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Global Burden of Typhoid Fever

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Published Disease Burden

- Ivanoff et al. (1994):
 - 16.6 million cases and 580,000 deaths
- Crump et al. (2004):
 - 21.6 million cases and 216,000 deaths
- Buckle et al. (2012):
 - 26.9 million cases and 269,000 deaths
- Lozano et al. (2012); Murray et al. (2012):
 - 190,000 deaths (Typhoid and Paratyphoid)
 - 12.2 million DALY lost

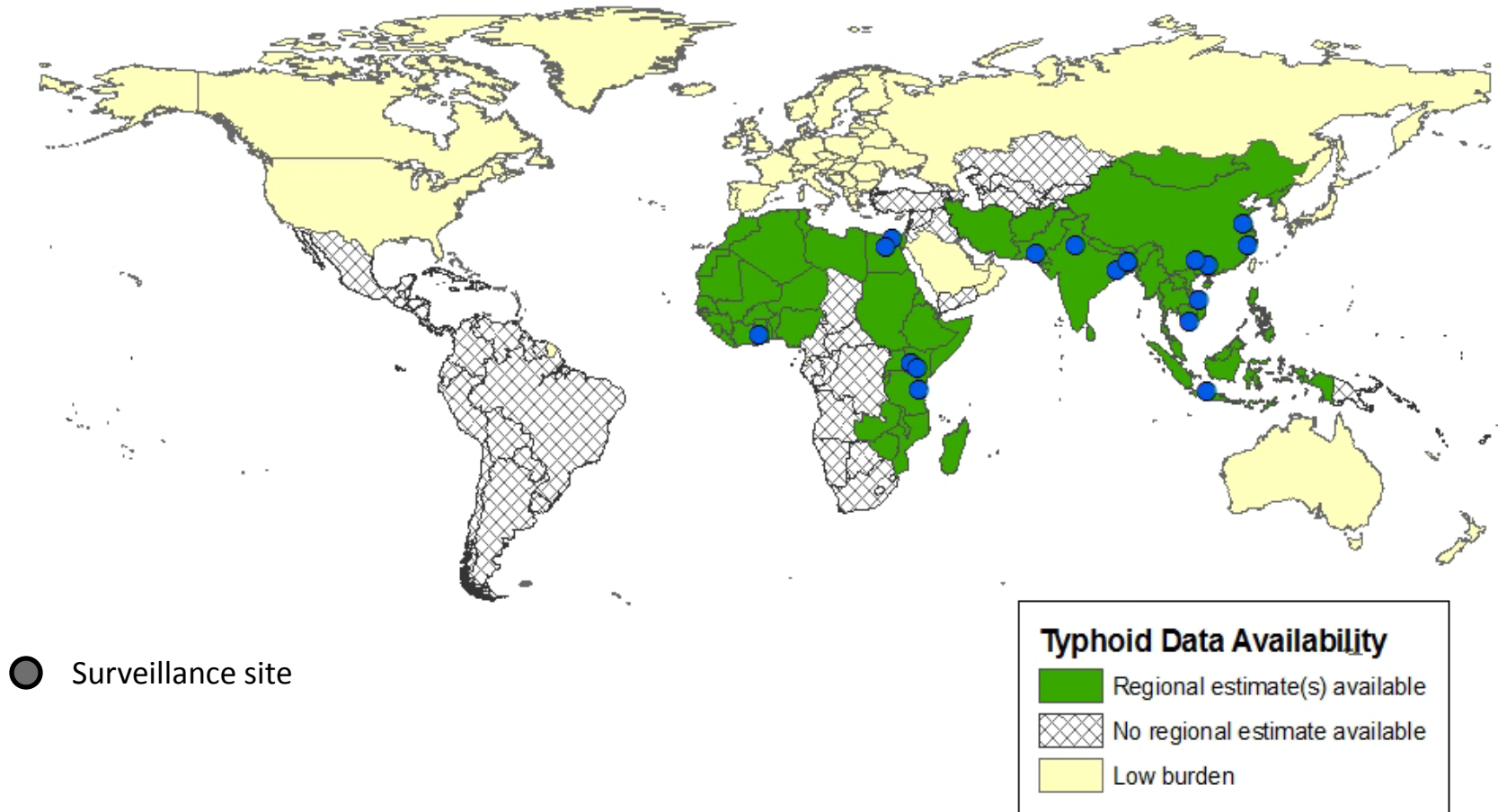


Analysis Gaps

