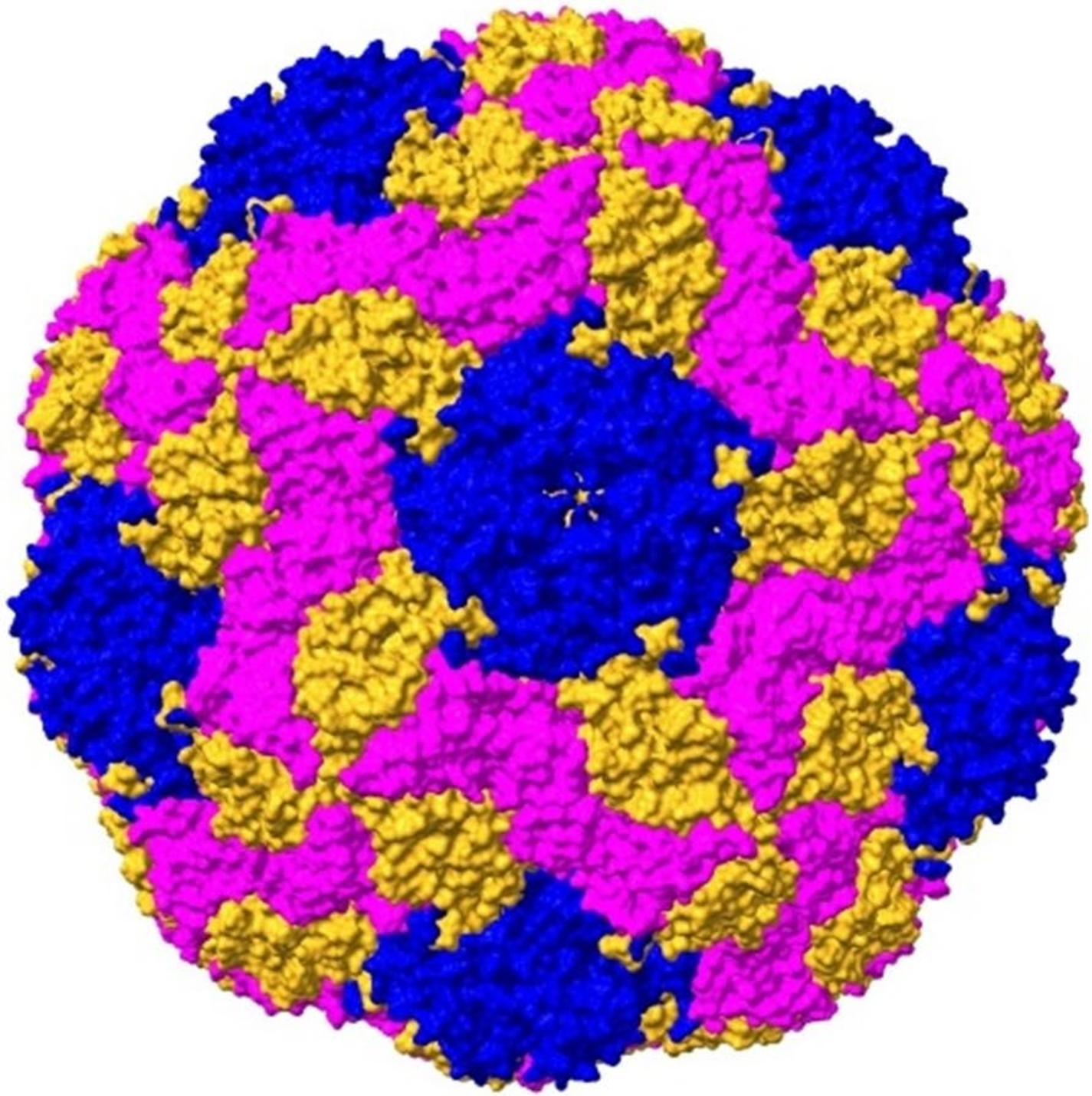
- Microneutralization assays



Neutralization of enteroviruses by murine enterovirus polyclonal sera

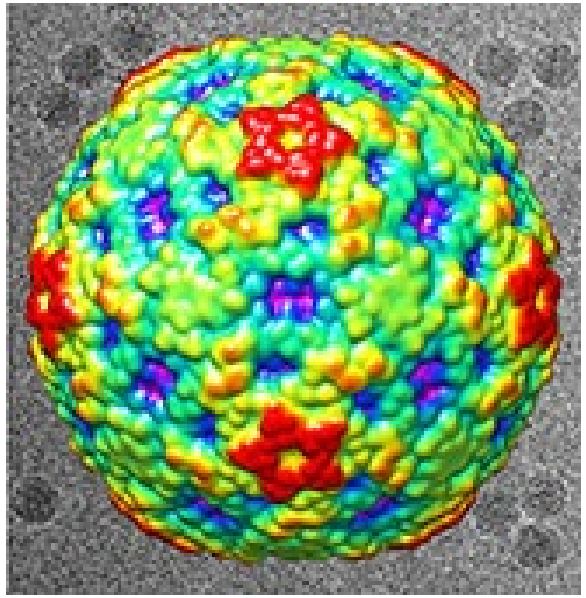
Virus	Neutralization titer (Reciprocal)	
Enterovirus D68 (209)	4096	
Poliovirus 1/ Mahoney	4096	
P414 (Mahoney/Lansing chimera)	32	
Coxsackievirus A24v	<2	
Coxsackievirus B3	<2	
Enterovirus B 1	<2	
Enterovirus D-68 NY-68	512	
IUH04 (2014, clinical isolate)	16	*Antigenic drift? New serotypes?*
Enterovirus D-94	<2	
Human rhinovirus A1A	256	
Human rhinovirus A16	<2	
Enterovirus D-70 (DNE)	<2	

Presence of a cross-reactive immune response suggests that results of serosurveys, seroconversion and seropositivity studies may be misleading



National Surveillance Data on Neonatal Enterovirus Infections in the United States

Miranda Delahoy, PhD MSPH
Acute Flaccid Myelitis and Domestic Polio Team
Polio and Picornavirus Branch, Division of Viral Diseases
Centers for Disease Control and Prevention



FDA Neonatal Enterovirus Infection and Congenital CMV Infection Workshop
May 7, 2024

Enterovirus (EV) infection data are reported to multiple national surveillance systems.

- National Enterovirus Surveillance System (NESS)
- National Respiratory and Enteric Virus Surveillance System (NREVSS)
- New Vaccine Surveillance Network (NVSN)

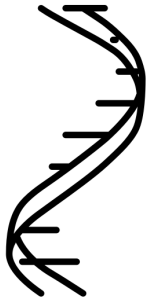
Data collected on enterovirus infections varies by surveillance system.

	National Enterovirus Surveillance System (NESS)	National Respiratory and Enteric Virus Surveillance System (NREVSS)	New Vaccine Surveillance Network (NVSN)
Type of system	passive, laboratory-based	passive, laboratory-based	active, prospective, population-based
EV reporting & typing	positive EV reports with virus types	aggregated rhinovirus (RV)/EV positivity reported	aggregated RV/EV & EV-D68
Years (with EV data)	1960s–present	2007–present	2000–2009 and 2015–present
Patient population	all ages	all ages	children <18 years with acute respiratory illness
Geographic scope	varies by year; CDC lab & labs from 4 states reported during 2022	varies by year; >90 labs reporting nationally	7 pediatric health systems

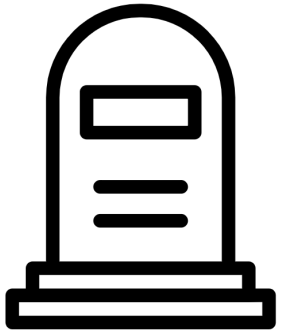
Neonatal Enterovirus Infections (2004–2022) — National Enterovirus Surveillance System (NESS)

