Antimicrobial therapy: every choice has consequences!

JOHN A. VANCHIERE, MD, PHD, FAAP
PROFESSOR OF PEDIATRICS
LSU HEALTH SHREVEPORT

Disclosures

- Pfizer: Clinical trial contracts, Principal Investigator
- Merck:Clinical trial contracts, Principal Investigator
- Enanta: Clinical trial contracts, Principal Investigator
- GSK: Clinical trial contracts, Principal Investigator
- Louisiana Healthcare Connections:Speaker
- Health Hero America: Medical Director
- Seqirus: Data Safety Monitoring Committee
- Biocryst: Clinical Trials, Data Safety Monitoring Committee

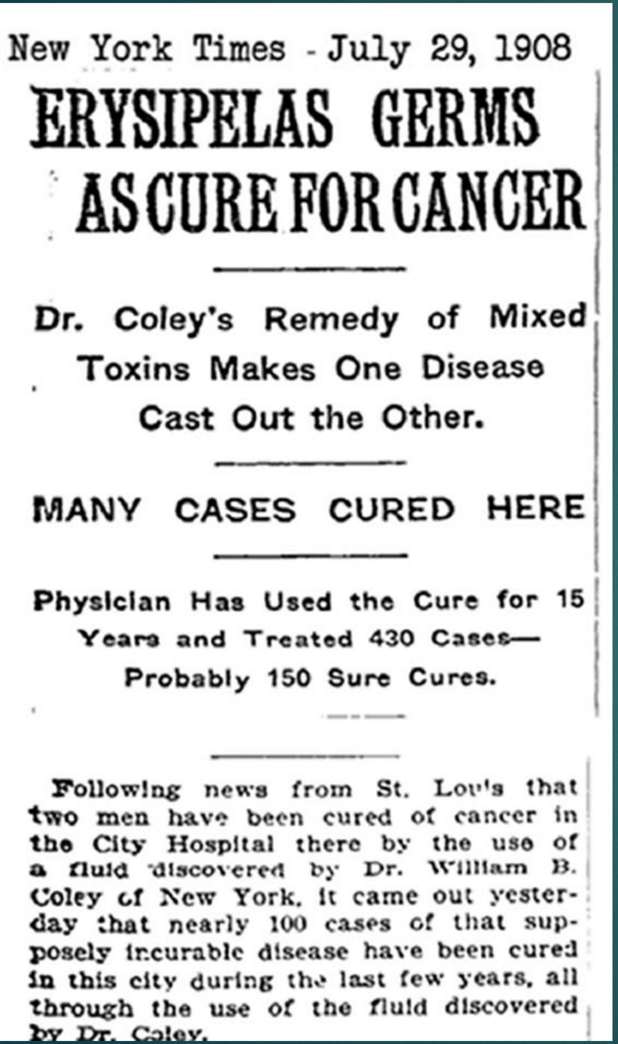
Outline of the presentation

- Impact of antibiotics on the microbiome
- Increasing antibiotic resistance in Group B Strep
- The complexity of homeostasis in pregnancy

The reality of a biomedical research career

"... .the born investigator no more needs encouragement to investigate than the fish does to swim. "

Thomas Dwight, M.D., Professor of Anatomy,
Harvard Medical School
December 20, 1899
Annual Meeting of the American Society
of Naturalists and Affiliated Societies


New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

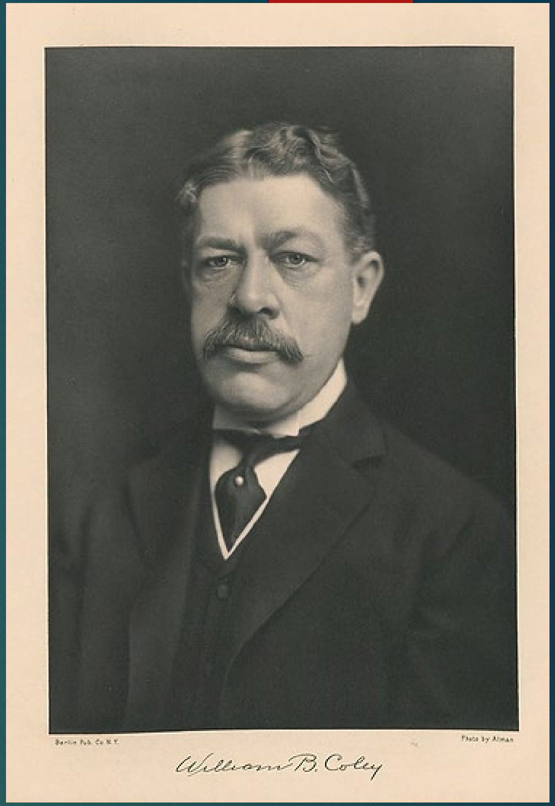
MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yesterday that nearly 100 cases of that supposely incurable disease have been cured in this city during the last few years, all through the use of the fluid discovered by Dr. Coley.

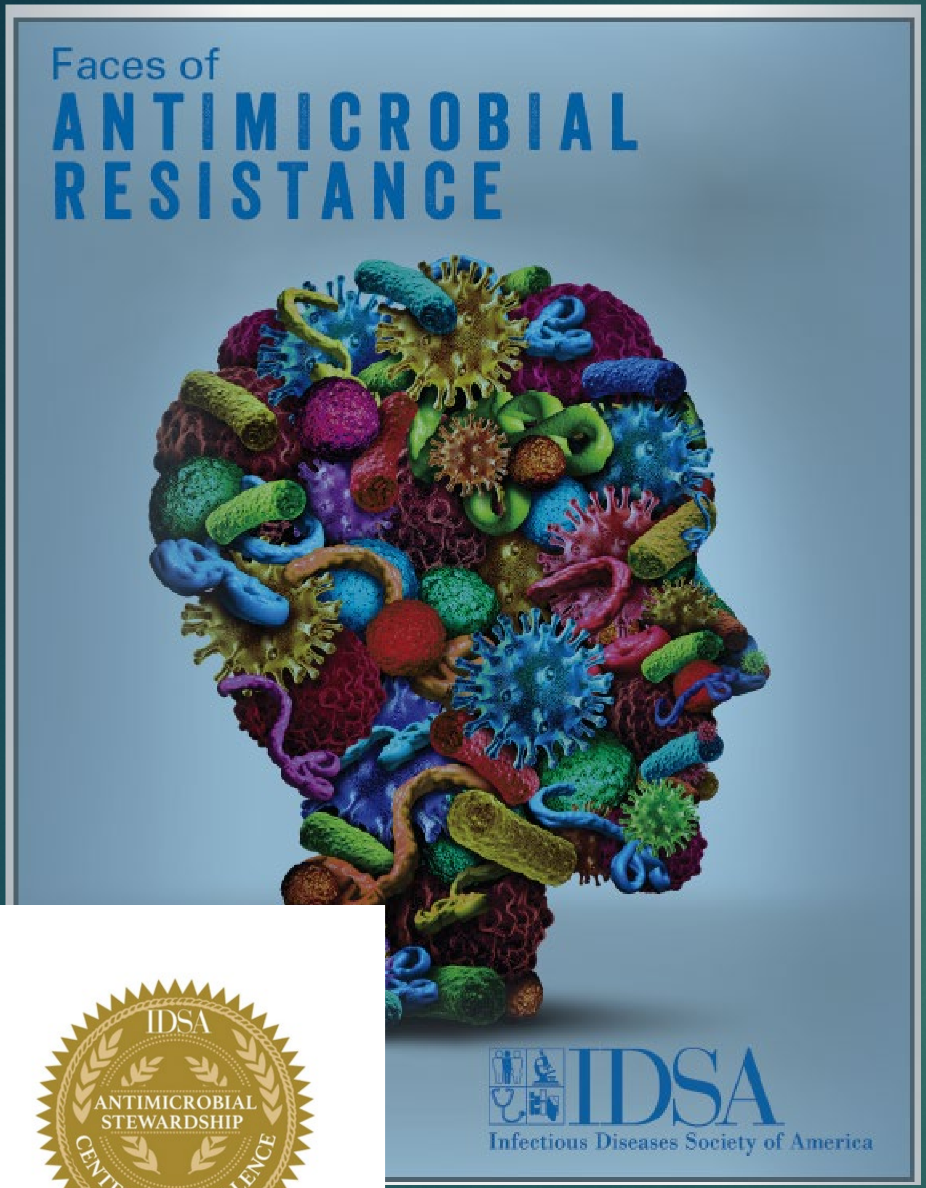
Nature often gives us hints to her profoundest secrets, and it is possible that she has given us a hint which, if we will but follow, may lead us on to the solution of this difficult problem.

– William Coley (1891)



Insights

- *Hippocrates* (460BCE-370BCE):
  - "Illnesses do not come out of the blue. They are developed from small daily "sins" against Nature. When enough "sins" have accumulated, illnesses will suddenly appear."
- Living, as a species, is now a race between genetics, the environment and germs...
  - Vaccines and antibiotics help compensate for "deficiencies" in our genetics .... and are our best hope to thwart the germs.
  - Changing the environment is a tough one!
- Evolution, broadly defined, is the key to a longer life...
  - Biomedical technology evolves faster than human genetics!!
- But germs evolve faster than we do!!



