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Proc. R. Soc. B 2014 **281**, 20132570, published 22 January 2014

PROCEEDINGS OF THE ROYAL SOCIETY B

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Cite this article: Earn DJD, Andrews PW, Bolker BM. 2014 Population-level effects of suppressing fever. *Proc. R. Soc. B* **281**: 20132570.
http://dx.doi.org/10.1098/rspb.2013.2570

Received: 22 October 2013
Accepted: 18 December 2013

Subject Areas:
health and disease and epidemiology, theoretical biology

Keywords:
influenza, transmission, fever, antipyretic drugs

Author for correspondence:
David J. D. Earn
e-mail: earn@math.mcmaster.ca

Electronic supplementary material is available at http://dx.doi.org/10.1098/rspb.2013.2570 or via http://rspb.royalsocietypublishing.org.

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Population-level effects of suppressing fever

David J. D. Earn[1,2], Paul W. Andrews[3] and Benjamin M. Bolker[1,2,4]

[1]Department of Mathematics and Statistics, [2]M. G. DeGroote Institute for Infectious Disease Research, [3]Department of Psychology, Neuroscience and Behaviour, and [4]Department of Biology, McMaster University, Hamilton, Ontario, Canada

Fever is commonly attenuated with antipyretic medication as a means to treat unpleasant symptoms of infectious diseases. We highlight a potentially important negative effect of fever suppression that becomes evident at the population level: reducing fever may increase transmission of associated infections. A higher transmission rate implies that a larger proportion of the population will be infected, so widespread antipyretic drug use is likely to lead to more illness and death than would be expected in a population that was not exposed to antipyretic pharmacotherapies. We assembled the published data available for estimating the magnitudes of these individual effects for seasonal influenza. While the data are incomplete and heterogeneous, they suggest that, overall, fever suppression increases the expected number of influenza cases and deaths in the US: for pandemic influenza with reproduction number $\mathcal{R} \sim 1.8$, the estimated increase is 1% (95% CI: 0.0–2.7%), whereas for seasonal influenza with $\mathcal{R} \sim 1.2$, the estimated increase is 5% (95% CI: 0.2–12.1%).

1. Introduction

For millennia, humans have suppressed fevers without understanding the potential effects [1,2] beyond the obvious alleviation of symptoms. Antipyretic drug treatment is extremely prevalent in Western countries—especially by parents [3], and also by healthcare professionals [4–6]. Even when treatment is not aimed at fever specifically, fever is likely to be reduced, because most common drugs that relieve other typical symptoms of infectious diseases also contain an antipyretic component [7].

Previous investigations of the effects of fever suppression have focused on the clinical benefits and costs to the individual [8,9]. The adaptive value of fever [10–13] is well known to immunologists; for example, *Janeway's Immunobiology* [14, p. 110] notes that 'At higher temperatures, bacterial and viral replication is less efficient, whereas the adaptive immune response operates more efficiently'. Others argue that the adaptive value of fever arises instead from activation and coordination of the immune response [12]. By contrast, a common view in the medical community, as expressed for example in *Harrison's Principles of Internal Medicine*, is that the 'treatment of fever and its symptoms does no harm and does not slow the resolution of common viral and bacterial infections' [15, p. 107]. Here, we consider some population-level effects of widespread fever suppression, effects that do not appear to have been investigated previously.

An individual whose fever has been reduced is likely to feel better and is therefore more likely to interact with others. In addition, fever suppression may increase both the rate and duration of viral shedding, further increasing the pathogen's transmission rate; this effect has been shown experimentally for influenza in ferrets [16]. A higher transmission rate will in general lead to larger epidemics [17,18] and hence to greater morbidity and mortality. The increase in epidemic size is larger for more weakly transmissible pathogens.

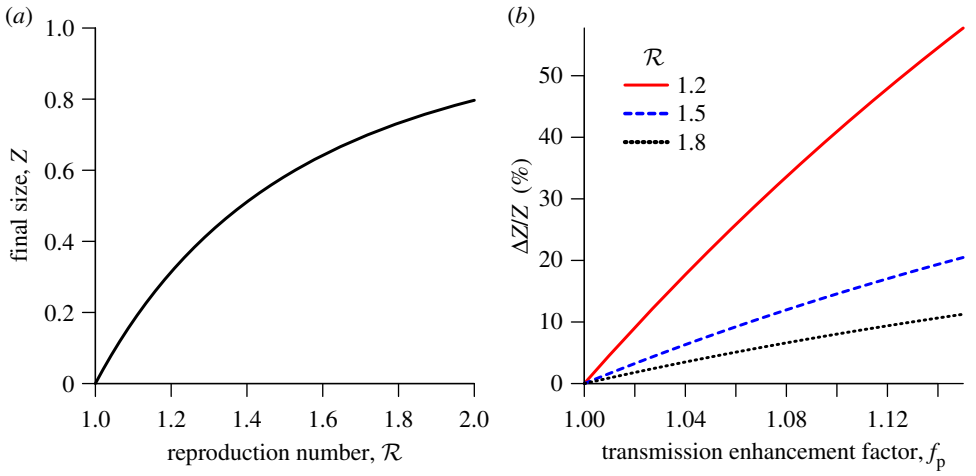


Figure 1. The effects of increases in transmission rate (by the factor f_p) on the expected proportion of the initially susceptible population that will be infected in a single influenza epidemic (the final size Z). (*a*) The standard final size relation (2.3), for the plausible range of (effective) reproduction number for influenza. (*b*) The relative increase in final size resulting from increasing the transmission rate by the factor f_p. For example, a 10% increase in the proportion of individuals infected during an epidemic will arise from a 2% transmission enhancement if $\mathcal{R} = 1.2$, a 6% enhancement if $\mathcal{R} = 1.5$ or a 12% enhancement if $\mathcal{R} = 1.8$. (Online version in colour.)

2. Theoretical argument

To make this idea more precise, suppose that (i) a proportion p of infected individuals develop a fever and are treated with antipyretics (the *treatment probability*) and (ii) on average, antipyretic treatment of febrile individuals increases their probability of infecting others by a factor f_i (the *individual transmission enhancement factor*). The proportion of infected individuals with enhanced transmission is then p, and the proportion without enhanced transmission (i.e. with transmission enhancement factor 1) is $1 - p$. Antipyretics therefore increase the overall transmission rate by the factor

$$f_P = (1-p)\cdot 1 + p\cdot f_i \tag{2.1a}$$

$$= 1 + p(f_i - 1)\,, \tag{2.1b}$$

which we call the *population transmission enhancement factor*. (Note that $f_P > 1$ given that $f_i > 1$ and $0 < p \leq 1$.)

Transmissibility of a pathogen is normally quantified by the basic reproduction number $\mathcal{R}_0$, the average number of secondary cases caused by a primary case in a wholly susceptible population [19]. In a population that is not wholly susceptible—which is always the situation for seasonal influenza—the effective reproduction number is reduced by the proportion susceptible at the start of the epidemic ($\mathcal{R} = S_{init} \times \mathcal{R}_0$). In these terms, antipyretic use has the effect of increasing the reproduction number

$$\mathcal{R} \to f_P \mathcal{R}\,. \tag{2.2}$$

We would like to estimate how many additional infections, and correspondingly how many severe illnesses and deaths, can be expected to result from this increase in $\mathcal{R}$ during an influenza epidemic or pandemic [20].

