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Passive vaccination as a global strategy for preventing RSV disease in infants

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Outline for Presentation

- Rationale for passive immunization for RSV prophylaxis
- Development of RSV monoclonal antibodies
- Passive vaccination with next generation monoclonal antibodies

RSV Described in Chimps in 1956

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First RSV literature citations in human populations

North America	1957	Africa	1966
United Kingdom	1963	Caribbean	1968
Europe	1963	China	1971
Australia/NZ	1965	India	1971
South America	1965	Pacific	1981
Japan	1965		

*Year when reports appeared in the literature

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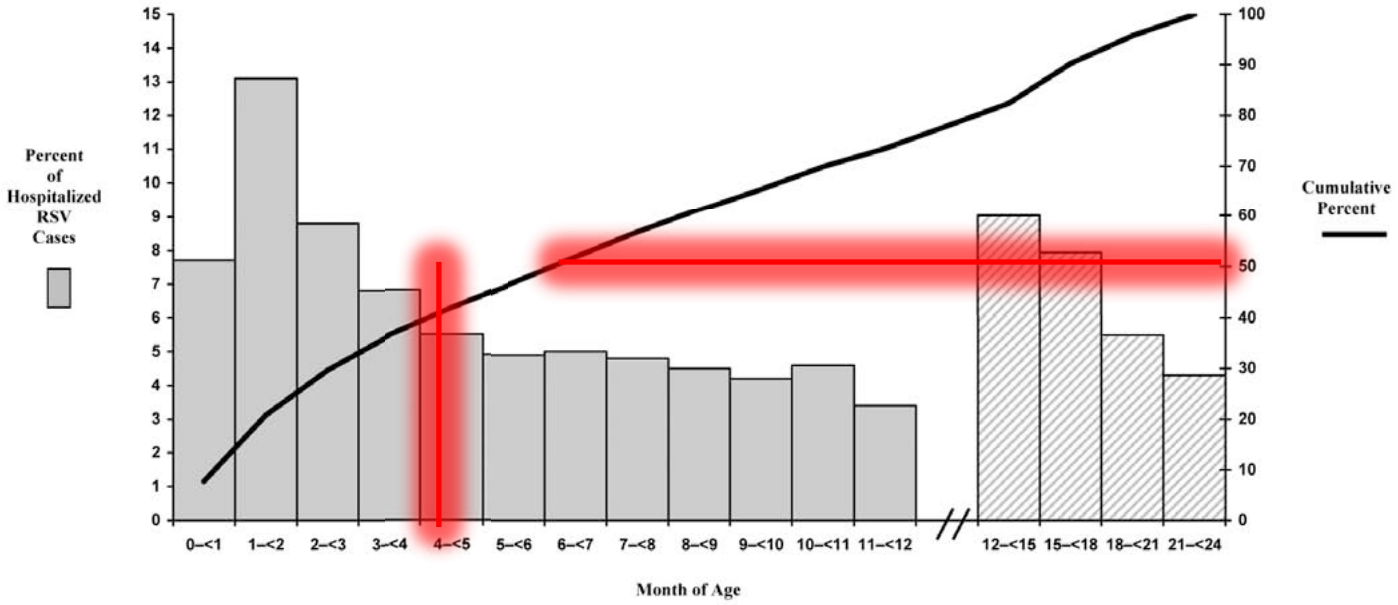
RSV disease is common but early neonatal disease reduces feasibility of active infant immunization



- Challenges in the very young infant
  - Protection needed at birth for infants born during the RSV season
  - Immature immune system
  - Inhibiting maternal antibodies
  - Safety of subunit and live attenuated vaccines
- Maternal immunization is a leading strategy for neonatal protection
- Passive vaccination is an alternative approach

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Hall Infect Disord Drug Target 2012

Early evidence for a passive antibody approach to RSV immunoprophylaxis

- Observation of later occurring and milder RSV illness in infants with higher maternal RSV neutralizing antibody levels
  - Glezen et al, 1981
- Antibody provides pulmonary protection and reduces RSV lung titers in cotton rat model
  - Prince et al, early 1980's

- The "Baby Moose" story, 1983
  - Native American infant with RSV received IGIV and improved
  - Prompted study of IGIV for RSV

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RSV-IGIV approved for prevention of serious RSV disease in preterm infants with and without BPD in 1996

