Chlamydia Management Updates: Advances and Vaccines Developments for STI Prevention

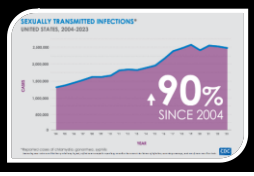


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Associate Professor of Medicine
University of Alabama at Birmingham

IAS–USA

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PART 1: EPIDEMIOLOGY

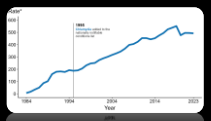


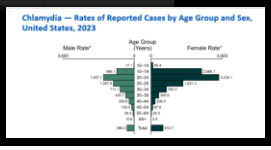


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CDC 2023 Surveillance Report: CHLAMYDIA



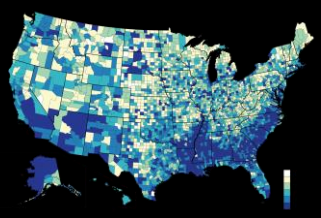


Disproportionate impact on adolescent girls and young women ages 15-34

Slide 5

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Chlamydia — Rates of Reported Cases by County, United States, 2023

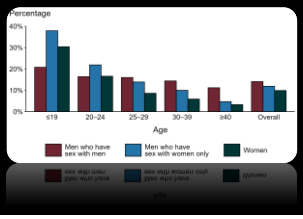


* Per 100,000

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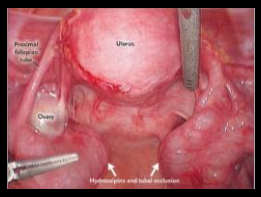
Chlamydia — Proportion of STI Clinic Patients Testing Positive by Age Group, Sex, and Sex of Sex Partners, STI Surveillance Network (SSuN), 2023



Slide 7

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Manifestations of Untreated Chlamydia trachomatis



Weisenfeld NEJM 2018

Slide 8

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CDC: CT Screening Guidelines

Chlamydia

Routine screening for *C. trachomatis* infection on an annual basis is recommended for all sexually active females aged <25 years (*149*). Rectal chlamydial testing can be considered for females on the basis of reported sexual behaviors and exposure, through shared clinical decision-making between the patient and the provider (*170,171*). Evidence is insufficient to recommend routine screening for *C. trachomatis* among sexually active young males, on the basis of efficacy and cost-effectiveness. However, screening of sexually active young males should be considered in clinical settings serving populations of young men with a high prevalence of chlamydial infections (e.g., adolescent service clinics, correctional facilities, and STD clinics). Chlamydia screening, including pharyngeal or rectal testing, should be offered to all YMSM at least annually on the basis of sexual behavior and anatomic site of exposure (see Men Who Have Sex with Men).

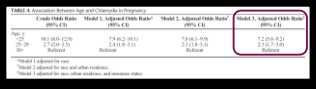
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Chlamydia Prevalence by Age and Correlates of Infection in Pregnancy



7.4% Prevalence



Slide 10

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CT Treatment

Recommended Regimen for Chlamydial Infection Among Adolescents and Adults

Doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens

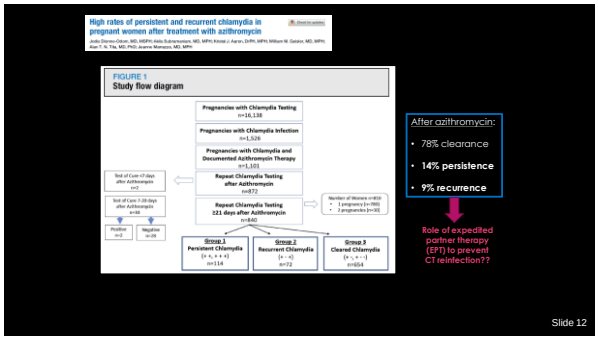
Azithromycin 1 g orally in a single dose
or
Levofloxacin 500 mg orally once daily for 7 days

- Treatment: Doxycycline had 3-7% higher efficacy compared to azithromycin single dose and 91% ITT (100% microbiologic) cure for rectal CT in MSM RCT (vs 74% AZ)
  - Azithromycin 1 gram PO alternative – DOT if significant adherence concerns
  - Levofloxacin alternative works - can be costly
  - Erythromycin no longer an alternative due to GI intolerance
  - Counsel to abstain from sex x 7 days
  - Partner therapy for sex partners in the past 60 days or most recent.
- **If pregnant - test of cure** in 4 weeks
- **Repeat testing for all** in 3 months. Re-infection common.

