CS 5035:
Pharmacokinetics of Benzathine Penicillin and Ceftriaxone In Pregnancy

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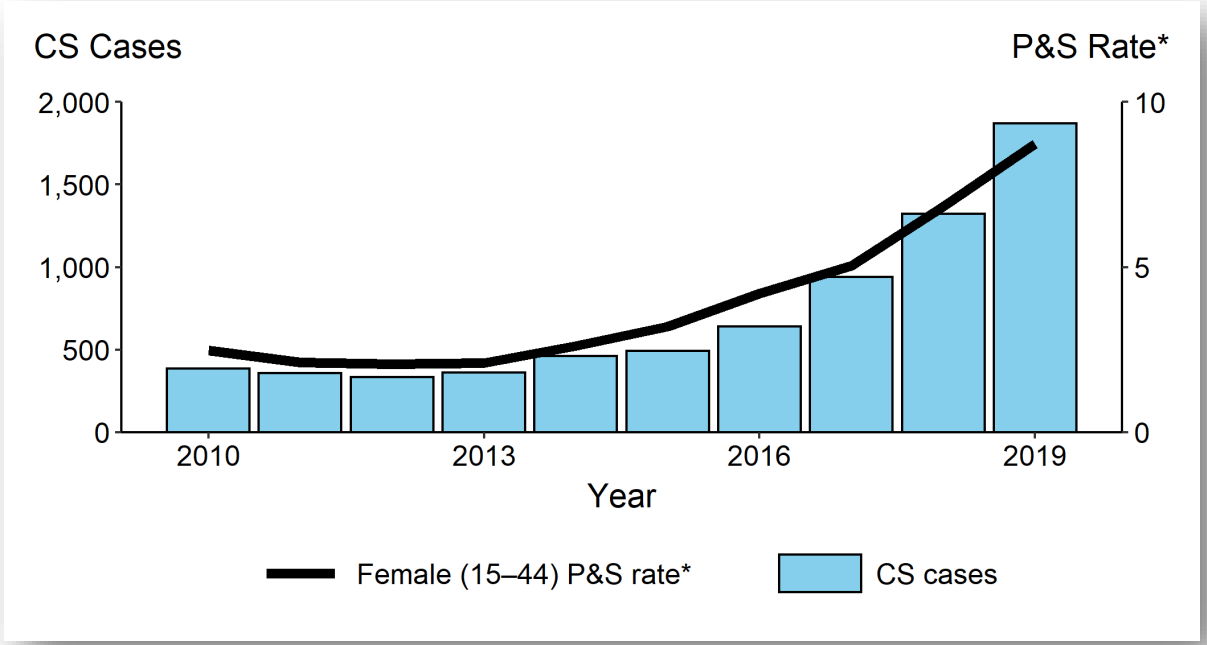
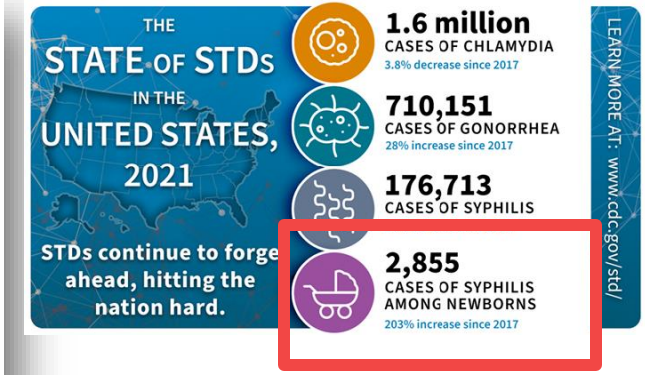
2 Study Summary

Design	Opportunistic Phase IV PK study of pharmacokinetic parameters of Ceftriaxone (arm 1) and Benzathine Penicillin (arm 2) in pregnancy
Study Population	Pregnant persons receiving any dose of either Ceftriaxone or Benzathine Penicillin for standard-of-care treatment for any indication
Agent	Arm 1: Ceftriaxone or Arm 2: Benzathine Penicillin
Sample Size	Arm 1a IV Ceftriaxone: 8 persons in each trimester (6 evaluable) Arm 1b IM Ceftriaxone: 4 persons in each trimester (2 evaluable) Arm 2 IM Benzathine Penicillin:12 persons in each trimester (8 evaluable)
1^0 Outcomes	Arm 1: Ceftriaxone area under the plasma concentration-time curve (AUC) at 24 hours Arm 2: Benzathine Penicillin AUC at 7 days
Enrollment	Six months
Duration	Active follow-up of up to 14 days for participants receiving penicillin Observational follow-up of up to 7 months for pregnancy outcomes

