Overview of NIAID's STI Research Portfolio

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Division of Microbiology and Infectious Diseases

NIAID, NIH, DHHS

National Institute of Allergy and Infectious Diseases

Presentation Overview

- Overview of NIAID STI Research Program
- Addressing antimicrobial resistance and diagnostics
- Accelerating STI vaccine development
- Advancing STI therapeutic options

U.S. Department of Health and Human Services

CDC

- Surveillance and Detection
- Train Local Response Teams
- Maintain Vaccine/Antimicrobial Stockpiles

NIH

- Conduct Basic Research
- Develop Medical Interventions
- Develop Research Infrastructure

FDA

- Regulatory Approval
  - Vaccines
  - Therapeutics
  - Diagnostics

Slide Source: A. S. Fauci

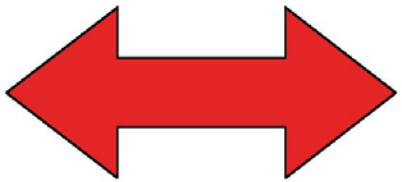
The National Institute of Allergy and Infectious Diseases (NIAID)

Conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases

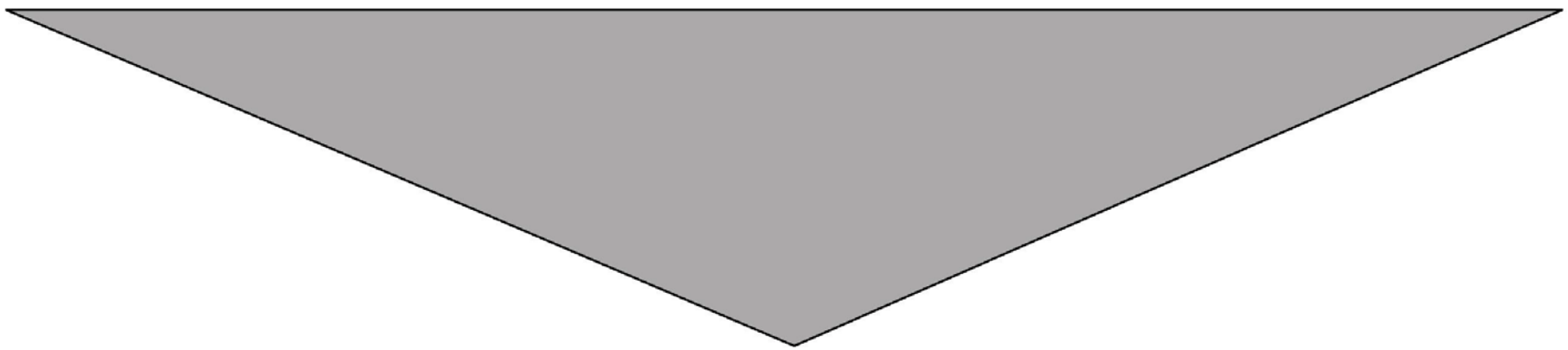
NIH National Institute of Allergy and Infectious Diseases

NIAID Research: A Dual Mandate

Maintain and "grow" a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases

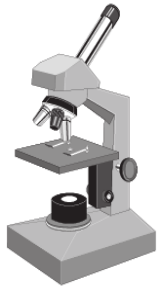


Respond rapidly to new and emerging disease threats



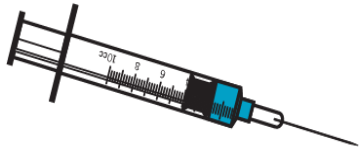
New/Improved Interventions

Slide source: AS Fauci



Diagnostics

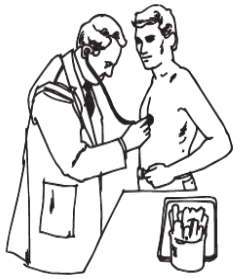
Therapeutics



Vaccines

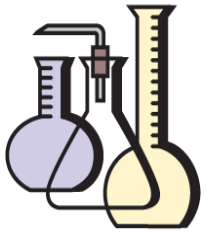
Research Resources

NIAID Research



Clinical Research

Basic Research



Slide source: AS Fauci

Published online
September 9, 2019

The Journal of Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

Refocusing Research on Sexually Transmitted Infections

RW Eisinger, E Erbelding, AS Fauci

- A refocused, dedicated, and intensive biomedical research program is needed that targets the development of innovative diagnostics, safe and effective vaccines, and new and improved therapeutics for STIs.

Slide source: AS Fauci

STI Research Program Scope

Pathogens

- *Neisseria gonorrhea**
- *Chlamydia trachomatis**
- *Treponema pallidum**
- Human papilloma virus*
- Herpes simplex virus*
- *Trichomonas vaginalis*
- Hepatitis C virus
- *Ureaplasma urealyticum*
- *Mycoplasma genitalum*

*Top funded pathogens

Multi-etiologic infections

- Bacterial vaginosis
- Non-gonoccocal urethritis
- Pelvic inflammatory disease
- Intra-amniotic infection

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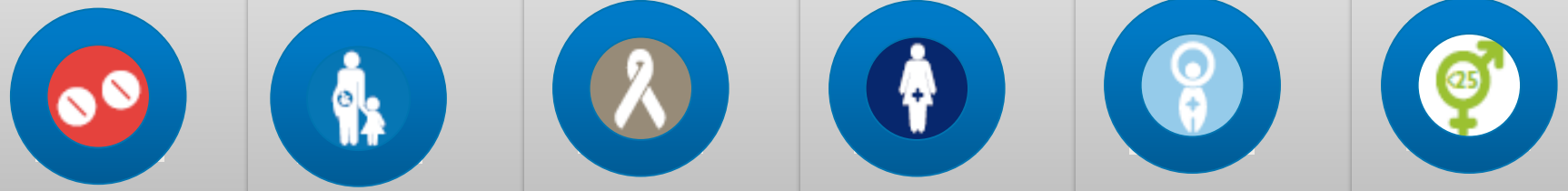
NIAID STI Research Program Goals