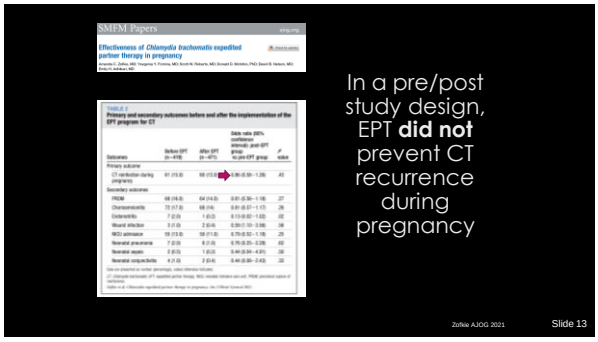
Kong CID 2014; Paez-Canro Cochrane 2019; Dombrowski CID 2021

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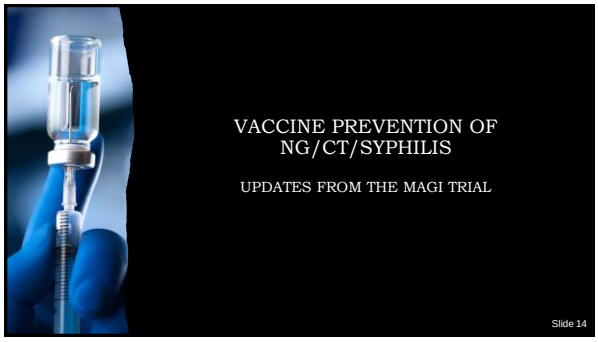
11


High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin
FIGURE 1
Study flow diagram
Pregnancies with Chlamydia Testing n=16,138
Pregnancies with Chlamydia Infection n=1,526
Pregnancies with Chlamydia and Documented Azithromycin Therapy n=1,101
Repeat Chlamydia Testing after Azithromycin n=872
Repeat Chlamydia Testing ≥21 days after Azithromycin n=840
Group 1 Persistent Chlamydia (+, +, + +) n=114
Group 2 Recurrent Chlamydia (+, −) n=72
Group 3 Cleared Chlamydia (+, −, + −) n=654
After azithromycin:
• 78% clearance
• 14% persistence
• 9% recurrence
Role of expedited partner therapy (EPT) to prevent CT reinfection??
Slide 12

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SMFM Papers
Effectiveness of Chlamydia trachomatis expedited partner therapy in pregnancy
In a pre/post study design, EPT did not prevent CT recurrence during pregnancy
Zofkie AJOG 2021
Slide 13

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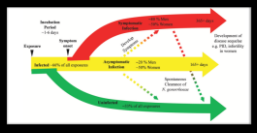

VACCINE PREVENTION OF NG/CT/SYPHILIS
UPDATES FROM THE MAGI TRIAL
Slide 14

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INCOMPLETE UNDERSTANDING OF GONOCOCCAL NATURAL HISTORY



601,319 NG cases reported to CDC in 2023



Lovett Front Immunol 2019

Slide 15

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CHALLENGES TO NG VACCINE DEVELOPMENT

- Antigenic variability of *Neisseria gonorrhoeae* surface Ag
- Variable expression and heterogeneous circulating strains
  - phase variation
- Absence of protective immunity following natural infection
  - Humoral response is weak and has limited durability
- Lack of defined correlate of protection
  - Early vaccine studies tested pilus, POR, LOS antigens w/o CoP
- Human restricted infection with murine model (prior NHP)
- Failed NG vaccine candidates: whole cell, pilus vaccine, OMV designed to enrich porin OMP.
  - **May need multiple Ab binding targets to trigger complement activation and lead to synergistic bactericidal response**

Williams CMR 2024

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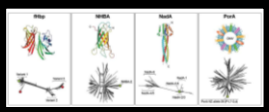
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REVERSE VACCINOLOGY

4 Component MenB vaccine (4C-MenB) contains Nm OMV and 3 other recombinant outer membrane proteins

4CMenB composition

1. Nm Group B D-OMVs (NZ98/254)
2. Factor H binding protein (fHbp) GNA 1870; not surface exposed
3. **Neisseria heparin binding antigen (NHBA) GNA 2132**
4. Neisserial adhesin A (NadA) GNA1994; absent in Ng
5. Minor: GNA2091 – OMP assembly – fused to fHbp
6. Minor: GNA1030 – ubiquinone binding protein – fused to NHBA
7. aluminum hydroxide



