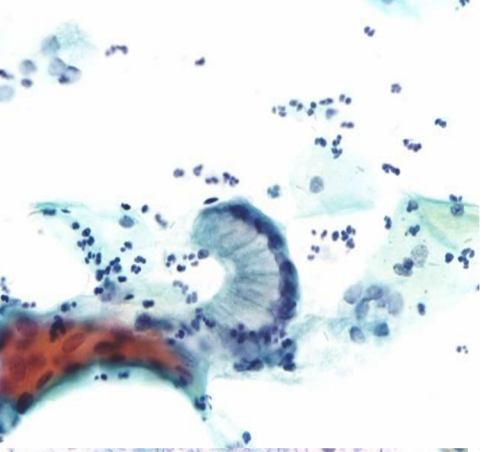
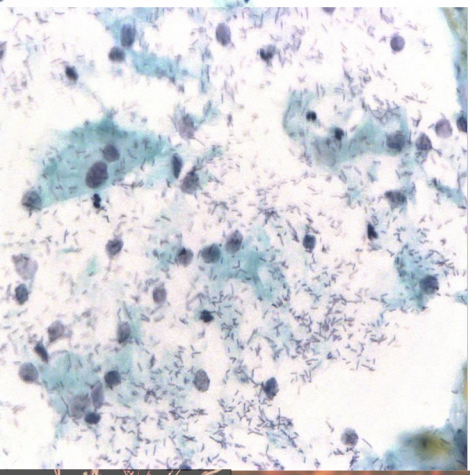
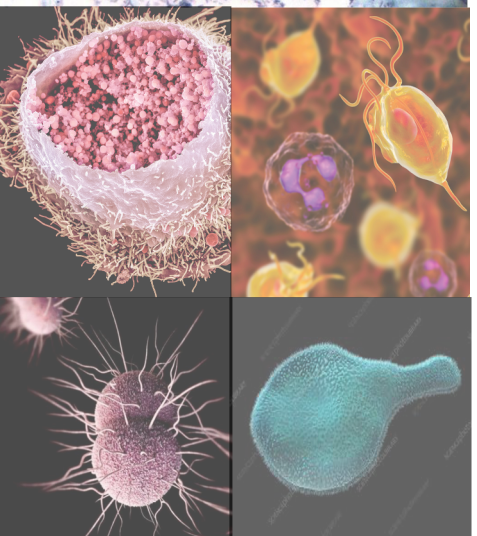






Chlamydia Vaccine Initiative
What, Who, How?

Toni Darville, MD

Feb 1, 2022

UNC MD-PhD Mini Medical School


Chlamydia
Is Not A
Flower.

Outline

What is *Chlamydia*?

What diseases does it cause?

Can we make a preventative vaccine?

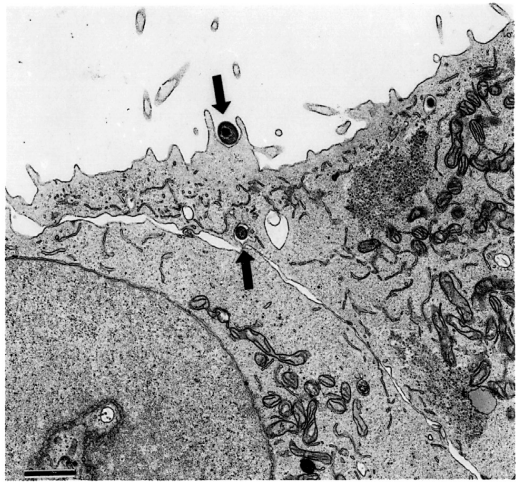
- What immune responses combat Chlamydia infection?
- Can we induce them with a vaccine?
- How would we test the vaccine?