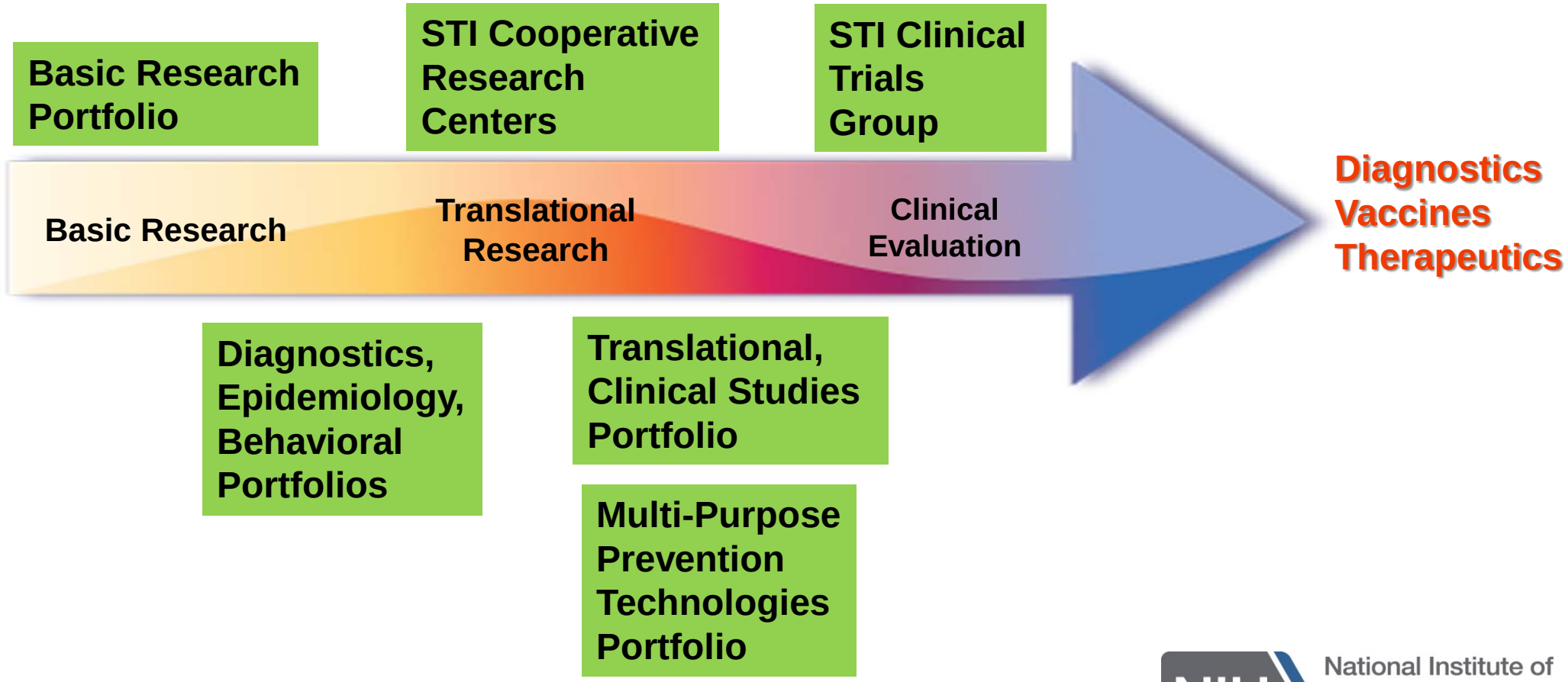
Effectively addressing STIs for the following outcomes:

- Combating antimicrobial resistance
- Eliminating adverse neonatal outcomes
- Reducing HIV transmission
- Preventing cancer
- Decreasing burden of infertility
- Supporting health of young people



Source: IPPF

Activities Throughout the Product Development Pathway



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NIAID STI Research Program Prioritization Principles

- Maintain a strong basic research base and product pipeline
- Support investigational products (e.g., vaccines, diagnostics, drugs, biotherapeutics) which fill scientific gaps for critical diseases
- Focus on critical pathway for licensure wherever possible
- Maintain strong collaborative partnerships with NIH Institutes and Centers, other government partners (CDC, WRAIR, UHSUS), WHO, academic institutions, and private foundations and industries

wellcome trust

USU Uniformed Services University

USAID FROM THE AMERICAN PEOPLE

World Health Organization

WRAIR

American Sexually Transmitted Diseases Association

CDC

Bill & Melinda Gates foundation

asha American Sexual Health Association

IDSA Infectious Diseases Society of America

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ADDRESSING ANTIMICROBIAL RESISTANCE AND DIAGNOSTICS

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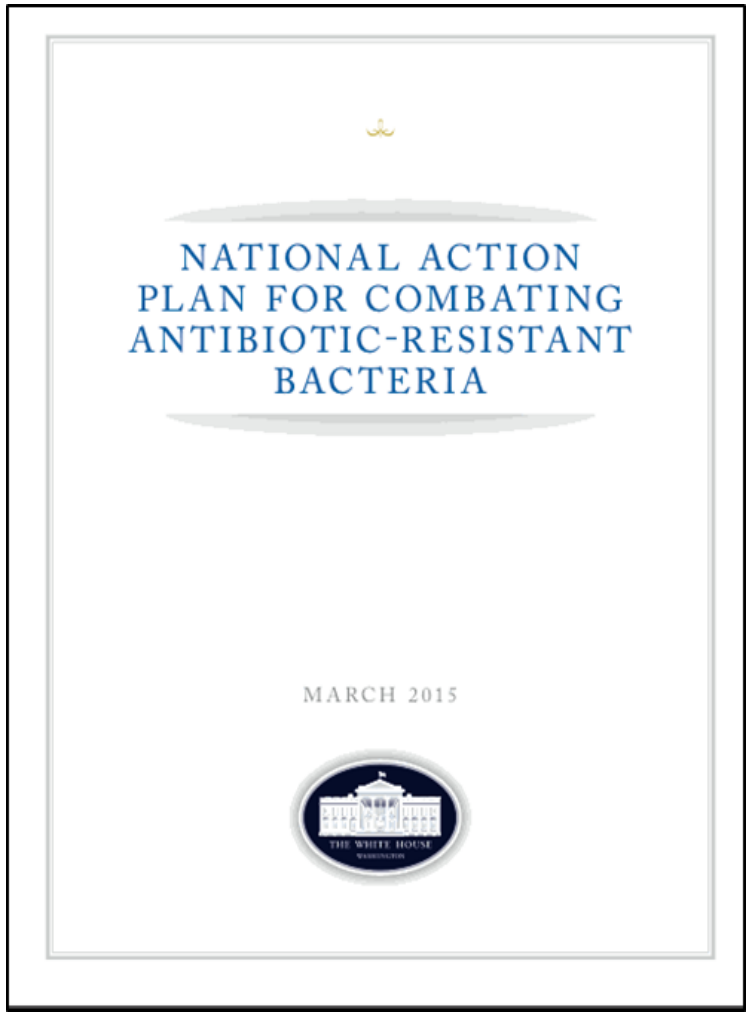
National Action Plan: 5 Goals