For a very large class of epidemic models, the proportion of the population that is expected to be infected during an epidemic (the expected *final size* Z) is related to the reproduction number by the classical final size relation [17,18],

$$Z = 1 - e^{-\mathcal{R}Z}, \tag{2.3}$$

which can be solved explicitly (see the electronic supplementary material). Note that Z is the final size as a proportion of those who were initially susceptible; if everyone were susceptible initially ($S_{init} = 1$), as is possible in a pandemic, then $\mathcal{R} = \mathcal{R}_0$ and Z is the proportion of the entire population infected.

Figure 1*a* shows this final size relation, $Z(\mathcal{R})$, and figure 1*b* shows the relative incremental change in final size,

$$\frac{\Delta Z}{Z} = \frac{Z(f_P\mathcal{R}) - Z(\mathcal{R})}{Z(\mathcal{R})}\,, \tag{2.4}$$

as a function of the population transmission enhancement factor f_P, for three values of $\mathcal{R}$ in the plausible range for influenza, $1.2 \lesssim \mathcal{R} \lesssim 1.8$ ($\mathcal{R}$ is likely near the lower end of this range for seasonal influenza [21,22] and the higher end for pandemic influenza [23–26]). Because the final size Z is a decelerating function of the reproduction number $\mathcal{R}$ (figure 1*a*), antipyresis always enhances transmission more for less transmissible diseases (which have smaller $\mathcal{R}_0$: figure 1*b*). The precise quantitative predictions in figure 1*b* depend on our use of the standard final size relation; however, the qualitative conclusions are very general because the expected final size always increases (typically in a decelerating fashion) as $\mathcal{R}$ increases [27–31].

3. Estimating the effect for influenza

To predict the magnitude of the effect in practice, we need an estimate of the population transmission enhancement factor f_P. We have insufficient data to estimate how all the relevant biological mechanisms contribute to increasing f_P; in particular, we expect the increase in social interaction owing to reduced symptoms to lead to a major increase in the epidemiological contact rate, but are unable to quantify this. Nevertheless, by focusing on how antipyretics affect individual infectivity, we can at least estimate a lower bound on f_P for influenza. Throughout all stages of the calculations described below, we propagate error estimates by randomly sampling 10 000 values from the sampling distribution of each of the estimated parameters (assumed normal unless otherwise specified), computing the relevant metric with each set of parameters in the random sample, and finding the lower 2.5% and upper 97.5% quantiles of the resulting

distribution. All computations were done in the R language [32] (see the electronic supplementary material).

The two components of f_P in equation (2.1) (p and f_i) are independent. Limited information is available concerning the treatment probability p: parents treat febrile children with antipyretics in approximately 90% of cases [3], and nurses treat fever with antipyretics in approximately 70% of cases [5,6]. We know that adults frequently take analgesics that are antipyretic, but we have little influenza-specific information. On these grounds, we propose a broad distribution for p (Beta(4,2)), with mean 0.67 (95% CI: 0.28–0.95). (Substituting a uniform [0,1] distribution for p instead to represent *complete* uncertainty does not change the results qualitatively; see the electronic supplementary material.) We must also adjust our estimate of p to take into account that only 67% (95% CI: 58–75%) of individuals show symptoms and only 35% (95% CI: 27–44%) develop a fever ([33]; see the electronic supplementary material).

To obtain a lower bound on individual transmission enhancement f_i, and hence to complete an estimate of a lower bound on population transmission enhancement f_P from equation (2.1), we consider two aspects of infectivity enhancement for which data exist.

First, antipyretics appear to increase viral shedding. To our knowledge, the only published experiment concerning the effects of antipyretic treatment on influenza viral shedding was conducted in ferrets (considered the best animal model for human influenza [34]). The study, conducted by Husseini *et al*. [16], considered two strains of influenza A/H3N2 that differed in virulence. For both strains, and regardless of whether fever was suppressed by shaving the ferrets or by administration of an antipyretic drug, the authors found that 'significantly more virus was shed in the nasal washes of ferrets whose febrile response was suppressed and the viral levels decreased less rapidly than in untreated ferrets or in those in which the treatments were ineffective' [16, p. 520]. This study was prompted by an earlier study from the same group showing that unmedicated ferrets with higher fevers shed less influenza virus [35]. The results are consistent with other studies showing that antipyretic treatment increases viral shedding in human volunteers infected with rhinovirus [36] and lengthens the infectious period in children with chickenpox [37]. Moreover, in a study of human volunteers infected with influenza A, the number of antipyretic doses received was positively correlated with the duration of illness [38]. Some cytokines reduce viral shedding, so a likely mechanism by which antipyresis increases viral shedding is the suppression of temperature-dependent cytokine responses to influenza infection (see the electronic supplementary material, §3.2). Based on these considerations, we assume that the clinical effects of fever suppression on nasal shedding in humans infected with influenza virus are similar to the effects measured in ferrets. Based on inverse-variance weighted mean values for the difference in the logarithm of viral titres between the antipyretic-treated and untreated ferrets, we estimate that antipyretic treatment increases influenza viral titres in nasal droplets by a factor of order 1.78 (95% CI: 1.35–2.35) (see the electronic supplementary material for further details).

Second, greater viral shedding increases infectivity. This is unsurprising, but estimating the strength of the effect is challenging. A recent review [39] describes 30 studies in which human volunteers were given various doses of a variety of influenza viruses. To analyse these data, we used a binomial generalized linear mixed model incorporating random effects of strain and study [40,41] to estimate the relationship between $\log_{10}$(dose) and probability of infection. We conclude (see the electronic supplementary material) that a dose that is larger by a factor 10 (which we assume would arise from an increase in viral titres in nasal droplets by the same factor) yields an increase of 0.28 (95% CI: 0.01–0.54) in the log-odds of infection. (This effect would correspond to an increase of 0.07 (95% CI: 0.004–0.13) in the proportion infected if we started from a baseline infection probability of 0.5.)

In order to infer the overall transmission implications, we need an estimate of the natural infectivity of influenza, i.e. the probability that a susceptible contacted by an (non-antipyretic-using) infectious individual will become infected. We are not aware of direct measurements of this probability, so we use published estimates [42] of the household secondary attack rate (SAR) as a proxy. We used a linear mixed model incorporating variation among strains and among studies to estimate the log-odds of the SAR, based on measurements of antibody response of individuals between the beginning and end of the influenza season. Based on the coefficients of this model, we estimate the expected SAR to be 0.14 (95% CI: 0.07–0.27). As study participants were not prevented from taking antipyretics, the reported SAR likely represents an overestimate of the natural infectivity (which will make our inferences more conservative; see the electronic supplementary material, §5).

Associating proportional changes in the viral titre of nasal washes in the ferret study [16] with proportional changes in viral titres in nasal sprays in the human challenge studies [39], and taking the household SAR to approximate natural infectivity, we estimated the antipyretic-induced individual transmission enhancement factor f_i using equation S22 in the electronic supplementary material. We infer a conservative lower bound of $f_i \approx 1.06$ (95% CI: 1.002–1.14).

