Prevalence and distribution of non-typhoidal *Salmonella enterica* serogroups and serovars from normally sterile sites: a global systematic review

John A. Crump, MB ChB, MD, DTM&H
Nienke N. Hagedoorn, MD, PhD

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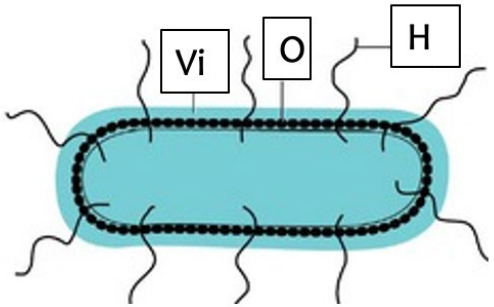
Background

- **Non-typhoidal *Salmonella* disease can develop in absence of diarrhea**
- **High case-fatality ratio of 15%**
- **Host factors: HIV infection, malaria, children with severe acute malnutrition**

Classification



- **67 serogroups → 'O-antigen'**
- **>2,500 non-typhoidal *Salmonella* serovars → the H antigen and Vi antigen**

- ***Salmonella* Typhimurium (serogroup O:4) and *Salmonella* Enteritidis (serogroup O:9) account for 78%-94% of invasive disease**

Background and Aim

- Various vaccines for iNTS disease in preclinical or clinical development

- Prevalence and regional distribution of non-typhoidal *Salmonella* serogroups and serovars is not well described

Aim

- To estimate the global prevalence and distribution of non-typhoidal *Salmonella enterica* serogroups and serovars isolated from normally sterile sites

Methods

- **Extension of our previous review**

Lancet Infect Dis 2022; 22: 692–705

Complications and mortality of non-typhoidal salmonella invasive disease: a global systematic review and meta-analysis

*Christian S Marchello, Megan Birkhold, John A Crump, on behalf of the Vacc-iNTS consortium collaborators**

- **Search to 4 June 2021**
  - **Embase, MEDLINE, Web of Science, PubMed**

- **Eligibility criteria**
  - **Report number of NTS isolates**
  - **At least one NTS strain by serogroup or serovar**
  - **Confirmed by culture of samples of normally sterile site**

Data analysis

- Prevalence of serogroup and serovar

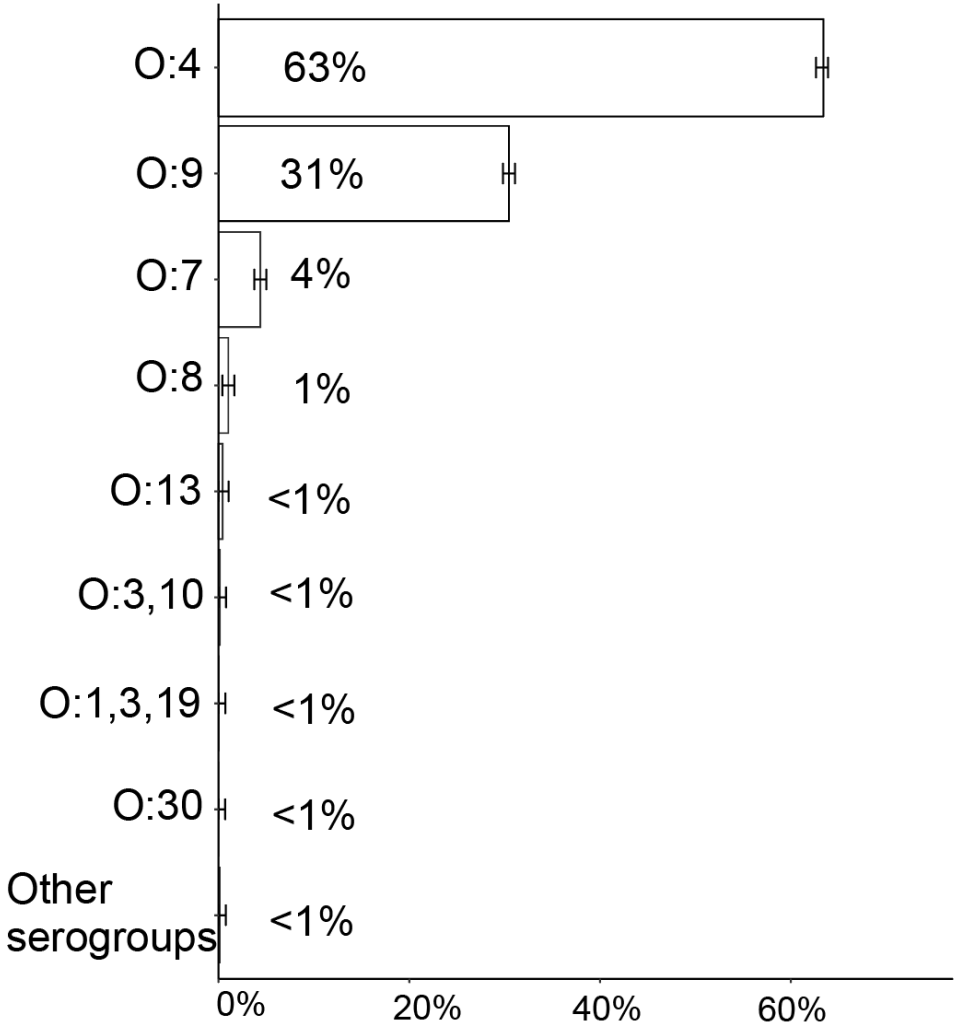
- Meta-analysis pooled prevalence
  - serogroup O:4, serogroup O:9, other serogroups
  - *Salmonella* Typhimurium, *Salmonella* Enteritidis, and other serovars

