Different gut microbiome dysbioses impact the evolutionary fate of hypervirulent *Klebsiella pneumoniae*



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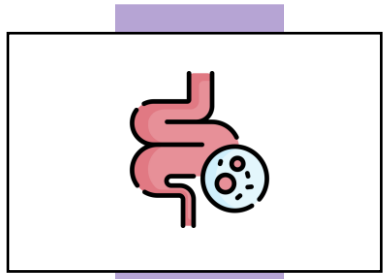
[2]Institute of Immunology, Zhejiang University School of Medicine, Hangzhou 310058, and Liangzhu Laboratory, Hangzhou 311121, China.

[3]Genome Institute of Singapore (GIS), Agency for Science, Technology and Research (A*STAR), Singapore 138672, Republic of Singapore.

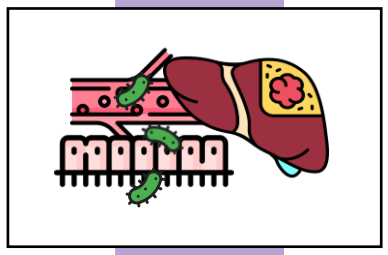
Carey Lim, Jialing Zheng, Guoxiang Cheam, Melvin Yong, Hanrong Chen, Andrew Ting, Yahua Chen, et al. 2026. Different gut microbiome dysbioses impact the evolutionary fate of hypervirulent *Klebsiella pneumoniae*. ***iMeta*** 5: e70175. https://doi.org/10.1002/imt2.70175

Introduction – Hypervirulent *Klebsiella pneumoniae*

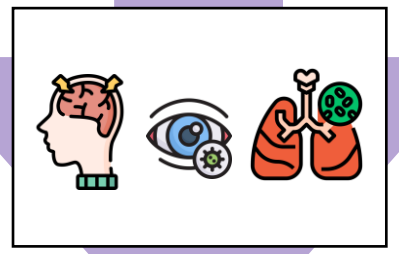
Hypervirulent *Kp*



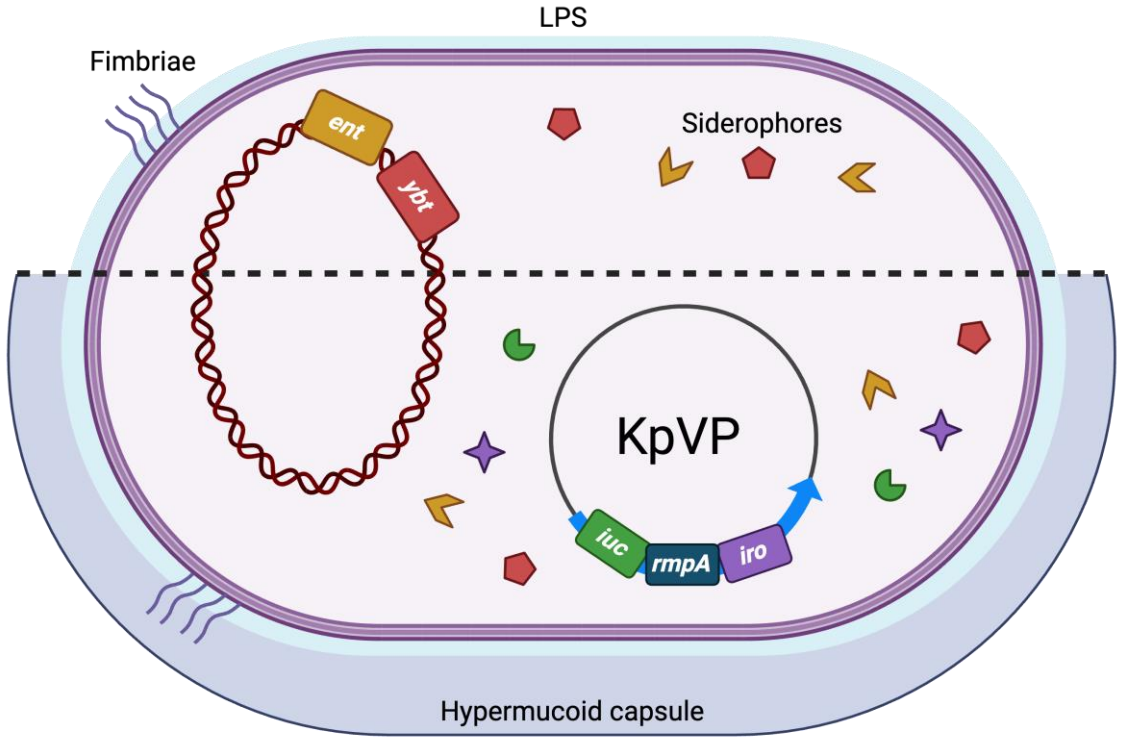
Intestinal colonization



Translocation, liver abscesses



Metastatic infections



strain

SGH10

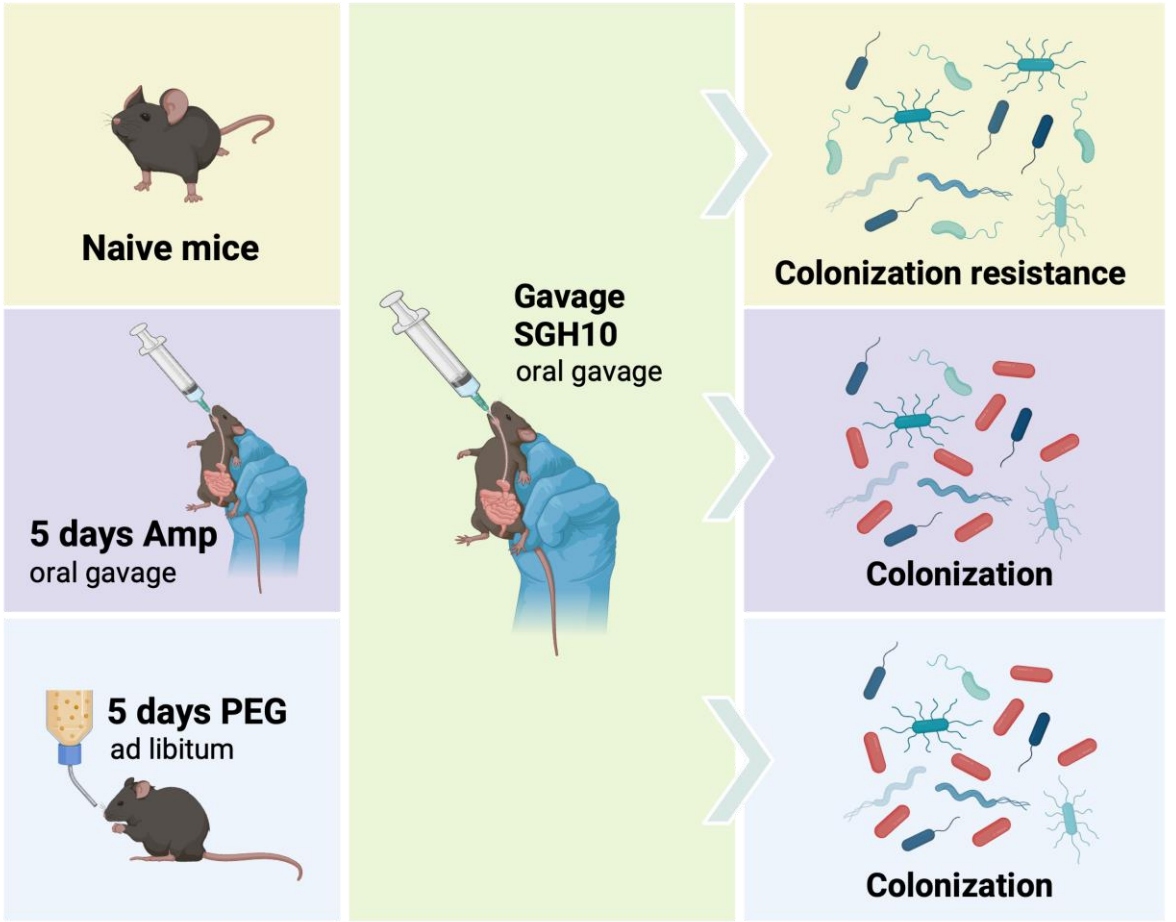
- **CG23 clade that represents >80% of Hv*Kp* strains that cause liver abscesses**
- **ST23 , K1 capsular strain**
- **Harbors virulence plasmid**