10,224

EV infections*



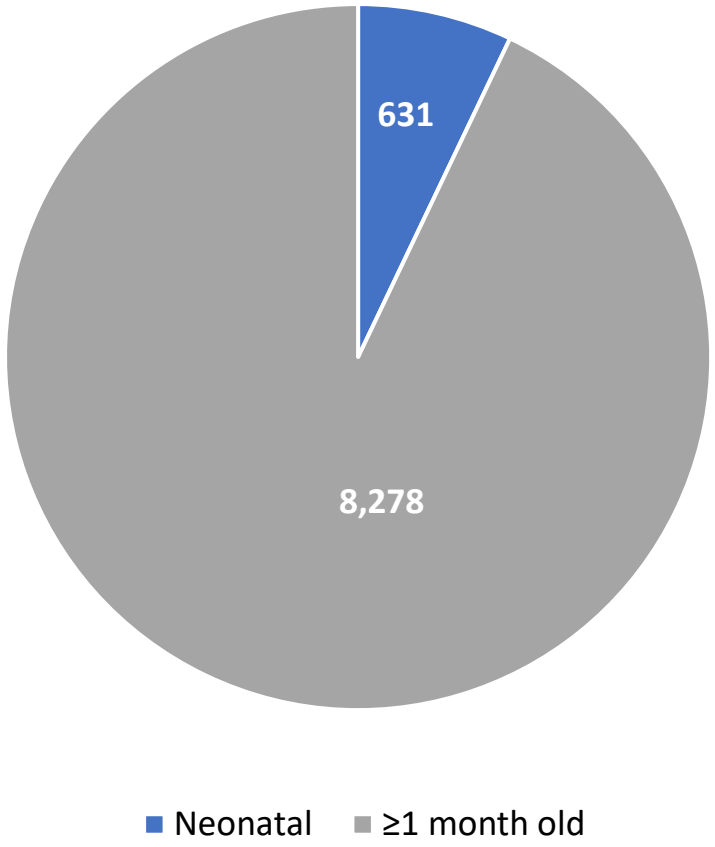
virus types



fatal outcomes

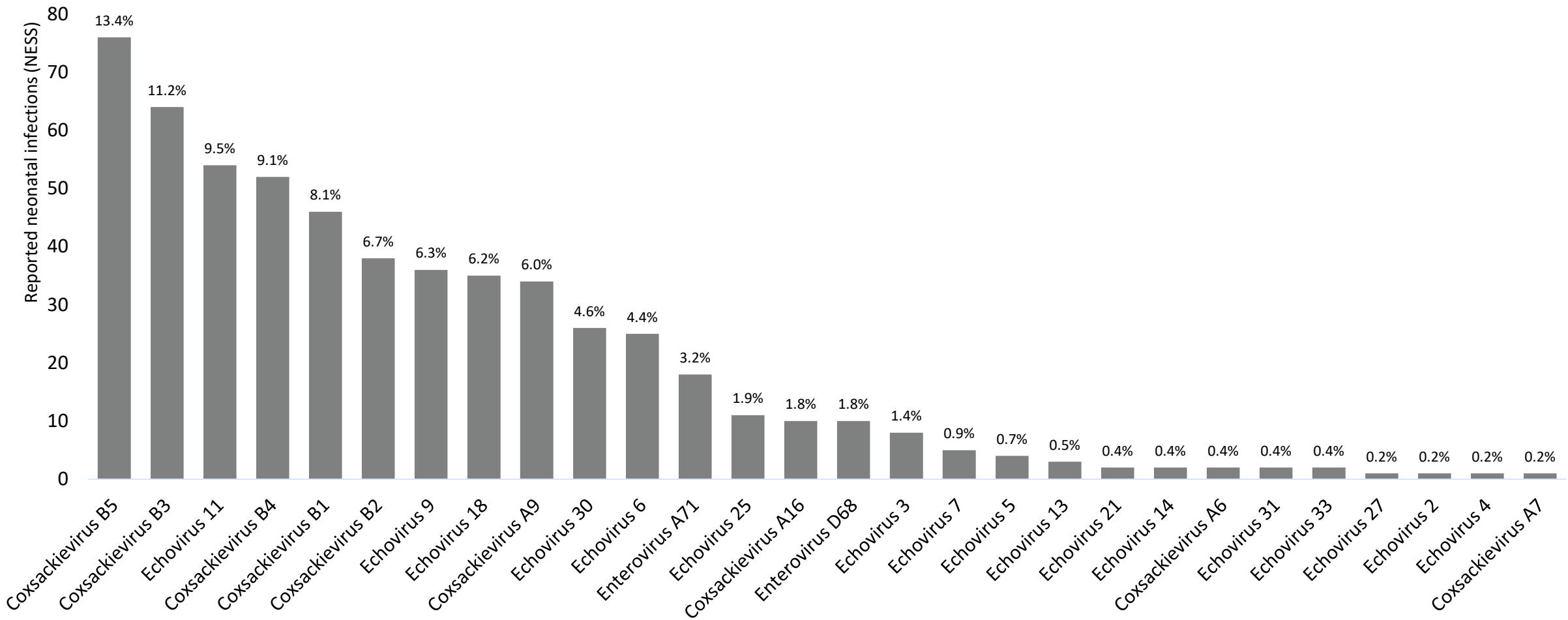
*nonpolio, all ages

7% of infections occurred among neonates (<1 month old).



Among 8,909 enterovirus infections with known patient age during 2004–2022

Coxsackievirus (CV)B5, CVB3, Echovirus (E)11, and CVB4 were detected most frequently among neonates.



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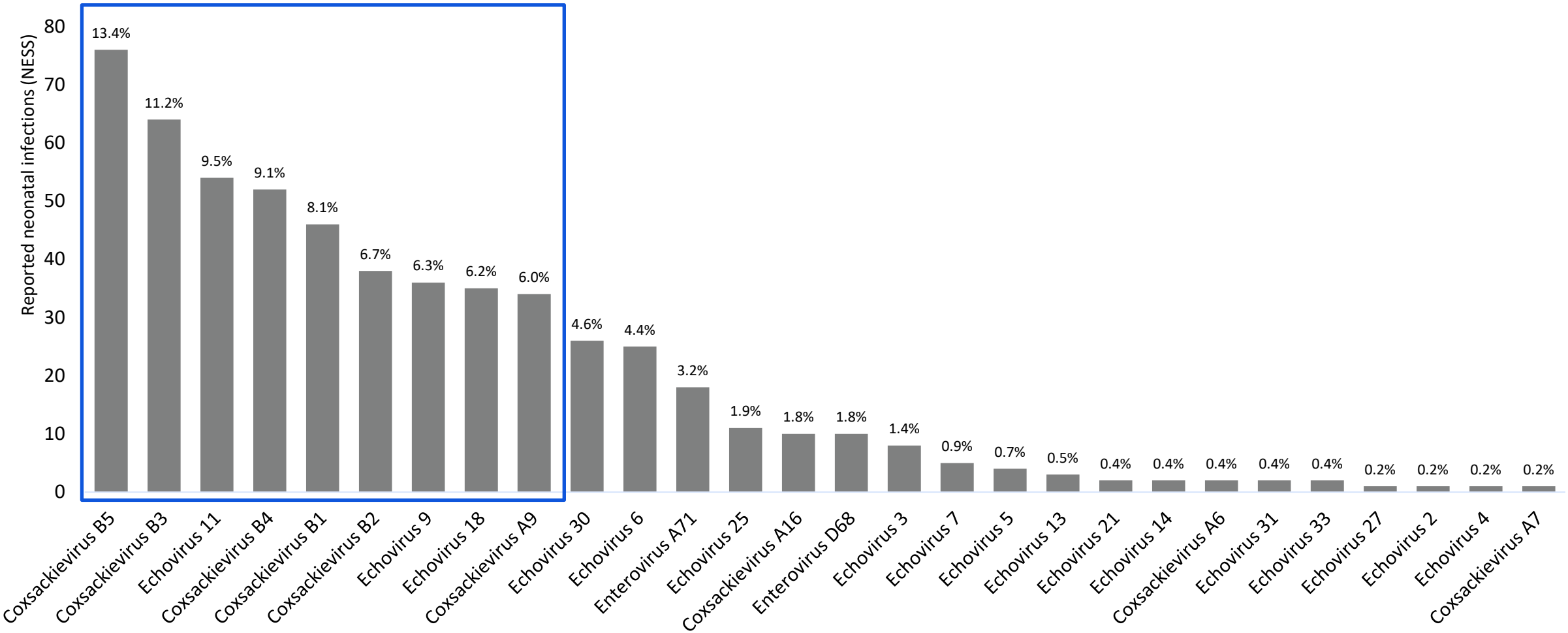
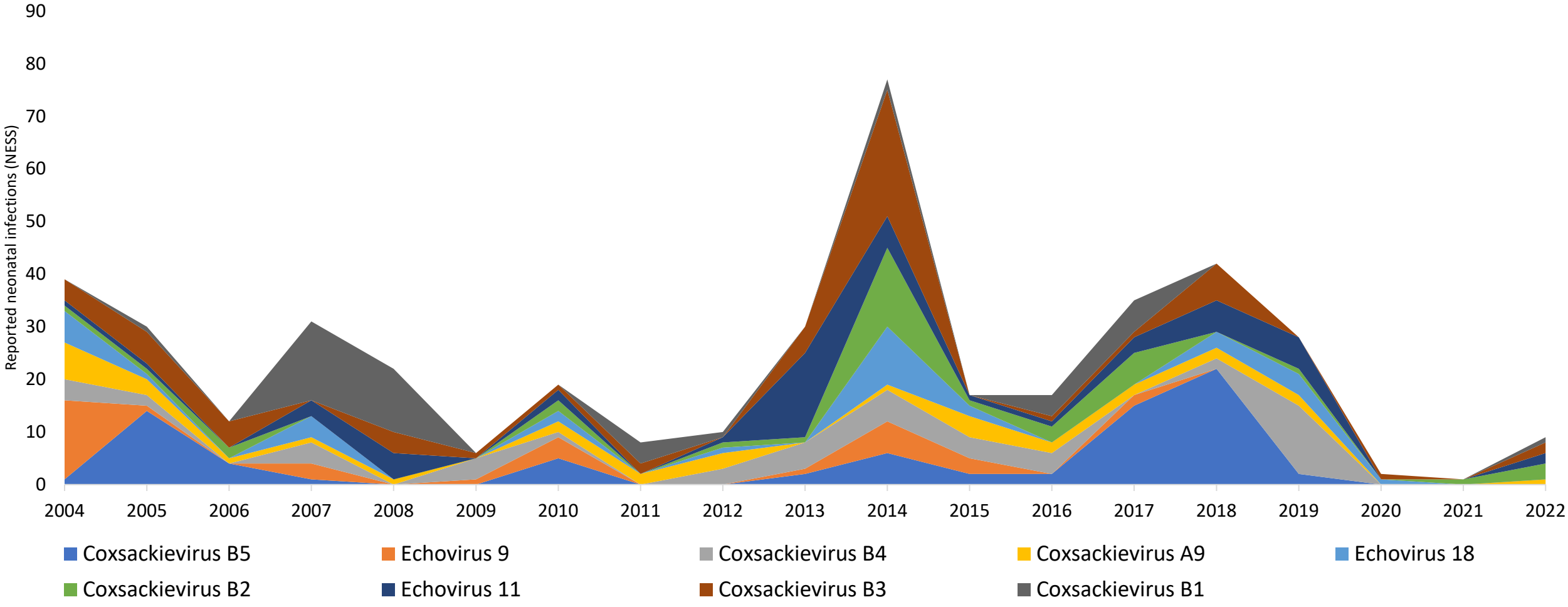


The EV types most commonly identified among neonates varied by year.



