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REPORT

Herald waves of cholera in nineteenth century London

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Deaths from cholera in London, UK, were recorded weekly from 1824 to 1901. Three features of the time series stand out: (i) cholera deaths were strongly seasonal, with peak mortality almost always in the summer, (ii) the only non-summer outbreaks occurred in the spring of 1832, the autumn of 1848 and the winter of 1853, and (iii) extraordinarily severe summer outbreaks occurred in 1832, 1849, 1854 and 1866 (the four 'great' cholera years). The non-summer outbreaks of 1832, 1848 and 1853 appear to have been herald waves of newly invading cholera strains. In addition, a simple mathematical model confirms that a non-summer introduction of a new cholera strain can result in an initial herald wave, followed by a severe outbreak the following summer. Through the analysis of the genomes of nineteenth-century specimens, it may be possible to identify the strains that caused these herald waves and the well-known cholera epidemics that followed.

Keywords: London cholera; herald wave; waterborne disease model; disease seasonality; John Snow

The birth of modern epidemiology is often attributed to John Snow's famous investigation of the 1854 cholera epidemic in London, and his identification of the Broad Street pump as the most important node in the cholera transmission network [1,2]. More than 150 years later, we still do not know what factors triggered the enormous cholera outbreaks in London in the summers of 1832, 1849, 1854 and 1866. In addition to the intrinsic interest of identifying the mechanisms of historical disease invasions, improving our understanding of cholera specifically is important because it remains a serious public health concern in areas where clean water is unavailable [3]. The recent cholera epidemics in Angola in 2006 [4], Zimbabwe in 2008–2009 [5] and Haiti in 2010 [6] are stark examples.

Previous studies of nineteenth century cholera have focused on the 'great' cholera years while paying little attention to the years between severe outbreaks [7–9]. Here, we consider the great cholera years in the context of London's weekly mortality over the course of the nineteenth century as a whole. Cholera deaths were recorded in the Weekly Returns of the Registrar General's Office from 8 January 1842 to 28 December 1901 (the date on which the last cholera death was reported in London). We digitized these and earlier cholera records from the London Bills of Mortality to obtain a contiguous weekly record of cholera deaths for 77 years from 24 August 1824 to 28 December 1901.

Figure 1 displays the London cholera data in two ways. Figure 1*a* shows the weekly time series, while Figure 1*b* shows an intensity plot of week-of-year against year to bring out the pattern of seasonality over the years. The three striking features highlighted above are readily apparent: (i) London's cholera epidemics were strongly seasonal and most intense in the summer, (ii) typical outbreaks were far milder than the devastating outbreaks in the summers of 1832, 1849, 1854 and 1866, and (iii) atypically timed outbreaks occurred in the few months preceding the major outbreaks in 1832, 1849 and 1854. The data clearly separate into regular, mild summer outbreaks, together with outliers corresponding to the non-summer outbreaks and the great cholera years. These features persist when cholera deaths are normalized to account for changes in population size and reporting coverage over the century (see figure 2 and the electronic supplementary material).

What factors might have been responsible for the unusual timing of the non-summer outbreaks in 1832, 1848 and 1853, and the unusual severity of the outbreaks in the following summers? The most obvious hypothesis is that these features of the London cholera time series resulted from the introduction of new cholera strains into the city at random times of year. It is natural to expect that a non-summer introduction would result in an initial outbreak, with severity tempered by the season [10], followed by a severe outbreak in the summer when environmental conditions most strongly promote cholera transmission. The non-summer outbreaks thus appear to have 'heralded' the arrival of new cholera strains in London in 1832, 1848 and 1853. The absense of a 'herald wave' before the major epidemic in 1866 may simply reflect the invasion of a new strain coincidentally near the start of the normal cholera season that year.

The idea of herald waves has largely been confined to influenza [11], where it has been discussed extensively in relation to the 1918 [12–14] and 2009 [15,16] pandemics. To our knowledge, herald waves have never been described for cholera. Our finding of herald waves for London cholera suggests that herald waves may be a common feature of seasonal diseases.