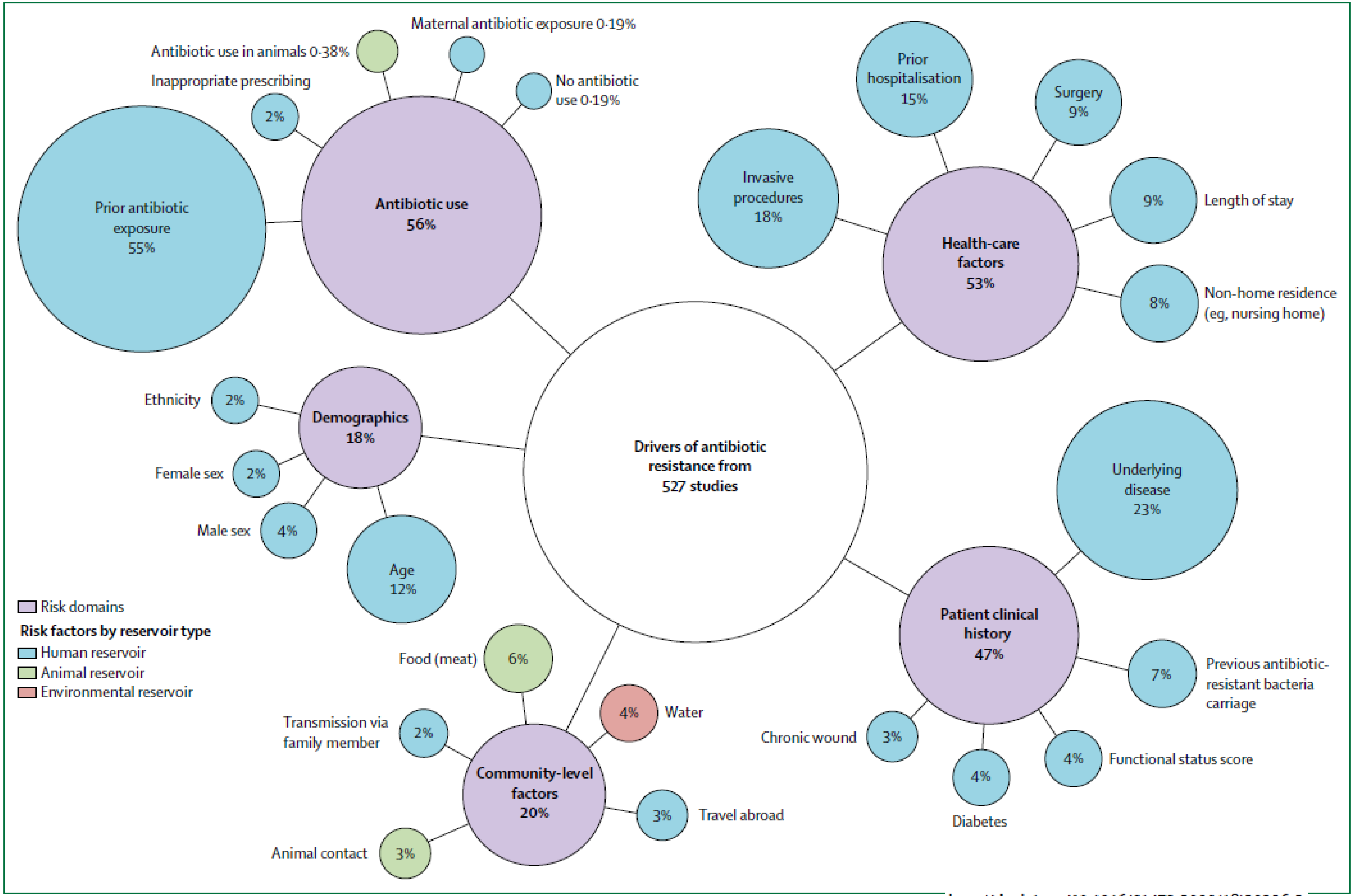
IDSA ANTIMICROBIAL STEWARDSHIP CENTER OF EXCELLENCE

BE ANTIBIOTICS AWARE

GET AHEAD OF SEPSIS

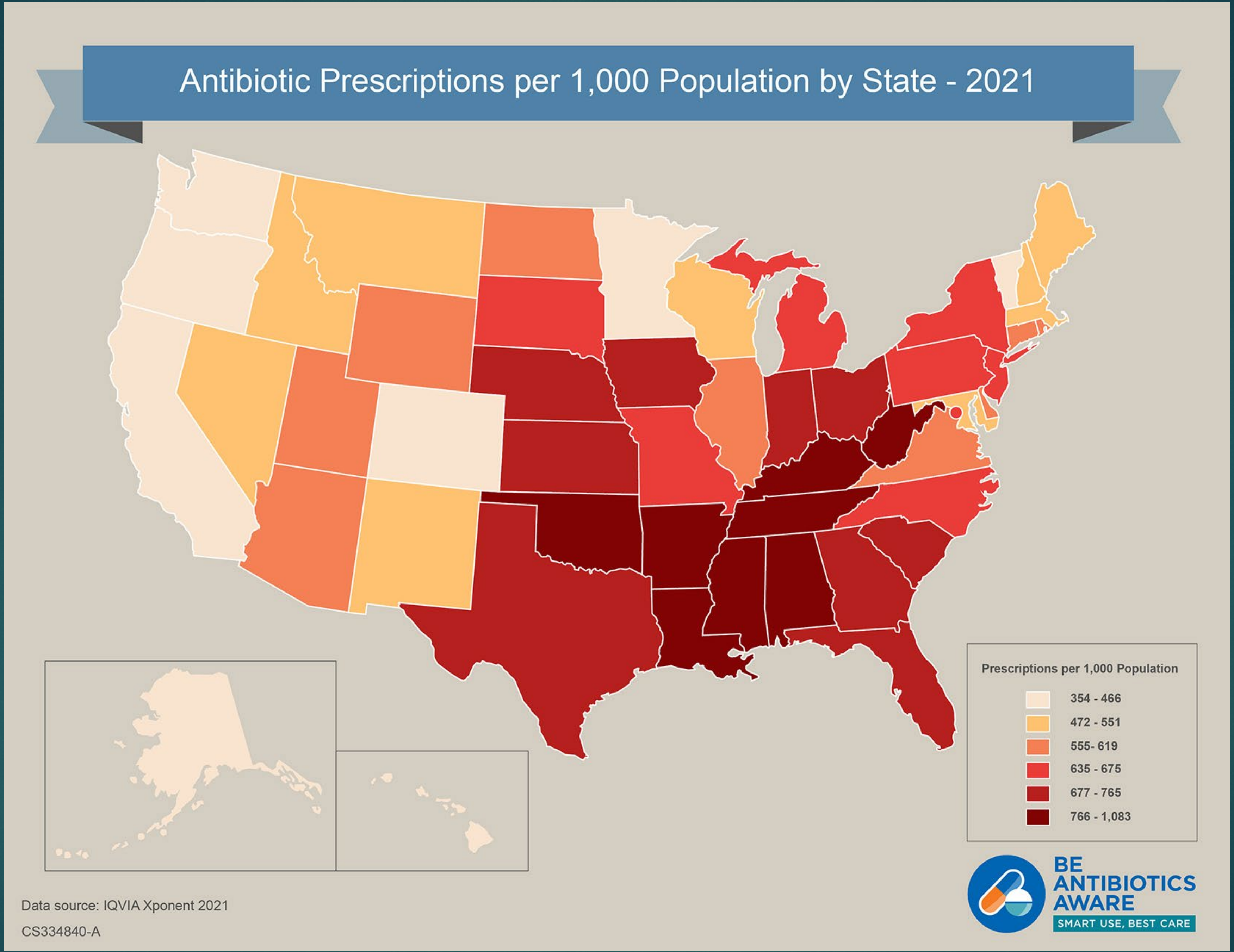
https://www.cdc.gov/antibiotic-use/index.html

Drivers of antimicrobial resistance



http://dx.doi.org/10.1016/S1473-3099(18)30296-2

Figure 3: Percentage of studies quantifying drivers of antibiotic resistance in humans



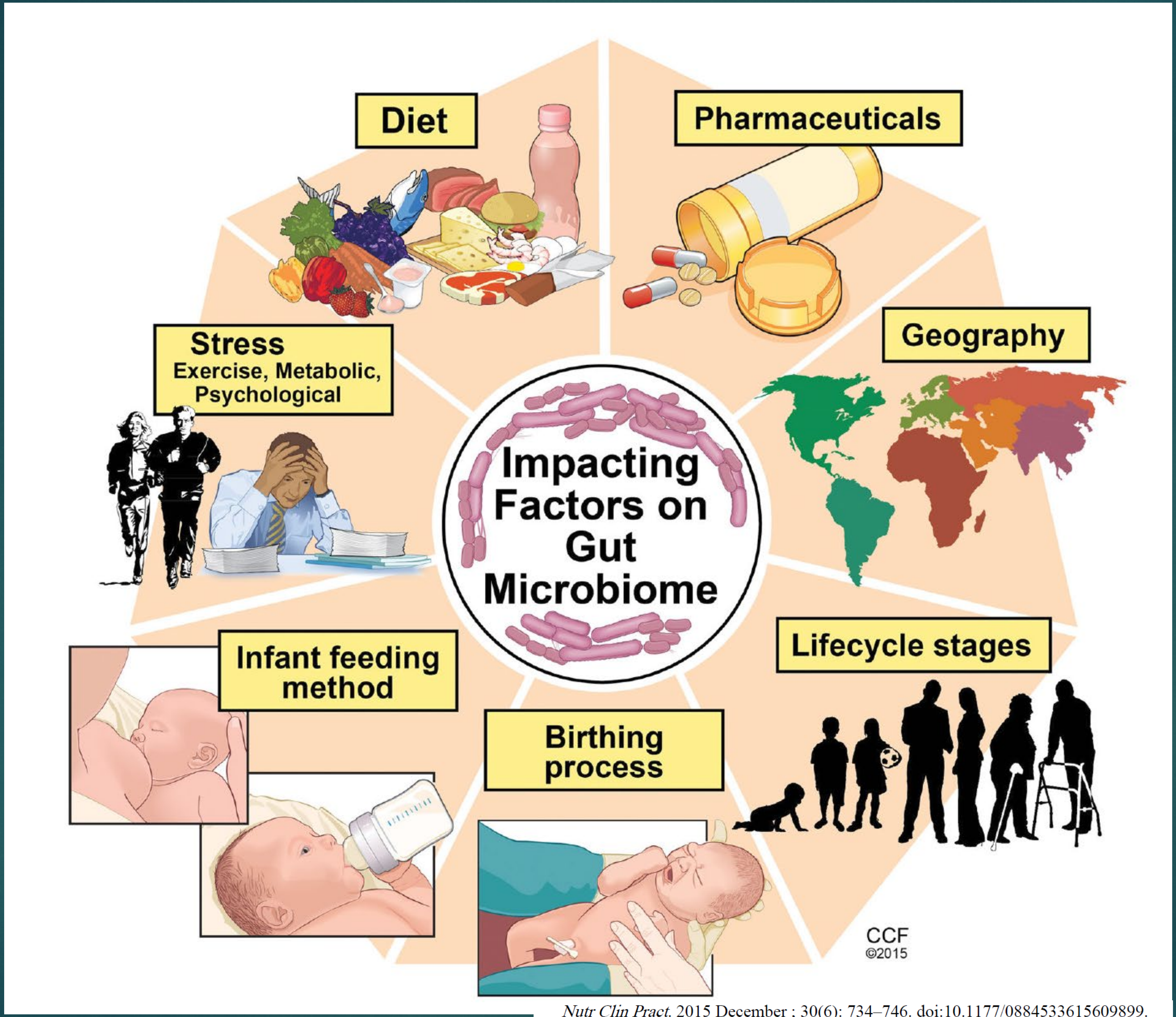
https://www.cdc.gov/antibiotic-use/images/2021-Report-Map.jpg

The Human Microbiome: Good germs help keep the bad germs in check

- Microbiome #1: (Rob Knight-- 8:25—11:48)

  https://www.youtube.com/watch?v=i-icXZ2tMRM

- How do we build resilience in the microbiome??
  - Prebiotics, probiotics, fermented beverages



Nutr Clin Pract. 2015 December ; 30(6): 734–746. doi:10.1177/0884533615609899.

Pammi *et al. Microbiome* (2017) 5:31
DOI 10.1186/s40168-017-0248-8

Microbiome

REVIEW Open Access

Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis

Mohan Pammi[1*], Julia Cope[2], Phillip I. Tarr[3], Barbara B. Warner[3], Ardythe L. Morrow[4], Volker Mai[5], Katherine E. Gregory[6], J. Simon Kroll[7], Valerie McMurtry[8], Michael J Ferris[8], Lars Engstrand[9], Helene Engstrand Lilja[10], Emily B. Hollister[11], James Versalovic[11] and Josef Neu[1]

Korpela *et al. Microbiome* (2017) 5:26
DOI 10.1186/s40168-017-0245-y

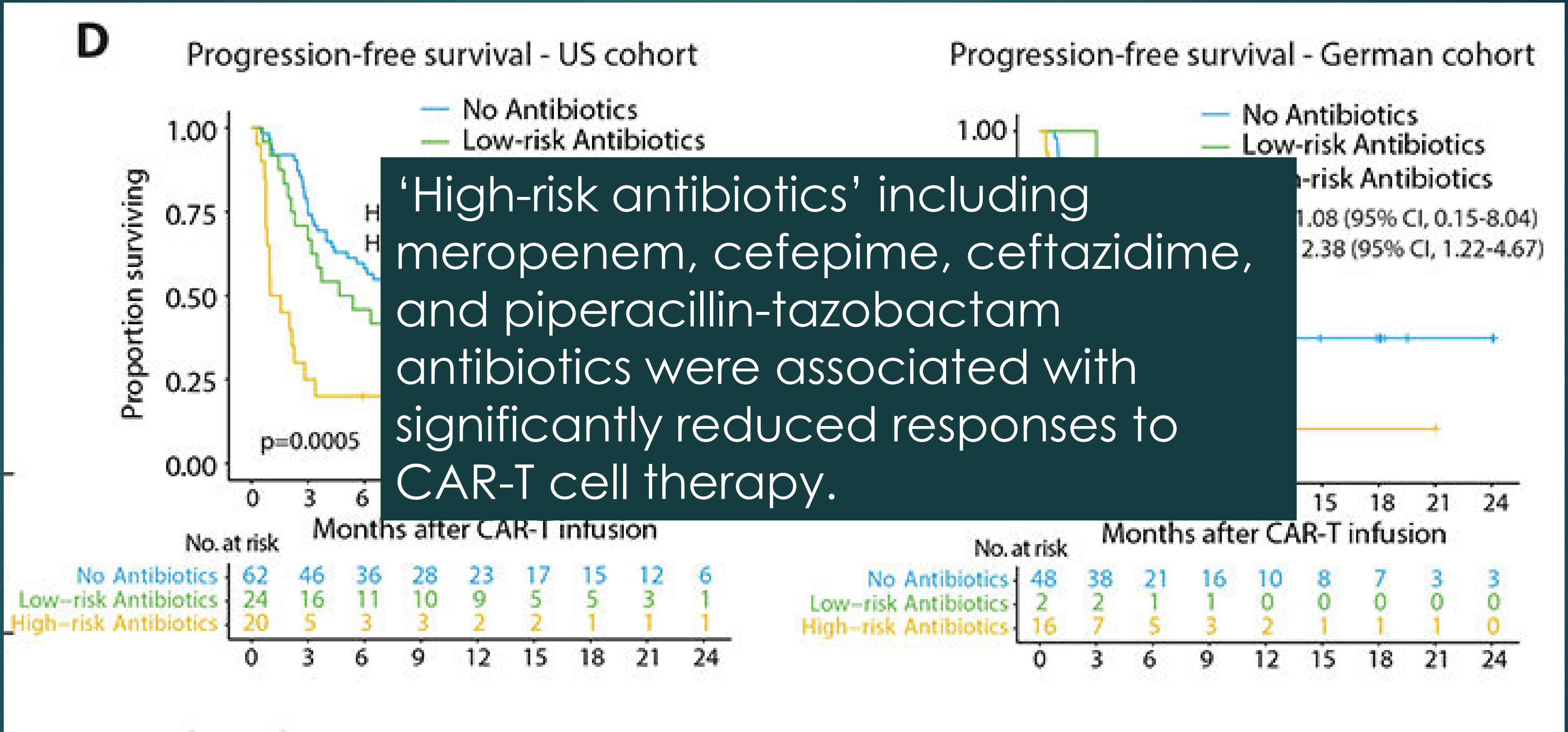
Microbiome

RESEARCH Open Access

Childhood BMI in relation to microbiota in infancy and lifetime antibiotic use

K. Korpela[1*], M. A. C. Zijlmans[2], M. Kuitunen[3], K. Kukkonen[4], E. Savilahti[3], A. Salonen[1], C. de Weerth[2] and W. M. de Vos[1,5]

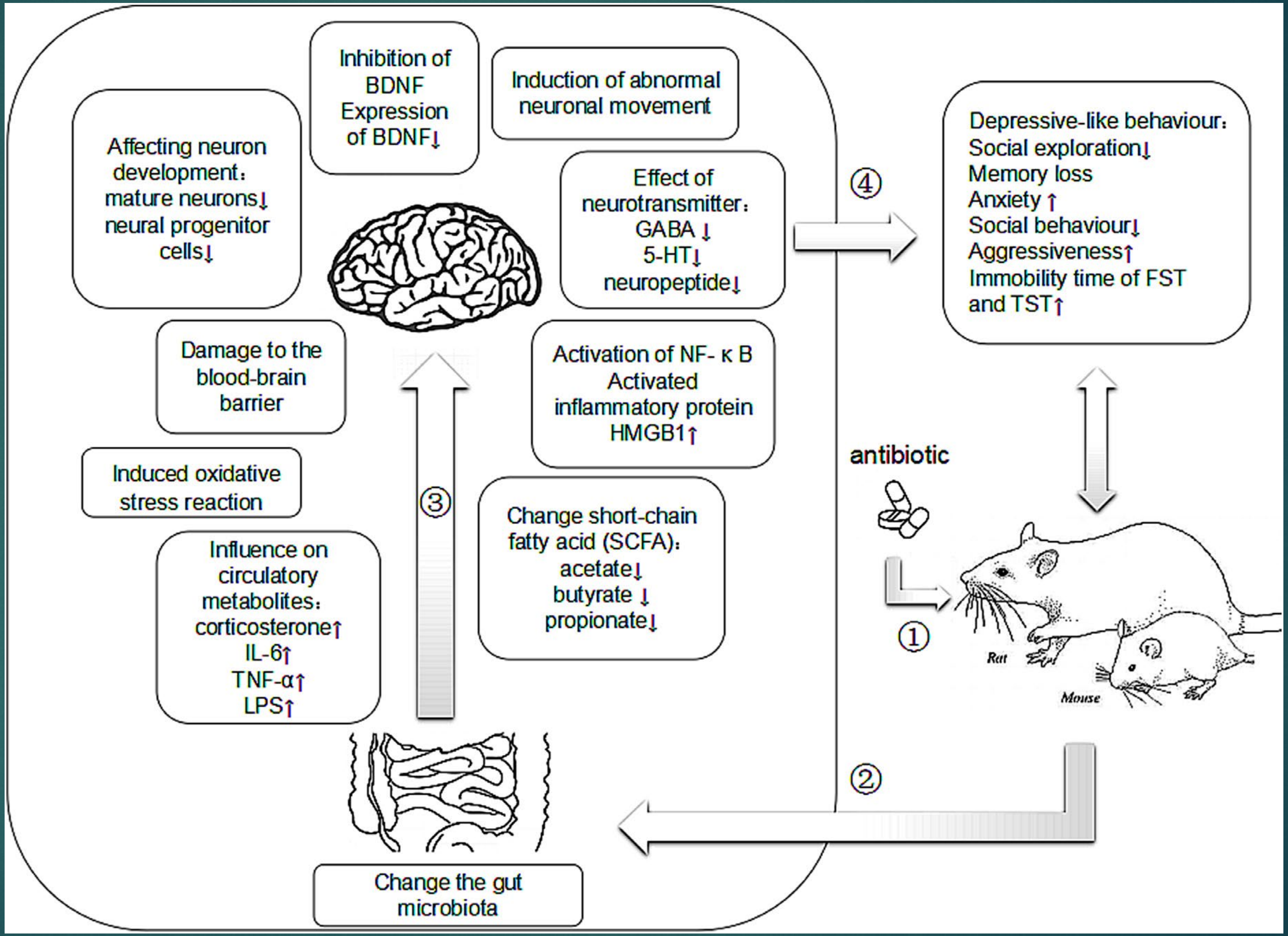
Prior antibiotic exposure affects survival after CAR-T cell therapy for B-cell Lymphoma



'High-risk antibiotics' including meropenem, cefepime, ceftazidime, and piperacillin-tazobactam antibiotics were associated with significantly reduced responses to CAR-T cell therapy.

