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FDA / CDC Workshop

Drug Development Considerations for the Prevention of HealthCare-Associated Infections—Virtual Public Workshop

Challenges and Lessons Learned Developing DAV132, a Novel Therapy Protecting Gut Microbiota from Antibiotic-Induced Dysbiosis

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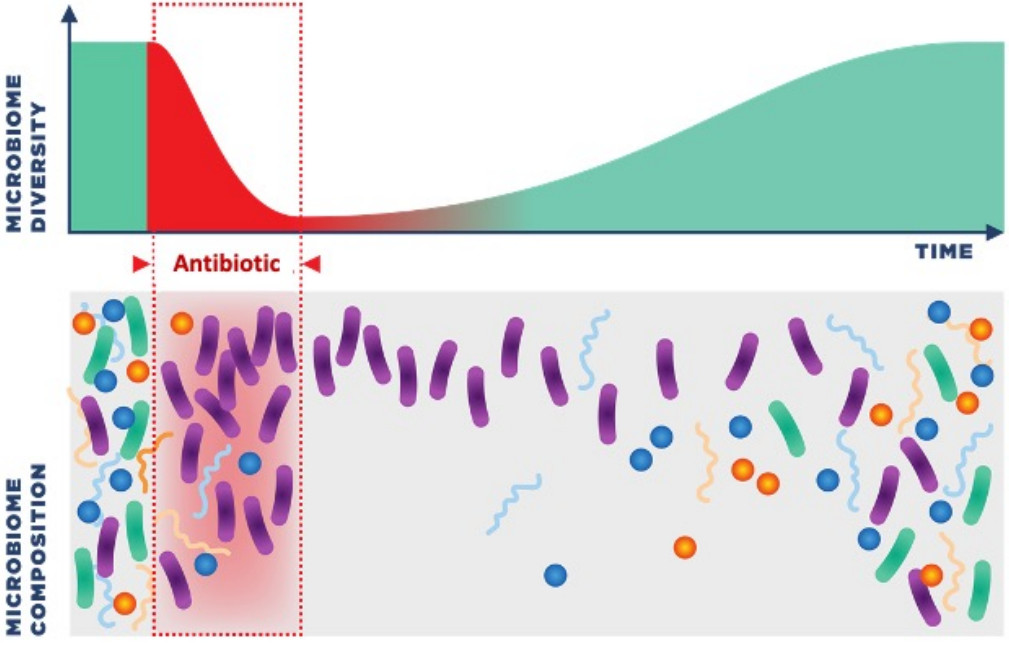
I August 30, 2022

All Antibiotics Provoke Intestinal Microbiota Dysbiosis

During oral and parenteral antibiotic treatments, antibiotic residues reach the colon where they kill numerous bacteria and provoke a strong **dysbiosis**.



Healthy Microbiota

High diversity:

- Beneficial to health,
- Symbiosis with human
- body functions

Disrupted Microbiota

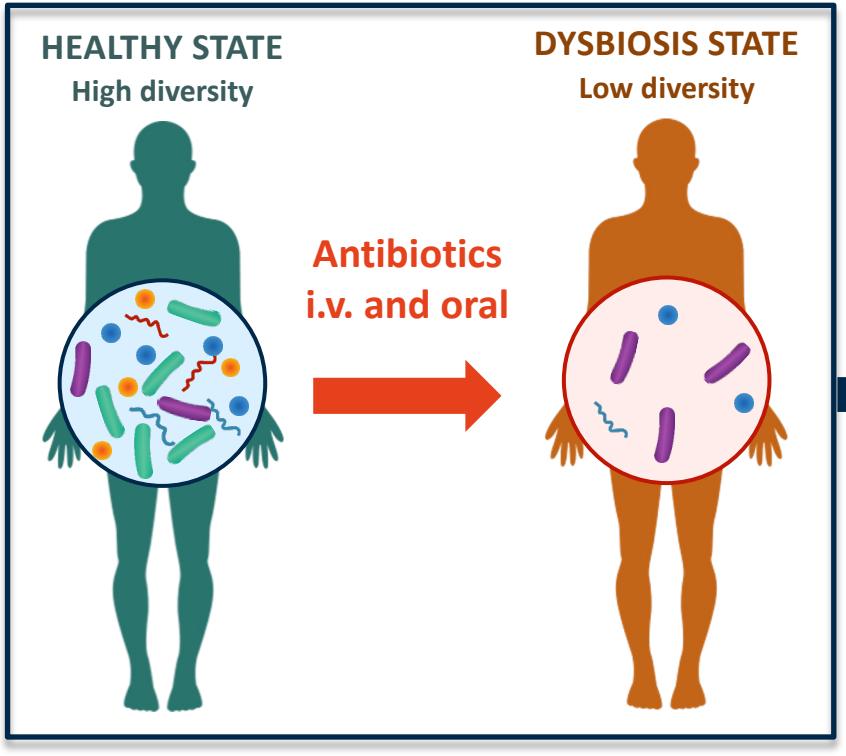
Strongly **decreased diversity, i.e. 'dysbiosis'** with human body:

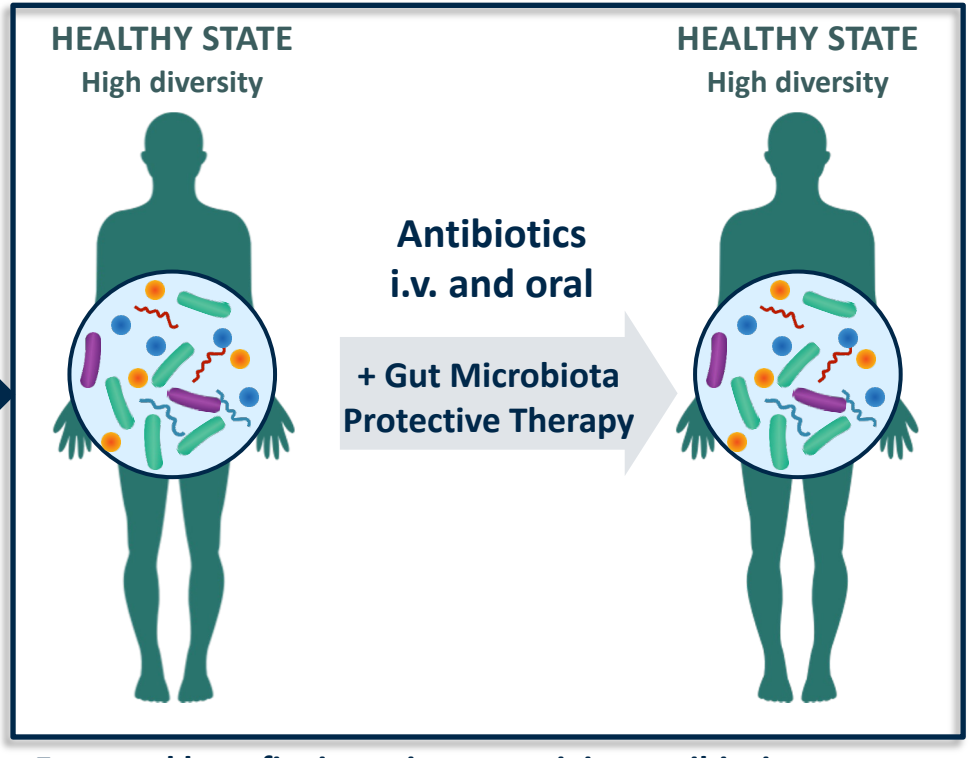
- Dysfunctional gut barrier and colonization by pathogenic bacteria such as *C. difficile*
- Multiplication of resistant clones
- Degraded immunity and immune response
- Oxidative stress increase
- Altered metabolism

Adapted from Jernberg C et al. Microbiology. 2010

Concept - Gut Microbiota Protective Therapies

Maintaining the Healthy Microbiota Function by Preventing Antibiotic-Induced Intestinal Disruption and Consequences





Expected benefits in patients receiving antibiotics

- Prevent *C. difficile* infections in patients at risk
- Limit emergence and dissemination of resistant strains
- Increase efficacy of immunity-based cancer treatments

DAV132 Mode of Action: Capturing Antibiotic Residues in the Colon

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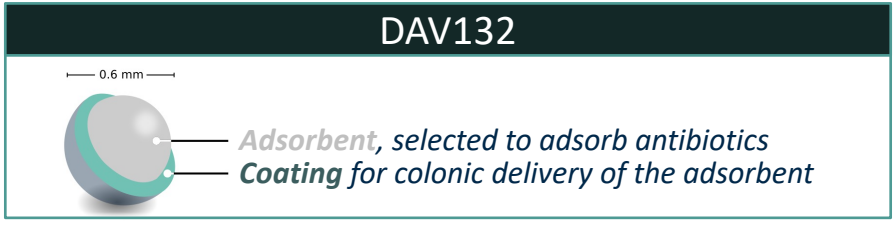
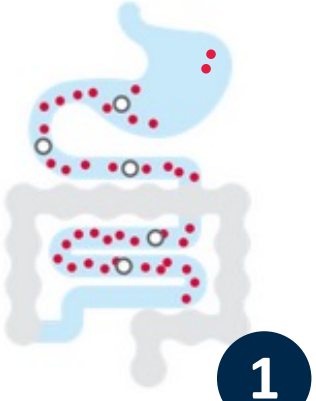
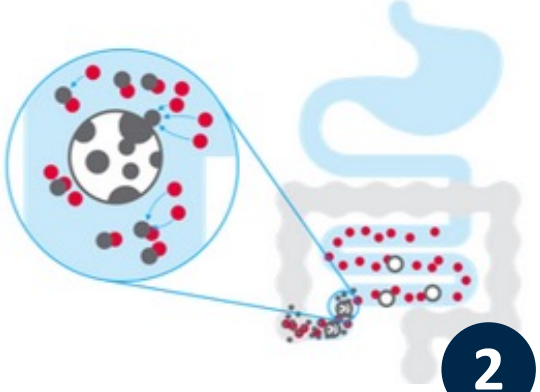


- ***DAV132***
- ***Antibiotics***



1

DAV132 is administered orally with antibiotics. The antibiotics reach the bloodstream from the upper gastrointestinal tract without interference with DAV132, whose coating remains intact



2

DAV132's coating opens in the colon and the adsorbent irreversibly captures (adsorbs) the antibiotic residues

3

Antibiotic residues bind to DAV132 and are eliminated in the patients' stools

✓ **No interference with systemic absorption and efficacy of co-administered antibiotics**

✓ **Inactivation of the antibiotic residues in the caecum and colon**

✓ **Microbiota protected from antibiotic-induced disruption**

DAV132 – Development Status

- ✓ Non-Clinical: Numerous preclinical proof of concept data on prevention of CDI in Hamster models + Breakthrough proof of concept in immuno-oncology
- ✓ Clinical: Data generated in **496 individuals exposed to DAV132 in six Phase 1 and one Phase 2 clinical trials** completed so far
  - ✓ Demonstrated **efficient and reproducible mode of action** in humans:
    - Free antibiotic fecal concentrations decreased by 99% with DAV132
    - No impact of DAV132 on the plasmatic concentration and efficacy of concomitant drugs taken by the patients
    - Very good protection of the intestinal microbiota diversity and functional colonization by *C. diff*
  - ✓ **Good safety profile**, even in severely-ill patients
- ✓ CMC: Product composition, process and characterization complete for Phase 3-stage

