

Μετεκπαιδευτικό Σεμινάριο Λοιμώξεων «Ενιαία υγεία και λοιμώξεις στη Λεκάνη της  
Μεσογείου / Οστικό Έλλειμμα και Λοίμωξη»  
Αθήνα, 10-11 Μαΐου 2019, Ξενοδοχείο Royal Olympic

Στρογγυλή Τράπεζα: «Διαρροϊκά σύνδρομα»  
**«ΣΑΛΜΟΝΕΛΛΑ, ΣΙΓΚΕΛΛΑ»**

ΓΑΡΥΦΑΛΛΙΑ ΠΟΥΛΑΚΟΥ  
ΠΑΘΟΛΟΓΟΣ ΛΟΙΜΩΣΙΟΛΟΓΟΣ  
ΕΠΙΚΟΥΡΗ ΚΑΘΗΓΗΤΡΙΑ  
Γ' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΕΚΠΑ  
ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ»



# ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

Καμία σχετική με αυτή την ομιλία

# ΟΞΕΙΑ ΔΙΑΡΡΟΙΑ – ΔΙΑΡΡΟΪΚΑ ΣΥΝΔΡΟΜΑ

## Οξεία διάρροια

- ΥΔΑΡΗΣ ΔΙΑΡΡΟΙΑ
- ΔΥΣΕΝΤΕΡΙΑ
- ΔΙΑΡΡΟΙΑ ΤΑΞΙΔΙΩΤΩΝ

- Οξεία διάρροια (ως 14 ημέρες)
- Χρόνια διάρροια (>1 μήνα)
- Εμμένουσα διάρροια (14ημ-1 μήνα)

# Κλινικά χαρακτηριστικά λοιμώδους διάρροιας

## Προσχηματισμένες τοξίνες

- Έναρξη συμπτωμάτων: 2-8 ώρες
- Εμετοί: συνήθεις
- Κοιλιακά άλγη: ήπια
- Πύο + αίμα: όχι
- Πυρετός: < 37.5

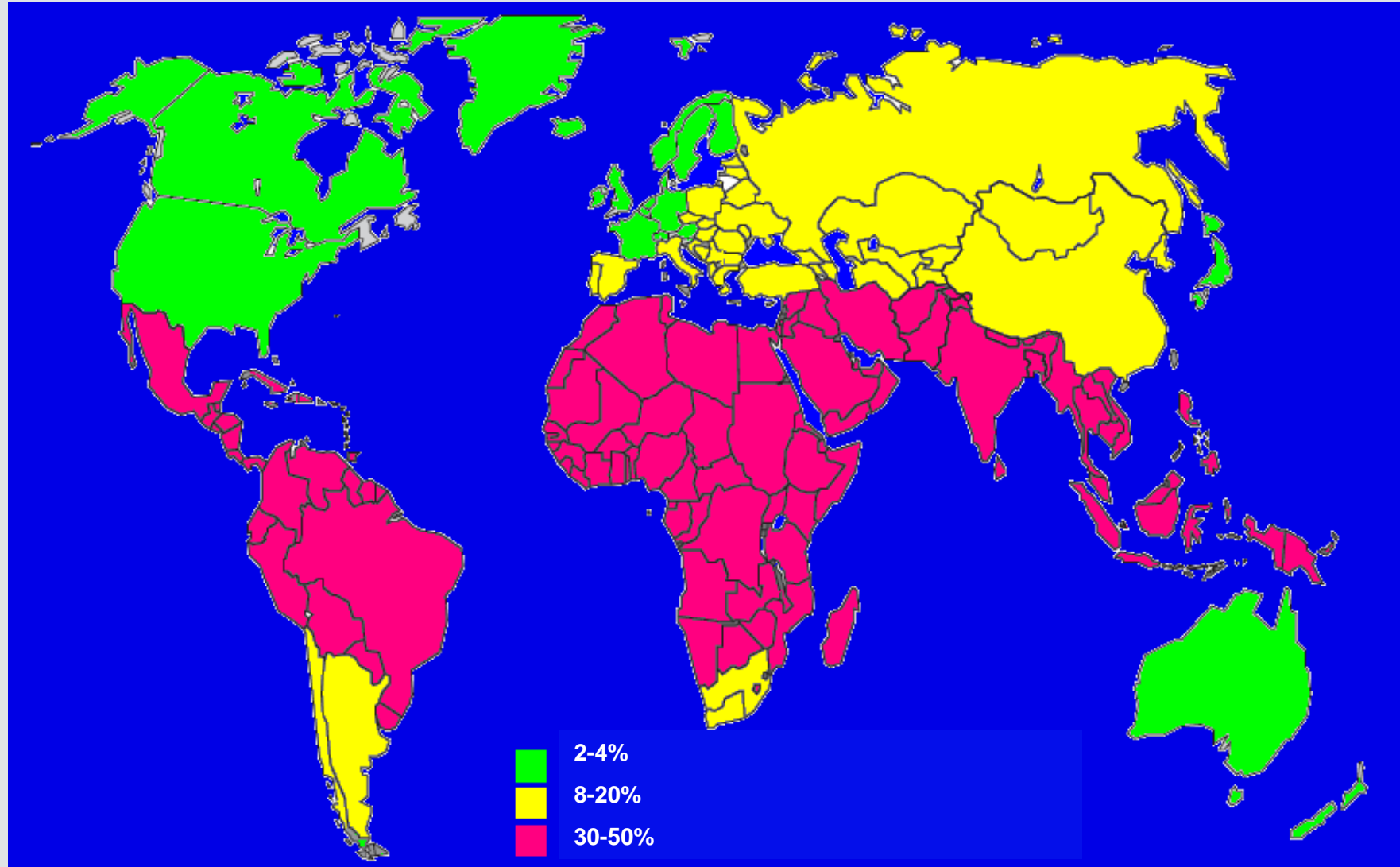
## Προσκολλητικά μικρόβια

- Έναρξη συμπτωμάτων: 5-72 ώρες
- Εμετοί: ασυνήθεις
- Κοιλιακά άλγη: ήπια
- Πύο + αίμα: όχι
- Πυρετός: < 37.5

## Διεισδυτικά μικρόβια

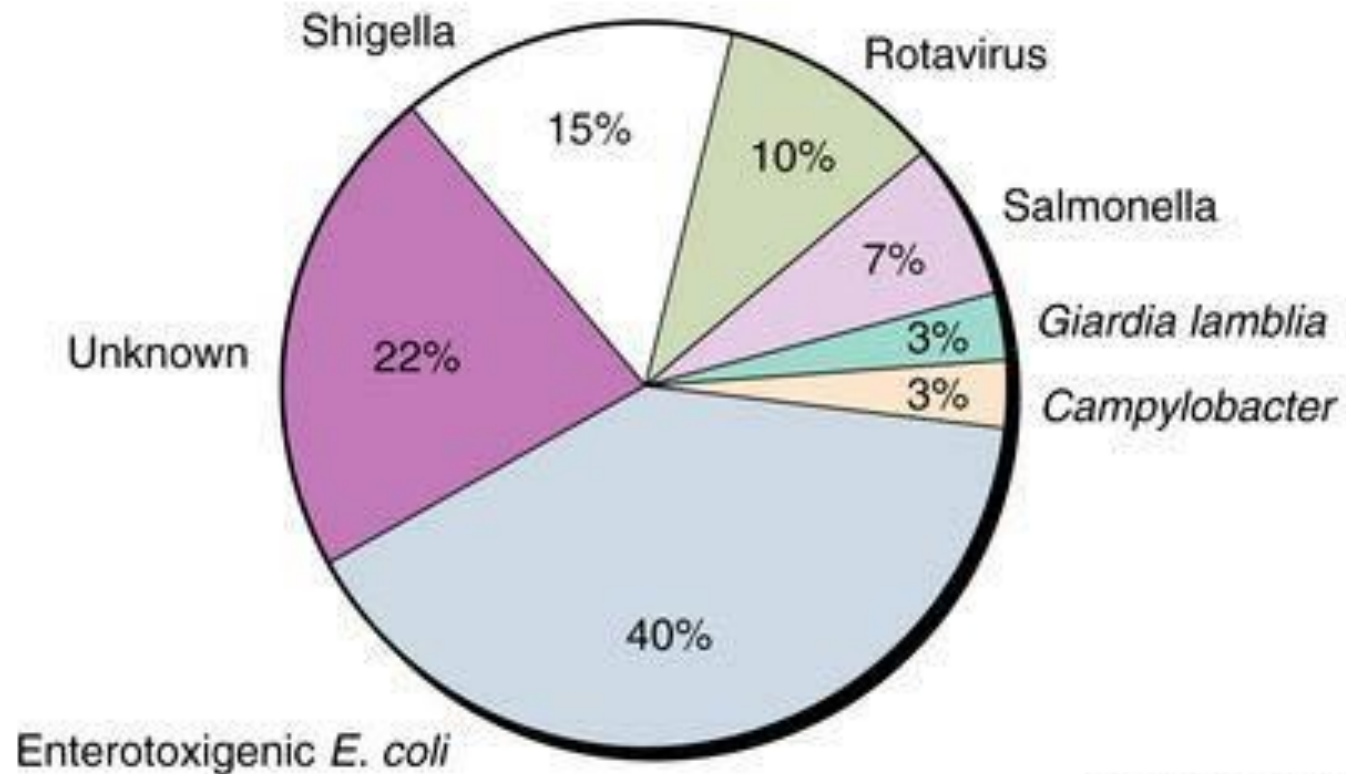
- Έναρξη συμπτωμάτων: 5-72 ώρες
- Εμετοί: ασυνήθεις
- Κοιλιακά άλγη: έντονα
- Πύο + αίμα: ναι
- Πυρετός: > 37.5

# ΔΙΑΡΡΟΙΑ ΤΑΞΙΔΙΩΤΩΝ



## ΔΙΑΡΡΟΙΑ ΤΑΞΙΔΙΩΤΩΝ

80% βακτηριακή  
90% υδαρής διάρροια  
10% μεταλοιμώδες ευερέθιστο έντερο



# ΚΛΙΝΙΚΗ ΠΡΟΣΕΓΓΙΣΗ

## ■ ΙΣΤΟΡΙΚΟ

### Τρόπος μετάδοσης

- Νερό (*Vibrio cholerae*, *Norwalk*, *Giardia*, *Cryptosporidium*)
- Πουλερικά (*Salmonella*, *Campylobacter* and *Shigella*)
- Βοδινό (*Enterohemorrhagic E. coli*, *Taenia saginata*)
- Χοιρινό (σκώληκες)
- Θαλασσινά (*Vibrio cholerae*, *Vibrio parahaemolyticus* *Vibrio vulnificus*; *Salmonella*; tapeworm and anisakiasis)
- Τυρί (*listeria*)
- Μαγιονέζες/κρέμες (*Staphylococcus*, *clostridium perfr*; *Salmonella*)
- Παιδικοί σταθμοί (ιοί, *Shigella*, *Campylobacter*, *Cryptosporidium*, *Giardia*)
- Νοσοκομείο, αντιβιοτικά, χημειοθεραπεία (*C. difficile*)
- Πισίνες (*Giardia* and *Cryptosporidium*)
- Ταξίδι (*E coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Giardia*, *Cryptosporidium*, *Entamoeba histolytica*)

