Adequate and Well-Controlled Trials in Neonates: Lessons Learned from Neonatal Candidiasis Program

FDA Workshop

Studies in Neonatal and Young Infants

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Agenda

- Mycamine® (micafungin sodium)
- Design and conduct of a Phase 3 study of invasive candidiasis in neonates and young infants
- Lessons learned

Astellas Antifungal Agents and Pediatric Experience

- Three systemic antifungals
  - AmBisome® (amphotericin B liposomal formulation)
    - Approved for pediatric patients, aged 1 month to 16 years
  - Mycamine® (micafungin sodium)
    - Approved for pediatric patients, aged 4 months to 16 years
  - Cresemba® (Isavuconazonium sulfate)
    - Recently approved for adults, no pediatric studies to date

Mycamine®(micafungin sodium)

- Member of the echinocandin class of antifungals

- Approved in the U.S. for adults and pediatric patients > 4 months of age for:
  - Treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses;
  - Treatment of esophageal candidiasis;
  - Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant

Neonatal and Young Infant Development Program

- Pediatric patients were included in the Mycamine development program prior to initial approval in 2005

- However, emerging data about invasive candidiasis in neonates necessitated further evaluation in this population

Key Question to Answer Before Proceeding with Pediatric Studies

- Is there something unique about the disease state or pathogenesis of the condition in neonates and young infants as compared to adult patients?

If the answer is yes, simply matching drug exposures to the efficacious and safe exposures in the adult population may not be adequate

Evolutions in the Field and Challenges to Face

- Pathogenesis of invasive candidiasis in neonates
  - CNS involvement is a prominent feature[1,2,3]
  - Requires a unique strategy for appropriate dose finding

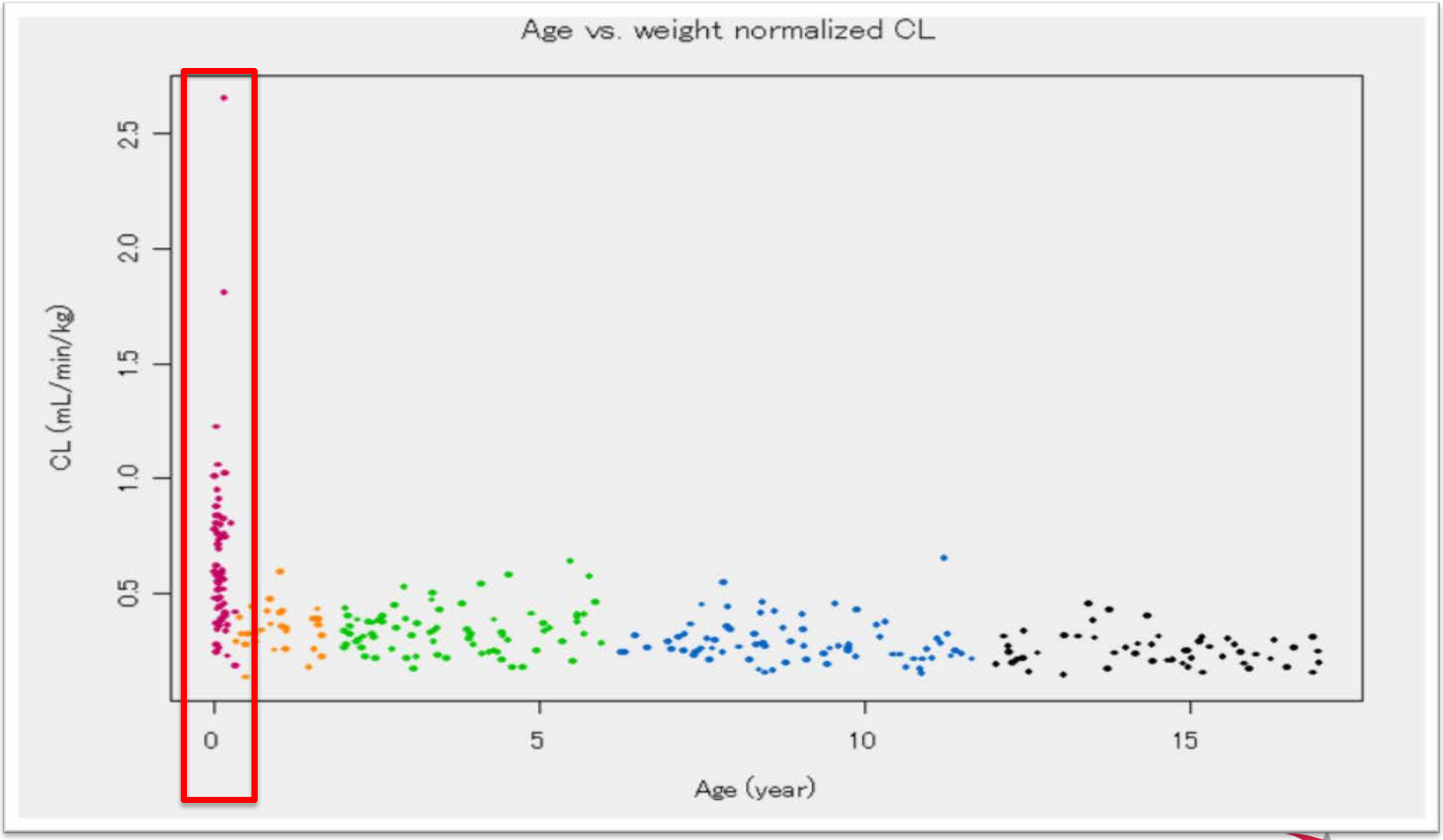
[1]*Pediatr Infect Dis J. 2012, June; 31(6): 635–637;* [2]*Pediatrics. 2006; 117:84–92;* [3]*Clin Infect Dis. 2012; 54:331–339*

Higher Exposures Required to Penetrate and Treat CNS Infection

- Rabbit model of hematogenous *Candida* meningoencephalitis mimics pathogenesis of neonatal candidiasis[1]
- The target Mycamine AUC to achieve efficacy in CNS infections is ≥ 170 mg▪h/L
- The average exposure achieved by the recommended clinical dosage regimen used to treat invasive candidiasis in adults and older children is 100 mg·h/L

