"Is there another possible way of controlling the spread of CPE ?

Pr Jean – Ralph Zahar
Infection Control Unit - French-Muslim Hospital
Bobigny - France
jrzahar@gmail.com

Hosted by Jim Gauthier

Conflicts of interest

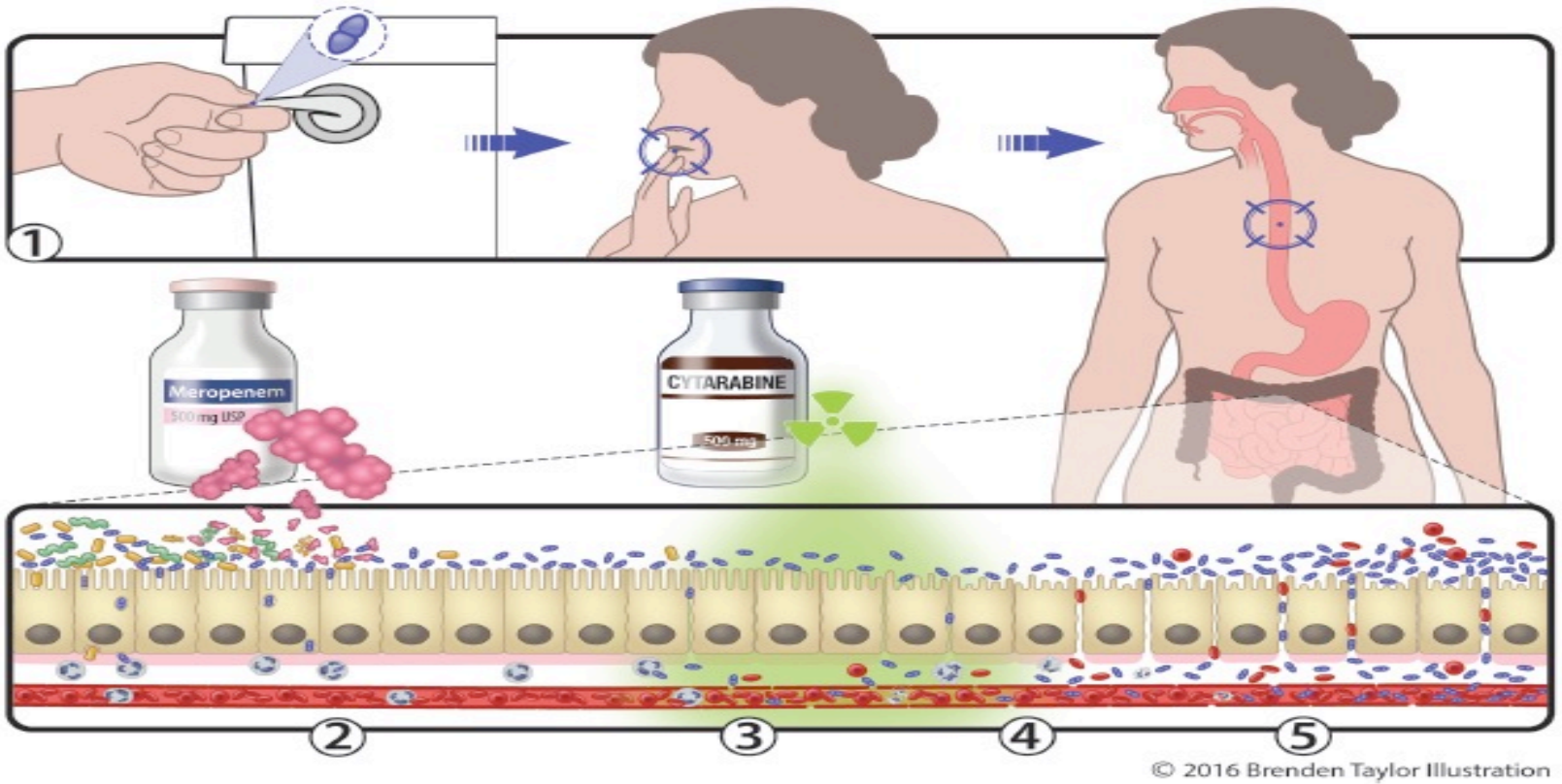
- None for this presentation

- Fees from :
  - MSD, Advanz Pharma, Pfizer, Biomérieux, Giléad

MDRO a huge Problem

- **Don't ignore this phenomenon !**
  - 1-acquisition is associated with a risk of secondary infection in 10 to 50% of cases
  - 2-acquisition is associated with a higher mortality and morbidity
  - 3-Our Policies to control the risk are costly for the community and are associated with adverse events at individual level

How are MDRO acquired and how do they persist?



Webb *et al*. Prediction of Bloodstream Infection Due to Vancomycin-Resistant Enterococcus in Patients Undergoing Leukemia Induction or Hematopoietic Stem-Cell Transplantation. Clin Infect Dis. 2017 Jun 15;64(12):1753-1759

Factors associated with the transmission within a ward unit

colonisation pressure

Type of ward

Workload

Compliance to preventive measures

Ward architecture

Leadership

Reservoir

Mode of transmission

R0

Patient characteristics

Microbial species

Amplifying factors

Antibiotic

Invasive procedures

MDRO a single entity ?

Species	Commensalism ?	Endemic situation ?	Role of antibiotic	Is it easy to identifiy carriers ?	Environmental survival ?
MRSA	+	-	-	+	+
ESBL	+	+	+	-	-
***Pseudomonas*-Resistant**	-	-	++	-	++
CPE	+	-/+	++	-	-
VRE	+	-	++	+	+++

Controlling MDROs in France and around the world

- Identifying the reservoir (MDRO colonised/infected patients)
- Isolate and when needed "cohort" colonised/infected patients
- Improve hand hygiene compliance
- Reinforce bio-cleaning
- And....sometimes.....control antibiotic prescribing

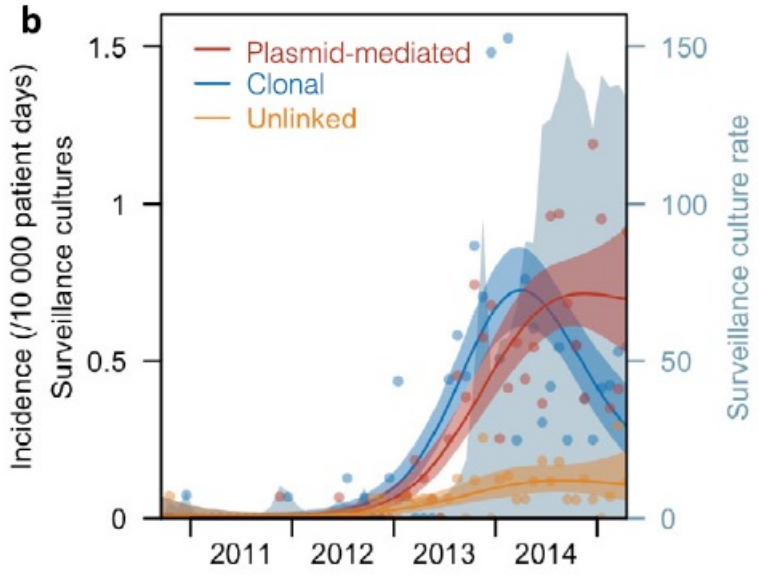
This "single" policy is difficult to apply

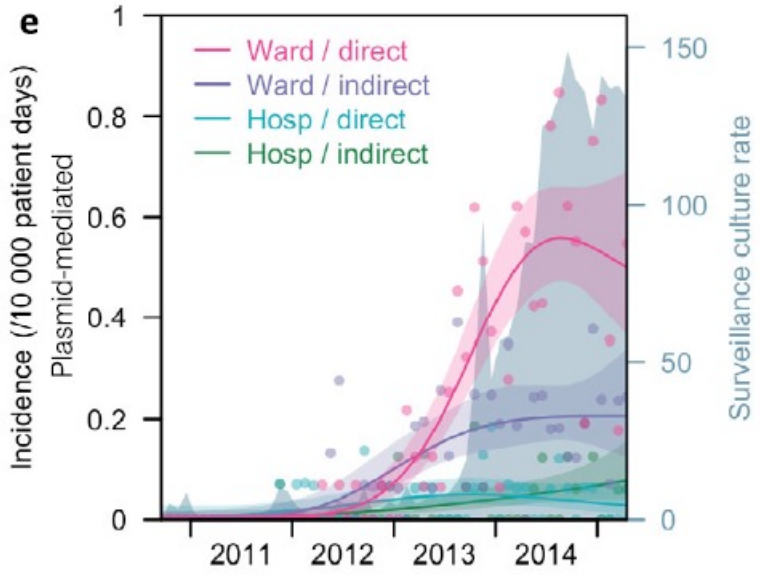
Strategy	Definition	
Single-room isolation	Separation of patients in MDRO wards and a series of other infection control measures. Patients received treatments in a single room; attended by specialist physicians and arrangement for specialised equipment for treatment.	Single room are scarce
Contact isolation	Contact isolation measures included bedside availability of disposable clothing, gloves, caps, shoe covers, etc. And with strict implementation of isolation-related procedures for patients, family and staff.	Compliance is difficult Cost are pohibitive
Hand hygiene	Access of medical staff having access to rapid-acting hand sanitizers, access to mobile devices and completion of HH self-assessments on mobile devices after high-risk procedures. Installation of cameras near sinks to monitor HH practice and to arrange managers to supervise procedures.	
Environmental surface cleaning and disinfection	Importance of disinfection of patient's surrounding environment. Frequency of intensive cleaning and disinfection of instruments and objects used by the patient, wiping down surfaces with chlorine-containing disinfectants (500 mg/l) or disinfection with wet paper towels more than three times a day and disinfection of bed units with ozone once a week.	Time consuming Inadequate ressources Cost are pohibitive