Introduction – Studying intestinal Hv*Kp* colonization

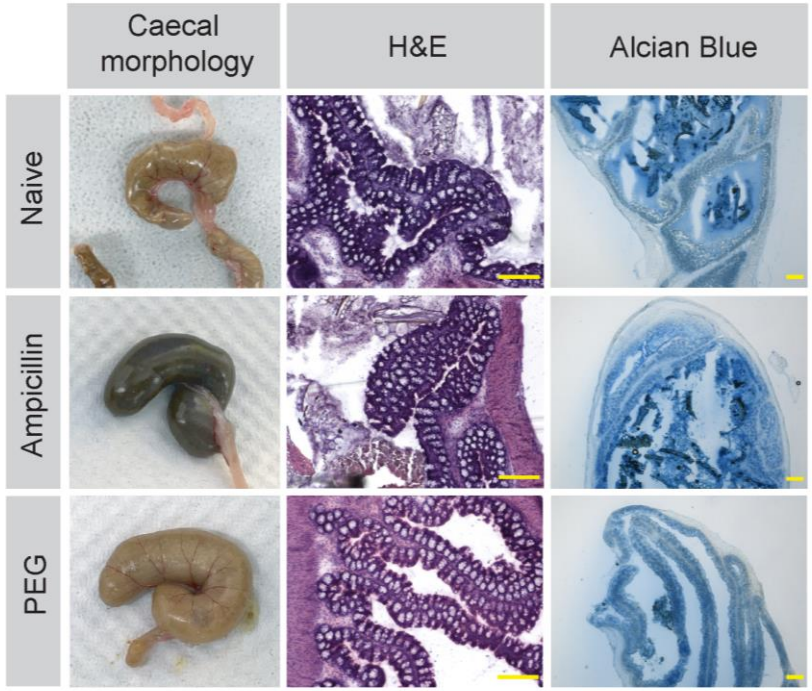
- **Gut carriage rates of hv*Kp* :**
  - Healthy donor gut, **4%–5.19%** (Yang et al, 2022, China)
  - Diarrheal patients, **7.8 %** (Zhang et al, 2018, China)
  - Hypervirulent K1 in the community, **4.5%** (Siu et al., 2011, Hong Kong, Taiwan, Singapore)

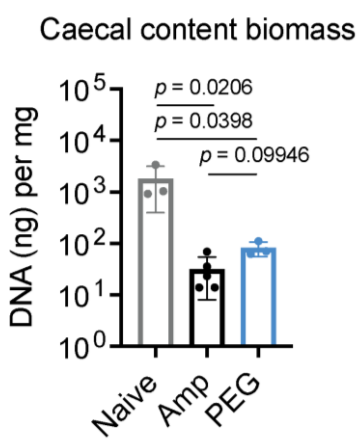
- **Naïve mice cannot be colonized with SGH10 due to colonization resistance from an intact microbiome**

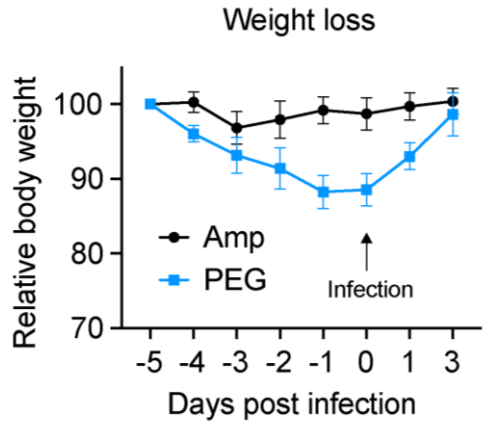
- **We used two models of gut perturbation to allow SGH10 to colonize**
  - Antibiotic perturbation (Ampicillin)
  - Osmotic perturbation (PEG3350)

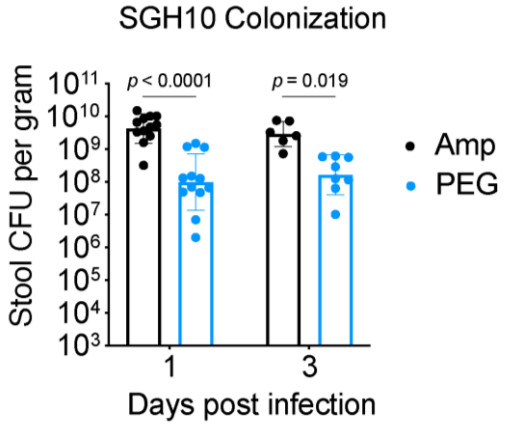


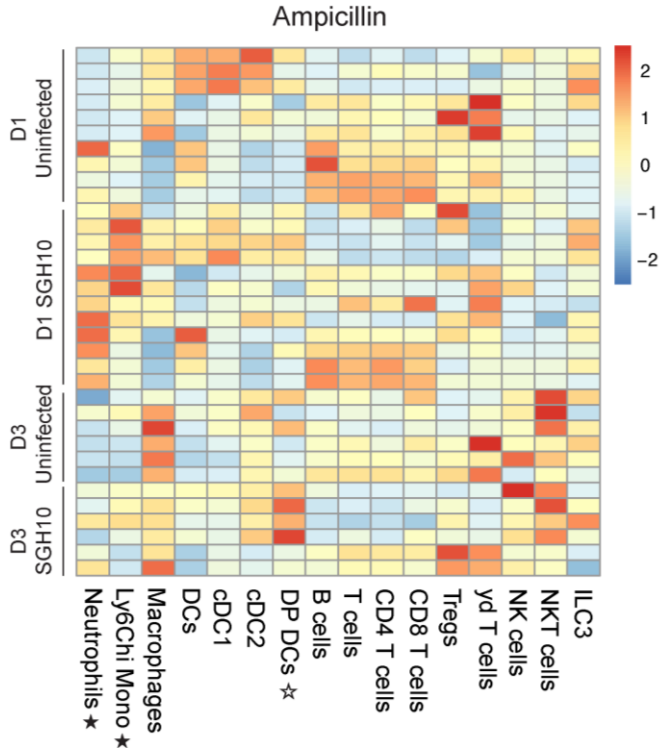
Characterizing the two models of perturbation

