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Waterborne transmission and the evolution of virulence among gastrointestinal bacteria

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SUMMARY

Diarrhoeal diseases are primary contributors to millions of deaths annually. Yet, little is known about the evolutionary reasons for the differences in virulence among gastrointestinal pathogens. Applying the comparative, cost/benefit approach of evolutionary biology this paper proposes that waterborne transmission should favour evolution towards high virulence. This hypothesis is supported by a cross-specific test, which shows that waterborne transmission is strongly correlated with the virulence of bacterial gastrointestinal pathogens of humans. Alternative explanations of this correlation are not supported by available data. These findings bear on public health policy because they draw attention to a previously unrecognized long-range benefit gained from purification of water supplies: diarrhoeal pathogens may evolve to lower levels of virulence.

INTRODUCTION

Severity of diarrhoeal diseases. During the last two decades diarrhoeal diseases have been primary contributors to about 5–18 million deaths per year [1–4]. Although host factors such as nutrition and age are associated with the severity of gastrointestinal infections (e.g. [5]), virtually nothing is known about the evolutionary reasons for the great differences in virulence within and between species of gastrointestinal pathogens. (In this paper 'virulence' refers to the level of negative effect on the host.) This vacuum in our knowledge is critical because only through a knowledge of the evolutionary determinants of pathogen virulence can we predict its future evolution and the influences of human activities on this evolution.

The health sciences have devoted relatively little attention to the evolution of virulence presumably because of misunderstandings about the levels at which natural selection acts. Until recent years authors writing on the subject generally concluded unjustifiably that coevolution between host and parasite should lead to very benign or commensal relationships (reviewed by [6]; I define 'parasite' as an organism that lives in or on another organism and has a negative effect on the fitness of that organism, and 'pathogen' as a subcellular or unicellular parasite.) Because the errors of traditional thinking about virulence have been addressed only relatively recently (see [7–10]), tests of tenable theory are just beginning.

The cost/benefit perspective and vector-borne transmission. This paper is one of a series that investigates the evolution of virulence using the comparative method

(*sensu* [1]). I first predict from theory situations in which extensive use of host resources should provide the pathogen with exceptionally great fitness benefits and exceptionally low fitness costs (fitness being measured by contribution of the relevant genes into future generations, *sensu* [11, 12]). I then test these predictions by comparing them with the actual relationships derived from the literature. The first paper using this approach confirmed the prediction that pathogens transmitted by biting arthropod vectors should be especially virulent [8].

Virulent genotypes should be favoured analogously by cultural vectors. A cultural vector is defined as a set of characteristics that allow pathogens to be transmitted from immobilized hosts when at least one of the characteristics is some aspect of human culture [6]. The cultural vector considered in this paper involves the transmission of gastrointestinal pathogens to susceptible hosts via contaminated water.

A positive association between vector-borne transmission and virulence is expected because evolution places two opposing pressures on pathogen genes that contribute to extensive reproduction in hosts.

Like pathogens transmitted by arthropod vectors, waterborne pathogens should incur relatively small fitness costs and large benefits from extensive reproduction inside hosts. A person immobilized by a severe case of diarrhoea will release pathogens into bedsheets, clothing and other objects that will tend to be washed. When the contaminated wash water mixes with unprotected drinking water, large numbers of susceptible people could become infected from the pathogens released from an immobilized host (for documentation of this process see [13–17]). In this case, the cultural vector includes the materials contaminated by the immobilized host, the person removing this material, the contaminated waters that flow into the drinking water, and agents contributing to this flow or delivering the contaminated water to susceptible people. (This cost/benefit argument is also applicable to pathogenicity due to enterotoxins and need not assume that mutations enhancing waterborne transmission precede those increasing pathogen virulence; see [6].)

The present paper tests a central prediction of this hypothesis: the virulence of gastrointestinal tract pathogens should be positively correlated with their tendencies for waterborne transmission. The test is restricted to bacteria because their pathogenicity and modes of transmission are well documented and variable. Pathogens species for which humans are dead-end hosts were excluded from the test because the level of virulence in a dead-end human host is irrelevant to the further transmission to other humans.

The test assumes that evolutionary changes in levels of pathogen characteristics relevant to virulence will occur over time scales in which the waterborne cultural vector has been present, that is, over years to millennia. This assumption seems reasonable considering the rapid rates of evolutionary changes documented in response to some cultural characteristics; for example, during the first 5 months of an epidemic of *Vibrio cholerae* in Tanzania, resistance to tetracycline changed from 0 to 76% of the isolates [18].

RANKING OF MORTALITY AS AN INDICATOR OF VIRULENCE

General methods. Because negative and positive effects of disease manifestations are often difficult to distinguish (see [8, 19]), mortality was used as an indicator of virulence. The total number of infections resulting in death was estimated by the following procedure. A literature search was initiated using medical texts and computer-accessed databases. Searching continued using these sources and cited references until 20 outbreaks yielding quantifications of mortality (see below) were found or until a 20-h period of searching time provided no new leads. Any outbreaks found inadvertently were also included, based on the assumption that the increased accuracy resulting from increased sample size would outweigh any potential biases associated with the subject matter of these papers. The data therefore represent all relevant information of which I am aware.

For an outbreak to be included, the number of deaths needed to be explicitly stated unless the qualitative description indicated that no deaths occurred. The number of cases or an explicit estimate thereof was also required. Because sporadic severe infections should tend to be reported more often than sporadic nonlethal infections, mortality figures included only outbreaks involving at least 10 infections. To correct for frequencies of inapparent infections, mortality per case was divided by infections per case (as indicated by bacteriological positivity). In using these calculations I assume that any deviations between estimates and actual values (e.g. infections per case) do not covary with the actual values of mortality. This assumption was evaluated whenever possible by comparing overall estimates with more restricted comparisons; for example, values from different pathogens could sometimes be compared using data from the same research group and the same epidemiological procedures.

To reduce effects of improved treatment on mortality, data gathered without use of antibiotics or other effective treatments (e.g. hypotonic saline for cholera) were used whenever possible. When such data were unavailable, direct comparisons between pathogens were made during similar time periods. If ambiguities in a ranking arose from differences in the effectiveness of treatment, the involved pathogens were assigned tied ranks in a supplemental conservative test. For some pathogens reliable estimates of mortality for untreated cases were so limited that mortality figures were obtained from governmental or hospital records, rather than outbreaks. Pair-wise comparisons were made within geographic areas when possible.

To reduce variability due to the health status of infected individuals, calculations excluded outbreaks within highly vulnerable groups (neonates, patients with underlying disease, and residents in institutions for the mentally handicapped and aged) and deaths attributed by authors to causes other than the pathogen under consideration. Hospital outbreaks were also excluded because transmission in hospitals often occurs by a different cultural vector, which seems to enhance virulence [6].

When comparing ratios of symptomatic to asymptomatic infections, and when comparing percentages of mortality, G tests were used with the Williams correction in accordance with the recommendations of Sokal and Rohlf [20].

Vibrio cholerae. Mortality associated with untreated acute cases of classical

cholera is generally between 50 and 75% [21]. The most reliable mortality figures that I located involved 1243 hospitalized cases between 1895 and 1905 from the Medical College and Campbell Hospital in Calcutta: 59 and 63% of these cases, respectively, were fatal [22]. These cases received supportive treatment but not hypertonic saline, which was introduced around 1905 and substantially reduced mortality rates. The patients were of different religious and racial groups, but the rates from all groups were similar (the low figure was 56·5% for 92 Europeans and Eurasians, and the high was 61·6% for 814 Hindus [22]). Another apparently reliable figure is 52% for the 7326 cases in the 1873 epidemic in the United States [23]. The average of these three values (58%) was used as the estimate of mortality from cases of untreated classical cholera. To obtain the mortality per infection, this value was divided by the infections per severe case (i.e. one in need of hospitalization).

Infections per severe case were estimated from frequencies of infection among contacts of index patients. For classical *V. cholerae* 3·7 infections occurred for every severe case (Table 1), yielding a mortality per infection of 15·7% (i.e. 58% divided by 3·7).

