

# *Escherichia coli* ST131: a versatile multidrug-resistant pathogen in and outside the gut

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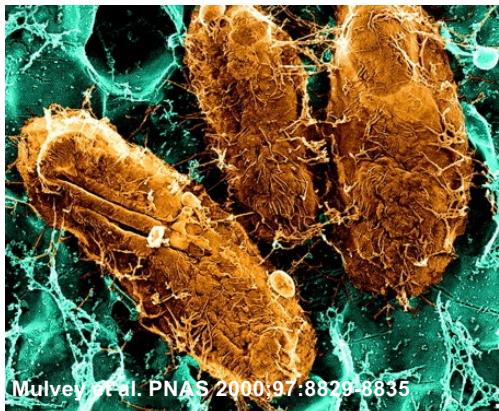


## 1. The Problem:



## Urinary Tract Infections (UTIs)

### 2. The Culprit:

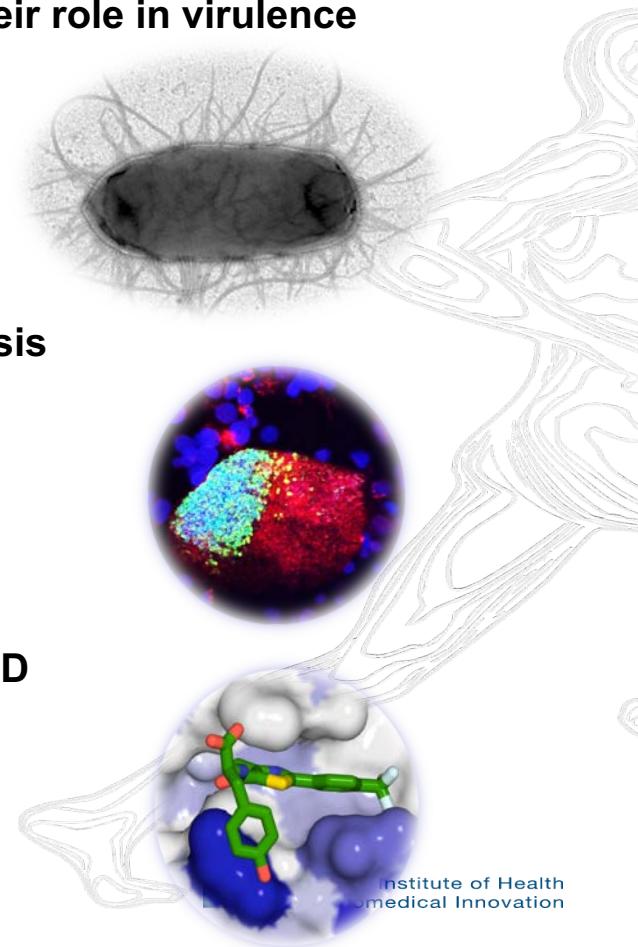


Mulvey et al. PNAS 2000;97:8829-8835

*Escherichia coli* (UPEC)

## 3. The Research:

### ◆ UPEC adhesins and their role in virulence



### ◆ MDR UPEC pathogenesis

### ◆ Anti-virulence drug R&D

# WHO Priority Pathogens List for New Antibiotics

## Priority 1: CRITICAL<sup>#</sup>

*Acinetobacter baumannii*, carbapenem-resistant  
*Pseudomonas aeruginosa*, carbapenem-resistant  
*Enterobacteriaceae\**, carbapenem-resistant, 3<sup>rd</sup> generation cephalosporin-resistant

## Priority 2: HIGH

*Enterococcus faecium*, vancomycin-resistant  
*Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant  
*Helicobacter pylori*, clarithromycin-resistant  
*Campylobacter*, fluoroquinolone-resistant  
*Salmonella* spp., fluoroquinolone-resistant  
*Neisseria gonorrhoeae*, 3<sup>rd</sup> generation cephalosporin-resistant, fluoroquinolone-resistant

## Priority 3: MEDIUM

*Streptococcus pneumoniae*, penicillin-non-susceptible  
*Haemophilus influenzae*, ampicillin-resistant  
*Shigella* spp., fluoroquinolone-resistant