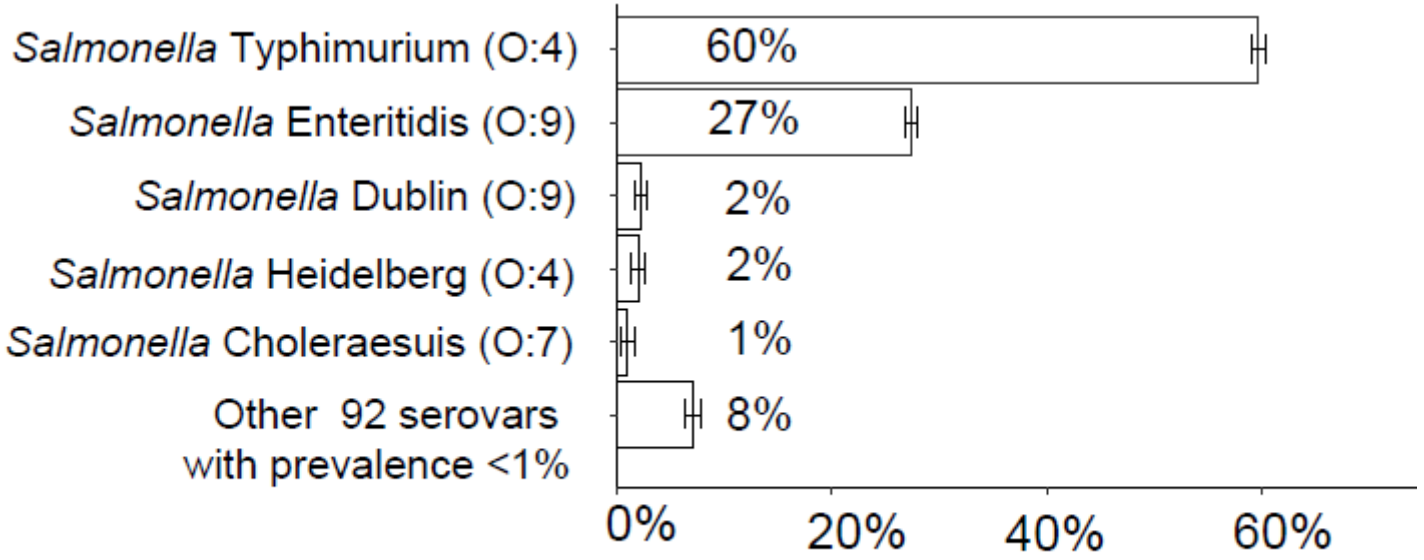
- Subgroup analysis
  - United Nations (UN) region
  - Income group
  - Age group
  - HIV infection status

Number of articles and serogrouped NTS isolates from normally sterile sites by income group and UN region, 1941 - 2019

Category	Articles n=82 n (%)	Serogrouped isolates n=24,253 n (%)
Income group		
High-income country	37 (45)	6,315 (26)
Lower- and middle-income country	45 (55)	17,938 (74)
UN region		
Africa	31 (38)	17,350 (72)
The Americas	9 (11)	2,645 (11)
Asia	21 (26)	1,083 (5)
Europe	20 (24)	3,172 (13)
Oceania	1 (1)	3 (<0.1)

Crude prevalence of NTS serogroups and serovars among 24,253 isolates from normally sterile sites, global, 1941 - 2019