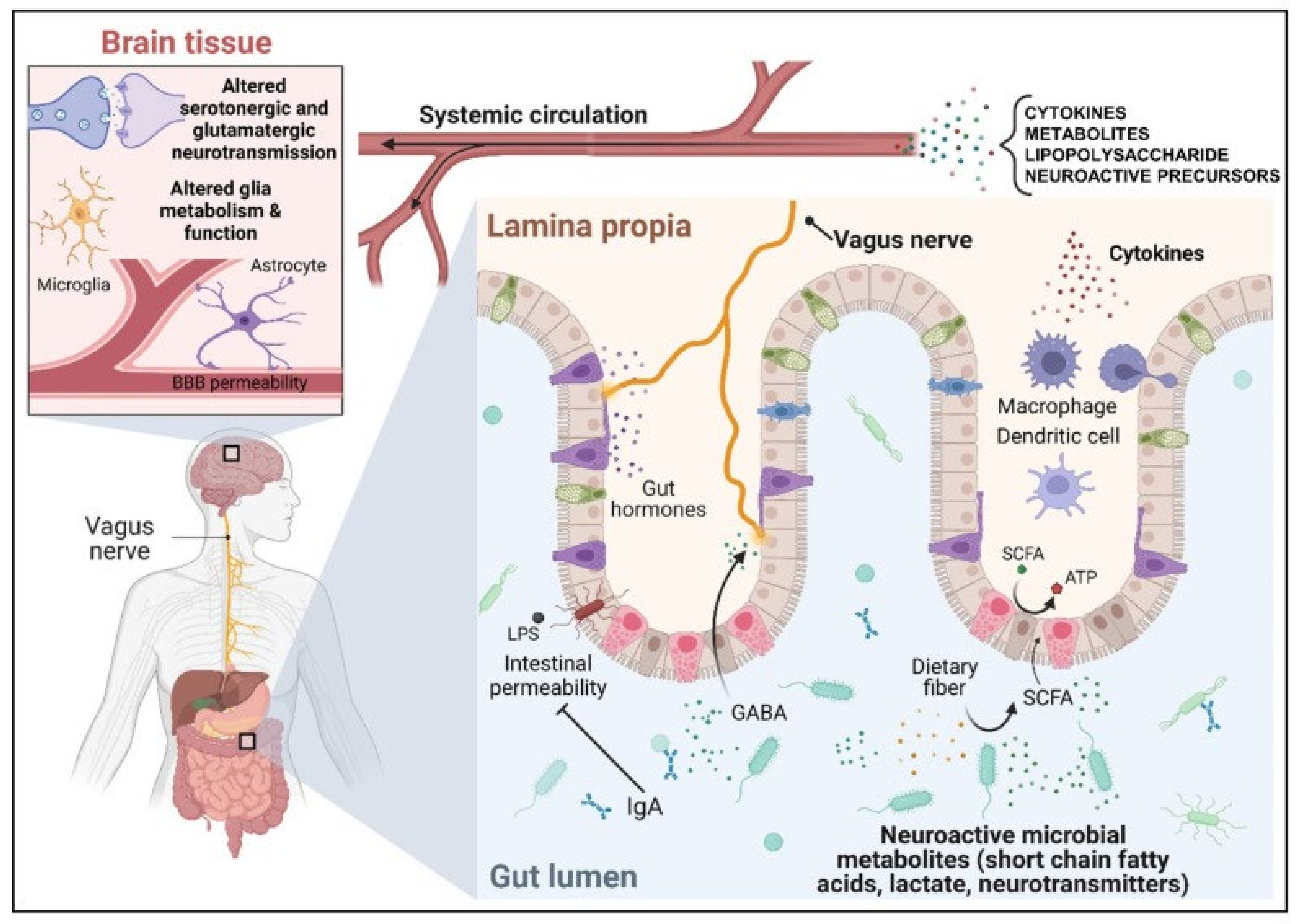
Nat Med. 2023 April ; 29(4): 906–916. doi:10.1038/s41591-023-02234-6.

Antibiotic impact on the Gut-Brain Axis



Psychiatry Research 284 (2020) 112691

The Human Gut-Brain Axis



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10146605/

British Journal of Hospital Medicine, VOL. 80, NO. 3 | Symposium on the Gut

normal

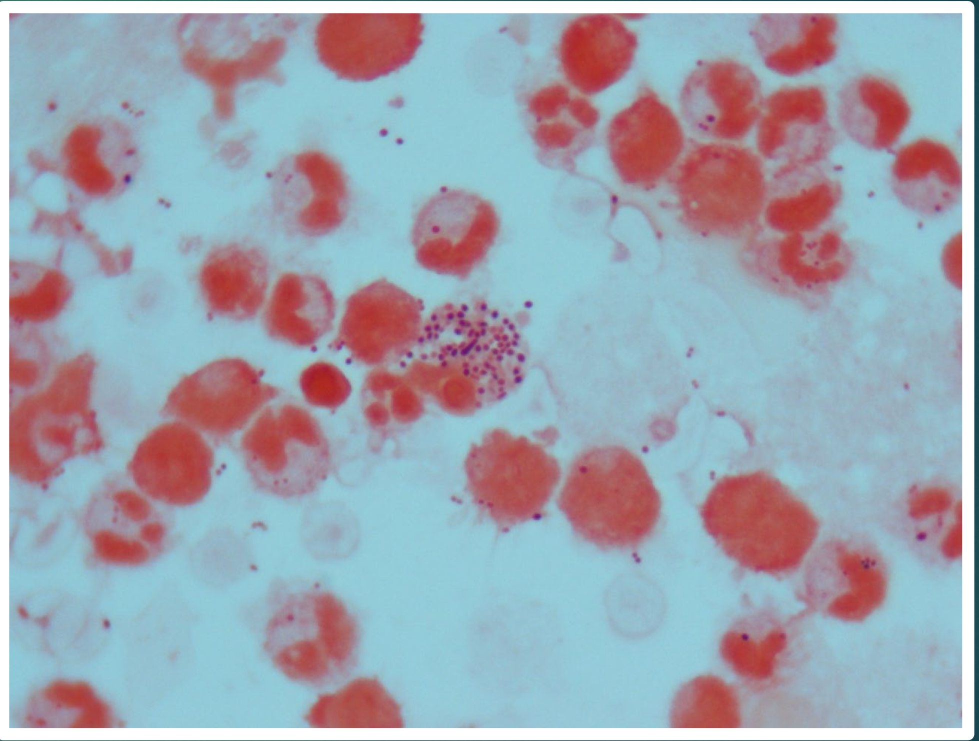
From isoniazid to psychobiotics: the gut microbiome as a new antidepressant target

Mary I Butler, Kiran Sandhu, John F Cryan, Timothy G Dinan

Published Online: 12 Mar 2019 | https://doi.org/10.12968/hmed.2019.80.3.139

Part 2. Antimicrobial resistance in Group B strep

Davie… 4-month-old with Late-Onset GBS Sepsis (June 2019)



CSF Gram Stain

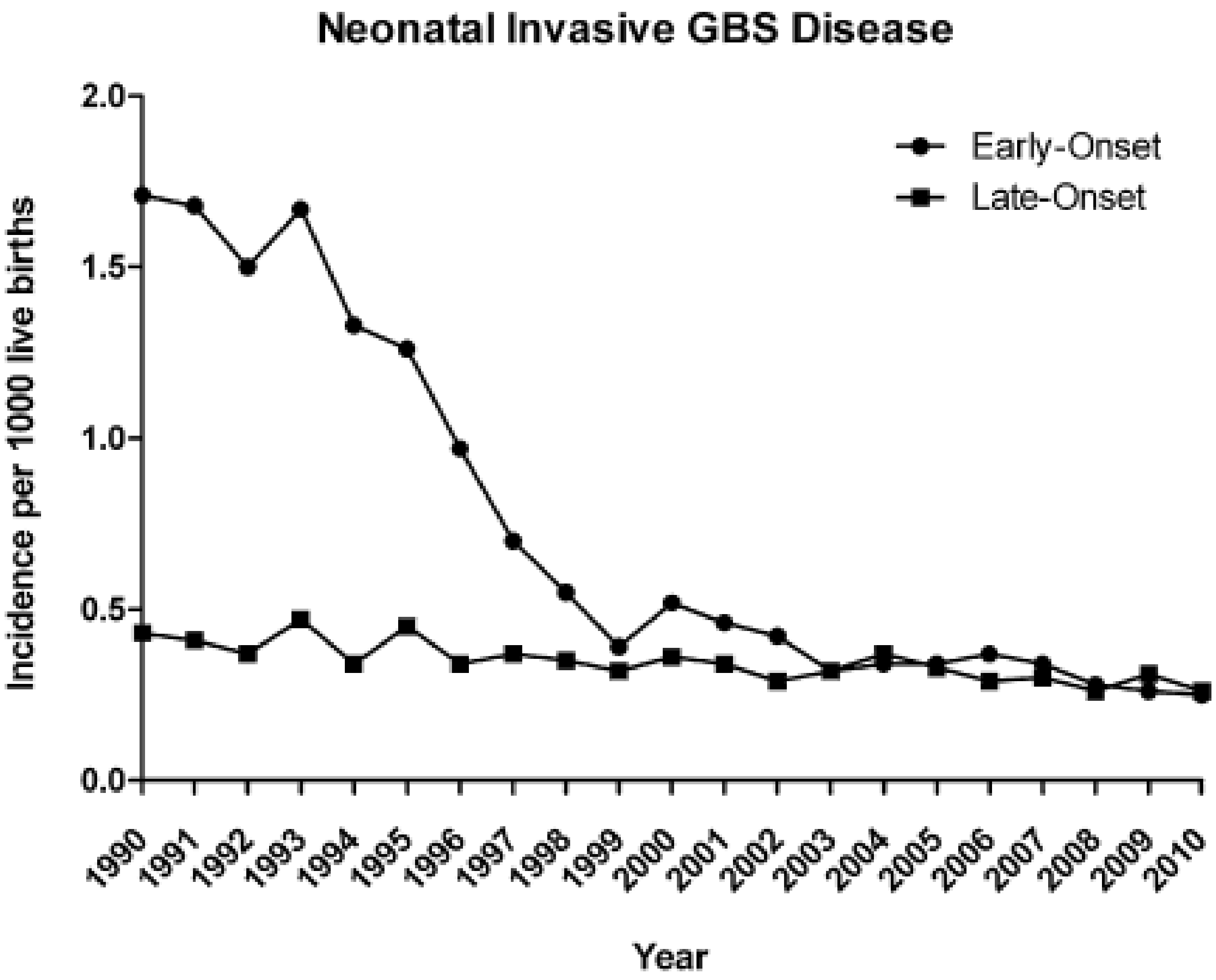
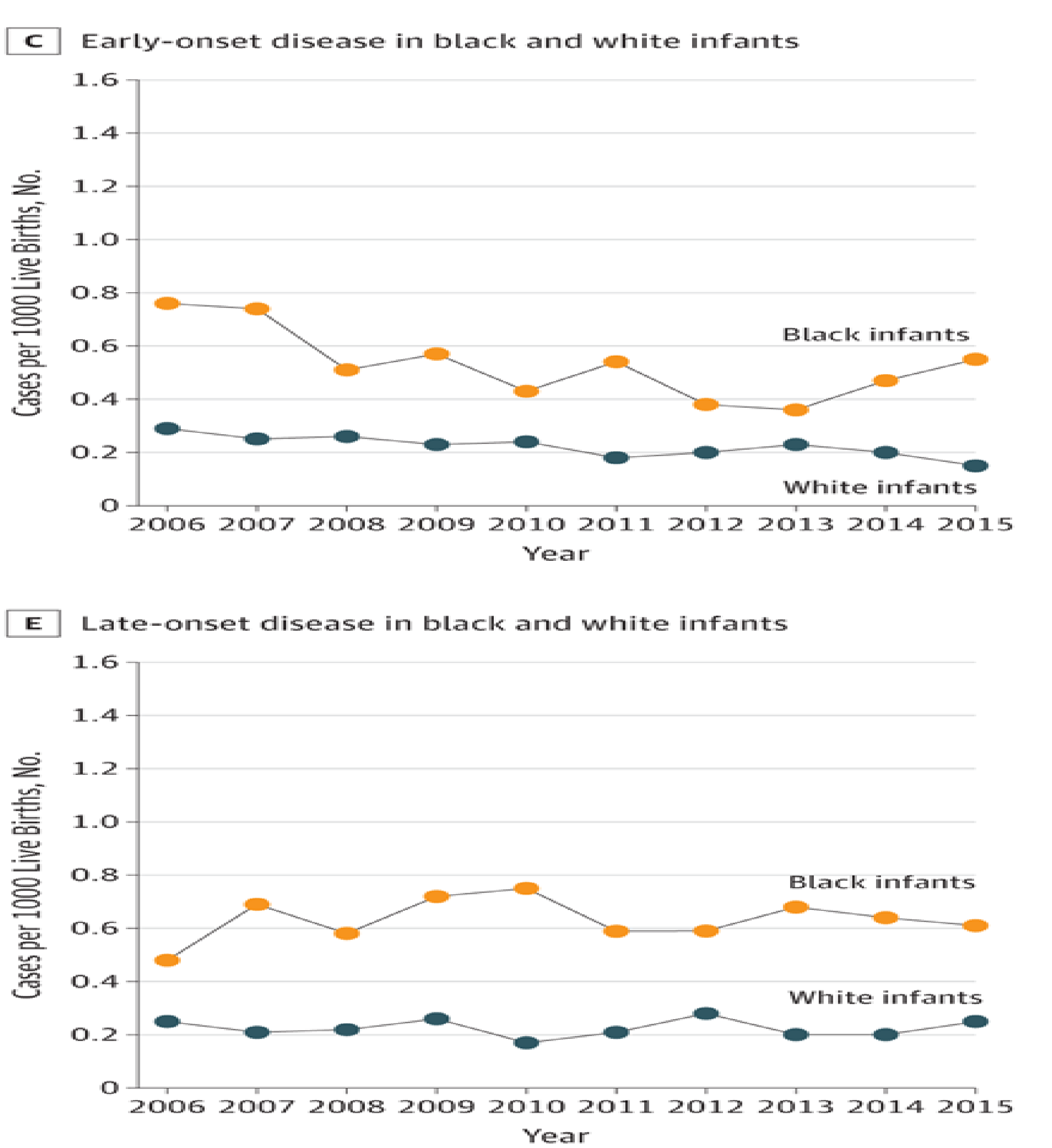