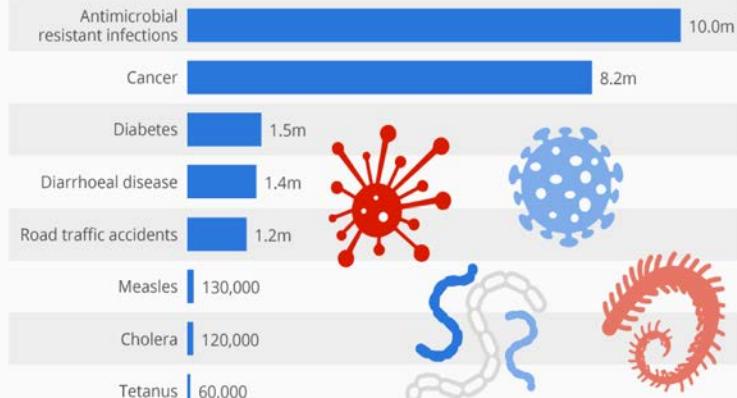
# AMR: A Political Priority

- *A global public health crisis*
- *Common infections once again lethal*



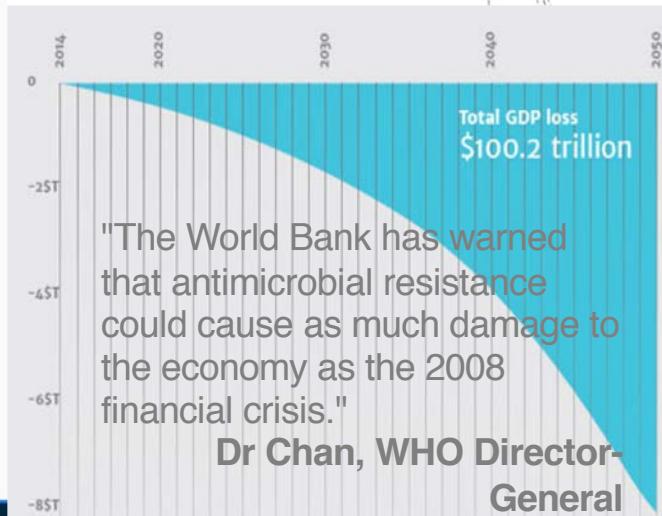
### Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