Surveillance culture

The current policy is not working

Retrospective Study
4,5 years; 779 patients acquired CPE
42% putative clonal transmission
15% putative plasmid transmission





Marimuthu K, Venkatachalam I, Koh V, Harbarth S, Perencevich E, Cherng BPZ, Fong RKC, Pada SK, Ooi ST, Smitasin N, Thoon KC, Tambyah PA, Hsu LY, Koh TH, De PP, Tan TY, Chan D, Deepak RN, Tee NWS, Kwa A, Cai Y, Teo YY, Thevasagayam NM, Prakki SRS, Xu W, Khong WX, Henderson D, Stoesser N, Eyre DW, Crook D, Ang M, Lin RTP, Chow A, Cook AR, Teo J, Ng OT; Carbapenemase-Producing Enterobacteriaceae in Singapore (CaPES) Study Group. Whole genome sequencing reveals hidden transmission of carbapenemase-producing Enterobacterales. Nat Commun. 2022 Jun 1;13(1):3052.

There are limitations to these policies

Swabs	Number of samples	Positive result by technique a (%)	Positive result by technique b (%)	Positive result by technique c (%)	Positive result by technique d (%)	Positive result whatever the technique
MC	176 (66.2%)	11/176 (6.3%)	14/176 (8%)	16/176 (9.1%)	14/176 (8%)	16/176 (9.1%)
BL	90 (33.8%)	2/90 (2.2%)	4/90 (4.4%)	5/90 (5.6%)	6/90 (6.6%)	6/90 (6.6%)
Total	266 (100%)	13 (4.9%)	18 (6.8%)	21 (7.9%)	20 (7.5%)	23 (8.6%)

Halouani H, Lomont A, Jaureguy F, Carbonnelle E, Seytre D, Zahar JR. Interest of broth enrichment for rectal screening in a low carbapenemase-producing Enterobacterales prevalence country. J Hosp Infect. 2023 Aug;138:97-98.

There are limitations to these policies

Screening result by technique and discordance of the different techniques with species and mechanism of resistance

Swabs	Screening pattern	Technique[a]				Species	Mechanism of resistance(s)
		A	B	C	D		
BL	Contact with carrier	+	+	+	+	*Enterobacter cloacae* & *Klebsiella aerogenes*	OXA-48
BL	Travelling abroad	−	−	+	+	*K. pneumoniae*	NDM
BL	Travelling abroad	−	+	+	+	*E. cloacae* & *K. pneumoniae*	OXA-48
BL	Former carrier	+	+	+	+	*Escherichia coli*	NDM
BL	Former carrier	−	−	−	+	*E. coli*	NDM
MC	Contact with carrier	+	+	+	+	*E. coli* & *K. pneumoniae*	KPC
MC	Travelling abroad	+	+	+	−	*E. coli* & *K. pneumoniae*	OXA-48
MC	Contact with carrier	+	+	−	−	*E. coli* & *Morganella morganii*	NDM
MC	Contact with carrier	−	−	+	+	*E. cloacae*	NDM
MC	Contact with carrier	+	+	+	+	*K. pneumoniae*	NDM
MC	Contact with carrier	−	−	+	+	*K. pneumoniae*	NDM
MC	Hospitalized abroad	+	+	+	+	*K. pneumoniae*	OXA-48
MC	Former carrier	−	+	+	+	*K. pneumoniae*	NDM
MC	Former carrier	−	+	+	+	*Escherichia coli*	OXA-48
MC	Former carrier	+	+	+	+	*K. pneumoniae*	NDM
MC	Former carrier	−	+	+	+	*E. cloacae*	OXA-48
MC	Hospitalized abroad	+	+	+	+	*E. coli*	NDM
MC	Contact with carrier	−	−	+	−	*E. coli*	OXA-48
MC	Contact with carrier	+	+	+	+	*E. coli*	NDM
BL	Contact with carrier	−	+	+	+	*K. pneumoniae*	OXA-48 & NDM

+, positive; −, negative; BL, blank; MC, macroscopically contaminated.

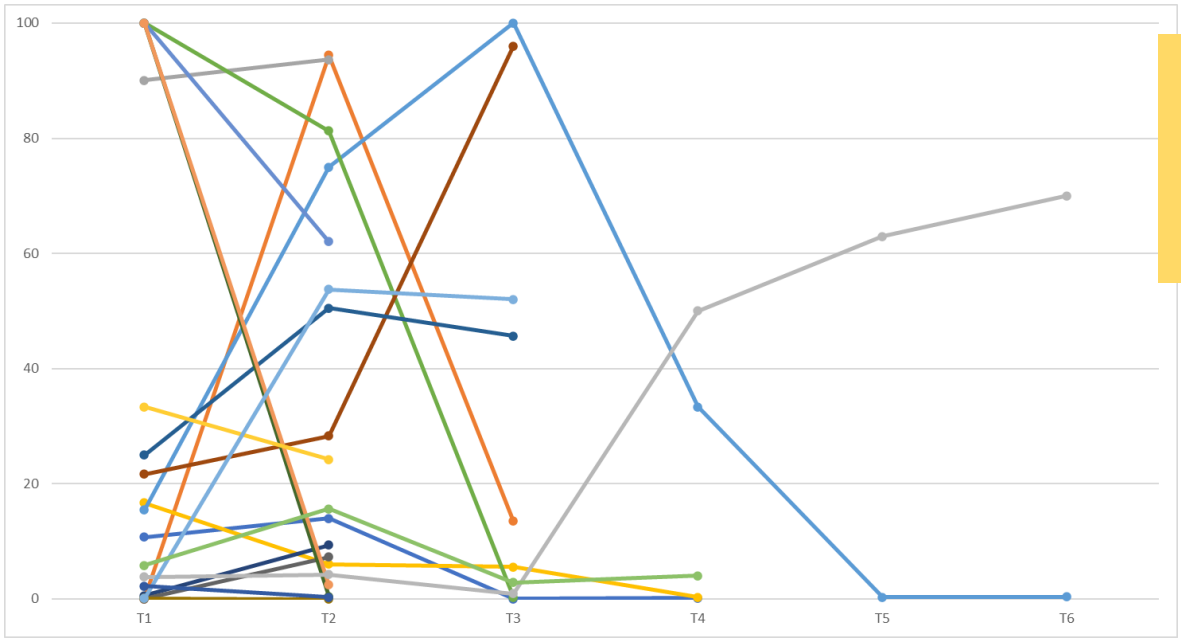
[a] Positivity: A: 13 (4.9%); B: 18 (6.8%); C: 21 (7.9%); D: 20 (7.5%). Positive result whatever the technique: 23 (8.6%).

it is impossible in clinical practice to identify colonised patients

Halouani H, Lomont A, Jaureguy F, Carbonnelle E, Seytre D, Zahar JR. Interest of broth enrichment for rectal screening in a low carbapenemase-producing Enterobacterales prevalence country. J Hosp Infect. 2023 Aug;138:97-98.