Fig. 1. Incidence of early- and late-onset invasive neonatal GBS disease, 1990–2010. Adapted from (1) Verani et al. [17], (2) [56] and (3) [57].

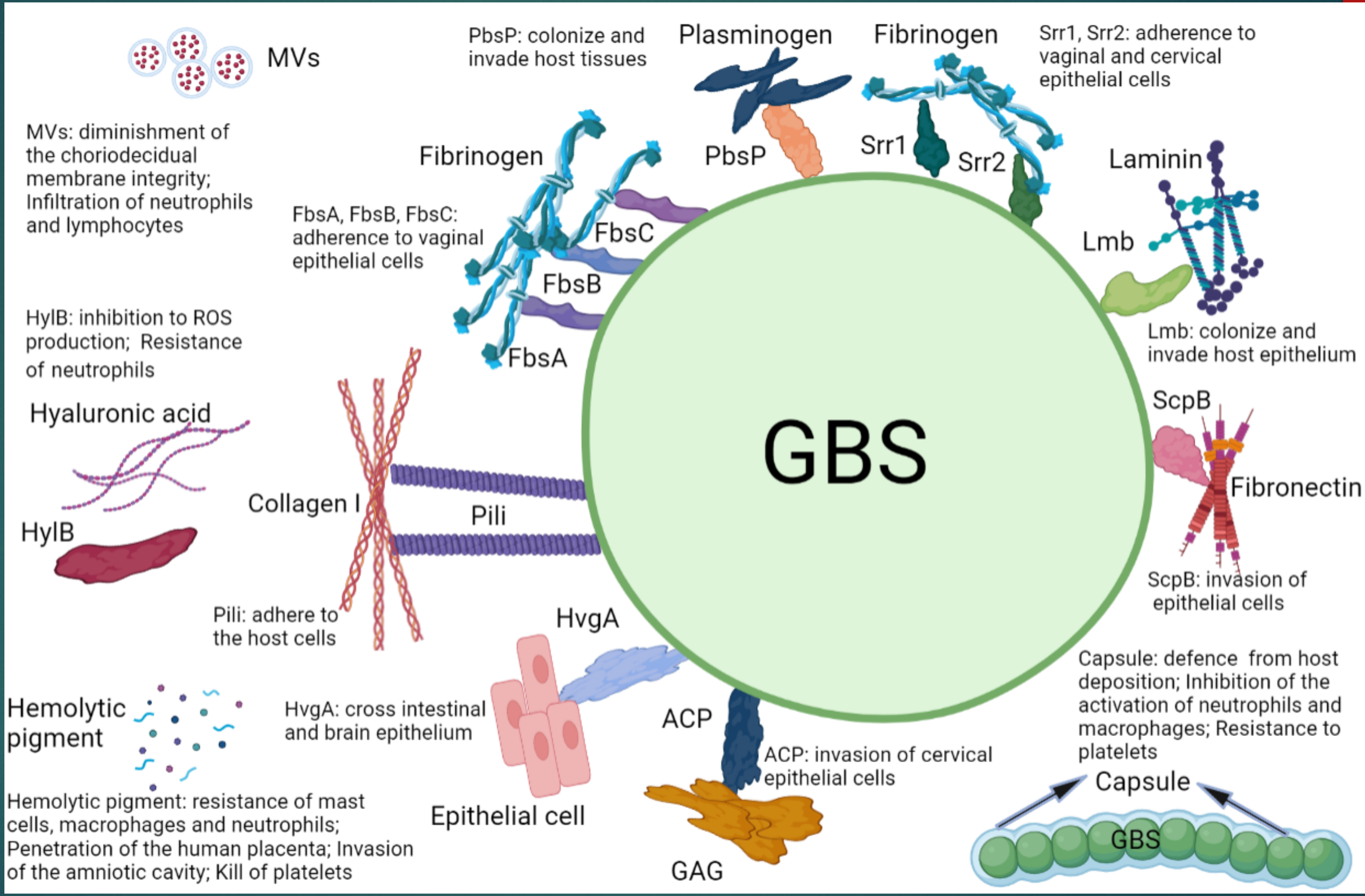
V.L. Chen et al. / Vaccine 31S (2013) D13–D19

African-American infants have ~3x the rate of GBS disease compared to white infants.



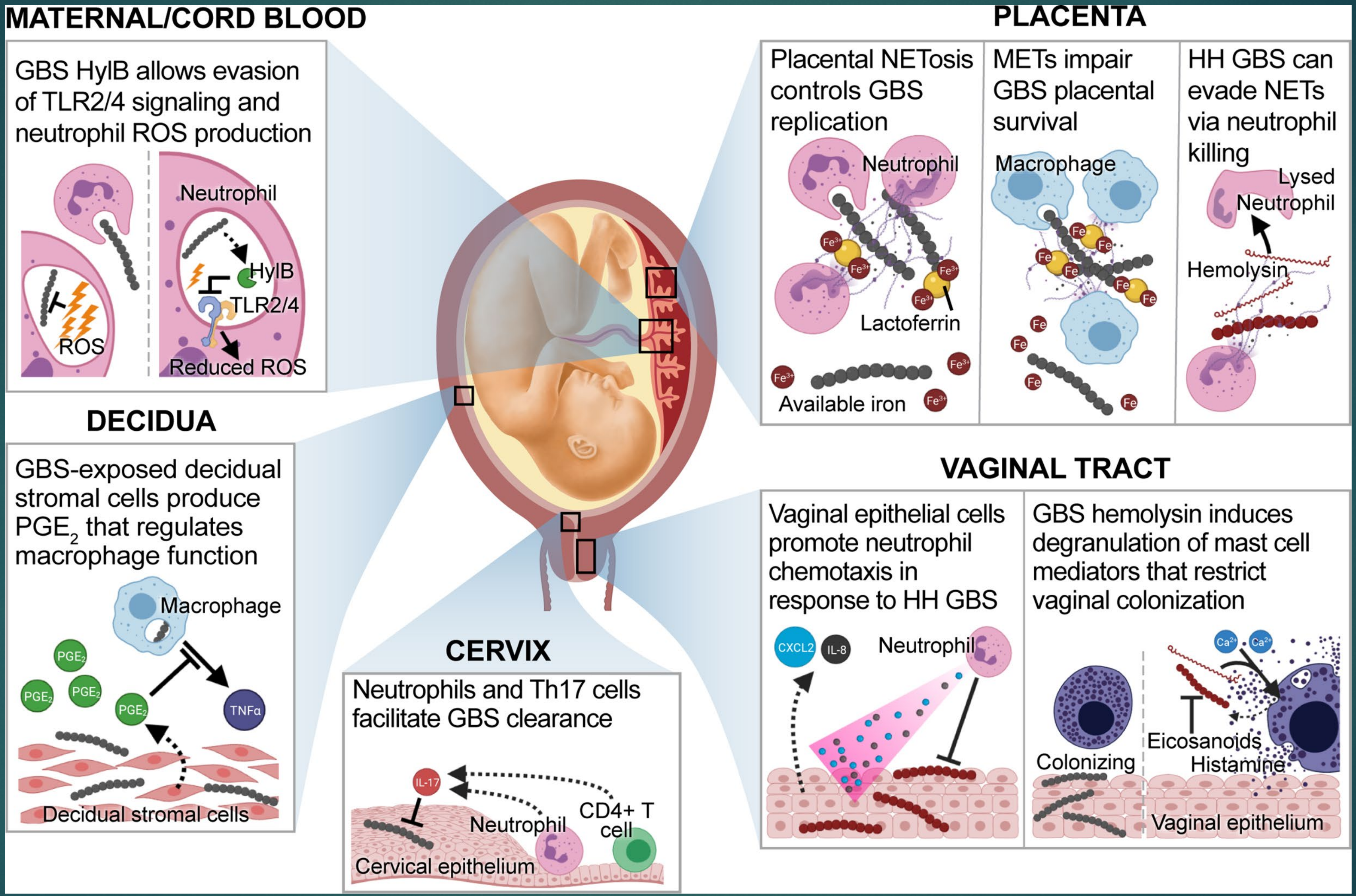
JAMA Pediatr. 2019;173(3):224-233. doi:10.1001/jamapediatrics.2018.4826

Figure 1. Summary of GBS virulence factors with their specific targets and mechanisms



Microorganisms 2022, 10, 2483

Host Immune Factors that mediate GBS infection and disease.



Brokaw A, et al.,*Front. Cell. Infect. Microbiol.* 11:720789.

Prior GBS studies at LSUHS

- Prior study by LSU Health group in 2009-10 (n=1500):
  - 35% GBS colonization
  - 24% iCLI resistance… highest reported in the literature at the time!!

- Azithromycin treatment for *Chlamydia trachomatis* infection and African American race were most significant risk factors for GBS with iCLI resistance ($p < 0.01$)

(Capraro, Rambin, Vanchiere, Bocchini, & Matthews-Greer, 2013; Capraro et al., 2019)

Methods – data per isolate…

managed by REDCap secure, HIPAA compliant software

Demographic	Clinical	Molecular	Serotype
• Age • Race • Ethnicity • Zip code	• Source of GBS • Parity • STI hx • Antibiotic hx • Delivery hx • AST	• GBS gene • *ermB* • *ermTR* • *ermT* • *MefA*	• Serotype Ia • Serotype Ib • Serotype II–IX

Age, race, ethnicity, and parity data as mean±SD, median, or N (%)
Categorical variable analysis by Chi-square (X^2) crosstabulation

Results – demographic and clinical, 2016-17

Characteristic	This study (n=333)	Prior LSU study (n=1513)
Age	26.9±7.04, 25.2	24.4±5.8, 23.0
Race:		
African-American	268 (80.5)	1114 (73.6)
White	49 (14.7)	201 (13.3)
Asian	3 (0.9)	
Other	13 (3.9)	35 (2.3)
Ethnicity:		
Hispanic	6 (1.8)	141 (9.3)
Non-Hispanic	323 (97.0)	1372 (90.7)
Unknown	4 (1.2)	
Parity	2.7±1.57, 2.0	
Urine isolates	68 (20.4)	
RV culture isolates	265 (79.6)	

Note. Data are N (%) or Mean±SD, Median. RV = rectovaginal swab.

