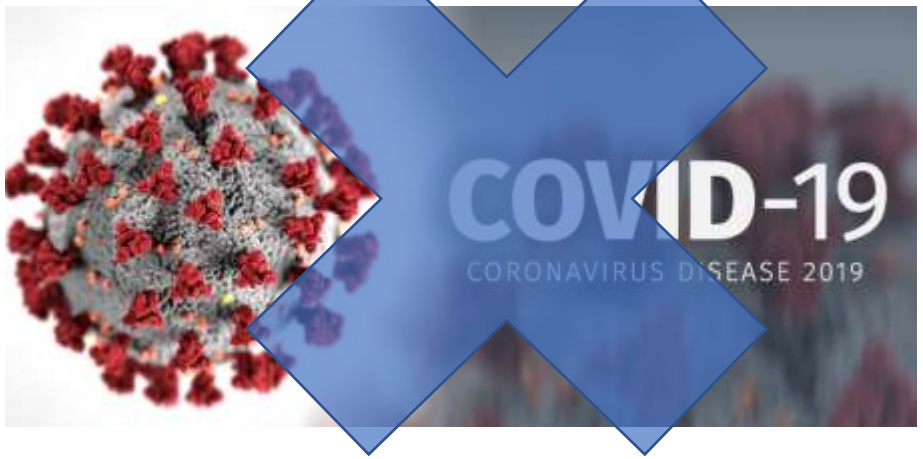


Top ID papers of 2024

NON-COVID!!

Prof Josh Davis, December 2024

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

menzies school of health research

NSW GOVERNMENT Health Hunter New England Local Health District

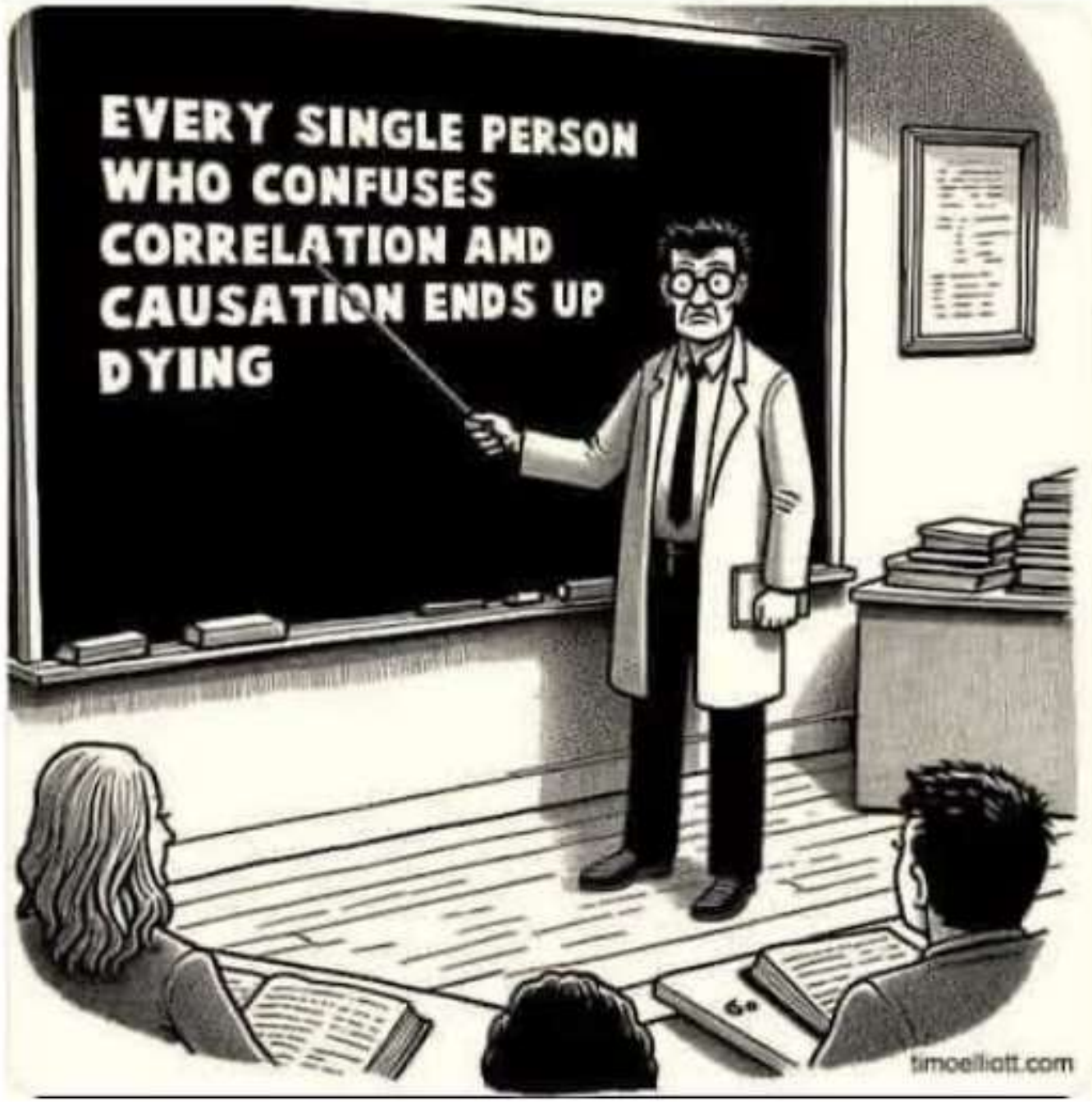
HMRI Hunter Medical Research Institute

Criteria

- IMHO
- COVID excluded
- Published during 2024
- Deal with diagnosis or treatment of infectious diseases
- Relevant to (my) clinical practice
- Practice-changing, paradigm-shifting, or dogma-challenging.
- **In alphabetical order by first author**

Type I Error

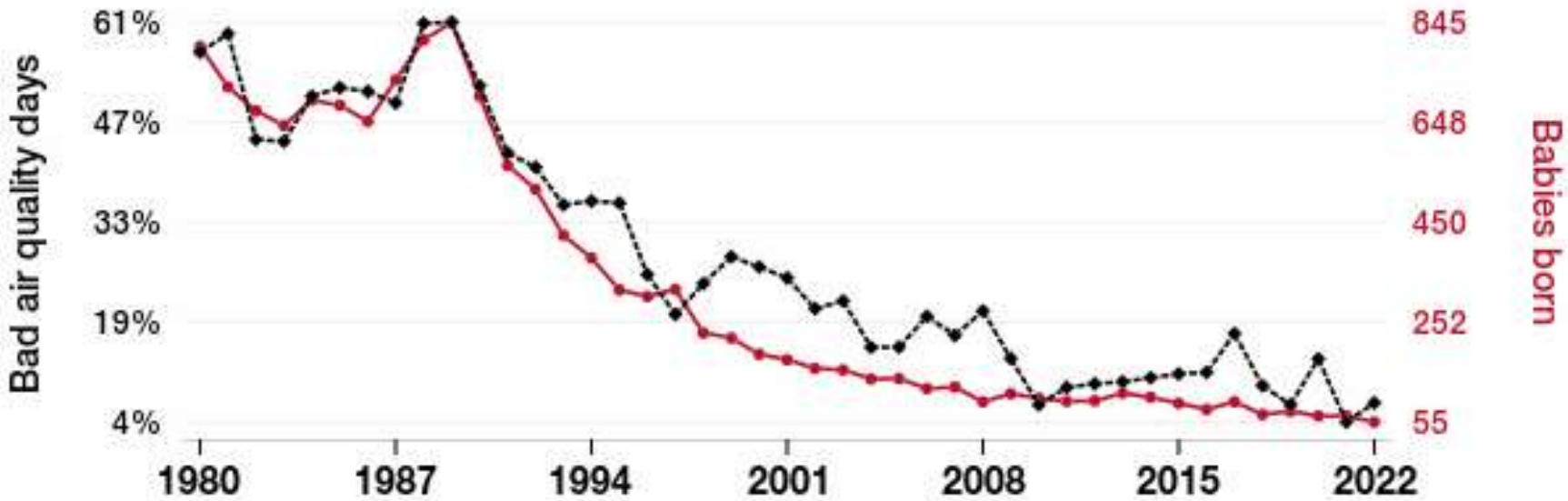
Type II Error


EVERY SINGLE PERSON WHO CONFUSES CORRELATION AND CAUSATION ENDS UP DYING
timoelliott.com

Air pollution in San Diego, California

correlates with

Popularity of the first name Kirk



Percentage of days with air quality at 'unhealthy for sensitive groups' or worse in San Diego-Carlsbad, CA · Source: Environmental Protection Agency

Babies of all sexes born in the US named Kirk · Source: US Social Security Administration

1980-2022, r=0.972, r^2=0.945, p<0.01 · tylervigen.com/spurious/correlation/5949

Honorable Mentions

Hayward	*D-Mannose to prevent recurrent UTI in women*	**JAMA Internal Medicine**	In 303 women at 99 primary care centres in the UK, with recurrent UTIs, D-Mannose daily did not significantly decrease the risk of recurrent UTIs
Lopez-Cortes	*SIMPLIFY trial*	**Lancet ID**	RCT in 21 Spanish hospitals, where 344 with GN bacteraemia Rxd with an antipseudomonal beta-lacatam were randomised to de-escalation or not; there was no difference in clinical cure or mortality
Okhuysen	*Ridinilazole vs Vancomycin for CDI*	**CID**	759 patients with CDI randomised to 10 days of Rid versus Vanco, Rid was non-inferior for clinical response but superior for relpase
Sie	*Azithromycin during routine well-infant visits to prevent death (CHAT)*	**NEJM**	Single dose of azithro at 5-12 weeks of age in 32,000 babies in Burkina Faso had no impact on mortality
Sprague	*PREP-IT trial*	**NEJM**	In 8485 adults with limb fractures, ETOH-iodine a bit better than ETOH-Chlorhex as skin prep for closed fractures but no difference for open
Wagenlehner	*Phase 3 RCT of geptidacin for uncomplicated UTI (EAGLE)*	**Lancet**	New

Honorable mentions implications

- Hayward – D-Mannose disappointing for UTI prevention
- Lopez-Cortes – De-escalate Abs in those with S GN bacteraemia
- Okhuysen – New (expensive) better CDAD drug: Ridinilazole
- Hozhev – Probiotics prevent antibiotic associated diarrhoea
- Sie – Don't give single dose Azithro to all babies in sub-Saharan Africa
- Sprague – Use ETOH-Iodine for closed fractures needing ORIF
- Wagenlehner – Gepticidan (+2 more)* new option for R UTI

*Pivmenicillin and Sulopenem/probenicid

Article

Gut microbiome strain-sharing within isolated village social networks

- WHY
  - Paradigm-shifting

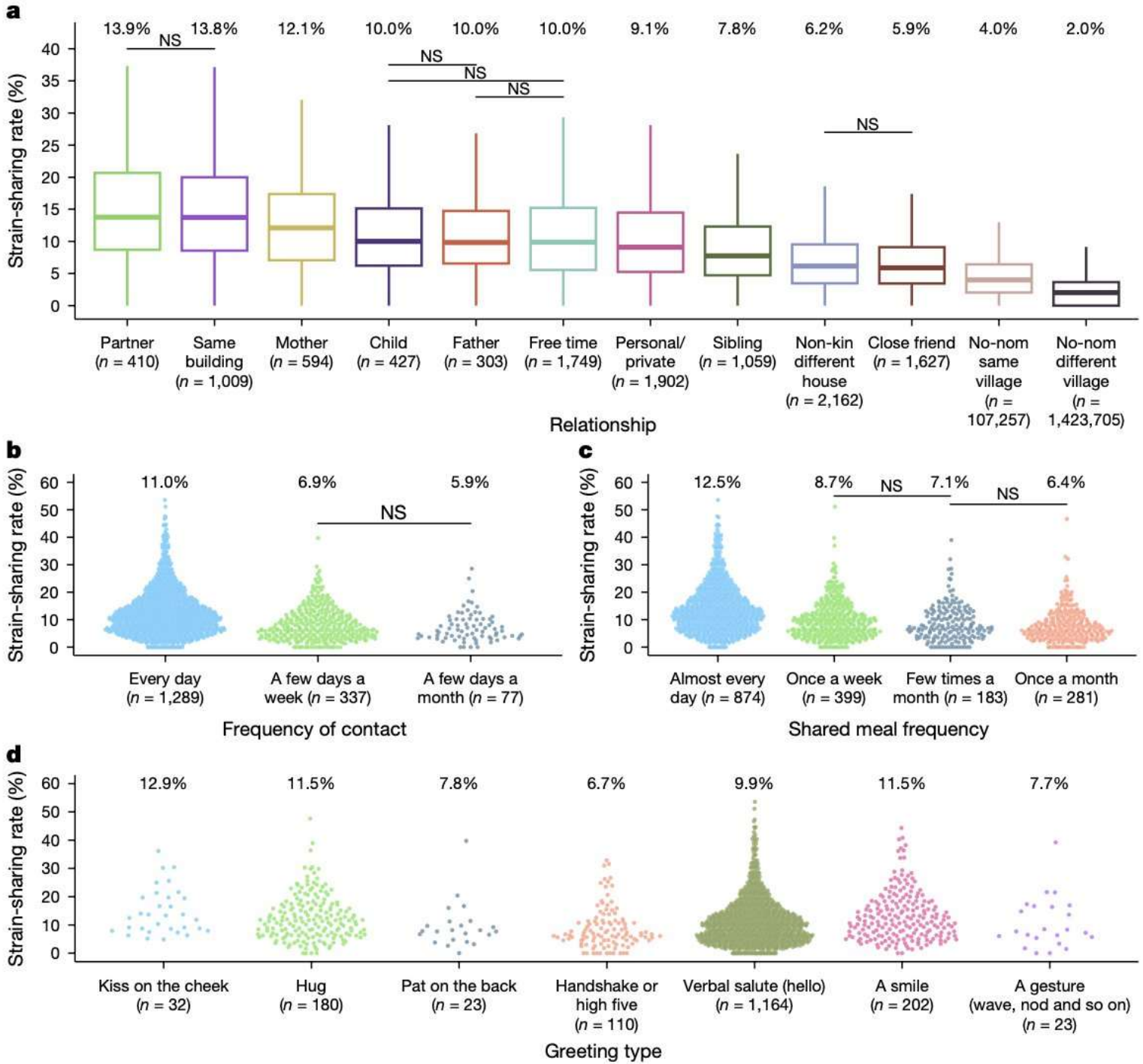
Francesco Beghini[1,10], Jackson Pullman[1,2,10], Marcus Alexander[1], Shivkumar Vishnempet Shridhar[1,3], Drew Prinster[4], Adarsh Singh[5], Rigoberto Matute Juárez[6], Edoardo M. Airoldi[7,8], Ilana L. Brito[5] & Nicholas A. Christakis[1,2,3,9] ✉