What we have learnt since:
A negative sample does not mean no acquisition

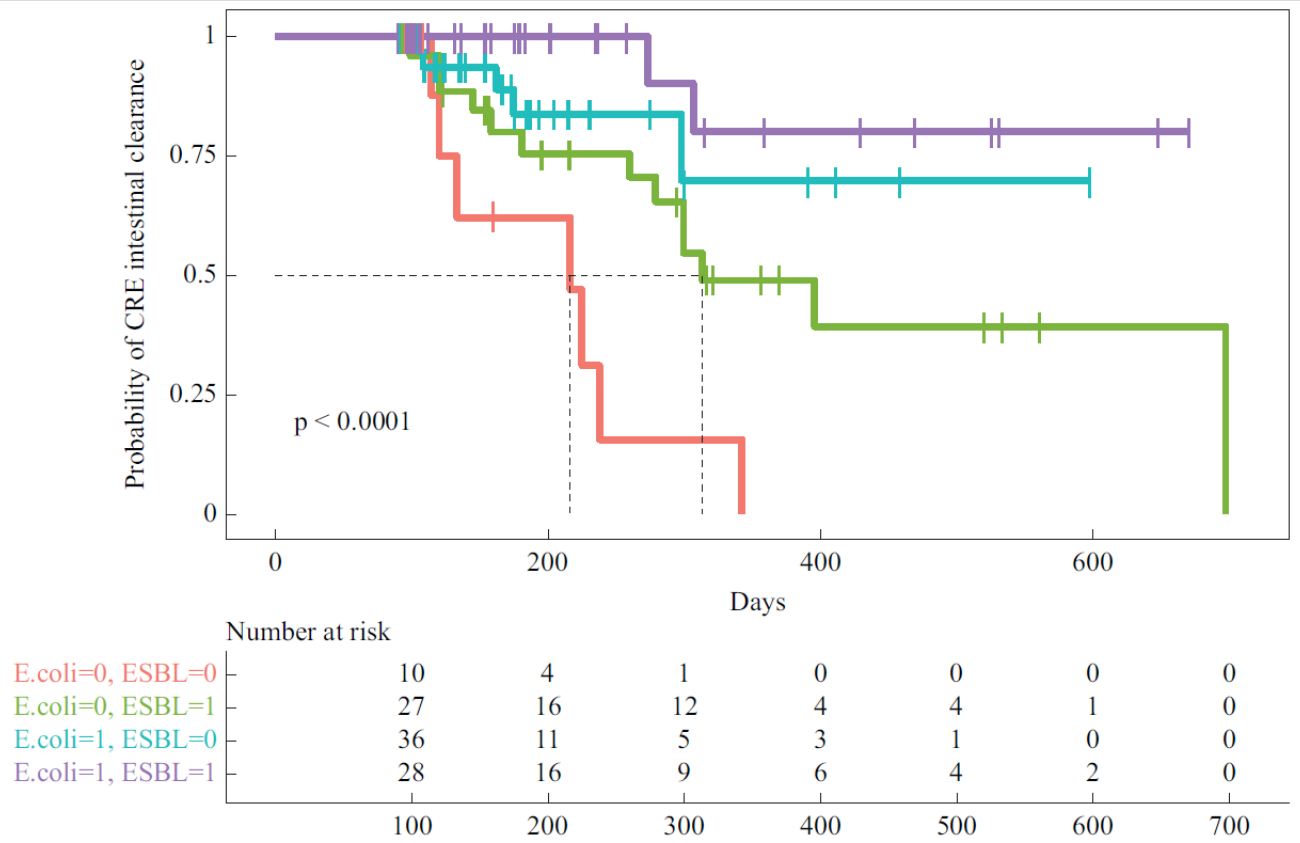
- Relative abundance is variable over time



19 patients
Study of the variation of RA
Sampling every 3 days
RA = 13,75% [1,26 – 53,8%]
Variation > 25% for 53% patients

Saliba R, *et al*. Significant variation in the faecal relative abundance of carbapenemase-producing Enterobacteriaceae of colonised patients during hospitalisation: a preliminary study. Int J Antimicrob Agents. 2022 Jan;59(1):106479.

What we have learnt since:
Time intestinal clearance is long, too long ….



Henoun Loukili N, Loquet A, Perrin A, Gaillot O, Bruandet A, Sendid B, Zahar JR, Nseir S. Time to intestinal clearance of carbapenemase-producing Enterobacterales in hospital patients: a longitudinal retrospective observational cohort study. J Hosp Infect. 2023 May;135:4-10.

Difficulty to implement these policies in LMIC

		High Compliance with Hand Hygiene	Antimicrobial Stewardship	Active Surveillance	Patient Isolation	Additional Contact Precautions	Cohorting
Multi-drug resistant bacterial species	*Escherichia coli*	✓	✓	×	×	×	×
	Other *Enterobacterales*	✓	✓	×	×	×	×
	VRE	✓	✓	✓	✓	✓	✓
	Pseudomonas aeruginosa producing carbapenemase	✓	✓	×	×	×	×
	Acinetobacter baumannii resistant to carbapenems	✓	✓	✓	✓	✓	✓
Hospital wards	Long term care facilities	✓	✓	×	×	×	×
	Intensive care units and reanimation	✓	✓	✓	✓	✓	✓*
	Other wards	✓	✓	×	×	×	×
Patient clinical characteristics	Diarrhea and or fecal incontinence	✓	✓	✓	✓	✓	✓
	High Katz score	✓	✓	✓	✓	✓	✓
	Other patients	✓	✓	×	×	×	×

✓: To adopt. ✓*: To adopt in an ongoing outbreak context. ×: Not to adopt. VRE: Vancomycin-resistant enterococci.

Saliba R, Zahar JR, Dabar G, Riachy M, Karam-Sarkis D, Husni R. Limiting the Spread of Multidrug-Resistant Bacteria in Low-to-Middle-Income Countries: One Size Does Not Fit All. Pathogens. 2023 Jan 14;12(1):144.

Nevertheless….

- Epidemics do not occur systematically
- The risk seems to depend on many "unknown" factors
- In intra-family situations, acquisition from a family member is not systematic
- Numerous papers suggest other pathsto explore ....

Outbreaks do not occur systematically

- **In hospital**: Transmission occurs in 5 to 10% of patients in contact with a patient case
- **In Household:** Transmission is a rare event, occurring in less than 5% of cases
- **Outbreaks:** depends on the species involved and probably on the resistance mechanism

Park JH, Choi HS, Yang H, Lee HJ, Kwak SH, Kim EO, Chong YP, Choi SH, Lee SO, Kim YS, Sung H, Kim MN, Kim SH, Jung J. Appropriate sites for active surveillance of carbapenemase-producing Enterobacterales. J Hosp Infect. 2022 Apr;122:211-213.
Chang E, Chang HE, Shin IS, Oh YR, Kang CK, Choe PG, Park WB, Choi EH, Oh MD, Park KU, Kim NJ. Investigation on the transmission rate of carbapenemase-producing carbapenem-resistant Enterobacterales among exposed persons in a tertiary hospital using whole-genome sequencing. J Hosp Infect. 2022 Jun;124:1-8.
Jamal AJ, Faheem A, Farooqi L, Zhong XZ, Armstrong I, Boyd DA, Borgundvaag E, Coleman BL, Green K, Jayasinghe K, Johnstone J, Katz K, Kohler P, Li AX, Mataseje L, Melano R, Muller MP, Mulvey MR, Nayani S, Patel SN, Paterson A, Poutanen S, Rebbapragada A, Richardson D, Sarabia A, Shafinaz S, Simor AE, Willey BM, Wisely L, McGeer AJ. Household Transmission of Carbapenemase-producing Enterobacterales in Ontario, Canada. Clin Infect Dis. 2021 Dec 6;73(11):e4607-e4615

Factors associated with the spread of CPE

Host Related
-Microbiota
-Atb selective pressure
-non atb selective pressure

Related to bacteria
-Species
-Specific bacterial clones
-Environmental contamination

Organisationnal
-Workload
-Environmental cleaning

Epidemiological
-Colonisation pressure

Can we stratify the risks?

- All bacteria (resistant or not), whatever their species, can be transmitted.
- Transmission occurs between hosts and within hosts
- There are conditions that favour transmission
  - A large reservoir (individual or collective)
  - A high concentration
  - A high-risk situation
  - A type of care

Lerner A,. Spread of KPC-producing carbapenem-resistant Enterobacteriaceae: the importance of super-spreaders and rectal KPC concentration. Clin Microbiol Infect. 2015 May;21(5):470.e1-7 . Ruppé E. Relative fecal abundance of extended-spectrum-β-lactamase-producing Escherichia coli strains and their occurrence in urinary tract infections in women. Antimicrob Agents Chemother. 2013 Sep;57(9):4512-7 . Blanco N. Transmission of resistant Gram-negative bacteria to healthcare personnel gowns and gloves during care of residents in community-based nursing. facilities.. Antimicrob Agents Chemother. 2017 Sep 22;61(10). pii: e00790-17; Bonten MJ. Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci. Lancet. 1996 Dec 14;348(9042):1615-9

Other factors associated with the risk of transmission

- **Workload**

  Legeay C, *et al*. Is cohorting the only solution to control carbapenemase-producing Enterobacteriaceae outbreaks? A single-centre experience. J Hosp Infect. 2018

- **Antibiotic pressure**

  Ruiz J. Influence of antibiotic pressure on multi-drug resistant Klebsiella pneumoniae colonisation in critically ill patients. Antimicrob Resist Infect Control. 2019 Feb 14;8:38

- **Colonisation pressure**

  Merrer J."Colonization pressure" and risk of acquisition of methicillin-resistant Staphylococcus aureus in a medical intensive care unit. Infect Control Hosp Epidemiol. 2000 Nov;21(11):718-23 . Ajao AO. Systematic review of measurement and adjustment for colonization pressure in studies of methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and clostridium difficile acquisition. Infect Control Hosp Epidemiol. 2011 May;32(5):481-9.