@StatistaCharts

Source: Review on Antimicrobial Resistance



Dr Chan, WHO Director-General

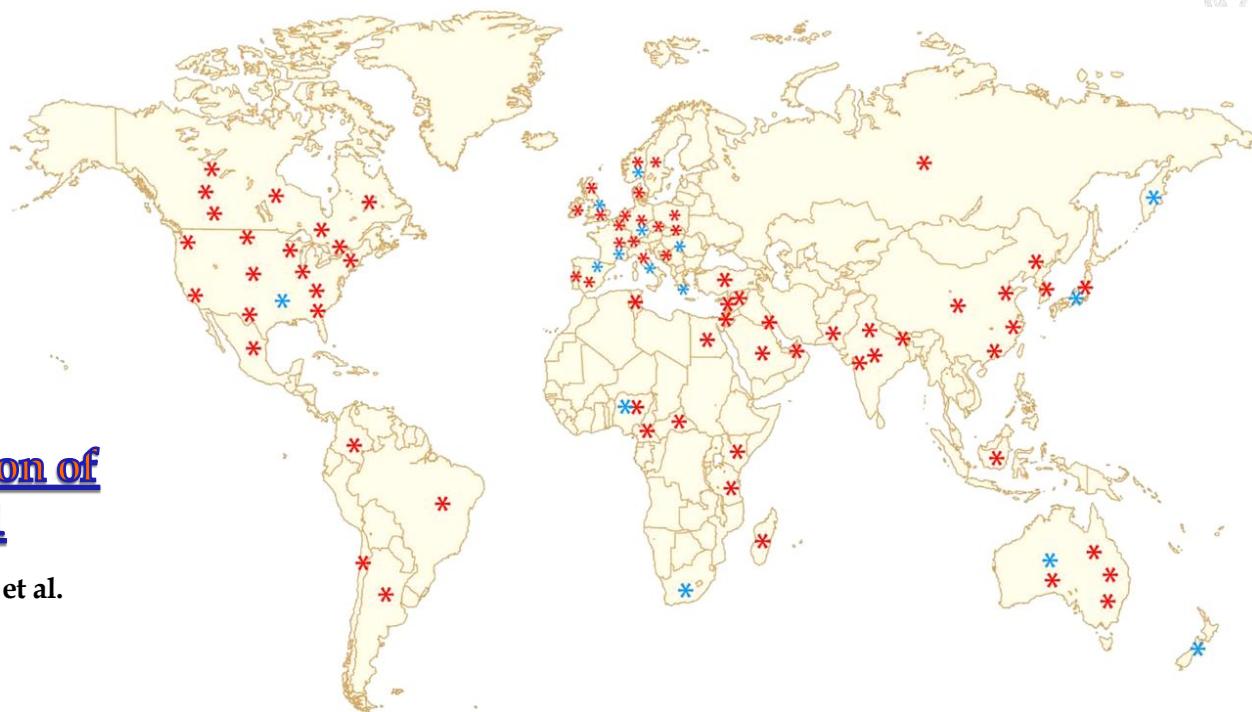
# *E. coli* ST131

*- the new global face of UPEC -*

- Recently emerged
- Multidrug resistant

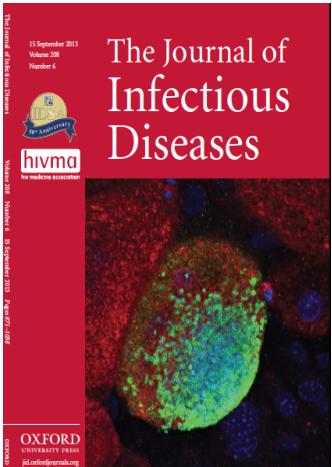
Pandemic

Virulent pathogen



2013 -  
Global  
Dissemination of  
*E. coli* ST131

Nicolas-Chanoine M et al.  
Clin. Microbiol. Rev.  
2014;27:543-574

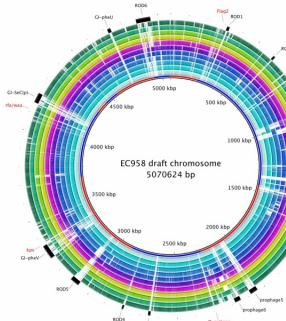


Totsika et al 2013 JID 208 (6)

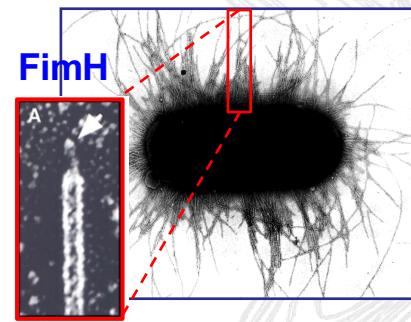


# Urinary Tract Infections (UTIs)

- *E. coli* ST131: are proficient MDR uropathogens
  - FimH adhesin : key driver for acute and chronic cystitis
  - FimH inhibitors : effective prophylaxis & treatment of cystitis in preclinical models
    - Clinical development of the first anti-adhesion therapeutics for drug resistant UTIs (Fimbrion-GSK)



Totsika et al PLoS One 2011



**FIMBRION**  
THERAPEUTICS

# Increasing prevalence of MDR *E. coli* in the gut

- significant clinical implications
- intestinal reservoir overlooked
- factors largely unknown

MAJOR ARTICLE

JID 2015:212 (15 December)

## Gut Colonization of Healthy Children and Their Mothers With Pathogenic Ciprofloxacin-Resistant *Escherichia coli*

Emily A. Gurnee,<sup>1,a</sup> I. Malick Ndao,<sup>1</sup> James R. Johnson,<sup>3,4</sup> Brian D. Johnston,<sup>3,4</sup> Mark D. Gonzalez,<sup>2</sup> Carey-Ann D. Burnham,<sup>2</sup> Carla M. Hall-Moore,<sup>1</sup> Jessica E. McGhee,<sup>1,a</sup> Alexander Mellmann,<sup>5</sup> Barbara B. Warner,<sup>1</sup> and Phillip I. Tarr<sup>1,6</sup>

J Antimicrob Chemother 2013; **68**: 562–568  
doi:10.1093/jac/dks429 Advance Access publication 9 November 2012

Journal of  
Antimicrobial  
Chemotherapy

Pediatric Infectious Disease Journal:  
May 2015 - Volume 34 - Issue 5 - p 469–475  
doi: 10.1097/INF.0000000000000623  
Original Studies

10-Fold increase (2006–11) in the rate of healthy subjects with extended-spectrum β-lactamase-producing *Escherichia coli* faecal carriage in a Parisian check-up centre