DAV132 Efficiently Captures Antibiotics Without Impacting their Plasma Concentrations

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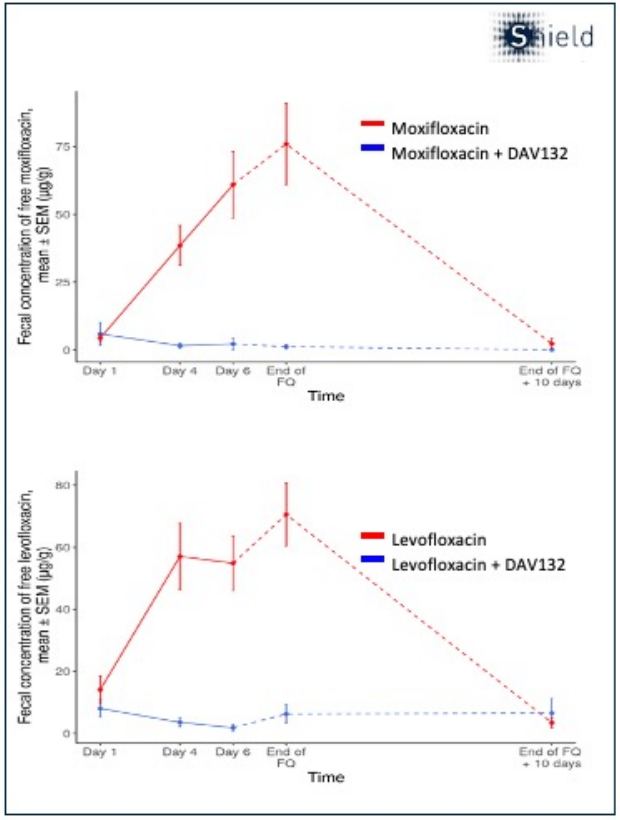
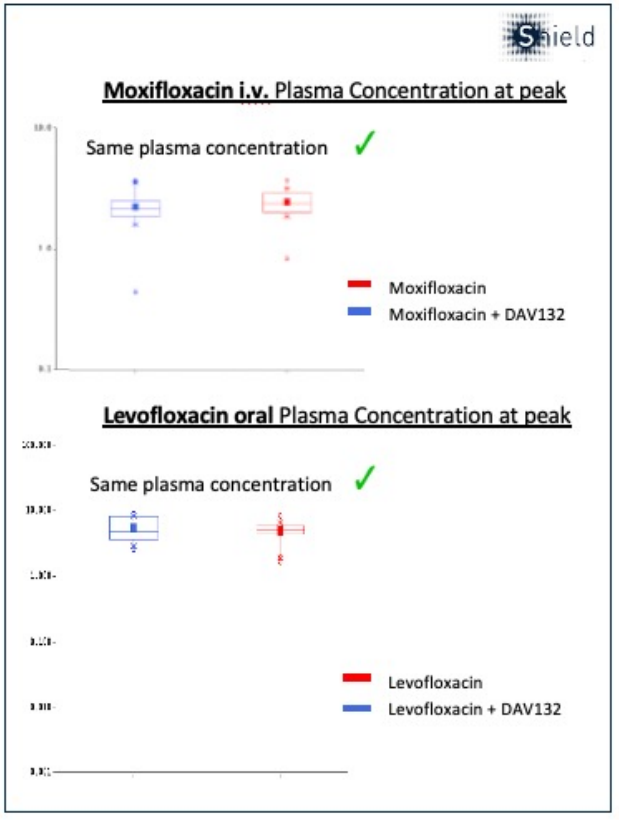
In vitro & Ex vivo experiments 85 antibiotics tested

Antibiotic Class	Antibiotic	Adsorption *in vitro* (%)	Adsorption *ex vivo* (%)
Penicillin	Amoxicillin	> 99	> 99
	Piperacillin	> 99	> 98
Cephalosporin	Cefalexin	> 98	97
	Cefazolin	97	
	Cefdinir	> 99	
	Cefixime	> 99	
	Cefotaxime	> 98	> 99
	Cefpodoxime	> 99	
	Ceftriaxone	> 99	96
	Cefepime	> 98	98
Carbapenem	Ertapenem	> 99	> 99
	Imipenem	> 97	> 99
	Meropenem	> 97	> 99
Fluoroquinolone	Ciprofloxacin	> 99	> 99
	Levofloxacin	> 99	99
	Moxifloxacin	> 99	99
	Lomefloxacin	> 99	> 99
Lincosamide	Clindamycin	> 95	97
Macrolide	Azithromycin	> 99	
	Clarithromycin	> 99	

