macaque monkeys, suggest that λ ranges between 3.2×10^{-6} and 8.1×10^{-5} per day[27,28]. Thus, λ is much smaller than θ. The dose to cause disease with probability $p = P/100$ is called the infectious dose ID(P) and is given by[20] $D = -(\lambda+\theta)\ln(1-p)/\lambda$. Substituting this expression for D into the formula for c and approximating $\lambda + \theta \approx \theta$, we find

$$c = 1 - (1-p)^{(1-e^{-\theta t_1}+e^{-\theta t_2}-e^{-\theta t_3})} \quad (1)$$

Thus, we have the surprising mathematical result that it is not necessary to have a precise value for λ to obtain our key results.

We divide the population into subgroups in which the periods of disease protection are the same for all persons in a subgroup. For example, consider a subgroup in which antibiotic protection begins at time t_1 and stops at time t_2, then we set t_3 to infinity in equation (1). Suppose further that post-exposure vaccine protection is achieved at t_v, which occurs before antibiotic protection stops ($t_v < t_2$), then t_2 and t_3 are set to infinity. If vaccine protection occurs after antibiotic protection stops then t_3 is set equal to t_v. The cumulative probability of disease in the population (c) is then a weighted average of the values of c for each subgroup, where the weights are the proportions of people in subgroups. These proportions are determined by the distributions of times in which vaccine immunity is achieved, and the antibiotic start and stop dates (determined by antibiotic adherence rates and efficacy). Among persons exposed to the ID(P), the percentage of cases prevented with post-exposure interventions is:

$$\left(1 - \frac{c}{p}\right)100 \quad (2)$$

Impact of pre-exposure vaccination

The impact of adding a pre-exposure vaccination programme is to reduce the cumulative probability of disease from c to $c(1-\beta\phi)$, in which ϕ is the vaccine efficacy (that is, the probability that the vaccine protects from disease), and β is the vaccine coverage (that is, the fraction of the population that receives pre-exposure vaccination). The fraction r of all cases prevented by adding a pre-exposure vaccination programme to the post-exposure prophylaxis strategy among persons exposed to the ID(P), is:

$$r = 1 - \frac{c(1-\beta\phi)}{p} \quad (3)$$

If we solve equation (3) for β we obtain $\beta = \{1 - [(p(1-r))/c]\}\phi^{-1}$.

The above equation for β was used to calculate the vaccine coverage rates given in Table 3 with $r = 0.75$ and 0.90.

Shortening antibiotic regimen by post-exposure vaccine

Consider two situations. In situation 1, antibiotics stop at time t_v, at which time vaccine protection begins with probability ϕ. In situation 2, antibiotics are continued for a longer period of time, until t_2, but there is no vaccine protection. We calculate by how much time antibiotics can be shortened ($t_2 - t_v$) in order that the disease risks in the two situations are equal. We set the two probabilities of disease conditional on being disease free at t_v equal to each other. Solving that equation and approximating $\lambda + \theta \approx \theta$, we obtain $t_2 - t_v = [-\ln(1-\phi)]/\theta$; this was used to produce Fig. 2.

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Transmissibility of 1918 pandemic influenza

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The 1918 influenza pandemic killed 20–40 million people worldwide[1], and is seen as a worst-case scenario for pandemic planning. Like other pandemic influenza strains, the 1918 A/H1N1 strain spread extremely rapidly. A measure of transmissibility and of the stringency of control measures required to stop an epidemic is the reproductive number, which is the number of secondary cases produced by each primary case[2]. Here we obtained an estimate of the reproductive number for 1918 influenza by fitting a deterministic SEIR (susceptible-exposed-infectious-recovered) model to pneumonia and influenza death epidemic curves from 45 US cities: the median value is less than three. The estimated proportion of the population with A/H1N1 immunity before September 1918 implies a median basic reproductive number of less than four. These results strongly suggest that the reproductive number for 1918 pandemic influenza is not large relative to many other infectious diseases[2]. In theory, a similar novel influenza subtype could be controlled. But because influenza is frequently transmitted before a specific diagnosis is possible and there is a dearth of global antiviral and vaccine stores, aggressive transmission reducing measures will probably be required.