Marie-Hélène Nicolas-Chanoine<sup>1-3\*</sup>, Coraline Gruson<sup>3</sup>, Suzanne Bialek-Davenet<sup>1-3</sup>, Xavier Bertrand<sup>4</sup>, Frédérique Thomas-Jean<sup>5</sup>, Frédéric Bert<sup>1</sup>, Mati Moyat<sup>1</sup>, Elodie Meiller<sup>1</sup>, Estelle Marcon<sup>1</sup>, Nicolas Danchin<sup>5</sup>, Latifa Noussair<sup>1</sup>, Richard Moreau<sup>3</sup> and Véronique Leflon-Guibout<sup>1</sup>

Emergence of Extended Spectrum-β-Lactamase-Producing *Escherichia coli* O25b-ST131: A Major Community-Acquired Uropathogen in Infants

Cheng, Ming-Fang MD<sup>\*†</sup>; Chen, Wan-Ling MD<sup>\*‡</sup>; Hung, Wan-Yu MS<sup>§</sup>; Huang, I-Fei MD<sup>\*¶</sup>; Chiou, Yee-Hsuan MD<sup>\*†</sup>; Chen, Yao-Shen MD<sup>\*¶</sup>; Lee, Susan Shin-Jung MD<sup>\*¶</sup>; Hung, Chih-Hsin PhD<sup>§</sup>; Wang, Jui-Ling MD<sup>\*||</sup>



Clinical Microbiology and Infection

Volume 22, Issue 10, October 2016, Pages 891.e1–891.e4



Research note

High rate of faecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in healthy children in Bangui, Central African Republic

A. Farra<sup>1</sup>, T. Frank<sup>1</sup>, L. Tondeur<sup>2</sup>, P. Bala<sup>3</sup>, J.C. Gody<sup>3</sup>, M. Onambele<sup>1</sup>, C. Rafai<sup>1</sup>, M. Vray<sup>2,4</sup>, S. Breurec<sup>1,5</sup>

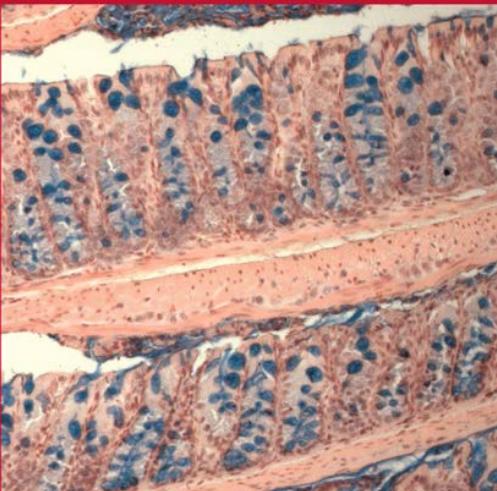
J Antimicrob Chemother 2015; **70**: 2223–2227  
doi:10.1093/jac/dkv114 Advance Access publication 9 May 2015

Journal of  
Antimicrobial  
Chemotherapy

Emergence and spread of O16-ST131 and O25b-ST131 clones among faecal CTX-M-producing *Escherichia coli* in healthy individuals in Hunan Province, China

Yi-Ming Zhong<sup>1</sup>, Wen-En Liu<sup>1,\*</sup>, Xiang-Hui Liang<sup>1</sup>, Yan-Ming Li<sup>1</sup>, Zi-Juan Jian<sup>1</sup> and Peter M. Hawkey<sup>2,3</sup>

# The Journal of Infectious Diseases



## Intestinal Colonization Traits of Pandemic Multidrug-Resistant *Escherichia coli* ST131

Sohinee Sarkar,<sup>1,2,a</sup> Melanie L. Hutton,<sup>5,6</sup> Dimitrios Vagenas,<sup>1,2</sup> Rinaldo Ruter,<sup>7</sup> Stephanie Schüller,<sup>7,8</sup> Dena Lyras,<sup>5,6</sup> Mark A. Schembri,<sup>3,4</sup> and Makrina Totsika<sup>1,2</sup>

<sup>1</sup>Institute of Health and Biomedical Innovation and <sup>2</sup>School of Biomedical Sciences, Queensland University of Technology, Queensland, Australia; <sup>3</sup>School of Chemistry and Molecular Biosciences and <sup>4</sup>Australian Infectious Diseases Research Centre, University of Queensland, Brisbane, and <sup>5</sup>Infection and Immunity Program, Monash Biomedicine Discovery Institute, and <sup>6</sup>Department of Microbiology, Monash University, Clayton, Australia; and <sup>7</sup>Gut Health and Food Safety Programme, Quadram Institute Bioscience, and <sup>8</sup>Norwich Medical School, University of East Anglia, Norwich, United Kingdom.

