SMT19969
A Selective Therapy for *C. difficile* Infection

Antibiotics 2015

September 14th, 2015

summit plc

SMT19969: A Selective Therapy for CDI

Novel antimicrobial with potential to significantly reduce recurrent CDI

- Potent, bactericidal inhibition of *C. difficile*
- Highly targeted spectrum of activity
- Superior to comparators in the hamster model of CDI

QIDP and Fast Track status granted

- 5 years additional market exclusivity

Phase 1 clinical trial completed

- SMT19969 considered safe and well tolerated at all administered doses
- GI restricted: Oral dosing associated with negligible systemic exposure
- Minimal effects against gut flora in humans

Phase 2 proof-of-concept clinical trial recruitment complete

- Top line data expected Q4 2015

Supported by wellcome trust

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CDI: A Significant Healthcare Problem

"C.difficile is an immediate public health threat that requires urgent and aggressive action"

US Department for Health and Human Services, 2013

Significant increase in global prevalence

> >900,000 cases p.a. in N. America and EU

> EUCLID Study – CDI 25% underdiagnosed

Emergence of hyper-virulent strains

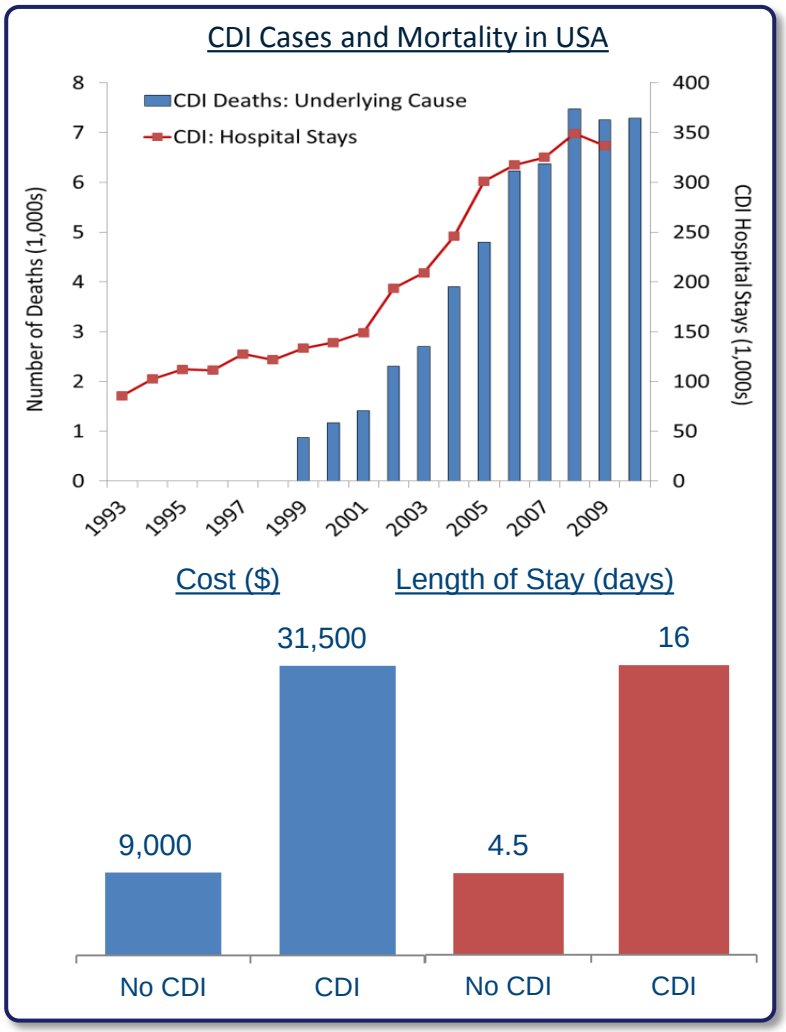
> Ribotypes 027 (US) and 078 (Europe)

Significant burden on healthcare systems

> US: $4.8bn in acute care direct cost

> Secondary CDI ≈ 3.5 fold increase in cost and length of stay

> UK: Cost of treating 2nd episode = $30,591



Healthcare Cost and Utilization Project
CDC NVSR Reports; J Pharm Pract 2013 p464

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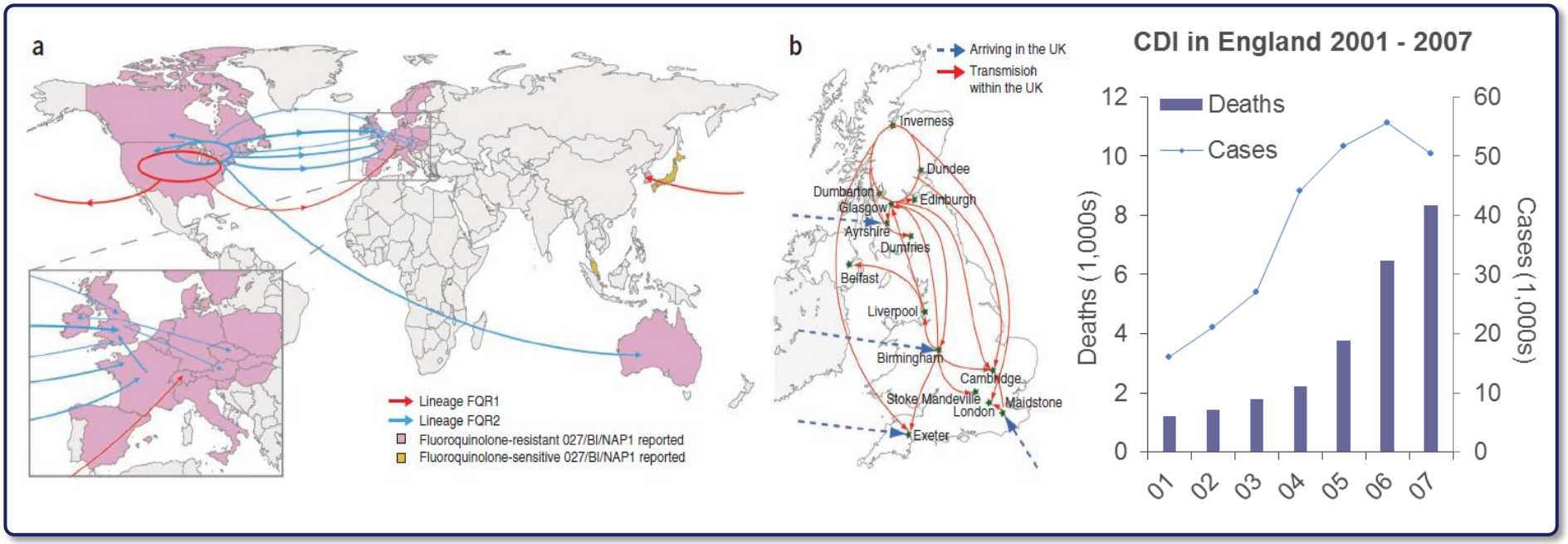
CDI: A Global Problem

Global spread driven by emergence of two distinct epidemic lineages

> FQR1 and FQR2: Fluoroquinolone resistant, hyper-virulent, ribotype 027 strains

FQR1: First large US outbreaks

FQR2: Rapid geographic spread ➔ outbreaks in UK, EU and Aus



He 2012 Nat Genetics; HPA Surveillance data

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CDI: A Global Problem

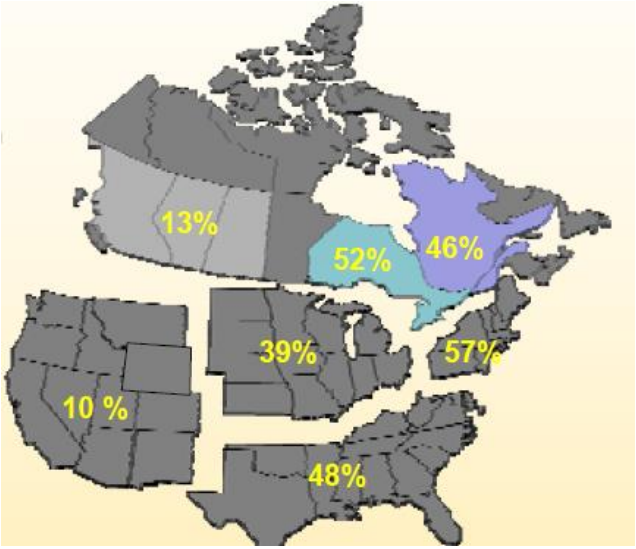
Europe: 2008 = 4.1 per 10,000 patient days ➔ 2014 = 6.6 per 10,000 patient days

Asia: CDI significantly under recognised. But look for CDI….

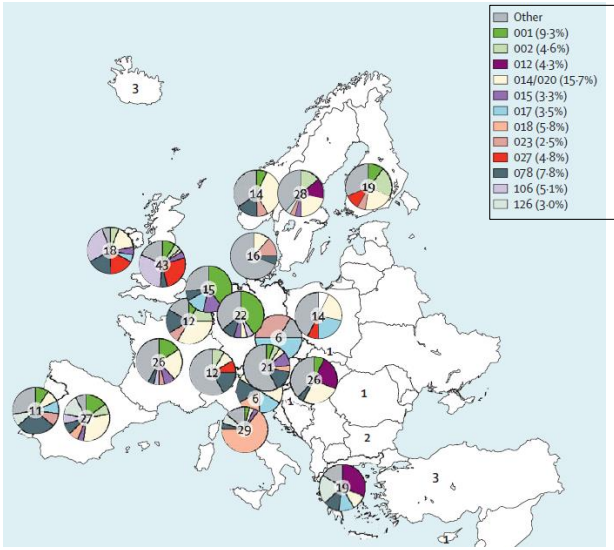
> Japan 2014 = 3.11 per 10,000 hospital days

Hyper-virulent strains continue to dominate in both US and EU

FDX Phase 3: % Isolates Typed as BI/027



EU Ribotype Distribution



Ribotype	2008	2014
014/020	16%	3%
001	10%	11%
078	8%	<1%
018	6%	3%
106	5%	<1%
027	5%	18%