Congenital Syphilis is Rising





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But Penicillin is on Shortage

Presentation	Availability and Estimated Shortage Duration	Related Information	Shortage Reason (per FDASIA)
Bicillin L-A Pediatric 600,000 Units/mL Prefilled Syringe (NDC 60793-700-10)	Next delivery: TBD; Estimated recovery 2024	Dear Patient Letter: Availability Update for Bicillin® L-A (penicillin G benzathine injectable suspension) and Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) Prefilled Syringes (HYPERLINK)	Demand Increase for the drug
Bicillin L-A 1.2 million Units/2 mL (600,000 units/mL) Prefilled Syringe (NDC 60793-701-10)	Limited Supply. Next delivery: July 2023; Estimated recovery: Q2 2024	On allocation. Check Wholesaler for Availability Dear Patient Letter: Availability Update for Bicillin® L-A (penicillin G benzathine injectable suspension) and Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) Prefilled Syringes (HYPERLINK)	Demand Increase for the drug
Bicillin L-A 2.4 million Units/4 mL (600,000 units/mL) Prefilled Syringe (NDC 60793-702-10)	Limited Supply. Next delivery: July 2023; Estimated recovery: Q2 2024	On allocation. Check Wholesaler for Availability Dear Patient Letter: Availability Update for Bicillin® L-A (penicillin G benzathine injectable suspension) and Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) Prefilled Syringes (HYPERLINK)	Demand Increase for the drug

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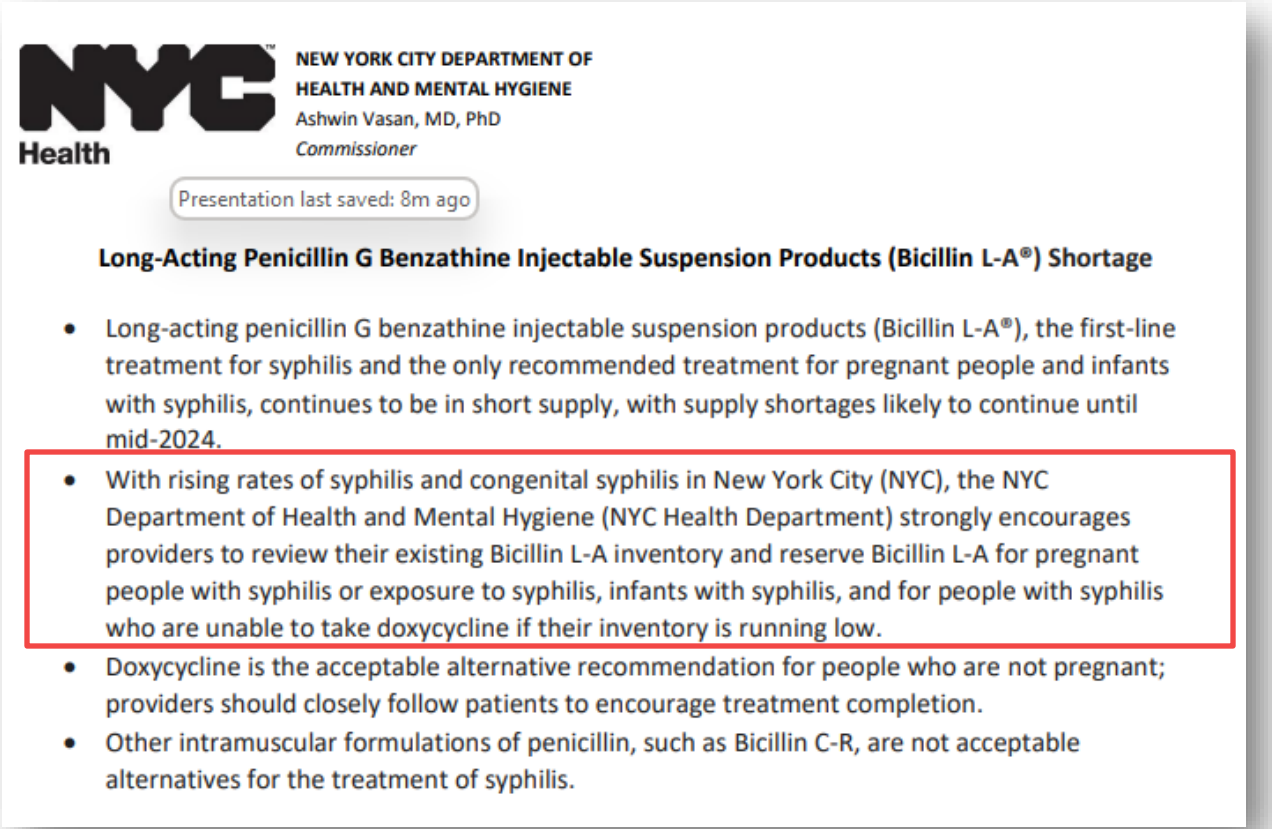
States Have Had to Restrict Supplies



NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
Ashwin Vasan, MD, PhD
Commissioner

Presentation last saved: 8m ago

Long-Acting Penicillin G Benzathine Injectable Suspension Products (Bicillin L-A®) Shortage

- Long-acting penicillin G benzathine injectable suspension products (Bicillin L-A®), the first-line treatment for syphilis and the only recommended treatment for pregnant people and infants with syphilis, continues to be in short supply, with supply shortages likely to continue until mid-2024.
- With rising rates of syphilis and congenital syphilis in New York City (NYC), the NYC Department of Health and Mental Hygiene (NYC Health Department) strongly encourages providers to review their existing Bicillin L-A inventory and reserve Bicillin L-A for pregnant people with syphilis or exposure to syphilis, infants with syphilis, and for people with syphilis who are unable to take doxycycline if their inventory is running low.
- Doxycycline is the acceptable alternative recommendation for people who are not pregnant; providers should closely follow patients to encourage treatment completion.
- Other intramuscular formulations of penicillin, such as Bicillin C-R, are not acceptable alternatives for the treatment of syphilis.

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Alternatives in Pregnancy Are Sparse

CDC Guidelines: Early Syphilis Treatment in Pregnancy

- Preferred
  - Benzathine penicillin G 2.4 million units x1 IM

"Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin G."

WHO Guidelines: Early Syphilis Treatment in Pregnancy

- Preferred
  - Benzathine penicillin G 2.4 million units x1 IM
- Alternative
  - ~~Procaine penicillin 1.2 million units IM daily x10d (preferred alt tx)~~
  - ***Ceftriaxone 1g IM QD x 10-14d***

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We Need An Alternative to Benzathine Penicillin for Treating Syphilis in Pregnant Persons

- Active against syphilis
- Easily administered via intramuscular injection
- Long-half life
- Crosses the placenta
- Long-acting IM Ceftriaxone would be the ideal agent
  - There is interest from the Preclinical Microbicide and Prevention Research Branch (PMPRB) in the Prevention Sciences Program Within the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) to develop this product

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Ceftriaxone Has Limited PK Data In Pregnancy

Ceftriaxone General PK Properties

- Absorption
  - F following IM administration ~100%
  - Tmax 1-2 hr
- Distribution
  - **Vd** is small: 6 to 14 L
  - **Plasma protein binding** 95% - but saturable
- Elimination
  - Not metabolized
  - **Significant biliary excretion**
  - **Urine elimination** 33-67%.
- Clearance
  - CL_{Total} 0.6-1.45 L/h
  - CL_{Renal}: 0.32-0.73 L/hr

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8 to 8.7	0.58 to 1.45	5.8 to 13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients With Renal Impairment			
Hemodialysis Patients (0 to 5 mL/min)*	14.7	0.65	13.7
Severe (5 to 15 mL/min)	15.7	0.56	12.5
Moderate (16 to 30 mL/min)	11.4	0.72	11.8
Mild (31 to 60 mL/min	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

*Creatinine clearance.