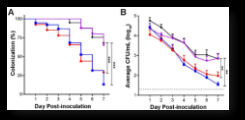
- Binds heparin and chondroitin sulfate
- Interacts with Ng and host cells

Tonsatto Expert Rev Vaccines. 2017

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4CMenB vaccination enhances clearance of *N. gonorrhoeae* in mouse infection model



- 2 dose vaccination
- NG F62 challenge 3 weeks
- 38-41 mice/group



Leduc, Jerse. PLOS Pathogens 2020

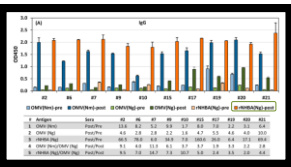
Slide 18

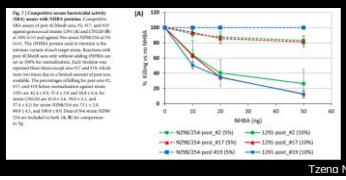
18

NHBA antibodies elicited by 4CMenB vaccination are key for serum bactericidal activity against *Neisseria gonorrhoeae*

n=10 vaccinated adults

IgG response by ELISA





Tzeng NPJ Vaccines 2024

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CLINICAL TRIALS DATA

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Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2×2 factorial design

DOXYVAC METHODS 1

INCLUSION:

- MSM age 18+.
- HIV negative participants in PrEP trial.
- History of bacterial STI in past 12 mo

EXCLUSION:

- Prior 4CMenB vaccination
- Current doxycycline treatment
- Doxycycline allergy/intolerance

Randomization Plan - 2x2 factorial design:

- 2:1 for doxy PEP
- 1:1 for 4CMen B vaccination - dosed at 0, 60 days

Molina Lancet ID 2024 Slide 21

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DOXYVAC METHODS 2

- FU at 2 mo, 3 mo and then every 3 months x 24 months total
- Three site screening for NG/CT NAAT (rectal, pharyngeal swab, urine) and syphilis serology.
- Sample size **n=720** to show HR 0.7 with vaccination
  - Power 85%, alpha 5%, LFU 18%. Assumed incident NG 52% at 18 months.
  - Assumed no effect of doxy PEP on vaccine efficacy.
  - Kaplan-Meier method with cox Ph test for interaction (P>0.1)
- **Co-primary outcomes:**
  - Risk of first GC episode starting one month after 2nd vaccine dose
  - Risk of first CT +/- syphilis episode after enrollment for doxy PEP

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RESULTS

PARTICIPANT CHARACTERISTICS

- Median age 40-41
- Median 10 partners in past 3 months
- IAI condom use 30%
- Most participants reported 2 STI in the past 12 months
  - **68% NG history**
- Incident STI at enrollment 20-23%
  - **13% NG**

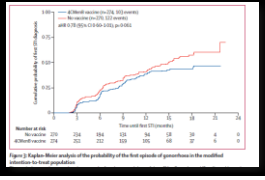


Figure 2: Kaplan-Meier analysis of the probability of the first episode of gonorrhoea in the modified intention-to-treat population

FINDINGS

- **aHR 0.78 (95 CI 0.6-1.0). P=0.061**
- 67% completed 12 mo follow up
- **Adverse Events**
  - 42% injection site reaction.
  - 6% asthenia
  - 3% HA
- Incident NG by site during FU:
  - 180 pharyngeal (58%)
  - 176 rectal (56%)
  - 35 urethral (11%)

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Mucosal Immunity Against Neisseria Gonorrhoeae After 4CMenB Vaccination

DMID IDCRC 19-0015

PI PHADKE
EMORY UNIVERSITY

N=40 4CMENB D1, 29
N=10 PLACEBO

PRIMARY OUTCOME: RECTAL MUCOSAL IGG (GMT) BY ELISA
OMV AG NG1291

D 1, 29, 43, 57, 181

Arm/Group Title	4CMenB	Placebo
Day 1		
Number Analyzed	12 participants	8 participants
Geometric Mean (95% Confidence Interval) | Unit of Measure: titer	0.07 (0.027 to 0.182)	0.072 (0.025 to 0.213)
Day 29		
Number Analyzed	16 participants	7 participants
*	0.089 (0.041 to 0.192)	0.057 (0.016 to 0.167)
Day 43		
Number Analyzed	23 participants	4 participants
*	0.078 (0.046 to 0.133)	0.047 (0.024 to 0.09)
Day 57		
Number Analyzed	24 participants	4 participants
*	0.135 (0.095 to 0.192)	0.062 (0.009 to 0.137)
Day 181		
Number Analyzed	23 participants	7 participants
*	0.162 (0.103 to 0.249)	0.055 (0.016 to 0.11)

