

Gender-Specific Aspects in Clinical Trials in Infectious Diseases

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Conflicts of Interest

Research and lecture funds Shionogi, Infectopharm, BBraun, Tillots und Pfizer

Memberships

ESICM (European Society of Clinical Microbiology and Infectious Diseases)

DGAI (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin)

Deutscher Ärztinnenbund

PEG (Paul Ehrlich Gesellschaft)

Spitzenfrauen Gesundheit

Aktionsbündnis Patientensicherheit

DGKImed (Deutsche Gesellschaft für Künstliche Intelligenz in der Medizin)

Und ich habe Kinder ...

The Core Problem

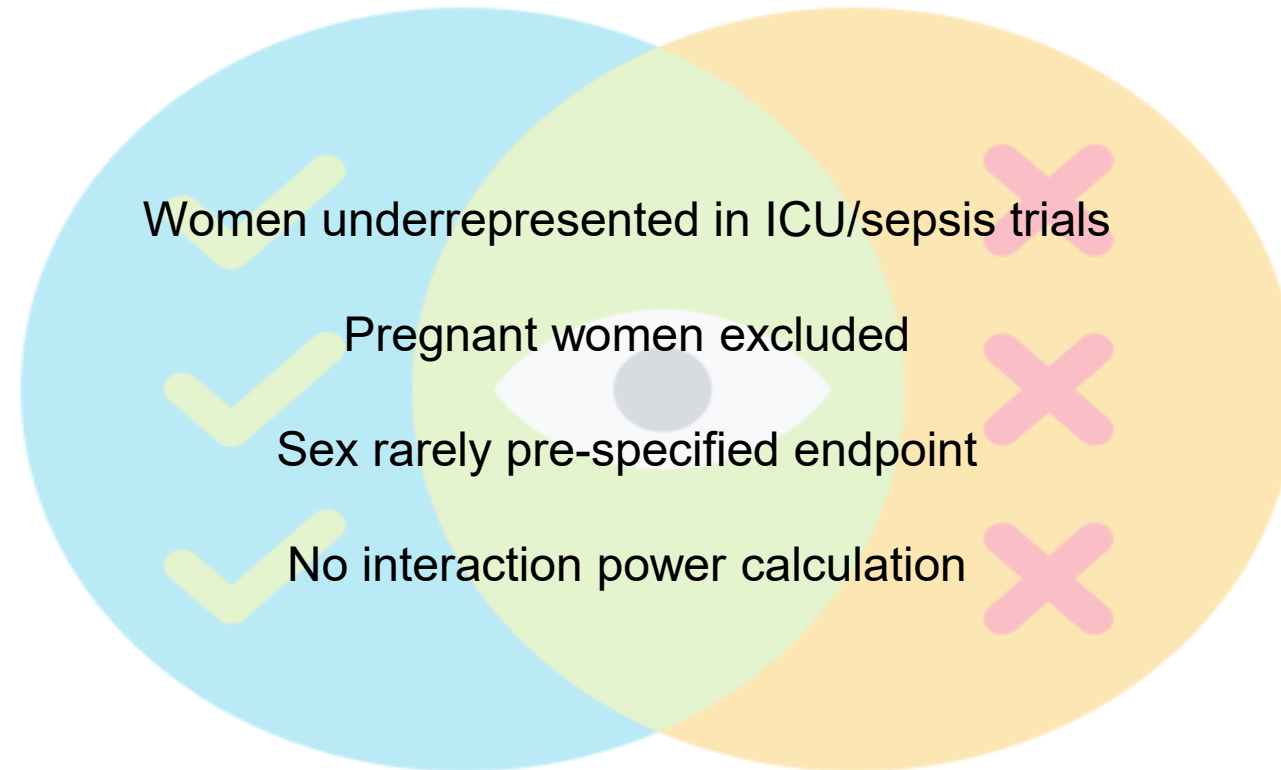
Sex mostly adjusted — rarely analyzed

Gender almost never measured

No predefined interaction testing

Risk: diluted treatment effects

Structural Bias in Infectious Disease Trials



Scott PE, et al. Inclusion of women in clinical trials: A review of FDA analyses. *JAMA*. 2018;319(13):1358–1359. doi:10.1001/jama.2018.0151

Mazure CM, Jones DP. Twenty years and still counting: including women as participants and studying sex and gender in biomedical research. *BMC Womens Health*. 2015 Oct 26;15:94. doi: 10.1186/s12905-015-0251-9. PMID: 26503700; PMCID: PMC4624369.

Krubiner CB, Faden RR, Karron RA, et al; PREVENT Working Group. Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response. *Vaccine*. 2021 Jan 3;39(1):85-120. doi: 10.1016/j.vaccine.2019.01.011. Epub 2019 May 3. PMID: 31060949; PMCID: PMC7735377.

Sex Differences in EU Infectious Disease Notifications

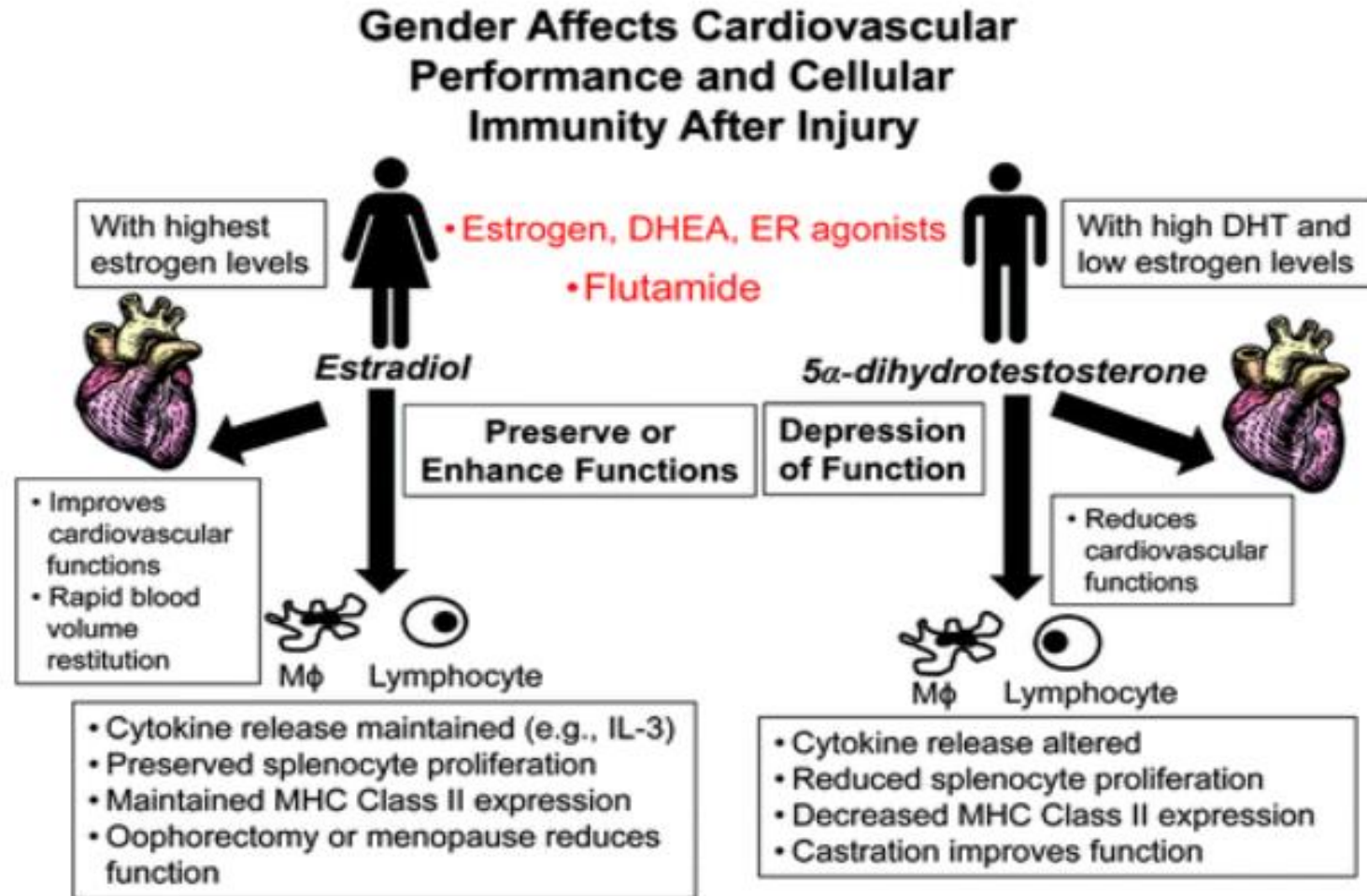
- 5.6 million cases | 30 EU/EEA countries | 2012–2021
 - **Up to 75% male** in HIV, AIDS, Legionnaires', HBV, TB
 - **Female predominance** in Chlamydia & Pertussis
 - Differences reflect **behaviour + screening**, not only biology
- **Surveillance data are shaped by testing policy.**
- What we measure depends on whom we test.
 - E.g. Listeriose or Hepatitis in pregnancy
 - Screening offered to specific populations may explain differences across countries

Gender differences in the perception of illness

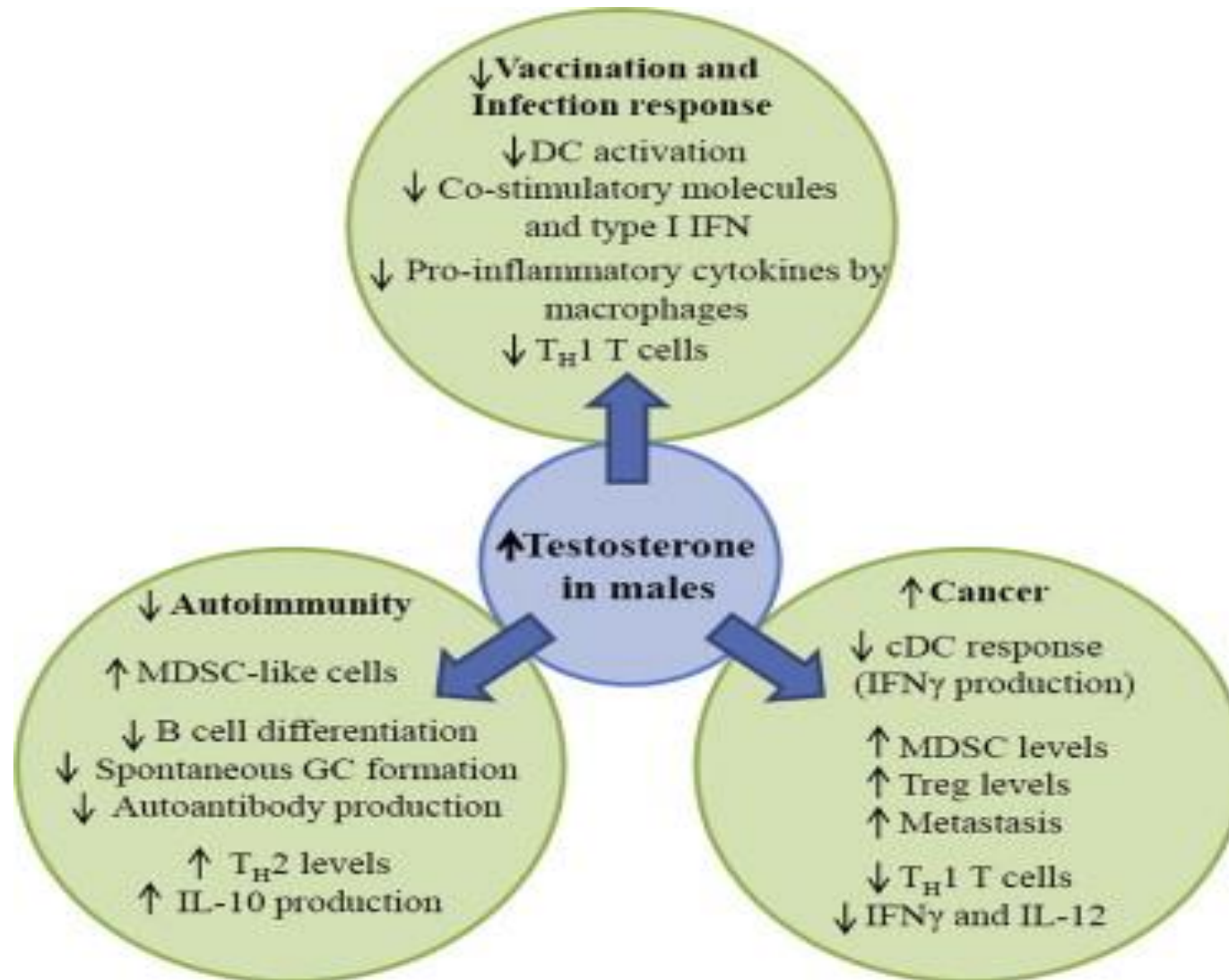
- Perception & communication
- Pain perception & reaction
- Awareness of illness
- 🌐 Cultural influences
 - Women are allowed to talk about symptoms
 - Men are expected to “persevere”