The emergence of a new pandemic influenza subtype is expected[3]. Pandemics have occurred regularly throughout this century (1918, 1957 and 1968)[4], and opportunities for the generation of new subtypes[5] have persisted and probably expanded[3]. Pandemic influenza spreads rapidly, has high attack rates and kills millions of people worldwide[1,4,6]. The 1918 pandemic was particularly destructive. The case fatality proportion (CFP) was ten times higher than in

all other influenza pandemics and was unusually high in young adults[4,7].

Understanding the great speed with which influenza is transmitted is crucial to effective preparation for pandemics. The doubling time for an epidemic curve (about three days in the 1918 pandemic) is a function of the reproductive number (R) and the serial interval (ν), which is the average time between a primary and secondary case. The magnitude of R determines the intensity of measures required to halt transmission. The components of ν, that is, the duration of the latent and infectious periods, determine how and when these measures must be applied. Estimates of R for pandemic influenza vary widely, ranging from 1.68 to 20 (refs 8–12), and are thus of limited value for pandemic preparation. Furthermore, R depends on both the infectious agent and the host population; for example, estimates for measles vary between rural and urban populations[2]. To our knowledge, there are no estimates of the range of R values that might be expected if a strain similar to 1918 pandemic influenza emerges.

We estimated R by fitting a deterministic SEIR model with homogeneous mixing to the excess pneumonia and influenza (P&I) death curves for 45 cities (Fig. 1). We assumed distributions of infectiousness consistent with previous studies[8] and with viral shedding data[4], giving mean latent and infectious periods of 1.9 days and 4.1 days, respectively. Infections in the SEIR model were transformed to P&I mortality by assuming a 2% CFP[7,13]. Time to death was based on influenza autopsy reports[14–16], with a mean survival time of two weeks (see Supplementary Information). Excess deaths were defined as the deaths above the median for 1910–16 (described previously[17], see Fig. 1 and Supplementary Information). The choice of baseline does not substantially affect the results; the 1918 influenza CFP was so much higher than for previous epidemics that any baseline is a small proportion of the 1918 P&I death curve (see Supplementary Information).

We estimate that R for 1918 pandemic influenza was approximately 2–3 (Fig. 2). The median estimated R for 45 cities was 2 (interquartile range 1.7, 2.3), based on the first three weeks of each epidemic curve with greater than one excess P&I death per 100,000 population. To address the possibility that these initial R estimates were biased downward—the model ignores the possibility of substantial slowing of exponential growth due to depletion of susceptible hosts, heterogeneous mixing and/or transmission-reducing interventions—we also fit, for each city, the two adjacent weeks of data with the greatest exponential growth rate. The median estimated R (2.7) increased and the interquartile range (2.3, 3.4) widened. The maximum initial (6.3) and extreme (6.5) R estimates were similar. The extreme R values serve as an upper bound; R estimates based on fits of other regions of the epidemic curves tended to be lower than the extreme R values (see Supplementary Information). These results strongly support the conclusion that the estimated R for 1918 pandemic influenza was not large relative to that for many other infectious diseases[2].

The initial R estimate was not significantly correlated with factors that included latitude, longitude, population size[18], population density[19,20], age distribution[21] or sex distribution[21]. These results are consistent with contemporary findings by Pearl, who sought correlates of an "epidemic index"[21]. The extreme R estimates were weakly positively correlated with population density in 1910 (Spearman correlation $\rho = 0.5, P = 0.001$) and 1920 ($\rho = 0.4, P = 0.011$), but only the former association remains statistically significant after the Bonferroni correction for multiple comparisons.

Our R estimates were based on excess P&I mortality data, which are surrogates for influenza case data. We assessed the potential bias of using mortality data in several ways. Sensitivity analyses indicated that the assumptions governing the case-to-death transformation in our model (the CFP and the time-to-death distribution) did not affect the magnitude of R estimates (see Supplementary Information). Furthermore, calculations described in the Supplementary Information indicate that mortality data will quickly (within two weeks of the start of the epidemic) reach exponential growth at a rate determined by R, even if transmission and mortality are concentrated in separate groups. Thus, mortality-based R estimates should not be biased. We also estimated R using symptomatic influenza reports from three of the 45 cities. They are consistent with these theoretical results, and are comparable to mortality-based estimates (see Supplementary Information).