CT.GOV: NCT04722003

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MAGI Study Update

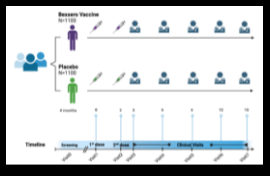
A Phase II randomized, observer-blind, placebo-controlled study, to assess efficacy of meningococcal Group B vaccine MenB+OMV NZ (Bexsero) in preventing gonococcal infection

DMID Protocol Number: 19-0004
Clinical Trials: NCT04350138

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MAGI STUDY DESIGN



- 1:1 randomization to Bexsero or placebo
- Phone call within 30 days of initial dose to assess for safety
- 5 in-clinic follow-up visits for safety, clinical, and laboratory assessments
- Target enrollment = 2,200 healthy men and women 18-50, to enroll to reach **202 participants** have experienced a least one urogenital or anorectal gonococcal infection

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MAGI STUDY OBJECTIVES

- **Primary:** To demonstrate efficacy of Bexsero in prevention of urogenital and/or anorectal gonococcal infection
  - **Secondary**:
    - To estimate efficacy of Bexsero in prevention of overall gonococcal infection and by anatomical site (urogenital, anorectal or pharyngeal)
    - To assess safety of Bexsero
  - **Exploratory**:
    - Ng strain type distribution and antimicrobial resistance (AMR) patterns
    - Measures of the immune response against Ng infection in participants with incident infection by SBA and other assays
    - Comparison of immune response to Ng and Nm

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MAGI OUTCOME MEASURES

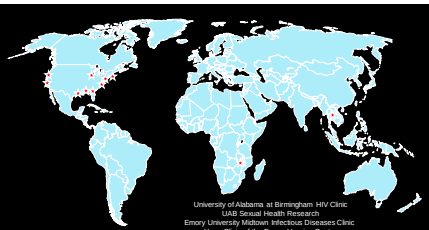
- PRIMARY: Number of participants in each treatment arm with diagnosis of urogenital or anorectal gonococcal infection confirmed by NAAT from 1 month after second vaccination with study product to study end (Day 451)

- SECONDARY:
  - Number of participants in each treatment arm with diagnosis of urogenital, anorectal, or pharyngeal gonococcal infection (overall and by individual site of infection) confirmed by NAAT from 1 month after second vaccination with study product to study end (Day 451)

  - Proportion of participants with at least one medically attended AE, AE leading to withdrawal from the study, SAE, or AESI

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MAGI STUDY SITES

University of Alabama at Birmingham HIV Clinic
UAB Sexual Health Research
Emory University Midtown Infectious Diseases Clinic
Hope Clinic of the Emory Vaccine Center
Louisiana State University
Royal Thai Army Clinical Research Center
Thai Red Cross AIDS Research Centre
Walter Reed Infectious Disease Clinic
UCLA Care Center
Bridge HIV, SFDPH
Harlem Prevention Center CRS
UPenn Prevention Research Unit
Ponce de Leon, CRS, Emory University
University of Illinois Chicago, Div. of Inf. Diseases
UNC Project, Lilongwe, Malawi

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SCREENING DATA AND PARTICIPANT CHARACTERISTICS*

Screening

3116 people screened

⇩

2606 people enrolled (84%)

Enrollment

- 75% male sex
- median age 31
- 8% Hispanic
- Race:
  - 45% Asian
  - 32% Black
  - 18% White
- >99% dose 1; 97% dose 2
- 56% completed study (day 451)

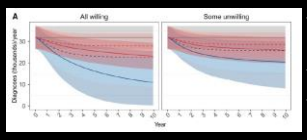
*As of 24 February 2025

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MODELING IMPACT OF PARTIALLY PROTECTIVE NG VACCINE

Data to support new UK Joint Committee on Vaccination and Immunization (JCVI) 4CMenB recommendations for MSM



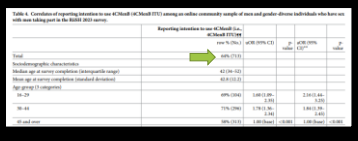
- Vaccination with NG diagnosis (red VoD) vs vaccination based on NG or risk (blue)
- Duration of protection 1.5 - 3 years
- Efficacy 26% and 40%