- Stewardship
- Surveillance (Sequencing)
- Diagnostics
- **Research**
- International Collaboration

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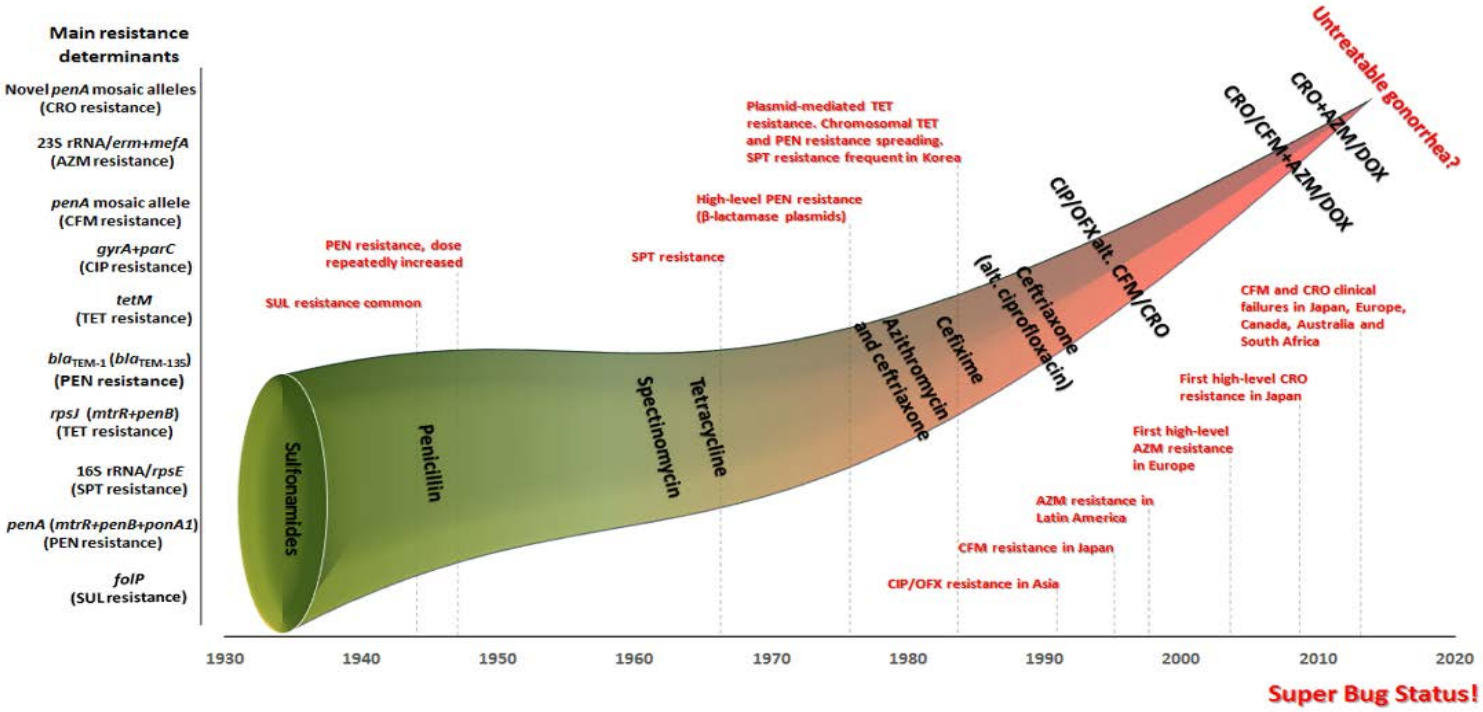
Identification of Pathways to Resistance



- Mechanisms of gonococcal resistance (P.I. Yonatan Grad)
  - Used population genomics and transcriptional analysis to demonstrate that gene transfer from multiple Neisseria species has contributed to gonococcal resistance
- Genetics of resistance (P.I. William Shafer)
  - 2 component MisR mutations lead to increased resistance
  - Cost to in vivo fitness by resistance mutations (mtrR, gyrA, and parC)