Immune Response

Immune response

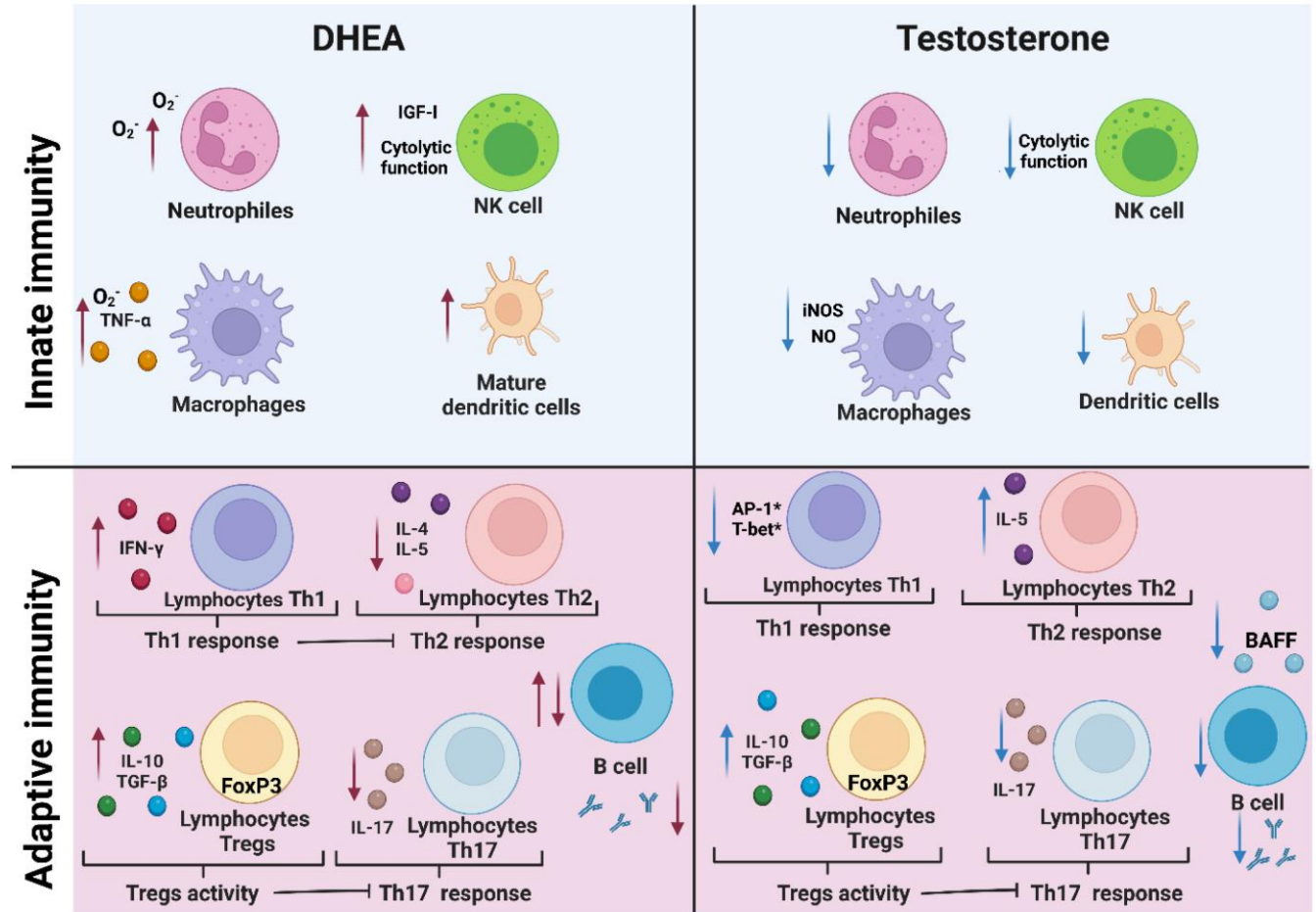


Testosterone in Males



Immune Response Differences

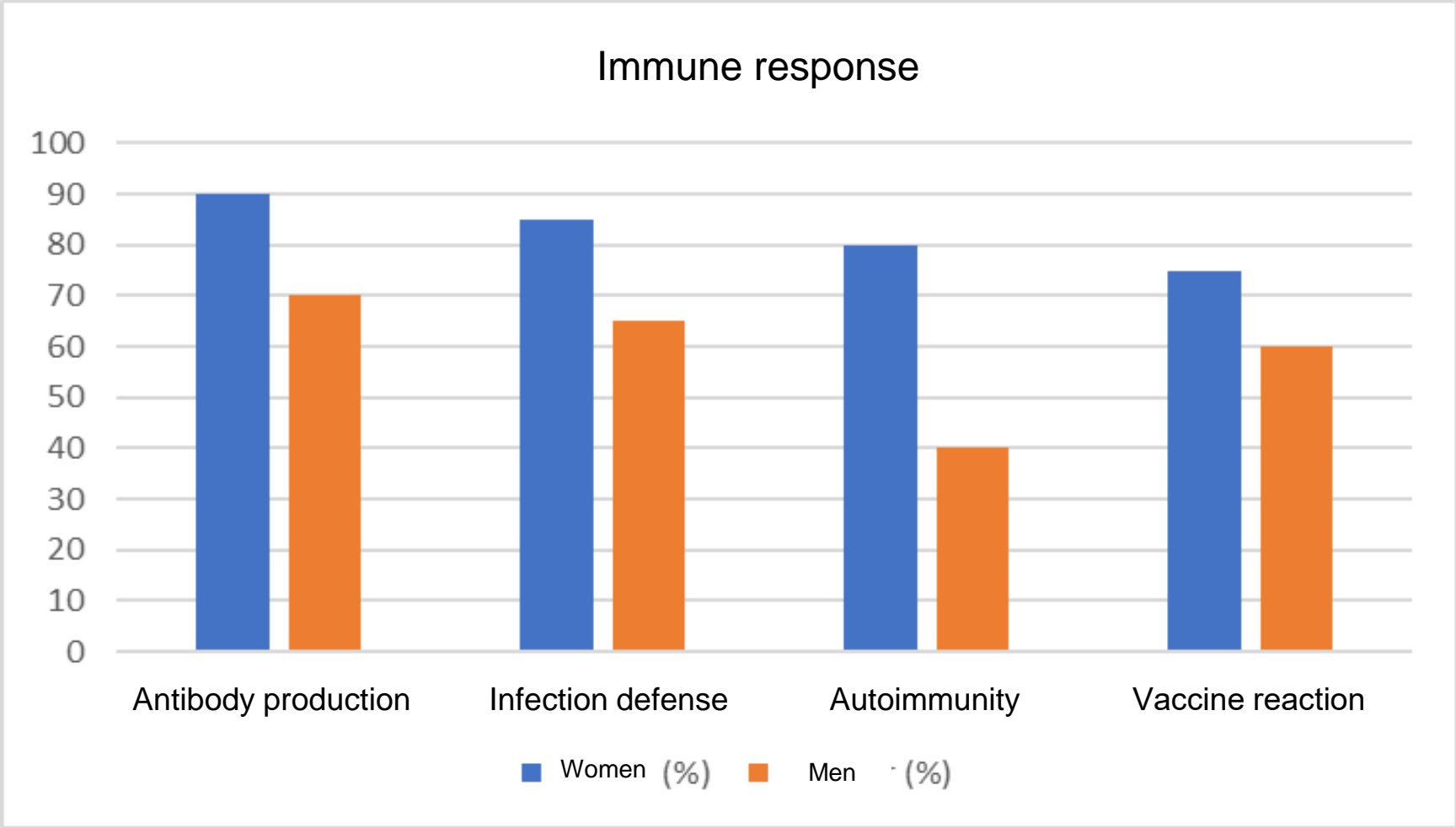
- Stronger humoral & cellular responses in females
- Higher antibody titers
- Higher cytokine response
- Higher autoimmune & vaccine ADR risk