[1]Hope et al, JID 2008; 197

Mycamine: Increased Weight-normalized Clearance in Infants < 4 Months of Age



Benjamin Clin Pharmacol Ther, 2010;87(1):93-9; Hope AAC, 2007

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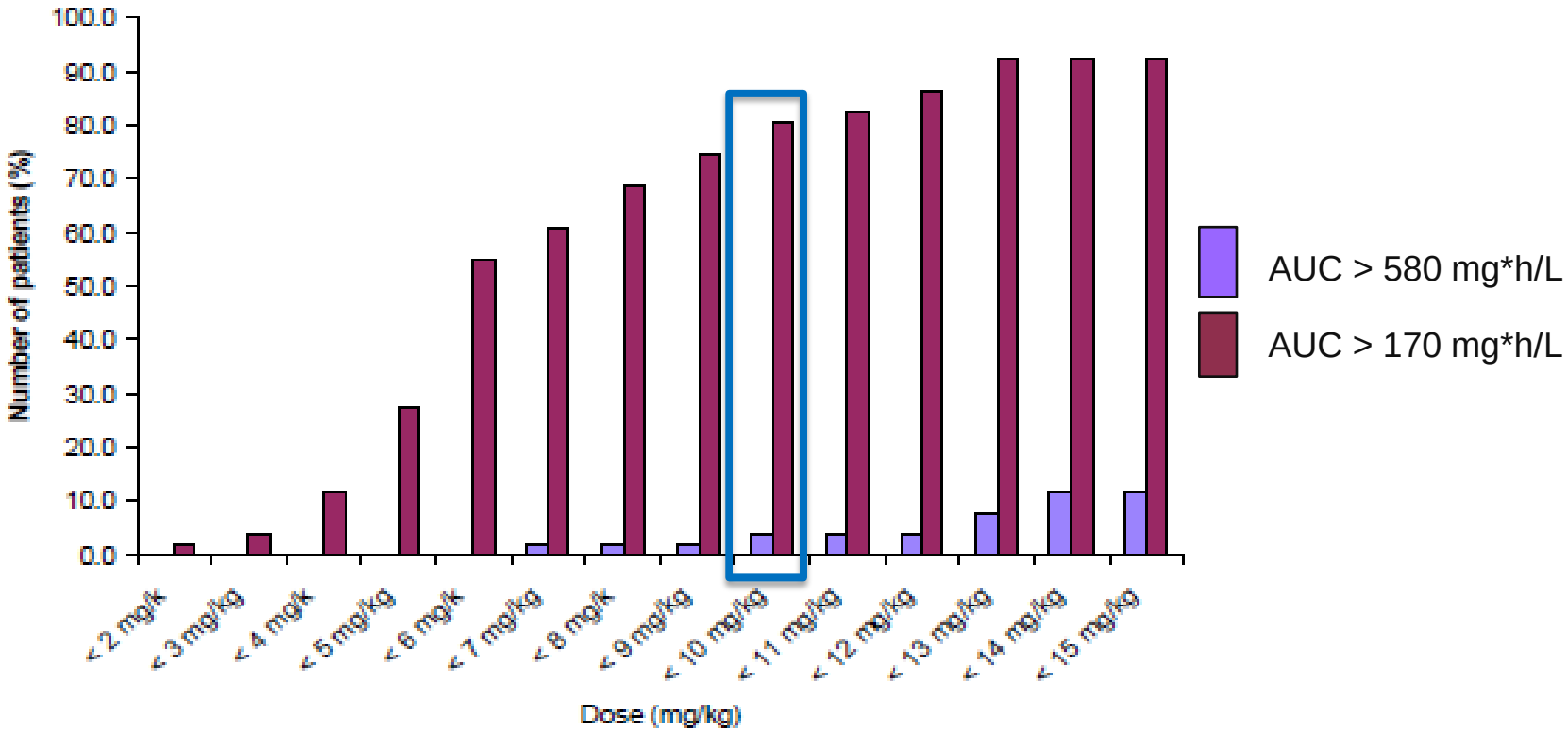
Population PK Bridging Study Demonstrates Dose of 10 mg/kg is Most Appropriate



- Monte Carlo simulations demonstrated that a Mycamine dose of 10 mg/kg achieves the target exposure in >85% of the population with <10% of the population at risk of reaching the range where non-clinical toxicities were seen, notably liver enzyme changes

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Further Investigation in Neonates and Young Infants May Be Necessary

- Unique drug disposition compared to older children and adults
- Prominent CNS disease in this population
  - CNS involvement requires higher target exposures for treatment
- There was limited safety and efficacy of this dose and exposure

Designing a Phase 3 Study in Neonates and Young Infants

- Close collaboration with FDA
  - FDA Special Protocol Assessment and Type C meetings
  - Aligned on the protocol and the dosage regimen for the Phase 3 study

- Also worked closely with experts in ID with specific interest in neonatal infections

- Our goal was to create a study design that followed standard of care as closely as possible so that there is minimal impact and risk to the infant while still gathering an informative dataset for analysis

Phase 3 Study Overview

Study Design: Phase 3, randomized (2:1), multi-center, double-blind, non-inferiority study comparing micafungin to conventional amphotericin B

Primary Endpoint: Fungal free survival (FFS) at one week following the last dose of study drug

Patient Population: 225 Infants: > 48 hours of life up to day of life (DOL) 120 with culture proven candidiasis

Randomization stratification: Estimated gestational age and Region

Independent Monitoring Committees: Independent Data and Safety Monitoring Board (DSMB); Safety and Data Review Panel (DRP); Diagnosis and adjudicate outcome

Phase 3 Study: Key Study Assessments

Assessments		Baseline	Treatment Period				Post-Treatment Period (+/- 3 days)
			Every 48 Hours	7 Days After 1st Dose of Study Drug	Every 4-7 Days	Day 1 - Last Dose of Study Drug	
End Organ Assessment	Retinal Exam	X		X			X
	Lumbar Puncture (LP)	X			X		
	Abdominal **U**ltrasound	X		X			X
	Echocardiogram	X		X			X
	Head Ultrasound, Computerized Tomography (CT), **or** Magnetic Resonance Imaging (MRI)	X		X			X
Urine & Blood Fungal Culture		X	X				
Plasma Pharmacokinetic Sampling						X	
CSF Pharmacokinetic Sampling						X	

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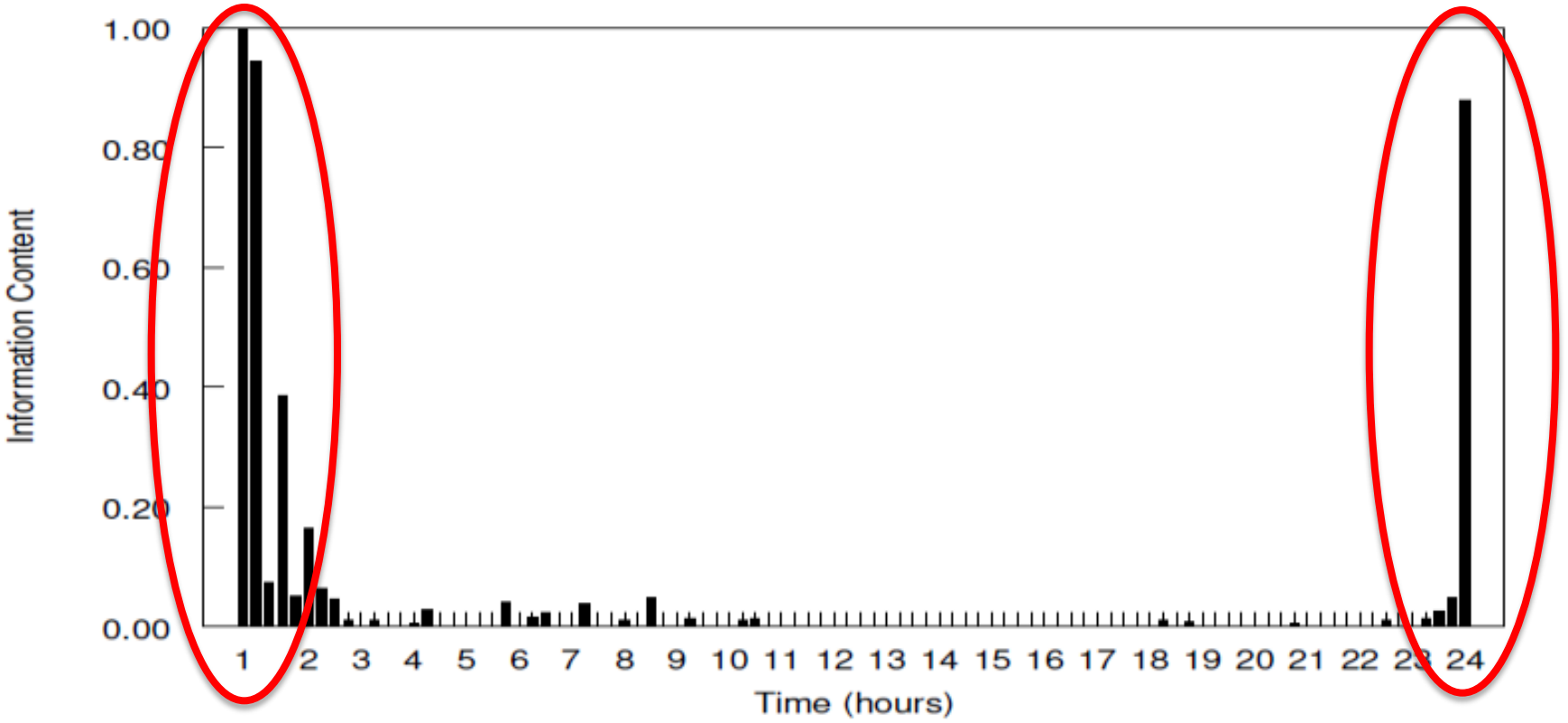
Identified Optimal Plasma Sampling Times from Population PK Modeling