	ΥΔΑΡΗΣ (ΜΗ ΦΛΕΓΜΟΝΩΔΗΣ)	ΦΛΕΓΜΟΝΩΔΗΣ (ΔΥΣΕΝΤΕΡΙΑ)
ΠΑΘΟΓΟΝΟΣ ΜΗΧΑΝΙΣΜΟΣ	Προσκόλληση Παραγωγή εντεροτοξινών	Διείσδυση εντερικό βλεννογόνο Παραγωγή κυτταροτοξινών
ΙΣΤΟΠΑΘΟΛΟΓΙΑ	Απουσία φλεγμονής	Καταστροφή κυττάρων βλεννογόνου → φλεγμονή
ΘΕΣΗ ΛΟΙΜΩΞΗΣ	Λεπτό έντερο, μικρόβια παραμένουν στον αυλό	Παχύ έντερο, μικρόβια διεισδύουν βλεννογόνο
ΚΕΝΩΣΕΙΣ	Μεγάλου όγκου, υδαρείς	Συχνές, μικρού όγκου με βλέννη, αίμα
ΠΜΝ ή ΛΑΚΤΟΦΕΡΡΙΝΗ	Όχι	Ναι
ΛΟΙΜΟΓΟΝΟΙ ΠΑΡΑΓΟΝΤΕΣ	<ul style="list-style-type: none"> <li>● <i>ETEC, EPEC</i></li> <li>● <i>B. cereus, C. perfringens, S. Aureus, V. cholerae</i></li> <li>● Caliciviruses (Noro-, Sapo-)</li> <li>● Rotavirus, Adenovirus</li> <li>● Giardia , Cryptosporidium</li> </ul>	<ul style="list-style-type: none"> <li>● <i>Campylobacter,</i></li> <li>● <i>Salmonella, Shigella,</i></li> <li>● <i>C. difficile, Yersinia spp</i></li> <li>● <i>Aeromonas, STEC,</i></li> <li>● <i>Plesiomonas</i></li> <li>● CMV</li> <li>● <i>E. histolytica</i></li> </ul>



# Ποιοι χρειάζονται ειδικές εξετάσεις;

- Βαριά αφυδάτωση – πυρετός
- Παρατεταμένη διάρροια
- Νοσοκομειακοί ασθενείς
- Αίμα στις κενώσεις
- Ανοσοκατασταλμένοι

# Ποιες εξετάσεις;

Έρευνα για λευκά και ερυθρά αιμοσφαίρια σε νωπά κόπρανα

( - ) : Συμπτωματική θεραπεία

( + ) : Καλλιέργεια κοπράνων

# The Big 4 found on 233,000 stool cultures

1.	<i>Campylobacter</i>	1.4 %
2.	<i>Salmonella</i>	0.9%
3.	<i>Shigella</i>	0.6%
4.	<i>E. coli</i> O157:H7 (STEC)	0.3%

**Total yield from stool cultures is 5.8%**

# Διαφορική Διάγνωση λοιμώδους διάρροιας

- *Campylobacter* Infections
- Shigellosis
- Salmonellosis
- Cryptosporidiosis
- *Cyclospora* Infection
- *Escherichia coli* (E coli) Infections
- *Listeria Monocytogenes* Infection
- *Vibrio* Infections
- *Yersinia Enterocolitica*

- **Με ποια κλινική εικόνα;**
- **Σε ποιο ξενιστή;**
- **Σε ποιο επιδημιολογικό σενάριο;**

## Κλινικά χαρακτηριστικά εντερικής λοίμωξης από τα κυριότερα εντεροπαθογόνα

Παθογόνο	Πυρετός	Κοιλιακός πόνος	Αιματηρές κενώσεις	Ναυτία έμετοι	Στοιχεία φλεγμονής στα κόπρανα
<i>Campylobacter</i>	Συχνά	Συχνά	Πιθανά	Πιθανά	Συχνά
<b><i>Salmonella</i></b>	<b>Συχνά</b>	<b>Συχνά</b>	<b>Πιθανά</b>	<b>Πιθανά</b>	<b>Συχνά</b>
<b><i>Shigella</i></b>	<b>Συχνά</b>	<b>Συχνά</b>	<b>Πιθανά</b>	<b>Συχνά</b>	<b>Συχνά</b>
STEC	Όχι πιθανό	Συχνά	Συχνά	Πιθανά	Όχι Συχνά
<i>C. difficile</i>	Πιθανά	Πιθανά	Πιθανά	Όχι πιθανό	Συχνά
<i>Vibrio</i>	Ποικίλλει	Ποικίλλει	Ποικίλλει	Ποικίλλει	Ποικίλλει
<i>Yersinia</i>	Συχνά	Συχνά	Πιθανά	Πιθανά	Πιθανά
Norovirus	Ποικίλλει	Συχνά	Όχι	Συχνά	Όχι



# ΔΙΑΓΝΩΣΤΙΚΗ ΠΡΟΣΠΕΛΑΣΗ ΛΟΙΜΩΔΟΥΣ ΔΙΑΡΡΟΙΑΣ

## ΙΣΤΟΡΙΚΟ-ΚΛΙΝΙΚΗ ΕΚΤΙΜΗΣΗ

Διάρκεια συμπτωμάτων (>48 ώρες)  
Στοιχεία φλεγμονής (πυρετός, αιματηρές κενώσεις, τεινεσμός), συνυπάρχοντα νοσήματα, ανοσοκαταστολή, ηλικία >70, σημεία αφυδάτωσης, συστηματική τοξικότητα



## ΕΠΙΔΗΜΙΟΛΟΓΙΚΑ ΣΤΟΙΧΕΙΑ

Κατανάλωση ύποπτης τροφής, ταξίδι, επιδημίες, νοσηλεία, λήψη φαρμάκων (αντιβιοτικά, αντιόξινα) εποχή του χρόνου, εργασία σε παιδικούς σταθμούς κ.λ.π.



# Καλλιέργεια κοπράνων

(McConkey, ειδικά-SS agar, 35-37°C, O<sub>2</sub>, 24h)

## Από την κοινότητα/ διάρροια ταξιδιωτών

Καλλιέργεια για *Salmonella*,  
*Campylobacter*, *Shigella*,  
*E. Coli* O157:H7  
Αντισώματα για *Yersinia*

## Επίμονη διάρροια

*Giardia*,  
Αμοιβάδα,  
*Cryptosporidium*,  
*Cyclospora*,  
*Isospora belli*  
**Κολονοσκόπηση!**

## Νοσοκομειακός ασθενής

Τοξίνη A & B *C. difficile*  
**Ανοσοκατασταλμένος/  
ουδετεροπενικός**  
*Salmonella*, *Shigella*.  
*Campylobacter*, *E. Coli* O157:H7

## HIV (+)

*Cryptosporidium*,  
*Microsporidia*,  
*Mycobacterium avium*  
complex, *Isospora belli*  
*Cytomegalovirus*

# Νέα επιδημιολογικά σενάρια

## New Food Vehicles

○ Bagged spinach

*E. coli* O157:H7

○ Carrot juice

**Botulism**

○ Peanut butter

○ Dog food

*Salmonella* spp

○ Pot pies

○ Broccoli powder on snack food

○ Hot peppers

○ White pepper

○ **Infant formula**

○ Canned chili sauce

○ Raw cookie dough

○ Whole, raw papaya

○ Hazelnuts

○ Pine nuts





## Θεραπεία

Η **ενυδάτωση** πρέπει να αρχίζει ακόμα και πριν την πλήρη αξιολόγηση του αρρώστου

### Αντιδιαρροϊκά

#### Λοπεραμίδη

- Η χορήγησή της σχετίζεται με παράταση του πυρετού σε ασθενείς με σιγκέλλωση
- Αυξημένο κίνδυνο αναπτύξεως τοξικού megacolon σε ασθενείς με διάρροια από *C. difficile*
- Αυξημένο κίνδυνο ανάπτυξης αιμολυτικού-ουραιμικού συνδρόμου σε παιδιά με διάρροια από στελέχη STEC



**Απαγορεύεται η χρήση της σε ασθενείς με αιματηρή διάρροια ή εικόνα φλεγμονώδους διάρροιας**

# Αντιμικροβιακή Θεραπεία:σε ποιους;

- Η κατάλληλη αντιμικροβιακή αγωγή είναι αποτελεσματική στη θεραπεία της :
  - Διάρροιας από *Shigella*
  - Σοβαρής μορφής διάρροιας ταξιδιωτών
  - *Clostridium difficile*-associated diarrhea (CDAD)
  - Διάρροιας από *Campylobacter* (εντός τεσσάρων ημερών από έναρξη συμπτωμάτων)
- Η αντιμικροβιακή θεραπεία ενδέχεται να :
  - Παρατείνει χρόνο φορέας nontyphoid *Salmonella*
  - Επάγει φάγους που κωδικοποιούν την παραγωγή shiga-τοξίνης από STEC (↑ κινδύνου εμφάνισης αιμολυτικού ουραιμικού συνδρόμου)

## Recommendations for the Treatment of Organism-Specific Enteric Infection in Adults

NEJM 2014

Παθογόνο	Αντιμικροβιακή Θεραπεία	Παρατηρήσεις
<i>Campylobacter</i>	Azithromycin, 500 mg X1, 3 ημ Erythromycin 500 mg X4, 5 ημ	Θεραπεία σε σοβαρές περιπτώσεις. Αντοχή κινολόνες
<i>Salmonella</i> (non typhoidal)	Δεν απαιτείται στις ήπιες μορφές	Σοβαρή διάρροια, υψηλός πυρετός Αυξημένο κίνδυνο βακτηριαμίας Levofloxacin, or Ciprofloxacin 7-10 ημ Azithro?
Enteric fever Bacteremic salmonellosis	Φθοριοκινολόνη ή iv κεφαλοσπορίνη 7 ημ	≥ 14 ημ ανοσοκαταστολή Μακρές θεραπείες σε επιπλεγμένη νόσο
<i>Shigella</i>	Ciprofloxacin, 750 mg X1, 3 ημ Azithromycin, 500 mg X1, 3 ημ	
<i>Vibrio cholerae</i>	Doxycycline, 300 mg εφάπαξ	Παιδιά: Azithromycin 3 ημ
Noncholeraic vibrio	Ciprofloxacin, 750 mg X1, 3 ημ Azithromycin, 500 mg X1, 3 ημ	Θεραπεία σε σοβαρές περιπτώσεις