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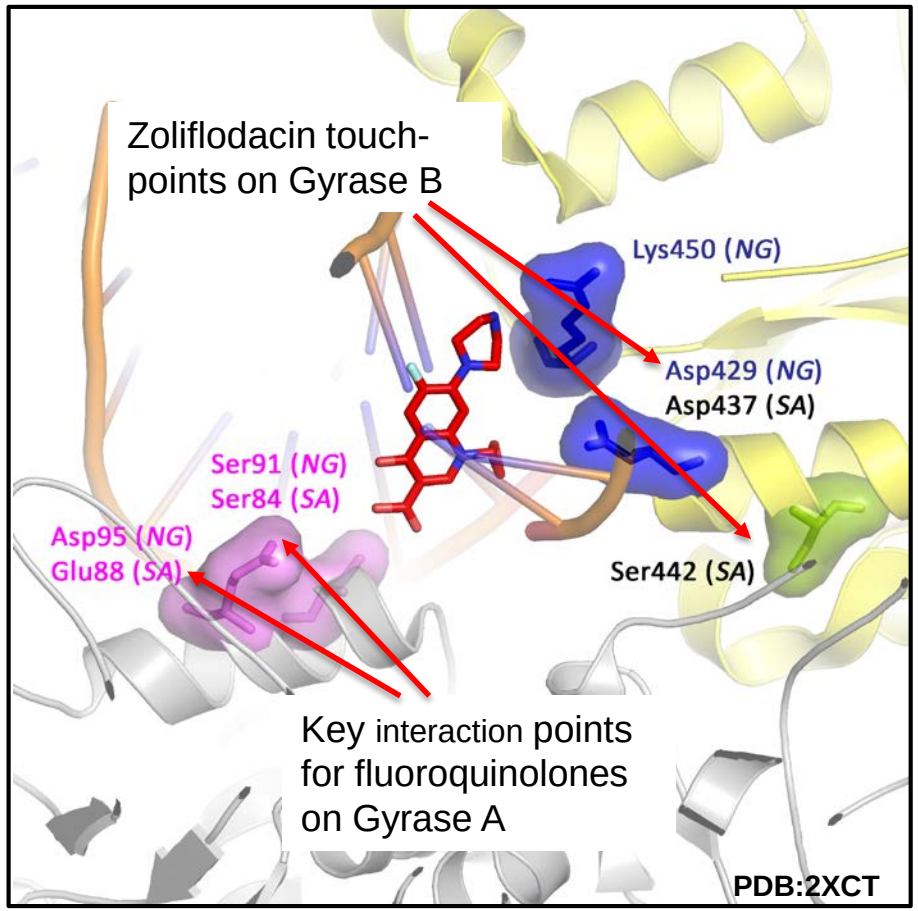
Public Private Partnership

- Zoliflodacin: A “first-in-class” antibiotic for treatment of uncomplicated gonorrhoea
- Non-quinolone topoisomerase
- Orally delivered
- Developer: Entasis
- QIDP* and Fast Track status granted by FDA
- Phase II trial of zoliflodacin
  - Single-dose oral zoliflodacin for treatment of uncomplicated urogenital gonorrhea
  - Safe and effective compared to ceftriaxone (98% at 2gm, 100% at 3 gm)



* Qualified Infectious Disease Product

Basarab G *Nature Scientific Reports* 2015. https://www.nature.com/articles/srep11827

Taylor S *N Eng J Med* 2018. https://www.nejm.org/doi/full/10.1056/NEJMoa1706988

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Clinical Pathway for Development of Alternative Treatment for Gonorrhea: Zoliflodacin

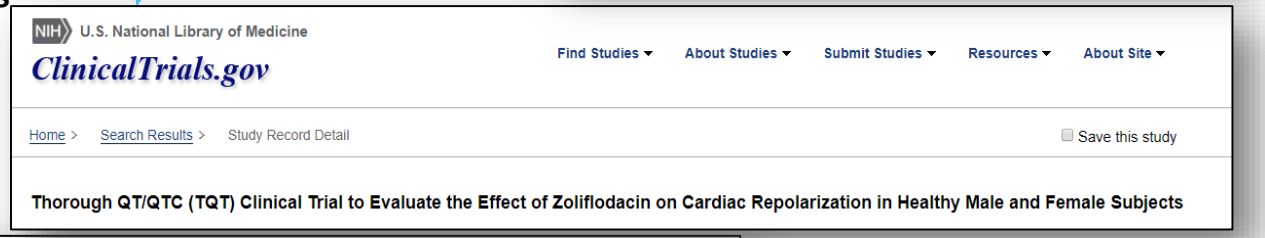
AZD0914 awarded fast track status by FDA

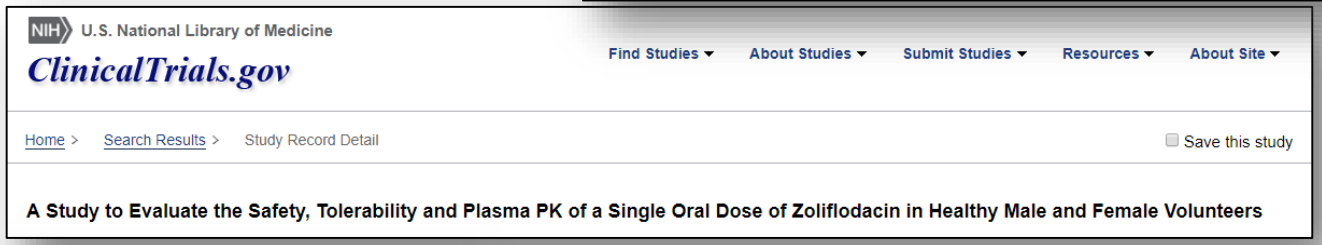
Phase II trial conducted by DMID STI Clinical Trials Group

NIAID supported trial to evaluate PK, safety and tolerability of modified formulation

NIAID supported required safety study to evaluate drug's potential to cause cardiac arrhythmia

Handoff to GARDP, who is expected to begin a Phase III trial in Netherlands, South Africa, Thailand, and U.S.





Antibiotic Sparing Strategy: Clinical Validation of test for Ciprofloxacin-susceptible *Neisseria gonorrhoeae*

- *N. gonorrhoeae* has rapidly developed resistance to most classes of antibiotics
- Wild-type gyrase A genotype of NG reliably predicts susceptibility to ciprofloxacin > 98%
  - Potential to identify infections that could be treated with older, oral antibiotic, ciprofloxacin
  - Facilitates antibiotic-sparing approach to treatment of gonorrhea infections
- STI Clinical Trial Group validated PCR assay of gyrase A genotype at 4 laboratories (UCLA, San Francisco, Philadelphia, and LSU)
- Status: enrollment complete, manuscript in development

ClinicalTrials.gov Identifier: NCT02961751

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FDA U.S. FOOD & DRUG ADMINISTRATION

FDA NEWS RELEASE

FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea

FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea

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For Immediate Release: May 23, 2019