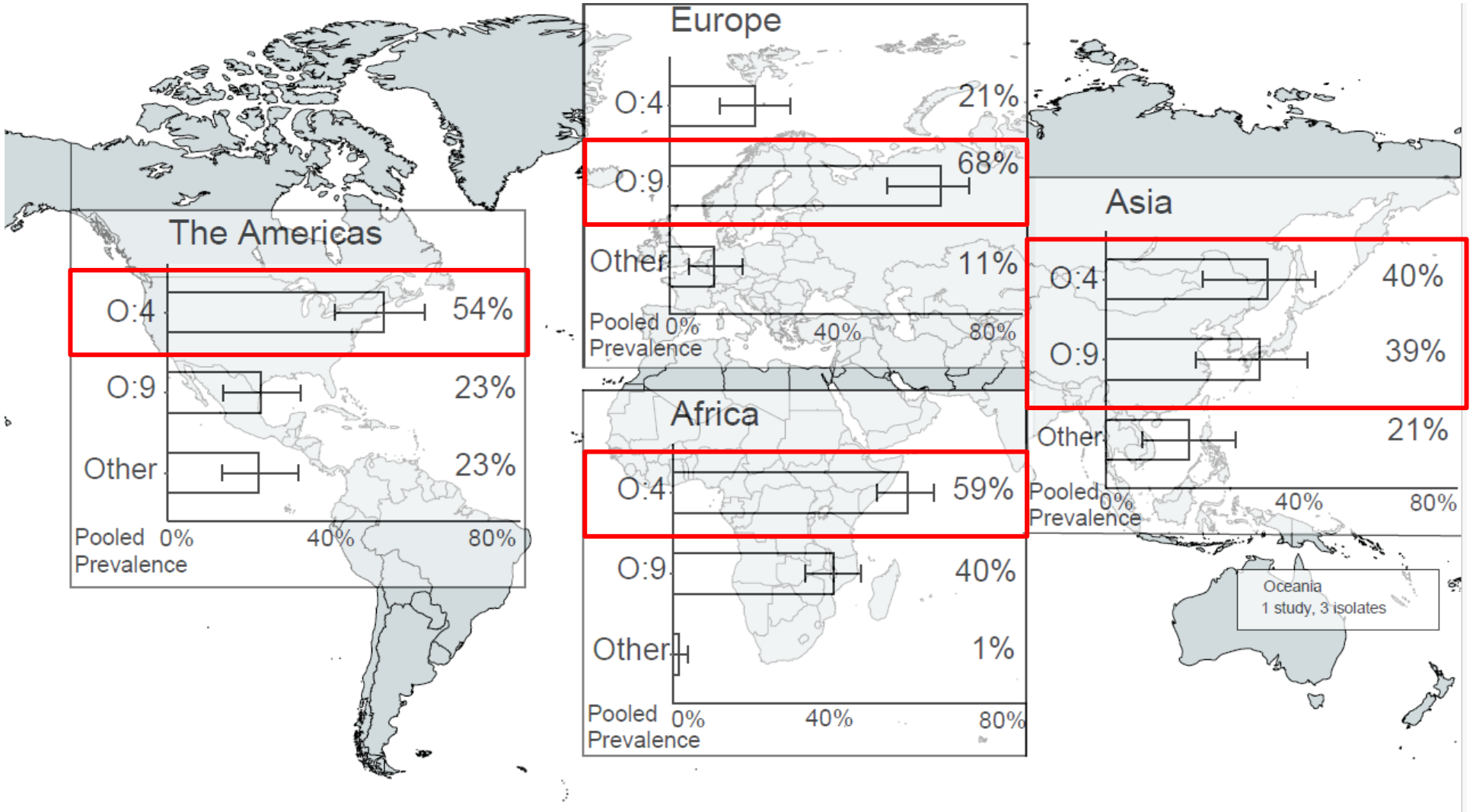


Pooled prevalence of NTS serogroups (82 articles) and serovars (79 articles) among isolates from normally sterile sites, global, 1941 - 2019

Serogroup	Pooled prevalence, %	(95% CI)
O:4	44.6	(36.2-48.2)
O:9	45.5	(37.0-49.1)
Others	9.9	(6.1-13.3)

Serovar	Pooled prevalence, %	(95% CI)
Typhimurium	40.2	(29.5-44.2)
Enteritidis	41.4	(30.5-45.3)
Others	18.4	(11.4-22.9)

Pooled prevalence of NTS serogroups among isolates from normally sterile sites by UN region, 1941 - 2019



Potential coverage of NTS invasive disease vaccine targets based on global systematic review of NTS serogroups and serovars

Vaccine target Serovar (serogroup)	Serogroup: Assuming cross-protection for serovars in same serogroup	Serovar: Without assuming cross-protection
Salmonella Typhimurium (O:4)	63%	60%
Salmonella Enteritidis (O:9)	31%	27%
Salmonella Typhimurium and *Salmonella* Enteritidis	94%	87%