**Background.** Epidemiological studies point to the gut as a key reservoir of multidrug resistant *Escherichia coli* multilocus sequence type 131 (ST131), a globally dominant pathogenic clone causing urinary tract and bloodstream infections. Here we report a detailed investigation of its intestinal lifestyle.

**Methods.** Clinical ST131 isolates and type 1 fimbriae null mutants were assessed for colonization of human intestinal epithelia and in mouse intestinal colonization models. Mouse gut tissue underwent histologic analysis for pathology and ST131 localization. Key findings were corroborated in mucus-producing human cell lines and intestinal biopsy specimens.

**Results.** ST131 strains adhered to and invaded human intestinal epithelial cells more than probiotic and commensal strains. The reference ST131 strain EC958 established persistent intestinal colonization in mice, and expression of type 1 fimbriae mediated higher colonization levels. Bacterial loads were highest in the distal parts of the mouse intestine and did not cause any obvious pathology. Further analysis revealed that EC958 could bind to both mucus and underlying human intestinal epithelia.

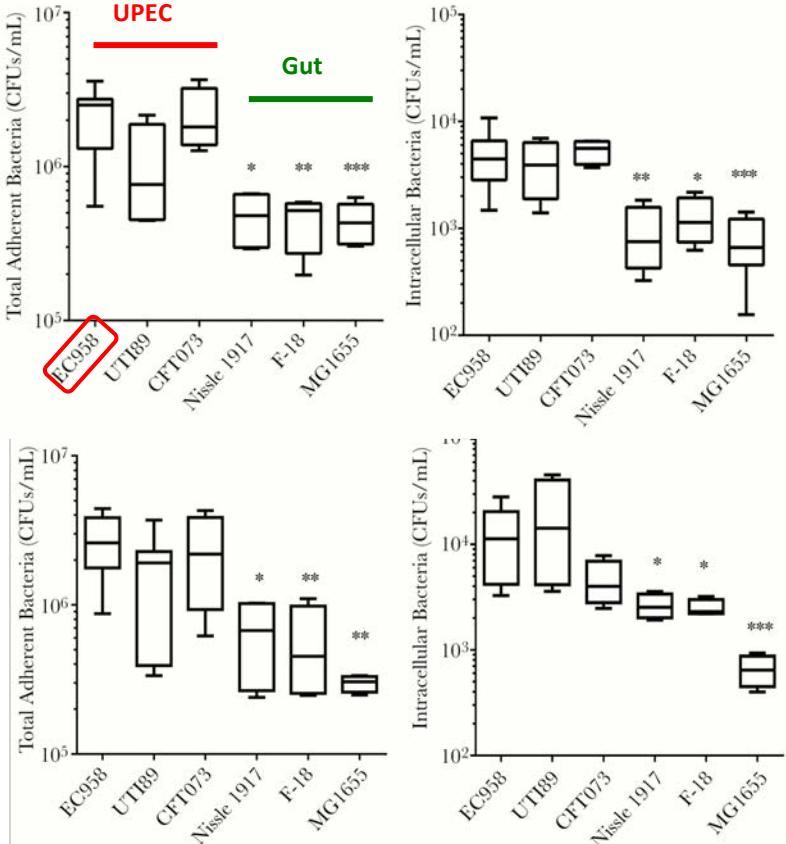
**Conclusions.** ST131 strains can efficiently colonize the mammalian gut and persist long term. Type 1 fimbriae enhance ST131 intestinal colonization, suggesting that mannoses, currently developed as therapeutics for bladder infections and Crohn's disease, could also be used to limit intestinal ST131 reservoirs.