- **Successful clones**

  Peirano G, Chen L, Kreiswirth BN, Pitout JDD. Emerging Antimicrobial-Resistant High-Risk Klebsiella pneumoniae Clones ST307 and ST147. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01148-20. https://eccmid-ondemand.acsvirtual.com/video/301/0830---0930-worldwide-spread-of-hypervirulent-clones-of-klebsiella-and-pseudomonas-aeruginosa-10-07?channelName=ECCMIDondemand, Del Barrio-Tofiño E, López-Causapé C, Oliver A. Pseudomonas aeruginosa epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents. 2020 Dec;56(6):106196.

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Epidemiological
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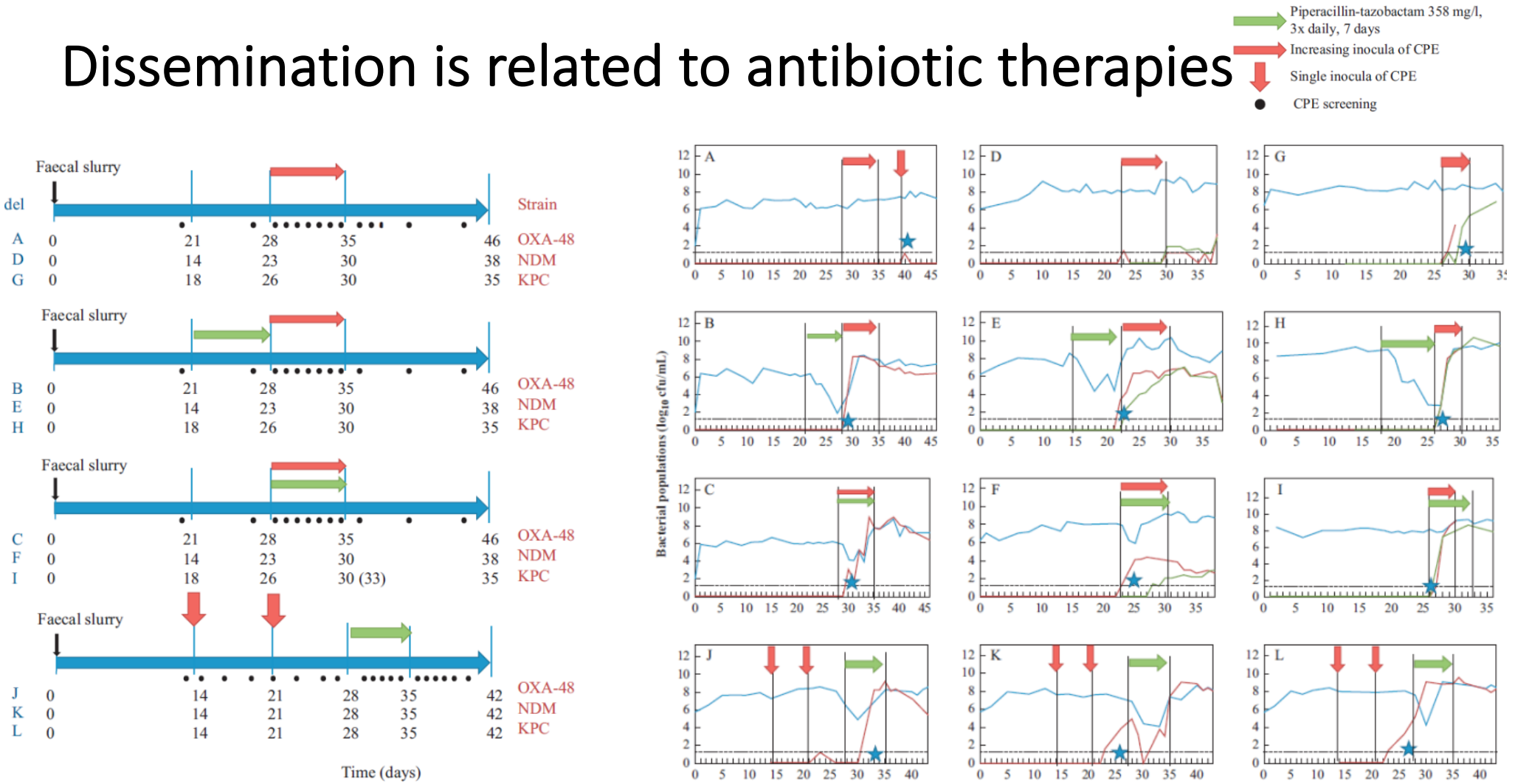
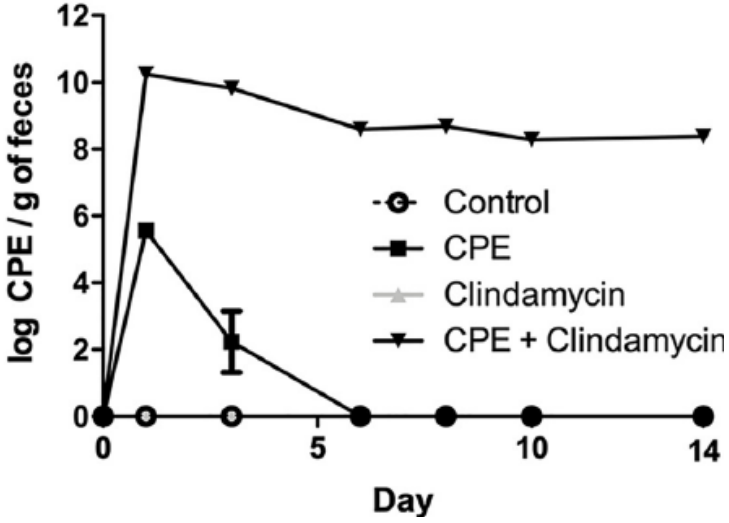
Role of antibiotics

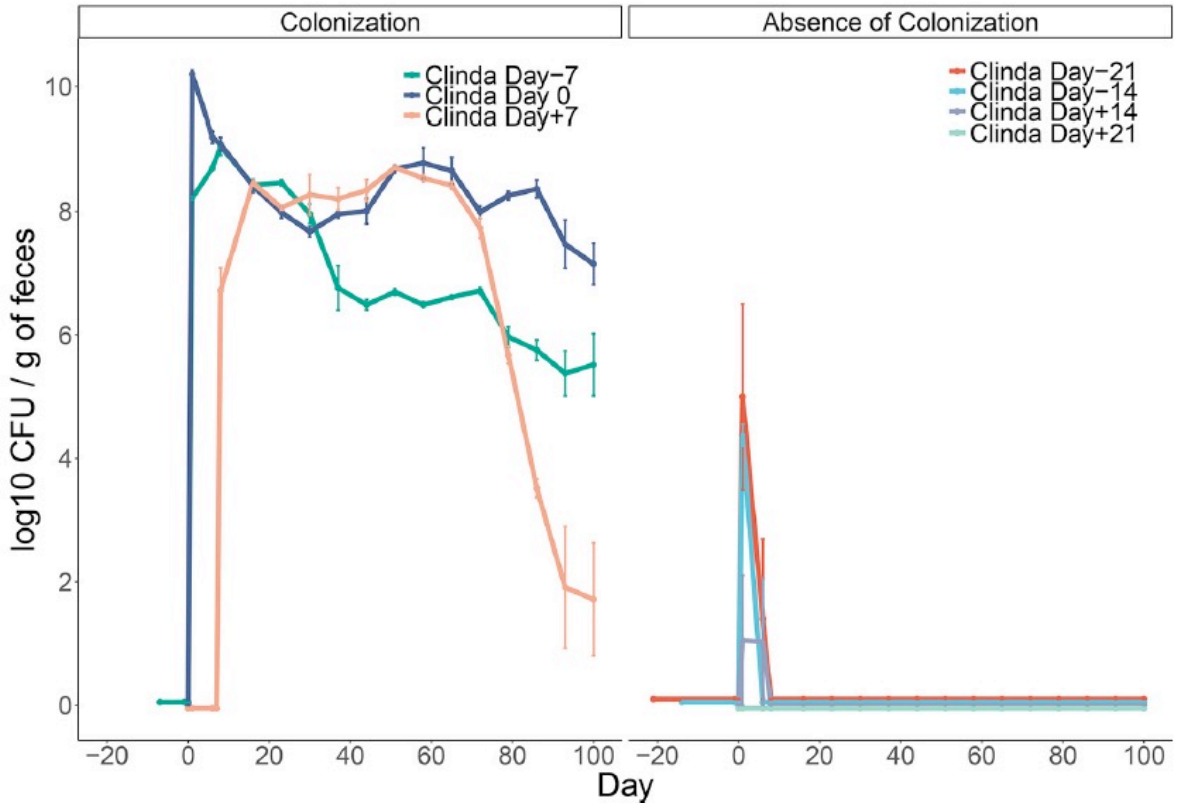
Dissemination is related to antibiotic therapies



Harris HC, Buckley AM, Spittal W, Ewin D, Clark E, Altringham J, Bentley K, Moura IB, Wilcox MH, Woodford N, Davies K, Chilton CH. The effect of intestinal microbiota dysbiosis on growth and detection of carbapenemase-producing Enterobacterales within an in vitro gut model. J Hosp Infect. 2021 Jul;113:1-9.