We note that the identity and origins of new cholera strains in the nineteenth century are not known. Current

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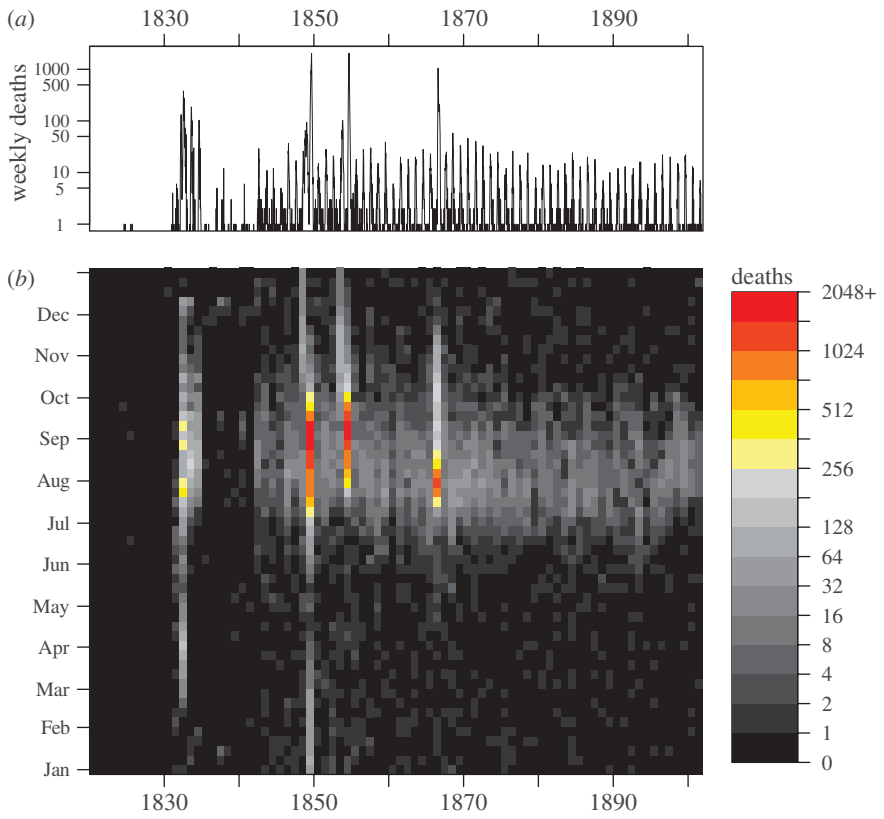

Figure 1. Weekly London cholera deaths from 1824 to 1901. (*a*) Weekly cholera deaths versus time and (*b*) cholera deaths versus time of year.