Bauer 2011; Davies 2015; Takahashi 2014

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CDI: Pathogenesis

Asymptomatic colonisation following exposure to the healthcare system

> 94% of cases associated with healthcare system contact

> 75% of cases have disease onset among patients not currently hospitalized

Antimicrobial therapy resulting in gut microbiota perturbation

Spore germination ➔ overgrowth of *C. difficile* ➔ toxin production

> Colonic mucosal inflammation and symptomatic disease

Broad range of disease symptoms

> Potentially life threatening infection of the colon

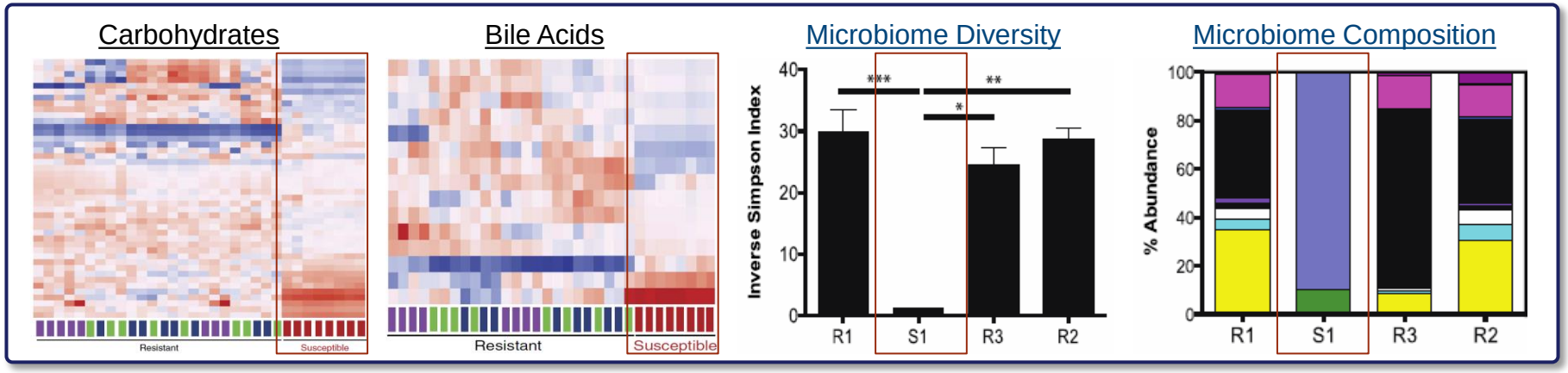
Moderate/non-severe	Severe	Severe complicated
Diarrhoea WBC < 15 Antimicrobial treatment required	Profuse diarrhoea WBC ≥ 15, SCr ≥ 1.5x baseline Abdominal pain	Hypotension, fever > 38.5°C, WBC ≥ 35 Ileus, fulminant colitis, megacolon Colectomy, ileostomy

Colonisation Resistance

Metabolome and microbiome assessed in CDI susceptible & resistant mice

CDI Susceptible State	CDI Resistant State (Recovery)
↓ Microbiome diversity	↑ Microbiome diversity
↓ 2^0 bile acids, SCFA	❑ Altered microbiome composition
↑ 1^0 bile acids, carbohydrates, amino acids	❑ Return to baseline metabolome

Different but diverse microbiome structures share similar metabolic function



Nature Comm 2013 (5) 1

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C. difficile Toxins

Primary virulence factors

Toxin A (TcdA) and Toxin B (TcdB)

> Glycosylate host GTPases

> No reports of naturally occurring A^+ B^- strains

> A^+ B^- strains cause lethal infection in hamsters

Binary toxin (CDT)

> Associated with more severe disease

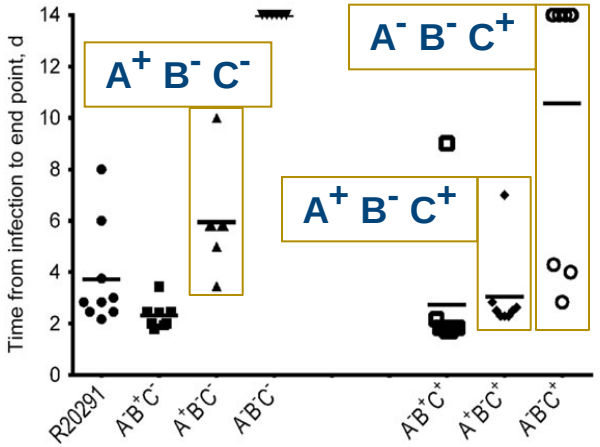
> May act with Tox A/B to increase virulence

CDT: Irreversibly modifies G-actin

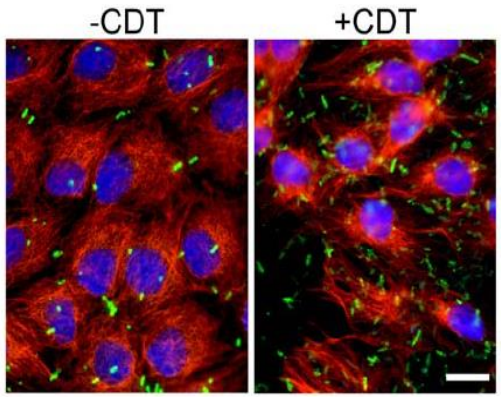
> ADP-ribosyltransferase

> Microtubule rearrangement ➔ dense mesh of cellular protrusions ➔ 4.5-fold increase in adherence

C. difficile Virulence in Hamsters



C. difficile Adherence to Caco-2 Cells



J Infect Dis 2013 1: PLoS Path 2009

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C. difficile Spores

Etiological agent, highly resistant and results in environmental persistence

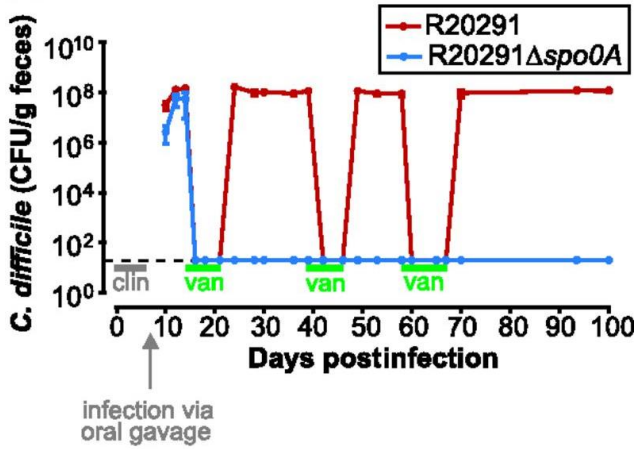
> Hyper-virulent strains may be associated with enhanced sporulation rates

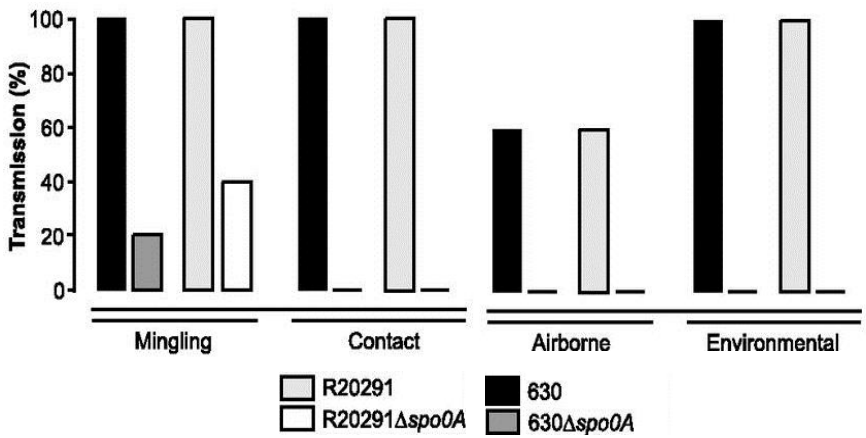
spo0A key transcriptional regulator of the early stages of sporulation

Infection with R20291 *Δspo0A* mutants results in:

> Virulent lethal infection in mice

> Inability to generate persistent infection or transmit infection between animals





Infect. Immun. 2012 (80) 2704

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Recurrent Disease – The Unmet Medical Need

Recurrent disease of particular concern

> Limited therapy options and difficult to manage

> Impacts on patient welfare and healthcare resources

Characterised by increased damage to GI microbiota

> CDI antibiotics can cause collateral damage

Each episode associated with

> Increased risk of further recurrence

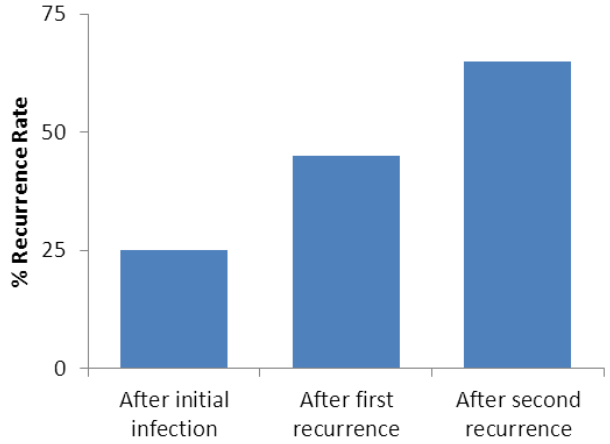
> Increased disease severity

> Increased mortality

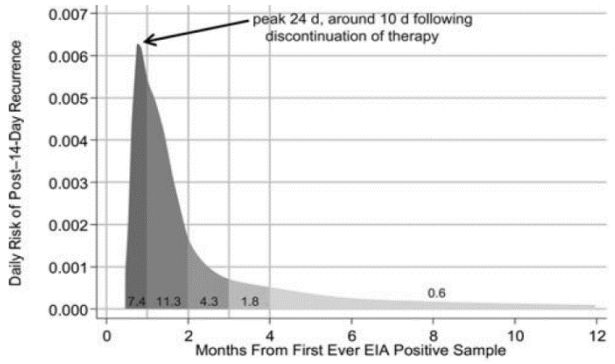
Risk peaks around 10 days post end of therapy

> High risk to 4-6 weeks post therapy

Increasing Risk of Recurrent Disease



Daily Risk of Recurrence



CMI 2012 p21; Clin Infect Dis 2012: 55(S2) S77
Am J Gastro 2002 p1769; CID 1997 p324

