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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Phrama scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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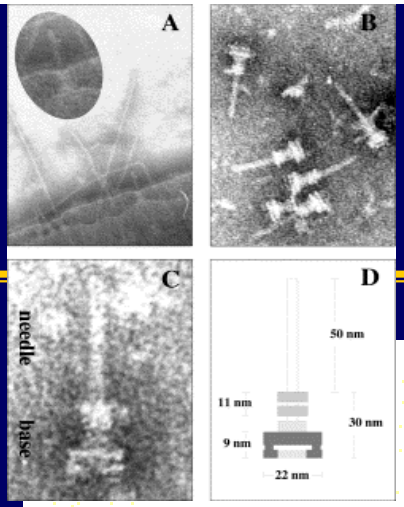
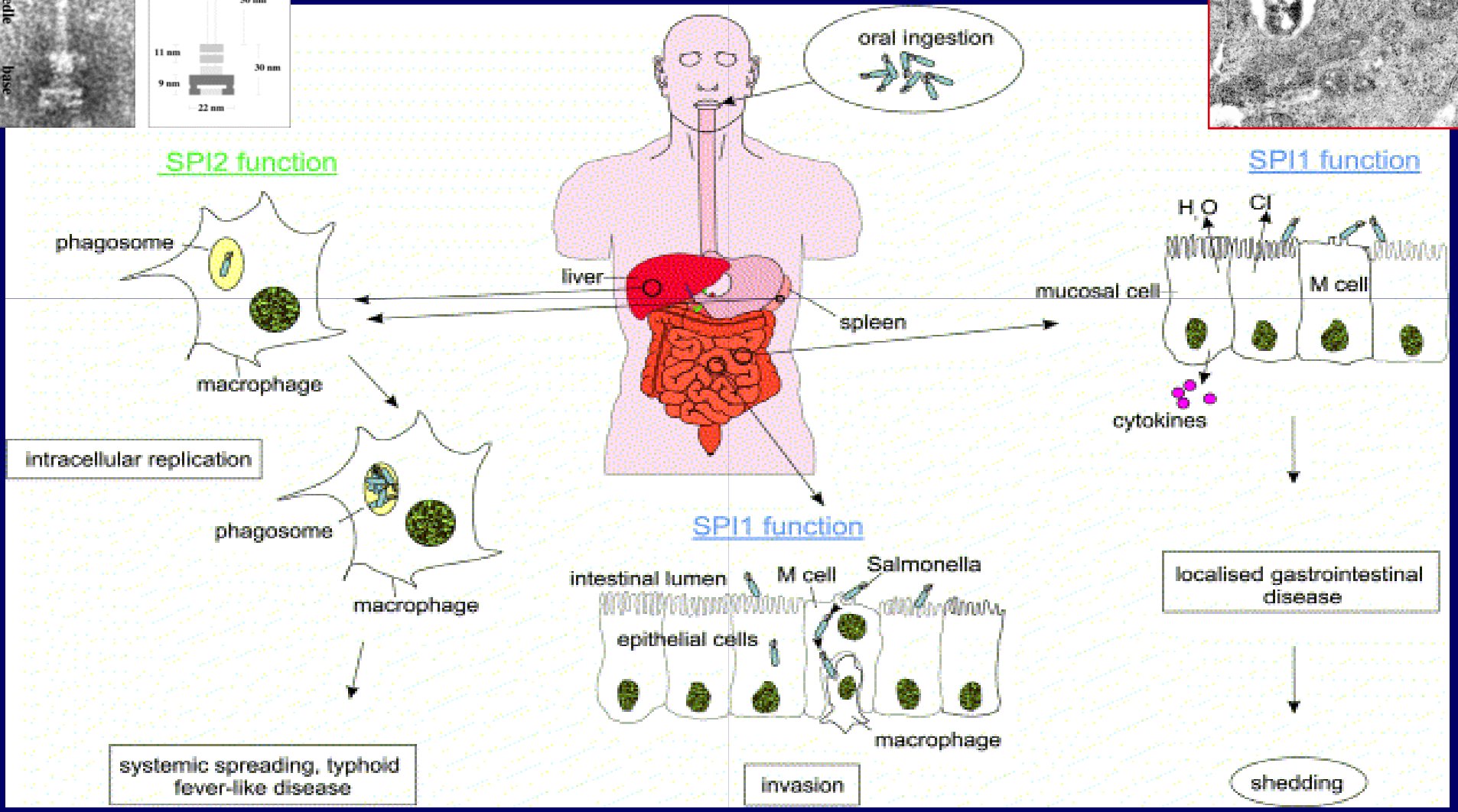
Biological and Pathogenic Regulatory Role of *Salmonella gidAB* Operon

Amin Fadl

University of Wisconsin-Madison

Pathogenesis

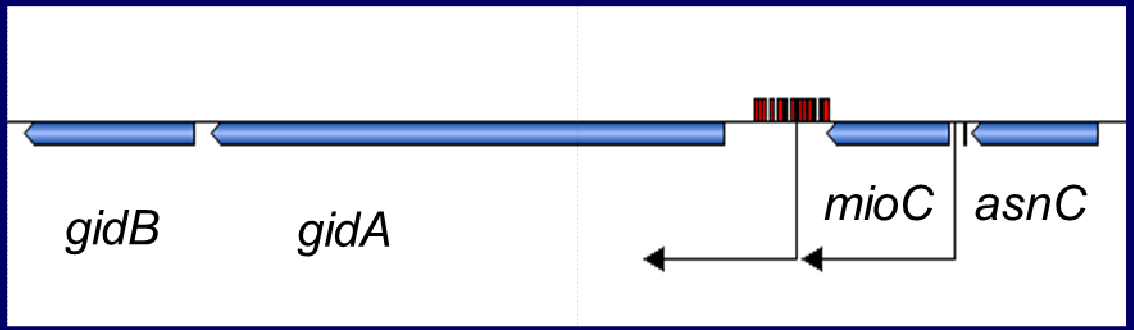




Hensel et al, 2001

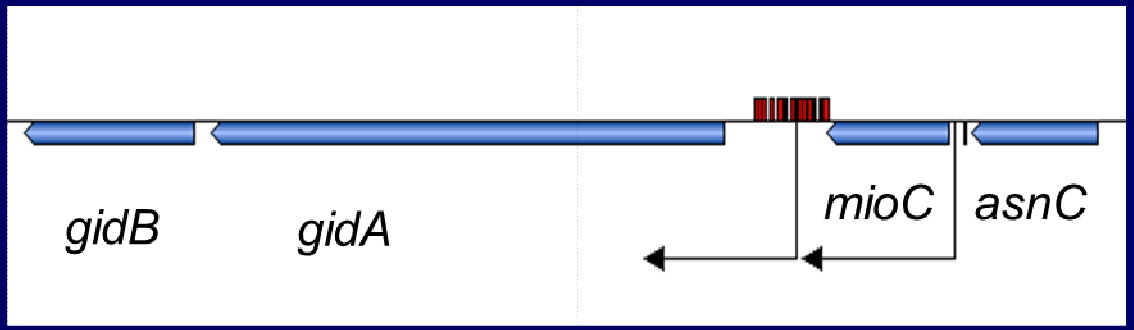
Salmonella gidAB operon

- Glucose-inhibited division gene (GidA, MnmG), methylaminomethyl (MnmE), Ribosomal Small Subunit Methyltransferase (RsmG, GidB)
- tRNAs are key molecules of translational machinery that ensure decoding of successive codons in mRNA inside the ribosome
- Post-transcriptional tRNA modification is found in all organisms and is required for tRNA functions, control gene expression