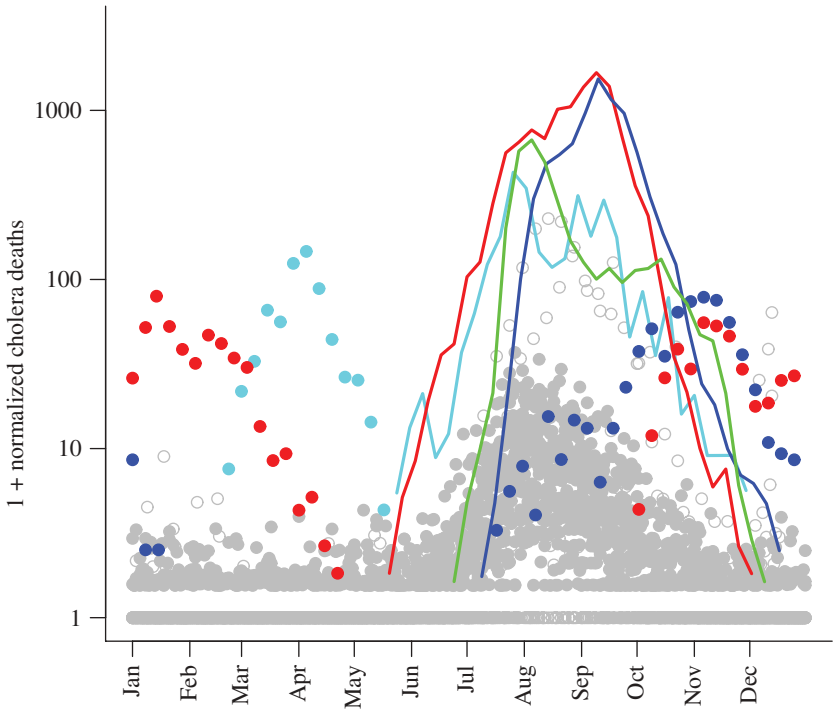

Figure 2. Weekly cholera deaths, normalized by all-cause mortality and plotted against time of year. Open circles correspond to Bills of Mortality data (years prior to 1842), filled circles to Registrar General data (1842 onwards). Filled light blue circles, 1832 herald; solid light blue line, 1832 summer; filled red circles, 1848 herald; solid red line, 1849 summer; filled dark blue circles, 1853 herald; solid dark blue line, 1854 summer; solid green line, 1866 summer.

evolution of new cholera strains appears to be facilitated by horizontal gene transfer among strains in different serogroups ([17]; see the electronic supplementary material). This mechanism might also account for the invasion of antigenically novel strains in the nineteenth century. Cyclical replacement of the predominant cholera serotype has also been observed [18], and may be relevant for London cholera.