Article

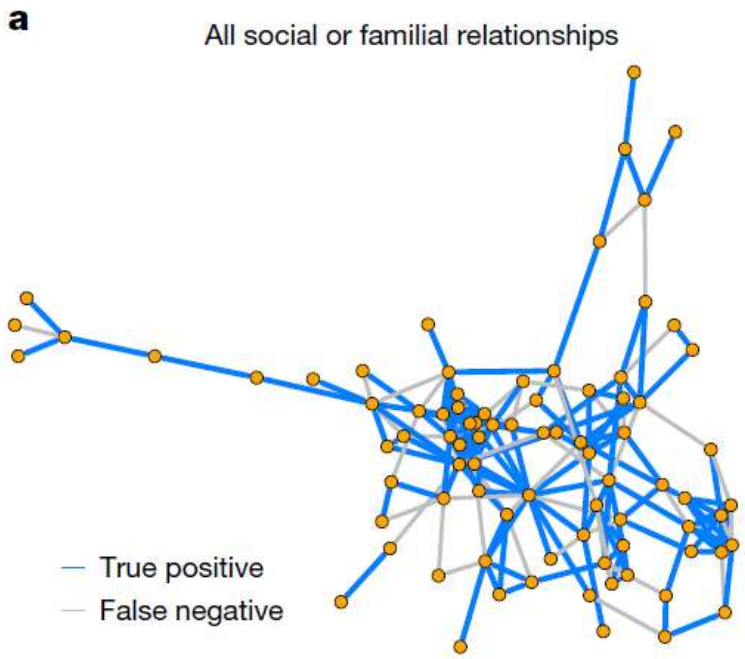
Gut microbiome strain-sharing within isolated village social networks

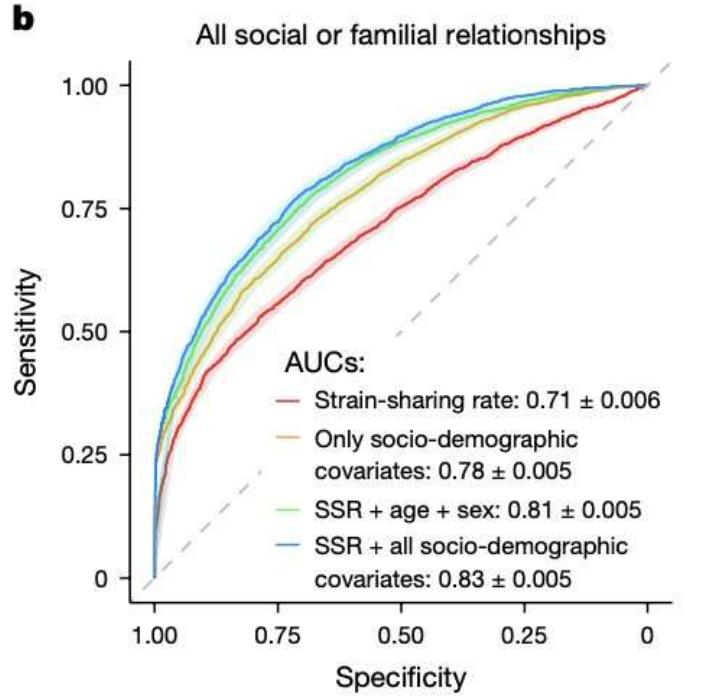
- WHY
  - Paradigm-shifting
- WHAT/HOW
  - 1787 adults in 18 isolated Honduran villages had social network mapping and gut microbiome sequencing
- KEY FINDINGS
  - Microbial-sharing occurs both within households and with other relationships
  - Socially central people are more microbiologically similar to the overall village than socially peripheral people

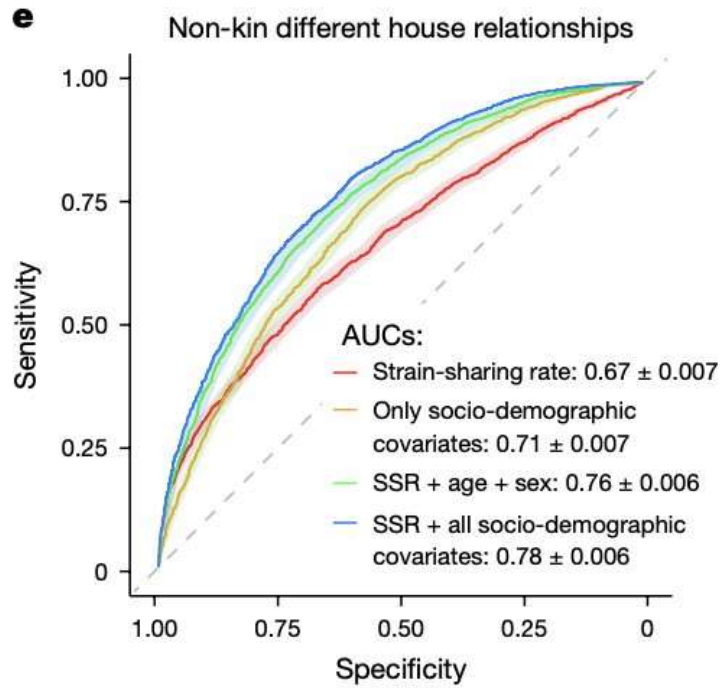
Francesco Beghini[1,10], Jackson Pullman[1,2,10], Marcus Alexander[1], Shivkumar Vishnempet Shridhar[1,3], Drew Prinster[4], Adarsh Singh[5], Rigoberto Matute Juárez[6], Edoardo M. Airoldi[7,8], Ilana L. Brito[5] & Nicholas A. Christakis[1,2,3,9] ✉


a
13.9%
NS
13.8%
12.1%
10.0%
NS
NS
NS
10.0%
9.1%
7.8%
6.2%
NS
5.9%
4.0%
2.0%
Strain-sharing rate (%)
Partner (n = 410)
Same building (n = 1,009)
Mother (n = 594)
Child (n = 427)
Father (n = 303)
Free time (n = 1,749)
Personal/ private (n = 1,902)
Sibling (n = 1,059)
Non-kin different house (n = 2,162)
Close friend (n = 1,627)
No-nom same village (n = 107,257)
No-nom different village (n = 1,423,705)
Relationship
b
11.0%
6.9%
NS
5.9%
Strain-sharing rate (%)
Every day (n = 1,289)
A few days a week (n = 337)
A few days a month (n = 77)
Frequency of contact
c
12.5%
8.7%
NS
7.1%
NS
6.4%
Strain-sharing rate (%)
Almost every day (n = 874)
Once a week (n = 399)
Few times a month (n = 183)
Once a month (n = 281)
Shared meal frequency
d
12.9%
11.5%
7.8%
6.7%
9.9%
11.5%
7.7%
Strain-sharing rate (%)
Kiss on the cheek (n = 32)
Hug (n = 180)
Pat on the back (n = 23)
Handshake or high five (n = 110)
Verbal salute (hello) (n = 1,164)
A smile (n = 202)
A gesture (wave, nod and so on) (n = 23)
Greeting type

- Strain-sharing rate can be used to guess who your friends are
- (Adding socio-demographic variables only increased this predictive ability a bit)







Article

Gut microbiome strain-sharing within isolated village social networks

- WHY
  - Paradigm-shifting
- IMPLICATIONS
  - Diseases formerly thought to be non-communicable (e.g. obesity, inflammatory arthritis) may actually be (at least partially) transmissible!

Francesco Beghini[1,10], Jackson Pullman[1,2,10], Marcus Alexander[1], Shivkumar Vishnempet Shridhar[1,3], Drew Prinster[4], Adarsh Singh[5], Rigoberto Matute Juárez[6], Edoardo M. Airoldi[7,8], Ilana L. Brito[5] & Nicholas A. Christakis[1,2,3,9]✉

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 3, 2024 VOL. 391 NO. 13

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

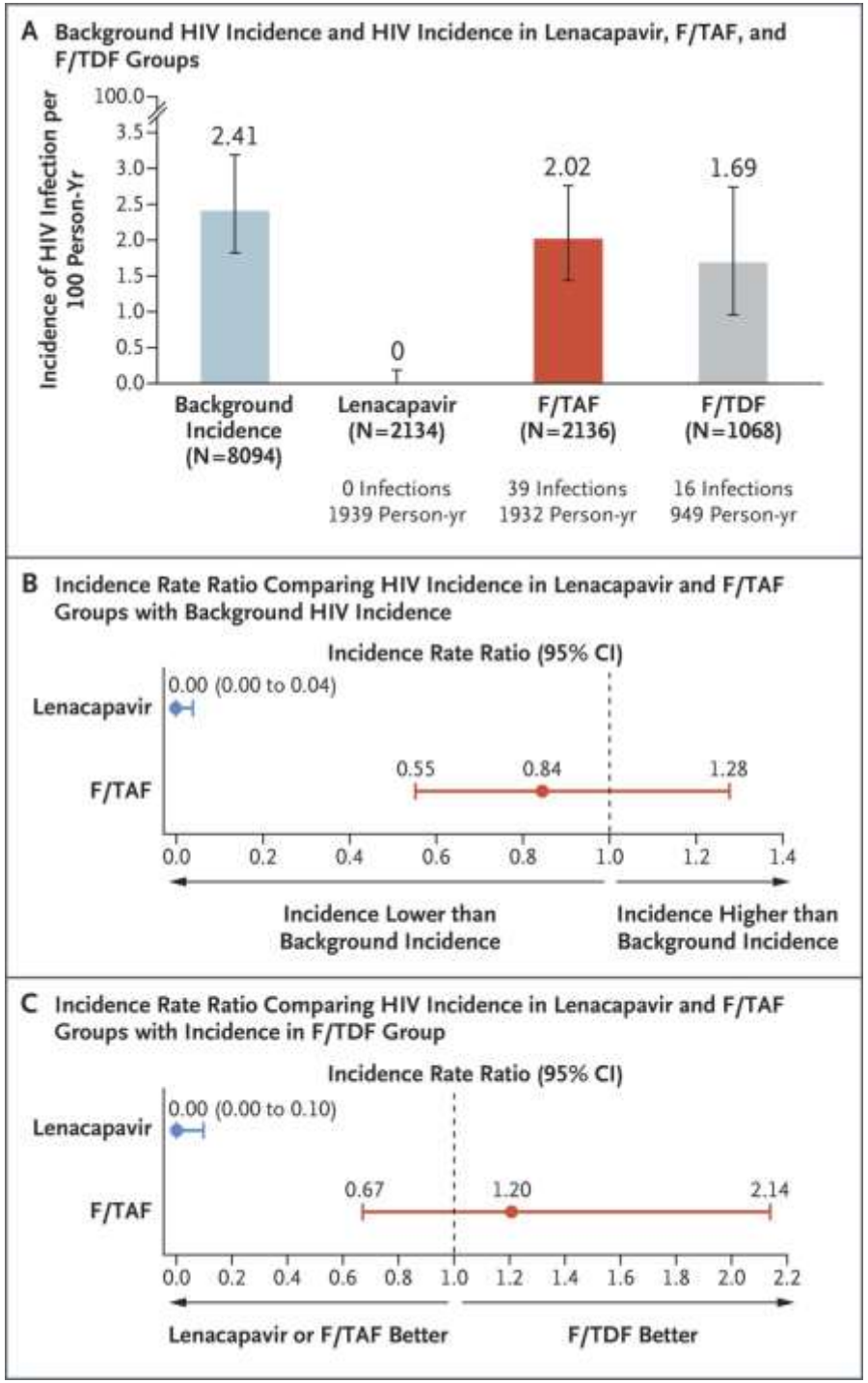
L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

- WHY
  - Practice-changing
- WHAT/HOW
  - Lenacapavir is an HIV capsid inhibitor with a long half life
  - 5338 HIV-ve women from Sth Africa and Uganda randomised to 6-monthly subcut lenacapvir, daily FTC/TAF or daily FTC/TDF OR matching placebo
  - 1ry outcome: incidence of new HIV infections

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Age			
Median(range) — yr	21 (16–25)	21 (16–26)†	21 (16–25)
16 or 17 yr — no. (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race — no. (%)‡	2135 (99.9)	2136 (>99.9)	1068 (99.8)
Education — no./total no. (%)			
No primary school	17/2136 (0.8)	19/2134 (0.9)	3/1069 (0.3)
Primary school	235/2136 (11.0)	223/2134 (10.4)	106/1069 (9.9)
Secondary school	1701/2136 (79.6)	1694/2134 (79.4)	851/1069 (79.6)
College or university	183/2136 (8.6)	198/2134 (9.3)	109/1069 (10.2)
Married — no./total no. (%)	26/2136 (1.2)	30/2134 (1.4)	17/1069 (1.6)
Living with primary partner — no./total no. (%)	148/2136 (6.9)	132/2134 (6.2)	73/1069 (6.8)
Sexually transmitted infection			
Chlamydia trachomatis	520 (24.3)	562 (26.3)	263 (24.6)
Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Any previous use of PrEP — no. (%)	143 (6.7)	121 (5.7)	71 (6.6)
Any previous HIV testing — no. (%)	1713 (80.1)	1731 (81.0)	860 (80.4)
Median time since last HIV test (IQR) — mo	6.8 (4.7–11.5)	6.6 (4.8–11.0)	6.5 (4.6–11.0)
Country — no. (%)			
South Africa	1809 (84.6)	1790 (83.8)	909 (85.0)
Uganda	329 (15.4)	347 (16.2)	161 (15.0)

* F/TAF denotes emtricitabine–tenofovir alafenamide, F/TDF emtricitabine–tenofovir disoproxil fumarate, HIV human immunodeficiency virus, IQR interquartile range, and PrEP preexposure prophylaxis.
† One person was screened at 25 years of age but was 26 years of age by the time of randomization. This was not a violation of the eligibility criteria.
‡ Race was reported by the participants. All non-Black participants were multiracial.


