

Persistent Infection by *Salmonella Enterica* *Typhimurium:* Are Synbiotics a Therapeutic Option? A Case Report

Last Update: 08 October 2020
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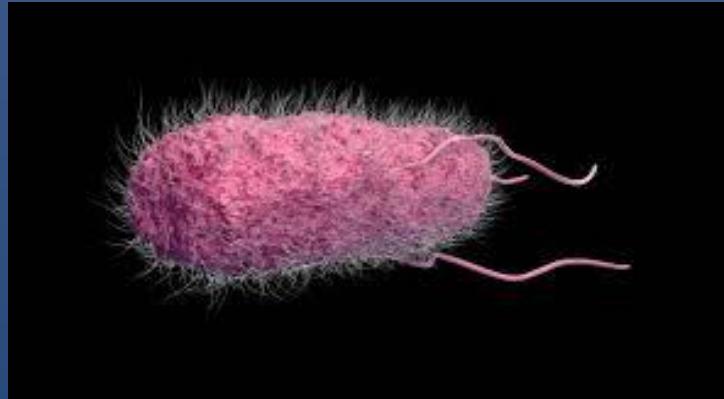
What Topics Will Be Covered In This Session?

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- 1** **Salmonella bacteria**
 - 2** **Non-typhoidal Salmonella (NTS): Sporadic and persistent Infections**
 - 3** **Persistent NTS infection: The patient case**
 - 4** **Synbiotics for managing persistent NTS infections**
 - 5** **Our Learnings**