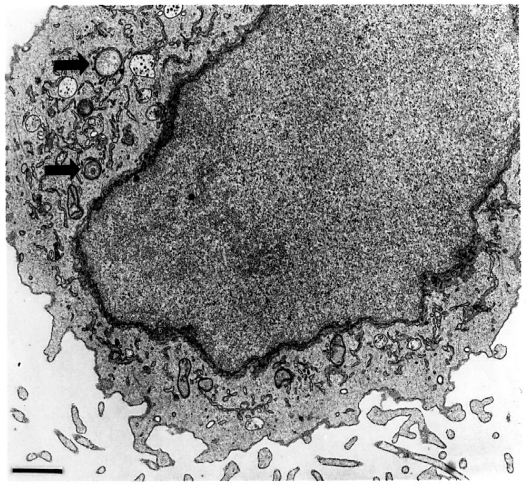
Chlamydia Bacteria Exist in Two Forms

Infectious elementary body -EB

Conversion to reticulate body - RB

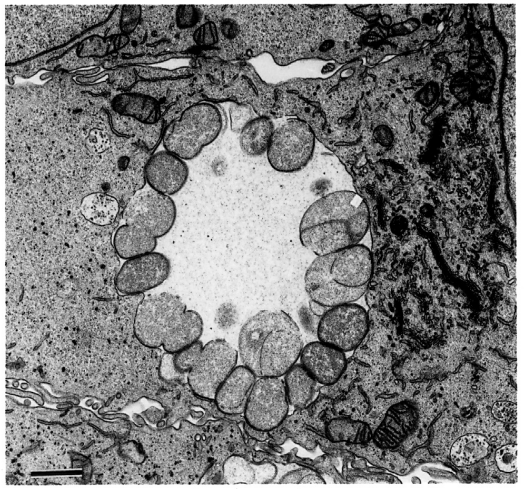
0 Hr

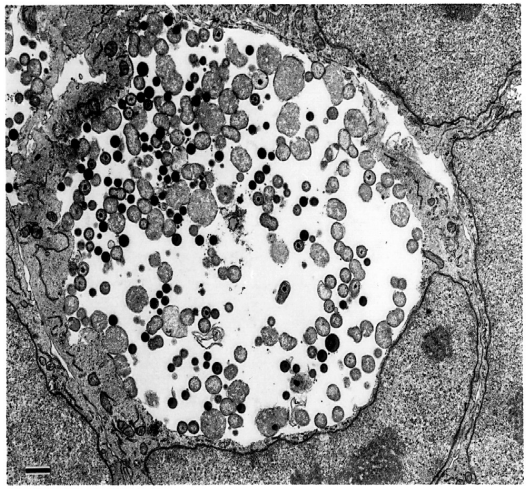




2 Hr

18 Hr

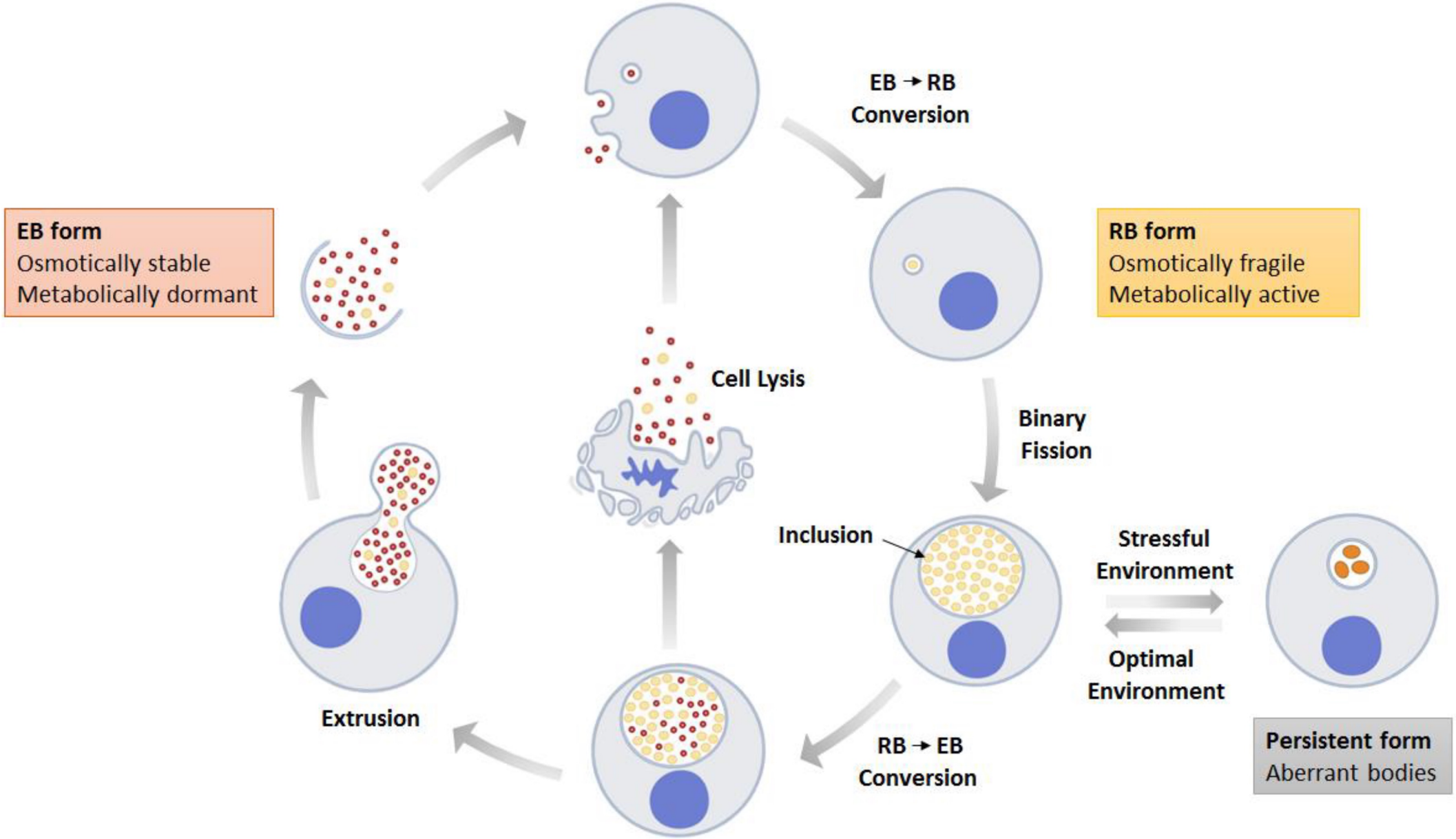




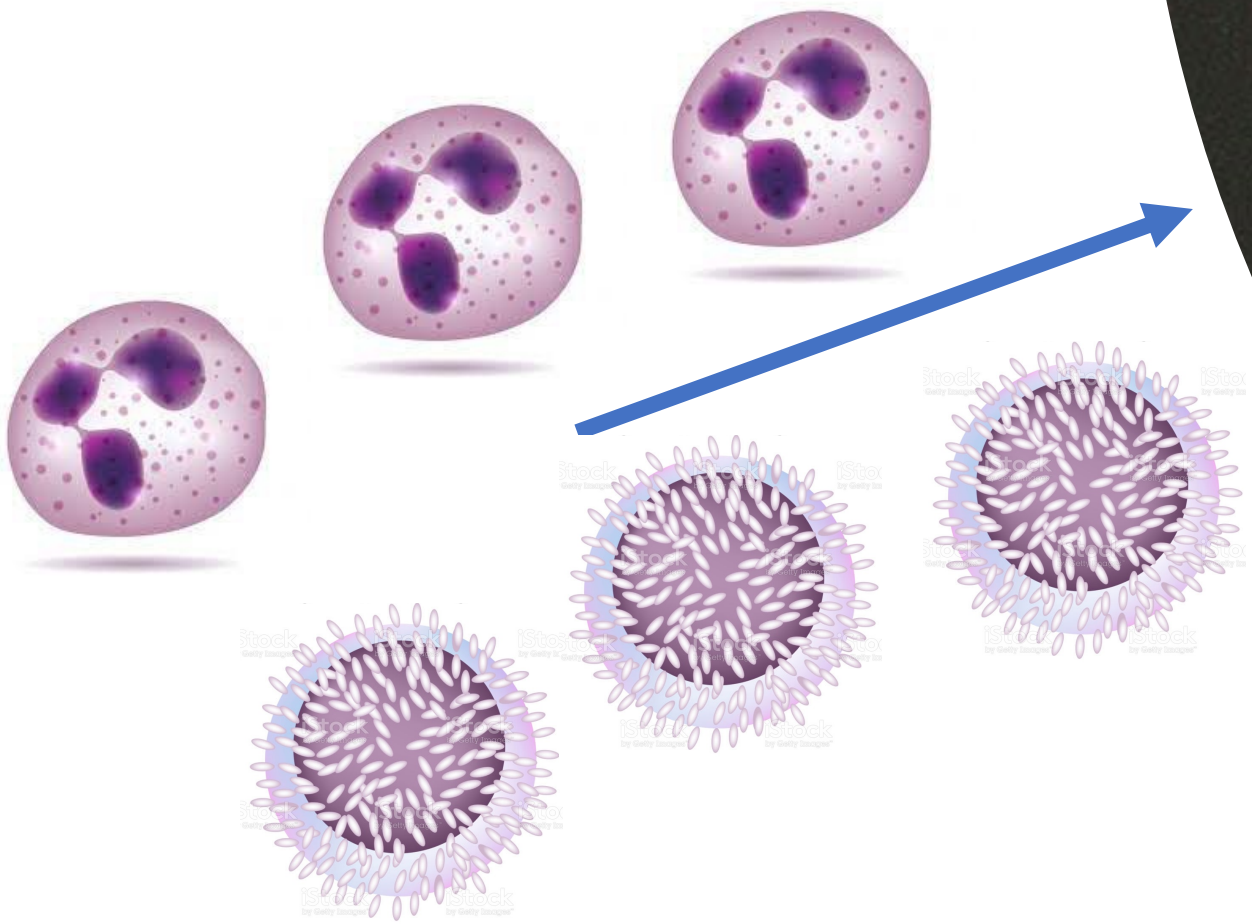
36 Hr

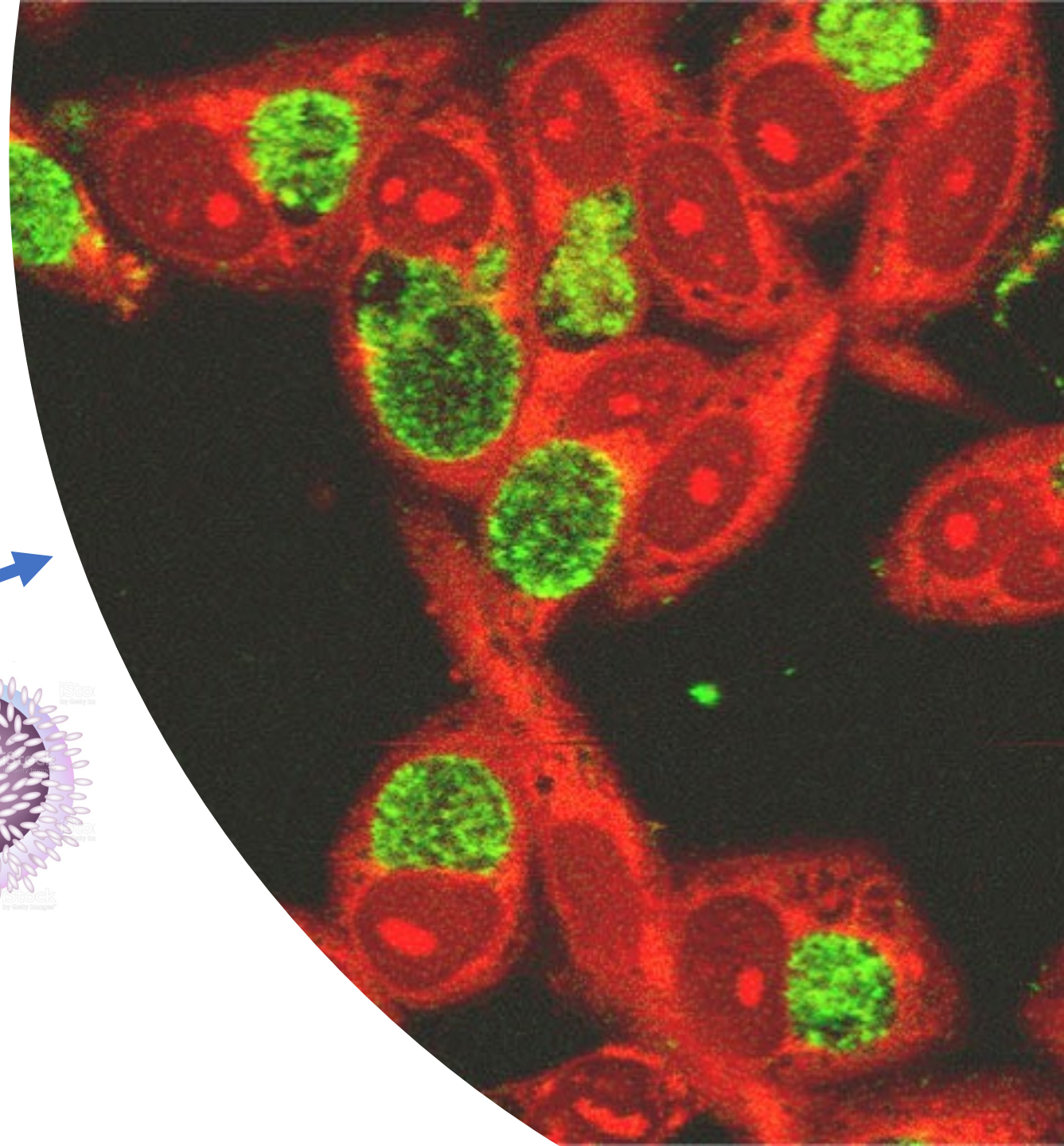
Replicating reticulate bodies

Mature inclusion with EBs and RBs

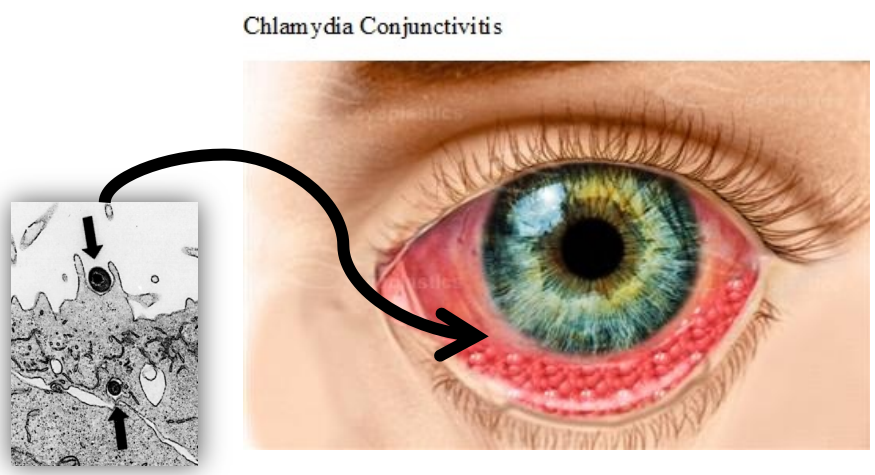

EB form
Osmotically stable
Metabolically dormant
EB → RB
Conversion
RB form
Osmotically fragile
Metabolically active
Binary
Fission
Inclusion
Stressful
Environment
Optimal
Environment
Persistent form
Aberrant bodies
RB → EB
Conversion
Cell Lysis
Extrusion

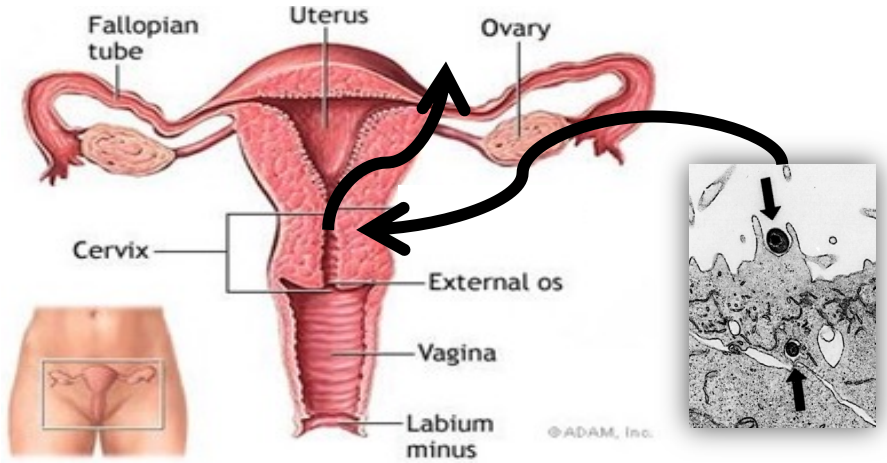
Chlamydia trachomatis bacteria in human cells