A Background HIV Incidence and HIV Incidence in Lenacapavir, F/TAF, and F/TDF Groups
Incidence of HIV Infection per 100 Person-Yr
100.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.41
0
2.02
1.69
Background Incidence (N=8094)
Lenacapavir (N=2134)
F/TAF (N=2136)
F/TDF (N=1068)
0 Infections 1939 Person-yr
39 Infections 1932 Person-yr
16 Infections 949 Person-yr
B Incidence Rate Ratio Comparing HIV Incidence in Lenacapavir and F/TAF Groups with Background HIV Incidence
Incidence Rate Ratio (95% CI)
Lenacapavir
0.00 (0.00 to 0.04)
F/TAF
0.55
0.84
1.28
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
Incidence Lower than Background Incidence
Incidence Higher than Background Incidence
C Incidence Rate Ratio Comparing HIV Incidence in Lenacapavir and F/TAF Groups with Incidence in F/TDF Group
Incidence Rate Ratio (95% CI)
Lenacapavir
0.00 (0.00 to 0.10)
F/TAF
0.67
1.20
2.14
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2
Lenacapavir or F/TAF Better
F/TDF Better

Bekker – PURPOSE trial - NEJM

- WHY
  - Practice-changing
- IMPLICATIONS
  - PURPOSE 2 trial showed the same in men (and gender diverse people) across 7 countries including USA
  - If you don't take a drug it doesn't work!
  - Lenacapavir should be the standard of care for PREP in those at high risk of HIV BUT cost and health economics are a barrier
  - Current estimated cost=$40,000/person/year, versus ~$1,500 for TDF/FTC

Browne – CLEEN trial – Lancet ID

- WHY
  - Practice-changing

Investigating the effect of enhanced cleaning and disinfection of shared medical equipment on health-care-associated infections in Australia (CLEEN): a stepped-wedge, cluster randomised, controlled trial

Katrina Browne, Nicole M White, Philip L Russo, Allen C Cheng, Andrew J Stewardson, Georgia Matterson, Peta E Tehan, Kirsty Graham, Maham Amin, Maria Northcote, Martin Kiernan, Jennie King, David Brain, Brett G Mitchell

- WHY
  - Practice-changing
- WHAT/HOW
  - Stepped-wedge cluster RCT in ten wards of Gosford hospital
  - Intervention: multimodal cleaning bundle of shared medical equipment – extra 3h per day by trained study staff
    - E.g. Shpygmos, walking frames, commodes, drip stands
  - Primary outcome incidence of new HAI (fortnightly point-prevalence survey)

Lancet Infect Dis 2024; 24: 1347–56

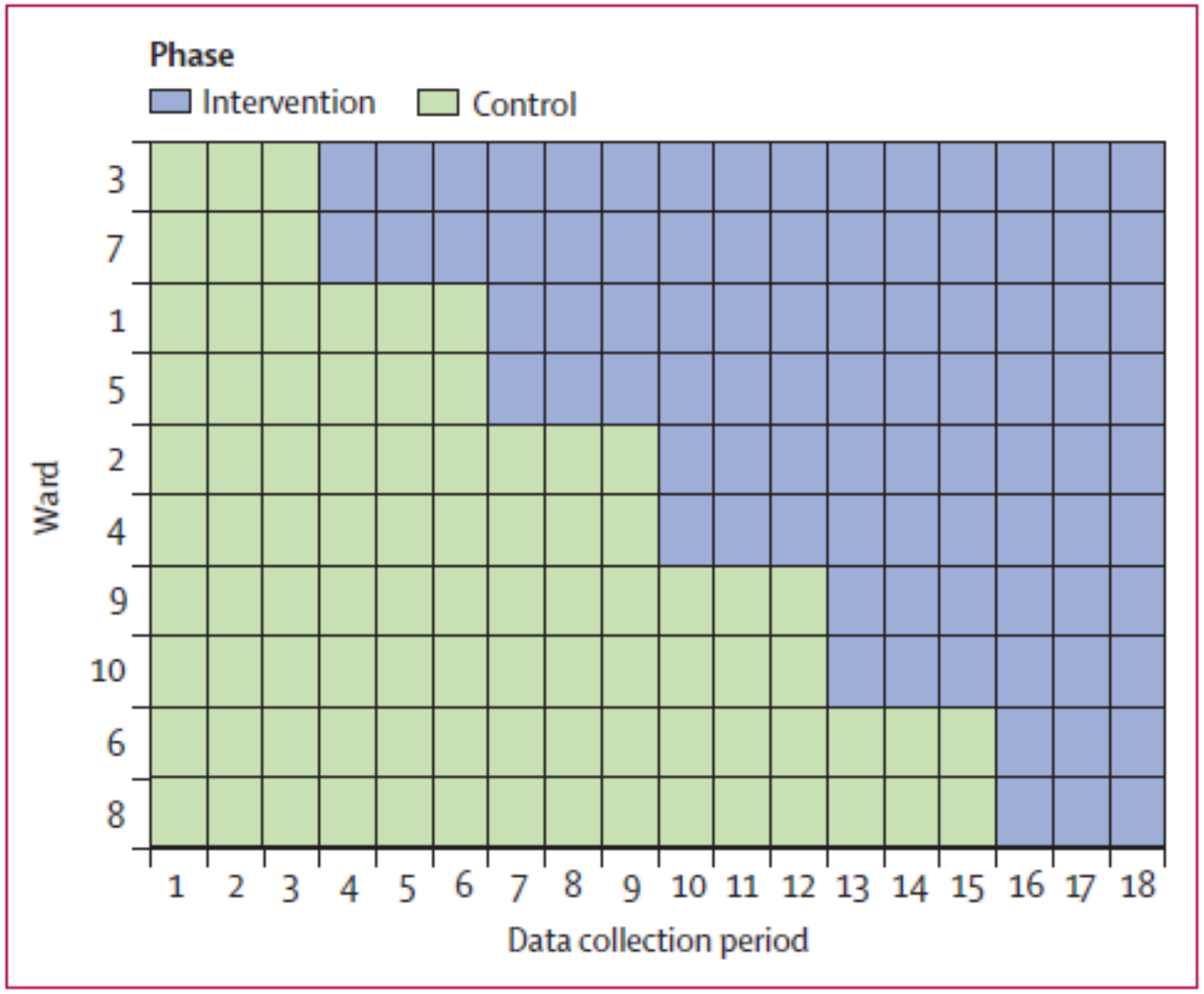


Figure 1: **Stepped-wedge trial design**
Each data collection period represents a 2-week period.

Lancet Infect Dis 2024;
24: 1347–56

	All patients (n=5002), n (%)	Patients without HAI (n=4417), n (%)	Patients with ≥1 HAI (n=585), n (%)	Control (n=2494), n (%)	Intervention (n=2508), n (%)
Sex					
Female	2524 (50·5%)	2235 (50·6%)	289 (49·4%)	1254 (50·3%)	1270 (50·6%)
Male	2478 (49·5%)	2182 (49·4%)	296 (50·6%)	1240 (49·7%)	1238 (49·4%)
Age, years					
Median (IQR)	75 (63–83)	75 (63–83)	75 (66–83)	75 (63–83)	75 (63–84)
Mean (SD)	71·6 (16·1)	71·4 (16·3)	73·2 (14·0)	71·4 (15·9)	71·9 (16·3)
Emergency admission	4159 (83·1%)	3710 (84·0%)	449 (76·8%)	2055 (82·4%)	2104 (83·9%)
Current colonisation or infection with multiresistant organism	610 (12·2%)	485 (11·0%)	125 (21·4%)	339 (13·6%)	271 (10·8%)
Ward duration of stay before survey, days					
Median (IQR)	7 (3–16)	6 (3–14)	14 (8–27)	7 (3–17)	7 (3–15)
Mean (SD)	15·8 (34·4)	14·7 (33·1)	24·2 (41·7)	16·8 (39·3)	14·8 (28·6)
Peripheral vascular access device present	2347 (46·9%)	2052 (46·5%)	295 (50·4%)	1192 (47·8%)	1155 (46·1%)
Central vascular access device present	316 (6·3%)	225 (5·1%)	91 (15·6%)	176 (7·1%)	140 (5·6%)
Indwelling urinary catheter present	785 (15·7%)	645 (14·6%)	140 (23·9%)	406 (16·3%)	379 (15·1%)
Ventilated	415 (8·3%)	343 (7·8%)	72 (12·3%)	197 (7·9%)	218 (8·7%)
Ward specialty					
Geriatric	530 (10·6%)	472 (10·7%)	58 (9·9%)	101 (4·0%)	429 (17·1%)
Neurology	555 (11·1%)	503 (11·4%)	52 (8·9%)	195 (7·8%)	360 (14·4%)
Oncology	588 (11·8%)	480 (10·9%)	108 (18·5%)	425 (17·0%)	163 (6·5%)
Orthopaedic	519 (10·4%)	460 (10·4%)	59 (10·1%)	412 (16·5%)	107 (4·3%)
Other	1 (0·0%)	1 (0·0%)	0	0	1 (0·0%)
Renal	442 (8·8%)	388 (8·8%)	54 (9·2%)	174 (7·0%)	268 (10·7%)
Respiratory	586 (11·7%)	532 (12·0%)	54 (9·2%)	311 (12·5%)	275 (11·0%)
Surgical	1675 (33·5%)	1488 (33·7%)	187 (32·0%)	828 (33·2%)	847 (33·8%)
Vascular	106 (2·1%)	93 (2·1%)	13 (2·2%)	48 (1·9%)	58 (2·3%)

Data are n (%) unless otherwise stated. Three patients had two separate admissions to hospital and are recorded only once in the baseline demographic information.
HAI=health-care-associated infection.

Table 1: **Baseline characteristics for all patients and stratified by HAI acquisition**

Lancet Infect Dis 2024;
24: 1347–56

- Control period HAIs
  - 433/2497 (17.3%, 15.9-18.8%)
- Intervention period HAIs
  - 301/2508 (12.0%, 10.7-13.3%)
- **Relative reduction of 34.5%**

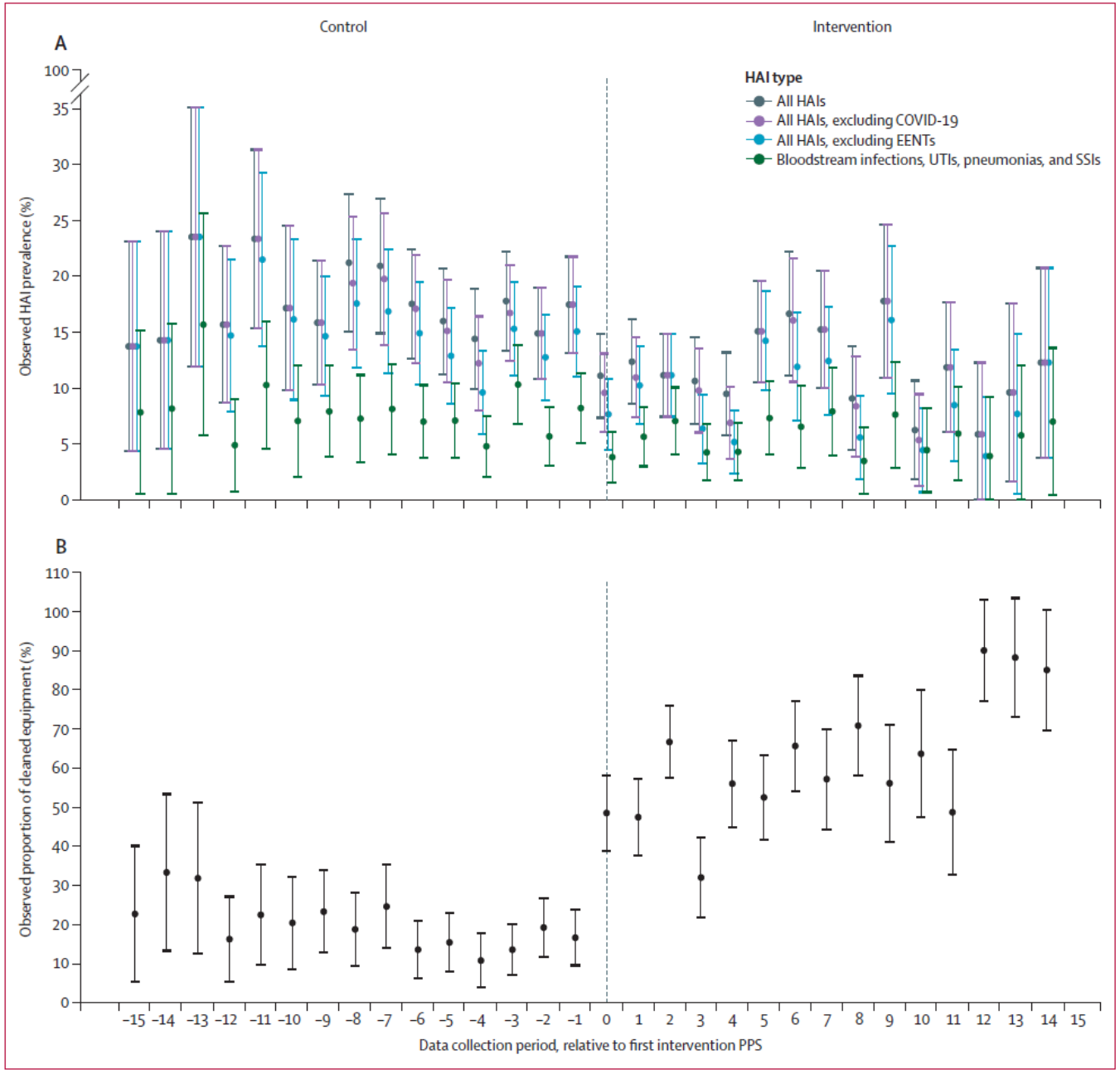


Figure 3: **Summary of outcomes relative to the first intervention PPS**
HAI prevalence (A) and proportion of cleaned equipment (B) in the control phase and intervention phase by HAI subtype. Each data collection period represents a 2-week period. EENT=ear, eye, nose, and throat infection. HAI=health-care-associated infection. PPS=point prevalence survey. SSI=surgical site infection. UTI=urinary tract infection.