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Salmonella enterica



Scientific Classification

Domain: Bacteria

Phylum: Proteobacteria

Class: Gammaproteobacteria

Order: Enterobacterales

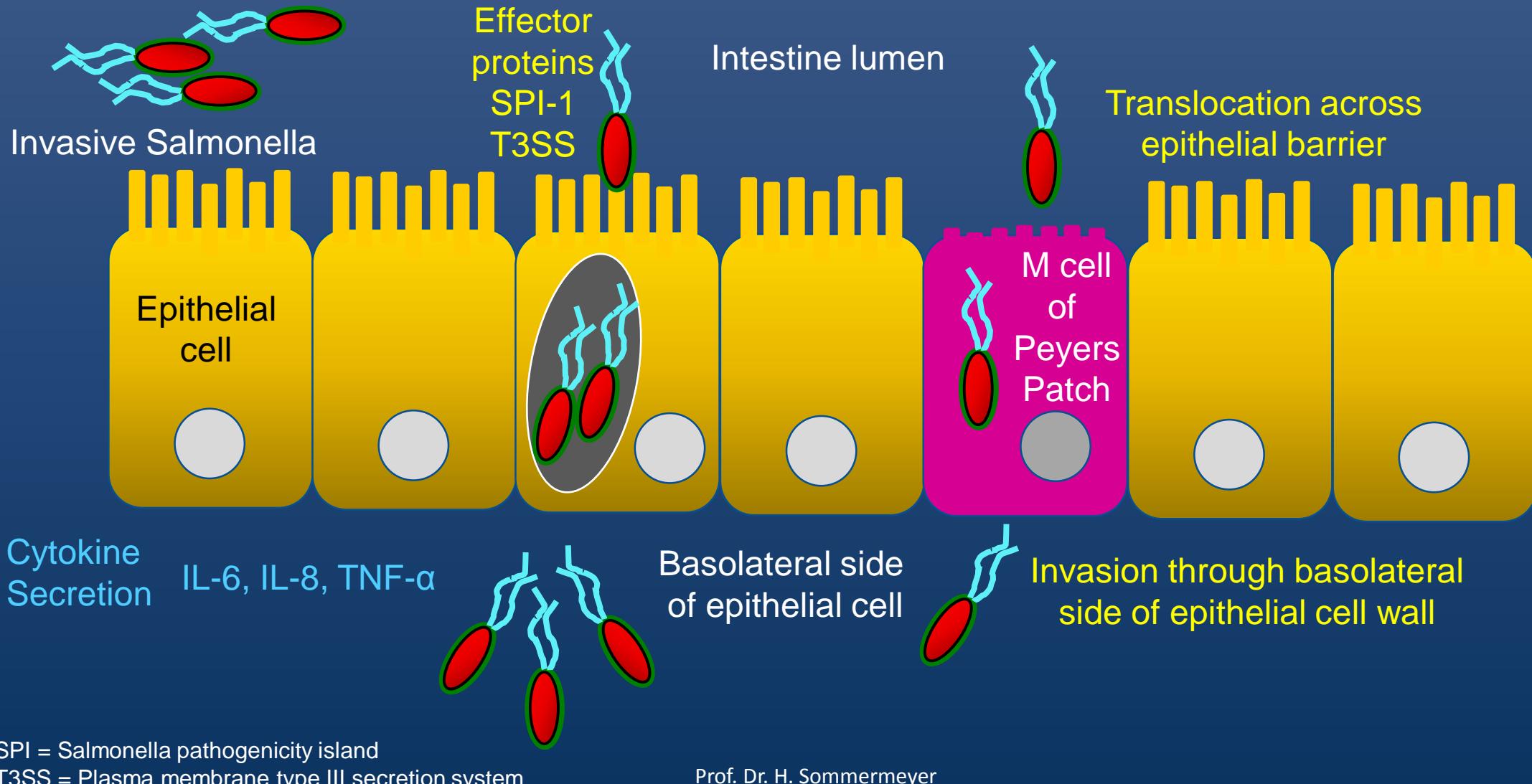
Family: Enterobacteriaceae

Genus: *Salmonella*

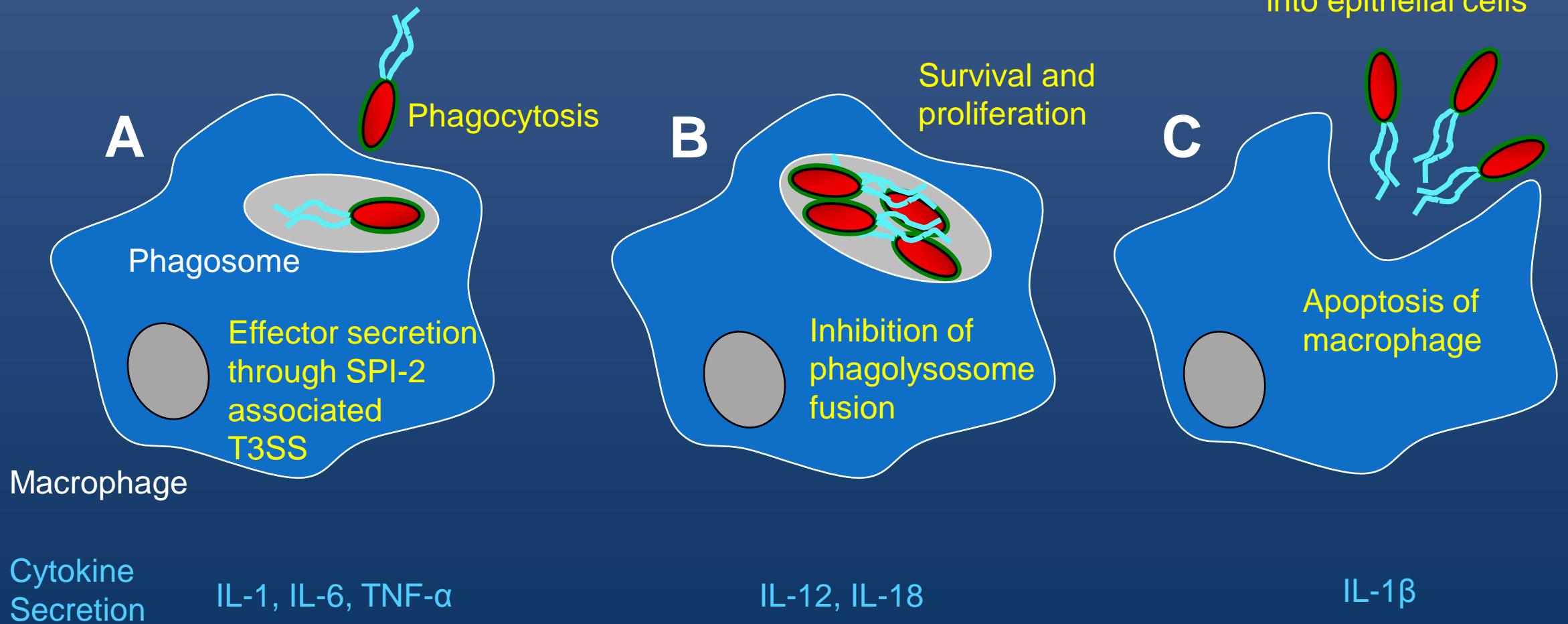
Species: *S. enterica*

- Gram-negative, flagellated, rod-shaped
- Aerobic, but facultatively anaerobic
- Routinely found in mammalian gastrointestinal tract
- Most cases of salmonellosis are caused by food infected with *S. enterica*
- *S. enterica* is an intracellular pathogen replicating and persisting in host gut epithelial cells, dendritic cells and macrophages of the innate immune system
- Secreted proteins play a major role of pathogenesis and are involved in host-cell invasion and intracellular proliferation

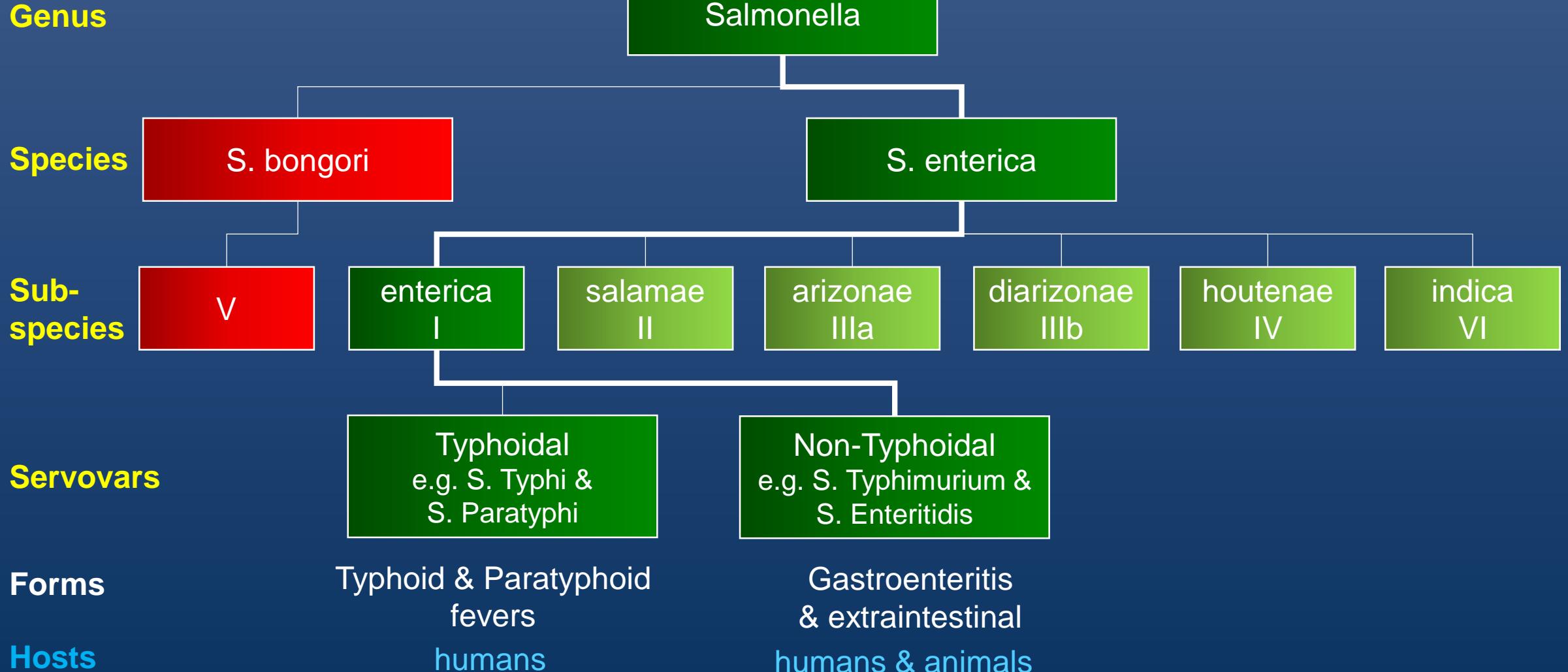
Salmonella Infection Step 1: Crossing the Epithelial Barrier



Salmonella Infection Step 2: Proliferation in Macrophages



Classification of *Salmonella* Species and Subspecies



Comparing Typhoidal and Non-Typhoidal Salmonella

	Typhoidal	Non-Typhoidal
Causing serovars	S. Typhi, S. Paratyphi	Non-typhoidal servovars
Hosts	Humans (and higher primates)	Humans and animals
Transmission	Fecal-oral	Primarily food-borne
Disease/Symptoms	Typhoid or paratyphoid fever, fever, abdominal pain, diarrhea and/or constipation, flu-like symptoms, fatigue	Diarrhea, nausea, vomiting
Chronic or prolonged infections	1-4% of all infections	?
Treatment of acute infection	7-10 days fluoroquinolone or 3rd generation cephalosporin	Self-limited infection, no antibiotic treatment indicated for uncomplicated cases
Treatment of chronic / prolonged infection	30 days fluoroquinolone or 3rd generation cephalosporin	?