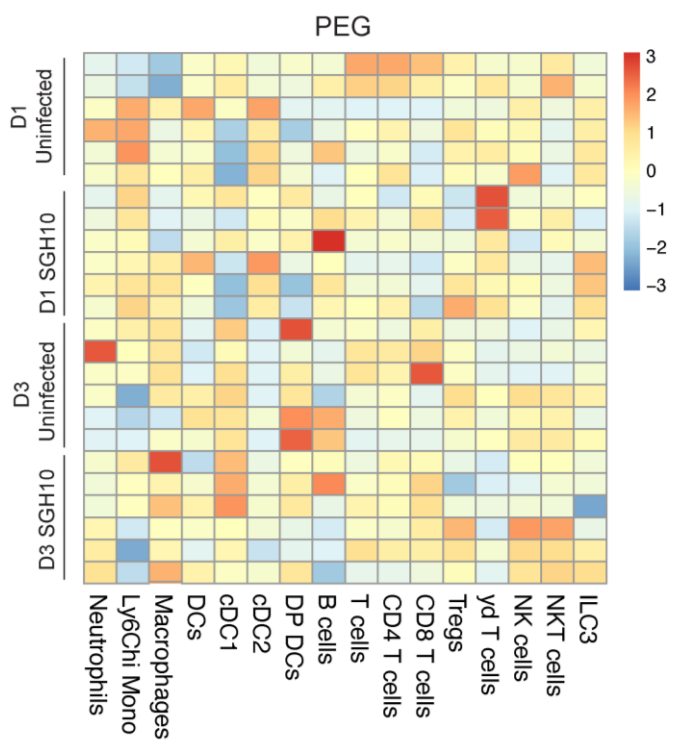








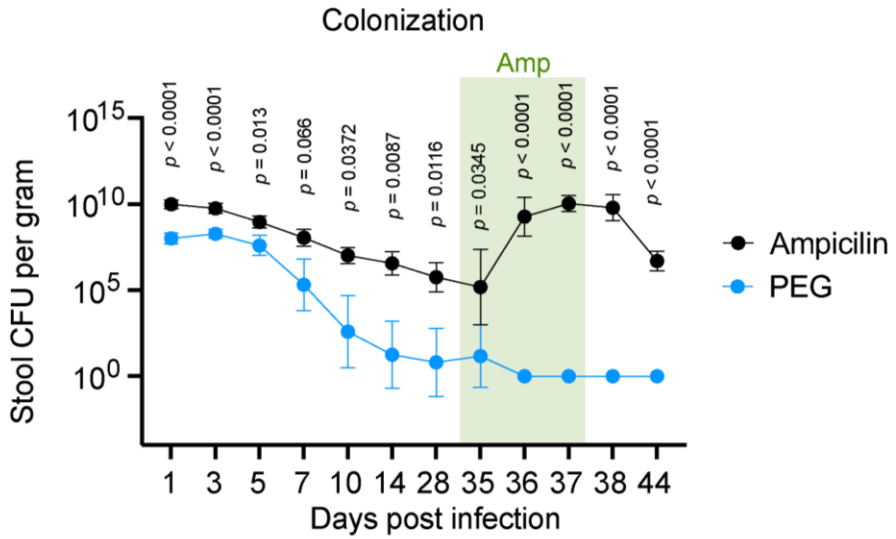


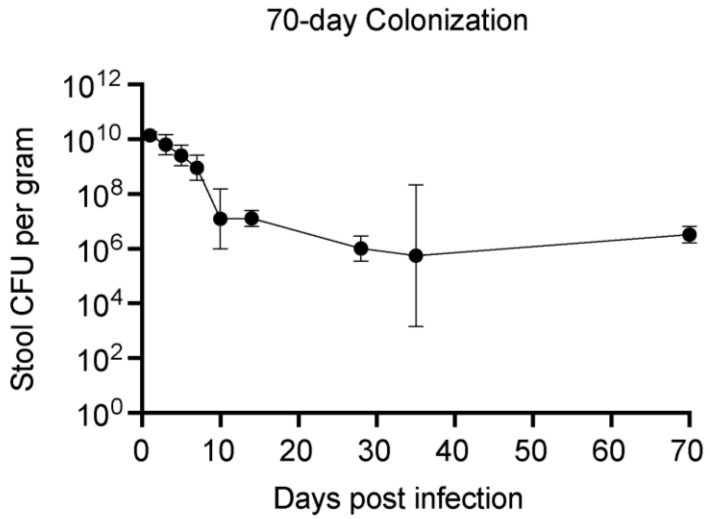


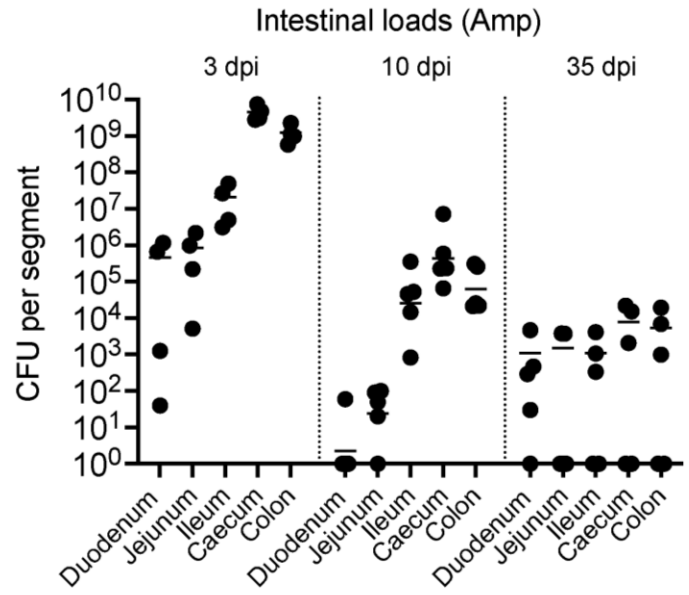
- Ampicillin and PEG models allow for bacterial colonization
- Ampicillin-mediated colonization leads to acute and transient inflammation in colon