- Utilized D-optimal design to define the most informative sampling times
- Allowing for flexibility in plasma sample acquisition and minimizing the number of samples (3) required

Hope AAC, June 2010;54(6):2633–2637

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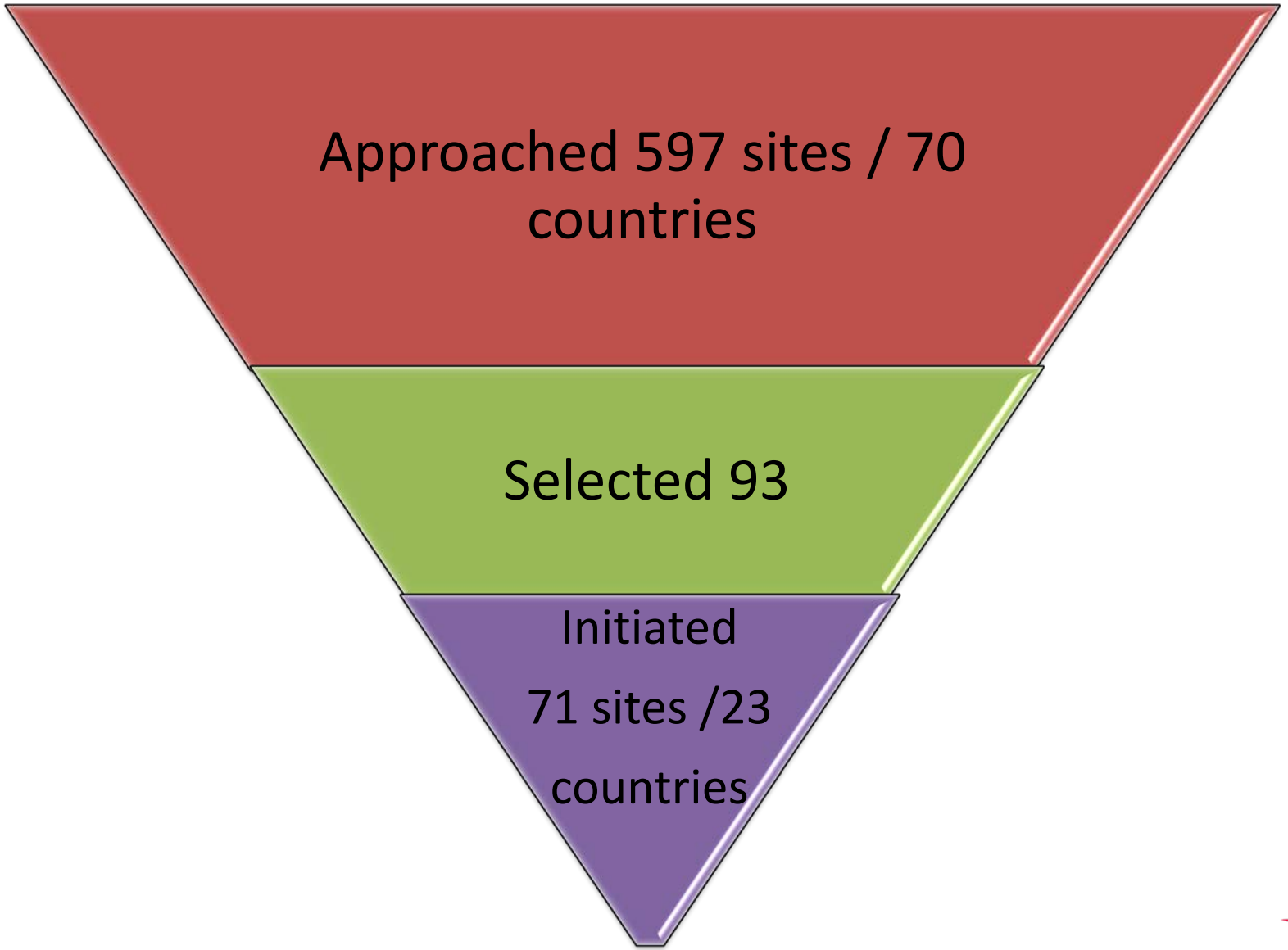
Study Conduct: Getting Started