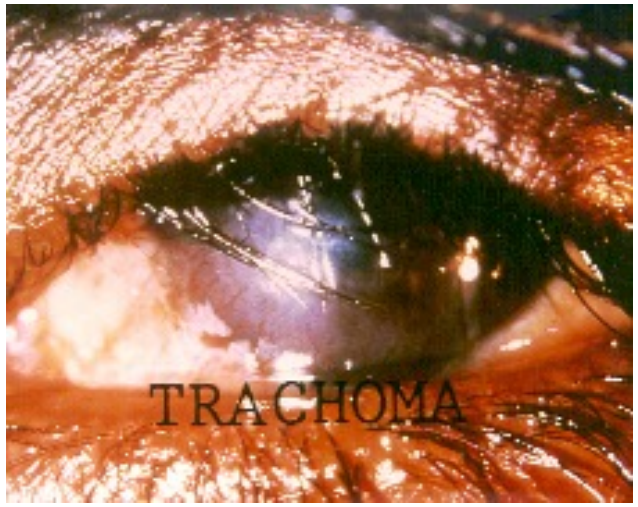




Chlamydia trachomatis - Human Disease

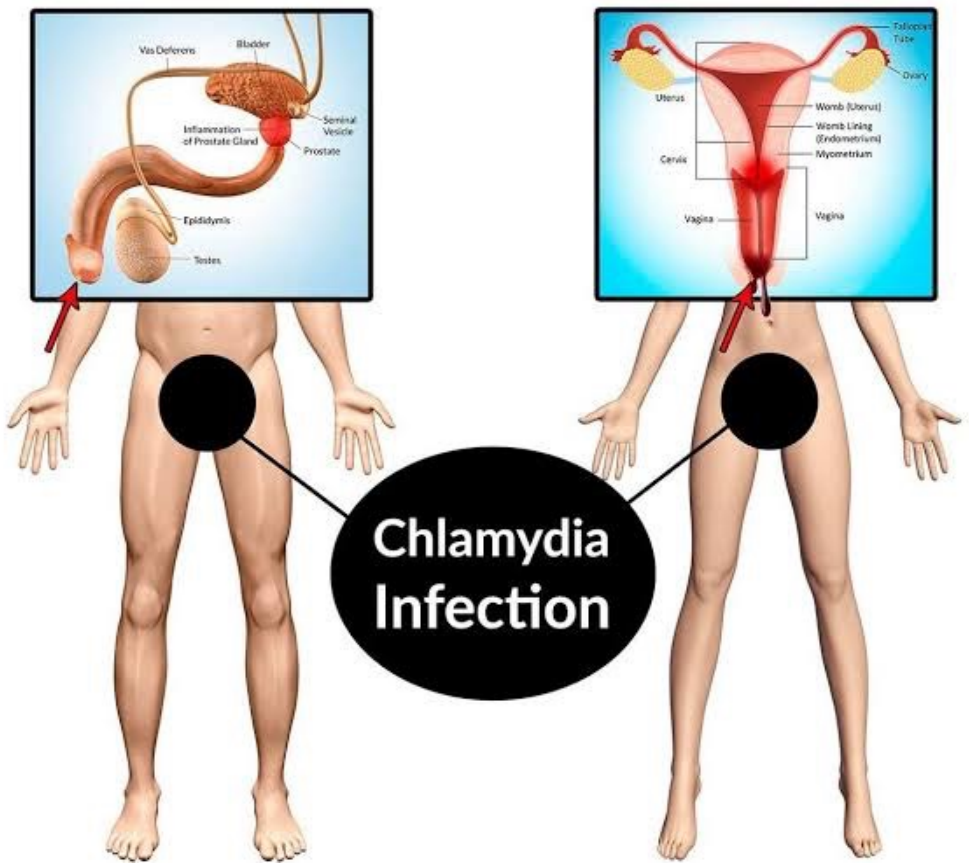


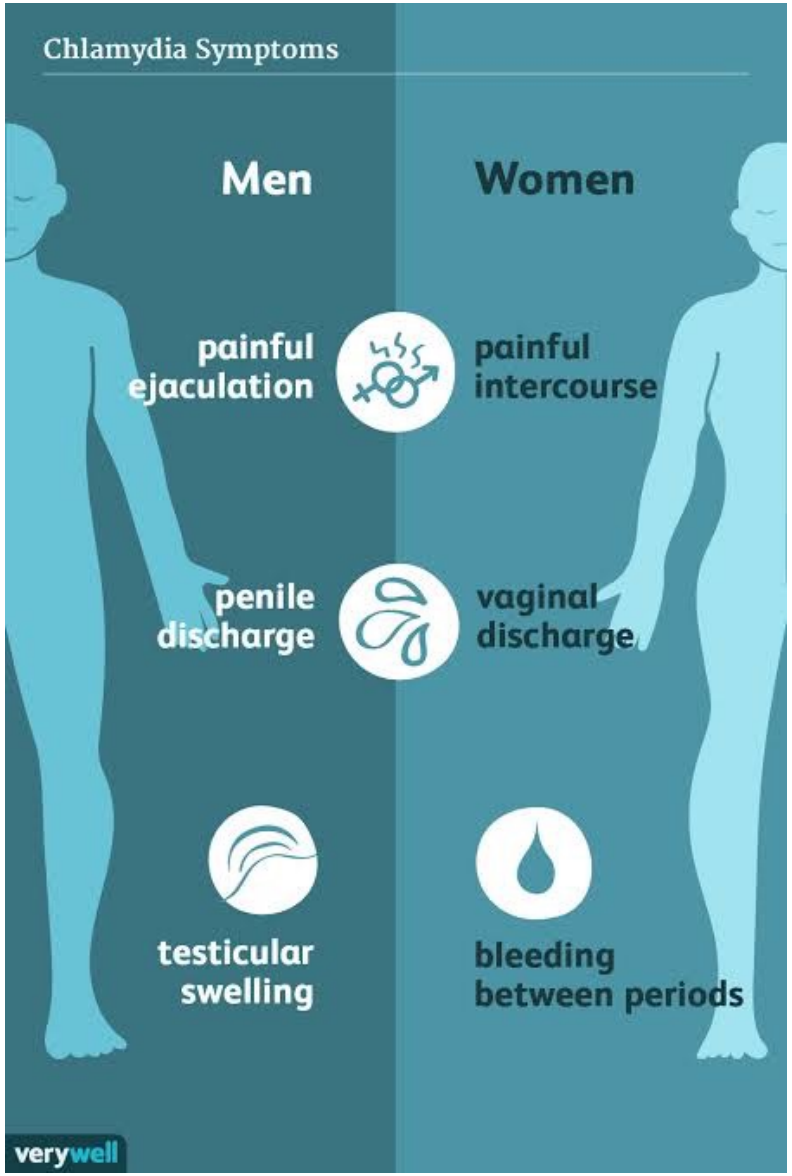




Sightsavers – Chlamydia trachoma is eliminated in Ghana

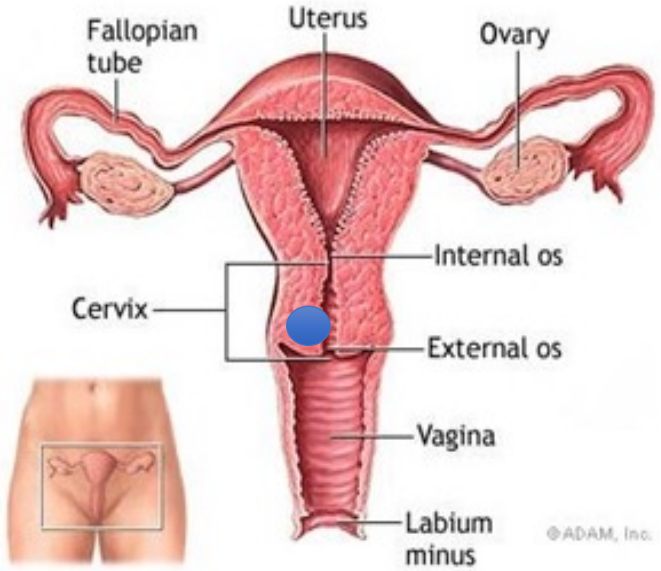
The Carter Center Chlamydia trachoma control program


Vas Deferens
Bladder
Seminal Vesicle
Inflammation of Prostate Gland
Prostate
Epididymis
Testes
Uterus
Womb (Uterus)
Womb Lining (Endometrium)
Myometrium
Cervix
Vagina
Vagina
Chlamydia Infection

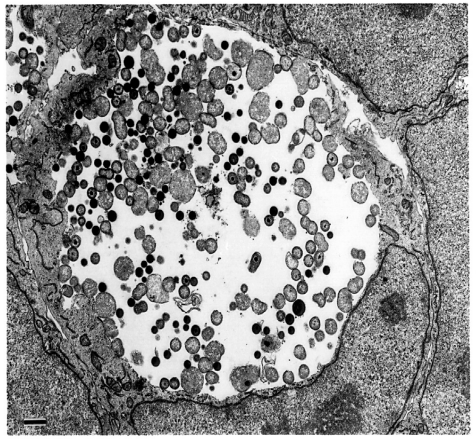

Chlamydia Symptoms
Men
Women
painful ejaculation
painful intercourse
penile discharge
vaginal discharge
testicular swelling
bleeding between periods
verywell

Chlamydia Infection & Differential Outcomes in Women

CT Cervix+



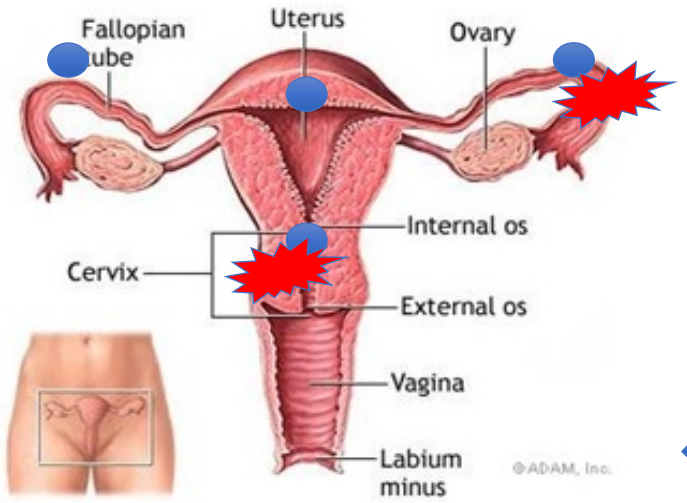
-Sexual transmission
-Cervicitis
-No chronic pathology



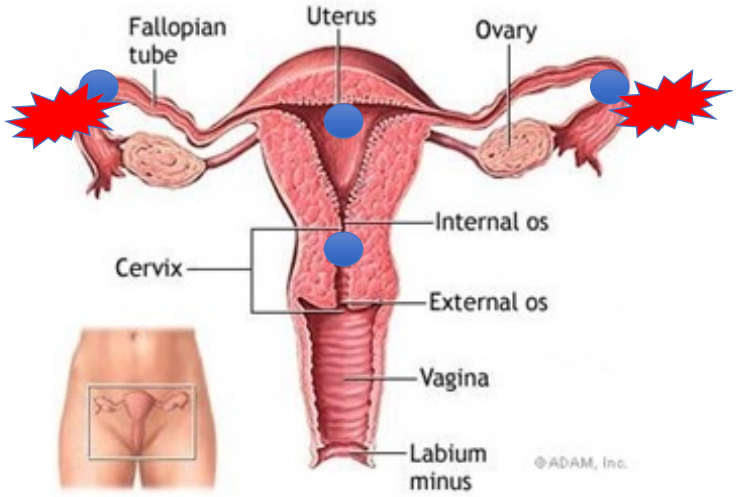
Mature inclusion with infectious Elementary Bodies (EBs) and replicating Reticulate Bodies (RBs)