Putting together our estimates of the treatment probability p and the individual transmission enhancement factor f_i using equation (2.1) (details in the electronic supplementary material), we conclude that the current practice of frequently treating fevers with antipyretic medication has the population-level effect of enhancing the transmission of influenza by at least 1% (95% CI: 0.04–3%) (i.e. $f_P > 1.01$ (95% CI: 1.00–1.03)). This estimate does not take into account the known effect that the infectious period of influenza is also increased by antipyresis [16], nor does it take into account the potentially large effect of increasing the rate of contact among infectious and susceptible individuals because antipyresis makes infectious individuals feel better.

4. Discussion

To put our lower bound for f_P into perspective, consider that approximately 41 400 (95% CI: 27 100–55 700) deaths per year are attributed to seasonal influenza epidemics in the United States [43] (and an order of magnitude more worldwide [44]). Taken at face value, our results indicate, for example, that if $\mathcal{R} = 1.5$ then at least 700 deaths per year (95% CI: 30–2100) (and many more serious illnesses) could be prevented in the US alone by avoiding antipyretic medication for the treatment of influenza (see table 1). While subject to large uncertainty, our estimates in table 1 should be considered conservative, as

Table 1. Percentage of influenza deaths attributable to common use of antipyretic medication (for the plausible range of reproduction number for influenza). See the electronic supplementary material for details.

	attributable influenza deaths	
$\mathcal{R}$	estimate (%)	95% CI
1.2	5	(0.3%, 12.6%)
1.5	2	(0.1%, 4.9%)
1.8	1	(0.1%, 2.8%)

we have ignored concomitant antipyretic-induced increases in infectious periods and contact rates.

The population-level effects of antipyretic treatment during influenza pandemics could be especially dramatic. It has been suggested that widespread use of aspirin in 1918 may have increased disease severity, and consequently death rates, during the pandemic [45], and experimental research in humans and other animals suggests that antipyretic use may increase the risk of death from serious infections [10,46]. Even without this individual-level effect, the population transmission-enhancing effect that we have highlighted here could have increased the final size of the 1918 pandemic significantly, suggesting that a non-negligible proportion of the 50–100 million [47] pandemic-related deaths could have been attributable to transmission enhancement from widespread use of antipyretic medication.

While our theoretical argument that links antipyretic treatment with an increase in epidemic size is straightforward, estimation of the magnitude of this effect is necessarily indirect, and our attempt here provides only a crude lower bound. We have been conservative in every step of our estimation of this lower bound, but we have not been able to quantify all potentially contributing factors. One further effect that could be important in principle is transmission of influenza by infected individuals before they show symptoms; however, evidence for this effect—and for asymptomatic transmission in general—is weak [48] and seems likely to be balanced in our calculations by ignoring the known lengthening of the infectious period caused by antipyresis [16]. Another potentially important effect that we have not considered is age-dependent mixing. Exceptionally high rates of antipyretic treatment in children [3] might contribute to the disproportionate role that children play in influenza transmission [26,49]; taking this into account would increase our estimated lower bound. Readers who want to consider the impact of including additional factors, or modifying our estimates, can use figure 1 to approximate the effect of changes to the population transmission enhancement factor f_P. Because the estimated absolute magnitude of f_P is fairly small, and because the curves in figure 1(*b*) are close to linear, most effects will be close to linear as well. For example, if amelioration of symptoms led to a lengthening of the infectious period by 20%, the number of estimated attributable cases would increase by 19.2%.

Experiments and observational studies designed specifically to estimate the magnitude of transmission enhancement by antipyresis could give much more precise constraints on the population-level effects of antipyretic use. In particular, randomized trials assigning individuals to antipyretic or placebo treatment could characterize increases in the infectious period and viral shedding owing to antipyretic drugs, while challenge experiments could better characterize the relationship between dosage and infection probability. Increases in contact rates caused by infectious individuals feeling well enough to go to work, school and other gathering places may be even more important in practice. These effects would best be estimated as part of the randomized trials discussed above, but even observational studies that survey individuals' symptoms and behaviour and correlate them with variation in use of medications could be a useful first step; we are beginning pilot studies of this sort.

We have shown that—as is well understood for antibiotics [50]—the use of antipyretics can have subtle and potentially important negative effects at the population level. Any medical intervention that aims to relieve the symptoms of an infectious disease in an individual should also be evaluated in light of potentially harmful effects at the population level. Practices that prevent infection (e.g. vaccination), or increase individual comfort without increasing transmission, are preferable from a population perspective. We hope that our analysis in this paper will spur further research to determine more precise estimates of the effects that we have discussed. Such estimates should assist in the development of evidence-based guidelines for antipyretic treatment practices.

Acknowledgements. We thank Susan Marsh-Rollo and Sangeeta Sutradhar for assistance in digitizing data, and Ali Ashkar, Sigal Balshine, Dawn Bowdish, David Champredon, Ferric Fang, Brian Lichty, Mark Loeb, Chai Molina, Karen Mossman, Marek Smieja, Gerry Wright and Dan Yamin for valuable discussions and correspondence.

Funding statement. D.J.D.E. and B.M.B. were supported by NSERC and the M.G. DeGroote Institute for Infectious Disease Research.

References

1. Jack DB. 1997 One hundred years of aspirin. *Lancet* **350**, 437–439. (doi:10.1016/S0140-6736(97)07087-6)
2. Mackowiak PA. 2000 Brief history of antipyretic therapy. *Clin. Infect. Dis.* **31**, S154–S156. (doi:10.1086/317510)
3. Walsh A, Edwards H, Fraser J. 2007 Over-the-counter medication use for childhood fever: a cross-sectional study of Australian parents. *J. Paediatr. Child Health* **43**, 601–606. (doi:10.1111/j.1440-1754.2007.01161.x)
4. Ipp M, Jaffe D. 1993 Physicians' attitudes toward the diagnosis and management of fever in children 3 months to 2 years of age. *Clin. Pediatr.* **32**, 66–70. (doi:10.1177/000992289303200201)
5. Thomas V, Riegel B, Andrea J, Murray P, Gerhart A, Gocka I. 1994 National survey of pediatric fever management practices among emergency department nurses. *J. Emerg. Nurs.* **20**, 505–510.
6. Plaisance KI, Mackowiak PA. 2000 Antipyretic therapy. *Arch. Intern. Med.* **160**, 449–456. (doi:10.1001/archinte.160.4.449)
7. Wood DM *et al*. 2010 Patient knowledge of the paracetamol content of over-the-counter (OTC) analgesics, cough/cold remedies and prescription medications. *Emerg. Med. J.* **27**, 829–833. (doi:10.1136/emj.2009.085027)
8. Mackowiak PA. 2000 Physiological rationale for suppression of fever. *Clin.*

Infect. Dis. **31**, S185–S189. (doi:10.1086/317511)

9. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R. 2010 The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analyis. *J. R. Soc. Med.* **103**, 403–411. (doi:10.1258/jrsm.2010.090441)
10. Kluger MJ. 1991 The adaptive value of fever. In *Fever: basic mechanisms and management* (ed. PA Mackowiak), pp. 105–124. New York, NY: Raven Press Ltd.
11. Hasday JD, Fairchild KD, Shanholtz C. 2000 The role of fever in the infected host. *Microbes Infect.* **2**, 1891–1904. (doi:10.1016/S1286-4579(00)01337-X)
12. Blatteis CM. 2003 Fever: pathological or physiological, injurious or beneficial? *J. Thermal Biol.* **28**, 1–13. (doi:10.1016/S0306-4565(02)00034-7)
13. Simon HB. 2003 Hyperthermia, fever, and fever of undetermined origin. In *Infectious diseases: the clinician's guide to diagnosis, treatment, and prevention.* (ed. DC Dale). New York, NY: WebMD Professional Publishing.
14. Murphy KM. 2011 *Janeway's immunobiology*, 8th edn. New York, NY: Garland Science.
15. Dinarello CA, Porat R. 2008 In *Harrison's principles of internal medicine* (eds AS Fauci, DL Kasper, DL LongoE Braunwald, SL Hauser, JL Jameson, J Loscalzo), 17th edn, p. 2958. New York, NY: McGraw-Hill.
16. Husseini RH, Sweet C, Collie MH, Smith H. 1982 Elevation of nasal viral levels by suppression of fever in ferrets infected with influenza viruses of differing virulence. *J. Infect. Dis.* **145**, 520–524. (doi:10.1093/infdis/145.4.520)
17. Kermack WO, McKendrick AG. 1927 A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond. A* **115**, 700–721. (doi:10.1098/rspa.1927.0118)
18. Ma J, Earn DJD. 2006 Generality of the final size formula for an epidemic of a newly invading infectious disease. *Bull. Math. Biol.* **68**, 679–702. (doi:10.1007/s11538-005-9047-7)
19. Anderson RM, May RM. 1991 *Infectious diseases of humans: dynamics and control*. Oxford, UK: Oxford University Press.
20. Earn DJD, Dushoff J, Levin SA. 2002 Ecology and evolution of the flu. *Trends Ecol. Evol.* **17**, 334–340. (doi:10.1016/S0169-5347(02)02502-8)
21. Chowell G, Miller MA, Viboud C. 2008 Seasonal influenza in the United States, France, and Australia: transmission and prospects for control. *Epidemiol. Infect.* **136**, 852–864. (doi:10.1017/S0950268807009144)
22. Chowell G, Viboud C, Simonsen L, Miller M, Alonso WJ. 2010 The reproduction number of seasonal influenza epidemics in Brazil, 1996–2006. *Proc. R. Soc. B* **277**, 1857–1866. (doi:10.1098/rspb.2009.1897)
23. Tuite AR *et al*. 2010 Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *Can. Med. Assoc. J.* **182**, 131–136. (doi:10.1503/cmaj.091807)
24. Katriel G, Yaari R, Huppert A, Roll U, Stone L. 2011 Modelling the initial phase of an epidemic using incidence and infection network data: 2009 H1N1 pandemic in Israel as a case study. *J. R. Soc. Interface* **8**, 856–867. (doi:10.1098/rsif.2010.0515)
25. He D, Dushoff J, Day T, Ma J, Earn DJD. 2011 Mechanistic modelling of the three waves of the 1918 influenza pandemic. *Theor. Ecol.* **4**, 283–288. (doi:10.1007/s12080-011-0123-3)
26. Earn DJD *et al*. 2012 Effects of school closure on incidence of pandemic influenza in Alberta, Canada. *Ann. Intern. Med.* **156**, 173–181. (doi:10.7326/0003-4819-156-3-201202070-00005)
27. Ludwig D. 1975 Final size distribution for epidemics. *Math. Biosci.* **23**, 33–46. (doi:10.1016/0025-5564(75)90119-4)
28. Drake JM. 2006 Limits to forecasting precision for outbreaks of directly transmitted diseases. *PLoS Med.* **3**, 57–62. (doi:10.1371/journal.pmed.0030003)
29. Brauer F. 2008 Age-of-infection and the final size relation. *Math. Biosci. Eng.* **5**, 681–690.
30. Katriel G. 2012 The size of epidemics in populations with heterogeneous susceptibility. *J. Math. Biol.* **65**, 237–262. (doi:10.1007/s00285-011-0460-2)
31. Miller JC, Slim AC, Volz EM. 2012 Edge-based compartmental modelling for infectious disease spread. *J. R. Soc. Interface* **9**, 890–906. (doi:10.1098/rsif.2011.0403)
32. R Development Core Team. 2012. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.
33. Carrat F *et al*. 2008 Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am. J. Epidemiol.* **167**, 775–785. (doi:10.1093/aje/kwm375)
34. Matsuoka Y, Lamirande EW, Subbarao K. 2009 The ferret model for influenza. In *Current protocols in microbiology*, vol. 13, pp. 15G.2.1–15G.2.29. Hoboken, NJ: John Wiley & Sons.
35. Toms GL, Davies JA, Woodward CG, Sweet C, Smith H. 1977 The relation of pyrexia and nasal inflammatory response to virus levels in nasal washings of ferrets infected with influenza viruses of differing virulence. *Br. J. Exp. Pathol.* **58**, 444–458.
36. Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V. 1975 Increased virus shedding with aspirin treatment of rhinovirus infection. *JAMA* **231**, 1248–1251. (doi:10.1001/jama.1975.03240240018017)
37. Doran TF, Deangelis C, Baumgardner RA, Mellits ED. 1989 Acetaminophen: more harm than good for chickenpox? *J. Pediatr.* **114**, 1045–1048. (doi:10.1016/S0022-3476(89)80461-5)
38. Plaisance KI, Kudaravalli S, Wasserman SS, Levine MM, Mackowiak PA. 2000 Effect of antipyretic therapy on the duration of illness in experimental influenza A, *Shigella sonnei*, and *Rickettsia rickettsii* infections. *Pharmacotherapy* **20**, 1417–1422. (doi:10.1592/phco.20.19.1417.34865)
39. Yezli S, Otter JA. 2011 Minimum infective dose of the major human respiratory and enteric viruses transmitted through food and the environment. *Food Environ. Virol.* **3**, 1–30.
40. Bolker BM *et al*. 2009 Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol. Evol.* **24**, 127–135. (doi:10.1016/j.tree.2008.10.008)
41. Bates D, Maechler M, Bolker B. 2012 *lme4: linear mixed-effects models using S4 classes*. R package v. 0.999375–42. See http://CRAN.R-project.org/package=lme4.
42. Yang Y *et al*. 2009 Transmissibility and control of pandemic influenza A (H1N1) virus. *Science* **326**, 729–733. (doi:10.1126/science.1177373)
43. Dushoff J, Plotkin JB, Viboud C, Earn DJD, Simonsen L. 2006 Mortality due to influenza in the United States: an annualized regression approach using multiple-cause mortality data. *Am. J. Epidemiol.* **163**, 181–187. (doi:10.1093/aje/kwj024)
44. World Health Organization. 2009 *Media centre: fact sheet 211*. See http://www.who.int/mediacentre/factsheets/fs211/en/.
45. Starko KM. 2009 Salicylates and pandemic influenza mortality, 1918–1919 pharmacology, pathology, and historic evidence. *Clin. Infect. Dis.* **49**, 1405. (doi:10.1086/606060)
46. Schulman CI *et al*. 2005 The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg. Infect.* **6**, 369–375. (doi:10.1089/sur.2005.6.369)
47. Taubenberger JK, Morens DM. 2006 1918 influenza, the mother of all pandemics. *Emerg. Infect. Dis.* **12**, 15–22. (doi:10.3201/eid1209.05-0979)
48. Patrozou E, Mermel LA. 2009 Does influenza transmission occur from asymptomatic infection or prior to symptom onset? *Public Health Rep.* **124**, 193–196.
49. Loeb M *et al*. 2010 Effect of influenza vaccination of children on infection rates in Hutterite communities. *JAMA* **303**, 943–950. (doi:10.1001/jama.2010.250)
50. DiazGranados CA, McGowan Jr JE. 2009 Antimicrobial resistance: an international public health problem. In *Antimicrobial drug resistance* (ed. DL Mayers), vol. 2, pp. 1267–1276. New York, NY: Springer Science+Business Media.