Some virus types were isolated more frequently among neonates compared with persons ≥1 month old.

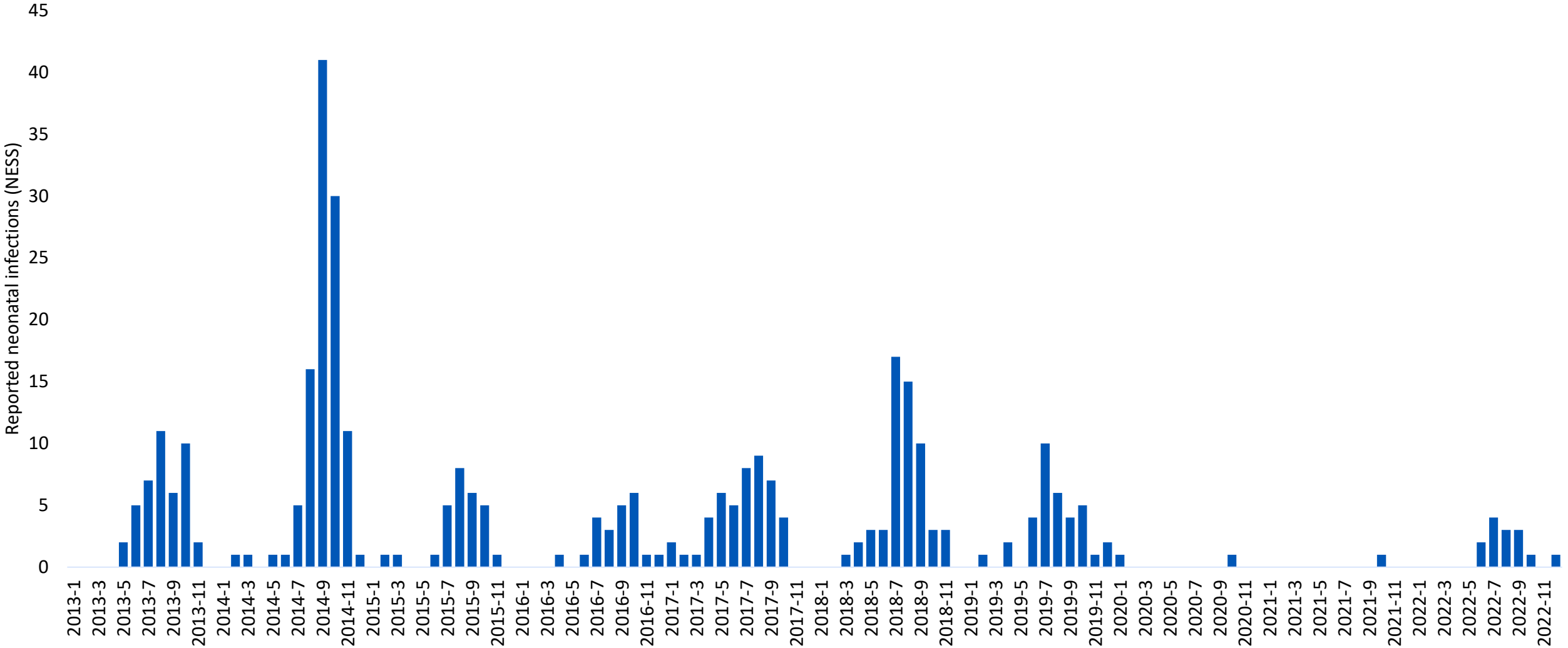
- Coxsackieviruses types B1–5
- Echovirus 11

MORE COMMON AMONG NEONATES

- EV-D68
- Echovirus 30

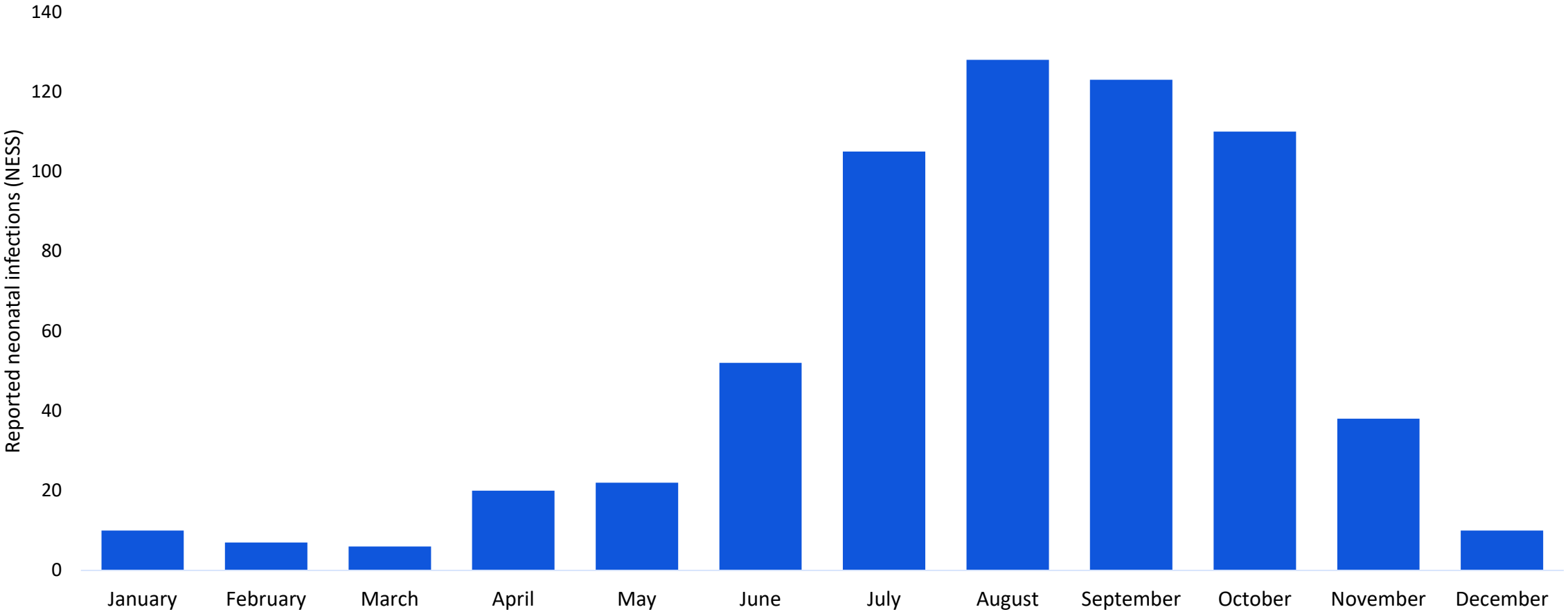
MORE COMMON AMONG PERSONS ≥1 MONTH OLD

Neonatal EV infections peak during late summer/early fall. Few infections were reported during 2020–2021.