Mortality data for untreated cases of el tor cholera are not available because the el tor biotype became prevalent only during the last three decades. Mortality due to el tor *V. cholerae* was therefore estimated as follows. The mortality per case of el tor cholera in south and southeast Asia from 1961 through 1966 (15·3%) was divided by the mortality per case of classical cholera in this geographic area during the same period (i.e. 40·5%; both figures from [33]). To estimate mortality per untreated case of el tor cholera, I multiplied the mortality per case of el tor relative to classical cholera ($15{\cdot}3/40{\cdot}5 = 0{\cdot}38$) by the fatality per untreated case of classical cholera (58·0%; see above). In making this calculation, I assume that the marginally effective treatment of cholera during this time period altered mortality per case by the same ratio for both biotypes (for classical cholera the reduction was about 58 to 41%; see above). The resulting mortality per untreated el tor case (21·9%) was divided by 15·2, which represents the infections per severe case (Table 1), yielding 1·44% as the mortality per infection. The difference in virulence between classical and el tor *V. cholerae* is also apparent when the biotypes occurred within a community, during adjacent years [26, 27] or simultaneously [28]; Table 1; $P < 0{\cdot}05$ for each difference.

Salmonella typhi. Data from a well-studied, localized outbreak of *S. typhi* in rural Georgia [34] were used to estimate the infections per apparent case. Eleven of the 80 *S. typhi* infections were asymptomatic. Two of these were probably chronic carriers infected prior to the outbreak [34]. One-third of the remaining 69 symptomatic cases were found through a house-to-house canvass; thus, 1·13 infections were documented per symptomatic case (78 infections divided by 69 symptomatic cases), and the number of infections for each case normally recognized by physicians was 1·70 (78 infections divided by 46 apparent cases). When mortality figures from outbreaks were based on intense efforts to identify all symptomatic cases they were therefore divided by 1·13 to obtain the mortality per infection. For all other outbreaks, mortality per case was divided by 1·70 (Table 2).

The average of these figures (5·8%) is below the mortality per infection of

Table 1. *Frequencies of infections with el tor and classical* Vibrio cholerae *categorized according to severity*

Number of infections			
Severe	Moderate-to-asymptomatic	Location	Reference
		Classical biotype	
31	84	Dhaka, Bangladesh	[24]
29	49	Dhaka, Bangladesh	[25]
7	28	Chittagong, Bangladesh	[26]
5	13	Meheran, Bangladesh	[27]
10	46	Dhaka, Bangladesh	[28]
82	220	All classical	
		El tor biotype	
5	50	Philippines	[29]
0	5	Calcutta, India	[30]
3	110	Chittagong, Bangladesh	[26]
2	33	Meheran, Bangladesh	[27]
9	33	Dhaka, Bangladesh	[31]
1	55	Matlab, Bangladesh	[32]
1	59	Dhaka, Bangladesh	[28]
21	319	All el tor	

classical *V. cholerae* (see above). Restricting the comparison temporally and geographically also yields a lower ranking of *S. typhi* relative to classical *V. cholerae*. The mortality associated with the five oldest outbreaks of *S. typhi* in the United States (18·6/1·70 = 9·7%; data from Table 2, 1885–94) is less than the mortality associated with the 1873 epidemic of cholera in the US: 14·1% (52% divided by 3·7).

Shigella spp. Case-fatality figures for *S. dysenteriae* 1, *S. flexneri*, and *S. sonnei* are presented in Table 3. Data from *S. boydii* and other serotypes of *S. dysenteriae* were insufficient for rankings of mortality and/or waterborne transmission. *Shigella dysenteriae* type 1 was analysed separately from the other serotypes of *S. dysenteriae* because its virulence is markedly different.

Infections per case were lowest for *S. dysenteriae* 1 and highest for *S. sonnei* (for *S. dysenteriae* 1 versus *S. flexneri*, $G = 6{\cdot}53$, $P < 0{\cdot}02$; for *S. flexneri* versus *S. sonnei*, $G = 17{\cdot}42$, $P < 0{\cdot}001$; for *S. dysenteriae* 1 versus *S. sonnei*, $G = 17{\cdot}95$, $P < 0{\cdot}001$; data from Table 3).

Because these differences were derived from several studies, they might have been influenced by differences in methods of detection, geographic location or year of study. To reduce interpretive ambiguities pair-wise comparisons were made within teams of researchers. Among contacts of index patients, Khan and Shahidullah [31] found more infections per case of *S. flexneri* than *S. dysenteriae* 1 ($G = 6{\cdot}78$; 2-tailed $P < 0{\cdot}01$). Hardy and his associates found more infections per case of *S. sonnei* than *S. flexneri* ($G = 10{\cdot}95$, 2-tailed $P < 0{\cdot}001$; data from Table 4): the results from the pair-wise comparisons are, therefore, consistent with the overall differences.

To obtain mortality per infection the mortality per case for each outbreak in

Table 2. *Mortality associated with* Salmonella typhi *infections*

Deaths	Cases	Mortality (%) Per case	Mortality (%) Per infection	Year	Location	References
21	352	6·0	3·5	1879	Caterham and Redhill, England	[13]
114	1604	7·1	4·2	1885	Plymouth, Pennsylvania	[13]
12	50	24·0	14·1	1890	Waterbury, Connecticut	[35]
61	323	18·9	11·1	1890–1	Lowell-Laurence, Massachusetts	[35]
25	150	16·7	9·8	1892	Springfield, Massachusetts	[35]
4	25	16·0	9·4	1894	Wesleyan, Connecticut	[35]
22	386	5·7	5·7	1895	Stamford, Connecticut	[35]
4580	20738	7·6	4·5	1898	Spanish–American War, U.S. camps	[35]
15	190	7·9	4·7	1901	Baraboo, Wisconsin	[35]
0	28	0	0	1902	Montclair and Bloomfield, New Jersey	[35]
16	196	8·2	4·8	1901–3	Lowell, Massachusetts	[35]
53	612	8·6	7·6	1902–3	Waterville and Augusta, Maine	[35]
611	4578	13·3	7·8	1903–4	Cleveland, Ohio	[35]
82	1350	6·1	5·4	1903	Ithaca, New York	[35]
13	164	7·9	4·7	1905	Basingstoke, England	[35]
111	1155	9·6	5·7	1906–7	Scranton, Pennsylvania	[35]
1	36	2·8	1·6	1911	Texarkana, Arkansas/Texas	[36]
24	199	12·1	7·1	1912	Rockford, Illinois	[37]
19	229	8·3	4·9	1912	Troy, Pennsylvania	[38]
16	202	7·9	4·7	1913	Quincy, Illinois	[37]
3	93	3·2	2·9	1914	Hanford, California	[39]
4	51	7·8	4·6	1917	Michigan	[40]
11	82	13·4	7·9	1919	E. Lansing, Michigan	[41]
	882	2·8	1·6	1919–20	Salem, Ohio	[42]
5	100	5·0	2·9	1920	Seneca Falls, New York	[43]
545	2423	22·5	13·3	1926	Hanover, Germany	[44]
488	5014	9·7	5·7	1927	Montreal, Quebec	[44, 13]
25	248	10·1	6·0	1928	Olean, New York	[45]
2–3	62	4·0	2·4	1930	Ecclefechan, Scotland	[46]
70	718	9·7	5·7	1936	Bournemouth, England	[47]
43	310	13·9	8·2	1937	Croydon, England	[47]
1	12	8·3	4·9	1939	DePue, Illinois	[48]
4	54	6·3	3·7	1940	St Boniface and St Anne, Manitoba	[49]

Table 3 was divided by the infections per case, which were 1·54 for *S. dysenteriae* 1, 2·22 for *S. flexneri* and 2·91 for *S. sonnei* (from Table 4), yielding 7·50, 1·32 and 0·65% mortality, respectively. In the United States, mortality associated with *S. dysenteriae* 1 was higher than that associated with the *S. typhi* outbreaks that occurred earlier in the century (Tables 2 and 3). Similarly, in the United Kingdom, mortality associated with *S. dysenteriae* 1 was generally higher than that associated with *S. typhi* (Tables 2 and 3). Although these outbreaks did not occur simultaneously the observed ranking is opposite to that expected from a temporal change in the quality of care: the *S. dysenteriae* 1 outbreaks occurred after the *S.*

Table 3. *Percent mortality associated with infection by* Shigella dysenteriae, S. flexneri *and* S. sonnei