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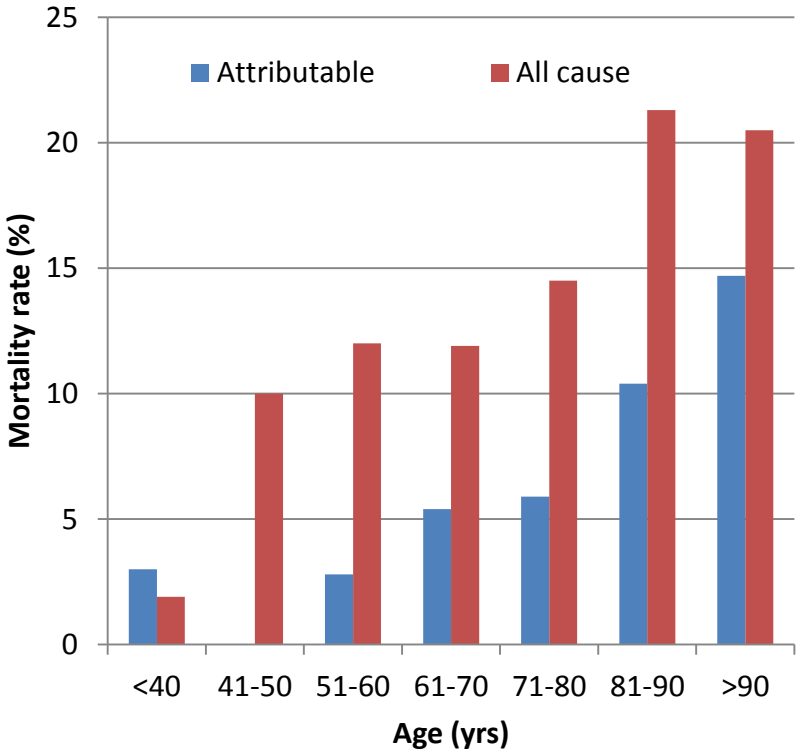
CDI Mortality: A Significantly Under Recognised Issue

Mortality a significantly under-recognised aspect of CDI

50% of cases are in <65 yrs of age - 90% of deaths are in the >65 yrs of age

- 7-15% of deaths due to HAIs in the US attributed to CDI
- CDC - 29,000 deaths in the US in 2011
- 1 in 9 patients ≥ 65 yrs with a HA-CDI die within 30 days of diagnosis
- 1.1% of annual deaths in the UK due to CDI
- 2.5 fold increase in all cause mortality following infection with *C. difficile*
- 30 days all-cause mortality overall 13%



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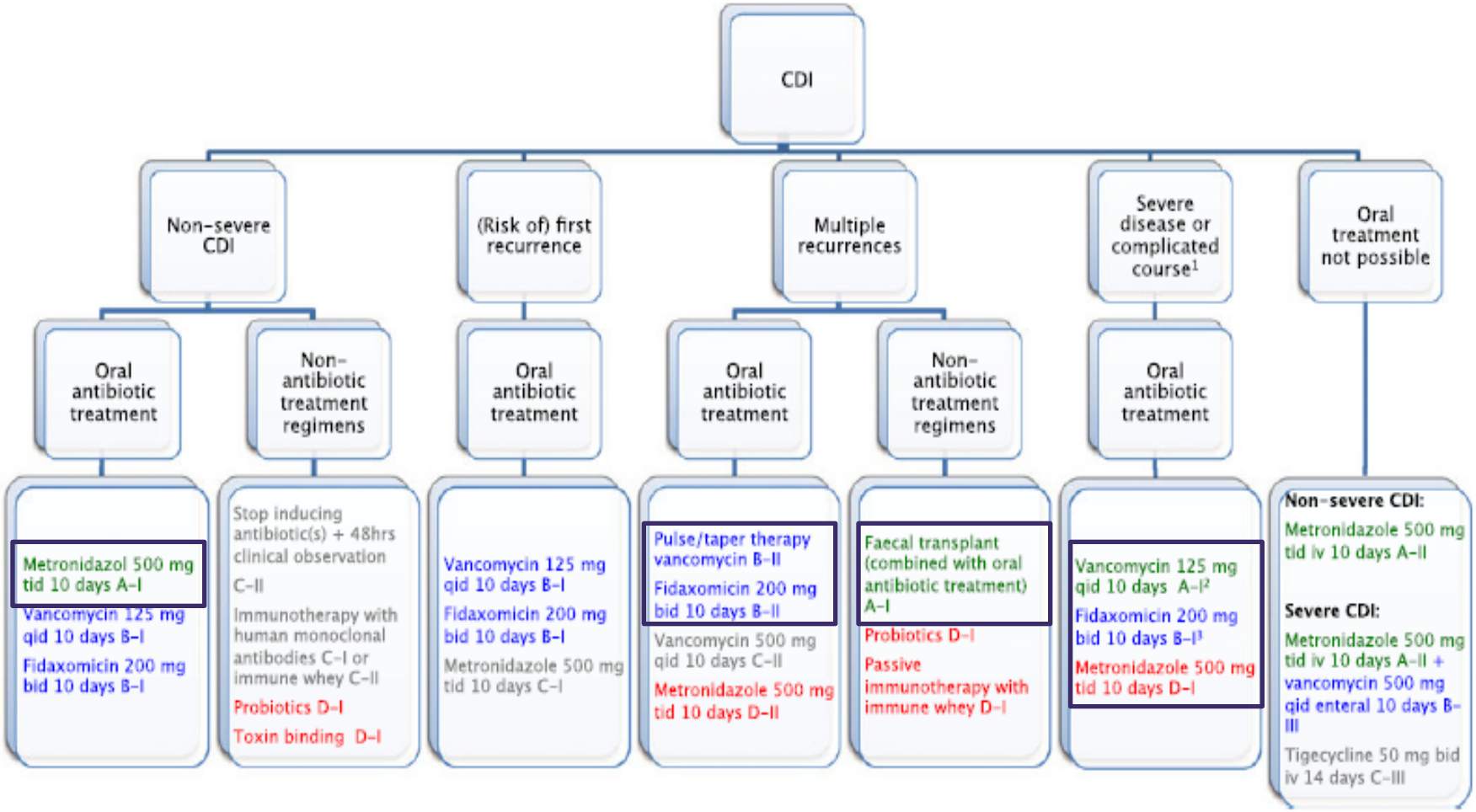
Current Treatment Approaches: ESCMID 2014 Guidelines



Strength of Recommendation: A Strong; B Moderate; C Marginal; D Against

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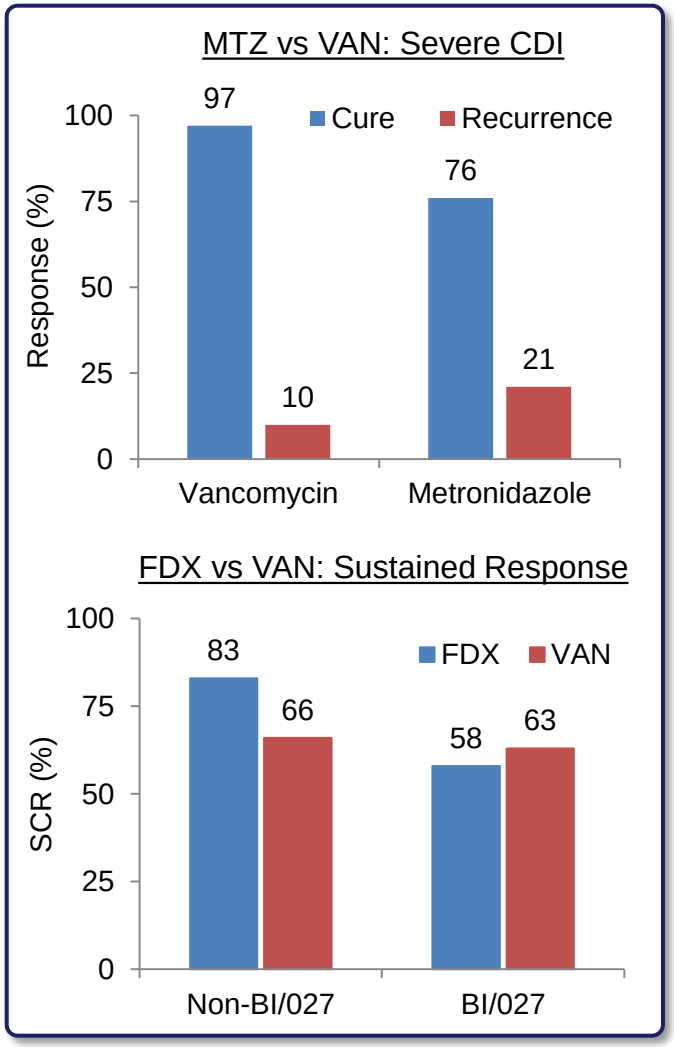
Limitations of Current Therapies

Vancomycin and metronidazole

- Inappropriate agents for CDI
- Metronidazole inferior for severe disease
- Eroding efficacy with metronidazole
- Recurrent disease of particular concern

New agent fidaxomicin

- Superior sustained clinical response (SCR) compared to vancomycin
  - SCR = Cure with no recurrence to 25 days post end of therapy
- Non-inferior recurrence rates for 027 infection
- Hypersensitivities; cost; multiple-recurrence data



Clin Infect Dis 2007 (45) 302; NEJM 2011 (364) 422
Lancet Infect Dis 2012 (12) 281; Clin Infect Dis 2014 (58) 537

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CDI Therapeutic Approaches

Bacteria	Antimicrobials	Active disease Prophylaxis
Spores	Germination/sporulation inhibitors	Recurrent disease Transmission Prophylaxis
Toxins	Toxin sequestering agents Antibodies	Active disease
Host immunity	Vaccine Antibodies	1º and 2º Prevention Active disease
Colonisation resistance	Faecal microbiota transplant Bacteriotherapy Pro/prebiotics NTCD	Recurrent disease

CDI Product Development Pipeline (Late Stage)