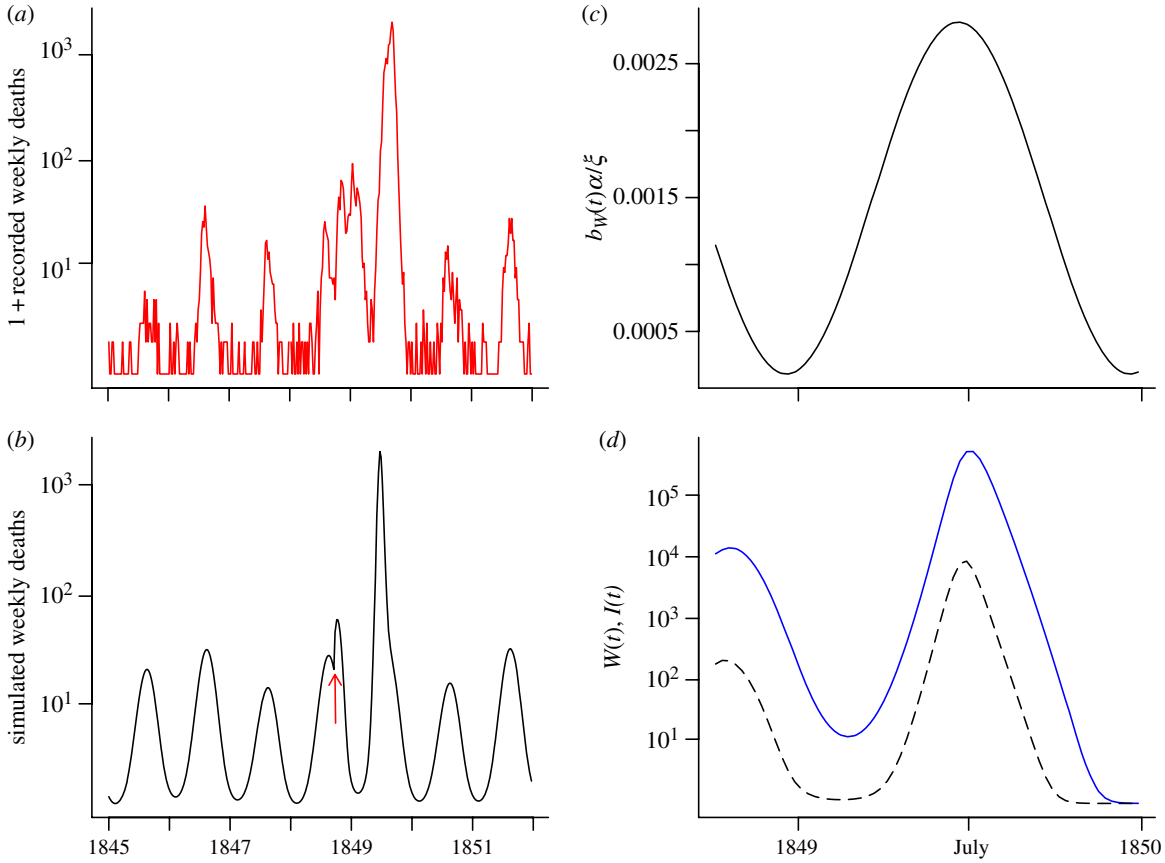

Figure 3. Model simulations of London cholera, compared with observed cholera deaths. (*a*) Observed weekly deaths from 1845 to 1852. (*b*) Simulation results corresponding to endemic cholera, together with the introduction of a new cholera strain in late September 1848 (arrow). (*c*) Seasonal variation in model disease transmission. (*d*) Simulated time courses of pathogen concentration in the water source ($W(t)$, in cells per millilitre) and individuals infected with the invading strain $I(t)$. $W(t)$ = solid blue curve, $I(t)$ = dashed black curve.

We used a simple mathematical model to verify theoretically that a non-summer introduction of a new cholera strain can result in a herald wave followed by a severe outbreak in the summer. The model extends the classical 'susceptible–infectious–recovered' (SIR) framework to include a water compartment (W), with transmission occurring through both person–person and person–water–person pathways ([19]; see appendix A for model equations).

As an example, figure 3 compares the London cholera mortality time series from 1845 to 1852 (figure 3*a*) with an SIWR simulation (figure 3*b*). Assuming the transmission rate in the water varies seasonally (peaking in the summer, as in figure 3*c*), simulated cholera time series resemble the typical pattern in London, with mild annual summer outbreaks (as in the period 1845–1848 in figure 3*b*). The arrow in figure 3*b* indicates the time at which we introduced a new cholera strain into the SIWR model (the end of September 1848). The population is completely susceptible to the new strain, resulting in an initial outbreak when the strain is introduced. However, owing to the season [10], disease transmissibility is waning at the time of introduction. Eventually transmission decreases past the point where an outbreak can be sustained (and the initial herald wave terminates), but the new cholera strain persists at low levels in the water (figure 3*d*).

Table 1. Variables for system (A 1), together with initial conditions used for simulations of endemic and introduced London cholera (figure 3).

		initial conditions	
		endemic	introduced
S	susceptible individuals	19 006	100 000
I	infected individuals	3	0
R	recovered individuals	80 991	0
W	pathogen concentration in water reservoir (cells ml^{-1})	610	14 000
D	individuals who have died from the disease	0	0
N	total population size	100 000	100 000

When transmissibility from the water rises again the following summer, it triggers an unusually severe epidemic owing to the large number of susceptible individuals (simulation details given in appendix A).

While the strain invasion hypothesis is simple—and appealing from the point of view of parsimony—many other explanations are possible, including misdiagnosis involving other diarrhoeal diseases. A direct test of the strain invasion hypothesis would require genetic information from the circulating cholera strains. Relevant

Table 2. Parameters for system (A 1), including values used for simulations of endemic and introduced London cholera (figure 3).

		units	endemic	introduced
demographic parameters				
ν	birth rate	yr^{-1}	0.044	0.044
μ	natural death rate	yr^{-1}	0.033	0.033
pathogen parameters				
γ^{-1}	mean infectious period	days	3	3
ξ^{-1}	mean pathogen lifetime in water reservoir	weeks	2	1
f	case fatality proportion	—	0.1	0.1
contact parameters				
b_I	person–person contact rate	$\mathrm{individuals}^{-1}\ \mathrm{yr}^{-1}$	9.12×10^{-4}	3.65×10^{-4}
α	rate of pathogen shedding into reservoir	$\mathrm{cells\ ml}^{-1}\ \mathrm{yr}^{-1}\ \mathrm{individuals}^{-1}$	3650	3650
$b_W(t)$	reservoir–person contact rate	$\mathrm{ml\ cells}^{-1}\ \mathrm{yr}^{-1}$		
B	average value of $b_W(t)$	$\mathrm{ml\ cells}^{-1}\ \mathrm{yr}^{-1}$	3.9×10^{-5}	2.14×10^{-5}
A	amplitude of seasonality of $b_W(t)$	—	0.5	0.88
t_1	time of maximum seasonal transmissibility	year	0.41 (May 31)	0.47 (June 20)
T	period of seasonal forcing	years	1	1