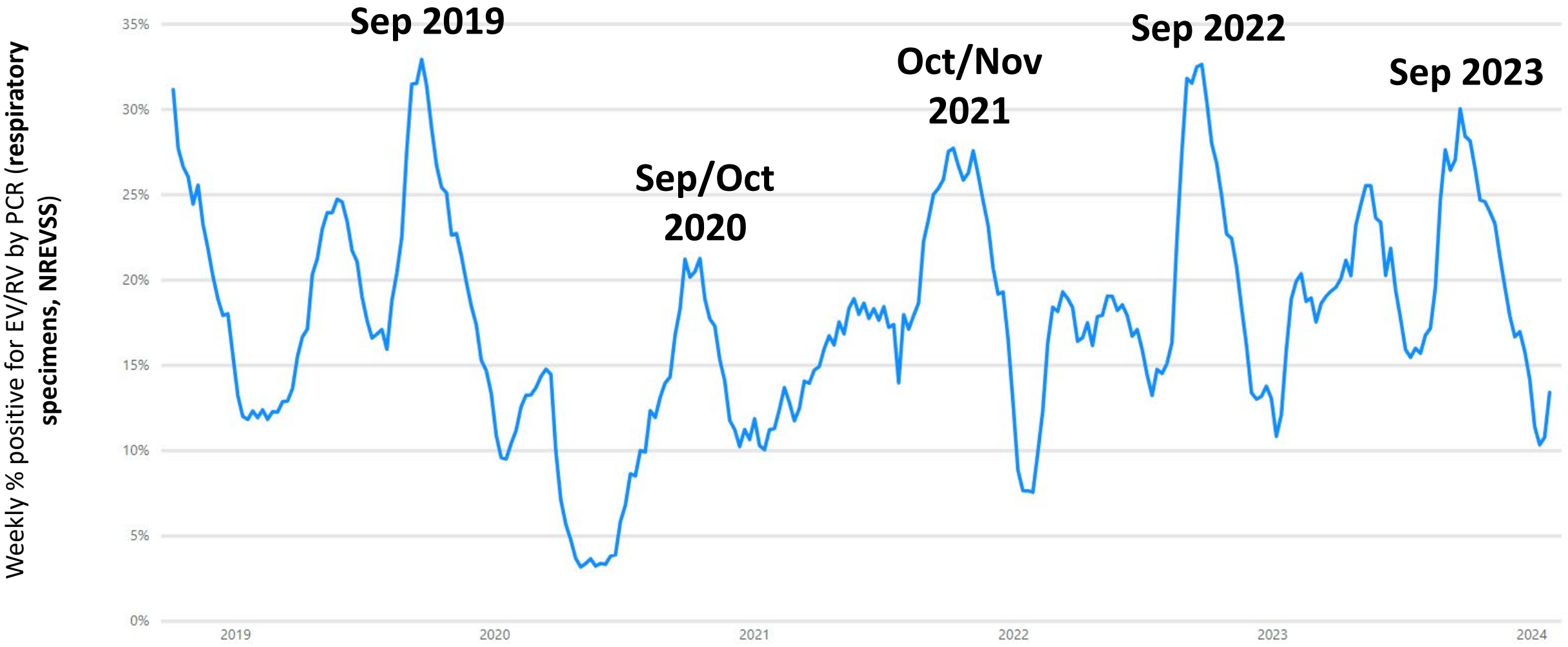
PRELIMINARY DATA (May 2024)

Reported infections were highest during July–October (2004–2022)*



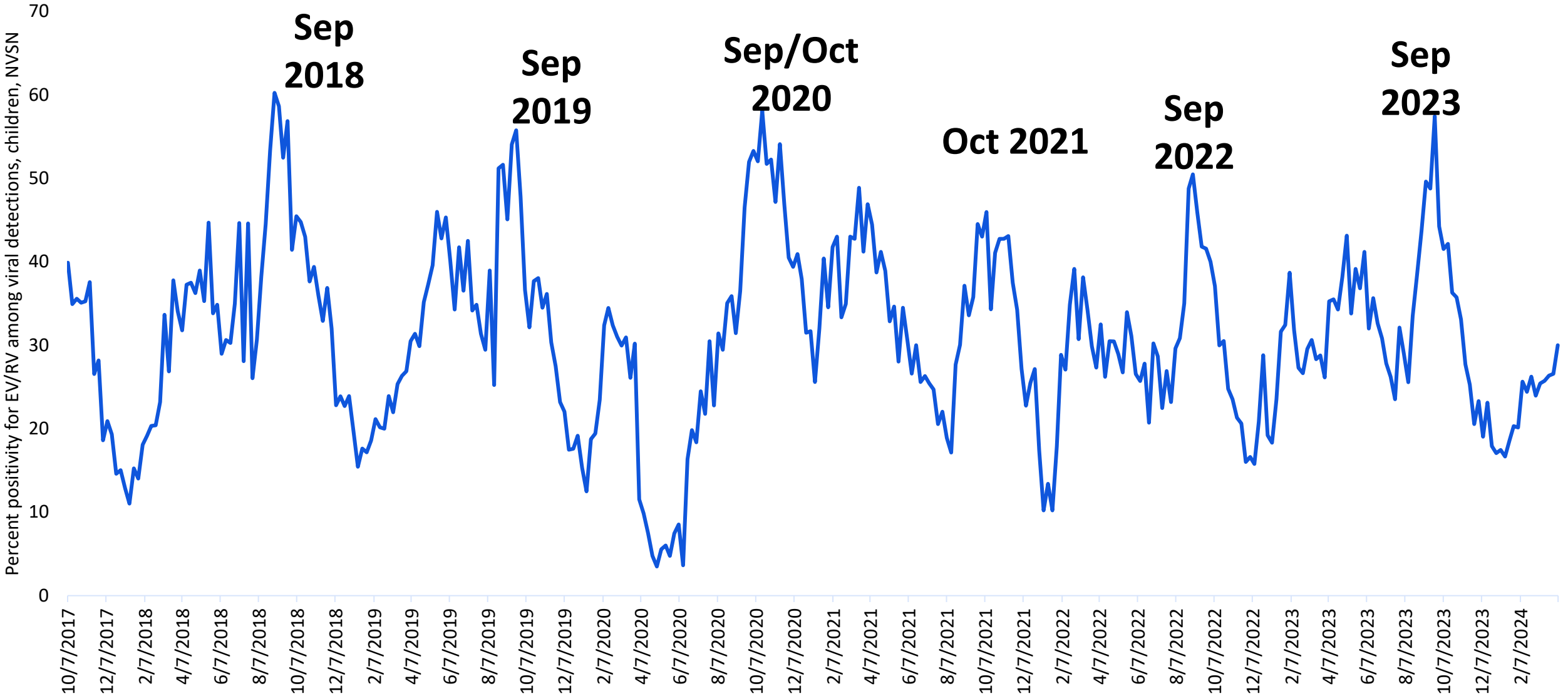
*infections summed by month across years

Similar seasonal patterns of EV/RV circulation were observed in NREVSS (respiratory specimens, all ages)



PRELIMINARY DATA (May 2024)

Similar seasonal patterns of EV/RV circulation were also observed in NVSN (children with respiratory infections)

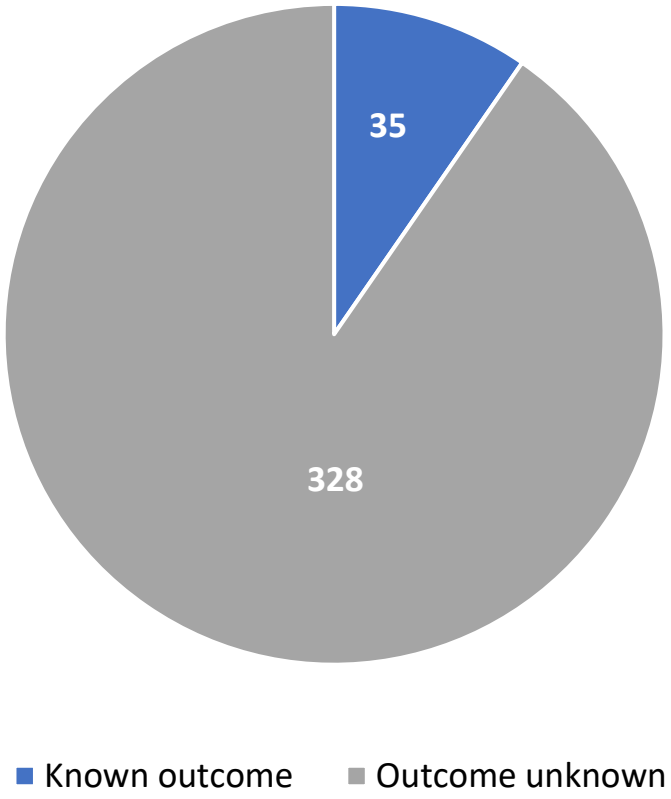


PRELIMINARY DATA (May 2024)

The specimen type for EV detections differed between neonates and persons ≥1 month old.