Lancet Infect Dis 2024; 24: 1347–56

Investigating the effect of enhanced cleaning and disinfection of shared medical equipment on health-care-associated infections in Australia (CLEEN): a stepped-wedge, cluster randomised, controlled trial

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- WHY
  - Practice-changing
- IMPLICATIONS
  - Hospital environmental cleaning is crucial and under-appreciated AND reduces acquisition of HAIs
  - BUT it is resource intensive to do it properly
  - Needs to be repeated in other/larger hospitals and settings to assess generalisability

Lancet Infect Dis 2024; 24: 1347–56

ORIGINAL ARTICLE

Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections

The BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network

- WHY
  - Practice-changing
- WHAT/HOW
  - RCT in 74 hospitals, 7 countries, 3608 patients (55% in ICU)
  - Randomised to 7 vs 14 days total antibiotic duration for bacteraemia
    - S.aureus and fungi excluded
    - Need for prolonged Rx excluded (e.g. endocarditis, BJI, undrained collections)
    - Timing of oral switch and choice of ABs at clinicians' discretion

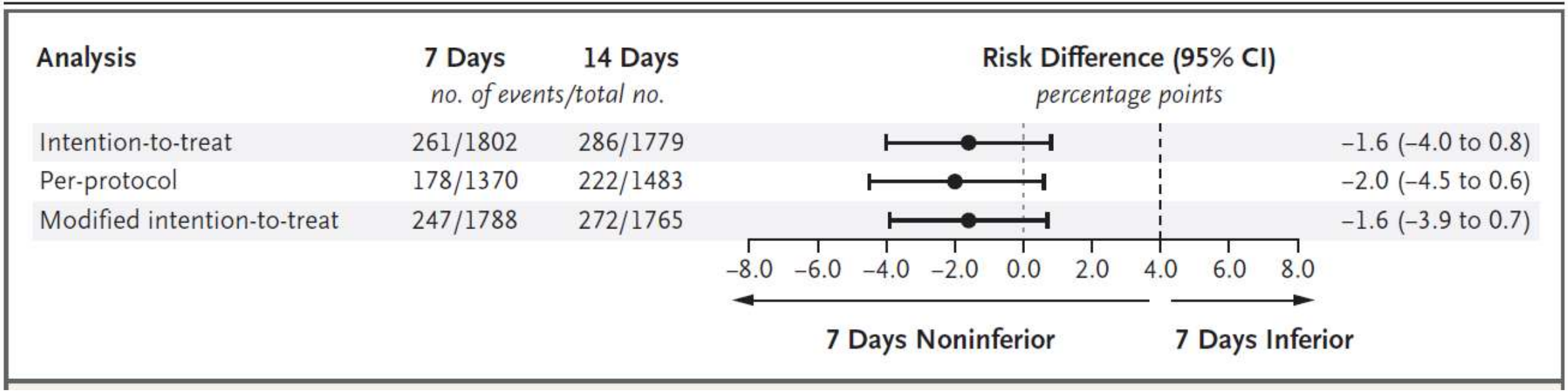
***COI and acknowledgement**

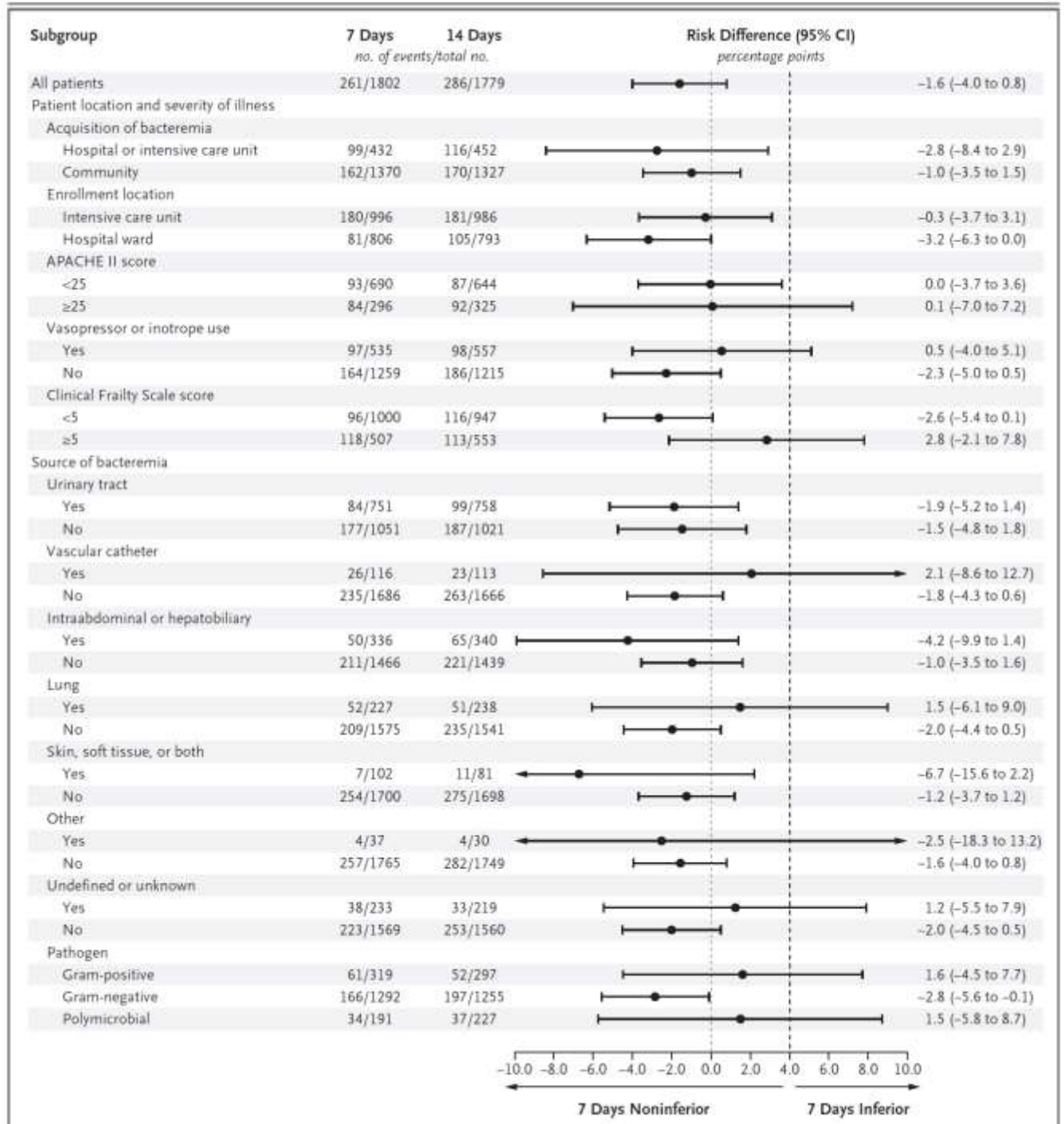
Top 11 pathogens*	Overall N=3608	7-day arm N=1814	14-day arm N=1794
Escherichia coli	1582 (43.8)	805 (44.4)	777 (43.3)
Klebsiella spp.	552 (15.3)	273 (15.0)	279 (15.6)
Enterococcus spp.	250 (6.9)	119 (6.6)	131 (7.3)
Coag. neg. staph.	174 (4.8)	81 (4.5)	93 (5.2)
Pseudomonas spp.	170 (4.7)	80 (4.4)	90 (5.0)
Strep. pneumoniae	164 (4.5)	86 (4.7)	78 (4.3)
Enterobacter spp.	157 (4.4)	80 (4.4)	77 (4.3)
Proteus spp.	133 (3.7)	58 (3.2)	75 (4.2)
Serratia spp.	86 (2.4)	38 (2.1)	48 (2.7)
Strep. pyogenes	74 (2.1)	39 (2.1)	35 (2.0)
Strep. agalactiae	75 (2.1)	40 (2.2)	35 (2.0)

*more than 70 different pathogens in total

Table 2. Primary and Secondary Outcomes.

	7-Day Group (N = 1814)	14-Day Group (N = 1794)	Difference (95% CI)*
			percentage points
Primary outcome, death from any cause by 90 days — no./ total no. (%)			
Primary analysis, intention-to-treat population	261/1802 (14.5)	286/1779 (16.1)	−1.6 (−4.0 to 0.8)
Secondary analysis, per-protocol population	178/1370 (13.0)	222/1483 (15.0)	−2.0 (−4.5 to 0.6)
Modified intention-to-treat analysis, survival ≥7 days	247/1788 (13.8)	272/1765 (15.4)	−1.6 (−3.9 to 0.7)
Secondary outcomes			
Death in hospital — no. (%)†	168 (9.3)	184 (10.3)	−1.0 (−2.9 to 0.9)

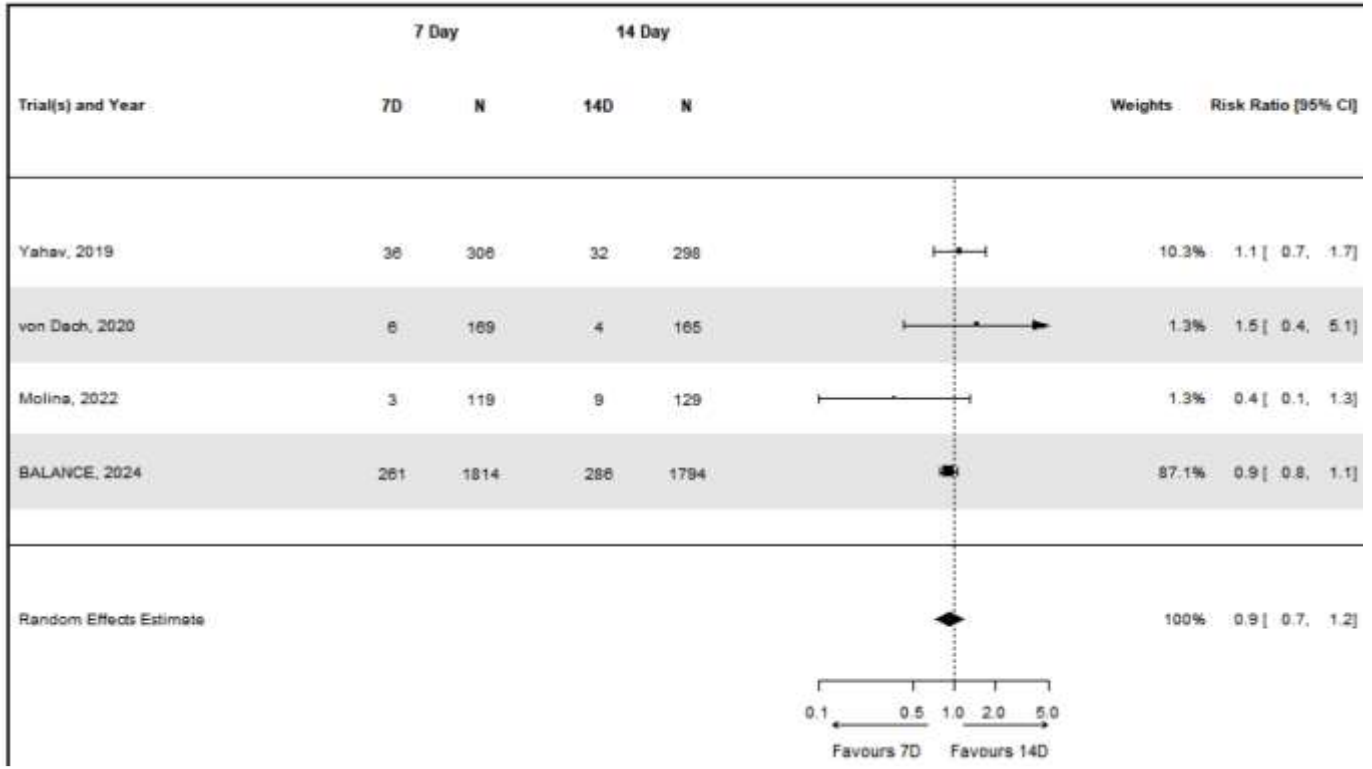



Subgroup
7 Days
no. of events/total no.
14 Days
Risk Difference (95% CI)
percentage points
All patients 261/1802 286/1779 −1.6 (−4.0 to 0.8)
Patient location and severity of illness
Acquisition of bacteremia
Hospital or intensive care unit 99/432 116/452 −2.8 (−8.4 to 2.9)
Community 162/1370 170/1327 −1.0 (−3.5 to 1.5)
Enrollment location
Intensive care unit 180/996 181/986 −0.3 (−3.7 to 3.1)
Hospital ward 81/806 105/793 −3.2 (−6.3 to 0.0)
APACHE II score
<25 93/690 87/644 0.0 (−3.7 to 3.6)
≥25 84/296 92/325 0.1 (−7.0 to 7.2)
Vasopressor or inotrope use
Yes 97/535 98/557 0.5 (−4.0 to 5.1)
No 164/1259 186/1215 −2.3 (−5.0 to 0.5)
Clinical Frailty Scale score
<5 96/1000 116/947 −2.6 (−5.4 to 0.1)
≥5 118/507 113/553 2.8 (−2.1 to 7.8)
Source of bacteremia
Urinary tract
Yes 84/751 99/758 −1.9 (−5.2 to 1.4)
No 177/1051 187/1021 −1.5 (−4.8 to 1.8)
Vascular catheter
Yes 26/116 23/113 2.1 (−8.6 to 12.7)
No 235/1686 263/1666 −1.8 (−4.3 to 0.6)
Intraabdominal or hepatobiliary
Yes 50/336 65/340 −4.2 (−9.9 to 1.4)
No 211/1466 221/1439 −1.0 (−3.5 to 1.6)
Lung
Yes 52/227 51/238 1.5 (−6.1 to 9.0)
No 209/1575 235/1541 −2.0 (−4.4 to 0.5)
Skin, soft tissue, or both
Yes 7/102 11/81 −6.7 (−15.6 to 2.2)
No 254/1700 275/1698 −1.2 (−3.7 to 1.2)
Other
Yes 4/37 4/30 −2.5 (−18.3 to 13.2)
No 257/1765 282/1749 −1.6 (−4.0 to 0.8)
Undefined or unknown
Yes 38/233 33/219 1.2 (−5.5 to 7.9)
No 223/1569 253/1560 −2.0 (−4.5 to 0.5)
Pathogen
Gram-positive 61/319 52/297 1.6 (−4.5 to 7.7)
Gram-negative 166/1292 197/1255 −2.8 (−5.6 to −0.1)
Polymicrobial 34/191 37/227 1.5 (−5.8 to 8.7)
−10.0 −8.0 −6.0 −4.0 −2.0 0.0 2.0 4.0 6.0 8.0 10.0
7 Days Noninferior
7 Days Inferior