Impact of the Timing of Antibiotic Administration on Digestive Colonization with Carbapenemase-Producing *Enterobacteriaceae* in a Murine Model





Le Guern R, Grandjean T, Bauduin M, Figeac M, Millot G, Loquet A, Faure K, Kipnis E, Dessein R. Impact of the Timing of Antibiotic Administration on Digestive Colonization with Carbapenemase-Producing *Enterobacteriaceae* in a Murine Model. Antimicrob Agents Chemother. 2019 May 24;63(6):e00360-19.

Role of gut microbiota

LETTERS
https://doi.org/10.1038/s41564-022-01221-w
nature microbiology
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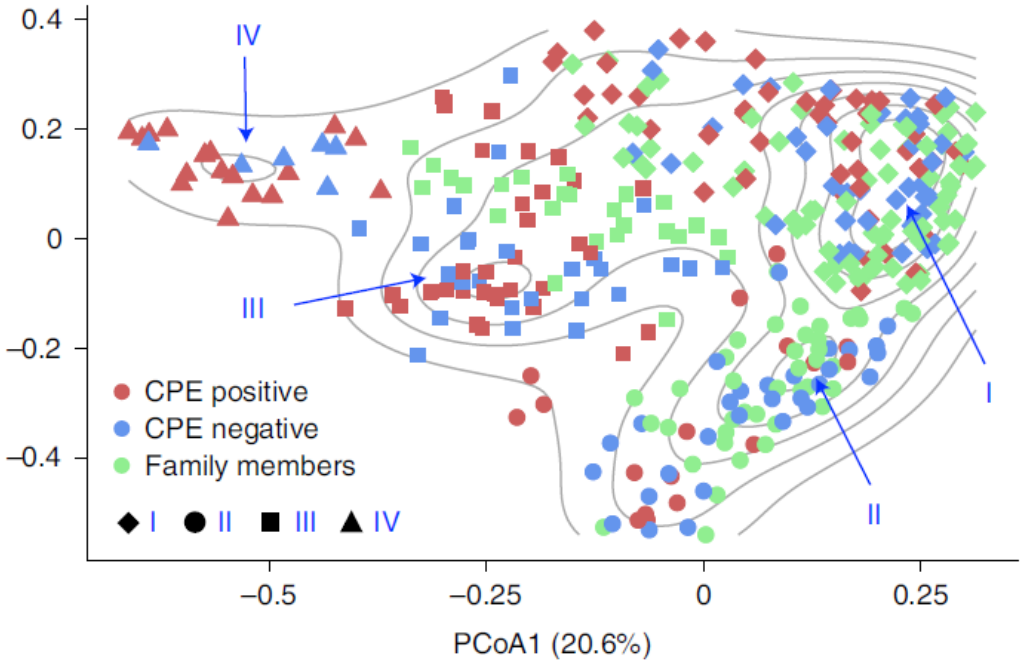
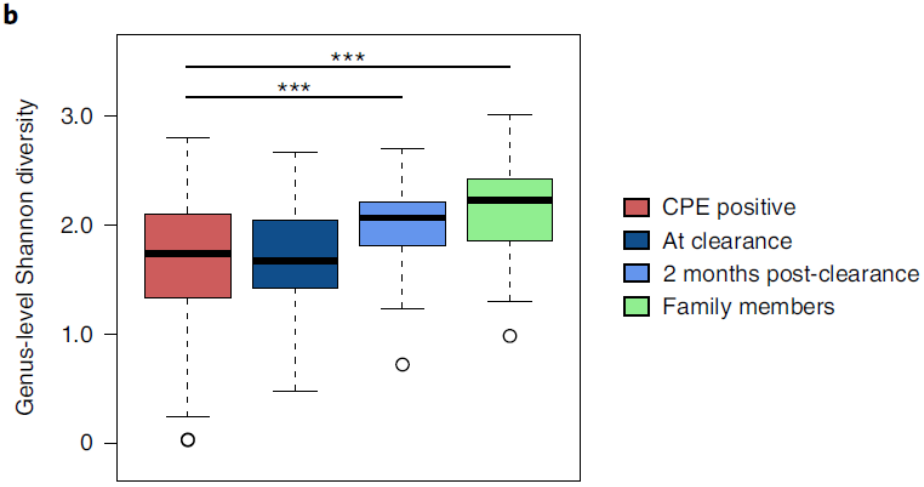
Long-term ecological and evolutionary dynamics in the gut microbiomes of carbapenemase-producing Enterobacteriaceae colonized subjects

Jonathan T. L. Kang[1,4], Jonathan J. Y. Teo[1,4], Denis Bertrand[1,4], Amanda Ng[1], Aarthi Ravikrishnan[1], Melvin Yong[2], Oon Tek Ng[3], Kalisvar Marimuthu[3], Swaine L. Chen[1,2], Kern Rei Chng[1], Yunn-Hwen Gan[2] and Niranjan Nagarajan[1,2]

29 colonised patients and 17 family members
12 months follow-up

A different composition





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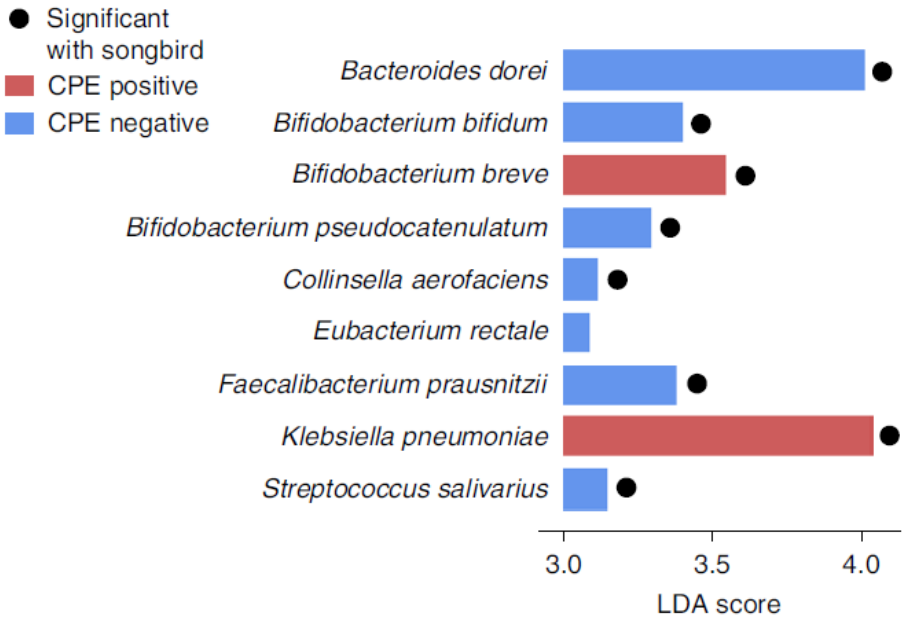