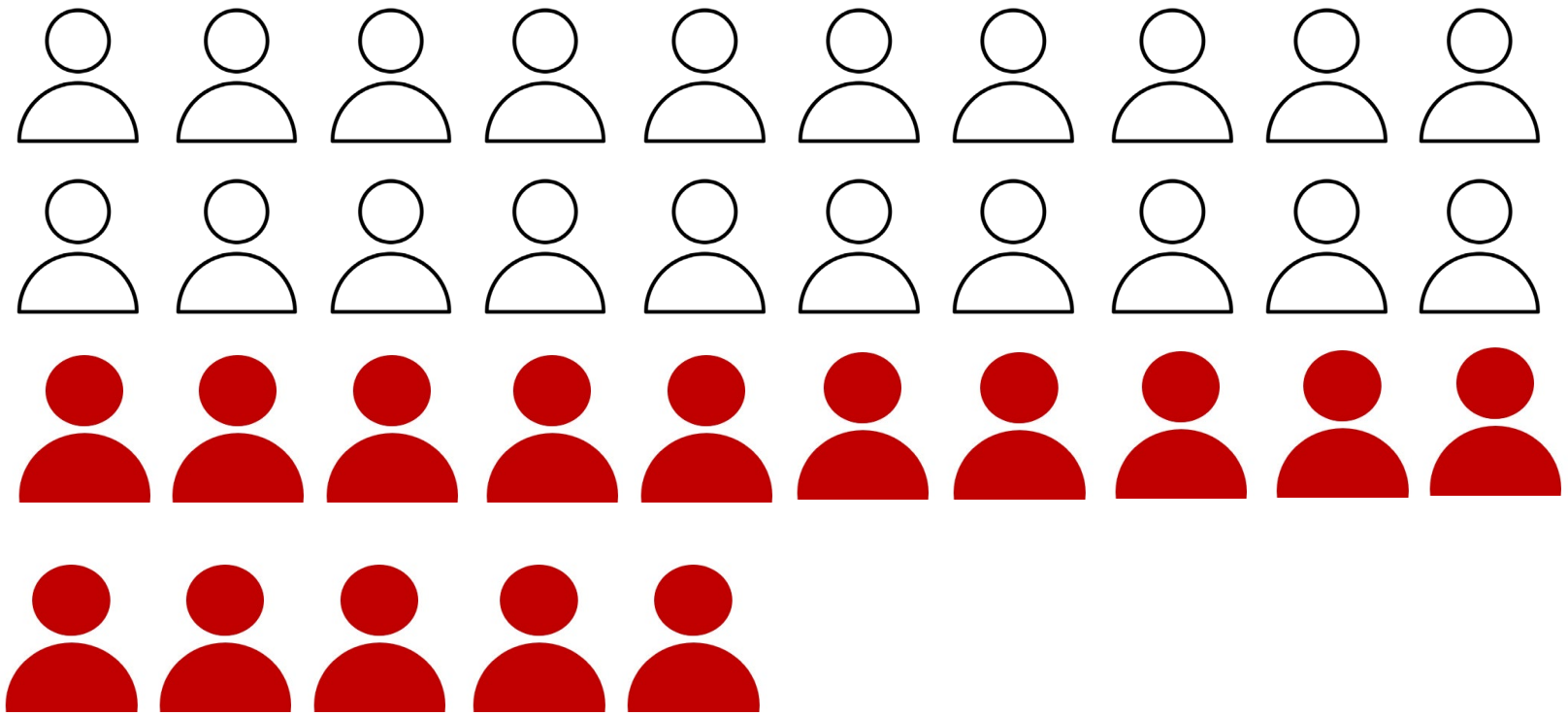
Specimen type	Neonatal	≥1 month
CSF (cerebrospinal fluid)	44%	34%
Throat/nasopharyngeal swab	22%	41%
Stool/rectal swab	15%	11%
Tissue Culture	3%	3%
Serum	2%	1%
Plasma	1%	<1%
Whole blood	<1%	<1%
Tissue (biopsy)	<1%	<1%
Urine	<1%	<1%
Lesion swab/scraping	<1%	1%
Tissue (postmortem)	0%	<1%
Other	5%	4%
Unknown	7%	5%

NESS data: 10% of neonates had known outcome (died vs. alive).



Among 363 neonates with enterovirus infections during 2014–2022

15 of 35 neonates with known outcome died (43%)



Limitations

- **A small number of laboratories perform and report EV typing**
  - Not nationally representative
- **EV testing and reporting are not systematic**
  - may be biased toward more severe infections and infections among younger patients
  - overall EV testing and testing specifically for EV-D68 may vary by age group
- **Outcome data are incomplete**
- **Limited clinical information**

Conclusions

- **EV types detected among neonates differ from those among persons ≥1 month old**
- **EV infections display a seasonal pattern typically peaking in late summer**
- **EV infections can cause severe disease among neonates**

- **National data on EV infections can be used to:**
  - observe seasonal trends and detect signals in year-to-year changes in EV infections
  - analyze circulating virus types by age

- **Strengthening capacity for EV typing and surveillance could be beneficial for:**
  - understanding burden of disease and clinical manifestations of EV infections
  - informing potential treatment options and prevention measures

Thank you.

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 cdc.gov

Neonatal Enterovirus Infections: Challenges and Opportunities

Mark Abzug, MD
University of Colorado School of Medicine and
Children's Hospital Colorado

Financial Disclosure

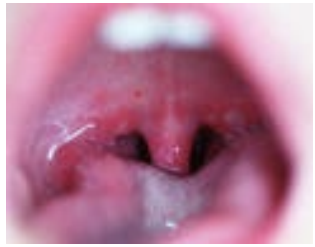
- No relevant financial relationships with any commercial interests.

Objectives

- Discuss clinical challenges presented by neonatal enterovirus infections that are driving the quest for antiviral therapies.

- Provide an update on the state of treatment for neonatal enterovirus infections.

Enterovirus Clinical Manifestations



- *Non-specific febrile illness*
- *Non-specific exanthems* – E9
- *Herpangina* – Cox A
- *Hand-foot-mouth disease*
  - Cox A16; EV-A71 pandemics (encephalitis, pneumonitis, myocarditis, shock); Cox A6
- *Hemorrhagic conjunctivitis* – EV70, CA24
  - Pandemics (tropics); neurologic signs
- *Respiratory illness* – EV-D68

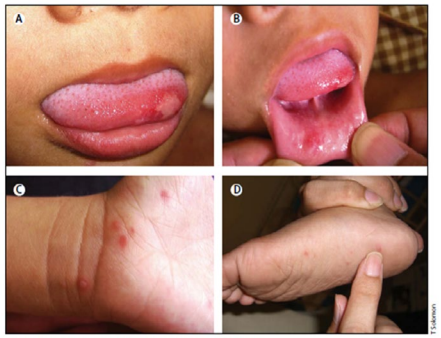
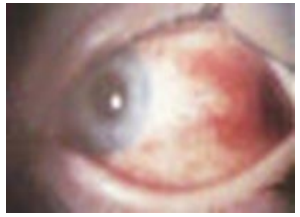
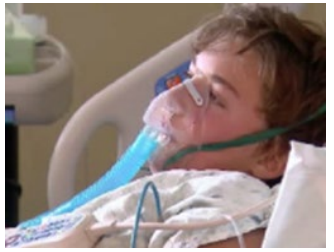


Figure 1: **Mucocutaneous lesions in hand, foot, and mouth disease**
Ulcers on (A) the tongue and (B) inside the lip, and vesicular and macular lesions on (C) the wrists and (D) the soles of children with enterovirus 71.

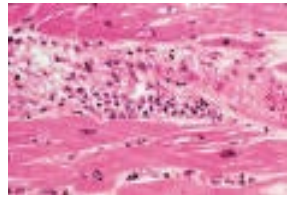
Ooi MH. Lancet Neurol 2010;9:1097.

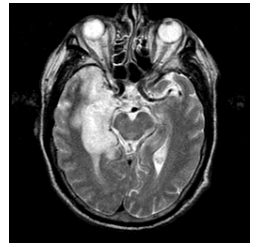




EV Clinical Manifestations

- *Myocarditis/Pericarditis* – Cox B
  - ~25-35% cases w/proven etiology
- *Neurologic diseases*
  - Meningitis, encephalitis, ADEM, GBS
  - Polio, brainstem encephalitis (EV-A71), AFM (EV-D68)
- *Immunocompromised host infections*
  - Chronic CNS infection, disseminated infection
- *Perinatal infections/neonatal viral sepsis*
- *Persistent/chronic infections?*
  - Type 1 diabetes, dilated cardiomyopathy, ALS, Sjögren syndrome, chronic fatigue syndrome





Neo. EV Infection > Symptomatic HSV, CMV, GBS

- **13% <1 mos. infected in summer/fall**
  - *Jenista JA. J Pediatr 1984;104:685.*
- **5% of neonates culture-positive during EV season**
  - *Cherry JD. Am J Dis Child 1968;116:245.*
- **4% of neonates with possible sepsis EV-infected**
  - *Rosenlew M. J Clin Virol 1999;12:211.*
- **Most common etiology of neonatal meningitis (~1/3)**
  - *Shattuck KE. Clin Pediatr 1992;31:130.*
- **2nd most common etiology of neonatal myocarditis**
  - *Bowles NE. J Am Coll Cardiol 2003;42:466.*
- **#1 virus in NICU (39%; Netherlands, 1992-2003)**
  - Verboon-Maciolek MA. *Pediatr Infect Dis J* 2005;24:901.
- **12% of neonates with sepsis, meningitis, encephalitis**
  - Piralla A. *Early Human Dev 2014;90S1:S75.*
- **39% of febrile neonates in summer/fall, China**
  - *Lv X. J Paediatr Child Health 2016;52:837.*

Neonatal EV Infection: Epidemiology

- Summer/fall seasonality in temperate regions
- Variability based on locally circulating viruses

OUTBREAKS

Increased reports of severe myocarditis associated with enterovirus infection in neonates, United Kingdom, 27 June 2022 to 26 April 2023 [CB3, CB4]

Anika Singanayagam[1], Catherine Moore[2], Susannah Froude[2], Cristina Celma[1], Julia Stowe[1], Erjola Hani[1], Khuen Foong Ng[3], Peter Muir[4], Marion Roderick[3], Simon Cottrell[2], David F. Bibby[1], Barry Vipond[4], Sophie Gillett[4], Peter J. Davis[5], Jack Gibb[6], Mai Barry[2], Phillippa Harris[2], Frances Rowley[2], Jiao Song[2], Ananda Giri Shankar[2], Danielle McMichael[7], Jonathan M. Cohen8, Abirami Manian[8], Ciaran Harvey[9], Louise Shaw Primrose[9], Stefanie Wilson[9], Declan T. Bradley[7], Karthik Paranthaman[1], Stuart Beard[1], Maria Zambon[1], Mary Ramsay[1], Vanessa Saliba[1], Shamez Ladhani[1], Christopher Williams[2]

RAPID COMMUNICATION

Severe and fatal neonatal infections linked to a new variant of echovirus 11, France, July 2022 to April 2023