- Study 1 NIAID study demonstrated protection in high-risk infants (Groothuis et al, *NEJM* 1993)
  - 249 children: 162 preterm and/or BPD, 87 with CHD
  - 150 mg/kg or 750 mg/kg IV monthly during RSV season
  - 63% relative reduction in RSV hospitalization with 750 mg/kg
  - 6 deaths: 5 in children with CHD
- Study 2 (PREVENT Study Group, *Pediatrics* 1997)
  - 510 children: preterm and/or BPD
  - 750 mg/kg IV monthly during RSV season
  - 41% relative reduction in RSV hospitalization

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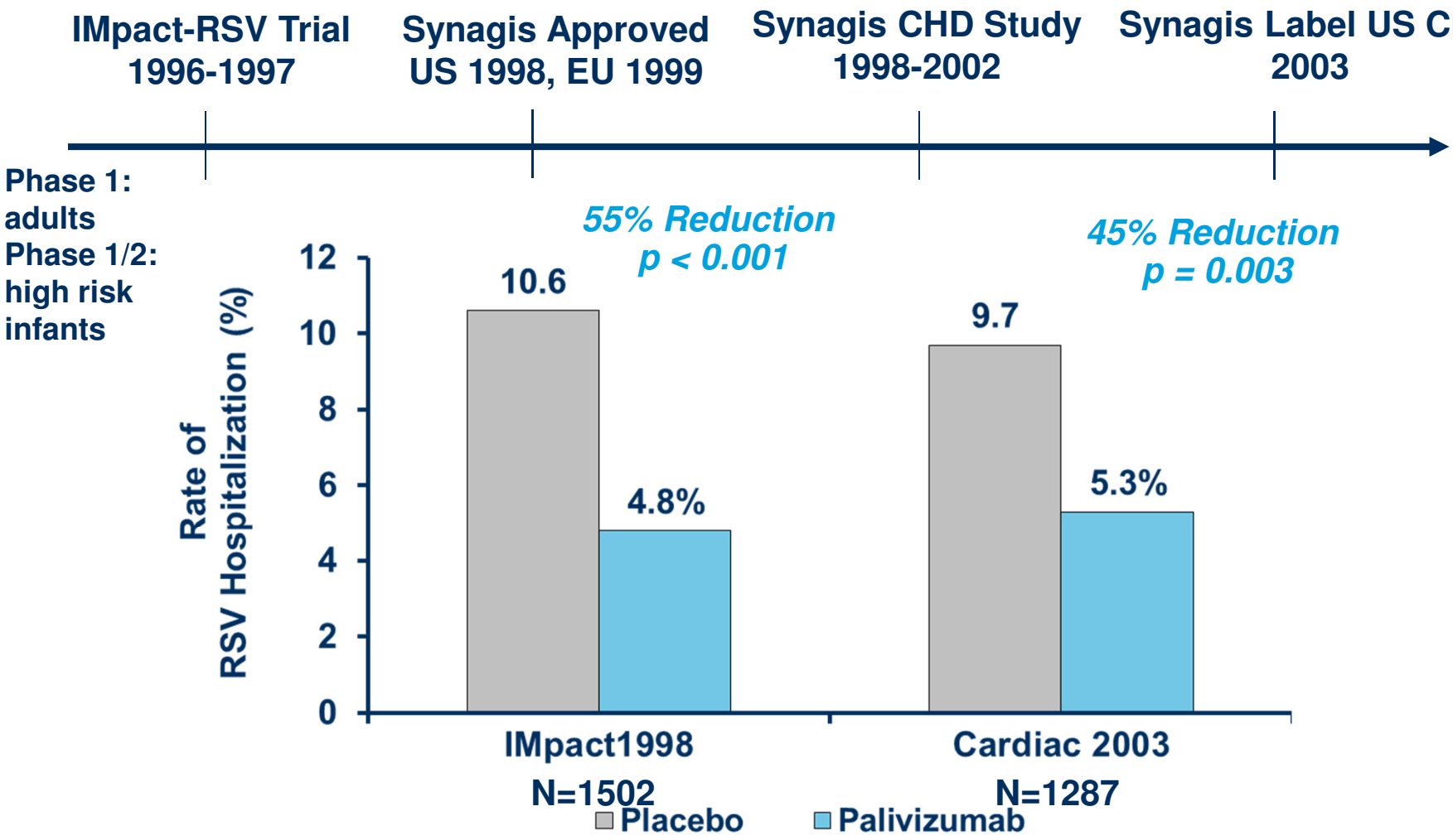
Why the need for development of palivizumab?