Approach	Product		Phase	Comments
Antibiotics	**Surotomycin** Cubist / Merck	G+ve antibiotic Daptomycin analogue	3	• Merck 10Q Filing *"…received unfavourable efficacy data from a clinical trial for Surotomycin…resulted in an IPR&D impairment of $50M"*
	Cadazolid Actelion	G+ve antibiotic Oxazolidinone-FQ hybrid	3	• P2 Non-inferior on cure and superior (trends) on recurrence to vancomycin - no data on 027 infection
Combination with antibiotics	**Actoxumab & bezlotoxumab** Merck	Monoclonal antibodies to Toxins A and B	3	• Adjunctive therapy with SOC • Phase 2: Reduction in recurrence (8% vs 32%) • Preliminary Phase 3 less positive • High cost • Use in high risk or multiple recurrence patients
Multiple recurrence High risk of recurrence	**SER-109** Seres Health	Oral ecobiotic	2/3	• Adjunct to antibiotic therapy. • Safety & efficacy trial in patients with multiple recurrences • 87% patients reached primary endpoint of no *C. difficile* diarrhoea during 8 wks follow-up
Primary prevention	**ACAM-CDIFF** Sanofi Pasteur	Vaccine	3	• Seroconversion in >65 yrs is often poor • IM injection of 3 doses on days 0, 7 and 30 • Primary prevention in high risk patients

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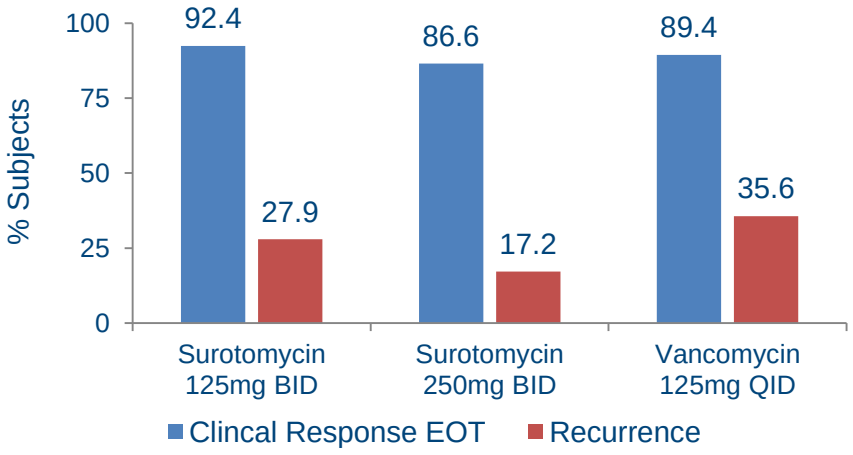
Phase 3 Antibiotics

Cubist: Surotomycin

- Lipopeptide
- *C. difficile* MIC_{90} = 0.5 µg/mL
  - *B. fragilis* > 8,192 µg/mL
  - *Bifidobacteria* = 2 µg/mL
  - *Lactobacillus* = 4 µg/mL
- Rapidly bactericidal

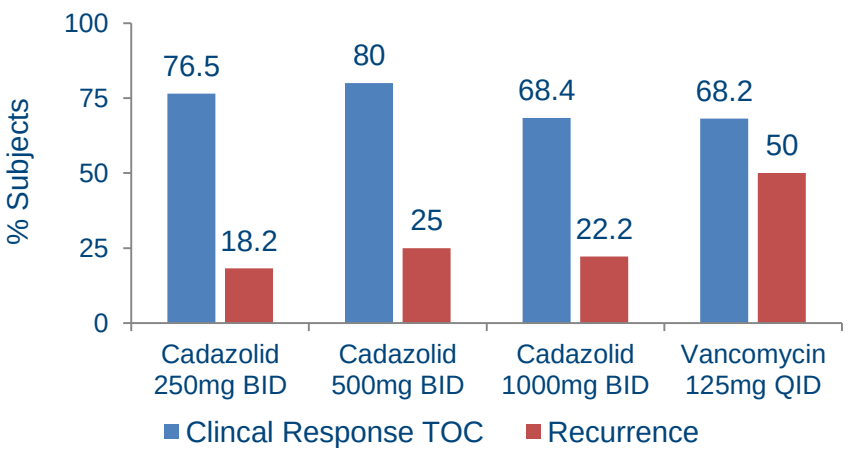
Phase 2 Efficacy



Actelion: Cadazolid

- FQ-oxazolidinone hybrid
- *C. difficile* MIC_{90} = 0.25 µg/mL
  - *B. fragilis* = 4 µg/mL
  - *Bifidobacteria* = 0.5 µg/mL
  - *Eubacteria* = 0.5 µg/mL
- ⬇ Toxin, sporulation *in vitro*

Phase 2 Efficacy



Patino ICAAC 2011 #K-205a; AAC 2012 (56) 1613;
ECCMID 2013 #C1-1347 and #LB 2956; ECCMID 2012 #E-808 .

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Merck: Actoxumab / Bezlotoxumab

Human Mabs against toxin A and B

Encouraging Phase 2 results

> Single infusion of antibodies or placebo with SoC

> Metronidazole or vancomycin as SOC

Significant reduction in recurrence

> 027 infection

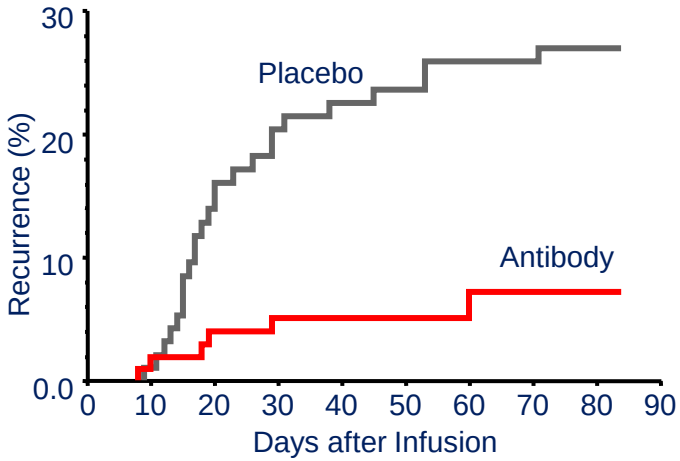
> Multiple recurrence

> Recurrence in antibody treated subjects not related to low serum levels of antibodies

Preliminary phase 3 data recently reported

> Possibly less encouraging than Phase 2

CDI Recurrence



Recurrence by Subgroup

	Antibody	Placebo
BI/NAP1/027		
• Yes	2/25 (8)	6/19 (32)
• No	4/52 (8)	11/55 (20)
Prior CDI Episodes		
• Single	2/29 (7)	12/66 (18)
• Multiple	5/72 (7)	12/32 (38)

N Engl J Med. 2010 (362) 197

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Merck: Actoxumab / Bezlotoxumab

Efficacy and Safety of Actoxumab (ACT) & Bezlotoxumab (BEZ) for Prevention of Recurrent *C. difficile* Infection (rCDI) in Patients on Standard of Care (SoC) Antibiotics (MODIFY I)

	ACT+BEZ n/N (%)	ACT n/N (%)	BEZ n/N (%)	Placebo n/N (%)
rCDI[†]	61/383 (15.9)	60/232 (25.9)	67/386 (17.4)	109/395 (27.6)
Global cure[‡]	225/383 (58.7)	109/232 (47.0)	232/386 (60.1)	218/395 (55.2)
rCDI by subgroup				
Metronidazole	26/189 (13.8)	23/112 (20.5)	32/190 (16.8)	43/192 (22.4)
Vancomycin	32/182 (17.6)	36/113 (31.9)	31/182 (17.0)	63/189 (33.3)
Fidaxomicin	3/12 (25.0)	1/7 (14.3)	4/14 (28.6)	3/14 (21.4)
Inpatient	40/254 (15.7)	36/158 (22.8)	40/257 (15.6)	66/261 (25.3)
Outpatient	21/129 (16.3)	24/74 (32.4)	27/129 (20.9)	43/134 (32.1)
History of CDI in past 6 months	24/96 (25.0)	23/69 (33.3)	27/103 (26.2)	43/109 (39.4)
Infected with 027 ribotype	4/37 (10.8)	8/24 (33.3)	12/46 (26.1)	13/36 (36.1)
Severe CDI at study entry	8/62 (12.9)	8/31 (25.8)	7/67 (10.4)	15/60 (25.0)
Age ≥65 years	34/200 (17.0)	32/122 (26.2)	28/185 (15.1)	66/199 (33.2)
Immunocompromised	9/78 (11.5)	10/55 (18.2)	15/87 (17.2)	26/92 (28.3)
Adverse events (AE) through Week 4				
One or more AE	231/387 (59.7)	158/235 (67.2)	255/390 (65.4)	248/400 (62.0)
One or more drug-related AE	24/387 (6.2)	17/235 (7.2)	32/390 (8.2)	20/400 (5.0)
Adverse events through Week 12				
One or more serious AE	94/387 (24.3)	104/235 (44.3)	120/390 (30.8)	126/400 (31.5)
Death	20/387 (5.2)	27/235 (11.5)	31/390 (7.9)	26/400 (6.5)

N = Number of subjects included in the analysis population or subgroup.

n = Number of subjects in the analysis population or subgroup meeting the definition of the endpoint.

[†] rCDI = New episode of diarrhea & positive stool test for toxigenic *C. difficile* after clinical cure of baseline CDI episode; evaluated in the Full Analysis Set, N=1396.

[‡] Global cure = Clinical cure of initial episode & no rCDI through Week 12.