Sex hormones in the immune response

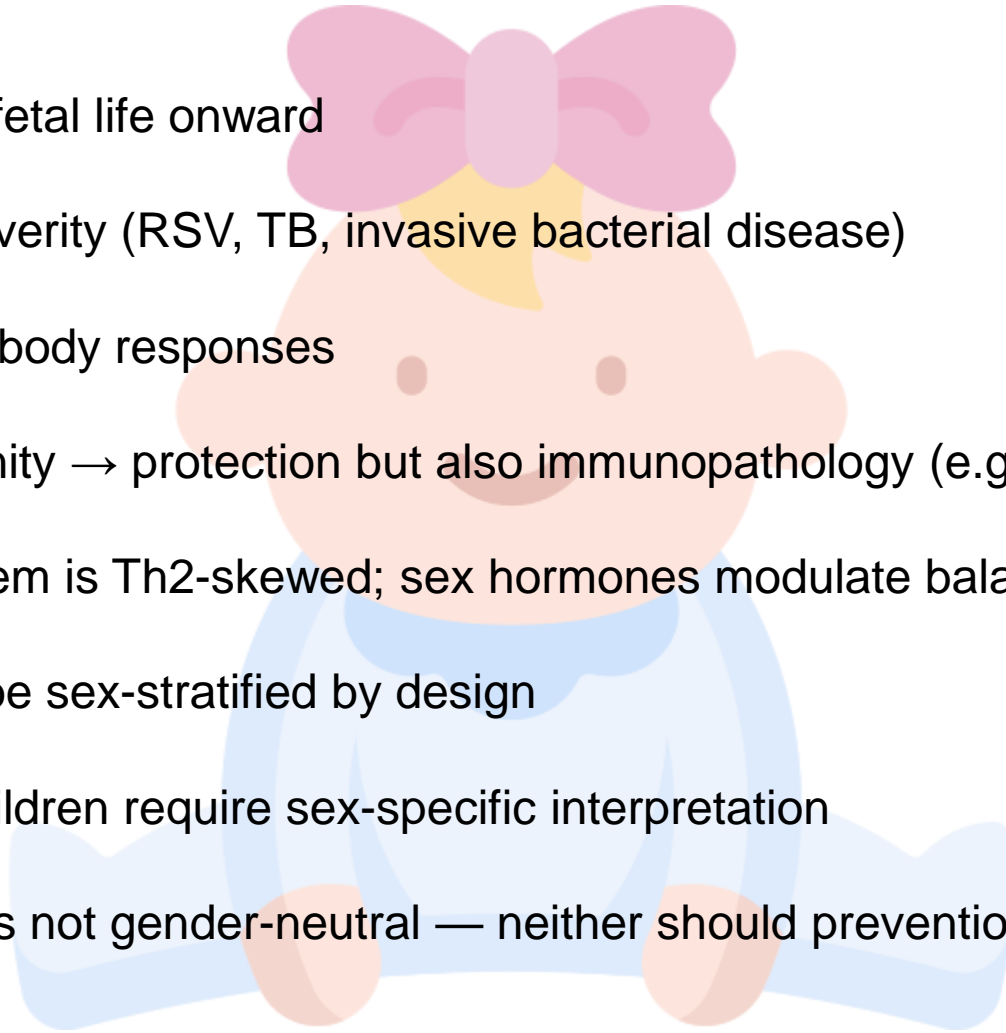
- ◇ Estrogen activates the immune system, while androgen suppress it.
 - Women have higher antibody production and a stronger response to infections.
- ◇ Autoimmune diseases & gender
 - Women are more frequently affected.
 - Hormone modulation as a therapeutic approach.
- ◇ Infections & allergies
 - Women show a stronger immune response to viruses.
 - Asthma & allergies fluctuate depending on hormones (e.g., pregnancy, menopause).

Sex hormones and gender-specific differences in immune responses



Sex Differences in Pediatric Infectious Diseases

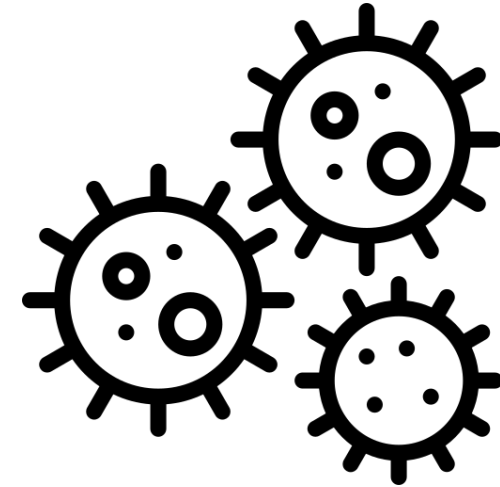
- Sex bias present from fetal life onward
- Boys: ↑ incidence & severity (RSV, TB, invasive bacterial disease)
- Girls: stronger Th1/antibody responses
- Stronger female immunity → protection but also immunopathology (e.g. congenital CMV)
- Neonatal immune system is Th2-skewed; sex hormones modulate balance early (“mini-puberty”)
- Pediatric trials should be sex-stratified by design
- Surveillance data in children require sex-specific interpretation
- Early-life immunology is not gender-neutral — neither should prevention be



Viral infections

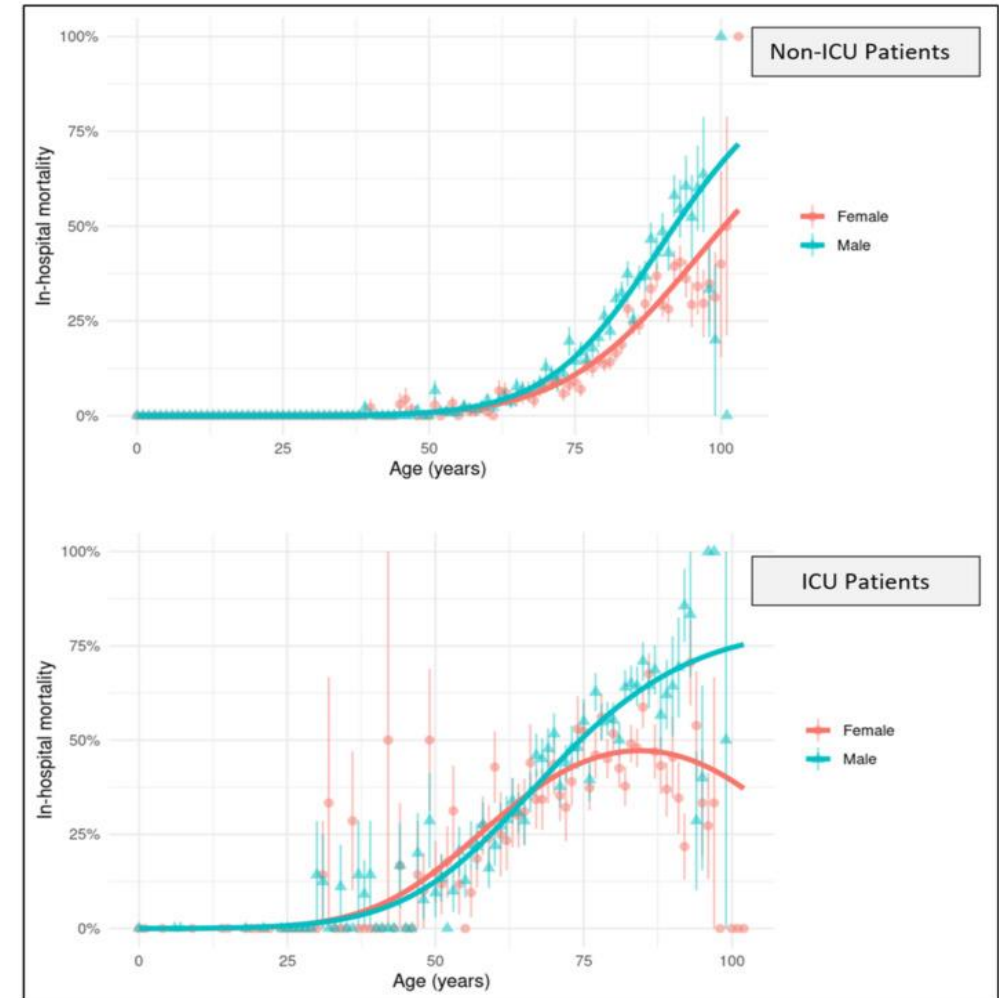
SARS-CoV-2 and Sex

- Men have a higher risk of severe disease progression and mortality.
- Women are more likely to experience long COVID.
- Differences in immune response influence course of the disease.
- Occupational exposure: Women are more likely to work in health and care professions.
- Care work: Higher stress levels can influence the risk of infection.
- Differences in access to healthcare: Men often seek medical help later.
- Gender-specific data analyses help to develop targeted prevention strategies..



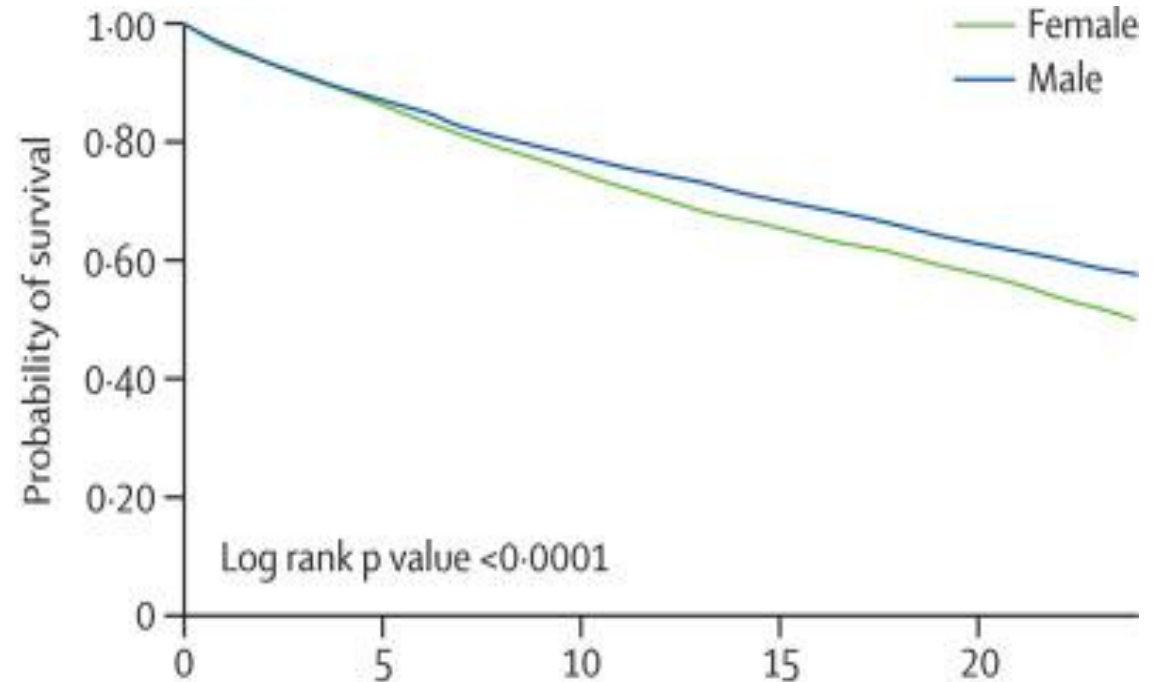
COVID-19 in intensive care

- Men have an increased risk of severe disease progression and higher mortality.
- Men require intensive care and mechanical ventilation more frequently.
- Up to the age of 60, mortality increases with age similarly for both sexes.
- From the age of 60 onwards, the risk of death increases more sharply for men than for women.
- The greatest gender difference is seen in the oldest patients. 75% of men over the age of 90 died, compared with 46% of women.