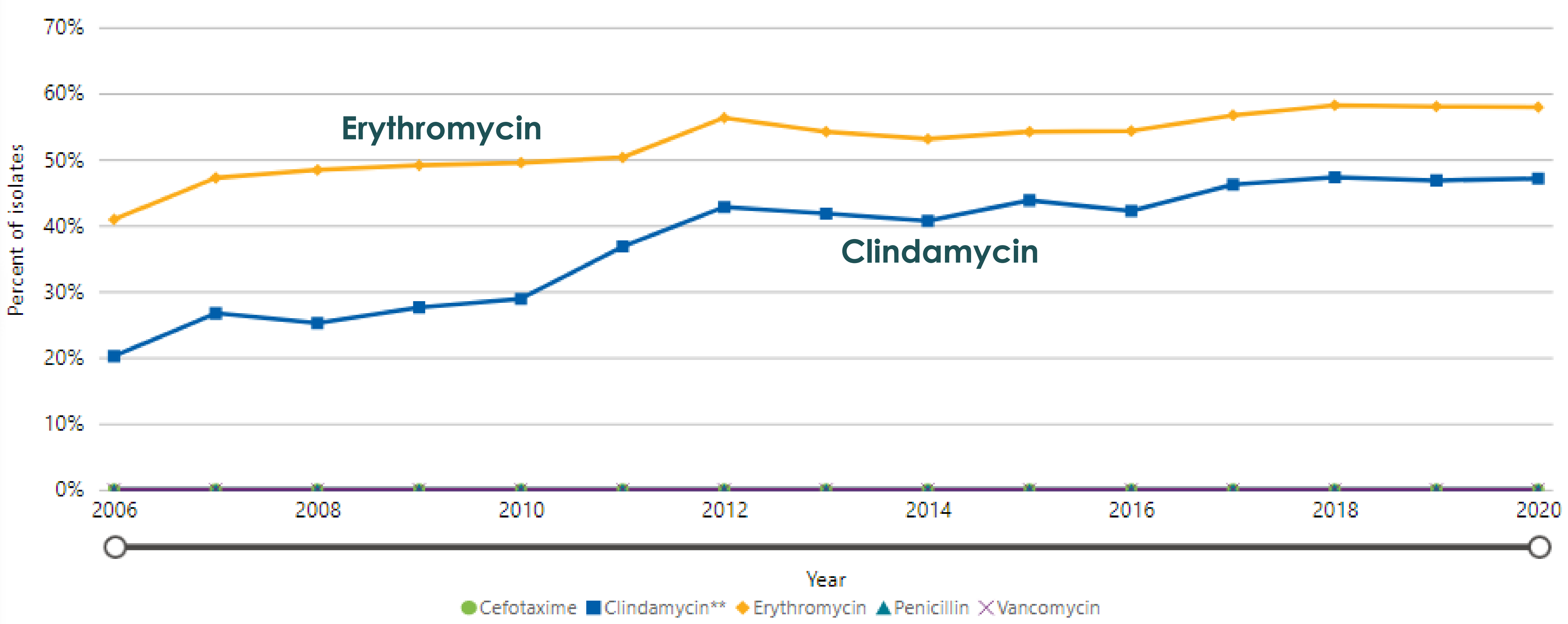
Results – frequency of erythromycin and clindamycin resistance, 2016-17

- AST Phenotype

(Amp, erythro, clinda, iCR)	N (%)	
A (S S S no)	135 (40.5)	
B (S R S no)	36 (10.8)	
C (S R R no)	147 (44.1)	
D (S R R yes)	12 (3.6)	⟵ *iCLI-R*
E (S S R no)	3 (0.9)	

Note. S = susceptible. R = resistant. No = iCR not detected. Yes = iCR detected

Percent of Invasive GBS isolates resistant to select antibiotics in ABCs areas



https://www.cdc.gov/abcs/bact-facts-interactive-dashboard.html

Results – resistance phenotypes and molecular phenotypes

	Molecular phenotype							
	B (+ + + -) *mef* & *ermB*	C (+ + - -) *mef* only	D (+ - - -) None	E (+ - + +) *ermB* and *ermTR*	F (+ - - +) *ermTR* only	G (+ + - +) *mef* and *ermTR*	H (+ - + -) *ermB* only	
AST phenotype								Total
A (SSS no)	1	22	96	3	3	0	10	135
B (SRS no)	2	27	6	1	0	0	0	36
C (SRR no)	5	6	22	7	13	3	73	147
D (SRR yes)	1	0	4	1	5	1	0	12
E (SSR no)	0	0	2	0	1	0	0	3
Total	9	55	130	12	40	4	83	333

Note. S = susceptible. R = resistant. No = iCR not detected. Yes = iCR detected. + denotes gene presence. - denotes absence of gene. AST Phenotype = (Ampicillin, erythromycin, clindamycin, iCR)

Results – serotype distribution

Serotype distribution of 2016-2017 LSU Health GBS isolates compared to U.S. and Canada reference populations

Serotype	**2016-2017 LSU Health GBS isolates (n=93)**	2010 U.S. Reference Population (n=175)	2017 Toronto population (n=102)
Ia	**16.1%**	33.7%	23%
Ib	**19.4%**	14.3%	9%
III	**39.8%**	32.0%	25%
V	**24.7%**	20.0%	19%

Note. 2010 U.S. reference population adapted from "Group B streptococcus serotype prevalence in reproductive-age women at a tertiary care military medical center relative to global serotype distribution," by D. Ippolito, W. James, D. Tinnemore, R. Huang, M. Dehart, J. Williams, M. Wingerd, and S. Demons, 2010, *BMC Infectious Diseases, 10,* 336. Copyright 2010 by BioMed Central Ltd. 2017 Toronto population adapted from "Serotype distribution, population structure, and antimicrobial resistance of group B *Streptococcus* strains recovered from colonized pregnant women," by S. Teatero, P. Ferrieri, I. Martin, W. Demczuk, A. McGeer, and N. Fittipaldi, 2017, *Journal of Clinical Microbiology, 55*(2), 412-422. Copyright 2017 by The American Society for Microbiology.

Results – serotype distribution

Correlation analysis between AST phenotype, molecular phenotype, and serotype

Variables	Spearman *rho*	*p*-value
AST and molecular phenotypes	*rho* (331) = .471	.0001*
AST phenotype and serotype	*rho* (93) = -.050	.634
Molecular phenotype and serotype	*rho* (93) = .070	.507

*Correlation is significant at the 0.01 level (2-tailed)

Results – resistance phenotypes and molecular phenotypes

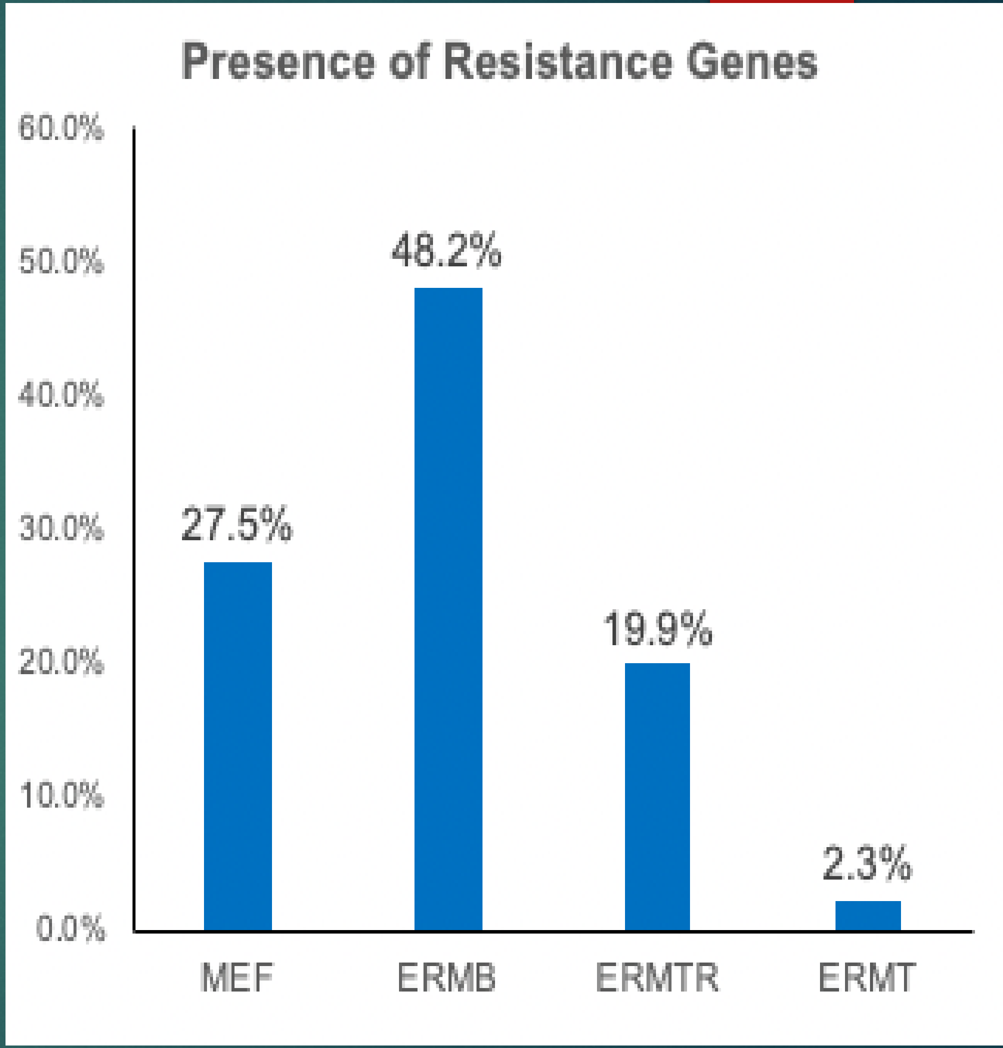
Analysis	X^2 (df)	*p*-value*
AST phenotype and GBS source	3.3 (4)	.502
AST phenotype and parity	35.6 (36)	.487
AST phenotype and race	12.4 (12)	.409
AST phenotype and antibiotic exposure	62.6 (64)	.526
AST phenotype and azithromycin exposure	228.3 (1)	.0001[a]
AST phenotype and antibiotic indication	51.3 (48)	.342
AST phenotype and chlamydia infection	246.2 (1)	.0001[a]
Molecular phenotype and GBS source	4.1 (6)	.656
Molecular phenotype and parity	33.3 (54)	.987
Molecular phenotype and race	13.5 (18)	.755
AST phenotype and molecular phenotype	268.9 (24)	.0001[a]

*X^2, $p < .05$.

[a]Significance in chi-square test of distribution

Results, 2019-2020

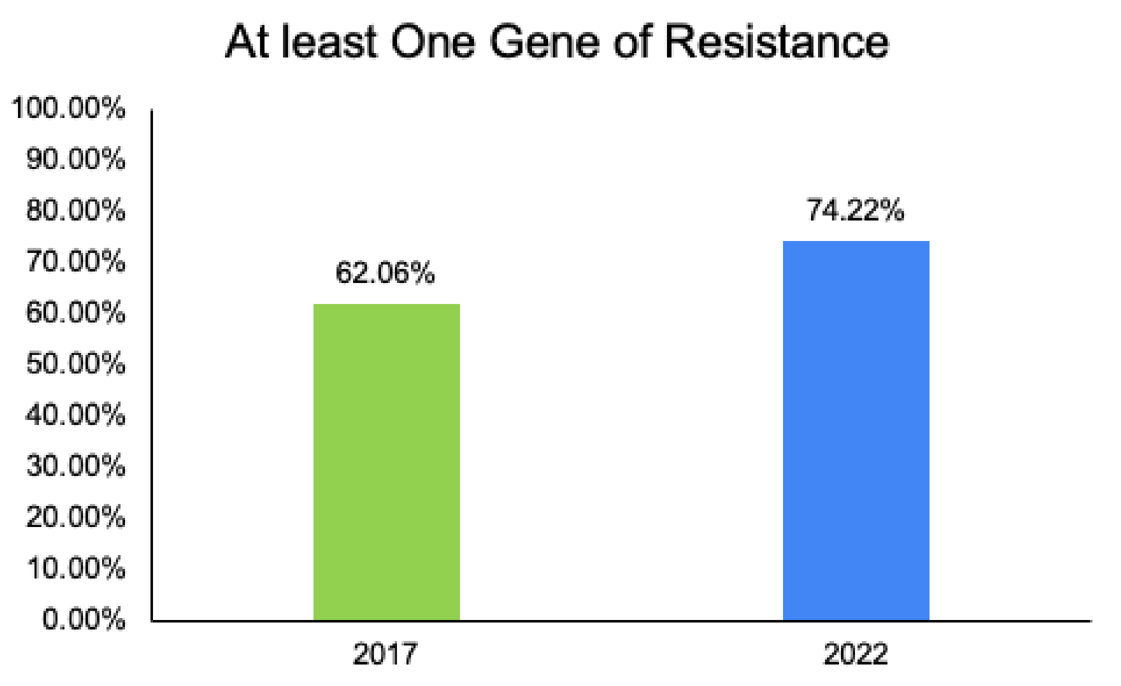
- *tkt* is a GBS specific housekeeping gene
  - *tkt* negative isolates were not included in statistical analysis
- Of the 547 total GBS isolates, 512 (93.6%) tested positive for *tkt*
- Overall, 384 (75.0%) of the *tkt*-positive isolates carried at least one resistance gene



Comparison of 2017 and 2022 data

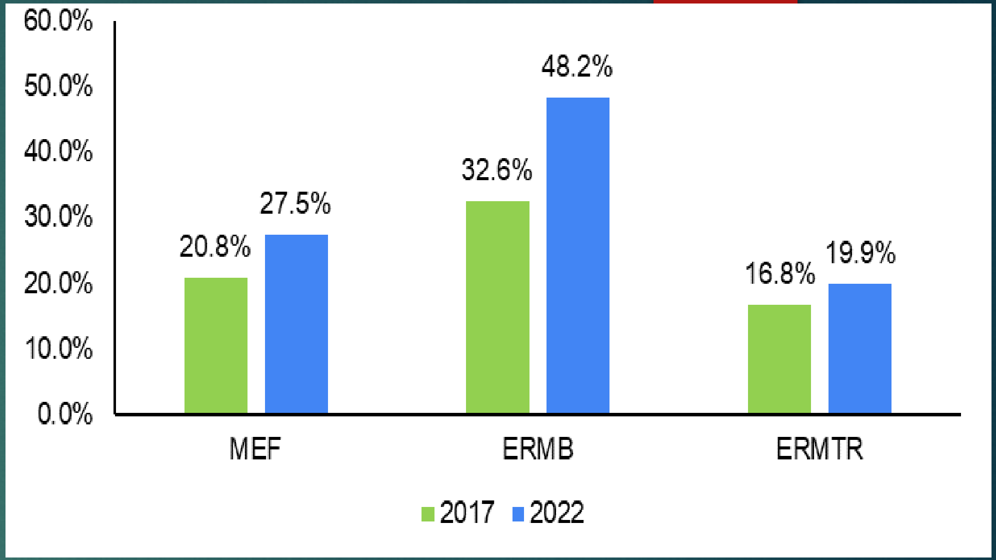
- When comparing *tkt*+ isolates that have at least one resistance gene, this study saw a 20.85% increase from the previous study
- (62.06% vs 74.22%, P<0.0001)