Estimates based on crude prevalence data

Conclusion

To prevent the majority of non-typhoidal *Salmonella* invasive disease vaccines should

- **serogroups O:4 and O:9, or**
- **serovars Typhimurium and Enteritidis**

Acknowledgements

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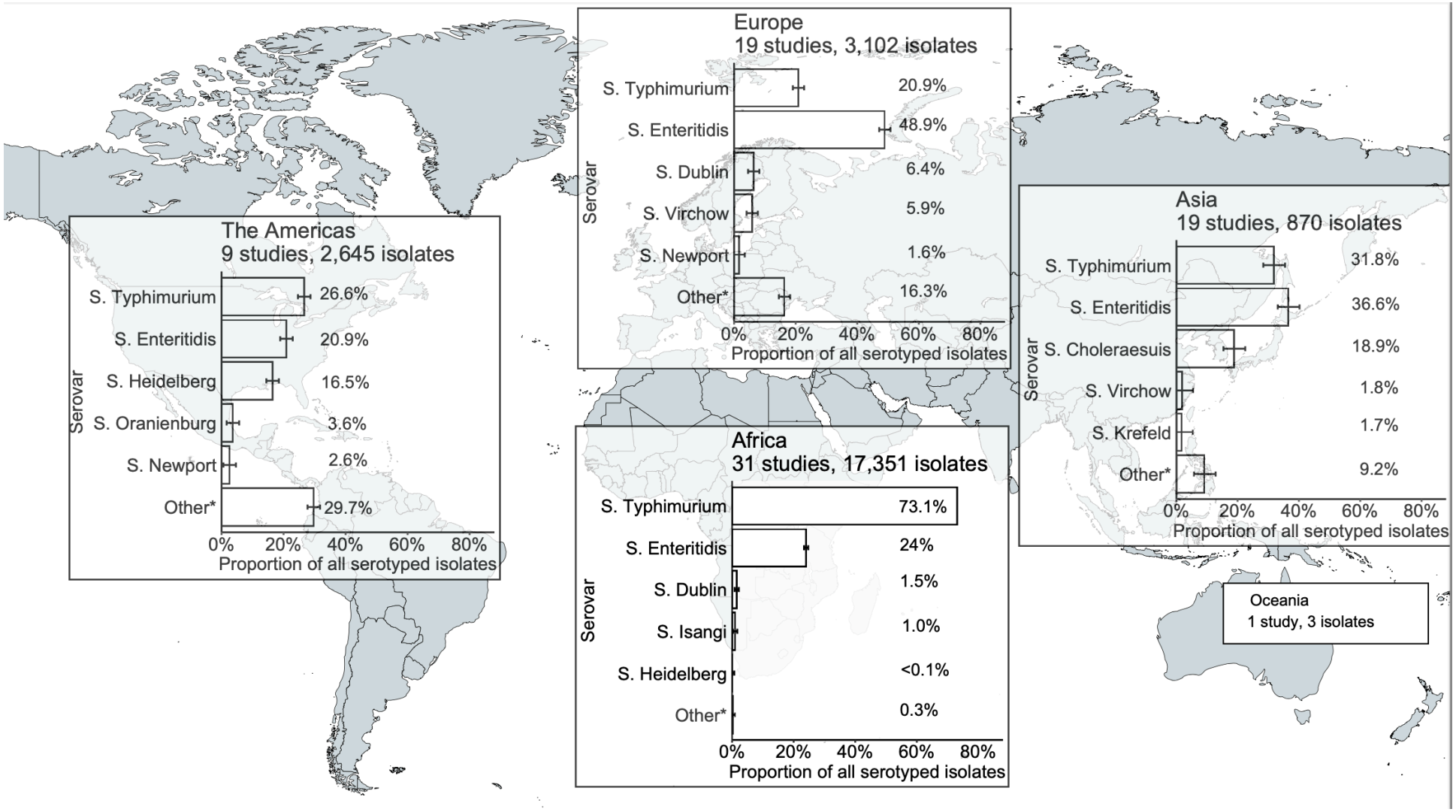
Additional slides

Incremental coverage of NTS invasive disease vaccine targets based on global systematic review of NTS serogroups and serovars