It is unknown how similar the recent and 1918 pandemic A/H1N1 influenza viral shedding patterns are, nor is it clear how these patterns translate into transmission probability. To better understand the dependence of R on assumptions about the serial interval and its components, we plotted R estimates based on a linearized SEIR model with an exponential growth rate corresponding to the median rate found in calculating the extreme values of R (Fig. 3, see Supplementary Information). R is less than 3 for most plausible mean ν, regardless of the fraction of ν that is spent in the latent period. To observe an R above 5, the mean ν for 1918 influenza would have had to be several times longer than that of more recent influenza strains[4].

The proportion of the population susceptible at the start of the pandemic determines the relationship between R and the basic reproductive number (R_0), which is the number of secondary cases generated by a primary case in a completely susceptible population[2]. Frost hypothesized that a 1918 pandemic-like strain spread throughout America in the spring of 1918 (ref. 22), and recent analyses support this 'herald wave' hypothesis[23]. Anecdotal evidence suggests that those who fell ill in the spring were protected from

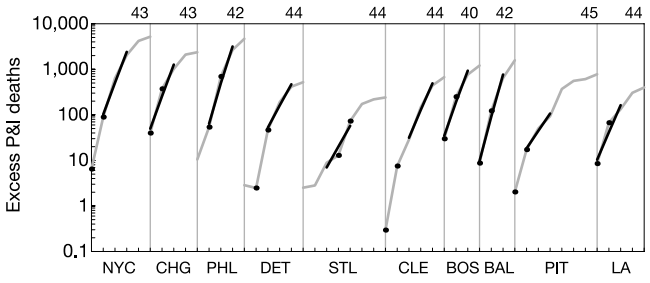

Figure 1 Graph of the logarithm of excess P&I deaths in 1918 for the ten most populous cities in the US. Curves from each city are separated by vertical bars for clarity, with the week number listed above each peak. Curves are shown from left to right, in order of decreasing population size: New York City (NYC), Chicago (CHG), Philadelphia (PHL), Detroit (DET), St Louis (STL), Cleveland (CLE), Boston (BOS), Baltimore (BAL), Pittsburgh (PIT) and Los Angeles (LA). Raw data are shown as grey lines. Black lines indicate model fits for the initial R estimates. Black dots indicate the weeks used for the extreme R estimates.

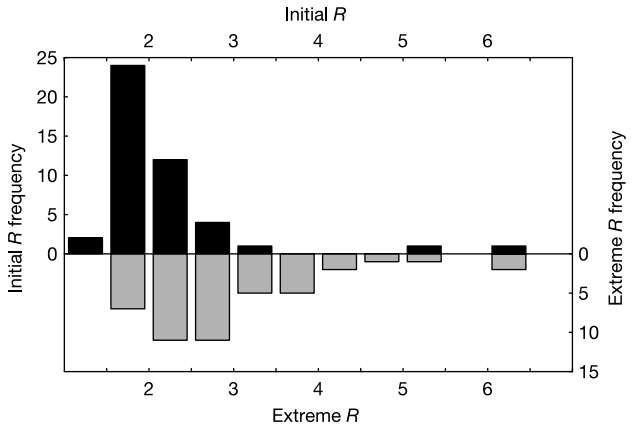

Figure 2 Histogram of initial and extreme estimated R values for 45 cities during the 1918 influenza pandemic. Dark bars show initial R estimates, grey bars show extreme R estimates.

disease in the autumn pandemic[24]. Nevertheless, a large majority of the population was probably susceptible to the A/H1N1 pandemic strain in September 1918. In a typical epidemic transmission season, 15–25% of the population becomes infected with influenza[4]. The herald wave is believed to have arrived late in the 1917–18 transmission season. Using 70% as a conservative lower bound for the fraction susceptible at the start of the autumn pandemic, the medians for our initial and extreme R_0 are 2.9 and 3.9.