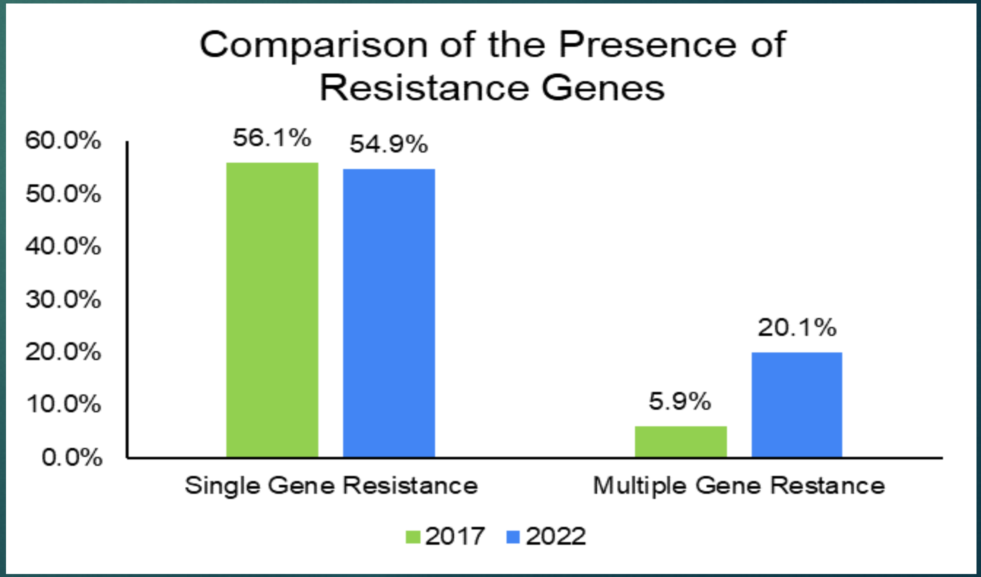
- Note: *ermT* was removed from statistical analysis when comparing the studies because the 2017 study did not include *ermT*



Comparison of 2017 and 2022 data

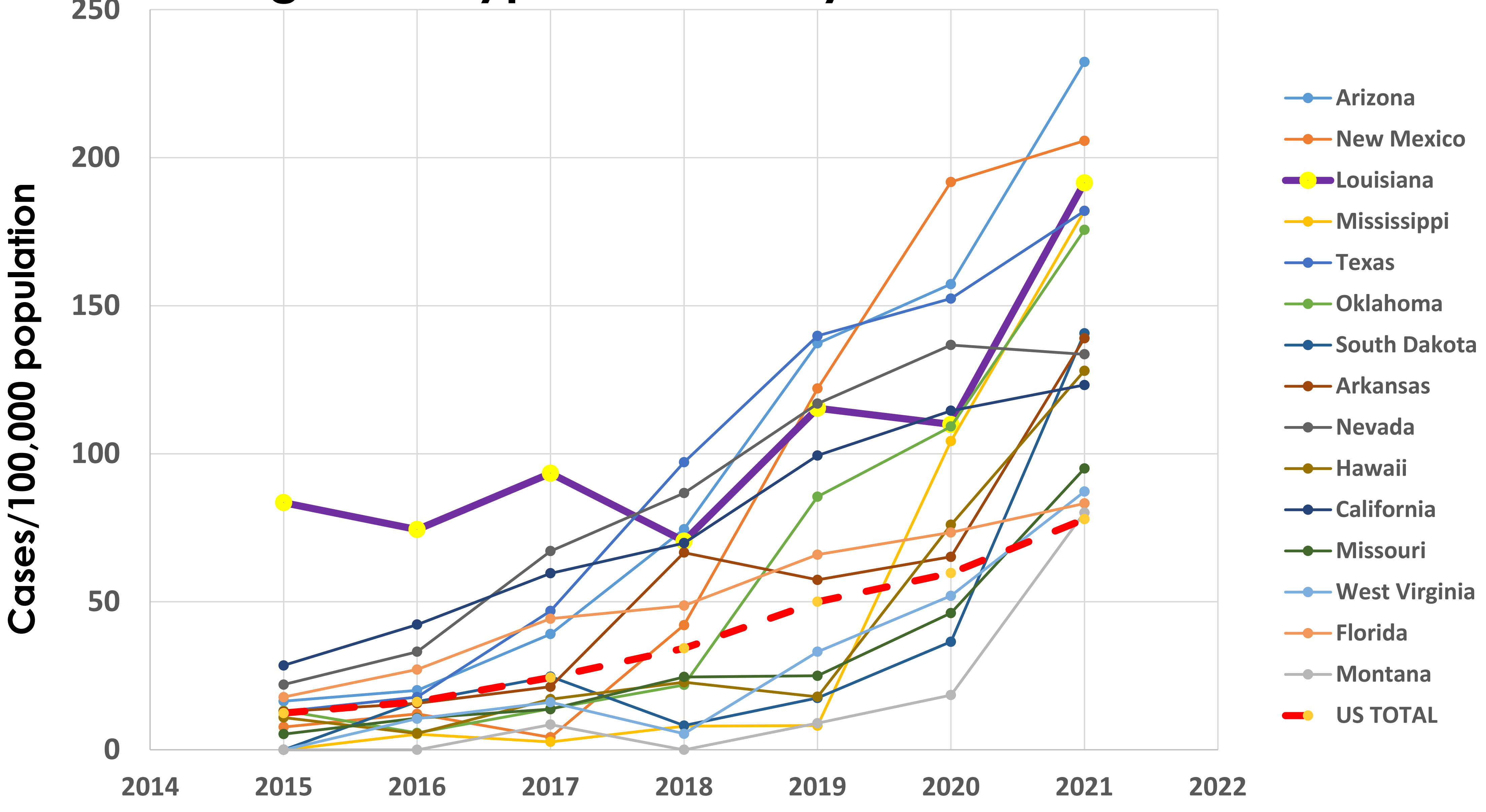
- There was an increase in the prevalence of each resistance gene when compared to the previous study
- When comparing the presence of isolates with only one resistance gene, there is not a statistically significant change
- However, this study showed a 2.4-fold increase in isolates with multiple resistance genes compared to the previous study (p-value <0.0001)





Part 3. The complexity of homeostasis in pregnancy

Congenital Syphilis Rates by State, 2015-2021

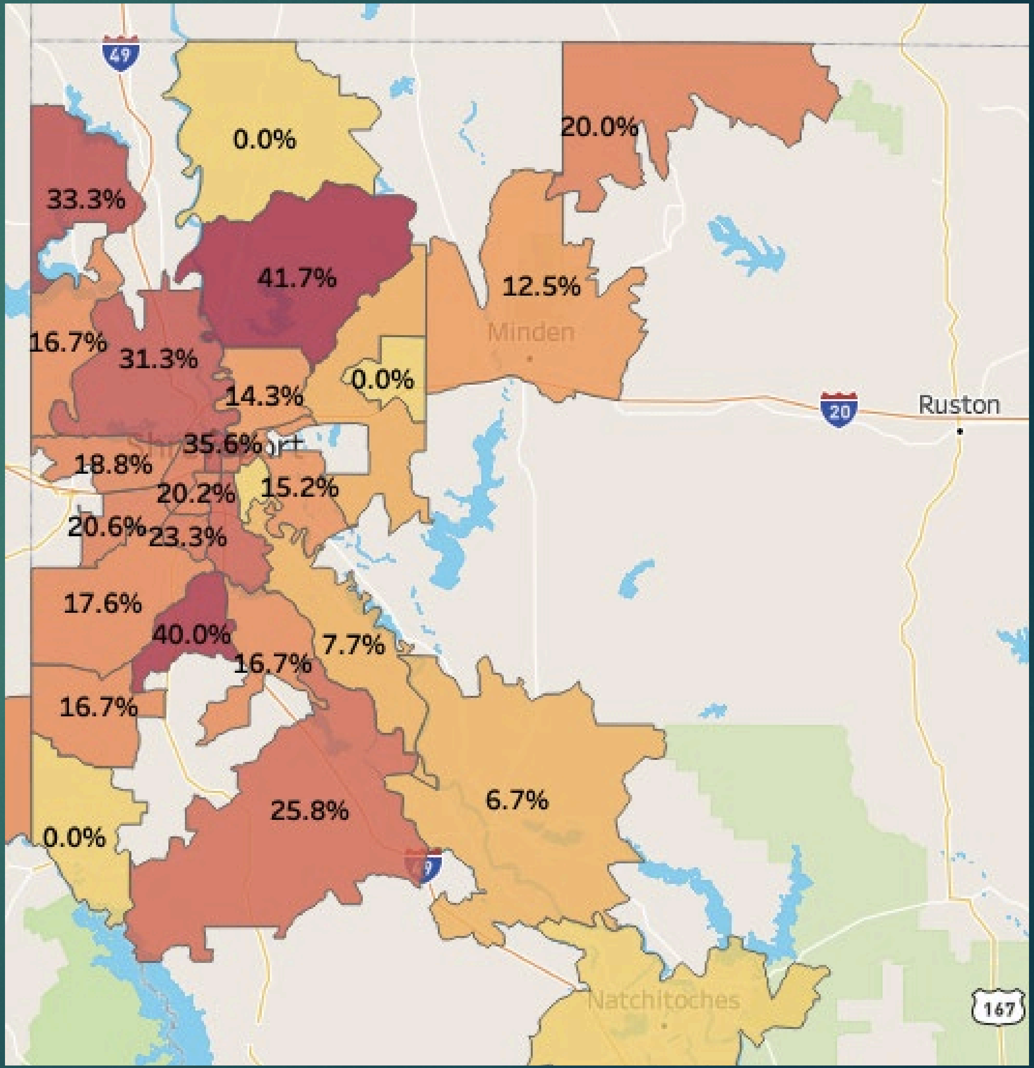


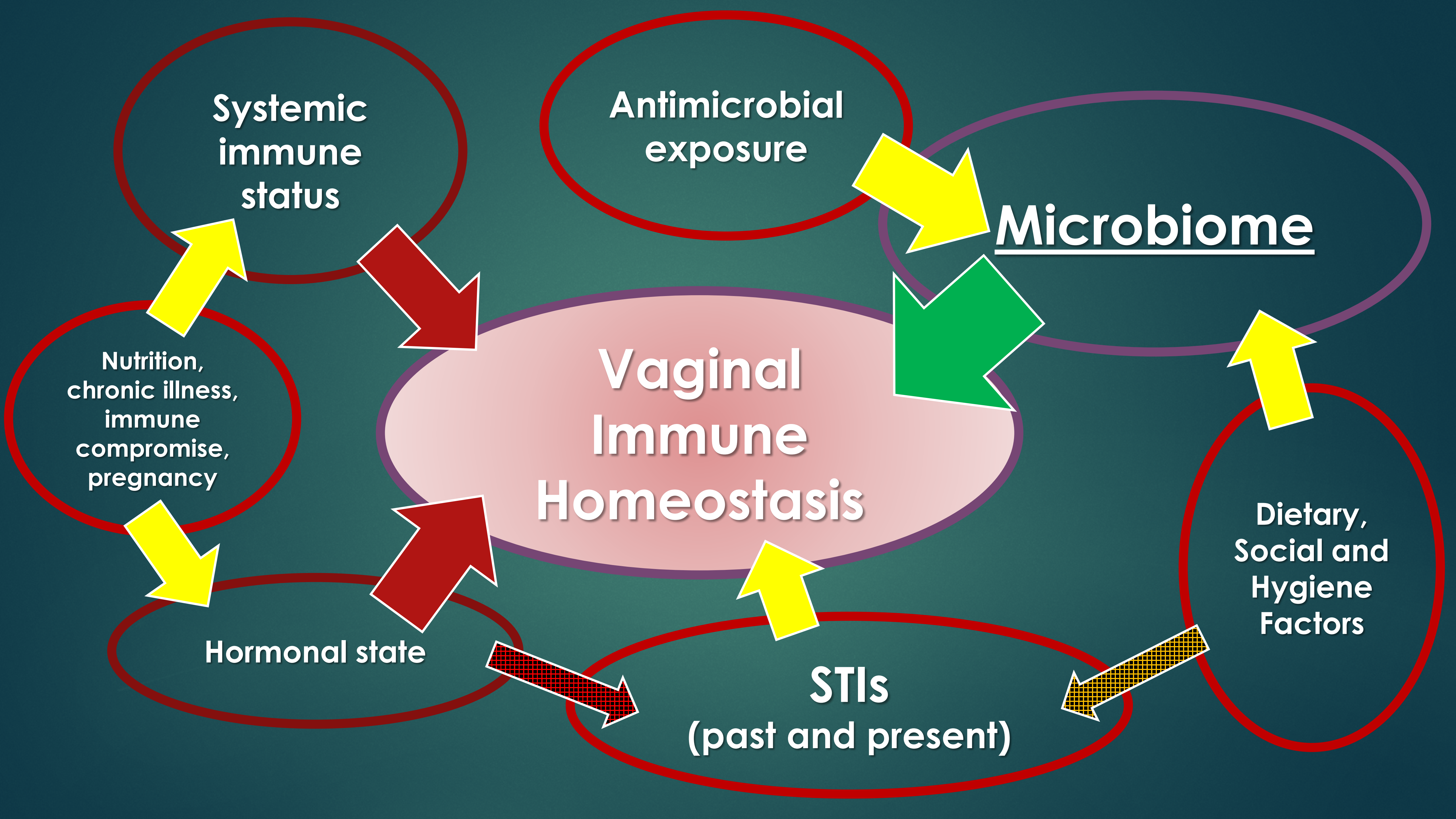
https://www.cdc.gov/std/statistics/2021/tables/21.htm

Endemic Infectious Diseases in Caddo Parish

- For 2021, Louisiana ranked 3rd in the nation for Gonorrhea, Chlamydia and Syphilis.
- Caddo Parish consistently experiences some of the highest rates of sexually transmitted illnesses (STIs) in Louisiana.
- Specific vulnerable communities have even higher rates than the overall population
- Rates in African-Americans are 5-7x greater than in European-Americans