DAV132 efficiently captures antibiotics in the colon



DAV132 does not impact the plasma PK of oral and IV antibiotics

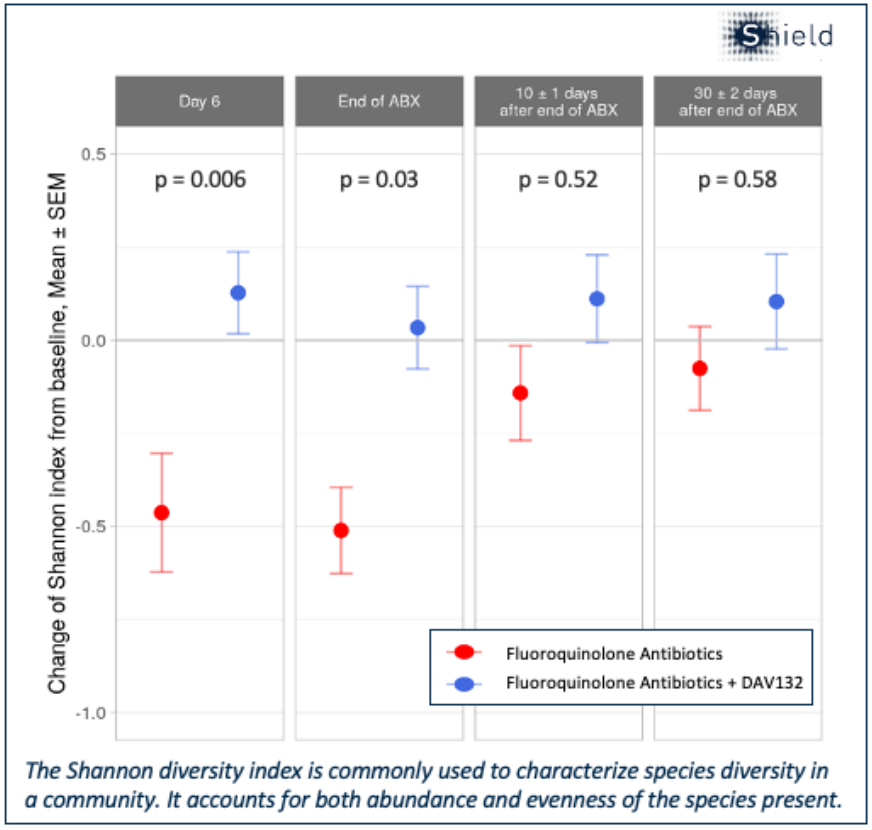


Similar results obtained with Ceftazidime, Piperacillin and Ciprofloxacin

Sources: de Gunzburg et al. JID 2018; Vehreschild, et al. JAC. 2022

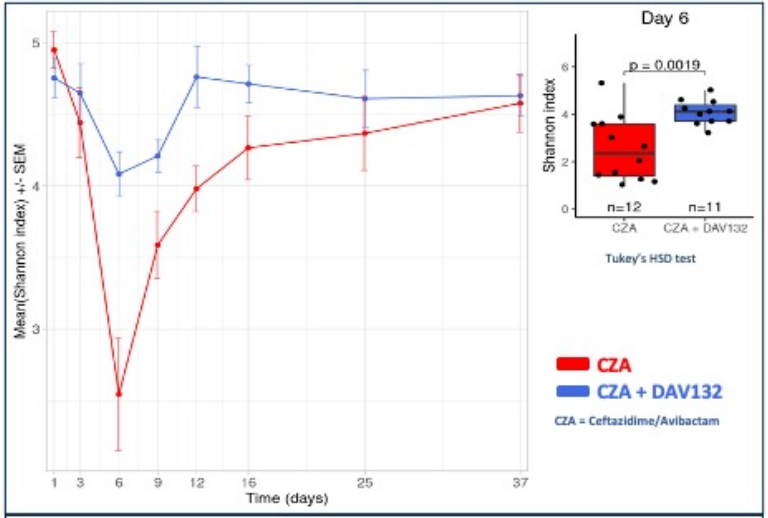
DAV132 Preserves the Gut Ecosystem from Dysbiosis

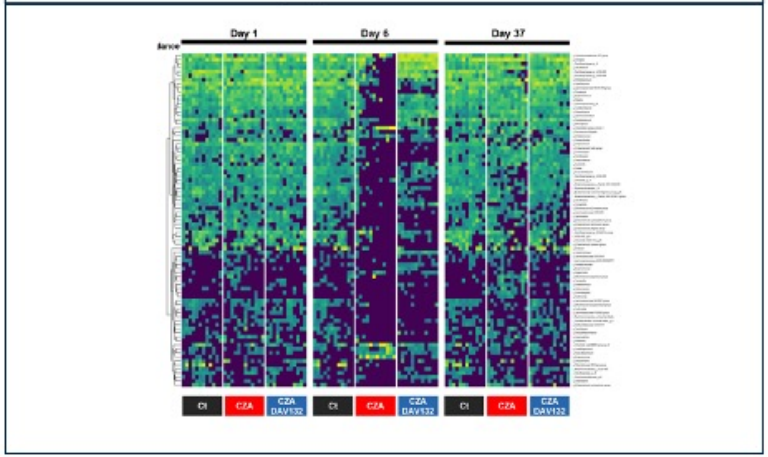
With Fluoroquinolones



The Shannon diversity index is commonly used to characterize species diversity in a community. It accounts for both abundance and evenness of the species present.