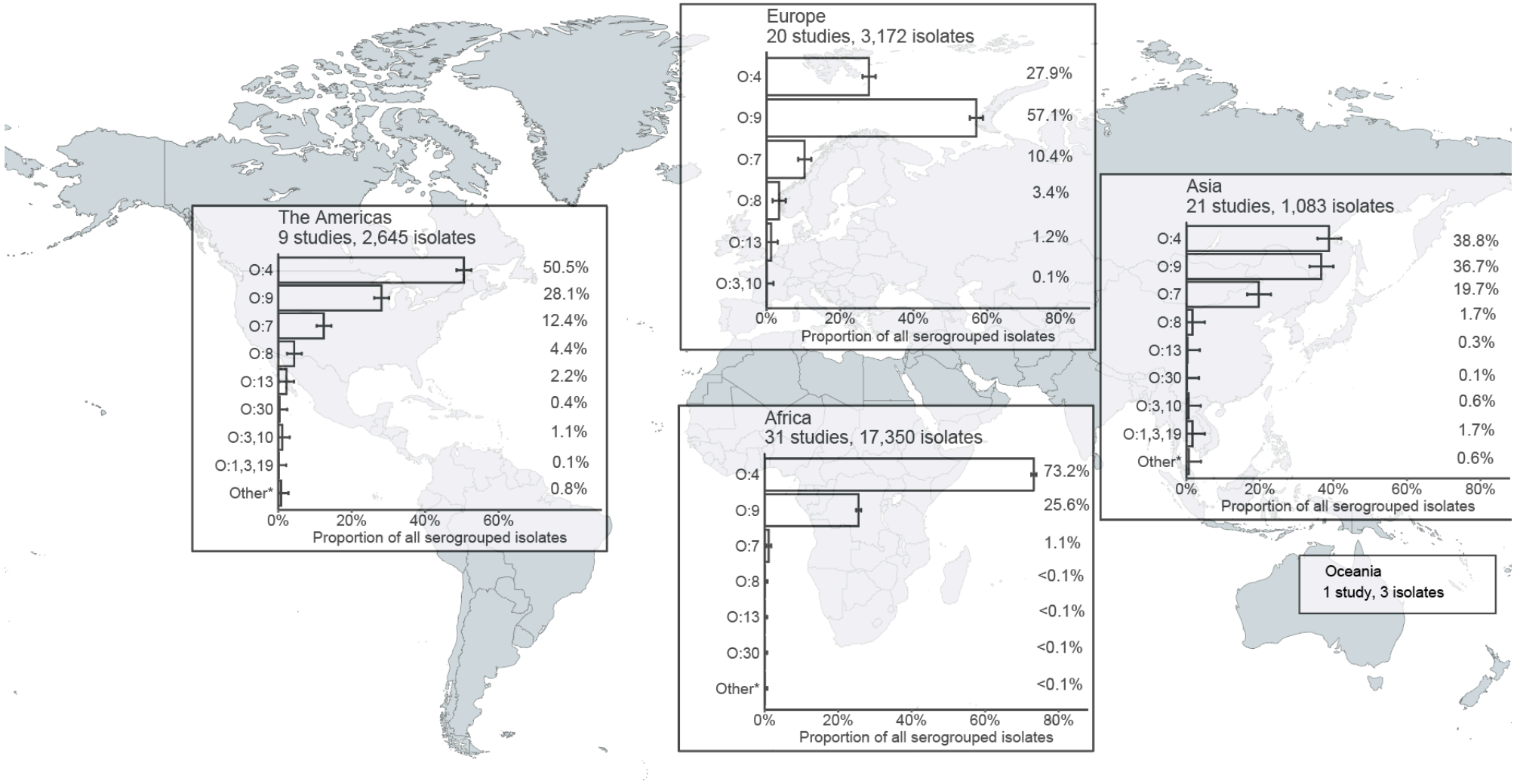
Serogroup	Overall	Africa	Americas	Asia	Europe
O:7	4%	1%	12%	20%	10%
O:8	1%	<1%	4%	2%	3%
O:13	<1%	<1%	2%	0.3%	1%

Serovar (serogroup)	Overall	Africa	Americas	Asia	Europe
Salmonella Dublin (O:9)	2%	2%	3%	0%	6%
Salmonella Heidelberg (O:4)	2%	<1%	17%	0%	1%
Salmonella Choleraesuis (O:7)	1%	<1%	2%	19%	<1%
Salmonella Virchow (O:7)	1%	<1%	1%	2%	6%

Prevalence of expanded NTS serovars among isolates from normally sterile sites by UN region, 1941 - 2019



Prevalence of expanded NTS serogroups among isolates from normally sterile sites by UN region, 1941 - 2019