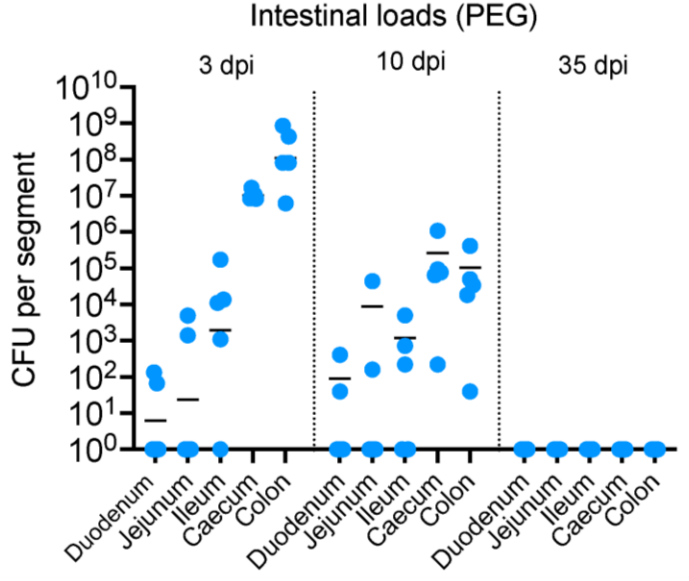
★ denotes significance

Amp permits SGH10 persistence while PEG promotes decolonization

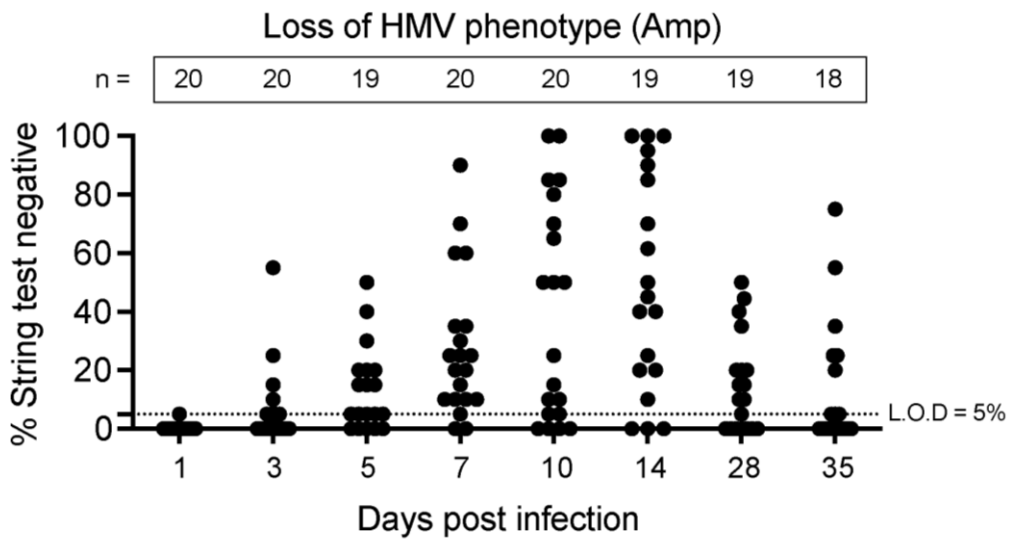


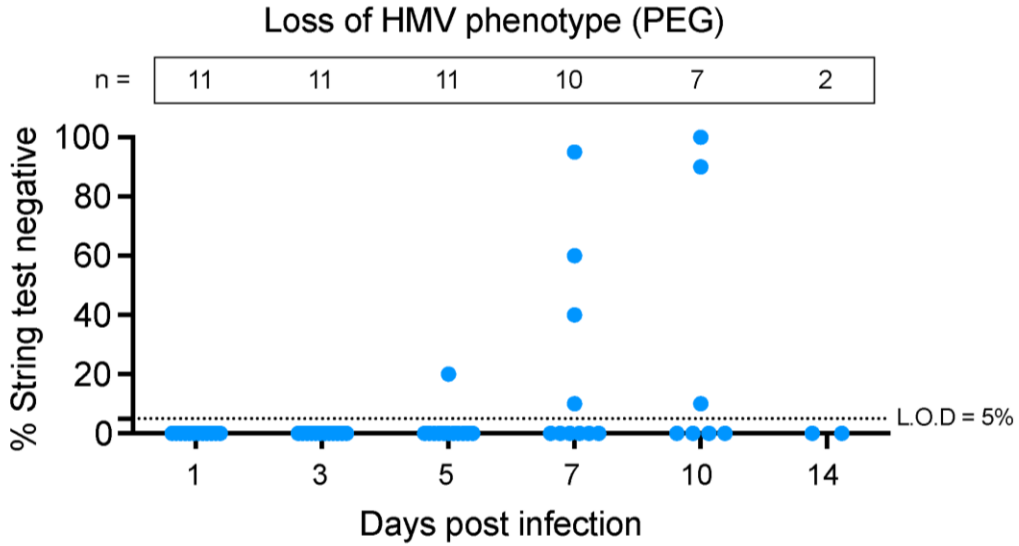


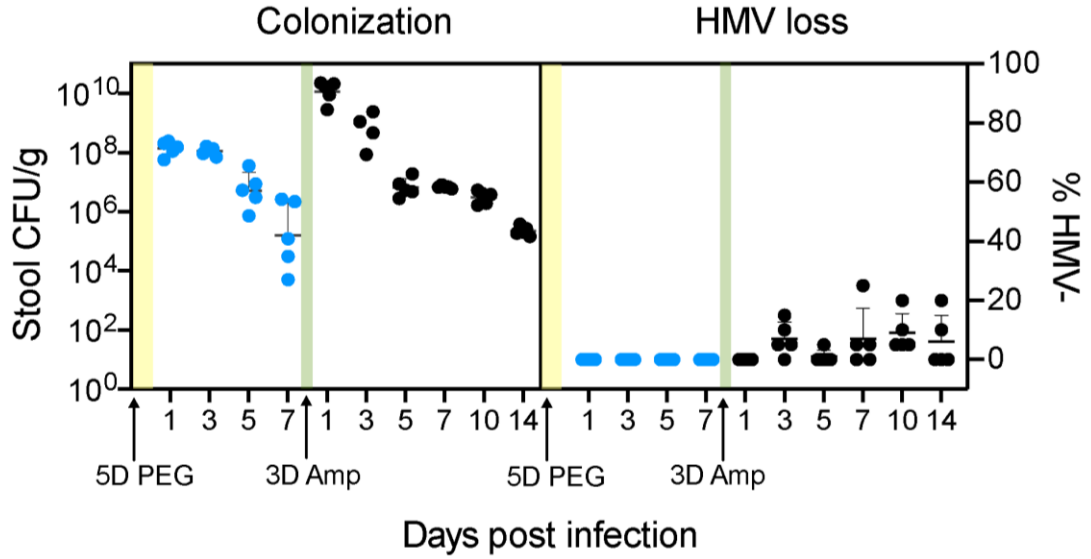




Hypomucoid variants accumulate in Amp-mediated colonization



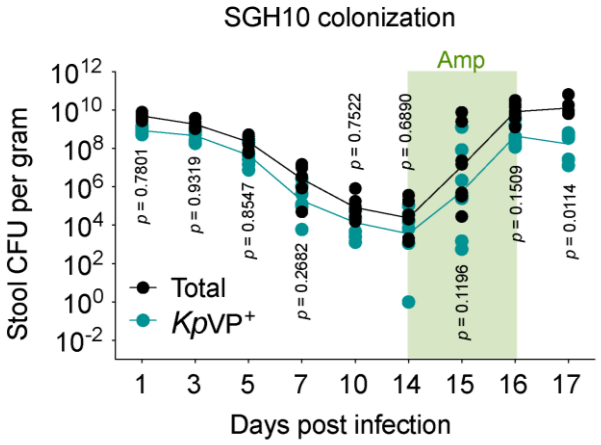


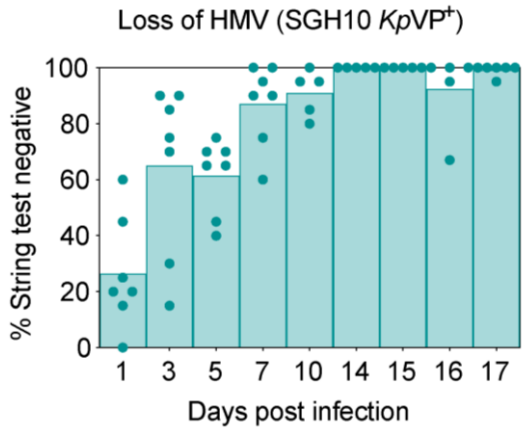


- String-test was used to check for HMV status of stool colonies
- Amp-mediated colonization favours emergence of hypomucoid phenotype

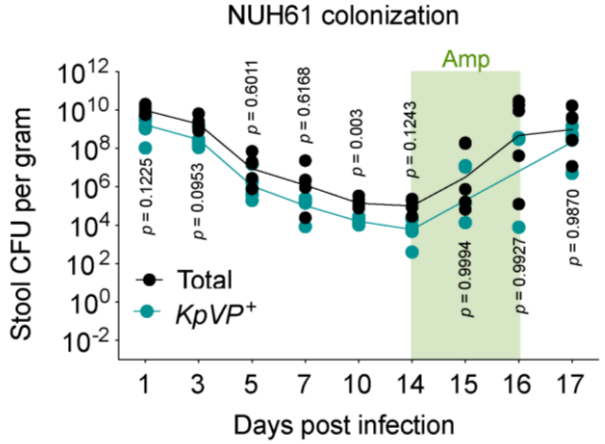
Hypomucoid variants also emerge in other hv*Kp* strains

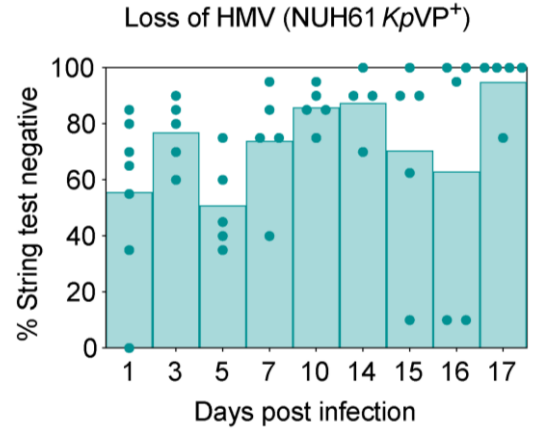
SGH10: K1 capsule
rmpA encoded on *Kp*VP



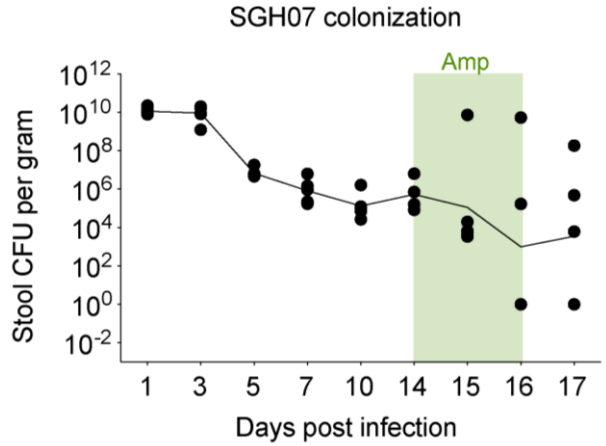


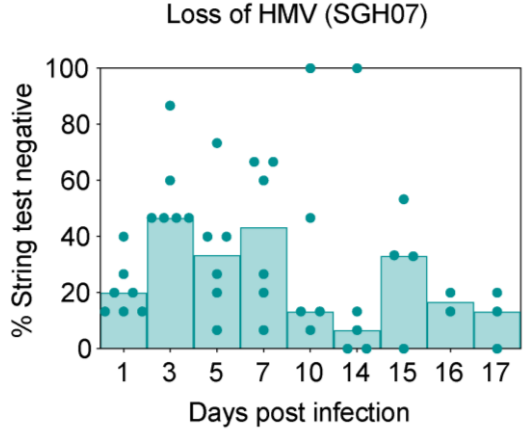
NUH61: K2 capsule
rmpA encoded on *Kp*VP