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Clinical Infectious Diseases

MAJOR ARTICLE



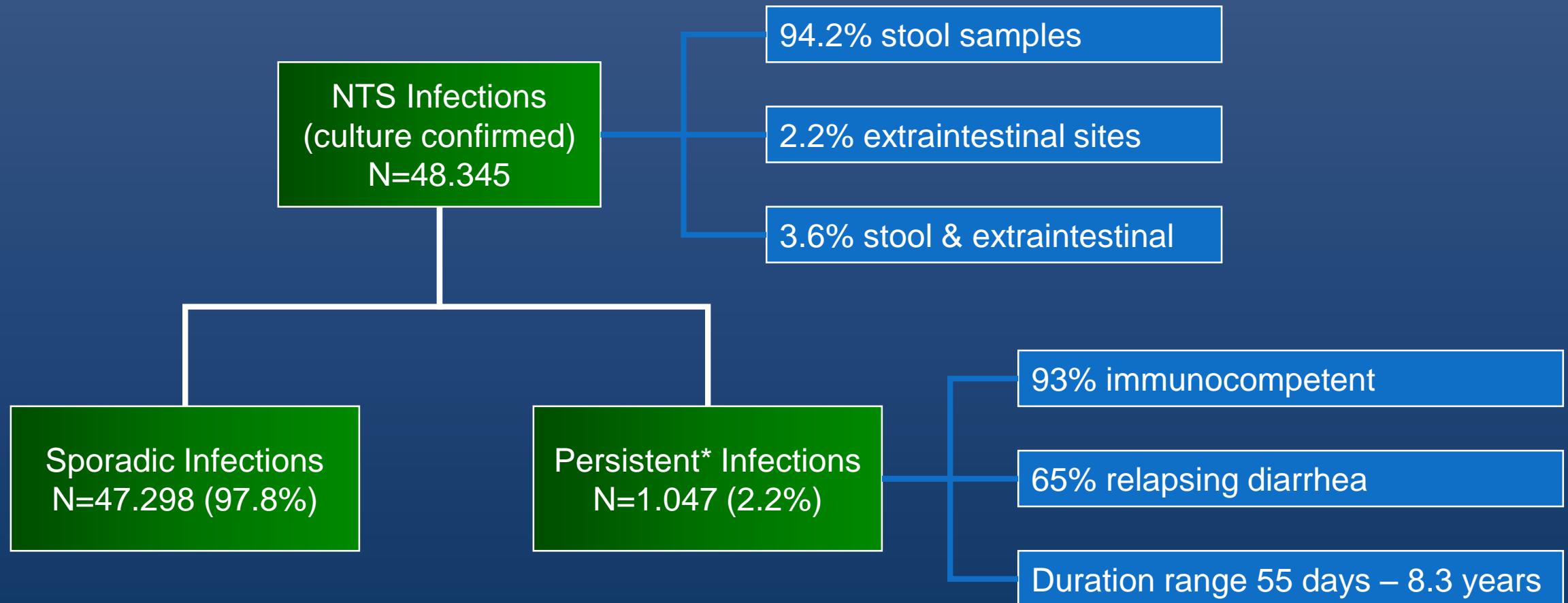
Persistent Infections by Nontyphoidal *Salmonella* in Humans: Epidemiology and Genetics

Alex Marzel,^{1,2,a} Prerak T. Desai,³ Alina Goren,^{1,4} Yosef Ilan Schorr,⁵ Israel Nissan,⁵ Steffen Porwollik,³ Lea Valinsky,⁵ Michael McClelland,³ Galia Rahav,^{1,6} and Ohad Gal-Mor^{1,4}

¹Infectious Diseases Research Laboratory, Sheba Medical Center, Tel-Hashomer, ²Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Israel;

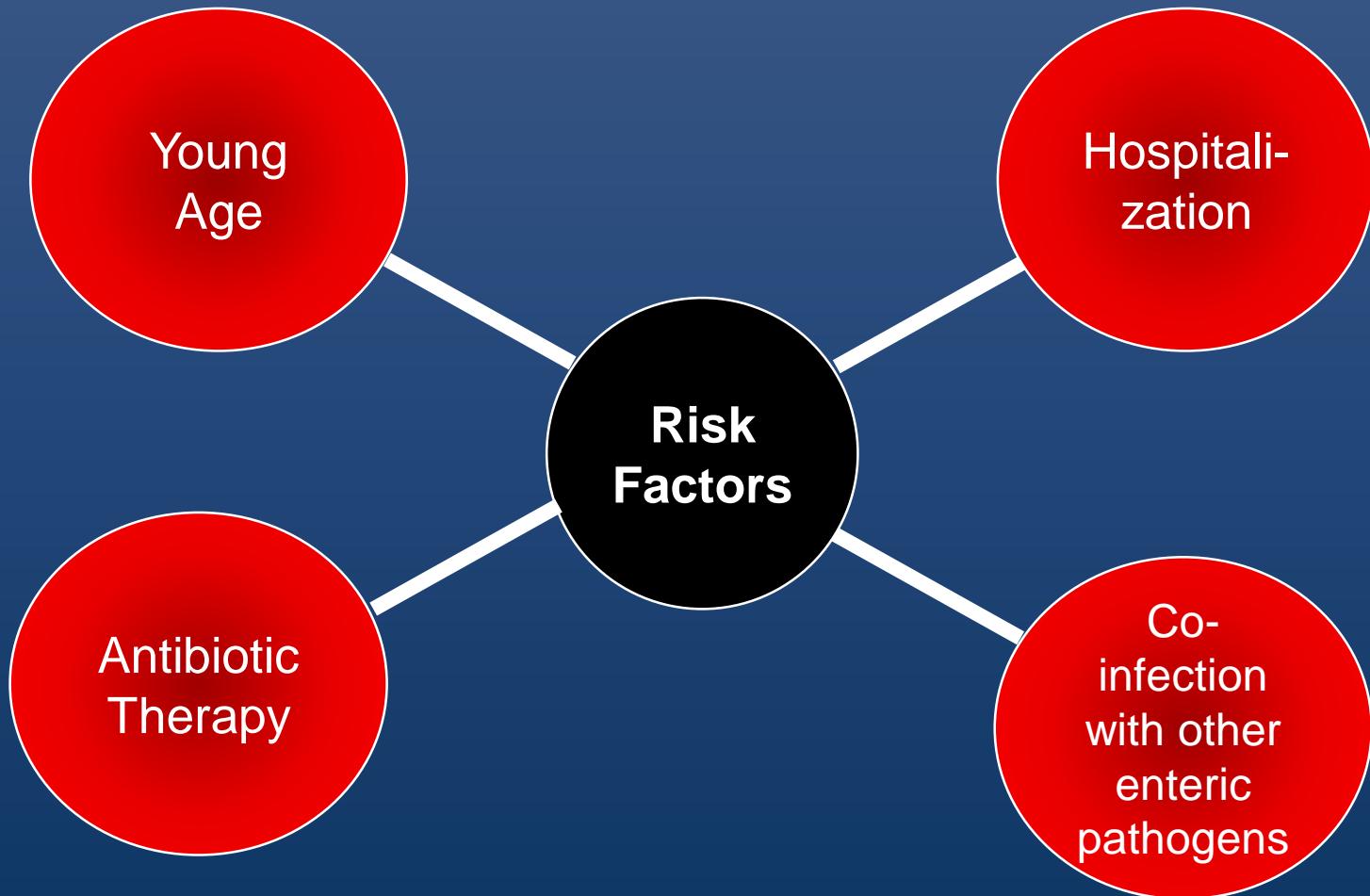
³Department of Microbiology and Molecular Genetics, University of California, Irvine; ⁴Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel Aviv University, ⁵Ministry of Health Central Laboratories, Jerusalem, and ⁶Sackler Faculty of Medicine, Tel Aviv University, Israel