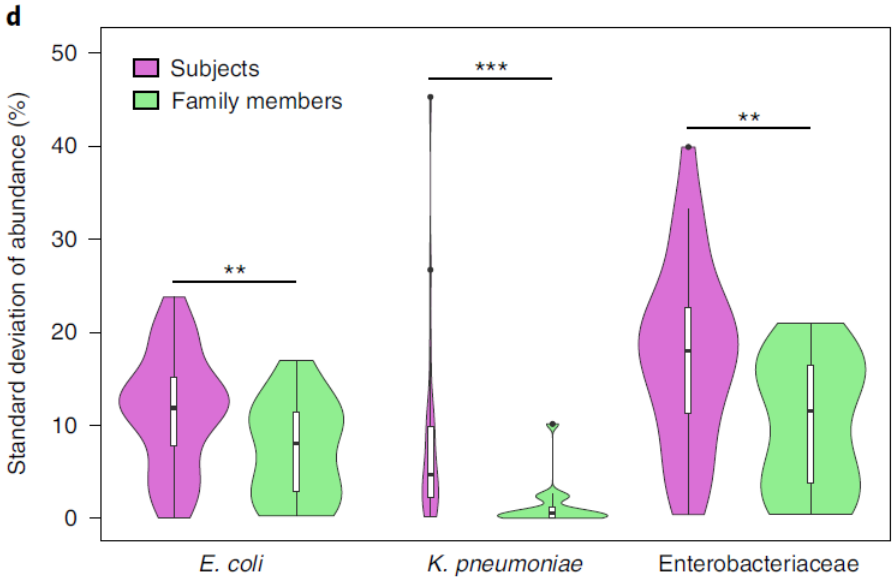

Successful clones

ARTICLES
https://doi.org/10.1038/s41564-021-00879-y
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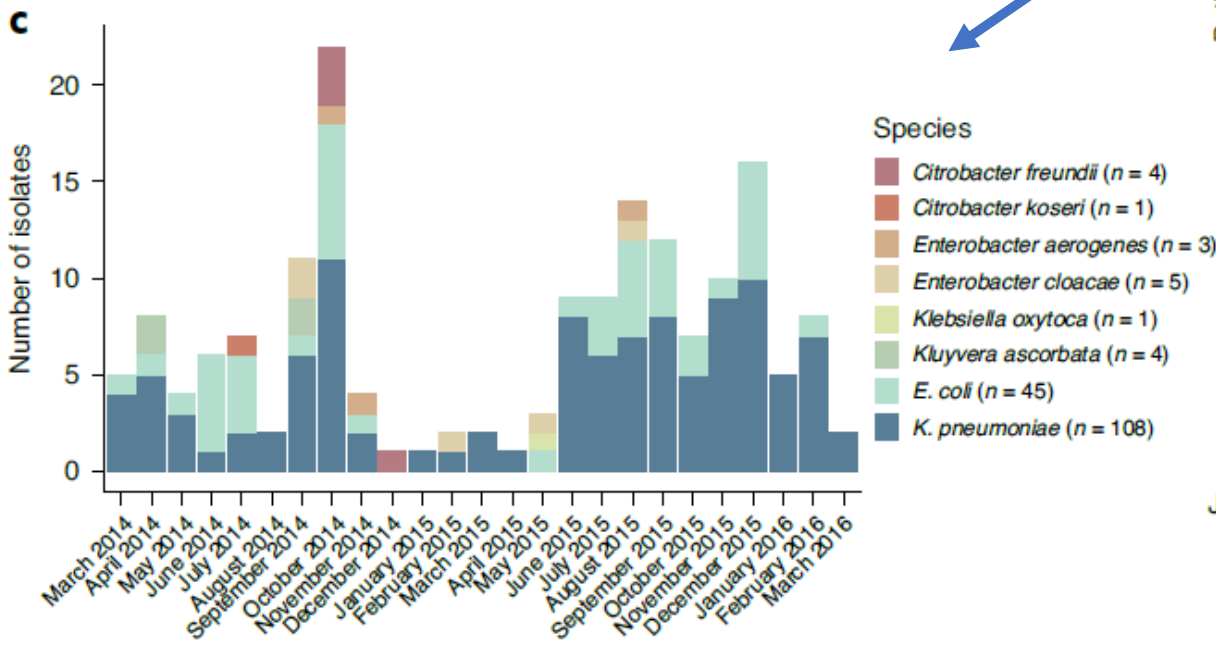
Pervasive transmission of a carbapenem resistance plasmid in the gut microbiota of hospitalized patients

Ricardo León-Sampedro[1,2,8], Javier DelaFuente[1,8], Cristina Díaz-Agero[3,8], Thomas Crellen[4,5], Patrick Musicha[4,5], Jerónimo Rodríguez-Beltrán[1,2], Carmen de la Vega[1], Marta Hernández-García[1,6], R-GNOSIS WP5 Study Group*, Nieves López-Fresneña[3], Patricia Ruiz-Garbajosa[1,6], Rafael Cantón[1,6], Ben S. Cooper[4,5] and Álvaro San Millán[1,2,7]

9,000 patients
250 clones (CPE)
Inter-patient and intra-patient dissemination

Specific species



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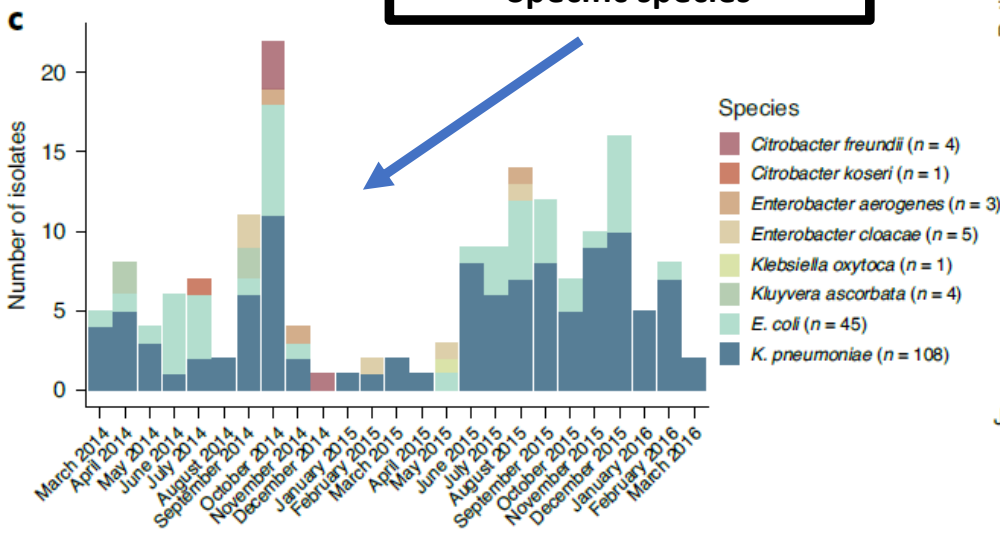
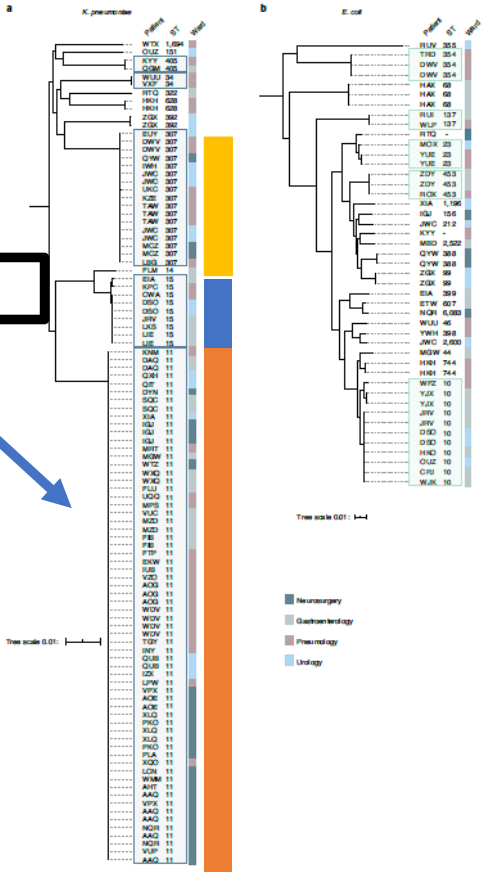