Deaths	Cases	Mortality (%) Per case	Per infection	Year	Location	Reference
			Shigella dysenteriae type 1			
15	108	13·8	9·0	1905	Kobe, Japan	[50]
2	38	5·3	3·4	1917–8	England	[51]
19	186	10·2	6·6	1919	Dublin, Ireland	[52]
10	45	22·0	14·2	1938	Michigan	[53]
NG	NG	12·0	7·8	1938	Mecklenberg, Germany	[54]
12	117	10·3	6·7	1941	Adair Co., Kentucky	[55]
13000	120000*	10·8	7·0	1968–9	Guatemala	[56]
27	330*	8·2	5·3	1973	St Martin Is., Bangladesh	[57]
			Shigella flexneri			
55	418	12·2	5·5	1905	Kobe, Japan	[50]
0	11	0	0	1921	Newcastle, England	[58]
12	1100†	1·1	0·5	1921	Og More Vale, Wales	[59]
0	10	0	0	1927	Smethwick, England	[60]
6	124	4·8	2·2	1927–9	Denmark	[61]
8	115	7·0	3·2	128–9	Newcastle and Durham, England	[62]
1	28	3·6	1·6	1929–31	Bangalore and Poona, India	[63]
0	40	0	0	1933–4	Bronx, New York	[64]
1	184	0·4‡	0·2	1934	Jersey City, New Jersey	[65]
2	70	2·9	1·3	1936	Yallaho	[54]
0	16	0	0	1938	New Mexico	[66]
			Shigella sonnei			
1	116	0·7	0·2	1927	Skanderborg, Denmark	[61]
0	150	0	0	1926	St Andrews, Scotland	[67]
4	167	2·4	0·8	1927–9	Denmark§	[61]
0	142	0	0	1928	Korsor, Denmark	[61]
0	75	0	0	1929	Rask Molle, Denmark	[61]
0	24	0	0		Lahore, Pakistan	[68]
3	26	3·9	1·3	1929	Newcastle and Durham, England	[62]
1	30	3·3	1·1	1929–30	Massachusetts	[69]
0	100†	0	0	1930	London, England	[70]
0	24	0	0	1931	Rugby, England	[71]
0	> 100	0	0	1931–2	Denton, England	[72]
1	15¶	—	6·7	1931	Glasgow, Scotland	[73]
0	40	0	0	1933–4	New York	[64]
0	59	0	0	1938	Bedford, England	[74]
1	132	0·8	0·3	1939	Tottenham, England	[75]
0	27	0	0	1942	Cardiff, Wales	[76]

* The value from Levine *et al.* [56] represents Mendizibal's unpublished estimates of the overall mortality in the epidemic prior to use of effective antibiotics (Sept. 1968– Aug. 1969). Levine *et al.* presented the estimated numbers of deaths and cases (13000 and 120000) but not the number of deaths and cases on which these estimates were based. The data from St Martin Island included only cases prior to medical intervention.

† These values are numbers of cases estimated by the authors.

‡ Felsen *et al.* [65] stated that 15–20 % of cases were severe and 2 % of severe cases were lethal, hence the mortality rate of 0·4 %. 184 cases had been observed at the time of their report.

§ Excluding the outbreaks at Korsor, Rask Molle, and Skanderborg listed above.

¶ Total number of infections.

Table 4. *Frequencies of total and asymptomatic* Shigella *infections*

No. infections	No. symptomatic	Location	Reference
	Shigella dysenteriae 1		
49	32	Bangladesh	[31]
5	3	Bangladesh	[77]
54	35	All *S. dysenteriae* 1	
	Shigella flexneri		
147	97	United States	[54]
66	44	United States	[78]
326	111	United States*	[79]
10	2	Bangladesh	[31]
131	52	Bangladesh	[77]
680	306	All *S. flexneri*	
	Shigella sonnei		
38	14	United States*	[79]
310	51	United States	[78]
118	38	England	[80]
107	92	United States	[81]
15	7	Scotland	[73]
588	202	All *S. sonnei*	

* A small minority of these cases was apparently from Puerto Rico.

typhi outbreaks and were more severe. *S. dysenteriae* 1 was, therefore, ranked above *S. typhi*.

The average mortality in the two outbreaks of *S. dysenteriae* 1 in the United States (10·5%) was lower than that of the 1873 outbreak of cholera (14·1%), in accordance with the overall difference between these two pathogens, but the large gap in time between these outbreaks weakens this comparison. The analysis of mortality across all species therefore ranked classical *V. cholerae* above *S. dysenteriae* 1 in one test and tied with *S. dysenteriae* in the second, more conservative test.

A more restricted comparison between *S. flexneri* and *S. typhi* is also consistent with the overall difference between these two species. During the 1920s and 1930s *S. typhi* infections were more lethal than *S. flexneri* infections in both the United States and the United Kingdom (Tables 2 and 3).

The mortality associated with *S. flexneri* was slightly lower than that of el tor *V. cholerae* (see above). Data gathered in Bangladesh during the late 1970s and early 1980s provide a temporally and geographically restricted comparison. For el tor *V. cholerae* 11 of 158 infections required hospitalization (Table 1). About 21·9% of hospitalized el tor cases would be expected to die without treatment (see preceding section on *V. cholerae*), yielding 1·5% mortality for untreated infections. For *S. flexneri* 38·3% of 141 infections were symptomatic (from Table 4). A 2·9% mortality for untreated cases (Table 3) yields 1·1% mortality for untreated infections. The more restricted comparison is therefore consistent with the overall comparison; however, because the difference is small, the cross specific analysis was run both with el tor *V. cholerae* ranked above *S. flexneri* and, in the more conservative test, with the two pathogens assigned a tied rank.

Campylobacter jejuni. No mortality occurred in the 21 outbreaks of *C. jejuni*

Table 5. *Mortality associated with infections by* Shigella sonnei *in outbreaks during or after 1970*

Deaths	Cases	Mortality: Per case	Mortality: Per infection	Year	Location	Reference
1	70	1·4	1·0*	1970	Kentucky (M)	[84]
0	11	0	0	1970	Utah	[84]
0	300	0	0	1970	Albuquerque, New Mexico	[85]
1	113	0·09	0·03	1971	Kansas (M)	[86]
0	242	0	0	1971	Atlanta, Georgia	[87]
0	667	0	0	1971	Florida	[87]
0	395	0	0	1971	Maui, Hawaii	[88]
0	89	0	0	1971	Anchorage, Alaska	[89]
0	86	0	0	1971	Gastonia, North Carolina	[89]
0	49	0	0	1971	Portsmouth, New Hampshire	[90, 91]
0	104	0	0	1974	Vermont (M)	[92]
0	51	0	0	1973	Chardon, Ohio	[90]
2	113	1·8	0·6	1972	Wood County, Ohio	[90]
0	21	0	0	1972	Washington, D.C.	[90]
0	45	0	0	1974	Dubuque, Iowa	[93]

* For this outbreak deaths per individuals exposed is given; multiplying the number of cases by the average infections per case would have yielded more infections than the number of people exposed.

that met the criteria for inclusion in the test; however, occasional deaths due to *C. jejuni* have occurred [82, 83].

Because the importance of *C. jejuni* as an enteric pathogen has become understood only since the mid-1970s, improved treatment and states of health complicate interspecific comparisons. To assess whether the overall mortality per infection was less than that for *S. sonnei* during a similar time period, *S. sonnei* outbreaks from 1970 onwards were compiled (Table 5).

If high-risk populations (i.e. institutions for elderly and mentally handicapped) are excluded, the mortality per *S. sonnei* infection was 0·05% (Table 5), which is higher than the analogous figure collected from studied outbreaks of *C. jejuni* (no deaths in about 4500 cases from 22 outbreaks). Including outbreaks from high-risk populations yields a mortality of 0·11% for *S. sonnei* (from Table 5) and 0·05% [4 deaths/(6740 cases × 1·3 infections per case)] for *C. jejuni*.

Antibiotics have substantial effects against *S. sonnei*, but little if any against *C. jejuni* [94–97]; consequently, if no infections had been treated, the observed difference in mortality would if anything increase. On the basis of these considerations, *C. jejuni* was ranked below *S. sonnei*.

Non-typhoid salmonella. Since the middle of this century the mortality associated with reported cases of non-typhoid salmonella in the United States ranged from about 5·3–0·4% [98–101]. The ratio of unnoticed infections to reported cases of non-typhoid salmonella is estimated to be at least 100:1 [102, 103]. The mortality per infection was therefore approximately 0·004–0·053%. This range is lower than that of *S. sonnei* but not distinguishable from *C. jejuni* (see above). Direct comparisons of these two pathogens suggest similar prevalences and deaths *per capita* [96, 83]. They were therefore assigned the same rank.