- Population based estimates
 - e.g. 2004 burden estimate for African continent derived from 2 studies
- Local heterogeneity
 - e.g. Regional differences were considered, but the derived estimates were applied to whole country
- Risk differences
 - e.g. No studies considered “high” or “low” risk within region/country
- Case Fatality Rate
 - e.g. Does it make sense to apply same CFR (1%) globally, when factors associated with CFR vary



Data Availability



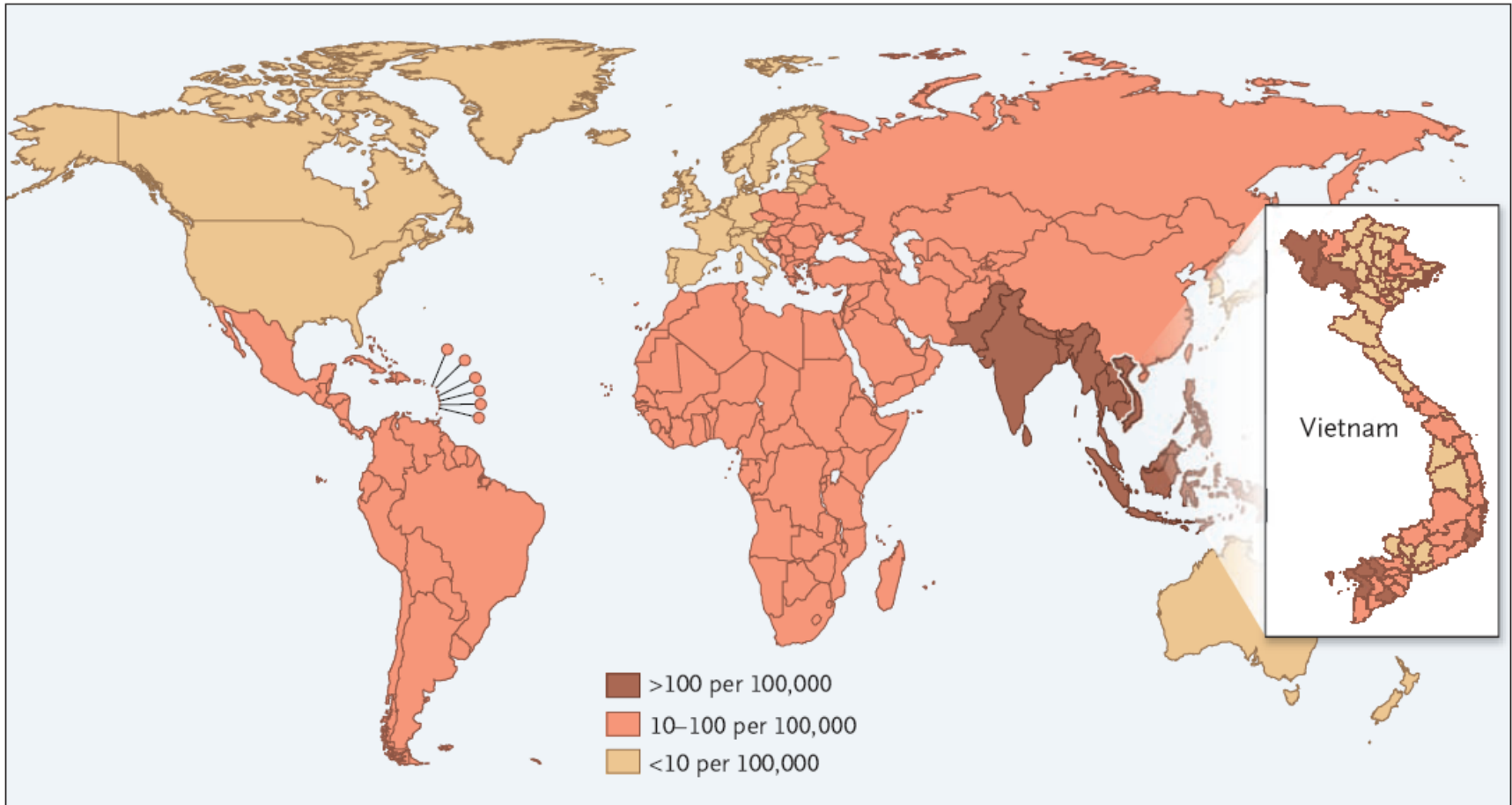
Surveillance Data as Proxy Incidence Rates