Βρέφη, άτομα άνω των 65 ετών, ασθενείς με λεμφοϋπερπλαστική νόσο, αιμοσφαιρινοπάθεια, καρκίνο, AIDS, μεταμοσχευμένοι, φέροντες αγγειακά μοσχεύματα ή άλλα προθέματα (πχ αρθροπλαστική, stents), ασθενείς με βαλβιδοπάθεια, λαμβάνοντες κορτικοειδή

## ΝΟΣΗΜΑΤΑ ΥΠΟΧΡΕΩΤΙΚΩΣ ΔΗΛΟΥΜΕΝΑ

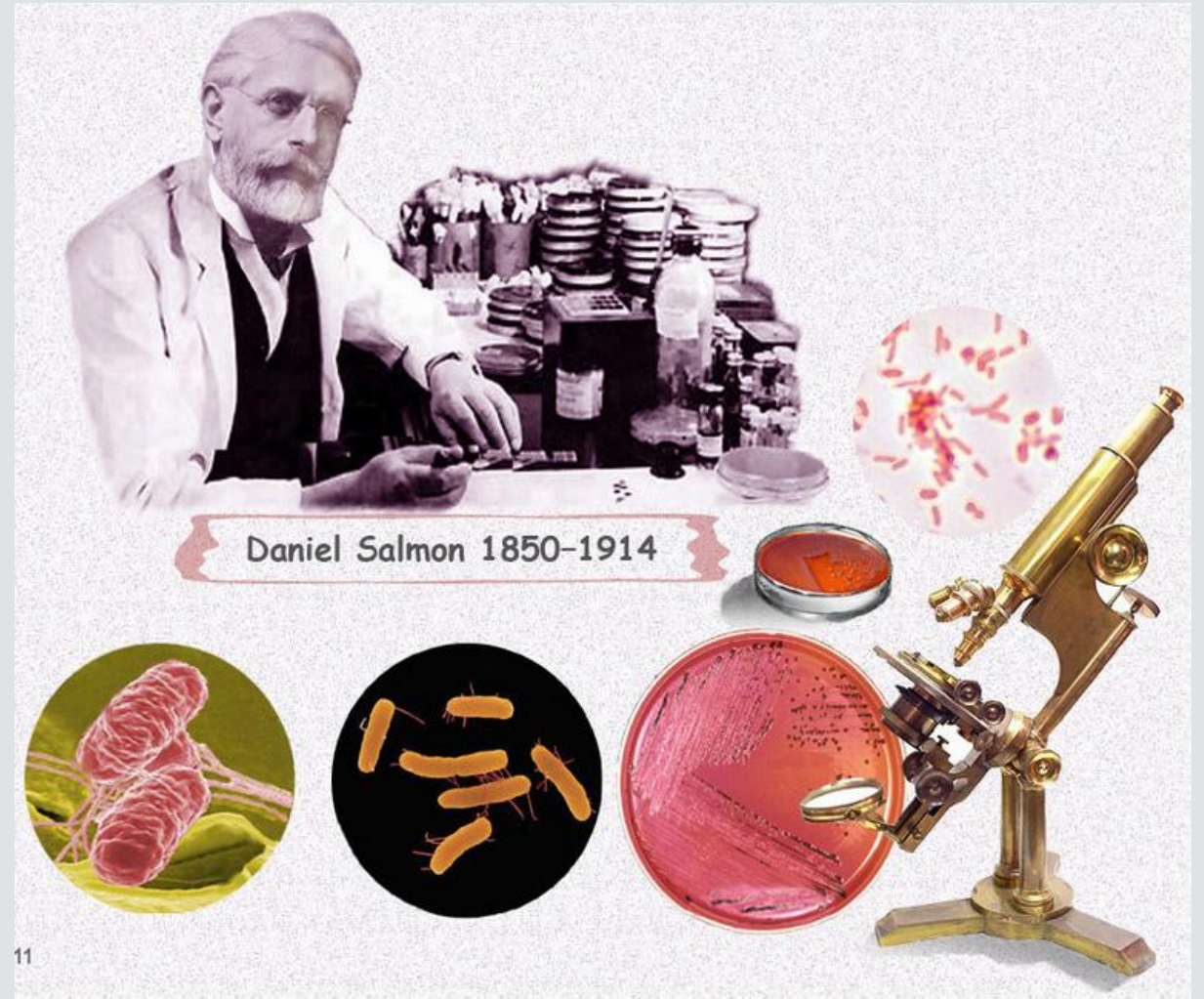
- **Συρροές κρουσμάτων** τροφιμογενούς-υδατογενούς νοσήματος (δύο ή περισσότερα συνδεδεμένα περιστατικά για τα οποία υπάρχει ένδειξη ότι είναι τροφιμογενούς ή υδατογενούς αιτιολογίας)
- *Salmonella*
- *Shigella*
- **STEC**
- *Vibrio cholerae*

Υποχρεωτική δήλωση στην οικεία Δ/νση Υγείας της Νομαρχιακής Αυτοδιοίκησης ή/και το Κέντρο Ελέγχου και Πρόληψης Νοσημάτων (ΚΕΕΛΠΝΟ)

- Σε περιπτώσεις επιδημιών τα καλλιεργήματα και τα δείγματα (κόπρανα) φυλάσσονται σε θερμοκρασία  $-70^{\circ}\text{C}$

# History

“Salmonella” derived from Dr. Salmon, a U.S. veterinary surgeon, who discovered and isolated the strain enterica or choleraesuis from the intestine of a pig in 1885





# More history

Some historical figures are believed to have been killed by *Salmonella*

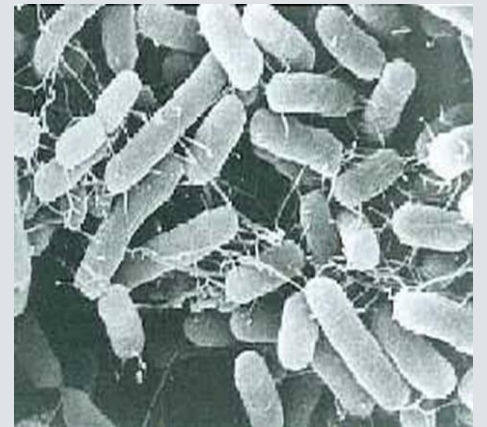


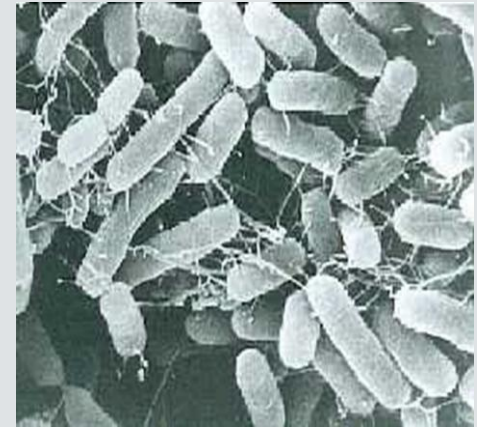
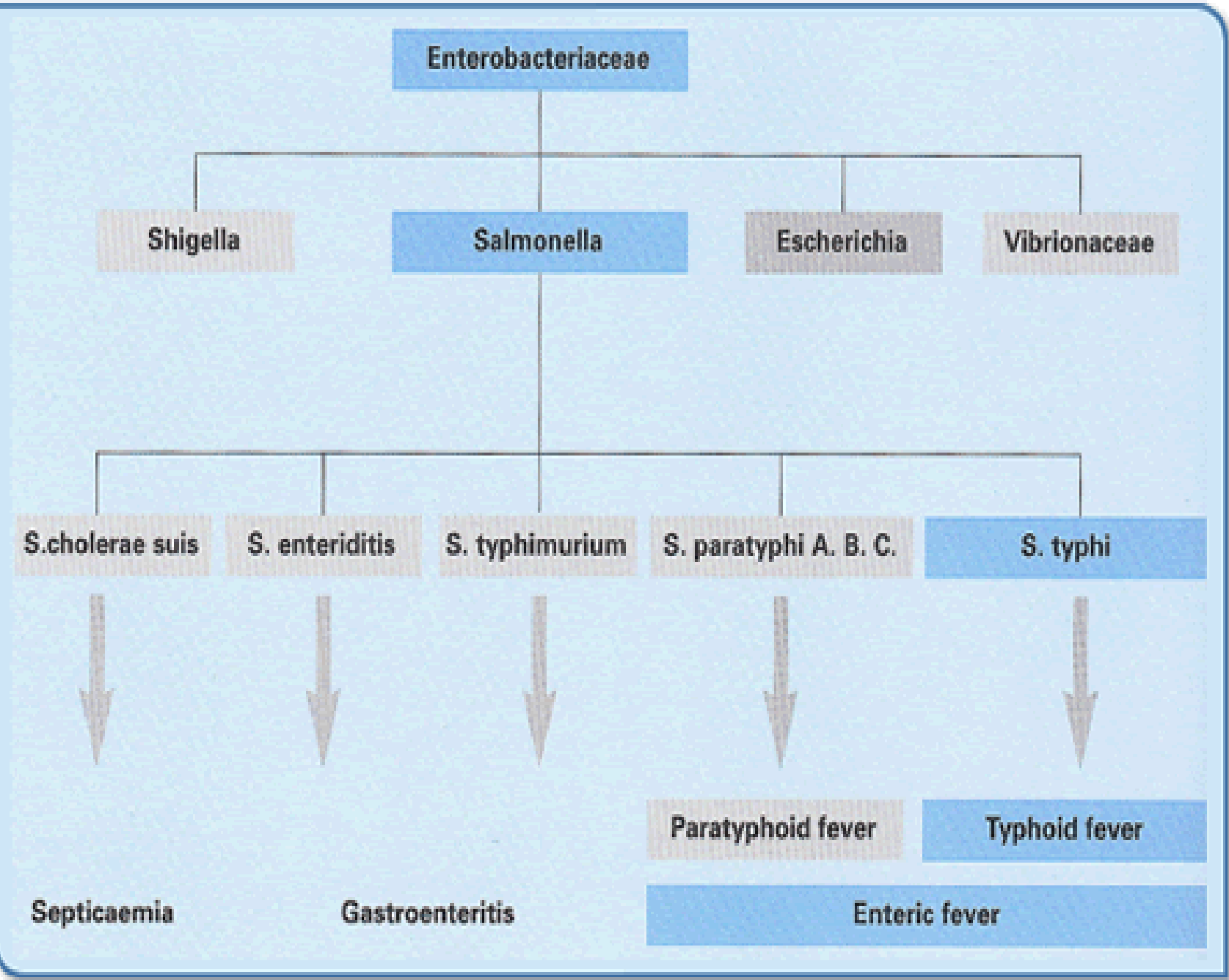
- Alexander the Great died mysteriously in 323 B.C. In 2001, a group of doctors at the University of Maryland suggested that *Salmonella* was the cause of death, based on a description of Alexander's symptoms written by the Greek author Arrian of Nicomedia
- Prince Albert, the consort of Queen Victoria, died of a *Salmonella* infection in 1861, a diagnosis made by his doctor, William Jenner. During the Victorian era, an estimated 50,000 cases per year occurred in England.
- Although the contemporary diagnosis was typhoid fever, symptoms starting 2 years prior to his death indicate an underlying chronic disease, such as Crohn's disease or abdominal cancer