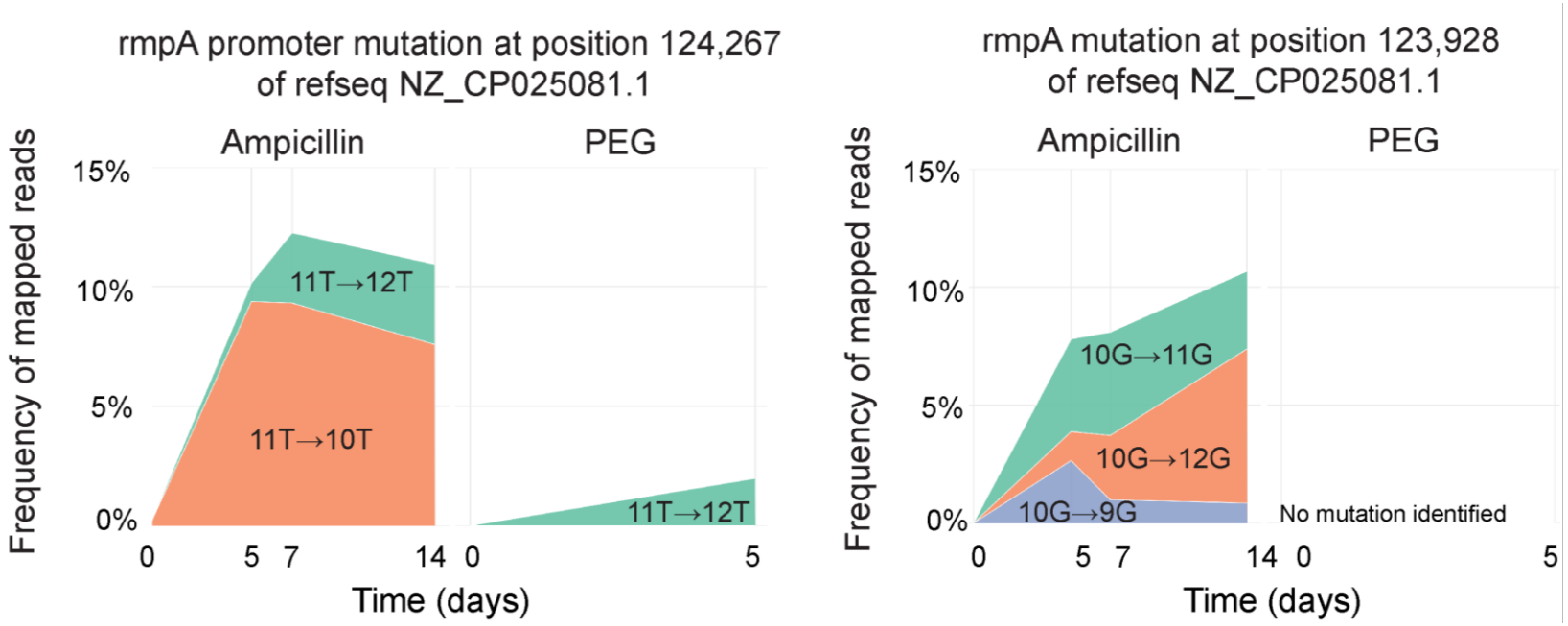
SGH07: K5 capsule
rmpA encoded on *chromosome*

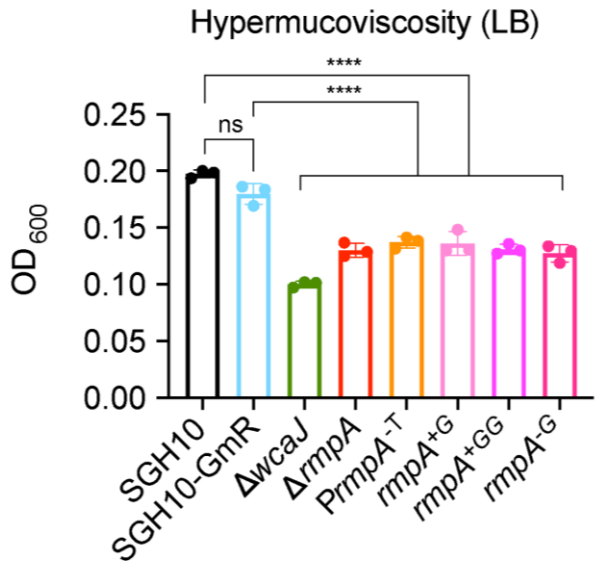




- *Kp*VP plasmid loss is maintained at around 10%, hypomucoid variants still arise in population that retains plasmid
- Hypomucoid variant emergence also occurs in other strains