GidAB Mutant

- The *gidA* mutant attenuated *in vitro* and in animals
- Immunization with the *gidA* mutant protected mice from a lethal dose of WT *Salmonella* by Th1/Th2 mechanism
- GidA modulates several pathogenic factors
- GidA complex with MnmE to modify tRNA and regulate virulence
- GidB catalyses the methylation of 16S rRNA in bacteria, a binding sites for aminoglycosides



Salmonella & Stress Response

Required for response to adverse conditions and survival

Closely associated with virulence gene expression

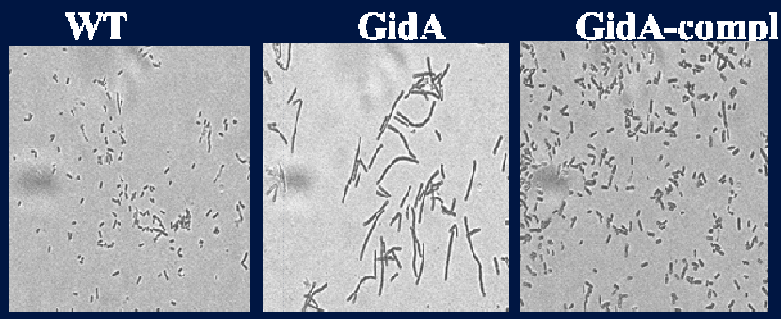
Overcome external environment, food matrices and host environment such as ability to survive inside macrophages

Regulated by genes/proteins network

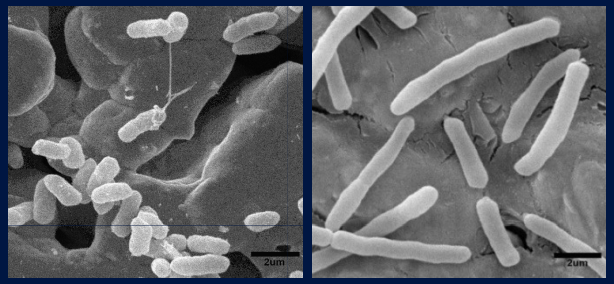
Objectives

- **Investigate the role of *gidAB* operon in stress response, overall effect on *Salmonella* virulence and mechanism of regulation**

GidA mutant: filamentous morphology specially under stress conditions

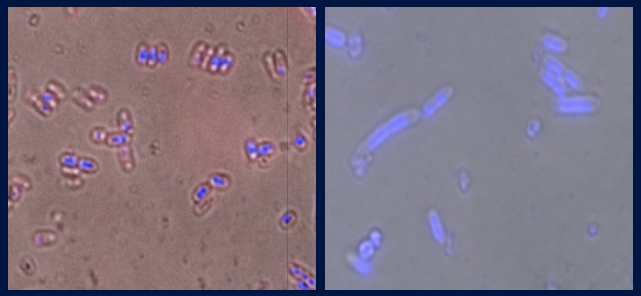


A



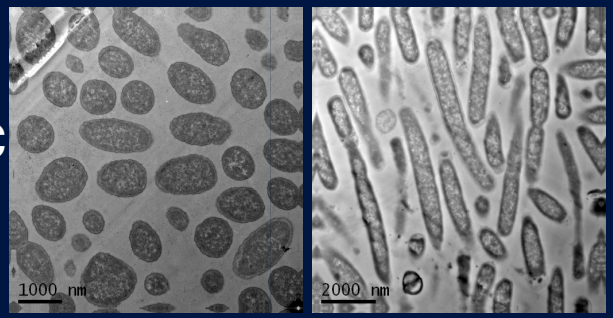
filaments with few signs of constriction.

B



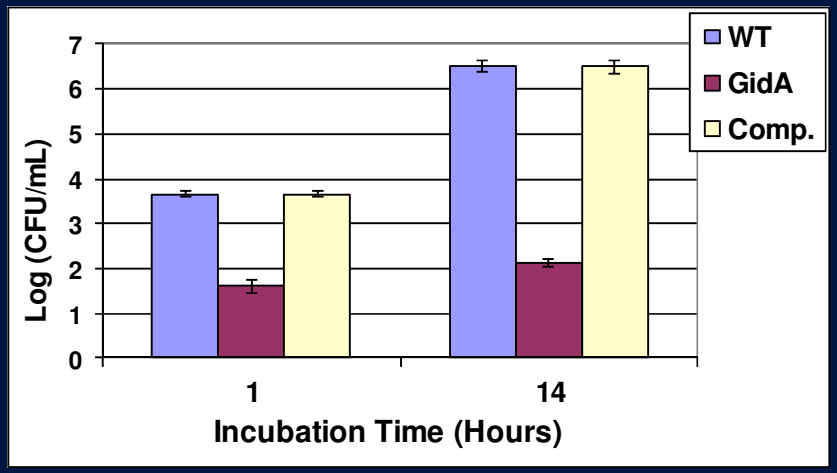
The *gidA* mutant: defect in chromosome segregation.