- RSV-IVIG (RespiGam) Limitations
  - Derived from enriched human immune globulin
  - Large dose (750 mg/kg) needed for protection
  - Required monthly IV administration
  - Concerns in CHD population and not approved for CHD

- Palivizumab Advantages
  - Humanized mAb specific to highly conserved epitope on RSV F-protein with broad neutralization of RSV A and B isolates
  - 50-100x more active than RSV-IGIV
  - Increased potency translated to a dose reduction (15 mg/kg) making IM administration possible
  - Resolved volume administration concerns in CHD population

Palivizumab clinical studies for approval



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The IMpact-RSV Study Group. *Pediatrics.* 1998;102:531–537; Feltes TF, et al. *J Pediatr.* 2003;143: 532–540;

Further anti-RSV monoclonal development

- Palivizumab (Synagis®)
  - FDA approved in June 1998
    - First and only approved mAb for RSV prophylaxis
    - Prevention of RSV hospitalizations in high risk children
- Motavizumab
  - Completed Phase 3
  - Not FDA approved (LRTI endpoint disallowed)
  - Discontinued
- MEDI-557 – extended half-life
  - 1st time in humans with an antibody with the YTE mutation
  - Discontinued after Phase 1
- MEDI8897
  - Fully human, extended half-life
  - Once per season dosing

Why the need for development of a next generation anti-RSV mAb?

- Palivizumab Limitations
  - Requires 15 mg/kg dose for protection
  - Formulation is 100 mg/mL
  - For infants ≥ ~ 7 kg, would require more than 1 injection per dose
  - Half-life is standard IgG antibody and requires monthly dosing
  - Not feasible for broader population of healthy infants

Overview for MEDI8897: Passive RSV Vaccine

Technology
- Fully human, high potency IgG1 mAb derived from human B-cells
- YTE half-life extension technology

Highlights
- Immediate protection at birth
- Once per season dosing
- Fixed IM dose (not weight based)
- Vaccine-like pricing

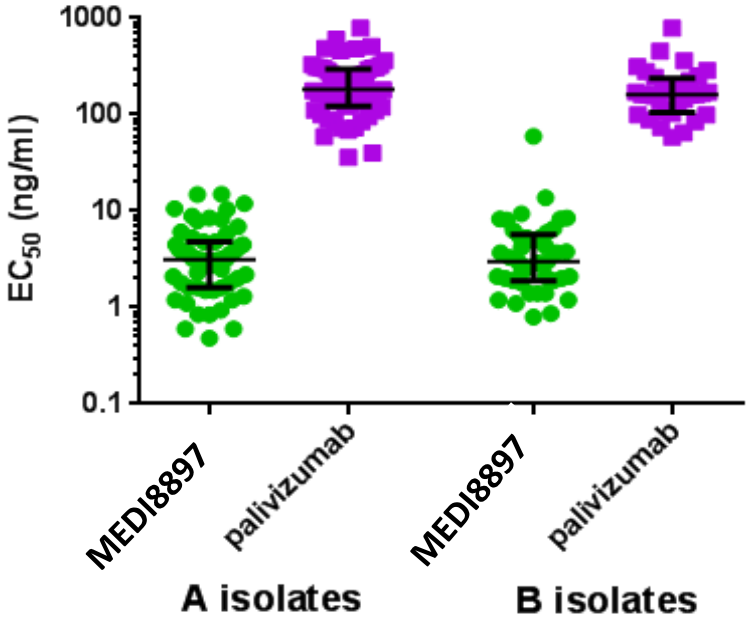
Clinical endpoint
- Prevention of lower respiratory tract infection due to RSV

Population & dosing scheme
- Seasonal RSV transmission: all infants immediately prior to their first RSV season
  - To protect during 6 month transmission window when infection is a possibility
- Year-round/sporadic transmission: all infants delivered as a birth-dose
  - To protect first 6 months of life when risk of severe disease is greatest