rmpA promoter and CDS mutations are associated with Amp-mediated colonization

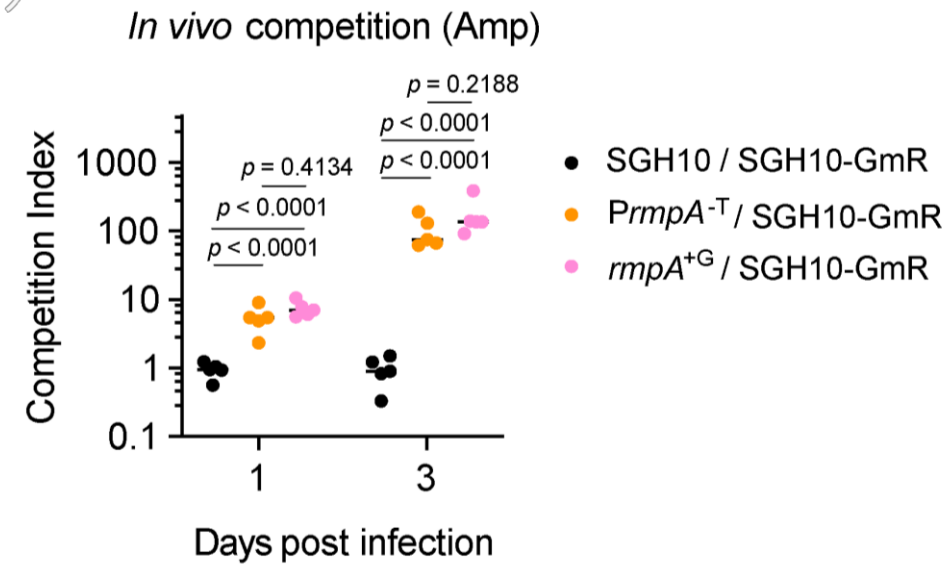


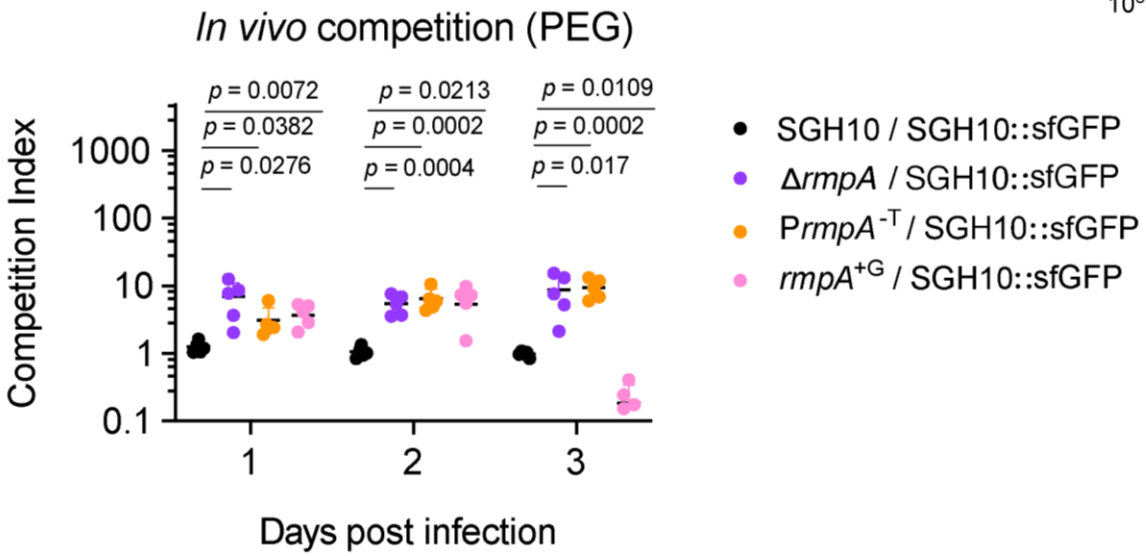


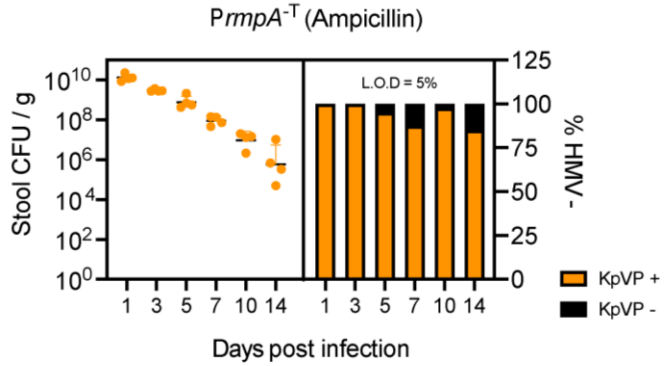
- Promoter mutation in PolyT region (11T→10T)
- CDS mutations in PolyG region (10G→9/11/12G, frameshift mutation)

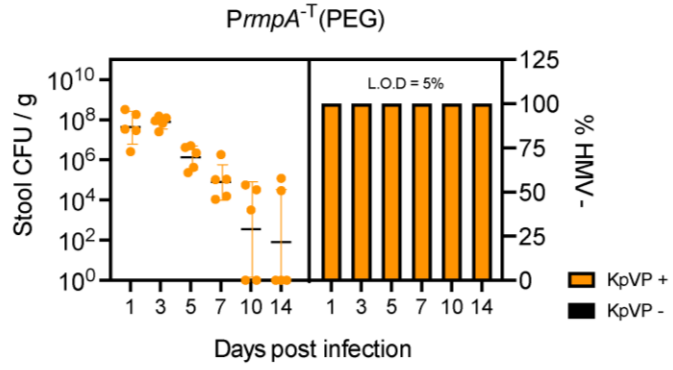
- Both mutations were associated only with Amp-mediated colonization and did not occur in PEG-mediated colonization

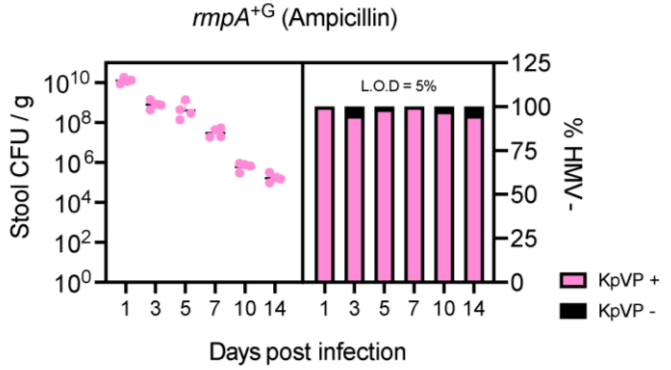
rmpA mutants have a greater competitive advantage in Amp-treated gut

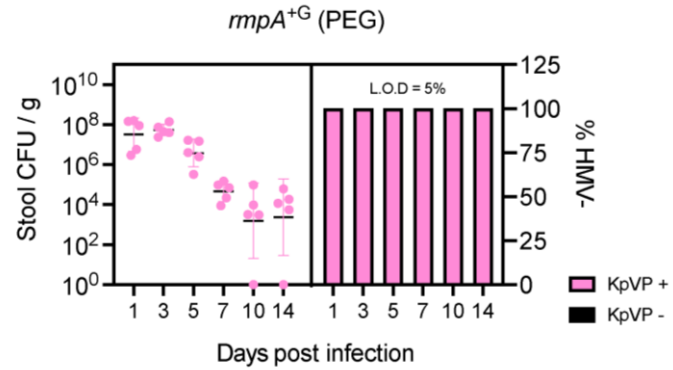








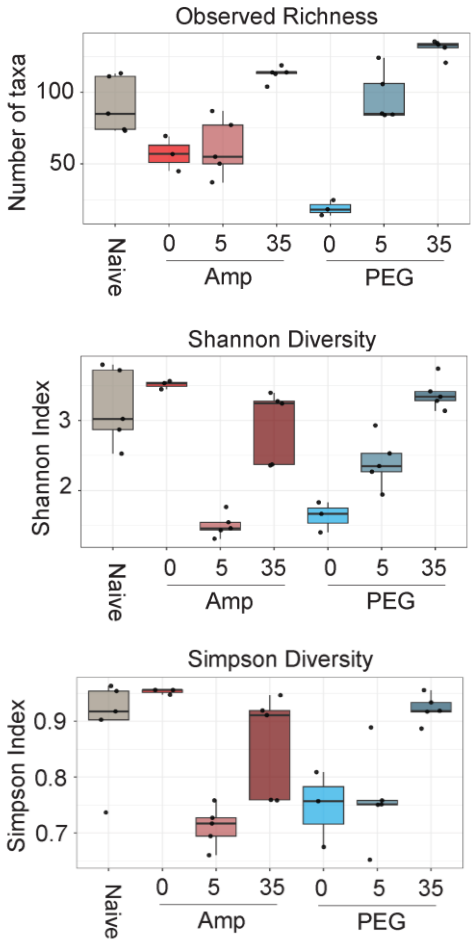


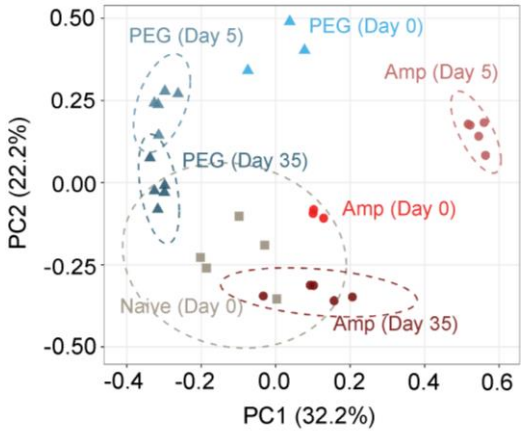


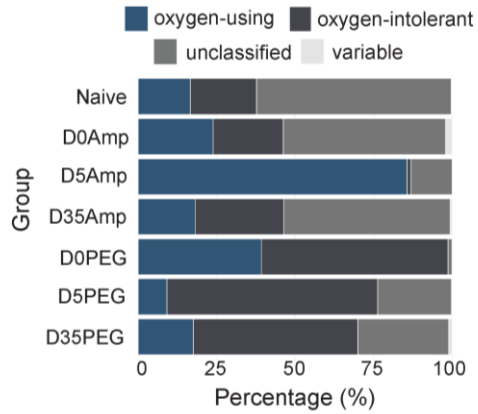
- *rmpA* mutants had significantly greater competitive advantage in Amp-treated gut
- We did not detect any revertant to wildtype in these experimental condition