Life expectancy and mortality among men and women with HIV

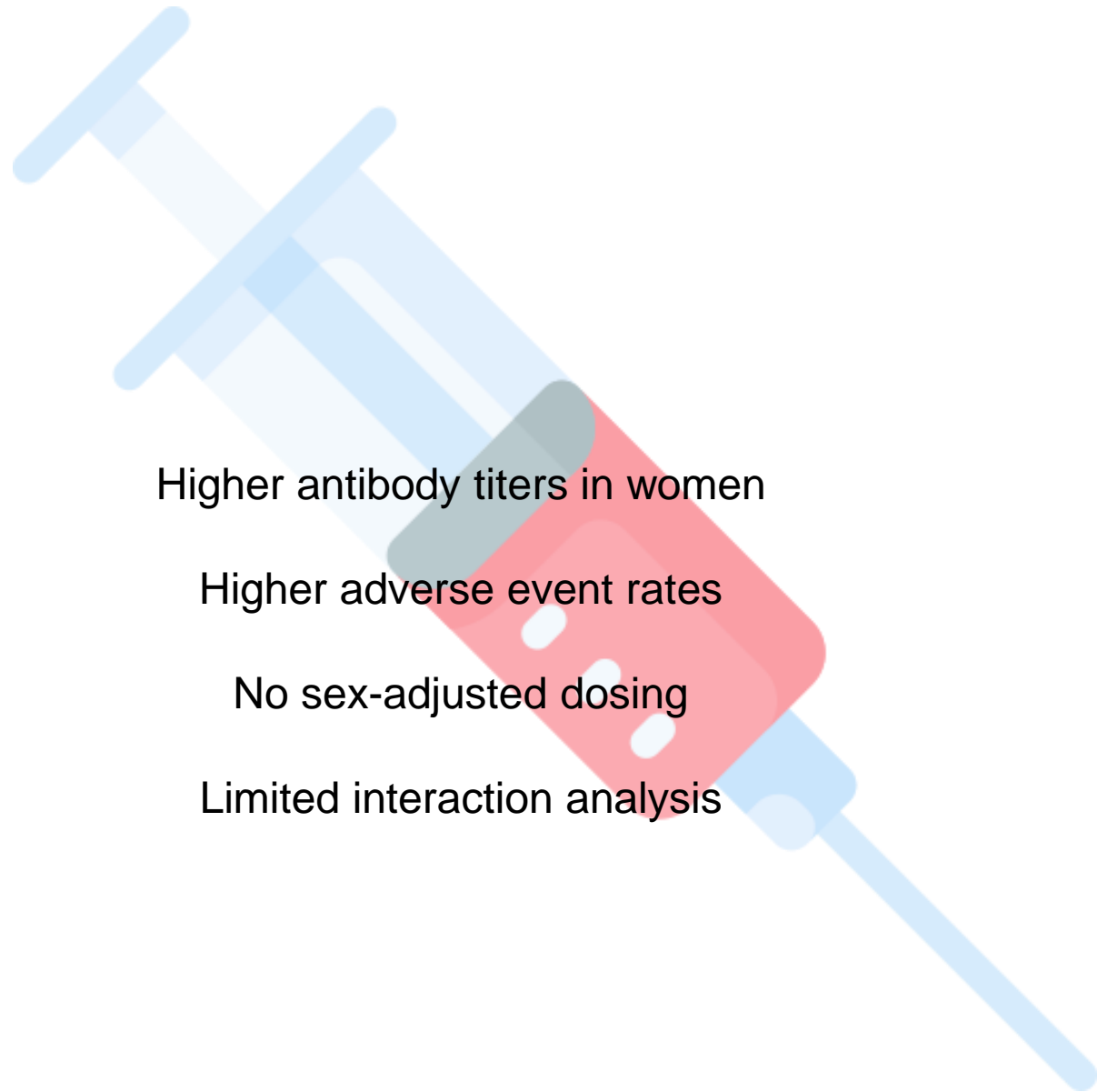
- ◇ Men (n = 11,738) → Life expectancy at age 20:
+23.54 years
- ◇ Women (n = 2,534) → Life expectancy at age 20:
+18.81 years
- ◇ Gender gap is widening
 - 1996–2001: 2.3-year difference
 - 2012–2020: 7.0-year difference
- ◇ Higher mortality among women despite taking social factors into account (HR 1.11).



	Follow-up time (years)				
Number at risk	0	5	10	15	20
Female	2534	1758	1263	777	429
Male	11738	8200	5823	3912	2337

Vaccination

Vaccine Trials



Higher antibody titers in women

Higher adverse event rates

No sex-adjusted dosing

Limited interaction analysis

Sex Differences in Viral Vector Vaccine Responses

- Biological sex influences vaccine immunogenicity and safety
- Traditional vaccines: often **stronger immune responses in females**
- Viral vector vaccines: **heterogeneous patterns** (female-, male-, or no bias)
- Differences depend on vector platform, replication, and innate activation
- Sex-stratified analyses remain insufficient

Sex matters — and should be integrated into vaccine design and evaluation.

Seasonal Influenza Vaccination & Sex

- 46 studies (1990–2018)
- No consistent sex difference in immunogenicity or effectiveness
- Clear signal: **higher adverse events in females**
- Major limitation: sex rarely stratified, mostly adjusted

- **Implication:**

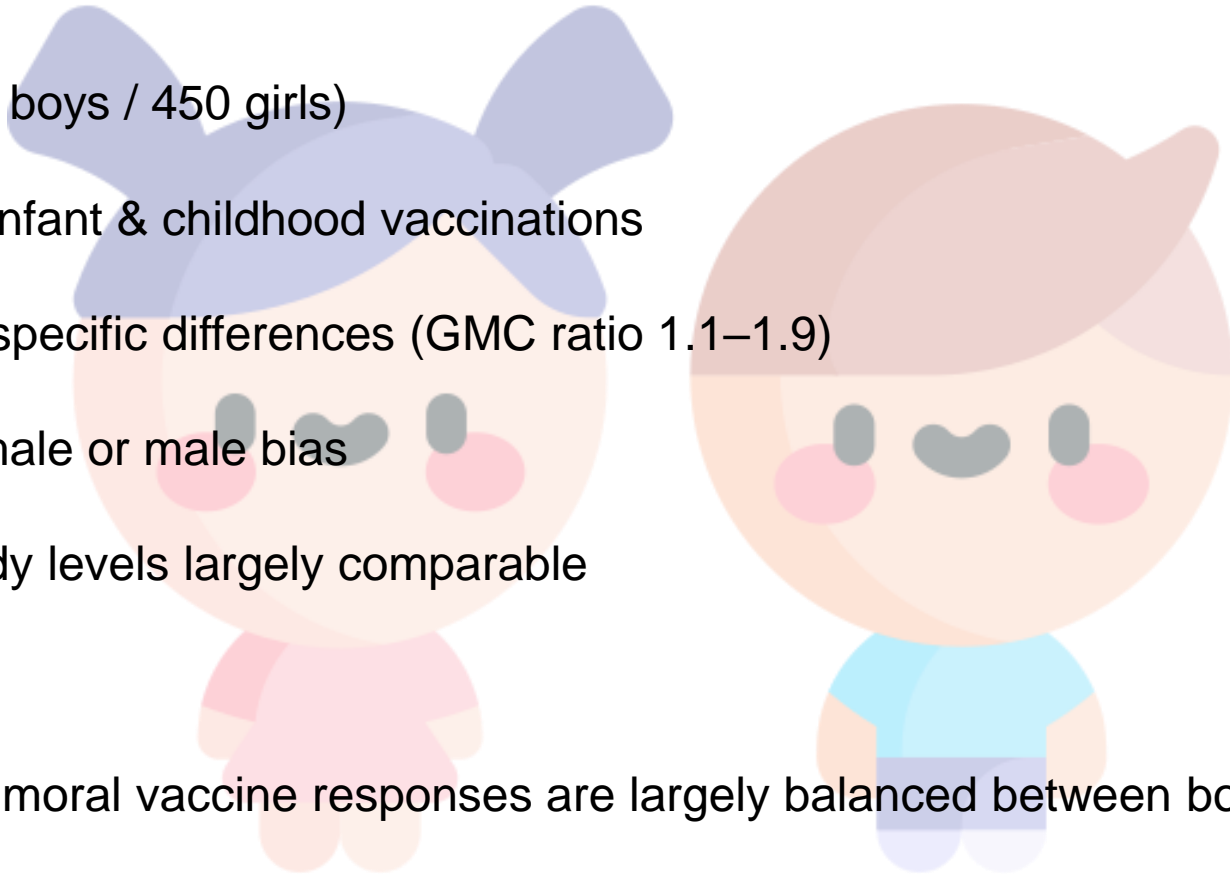
Sex is treated as a confounder — not as a biological variable.

If we want precision vaccination strategies, we need sex-stratified phase III data — not post-hoc adjustments.

Antibody Responses Before Puberty

- 885 children (435 boys / 450 girls)
- IgG after routine infant & childhood vaccinations
- Small, pathogen-specific differences (GMC ratio 1.1–1.9)
- No consistent female or male bias
- Protective antibody levels largely comparable

Before puberty, humoral vaccine responses are largely balanced between boys and girls.



Bacterial infections

Different pathogen distribution

> [J Hosp Infect.](#) 2024 Oct 10:S0195-6701(24)00327-X. doi: 10.1016/j.jhin.2024.07.021.

Online ahead of print.

Males are at Higher Risk for Colonizations and Infections with Multidrug Resistant Organisms than Females

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Affiliations + expand

PMID: 39395464 DOI: [10.1016/j.jhin.2024.07.021](#)

Abstract

Background: Global rise of multidrug-resistant organisms (MDRO) is alarming and antimicrobial resistance (AMR) poses a significant public health threat globally. Although certain risk factors are known including recent antimicrobial therapy, inappropriate use and hospitalization, the focus on gender-specific aspects in MDRO is scarce. Our aim was to show gender-specific differences in colonization and infections of multiple MDRO and their detection sites.

Different pathogen distribution

Multidrug-resistant organisms	N	p- value
MRSA	85.063 (45.33%)	p < .001
Male	48.088 (1.403%)	
Female	36.975 (1.012%)	
E. coli	41.632 (22.2%)	p= .008
Male	20.425 (0.596%)	
Female	21.207 (0.581%)	
VRE	31.767 (16.93%)	p < .001
Male	18.552 (0.541%)	
Female	13.215 (0.362%)	
Klebsiella spp.	12.804 (6.82%)	p < .001
Male	7.915 (0.231%)	
Female	4.889 (0.134%)	
Pseudomonas aeruginosa	7.687 (4.10%)	p < .001
Male	5.252 (0.153%)	
Female	2.435 (0.067%)	
Enterobacter spp.	3.651 (1.95%)	p < .001
Male	2.327 (0.068%)	
Female	1.324 (0.036)	
Acinetobacter baumannii	1.608 (0.86%)	p < .001
Male	943 (0.028%)	
Female	665 (0.018)	

Sex and Gender Differences in Bacterial Infections

Most bacterial infections show a male predominance

(e.g., tuberculosis, pneumonia, invasive pneumococcal disease, Q fever, brucellosis)

Females:

Higher incidence of UTIs and *Clostridioides difficile* infection

Higher risk of STI-related reproductive complications

Pregnancy: increased susceptibility to pathogens such as *Listeria monocytogenes*

Sepsis: higher incidence in men; outcome differences inconsistent

Incidence, severity, and outcomes of bacterial diseases differ by sex

— driven by immune biology, hormones, anatomy, and gender-related exposure.

Sex Hormones and Tuberculosis

- Adult males have ~1.7-fold higher risk of active TB (sex difference emerges after puberty)
 - Th1 cytokines (IFN- γ , TNF- α , IL-1 β , IL-6) → protective
 - Th2 cytokines (IL-4, IL-5, IL-10) → impaired bacterial control
 - Estrogen: enhances Th1 immunity (physiologic levels); may shift to Th2 at high levels (e.g., pregnancy)
 - Progesterone: immune homeostasis at baseline; suppresses Th1/DC function when elevated
 - Testosterone: attenuates Th1 responses; promotes anti-inflammatory pathways
- ☞ Sex hormone-mediated immune modulation contributes to TB susceptibility and pathogenesis

Future TB research and host-directed therapies should be sex- and hormone-aware.