C

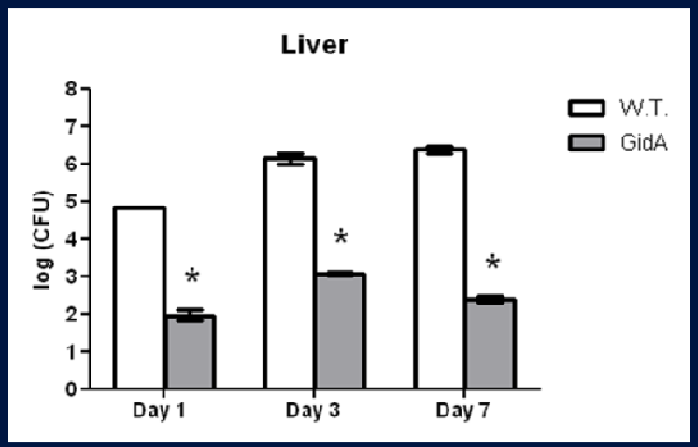


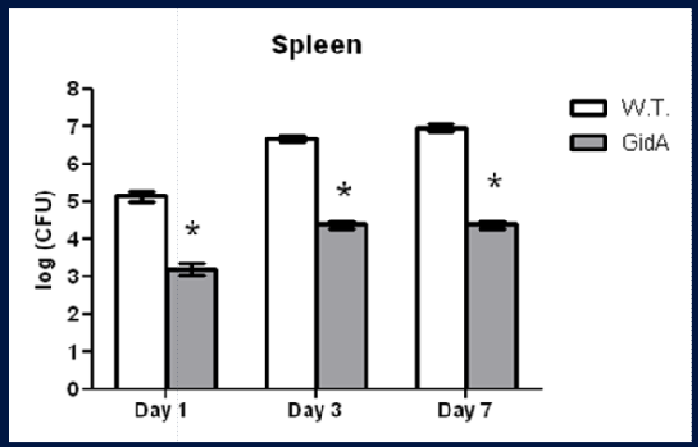
defect in chromosome segregation

GidA mutant: defective in intracellular & systemic replication



Cultured macrophages



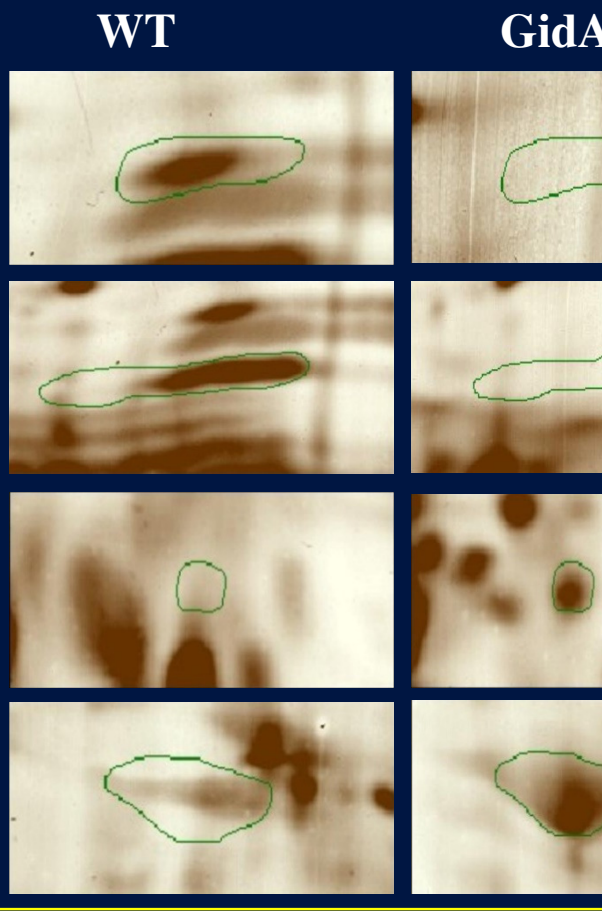


Mice

nscriptome and proteome analyses of *gidA* mutant

Gene Name	Gene #	Microarray FC	RT-PCR FC
spaP	STM2890	-9.61	-10.85
prgJ	STM2872	-4.36	-9.85
fepE	STM0589	4.53	4.54
hscC	STM0659	3.78	2.63
yhjC	STM3607	4.22	2.46
ssaN	STM1415	2.96	4.59
yebK	STM1887	2.86	2.36
invF	STM2899	-11.79	-9.83
invE	STM2897	-12.20	-7.57
motA	STM1923	-5.05	-2.09
spaQ	STM2889	-9.49	-3.50
invA	STM2896	-10.21	-2.16
prgH	STM2874	-6.86	-3.82
fliD	STM1960	-4.79	-4.26
fliC	STM1959	-5.64	-14.89
cheW	STM1920	-8.71	-4.86
mukB	STM0994	2.10	3.46
mreB	STM3374	-2.54	-2.27
parA	PSLT052	7.07	18.64
parB	PSLT053	5.45	5.08

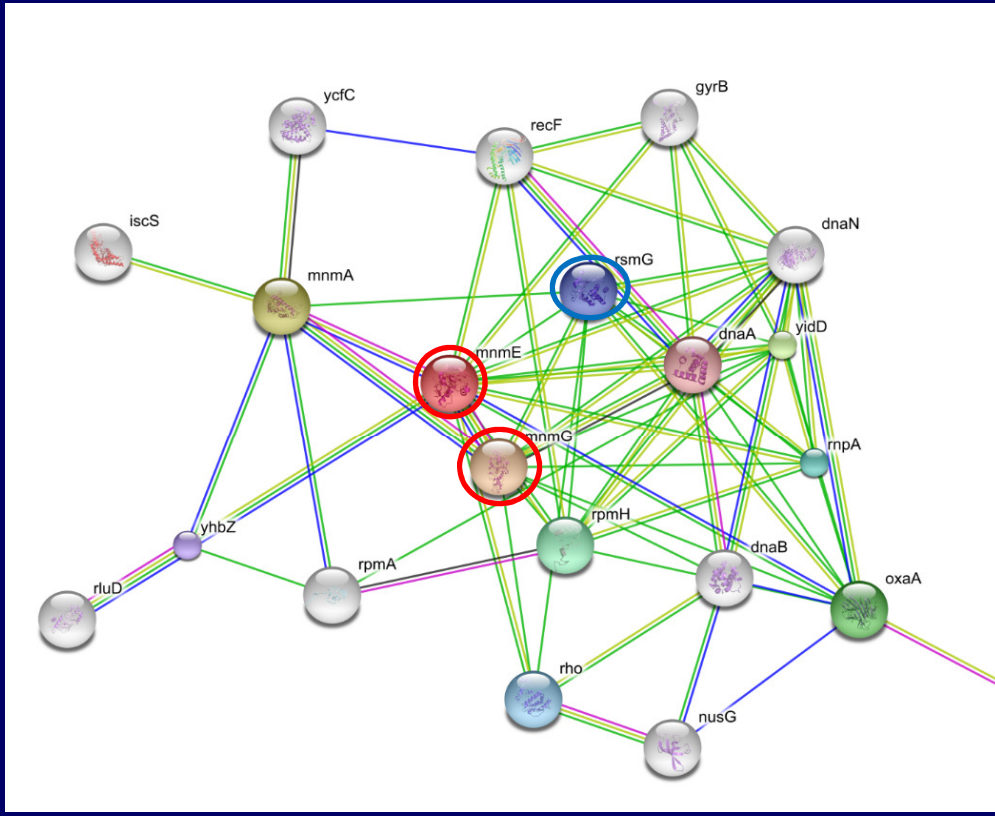
Down-regulation in stress related genes including heat-shock proteins (e.g. *hscC*)