ELECTRONIC SUPPLEMENTARY MATERIAL
Population-level effects of suppressing fever

David J.D. Earn[1,2,*], Paul W. Andrews[3] and Benjamin M. Bolker[1,2,4]

[1]Department of Mathematics and Statistics, McMaster University
[2]M. G. DeGroote Institute for Infectious Disease Research, McMaster University
[3]Department of Psychology, Neuroscience and Behaviour, McMaster University
[4]Department of Biology, McMaster University

*Corresponding author: earn@math.mcmaster.ca

December 26, 2013 @ 19:45

Published in *Proceedings of the Royal Society* B
http://dx.doi.org/10.1098/rspb.2013.2570

Contents

1 Introduction

This supplement is written in `knitr` (3), an R (4) package for reproducible research inspired by Knuth's *Literate Programming* (5). All graphs, computations and statistics are computed at the same time that the text is typeset, so everything is exactly reproducible. This document is lengthy because it contains (hopefully) pedagogical explanations and statistical code. A few finicky details—such as code to read data files and plot graphs—are suppressed in this document, but all details are visible in the source code (`feversupp.Rnw`), which is available upon request from `earn@math.mcmaster.ca`. Readers who have no interest in reproducing our results can skim over most of the details.

One graphics detail perhaps worth noting is that we use the `tikz` package, which allows us to use LaTeX within figures.

```
require("tikzDevice")
```

We used R version 2.15.2 (2012-10-26) and package versions:

```
##      bbmle  coefplot2    emdbook      gdata    ggplot2       lme4
##    1.0.5.2    0.1.3.2      1.3.4     2.12.0    0.9.3.1     1.0-4
##       plyr   reshape2 tikzDevice
##        1.8      1.2.2      0.6.2
```

The `coefplot2` package must be installed from `http://r-forge.r-project.org` or `http://www.math.mcmaster.ca/bolker/R`.

2 Epidemic final size

The expected final size Z (the proportion of initially susceptible individuals infected during a given epidemic) can be expressed explicitly as a function of the reproduction number $\mathcal{R}$ using Lambert's W function (6, 7),

$$Z(\mathcal{R}) = 1 + \frac{1}{\mathcal{R}} W[-\mathcal{R}\, e^{-\mathcal{R}}]\,. \tag{S1}$$

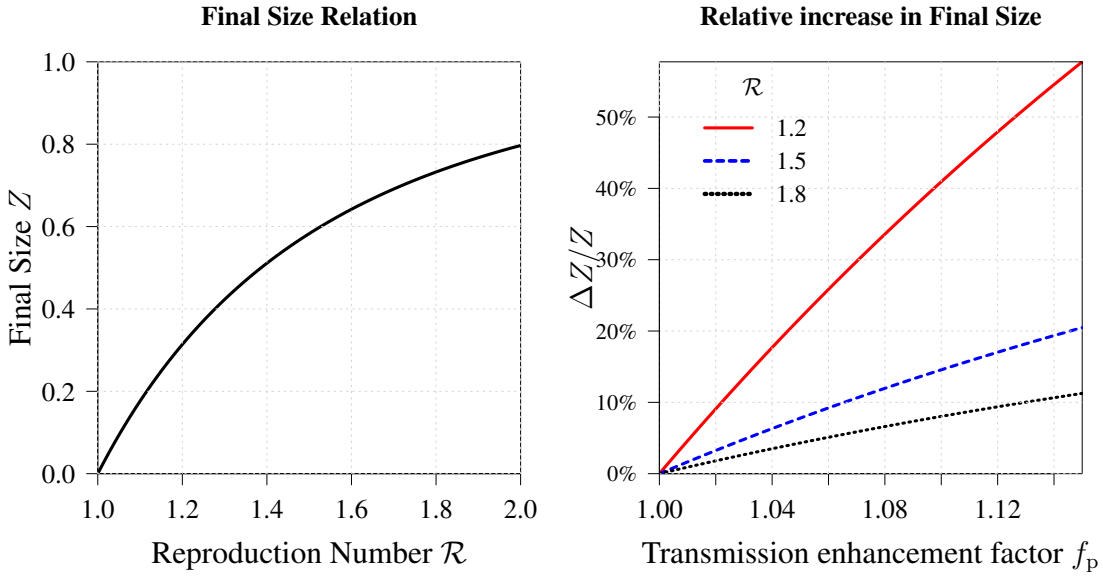
This avoids having to solve the implicit final size relation:

```
require(emdbook) # implements lambertW
Z <- function(R) {
   1+1/R*lambertW(-R*exp(-R))
}
```

We also define a function for the incremental increase in final size due to an increase in transmission rate by factor `f`:

```
dZ <- function(f,R) {
  Z(f*R) - Z(R)
}
```

The relative increase in final size—equation (4) of the main text—is then `dZ(f,R)/Z(R)`. We are now able to produce the plot shown in Figure 1 of the main text (plotting code suppressed).



3 Antipyretics increase viral shedding

3.1 Animal model

Some studies suggest that antipyretic medications may have antiviral properties in laboratory mice (8, 9). However, mice do not develop a febrile response to influenza (10), which makes them poor models for examining the effects of antipyretic medications on influenza transmission in humans. Since we are interested in the effects of suppressing fever on influenza transmission, ferrets are a better animal model (10).

3.2 Immunological mechanism

With many influenza viruses, viral shedding is inhibited by the interferon-alpha (IFNα) cytokines, which play a key role in the innate immune response to viral infections (11, 12). IFNα reduces the shedding of influenza virus in guinea pigs (13) and ferrets (14), and it appears to have a similar effect in humans (15, 16). Since the production of IFNα is enhanced at higher febrile temperatures (17, 18), fever suppression is likely to increase viral shedding, at least in part, by inhibiting the IFNα response to influenza.

3.3 Data from the study of Husseini *et al.* (1)

We begin by reading the data:

```
Huss1 <- read.Huss( fignum=1, clonename="7a" )
Huss2a <- read.Huss( fignum=2, clonename="7a" )
Huss2b <- read.Huss( fignum=2, clonename="64d" )
```

All the graphs published by Husseini *et al.* (1) are replotted here in Figures S1, S2 and S3. Because the original data were not available to us, each plotted data point (and associated standard error) was extracted from the published graphs.