ORIGINAL ARTICLE

Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections

The BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network



- WHY
  - Practice-changing
- IMPLICATIONS
  - 7 days of antibiotics should be the standard duration for bacteraemia UNLESS it is S.aureus or is a defined syndrome with a clear need for longer durations
  - Regardless of disease severity, ICU admission, focus of infection

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Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis The BLING III Randomized Clinical Trial

Joel M. Dulhunty, MD, PhD; Stephen J. Brett, MD; Jan J. De Waele, MD, PhD; Dorrilyn Rajbhandari, PGDip(Clinical Nursing); Laurent Billot, MRes; Menino O. Cotta, PhD; Joshua S. Davis, MD, PhD; Simon Finfer, MD; Naomi E. Hammond, RN, PhD; Serena Knowles, RN, PhD; Xiaoqiu Liu, PhD; Shay McGuinness, MD; Jayanthi Mysore, MS; David L. Paterson, MD, PhD; Sandra Peake, MD, PhD; Andrew Rhodes, MD, MD(Res); Jason A. Roberts, BPharm, PhD; Claire Roger, MD, PhD; Charudatt Shirwadkar, MD; Therese Starr, RN; Colman Taylor, PhD; John A. Myburgh, MD, PhD; Jeffrey Lipman, MD, DMed(Res); for the BLING III Study Investigators

- WHY
  - Practice-changing
- WHAT/HOW
  - RCT in 104 ICUs in 7 countries
  - 7,202 adults with sepsis treated with pip/tazo or meropenem randomised to continuous infusion or intermittent dosing
  - Primary outcome=90 day all-cause mortality

***COI and acknowledgement**

JAMA

QUESTION Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

CONCLUSION In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-day mortality in the primary analysis. A clinically important benefit with continuous infusions is possible.

POPULATION

4608 Men
2423 Women

Critically ill adults aged ≥18 years treated for sepsis

Mean age: 59 years

LOCATION

104
ICUs worldwide

INTERVENTION

7031 Patients randomized

3498

Continuous infusion

Continuous infusion (over 24 hours) of either piperacillin-tazobactam or meropenem

3533

Intermittent infusion

Intermittent infusion (over 30 minutes) of either piperacillin-tazobactam or meropenem

PRIMARY OUTCOME

All-cause mortality within 90 days after randomization

FINDINGS

All-cause mortality at day 90

Continuous infusion
864 of 3474 patients

Intermittent infusion
939 of 3507 patients

Absolute difference, −1.9% (95% CI, −4.9% to 1.1%)
Odds ratio, 0.91 (95% CI, 0.81 to 1.01); *P* = .08

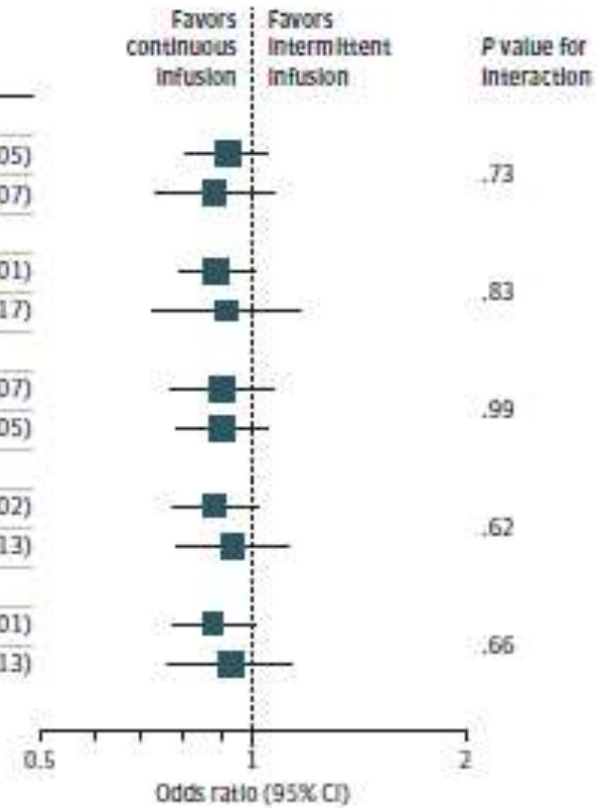
Dulhunty JM, Brett SJ, De Waele JJ, et al; BLING III Study Investigators. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA*. Published June 12, 2024. doi:10.1001/jama.2024.9779

Table 2. Reporting of Primary, Secondary, and Tertiary Outcomes

Outcome	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds ratio or mean difference (95% CI)	*P* value[b]
Primary outcome					
All-cause mortality at day 90, No./total (%)	864/3474 (24.9)	939/3507 (26.8)	−1.9 (−4.9 to 1.1)	0.91 (0.81 to 1.01)	.08
Adjusted analysis			−2.2 (−5.5 to 1.1)	0.89 (0.79 to 0.99)	.04
Secondary outcomes					
Clinical cure at day 14, No./total (%)	1930/3467 (55.7)	1744/3491 (50.0)	5.7 (2.4 to 9.1)	1.26 (1.15 to 1.38)	<.001
New acquisition, colonization, or infection with an MRO or *C difficile*, No./total (%)[c]	253/3498 (7.2)	266/3533 (7.5)	−0.3 (−1.9 to 1.4)	0.96 (0.80 to 1.15)	.65
All-cause ICU mortality, No./total (%)	595/3474 (17.1)	645/3507 (18.4)	−1.3 (−4.0 to 1.4)	0.92 (0.81 to 1.04)	.35
All-cause hospital mortality, No./total (%)	808/3474 (23.3)	878/3507 (25.0)	−1.8 (−4.8 to 1.2)	0.91 (0.81 to 1.02)	.27

Figure 2. Subgroup Analysis of Mortality at Day 90

	Group, No./total (%)				
	Continuous infusion	Intermittent infusion	Absolute difference, % (95% CI)[a]	Odds ratio (95% CI)[b]	*P* value for interaction
Pulmonary infection					
Yes	593/2178 (27.2)	647/2249 (28.8)	−1.7 (−5.2 to 1.9)	0.92 (0.81 to 1.05)	.73
No	271/1296 (20.9)	292/1258 (23.2)	−2.1 (−6.0 to 1.7)	0.88 (0.73 to 1.07)	
β-Lactam antibiotic					
Piperacillin-tazobactam	667/2749 (24.3)	722/2746 (26.3)	−2.2 (−5.3 to 1.0)	0.89 (0.79 to 1.01)	.83
Meropenem	183/696 (26.3)	203/714 (28.4)	−1.7 (−7.0 to 3.7)	0.92 (0.73 to 1.17)	
Age, y					
<65	348/1935 (18.0)	375/1938 (19.3)	−1.5 (−4.5 to 1.6)	0.91 (0.77 to 1.07)	.99
≥65	516/1539 (33.5)	564/1569 (35.9)	−2.2 (−6.5 to 2.0)	0.91 (0.78 to 1.05)	
Sex					
Male	563/2290 (24.6)	612/2279 (26.9)	−2.3 (−5.7 to 1.1)	0.89 (0.78 to 1.02)	.62
Female	301/1184 (25.4)	327/1228 (26.6)	−1.2 (−5.4 to 3.0)	0.94 (0.78 to 1.13)	
APACHE II score					
<25	543/2599 (20.9)	610/2661 (22.9)	−2.2 (−5.2 to 0.8)	0.88 (0.77 to 1.01)	.66
≥25	320/872 (36.7)	328/842 (39.0)	−1.7 (−7.1 to 3.7)	0.93 (0.76 to 1.13)	



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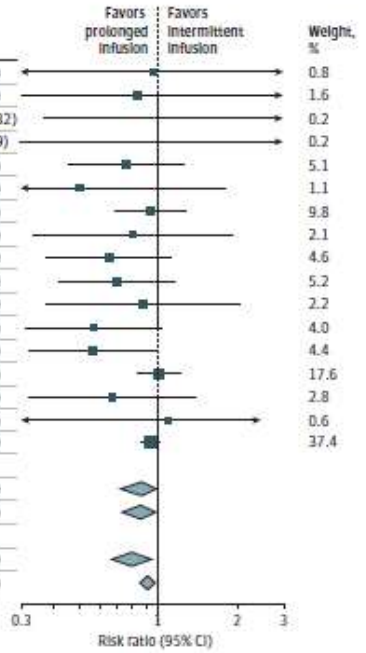
Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock
A Systematic Review and Meta-Analysis

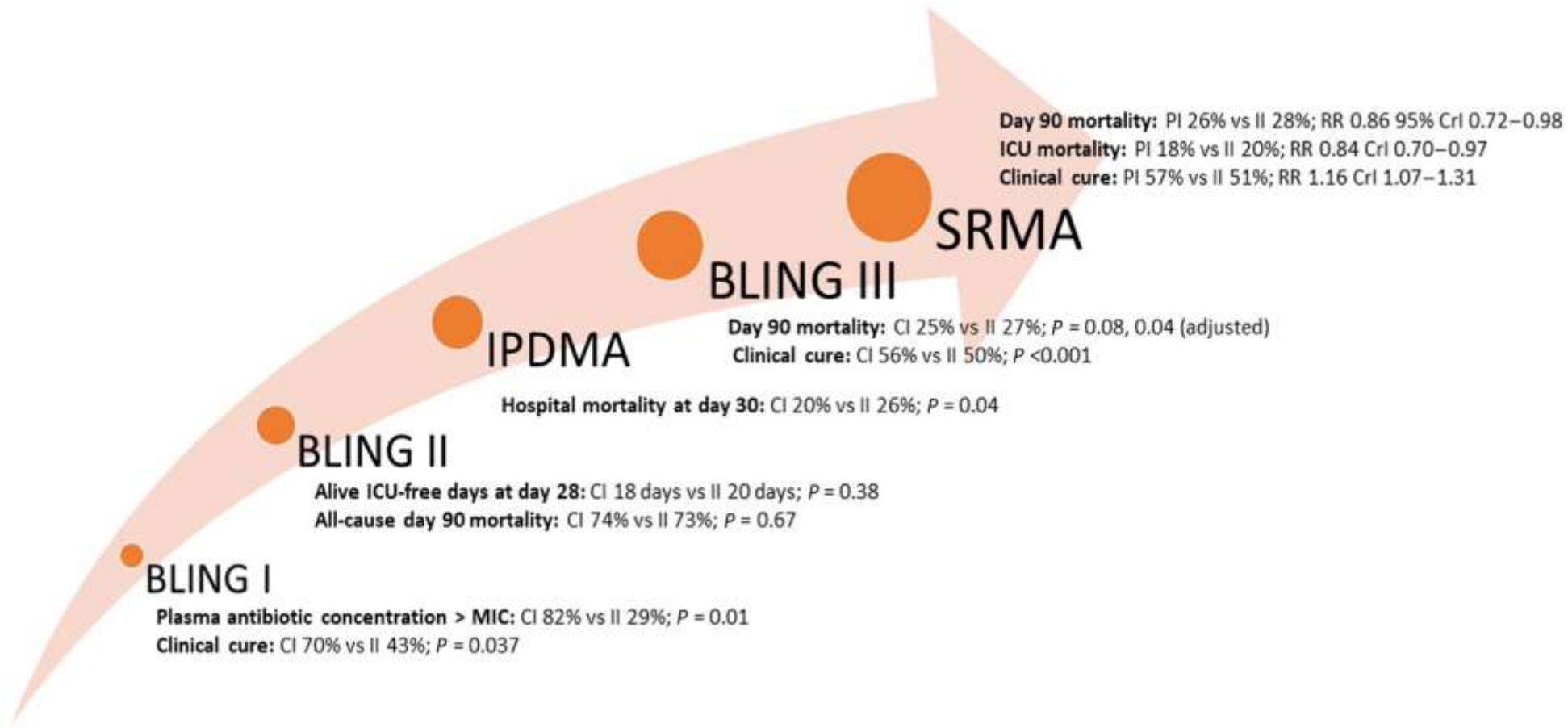
Figure 1. All-Cause 90-Day Mortality for the Comparison Between Prolonged Infusions of β-Lactam Antibiotics vs Intermittent Infusions

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.02 to 0.01)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.09 to -0.01)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (0.09 to 0.11)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (0.23 to 0.44)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.06 to -0.05)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.12 to -0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.02 to -0.01)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.24 to -0.01)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.40 to -0.27)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.13 to -0.10)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.07 to -0.01)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.19 to -0.16)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.17 to -0.15)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (0.00 to 0.00)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.16 to -0.10)	0.67 (0.32 to 1.39)	2.8
Alvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.03 to 0.06)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.02 to -0.02)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



- 9,108 critically ill adults across 18 RCTs
- Pooled risk ratio 90-day mortality=0.86 (95% CI 0.70-0.97)
- Pooled risk of clinical cure 1.16 (95% CI 1.07-1.31)

Is it time to implement prolonged infusions of beta-lactam antibiotics in and beyond critical care settings?