Epidemiology of Persistent Non-Typhoidal Salmonella Infections Israel 1995-2012



*Persistent infection based on the submission of two or more isolates of the same serovar, separated by 30 days or more.

Risk Factors for Symptomatic Persistent Non-typhoidal Salmonella (NTS) Infections

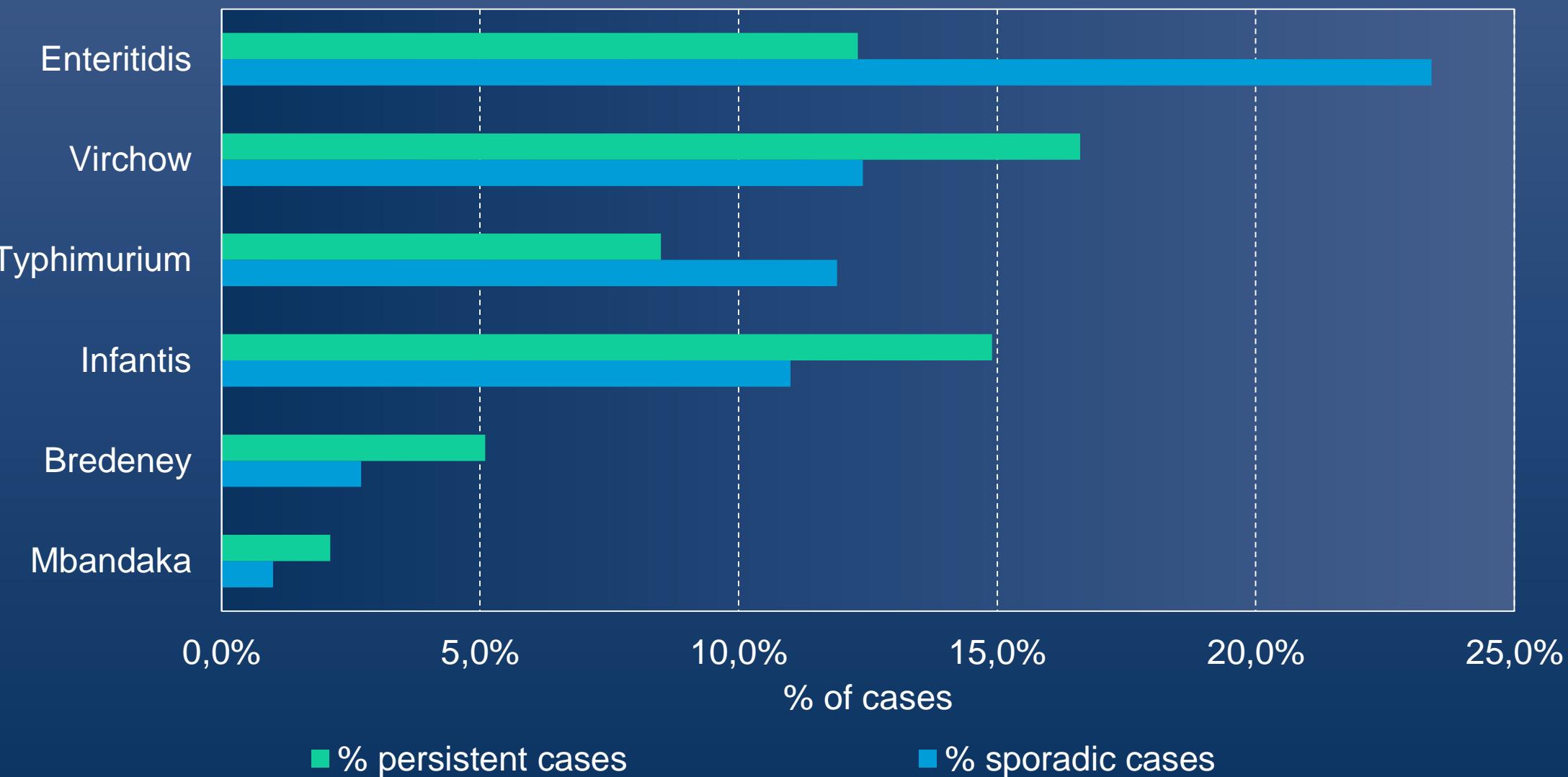


Frequency of Antibiotics Prescribed for Uncomplicated Salmonella Infections

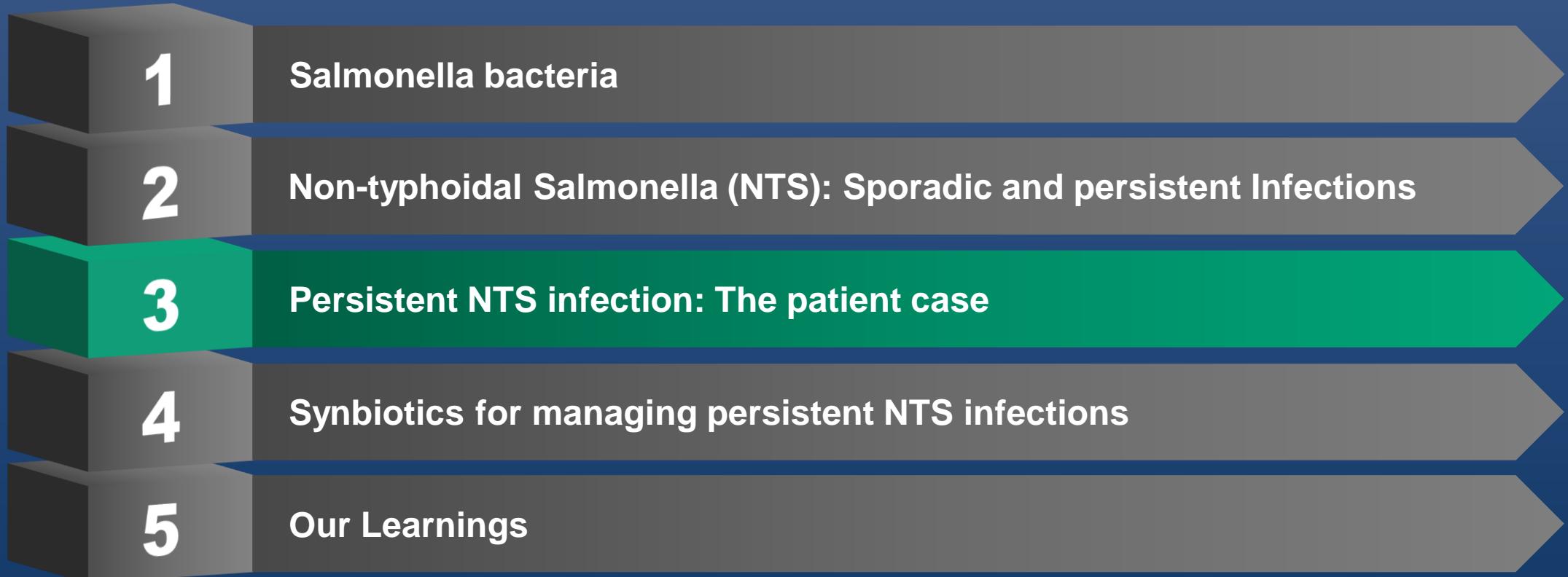
55%

Source: Marzel A, Desai PT, Goren A, et al. Persistent Infections by Nontyphoidal *Salmonella* in Humans: Epidemiology and Genetics. *Clin Infect Dis.* 2016;62(7):879-886.

NTS Servovars and Their Association With Sporadic and Persistent Infections in Humans in Israel



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Africa – Patient Volunteered in an Animal Rescue Centre in Namibia



The image consists of three separate photographs arranged horizontally, all set against a red background. The top-left photograph shows a person in a red shirt holding a large tortoise. The bottom-left photograph is a close-up of a pink, rod-shaped bacterium with cilia, labeled "Salmonella?". The right photograph shows people preparing food in a kitchen setting with various containers and ingredients.

Reptiles

Salmonella?

Food Preparation

Africa – Patient volunteers in an Animal Rescue Centre in Namibia



After several days staying in the camp patients developed the symptoms of infection

Day
1-3

- Extensive diarrhea
- Vomiting
- Stomach cramps
- Fever

On day three patient is visiting a doctor who administered the following treatments

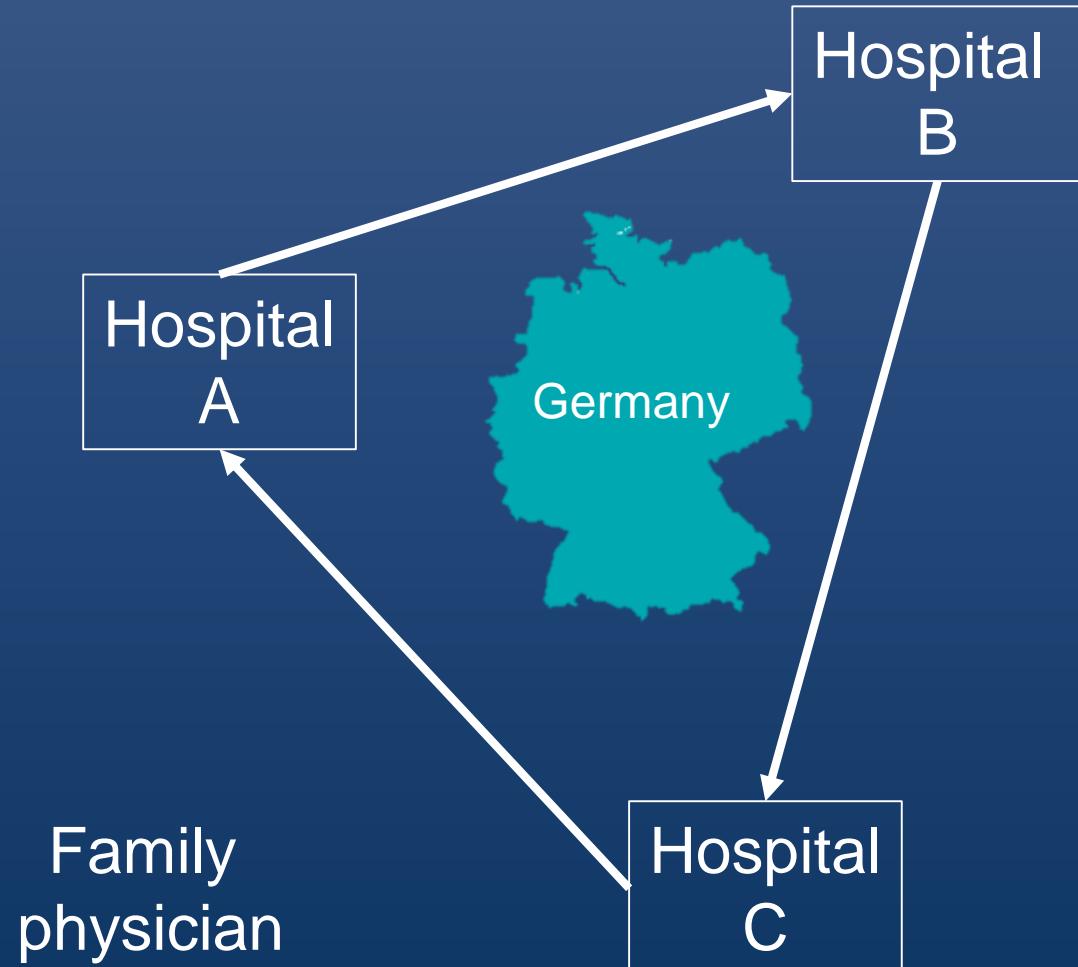
Day
3

- Electrolyte fluid
- Product against stomach pain (product details unknown)
- Injection of an antibiotic (product details unknown)