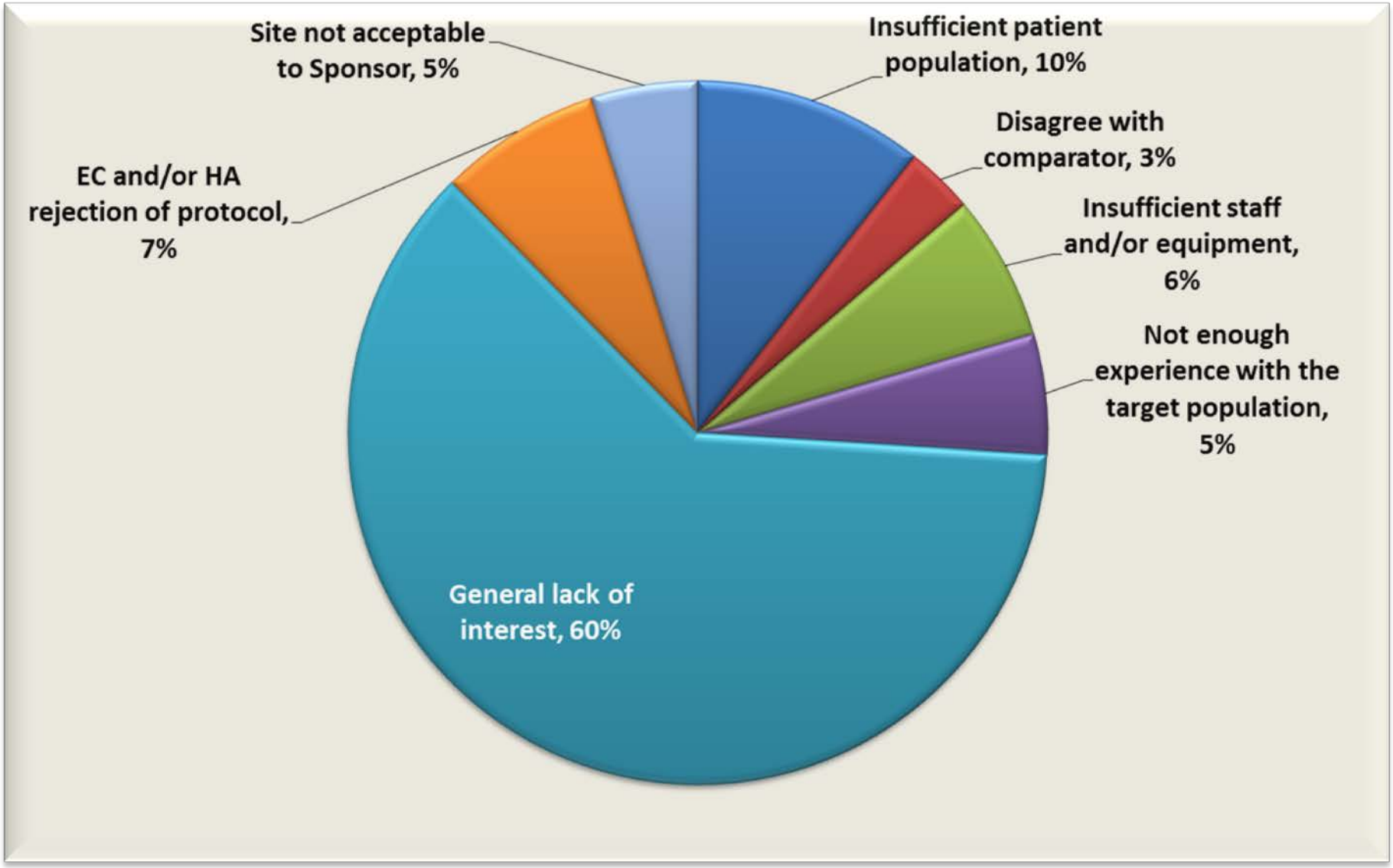
- Contacted pediatric clinical trial networks globally experienced with disease state, including:
  - Pediatric Trials Network, Pediatric Fungal Network, PediatriX, Children's Research Network (UK), International Conference of Clinical Neonatology (ICCN), Treat Infections in Neonates (TINN) (EU)

- Established a Scientific Committee to advise on study
  - Daniel Benjamin, MD, PhD (Protocol Chair); Duke University Medical Center Durham, North Carolina, USA
  - William Hope, MD University of Liverpool Liverpool, UK
  - P. Brian Smith, MD Duke University Medical Center Durham, North Carolina, USA
  - David Kaufman, MD University of Virginia Charlottesville, Virginia, USA
  - Thomas J. Walsh, MD Weill Cornell Medical Center New York, New York, USA
  - Antonio Arrieta, MD Children's Hospital of Orange County, Orange, California, USA