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Benzathine Penicillin Has Limited PK Data In Pregnancy

- Detailed pharmacokinetics in pregnancy are limited
- We know that it works…
- A complete understanding of the PK/PD of Benzathine Penicillin in pregnancy is necessary to design potential alternatives

Ceftriaxone PopPK Modeling Completed For Pregnancy

- Current Approach Represents a Semi-Physiologic Population PK Model
  - Compartmental parameters and linked to known physiologic processes
  - Non-pregnant models show linkage between Ceftriaxone and CrCL and eGFR that can be applied to other populations
  - Large existing repository of anatomic, physiologic, and biological parameters for the pregnancy PK models

Table 1 Main Anatomical, Physiological, and Biological Parameters Needed for p-PBPK Model and Equations Used to Calculate Parameter Values During Different Gestation Ages (GA) (14)

Parameter	Unit	Equation
Today body weight (kg)	kg	$TBW=61.1+0.2409\ GA+0.0038\ GA^2$
Cardiac output (CO)	L/h	$CO=301+5.916\ GA-0.088\ GA^2$
Total body fat mass (TFM)	kg	$TFM=17.14+0.1305\ GA+0.0008\ GA^2$
Weight of the uterus	g	$\text{Weight of the uterus}=80+8.2931\ GA+0.3546\ GA^2$
Fetal volume	mL	$\text{Fetal volume}=0.01\ \exp(13.604(1-\exp(-0.0702GA)))$
Placental volume	mL	$\text{Placenta volume}=0.0-0.0716+0.9146\ GA^2-0.0122\ GA^2$
Amniotic fluid	mL	$\text{Aminotic fluid volume}=0+1.9648\ GA-1.2056\ GA^2+0.2064GA^3-0.0061\ GA^4+0.00005\ GA^5$
Volume of fetoplacental unit	mL	Fetoplacental volume = Uterus weight + Placenta volume + Fetal volume + Amniotic fluid volume
Blood flow of uterine	L/h	$\text{Uterine blood flow}=1.71+0.2068\ GA+0.0841\ GA^2-0.0015\ GA^3$
Plasma volume	L	$\text{Plasma volume}=2.5-0.0223\ GA+0.0042\ GA^2-0.00007\ GA^3$
Red blood cell (RBC) volume	L	$\text{RBC volume}=1.49+0.0098\ GA$
Total blood volume	L	Total blood volume = plasma volume + RBC volume
Glomerular filtration rate (GFR)	mL/min	$GFR=114+3.2367\ GA-0.0572\ GA^2$

Citation: Dallmann A, Ince I, Meyer M, Willmann S, Eissing T, Hempel G. Gestation-Specific Changes in the Anatomy and Physiology of Healthy Pregnant Women: An Extended Repository of Model Parameters for Physiologically Based Pharmacokinetic Modeling in Pregnancy. Clin Pharmacokinet. 2017 Nov;56(11):1303-1330. doi: 10.1007/s40262-017-0539-z. PMID: 28401479

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Ceftriaxone Modeling 2gm IM Q24

Figure 1: Ceftriaxone Concentration By Time

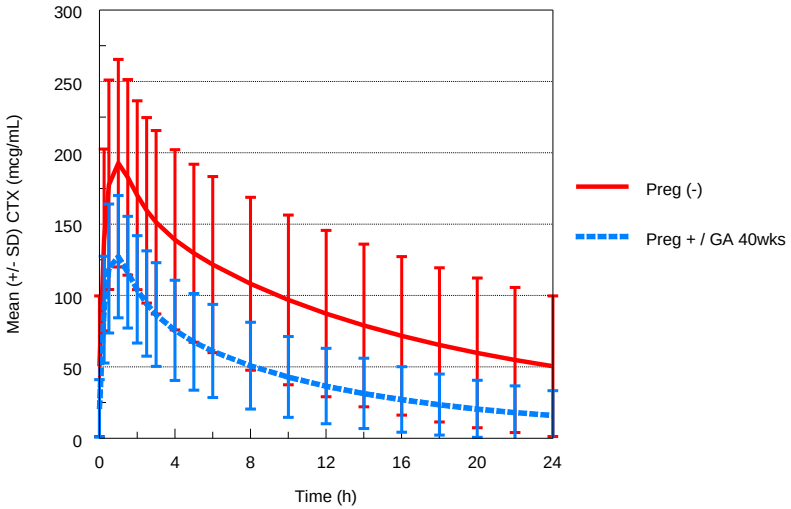
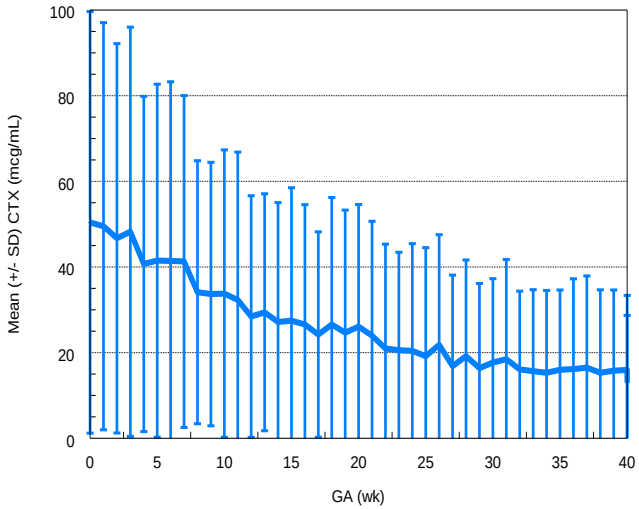