Transfer of patient from Namibia to Germany (Day 5)



Germany – The Hospital Odysee



Day 6-21 and three hospitals later:

Laboratory tests performed in all three hospitals confirm:

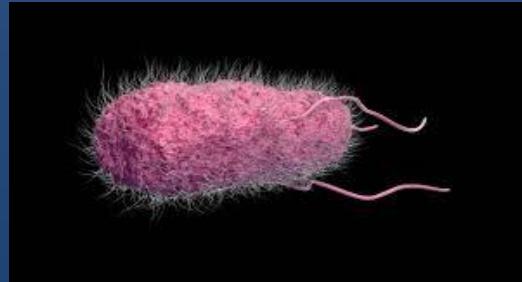
- | | |
|---------------------------|--------------|
| • Salmonella Typhimurium: | high amounts |
| • Shigella: | negative |
| • Yersinia: | negative |
| • Campylobacter: | negative |

Patient situation

- Persistent infection
- Persistent diarrhea

Characterising the Pathogen - Antibiogramm

ANTIBIOTIC RESISTANCE



Salmonella Typhimurium

S. Typhimurium isolated from patient is resistant against

- Penicillin
- Cefaclor
- Cefuroxim
- Doxycyclin
- Erythromycin
- Azithromycin
- Clindamycin
- Gentamycin
- Amikacin

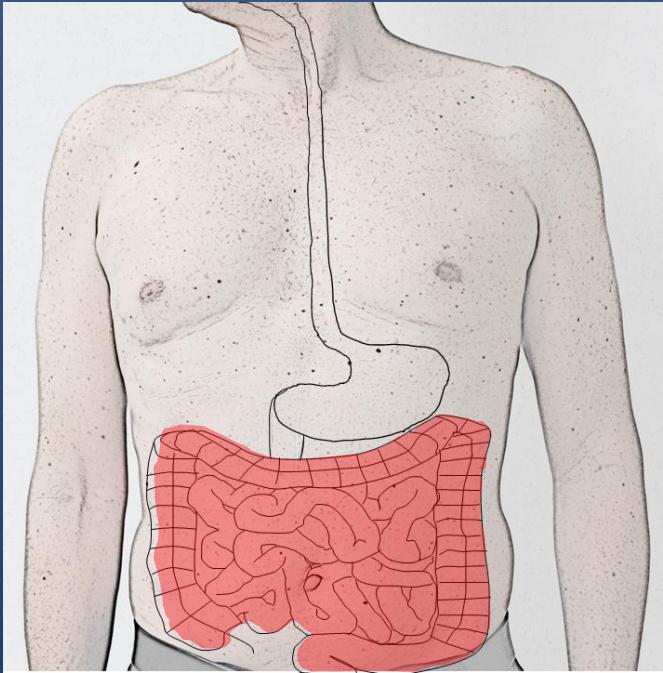
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After 6 Weeks Patient was Treated with a Multistrain Synbiotic

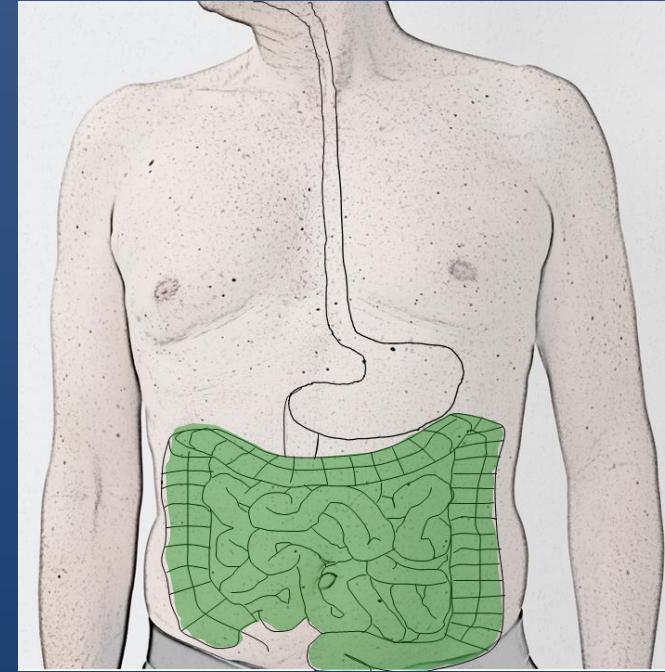


Patient Treatment with Synbiotic Eliminated S. Typhimurium (Induction of Colonization Resistance)



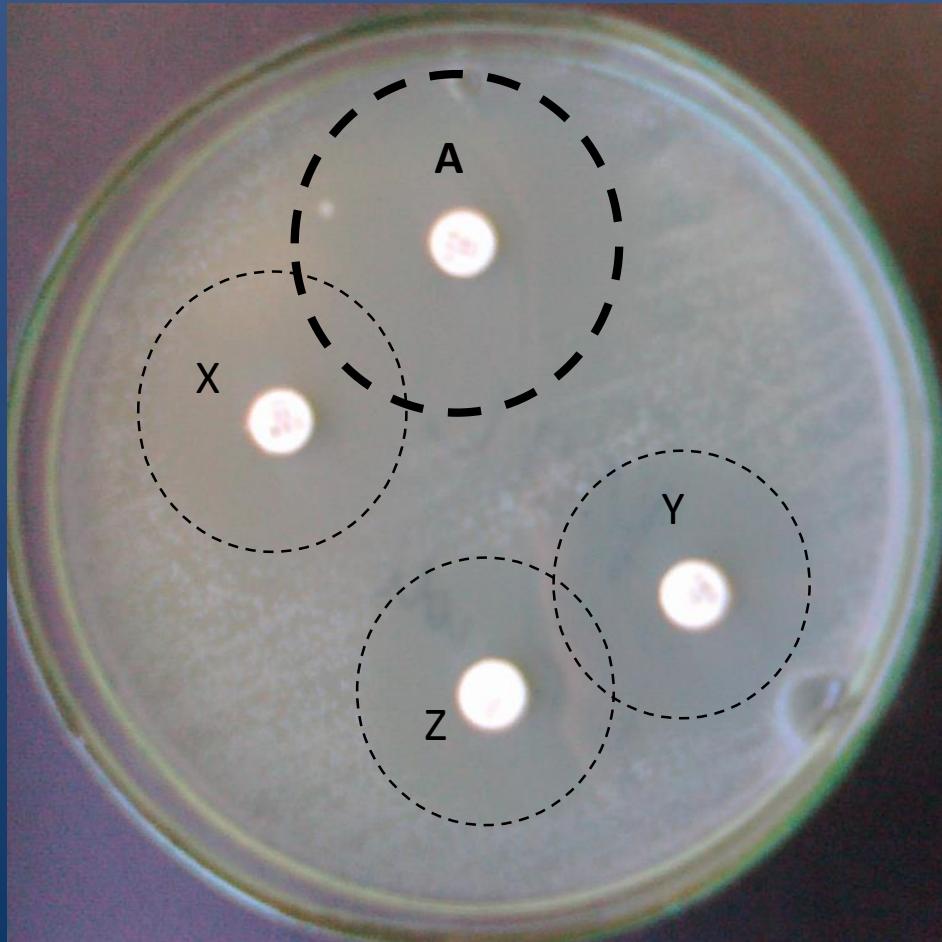
Symptomatic
Patient with persistent
S. Typhimurium
Infection