Husseini *et al.* (1) conducted three experiments in which ferrets where infected with one of two influenza viruses (clones 7a or 64d of influenza A/Puerto Rico/8/34-A/England/939/69 (H3N2)) and then followed for 72 hours. In each experiment, some ferrets were treated and others were not. Treatment consisted either of shaving before being infected (Figure S1) or administration of an antipyretic drug every 3–4 hours (Figures S2 and S3). We analyze only the experiments involving the antipyretic drug, since shaving (which reduces core body temperature in ferrets) is not a common treatment for human influenza.

In each experiment, Husseini *et al.* (1) divided the ferrets into three groups after the trials were completed: those that were untreated (blue circles in the figures), treated and responded (red squares) and treated but did not respond (black triangles). The upper panels of Figures S1, S2 and S3 show the mean rectal temperature in each of the groups during the course of the experiment, while the lower panels show the corresponding mean viral titers in each of the groups.

We denote the sequence of mean viral titers for the untreated group by U_i and their standard errors by ΔU_i. Similarly, for the group treated with antipyretics, we denote the mean $\pm$ SEM by $A_i \pm \Delta A_i$ for the subgroup that "responded" and $B_i \pm \Delta B_i$ for the subgroup that "did not respond".

We combine the data from Figures S2 and S3 and treat each data point as independent. Note that we must omit `NA` ("not available"/missing) values that occur because measurements of viral titer were not taken at some times when temperatures were measured.

```
time <- c( Huss2a$time[!is.na(Huss2a$A)],
           Huss2b$time[!is.na(Huss2b$A)] )
A <- c(na.omit(c(Huss2a$A, Huss2b$A))) # treated, responded
B <- c(na.omit(c(Huss2a$B, Huss2b$B))) # treated, did not respond
U <- c(na.omit(c(Huss2a$U, Huss2b$U))) # untreated
```

(The additional `c()` outside of `na.omit()` is used here, and below, for its side effect of dropping attributes, in this case additional information stored by R about which values were dropped — this is purely cosmetic.)

We restrict attention to measurements made after antipyretic treatment was initiated (18 hours post-infection) and before the effects of the final treatment (48 hours post-infection) had worn off.

```
tmin <- 18 # hours
tmax <- 54 # hours
A <- A[time>tmin & time<tmax]
B <- B[time>tmin & time<tmax]
U <- U[time>tmin & time<tmax]
t.treat <- time[time>tmin & time<tmax]
```

3.4 Dose units

The unit used by Husseini *et al.* (1) to quantify viral titer was the base 10 logarithm of the number of 50% egg bit infectious doses ($\log_{10}\texttt{EBID}_{50}$), as indicated in Figures S1, S2 and S3. A detailed discussion of this method of virus quantification (which is no longer in common use) is given by Fazekas de St. Groth and White (19).

The most common current method of virus quantification yields estimates in units of Tissue Culture Infectious Doses (TCID). For example, one $\texttt{TCID}_{50}$ is the amount of virus that will produce infection in 50% of inoculated tissue cultures. Most of the studies reviewed by Yezli and Otter (2) (§4 below) used TCID.

Different methods of virus quantification are not directly comparable. However, for our purposes we need only quantify proportional changes in viral titers, which avoids the need to convert units.

3.5 Estimation of $\bar{\delta}$

We now consider the difference in viral titers between groups,

$$\delta_i^A = A_i - U_i\,, \qquad i = 1, \ldots, n, \tag{S2a}$$

$$\delta_i^B = B_i - U_i\,, \qquad i = 1, \ldots, n. \tag{S2b}$$

```
deltaA <- A - U
deltaB <- B - U
```

The *post hoc* separation of the "treated" group into "responded" and "did not respond" subgroups could represent an inappropriate bias that inflated the effect reported by the authors (1). To be as conservative as possible, we combine the two "treated" subgroups by taking the inverse-variance weighted mean (which gives greater weight to observations with smaller errors). To do so, we first need the relevant variances. The variance of δ_i^A is the sum of the variances of A_i and U_i, i.e.,

$$\text{var}\left(\delta_i^A\right) = \text{var}\left(A_i\right) + \text{var}\left(U_i\right) = \left(\Delta A_i\right)^2 + \left(\Delta U_i\right)^2\,, \tag{S3}$$

and similarly for δ_i^B.

```
sem.A <- c(na.omit(c( Huss2a$dA, Huss2b$dA )))
sem.B <- c(na.omit(c( Huss2a$dB, Huss2b$dB )))
sem.U <- c(na.omit(c( Huss2a$dU, Huss2b$dU )))
sem.A <- sem.A[time>tmin & time<tmax]
sem.B <- sem.B[time>tmin & time<tmax]
sem.U <- sem.U[time>tmin & time<tmax]
var.deltaA <- sem.A^2 + sem.U^2
var.deltaB <- sem.B^2 + sem.U^2
```

We now compute

$$\delta_i = \left(\frac{\delta_i^A}{\mathrm{var}\,(\delta_i^A)} + \frac{\delta_i^B}{\mathrm{var}\,(\delta_i^B)} \right) \Bigg/ \left(\frac{1}{\mathrm{var}\,(\delta_i^A)} + \frac{1}{\mathrm{var}\,(\delta_i^B)} \right) , \tag{S4}$$

and

$$\mathrm{var}\,(\delta_i) = 1 \Bigg/ \left(\frac{1}{\mathrm{var}\,(\delta_i^A)} + \frac{1}{\mathrm{var}\,(\delta_i^B)} \right) . \tag{S5}$$

(The justification for the formula for the variance in δ_i is identical to that given for the variance in $\bar{\delta}$ below.)

```
if (any(var.deltaA==0)) stop("some var(deltaA) is zero")
if (any(var.deltaB==0)) stop("some var(deltaB) is zero")
var.delta <- 1/(1/var.deltaA + 1/var.deltaB)
delta <- (deltaA/var.deltaA + deltaB/var.deltaB) * var.delta
```

The standard error in the mean for each δ_i is $\Delta\delta_i = \sqrt{\mathrm{var}\,(\delta_i)}$,

```
sem.delta <- sqrt(var.delta)
```

We now estimate the average difference between treated and untreated groups, defining $\bar{\delta}$ to be the inverse variance weighted mean,

$$\bar{\delta} = \sum_{i=1}^{n} \frac{\delta_i}{\mathrm{var}\,(\delta_i)} \Bigg/ \sum_{i=1}^{n} \frac{1}{\mathrm{var}\,(\delta_i)} . \tag{S6}$$

To compute the error in $\bar{\delta}$, note that since the individual variances $\mathrm{var}\,(\delta_i)$ are constants, we have

$$\mathrm{var} \left(\sum_{i=1}^{n} \frac{\delta_i}{\mathrm{var}\,(\delta_i)} \right) = \sum_{i=1}^{n} \frac{\mathrm{var}\,(\delta_i)}{[\mathrm{var}\,(\delta_i)]^2} = \sum_{i=1}^{n} \frac{1}{\mathrm{var}\,(\delta_i)} . \tag{S7}$$