tissue samples from patients who died of cholera do exist in museum collections, and recent advances in the recovery and sequencing of DNA as well as the reconstruction of complete genomes from fossil materials [20,21] make sequencing substantial portions of the genomes of nineteenth century cholera strains a realistic goal (see the electronic supplementary material).

Given the fame and historical importance of the four major London cholera epidemics in the nineteenth century, it is surprising that the herald waves we have identified here have not been highlighted previously. Unravelling the mechanisms behind these herald waves will deepen our understanding of the evolutionary and ecological history of this important disease, and in turn help us understand the factors underlying severe cholera outbreaks in modern times. Our study of London cholera also suggests that herald waves may occur for more diseases than has been previously realized, and emphasizes the need for further work examining the relationship between the timing and magnitude of seasonal outbreaks [10]. The systematic digitization of lengthy historical records of disease incidence and mortality will be invaluable for this endeavour. In particular, evidence that herald waves have preceded major epidemics of other diseases may be hidden in untapped historical sources.

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APPENDIX A. MATHEMATICAL MODEL

A.1. Model equations

Our SIWR model for waterborne disease modelling is expressed as a simple system of ordinary differential equations [19],

$$\left.\begin{aligned} \dot{S} &= \nu N - b_W(t)SW - b_I SI - \mu S, \\ \dot{I} &= b_W(t)SW + b_I SI - \gamma I - \mu I, \\ \dot{W} &= \alpha I - \xi W, \\ \dot{R} &= (1-f)\gamma I - \mu R, \\ \dot{D} &= f\gamma I, \end{aligned}\right\} \qquad \text{(A 1)}$$

where the host population is divided into susceptible (S), infectious (I) and recovered (R) compartments. The variable W tracks pathogen concentration in a water compartment (e.g. the River Thames and natural wells), and D is the number of individuals killed by the disease. Recovered individuals are immune to further infection. The total host population size is $N = S + I + R$. The parameter ν is the birth rate, μ is the natural death rate, $1/\gamma$ is the mean infectious period and $1/\xi$ is the mean pathogen lifetime in the water compartment. The parameter α is the pathogen shedding rate into the water, and f is the case fatality proportion. Disease transmission can occur either through person–person contact, with rate parameter b_I, or through the water, with rate parameter $b_W(t)$. Seasonality in waterborne transmission is modelled using sinusoidal forcing,

$$b_W(t) = B\left(1 + A\cos\left[\frac{2\pi(t-t_1)}{T}\right]\right) \qquad \text{(A 2)}$$

A.2. Simulation details

Model variables and parameters for system (A 1) are summarized in tables 1 and 2, together with initial conditions and parameter values for simulating endemic and introduced cholera (figure 3). The birth and natural death rates were chosen to match London's population growth between 1801 and 1901 (http://www.demographia.com/dm-lon31.htm). An expected infectious period of 3 days was used in the model (the typical infectious period is 1–5 days for cholera patients [22]). The ability of *Vibrio cholerae* to persist outside of human hosts depends upon environmental factors such as salinity [23] and temperature

[24]. Under appropriate conditions, *V. cholerae* can persist for extended periods of time in environmental water sources [25]. Here, we model the expected pathogen lifetime in the water to be of the order of one to two weeks. Case fatality rates for cholera in modern times range from a few per cent to as high as 50 per cent [26], and was fixed at 10 per cent for our model. We set α, the rate at which infected individuals shed pathogen into the water compartment, to 10 cells $\mathrm{ml}^{-1}\,\mathrm{d}^{-1}$, a value that has been used in previous modelling efforts [27,28]. The transmission parameters were tuned to give reasonable fits to the cholera mortality data. This tuning was accomplished by first locating a periodic orbit for the model when $\nu = \mu$, such that this orbit matched the general seasonal pattern of London cholera in 'typical' years. Initial conditions for endemic cholera were taken from this periodic orbit. An initial population size of 100 000 was used in the simulations, rather than the population size of the entire city of London, since only a portion of the city's population was at risk for cholera (e.g. John Snow's finding that Vauxhall and Southwark Waterworks customers were at greatly elevated risk of infection [29]).