Treatment with
multistrain
synbiotic
(10 days)



Absence of
S. Typhimurium
in samples
taken from patient

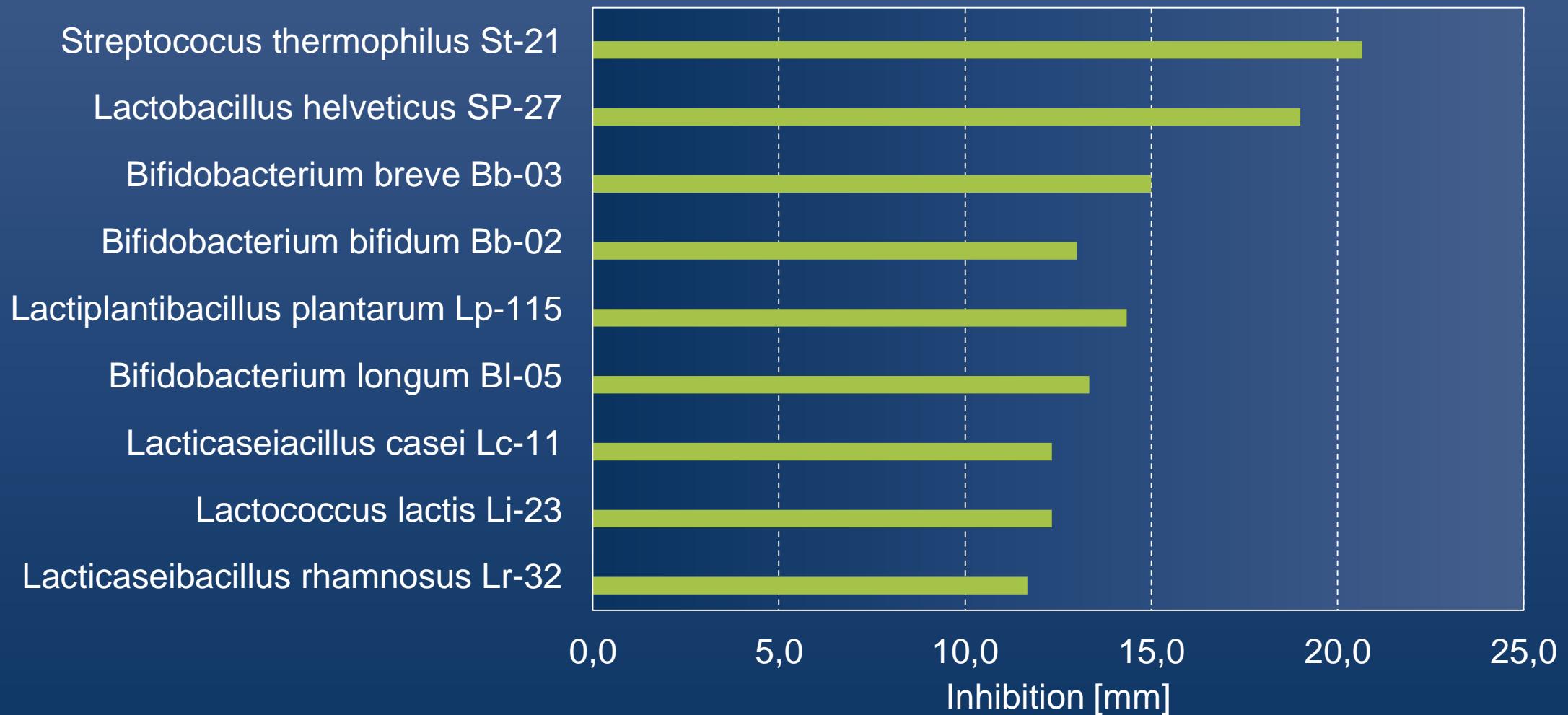
In-vitro Growth Inhibition of S. Typhimurium – Multistrain Synbiotic



A: Inhibition of *S. typhimurium* by a synbiotic mixture containing *Lactobacillus helveticus* SP-27, *Lactococcus lactis* Li-23, *Lacticaseibacillus casei* Lc-11, *Lactiplantibacillus plantarum* Lp-115, *Lacticaseibacillus rhamnosus* Lr-32, *Bifidobacterium longum* Bl-05, *Bifidobacterium breve* Bb-03, *Bifidobacterium bifidum* Bb-02, *Streptococcus thermophiles* St-21 and fructooligosaccharides

X,Y,Z: Inhibition caused by other probiotic and synbiotic mixtures containing a smaller number of probiotic bacterial strains.