With Beta-Lactams



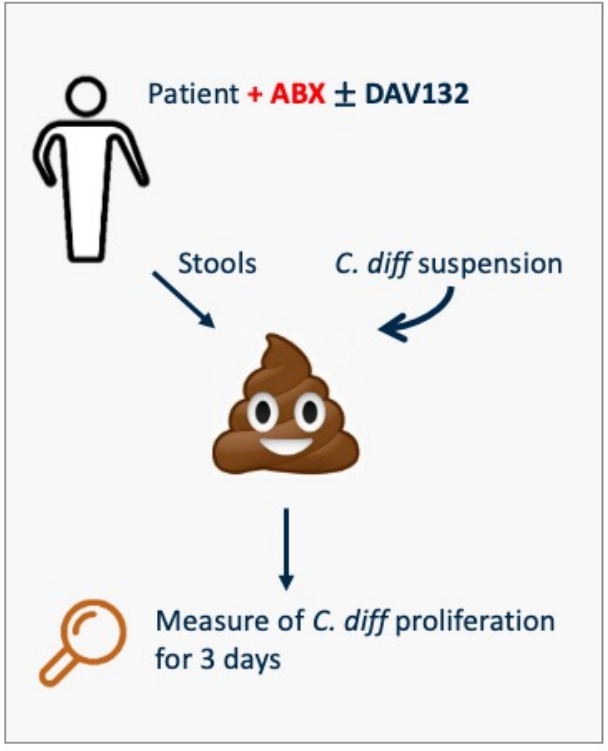


Sources: Harris et al. AAC. 2020; Mark Wilcox Lab; Vehreschild, et al. JAC. 2022

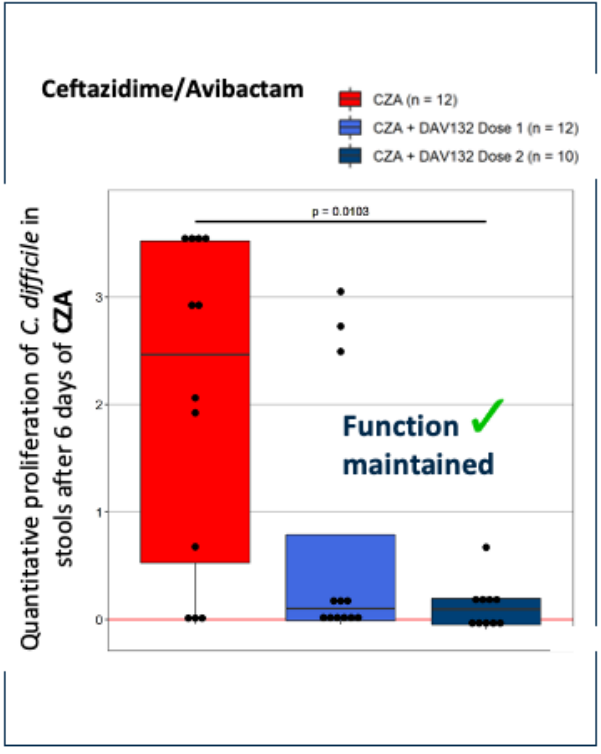
DAV132 Maintains the Functions of the Microbiota

Resistance to Colonization by *C. diff*

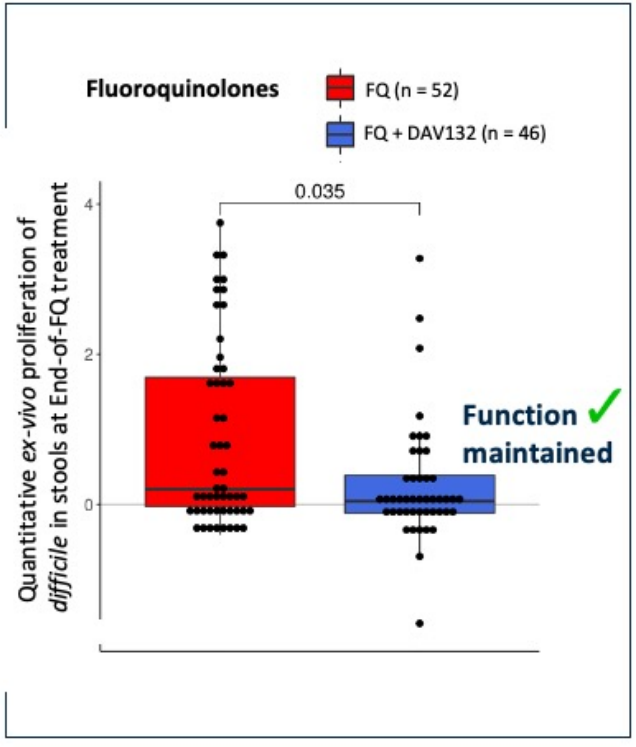
Design: Colonization Resistance Assay for *C. diff* in Stool (CRACS)



Phase 1 Clinical Trial
Healthy Volunteers



Phase 2 Clinical Trial
Patients



Sources: Harris et al. AAC. 2020 ; Mark Wilcox Lab ; Vehreschild, et al. JAC. 2022 ; Unpublished data

DAV132 Significantly Reduces the Counts of Vancomycin-Resistant *Enterococci* (VRE) at the End of FQ Antibiotics Treatment