Chlamydia Infection & Differential Outcomes in Women

CT Endo+ Pelvic Pain
"Acute" PID

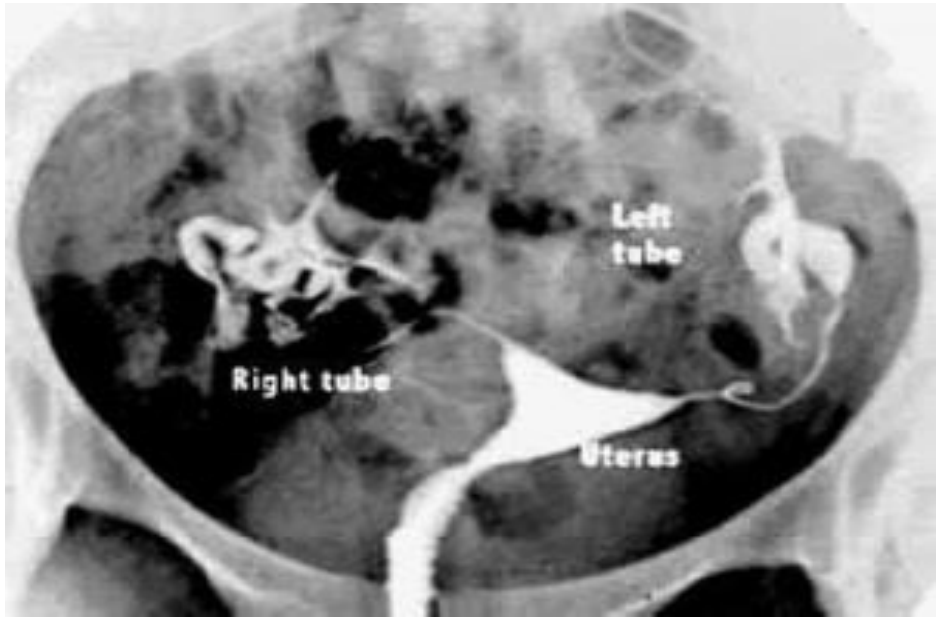


CT Endo+ Asymptomatic
Subacute "Silent" PID

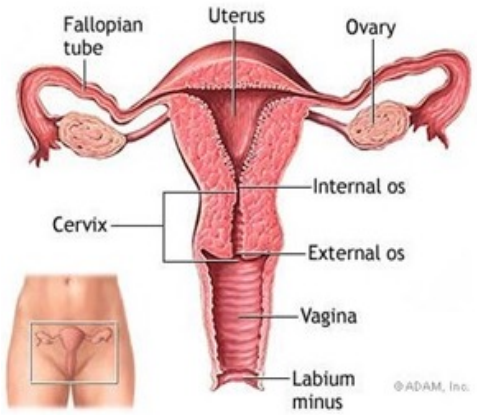


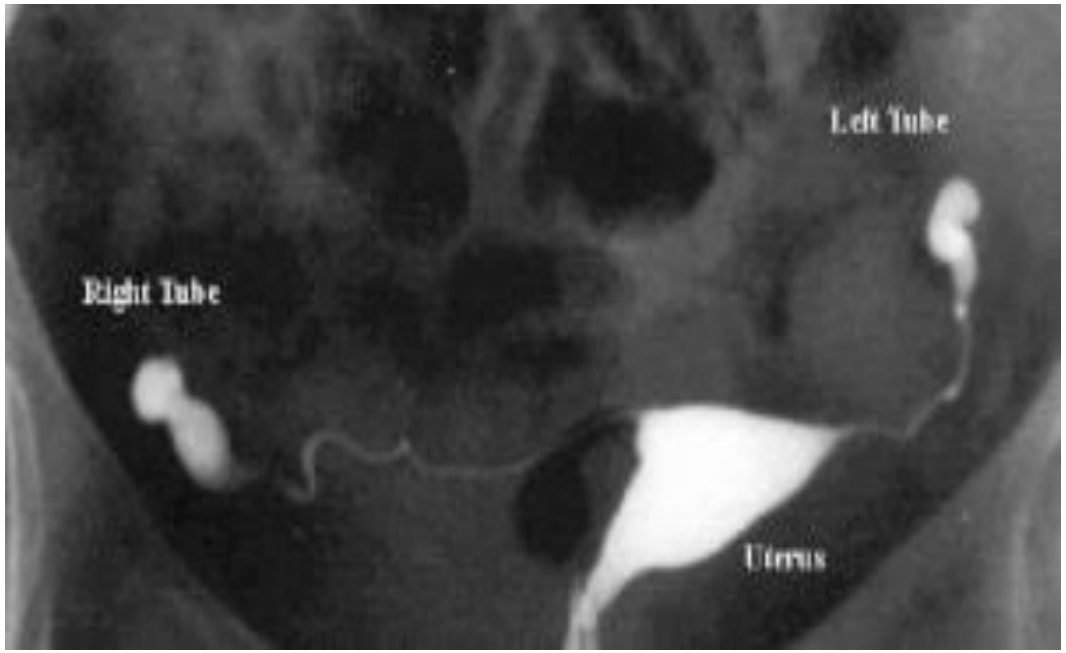
-Sexual transmission
-Lower abdominal/pelvic pain
-Chronic sequelae
- Infertility
- Chronic Pelvic Pain
- Ectopic Pregnancy

Infertility due to Tubal Scarring and Blockage



Normal Study – A smooth triangular uterine cavity and spill from both tubes.





Blocked tubes – No spill of dye is seen and both tubes are slightly dilated and fluid filled.

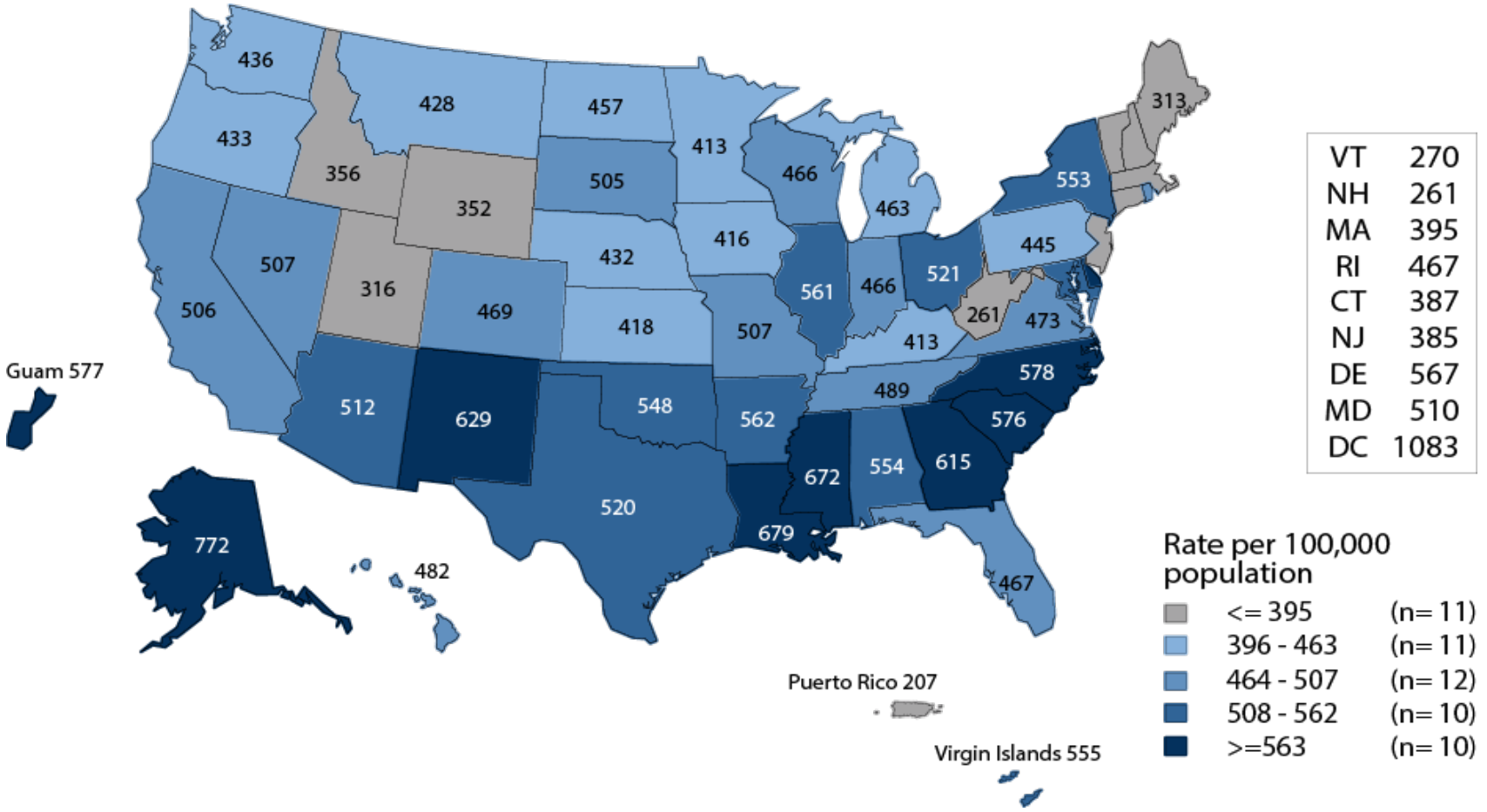
Long-term complications
Infertility
Chronic pelvic pain

- If untreated, 10% of infected girls develop pelvic inflammatory disease (PID) with lower abdominal pain, pain or bleeding with intercourse
- Chronic complications include, chronic pelvic pain, infertility and ectopic pregnancy

Chlamydia in newborns

- Infants born to infected mothers may develop
- Conjunctivitis
- Afebrile pneumonia

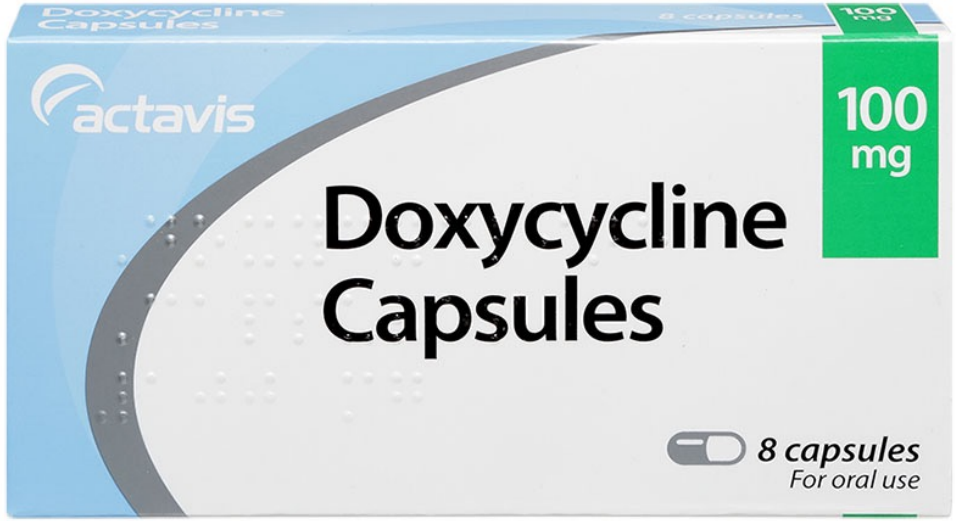
Chlamydia — Rates of Reported Cases by State, United States and Outlying Areas, 2019



Chlamydia trachomatis

- #1 bacterial STI; highly prevalent
- As many as 1 in 10 sexually active adolescent girls test positive for *Chlamydia trachomatis.*
- 90% of infected female teens and women are asymptomatic.
- Diagnosed primarily through STI screening programs.