In-vitro Growth Inhibition of S. Typhimurium – Individual Probiotics



Our publication is available as open access

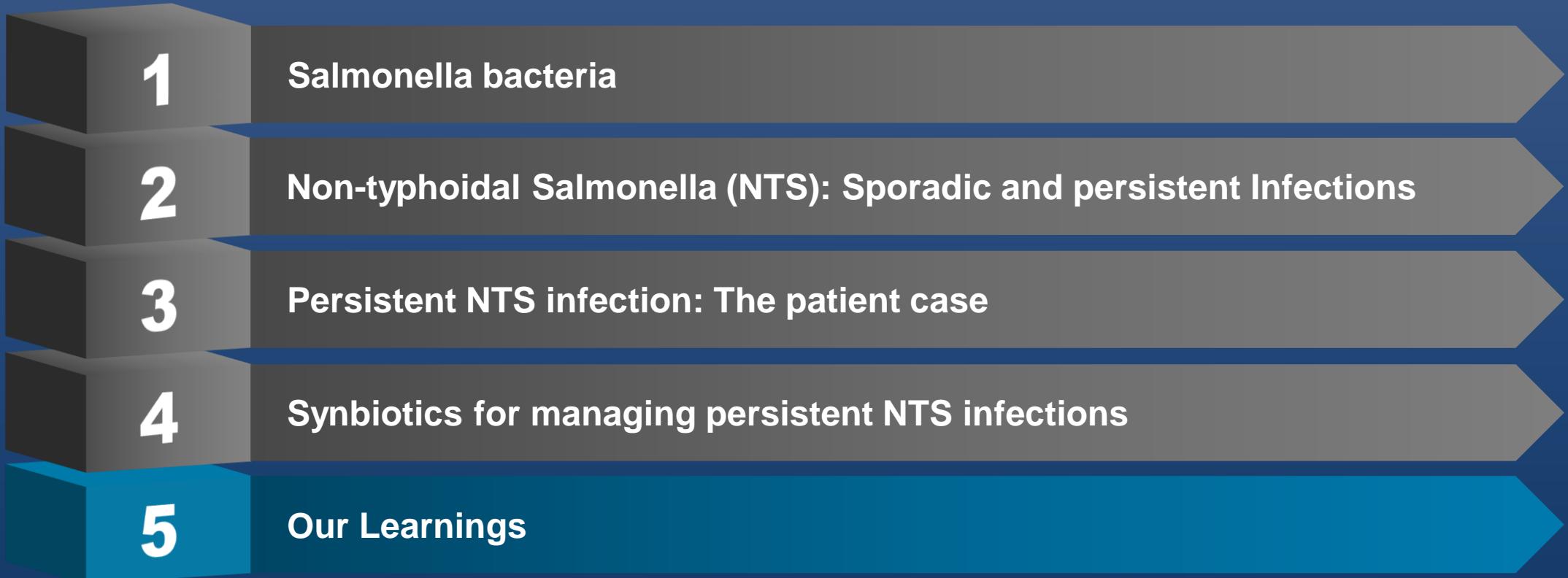
Persistent infection by *Salmonella enterica* serovar Typhimurium: are synbiotics a therapeutic option? – a case report

J. Piatek^{1*}, H. Sommermeyer², M. Bernatek³, A. Ciechelska-Rybarczyk⁴, B. Oleskow⁴, L. Sommer Mikkelsen⁵ and K. Bundvig Barken⁵



<https://www.wageningenacademic.com/doi/10.3920/BM2018.0080>

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Filling two Gaps

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Hosts	Humans (and higher primates)	Humans and animals
Transmission	Fecal-oral	Primarily food-borne
Disease	Typhoid or paratyphoid fever Fever, abdominal pain, diarrhea and/or constipation, flu-like symptoms	Diarrhea, nausea, vomiting
Chronic or prolonged infections	1-4% of all infections	2.2%
Treatment of acute infection	7-10 days fluoroquinolone or 3rd generation cephalosporin	Self-limited infection, no antibiotic treatment indicated for uncomplicated cases
Treatment of chronic / prolonged infection	30 days fluoroquinolone or 3rd generation cephalosporin	Synbiotics

Objectives of Our Awareness Campaign



Awareness

AWARENESS

1

Persistent Non-typhoidal Salmonella Infections is a problem that can be encountered in daily practise

2

Patients with persistent NTS infections are potential sources of community spreading of Salmonella

3

Best practice for management of patients with persistent NTS infections

Antibiotics?

1

Non-typhoidal salmonella infections are normally self-limiting, no need for antibiotic therapy

2

Antibiotic therapy of persistent non-typhoidal Salmonella infection is not recommended

3

Antibiotic therapy is a risk factor for the development of persistent non-typhoidal salmonella infections

Synbiotics?

1

Supporting a diverse and balanced gut-microbiota will limit the risk of salmonella infection (support of colonization resistance)

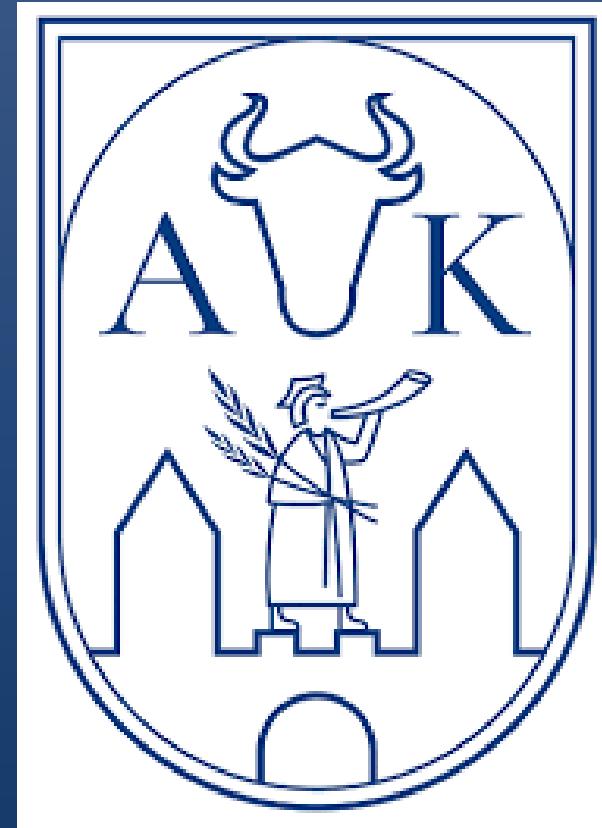
2

Strengthening of colonization resistance will contribute to the eliminate of salmonella from the gut

3

Management of persistent non-typhoidal Salmonella infections should involve administration of a multistrain synbiotic

Questions, Comments & Suggestions



E-mail: h.sommermeyer@akademiakaliska.edu.pl

Components of the Immune System

Innate immune system

- Early response
- Unspecific
- Physical (epithelia) and chemical barriers (antimicrobial chemicals, e.g. bacteriocins)
- Phagocytic cells (neutrophils, macrophages), dendritic cells, natural killer (NK) cells
- Blood proteins (complement system & other mediators of inflammation)

Adaptive immune system

- Late response
- Specific or acquired
- Ability to distinguish (specificity) and to respond more vigorously to repeated exposures to the same antigen (memory)
- Lymphocytes (T-cells, B-cells)
- Products secreted by lymphocytes (antibodies, mediator proteins and peptides)