Site Selection Challenges

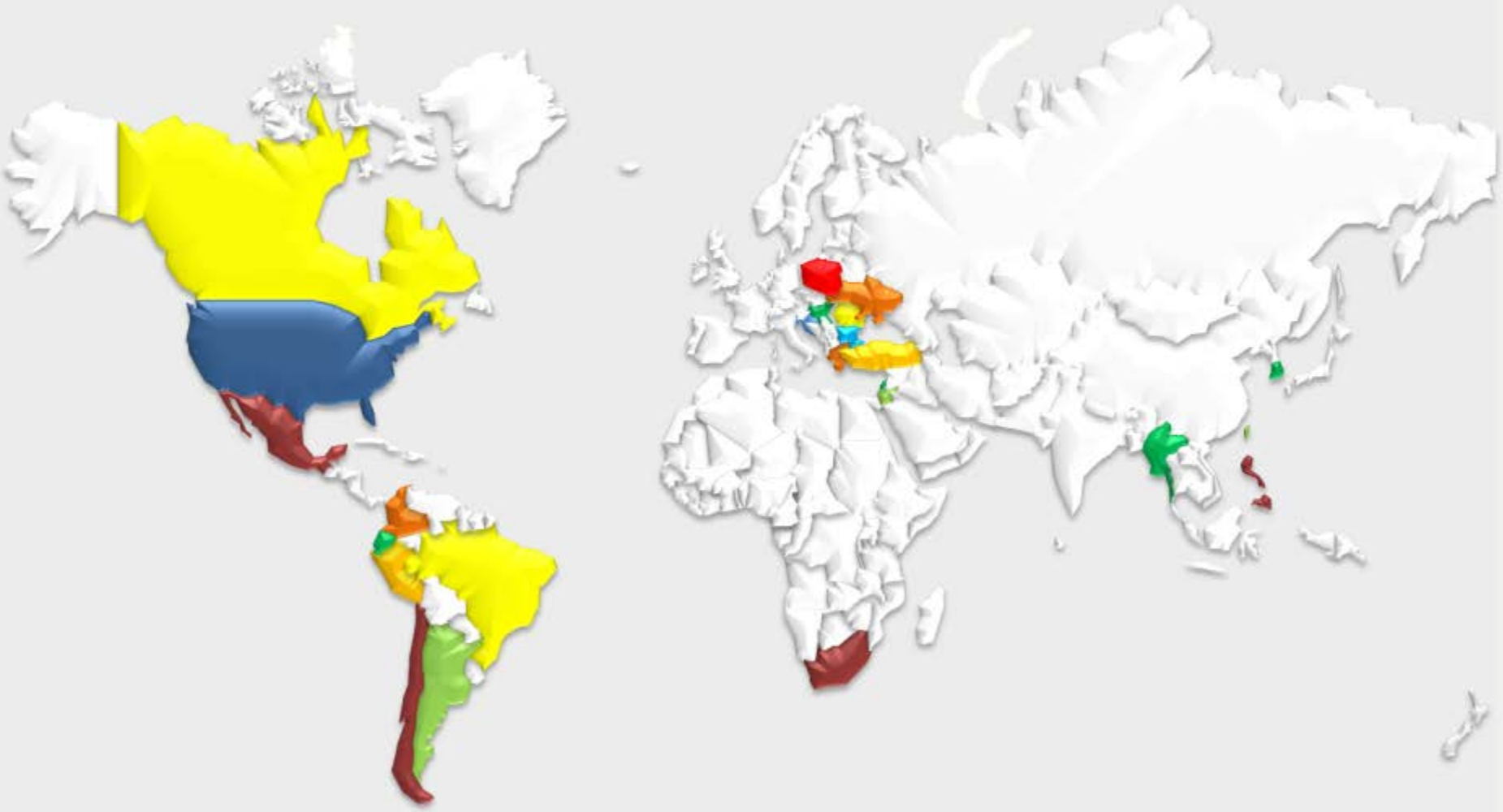


Reasons for Not Participating

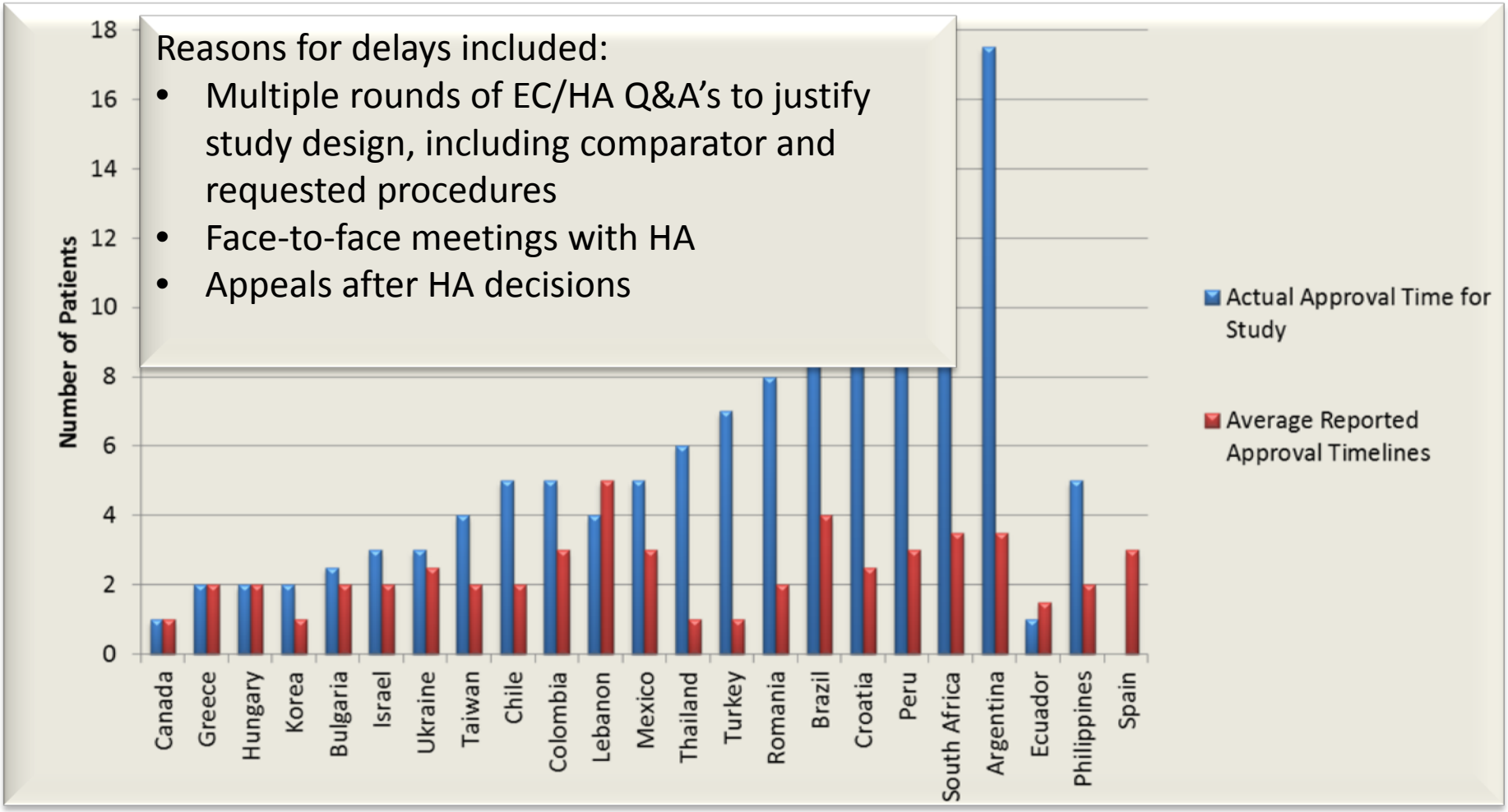


Global Study

71 sites participating from 23 countries



Longer than Average Start-up Timelines