Africa; annual per 100,000; unadjusted for blood culture sensitivity

Location	Region	Year	Rural/ urban	0-1	2-4	5-9	10-14	15-19	20+	Overall	Source
Sharkia, Egypt	N Africa	2001	Rural+ Urban	6.5						6.5	(Crump, et al. 2003)
Fayoum, Egypt	N Africa	2002	Rural+ Urban	3		72	80	17		30	(Srikantiah, et al. 2006)
Regional	N Africa			6		53		9		18	
Ashanti region, Ghana	W Africa	2007-2009	Rural	54	286	83					(Marks, et al. 2010)
Regional	W Africa			188		83		26		63	
Kibera, Kenya	E Africa	2007-2009	Urban	821	2243	1788	870	231		822	(Breiman, et al. 2012)
Lwak, Kenya	E Africa	2006-2009	Rural	345	742	215	260	608		444	(Breiman, et al. 2012)
Pemba, Zanzibar Tanzania	E Africa	2009-2010	Rural	42		51		64		55	(Thriemer, et al. 2012)
Regional	E Africa			719		662		296		465	
N. Province, South Africa	S Africa	1985-88	Rural+ Urban			386					(Klugman, et al. 1996)
Regional	S Africa			428		387		61		164	



Geographic Heterogeneity



Mean Annual Incidence of Typhoid Fever per 100,000 Persons.

Country-specific incidence rates, some of which are estimates, are for 2000. Province-specific incidence rates for Vietnam are for children 5 to 14 years of age, between 1999 and 2003 (inset). Country data are from Crump et al.² Provincial data for Vietnam are from a meta-analysis conducted by the DOMI Program.

High-Risk vs. Non-High-Risk Populations

	Total population	Urban slum % (of total pop.)	Rural, lacking access to improved water (% of total pop.)	Fraction (of total pop.)	High-risk Population
AFRICA					
East Africa	326,151,000	15%	43%	58%	187,816,425
Middle Africa	128,209,000	30%	38%	68%	87,276,422
North Africa	212,387,000	16%	9%	25%	53,836,931
West Africa	306,044,000	26%	32%	58%	178,129,405
South Africa	57,967,000	17%	8%	25%	14,472,788
ASIA					
East Asia	1,380,837,000	13%	11%	24%	334,633,289
South Asia	1,719,118,000	12%	11%	23%	398,354,439
Central Asia	61,346,000	1%	12%	13%	8,011,657
Southeast Asia	584,372,000	15%	10%	25%	144,837,488
West Asia	180,898,000	17%	9%	25%	45,610,731
TOTAL	5,557,307,000	15%	14%	29%	1,608,592,886