Hence the variance in $\bar{\delta}$ is

$$\mathrm{var}\,(\bar{\delta}) = \sum_{i=1}^{n} \frac{1}{\mathrm{var}\,(\delta_i)} \Bigg/ \left[\sum_{i=1}^{n} \frac{1}{\mathrm{var}\,(\delta_i)} \right]^2 \tag{S8a}$$

$$= 1 \Bigg/ \sum_{i=1}^{n} \frac{1}{\mathrm{var}\,(\delta_i)} , \tag{S8b}$$

and the standard error in $\bar{\delta}$ is

$$\Delta\bar{\delta} = \sqrt{\mathrm{var}\left(\bar{\delta}\right)}\,. \tag{S9}$$

```
if (any(var.delta==0)) stop("some var(delta) is zero")
harmonic.sum <- function(x) 1/(sum(1/x))
var.delta.bar <- harmonic.sum(var.delta)
(delta.bar <- sum(delta/var.delta)*var.delta.bar)

## [1] 0.2498
```

```
(sem.delta.bar <- sqrt(var.delta.bar))

## [1] 0.06154
```

Thus, we estimate that the average increase in viral titer induced by antipyretic medication is

$$\bar{\delta} \simeq 0.25 \pm 0.062 \quad \log_{10} \mathtt{EBID}_{50}\,. \tag{S10}$$

Rather than a standard error, it will be more convenient to have a confidence interval on $\bar{\delta}$:

```
delta.bar.lwr <- delta.bar - 1.96*sem.delta.bar
delta.bar.upr <- delta.bar + 1.96*sem.delta.bar
```

$$\bar{\delta} \simeq 0.25 \qquad [0.129, 0.37] \quad \log_{10} \mathtt{EBID}_{50}\,. \tag{S11}$$

More intuitively, antipyresis causes viral titer in nasal washes to increase by a factor of order

```
ten.to.the.delta.bar <- 10^delta.bar
ten.to.the.delta.bar.lwr <- 10^delta.bar.lwr
ten.to.the.delta.bar.upr <- 10^delta.bar.upr
round(ten.to.the.delta.bar,2)

## [1] 1.78
```

$$10^{\bar{\delta}} = 1.78 \qquad [1.35, 2.35]\,. \tag{S12}$$

Note here that $10^{\bar{\delta}}$ is dimensionless, because $\bar{\delta}$ is a difference (each term of which has the same unit). Hence exponentiation converts the difference to a ratio, in which the units cancel out.

4 Greater viral shedding increases infectivity

4.1 Data from the review of Yezli and Otter (2)

We begin by reading the data from Table 1 of Yezli and Otter (2). These data are plotted in Figure S4.

```
require("gdata") # enable reading of Excel spreadsheets
Yezli <- read.xls("data/Yezli2011_Table1.xlsx")
nexpts <- nrow(Yezli) ## number of distinct experiments listed
nstudies <- length(unique(Yezli[,"Reference"])) ## distinct studies
nstrains <- length(unique(Yezli[,"Influenza.strain"])) ## distinct strains
nreport <- sum(!is.na(Yezli[,"P.infected"]))
    ## experiments that reported proportion infected
```

This table reports 34 experiments from 30 studies, which involved a total of 20 distinct influenza strains. In 2 experiments, the proportion of individuals who were infected was not given, so we exclude these:

```
## utility function: subset() does not automatically
##    remove unused/empty levels
dsubset <- function(x,...) droplevels(subset(x,...))
Yezli <- dsubset(Yezli,!is.na(P.infected))
```

Here, `droplevels()` removes empty levels everywhere in the data frame, hence in particular removes the 2 levels associated with strains for which proportion infected was not given. We also drop studies that (unusually) used eggs rather than tissue culture to quantify virus:

```
Yezli <- dsubset(Yezli,Dose.unit=="TCID50")
nreport <- sum(!is.na(Yezli[,"P.infected"]))
```

This leaves only 17 of the original 20 influenza strains. The remaining list of strains in Table 1 of Yezli and Otter (2011) for which the associated study reported the proportion infected is:

```
unique(Yezli$Influenza.strain)
```

```
##  [1] A/Alaska/6/77 (H3N2)
##  [2] A/California/10/78 (H1N1)
##  [3] A/England/42/72 (H3N2)
##  [4] A/England/40/83 (H3N2)
##  [5] A2/Bethesda/10/63 (H2N2)
##  [6] A/Equi 2/Miami/1/63 (H3N8)
##  [7] A2/Hong Kong/1/68 (H3N2)
##  [8] A/Kawasaki/9/86 (H1N1)
##  [9] A/Korea/1/82 (H3N2)
## [10] A2/Rockville/1/65
## [11] A/Shangdong/9/93 (H3N2)
## [12] A/Texas/36/91 (H1N1)
## [13] A/Texas/1/85 (H1N1)
## [14] A/University of Maryland/1/70 (H3N2)
## [15] A/Victoria/3/75 (H3N2)
## [16] B/Panama/45/90
## [17] B/Yamagata/16/88
## 17 Levels: A/Alaska/6/77 (H3N2) ... B/Yamagata/16/88
```

Of these 17 strains, some were used in more than one experiment:

```
(multi.expt.strains <- names(which(table(Yezli$Influenza.strain)>1)))
```

```
## [1] "A/England/42/72 (H3N2)"     "A/Equi 2/Miami/1/63 (H3N8)"
## [3] "A/Kawasaki/9/86 (H1N1)"     "A/Texas/36/91 (H1N1)"
## [5] "A2/Bethesda/10/63 (H2N2)"   "A2/Rockville/1/65"
## [7] "B/Yamagata/16/88"
```

Yezli and Otter (2) report a single dose for most experiments but report a range of doses for the following experiments:

```
Yezli.dose.range <- Yezli[Yezli[,"Low.dose"] != Yezli[,"High.dose"],]
Yezli.dose.range[,c("Influenza.strain","Low.dose","High.dose","Dose.unit",
                    "P.infected")]
```

```
##             Influenza.strain Low.dose High.dose Dose.unit P.infected
## 7   A2/Bethesda/10/63 (H2N2)    80000    180000    TCID50     1.0000
## 9 A/Equi 2/Miami/1/63 (H3N8)    40000    200000    TCID50     0.6364
```

Our analysis is based on doses on a logarithmic scale, so we replace the ranges in these 2 experiments with midpoints of their logarithms, and save this new variable in our data frame:

```
Yezli <- transform(Yezli,
                   log10dose=(log10(Low.dose)+log10(High.dose))/2)
```

For each experiment, we want to predict the proportion infected:

```
pinfected <- Yezli[,"P.infected"]
```

Figure S4 shows the data (`pinfected` vs `log10dose`). Strains that were used in multiple experiments are colour-coded as indicated.

```
col.list <- c("red","blue","brown","cyan","magenta","orange","yellow")
stopifnot(length(col.list) == length(multi.expt.strains))
names(col.list) <- multi.expt.strains
```

4.2 Completely naïve linear regression

Although technically inappropriate (since the response variable is a proportion) we begin with a simple linear regression of `log10dose` against `pinfected`.

```
fit.lm <- lm( P.infected ~ log10dose, data=Yezli )
coef(summary(fit.lm))

##             Estimate Std. Error t value  Pr(>|t|)
## (Intercept)  0.62714    0.11007   5.698 3.662e-06
## log10dose    0.03278    0.01983   1.654 1.090e-01

slope.lm <- coef(summary(fit.lm))[2]
sem.slope.lm <- coef(summary(fit.lm))[4]
```

Although this linear regression is not significant at $p < 0.05$ ($\Pr(>|t|) = 0.109$), we proceed to use it as a pedagogical exercise. The fitted slope of the linear regression is

$$a = 0.033 \pm 0.02\,. \tag{S13}$$

Confidence bands on the linear regression are obtained as follows.

```
## Create a new data frame with log10dose values
##    increasing in sequence over the range of interest:
pframe <- data.frame( log10dose=seq(0,10,length=50) )
## Compute a matrix with columns fit,lwr,upr for each log10dose
##   value in pframe:
ci.lm <- predict(fit.lm, interval="confidence",newdata=pframe)
## Combine as matrix with columns log10dose,fit,lwr,upr for plotting:
confbands.lm <- cbind(as.vector(pframe),ci.lm)
```

Figure S4(b) shows the linear fit (heavy black line) and associated confidence bands (grey).