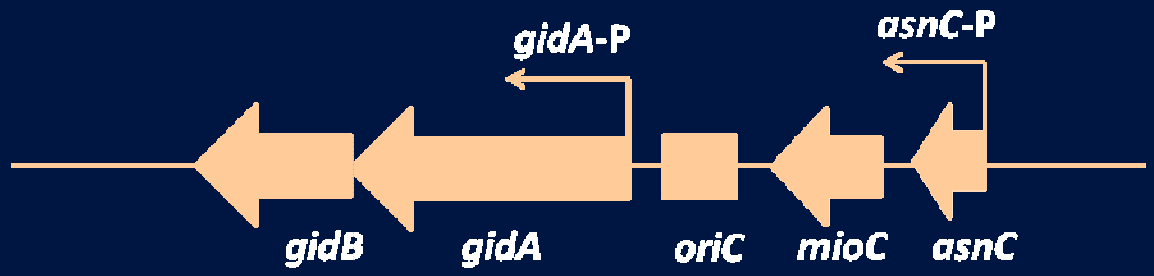
Identified stress related proteins including YghA (an oxidoreductase help *Salmonella* survive inside macrophages), Tpx (a thiol peroxidase, help *Salmonella* survive within macrophages), tpx (H_2O_2 survival)

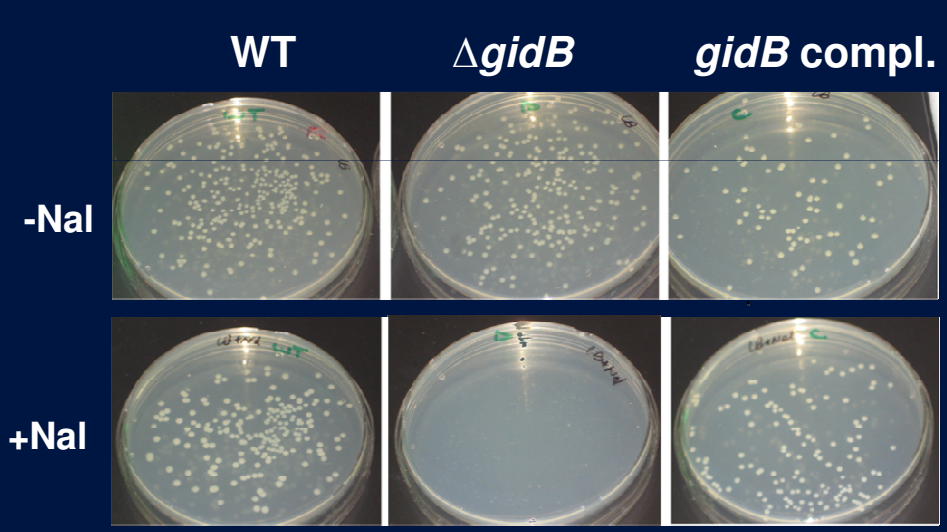
Predicted functional association for GidA mutant with other proteins using STRING 8.3 software (Jensen et al, 2009)

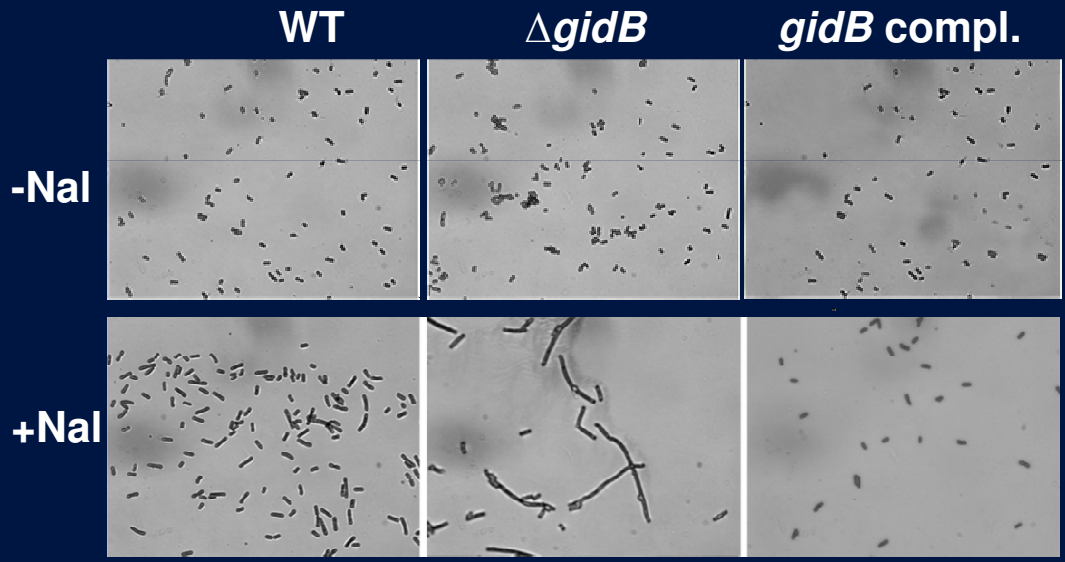
idA interacts with proteins involved in
ress response and replication (e.g. DnaA,
naN, YhbZ, GyrB) and RNA modification
zymes (MnmE, MnmA, and RsmG).



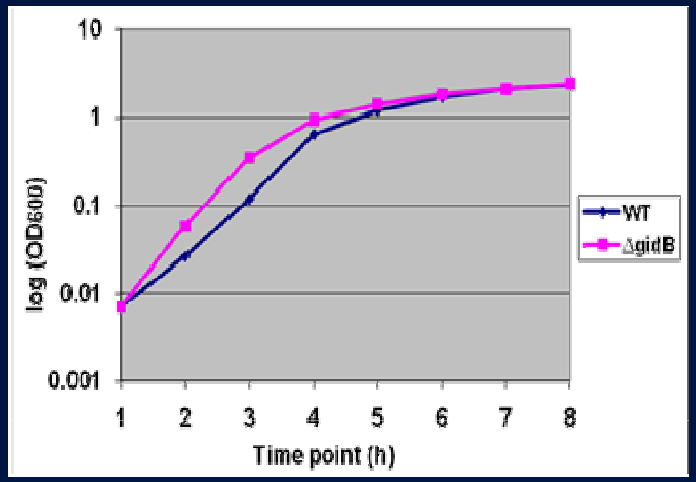
Deletion of *gidB* altered colony and cellular morphology under stress conditions