**Keywords.** *E. coli* ST131; intestinal colonization; type 1 fimbriae; *fimH*; multidrug resistance.

# UPEC adhere and invade into human intestinal epithelial cells

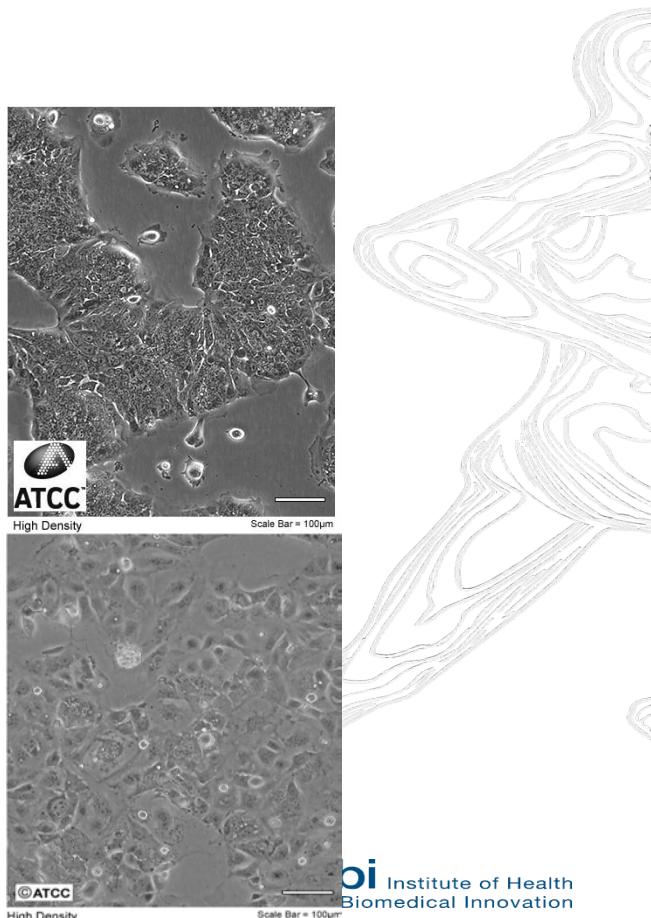
T84

ATCC: CCL-248



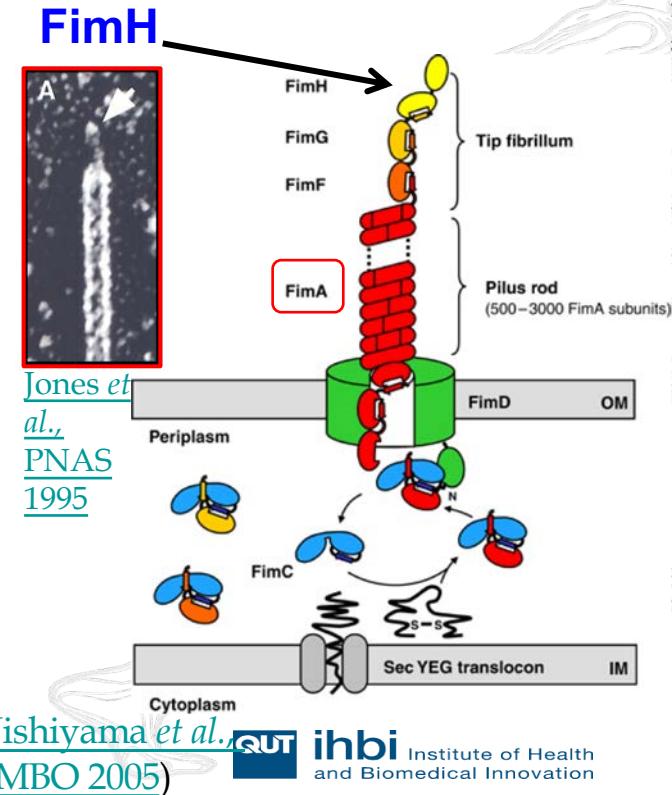
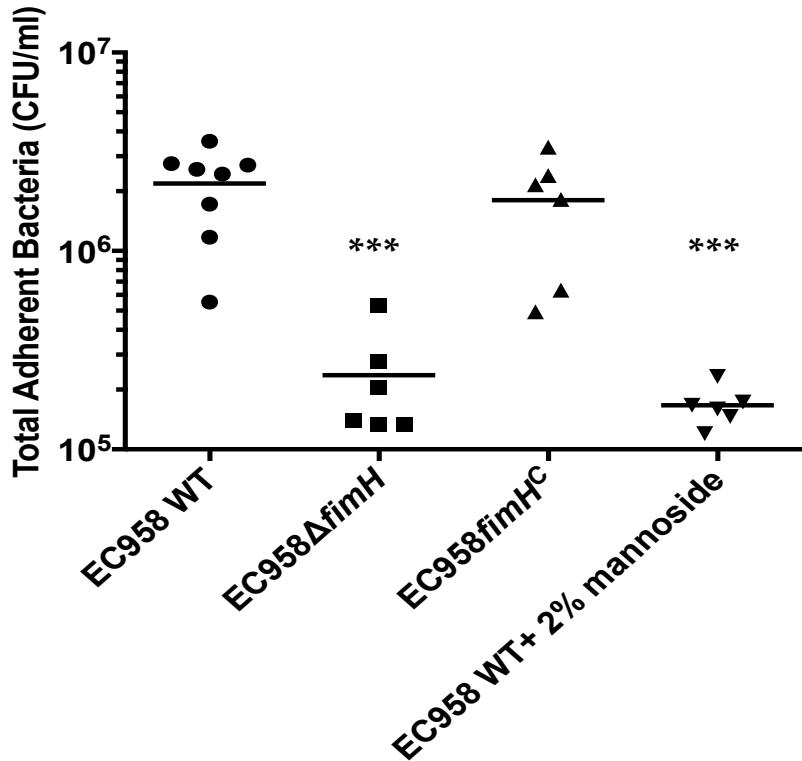
Caco-2