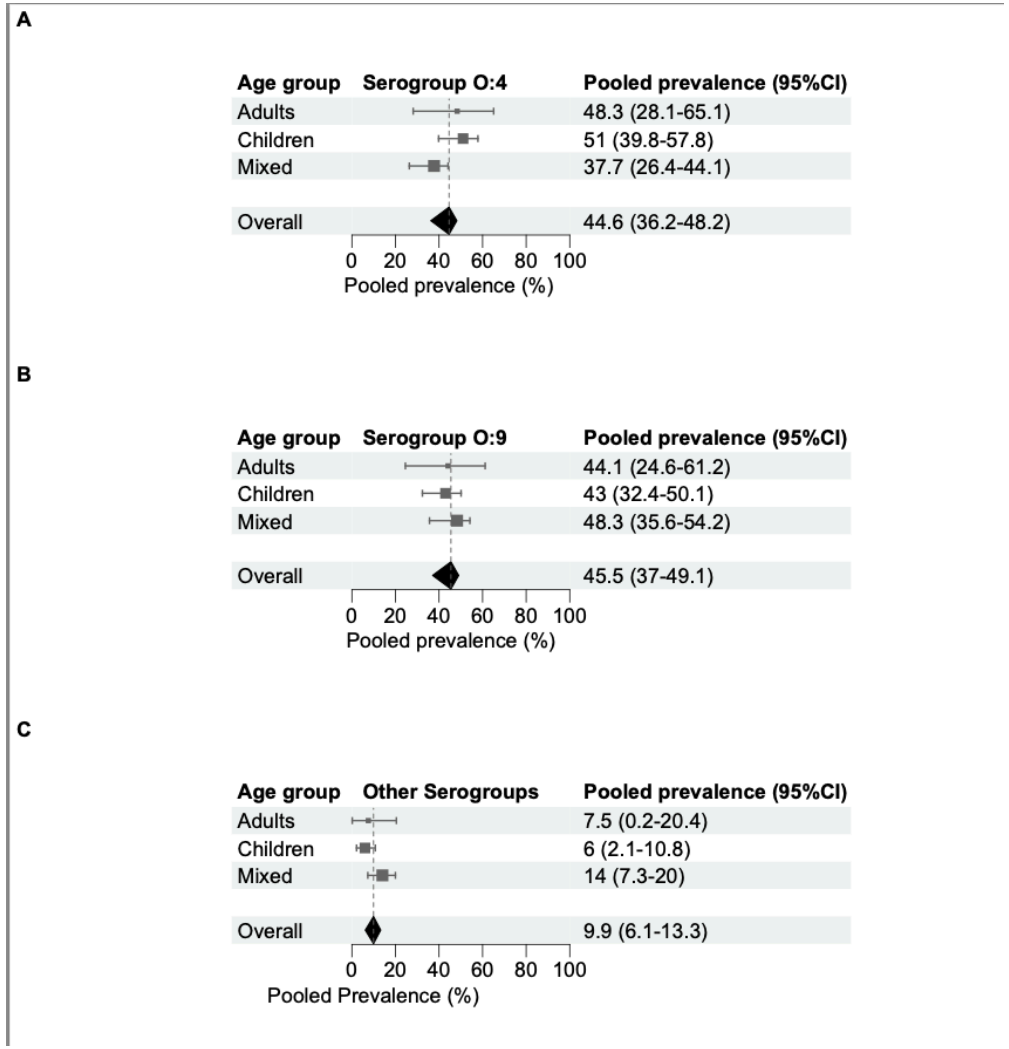


Vaccines against non-typhoidal *Salmonella* invasive disease in development, Baliban, 2020

Type of vaccine	Vaccine description	Vaccine antigen Serovar (serogroup)
Generalized Modules for Membrane Antigens (GMMA)	*Salmonella* Typhimurium GMMA, as part of a 2-component *Salmonella* Enteritidis/*Salmonella* Typhimurium GMMA vaccine	*Salmonella* Enteritidis (O:9) *Salmonella* Typhimurium (O:4)
Glycoconjugate	Non-typhoidal *Salmonella* core and O-polysaccharide conjugated to the flagellin protein	*Salmonella* Enteritidis (O:9) *Salmonella* Typhimurium (O:4) *Salmonella* Typhi Vi (O:9)
	Trivalent *Salmonella* conjugate caccine	
Live-attenuated	*Salmonella* Typhimurium strain LH1160 chicken isolate	*Salmonella* Typhimurium (O:4)
	Human *Salmonella* Typhimurium enterocolitis isolate	*Salmonella* Typhimurium (O:4)

Baliban et al. Overview of the nontyphoidal and paratyphoidal *Salmonella* vaccine pipeline: current status and future prospects. Clin Infect Dis 2020; 71 (suppl 2): S151-154

Pooled prevalence of NTS serogroups among isolates from normally sterile sites by age group, 1941 - 2019



Pooled prevalence of NTS serogroups among isolates from normally sterile sites by income group, 1941 - 2019