Female Sex and Mortality in *Staphylococcus aureus* Bacteremia

- 89 studies | 132,582 patients

- Mortality ≤ 90 days

- Unadjusted OR: 1.12 (1.06–1.18)

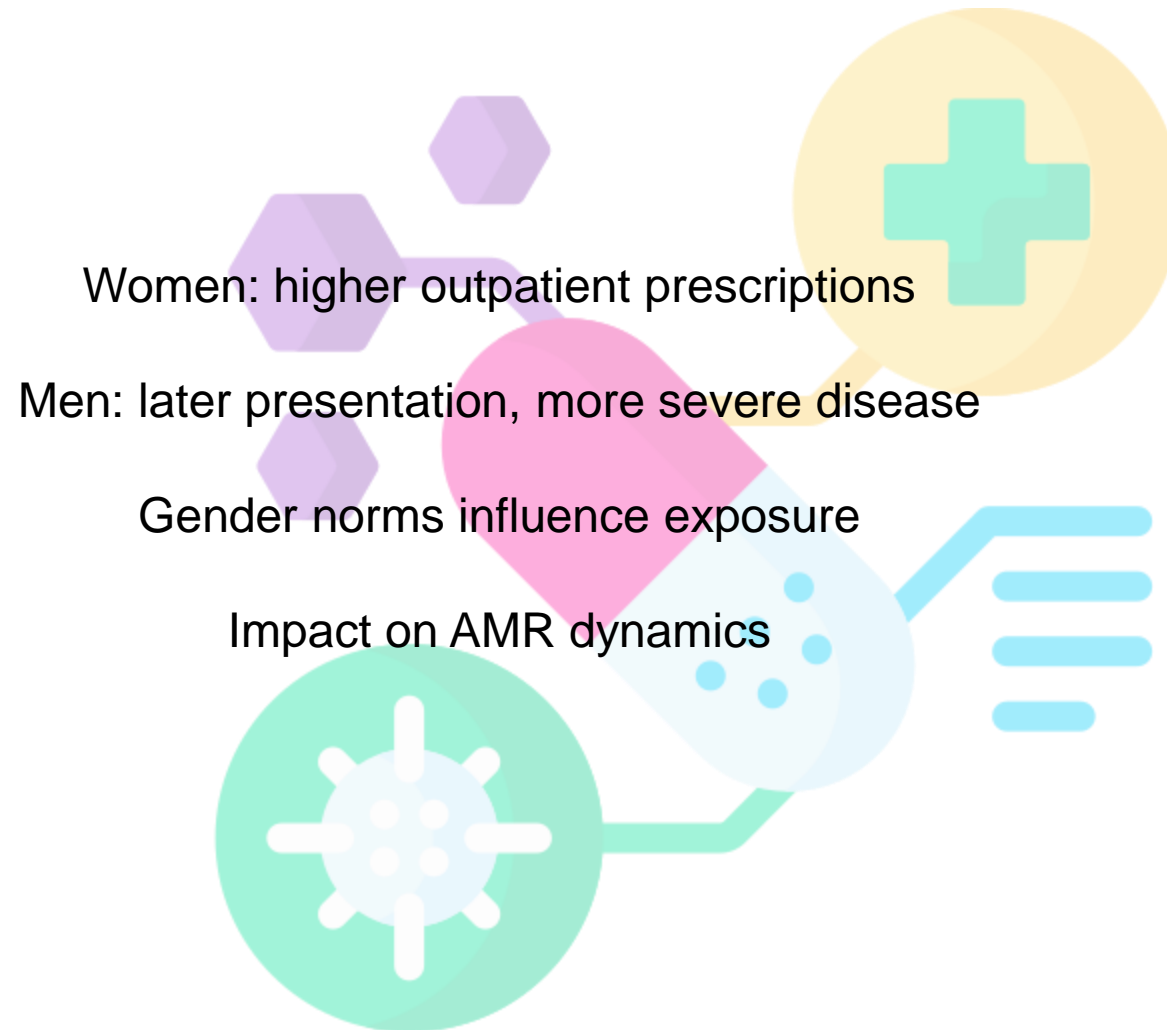
- Adjusted OR: 1.18 (1.11–1.27)

- ☞ Female patients had ~18% higher odds of death

Sex differences in SAB outcomes are clinically relevant; mechanisms remain unclear.

Antibiotic therapy

Gendered Antibiotic Use

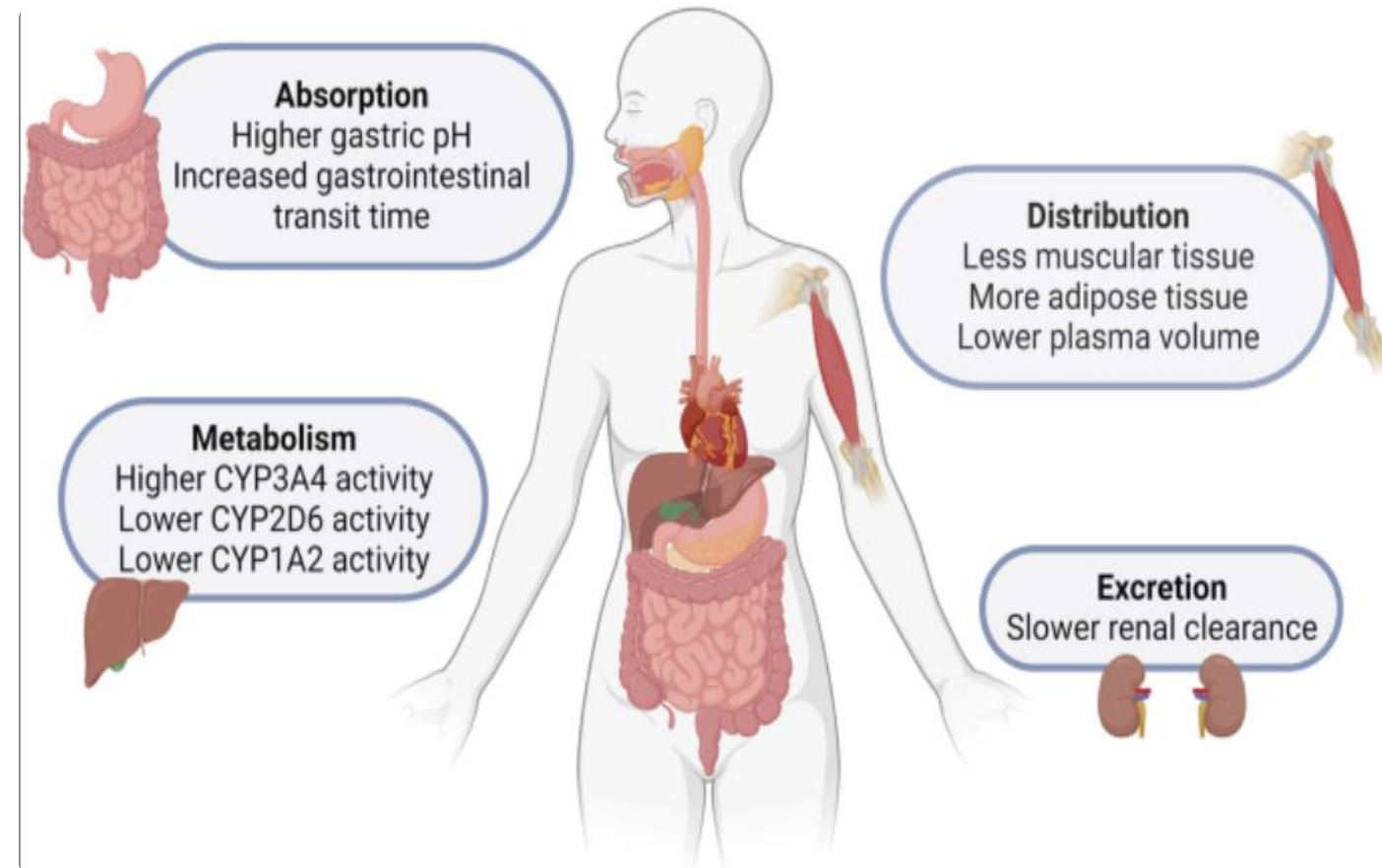


Schröder W, Sommer H, Gladstone BP, Foschi F, Hellman J, Evengard B, Tacconelli E. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2016 Jul;71(7):1800-6. doi: 10.1093/jac/dkw054. Epub 2016 Apr 3. PMID: 27040304.

Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A.* 2018 Apr 10;115(15):E3463-E3470. doi: 10.1073/pnas.1717295115. Epub 2018 Mar 26. PMID: 29581252; PMCID: PMC5899442.

Pharmacokinetics & Pharmacodynamics

- Higher body fat % → lipophilic distribution
- CYP450 variability
- Renal clearance differences
- ADRs more frequent in women
- QT prolongation risk



Gender differences in antibiotic prescribing in primary care

Systematic review and meta-analysis (11 studies, >44 million individuals, 10 countries)

Women are **27% more likely** to receive at least one antibiotic prescription than men

The largest gender gap is observed in adults aged **16–54 years**:

16–34 years: +36% higher prescribing in women (*IRR* = 1.36)

35–54 years: +40% higher prescribing in women (*IRR* = 1.40)

Pronounced differences by antibiotic class:

Cephalosporins: +44% in women (*IRR* = 1.44)

Macrolides: +32% in women (*IRR* = 1.32)

Quinolones: no relevant gender difference

The observed differences **cannot be fully explained by known epidemiology** of infectious diseases.

Antibiotic stewardship programmes should explicitly address **gender-related prescribing patterns**.

Gender inequality and antibiotic consumption

Key findings (70 countries, 2000–2022)

Design: Country-level fixed-effects analysis using IQVIA MIDAS® data (70 countries; outcome: DDDs/1,000 population/day)

Average consumption: 19.13 DDDs / 1,000 population / day

Lower antibiotic consumption was associated with

higher female education ($p < 0.05$)

higher female-to-male labour force participation ratio ($p < 0.01$)

Slightly higher consumption with a higher share of females in the population ($p < 0.01$)

Gender inequalities are associated with national antibiotic consumption patterns → AMR strategies should be gender-responsive and community-based.