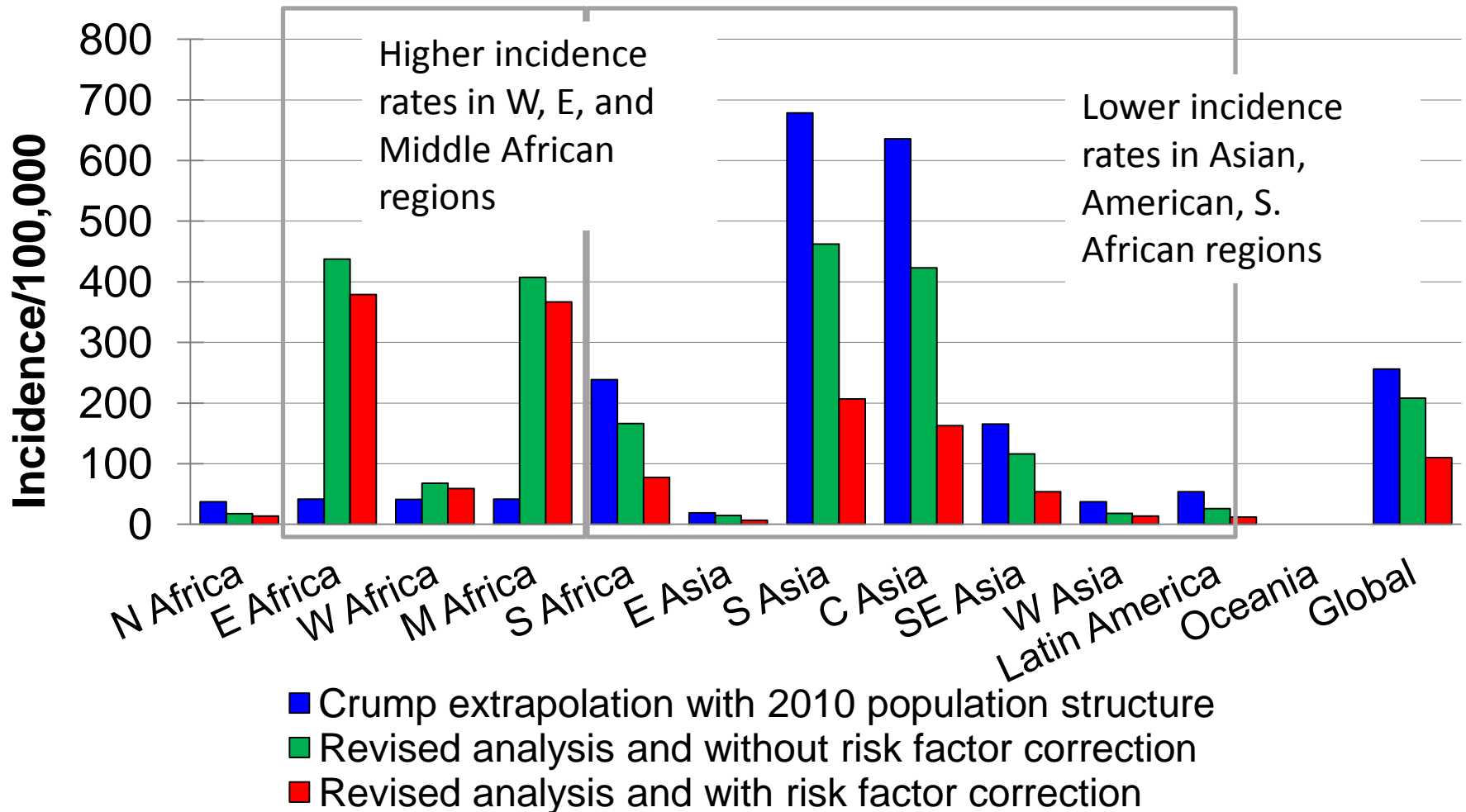
Risk Factor Analysis

Significant risk factors	Odds ratio	95% CI	Case group	Control group	Model	Location/Sources
Piped water supply at home	0.4	0.2-0.9	42/123	53/123	Univariate analysis	Darjeeling, West Bengal, India (Sharma, et al. 2009)
Latrine at home	0.5	0.3-0.8	58/123	79/123		
No education	2	1.0-3.7	35/90	47/180	Logistic regression (LR)	Son La province, northern Vietnam (Tran, et al. 2005)
Drinking untreated water	3.9	2.0-7.5	70/90	79/180		
Low economic level	2.9	1.5-5.3	54/141	32/136	LR	Mekong delta, southern Viet Nam (Luxemburger, et al. 2001)
Drinking unboiled water	4.3	1.3-14.5	25/147	11/142		
Drinking unboiled water at home	12.1	2.2-65.6	36/41	48/82	LR	Dhaka slum, Bangladesh (Ram, et al. 2007)
Using foul-smelling water	7.5	2.1-25.4	23/41	21/82		
Drinking water from a community tap	0.03	0.003-0.331	1/100	14/200	LR	Karachi, Pakistan (Luby, et al. 1998)
No municipal water supply in house	29.18	2.12-400.8	67/75	57/75	LR	Semarang, Indonesia (Gasem, et al. 2001)
Open or without drainage system of house	7.19	1.33-38.82	65/75	57/75		
Unemployed or part time job	31.1	3.08-317.4	22/75	10/75		
No toilet in the household	2.2	1.06-4.55	15/69	33/378	LR	Jakarta, Indonesia (Vollard, et al. 2004)
Consumption of unboiled surface water outside the home	3	1.1-8.2	35/97	51/190	LR	Samarkand Oblast, Uzbekistan (Srikantiah, et al. 2007)
Selected Odds Ratios for drinking unimproved water						
	Odds ratio					
Variance-weighted mean	3.72					
Simple mean	3.73					