ATCC: HTB-37

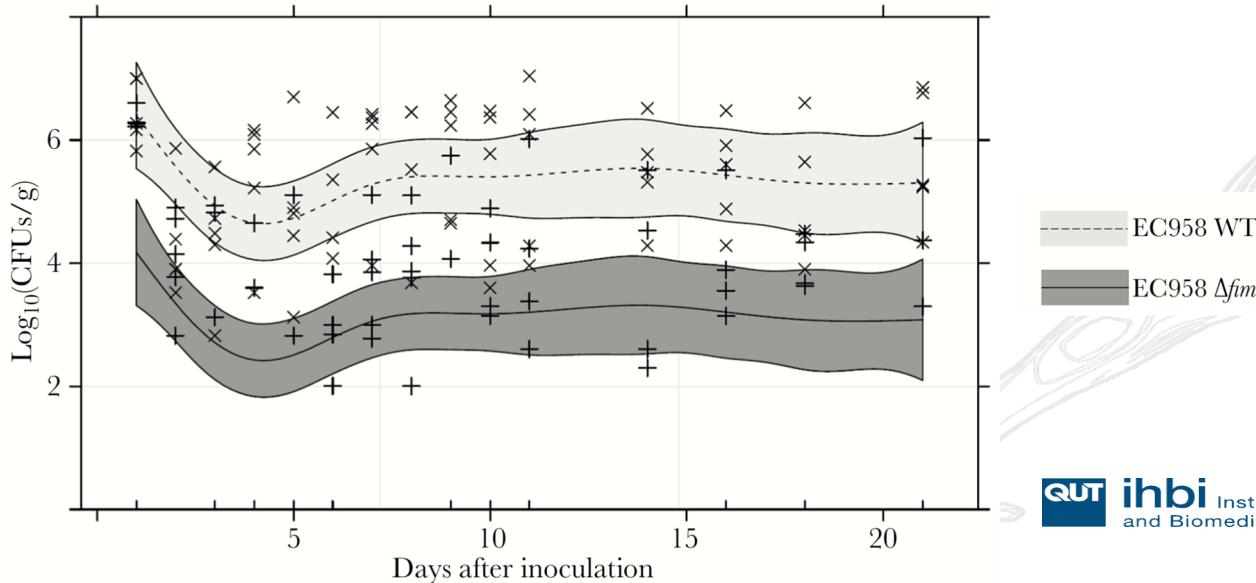
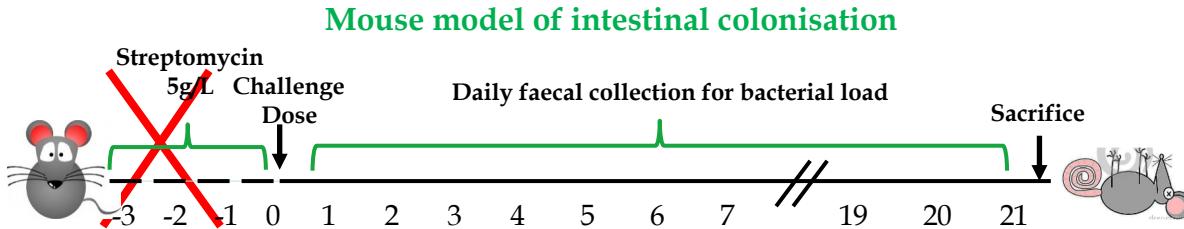