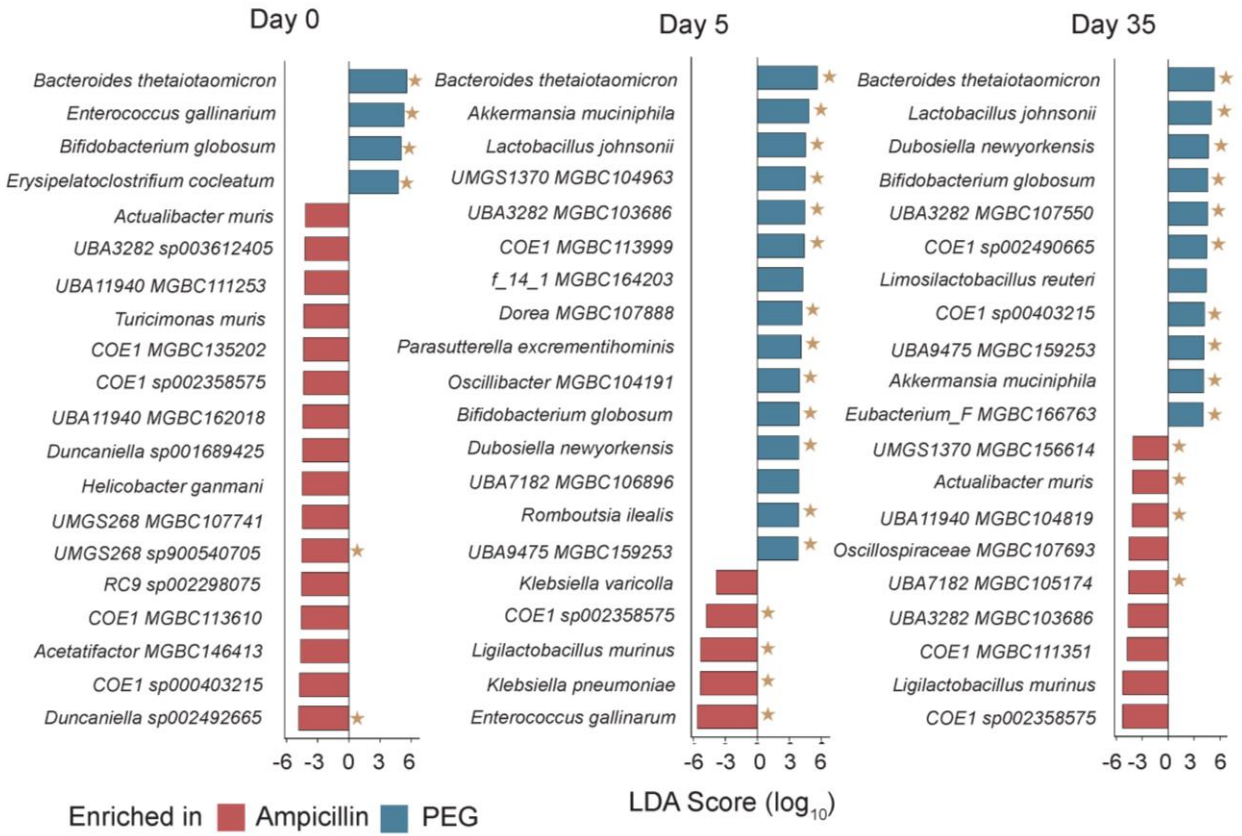
Different perturbations result in distinct community compositions

- Ampicillin-mediated colonization skewed towards Firmicutes and oxygen-using Proteobacterial bloom
- PEG-mediated colonization favoured Bacteroidota dominance, oxygen-intolerant anaerobes



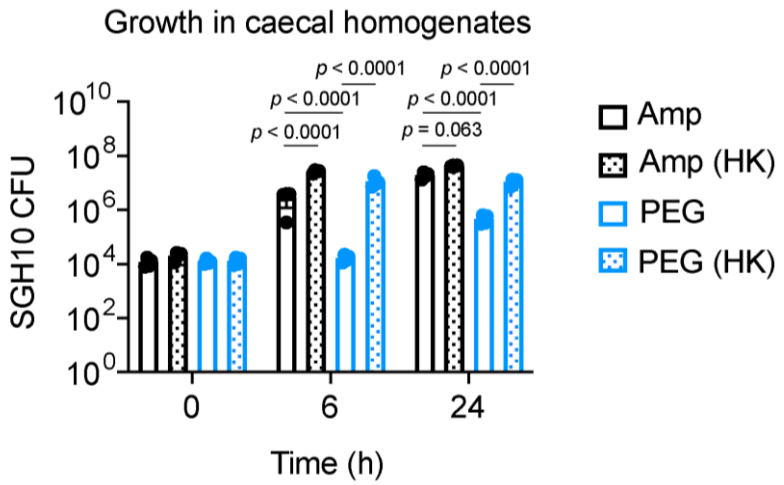


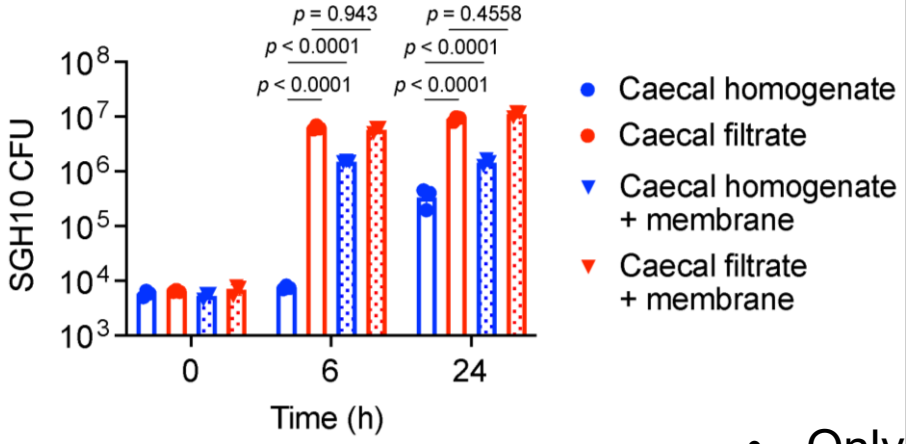


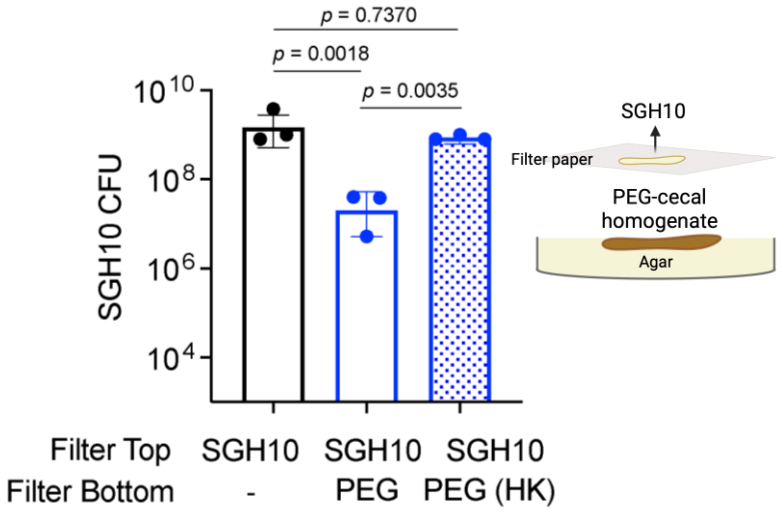


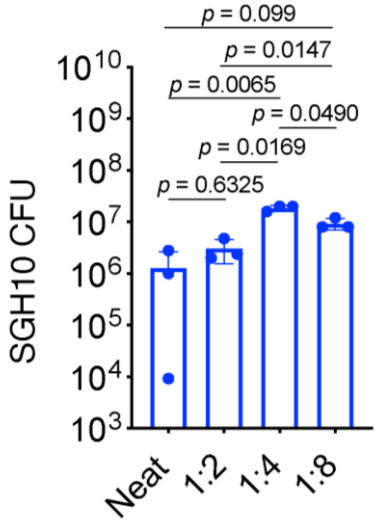
Live PEG-mediated microbiome community mediates SGH10 inhibition