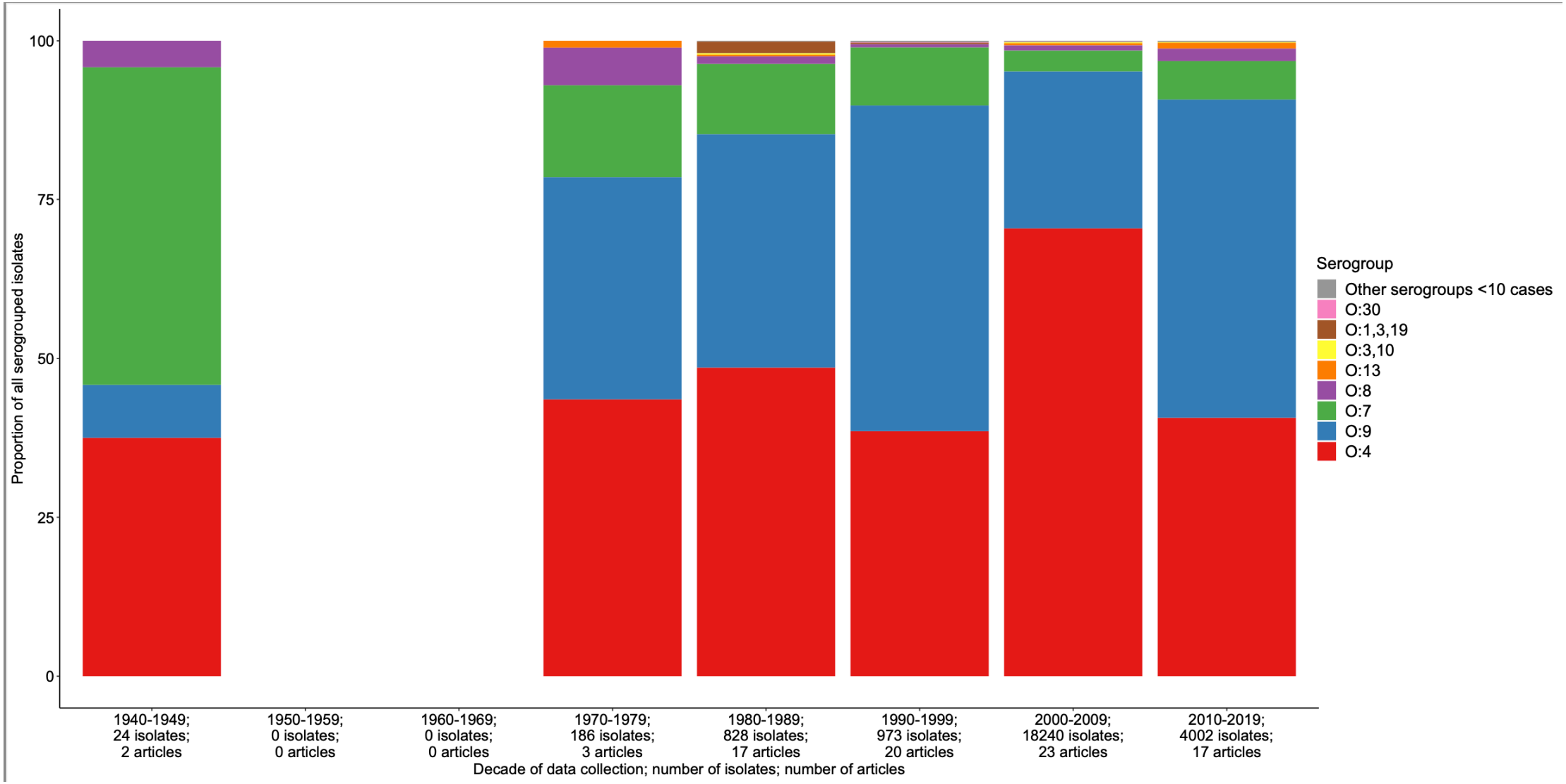
Serogroup	High-income countries 37 studies Pooled prevalence, % (95% CI)	Low- and middle-income countries 45 studies Pooled prevalence, % (95% CI)
O:4	31.4 (22.3-37.8)	54.7 (45.6-59.2)
O:9	51.1 (40.0-56.9)	40.3 (32.1-45.3)
Other	17.5 (10.8-23.4)	5.0 (2.2-8.2)

Prevalence of NTS serogroups and serovars among isolates from normally sterile sites by HIV-infection status, 1941 - 2019