Specific clone



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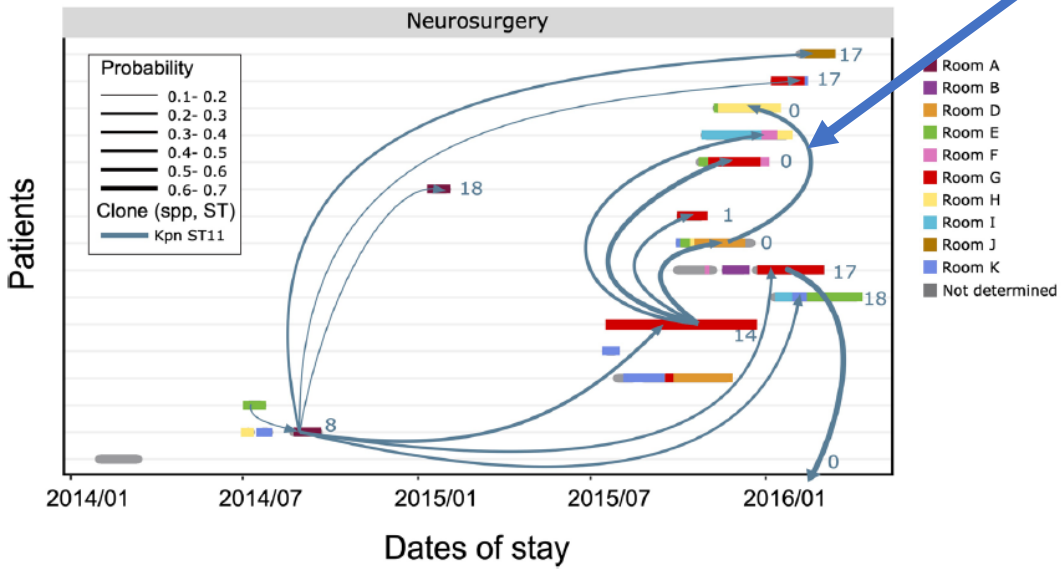
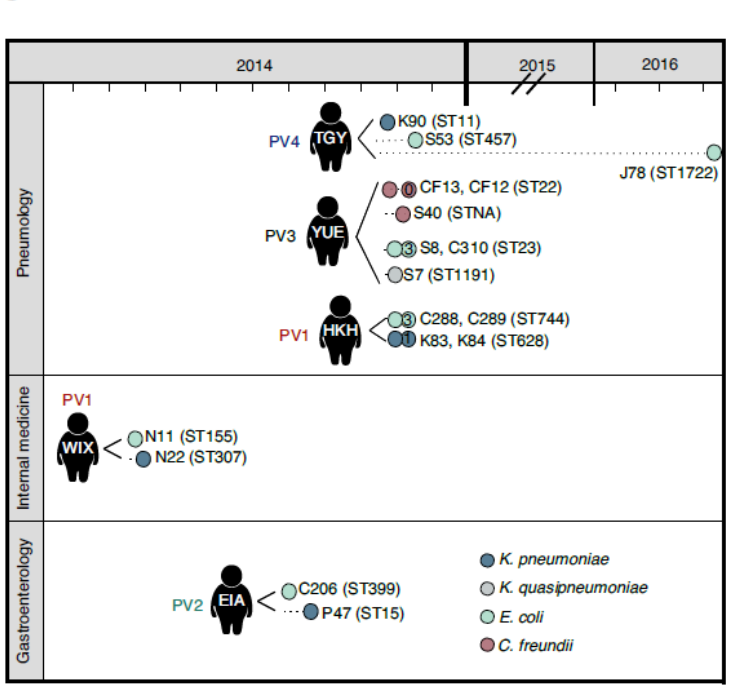
9000 patients
250 clones (CPE)
Dissemination inter patient et intra patient

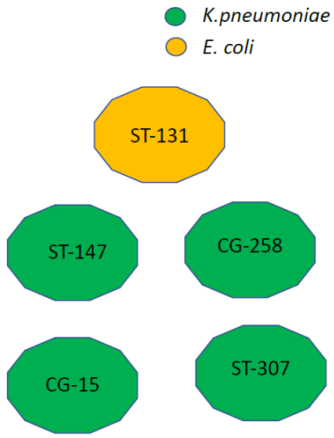
Specific situation

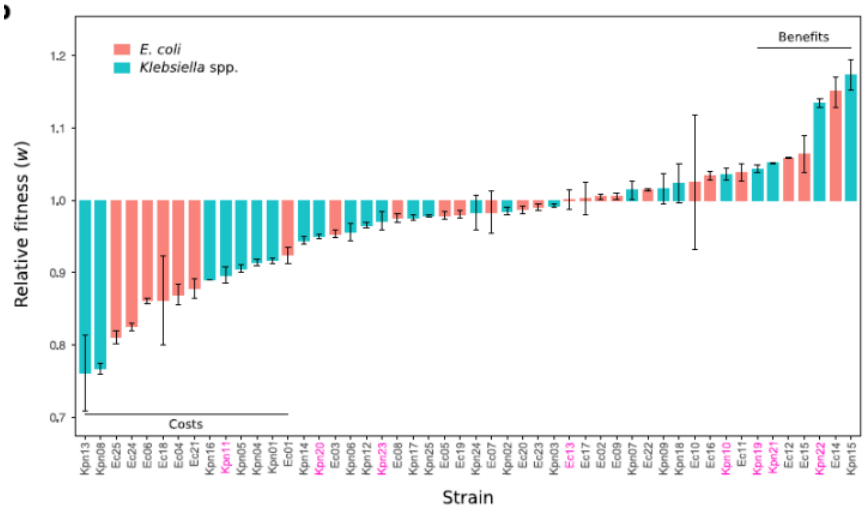




Carbapenemases: dissemination within successful clones!

- Plamids can be transferred
- High-risk clones Global
  - Global distribution
  - High power of colonisation
  - Low fitness cost





- Diffusion of résistance in hypervirulent clone (ST-235 – *Pseudomonas aeruginosa* , St-101 *Klebsiella pneumoniae*)

Alonso-Del Valle A, León-Sampedro R, Rodríguez-Beltrán J, DelaFuente J, Hernández-García M, Ruiz-Garbajosa P, Cantón R, Peña-Miller R, San Millán A. Variability of plasmid fitness effects contributes to plasmid persistence in bacterial communities. Nat Commun. 2021 May 11;12(1):2653. Peirano G, Chen L, Kreiswirth BN, Pitout JDD. Emerging Antimicrobial-Resistant High-Risk Klebsiella pneumoniae Clones ST307 and ST147. Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01148-20. https://eccmid-ondemand.acsvirtual.com/video/301/0830---0930-worldwide-spread-of-hypervirulent-clones-of-klebsiella-and-pseudomonas-aeruginosa-10-07?channelName=ECCMIDondemand, Del Barrio-Tofiño E, López-Causapé C, Oliver A. Pseudomonas aeruginosa epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents. 2020 Dec;56(6):106196.

Are there any solutions

Antimicrobial stewardship

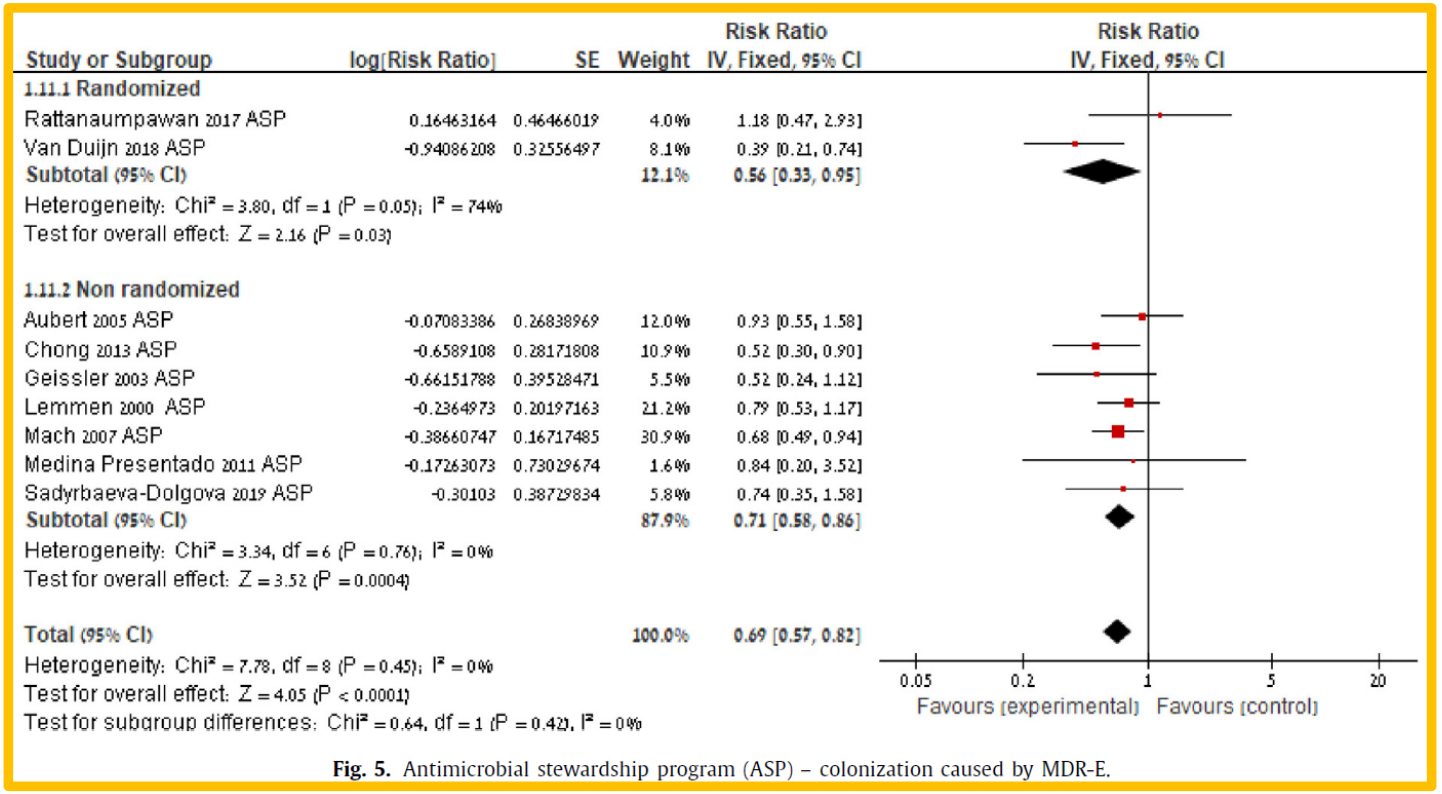


Fig. 5. Antimicrobial stewardship program (ASP) – colonization caused by MDR-E.