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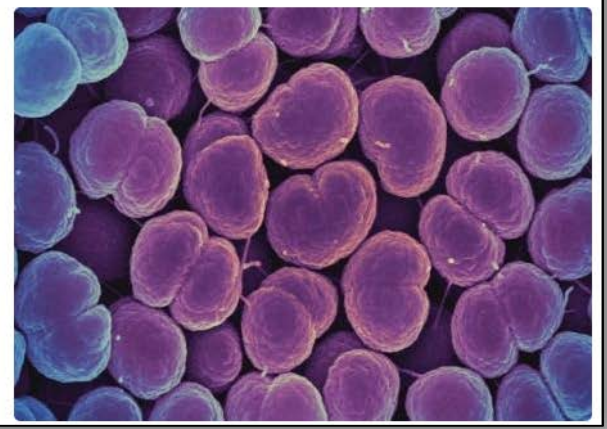
News & Events > Newsroom > Blog

New Study Supports Expanded Testing for Gonorrhea and Chlamydia

NIAID Now | July 01, 2019

A new study from the NIAID-funded Antibacterial Resistance Leadership Group (ARLG) found that two diagnostic tests accurately detected gonorrhea and chlamydia in samples from the pharynx (throat) and rectum. The findings informed the Food and Drug Administration's (FDA) recent decision to approve the diagnostics for use in these extragenital sites. Now, the tests may be more readily available to clinics across the country. The findings were presented at ASM Microbe in San Francisco on June 23, 2019, by Sarah Doernberg, M.D., associate professor in the Division of Infectious Diseases at the University of California, San Francisco.



Doernberg SB, Komarow L, *et al.,* ASM Microbe 2019. (manuscript in preparation)

The Binx io Diagnostic Platform

- The first FDA 510(k) cleared, 30-minute, genetic test for *Chlamydia trachomatis* and *Neisseria gonorrhoea* in women.
- Onsite testing enables diagnosis and treatment in a single visit. This new paradigm offers the potential to improve health outcomes by increasing treatment compliance and reducing transmission and the potential serious consequences of untreated infections.
- NIAID and NIBIB co-funded JHU's Point-of-Care Technology Research Network (POCTRN), which developed the technology for this product.

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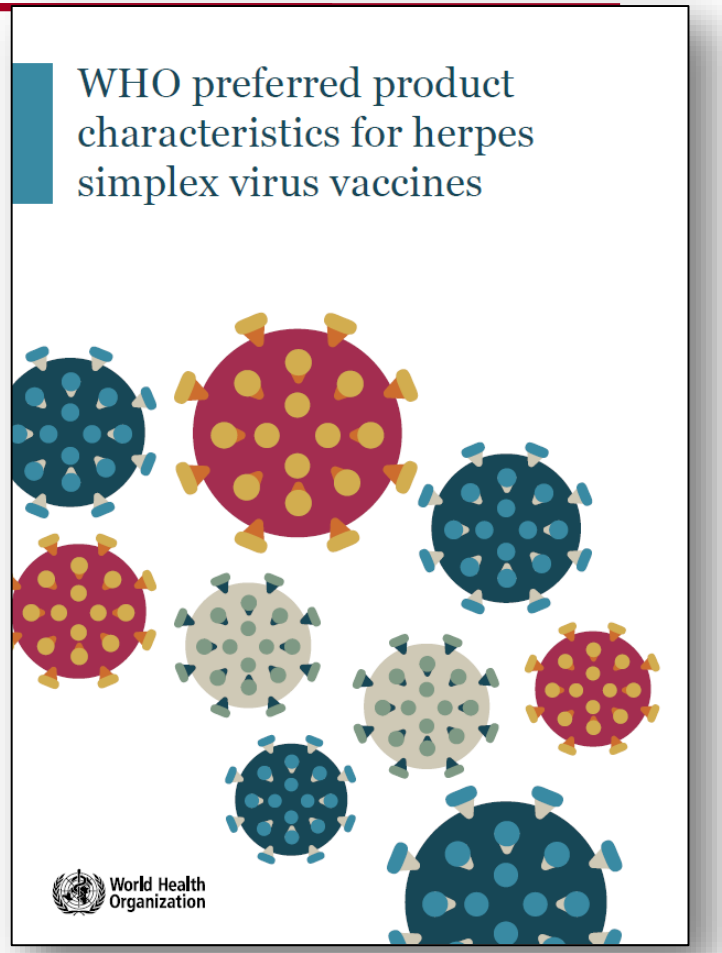
STI VACCINE DEVELOPMENT

National Institute of Allergy and Infectious Diseases

STI Vaccines - A Needed Intervention

- **Rationale:**
  - Despite diagnostics and treatment, epidemics of these diseases continue
  - Growing concern about antibiotic resistant *N. gonorrhoeae*
  - Limited commercial development (except for HBV & HPV)
- **WHO & NIAID developed an STI Vaccine Roadmap**
  - Collaboration with CDC & multiple international partners
  - Outlines need, development status, & future prospects for STI vaccines (HSV, CT, GC, TV, syphilis)
  - https://doi.org/10.1016/j.vaccine.2014.01.053
- **WHO Product Development Vaccine Advisory Committee**
  - HSV, CT, & GC highlighted at meetings
  - Published Preferred Product Characteristics (PPC) for HSV vaccines (https://www.who.int/reproductivehealth/publications/HSV-Vaccine-PPCs/en/)
  - Ongoing development of PPC for GC vaccines