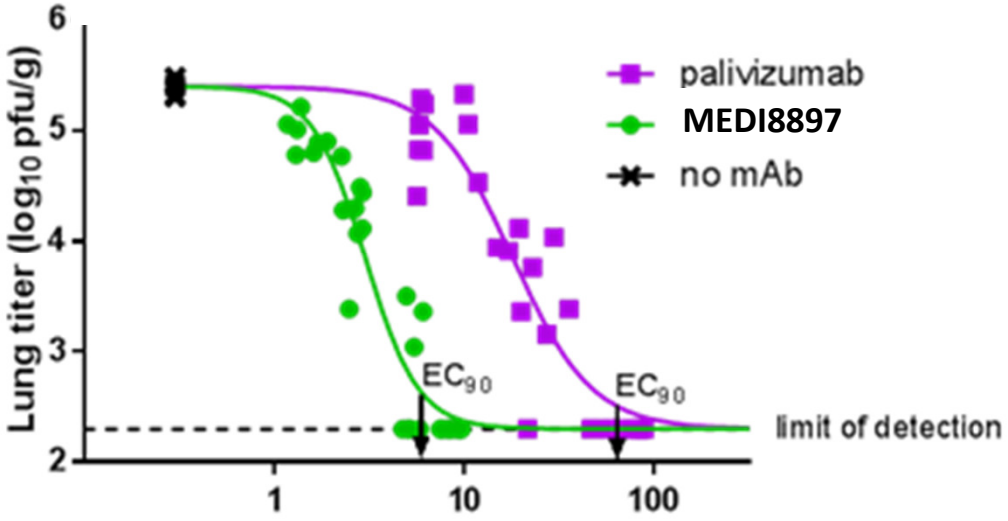
Program Status
- Phase 1a adult FTIH complete (N=136)
- Phase 1b/2a in 32-35 week preterm infants (N=89); enrollment complete, follow-up ongoing
- Phase 2b clinical efficacy in 29-35 week preterm infants planned for 2016
- FDA fast track designation granted

MEDI8897 demonstrates enhanced activity *in vitro* and *in vivo*

RSV Clinical Isolates (N=99)



RSV lung titers vs serum mAb concentration



- MEDI8897 targets a unique antigenic site on pre-fusion RSV F
- MEDI8897 neutralizes all RSV A and B clinical isolates tested

- MEDI8897: 9-fold increase in *in vivo* potency compared to palivizumab
- MEDI8897 target concentration identified as 6.8 µg/mL