# Epidemiology-Microbiology *Salmonella*

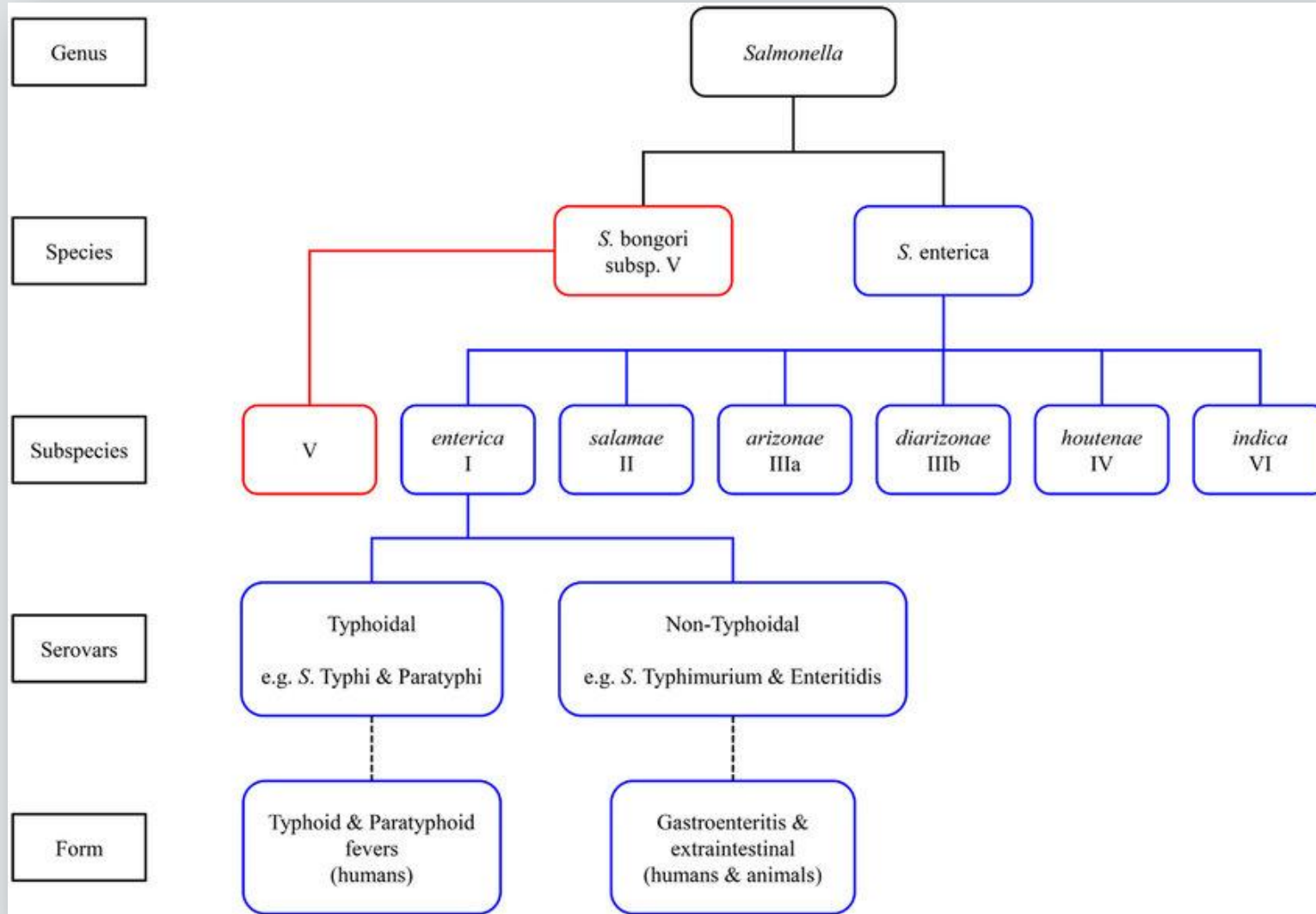
- *Salmonella* is a rod-shaped, gram-negative, facultative anaerobe in the family Enterobacteriaceae
- 2 species, *Salmonella bongori* and *Samonella enterica*, over 2500 different serotypes or serovars have been identified to date.
- *Salmonella* is a ubiquitous and hardy bacteria that can survive several weeks in a dry environment and several months in water
- They are ingested orally by contaminated food or water
- Refrigeration prevents growth but does not kill bacteria
- Heating at 57-60°C has shown to be effective in killing the bacteria
- Optimal growth: 37°C







# Salmonella taxonomy



# Principal habitats in different types of Salmonella

## The WHO groups Salmonella into 3 types:



### 1. Typhoidal (enteric) *Salmonella* (example: *S. typhi*)

- causes typhoid and paratyphoid fever
- **restricted to growth in human hosts**
- principal habitat is in intestinal tracts and the bloodstream

### 2. Nontyphoidal *Salmonella* (example: *S. enteritidis*, *S. typhimurium*)

- Prevalent in gastrointestinal tracts of various animals, including mammals, reptiles, birds and insects, house and exotic pets
- **Cause a whole range of diseases in animals and humans, mainly gastroenteritis**
- usually transferred animal-to-person, through certain food products: fresh meat, poultry, eggs and milk, fruits, vegetables, seafood, contamination through contact with pets' feces

### 3. *Salmonella* restricted to animals

- *Salmonella enterica* serotype Dublin in cattle and *Salmonella enterica* serotype Choleraesuis in pigs
- **Rarely in humans but very severe disease**



# Non typhoidal *Salmonella*



World Health  
Organization

- The onset of disease symptoms occurs 6–72 hours (usually 12–36 hours) after ingestion of *Salmonella*, and illness lasts 2–7 days
- Symptoms of salmonellosis are relatively mild and patients will recover without specific treatment
- Severe and life-threatening disease: in children and elderly patients (associated dehydration)
- Antimicrobial resistance is a global public health concern
- *Salmonella* is one of the microorganisms in which resistance affects the food chain
- Basic food hygiene practices, such as "cook thoroughly", "preserve in high temperatures" are recommended as a preventive measure against salmonellosis

[https://www.who.int/en/news-room/fact-sheets/detail/salmonella-\(non-typhoidal\)](https://www.who.int/en/news-room/fact-sheets/detail/salmonella-(non-typhoidal))

# Non typhoidal-*Salmonella* type of infection

- **Enteric:** an infection of the gastrointestinal tract
- **Extra-intestinal:** an infection occurring outside the intestine
- **Gastroenteritis:** inflammation of the stomach and large and small intestines that may result in vomiting or diarrhea
- **Invasive infection:** an infection of the bloodstream, bone, joint, brain, or nervous system

[https://www.who.int/en/news-room/fact-sheets/detail/salmonella-\(non-typhoidal\)](https://www.who.int/en/news-room/fact-sheets/detail/salmonella-(non-typhoidal))



# Salmonellosis



## Key facts

- Salmonellosis is the second most commonly reported gastrointestinal infection and an important cause of foodborne outbreaks in the EU/EEA.
- In 2016, 95 326 laboratory-confirmed cases were reported out of which 134 were fatal.
- The EU/EEA notification rate was 20.4 cases per 100 000 population.
- Salmonellosis notification rates have stabilised in the last five years after a long period that was marked by a declining trend.
- The reported case rate was highest in young children 0–4 years with 89.9 cases per 100 000 population, seven times higher than in adults 25–64 years.

# Σαλμονέλλωση στην Ευρώπη: Επιδημιολογικά δεδομένα

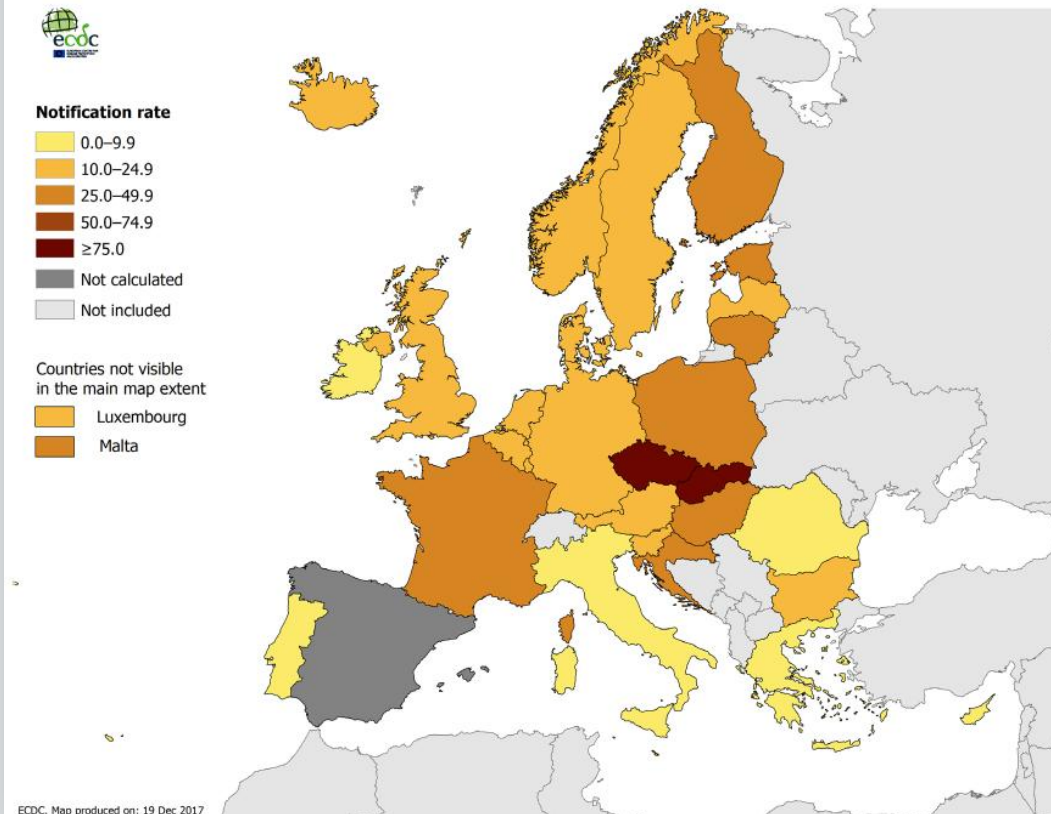


- **In 2016, Salmonella was the most common cause of foodborne outbreaks, accounting for 22% of all reported foodborne outbreaks (1 067)**
- **Eggs and egg products continued to be the most commonly identified vehicles in these outbreaks and were also the source in the large multi-country outbreak linked to eggs from Poland**
- **The large egg outbreak affected at least 14 EU/EEA countries and possibly even more since the outbreak case definition was based on typing methods (WGS and MLVA) not yet applied in all countries**
- **The highest notification rates were reported by the Czech Republic (110.0 cases per 100 000 population) and Slovakia (97.7), followed by Hungary (48.0) and Lithuania (37.3). The lowest rate was reported by Portugal (3.6 cases per 100 000).**
- **The largest increase in rates from 2015–2016 was observed in Estonia (213%) and Greece (59%)**