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Sanofi: ACAM-CDIFF

Toxoid vaccine - formalin inactivated toxins A and B

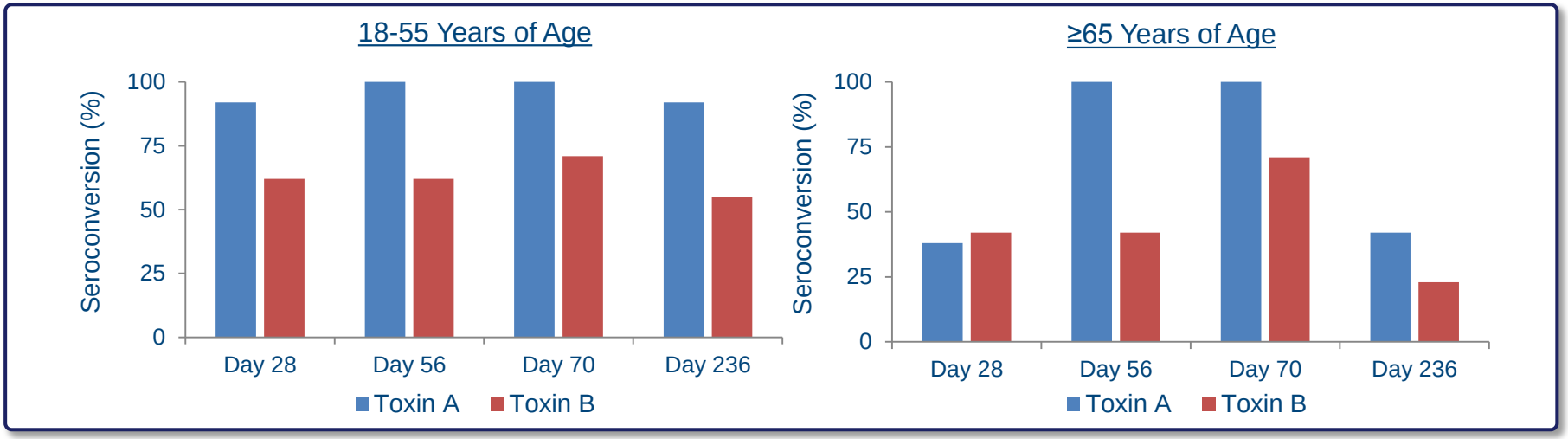
Phase 1: 100% seroconversion for Toxin A on day 56 at 50µg dose

> Lower seroconversion rates for Toxin B and in subjects ≥65 years old

> Reduction in antibody titres by day 236

Currently in Phase 3 trials for primary prevention of CDI

> Enrolment ≈ 15,000 subjects; IM injection of 3 doses on days 0, 7 and 30



Vaccine 2012;30:2245-9

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ViroPharma: Non-toxigenic *C. difficile* (NTCD)

Colonisation with a non-toxigenic strain of *C. difficile*

In a Phase 2 study 168 patients, post treatment for CDI, randomised to:

> Low dose (10^4 spores) NTCD for 7 days

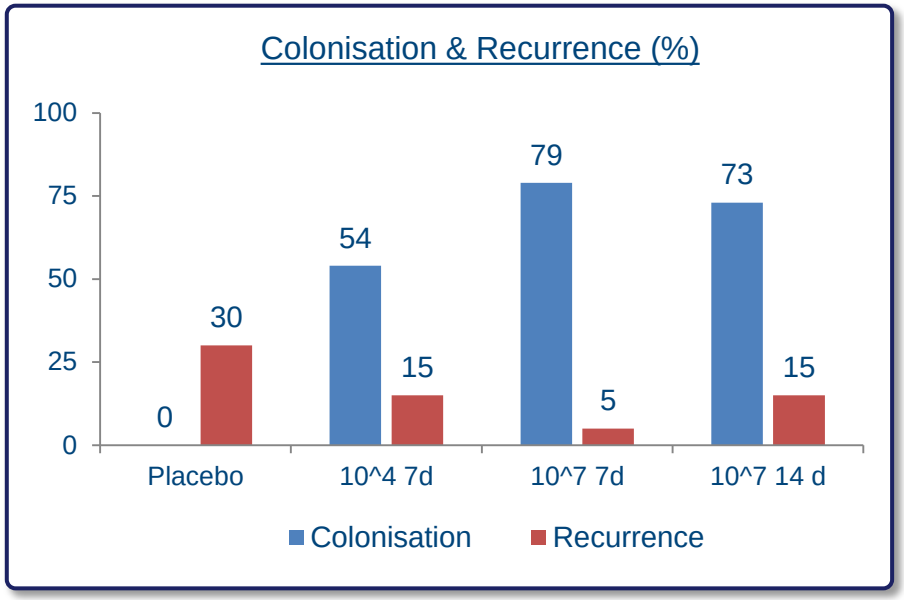
> High dose (10^7 spores) NTCD for 7 or 14 days

> Placebo

Colonisation rates of 79% in subjects treated with high dose for 7 days

Recurrent CDI reduced by ≥ 50% over placebo

Recurrence rate of 2% for colonised subjects



AAC 2012 (56) p5244;
ViroPharma Press Release April 22, 2013

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Faecal Microbiota Transplant (FMT)

First described in 1958 to successfully treat 4 subjects with PMC

Highly effective at treating recurrent CDI. Recent systematic reviews:

> 317 cases: 92 % resolution; 273 cases: 90% resolution

FECAL: First randomised trial

> 93.8% cure without recurrence

Some concerns remain

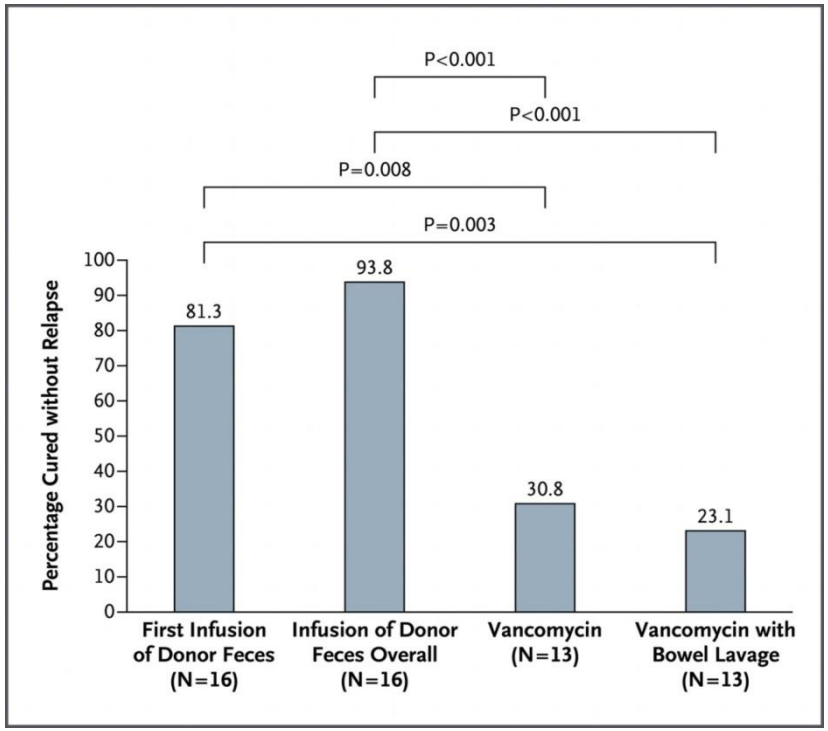
> Infection transmission

> Standardisation of delivery, donor screening and donor selection

> Patient and health care worker acceptance

> Appropriate subjects

> FDA – IND strongly encouraged



CID 2011 (53) 994; NEJM 2013 (368) 407;
Am J Gastro 2013 (108) 500

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“Synthetic” FMT

Rational, predefined and controlled mixture of bacteria - overcomes issues with FMT?

SERES Therapeutics: SER-109 Phase 1b/2

- *“ecology of commensal spores….developed to treat recurrent CDI and repair gut dysbiosis.”*
- 26 of 30 patients achieved primary endpoint of no CDI recurrence to 8 weeks post-therapy
- For 3 subjects who failed endpoint investigator recommended they refrain from antibiotic use and condition resolved.
- Loss of *Klebsiella* spp., VRE, or imipenem resistant Enterobacteriacea colonisation

RePOOPulate Study

- Stool substitute prepared from purified cultures of a single healthy donor
- Subject 1: Six prior CDI episodes over 18 months
- Subject 2: Three prior CDI episodes
- Resolution of diarrhoea by 3 days post administration; Symptom free after 6-8 months

FMT: High Levels of Efficacy
Microbiome Fundamental When Considering CDI Therapy

In contrast, evidence for efficacy with single organism probiotics is limited

Demonstrates importance of considering entire microbiota not single bacterial group

BBC Sign in News Sport Weather

NEWS MAGAZINE

The brave new world of DIY faecal transplant

By William Kremer
BBC World Service

THE INDEPENDENT MONDAY 01 DECEMBER 2014

Sausages made with baby poo are completely normal and super healthy, say scientists

Don't expect to see them on supermarket shelves any time soon, but this sort of bacterial innovation might be key to making healthier fermented sausage

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SMT19969: A Selective Therapy for CDI

Novel antimicrobial with potential to significantly reduce recurrent CDI

- Potent, bactericidal inhibition of *C. difficile*
- Highly targeted spectrum of activity
- Superior to comparators in the hamster model of CDI

QIDP and Fast Track status granted

- 5 years additional market exclusivity

Phase 1 clinical trial completed

- SMT19969 considered safe and well tolerated at all administered doses
- GI restricted: Oral dosing associated with negligible systemic exposure
- Minimal effects against gut flora in humans

Phase 2 proof-of-concept clinical trial recruitment complete

- Top line data expected Q4 2015

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Phase 1: Clinical Trial Successfully Completed

First in human Phase 1 clinical trial complete

> 56 healthy male volunteers - Single and multiple ascending oral doses

SMT19969 considered safe and well tolerated at all doses tested

No clinically significant findings from biochemistry, haematology, urinalysis, vital sign, ECGs and Faecal Occult Blood

All adverse events mild in severity and resolved without intervention

> No dose dependent relationship between AEs and SMT19969

> Comparable rate of AEs in SMT19969 and placebo groups

> One SAE (appendicitis) - not considered drug-related

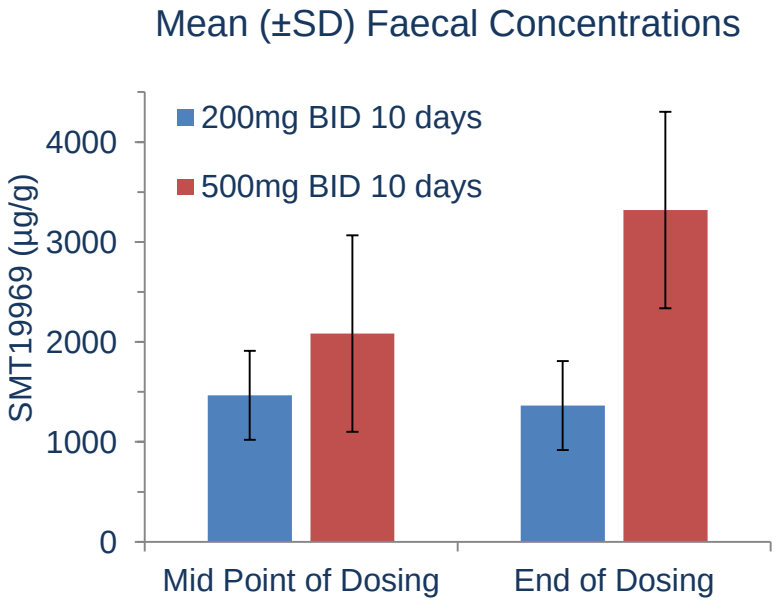
Oral dosing associated with negligible systemic exposure