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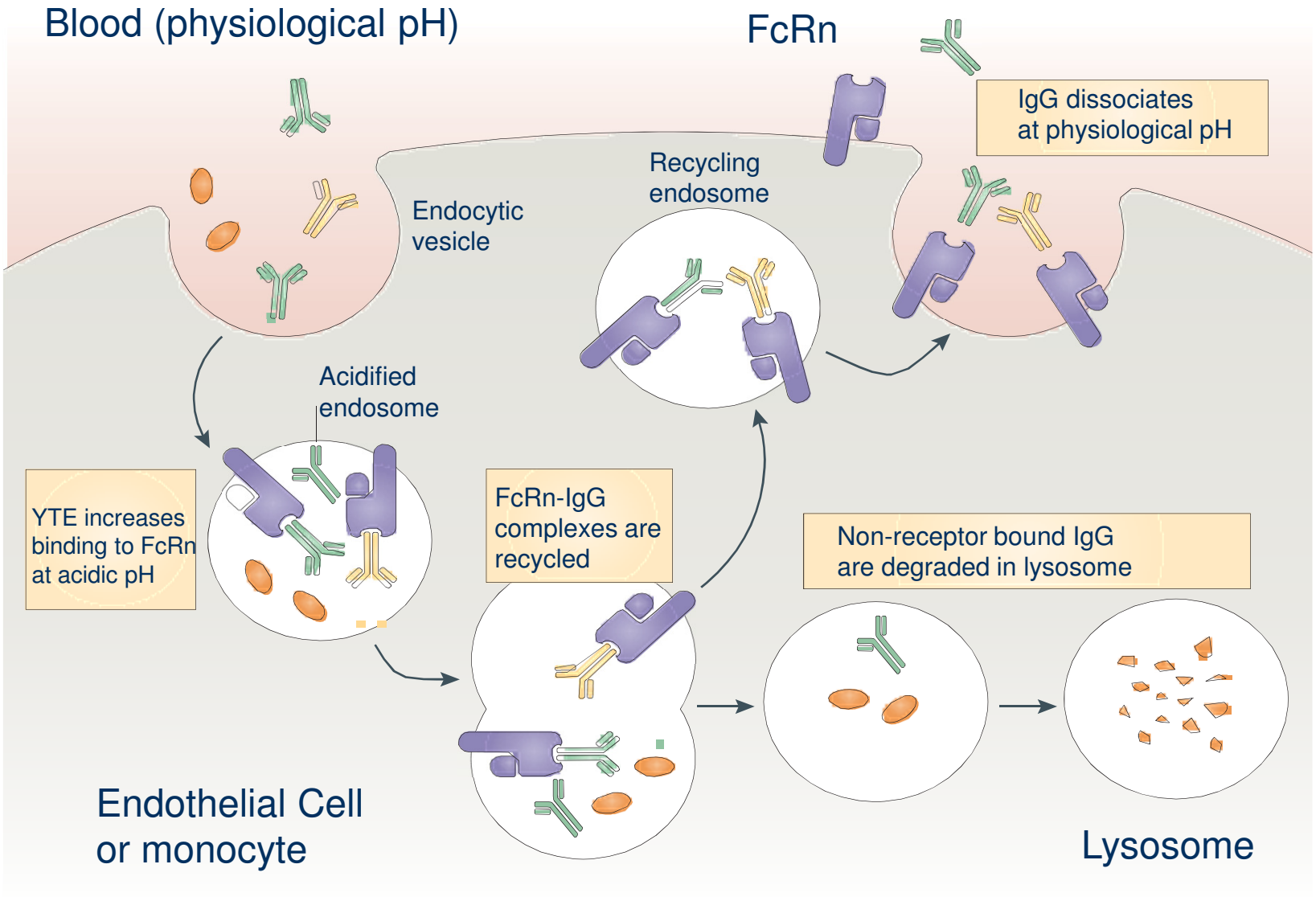
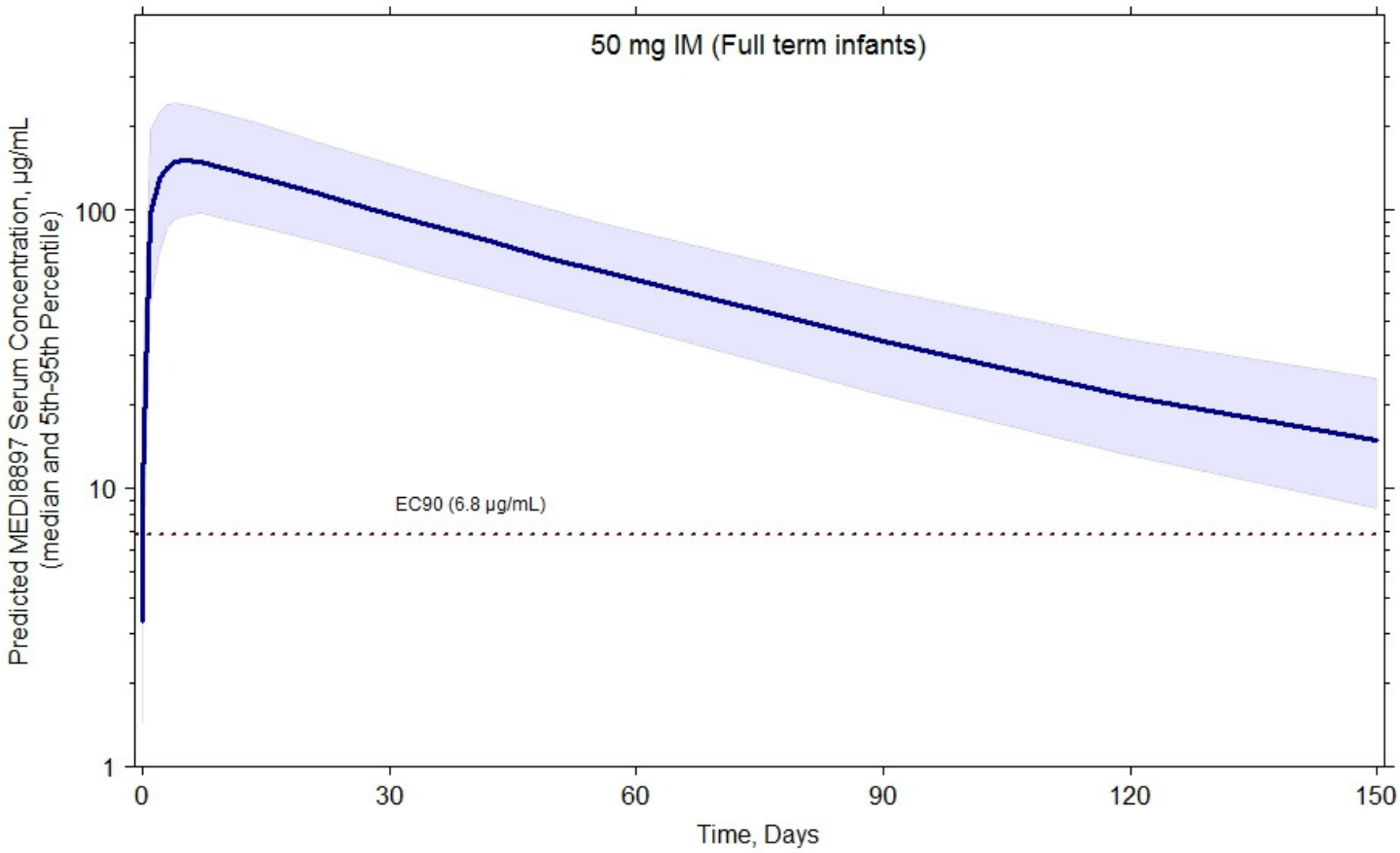
Half-life extended with YTE modification in Fc region