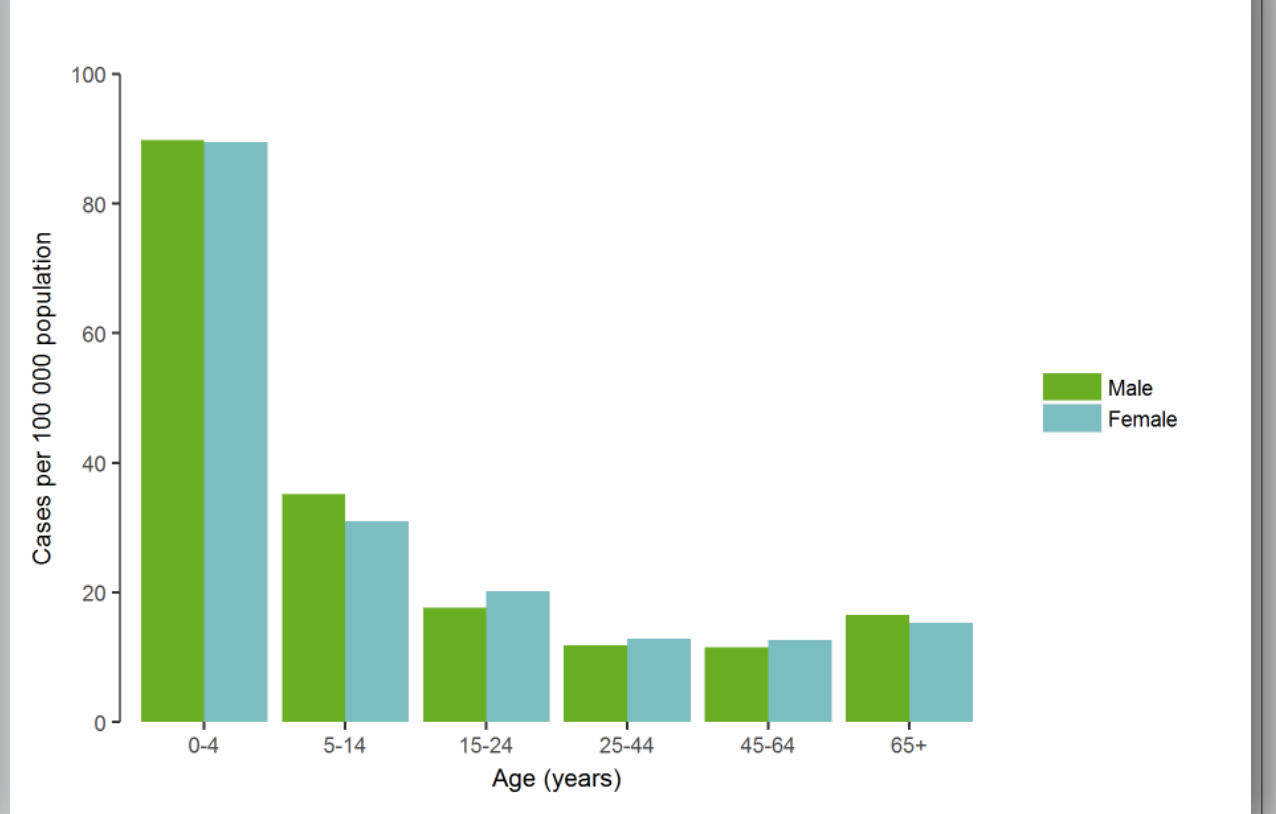


# Distribution of salmonellosis by country and age

**Figure 1.** Distribution of confirmed salmonellosis cases per 100 000 population by country, 2016



**Figure 4.** Distribution of confirmed salmonellosis cases per 100 000 population by age and gender, EU/EEA, 2016



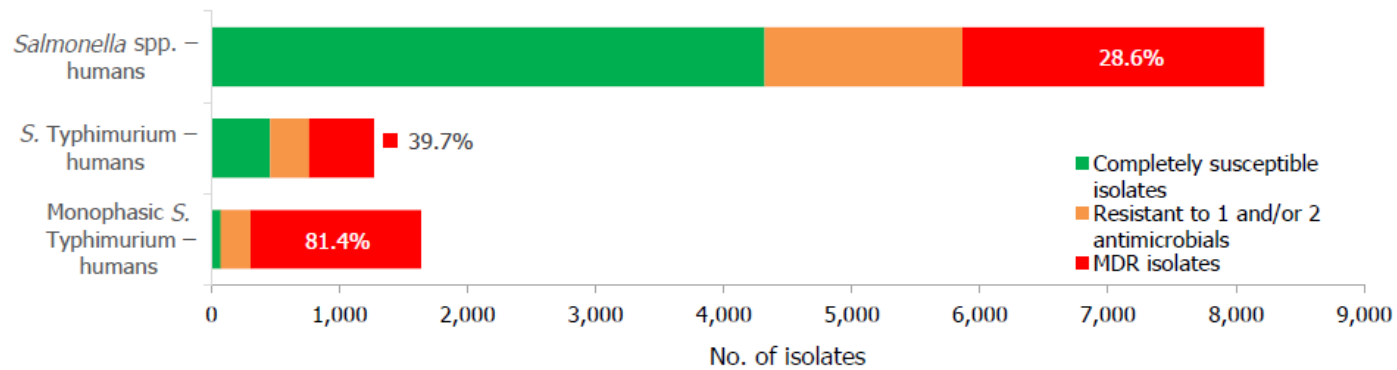
# Salmonella in Europe: travel or domestic?



- **Of 61 014 cases with known travel history, 9 908 (16%) were reported as travel-associated.**
- **The highest proportions of domestic cases ranging from 93% to 100% were reported in the Czech Republic, Estonia, **Greece**, Hungary, Latvia, Lithuania, Malta, the Netherlands, Portugal, Romania, Slovakia and Spain.**
- **The highest proportions of travel-related cases were reported by three Nordic countries: Finland (79%), Norway (78%) and Sweden (71%).**
- **Among the 8 337 travel-associated cases with known information on probable country of infection, Thailand, Turkey and India were the most frequently reported travel destinations (16%, 10% and 6% respectively), followed by two EU Member States: **Spain (6%) and Greece (4%).****



## Annual Epidemiological Report for 2016 Salmonellosis

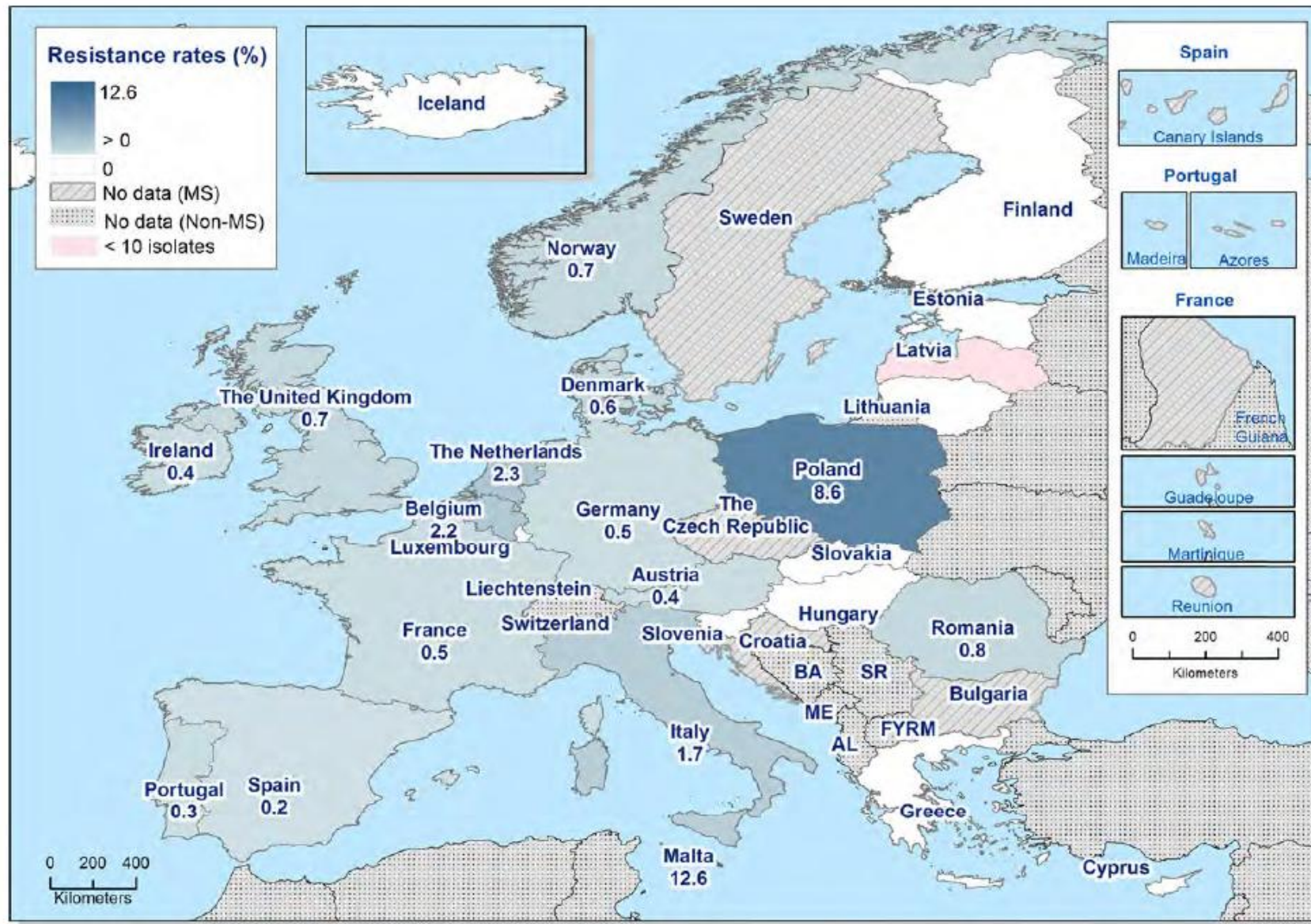


**Figure 1:** Number of MDR isolates, isolates resistant to 1 and/or 2 antimicrobials and completely susceptible *Salmonella* isolates from humans in 2017