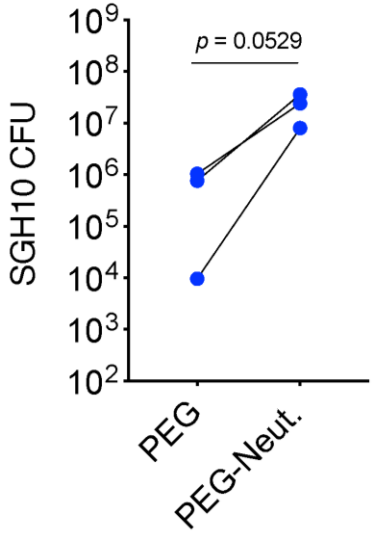
HK : heat-killed







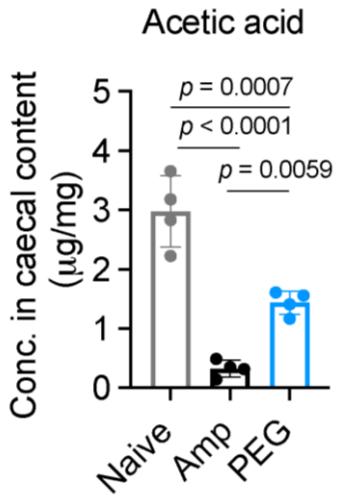


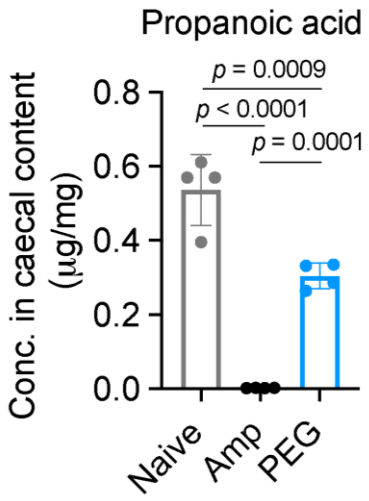


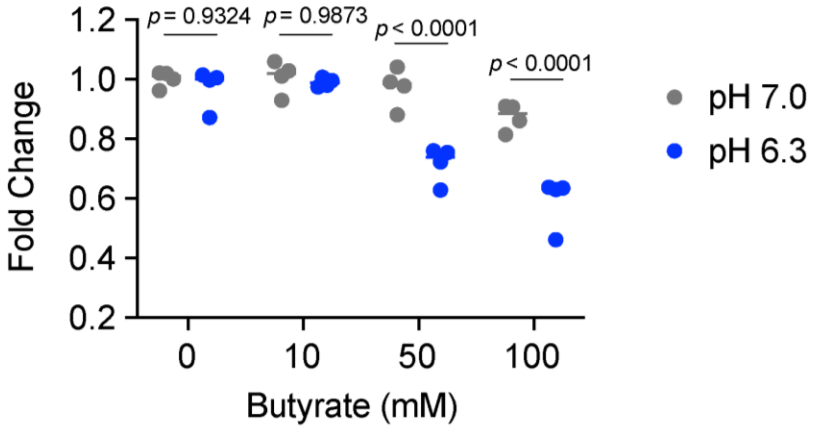
- Only live PEG-communities could inhibit SGH10
- PEG-mediated inhibition :
  - Was not due to nutrient limitation
  - May require close proximity but did not require direct contact
  - Was lifted by neutralization of PEG-cecal homogenate spent filtrates

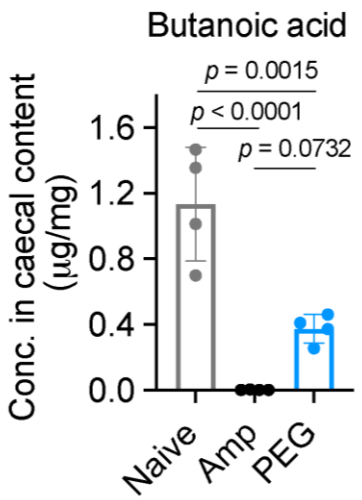
Higher SCFA production in PEG-treated ceca may inhibit SGH10 and *rmpA* mutants

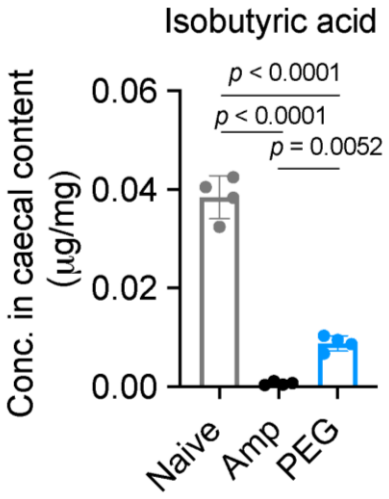
- PEG-treated gut contains many SCFA-producing species
- Higher SCFA production in PEG-treated ceca
- Butyrate was able to inhibit SGH10
- *rmpA* mutants were more susceptible to SCFA inhibition

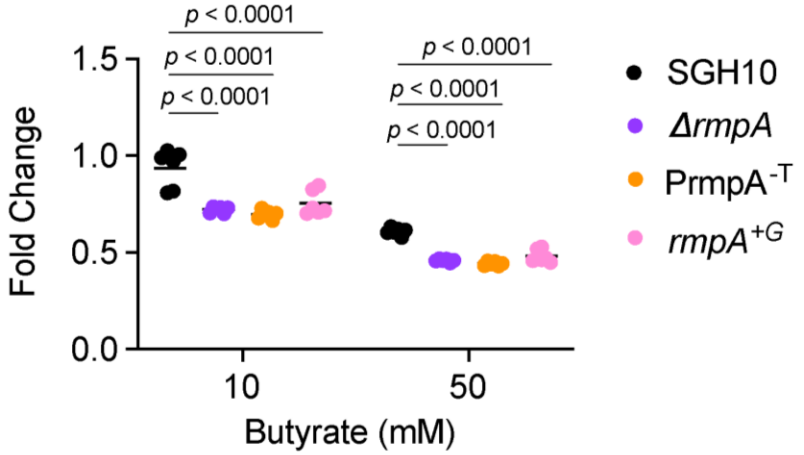












Summary

- Different transient physiological perturbations of the gut such as ampicillin or osmotic laxative exposure result in hypervirulent *K. pneumoniae* colonisation persistence or decolonisation respectively.

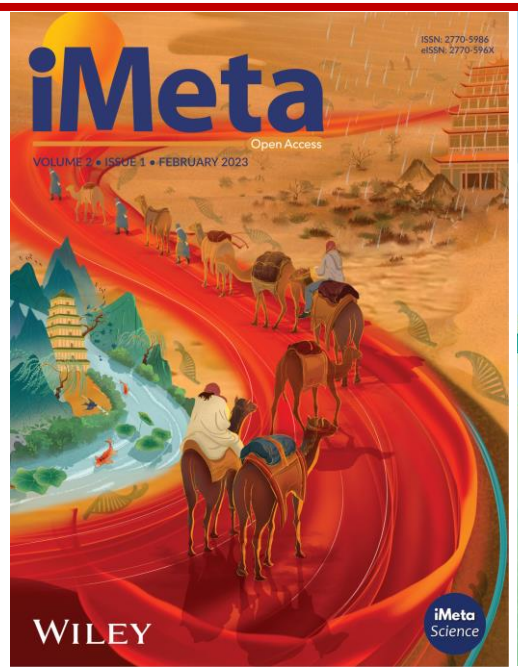
- Ampicillin exposure favours the emergence of hypomucoid variants through promoter polyT and coding sequence polyG contraction/expansion in the *rmpA* gene.

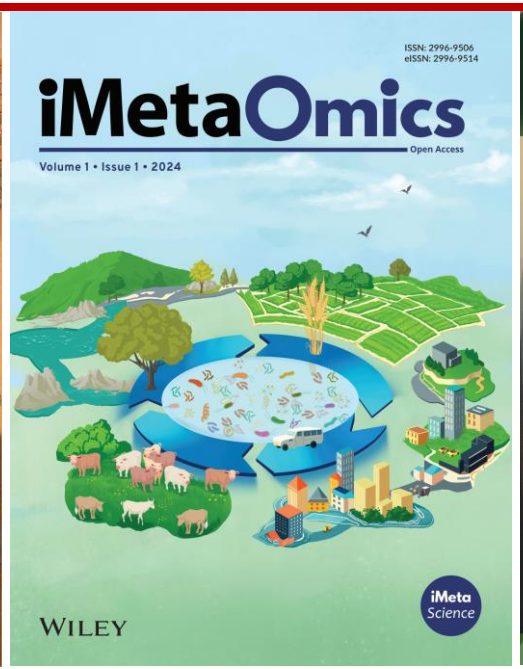
- Short-chain fatty acids produced by gut microbiome from laxative-exposed gut microbiome may help constrain the expansion of *rmpA* hypomucoid variants.

Carey Lim, Jialing Zheng, Guoxiang Cheam, Melvin Yong, Hanrong Chen, Andrew Ting, Yahua Chen, et al. 2026. Different gut microbiome dysbioses impact the evolutionary fate of hypervirulent *Klebsiella pneumoniae*. ***iMeta*** 5: e70175.
https://doi.org/10.1002/imt2.70175

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