Mathilde Grapin[1,*], Audrey Mirand[2,3,*], Didier Pinquier[4], Aurélie Basset[5], Matthieu Bendavid[1], Maxime Bisseux[2,3], Marion Jeannoël[6], Bérengère Kireche[7], Manoelle Kossorotoff[8], Anne-Sophie L'Honneur[9], Lila Robin[7], Yves Ville[10], Sylvain Renolleau[1], Véronique Lemee[11], Pierre-Henri Jarreau[5], Isabelle Desguerre[8], Florence Lacaille[12], Marianne Leruez-Ville[13], Clémence Guillaume[14], Cécile Henquell[2,3], Alexandre Lapillonne[15], Isabelle Schuffenecker[6,**], Mélodie Aubart[8,16,**]

www.eurosurveillance.org

Neonatal EV Infections: Transmission

- Prenatal
  - Cx from amniotic fluid, placenta, umbilical cord blood
  - Illness, viremia w/in hours-2d following delivery
- Intra/Post-Partum *(majority)*
  - Mothers
    - 3-4% shed at delivery during season (± symptomatic)
    - Maternal illness in week PTD → 20-50% infants infected
    - Vaginal or cesarean; breast milk? (⊕ culture, PCR)
  - Family contacts
  - Nursery (sporadic & epidemic)

Neonatal EV Infections: Clinical Presentations

- Asymptomatic – majority
- Benign illness
  - Fever - ~3 days
  - Other symptoms - ~7 days
  - Occasionally biphasic
  - Uncomplicated meningitis
    - Generally good outcome
- Severe disease

Neonatal EV Infections: History

- Nl pregnancy, FT, uncomplicated
- Maternal viral illness: 59-68%
  - Preceding or following delivery
  - Fever, respiratory or GI sx's, abdominal pain
  - May mimic chorioamnionitis, abruption
- Viral illness in other family members
- Illness onset day 1-30
  - Severe disease days 1-14

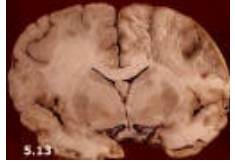
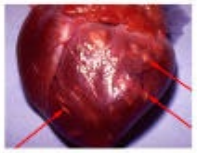
Neonatal EV Infections: Symptoms & Signs

- Fever/hypothermia
- Irritability
- Lethargy
- Anorexia/poor feeding
- ↓ perfusion
- Jaundice
- Rash
  - Macular
  - Maculopapular
  - Petechia/purpura
  - (Papulovesicular)
  - (Nodular)
  - (Bullous)
  - (Ulcerated)
- Abdominal distension
- Emesis
- Diarrhea (preemies)
- Respiratory
  - Tachypnea
  - Cough
  - Grunting
  - Retraction
  - Wheezing
  - Rhinorrhea
  - Apnea

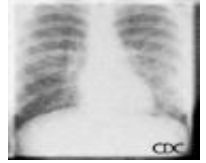
Neonatal EV Infections: Severe Disease

- Meningoencephalitis
- Myocarditis
- Pneumonitis
- Hepatitis
- Coagulopathy
- Sepsis

- Uncommon
  - Myositis
  - Arthritis
  - Necrotizing enterocolitis
  - SIADH
  - Pancytopenia/BM failure
  - Hemophagocytic lymphohistiocytosis
  - Sudden Infant Death

Severe EV Disease




Meningoencephalitis (E;CB;EV71)

- Δ consciousness, seizures, focal abnormalities, paralysis
- WM injury, periventricular echogenicity, microcephaly, hydrocephaly
- Variable prognosis
  - Intellectual, motor, speech & language, seizures

Myocarditis (CB1-5)

- Resp. distress, CHF, shock, arrhythmias, infarction
- 30-50% mortality; residual dysfn, chronic calcific myocarditis; DCM; aneurysm
- *May lack long-term sequelae*

Pneumonitis (E6,9,11,7,22; CB)

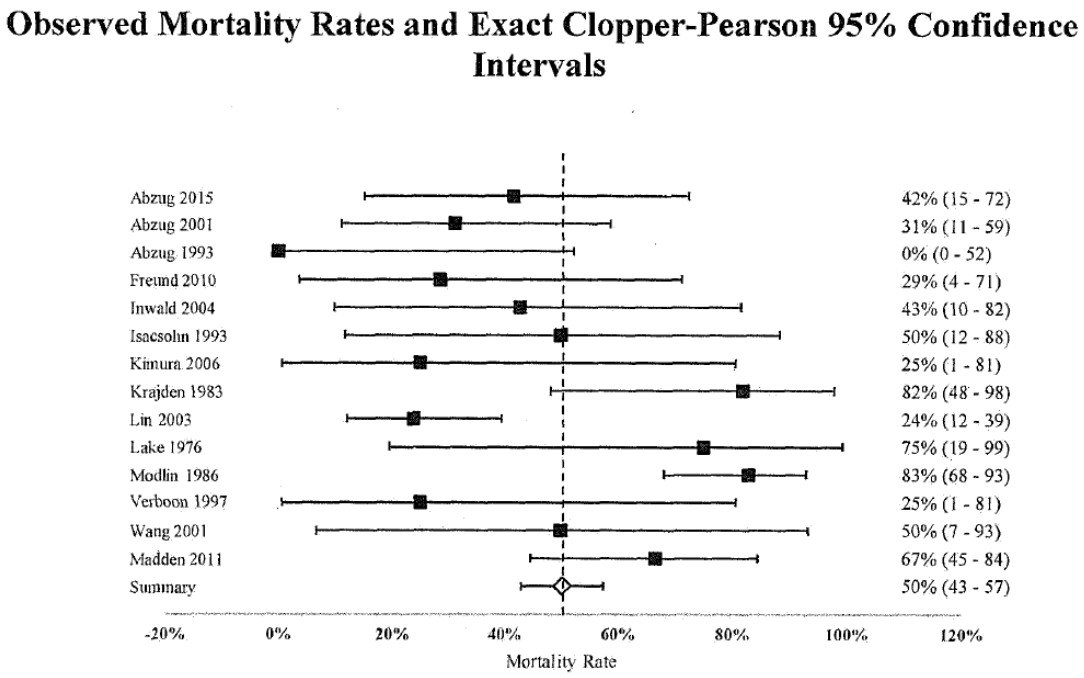
- Primary or associated; w/in hours of birth
- Rapid; pulm. hypertension, pulm. hemorrhage
- Severe; high mortality

Hepatitis & Coagulopathy

(E11,3,5,6,7,9,14,17,19,21,30; CB1-5)

- Acute hepatic necrosis, ALF
- ↓ plts, prolonged clotting
- 24-83% mortality; bleeding
- Persistent hepatic dysfn, fibrosis, calcification
- *Majority of survivors - nl fn*

Severe Neonatal EV Mortality Rates



Byron D, personal communication

- PHIS database
  - 45 children's hospitals, 1999-2015
  - Neo. EV hepatitis, coagulopathy, or myocarditis codes
  - Mortality: 20/84 (24%)
- Lit. review, 2000-2020
  - 237 severe cases
  - Mortality: 30%
  - Zhang M. BMC Pediatr 2021

Risk Factors/Markers for Severe Neonatal Disease

- Onset <7 days
  - esp. first few days
- Absence of nAb
- Maternal illness before/at delivery
- Prematurity
- Male
- Multisystem disease
  - (e.g., hepatitis + myocarditis)
- Severe hepatitis
- ⊕ serum viral culture
- E11, CB