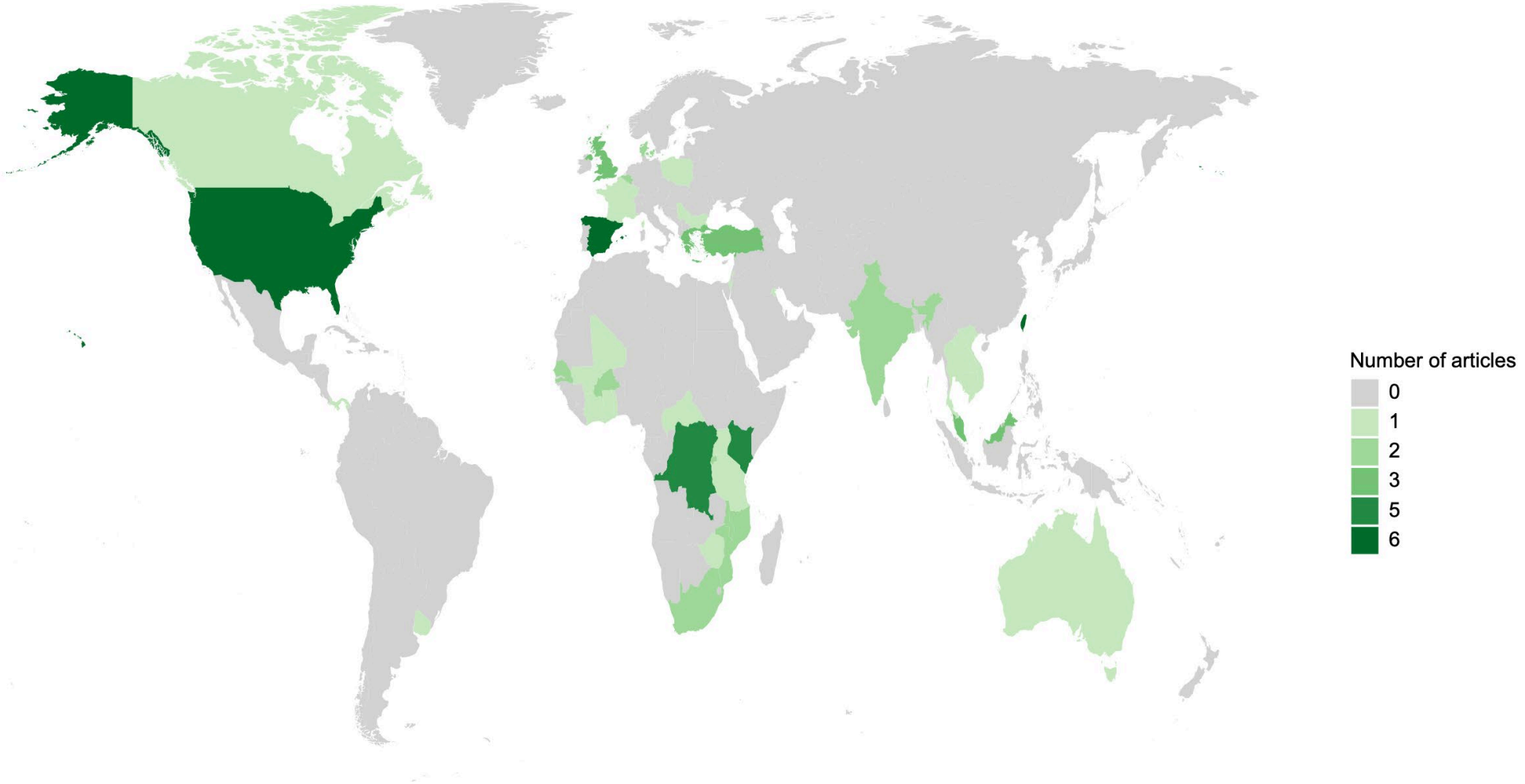
Salmonella serogroup	HIV-infected 1,743 participants n (%)	HIV-uninfected 257 participants n (%)	p-value
O:4	1,174 (67.4)	89 (34.6)	<0.01
O:9	559 (32.1)	157 (61.1)	<0.01
Other	10 (0.6)	11 (4.3)	<0.01

Salmonella serovar	HIV-infected 1,743 participants n (%)	HIV-uninfected 258 participants n (%)	p-value
Typhimurium	1,174 (67.4)	88 (34.1)	<0.01
Enteritidis	493 (28.3)	147 (57.0)	<0.01
Other	76 (4.4)	23 (8.9)	<0.01

Prevalence of NTS serovars from normally sterile sites by decade, 1940 - 2019



Systematic review of prevalence and distribution of NTS serogroups and serovars eligible articles by country



Systematic review of prevalence and distribution of NTS serogroups and serovars bias assessment