oi Institute of Health  
Biomedical Innovation

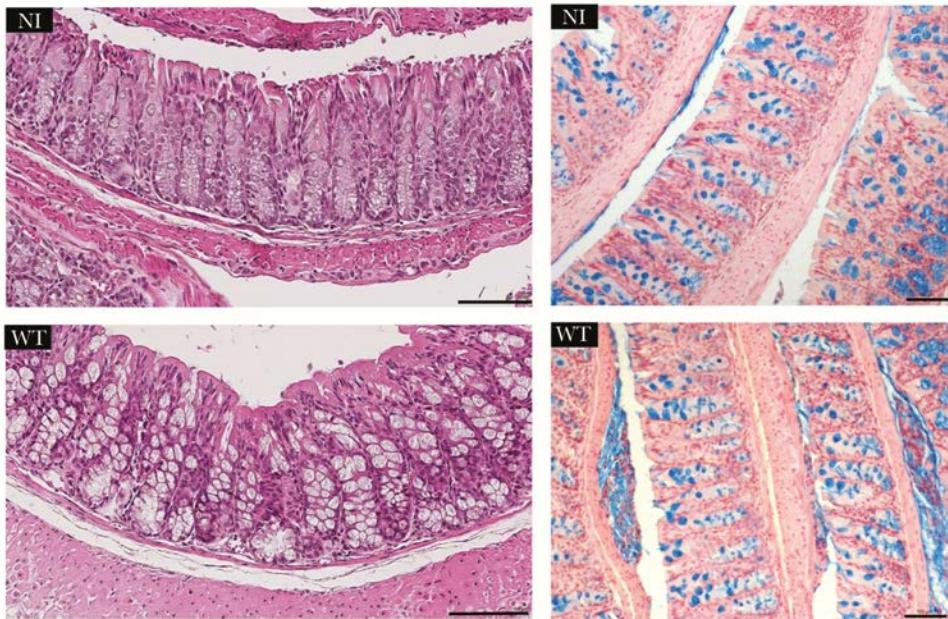
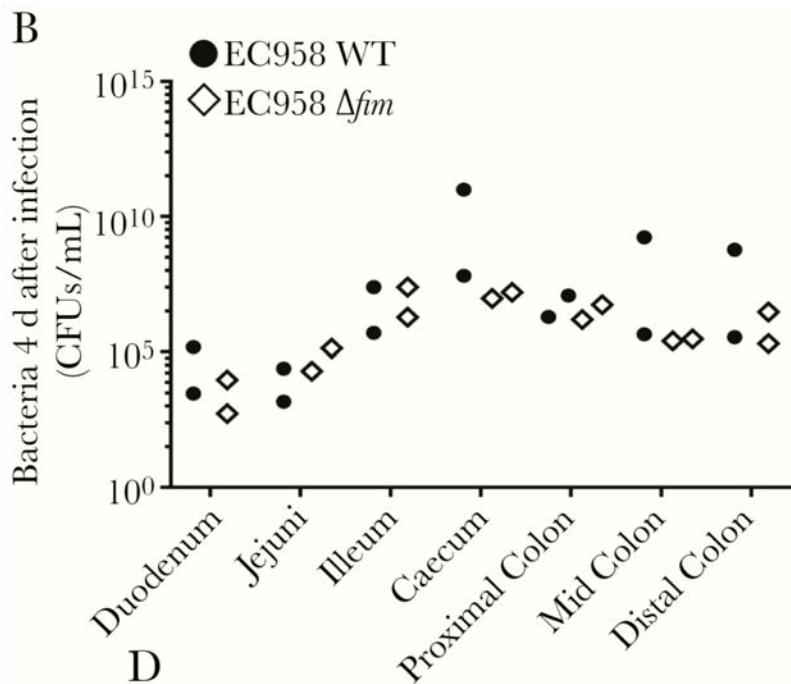
# Type 1 fimbriae and the FimH adhesin contribute to ST131 intestinal colonisation



# ST131 overcome colonisation resistance in the mouse intestine & type 1 fimbriae contribute to colonisation



# High EC958 numbers in distal parts of the mouse intestine are tolerated without obvious pathology



# Conclusions & Clinical Implications

- ST131 are proficient uropathogens and capable of overcoming colonisation resistance in the mammalian gut and persist long-term
- ST131 are dependent on the FimH adhesin for successful colonisation in and out of the gut
- FimH antagonists could serve as therapeutics for prevention and treatment of UTIs, Crohn's and IBD

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