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Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis The BLING III Randomized Clinical Trial

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- WHY
  - Practice-changing
- IMPLICATIONS
  - In critically ill adults treated with beta-lactams for suspected or proven sepsis, antibiotics should be administered by continuous infusion wherever possible
  - Unclear if this applies to children or to non-critically ill people

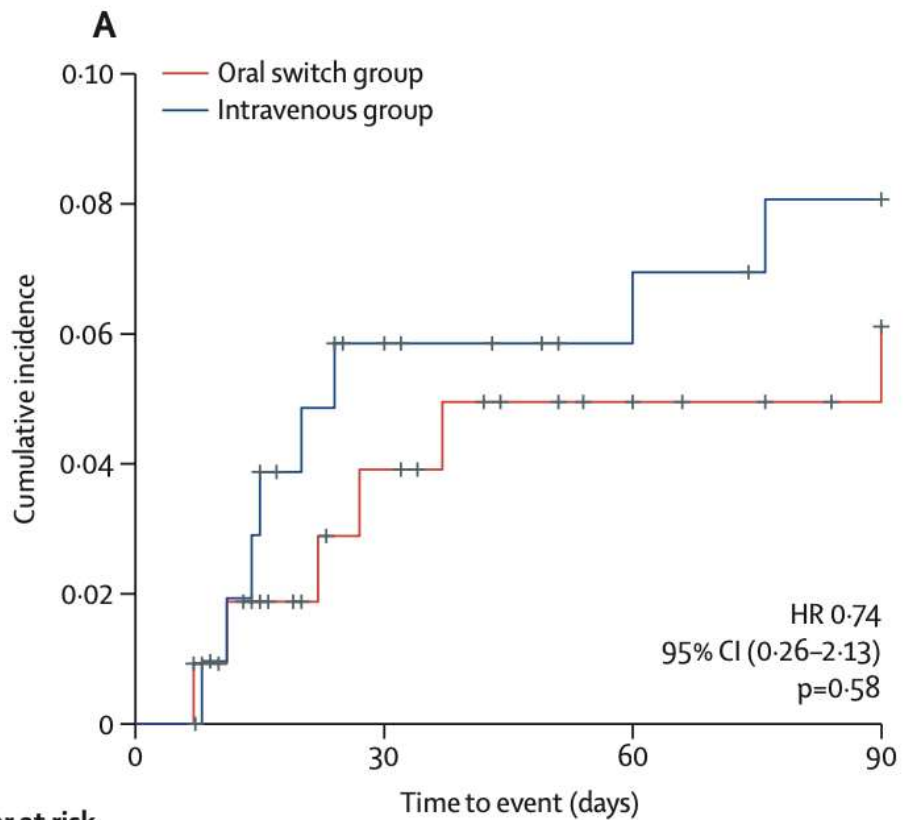
Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

*Achim J Kaasch, Luis Eduardo López-Cortés, Jesús Rodríguez-Baño, José Miguel Cisneros, M Dolores Navarro, Gerd Fätkenheuer, Norma Jung, Siegbert Rieg, Raphaël Lepeule, Laetitia Coutte, Louis Bernard, Adrien Lemaignen, Katrin Kösters, Colin R MacKenzie, Alex Soriano, Stefan Hagel, Bruno Fantin, Matthieu Lafaurie, Jean-Philippe Talarmin, Aurélien Dinh, Thomas Guimard, David Boutoille, Tobias Welte, Stefan Reuter, Jan Kluytmans, Maria Luisa Martin, Emmanuel Forestier, Hartmut Stocker, Virginie Vitrat, Pierre Tattevin, Anna Rommerskirchen, Marion Noret, Anne Adams, Winfried V Kern, Martin Hellmich, Harald Seifert, for the SABATO study group**

- WHY
  - (Potentially) Practice-changing
  - Dogma challenging
- WHAT/HOW
  - RCT in 31 hospitals in 4 Germany, Spain, France and the Netherlands
  - 213 patients with low-risk SAB randomised to switch to oral antibiotics after 5-7 days or to complete 14 days IV
  - Outcome was composite of SAB complication by day 90
    - Attributable death, relapse, new deep-seated infection
  - Used cotrimoxazole, clindamycin or linezolid PO (in that heirarchy)

Lancet Infect Dis 2024; 24: 523–34

	Intention-to-treat population			Clinically evaluable population		
	Oral switch group (n=108)	Intravenous group (n=105)	Percentage-point difference (95% CI)	Oral switch group (n=86)	Intravenous group (n=79)	Percentage-point difference (95% CI)
Primary endpoint						
SAB-related complication within 90 days	14 (13%)	13 (12%)	0·7 (–7·8 to 9·1)	3 (4%)	4 (5%)	–2·9 (–9·6 to 3·9)



Number at risk

Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

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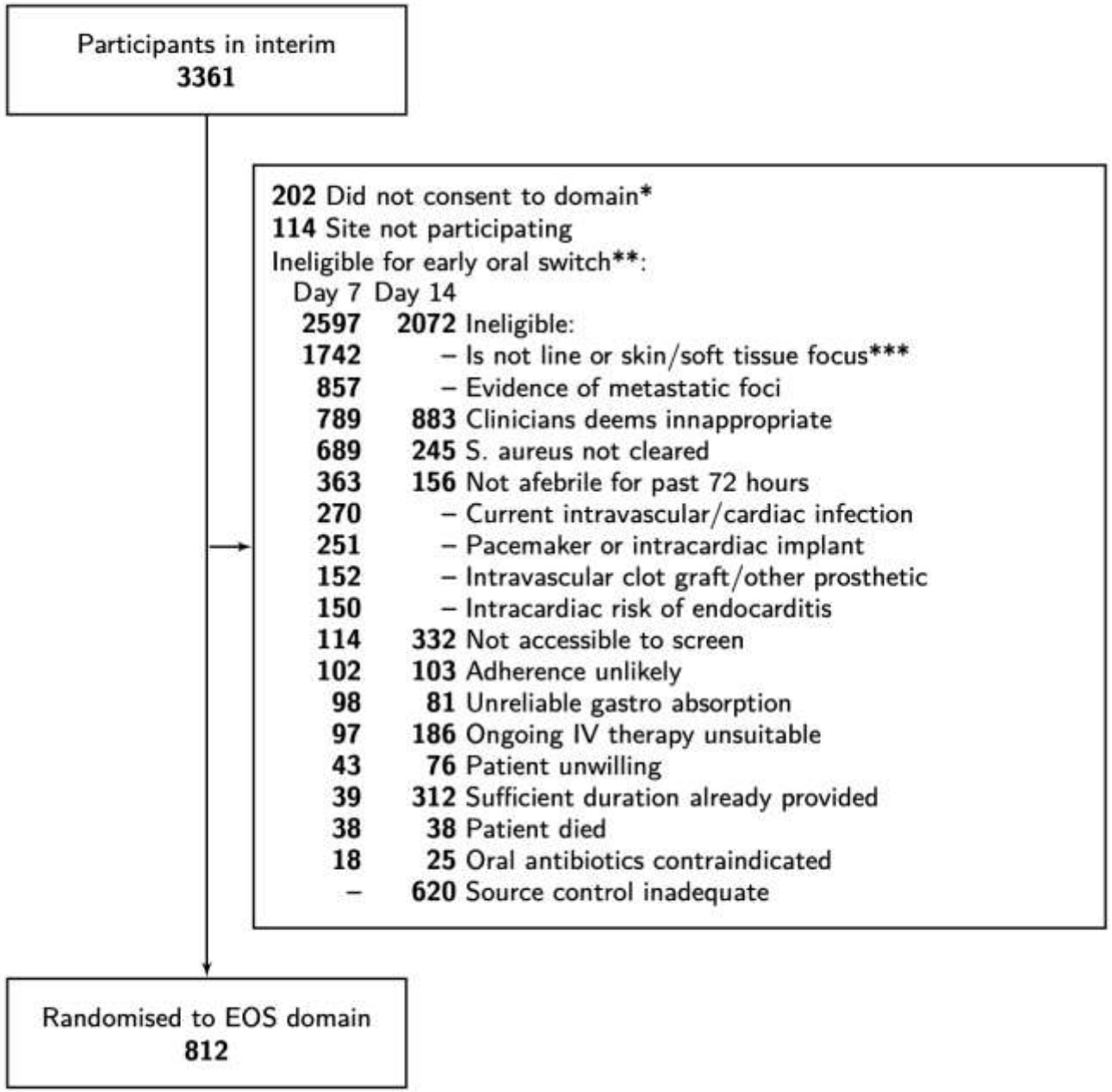
- WHY
  - (Potentially) Practice-changing
  - Dogma challenging
- IMPLICATIONS
  - Note 5063 patients screened to get 213 enrolled
  - Note trial stopped early; original sample size=430; Non-inferiority margin=10%
  - i.e. it is very hard to do these trials, and it doesn't apply to most SAB patients!
  - BUT gives us confidence to keep enrolling in SNAP EOS domain

Lancet Infect Dis 2024; 24: 523–34

Figure 6: Flowchart of participants' progress through the early oral switch domain.



SNAP
Staphylococcus aureus
Network Adaptive Platform

Early Oral Switch

n = 812 (23%)
(includes n = 6 paediatric)

384 Day 7:
201 Continued IV
183 Oral Switch

428 Day 14:
203 Continued IV
225 Oral Switch

Nasal sprays and behavioural interventions compared with usual care for acute respiratory illness in primary care: a randomised, controlled, open-label, parallel-group trial

Paul Little, Jane Vennik, Kate Rumsby, Beth Stuart, Taeko Becque, Michael Moore, Nick Francis, Alastair D Hay, Theo Verheij, Katherine Bradbury, Kate Greenwell, Laura Dennison, Sian Holt, James Denison-Day, Ben Ainsworth, James Raftery, Tammy Thomas, Christopher C Butler, Samantha Richards-Hall, Deb Smith, Hazel Patel, Samantha Williams, Jane Barnett, Karen Middleton, Sascha Miller, Sophie Johnson, Jacqui Nuttall, Fran Webley, Tracey Sach, Lucy Yardley, Adam W A Geraghty

- WHY
  - Practice-changing
  - Paradigm-shifting
- WHAT/HOW
  - RCT at 332 UK general practices
  - 13,799 adults with URTI symptoms and >=1 risk factor for adverse outcomes randomised to
    - Usual care
    - Gel-based nose spray 6x/day
    - Saline nose spray 6x/day
    - iv) Behavioural intervention (website)

	Usual care (n=3451)	Gel-based spray (n=3448)	Saline spray (n=3450)	Behavioural website (n=3450)
Number of days of illness due to self-reported respiratory tract illness in previous 6 months				
n	1626	1587	1613	1422
Median (IQR)	10 (5–16)	7 (4–14)	7 (5–14)	8 (5–15)
Mean (SD)	15·1 (19·2)	12·0 (15·3)	11·8 (14·9)	14·2 (17·9)
Number of days of illness among all participants in previous 6 months				
n	2983	2935	2967	2727
Missing, n (%)	468 (13·6%)	513 (14·9%)	483 (14·0%)	723 (21·0%)
Median (IQR)	3 (0–10)	3 (0–8)	3 (0–8)	2 (0–9)
Mean (SD)	8·2 (16·1)	6·5 (12·8)	6·4 (12·4)	7·4 (14·7)
Adjusted IRR*† (99% CI); p value	1 (ref)	0·82 (0·76–0·90); p<0·0001	0·81 (0·74–0·88); p<0·0001	0·97 (0·89–1·06); p=0·46

IRR=incidence rate ratio. *Adjusted for baseline number of days of respiratory tract infection symptoms and stratum. †Complete cases analysis; IRR for intervention *vs* usual care.

Table 2: **Primary outcome (total days of illness in previous 6 months)**

	Usual care (N=3451)	Gel-based spray (N=3448)	Saline spray (N=3450)	Behavioural website (N=3450)
Days with moderately bad symptoms				
Participants with data available, n	2986	2934	2964	2725
Median (IQR)	0 (0–3)	0 (0–3)	0 (0–3)	0 (0–3)
Mean (SD)	3·0 (7·9)	2·4 (7·0)	2·3 (5·8)	2·6 (6·6)
Adjusted effect estimate* (95% CI); p value	1 (ref)	IRR 0·82 (0·73 to 0·91); p<0·0001	IRR 0·82 (0·74 to 0·92); p<0·0001	IRR 0·89 (0·80 to 0·99); p=0·04

Nasal sprays and behavioural interventions compared with usual care for acute respiratory illness in primary care: a randomised, controlled, open-label, parallel-group trial

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- WHY
  - Practice-changing
  - Paradigm-shifting
- IMPLICATIONS
  - Saline-based nasal spray should be routinely recommended for URTI (in addition to rest, simple analgesia etc.)