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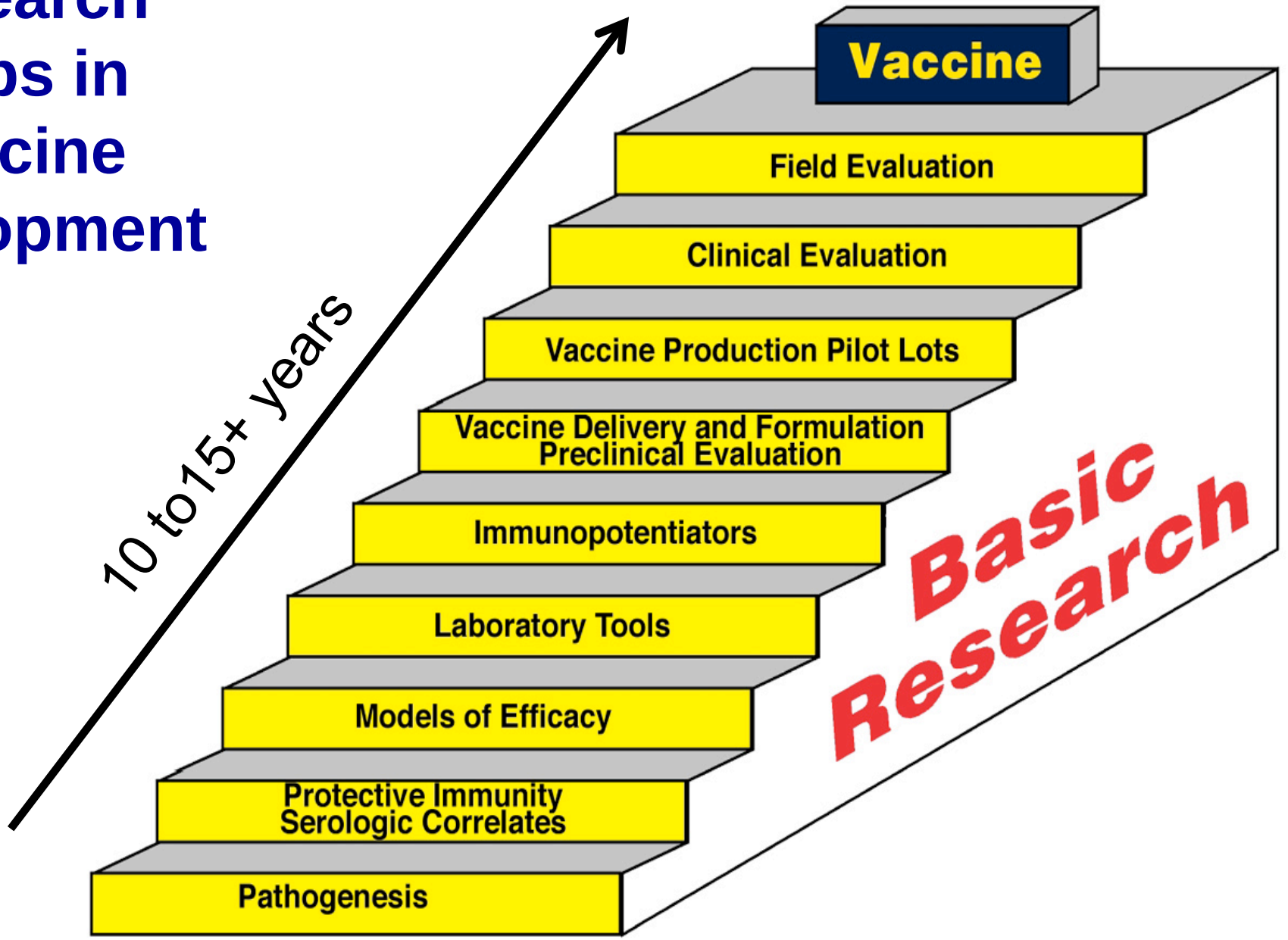
Research Steps in Vaccine Development



Slide source: AS Fauci

Basic Research & Pre-clinical HSV Vaccine Development

- Subunit vaccine based on glycoprotein D of HSV-2 (gD2), gC2 and gE2
  - University of Pennsylvania (PI: Friedman)
  - R01
- Live attenuated HSV-2ΔgD vaccine
  - Albert Einstein College of Medicine (PI: Jacobs)
  - R01
- Recombinant vaccine based on gD2/gB2 in proprietary nanoemulsion for intranasal administration
  - BlueWillow Biologics (formally NanoBio , Inc.) (PI: Fattom)
  - SBIR
- DNA vaccine followed by intranasal administration of recombinant gD2
  - Biomedical Research Models, Inc. (PI: Yang)
  - gD2-based heterologous vaccine strategy
  - SBIR

Image source: CDC

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Public Private Partnership to Test HSV Vaccine

Image source: NIAID Flickr

- Phase I randomized, double-blind, placebo-controlled trial of 3 doses of HSV-2 replication defective virus *dl*5-29
  - Developed by David Knipe at Harvard, produced by Sanofi Pasteur
  - Trial PI: Jeff Cohen, NIAID/DIR
  - Enrolled 60 subjects in 3 arms: HSV1- /HSV2- , HSV1+ /HSV2+ , and HSV1+ /HSV2-
  - Primary endpoint: Safety
  - Secondary endpoint: HSV-2 specific immunogenicity
- Conclusion: HSV529 vaccine was safe and elicited neutralizing antibody and modest CD4+ T-cell responses in HSV seronegative vaccinees
- Next steps: Sanofi pursuing further advancement of HSV vaccine development

https://www.ncbi.nlm.nih.gov/pubmed/31058977, ClinicalTrials.gov identifier: NCT01915212

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Gonorrhea vaccine candidates under development

- **Peptide vaccines**
  - 2C7 LOS epitope (peptide mimetic)
  - PorB and MtrE peptide/virus-like particles

- **Outer membrane vesicle vaccines**
  - **Meningococcal (*Nm*) OMVs**
    - 4CMenB (Bexsero®)
    - MC58ΔABR (FDA/CBER)
  - **Gonococcal (*Ng*) OMVs**
    - With microencapsulated IL-17

Reviewed in Rice PA, Shafer WM, Ram S, Jerse AE. *Annu Rev Microbiol*. 2017

Matthias et al, IPNC 2018 abstract #0113

Connolly et al, IPNC 2018 abstract #0110

- **Purified Protein Subunit Vaccines**
  - **Antigens involved in physiology or metabolism**
    - Transferrin receptors (TbpA,B)
    - Methionine transporter (MetQ) (Seib, Griffith U)
    - MsrA/B – repairs oxidatively damaged proteins (M. Jennings, Griffith U)
  - **Antigens involved in evasion of innate effectors**
    - MtrE (outer membrane channel of 2 active efflux pumps)
    - SliC (lysozyme inhibitor) (OSU)
    - Acp (lysozyme inhibitor) (U of Southampton (M. Christodoulides)
  - **Antigens involved in bacterial structure; identified by proteomics**
    - BamA (Oregon State U)