- Non-U.S. average HA/EC review time = 6.25 months (range 1-17.5 months)
- U.S. average IRB review time = 2.6 months (range 0.2-17.1 months)

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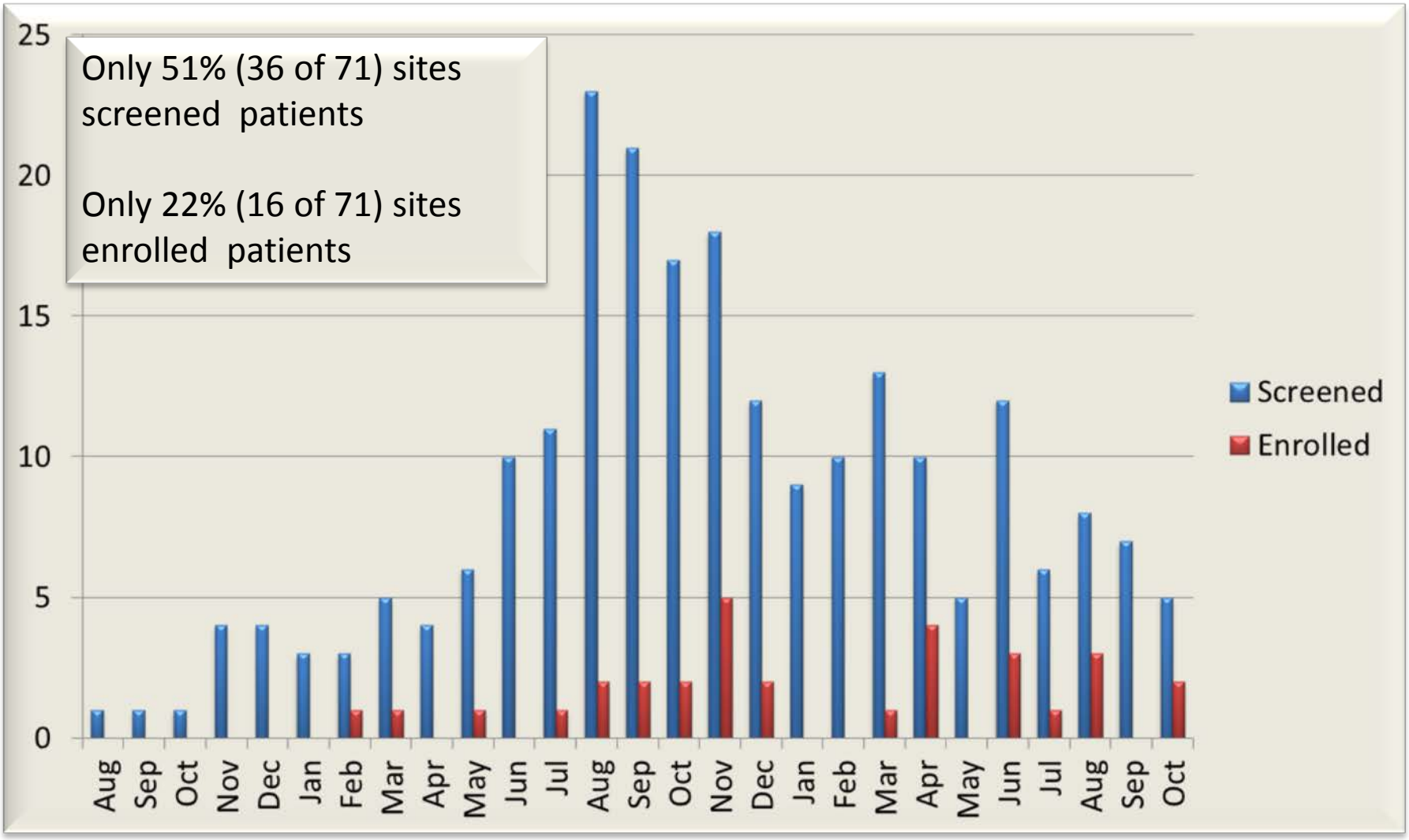
Low Yields from Monthly Screening