Atamna-Mawassi H, Huberman-Samuel M, Hershcovitz S, Karny-Epstein N, Kola A, Cortés LEL, Leibovici L, Yahav D. Interventions to reduce infections caused by multidrug resistant Enterobacteriaceae (MDR-E): A systematic review and meta-analysis. J Infect. 2021 May 14:S0163-4453(21)00246-2.

Modifying the microbiota....and decolonisation?

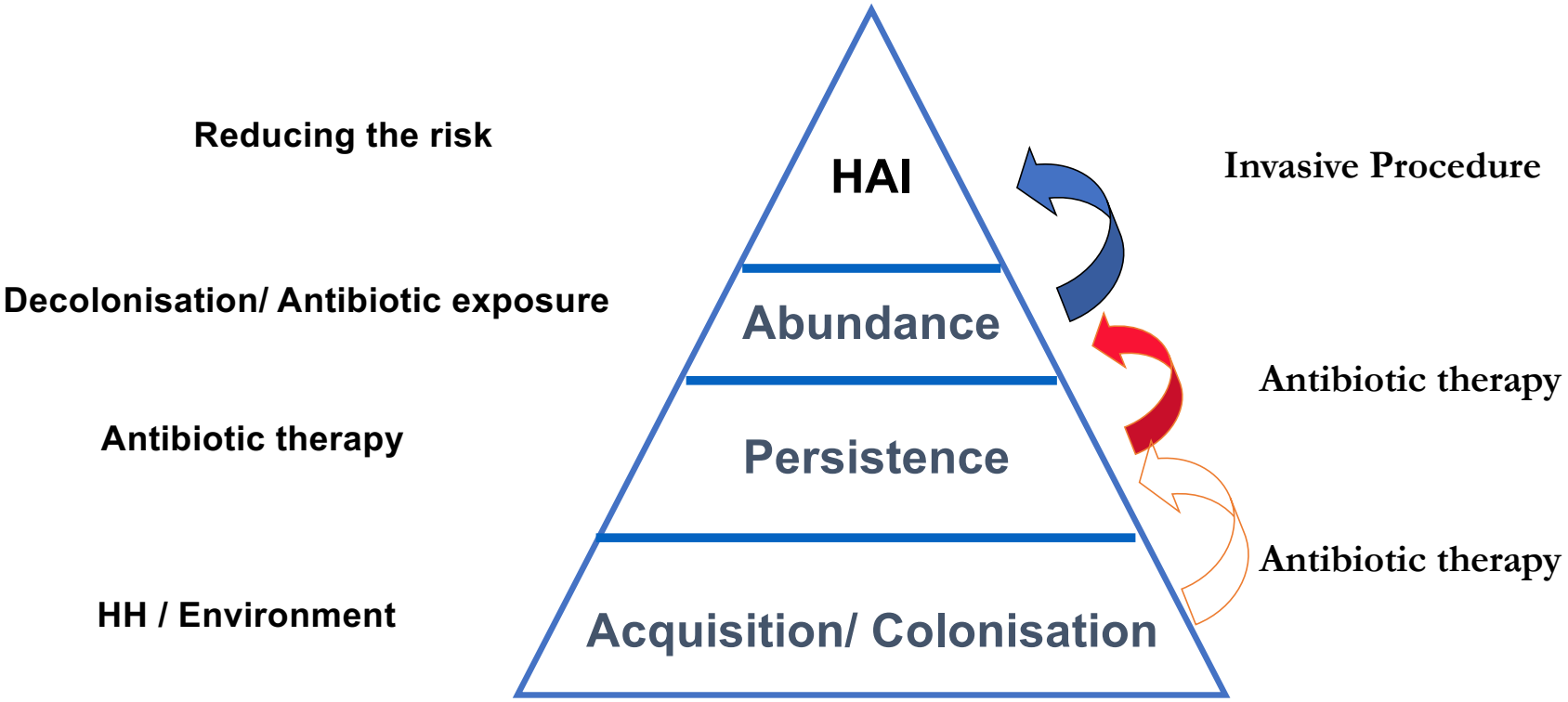
Intervention and outcomes

Study	Primary indication for FMT (CDI/other)	Stool delivery	Stool quantity	Stool type	Donor type	Patients receiving FMT	Patients with eradication of MDRO	Eradication rate (%)
Battipaglia (in press) [10]	Other	Nasogastric or enema	Variable; median, 84 g (range, 43–104 g)	Fresh or frozen	U or R	10	6	60.0
Huttner (2019) [11]	Other	Oral capsule or nasogastric	Nasogastric, about 40 g; oral, about 15–30 g	Frozen	U	21	14	66.7
Davido (2019) [12]	Other	Nasoduodenal	250 g	Frozen	U	8	7	87.5
Dinh (2018) [13]	Other	Nasogastric	70–100 g	Frozen	U	17	10	62.5
Singh (2018) [14]	Other	Nasoduodenal	>150 g	Fresh	U	15	6	40
Bilinski (2017) [15]	Other	Nasoduodenal	100 g	Fresh	U	20	15	75
Davido (2017a) [16]	Other	Nasoduodenal	250 g	Frozen	U	8	3	37.5
Davido (2017b) [17]	Other	Nasoduodenal	250 g	Frozen	U	8	7	87.5
Innes (2017) [18]	Other	Nasogastric	100 mL	Frozen	U	1	1	100.0
Ponte (2017) [19]	CDI	Endoscopy	50 mL	NA	NA	1	1	100.0
Tariq (2017) [20]	CDI	Colonoscopy	50 g	NA	U	8	3	37.5
Bilinski (2016) [21]	Other	Nasoduodenal	100 g	Fresh	U	1	1	100.0
Dubberke (2016) [22]	CDI	Enema	50 g	Frozen	U	11	8	72.7
Garcia-Fernandez (2016) [23]	CDI	Colonoscopy	100 g	NA	R	1	1	100.0
Sohn (2016) [24]	Other	Retention enema	100 g	NA	R	3	1	33.3
Crum-Cianflone (2015) [25]	CDI	Colonoscopy	480 mL	NA	R	1	1	100.0
Jang (2015) [26]	CDI	Enema, nasoduodenal tube	300 g	Fresh	R	1	0	0.0
Lagier (2015) [27]	Other	Nasogastric	50 g	NA	U	1	1	100.0
Stripling (2015) [28]	CDI	Nasogastric	25–30 g	NA	R	1	1	100.0
Wei (2015) [29]	Other	Jejunal	60 g	Fresh	U/R	5	5	100.0
Singh (2014) [30]	Other	Nasoduodenal	150 g	Fresh	U	1	1	100.0

CDI, *Clostridium difficile* infection; FMT, faecal microbiota transplantation; MDRO, multidrug-resistant organism; NA, not applicable; R, related donor; U, unrelated donor.

Saha S, Tariq R, Tosh PK, Pardi DS, Khanna S. Faecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. Clin Microbiol Infect. 2019 Aug;25(8):958-963

HAI related to MDRO : How does it happen



Take home message

- Dissemination within a community depends on a number of factors
  - Environmental factors linked to practices (and therefore modifiable)
  - Can microbial communities (microbiota) be modified?

- Standardising our measures of prevention will not make it possible to control the phenomena (reduce them ... perhaps).

- To understand the transmission phenomena, we need to look at patients who are "resistant to acquisition" ..... and perhaps at the bacterial clone !!!!.

Take home message

- **Practical ways of controlling the in-hospital risk**
  - Avoid acquisition in hospitals ➔ Improving hand hygiene
  - Avoiding persistence in the microbiota ➔ Reducing antibiotic therapy

- **How to better understand the phenomenon**
  - Identifying "protective" microbiota
  - Identifying treatments (antibiotic and non antibiotic) that amplify the phenomenon
  - Assess the role of microbiota modulation

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