Sepsis

DISPARITY-II Study – Delayed antibiotic therapy in women

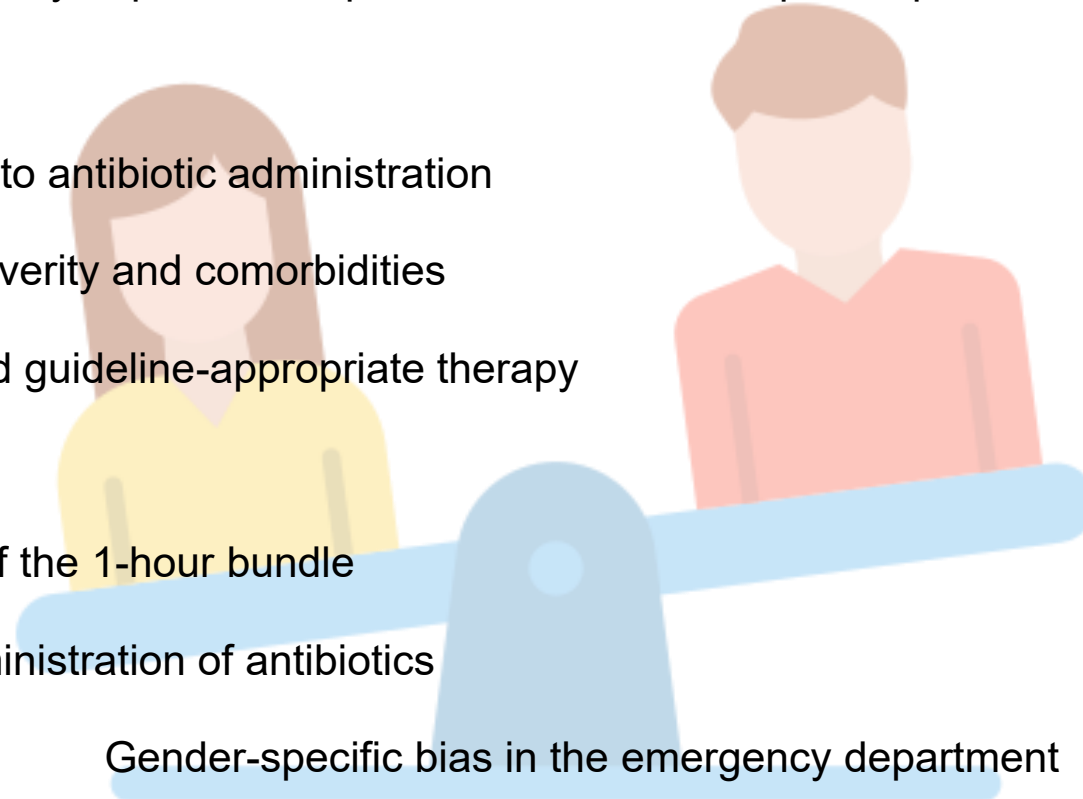
Multicentre study in US emergency departments, patients with severe sepsis/septic shock

Women:

- Significantly longer time to antibiotic administration
- Delay independent of severity and comorbidities
- Increased risk of delayed guideline-appropriate therapy

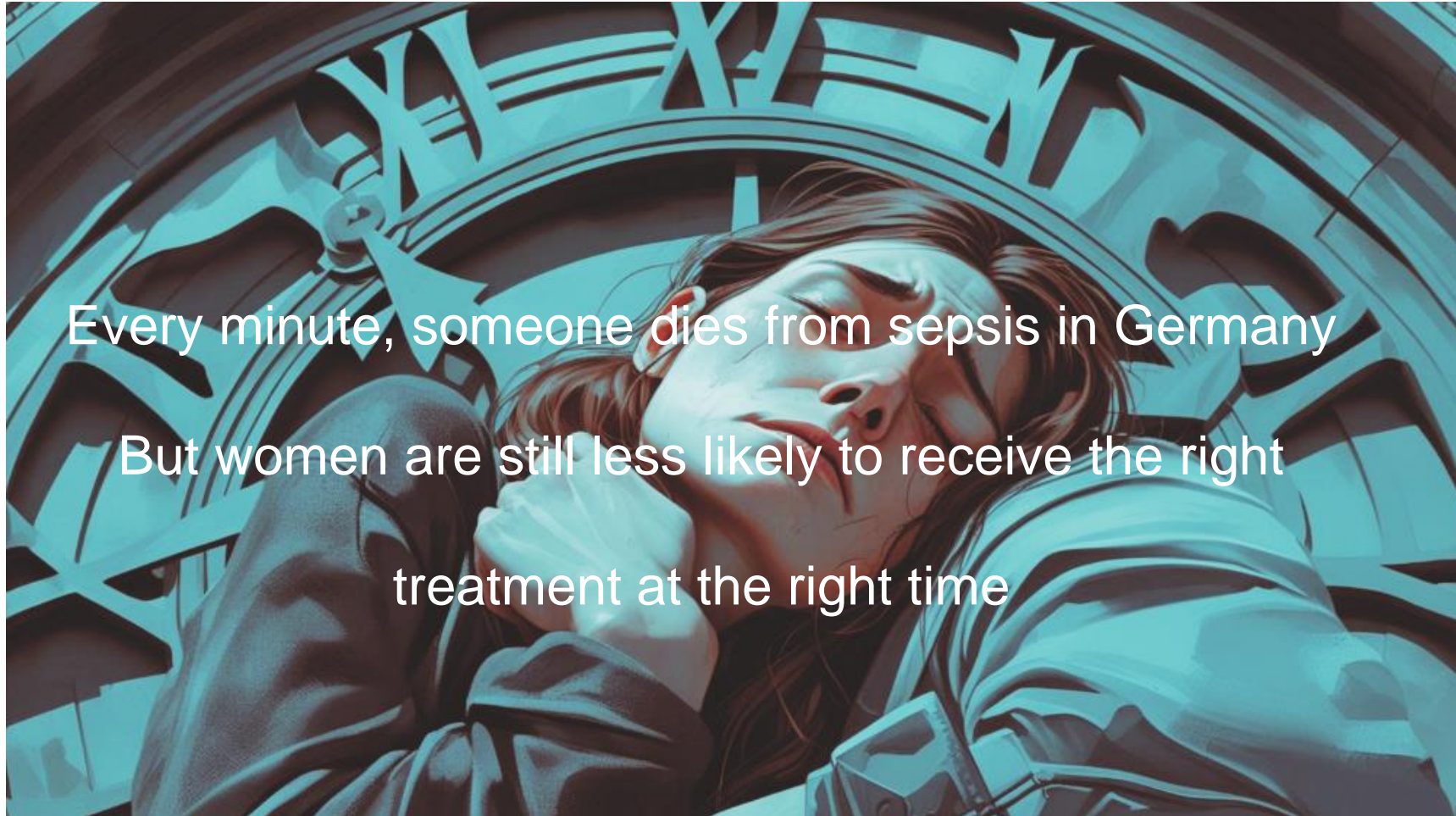
Men:

- Faster implementation of the 1-hour bundle
- More frequent early administration of antibiotics



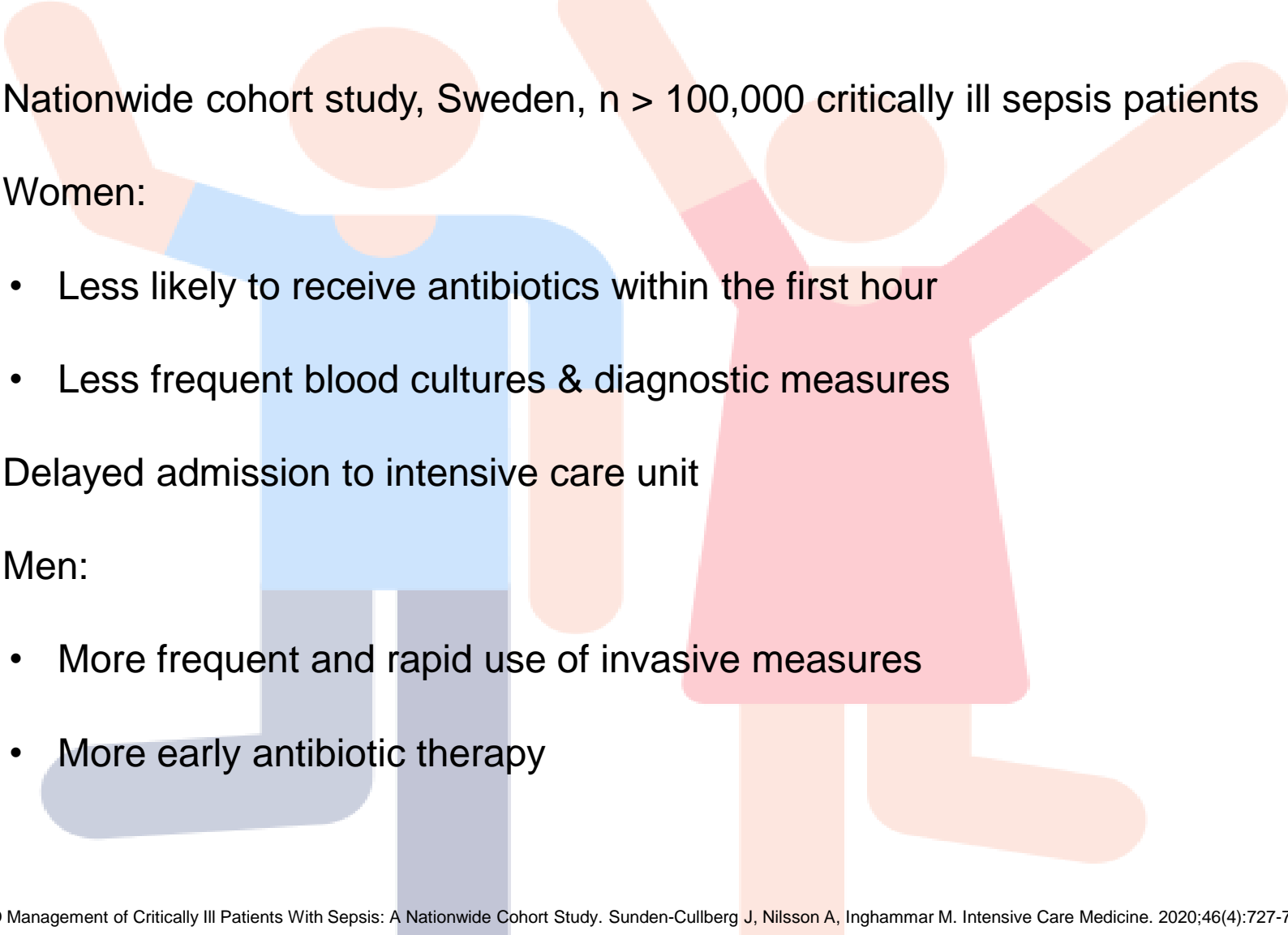
➔ Urgent need for gender-sensitive sepsis protocols

Sepsis & Gender Data Gap – a patient safety problem



Every minute, someone dies from sepsis in Germany
But women are still less likely to receive the right
treatment at the right time

Gender differences in ED management of sepsis

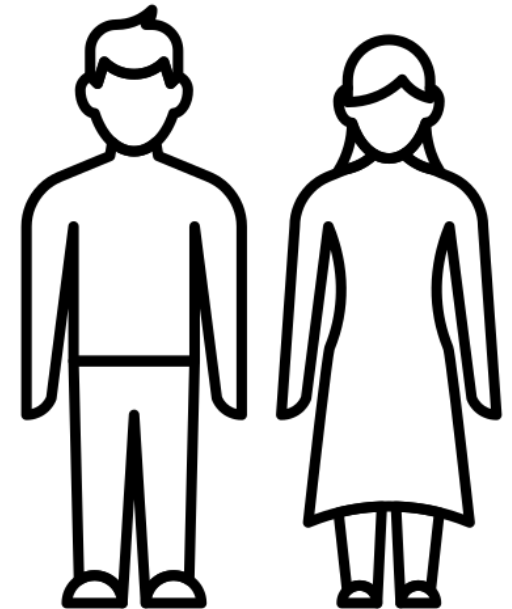
- 
- Nationwide cohort study, Sweden, n > 100,000 critically ill sepsis patients
 - Women:
 - Less likely to receive antibiotics within the first hour
 - Less frequent blood cultures & diagnostic measures
 - Delayed admission to intensive care unit
 - Men:
 - More frequent and rapid use of invasive measures
 - More early antibiotic therapy

Differences in invasive intensive care

- (n = 26,711) Proportion of men: 64.8%
- Tracheotomy: 8.8% vs. 7.0% → OR 1.39 (1.26–1.54)
- ECMO: 1.1% vs. 0.7% → OR 1.37 (1.02–1.83)
- Dialysis: 12.1% vs. 9.8% → OR 1.29 (1.18–1.41)
- PAC: 1.9% vs. 0.8% → OR 1.81 (1.40–2.33)
- Duration of ventilation: IRR 1.07 (1.02–1.12)
- ICU mortality: 8.8% vs. 8.7% (no difference)
- More invasive therapy in men – mortality remains the same
- This indicates different decision-making processes, not poorer outcomes.