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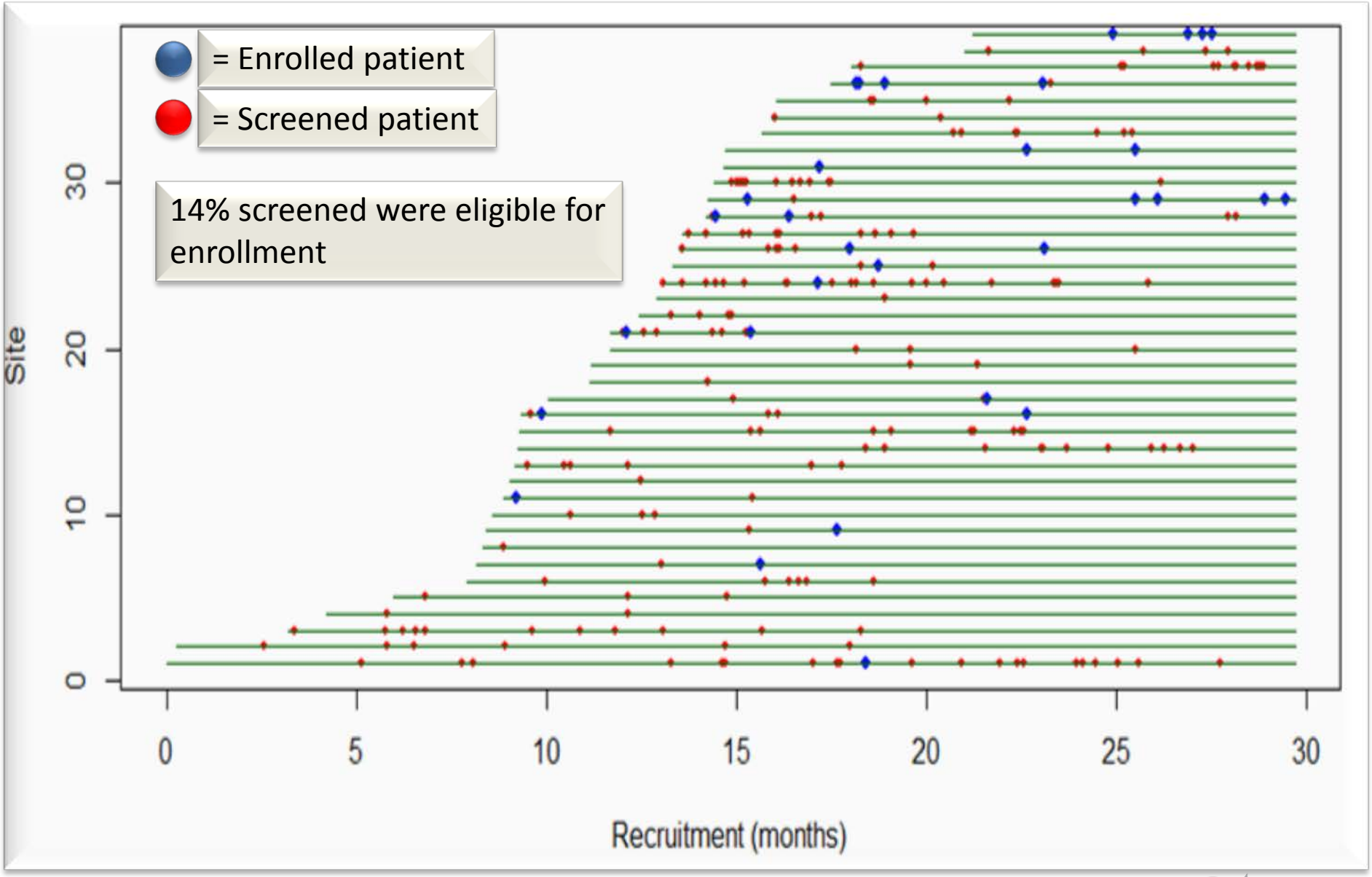
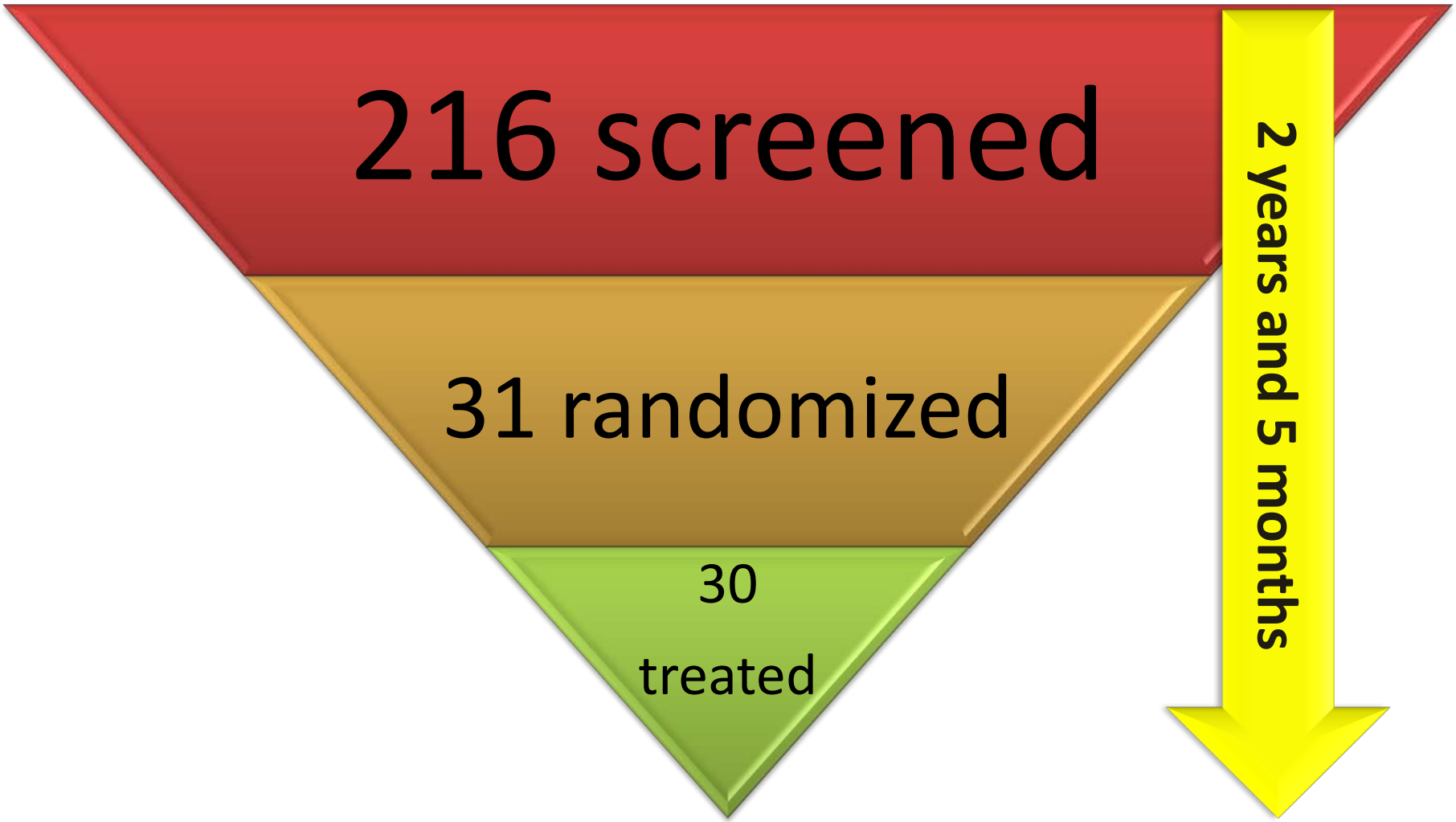
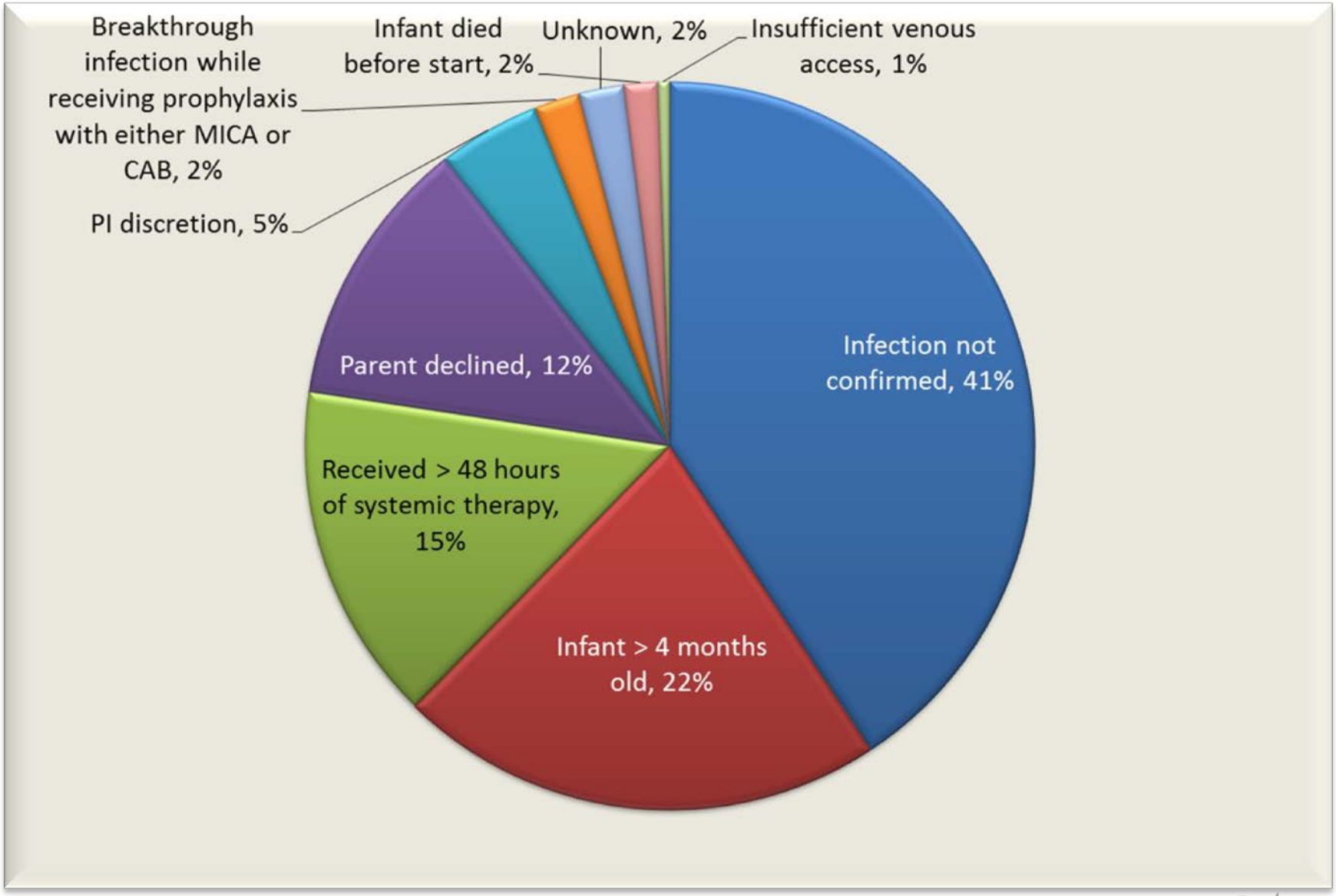
Enrollment and Screening by Site