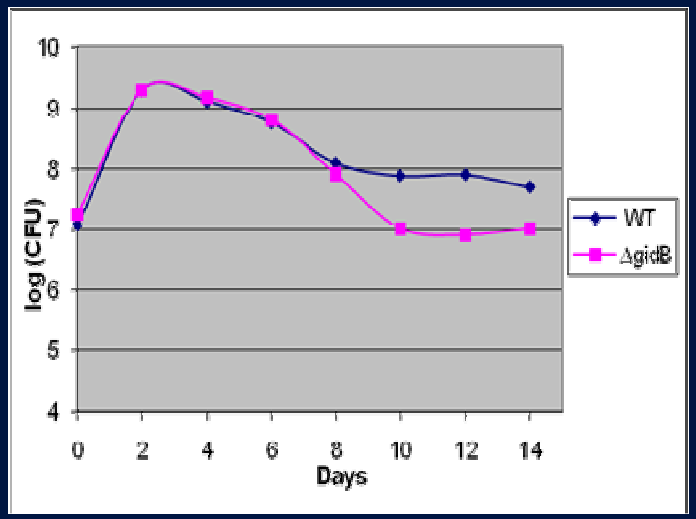


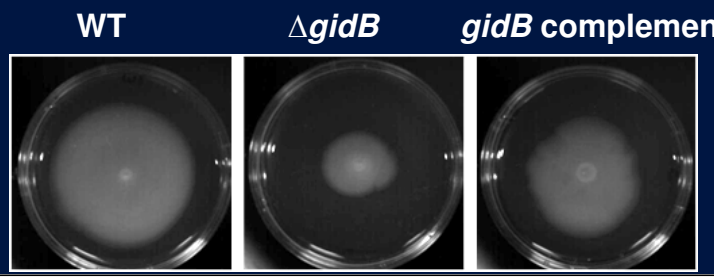




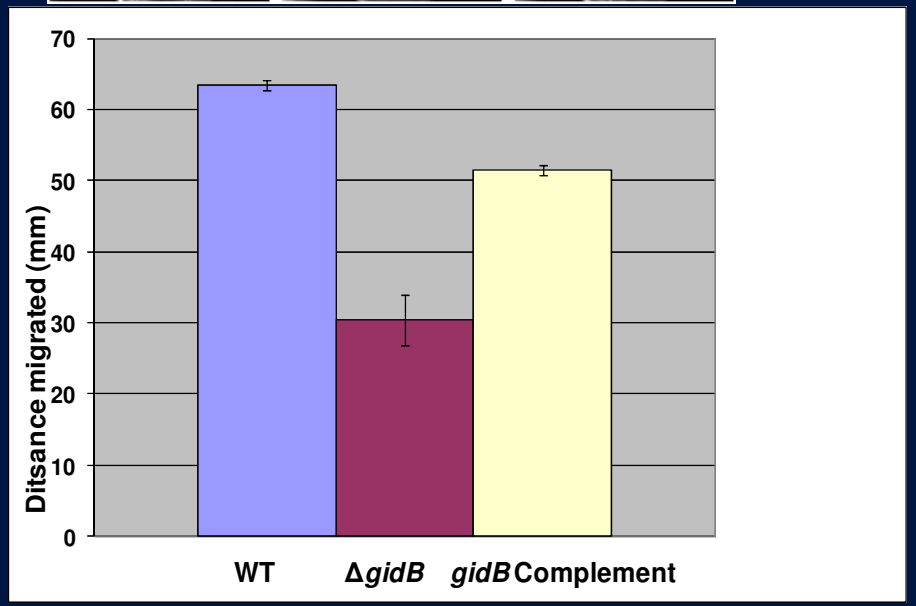
Deletion of *gidB* decreased survival and motility under stress







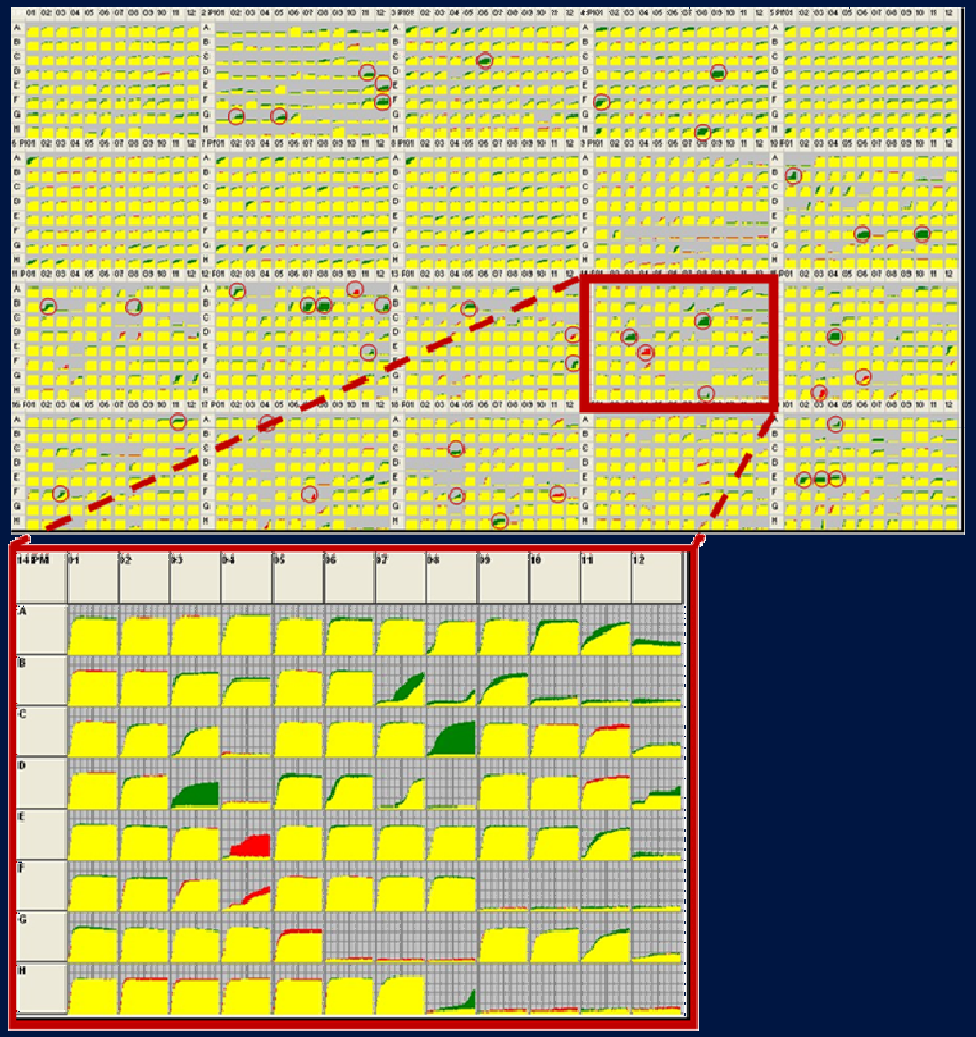
+Nal



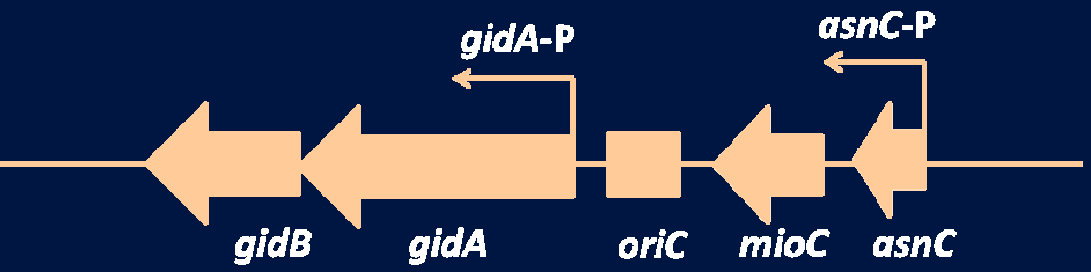
GidB Mutant Phenotype Microarray: stress, antibiotic susceptibility