Risk of typhoid is estimated to be 3.7 times greater in high risk areas



Results

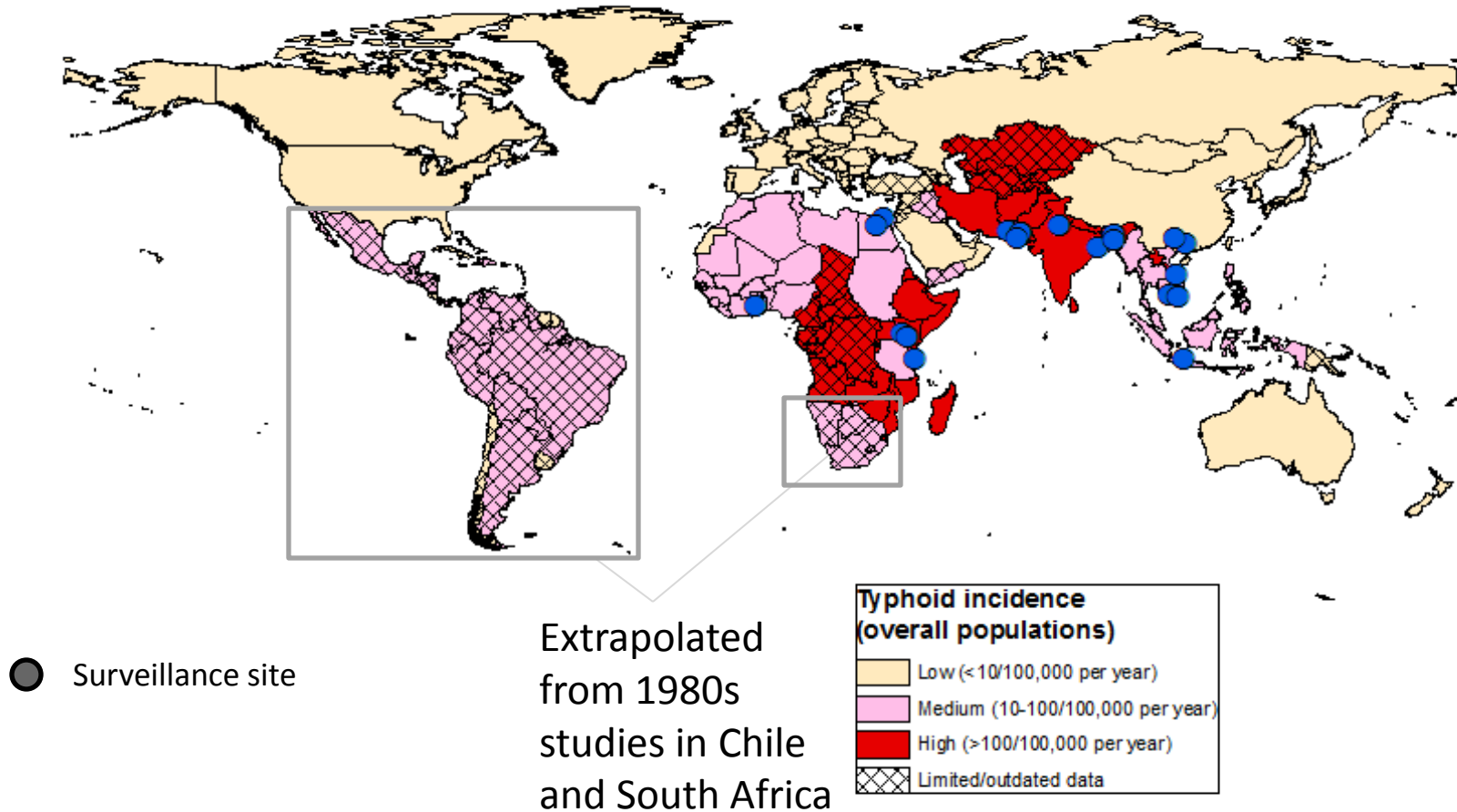


All incidence rates assume blood culture sensitivity is 50%, Beta-PRT (0.4, 0.5, 0.6)