Early Age of Onset & Severe Neonatal Disease

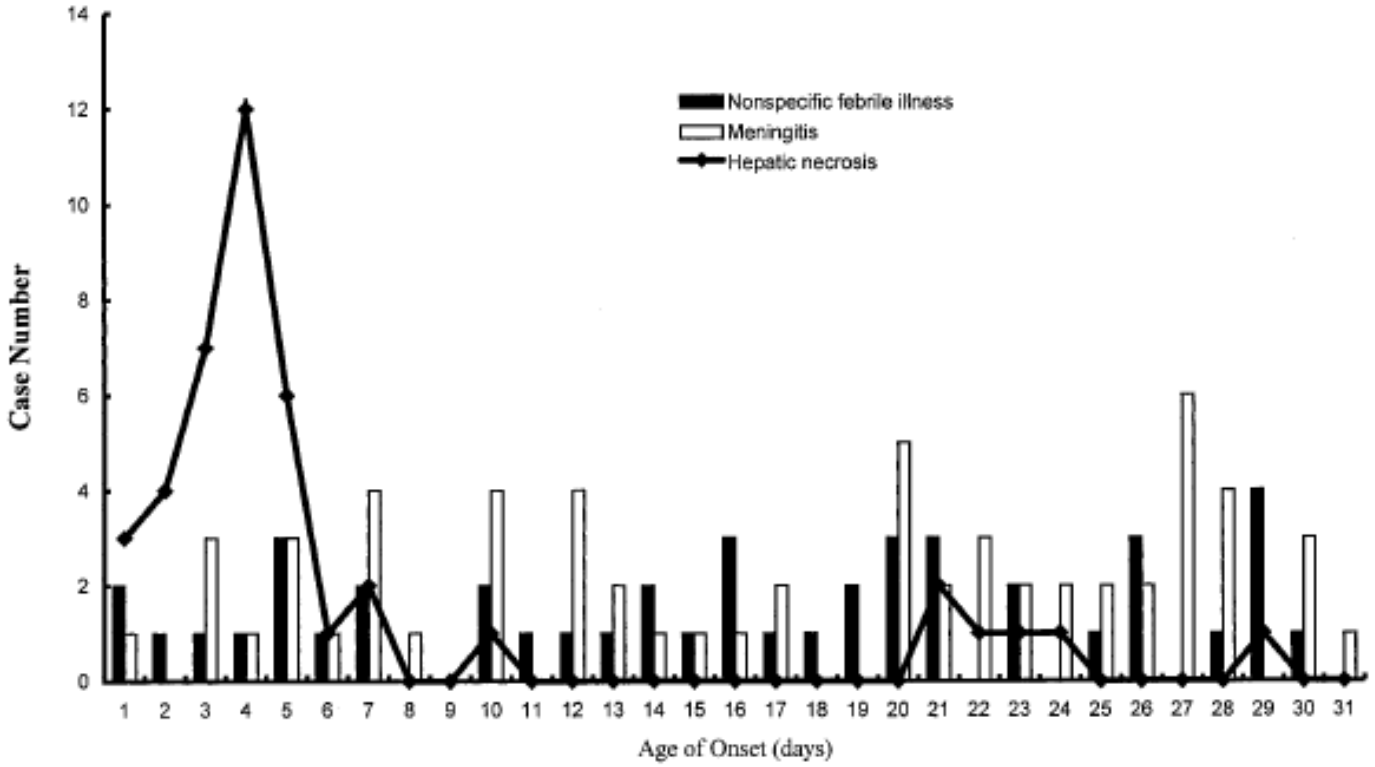


FIG. 2. Age of onset among three clinical syndromes of neonatal enterovirus infection. Cases of hepatic necrosis had significantly earlier age of onset than the other two syndromes ($P = 0.001$).

- 10 yr neonatal review, China
  - 83% hepatic necrosis @ <7d

Lin TY. Pediatr Infect Dis J 2003;22:889.

Severe Neonatal EV Disease: Standard Tx

- Empiric antibacterial tx
- Empiric tx for HSV
- Supportive Care
  - Respiratory
  - Cardiovascular
  - Blood products
  - Renal
  - ECMO
  - LVAD
  - Transplantation (liver, heart)

Severe Neonatal EV Disease: Immune Globulin

- **Rationale**
  - Key defense v. EVs
  - Lack of nAb → ↑ risk
  - nAb in IVIG (variable)
- **Neonatal**
  - IVIG, maternal convalescent plasma
    - Anecdotal/retrospective (treatment, prophylaxis)
  - Randomized trial: IVIG, n=16 (Abzug MJ. Clin Infect Dis 1995)
    - Age ≤ 14d; IVIG (750 mg/kg) v. no tx
    - Faster cessation of viremia & viruria if NT ≥ 1:800
  - Retrospective study (hepatitis & coagulopathy): IVIG <3d after illness onset assoc. w/↓ mortality (Yen MH. J Clin Virol 2015)

Severe Neonatal EV Disease: Antiviral Tx

- Capsid binders → inhibit attachment & uncoating
- 3 in clinical development
  - **Pleconaril** [neonatal EV cases & RCT]
  - **Pocapavir** [polio antiviral; variable activity v. non-polio EVs; neonatal EV cases]
  - **Vapendavir**

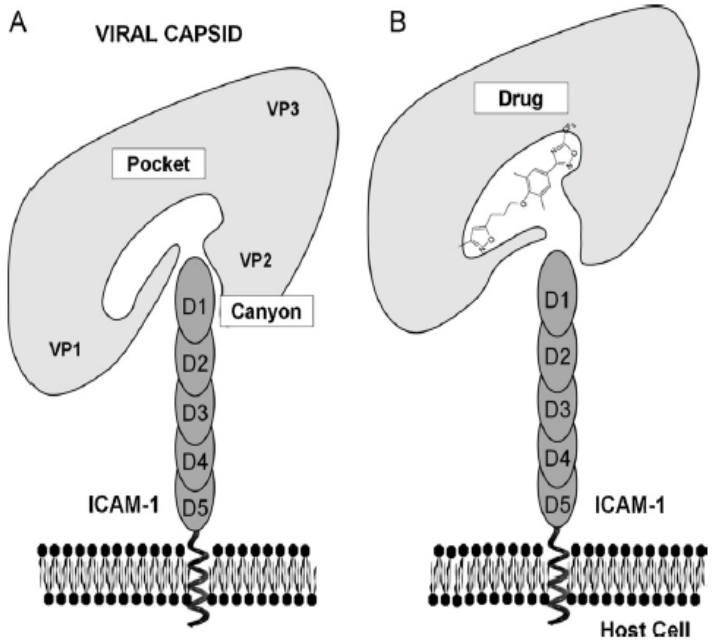


Fig. 2. Mechanism of action of capsid binders. Schematic representation of the interaction between ICAM-1 and major group rhinoviruses. Left (A): ICAM-1 binds into the canyon, surrounding each fivefold axis, inducing conformational changes that eventually lead to uncoating of the virus and release of the viral RNA. Right (B): Binding of a "capsid binder" into the hydrophobic pocket, underneath the canyon floor. This binding event induces conformational changes, thereby (i) increasing the rigidity of the virion (preventing uncoating and subsequent release of viral RNA) and at the same time (ii) decreasing the ability of the virion to interact with its receptor.

Thibaut HJ. Biochem Pharmacol 2012;83:185.

A Randomized, Double-Blind, Placebo-Controlled Trial of Pleconaril for the Treatment of Neonates With Enterovirus Sepsis

Mark J. Abzug,[1] Marian G. Michaels,[2] Ellen Wald,[3] Richard F. Jacobs,[4] José R. Romero,[5] Pablo J. Sánchez,[6] Gregory Wilson,[7] Paul Krogstad,[8] Gregory A. Storch,[9] Robert Lawrence,[10] Mark Shelton,[11] April Palmer,[12] Joan Robinson,[13] Penelope Dennehy,[14] Sunil K. Sood,[15] Gretchen Cloud,[16] Penelope Jester,[16] Edward P. Acosta,[16] Richard Whitley,[16] and David Kimberlin[16] the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

Journal of the Pediatric Infectious Diseases Society, Vol. 5, No. 1, pp. 53–62, 2016. DOI:10.1093/jpids/piv015

Neonatal EV Sepsis: Pleconaril RCT

- Onset ≤15 days
- BW ≥1500 gms & GA ≥32 wks
- Presumed EV infection w/at least 1 of:
  - **Hepatitis** [ALT >3 X ULN]
  - **Coagulopathy** [plts <100,000/mm^3, PT >1.5 ULN, FSPs]
  - **Myocarditis** [SF <25% or EJ <50%]
- 2:1 pleconaril: placebo randomization; 7d oral tx
- Virologic, clinical, PK, safety endpoints
- Enrolled: 43 pleconaril, 18 placebo
- EV-confirmed: 31 pleconaril, 12 placebo

Figure 1. Time to culture negativity from all anatomic sites combined among culture-positive subjects. [OP, rectum, serum, urine]