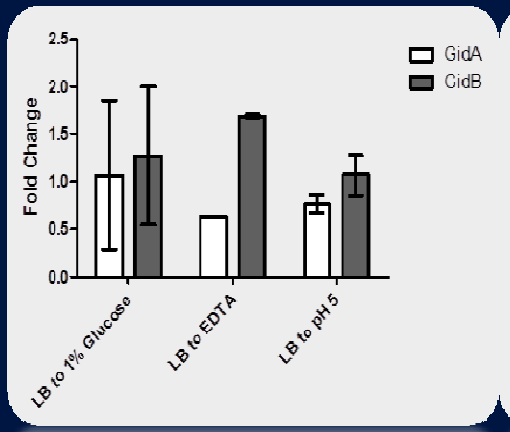
Δ*gidB* was resistant to many antimicrobial agents such as amoxicillin, cloxacillin, and polymyxin B

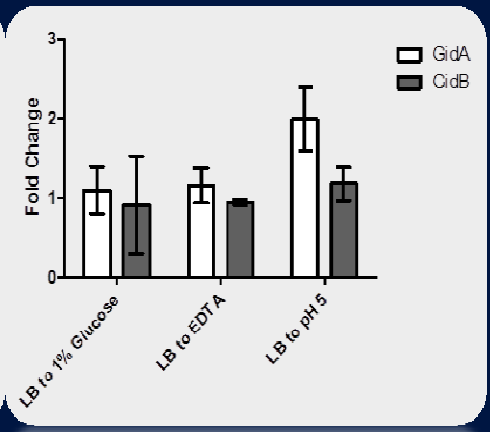
Differential phenotypes for *gidB* mutant: utilization of carbon, nitrogen, phosphorus, or sulfar sources, compared to WT *Salmonella*

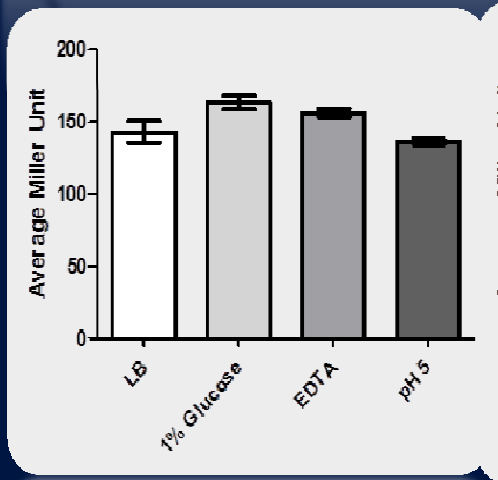


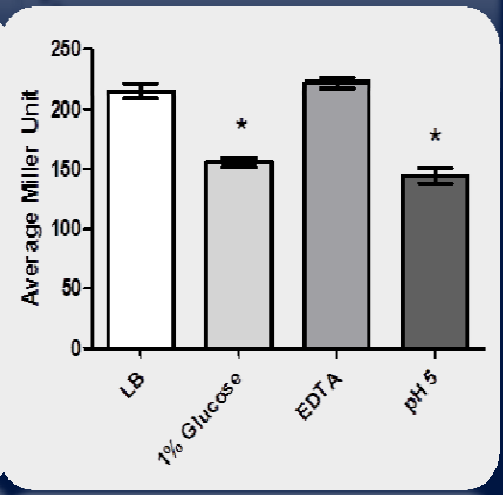
How *gidAB* operon is regulated?







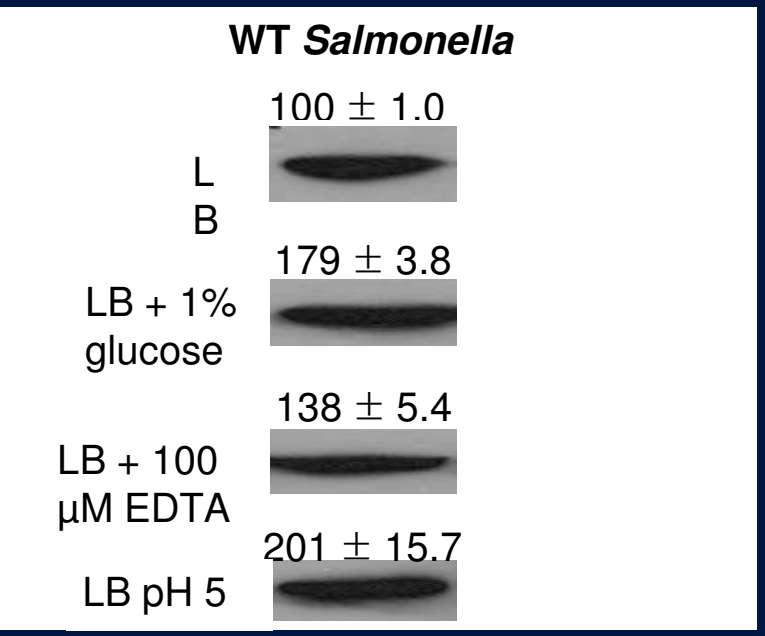


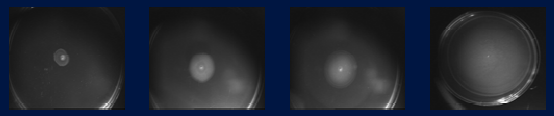


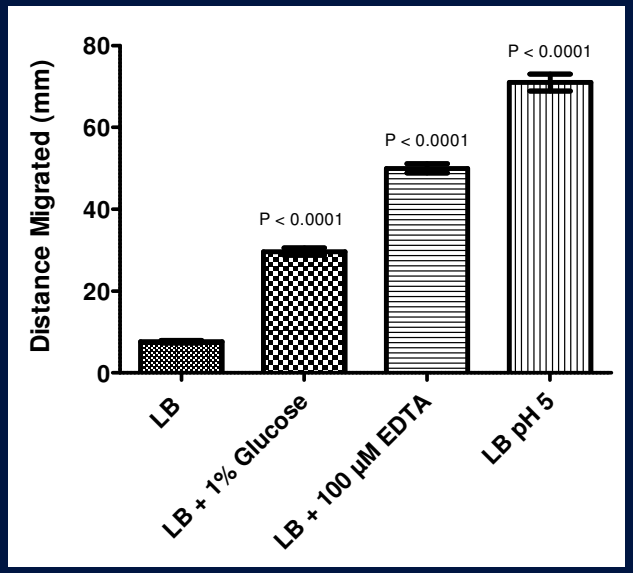
Increased filamentation under high glucose

Bioinformatic indicated AsnC as potential regulator and showed two promoters

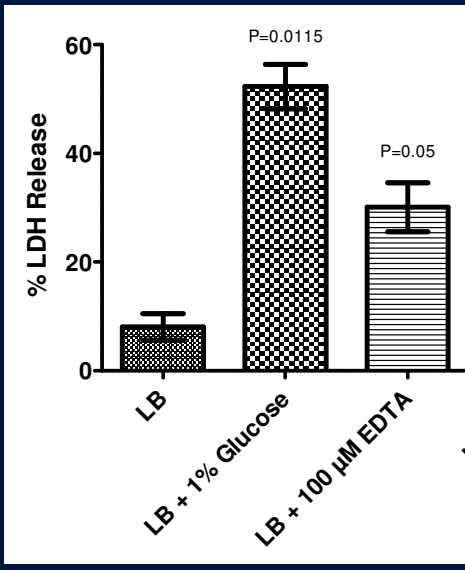
How *gidAB* operon is regulated?