Revised Map of Typhoid Incidence (1)

(with risk factor adjustment)

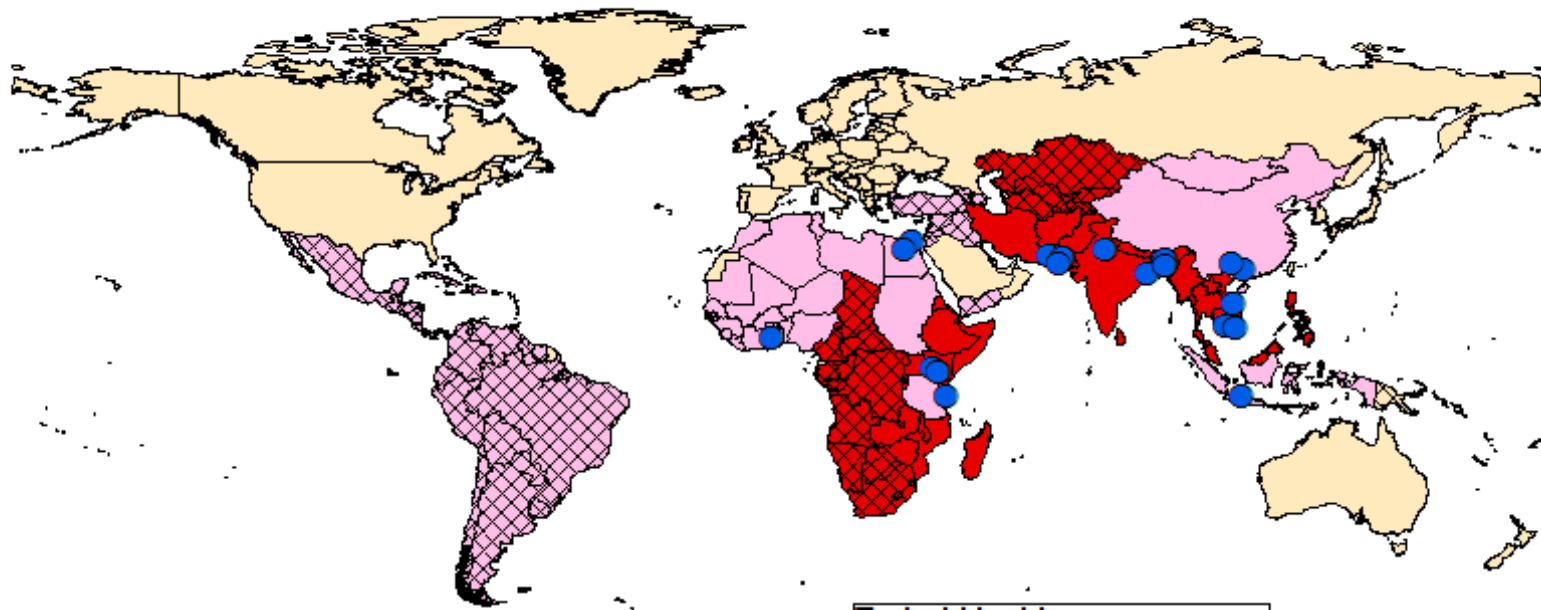


* Not adjusted for blood culture sensitivity



Revised Map of Typhoid Incidence (2)