Figure 2:Changes in Ceftriaxone Troughs by Gestational Age



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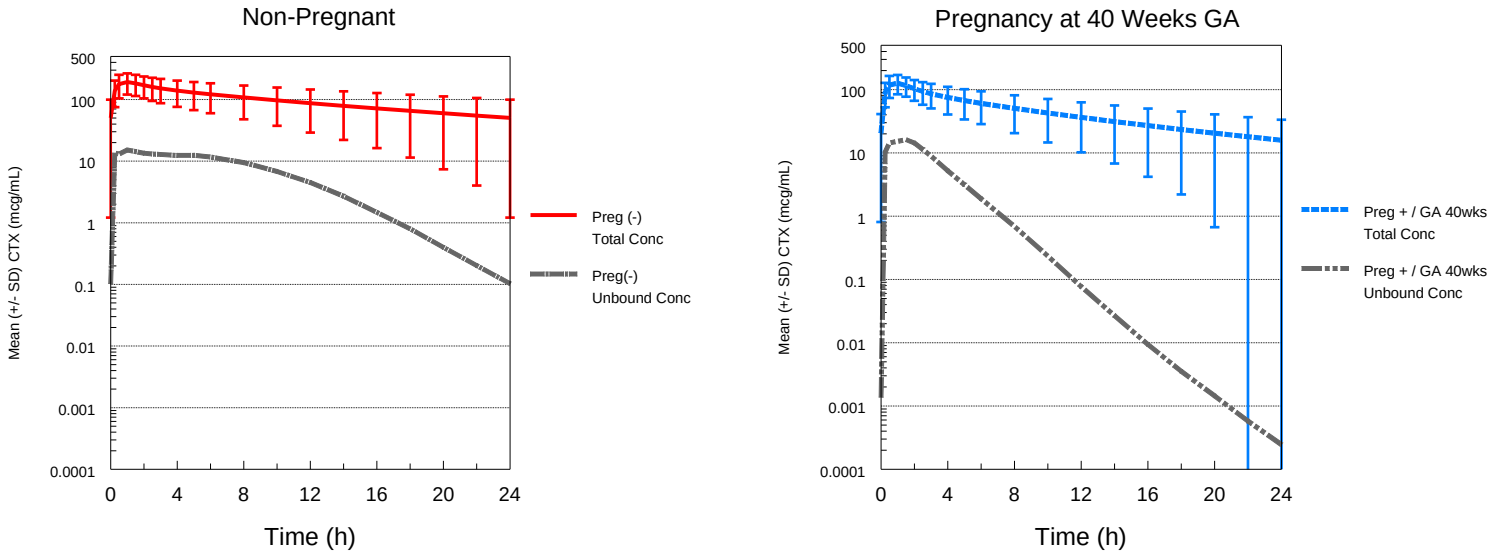
Ceftriaxone Bound and Unbound Concentrations

Figure 3: Ceftriaxone Bound and Unbound Concentrations



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Model Conclusions

Current Conclusions:

- Infrequent high dose CTX **may not maintain adequate concentration** of Ceftriaxone to treat syphilis in pregnant and non-pregnant persons per modeling.
- **Late pregnancy** may require **different dosing approaches** to maintain target trough concentrations.