Gender differences in sepsis treatment

- Women received 1-hour bundle therapy less frequently than men (13.0% vs. 19.2%, $p < 0.001$).
- Antibiotics were prescribed less frequently to women than to men (25.4% vs. 31.6%, $p < 0.001$).
- Women receive adequate fluids more often than men (96.8% vs. 95.0%, $p = 0.029$).
- Blood pressure monitoring using invasive arterial measurement is less common in women (76.0% vs. 80.2%, $p = 0.013$).
- ✎ Lower antibiotic administration in women could lead to delayed treatment and poorer outcomes.
- Fluid administration is more often adequate in women – possibly due to differences in body weight.
- Gender-specific unequal treatment indicates unconscious bias in clinical decision-making.

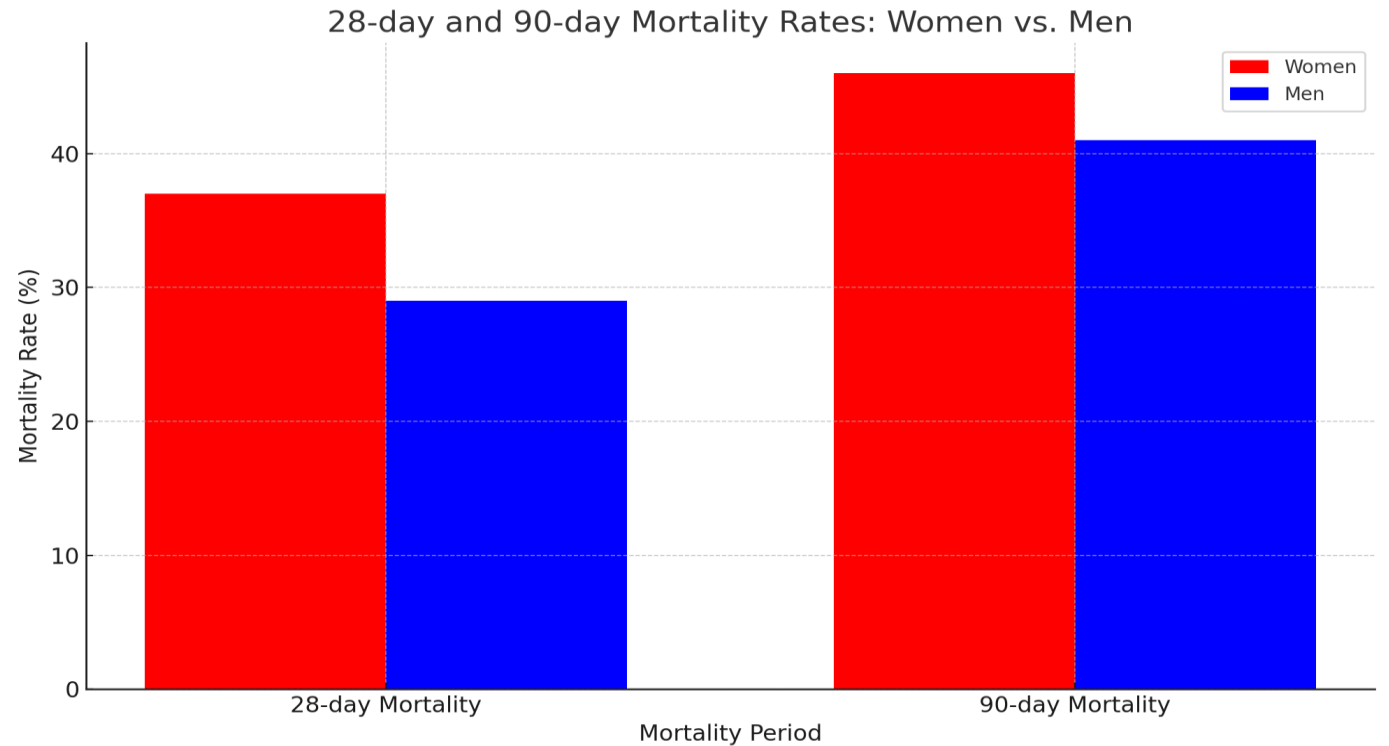
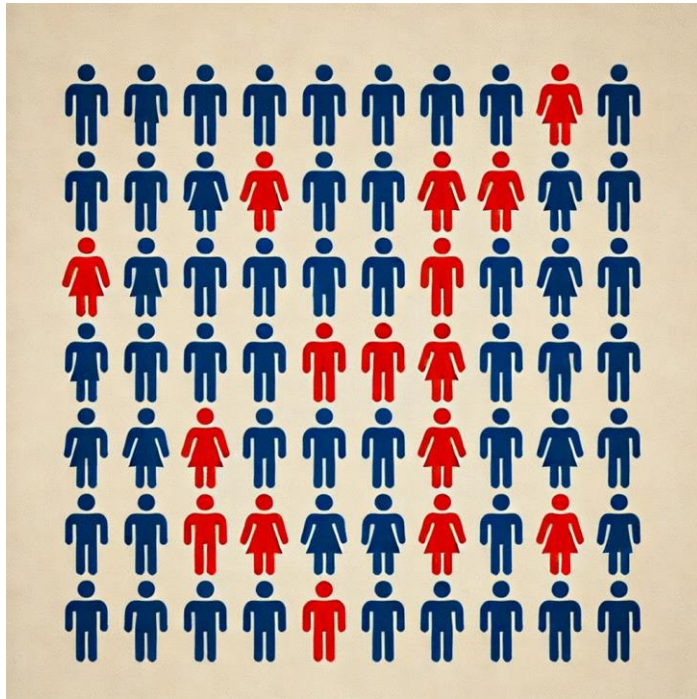


Gender differences in sepsis

A cohort of 1,448 septic patients

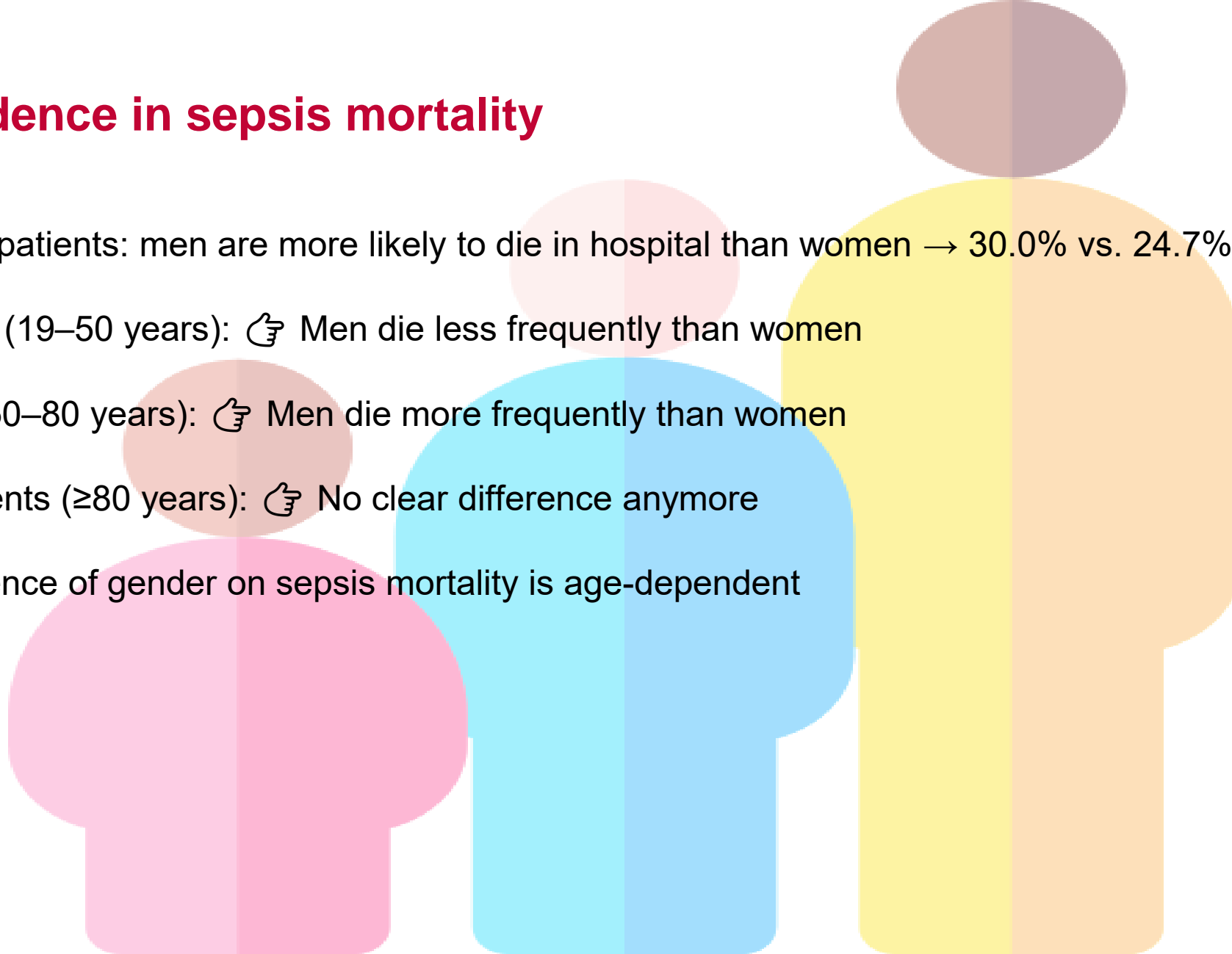
525 women and 923 men with sepsis in intensive care

Mortality (28/90 days) Women 37%/46% versus Men 29%/41%




Age dependence in sepsis mortality

- 6,442 sepsis patients: men are more likely to die in hospital than women → 30.0% vs. 24.7%
- Young adults (19–50 years): ☞ Men die less frequently than women
- Middle age (50–80 years): ☞ Men die more frequently than women
- Very old patients (≥80 years): ☞ No clear difference anymore
- ➡ The influence of gender on sepsis mortality is age-dependent



Metaanalysis ...