Oral versus intravenous empirical antibiotics in children and adolescents with uncomplicated bone and joint infections: a nationwide, randomised, controlled, non-inferiority trial in Denmark

Allan Byback Nielsen, Mette Holm, Morten S Lindhard, Jonathan P Glenthøj, Luise Borch, Ulla Hartling, Lisbeth S Schmidt, Maren J H Rytter, Annett H Rasmussen, Mads Damkjær, Grethe Lemvik, Jens J H Petersen, Mia J Søndergaard, Jesper Thaarup, Kim Kristensen, Lise H Jensen, Lotte H Hansen, Marie C Laweetz, Martin Gottliebsen, Tanja H Horsager, Tatjana Zaharov, Thomas U Hoffmann, Tobias Nygaard, Ulrik S Justesen, Lone G Stensballe, Nadja H Vissing, Paul Blanche, Kjeld Schmiegelow, Ulrikka Nygaard

Summary

Background Bone and joint infections (BJIs) are treated with intravenous antibiotics, which are burdensome and costly. No randomised controlled studies have compared if initial oral antibiotics are as effective as intravenous therapy. We aimed to investigate the efficacy and safety of initial oral antibiotics compared with initial intravenous antibiotics followed by oral antibiotics in children and adolescents with uncomplicated BJIs.

Lancet Child Adolesc Health 2024
Published Online
July 15, 2024
https://doi.org/10.1016/
S2352-4642(24)00133-0

- WHY
  - Practice-changing
- WHAT/HOW
  - RCT at 18 Danish paediatric hospitals
  - Children with BJI and <24h of antibiotics were randomised to oral ABs (Augmentin <5 years, Diclox>5 years) from day 1 or IV Ceftriaxone for >=3 days until clinical improvement and falling CRP, then oral.
  - Primary endpoint=sequelae after 6 months (assessed blindly – affected mobility or joint function)

	Initial oral antibiotics	Initial intravenous antibiotics	Risk difference (CI*)	$p_{non\text{-}inferiority}$
Primary outcome, clinical sequelae at 6 months				
Main analysis†	0/98	0/84	0 (0·0 to 3·8)	0·012
Per protocol‡	0/81	0/76	0 (0·0 to 4·6)	0·021
Secondary outcomes				
Switch of antibiotics within 28 days due to suspicion of non-acute treatment failure	5/101 (5·0%)	3/91 (3·3%)	1·7% (–5·2 to 8·3)	NA
Recurrent infection within 6 months	0/101	1/91 (1·1%)	–1·1% (–6·2 to 2·7)	NA
Safety outcomes				
Serious complications	0/123	0/125	0 (–3·2 to 3·2)	NA
Surgical intervention after treatment initiation§	12/123 (9·8%)	7/125 (5·6%)	4·2% (–2·7 to 11·5)	NA
Parent-reported adverse events related to antibiotics¶				
One or more¶	58/89 (65·2%)	49/80 (61·2%)	3·9% (–10·9 to 18·5)	NA
Stomach pain	9/89 (10·1%)	6/80 (7·5%)	2·6% (–6·7 to 11·9)	NA
Nausea	10/89 (11·2%)	2/80 (2·5%)	8·7% (0·9 to 17·5)	NA
Frequent stools	15/89 (16·9%)	18/80 (22·5%)	–5·6% (–18·2 to 6·5)	NA
Loose stools	45/89 (50·6%)	33/80 (41·2%)	9·3% (–6·0 to 24·2)	NA
Rash	5/89 (5·6%)	4/80 (5·0%)	0·6% (–7·7 to 8·4)	NA

BJIs=bone and joint infections. NA=not applicable. *CIs were 97·5% (one-sided) for the primary outcome and 95% for secondary and safety outcomes. †The main analysis was assessed in patients with BJIs who had a primary outcome evaluation. ‡The per-protocol analysis was assessed in patients with BJIs who did not switch the initial treatment from oral to intravenous treatment, or from intravenous to oral treatment. §Surgical intervention was primarily assessed in all randomised patients. Among those with BJIs, the proportion of surgical intervention was ten (9·9%) of 101 and seven (7·7%) of 91 (risk difference 2·2%, 95% CI –6·5 to 10·8). The surgical procedures were joint puncture with lavage for seven patients in the oral group and five patients in the intravenous group, including fenestration for four patients in the oral group and three in the intravenous group and draining and debridement of bone abscess for three patients in the oral group and two in the intravenous group. ¶Reported only during the first 7 days of treatment initiation. The denominators were 89 instead of 123 and 80 instead of 125, which reflects that 34 (28%) and 45 (36%) patients or their relatives did not answer the questions about adverse events in the questionnaire.

Table 3: **Primary, secondary, and safety outcomes**

Nielsen – Oral vs IV Abs for kids with BJIs – Lancet ACH

- WHY
  - Practice-changing
- IMPLICATIONS
  - Lots of cross-over (17% PO→IV and 9% IV→PO)
  - ?Wrong primary endpoint?
  - Complex/difficult BJIs excluded
  - **Key point**: there is no need for <u>any</u> minimum duration of IV antibiotics in kids with BJI
  - BEST trial ongoing in Australia

JAMA | Original Investigation

Tenofovir and Hepatitis B Virus Transmission During Pregnancy
A Randomized Clinical Trial

Calvin Q. Pan, MD; Erhei Dai, MD; Zhongfu Mo, MD; Hua Zhang, MD; Thomas Q. Zheng, MD; Yuming Wang, MD; Yingxia Liu, MD; Tianyan Chen, MD; Suwen Li, MD; Cuili Yang, MD; Jinjuan Wu, MD; Xiuli Chen, MD; Huaibin Zou, MD; Shanshan Mei, MD; Lin Zhu, MD

- WHY
  - Practice-changing
- WHAT/HOW
  - Standard MTCT Rx for HBV and a high VL is TDF in the 3rd trimester plus HBIG (and vaccination) at birth, but HBIG unavailable in some LMICs
  - 280 pregnant women with HBV VL>200,000 randomised to TDF from 16/40 and no HBIG or TDF from 28/40 with HBIG at birth

JAMA | Original Investigation

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Figure 2. Assessment of Outcome Difference Between Groups and Noninferiority

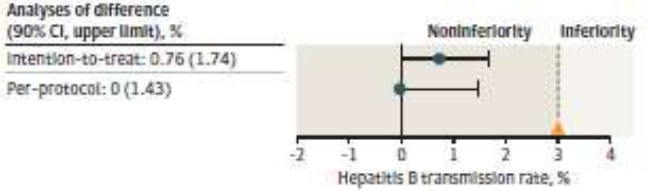

Table 2. Efficacy Outcome Assessments

HBV infection cases	No./total No. (%) [95% CI][a]		Difference in mother-to-child transmission rates, %	
	Experimental group	Standard care group	Upper limit of 90% CI	Upper limit of post hoc 95% CI
Primary outcome (HBV transmission rates in infants aged 28 wk)				
Analysis of all live-born infants (intention-to-treat analysis)[b]	1/131 (0.76)	0/142	0.76 (1.74)	0.76 (2.23)
Per-protocol analysis[c]	0/124	0/141	0 (1.43)[d]	0 (2.15)[d]
			P value	Difference (95% CI), %[e]
Secondary outcomes for mothers				
HBV DNA levels <200 000 IU/mL at delivery	130/131 (99.2) [95.2 to 99.96]	130/138 (94.2) [88.5 to 97.3]	.02[f]	5.00 (0.1 to 10.0)
HBeAg negativity at postpartum week 28	3/140 (2.1) [0.6 to 6.6]	3/140 (2.1) [0.6 to 6.6]	>.99	0 (−3.4 to 3.4)
HBeAg conversion at postpartum week 28	3/140 (2.1) [0.6 to 6.6]	2/140 (1.4) [0.3 to 5.6]	>.99	0.7 (−3.1 to 4.5)
Postpartum ALT >5 × ULN	5/140 (3.6) [1.3 to 8.6]	6/140 (4.3) [1.8 to 9.5]	.76[f]	0.7 (−6.0 to 4.6)
Postpartum ALT >10 × ULN[g]	5/140 (3.6) [1.3 to 8.6]	4/140 (2.9) [0.9 to 7.6]	>.99	0.7 (−4.1 to 5.6)
Other efficacy outcomes for mothers[h]				
HBV DNA levels <20 000 IU/mL at delivery	124/131 (94.7) [88.9 to 97.6]	91/138 (65.9) [57.3 to 73.7]	.001[f]	28.8 (19.2 to 38.3)

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; ... This per-protocol dataset analysis represents the primary outcome ...

JAMA | Original Investigation

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- WHY
  - Practice-changing
- IMPLICATIONS
  - In the absence of HBIG, TDF alone is very effective at preventing MTCT of HBV if started early
  - We probably don't actually need HBIG at all in this setting

Preventing New Gram-negative Resistance Through Beta-lactam De-escalation in Hospitalized Patients With Sepsis: A Retrospective Cohort Study

Besu F. Teshome,[1,2] Taehwan Park,[3] Joel Arackal,[2] Nicholas Hampton,[4] Marin H. Kollef,[5] and Scott T. Micek[1,2]

- WHY
  - Paradigm-shifting, proof of concept
- WHAT/HOW
  - Retrospective cohort study including 7742 hospitalised patients at one US hospital with “broad spectrum” beta-lactam use for >=3 days
  - “Spectrum” defined using BLSS
  - Grouped into: i) De-escalation occurred; ii) No change; or iii) Escalation
  - Primary endpoint=isolation of a new resistant Gram negative w/i 60 days

Clinical Infectious Diseases® 2024;79(4):826–33

Antibiotic	MSSA	MRSA	Enterococcus	VRE	DRSP	Moraxella, H. flu	E. coli, Klebsiella	ESBL	CRE	Citrobacter, Enterobacter, Serratia	Pseudomonas	MDRO	Anaerobes	B. fragilis	Atypicals	Spectrum Score
Oxacillin	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dicloxacillin	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Amoxicillin	0	0	1	0	0	0	0.5	0	0	0	0	0	0	0	0	1.5
Ampicillin	0	0	1	0	0	0	0.5	0	0	0	0	0	0	0	0	1.5
Cephalexin	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2
Penicillin	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	2
Aztreonam	0	0	0	0	0	1	1	0	0	0	1	0	0	0	0	3
Cefazolin	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	3
Cefdinir	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	3
Ceftazidime	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	4
Ceftriaxone	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	5
Amox/clav	1	0	1	0	0	1	1	0	0	0	0	0	1	1	0	6
Pivotal beta-lactam antibiotics																
Amp/sulb	1	0	1	0	0	1	1	0	0	0	0	1	1	1	0	7
Cefepime	1	0	0	0	1	1	1	0	0	1	1	1	0	0	0	7
Ceftaroline	1	1	1	0	1	1	1	0	0	0	0	1	0	0	0	7
Ceftol/tazo	0	0	0	0	0	1	1	1	0	1	1	1	1	1	0	8
Ceftaz/avi	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	8
Pip/tazo	1	0	1	0	0	1	1	0	0	1	1	0	1	1	0	8
Ertapenem	1	0	0	0	1	1	1	1	0	1	0	1	1	1	0	9
Meropenem	1	0	0	0	1	1	1	1	0	1	1	1	1	1	0	10
Mero/vabor	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	11
Imipenem	1	0	1	0	1	1	1	1	0	1	1	1	1	1	0	11

MSSA = methicillin-sensitive Staphylococcus aureus, MRSA = methicillin-resistant Staphylococcus aureus, VRE = vancomycin-resistant Enterococcus, DRSP = Drug-resistant Streptococcus pneumoniae, H. flu = Haemophilus influenzae, ESBL = Extended spectrum beta-lactamase, CRE = Carbapenem-resistant Enterobacterale, MDRO = Multidrug-resistant organism, Amox/clav = amoxicillin/clavulanate; Amp/sulb = ampicillin/sulbactam; Ceftol/tazo = ceftolozane/tazobactam; Ceftaz/avi = ceftazidime/avibactam; Pip/tazo = piperacillin/tazobactam; Mero/vabor = Meropenem/vaborbactam

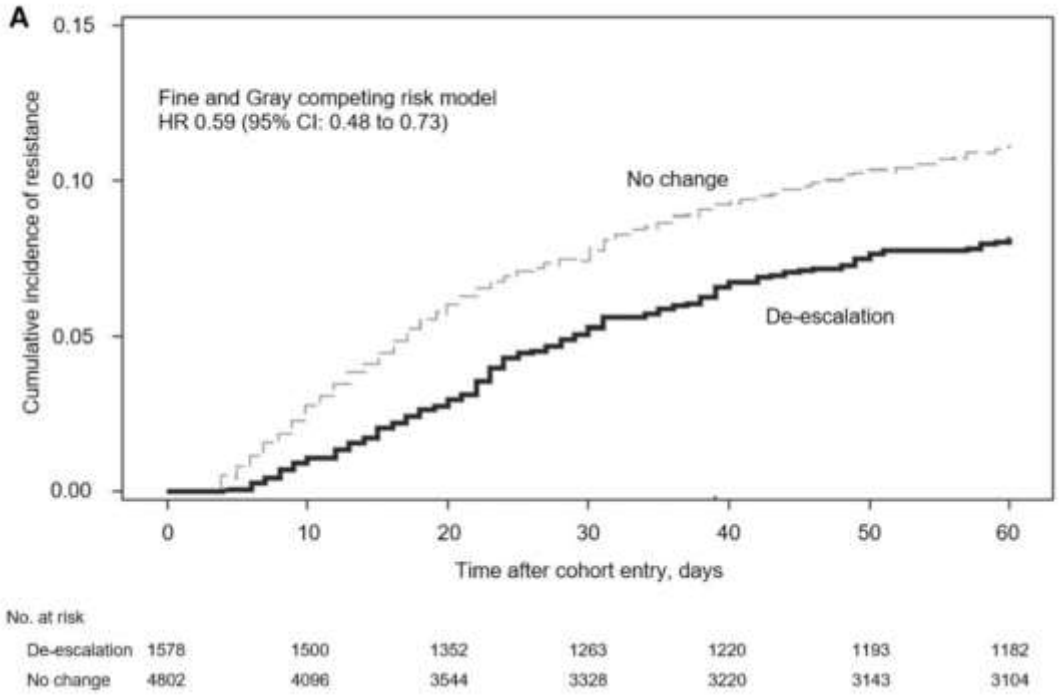
Table 3. Bacterial Pathogens that Developed New Resistance

	Overall (n = 644)	De-escalation (n = 112)	No Change (n = 431)	Escalation (n = 101)
Incidence rate per 1000 person-d (95% CI)	1.85 (1.71–2.00)	1.42 (1.16–1.68)	2.03 (1.84–2.22)	1.80 (1.45–2.15)
Time to new resistance, d, mean ± SD	23.7 ± 15.0	26.0 ± 14.1	22.0 ± 15.1	28.4 ± 14.4
Pathogens				
Acinetobacter baumannii complex				
Carbapenem resistant	39 (6.0)	4 (3.6)	29 (6.7)	6 (5.9)
MDR	43 (6.7)	6 (5.4)	30 (7.0)	7 (6.9)
Enterobacterales				
3rd generation cephalosporin resistance	329 (51.0)	63 (56.3)	229 (53.1)	37 (36.3)
Carbapenem resistant	51 (7.9)	7 (6.3)	36 (8.4)	8 (7.8)
MDR	251 (38.9)	41 (36.6)	175 (40.6)	35 (34.3)
Pseudomonas aeruginosa				
Carbapenem resistant	155 (24.0)	23 (20.5)	92 (21.3)	40 (39.2)
MDR	125 (19.4)	20 (17.9)	72 (16.7)	32 (31.4)
Other MDR non-fermenting GNR	29 (4.5)	7 (6.3)	18 (4.2)	4 (3.9)
Source of isolation[a]				
Blood	94 (14.6)	13 (11.6)	70 (16.2)	11 (10.8)
Respiratory specimen	262 (40.6)	51 (45.5)	160 (37.1)	51 (50.0)
Urine	163 (25.3)	28 (25.0)	111 (25.8)	24 (23.5)
Other	133 (20.6)	22 (19.6)	94 (21.8)	17 (16.7)

Data are presented as number (%).