Phase 1: Exposure Exclusively in Gastrointestinal Tract

SMT19969 retained in the gastrointestinal tract - site of infection

- Plasma levels of SMT19969 typically at or below limit of quantification
- Minimal metabolism with > 97% excreted as unchanged parent drug
- Mean faecal concentrations >1,000 fold above MIC at 200mg BID

Dose Regimen	Plasma Pharmacokinetics	
	C_{max} Range (ng/mL)	Mean AUC (ng.hr/mL)
200mg BID 10 days	0.103 - 0.243	0.653
500mg BID 10 days	0.102 - 0.305	1.42



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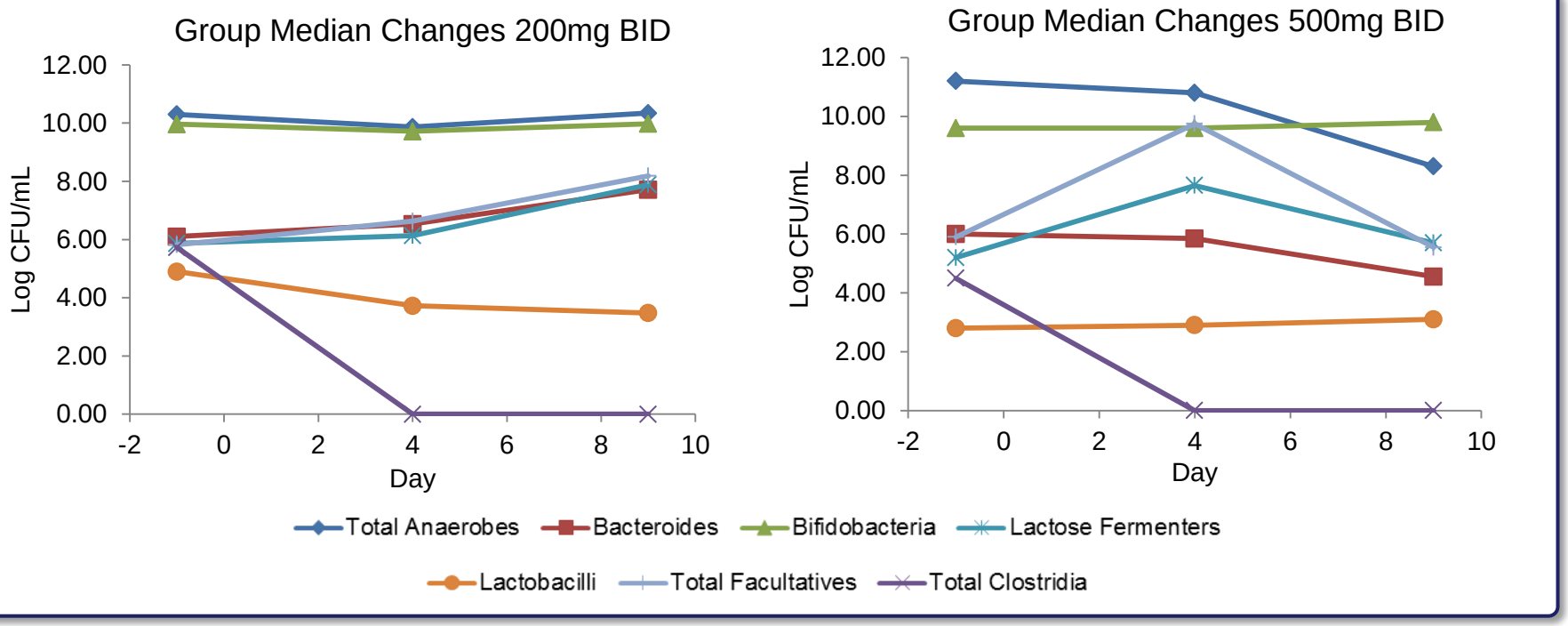
Phase 1: SMT19969 Preserves Healthy GI Microbiota

Faecal samples from MAD phase analysed for gut flora composition

> SMT19969 shown to be highly sparing of key bacterial groups

> Total Clostridia only group where marked changes in counts were seen



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CoDIFy: Phase 2 Proof of Concept Trial

100 subjects ~30 US/Canadian sites

Primary outcome parameter:

> Sustained Clinical Response (SCR)

> *Defined as clinical cure at Test of Cure and absence of recurrence within 30days after end of treatment*

Group Design			
Group	N	Agent	Regimen
1	50	SMT19969	200mg BID 10 days
2	50	VAN	125mg QID 10 days

Secondary outcome parameters:

> Clinical response at TOC

> Time to resolution of diarrhoea (TTROD)

> Time to hospital discharge

Exploratory analysis:

> Clinical microbiology

> Inflammatory markers

> Detailed examination of the microbiome during and post therapy by 16S rRNA sequencing

CoDIFy

CoDIFy: Detailed Understanding of Efficacy

Study to provide detailed picture beyond basic safety and efficacy

> Provide differentiating data and input in to subsequent clinical development

Detailed qualitative and quantitative analysis of the microbiome

> All subjects during and post therapy

Time to disease resolution

> Symptomatic resolution – TTROD and inflammatory markers

> Microbiological clearance – *C. difficile* viable counts

	Visit Day						
	-1	5	End of Therapy	Recurrence	25	40	
C. difficile viable counts	x	x	x	x	x	x	Resolution
C. difficile spore counts	x	x	x	x	x	x	Recurrence Transmission
Microbiome	x	x	x	x	x	x	Recurrence
Inflamatory markers	x	x	x	x	x	x	Resolution Severity

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SMT19969: Potent Inhibition of *C. difficile*

Potent growth inhibition of *C. difficile* - MIC_{90} = 0.125 - 0.25µg/mL

> No significant differences in MICs between ribotypes

> No increase in MIC against isolates with reduced VAN or MTZ susceptibility

C. difficile Group (№ Isolates)		SMT19969	Metronidazole	Vancomycin	Fidaxomicin
		MIC_{90}	MIC_{90}	MIC_{90}	MIC_{90}
UK Isolates	Overall Total (82/82)	0.125	8	2	0.06
	• Genotypically distinct group (30)	0.125	2	2	0.06
	• Ribotype 001 (10)	0.125	1	4	0.06
	• Ribotype 027 (11)	0.125	2	2	0.06
	• Ribotype 106 (10)	0.125	2	2	0.125
	• Reduced MET susceptibility (21)	0.125	8	2	0.03
US Isolates	Overall Total (50/50)	0.25	2	4	0.5
	• Ribotype 027 (11)	0.25	8	4	0.5
	• Non-027 ribotypes (39)	0.25	0.5	2	0.5
	• Reduced VAN susceptibility (10) ▪ Ribotypes 027, 137,190	0.25	4	8	0.5

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SMT19969: Highly Targeted Spectrum of Activity

Minimal growth inhibition of Gram negative anaerobes

> No growth inhibition of *Bacteroides* spp.

Organism	N	MIC_{90} (µg/mL)			
		SMT19969	FDX	VAN	MTZ
Bacteroides fragilis	20	>512	>512	64	2
Bacteroides ovatus	10	>512	>512	256	2
Bacteroides thetaiotaomicron	10	>512	>512	128	2
Bacteroides vulgatus	10	>512	>512	128	1
Parabacteroides spp.	10	>512	>512	128	2
Fusobacterium nucleatum	10	64	>512	512	0.25
Fusobacterium spp.	10	>512	>512	>512	0.5
Prevotella spp.	23	>512	>512	512	1
Veillonella spp.	20	>512	256	>512	2

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SMT19969: Highly Targeted Spectrum of Activity

Significantly more selective than comparators vs. Gram positive bacteria

> Anaerobic and aerobic bacteria

Organism	N	MIC_{90} (µg/mL)			
		SMT19969	FDX	VAN	MTZ
Bifidobacterium spp.	20	>512	0.125	1	128
Lactobacillus spp.	20	>512	>512	>512	>512
Eggerthella lenta	20	>512	≤0.03	4	0.5
Various Gram positive rods	23	>512	128	4	2
Finegoldia magna	20	64	2	0.5	1
Peptostreptococcus anaerobius	20	64	≤0.03	0.5	1
Staphylococcus aureus	10	>512	16	1	>512
Enterococcus faecalis	10	>512	8	4	>512
Enterococcus faecium	10	128	128	256	>512
Streptococcus spp.	10	>512	128	1	>512