Table 6. *Modes of transmission for classical cholera* (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
Tockwith and Moor Monkton, England	1838	c	[16]
Glasgow, Scotland	1832	w	[16]
Moscow, Russia	1847	w	[16]
Pocklington and York, England	1849	c	[16]
Horsleydown	1849	w	[16]
Albion Terrace, London, England	1849	w	[16]
Rotherhithe, London, England	1849	w	[16]
Manchester, England	1848–9	w	[16]
Golden Square, London, England	1854	w	[16]
London, England	1849	w	[16]
York, England	1849	w	[16]
Shoreditch, London, England	1848–9	w	[108]
London, England	1853	w	[16]
Baljik, Black Sea	1854	w	[16]
Millbank Prison, England	1854	w	[16]
Deptford, England	1855	w	[16]
Eastern London, England	1866	w	[108]
Southampton, England	1866	w	[108]
Calcutta, India	1870	w	[15]
Reval, Russia	1871	w	[15]
Rural, India	< 1885	w	[15]
Pondicherry	NG	w	[15]
Tong King, Japan	1885	c	[15]
Hamburg, Germany	1892	w	[15]
Nietleben, Germany	1893	w	[15]
Grimsby and Cleethorpes, England	1893	wsf	[15]
Indian jail	< 1895	f, fl	[15]
Philippines	1907	wsf	[15]
Sori, Italy	1911	w	[15]
Berlin, Germany	1918	f	[15]
Syriam, Burma	1920	fl ?	[15]
Tokyo, Japan	1922	wsf	[15]
Romblon, Philippines	1926	w	[109]
Changteh, China	1938–9	w	[15]
Newcastle, UK	≈ 1850	w	[22]
London, UK	1854	w	[15]
Rotterdam and Utrecht, Netherlands	NG	w	[108]
Assam, India	1964–5	w	[110]
Bangladesh	1964–74	w	[17, 111]
Bangladesh	1966–75	w	[112]
Meheran, Bangladesh	1968–69	w	[113]

Escherichia coli. Determination of mortality due to *E. coli* is complicated by the broad spectrum of interactions between this species and humans. Calculation of accurate mortality per infection is not feasible for the entire species because frequencies of non-pathogenic infection are high and not accurately quantified. Unbiased calculation of mortality due to 'enteropathogenic' *E. coli* is not feasible because associations between these serotypes and pathogenicity are uncertain [104]. Use of the traditional 'enteropathogenic' serotypes would probably strongly bias the sample toward high virulence. Restriction of the analysis to invasive and haemorrhagic serotypes [105] is not feasible because of insufficient data.

For enterotoxigenic *E. coli*, these problems are relatively unimportant. Genetic

Table 7. *Modes of transmission for el tor* V. cholerae (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
Celebes, Indonesia	1939	w	[114]
Ubol, Thailand	1960	w	[115]
Bacolod City, Philippines	1961	wsf	[116]
Lucdo, Philippines	1962	c	[117]
Rural New Territories, Hong Kong	1962	c	[118, 119]
Temple St., Hong Kong	1964	w, wf	[120]
North Kowloon, Hong Kong	1966	f, c	[118]
Can Itom, Philippines	1967	w	[212]
Calcutta, India	1968	nw	[122]
Kelantan, Malaysia	1969	wsf, w	[123]
Chad and Cameroon	1970	c	[124]
Mali and neighbouring areas	1970–1	c	[125]
Airline flight through Bahrain	1972	f	[126]
Italy	1973	wsf	[124]
Sri Lanka	1973–4	w	[127]
Bangladesh	1973–4	w	[32]
South Africa	1974	wh	[128]
Portugal	1974	wsf, w	[129, 130]
Bangladesh	1976–7	w	[131]
Kiribati	1977	wsf	[132]
Tanzania	1977–8, 1981, 1983	w; c; c; c	[133, 134]
Nias, Indonesia	1978	w	[135]
Bahrain	1978–9	wh	[136]
Congo	1978–9	c	[137]
Moherong, South Africa	1981	2	[138]
Gaza Strip	1981	nw	[139]
Truk, Micronesia	1982	f	[140]

instructions for toxin production are either present or absent [106, 107] and many outbreaks have been studied.

As with *C. jejuni*, no deaths from enterotoxigenic *E. coli* were reported in the nine outbreaks conforming the criteria for inclusion in the test, but deaths have occurred in vulnerable individuals and institutional settings in which attendants act as cultural vectors (e.g. among infants in nursery wards; see [6]). Enterotoxigenic *E. coli* was therefore assigned the same rank as *C. jejuni* and non-typhoid salmonella.

RANKING OF TENDENCIES FOR WATERBORNE TRANSMISSION

General methods. If waterborne transmission was implicated for any portion of the infections, the outbreak was assigned to the waterborne category; if waterborne transmission was rejected as a possibility, or if an alternative mode was clearly implicated while water was not, the outbreak was placed in the non-waterborne category. If a food-borne outbreak resulted from contamination of the food with water, the outbreak was included in the waterborne category because such transmission conforms to the definition of a cultural vector (see Introduction). Food-borne outbreaks in which water contamination was neither documented nor suspected were counted as non-waterborne. Food-borne outbreaks generally do

Table 8. *Modes of transmission for* Salmonella typhi (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
Bristol, England	1847	w	[108]
Salisbury, England	1852–3	w	[108]
Croydon, England	1852–3	w	[108]
Cowbridge, South Wales	1853	w	[108]
Millbank Prison, England	1854	w	[108]
Munich, Germany	1860	w	[108]
Congleton	1866	w	[108]
Frankfurt, Germany	1870–5	w	[142]
Lausen, Switzerland	1872	w	[13, 35]
Caterham and Redhill, England	1879	w	[13, 108]
Burlington, Vermont	1880s–90s	w	[35]
Plymouth, Pennsylvania	1885	w	[13, 35, 143]
Zurich, Switzerland	1885	w	[35, 142]
Lowell and Lawrence, Massachusetts	1890–93	w	[13, 142, 144]
Chicago, Illinois	1890–92	w	[35, 142]
Newark, New Jersey	1892	w	[142, 144]
Springfield, Massachusetts	1892	wm	[35]
Worthing, England	1893	w	[145]
Hamburg, Germany	1893	w	[142, 144]
Marlborough, Massachusetts	1894	mh	[35]
Middletown, Connecticut	1894	wsf	[13, 35]
Lowell, Massachusetts	1894	w	[144]
Stamford, Connecticut	1895	wm	[35]
Jersey City, New Jersey	1896	w	[144]
Loraine, Ohio	1897	w	[144]
Maidstone, England	1897	w	[143, 145]
Albany, New York	1899	w	[35, 144]
Williamstown, Massachusetts	NG	fh	[35]
Gelsenkirchen, Germany	NG	w	[35]
U.S. Military camps, Spanish–American War	1898	fl, c	[35, 47, 143]
Newport, Rhode Island	1900	w	[35]
Pittsburg and Allgeheny, Pennsylvania	1900	w	[35]
Baraboo, Wisconsin	1901	w	[35]
New Haven, Connecticut	1901	w	[35]
Ithaca, New York	1901	w	[35]
New York (typhoid Mary)	1910–14	fh	[146]
Patterson, New Jersey	1902	w	[35, 144]
Somerville, Massachusetts	1902	mh	[35]
Auxerre, France	1902	w	[35]
Montclair and Bloomfield, New Jersey	1902	m	[35]
Lowell, Massachusetts	1902	w	[35]
Winchester and Southampton, England	1902	wsf	[35]
Binghamton, New York	1902	w	[35, 144]
Waterville and Augusta, Maine	1902–3	w	[35]
Cleveland, Ohio	1903	w	[35]
Butler, Pennsylvania	1903	w	[35]
Watertown, New York	1904	w	[35]
Lawrence, New York	1904	wsf	[35]
New Haven Co. Jail, Connecticut	1904	nw	[35]
Mt. Savage, Maryland	1904	w	[35]
Millenocket, Maine	1904	w	[35]
Winnipeg, Manitoba	1904	c, fl	[35]
Lincoln, England	1904–5	w	[145]

Table 8. (*cont.*)

Winnipeg, Manitoba	1904	w	[35]
Springfield, Massachusetts	1905	c, f	[35]
Basingstoke, England	1905	w	[35]
Philadelphia, Pennsylvania	1906	w	[147]
Steamer 'Northwest', Michigan	1906	w	[35]
Scranton, Pennsylvania	1906–7	w	[35]
Trenton, New Jersey (M)	1907	w	[35]
Des Moines, Iowa	1910	w	[148]
Cedar Falls, Iowa	1911	w	[149]
Lincoln, Nebraska	1911	w	[150]
Rockford, Illinois	1912	w	[37]
Troy, Pennsylvania	1912	w	[38]
Quincy, Illinois	1913	w	[37]
Hanford, California	1914	f	[39]
Michigan	1917	mh	[40]
Lansing, Michigan	1919	w	[41]
Salem, Ohio	1919–20	w	[42]
Seneca Falls, New York	1920	w	[43]
Harrowgate, Tennessee	1924	m	[151]
Lincoln, Massachusetts	1926	mh	[13]
Montreal, Quebec	1927	mh	[13]
Olean City, New York	1928	w	[45]
Ecclefechan, Scotland	1930	w	[46]
Malton, Yorkshire, England	1932	w	[145]
Manteno, Illinois	1939	w	[152, 153]
DePue, Illinois	1939	m	[48]
St Boniface and St Anne, Manitoba	1940	f	[49]
New York City	1952	fh	[100]
Argentina/Scotland	1964	wf	[154]
Mexico	early 1970s	w	[154]
New Jersey	1973	sfh	[155]
Florida	1973	w	[155, 156]
Texas	1975	f	[157]
New York City	1975	f	[157]
Sangli, India	1985–6	w	[158]
Tennessee	1977	f	[159]
San Antonio, Texas	1981	fh	[160]

not involve cultural vectors because infected food handlers generally must be mobile in order to contaminate food. If transmission occurred through contamination of water within a household or institution, the outbreak was counted as non-waterborne, because such transmission should rely upon host mobility in a manner analogous to transmission through contamination of food by food handlers.