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Supplementary Material

Mortality data normalization. Let $c(t)$ denote the cholera time series, and $\widehat{a}(t)$ the all cause mortality time series after smoothing using loess (Cleveland, 1979). Then the normalized cholera time series is given by $\tilde{c}(t) = c(t) \cdot (\widehat{a}(t_0)/\widehat{a}(t))$, where t_0 is the first time point of the cholera time series. The scaling factor $\widehat{a}(t_0)/\widehat{a}(t)$ accounts for changes in population size and reporting coverage over time. The effect of the normalization is to count cholera deaths at time t in the "units" of cholera deaths at time t_0.

Figure **2** plots normalized weekly cholera deaths against time of year. As in Figure **1**, the data clearly separate into regular, mild summer outbreaks, together with outliers corresponding to the non-summer outbreaks and the great cholera years.

Origin of new strains

Many different cholera strains exist (Kaper et al., 1995), and changes in circulating strains have been documented in modern times at the level of serogroup (defined by surface antigen structure), serotype (defined by subunit composition of the O1 antigen), and biotype (based upon a collection of bioassays; (Albert et al., 1993; Koelle et al., 2006; Longini, Jr. et al., 2002)). Cross-immunity among different serogroups is likely to be low (Qadri et al., 1997; Mooi and Bik, 1997).

Prior to 1992, all known pathogenic cholera strains were thought to belong to the O1 serogroup. In 1992, a new serogroup (O139) of pathogenic cholera appeared in the Bay of Bengal region (Albert et al., 1993), likely as the result of horizontal gene transfer between an ancestral O1 strain and a non-pathogenic *V. cholera* O139 strain (Faruque et al., 2003). This type of horizontal gene transfer may be common: more than 200 serogroups of *V. cholerae* have been identified, and the cholera genome possesses a class of integrons that facilitate the capture and integration of foreign genes (Faruque et al., 1998). In fact, the O antigen does not appear to group monophyletically in phylogenetic trees (Karaolis et al., 1995).

Potential to sequence cholera genomes from 19th century samples

Perhaps the most direct way to assess the novelty of cholera epidemics from the past would be to isolate and sequence portions of the genomic DNA from archival samples of patients who died during these outbreaks. Such samples do exist (i.e. those stored in pathological collections such as the Mütter museum in Philadelphia), and the DNA can be extracted using slightly modified versions of standard methods applied for formalin-fixed or alcohol-preserved tissue samples (Okello et al., 2010). While the majority of DNA within these extracts will likely stem from human DNA, bacterial DNA should also be preserved, albeit at appreciably lower concentrations. Despite these "needle in a haystack" scenarios, recent advances in ancient DNA analysis (Poinar et al., 2006), including enrichment techniques such as those used to fish out complete mitochondrial genomes of Neanderthals from fossil remains (Briggs et al., 2009), are the way forward. Genes and their upstream regulators (promoters) involved in pathogenicity, such as the Cholera Toxin gene or the toxin-coregulated pilus (TCP) gene, can be enriched specifically by fishing with heterogenous mixtures of overlapping probes/primers spanning consecutive 20bp (base pair) sections of the genes and their promoter regions. Changes in these genes or their regulators might explain the underlying genetic component and the differential susceptibilities to the novel strains. Alternatively these experiments, potentially biased towards looking for changes/similarities in known pathogenic genes, can be modified with the recent advent of rapid, large scale enrichment strategies using microdroplet emulsion PCRs (Tewhey et al., 2009), which will enable us to enrich for entire chromosomal sections and thus allow us to compare partial or complete genomes of cholera over both space and time.

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