We have presented a range of R estimates for 1918 pandemic influenza in 45 US cities. We know of one previous R estimate for 1918 pandemic influenza, obtained by fitting the entirety of a single curve of influenza deaths from cities across England and Wales[10]. Although the previous estimate was described by its author as having a poor fit to data[10], and despite the additional assumptions implicit in that analysis, it is reassuring that our R estimates for 1918 A/H1N1 are similar. The median initial and extreme R values are slightly higher than 1957 A/H2N2 and 1968 A/H3N2 pandemic R estimates[8,11] (see Supplementary Discussion), but are well below that of many other infections[2]. It is likely that an exceptionally high CFP in young adults, rather than an unusually high R, is what distinguishes the epidemic curve of 1918 from more recent pandemics.

For many infectious agents, explosive epidemics indicate high transmissibility. While the 1918 pandemic progressed quite rapidly, our results indicate that 1918 pandemic influenza A/H1N1 was not highly transmissible relative to other influenza subtypes[8,11] and infectious agents[2]. A similar pandemic with an R_0 of 2–4 could in principle be prevented by vaccinating or administering antiviral prophylaxis to 50–75% of the population, a figure that may require some adjustment owing to heterogeneous mixing patterns in real populations[25]. Unfortunately, controlling a future pandemic will not be so simple. At present, vaccine production capacity and antiviral medication stockpiles are insufficient to provide such broad coverage, even in wealthy countries[3], although judicious use of available supplies may nevertheless reduce mortality during a pandemic[8]. Control measures based on case identification (for example, contact tracing, isolation, targeted prophylaxis and treatment) that were central to the control of severe acute respiratory syndrome (SARS), whose R was similar to that for 1918 influenza[26–28], will only be partially successful for influenza[12]. For influenza, unlike SARS, substantial transmission occurs before the onset of case-defining symptoms[12]. This implies that measures that generally reduce contacts between persons, regardless of infection status, may be our most powerful protection against a pandemic until adequate vaccine and antiviral medicines can be produced, at which point mass-vaccination and prophylaxis may be more effective than targeted approaches.

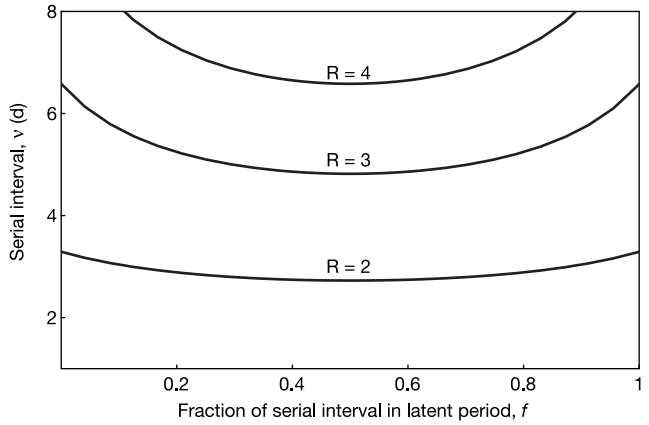

Figure 3 Graph of the relationship between the serial interval (ν) and the magnitude of R. Lines indicate combinations of ν and the fraction of ν in the latent period (f) that yield constant values of R. These R estimates assume a linearized SEIR model and the median extreme exponential growth rate.

Rapid application of control measures for a 1918-like influenza pandemic will be crucial. The short time between primary and secondary cases (ν) means that case numbers in a 1918-like pandemic will rise rapidly, with incident infections and the ensuing deaths doubling about every three days. Increased passenger travel relative to 1918 will facilitate the spread of a new virus across the globe. It is imperative that real-time surveillance information be shared freely, and that preventive measures be taken very early in a new pandemic. Therefore, while the relatively modest reproductive number estimated for 1918 pandemic influenza suggests the feasibility of controlling a similar future pandemic, significant planning and investment will be required to facilitate a rapid and effective response. □

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