For some outbreaks, authors or agencies (e.g. the Centre for Disease Control of the US Public Health Service) stated a mode of transmission without presenting the evidence for their conclusions. For these outbreaks, I trusted the published conclusions unless the available data raised serious doubts; such outbreaks were excluded from the analysis. Other details of the literature search were as described for quantification of mortality.

V. cholerae. During the last two decades, several investigators have concluded that cholera outbreaks involved waterborne transmission (see Tables 6 and 7):

Table 9. *Modes of transmission for* Shigella dysenteriae *(see Appendix for abbreviations)*

Location	Year	Mode	Reference
England	1917–18	w	[51]
Missouri	1934	nw?	[171]
Michigan	1939	nw?	[53]
Kentucky	1941	nw	[55]
Giohor, Somalia	1964	w?	[172]
Guatemala	1969	w?	[167]
El Coco, Guatemala	1969	nw?	[173]
Pueblo Nuevo, Guatemala	1969	w	[173]
El Salvador	1969–70	wf?	[174]
Dhaka, Bangladesh	1972	w	[175]
Tamil Nadu, India	1972	w	[176]
St Martin Island, Bangladesh	1973	w?	[57]

however, many of these conclusions have been questioned by Feachem [141], who proposed that although the outbreaks may have involved contaminated water, non-waterborne transmission is consistent with the results. Because of the uncertainties associated with these arguments the percentages of waterborne outbreaks were calculated in two ways. In the first calculation I assumed that water played a role in transmission in all of the outbreaks for which waterborne transmission was supported. In the second calculation I excluded these outbreaks from the waterborne category, but counted them as non-waterborne only if epidemiological evidence for non-waterborne transmission existed.

The difference between the percentages in Tables 6 and 7 indicates that classical *V. cholerae* has been waterborne more often than el tor *V. cholerae*. Sommer and Woodward's [113] data show a similar difference within a single community where a classical outbreak was followed by an el tor outbreak in successive years.

Salmonella typhi. Seventy-four percent of the *S. typhi* outbreaks involved waterborne transmission (Table 8). This percentage places *S. typhi* slightly below classical *V. cholerae* in terms of waterborne transmission.

The available data permit some temporally and geographically restricted comparisons between *S. typhi* and classical *V. cholerae*. Prior to 1900 the percentage of waterborne outbreaks in the United States and western Europe were virtually the same for these pathogens (17 out of 20 from Table 8, and 16 out of 19 from Table 6). In the United States improvements in water purification began near the turn of the century [35, 144] and continued through the mid-century [44, 161, 162]. Classical *V. cholerae* infections virtually vanished from the United States after the initial improvements in water supplies; *S. typhi* outbreaks did not vanish, but the proportion of waterborne outbreaks become rarer as the water supplies were purified ($P < 0{\cdot}01$, Cochran-ordered $\chi^2 = 8{\cdot}34$, 1 D.F. [163]; Table 8; outbreaks were grouped chronologically, maximizing the number of groups under two constraints: null hypothesis frequencies were > 5 and the standard deviation of outbreaks per group was minimized).

Data from England permit a more temporally and geographically restricted comparison. Between 1843 and 1847 water supply improvements in 24 towns reduced the death rates from typhoid by up to about 50%; cholera death rates

Table 10. *Modes of transmission for* Shigella flexneri *(see Appendix for abbreviations)*

Location	Year	Mode	Reference
Wakefield, England (M)	1913	c	[177]
Meurthe-Moselle, France	1918	w	[178]
Claybury, England (M)	1919	nw	[179]
Aberdeen, Scotland	1919	m	[180]
Ogmore Vale, Wales	1921	w	[59]
Smethwick, England	1927	w	[60]
Newcastle and Durham, England	1928–9	nw	[62, 181]
Yugoslavia	1931	w	[182]
St Louis, Missouri	1934	f	[183]
England (A)	1934	w	[184]
Elgin, Illinois (M)	1935	f	[185]
Matane, Quebec	1935	w	[186]
St Gerome, Quebec	1935	w	[187]
Locke, California	1936	w	[187]
Yallaho	1936	w	[54]
Connecticut	1937	w	[188]
New York, New York	1939	f	[55]
Georgia (M)	1940	nw	[66]
Vermont (M)	1940	nw	[66]
New York (M)	1940	nw	[66, 78]
Newton, Kansas	1942	w	[189]
Philippines	1945	w	[190]
Germany	1945	w	[191]
Guam	1947	w	[192]
Yugoslavia	1951	w	[193]
Yugoslavia	1954	w	[193]
Hungary	1954	w	[194]
Utah	1956	w	[195]
Omaha, Nebraska	1961–2	nw	[196]
California	1964	f	[197]
North Carolina	1964	w	[197]
Hawaii	1964	f	[197]
Yugoslavia	1962–4	w; w; w	{193[
Texas	1965	f	[197]
Hawaii	1965	f	[197]
Florida	1966	m	[197]
Washington	1968	f	[197]
North Carolina (M)	1968	f	[198]
Utah (M)	1968	c	[199]
Cleveland, Ohio	1969	c	[200]
Willowbrook and Rosewood, New York	1969	nw	[201]
New Mexico	1969	c	[202]
Alaska	1970	w	[202]
Roxboro, North Carolina	1970	c	[203]
Lufkin, Texas (M)	1970	c	[203]
Tululasak, Alaska	1970	w	[84]
Scotland	1972	nw	[204]
Caribbean cruise ship	1973	w	[205]
Hawaii	1973	f	[155]
Arkansas	1973	f	[155]
Connecticut	1973	sfh	[155]
California	1975	f	[206]
Washington	1976	w	[206]
Connecticut	1981	f	[207]
Minnesota	1981	f	[207]

Table 11. *Modes of transmission for* Shigella sonnei (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
St Andrews, Scotland	1926	m	[67]
Skanderborg, Denmark	1927	m	[61]
Korsor, Denmark	1928	m	[61]
Glasgow, Scotland	1928	c	[215]
London, England	1930	fh	[70]
Scotland	1931	nw	[734]
Surrey, England	1935	nw	[216]
New Mexico	1938	nw	[66]
Bedford, England	1938	m	[74]
England	1939	c	[75]
New York	< 1941	m	[217]
Norway	< 1941	w	[218]
Penrith, England	1942	m	[219]
Carlisle, England	1942	m	[220]
Cardiff, Wales	1942	c	[76]
Somerset, England	1942	w	[221]
Ukraine	apx1945	w	[222]
England	1948	f	[223]
Leicester, England	1950	w	[224]
Oxford, England	1951	c	[80]
Ohio	1954	f	[81]
Mansfield, Australia	1958	nw	[225]
Albany Co., New York	1959–60	w	[226]
Yugoslavia	1963	w	[193]
Iowa	1965	w	[227]
Montrose, Scotland	NG	w	[228]
Vermont	1967	w	[227]
Ohio	1968	f	[227]
Kansas City, Kansas	1968	c	[199]
Lexington, Kentucky	1969	f	[229]
Russelville, Arkansas	1969	c	[200]
Jersey City, New Jersey	1969	fh	[200]
Medford, Oregon	1969	w	[229, 230]
Prineville, Oregon	1969	w	[200, 230]
Frederic Co., Maryland	1969	w	[200]
South Carolina	1969	c	[202]
Maui, Hawaii 1972	1970	f	[86, 88, 231]
Texas	1970	fh, c	[84]
Albuquerque, New Mexico	1970	fh	[85, 231]
Le Seur Co., Minnesota	1970	f	[85, 231]
Kansas	1971	c	[86]
California	1971	a	[232]
Pennsylvania	1971	f	[232]
Portsmouth, New Hampshire	1971	c	[90]
Turkey Creek, Florida	1971	f	[87, 232]
Kahului, Hawaii	1971	f	[232]
Gastonia, North Carolina	1971	c	[89]
Anchorage, Alaska	1971	w	[89, 233]
England	1971–2	c	[234]
Washington, D.C.	1972	c	[90]
Wood Co., Ohio	1972	c	[90]
Stockport, Iowa	1972	w	[233]
St Louis, Missouri	1972	w	[233]

Table 11. (*cont.*)

New Jersey	1972	w	[233]
Chardon, Ohio	1973	c	[90]
California	1973	f; f	[155]
Illinois	1973	f	[155]
Dubuque, Iowa	1974	w	[93]
Vermont	1974	c	[92]
Iowa	1974	f	[235]
Washington	1974	f	[235]
Florida	1974	w	[235, 236]
Pennsylvania	1974	w	[235]
Montana	1974	f; w	[157]
Oregon	1975	f	[155]
Washington	1976	f	[206]
Puerto Rico	1976	w	[206]
Hawaii	1977	f	[159]
Pennsylvania	NG	fh	[237]
Illinois	1978	f	[238]
Virginia	1981	f	[207]

were more markedly reduced, by more than 90% in at least two communities [108].