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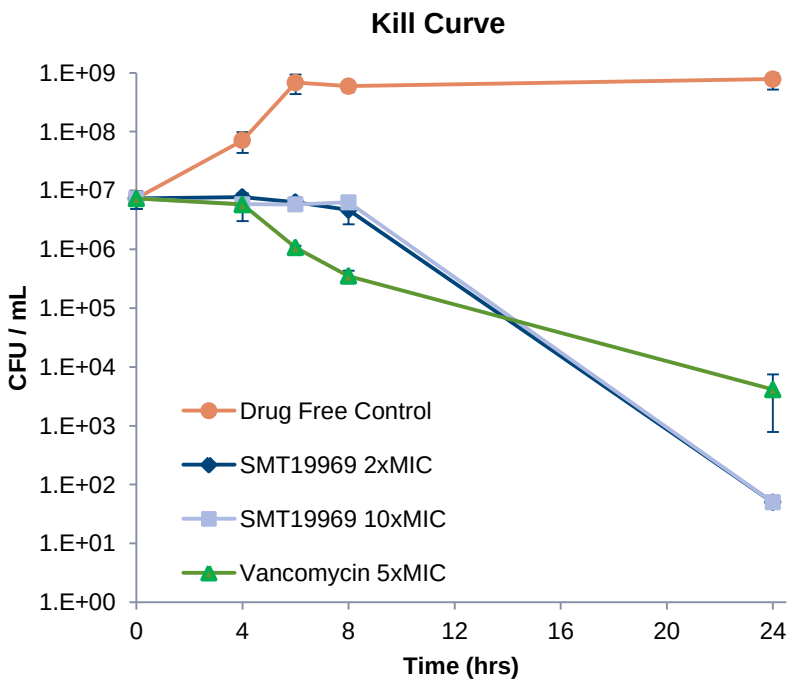
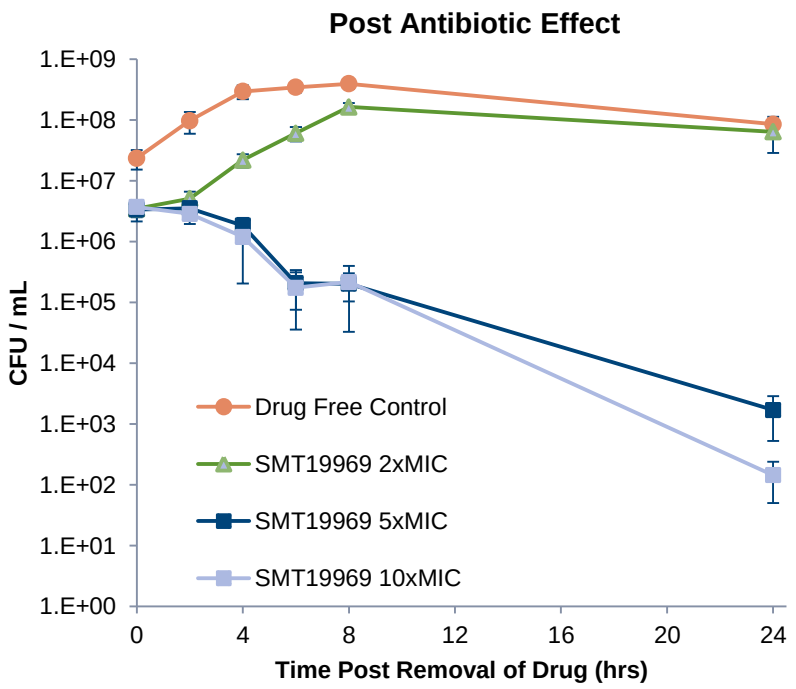
SMT19969: Bactericidal with Pronounced PAE

Bactericidal activity with > 5 log reduction in CFU/mL after 24 hours

No recovery of growth at ≥ 5 x MIC following 3 hrs pre-incubation





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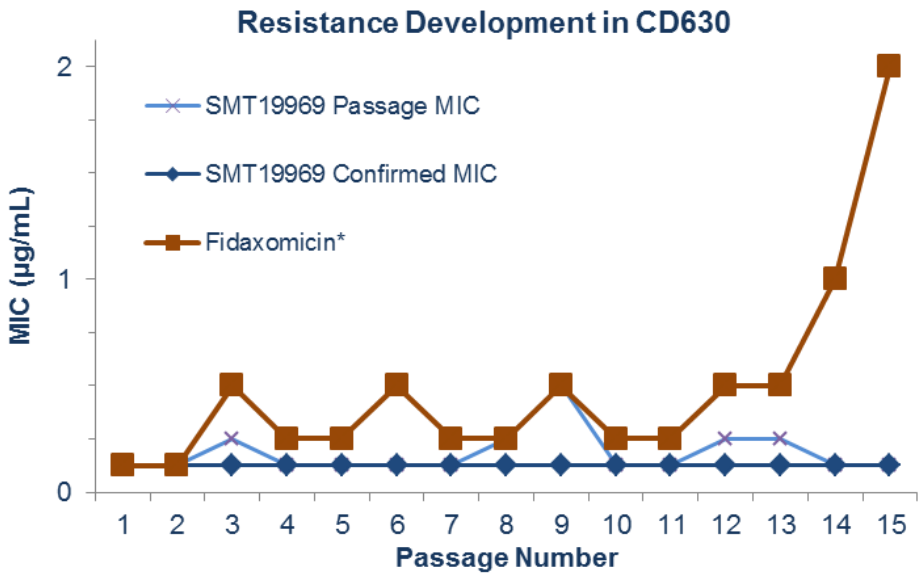
SMT19969: Low Resistance Potential

C. difficile shown to have low propensity to develop SMT19969 resistance

> No increase in MIC following 14 serial passages

> Spontaneous resistant mutants have not been isolated against clinical isolates



C. difficile	Mutation Frequency	
	4 x MIC	8 x MIC
CD630	$<6.9 \times 10^{-9}$	$<6.9 \times 10^{-9}$
R20291	$<3.17 \times 10^{-9}$	$<3.17 \times 10^{-9}$

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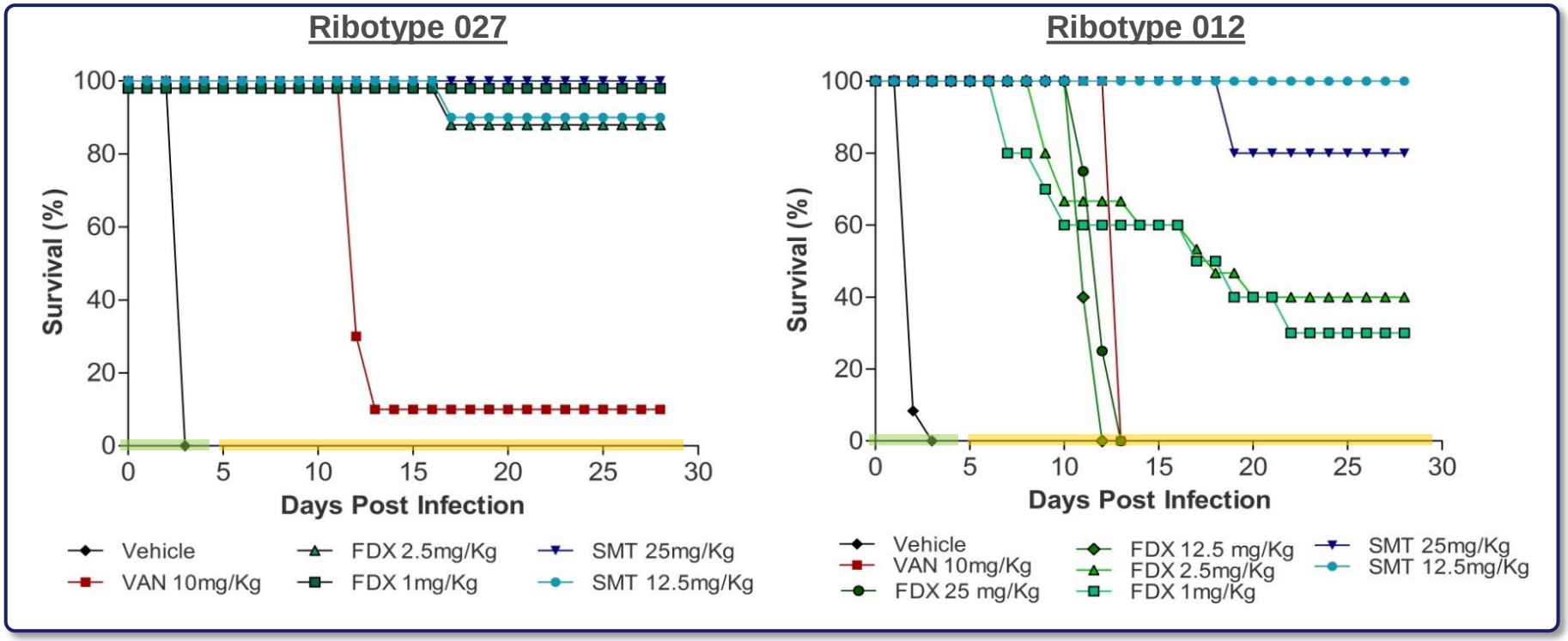
SMT19969: *In vivo* Protection from Recurrent Disease

Significant protection from acute and recurrent infection

> Consistent activity against multiple strains including hyper-virulent 027 strains

> 100% survival during acute infection; 80-100% survival during recurrence period



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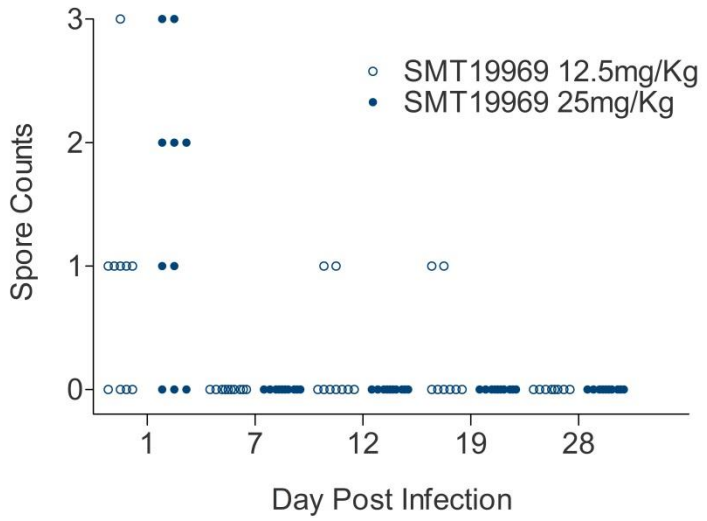
SMT19969: *In vivo* Reduction in Spores

Marked reduction in spores from faecal samples

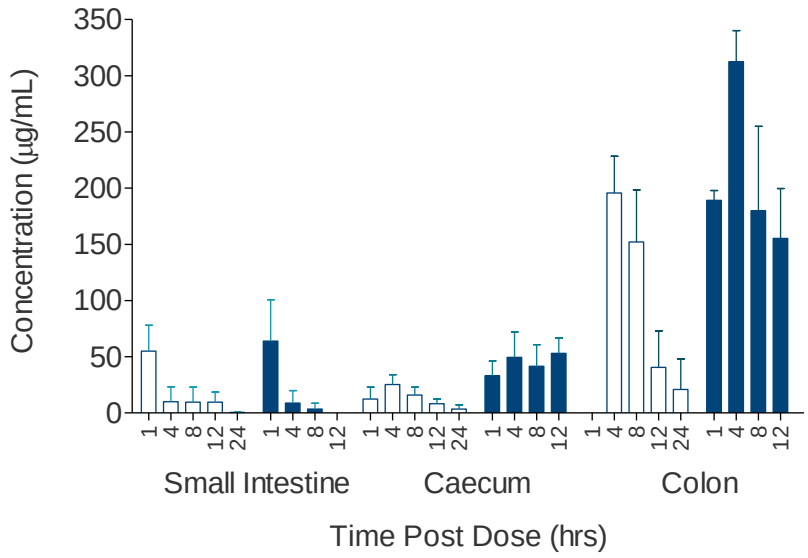
SMT19969 plasma levels below limit of quantification (1ng/mL) in infected animals