Modified from Roopenian D et al

Model of predicted PK profile in term infants



- Single 50 mg intramuscular dose predicted to protect through winter respiratory viral season

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MEDI8897: Clinical Development Plan – Overview

- Primary indication:

  Passive immunization of all infants entering their first RSV season for the prevention of lower respiratory tract illnesses (LRI) caused by RSV

- Clinical studies:

  - Phase 1a First-in-Human: Safety and PK in healthy adult volunteers
  - Phase 1b/2a: Safety and PK, dose escalation in healthy preterm infants (32 – 35 wks GA)
  - Phase 2b: Study in healthy preterm infants (29 – 35 wks GA)
  - Phase 3: Study in healthy infants > 35 wks GA
  - Additional study in the Synagis population

MEDI8897 Clinical development overview

Phase 1a First-Time in Human study in healthy adults

- Double-blind (3:1) placebo controlled study (N = 136)
- Evaluated multiple IV and IM dose levels
- Subjects followed for 1 year

Safety

- AEs balanced (MEDI8897 62% vs placebo 63%)
- 2 SAEs: Gun shot & appendicitis

Pharmacokinetics

- Bioavailability 87%
- Half-life extended to 85-117 days

Anti-drug antibody

- Incidence of ADA was similar (MEDI8897 14% vs placebo 15%) , titers were low, no observed impact on safety or PK