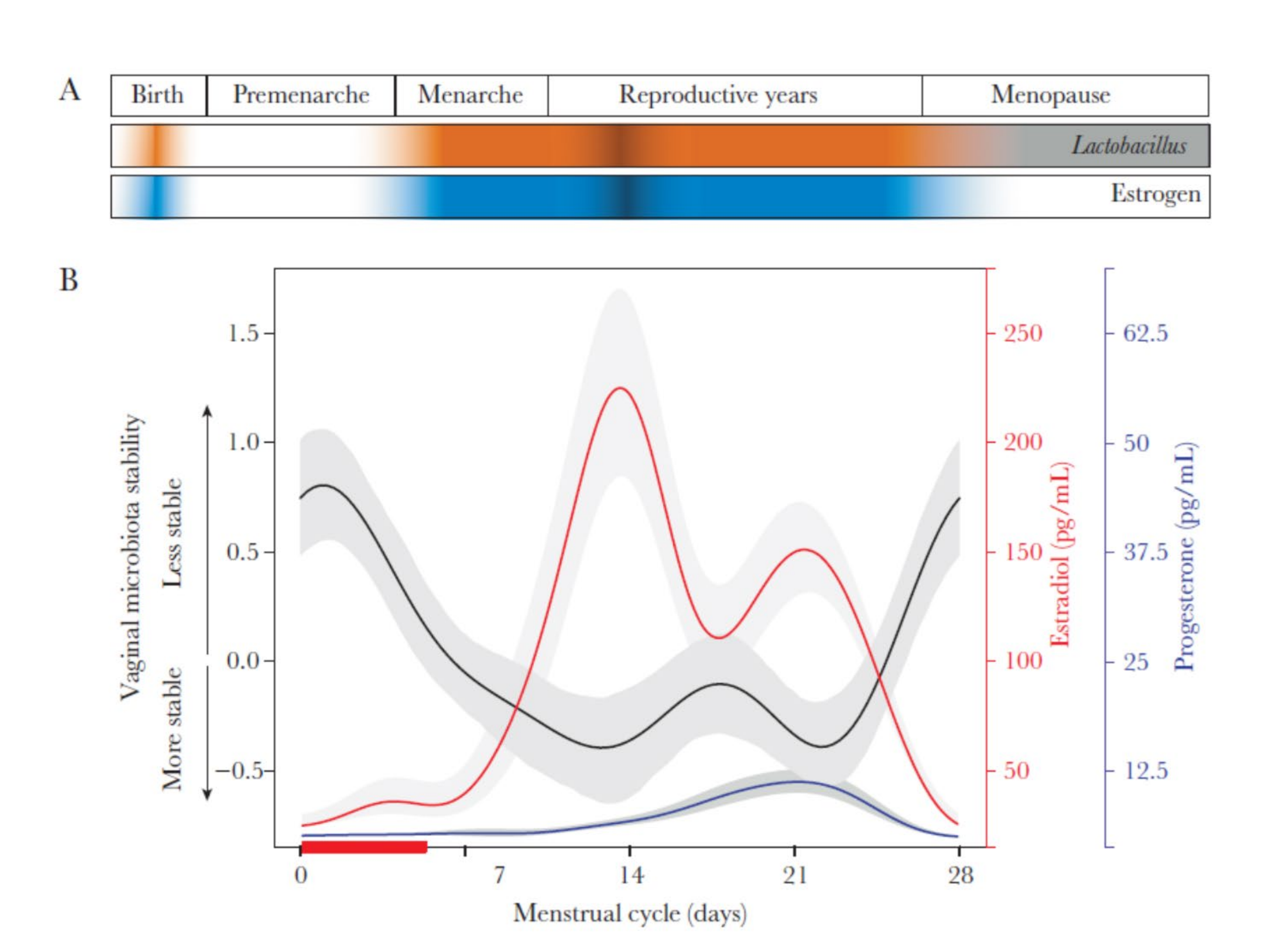
% positive for C. *trachomatis* among pregnant women receiving care at LSUHS, 2009-11



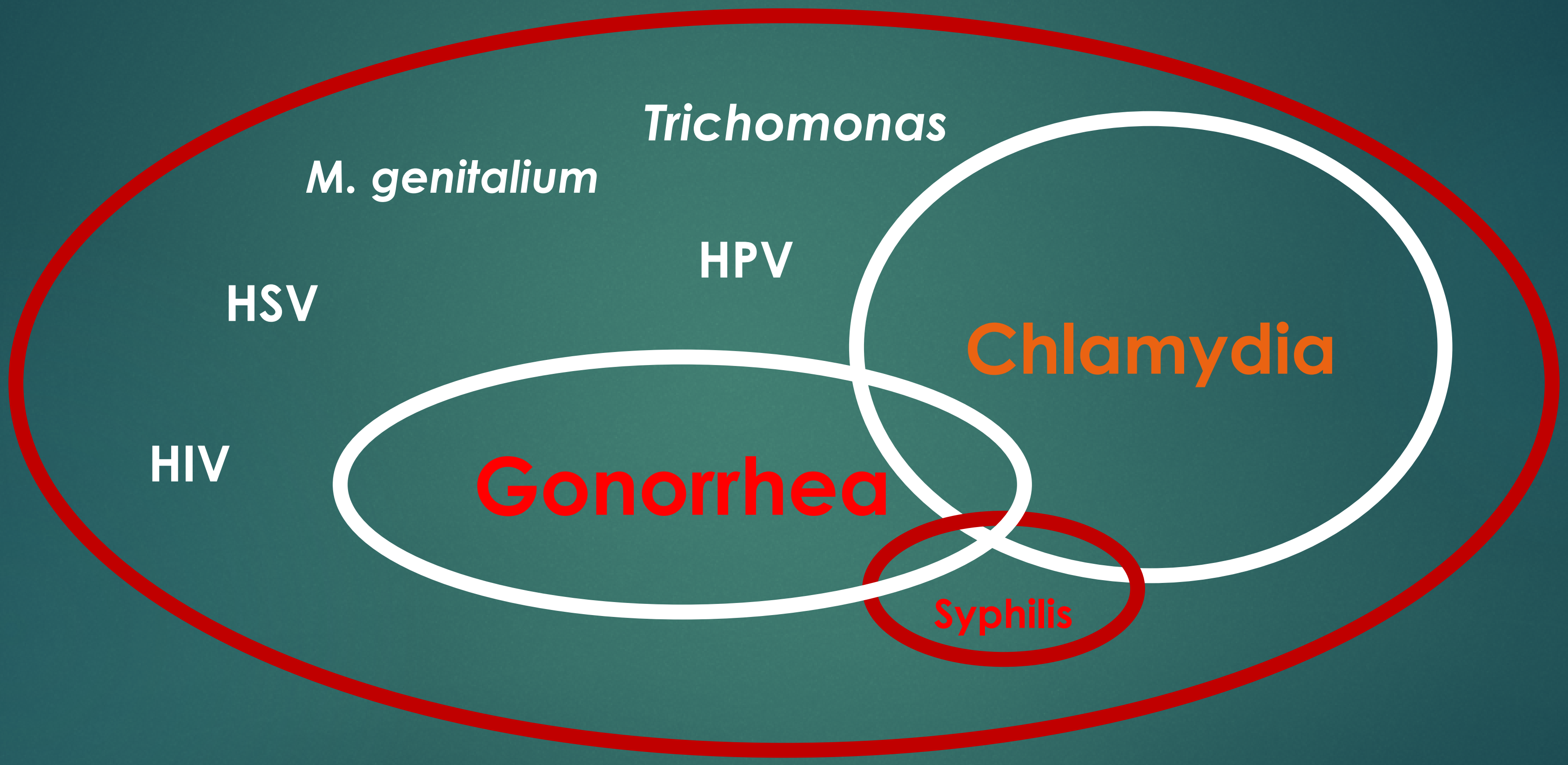

Systemic immune status
Antimicrobial exposure
Microbiome
Nutrition, chronic illness, immune compromise, pregnancy
Vaginal Immune Homeostasis
Dietary, Social and Hygiene Factors
Hormonal state
STIs
(past and present)