Slide courtesy of Ann Jerse, USU

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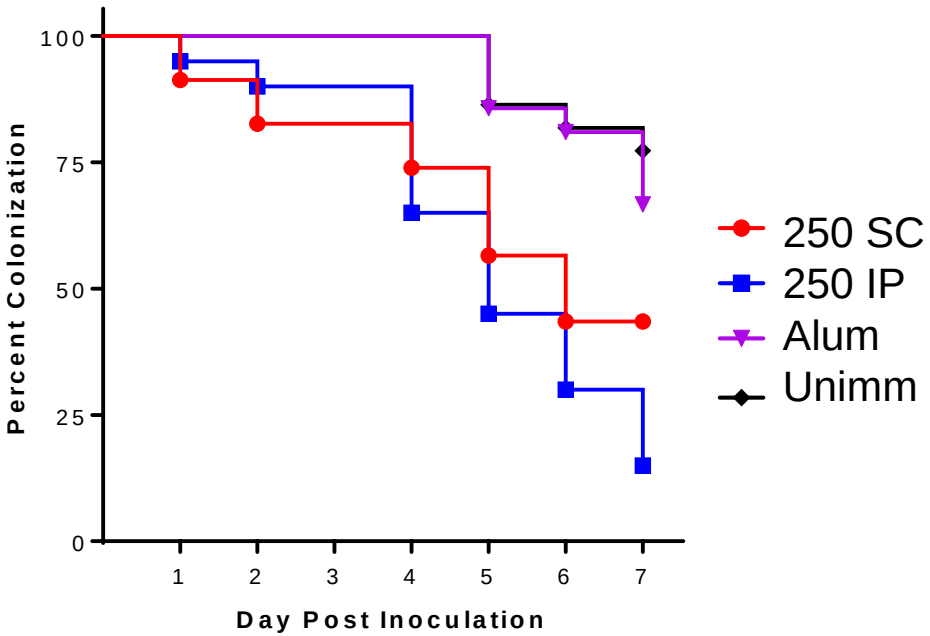
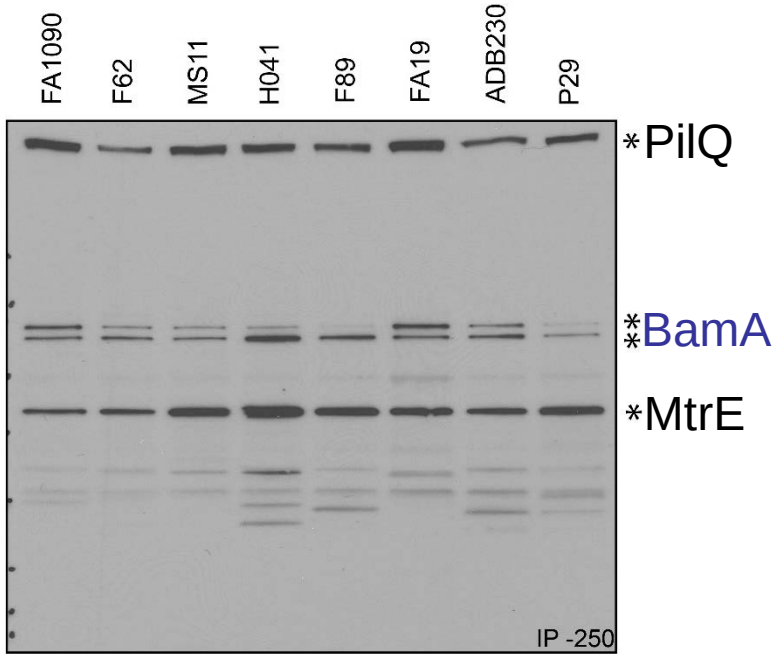
Gonococcal Vaccine: Proof of Concept Studies

- In the gonococcal mouse model, Bexsero immunization
  - Reduced colonization
  - Immune serum recognized GC OMV proteins





Connolly KL, Leduc I, *et al.,* IPNC 2017 (manuscript in preparation)
Slide courtesy of Ann Jerse, USU

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Proof of Concept
Gonococcal Vaccine

- Effectiveness of a group B outer membrane vesicle (OMV) meningococcal vaccine against gonorrhea in New Zealand: a retrospective case-control study
  - Outer membrane vesicle for the epidemic strain in New Zealand
  - Vaccinated people were about one third less likely to contract gonorrhea as compared to chlamydia
- US FDA licensed rMenB+OMV NZ vaccine in 2015 to prevent Group B meningococcal infection (Bexsero, Novartis/GSK)
- NIAID exploring opportunities for clinical trials to prospectively evaluate efficacy of OMV vaccines in prevention of gonorrhea

Petousis-Harris H *Lancet* 2017. https://www.ncbi.nlm.nih.gov/pubmed/28705462.

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Sexually Transmitted Infections Cooperative Research Centers (STICRCs)

- University of Connecticut
  - Structural biology approaches to investigate surface-exposed proteins within the outer membrane of *T. pallidum* as vaccine antigens
- Georgia State University
  - Using vaccination to interfere with the acquisition of metal ions by *Neisseria gonorrhoeae*
- Henry M. Jackson Foundation
  - Outer membrane protein-based vaccine design for *N. gonorrhoeae*; integrating human immune responses to 4CMenB, the outer membrane vesicle-based meningococcal vaccine
- University of North Carolina
  - Vaccine development through the identification of protective antigens from women at high risk for *Chlamydia trachomatis* infection
- University of Washington
  - Targeting *T. pallidum* attachment, invasion and dissemination factors as vaccine antigens
- Lawrence Livermore National Laboratory
  - MOMP and other outer membrane proteins as a vaccine for *C. trachomatis* infection


NIH Awards Will Advance Development of Vaccines for Sexually Transmitted Infections

NIAID Announces Four New Cooperative Research Centers

May 9, 2019

Colorized scanning electron micrograph of *Neisseria gonorrhoeae* bacteria, which causes gonorrhea