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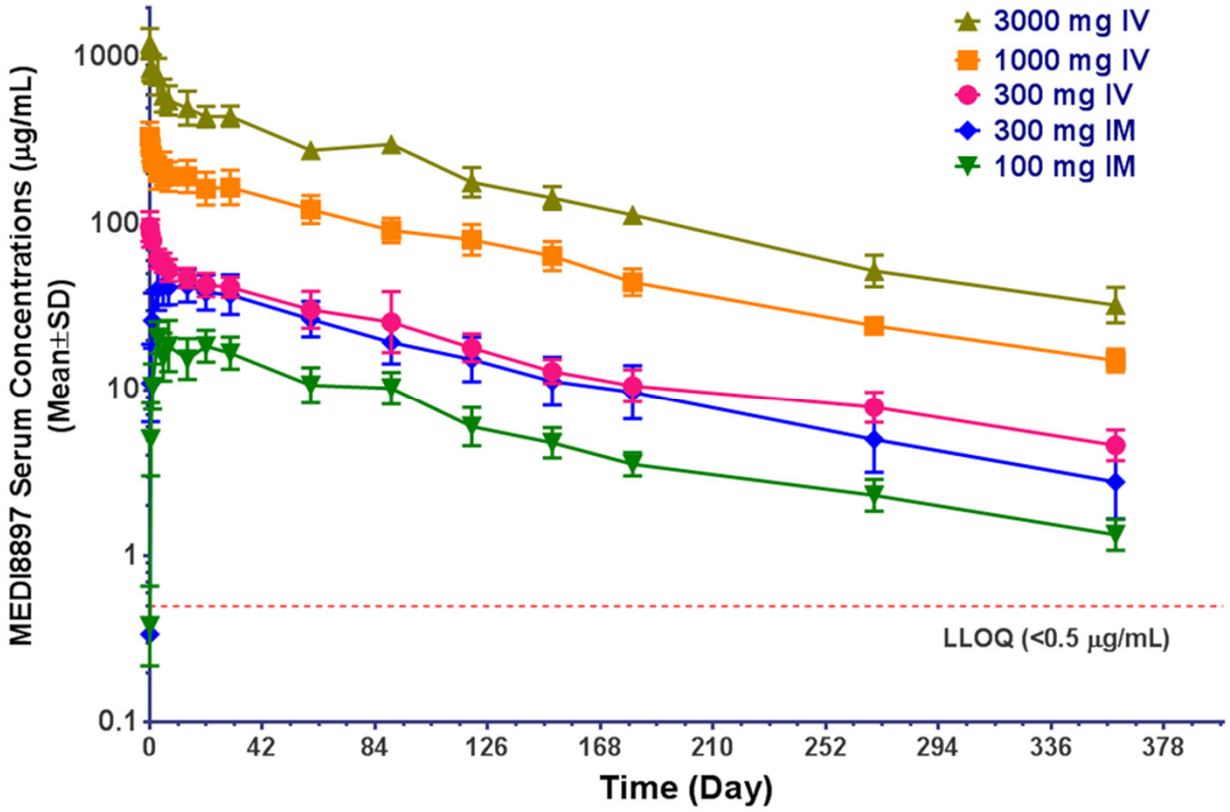
MEDI8897 Serum Concentration-Time Profiles



- Peak concentrations increased dose-proportionally
- Time to peak concentration upon IM administration was 5 – 9 days
- Half-life values ranged from 85 to 117 days across dose groups

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MEDI8897 Clinical development overview

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Phase 1b/2a safety, PK in 32-35 week GA infants

- Double-blind (4:1) placebo controlled study in USA, SA, Chile (N=89)
- Three IM dose levels evaluated
- Subjects followed for 1 year

Safety

- Day 30 safety and tolerability profile reassuring

Pharmacokinetics

- Day 30 interim PK models support single 50mg intramuscular dose administration

Anti-drug antibody

- Day 30 incidence of ADA was low and balanced between groups, no observed impact on safety or PK