Next Steps:

- Compare Ceftriaxone PK/PD to Benzathine Penicillin PK/PD with **collected biologic data**
- Model with biological data a **theoretical Long Acting (LA) intramuscular formulation of Ceftriaxone** that can maintain appropriate trough concentrations for at least 1 week

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Objectives

Primary

- Describe the pharmacokinetic parameters during pregnancy of Benzathine Penicillin administered to pregnant persons

- Describe the pharmacokinetic parameters during pregnancy of Ceftriaxone administered to pregnant persons.

Inclusion

- Age >=18 and Age <55
- Receiving or expecting to receive Ceftriaxone or Benzathine penicillin prescribed by their clinical care provider and documented in the medical records
  - Accurate dosing history available for those who have received prior doses
- For pregnancy defined as:
  - At study entry, viable **single** intra-uterine pregnancy of any gestational age based on medical records

Exclusion

- Receiving any medications known to interfere with the absorption, distribution, metabolism, and excretion of Ceftriaxone or Benzathine Penicillin
- Requiring ICU level of care
- Hemodialysis
- Requiring desensitization

Sample Size = 72

	1st Trimester	2nd Trimester	3rd Trimester
Arm 1: IV Ceftriaxone	8	8	8
Aim 1b IM Ceftriaxone	4	4	4
Arm 2: Benzathine Penicillin	12	12	12

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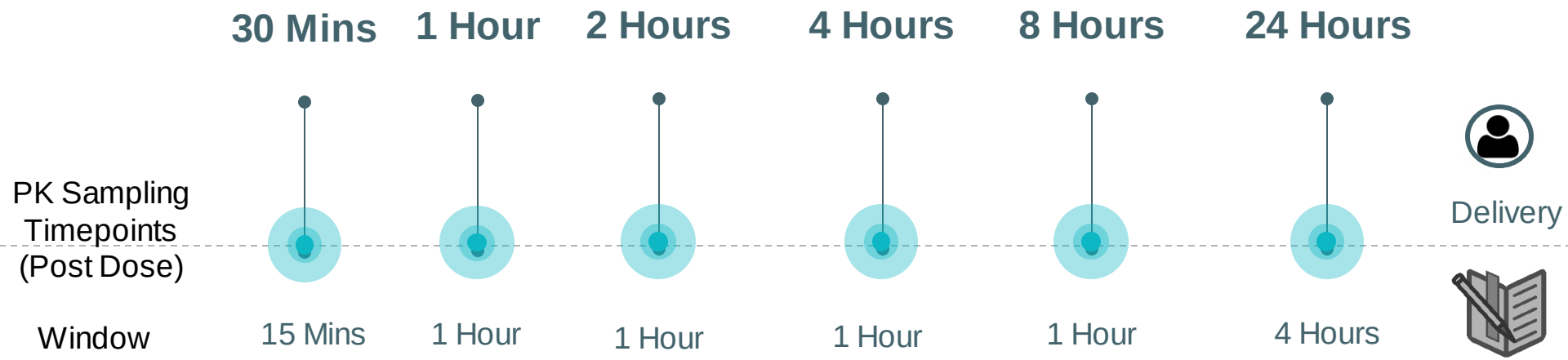
Schedule of Evaluations
Arm 1a: IV Ceftriaxone



Urine fractional excretion to be collected with the 2 and 4 hour blood collection

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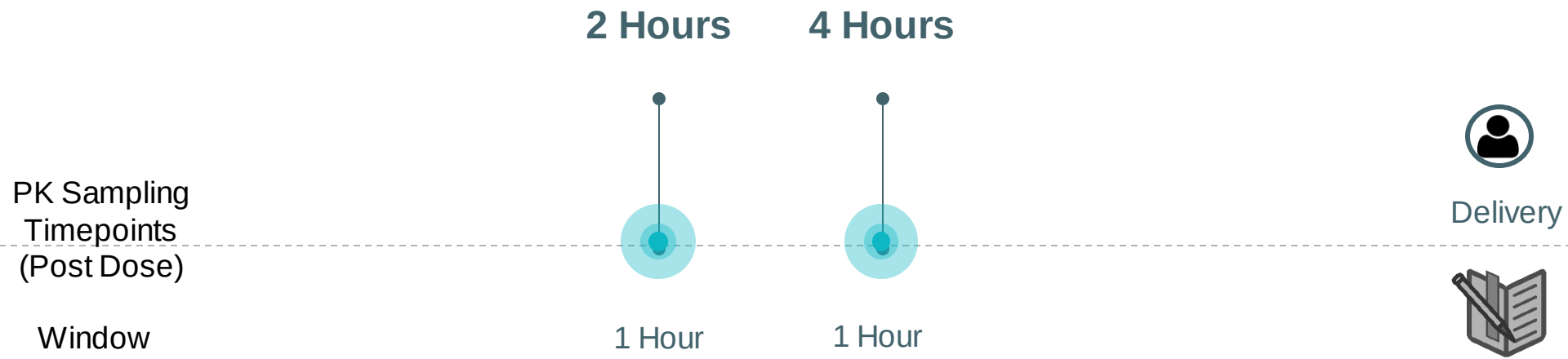
*Pre-dosage samples will be obtained for patients enrolling after receiving their first dose of the antibiotic