The difference between *S. typhi* and classical *V. cholerae* with regards to long-term carriage may be one factor resulting in the more abrupt decline in classical *V. cholerae* than in *S. typhi* following water purification. Long-term excretion of classical *V. cholerae* is extremely rare. Virtually all cases and carriers generally cease excretion within days to a few weeks [15, 24, 27], the longest documented duration being about 40 days [15]. In contrast, approximately 2–5% of *S. typhi* cases continue excretion for several months to many years after symptomatic recovery [144, 164, 47]. Since carriers are known to contribute to non-waterborne transmission (e.g. [146]), *S. typhi*'s greater carriage rates help explain its persistence after water purification.

On the basis of these considerations, *S. typhi* was ranked as less waterborne than classical *V. cholerae*; however, because of the uncertainty associated with this ranking, *S. typhi* and classical *V. cholerae* were assigned tied ranks in the more conservative cross-specific test.

Shigella spp. Like classical *V. cholerae* and *S. typhi*, the frequency of *S. dysenteriae* declined strongly in industrialized countries as drinking water was purified. In countries with persistently contaminated water (e.g. Guatemala; see [165]) *S. dysenteriae* 1 has continued to cause disease generally at low-to-moderate prevalences [166–169]. When it was introduced into the United States during a massive Central American epidemic (Table 3), the secondary spread (i.e. in the absence of waterborne transmission) was insufficient to maintain the pathogen; the number of new infections from a given infection was approximately 0·4 (calculated from [170]).

Because of the paucity of information about modes of transmission for *S. dysenteriae* 1, some tentative identification of modes of transmission were included in the analysis (signified by a question mark in column 3 of Table 9). Four of the five outbreaks with reliable identification of transmission mode were waterborne, placing *S. dysenteriae* 1 between classical *V. cholerae* and *S. typhi*. On the basis of

all 12 outbreaks listed in Table 9, *S. dysenteriae* 1 would be less waterborne than *S. typhi*. In the conservative comparison all three species were therefore assigned tied ranks.

The greater waterborne transmission of *S. dysenteriae* 1 relative to *S. flexneri* (Tables 9 and 10) is supported by a more restricted study in Bangladesh showing that contaminated water was a risk factor for *S. dysenteriae* 1 but not *S. flexneri* [208].

When outbreaks are combined over all years, the percentage involving water was significantly greater for *S. flexneri* than for *S. sonnei* ($P = 0{\cdot}02$, $G = 5{\cdot}4$). One might argue, however, that the lower percentage of waterborne outbreaks associated with *S. sonnei* is unreliable because of the disproportionate number of *S. sonnei* outbreaks during the last two decades, when water supplies were relatively pure. This hypothesis can be evaluated by taking time periods into account. If a pathogen is often waterborne but can be maintained without waterborne transmission, the percentage of outbreaks involving water should decline as water supplies are improved (e.g. see the preceding analysis of *S. typhi*). If, however, a pathogen is generally not transmitted by water, the proportion of waterborne outbreaks might not decrease perceptibly as the purity of drinking water increases (e.g. if a pathogen could be transmitted only by direct contact purification of water should not directly affect its proportion of waterborne outbreaks).

S. sonnei survives longer than *S. flexneri* on surfaces exposed to air [75, 209, 84, 84] but apparently not in water [210, 205]. The two species have similar durations of excretion per infection [211, 212, 81], but the frequency of asymptomatic infections, which are associated with low excretion rates of shigella [213, 214], are higher for *S. sonnei* than for *S. flexneri* (Table 4). On the basis of these characteristics and the differences between the species in mortality (Table 3), the degree of waterborne transmission should have declined more strongly through this century for *S. flexneri* than for *S. sonnei*. The decline in waterborne *S. flexneri* was statistically significant ($P < 0{\cdot}05$, $\chi^2 = 4{\cdot}51$, Table 10; grouping as described above for *S. typhi*). Analogous analyses of *S. sonnei* outbreaks (Table 11) yielded nonsignificant trends in the opposite direction, whether based on the same temporal divisions used for *S. flexneri* ($P < 0{\cdot}3$; $\chi^2 = 1{\cdot}65$); or the same rules for temporal division ($P < 0{\cdot}3$; $\chi^2 = 0{\cdot}62$).

To compare directly waterborne transmission of these two species, the combined data from both species were divided according to the median outbreak. The degree of waterborne transmission prior to the median is significantly greater for *S. flexneri* than for *S. sonnei* (54 versus 24%, $P < 0{\cdot}02$, $G = 5{\cdot}62$), but no significant difference between the species existed after the median outbreak (21 versus 27%, $P > 0{\cdot}5$; $G = 0{\cdot}26$).

The data in Tables 10 and 11 are insufficient for a highly temporally and geographically restricted comparison early in this century when waterborne outbreaks were relatively common, but moderately restricted comparisons are consistent with the overall trend; for example during the second quarter of this century, 43% of the *S. flexneri* outbreaks in western Europe and North America involved waterborne transmission compared with 13% of the *S. sonnei* outbreaks ($G = 3{\cdot}71$, 1-tailed $P < 0{\cdot}05$). On the basis of the preceding analyses, *S. sonnei* was considered less waterborne than *S. flexneri*.

The ranking of *S. dysenteriae* 1 as the most waterborne shigella and *S. sonnei* as the least is consistent with a recent study of the effects of handwashing on transmission of shigellosis. Infection through direct contact, contact with fomites, and contamination by food handlers and water handlers are the routes of transmission that should be reduced by handwashing. Infection through contamination of drinking water outside of the house should not be reduced to the same degree by handwashing if it is reduced at all. Among family contacts of index cases in Dhaka, Bangladesh, handwashing reduced *S. dysenteriae* 1 by 33% relative to controls, *S. flexneri* by 67%, and other *Shigella* by 87% [239]. About half of the 'other *Shigella*' in Dhaka at about this time were *S. sonnei*; the other half were *S. boydii* and the relatively benign serotypes of *S. dysenteriae* [240, 77].

Campylobacter jejuni. Outbreaks of *C. jejuni* are classified according to waterborne transmission in Table 12. To permit comparison with *S. sonnei*, the proportion of outbreaks of *S. sonnei* attributable to water was calculated for all outbreaks of this species during the 1970s and 1980s (from Table 11). As this percentage (24·3%) is above the analogous figure for *C. jejuni* (10·7%), *C. jejuni* was ranked below *S. sonnei*.

Enterotoxigenic *Escherichia coli*. Waterborne transmission was implicated in 20% of the 15 outbreaks due to enterotoxigenic *E. coli* (Table 13). This percentage is less than both the overall and the more recent percentages for *S. sonnei* (see above) and greater than the percentage for *C. jejuni*. Enterotoxigenic *E. coli* was, therefore, ranked between these two pathogens.

Non-typhoid salmonella. Of the 258 outbreaks of non-typhoid salmonella for which the CDC [175] could ascribe modes of transmission, only 1·6% were ascribable to water. The corresponding figure from the United States for *S. sonnei* during this time period is 29·5% (based on the 44 outbreaks in Table 11 referenced by CDC, Reller *et al.*, Rosenberg *et al.* or Weissman *et al*). This percentage for non-typhoid salmonella is also less than the percentage for *C. jejuni* in the United States (15·4% of 26 outbreaks) and enterotoxigenic *E. coli* (25% of 4 outbreaks). Non-typhoid salmonella was therefore ranked as the least waterborne pathogen.