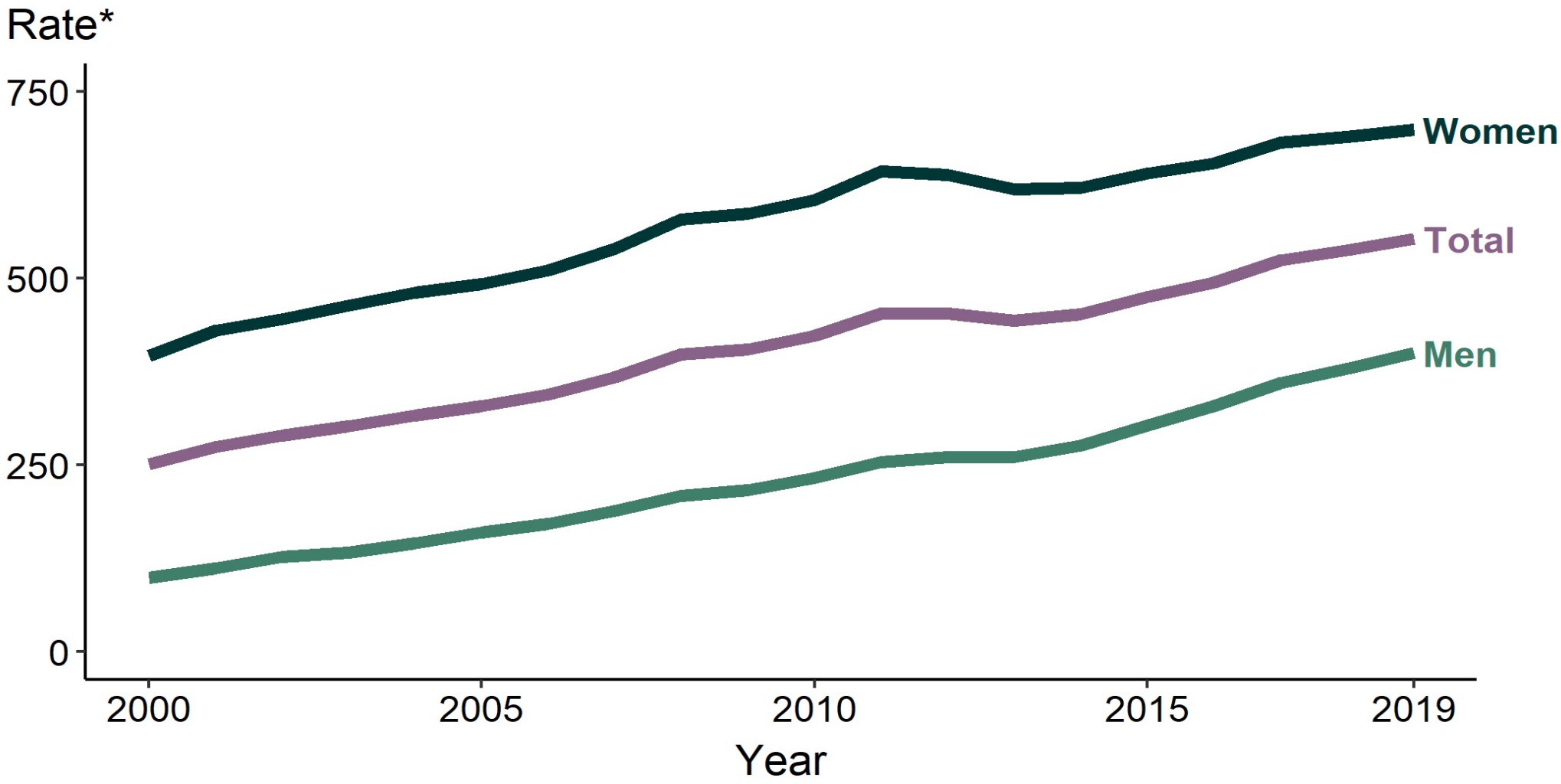
Prevention – Why not just screen and treat with antibiotics?



Do screening and treatment programs work to reduce disease?

- *Yes, but they are extremely expensive and logistically difficult to maintain due to the need for repeated and ongoing screening.*

Rising Rates of Reported Chlamydia Cases by Sex, United States, 2000-2019, Centers for Disease Control and Prevention



Outline

What is *Chlamydia*?

What diseases does it cause?

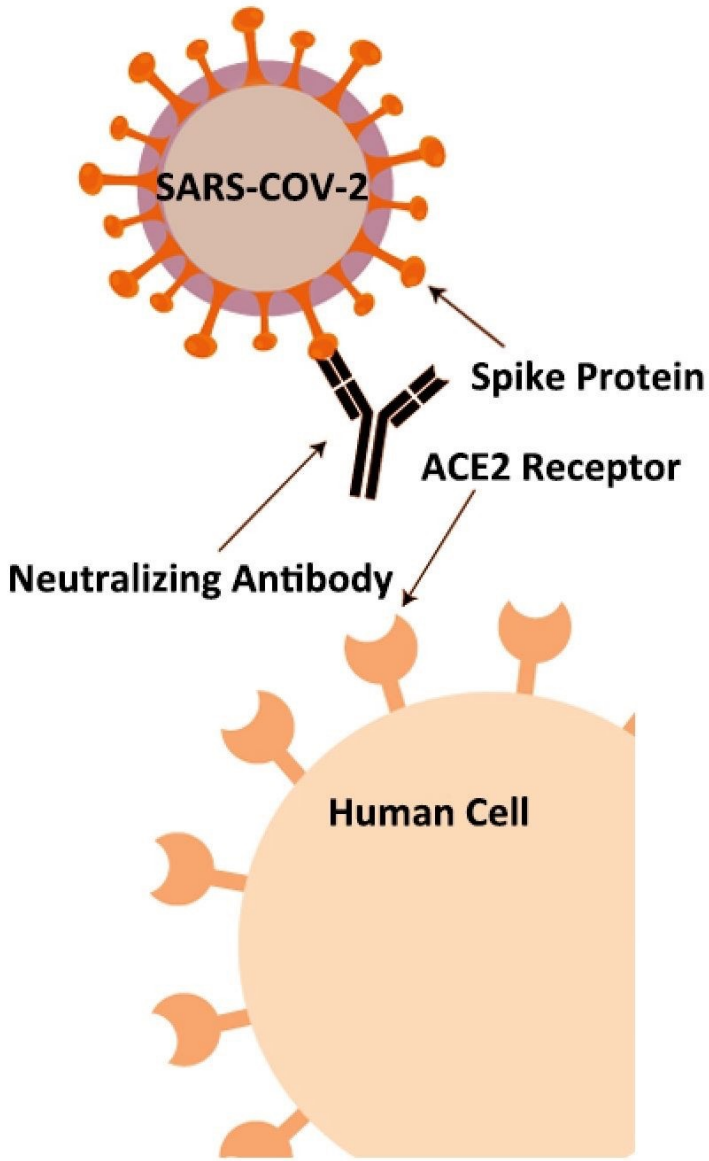
Can we make a preventative vaccine?

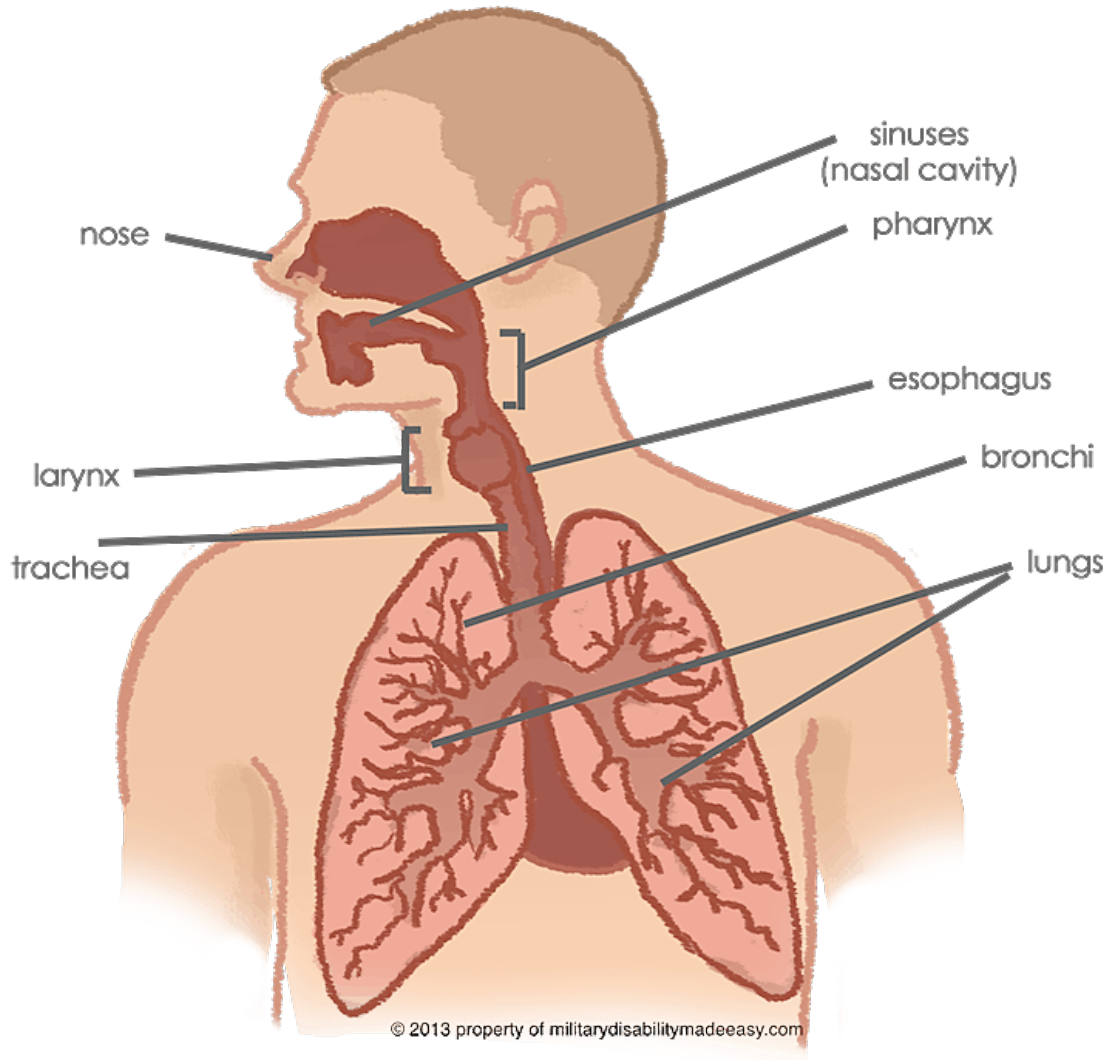
- What immune responses combat Chlamydia infection?
- Can we induce them with a vaccine?
- How do we test the vaccine?