(no risk factor adjustment)



● Surveillance site

* Not adjusted for blood culture sensitivity



Summary of CFR Over Time from a Review

Data period	1980-1989	1990-1999	2000-2005	Comment
Average CFR	2.45%	1.77%	0.95%	19 studies (>1990)
CFR in hospitalized	2.21%	1.77%	0.99%	18 studies (>1990)
CFR in community based studies	NA	NA	0%	1 study (>1990)

Non-MDR CFR: 1.23%, MDR CFR 1.60%

Source: Prof. Zulfiqar Bhutta, manuscript in preparation

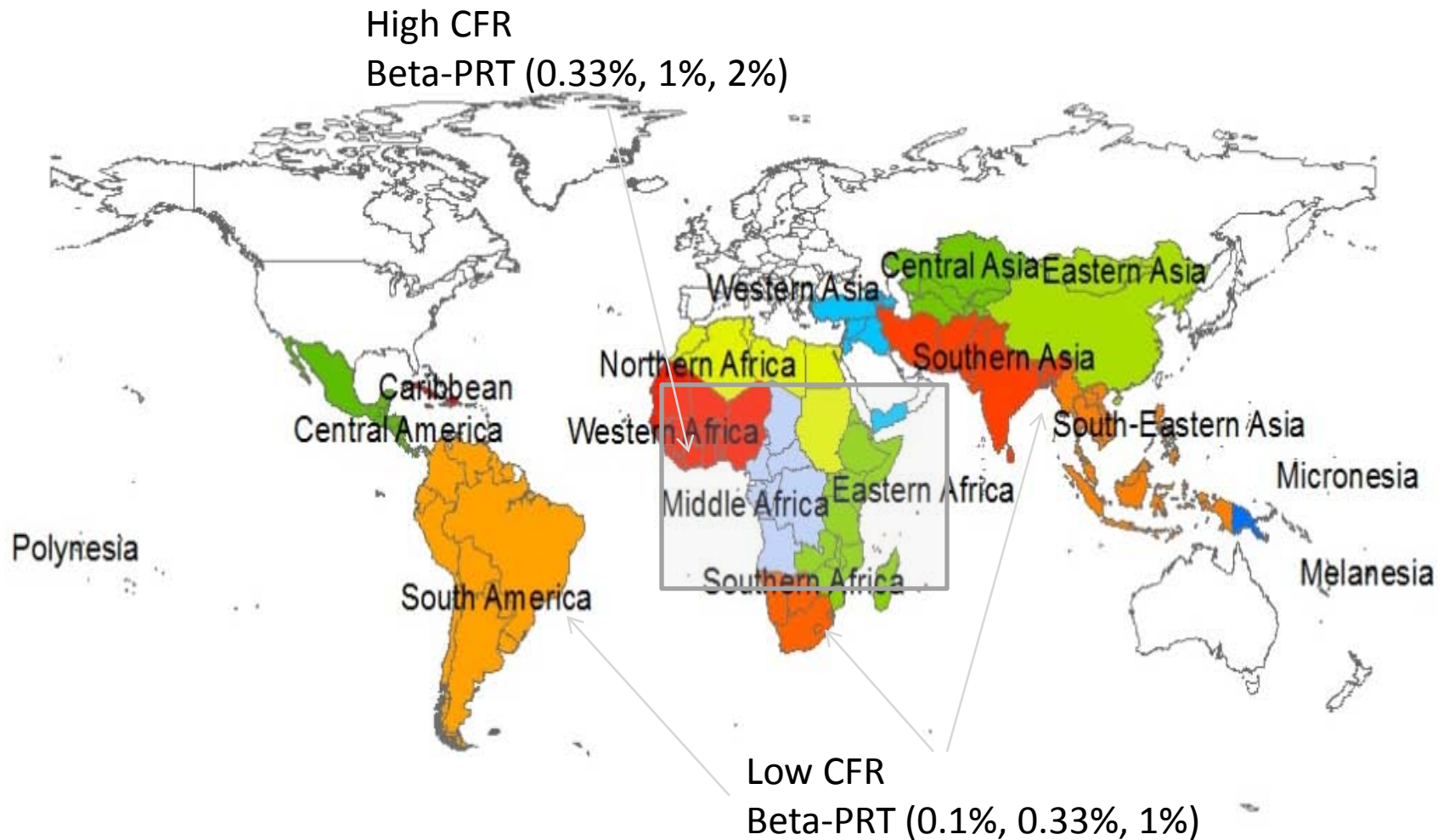


Case Fatality Rate by Region

- In systematic review of intestinal perforation cases
 - Asian CFR 7%
 - African CFR 16%
- High CFR in rural African outbreaks
 - 8.1% in Uganda (intestinal perforation)
 - 3.6% in Malawi (encephalopathy)
- Lower CFR in urban outbreaks
 - <0.1% in Harare
- Misdiagnosis (both under and over reporting) seems to be an issue in Africa



Risk Factor Correction (Case Fatality Rate)



Global Burden Summary with CI

Region		Median	CI Lower	CI Upper
AFRICA				
North Africa	Cases	58,191	38,997	84,986
	Deaths	272	257	2,200
East Africa	Cases	2,507,843	1,887,499	3,383,796
	Deaths	24,368	11,251	88,884
West Africa	Cases	366,156	204,027	606,819
	Deaths	3,558	1,436	14,019
Middle Africa	Cases	954,089	735,129	1,252,795
	Deaths	9,271	4,316	33,377
Southern Africa	Cases	90,892	98,246	227,809
	Deaths	424	647	5,650
AFRICA TOTAL	Cases	3,977,170	3,142,292	5,455,454
	Deaths	37,892	18,193	146,434



Global Burden Summary with CI

Region		Median	CI Lower	CI Upper
ASIA				
East Asia	Cases	184,869	95,270	377,090
	Deaths	863	219	2,321
South-central Asia	Cases	7,444,029	5,555,429	10,931,279
	Deaths	34,739	10,415	79,501
South-East Asia	Cases	634,728	490,308	900,062
	Deaths	2,962	899	6,560
West Asia	Cases	50,318	23,072	44,565