- Sepsis is more common in men than in women (1.3 times higher risk).
- Men have longer hospital stays, higher ICU mortality, and an increased risk of rehospitalisation within one year.
- Sources of bacterial infection differ:
- Men: more frequent gastrointestinal, lung and skin infections.
- Women: more frequent urinary tract infections.
-  Sepsis therapy should be tailored to gender with regard to immunomodulation and hormonal influence.

Symptoms vary depending on gender

- These differences mean that AI models trained on predominantly male data may overlook or misinterpret symptoms in women.
- Women may describe symptoms more subtly or focus on general feelings (e.g., “foggy”, “unwell”), which can delay diagnosis.
- Men tend to describe physical and measurable symptoms (e.g. fever, rapid heart rate) more directly..

Symptom	Men	Women
Fever	Often high fever, above 38°C (100.4°F)	Similar presentation with fever, but sometimes less pronounced or delayed onset
Chills/Shivering	Intense and frequent chills	Similar chills, but sometimes reported less frequently
Confusion/Disorientation	Men may experience sudden confusion, agitation, or delirium	Confusion and mental changes also common, but women may describe this as feeling “foggy”
Shortness of Breath	Rapid or shallow breathing is common	Women may report this, but can also experience a more generalized feeling of breathlessness
Rapid Heart Rate	Tachycardia (fast heart rate) often noticeable	Tachycardia may occur, but could be less emphasized in initial symptoms
Low Urine Output	Reduced urine production is a key sign	Similarly, reduced urine output, sometimes less frequently reported early on
Extreme Weakness	Profound fatigue and inability to move easily, often an early and intense symptom	Extreme weakness is often described, but may be mistaken for other conditions in women
Pale or Discolored Skin	Pale, mottled, or cold skin	Women may exhibit pale skin but also report more subtle discoloration or clammy feeling
Pain and Discomfort	Localized pain often around the site of infection	More likely to describe generalized pain or discomfort, not always localized
Nausea/Vomiting	Sometimes reported, though not as prominent	Nausea, vomiting, and gastrointestinal discomfort may be more frequent in women
Swelling	Local swelling around infection site may be noticed	Similar presentation, but may be described as generalized swelling rather than localized
Fatigue and Malaise	Fatigue may be reported, but men often focus on physical symptoms	Women may report fatigue and general unwellness more prominently

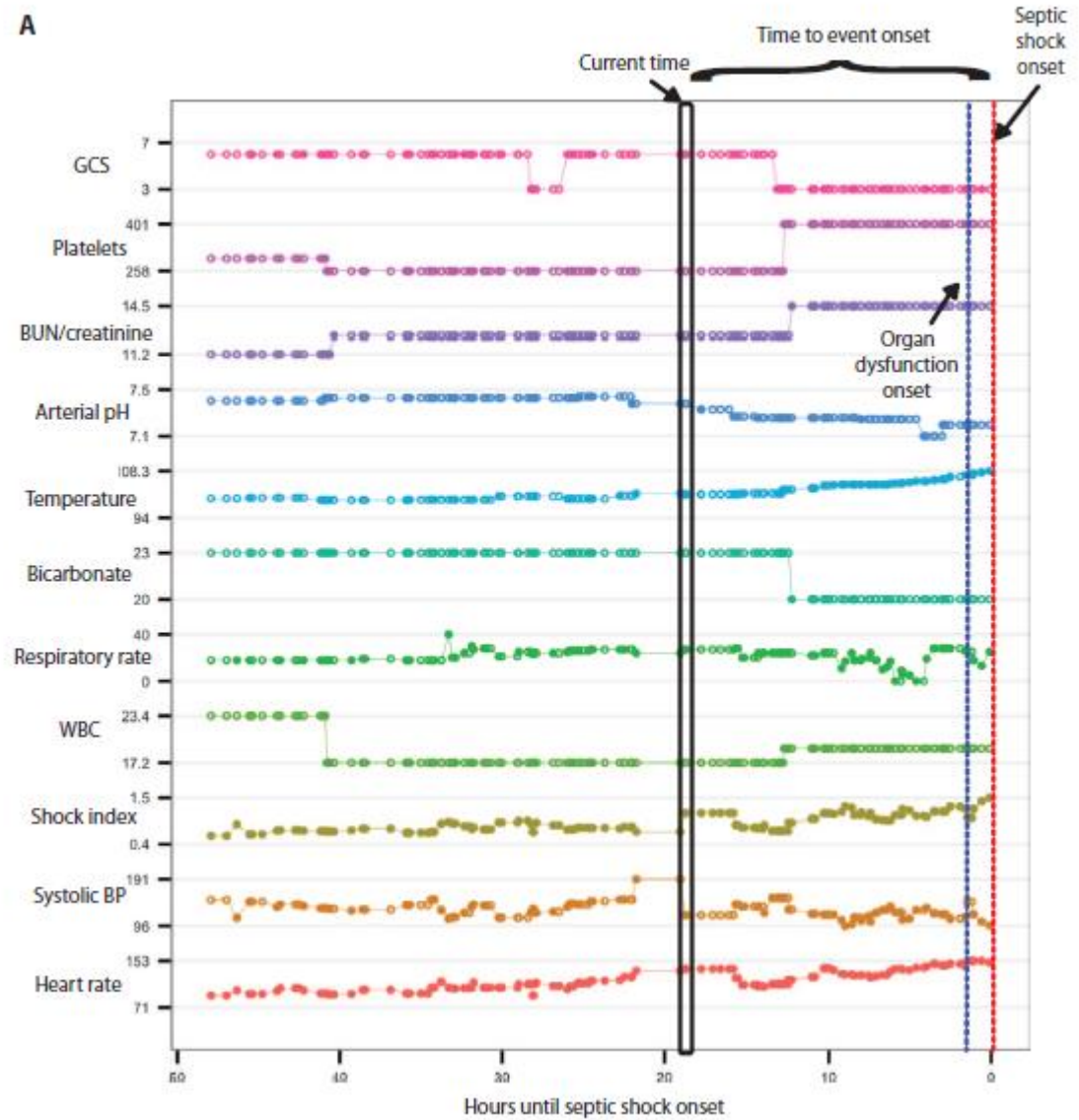
AI

AI & Early Warning Systems



AI in Sepsis Research

- AI is increasingly being used to predict and detect sepsis based on patient data.
- One challenge is gender bias:
- AI models may not perform equally well for men and women due to skewed training data.



AI system misdiagnoses sepsis in women

- AI system for detecting sepsis had a 30% higher error rate when diagnosing women
- Model was trained mainly on male data and overlooked women's immune response to infection.
- Women's symptoms change with their menstrual cycle



When AI is trained for the period before a blood culture is taken

Patients from 01.01.2020 till 31.12.2023:

(in-hospital and outpatients)

Women	1.597.131
Men	1.381.988

blood cultures

51.614
67.700

Sepsis diagnosed

8.956
12.564



AI in Infectious Disease Surveillance – Why Gender Matters

- AI models perform well (e.g. HIV AUC ~0.91)
- But: data are not gender-neutral

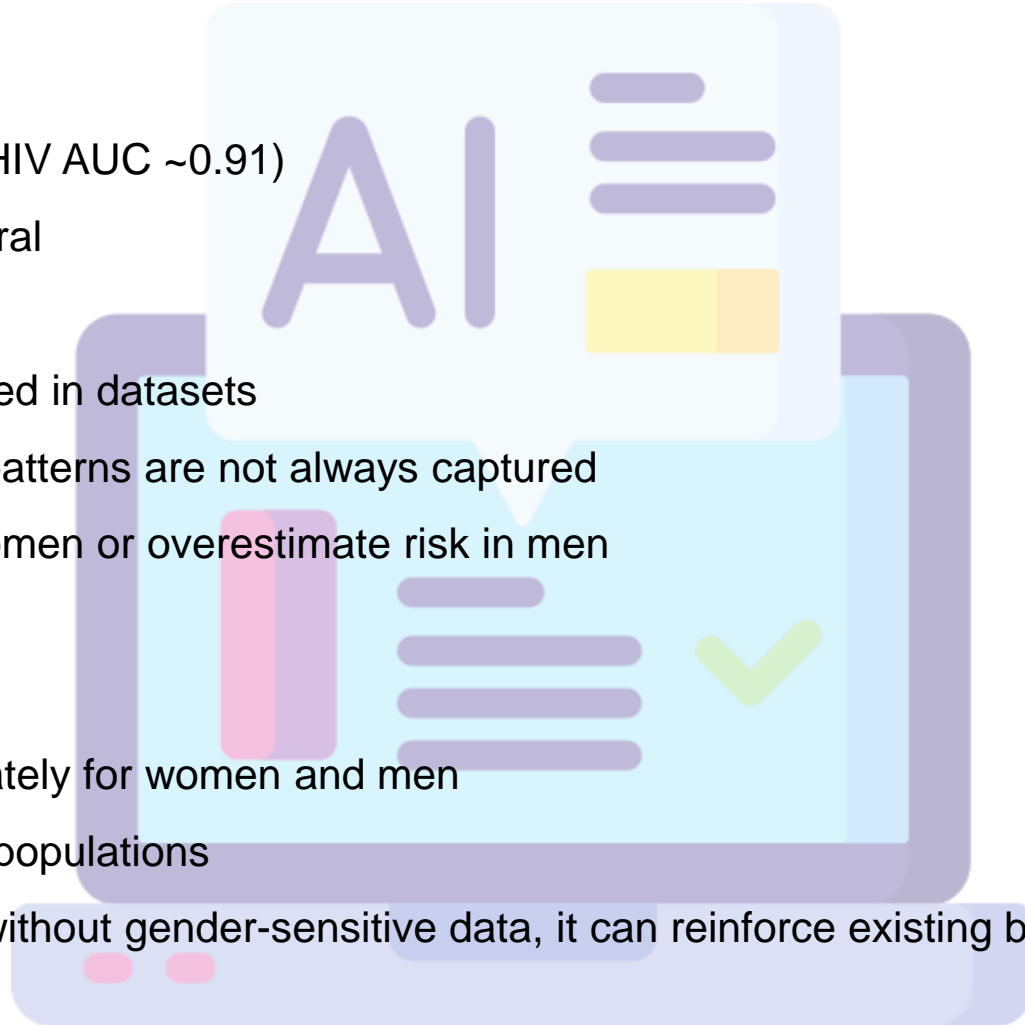
Risks

- Women often underrepresented in datasets
- Different symptoms and risk patterns are not always captured
- Models may miss cases in women or overestimate risk in men

What we need

- Sex-disaggregated data
- Performance reporting separately for women and men
- External validation in diverse populations

AI improves surveillance — but without gender-sensitive data, it can reinforce existing bias.



A hand is shown holding a broken alarm clock. The clock is shattered, with numerous small, dark particles flying out from the broken pieces. The background is a light, neutral color.

Pathogens do not choose a gender.

But our evidence does.

It is time we correct that.

The background of the slide is an aerial photograph of Berlin, Germany, taken during the golden hour. The Spree river flows through the city, with a large cargo ship visible in the water. The city skyline is filled with various buildings, including the prominent Fernsehturm (TV Tower) in the center. The sky is a clear, bright blue with some light clouds.

**Vielen Dank für Ihre
Aufmerksamkeit!**

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