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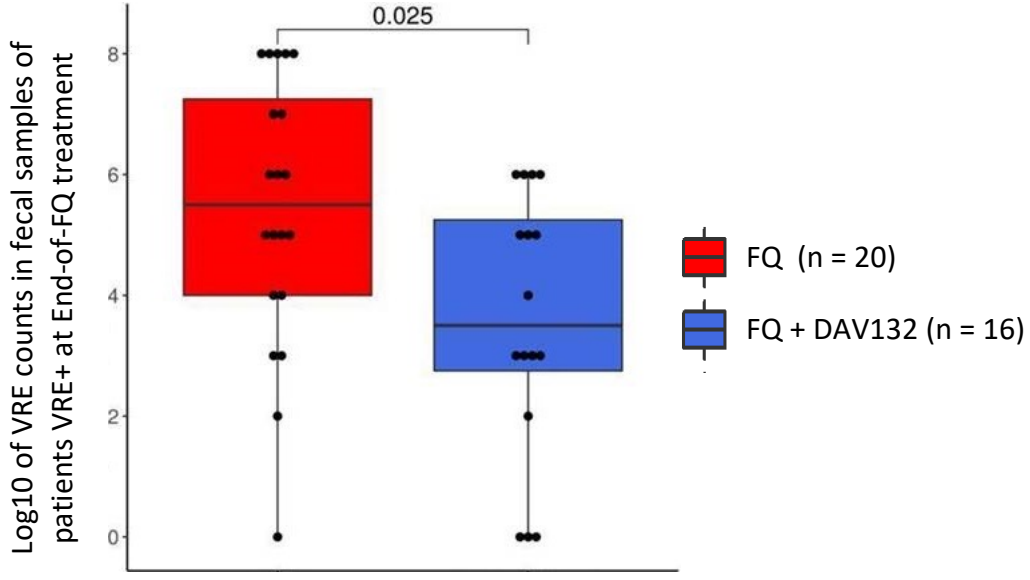
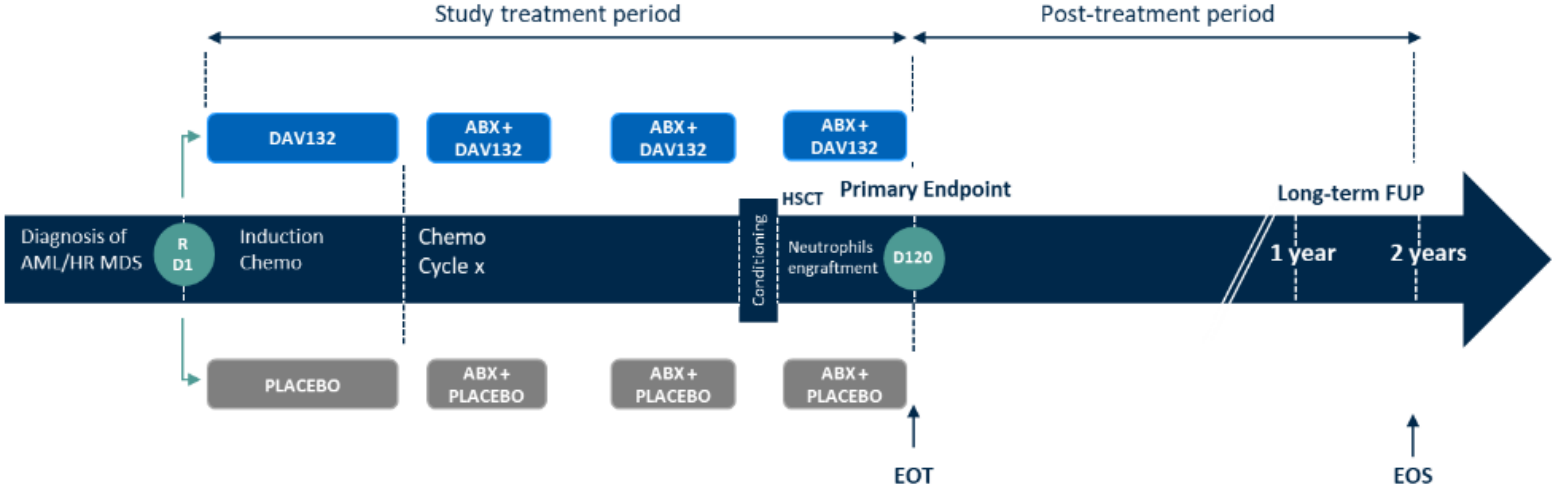
Phase 2 Clinical Trial: VRE counts at End-of-FQ treatment are reduced in the feces of patients treated with DAV132 (not carriers at Day 1)



Sources: Vehreschild, et al. JAC. 2022

Phase 3 Design for DAV132 to Demonstrate the Prevention of CDI in an Enriched Patient Population (AML)

- A multicenter, randomized, placebo-controlled, parallel-arm clinical trial (phase III)
- To assess the efficacy of DAV132, compared to placebo, in preventing *C. difficile* infection in newly diagnosed AML or high-risk MDS patients treated with intensive chemotherapy



Primary endpoint : **occurrence of CDI during the 120 days following randomization**

Lessons Learned – Regulatory and Clinical Operations

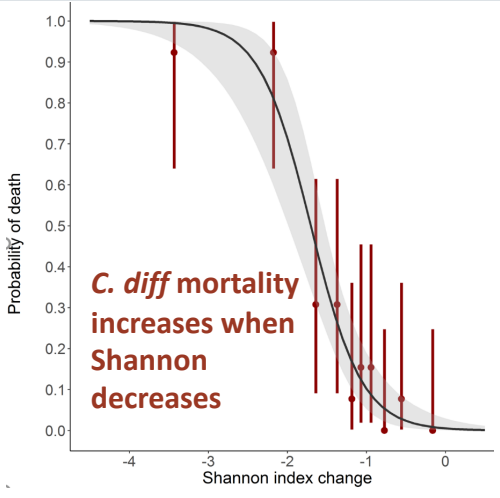
- Primary analysis: **competing risks analysis with CDI occurrence as the event of interest and death as a competing risk, with cause-specific hazard ratio as a statistical outcome**, "Time to CDI" being the variable of interest on which the competing risks approach is based.
  - ✓ Cause-specific hazard ratio and cumulative incidence do not focus on the time to CDI but they express the **actual risk of developing a CDI at any point in time in the study,** thus informative on the incidence of CDI.
  - ✓ Simulations performed that showed that the competing risks approach does not lead to over-conclude in the unlikely case DAV132 only delays (but not prevents) CDI occurrence.
  - ✓ Approach developed in partnership with experts from STAT-NET as appropriate to conclude on a meaningful clinical benefit.
  - ✓ Sample size re-estimation planned with 2 interim analyses to optimize futility decision*.
- Study initiated in Europe as a public-private partnership in COMBACTE-NET but **which had to stop in July 2022 for operational futility** (not enough sites, low recruitment rate)

* Marlieke de Kraker, *Which design aspects can enhance clinical trial efficiency?* **ECCMID Educational Workshop 2022**