Vaccine Development

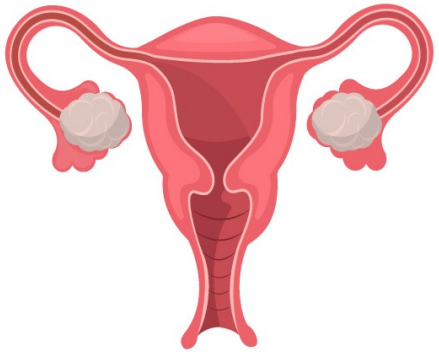
What immune responses are required for protection?

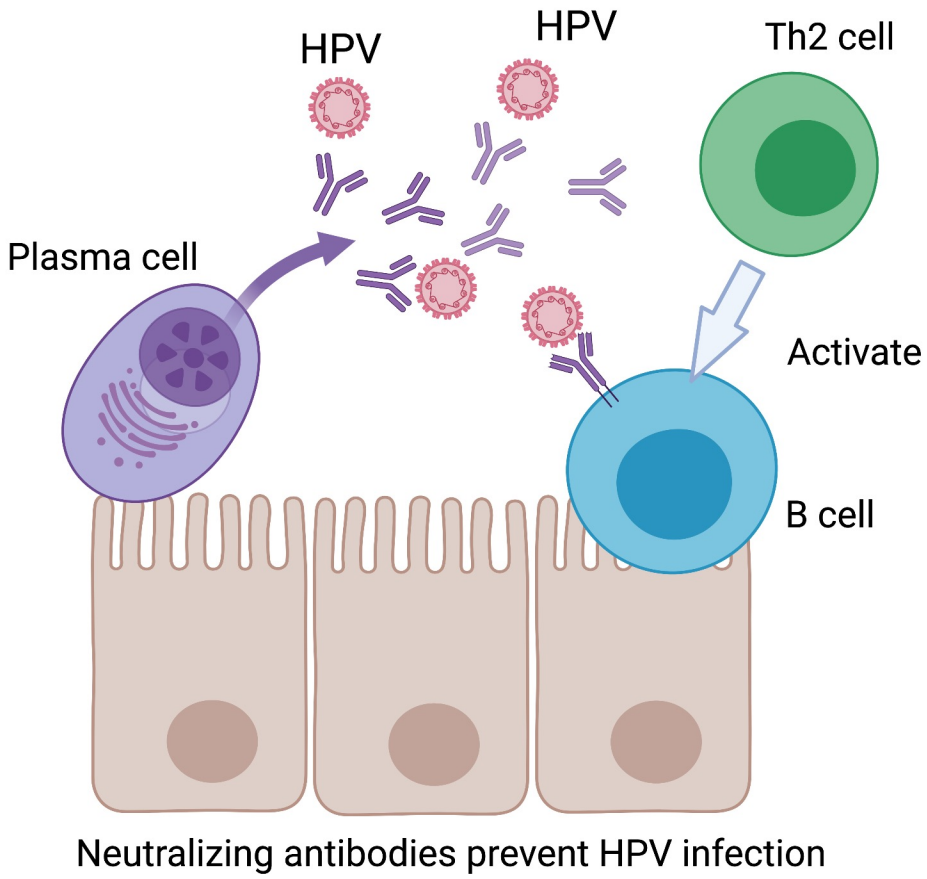
- Guides vaccine components and vaccine platforms for delivery.

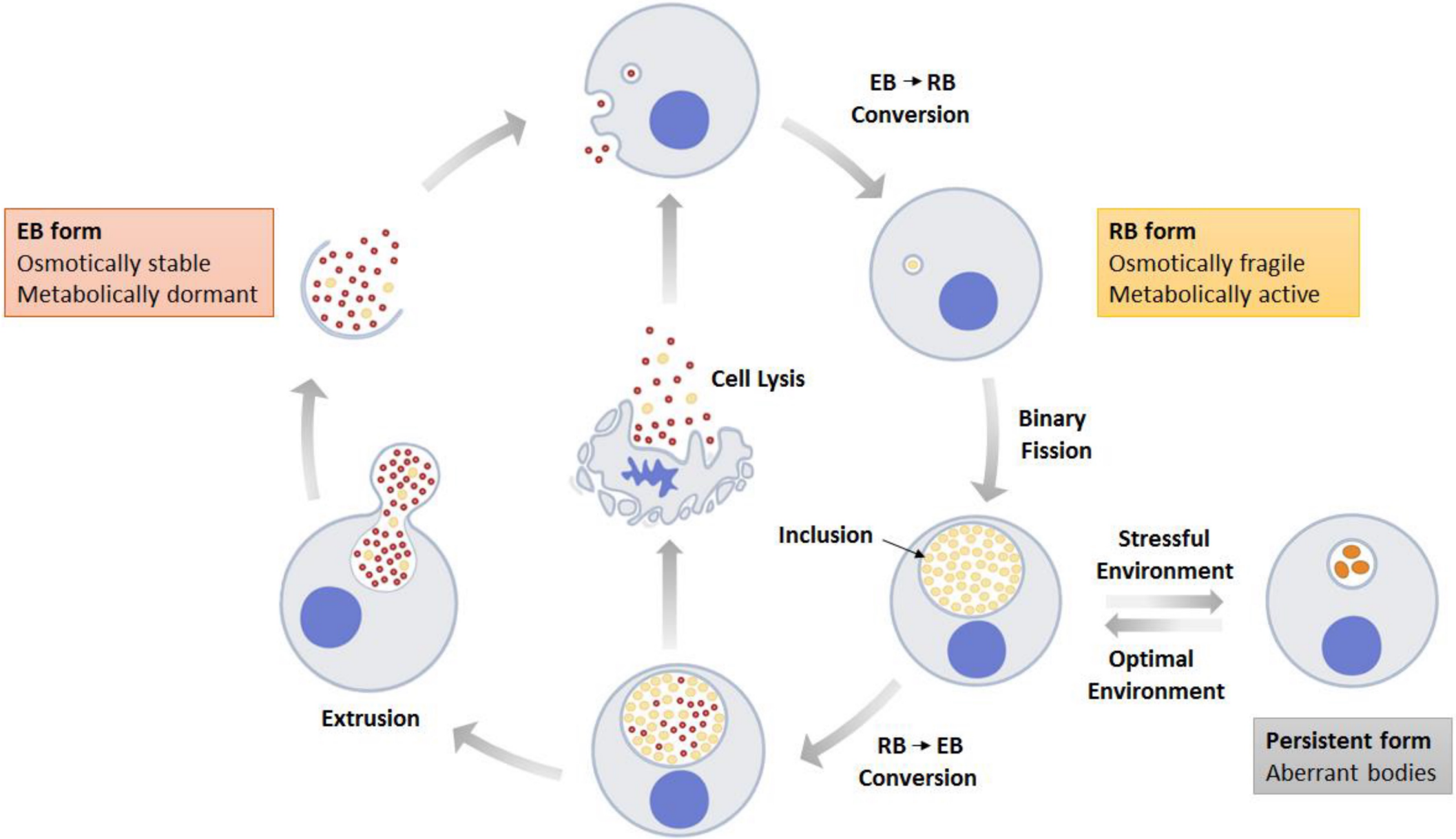

SARS-COV-2
Spike Protein
ACE2 Receptor
Neutralizing Antibody
Human Cell


sinuses
(nasal cavity)
nose
pharynx
esophagus
larynx
bronchi
trachea
lungs
© 2013 property of militarydisabilitymadeeasy.com

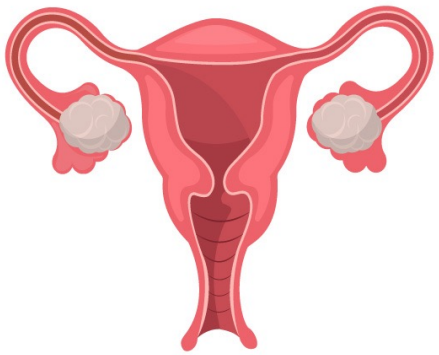
Human Papilloma Virus (HPV) Vaccine Strategy
Antibodies Block Infection