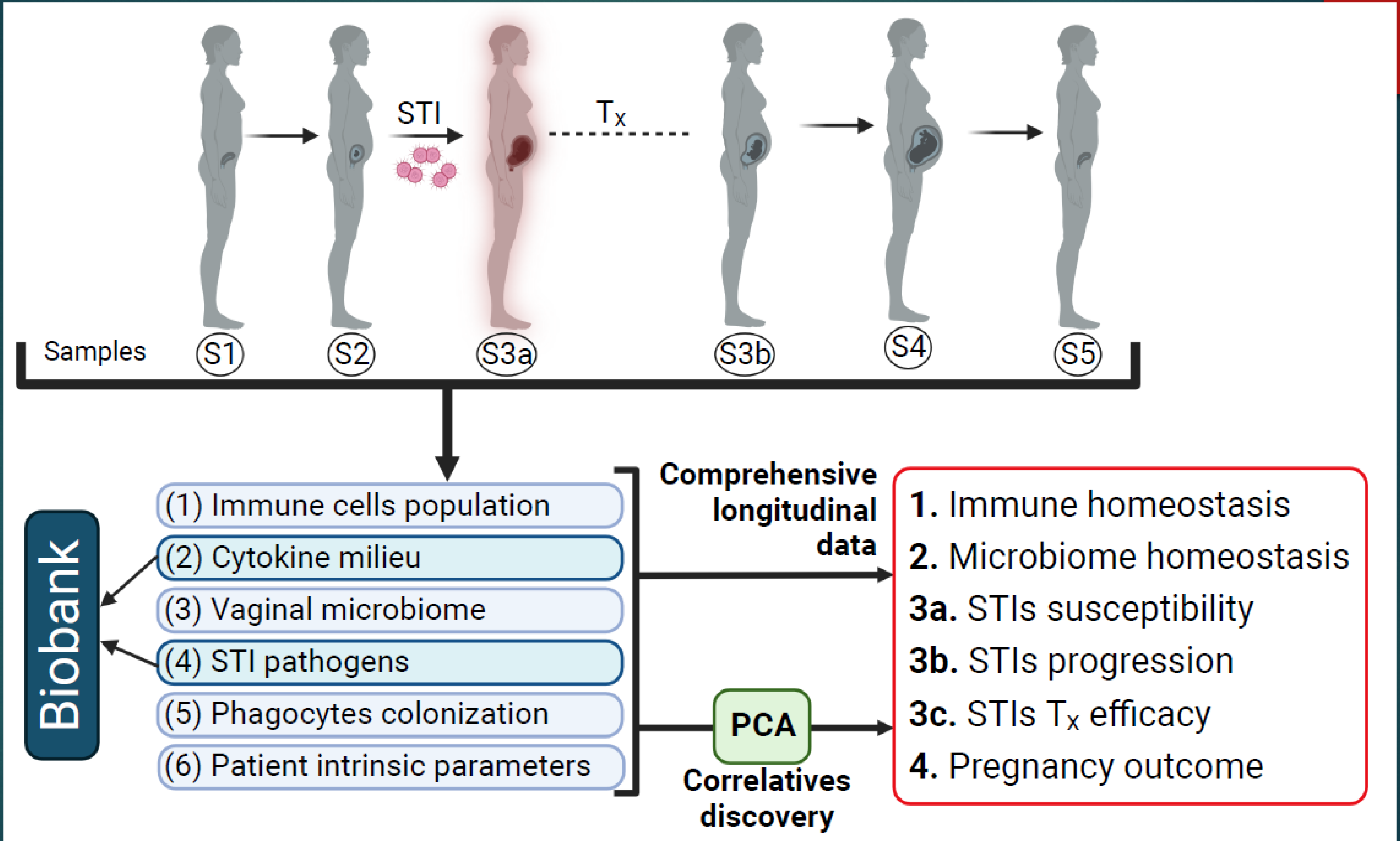
The importance of *Lactobacilli*

- *L. crispatus*
- *L. iners*
- *L. jensenii*
- *L. gasseri*

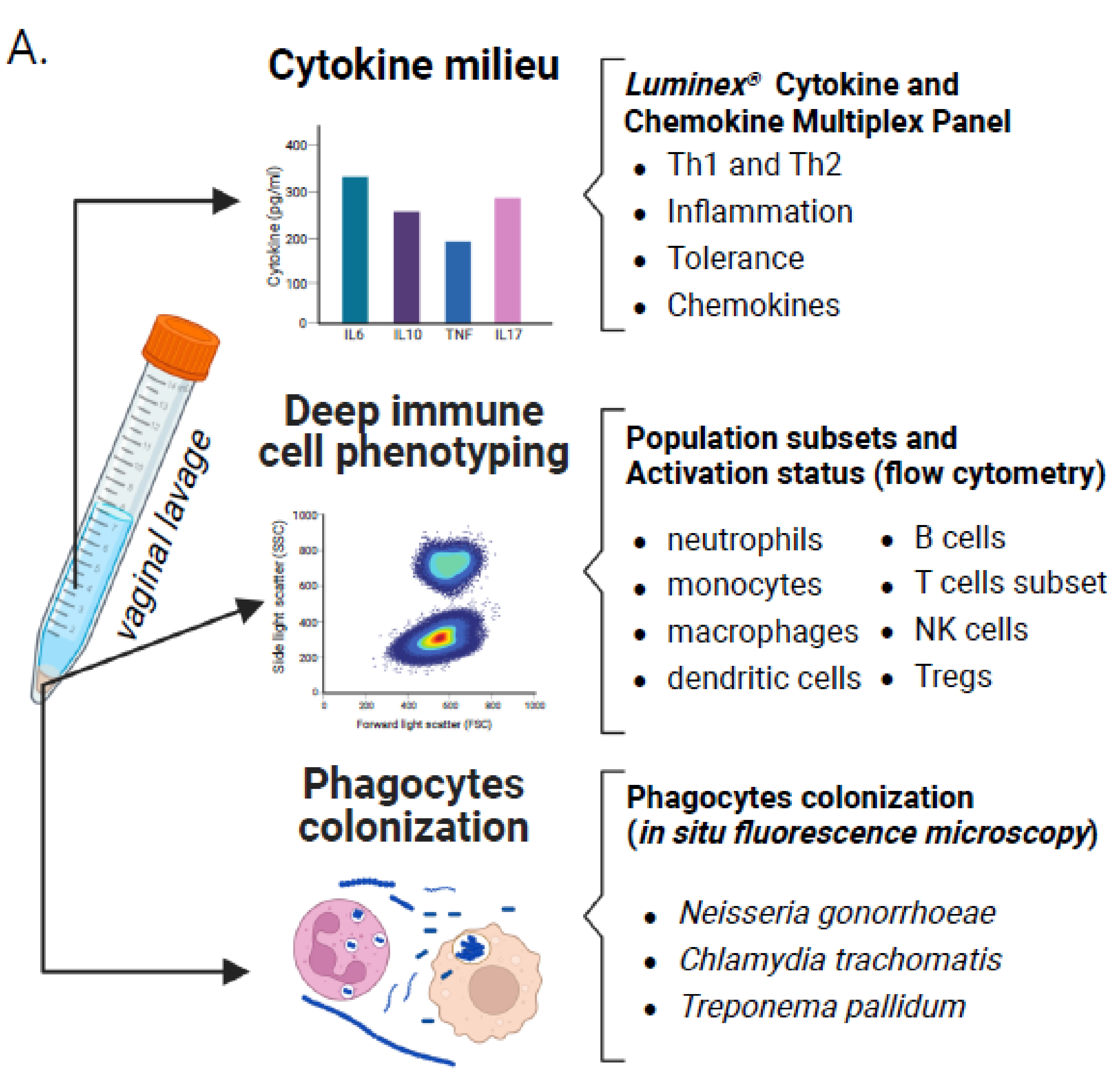


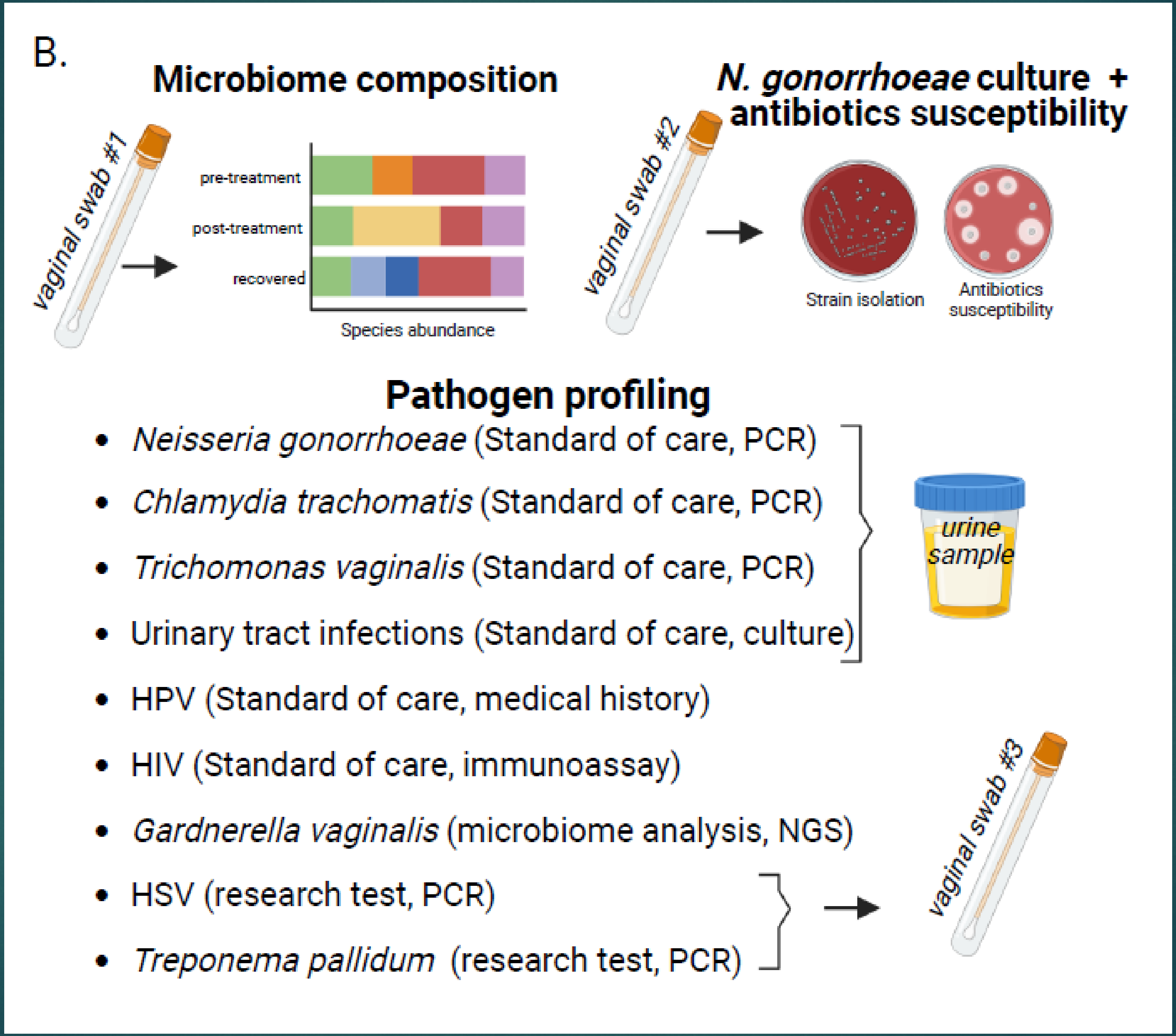
Understanding the "natural history" of STIs is a complex adventure!!



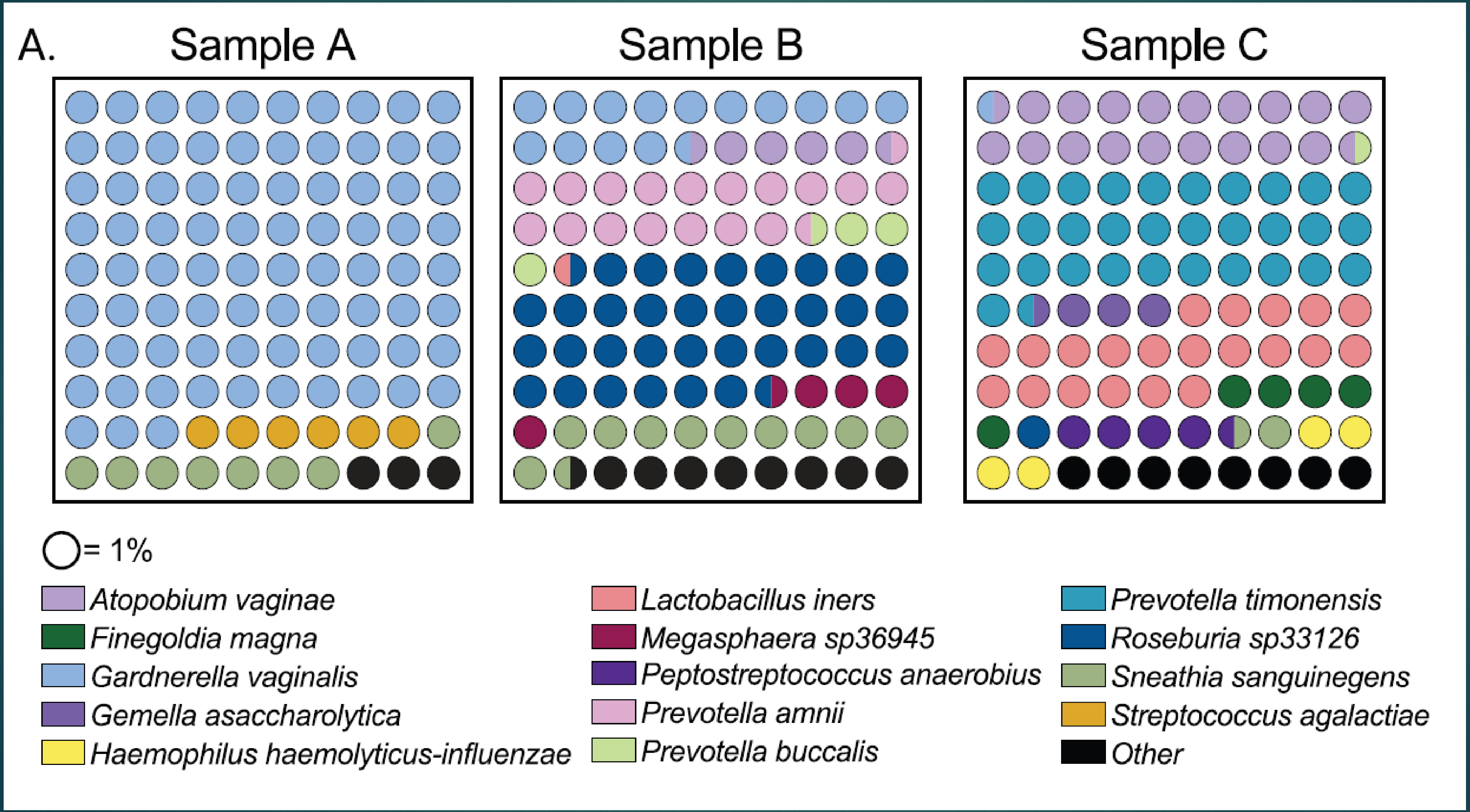


STI
T_X
Samples
S1
S2
S3a
S3b
S4
S5
Biobank
(1) Immune cells population
(2) Cytokine milieu
(3) Vaginal microbiome
(4) STI pathogens
(5) Phagocytes colonization
(6) Patient intrinsic parameters
Comprehensive longitudinal data
PCA
Correlatives discovery
1. Immune homeostasis
2. Microbiome homeostasis
3a. STIs susceptibility
3b. STIs progression
3c. STIs T_X efficacy
4. Pregnancy outcome

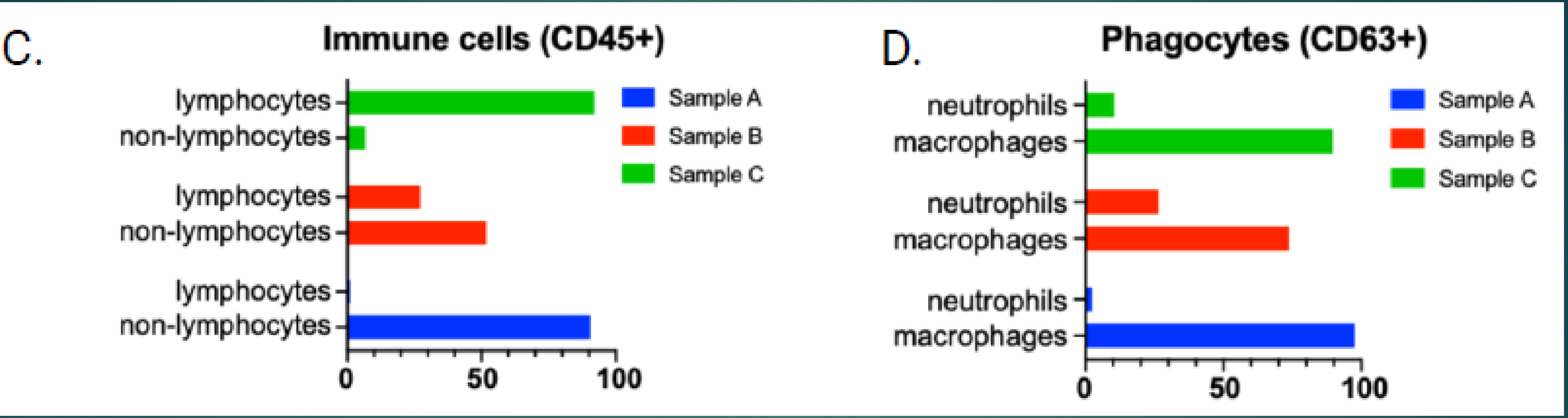

A.
Cytokine milieu
Cytokine (pg/ml)
400
300
200
100
0
IL6
IL10
TNF
IL17
Luminex® Cytokine and Chemokine Multiplex Panel
Th1 and Th2
Inflammation
Tolerance
Chemokines
vaginal lavage
Deep immune cell phenotyping
Side light scatter (SSC)
Forward light scatter (FSC)
Population subsets and Activation status (flow cytometry)
neutrophils
monocytes
macrophages
dendritic cells
B cells
T cells subset
NK cells
Tregs
Phagocytes colonization
Phagocytes colonization (in situ fluorescence microscopy)
Neisseria gonorrhoeae
Chlamydia trachomatis
Treponema pallidum


B.
Microbiome composition
vaginal swab #1
pre-treatment
post-treatment
recovered
Species abundance
N. gonorrhoeae culture + antibiotics susceptibility
vaginal swab #2
Strain isolation
Antibiotics susceptibility
Pathogen profiling
• Neisseria gonorrhoeae (Standard of care, PCR)
• Chlamydia trachomatis (Standard of care, PCR)
• Trichomonas vaginalis (Standard of care, PCR)
• Urinary tract infections (Standard of care, culture)
urine sample
• HPV (Standard of care, medical history)
• HIV (Standard of care, immunoassay)
• Gardnerella vaginalis (microbiome analysis, NGS)
• HSV (research test, PCR)
• Treponema pallidum (research test, PCR)
vaginal swab #3

Quantitative vaginal microbiome analysis from non-pregnant women



Flow cytometry analysis of vaginal leukocyte populations from non-pregnant women



What's on the horizon?

A recent randomized placebo-controlled trial compared periodic vaginal repletion with a human *L. crispatus* strain (LACTIN-V), and demonstrated a modest reduction in recurrent BV among those who used the active study product.

The use of novel agents to disrupt the tenacious biofilm that characterizes BV might offer another avenue for intervention: in a small study, the boric acid and EDTA-based intravaginal product TOL-463 had some efficacy for treatment of both acute BV and vulvovaginal candidiasis, and is currently under study for the prevention of recurrent BV

A recent small case series reported 5 women who received vaginal microbiota transplants for recurrent BV

<u>Conclusions</u>

- **Life is complex!**
- **Ok… life is VERY complex!**
- **Life happens… to all of us!**
- **Life is short... the impact of our work is infinite!**
- **Laughter is still <u>great</u> medicine!!**

Acknowledgements

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  - Jake Smith, Maggie Aucoin
  - Jenae Dykes, Savannah Ellis
  - Rithika Thirumal
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Olivia Desire
Theresa Boston
Will Barlow*
Lacie Melder*

Ochsner-LSU Hospital Clinical Microbiology Laboratory

Michelle Dillard-Wayne
Ada Jones

Dr. Adam Ratner Lab (NYU) – Serotyping

From Davie's mom…. November, 2022

We found out we were expecting on our Anniversary trip last January, and to say we've had a lot of anxiety since then would be an understatement. But God in His mercy gave us a healthy baby girl in September. Kinsley Grace Dunavent. The angst continued every time she felt warm or had an odd cry, but yesterday we hit a milestone.

Yesterday she turned 64 days old - one day older than Davie was when we said goodbye.

Thank you for guarding the microbiome!!

Evaluation Reminder

Evaluation reminder for the 2023 Louisiana Office of Public Health Antimicrobial Stewardship Summit

Please use this QR code or log-on/type in the following URL:
https://bit.ly/AMR2023

To use QR code:

- Open your phone Camera app from the Home screen, Control Center, or Lock screen.
- Select the rear-facing camera. Hold your device so that the QR code appears in the viewfinder in the Camera app.
- Tap the notification to open the link associated with the QR code.