Enrollment Challenges



Main Reasons for Screen Failures



MICA: Mycamine; CAB: conventional amphotericin B; PI: principal investigator

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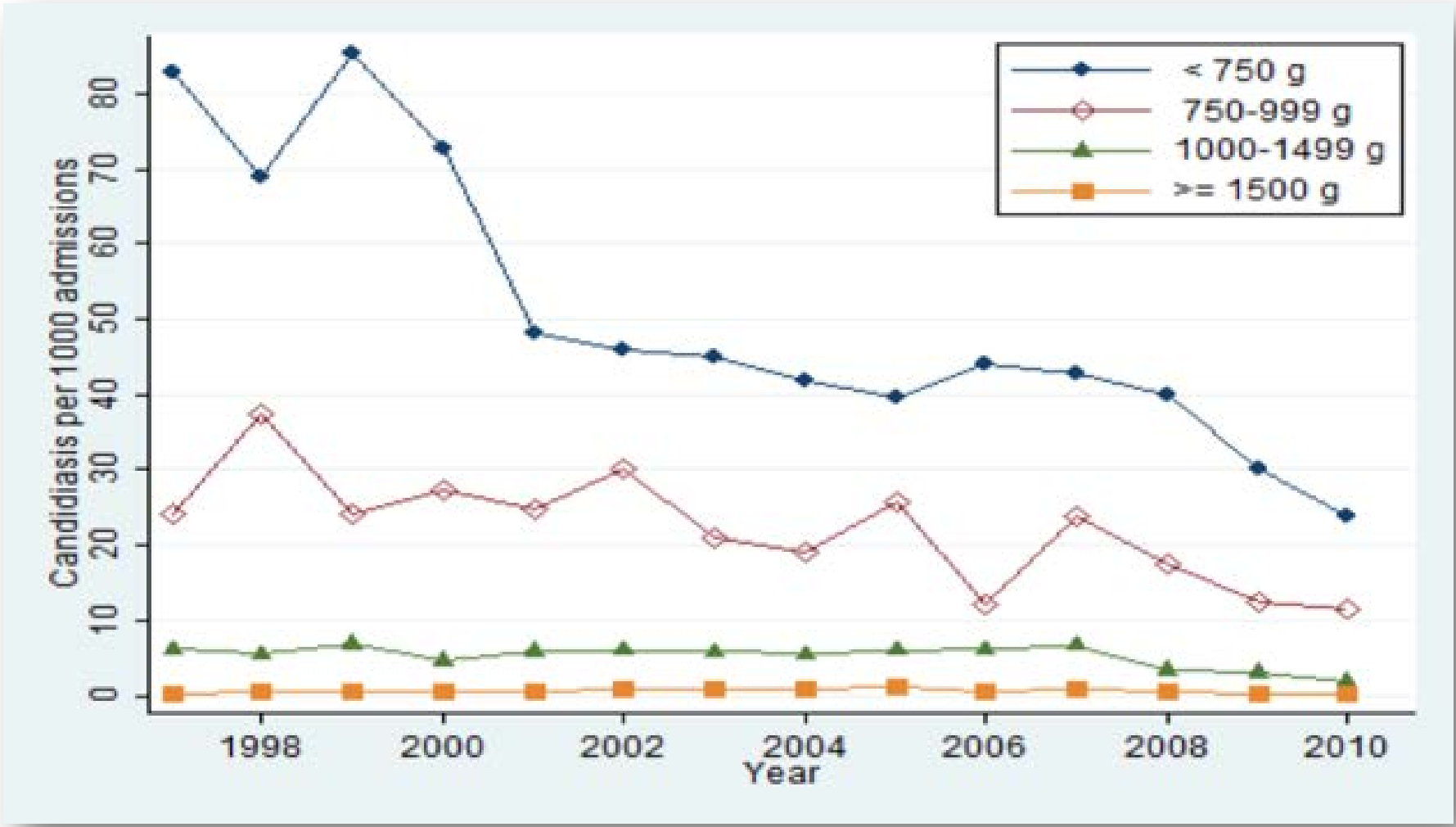
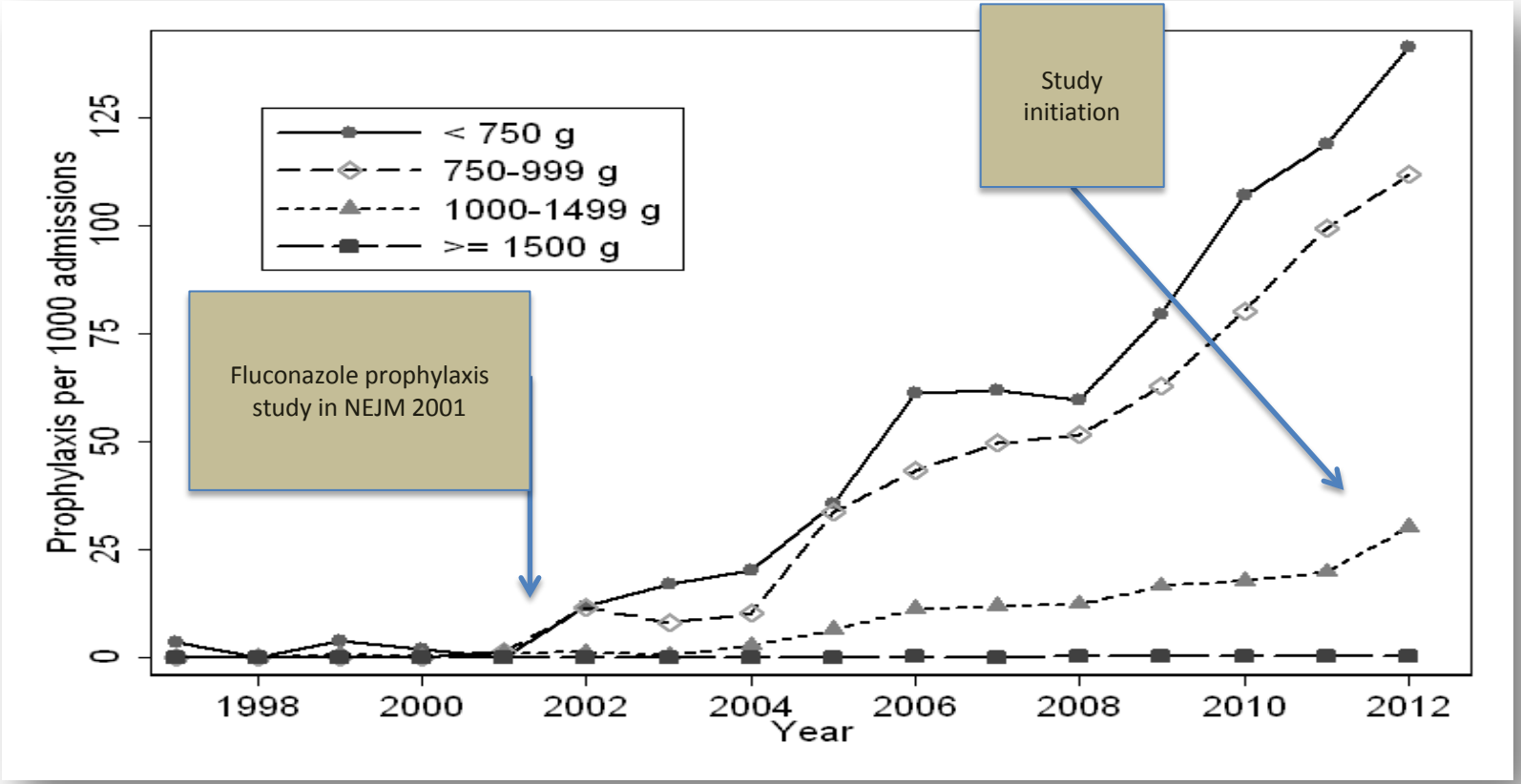
Declining Incidence of IC in the NICU (1997-2010)



Paradigm Shifts in Treatment Practices



- Increased use of prophylactic treatment of high risk neonates

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Challenges During Study Conduct

Compliance with Protocol Procedures is Challenging

Assessments		Baseline	Treatment Period	Post-Treatment
Blood Fungal Culture		100%	67%	n/a
CSF Culture		57%	10%	17%
Urine Fungal Culture		87%	27%	n/a
End Organ Assessment	Retinal Exam	80%	37%	47%
	Lumbar Puncture (LP) for CSF Analysis	83%	17%	13%
	Abdominal Ultrasound	100%	47%	60%
	Echocardiogram	0	3%	0
	Head Ultrasound	97%	50%	60%

CSF Cultures Performed on Half of the Patients and None were Positive

- 57% (17) infants had a baseline CSF culture
  - 30% (9) infants had only a baseline CSF culture
  - 23.3% (7) infants had a baseline CSF culture plus at least one follow-up
    - Only 3 were done while on therapy

- All CSF cultures collected were negative
  - Consistent with the reported low yield of CSF cultures in this population.
  - Of the 3 cases with CNS involvement in the study, all 3 were diagnosed based on head ultrasounds.

Pharmacokinetic Sampling

- Plasma PK
  - 17 patients (57%)
- CSF PK
  - 2 patients (7%)

Lessons Learned

Lessons Learned

- Evolving epidemiology was not fully defined at the onset of the neonatal program
  - Finding eligible patients was difficult due to low incidence
- Well-established PK-PD models with data rich PK bridging studies provide valuable information to establish dosage regimens
- Regulatory acceptance of study design globally was a huge hurdle
  - Standard of care differs globally
- Neonatal population is vulnerable and parental consent is difficult to obtain
- Eligibility criteria increased the challenges in enrollment and sites ability to participate
- Data requirements and efficacy definitions require careful consideration and the expectations need to balance practical and logistical issues with the need for level of proof for regulatory assessment (e.g. 2 negative cultures to define eradication)

Future Direction

- A combination of well-established *in vivo* PK-PD models with data rich PK bridging studies, and an open-label clinical trial / registry leveraging comparisons to contemporaneous historical controls may be an appropriate development path