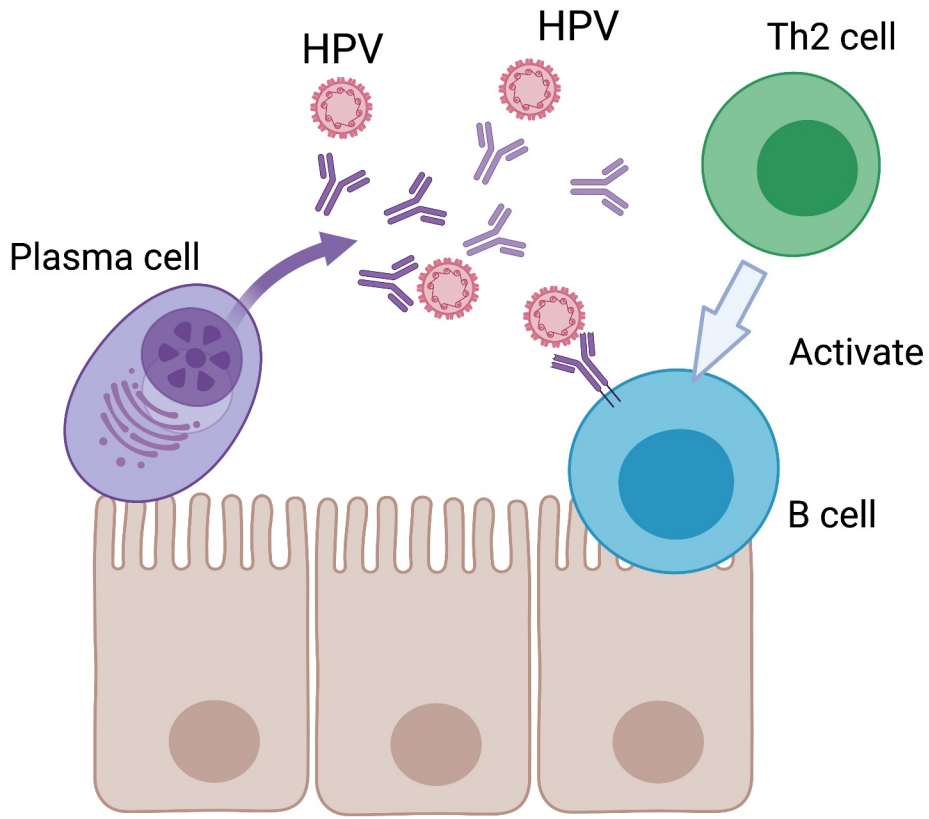




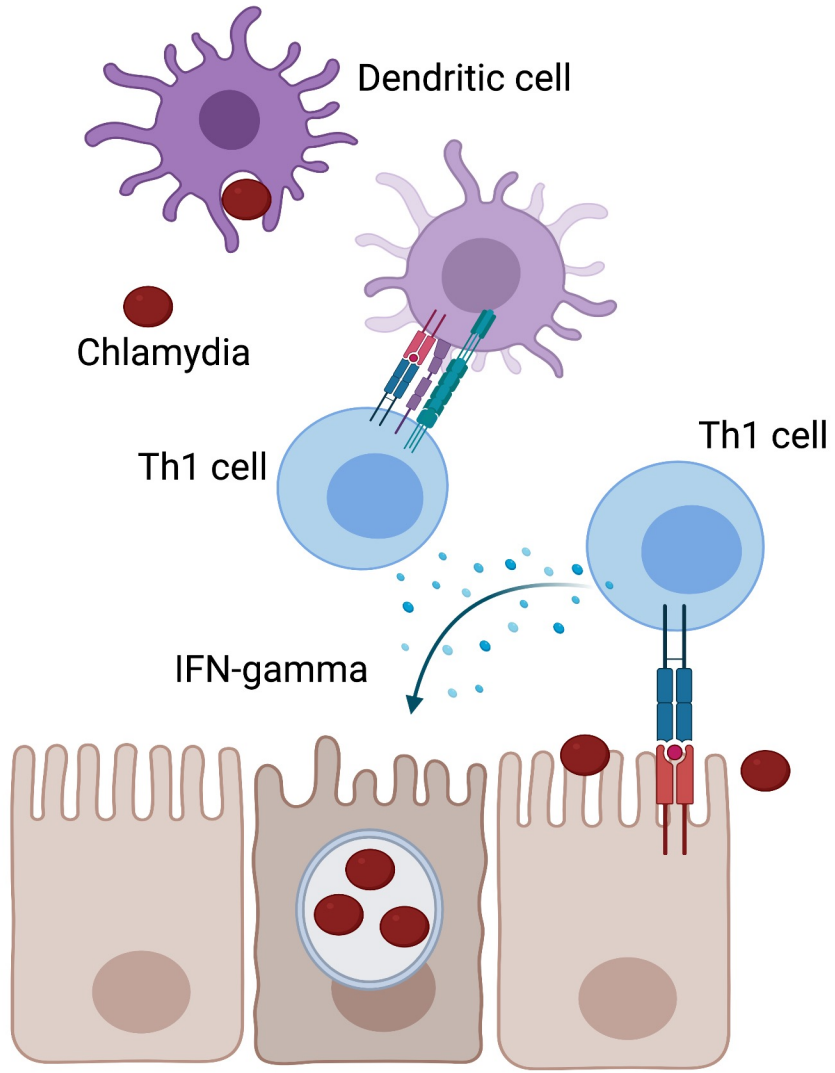

EB form
Osmotically stable
Metabolically dormant
EB → RB
Conversion
RB form
Osmotically fragile
Metabolically active
Binary
Fission
Inclusion
Stressful
Environment
Optimal
Environment
Persistent form
Aberrant bodies
RB → EB
Conversion
Cell Lysis
Extrusion

HPV versus Chlamydia Vaccine Strategy



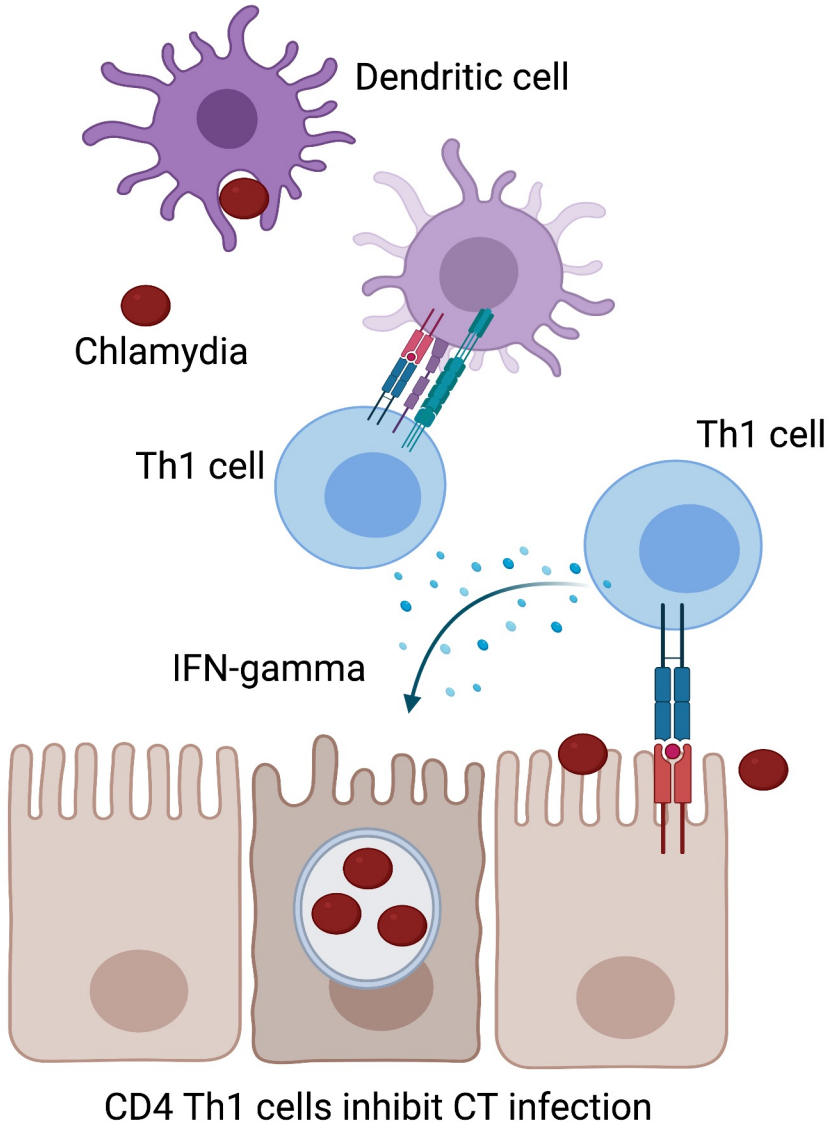


Neutralizing antibodies prevent HPV infection



CD4 Th1 cells inhibit CT infection

Chlamydia Vaccine Strategy



CD4 Th1 cells inhibit CT infection

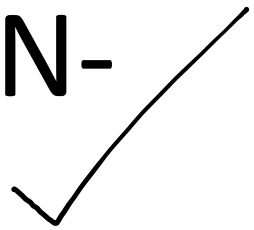
What chlamydia proteins or *antigens* excite or “activate” Th1 cells?

What chlamydia proteins or *antigens* cause T cells to make IFN-gamma?

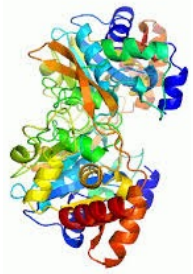
Vaccine Development

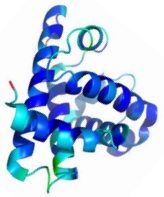
What immune responses are required for protection?

- Th1 cells making IFN-gamma



Antigen Selection





Preclinical Chlamydia Vaccine Development

Pittsburgh **T** Cell **R**esponse **A**gainst **C**hlamydia (TRAC) Cohort N = 247

Recruitment

Women 18-35 yo with :

- Recent exposure to Chlamydia
- Positive Chlamydia screening test

Enrollment

- Behavioral questionnaire
- Blood samples
- Vaginal and Cervical and Uterine samples

65% infected at enrollment
47% Uterus+

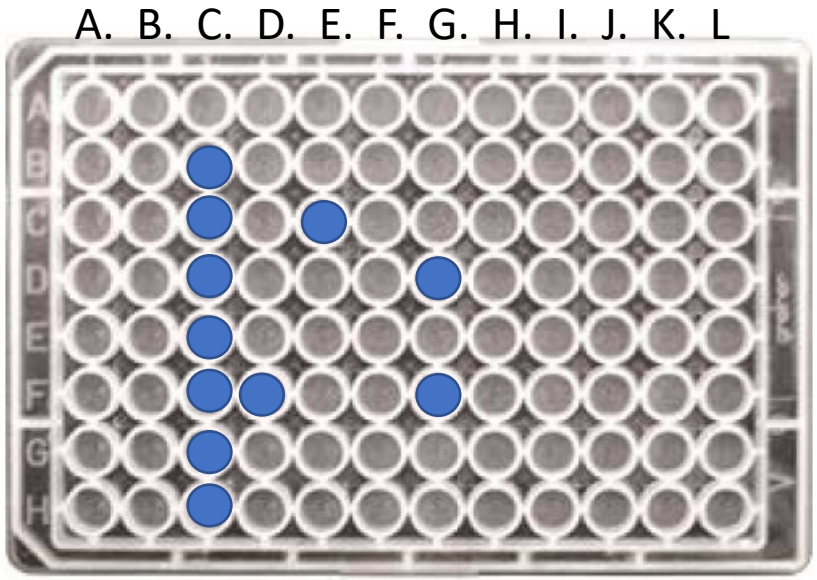
Follow-up

- Intervals: 1, 4, 8, 12 months after enrollment
- Testing as above, except without endometrial biopsy

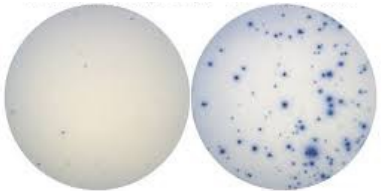
35% with positive Chlamydia test during follow-up

Test Chlamydia Exposed Patients' Blood

Patient blood cells +
Chlamydia Proteins;
Measure IFN-gamma



PROTEIN "C" induces
IFN-gamma!!!

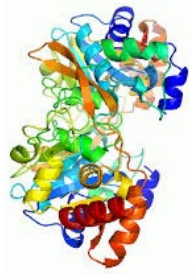


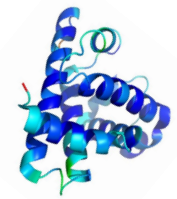
Vaccine Development

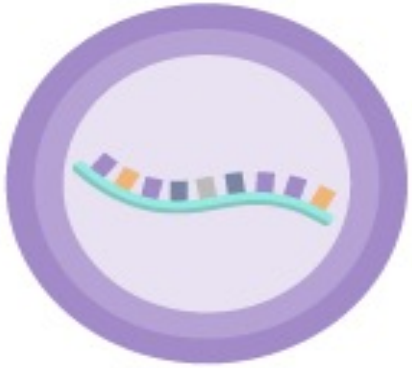
Can we induce protective responses with a vaccine?

- New vaccines stimulate Th1 cells

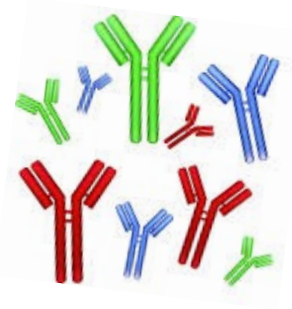
Antigen Selection



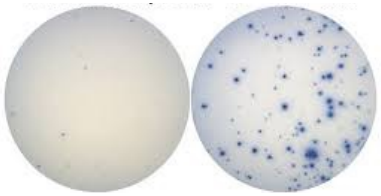




mRNA vaccine in lipid nanoparticle

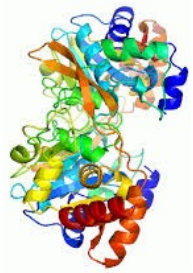


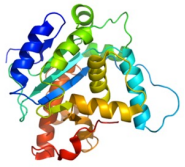
These vaccine platforms induce antibodies AND Th1 cells that make IFN-gamma!