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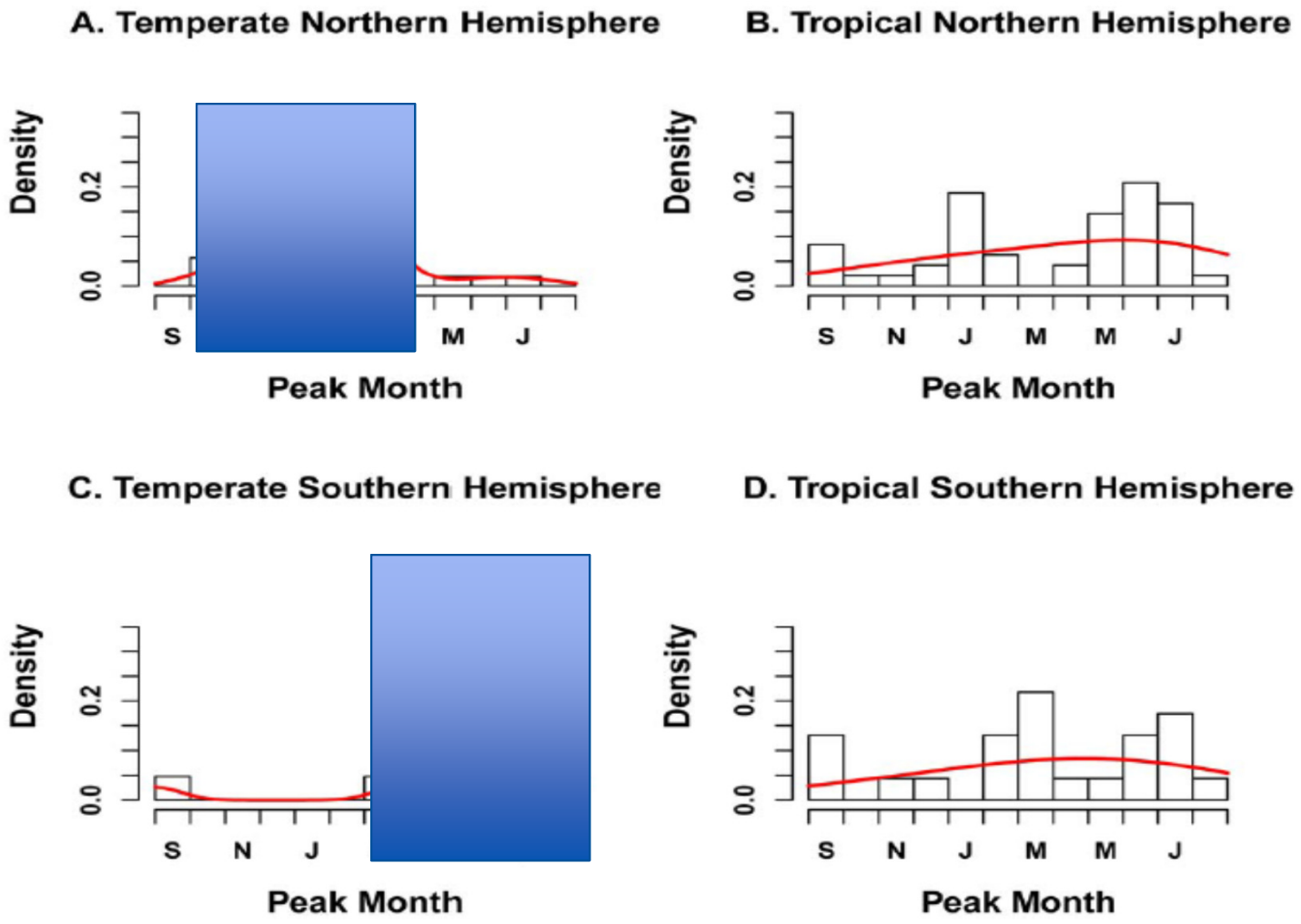
RSV peak transmission by geographic zone, n=96



Bloom-Fesbach et al. PLOS*One* 2013; e54445 1-12

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Alternative MEDI8897 dosing strategy

- Deliver MEDI8897 as birth dose in term infants
  - Provides protection through first half-year of life where risk of serious RSV disease is greatest
  - Eliminates need for RSV surveillance to identify timing of seasonal dosing
  - Takes advantage of pre-existing medical contacts eliminating need to establish seasonal vaccination campaigns
- Pursue parallel clinical development as birth-dose in tropical regions with irregular RSV transmission
  - Massive unmet medical need and mortality in developing countries
  - Accelerate availability in developing countries
  - Seek label indication for use as birth-dose
  - Generate relevant safety & efficacy data to facilitate deployment in individual countries

Passive RSV vaccination in term infants should be beneficial when given as a birth dose in regions of non-seasonal transmission

- Passive vaccination with motavizumab effective in term infants[1]
  - Randomized 2:1 Native American term infants to 5 monthly doses (N=2,127)
  - Mean age at dosing approximately 2 months of age (SD± 1.9 months)
  - RSV Hospitalization: 11% placebo vs 1% motavizumab; 87% relative reduction
  - RSV Outpatient LRI: 10% placebo vs 3% motavizumab; 71% relative reduction

- Passive vaccination with palivizumab effective as birth doses in tropics[2]
  - Taiwan has a blend of year-round and twice-yearly RSV epidemics
  - 6 monthly doses initiated at hospital discharge irrespective of season (N=127)
  - Compared to historical rates of RSV hospitalization
  - Median age at dosing approximately 3 months (IQR 1-6 mo)
  - RSV Hospitalization within 6 months 86% (95% CI: 36-97)
  - RSV Hospitalization within 12 months 78% (95% CI: 40-92)

1: O'Brien et al Lancet October 2015
2: Chi et al PLoS One June 2014

MEDI8897: passive RSV vaccine to address global public health needs

- Validated target and approach to address a high unmet medical need
- Novel use of a monoclonal antibody leveraging technological advances
  - Passive vaccination for general population
  - Once per season dosing
  - Tiered vaccine-like pricing
- Opportunity to execute a parallel developed/ developing world strategy to facilitate availability in LICs/LMICs on similar timeline to developed countries