## ECDC: antibiotic-resistant *Salmonella*

- Most countries reported that *Salmonella* in humans is increasingly resistant to fluoroquinolones.
- Multidrug resistance (resistance to three or more antimicrobials) is high in *Salmonella* found in humans (28.3%) and animals, particularly in *S. Typhimurium*.
- The proportions of *Salmonella* isolates resistant to either of the clinically important antimicrobials ciprofloxacin and cefotaxime were relatively low overall (13.0% resistant to ciprofloxacin and 1.9% to cefotaxime), except for *S. Kentucky*: 92.6% of the isolates were high-level ciprofloxacin resistant
- No isolates resistant to meropenem were reported in 2017
- Resistance to colistin was detected in 4.7% of isolates, although 88.9% of the resistant isolates were either *S. Enteritidis* or *S. Dublin* which have been reported to have higher natural tolerance to colistin

# Annual Epidemiological Report for 2016 Salmonellosis



**Figure 16:** Spatial distribution of combined 'microbiological' resistance to ciprofloxacin and cefotaxime among *Salmonella* spp. from human cases in reporting countries in 2017

**Table 9:** Antimicrobial resistance in *Salmonella* spp. (all non-typhoidal serovars) from humans per country in 2017

Country	Gentamicin		Chloramphenicol		Ampicillin		Cefotaxime		Ceftazidime		Meropenem		Tigecycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res
Austria	1,697	0.9	1,697	3.3	1,697	14.8	1,697	0.5	1,697	0.4	1,697	0	1,697	0.1
Belgium	980	3.4	980	12.8	980	51.8	980	7.7	980	0.8	980	0	969	2.9
Cyprus	74	13.5	–	–	76	27.6	29	0	76	0	76	0	–	–
Denmark	310	2.9	310	9.0	310	40.6	310	1.3	310	1.0	310	0	310	0.3
Estonia	265	0	265	0.8	265	6.4	265	0.8	265	0.8	265	0	10	0
Finland	214	0.9	214	4.2	214	24.8	214	0	–	–	214	0	–	–
France	870	1.8	870	7.2	870	35.3	870	0.8	870	0.3	870	0	870	0
Germany <sup>(a)</sup>	652	2.0	652	6.3	652	30.1	651	2.3	650	1.7	652	0	–	–
Greece	130	0	130	30.0	129	81.4	129	0.8	130	0	130	0	–	–
<b>Total (MSs 24)</b>	<b>10,816</b>	<b>2.2</b>	<b>12,328</b>	<b>8.5</b>	<b>15,798</b>	<b>27.5</b>	<b>12,582</b>	<b>1.9</b>	<b>10,848</b>	<b>1.1</b>	<b>11,051</b>	<b>0</b>	<b>5,496</b>	<b>0.8</b>

Country	Nalidixic acid		Ciprofloxacin <sup>(b)</sup>		Azithromycin		Colistin		Sulfamethoxazole <sup>(c)</sup>		Trimethoprim		Co-trimoxazole		Tetracycline	
	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res	N	% Res
Austria	1,697	14.9	1,697	15.9	–	–	–	–	1,697	16.9	1,697	2.5	–	–	1,697	17.5
Belgium	11	9.1	980	18.1	980	4.3	–	–	980	47.6	969	19.8	–	–	980	45.9
Cyprus	–	–	76	30.3	–	–	44	0	–	–	–	–	74	14.9	3	NA
Denmark	310	1.9	310	6.8	310	0.3	310	3.2	310	41.6	310	3.9	–	–	310	39.0
Estonia	265	9.8	265	9.8	–	–	265	0.4	265	7.2	265	1.5	–	–	265	8.7
Finland	214	4.7	214	5.6	–	–	–	–	–	–	214	2.8	–	–	214	24.3
France	870	10.3	870	12.2	870	0.3	870	4.8	870	40.5	870	6.4	–	–	870	38.5
Germany <sup>(a)</sup>	652	10.0	651	1.8	–	–	–	–	–	–	–	–	652	5.7	651	23.0
Greece	130	0	109	0	–	–	–	–	130	82.3	130	73.8	–	–	130	80.0
<b>Total (MSs 24)</b>	<b>9,235</b>	<b>12.1</b>	<b>14,864</b>	<b>13.0</b>	<b>3,801</b>	<b>2.5</b>	<b>2,874</b>	<b>4.7</b>	<b>8,980</b>	<b>32.8</b>	<b>11,052</b>	<b>7.6</b>	<b>4,709</b>	<b>5.3</b>	<b>11,126</b>	<b>30.2</b>



# Salmonella Poona infections in humans

- **Salmonella Poona is the 36th most common *Salmonella* serotype causing human infection reported in the European Surveillance System (TESSy). During the period 2013–2017 it was reported by 23 EU/EEA countries with 147–206 cases per year.**
- **In the five-year period, France accounted for 34% of the cases, followed by the United Kingdom with 26%. Cases were most common in children 0–4 years old (37% of cases). Travel information was available for 55% cases and of these, 45% were imported.**
- **Thailand was the most common destination, accounting for 21% of the travel-associated cases**

## Salmonella Poona in infant products - Multicountry - 2018 - 2019

Opening date: 28 January 2019

Latest update: 22 February 2019

French authorities have reported cases of *Salmonella* Poona infection in infants with genome sequences (cgMLST) belonging to the same cluster. All patients consumed infant formula from the same brand before developing symptoms.

→ Update of the week

Luxembourg and Belgium reported one case each of *S. Poona* infection in January 2019 in infants who had consumed the same brand of infant formula. The human isolates are 0–1 allelic difference from the French representative sequences.



# *Salmonella* Poona infections in humans

- In 2011, an outbreak of *S. Poona* in Spain was associated with milk-based infant formula, which was produced by the same company as this outbreak (Spanish processing company B).
- Furthermore, the French and Spanish National Reference Laboratories reported that the sequences of the French human isolates from the current outbreak and the sequences from the Spanish human isolates for the outbreak in 2011 are genetically related. The possible persistence of *S. Poona* in the processing line warrants further investigation.





## Plasmid-Mediated Colistin Resistance in *Salmonella enterica*: A Review

[Tiago Lima](#),<sup>1,2</sup> [Sara Domingues](#),<sup>1,2</sup> and [Gabriela Jorge Da Silva](#)<sup>1,2,\*</sup>

The study summarizes >20 reports on mcr-like genes and their variants

- Plasmid-mediated colistin resistance conferred by mcr-1, mcr-2, mcr-3, mcr-4 and mcr-5 genes have been already identified in different serovars of *S. enterica*. Recent reports highlight *S. Typhimurium* as the most prevalent serotype harbouring mcr genes. This serotype is also one of the most frequent to cause human infections
- Like in other bacterial species, mcr-like genes have been detected in isolates from different origin, such as food-producing animals, food products and human samples, and are inserted in diverse genetic environments and plasmid backbones.
- It is of note that the presence of the mcr genes can be associated with low level of resistance to colistin

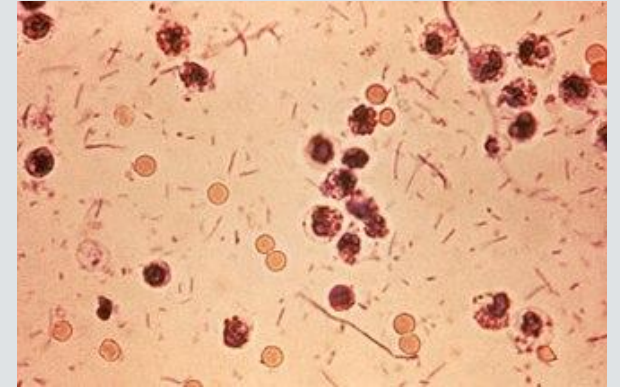
# More history: *Shigella* spp

- Kiyoshi Shiga (志賀 潔 Shiga Kiyoshi, February 7, 1871 – January 25, 1957) was a Japanese physician and bacteriologist.
- Shiga became famous for the discovery of *Shigella dysenteriae*, the organism that causes dysentery, in 1897, during a severe epidemic in which more than 90,000 cases were reported, with a mortality rate approaching 30%.
- The bacterium *Shigella* was thus named after him, as well as the Shiga toxin, which is produced by the bacterium.
- After the discovery of *Shigella*, Shiga worked with Paul Ehrlich in Germany from 1901 to 1905

Source: Wikipedia



# Shigella Taxonomy and microbiology



Family *Enterobacteriaceae*

- 1. *Shigella flexneri* (6 serotypes):** the most frequent species worldwide, 60% of shigellosis underdeveloped countries
- 2. *Shigella sonnei* (one serotype):** 77% of shigellosis in developed countries and 15% in developed world
- 3. *Shigella dysenteriae* (15 serotypes):** most serious form of bacillary dysentery cause of epidemics of dysentery, particularly in confined populations such as refugee camps
- 4. *Shigella boydii* (19 serotypes)**



# Microbiology-taxonomy epidemiology: *Shigella*

Short rods- Gram-negative

- Nonencapsulated-Non-sporeformer
  - Non-motile
  - Facultative anaerobes
- Phylogenetic studies indicate *Shigella* is more appropriately treated as subgenus of *Escherichia*, and that certain strains generally considered *E. coli*—such as *E. coli* O157:H7—are better placed in *Shigella*
  - Non lactose fermenters (distinction to *E.coli*)
- *Shigella* is one of the leading bacterial causes of diarrhea worldwide, causing an estimated 80–165 million cases
  - The number of deaths it causes each year is estimated at between 74,000 and 600,000
  - It is one of the top four pathogens that cause moderate-to-severe diarrhea in African and South Asian children

# *Shigella: Κλινική Εικόνα*



Η σιγκέλλωση (shigellosis) έχει δύο βασικά κλινικά συμπτώματα:

- (1) διάρροια που συνοδεύεται από εμετό και ελαφριά ή μέτρια αφυδάτωση,
- (2) δυσεντερία που χαρακτηρίζεται από αίμα και βλέννα στα κόπρανα και κοιλιακούς πόνους.