	Deaths	235	43	321
ASIA TOTAL	CASES	8,353,453	6,294,103	12,206,279
	DEATHS	38,983	11,635	89,129
LATIN AMERICA/CARIBBEAN				
TOTAL	CASES	143,005	88,415	228,476
	DEATHS	667	189	1,611
GLOBAL CASES		12,473,628	10,096,655	16,785,238
GLOBAL DEATHS		77,542	42,314	197,910



Greatest Sources of Uncertainty

- Risk factor correction
- Blood culture sensitivity
- Case fatality rate (deaths only)
- Studies/age groups with high incidence rates, which are extrapolated to large populations



Comparison of Results

Risk factor correction	No	No	Yes	Yes
CFR assumption	1%- all	0.33%/1%	1%- all	0.33%/1%
Cases	23,431,898	23,431,898	12,473,628	12,473,628
Deaths	234,319	131,429	124,736	77,542



Limitations

- Correction factor and CFR estimation are somewhat ad-hoc due to data limitations
 - Hospitalization rates
 - CFR outside study hospitals may be higher (especially rural areas)
 - No. of deaths due to misdiagnosis or lack of access to treatment (outpatient deaths)
 - Risk factor correction based on data from co-located, not separate populations
- African data will be improved with TSAP results



Conclusions

- Burden of typhoid remains high
- Incidence estimate is reduced compared to previous estimate
 - Lower incidence studies in Asia
 - Risk factor correction applied to non-high-risk population
 - Higher burden in E/W/M Africa
- Case fatality rate
 - Reduced for Asian and N/S Africa in part due to recent systematic review



Typhoid Trends

- Improvements in economic status, access to water and sanitation, and access to care should reduce cases and deaths (especially Asia)
- Increased urbanization may lead to increased incidence if infrastructure cannot be maintained



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