Nitikin JID 2024

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INTENTION TO RECEIVE 4CMENB AMONG MSM SURVEYED IN UK



Ogaz PLOS Global PH 2024

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4CMEN B PHASE 2-3 TRIALS

	Sponsor	Location	Objective	Primary endpoints	Population	Study period	Study
Phase 2 mucosal immunity trial	NIAID	USA	4CMenB systemic and mucosal immunogenicity against gonorrhoea	Rectal mucosal IgG concentrations against gonococcal OMV antigens	Men and women aged 18–45 years	November, 2021–March, 2023	NCT04222003
Phase 2 RCT	NIAID	USA and Thailand	4CMenB efficacy in preventing urogenital or anorectal gonococcal infection, or both	Number of pooled swabs diagnosed with urogenital or anorectal gonococcal infection post-second vaccination	Adults at risk of gonorrhoea aged 18–55 years (N=~2200)	December, 2020–September, 2023	NCT04201158
Observational, prospective cohort study (part B of II RT)	University of Adelaide	Northern Territory, Australia	4CMenB effect and efficacy against IMD and gonorrhoea	Notifications of gonorrhoea; effect of 4CMenB on carriage of pathogenic Nglab	Adolescents and young adults aged 14–19 years (N=2500)	March, 2021–December 2026	NCT04288856
Phase 3 RCT (MenGO)	Gold Coast Hospital	Queensland, Australia	4CMenB efficacy and immunogenicity against gonorrhoea	Number of gonorrhoea infections during study period; gonorrhoea-specific immune responses	MSM aged ≥18 years at risk of gonorrhoea (N=~720)	January, 2020–January, 2025	ACTRN12619300147(B)
Phase 3 RCT (GeGoVac)	Kirby Institute	New South Wales, Australia	Efficacy of 4CMenB in preventing gonorrhoea	Change in incidence of the first episode of gonorrhoea; comparison of incidence of gonorrhoea episodes during study period	GBM+; N=730, aged 18–40 years	July, 2021–February, 2025	NCT04415814
Phase 2 human challenge RCT	University of North Carolina, Chapel Hill	North Carolina, USA	4CMenB efficacy against experimental urethral N gonorrhoeae inoculation	Infectivity of N gonorrhoeae inoculum between 1 day and 10 days post inoculation	Men aged 19–35 years (N=~140)	April, 2022–February, 2028	NCT05256589
Phase 3 RCT	Chinese University of Hong Kong	Hong Kong	Efficacy of 4CMenB in preventing gonorrhoea	Comparison of gonorrhoea incidence between 4CMenB and placebo groups	MSM aged 18–59 years at risk of gonorrhoea (N=~720)	May, 2023–September, 2025	NCT05769764

Ladhani Lancet ID 2024 Slide 33

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KEY SCIENTIFIC QUESTIONS

Box 1: Next Steps in Development of a Gonococcal Vaccine

Ongoing trials of MenB vaccine in preventing gonorrhea can provide good infrastructure and opportunity for further research:

- Study of *Neisseria gonorrhoeae* Th17-driven responses and suppression of Th1- and Th2-driven responses
- Study of the immunogenetics of vaccinated individuals to understand and identify the immunodominant epitopes in the vaccine that explain the improved immune protection against gonococcal infection compared with naturally infected individuals
- Immune evasion in vaccinated individuals who acquire gonococcal infection
- Identification of correlates of protection

Confirm that the immunosuppressive pathways identified in mice are repeated in humans

Investigate Th1-driven responses induced by new vaccine candidates

Evaluate novel adjuvants and delivery systems to optimize mucosal responses to candidate vaccines

Adapt multiorgan cultures to combine primary human epithelial and immune cells to study human immune responses during infection

Further investigate the pathogenesis of *N gonorrhoeae* in the absence and presence of *Chlamydia trachomatis*

Garcia JID 2024 Slide 34

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ON BEHALF OF THE MAGI TEAM, STAY TUNED



- Eric Garges
- Shay Lovette
- FHI-360
- EMMES
- GSK
- Ned Hook
- Lisa Forte
- Quique Mejia-Galvis
- Letha Healey
- Peter Wolff
- Carolyn Deal
- DSMB Committee