Low-Diversity Microbiota is a Biological Marker Correlated to CDI Risk

Correlation between **low-diversity microbiota** (alpha-diversity Shannon Index) and **occurrence of *C. difficile* infections** (CDI) has been validated in the scientific literature:

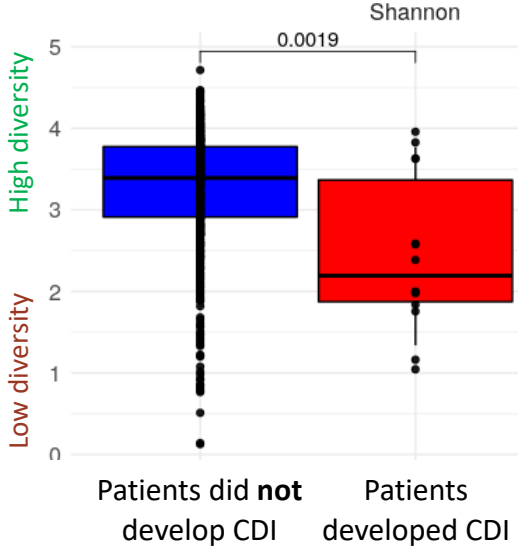
Powerful Predictor for *C. difficile* Infection Severity in Hamsters



Logistic models of mortality according to the change of Shannon index between D_0 and D_3 after pooling data from antibiotic-treated animals

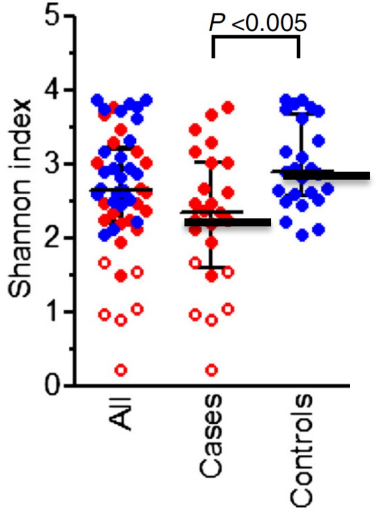
Burdet C, et al. Antimicrob Agents Chemother. 2018.

A lower microbiota diversity is predictive of CDI



van Werkhoven CH, et al. ANTICIPATE Study. Nat Commun. 2021

Patients who develop CDI have significantly lower Shannon index

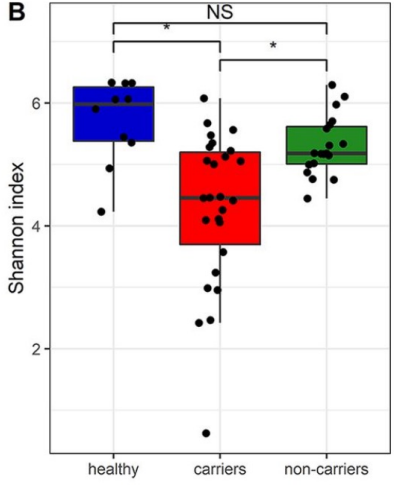


Vincent C, et al. Microbiome. 2013

Low-Diversity Microbiota & Antibiotic Use are Associated to Colonization to MDROs

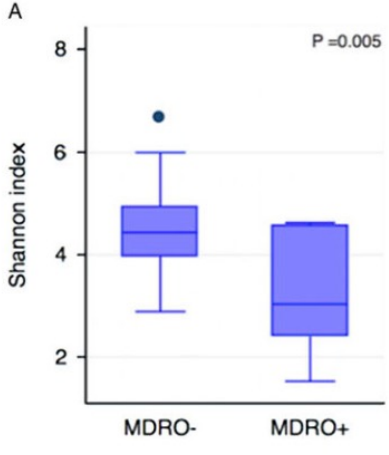
Association between **low-diversity microbiota** (alpha-diversity Shannon index)/**antibiotic use** and **colonization to Multi-Drug Resistant Organisms** (MDROs) is well described in the literature:

Carbapenem resistant *Enterobacteriaceae* carriers have significantly lower microbiota diversity compared to other groups



Korach-Rechtman H, et al. mSphere. 2020

Hospitalized patients colonized with MDROs have significantly lower microbiota diversity compared to hospitalized, non-colonized patients



Araos R, et al. Infect Control Hosp Epidemiol. 2017

Prior antibiotic treatment is independently associated with ESBL colonization in ICU patients

Study	Patients colonized to ESBL-PE among prior ABX users	Patients colonized to ESBL-PE among patients who did not use ABX	RR [95% CI]	ABX exposure TW
Moustaoui	1/4 (25%)	16/71 (22.5%)	1.1 [0.19-6.39]	NA
Razazi	16/110 (14.6%)	12/102 (11.8%)	1.24 [0.62-2.49]	Previous year
Ma.	37/175 (21.1%)	32/287 (11.2%)	1.90 [1.23-2.93]	Last 3 months
All			**1.65 [1.15-2.37]**	

Detsis M, et al. Crit Care Med. 2017

ABX: Antibiotic, CI: Confidence interval, ESBL-PE: Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, NA: Not available, RR: Relative risk, TW: Time window

Colonization by Resistant Bacteria is Associated with an Increased Risk of Hospital-Acquired Infections (HAI)

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ESBL Producing Enterobacteriaceae (ESBL-PE)

Labelled as Serious Threat by US CDC

197,400 cases in-hospital | **9,100** deaths | **$1.2B** attributable healthcare costs

Vancomycin-Resistant Enterococci (VRE)

Labelled as Serious Threat by US CDC

54,500 cases in-hospital | **5,400** deaths | **$539M** attributable healthcare costs

Cancer patients with ESBL-PE colonization were **12.98 [95% CI 3.91-43.06] times more likely to develop a BSI with ESBL-PE** compared with non-colonized patients

ICU patients with ESBL-PE colonization were **49.62 [95% CI 20.42-120.58] times more likely to develop an ESBL-PE infection** compared with non-colonized patients

Dialysis patients with VRE colonization were **21.62 [95% CI 4.33-87.69] times more likely to develop a VRE infection** compared with non-colonized patients

Sources: CDC. Antibiotic Resistance Threats in the United States, 2019 ; Alevizakos M et al., Int J Antimicrob Agents. 2016; Detsis et al., Crit Care Med. 2017; Zacharioudakis et al., Am J Kidney Dis. 2014

Challenges Met Today Leading to Considering New Endpoints?