Μελέτες σε εθελοντές έχουν δείξει ότι τα συμπτώματα μπορεί να εμφανιστούν από τη λήψη πολύ μικρού πληθυσμού του παθογόνου (10-100 κύτταρα), και ο χρόνος εμφάνισης είναι συνήθως 24-48 ώρες

Η μέση διάρκεια των συμπτωμάτων στους ενήλικες είναι 7 ημέρες

# Pathogenesis Shigella

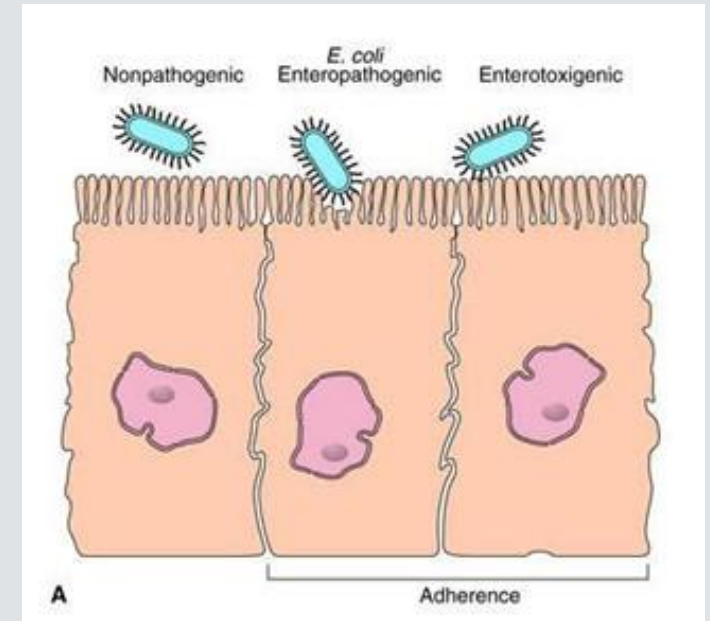
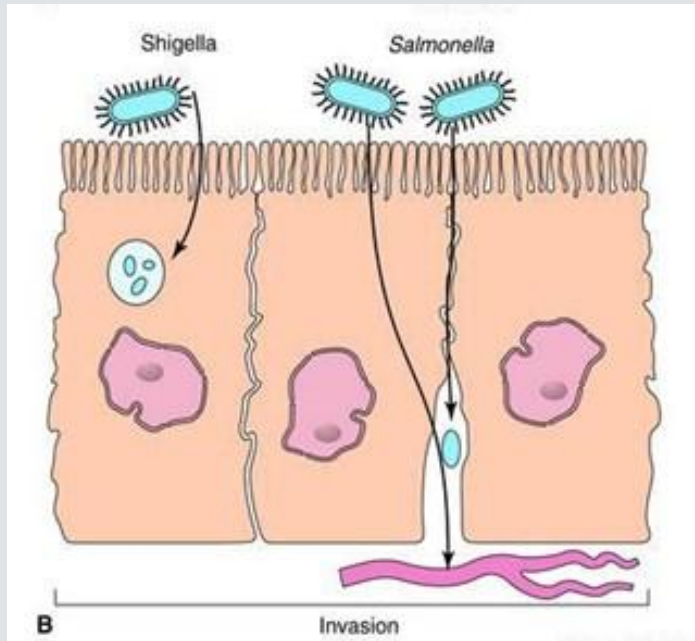
- **Shigella species generally invade the epithelial lining of the colon, causing severe inflammation and death of the cells lining the colon.**
- **This inflammation results in the diarrhea and even dysentery that are the hallmarks of Shigella infection**
- **Some strains of Shigella produce toxins which contribute to disease during infection.**
  - ***S. flexneri* strains produce ShET1 and ShET2, which may contribute to diarrhea.**
  - ***S. dysenteriae* strains produce the enterotoxin Shiga toxin, which is similar to the verotoxin produced by enterohemorrhagic *E. coli*.**
- **Both Shiga toxin and verotoxin are associated with causing potentially fatal hemolytic-uremic syndrome.**

# Pathogenesis & Immunity

**Exotoxin (Shiga toxin)** is neurotoxic, cytotoxic, and enterotoxic, encoded by chromosomal genes

- **Enterotoxic effect:** Shiga toxin adheres to small intestine receptors
  - Blocks absorption (uptake) of electrolytes, glucose, and amino acids from the intestinal lumen
- **Cytotoxic effect:** B subunit of Shiga toxin binds host cell glycolipid in large intestine
  - Inactivate the 60S ribosomal subunit,
  - Inhibit protein synthesis, causing cell death, microvasculature damage to the intestine, and hemorrhage (blood and fecal leukocytes in stool)
- **Neurotoxic effect:** Fever, abdominal cramping are considered signs of neurotoxicity
- **1<sup>st</sup> cause of reactive arthritis worldwide**

# Pathogenesis *Shigella*



- *Shigella* species invade the host through the M-cells interspersed in the gut epithelia of the small intestine, as they do not interact with the apical surface of epithelial cells, preferring the basolateral side.
- *Shigella* uses a type-III secretion system, which acts as a biological syringe to translocate toxic effector proteins to the target human cell.
- M cells typically transport foreign antigens from the intestine to underlying macrophages, but *Shigella* can lyse the phagocytic vacuole (phagosome) and replicate in the cytoplasm

Note: This contrasts with *Salmonella* which multiplies in the phagocytic vacuole

# Transmission *Shigella*

- *Shigella* species are found only in the human intestinal tract
- Carriers of pathogenic strains can excrete the organism up to two weeks after infection and occasionally for longer periods
- *Shigella* are killed by drying
- Spread is always from a human resource and generally involves one of the five f`s:
  - – food,
  - – fingers,
  - – feces,
  - – flies,
  - – fomites
- This is in contrast to salmonellae, which are often spread to human from infected animals

# Treatment, Prevention & Control shigella:

- Dehydration is problem to attend
- Antibiotic resistance is an increasing problem
- Proper sewage disposal and water chlorination
- Oral vaccines of *Shigella*: *E. coli* hybrids or *Shigella* mutants offers immunity for six months to one year – Need more studies

# Shigellosis epidemiology in Europe

## Key facts

- Shigellosis is a relatively uncommon disease in the EU/EEA, but remains of concern in some countries and for some population groups.
- In 2016, 29 EU/EEA countries reported 5 631 confirmed shigellosis cases.
- The overall notification rate was 1.5 cases per 100 000 population in 2016, slightly below the rates observed for the period 2012–2015.
- The highest notification rate was noted in children under five years of age, followed by adults aged 24–44 years.
- Sexual transmission of shigellosis among men who have sex with men (MSM) increased in several European countries in recent years.