Questions

NIH National Institute of Allergy and Infectious Diseases

Funding:75N93019F00131
STI Clinical Trials Group

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

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CHLAMYDIA VACCINES: PHASE 1



OXFORD FEMS

Pathogens and Disease, 2024, 82, ftae017

Advance access publication date: 23 July 2024

Minireview

Advances in vaccine development for *Chlamydia trachomatis*

Taylor R. Poston

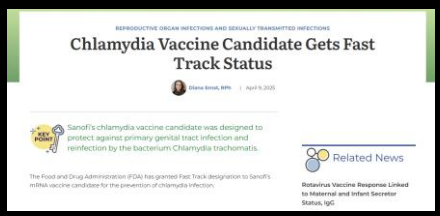
Abstract

Chlamydia trachomatis is the most prevalent bacterial sexually transmitted infection globally. Antibiotic treatment is highly effective, but infection is often asymptomatic resulting in most individuals going undetected and untreated. This untreated infection can ascend to cause pelvic inflammatory disease, infertility, ectopic pregnancy, and chronic pelvic pain. Despite these severe outcomes, screening and treatment programs have failed to control this epidemic and demonstrate the need for an efficacious vaccine to prevent transmission and disease. Animal models and human epidemiological data reveal that natural immunity can provide partial or short-lived sterilizing immunity. These data further demonstrate the importance of eliciting interferon gamma (IFN-γ)-producing cluster of differentiation 4 (CD4) T cells (Th1 and Th17 cells) that can likely synergize with antibody-mediated opsonophagocytosis to provide optimal protection. These studies have guided preclinical maternal vaccine design for decades and the first Phase 1 clinical trials have recently been completed. Recent advances have led to improvements in vaccine platforms and clinically safe adjuvants that help induce protective T cells. This review discusses animal models, correlates of immunity, antigen and adjuvant selection, and future clinical testing for *Chlamydia* vaccine development.

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CT VACCINE: LATEST NEWS



REPRODUCTIVE ORGAN INFECTIONS AND SEXUALLY TRANSMITTED INFECTIONS

Chlamydia Vaccine Candidate Gets Fast Track Status

Diana Ernst, MPH | April 9, 2025

KEY POINT

Sanofi's chlamydia vaccine candidate was designed to protect against primary genital tract infection and reinfection by the bacterium Chlamydia trachomatis.

The Food and Drug Administration (FDA) has granted Fast Track designation to Sanofi's mRNA vaccine candidate for the prevention of chlamydia infection.

Related News

Rotavirus Vaccine Response Linked to Maternal and Infant Secretor Status, IgG

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SYPHILIS VACCINES: CHALLENGES TO VACCINE DEVELOPMENT

- *T pallidum* excels at immune evasion and antigenic variability
- Rabbit model – *Treponema paraluiscuniculi*
  - Ideal model would recapitulate all human stages and congenital syphilis
- No known correlate of immunity in humans
- More to learn about pathogenesis of fetal infection
- Vaccine induction of full protection before primary disease and wide dissemination
- Broad protection against diverse *T pallidum* strains
- Induction of immunity in all hosts including pregnant women and people living with HIV



Lukehart Vaccine 2014; Cameron STD 2018

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RATIONAL VACCINE DESIGN:

IDENTIFYING *T PALLIDUM* OUTER MEMBRANE PROTEIN ANTIGENS VIA BIOINFORMATICS

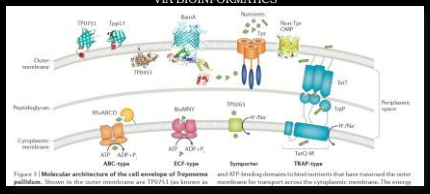


Figure 1 | **Molecular architecture of the cell envelope of Treponema pallidum.** Shown in the outer membrane are TP0751 (as known as ... and ATP-binding domains to bind nutrients that have traversed the outer membrane for transport across the cytoplasmic membrane. The energy

Peeling, Nat Rev 2017

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CONCLUSIONS

- CT is the most common reportable STI in the US.
  - 1.6M cases reported to CDC in 2023.
- CDC treatment guidelines in 2021 updated recommendations to doxycycline 100 mg po bid x 7d
- Recent ecologic and lab data suggesting 4CMenB cross protection have led to enthusiasm for vaccine prevention of gonorrhea
  - Several phase I-III 4CMenB and other NG vaccine clinical trials are underway with results expected 2024-2026.
  - Future trials to include more adolescents and young adults, pregnant women, and people with HIV who are at highest risk of NG acquisition.
- CT and syphilis vaccines are in early stages with promising recent developments

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Q and A Session

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