Credit: NIAID

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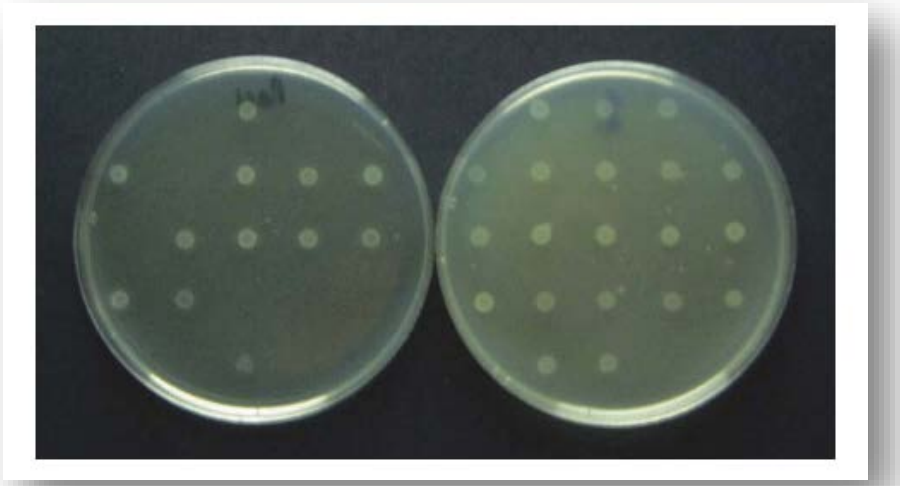
ADVANCING THERAPEUTIC OPTIONS

MIC Testing

- As part of NIAID's Preclinical Services, the minimal inhibitory concentration (MIC) assay involves exposing the bacterial pathogen to increasing concentrations of a candidate antibiotic and determining the minimal concentration required to clear the infection.
- Used to judge the potential of the candidate to treat the infections, and helps determine a dose range needed for future animal and/or human studies.
- Candidate drugs are tested against a panel of 96 *N. gonorrhoeae* isolates.
- So far, 14 compounds have been tested for 9 companies.



Agar dilution plates

Photo credit:
www.sciencedirect.com.

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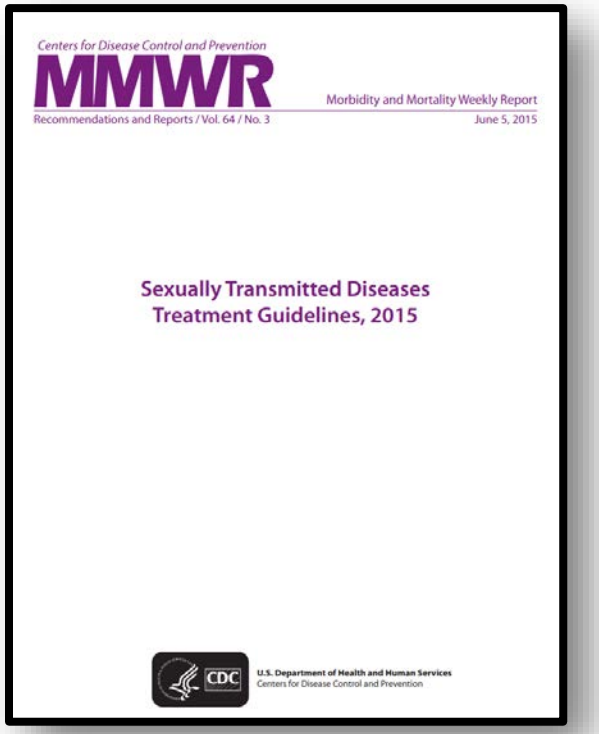
Clinical Trials to Provide Options for Treatment of Bacterial Vaginosis

- Challenge: high treatment failure rate for BV
- LACTIN-V: Osel, Inc., live bio-therapeutic
  - *Lactobacillus crispatus* powder applied via modified gel applicator
  - Prevention of BV reinfection after metronidazole treatment
  - Phase 2b trial to inform their Phase 3
  - Enrollment complete, analysis is underway, results due Jan 2020
- TOL-463: Toltec Pharmaceuticals, boric acid/EDTA
  - CDC Guidelines allow use of boric acid in BV treatment, but no commercially available product
  - Ongoing Phase 2 trial with vaginal insert formulation
    - Study PI: Dr. Jeanne Marrazzo (UAB)
    - Site PI: Dr. Harold Wiesenfeld (Pitt)
  - Enrollment is underway

Generation of evidence for CDC Treatment Guideline Development



- Rectal chlamydia: Clinicians have reported improved efficacy of doxycycline over azithromycin for treatment
  - Phase 4, randomized, double-blind, placebo-controlled trial of azithromycin vs. doxycycline for treatment of rectal chlamydia in MSM (enrollment ongoing)
- Mycoplasma genitalium (MG): Study evaluated the frequency of MG among men with urethritis, prevalence of mutations associated with antimicrobial resistance of MG, and post-treatment symptom persistence
- Syphilis: Recent clinical trial demonstrated that doxycycline post exposure prophylaxis (PEP) reduced syphilis rates in HIV negative MSM on PrEP (Ipergay Study, France)
  - Randomized, open-label trial of 380 HIV+ and 380 HIV- (PrEP users) to evaluate effectiveness, tolerability, acceptability, and adherence to doxycycline PEP, and to monitor effect of doxycycline PEP on emergence of AR *N. gonorrhoeae*, *S. aureus,* and other *Neisseria* spp.

Supporting National Efforts to Eliminate Syphilis

- Basic research advances
  - "Factors affecting long-term in vitro culture of *T. pallidum*" (P.I. Steven Norris)
  - Developed a method for long-term in-vitro culture of *T. pallidum* where bacterium remains viable, multiplies, and remains infectious
  - Potential to accelerate future research

Diagnostics
Vaccines
Therapeutics

Edmondson D, *mBio,* 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020297/

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Ongoing Public Health Needs: New Interventions for the Future!

Thank You

DMID/ESTIB/STD Section Team
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