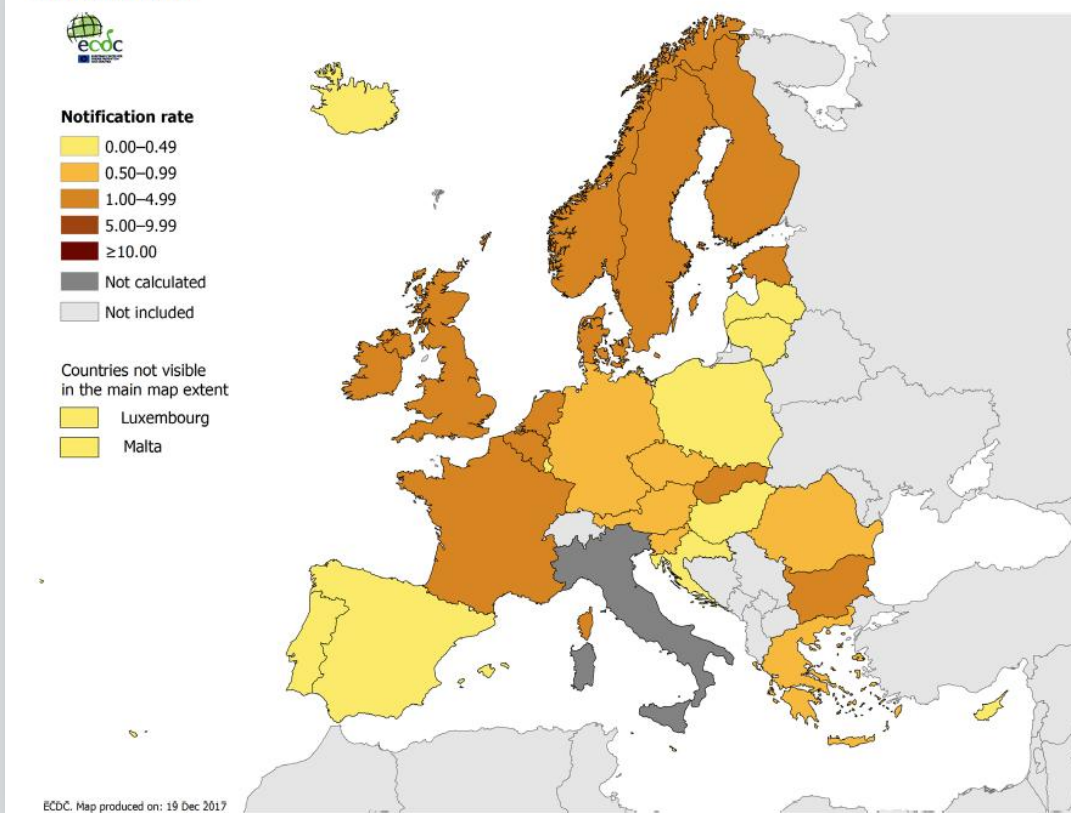


**Table 1. Distribution of confirmed shigellosis cases, EU/EEA, 2012–2016**

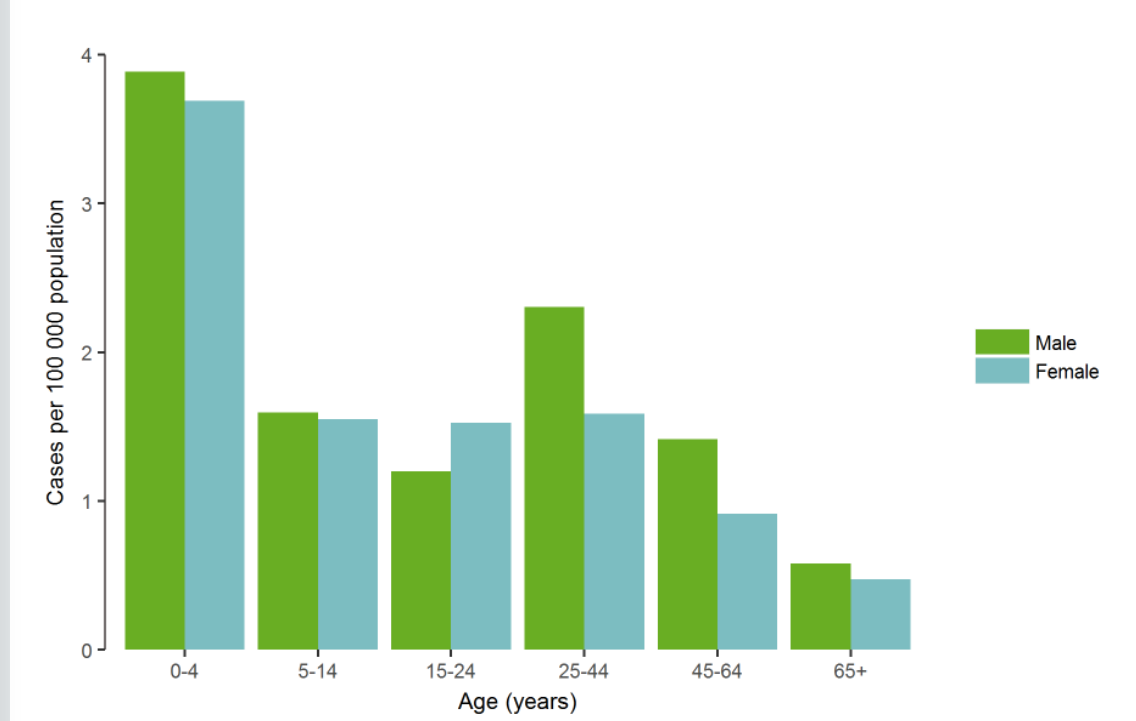
Country	2012		2013		2014		2015		2016			
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Confirmed cases	Rate	ASR	Reported cases
Austria	57	0.7	70	0.8	75	0.9	96	1.1	62	0.7	0.8	62
Belgium	340	3.1	323	2.9	403	3.6	391	3.5	353	3.1	3.1	353
Bulgaria	777	10.6	486	6.7	512	7.1	410	5.7	291	4.1	4.4	291
Croatia	26	0.6	19	0.4	0	0.0	12	0.3	6	0.1	0.1	6
Cyprus	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0.1	1
Czech Republic	266	2.5	247	2.3	92	0.9	88	0.8	68	0.6	0.6	70
Denmark	105	1.9	109	1.9	110	2.0	170	3.0	212	3.7	3.9	212
Estonia	34	2.6	12	0.9	10	0.8	12	0.9	17	1.3	1.3	17
Finland	88	1.6	111	2.0	89	1.6	86	1.6	59	1.1	1.1	66
France	686	2.4	662	2.3	873	3.0	822	2.8	828	2.8	2.9	828
Germany	523	0.7	562	0.7	509	0.6	553	0.7	418	0.5	0.5	426
Greece	89	0.8	112	1.0	90	0.8	78	0.7	72	0.7	0.7	72
<b>EU/EEA</b>	<b>7 143</b>	<b>1.8</b>	<b>6 356</b>	<b>1.6</b>	<b>6 531</b>	<b>1.7</b>	<b>6 723</b>	<b>1.7</b>	<b>5 631</b>	<b>1.5</b>	<b>1.5</b>	<b>5 699</b>

# Shigellosis distribution by country and age, Europe

**Figure 1.** Distribution of confirmed shigellosis cases per 100 000 population by country, EU/EEA, 2016



**Figure 4.** Distribution of confirmed shigellosis cases per 100 000 population, by age and gender, EU/EEA, 2016



# Shigellosis epidemiology in Europe

- **Several food-borne outbreaks of shigellosis in recent years have been attributed to fresh vegetables or herbs imported from outside the EU/EEA**
- **Sexual transmission of shigellosis among MSM increased among domestically acquired cases in several European countries in recent years, particularly in the UK. This could be an explanation for the overrepresentation of male cases in the 24–44- and 45–64-year age groups. Oral-anal contact was often reported and many cases were immunocompromised due to other infections (e.g. HIV)**
  - **The spread of a multidrug-resistant lineage of *S. flexneri* serotype 3a, which has been described among the MSM population**
- **Sporadic cases in migrants, refugees and asylum seekers have been reported in recent years and these populations may be at increased risk due to reception and transit centre conditions**
  - **In Germany, it was reported that importation of *Shigella* by asylum seekers was negligible and had no impact on the incidence of notified *Shigella* infections**

# Shigella Infections among Gay and Bisexual Men

Note: Content below contains mature language.



Gay, bisexual, and other men who have sex with men (MSM)<sup>†</sup> are at risk for *Shigella* infections.

## What is *Shigella*?

- Shigellosis is a common diarrheal disease caused by a group of bacteria called *Shigella*. Symptoms of shigellosis typically start 1–2 days after exposure and include:
  - Diarrhea (sometimes bloody)
  - Fever
  - Abdominal pain
  - Tenesmus (a painful sensation of needing to pass stools when bowels are empty)

## How is *Shigella* spread?

*Shigella* germs are present in the feces (poop) of people with shigellosis while they have diarrhea and up to a few weeks after the diarrhea has gone away. *Shigella* is very contagious; exposure to even a tiny amount of fecal matter with *Shigella* in it can cause infection. Symptoms usually start 1–2 days after exposure, but may range from 12–96 hours.

<https://www.cdc.gov/shigella/msm.html>



Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™

# Update – CDC Recommendations for Managing and Reporting *Shigella* Infections with Possible Reduced Susceptibility to Ciprofloxacin



Distributed via the CDC Health Alert Network

June 7, 2018, 1100 ET (11:00 AM ET)



- People who are at high risk for multidrug-resistant *Shigella* infections and are more likely to require antibiotic treatment, such as men who have sex with men, patients who are homeless, and immunocompromised patients.
- These patients often have more severe disease, prolonged shedding, and recurrent infections.

- **Ciprofloxacin resistance on the rise**
- **An increasing number of *Shigella* isolates that test within the susceptible range for the fluoroquinolone antibiotic ciprofloxacin (minimum inhibitory concentration [MIC] values of 0.12-1 µg/mL), but harbor one or more resistance mechanisms.**
- **CDC remains concerned about potential clinical failures with fluoroquinolone treatment (8.5%>16.5% from 2016 to 2017)**
- **Azithromycin: not established breakpoints for *Shigella* (reduced susceptibility ECV 9.5%>22.1% from 2016 to 2017)**



# Treatment and control: *Shigella*

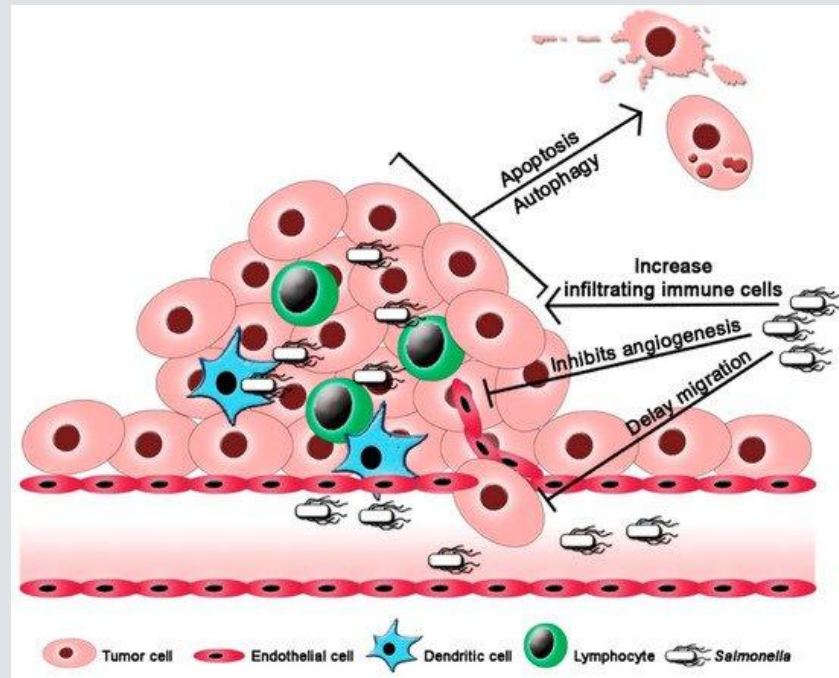
- **Ciprofloxacin, Fluoroquinolones, Azithromycin, Pivmecillinam, Ceftriaxone**
- **Preventing infected individuals from handling food**
- **Thoroughly washing hands after changing and disposing of an infant's diaper**
- **Disinfecting surfaces handled by infected individuals**
- **Not allowing infected children to play in community swimming areas**
- **If traveling, consuming boiled or filtered water, fruits peeled by self, and hot meals**
- **Proper storage of food**



**ΤΑ ΚΑΛΑ ΝΕΑ ΣΤΟ  
ΤΕΛΟΣ...**



# From bioterrorism to anti-tumor treatment



- **Salmonella-mediated tumor immunotherapy**
- **Salmonella triggers immune cells infiltration into tumor tissue and coax tumor cells self-destruction while preventing tumor microvascularization and delaying tumor cell migration**
- **Συνέργεια με αντινεοπλασματικούς παράγοντες, μείωση της αγγειογένεσης του όγκου, μείωση της δυνατότητας για μετάσταση κλπ**

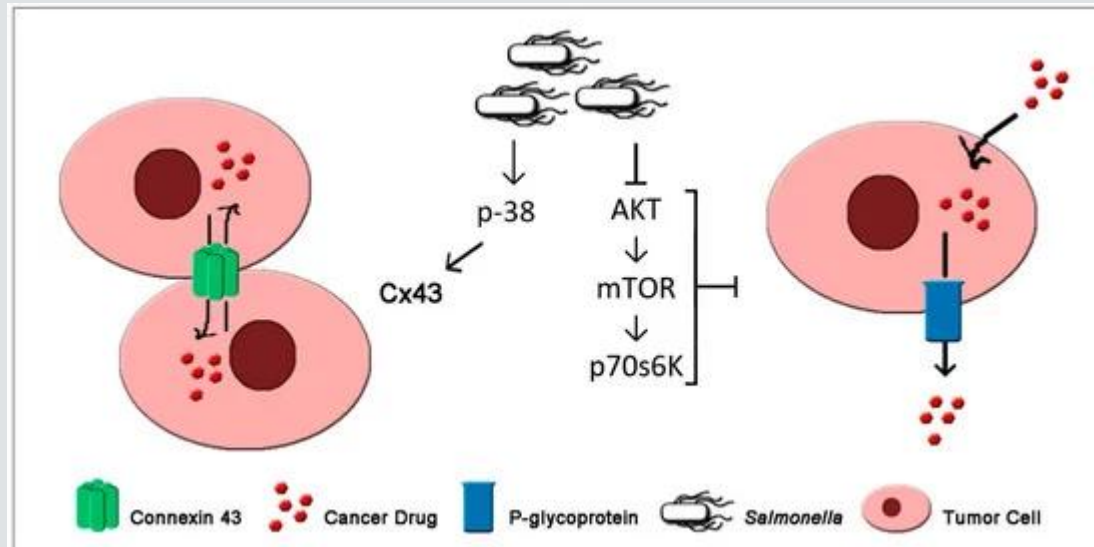
Review

# ***Salmonella*-Based Targeted Cancer Therapy: Updates on A Promising and Innovative Tumor Immunotherapeutic Strategy**

**Christian Ronquillo Pangilinan** <sup>1</sup>  and **Che-Hsin Lee** <sup>1,2,\*</sup> 

<sup>1</sup> Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung 80424, Taiwan

<sup>2</sup> Department of Medical Research, China Medical University Hospital, China Medical University, Taichung 404, Taiwan



**Salmonella enhances gap intercellular communication (GJIC) via gap junctions and alters membrane permeability to re-sensitize drug-resistant tumor cells**



**ΣΑΣ ΕΥΧΑΡΙΣΤΩ**