Abbreviations: GNR, Gram-negative rod; MDR, multidrug resistant.

[a]Some pathogens were isolated from multiple sites in the same patient.



Preventing New Gram-negative Resistance Through Beta-lactam De-escalation in Hospitalized Patients With Sepsis: A Retrospective Cohort Study

Besu F. Teshome,[1,2] Taehwan Park,[3] Joel Arackal,[2] Nicholas Hampton,[4] Marin H. Kollef,[5] and Scott T. Micek[1,2]

- WHY
  - Paradigm-shifting, proof of concept
- IMPLICATIONS
  - De-escalating doesn't only make ID physicians feel good – it decreases the emergence/acquisition of resistant Gram negatives

Clinical Infectious Diseases® 2024;79(4):826–33

Top 10 Non-COVID ID papers 2024+implications

1. Beghini – *Many "non-communicable" diseases are probably communicable*
2. Bekker – *6 monthly S/C lenacapavir should be standard for PEP if/where affordable*
3. Browne – *Shared hospital equipment should be cleaned daily*
4. Daneman – *7 days antibiotics is enough for nearly all uncomplicated bacteraemias*
5. Dulhunty – *Beta-lactams should be used by continuous infusion in ICU for sepsis*
6. Kaasch – *Early oral switch is probably safe for uncomplicated SAB (more data needed)*
7. Little – *Saline nasal spray should be recommended for all URTIs*
8. Neilsen – *There is no minimum duration of IV ABs for kids with BJI – just use oral*
9. Pan – *HBIG not needed to prevent MTCT of HBV if TDF started early enough*
10. Teshome– *Antibiotic de-escalation has tangible benefits*

Prof Josh Davis, December 2024 @gurujosh.bsky.social joshua.davis@health.nsw.gov.au

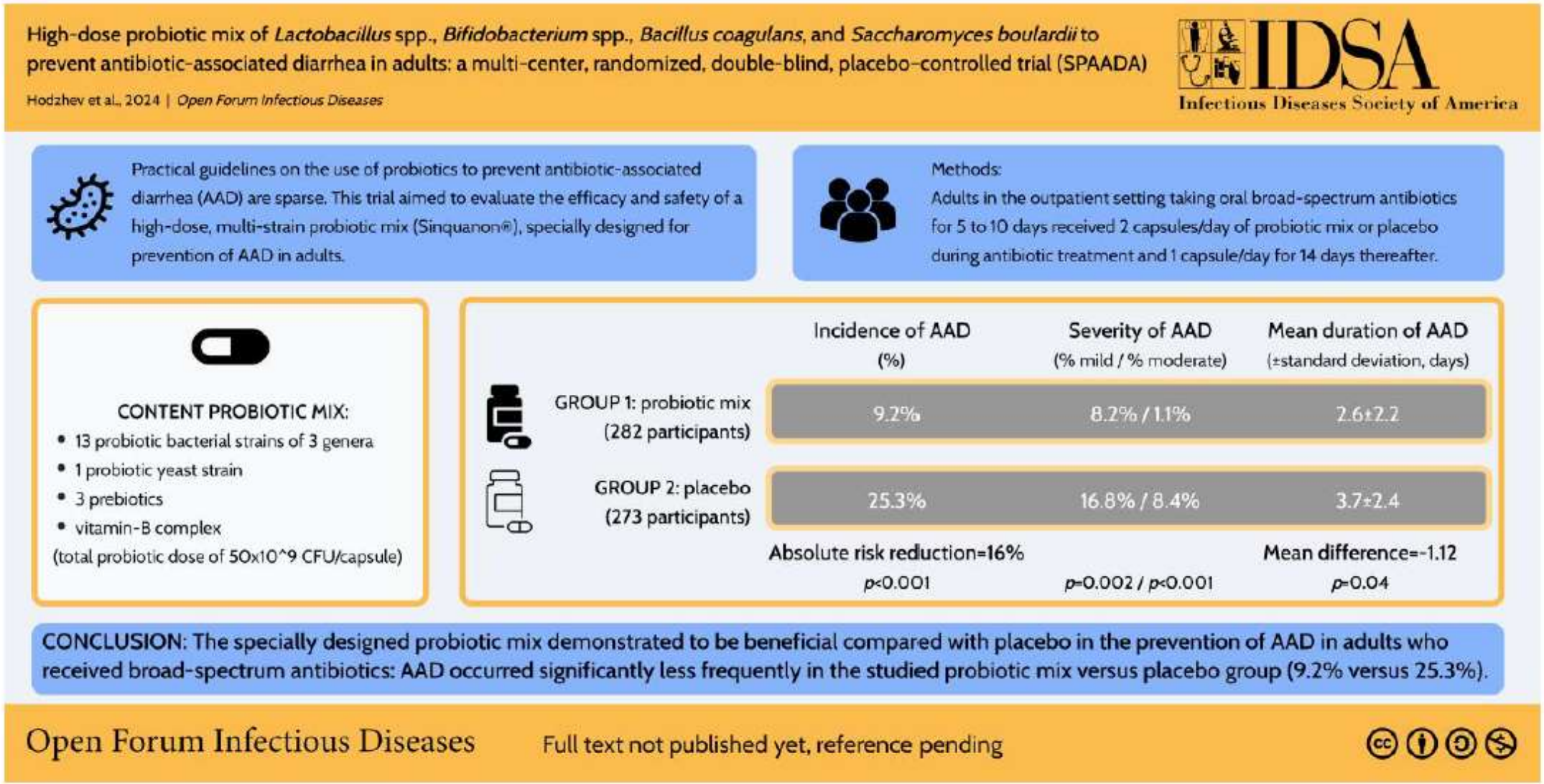
High-dose Probiotic Mix of *Lactobacillus* spp., *Bifidobacterium* spp., *Bacillus coagulans*, and *Saccharomyces boulardii* to Prevent Antibiotic-associated Diarrhea in Adults: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial (SPAADA)

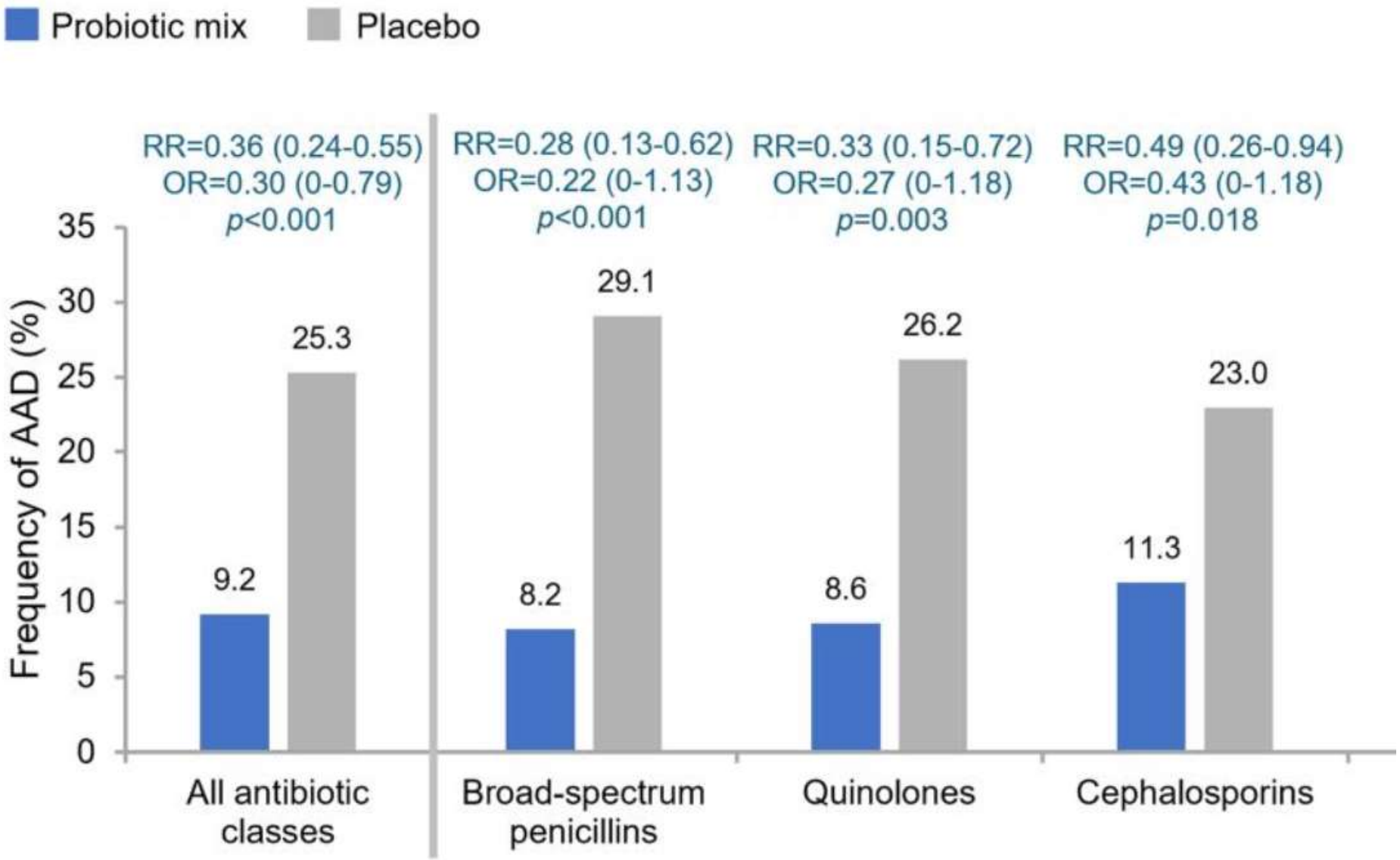
Vladimir Hodzhev,[1] Karen Dzhambazov,[1] Nikolay Sapundziev,[2] Milena Encheva,[3] Spiridon Todorov,[4] Vania Youroukova,[5] Rumen Benchev,[6] Rosen Nikolov,[7] Boris Bogov,[8] Georgi Momekov,[9] and Veselin Hadjiev[10]

- WHY
  - (Potentially) Practice-changing
  - Dogma challenging
- WHAT/HOW
  - 564 adult outpatients from Bulgarian Resp and ENT clinics receiving broad spectrum antibiotics were randomised to 2 probiotic capsules PO daily for the duration of AB treatment plus 14 more days OR placebo.
  - Primary outcome=number of participants who had >=1 day of diarrhoea (>=3 loose stools/24h)

- 13 selected bacterial strains
- 100 billion CFU per dose (2 capsules)
- Plus ”prebiotic blend” of oligosaccharides
- Plus B vitamins
- A$37 per 14 day course on eBay
- Note trial sponsor was Neopharm Bulgaria but they played no role etc.
- Author CoI statement: All authors have delivered scientific lec- tures on a given problem for various pharmaceutical companies, including Neopharm Bulgaria.

Graphical Abstract




Probiotic mix
Placebo
RR=0.36 (0.24-0.55)
OR=0.30 (0-0.79)
p<0.001
RR=0.28 (0.13-0.62)
OR=0.22 (0-1.13)
p<0.001
RR=0.33 (0.15-0.72)
OR=0.27 (0-1.18)
p=0.003
RR=0.49 (0.26-0.94)
OR=0.43 (0-1.18)
p=0.018
Frequency of AAD (%)
35
30
25
20
15
10
5
0
9.2
25.3
8.2
29.1
8.6
26.2
11.3
23.0
All antibiotic classes
Broad-spectrum penicillins
Quinolones
Cephalosporins

High-dose Probiotic Mix of *Lactobacillus* spp., *Bifidobacterium* spp., *Bacillus coagulans*, and *Saccharomyces boulardii* to Prevent Antibiotic-associated Diarrhea in Adults: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial (SPAADA)

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- WHY
  - (Potentially) Practice-changing
  - Dogma challenging
- IMPLICATIONS
  - Shifts the needle on probiotics but the jury is still out for me
  - Opposes many previous RCTs of other products
  - Need to replicate this in an independent trial and in hospital settings


РЕПУБЛИКА БЪЛГАРИЯ
ПРЕЗИДЕНТ