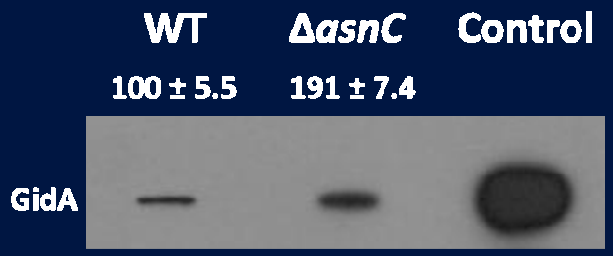




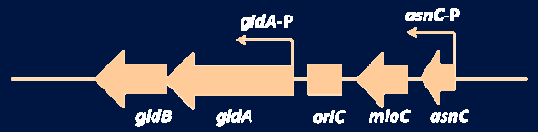
Motility



Cytotoxicity



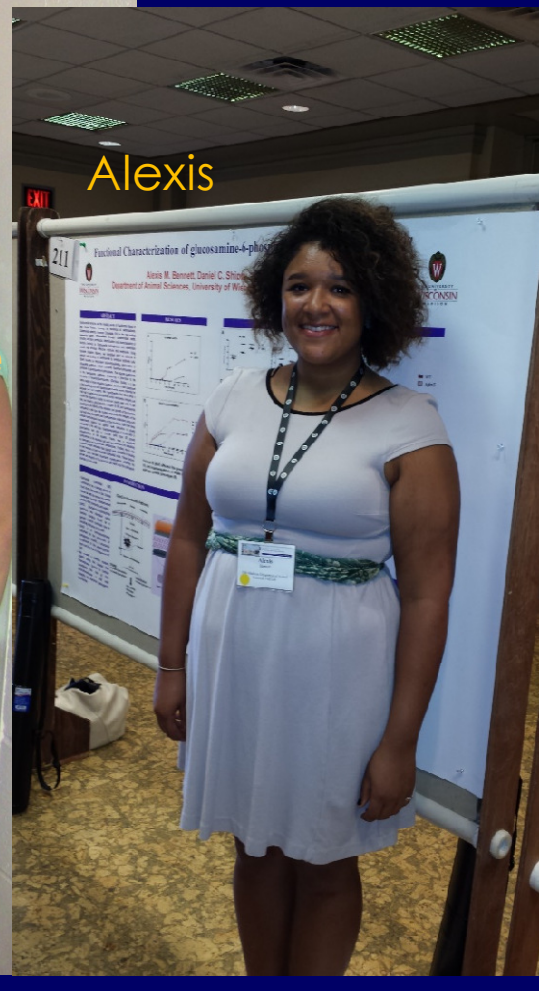
AsnC mutant



Summary

- Deletion of *gidA* rendered *Salmonella* defective in survival and replication inside macrophages and animal host. Phenotype associated with down-regulation in genes/proteins required for survival and stress response.
- GidB mutant showed filamentation, smaller size colonies, and reduced motility in the presence under stress conditions, compared to the WT
- Competitive growth assay: deletion of *gidB* significantly affected overall fitness of *Salmonella* under limited nutrient conditions.
- GidA expression is regulated by environmental conditions and the AsnC at post-transcriptional level
- GidAB operon play important role for survival under stressful conditions

Acknowledgements



Thank you. Question…comment?

Why *Salmonella*

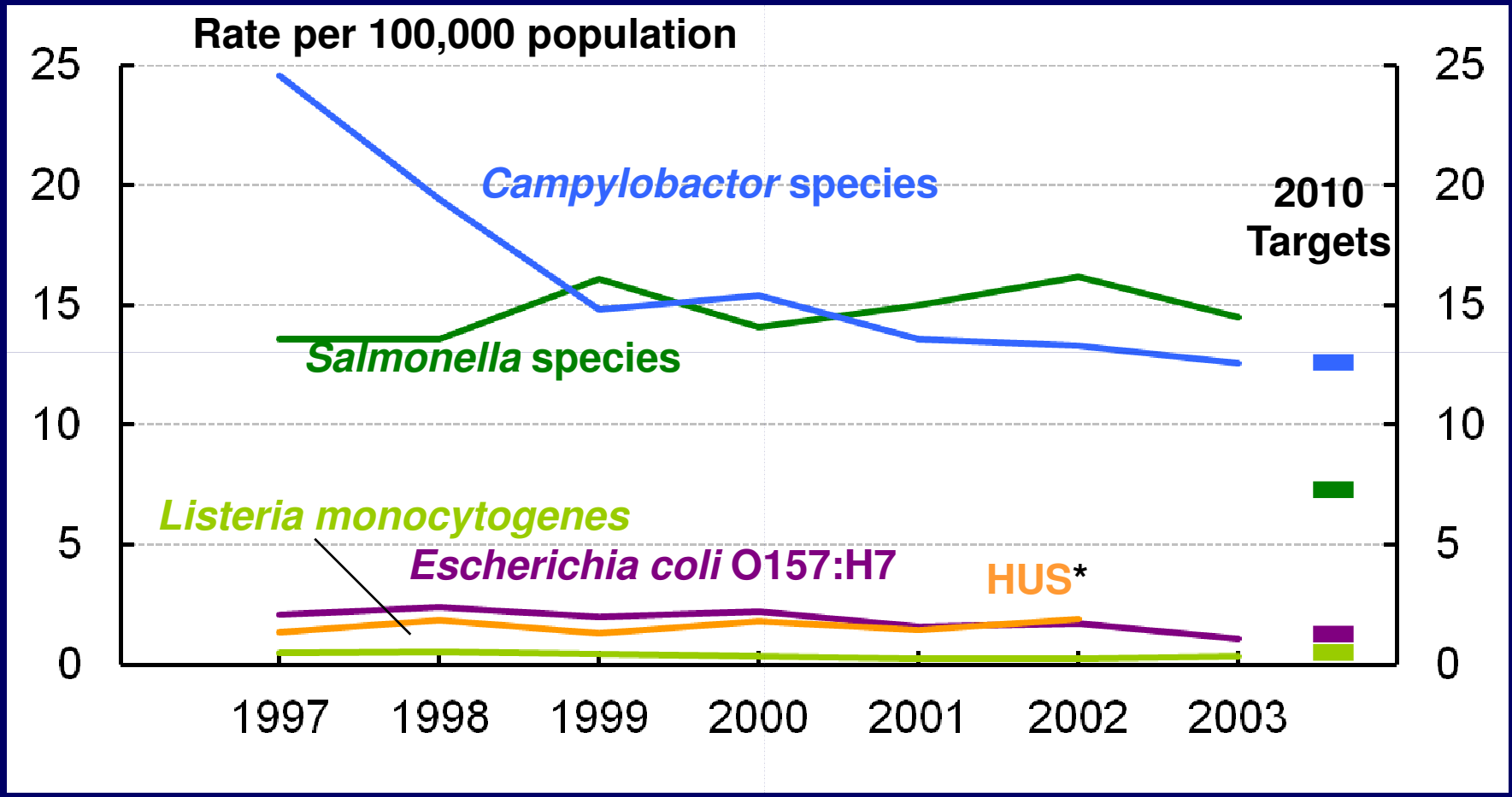
	Cases	%
Overall foodborne illness	76,000,000	
Bacterial foodborne illness	4,200,000	5.5
Foodborne salmonellosis	1,400,000	1.7
salmonellosis from SE	194,408	0.25
Egg association: 40 to 80%	77,000-155,000	< 0.20