Schedule of Evaluations
Arm 1b: IM Ceftriaxone



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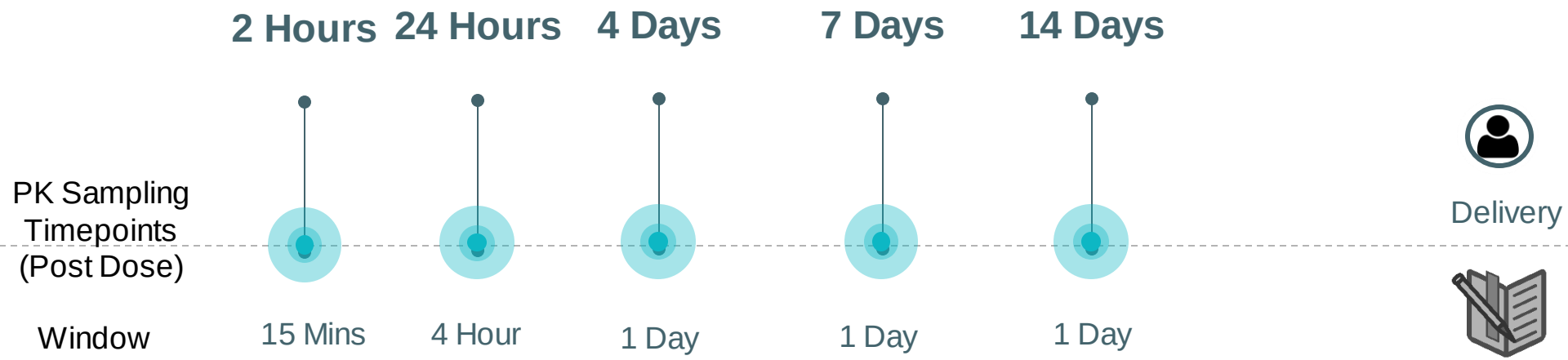
Schedule of Evaluations
Arm 2: Benzathine Penicillin



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Primary Outcome Measures

- Arm 1a/1b: IV/IM Ceftriaxone
  - CTX area under the plasma concentration-time curve (AUC) at 24 hours

- Arm 2: IM Benzathine Penicillin
  - Penicillin area under the plasma concentration-time curve (AUC) at 7 days

Secondary Outcome Measures

- Arm 1a/b: Ceftriaxone
  - Ceftriaxone elimination half-life ($t_{1/2}$)
  - Ceftriaxone 24 hour trough concentration (C_{trough})
- Arm 1b: Ceftriaxone
  - Absolute IM bioavailability
  - Absorption rate constant
- Arm 2: Benzathine Penicillin
  - Plasma concentration at 2 hours, 24 hours, Day 7, and Day 14

Clinical Outcome Measures

- Safety Outcomes
  - DAIDS Grade 3 or higher maternal adverse events
  - DAIDS Grade 3 or higher maternal adverse events assessed as related to the drug under study

- Change in maternal quantitative syphilis serology (observational)
- Congenital syphilis (yes/no, observational)

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Summary

- Congenital syphilis is increasing rapidly
- We need a reasonable alternative to Benzathine Penicillin for pregnant persons
- However limited data is available on the PK/PD of Benzathine Penicillin and Ceftriaxone to inform the development of that agent

- **This study will allow us to model the needed PK of a theoretical Long-Acting (LA) formulation of ceftriaxone that can be given IM and maintain appropriate trough concentrations**

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Thanks

- Cassandra Heiselman
- Jeremiah Momper
- Aaron Devanathan
- Edmund Capparelli
- Sharon Nachman

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Questions?

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