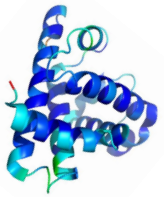


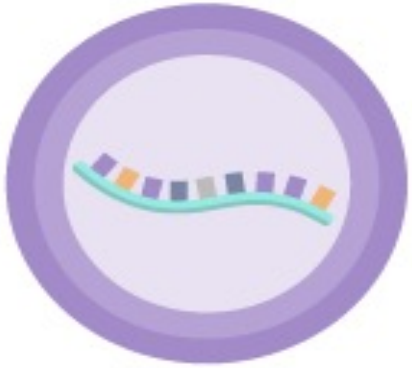
Preclinical Chlamydia Vaccine Development

Antigen Selection



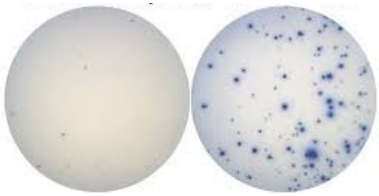






mRNA vaccine in lipid nanoparticle

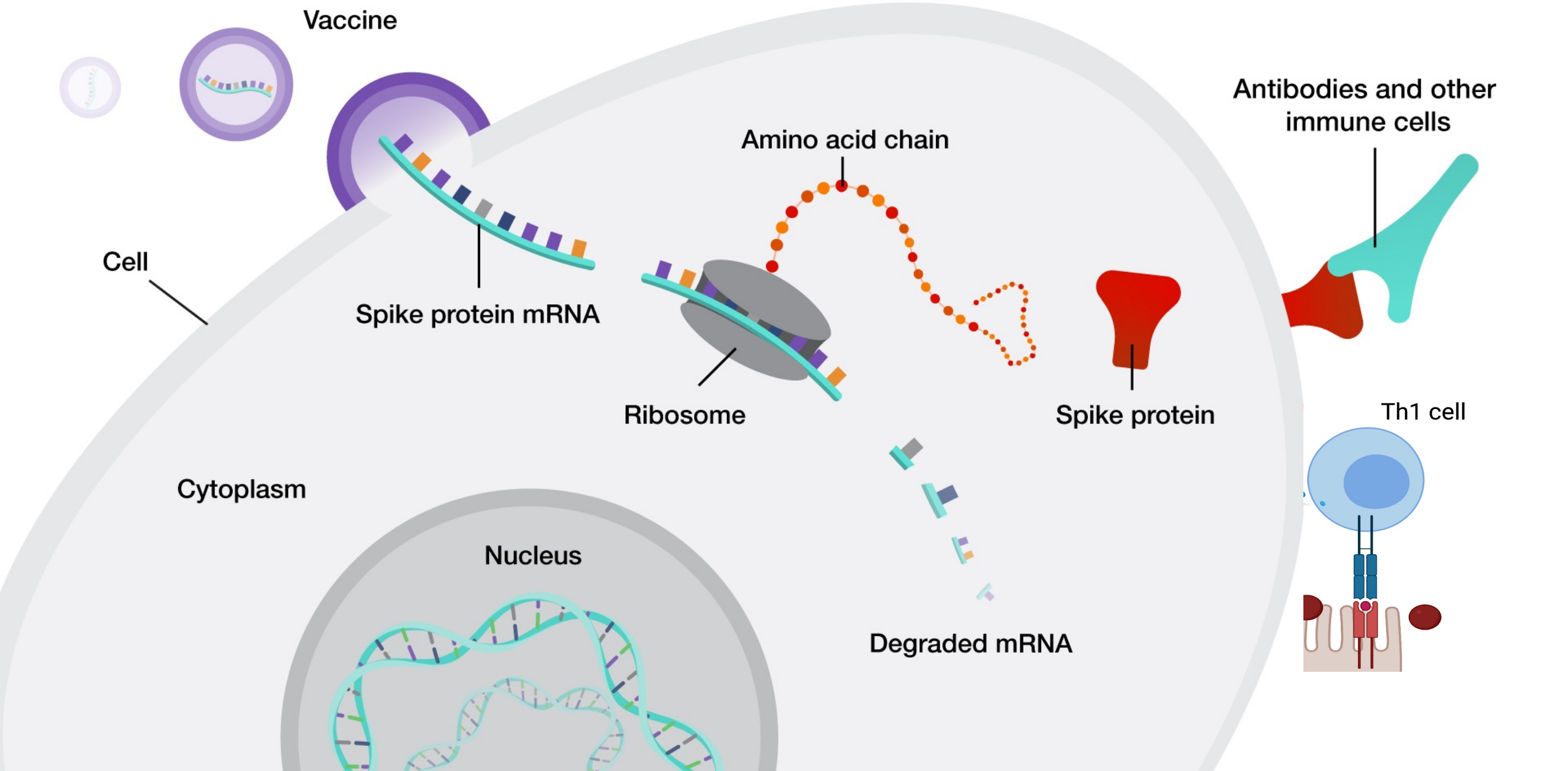
Testing in Mice



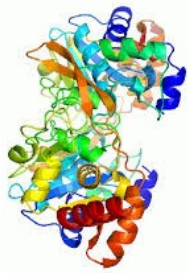
PROTEIN induces IFN-gamma!!!

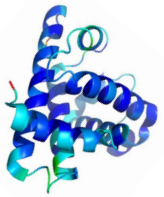
Preclinical Chlamydia Vaccine Development

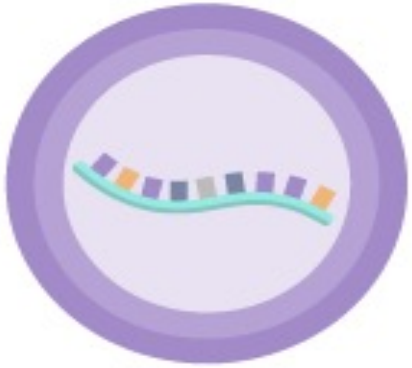
mRNA vaccine – COVID as an example



Antigen Selection

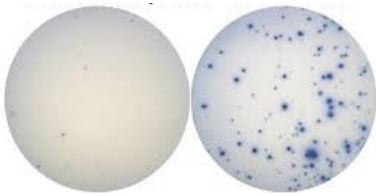






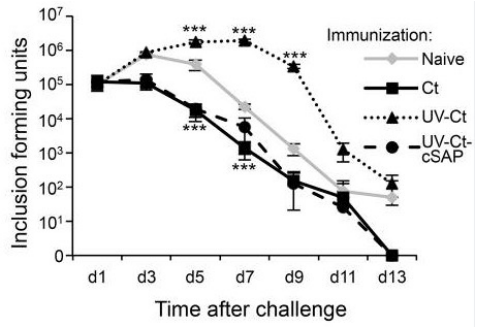
mRNA vaccine in lipid nanoparticle

Testing in Mice



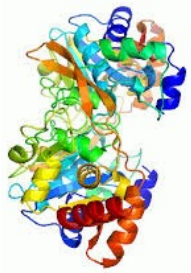
PROTEIN induces IFN-gamma!!!

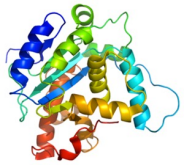
Preclinical Chlamydia Vaccine Development

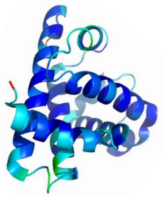


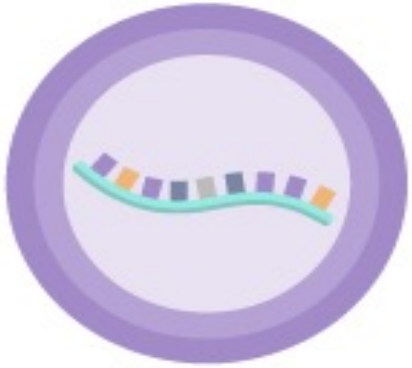
Challenge Experiments

Antigen Selection









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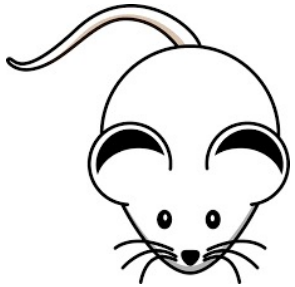
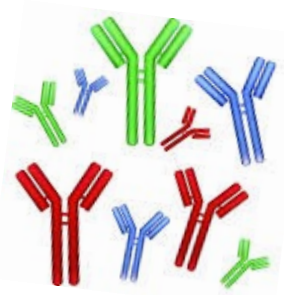
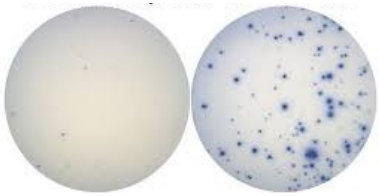
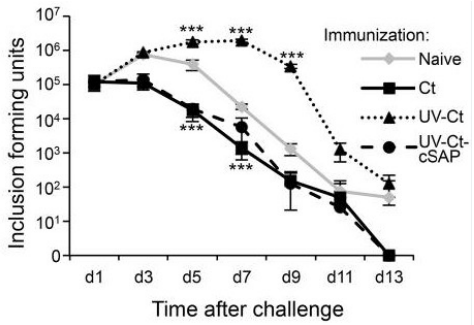


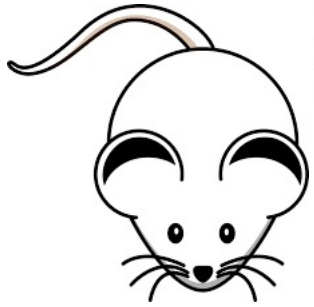




PROTEIN induces IFN-gamma!!!

Preclinical Chlamydia Vaccine Development





Challenge Experiments

Immunogenicity, Challenge (Transmission)

Vaccine Development

How do we test the vaccine?

- Phase I – safety and immune response evaluation
- Phase II - protection

How to measure efficacy?

- Phase I vaccine trial
  - Recruit 18 to 25 yo sexually active adults and assess safety and immune response – need to see IFN-gamma + Th1 cells
- Phase II vaccine trial
  - Recruit 18 to 25 yo sexually active adults; past Chlamydia infections; adjust for prior exposure
  - Tetanus booster versus Chlamydia vaccine

Chlamydia Vaccine Phase II Trial Design

- Efficacy monitoring-
  - Monitor for infection via self obtained urethral swab or urine testing (men) and self-obtained vaginal swabs (women) at 1, 3, 6, 9, and 12 months.
  - Questionnaires assess for potential sexual exposure.
  - At detection of positive test, treat with antibiotics.
  - If +, can determine amount of chlamydia by PCR.

Outline

What is *Chlamydia*?

What diseases does it cause?

Can we make a preventative vaccine?

- What immune responses prevent Chlamydia infection?
- Can we induce protective responses with a vaccine?
- How do we test the vaccine?

Questions/Discussion