- **Co-administered prevention approaches reducing dysbiosis and colonization by bacteria and yeasts caused by antibiotics** like DAV132 make medical sense.

➔ *How to envision facilitating their access to market considering microbiological markers as surrogate endpoints to combat urgent threat infections and AMR dissemination?*

- Similarly, some **Pathogen-Specific Antibacterials** in development have shown to have **microbiota-sparing properties,** expected to lead to reduced risk of selecting for resistance or other colonizing bacterial species, potentially minimizing the overall burden of resistance and subsequent healthcare-associated infections. This represents a very important competitive advantage in classical equivalence phase 3 efficacy study performed for the development of new antibiotics and justifies higher economic valuation on the expected/modelized reduction of secondary infections and hospital dissemination.

➔ *How to include new achievable biomarkers, such as colonization with bacterial species associated with morbidity and mortality risks (MRSA, VRE, C. diff, etc.), which could then be described within the clinical section of the label?*

- Finally, decolonization strategies make medical sense too.

➔ *Would microbiological carriage endpoints could be considered for clinical development of HAI prevention products via decolonization MoA? Alignment with EMA guideline*?*

*EMA Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3)

Take-Home Messages

- Sparing the microbiota from antibiotic-associated dysbiosis and colonisation by resistant micro-organisms is possible technically and pharmacologically, however not yet financially

- Current regulations do not allow for feasible clinical developments because demonstrating a reduction of colonisation followed by a reduction of secondary infections and dissemination necessitates too large and expensive studies

- New regulations accepting prevention of colonisation as an endpoint for clinical development are a necessity to make available such a strategy for the benefit of individual patients and the global control of AMR

Da Volterra Publications & Posters

About DAV132

- Vehreschild, et al. *An open randomized multicentre Phase 2 trial to assess the safety of DAV132 and its efficacy to 1 protect gut microbiota diversity in hospitalized patients treated with fluoroquinolones*. Journal of Antimicrobial Chemotherapy. 2021. Link
- Andremont A, et al. *Spare and repair the gut microbiota from antibiotic-induced dysbiosis: state-of-the-art*. Drug Discovery Today. 2021. Link
- Ducher A, et al. *DAV132 protects intestinal microbiome of patients treated with quinolones. A European phase II randomized controlled trial*. IDWeek, Oral presentation. 2020. Link
- de Gunzburg et al. *Protection of the human gut microbiome from antibiotics.* The Journal of Infectious Diseases. 2018. Link
- Guk J, et al. *Modeling the Effect of DAV132, a Novel Colon-Targeted Adsorbent, on Fecal Concentrations of Moxifloxacin and Gut Microbiome Diversity in Healthy Volunteers*. Clin Pharmacol Ther. 2021. Link
- Pinquier et al. *A Colon-Targeted Adsorbent (DAV132) Does Not Affect the Pharmacokinetics of Warfarin or Clonazepam in Healthy Subjects*. Clin Pharmacol Drug Dev. 2021. Link
- de Gunzburg et al. *Targeted Adsorption of Molecules in the Colon with the Novel Adsorbent-Based Medicinal Product, DAV132: A Proof of Concept Study in Healthy Subjects*. J Clin Pharmacol. 2015. Link
- Saint-Lu N et al. *DAV131A protects hamsters from lethal Clostridioides difficile infection induced by fluoroquinolones*. Antimicrobial Agents and Chemotherapy. 2019. Link
- Grall et al. *Oral DAV131, a Charcoal-based Adsorbent, Inhibits Intestinal Colonization by Beta-lactam Resistant Klebsiella pneumoniae in Cefotaxime-Treated Mice*. AAC. 2013. Link

About Immuno-Oncology

- Zalcman G, et al. *Systematic Review and Meta-analysis Evaluating the Impact of Antibiotic Use on the Clinical Outcomes of Cancer Patients Treated with Immune Checkpoint Inhibitors*. ASCO Annual meeting. 2022. Link
- Crespin A, et al. *Systematic Review and Meta Analysis Evaluating the Impact of Antibiotic Use on Survival Outcomes and Treatment Response of Non Small Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors.* SITC Virtual Congress. 2021. Link
- Lurienne L, et al. *Non-small-cell lung cancer immunotherapy efficacy and antibiotic use: a systematic review and meta-analysis*. J Thorac Oncol. 2020. Link

About Hemato-Oncology

- Lurienne L, et al. *Incidence of CDI in a cohort of US patients with newly diagnosed Acute Myeloid Leukemia receiving intensive chemotherapy*. ASH 2020, poster 3406. Link
- Duhalde L, et al. *The economic burden of Clostridioides difficile infection in patients with hematological malignancies in the United States: A case-control study*. Infect Control Hosp Epidemiol. 2020. Link
- Duhalde et al. *Excess burden associated with Clostridioides difficile infection in haematological patients occurring during hospitalization with induction chemotherapy in the United States*. J Hosp Infect. 2019. Link