THE OVERALL TREND AND ALTERNATIVE HYPOTHESES

The overall trend. The positive correlation between mortality and waterborne transmission is statistically significant ($P < 0{\cdot}01$, $r_s = 0{\cdot}98$ Spearman rank test; Table 14). Exclusion of the outbreaks whose modes of transmission were challenged (see *Vibrio cholerae* section of 'Ranking of tendencies for waterborne transmission') reversed the ranking of el tor *V. cholerae* and *S. flexneri*, but still yielded a significant correlation ($P < 0{\cdot}01$, $r_s = 0{\cdot}97$).

One might argue that campylobacter and salmonella should not be included in this test because they are prevalent in animal reservoirs. A statistically significant correlation between mortality and waterborne transmission still exists, however, even if these two pathogens are excluded ($P < 0{\cdot}01$, $r_s = 1{\cdot}0$ using ranks of Table 14).

One could argue that the quantifications of waterborne transmission in Table 14 were gross overestimates of the actual levels of waterborne transmission due, for example, to preferential reporting of waterborne outbreaks in the literature. If so, waterborne transmission among the most waterborne pathogens in Table 14 might

Table 12. *Modes of transmission for* Campylobacter jejuni (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
California	1976	m	[241]
England (A)	1976	nw	[242]
Sweden	1978	w	[243]
Bennington, Vermont	1978	w	[95]
Colorado	1978	m; d; f	[244]
Somerset, England	1978	m	[245]
Cumbria, England	1978	m	[246]
Bradford, England	1978	m	[246]
Belgium	1979	f	[247]
Lincoln, England	1979	m	[245]
Long Sutton, England	1979	m	[245]
Maidstone, England	1979	m	[245]
Yorkshire, England	1979	m	[245]
Aberdeen, Scotland	1979	m	[245]
Kincardinshire and North Angus, Scotland	1979	m	[248]
Luton, England	1979	m	[249]
Breda, Netherlands	1979	f	[250]
Netherlands	1979	f	[251]
Tokyo, Japan	1979	f	[252]
Goteborg, Sweden	1979–80	f	[253]
Freiburg, Germany	1979–81	f	[254]
Connecticut	1980	f	[255, 256]
Wyoming	1980	w	[257]
Connecticut	1980	w	[94]*
California	1980	f	[94]*
Netherlands	1980	f	[94]*
Essex, England	1980	m	[245]
Kent, England	1980	m	[245]
Blackburn, England	1980	m	[245]
Cumbria, England	1980	m	[245]
England	1980	f	[258]
Alberta	1980	m	[259]
Oregon	1980–1	m	[256]
Arizona	1981	m; m	[256]
Georgia	1981	m	[256, 260]
Kansas	1981	m	[261, 262]
New York	1981	f	[256]
DeDrakenver/Fort Collins, Colorado	1981	w	[263]
Maine	1981	m	[256]
Minnesota	1981	m	[264]
England	1981	w	[265]
England	1982	m	[266]
Colorado	1982	f; f	[267, 268]
Maine	1982	m	[256]
Maryland	1982	m	[256]
Michigan	1982	m	[256]
Minnesota	1982	f	[256]
Vermont	1982	m	[256]
Wisconsin	1982	m	[269]
Rotterdam, Netherlands	1982	f, d	[270]
Switzerland	NG	m	[271]
Vermont	1983	m	[272]
England	1983	m	[273]
Switzerland	1985	c	[274]

* Cited by Blaser & Reller, 1981 [94].

Table 13. *Modes of transmission for enterotoxigenic* Escherichia coli (*see Appendix for abbreviations*)

Location	Year	Mode	Reference
Arizona	1972–3	c	[276]
Mexico	1973	f	[277]
Mexico	1974	f	[278]
Virginia/Maryland (A)	1974	c	[279]
Texas	1974–5	f	[280]
Japan	1974–5	w; w; f	[281]
Oregon	1975	w	[282]
Mexico	1975	f	[283]
Mexico	1977	f	[284]
Wisconsin	1980	f	[285]
Texas	1981	f	[286]
England	1983	f	[287]
France/U.S.	1983	m	[288]

Table 14. *Ranking of mortality and tendencies for waterborne transmission across species*

	Mortality		Waterborne outbreaks	
Pathogen	%	rank	%	rank
V. cholerae, classical biotype	15.7	1	83·3	1
Shigella dysenteriae type 1	7·5	2	80·0	2
Salmonella typhi	5·8	3	74·0	3
V. cholerae, el tor biotype	1·44	4	50·0	4
Shigella flexneri	1·32	5	48·3	5
Shigella sonnei	0·65	6	27·8	6
Enterotoxigenic *E. coli*	< 0·1	8*	20·0	7
Campylobacter jejuni	< 0·1	8*	10·7	8
Non-typhoid salmonella	< 0·1	8*	1·56	9

* See text for discussion of ranking.

be too rare to favour the evolution of increased virulence. The disappearance of classical *V. cholerae* immediately following the first major improvements in water purification (see 'Rankings of tendencies for waterborne transmission', subsection *Salmonella typhi*) and the dramatic decline the prevalence of *S. typhi* and *S. dysenteriae* during decades of water purification [6], however, support the importance of waterborne transmission as indicated in Table 14.

The correlation between mortality and waterborne transmission does not prove that the two are linked evolutionarily. One could hypothesize that other variables correlated with both waterborne transmission and mortality cause the correlation shown in Table 14.

Temporal correlates. Time is one possible correlate of waterborne transmission and mortality. The more virulent pathogens would tend to be noticed earlier when water supplies were generally more contaminated. Mortality at this time might also be inflated by variables such as poor nutrition. As noted in the preceding sections, temporally and geographically restricted comparisons confirm virtually every comparison. In the conservative test referred to throughout this paper, tied rankings were given to pathogens whose virulence or mortality could not be

distinguished in temporally and geographically controlled comparisons. The resulting correlation was still statistically significant ($P < 0{\cdot}01$, $r_s = 0{\cdot}97$).

Fly-borne transmission. Another possible correlate of waterborne transmission and mortality is the degree of transmission by flies that contaminate objects and food. One could argue that fly-borne transmission favours virulent genotypes, using an argument analogous to that used for biting, terrestrial arthropods (see Introduction).

Flies have long been suggested as important transmitters of gastrointestinal pathogens, often on the basis of associations between fly abundance and disease prevalence (e.g. [289–292]). Such evidence is weak because environmental conditions favouring growth of fly populations may correspond to those favouring transmission by other routes. Flies did seem to contribution to transmission in two outbreaks of shigellosis, when *S. sonnei* and especially *S. flexneri* were the common *Shigella* species [293–295].

Flies harbour all of the pathogen species in Table 14 [15, 289, 290, 296–298], except possibly *C. jejuni*, which has been recognized only recently as a common pathogen of humans [242]. In Thailand, enterotoxigenic *E. coli*, the relatively benign non-O1 *V. cholerae*, and *Shigella* sp. were isolated from flies [299], which were tested for all genera in Table 14 except *Campylobacter*. In Bangladesh, *E. coli* was isolated from most body washes and excreta of flies; *S. flexneri* and *V. cholerae* (almost certainly not the classical biotype) were isolated rarely from body washes and never from fly excreta. None of the other pathogens in Table 14 were isolated.

In general, fly-borne transmission seems strongly dependent on infectivity with low doses (e.g. as in *Shigella* species) and the ability of organisms to grow on food (e.g. as in *Salmonella typhimurium*, [300]). The data do not support the idea that the relatively benign gastrointestinal bacteria (e.g. *E. coli*, *Shigella sonnei*, and non-typhoid salmonella are less fly-borne than the same virulent bacteria (see also [300]).

Aqueous inocula. One might hypothesize that the relationship between mortality and waterborne transmission results from the aqueous medium (e.g. diluting stomach acidity) or the large dosages ingested in water. This alternative can be evaluated by comparing mortality of waterborne outbreaks with non-waterborne outbreaks of the same pathogen.

Snow [16] provided detailed case:fatality data on four of the cholera outbreaks in Table 6. The outbreaks involving transmission by contact were not associated with a lower mortality than the waterborne outbreaks: deaths occurred in 5 of 11 cases and 8 of 11 cases in the two non-waterborne outbreaks (in Moor Monkton and Pocklington/York respectively) as compared with 38 of 80 cases and 25 of 45 cases (in Rotherhithe and Manchester respectively).

The waterborne outbreaks of *S. typhi* had a slightly but not significantly greater mortality than the non-waterborne outbreaks: $5{\cdot}7 \pm 2{\cdot}4$ (S.D.) *vs.* $4{\cdot}4 \pm 1{\cdot}2$ ($P \gg 0{\cdot}05$. Mann–Whitney U test; data from Tables 2 and 8); however, even if the non-waterborne value were used in Table 14, the ranking would remain unchanged.