Out of 1.4 million cases of salmonellosis, 95% (1.3 million) associated with food; 20% (234,000) from SE (about 75% associated with eggs).

* Cost $23 billion (*Salmonella* $2.65 billion)

CDC, 2002

Significance

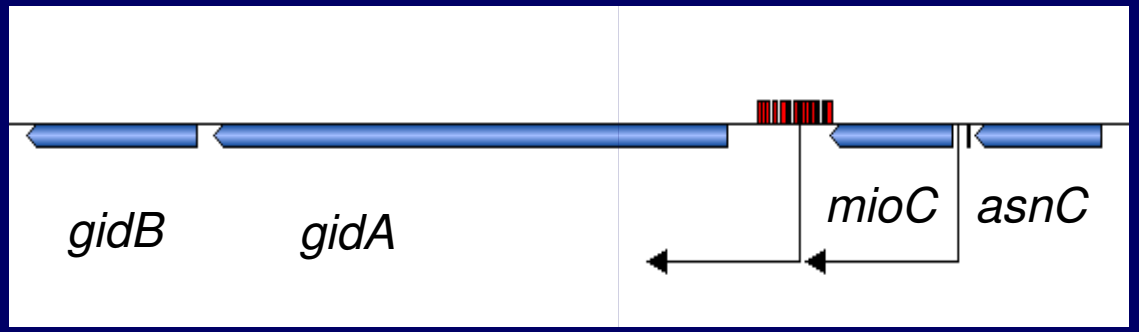


Source: Foodborne Disease Active Surveillance Network (FoodNet)

Significance

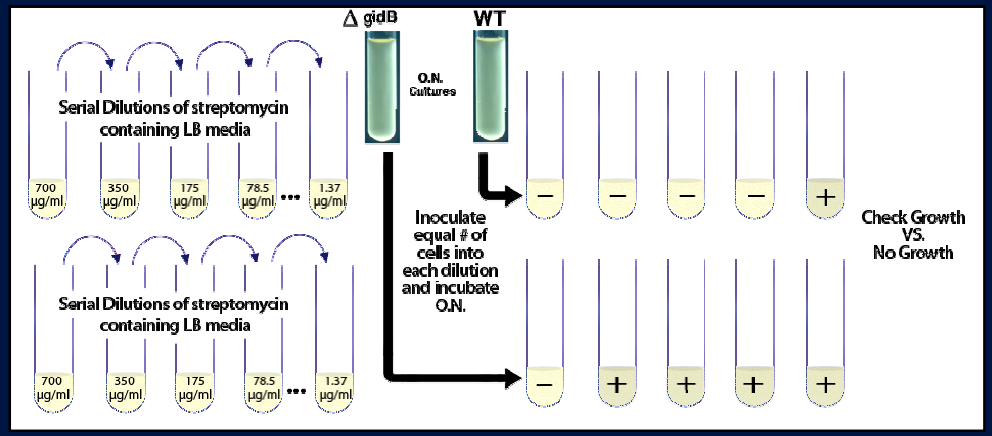
- Major cause of food-borne diseases (poultry, meat, dairy products), use as an indicator of how safe a country's food supplies are
- Multiple antibiotic-resistance strains: use in animal feed
- Model organism to study bacterial genetics and virulence

gidAB operon

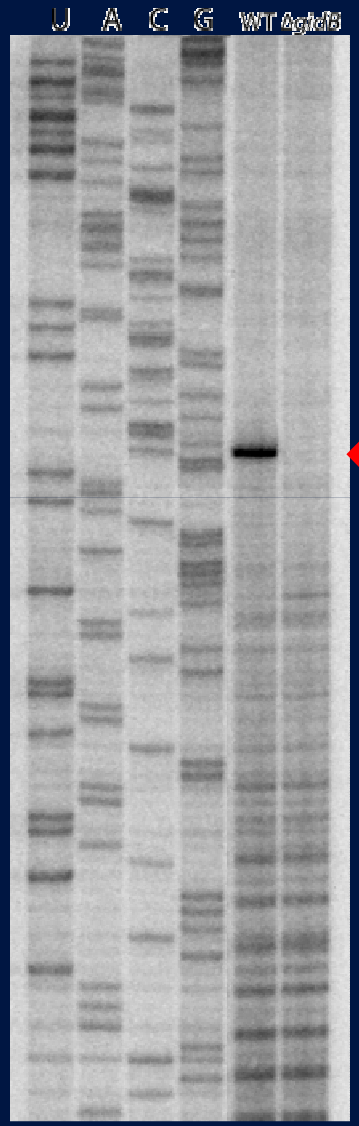


- **GidB (RsmG) is an enzyme that catalyses the methylation of 16S rRNA in bacteria, a binding sites for aminoglycosides e.g. Streptomycin**

Deletion of *gidB* affects susceptibility of *Salmonella* to aminoglycosides



	WT	Δ*gidB*
Antibiotic	MIC (Sensitivity)	MIC (Sensitivity)
Florfenicol	4 (I)	2 (S)
Neomycin	<=4 (S)	>32 (R)
Spectinomycin	64 (R)	32 (I)
Streptomycin	16 (R)	128 (R)



Current and Future Work

- Role of *gidAB* & mechanism in systemic infection and survival in food matrices and animal hosts
- Examine effect of GidB on ribosomal function and effects on antibiotic resistance in *Salmonella*
- Role of GidB in stress response & metabolic pathways as suggested by the PM

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