> GI concentrations significantly above MIC during dosing interval

Semi-quantitative Spore Counts Following Infection with *C. difficile* (ribotype 027)



Mean SMT19969 Concentrations in Sections of GI Tract Following Single or BID Dosing



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SMT19969: A Selective Therapy for CDI

Novel antimicrobial with potential to significantly reduce recurrent CDI

- Potent, bactericidal inhibition of *C. difficile*
- Highly targeted spectrum of activity
- Superior to comparators in the hamster model of CDI

QIDP and Fast Track status granted

- 5 years additional market exclusivity

Phase 1 clinical trial completed

- SMT19969 considered safe and well tolerated at all administered doses
- GI restricted: Oral dosing associated with negligible systemic exposure
- Minimal effects against gut flora in humans

Phase 2 proof-of-concept clinical trial recruitment complete

- Top line data expected Q4 2015

Supported by wellcome trust

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Human Microbiota

$10^{13\text{-}14}$ microbes make up the human microbiota

> Bacterial cells outnumber human cells by 10^3

> 150x more unique genes than that encoded by the human genome

GI tract contains ≈1,000 different species

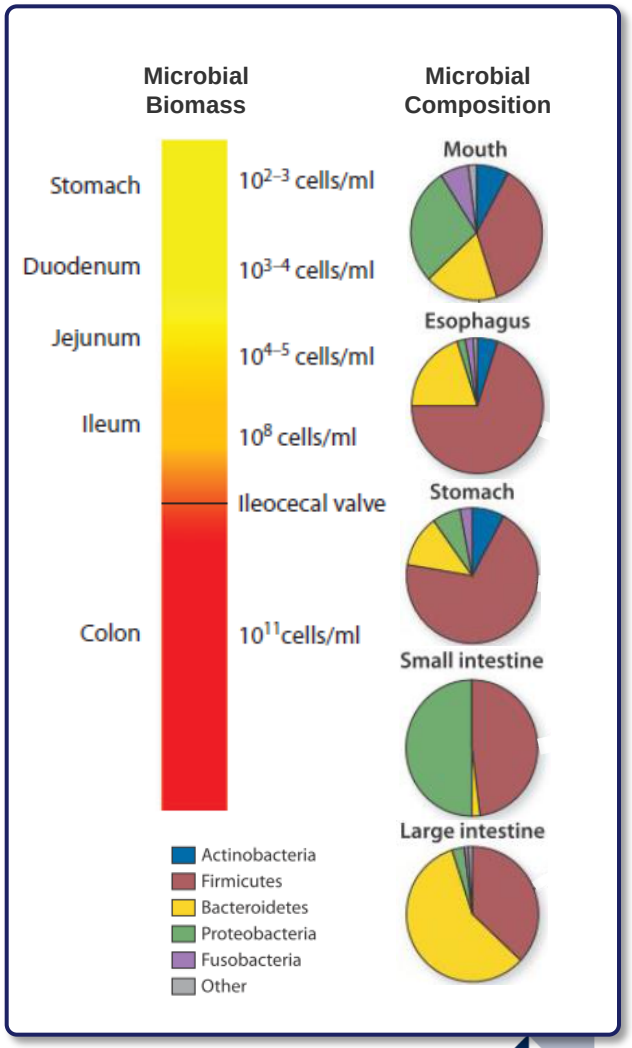
Complex community playing important role in health

> Metabolism, digestion, immune function….

> Protection from infection: *Colonisation Resistance*

Dysymbiosis associated with numerous disease states

> Obesity, cancer, IBD, neurological disorders…



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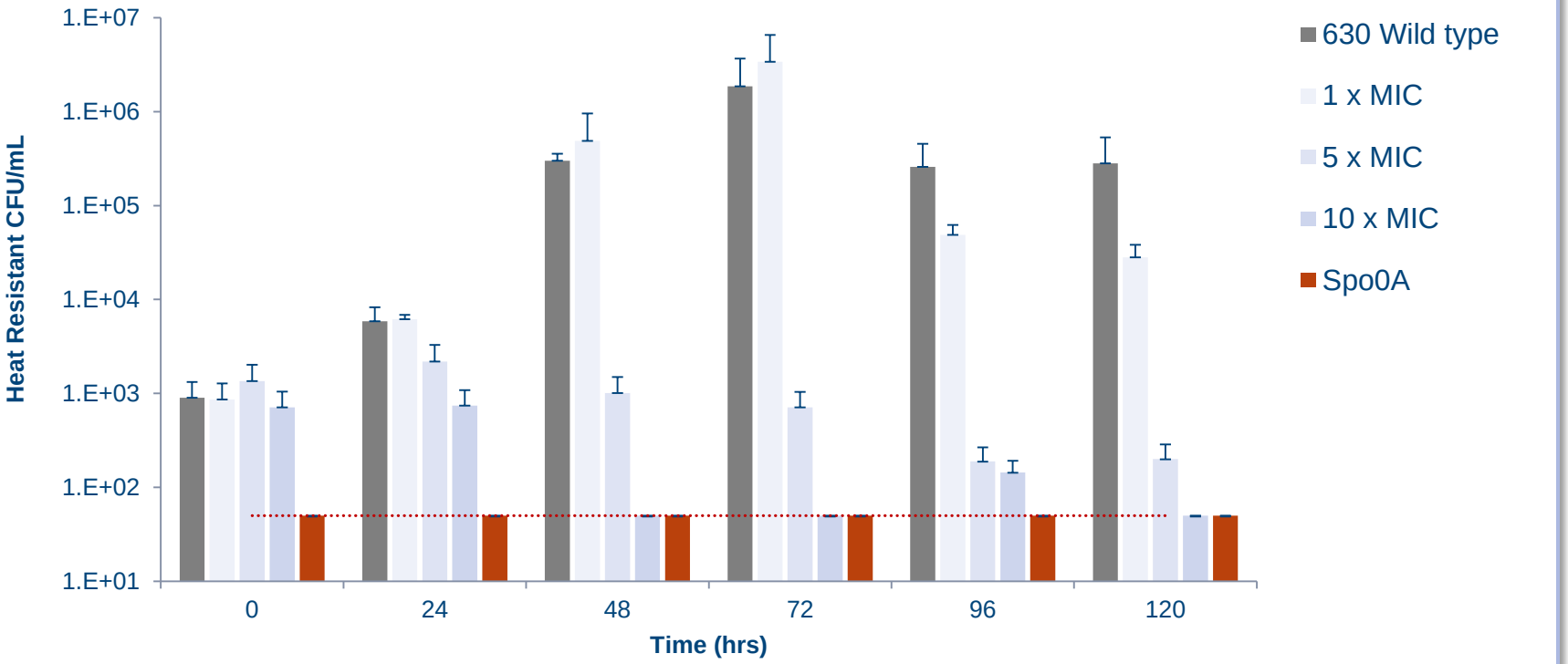
SMT19969: Inhibition of Sporulation

At ≥5xMIC significant reduction in spore formation

At 10xMIC spores numbers at 48hrs reduced to below the limit of detection



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Clostridium difficile

Anaerobic endospore forming bacteria

> 1935: *Bacillus difficilis* isolated by Hall & O'Toole from the stool of healthy neonates

> 1978: Identified as causative agent of pseudomembranous colitis

Ubiquitous in the environment

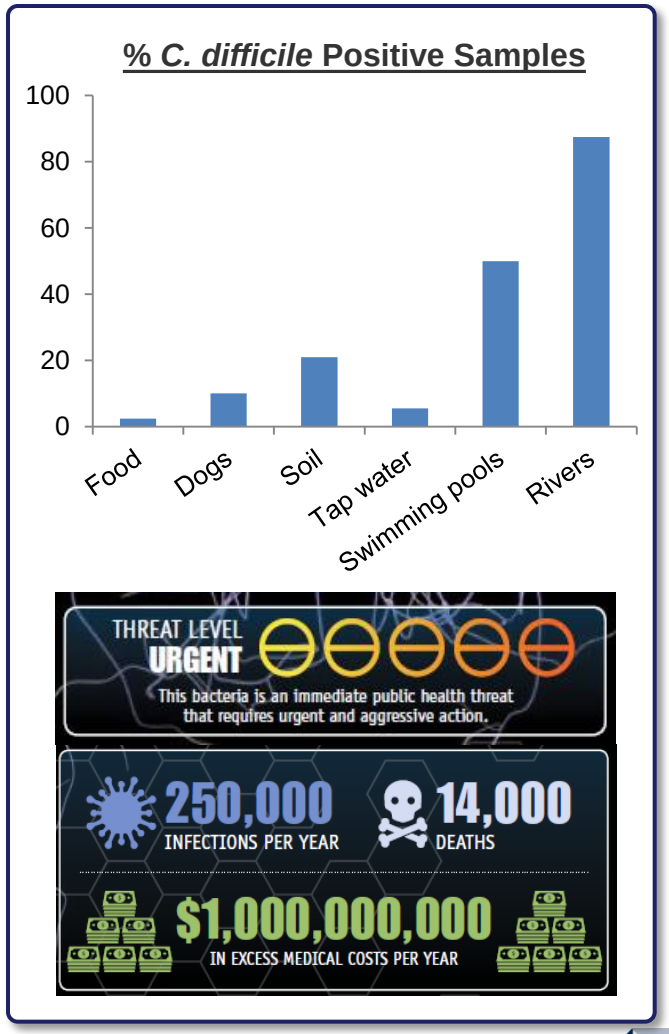
> Soil, water, food, animals, healthcare system

Can be a harmless resident of the GI tract

> 1-3% of healthy adults colonised

> 60% of children <12 months colonised

CDC: Top 3 Urgent Level AMR Threat



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