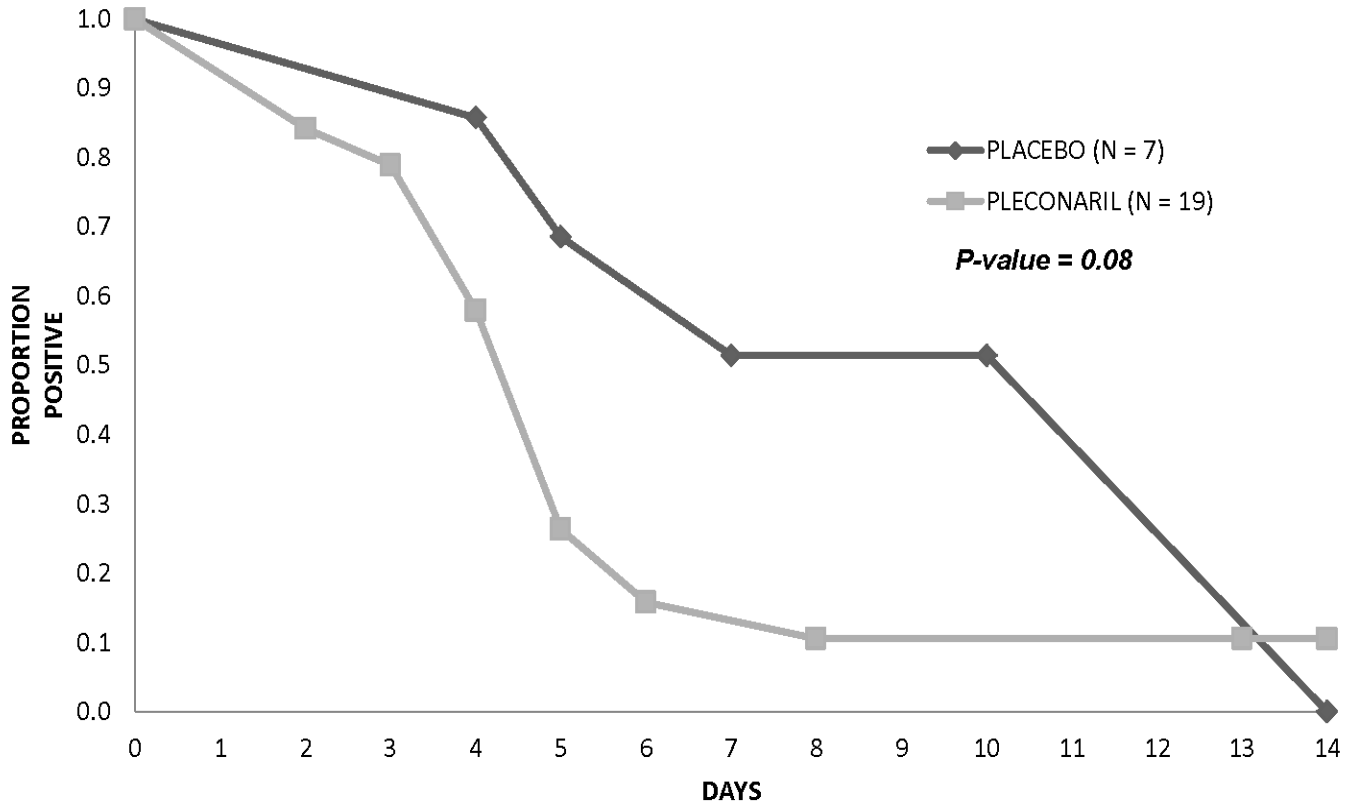
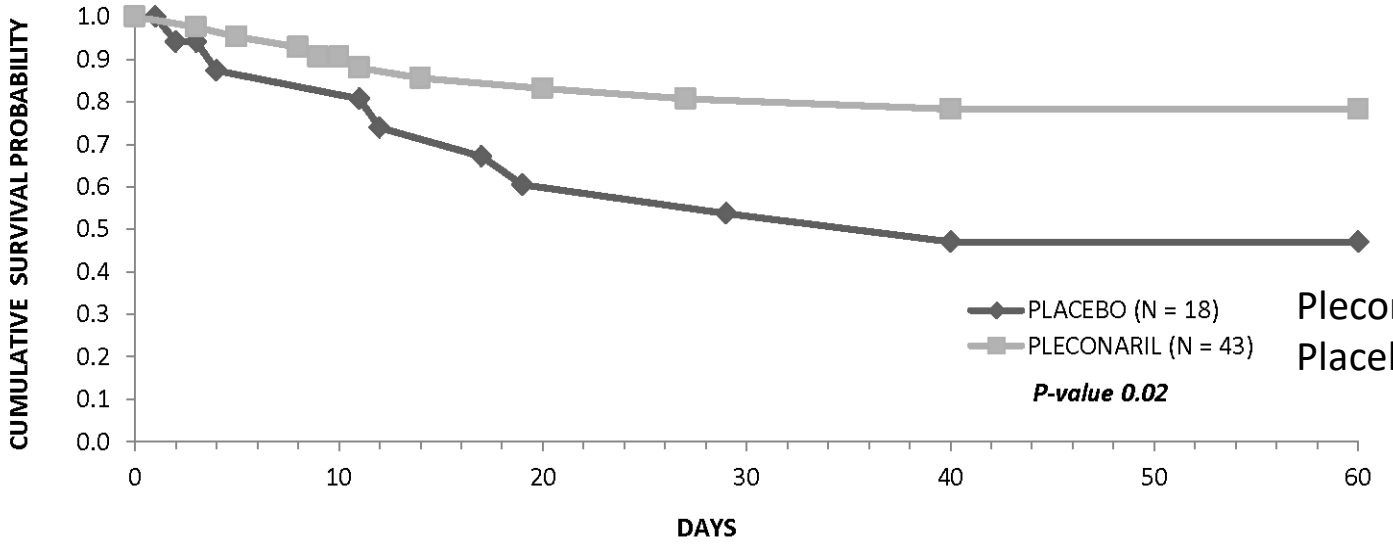


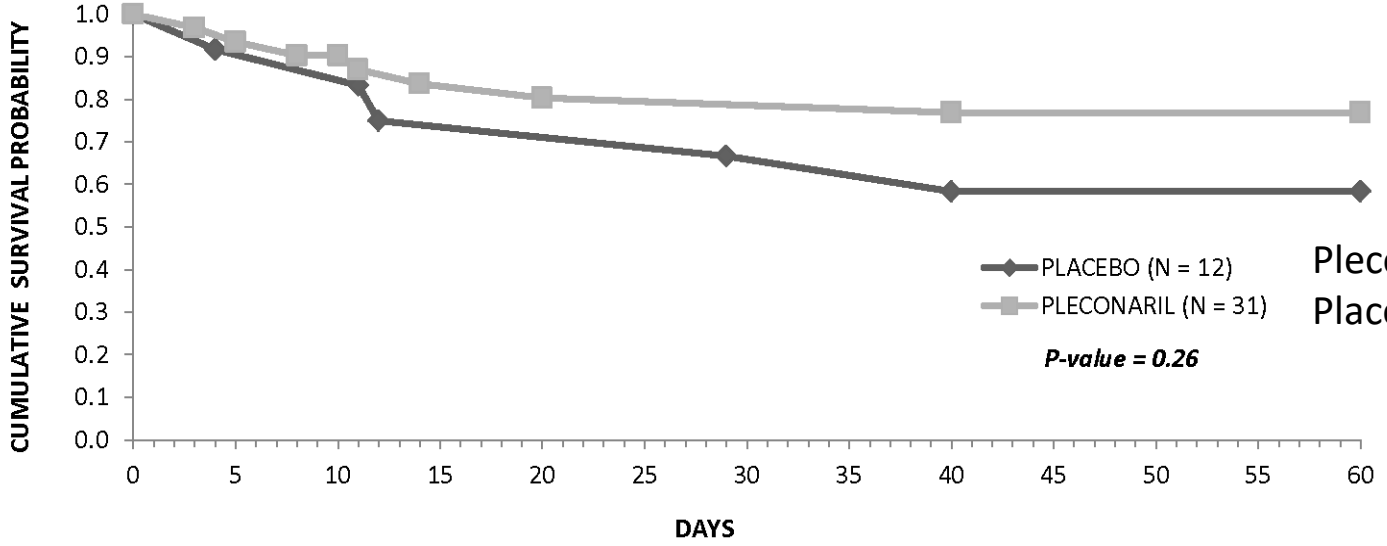
Figure 2. Survival over two months among all enrolled subjects (panel A) and among enterovirus-confirmed subjects (panel B).

Panel A



Pleconaril: 10/43 (23%) deaths
Placebo: 8/18 (44%) deaths

Panel B



Pleconaril: 7/31 (23%) deaths
Placebo: 5/12 (42%) deaths

Severe Neonatal EV Disease: Current Tx Status

- **Supportive Care**
- IVIG; maternal convalescent plasma
- Antiviral
  - Pleconaril - not FDA-approved; not available in US
  - Pocapavir - FDA expanded access
- Neonatal EV & HPeV Viral Sepsis Natural Hx Study
  - Congenital & Perinatal Infections Consortium (CPIC), NIH Rare Diseases Clinical Research Network (RDCRN)
  - Better define mortality rates of neonatal EV & HPeV sepsis for antiviral clinical trial design
  - Identify predictors of morbidity & mortality (e.g., qPCR)

U.S. FOOD & DRUG ADMINISTRATION

Clarifying Questions and Answers

U.S. FOOD & DRUG ADMINISTRATION

Lunch Break

U.S. FOOD & DRUG ADMINISTRATION

Panel Discussion on Drug Development Considerations for Products to Treat Neonatal Enterovirus Infection

Session 3:
Enterovirus Trial Design Challenges Panel

- Prabha Viswanathan, MD; FDA
- An Massaro, MD; FDA
- Kunyi Wu, PharmD; FDA
- Betsy Pilon, Hope for HIE
- Lily (Yeruk) Mulugeta, PharmD; FDA
- John Concato, MD, MS, MPH; FDA

- Amy Rosenfeld, PhD; FDA
- Miranda Delahoy, PhD; CDC
- Mark Abzug, MD; University of Colorado School of Medicine

- David Byron; AntiVirus Therapeutics
- Jeffrey Hincks, PhD; ViroDefense, Inc
- David Kimberlin, MD; University of Alabama at Birmingham
- Steve Oberste, PhD; CDC
- Matthew Vogt, MD, PhD; UNC at Chapel Hill School of Medicine
- Kevin Messacar, MD, PhD; University of Colorado, Children's Hospital of Colorado

Panel Discussion on Drug Development Considerations for Products to Treat Neonatal Enterovirus Infection

1. Please discuss the key challenges in antiviral drug development for the treatment of enterovirus infection in infants and neonates
    - Comment on what additional nonclinical or basic science work may be needed to help drive therapeutic development for treatment of enterovirus infection in infants and neonates
2. Please discuss potential strategies that could be considered to improve collaboration between industry, academia, and parents/caregivers to facilitate antiviral therapeutic development for the treatment of enterovirus infection in infants and neonates

U.S. FOOD & DRUG ADMINISTRATION

Panel Discussion on Clinical Trial Designs to Evaluate Treatment of Neonatal Enterovirus Infection

1. Discuss the ideal study populations for enrollment into clinical trial
   - Age group (e.g., neonates only; infants and neonates)
   - Infection severity (mild symptomatic infection or severe infection/disease)
2. Considering the ideal population, please discuss the appropriate trial endpoints (e.g., mortality, time to hospital discharge, etc.)
3. Please discuss the most appropriate comparator treatment group
   - Please comment on the potential role of real-world data and real-world evidence

End of Day 1