Only two outbreaks of *S. dysenteriae* 1 with mortality data were ascribed a mode of transmission: the waterborne outbreak [51] was associated with a slightly lower mortality than the outbreak in which water was not implicated [55]. The mortality associated with the waterborne outbreak of *S. flexneri* (in Ogmore Vale, Smethwick and Yallaho) was lower than that of the outbreak in which water was

not implicated (in Newcastle/Durham; see Table 3). None of the *S. sonnei* outbreaks in Table 3 were documented as waterborne; those for which a mode was ascribed were associated with an average mortality of $0{\cdot}36 \pm 0{\cdot}79\,\%$ (S.D.), which is below the corresponding figure for non-waterborne outbreaks as well as for all outbreaks of *S. flexneri* (see above).

Comparisons of mortality in waterborne and non-waterborne outbreaks are not useful for the remaining pathogens because their mortality rates were essentially zero; either untreated mortality was zero in both waterborne and non-waterborne outbreaks (e.g. *C. jejuni*, enterotoxigenic *E. coli*) or the outbreaks involved effective treatment (e.g. el tor *V. cholerae*).

The evidence therefore does not support the argument that the higher mortality associated with waterborne disease results from ingesting pathogens in an aqueous medium.

Desiccation resistance. One could hypothesize that variation in desiccation resistance caused the correlation in Table 14 by diverting pathogen resources from reproduction. A negative association between waterborne transmission and desiccation resistance does exist among *Shigella* sp. [6] and between el tor and classical *V. cholerae* [26, 301, 302]. These associations, however, are also consistent with the cultural vectors hypothesis, because contact transmission, desiccation resistance, and benignness should favour each other evolutionarily.

The desiccation resistance hypothesis is weakened by current knowledge about virulence genes and growth of bacterial cultures. Virulence depends directly on the presence of genes for adhesiveness, toxin production, and invasiveness and other genes which regulate or complement these characteristics [105, 303, 304–309]. When such genes are transferred from *Shigella* sp. to *Escherichia coli*, the latter develops the former's virulence characteristics [303]. Similarly, transfer experiments show that one of *V. cholerae*'s plasmids increases fluid accumulation, although it did not contain the gene for cholera toxin, and did not increase intestinal colonization [310]; the virulence enhancement, therefore, did not result from a diversion of resources from desiccation resistance to colonization ability.

When el tor and classical *V. cholerae* are grown in culture the less virulent el tor predominates [311, 312], even in aqueous media [312] and *in vivo* when the hypothesized competitive benefits of toxin production [6] were eliminated through intestinal ligation [311]. These greater growth rates of the more benign pathogens are contrary to the desiccation hypothesis and consistent with the cultural vectors hypothesis given a biochemical cost of virulence, which occurs among *V. cholerae*: the classical biotype has nontandem chromosomal duplication of the cholera toxin operon and produces greater concentrations of cholera toxin than the el tor biotype, which usually has only a single copy [312, 313].

Data from *Shigella* spp. provide further support of the cost of virulence genes. When *S. flexneri* are grown in cell free culture, mutants lacking functional genes for cell invasiveness outcompete invasive genotypes [314]; however, when grown in cell culture *Shigella* spp. containing virulence plasmids both infected cells at greater rates and had greater haemolytic activity than strains without virulence plasmids [307]. The most lethal serotype, *S. dysenteriae* 1, more negatively affected host protein synthesis and intracellular multiplication than did the less virulent *S. flexneri* and *S. sonnei* [315]. This inhibition presumably results from the much greater production of cytotoxin by *S. dysenteriae* 1 [315].

These considerations indicate that virulence among gastrointestinal bacteria has specific genetic bases and is not simply a consequence of variation in desiccation resistance.

Taxonomic relationships. The taxonomic division of the pathogens also needs to be considered. If taxonomically similar species were clustered with regards to mortality and degrees of waterborne transmission then one might argue that a higher taxonomic division was a more appropriate unit of grouping. The taxonomically related pathogens, however, do not appear to be clustered any more than would be expected by a random grouping: classical and el tor *V. cholerae* differ substantially from each other, as do *S. typhi* and non-typhoid salmonella. The *Shigella* species are relatively evenly distributed according to mortality rates. *S. flexneri* and *S. sonnei* are similar in terms of both mortality and waterborne transmission, but among the entire group of taxonomically similar pathogens one such adjacent ranking of taxonomically similar pathogens is probable if the rankings are independent of taxonomic relatedness. *Shigella* sp. and *Escherichia coli* are so similar taxonomically that polynucleotide hybridization fails to distinguish them [316], yet the four species in these genera span nearly the entire range of mortality. The tribe to which these two genera and *Salmonella* sp. belong show a similarly broad distribution in mortality and waterborne transmission.

RELEVANCE OF THE CORRELATION

The preceding analyses suggest that virulence of gastrointestinal bacteria is evolutionarily linked to waterborne transmission. This result draws attention to the need for controlled field studies to determine whether purification of drinking water decreases frequencies of virulent species of pathogens and virulence genes within species of pathogens.

Recent evaluations of intervention studies have concluded that it is less cost effective to combat diarrhoeal diseases through water purification than through increases in water quantity or improving excreta disposal [317–319]. The results of this study emphasize the need to distinguish between, rather than lump together, the various diarrhoeal pathogens when making conclusions. Where severe pathogens such as classical *V. cholerae*, *Salmonella typhi*, and *Shigella dysenteriae* predominate, purification of water should reduce morbidity and mortality more strongly than where more benign pathogens such as el tor *V. cholerae*, *Shigella sonnei*, and enterotoxigenic *E. coli* predominate. In accordance with the arguments presented in this paper, studies implicating greater effectiveness of water quantity or improved excreta over water purification typically occur in areas where the latter group of pathogens predominates. The correlation between increased benignity and increased effectiveness of methods other than water purification is well illustrated by Khan and Shahidullah's [239] study of shigella (see the *Shigella* spp. subsection under 'Ranking of tendencies for waterborne transmission').

Resolution of these relationships should eventually improve allocations of economic resources for control of disease. As suggested above, disadvantages of contaminated water generally have been assessed in terms of prevalences of particular pathogen species or short-term effects on morbidity and mortality (e.g. [317, 318]). The results of this paper suggest an additional long-term cost: the

average virulence per infection should increase over evolutionary time scales because pathogen genotypes of greater virulence will be favoured over more benign genotypes. Once pathogens have evolved increased virulence the costs of this virulence will be suffered not just until the contamination is remedied, but rather throughout a period determined by (i) the relative prevalences of the different genotypes and (ii) the differences between the fitness of the genotypes in the corrected environment.

In this regard, the failure to consider evolutionary effects may result in underestimates of the long-term net benefits of pure water and, as a consequence, underestimates of the appropriate level of economic investment in water purification. The recent advocacy of increasing water quantity rather than water quality [317, 318] might have grave long-term effects: provisioning of contaminated water might favour the most virulent genotypes, reversing the general tendency observed during decades of water purification, for replacement of the most deadly pathogens (classical *V. cholerae*, *Salmonella typhi*, and *Shigella dysenteriae* 1) by less virulent pathogens [6]. Determinations of appropriate allocations of economic resources [4, 317, 318, 320], therefore, need to be temporally broadened to consider evolutionary effects of investments in alternatives such as treatment, vaccination, excreta disposal, increasing quantities of water and provisioning of pure water.

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Appendix. *Abbreviations used in tables*

Symbol	Meaning
w	ingestion of contaminated water
f	ingestion of contaminated food not directly or indirectly waterborne
nw	vehicle not identified or multiple vehicles other than water
wsf	seafood contaminated by water
m	milk-borne or cheese-borne transmission with no evidence of contamination of milk by water
mh	milk-borne or cheese-borne transmission with contamination of milk by milk handlers

wm	milk-borne or cheese-borne transmission with contamination of milk by water
wf	other foods contaminated by water
fh	foods contaminated by food handlers who were infected or in contact with infected materials
c	spread by direct person-to-person contact or fomites
fl	contamination by flies
d	direct contact with dogs
NG	information not given
(M)	outbreak occurred in an institution for mentally subnormal, aged or inform
(A)	geographic location ascribed based on authors' addresses
;	separates modes associated with different outbreaks
,	separates different modes identified within a single outbreak

Numbers in front of abbreviations indicate the number of outbreaks attributable to that mode of transmission. When no number is given, the symbol represents only one outbreak.

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