4.3 Naïve logistic regression

Our aim is to fit a model that predicts the proportion infected (`P.infected`) for a given dose of virus (`log10dose`). This dose-response problem (with a proportional response) is a standard setting for the application of logistic regression (20–22). If our data were based on a single study involving a single influenza strain, and only the infectious dose varied among trials, then a simple logistic regression would be appropriate. The data that we have are more complicated since they come from many different studies involving many different influenza strains (2); some studies include more than one strain, and some strains are included in more than one study. In §4.4 we account for this variation by constructing a generalized linear mixed model (23) (GLMM). As it turns out, the predictions made by a simple logistic regression are very similar to those from a more sophisticated GLMM applied to our data.

In this section, we present a simple logistic regression, which will be more familiar to most readers and is based on standard theory (20–22).

A logistic regression is a particular type of generalized linear model (GLM), namely a binomial regression in which the link function is the logit,

$$\text{logit}(y) = \log\left(\frac{y}{1-y}\right) . \tag{S14}$$

The logit converts probabilities to log-odds, whereas the inverse-logit (the logistic function, $y = 1/(1+e^{-x})$) converts log-odds to probabilities. R's built in `qlogis()` function implements the logit, while `plogis()` implements the inverse-logit or logistic function.

There are two equivalent ways to specify a binomial regression using R's `glm()` function:

1. The response variable can be expressed as a two-column matrix containing successes and failures. In our case, the R syntax for the model is

   `cbind(N.infected,N.total-N.infected)  log10dose.` (S15)

2. The response variable can be expressed as the proportion of successes. In this case, the sizes of the samples must be specified. The R syntax for the model is

   `P.infected  log10dose` (S16a)

   and the sample sizes are specified with the argument

   `weights=N.total.` (S16b)

We use the second option, which is slightly more readable:

```
fit.glm <- glm( P.infected ~ log10dose, weights=N.total,
                family=binomial(link="logit"), data=Yezli )
```

```
summary(fit.glm)

##
## Call:
## glm(formula = P.infected ~ log10dose, family = binomial(link = "logit"),
##     data = Yezli, weights = N.total)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -2.619  -1.598   0.606   1.823   3.534
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   0.1870     0.3145    0.59     0.55
## log10dose     0.2437     0.0606    4.02  5.8e-05 ***
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 116.95  on 30  degrees of freedom
## Residual deviance: 100.81  on 29  degrees of freedom
## AIC: 167
##
## Number of Fisher Scoring iterations: 5

(slope.glm <- coef(summary(fit.glm))["log10dose","Estimate"])

## [1] 0.2437

## OR slope.glm <- coef(fit.glm)["log10dose"]
(sem.slope.glm <- coef(summary(fit.glm))["log10dose","Std. Error"])

## [1] 0.06062
```

We now make predictions based on this logistic regression.

4.3.1 Prediction from logistic regression

Assume the sampling distribution of the intercept and slope parameters above is bivariate normal. Generate samples:

```
## generate a 1000x2 matrix:
my.sample <- mvrnorm(1000,mu=coef(fit.glm),Sigma=vcov(fit.glm))
summary(my.sample)

##   (Intercept)        log10dose
##  Min.   :-1.2841   Min.   :0.0049
##  1st Qu.:-0.0546   1st Qu.:0.2068
##  Median : 0.1836   Median :0.2482
##  Mean   : 0.1748   Mean   :0.2464
##  3rd Qu.: 0.3862   3rd Qu.:0.2855
##  Max.   : 1.4517   Max.   :0.5229
```

4.3.2 Confidence bands for logistic regression

Obtaining confidence bands on our fit is slightly more complicated than for the naïve linear regression (§4.2). Unlike `predict.lm()`, `predict.glm()` has no `interval` argument, so we must actually compute the 95% confidence intervals ourselves from the standard errors at each point we require (which were defined as `pframe` in §4.2):

```
ci.glm <- predict( fit.glm, se.fit=TRUE, newdata=pframe )
ci.glm$lwr <- ci.glm$fit - 1.96*ci.glm$se.fit
ci.glm$upr <- ci.glm$fit + 1.96*ci.glm$se.fit
## translate back to the probability scale:
pglm <- lapply(ci.glm[c("fit","lwr","upr")],plogis)
confbands.glm <- cbind( as.vector(pframe), pglm )
```

To obtain the predicted proportion infected (and standard error or confidence interval) for any given dose we would simply redefine `pframe` in the above. For example, to obtain predicted proportion infected for a dose of 100 $\mathtt{TCID}_{50}$) we would set

```
pframe <- data.frame( log10dose=2 )
```

Note that the `newdata` passed to `predict()` must have the same name (`log10dose`) as the original data in order to replace it in the prediction.

4.4 Generalized Linear Mixed Models

4.4.1 Why GLMMs?

If the data plotted in Figure S4 had come from a single experiment in which the experimenter had many treatments involving the same influenza strain but different doses, and looked for the response in terms of proportion infected, then the simple logistic regression we performed would be appropriate. In fact, the data that Yezli and Otter (2) summarize come from many different studies, and involve many different influenza strains. To account for this properly, we require a generalized linear mixed model (23).

4.4.2 Fitting

Logistic regression with strain as a random effect We first fit a logistic (binomial) regression with strain as a random effect. We use `weights` to specify the number of subjects per trial and `nAGQ=8` to specify that we want to fit the model using Gauss-Hermite quadrature with 8 quadrature points (this is slightly more accurate than the default method, Laplace approximation).

```
library(lme4pkg,character.only=TRUE)
```

For the benefit of readers unfamiliar with R's formula notation for GLMMs, we note: On the RHS of the vertical bar | is the grouping variable. On the LHS of | is the parameter that varies across groups. Parameter `1` refers to the intercept (the LHS is interpreted according to R's formula language [Wilkinson-Rogers notation: see the *Introduction to R* (24, p.76) for basic information]). Any predictor variable can be on the LHS. Any factor can be on the RHS.

```
fit.glmm.bystrain <- glmer(P.infected~log10dose+(1|Influenza.strain),
                     weights=N.total,family=binomial,data=Yezli)
fixef(fit.glmm.bystrain)

## (Intercept)   log10dose
##      0.1584      0.2815
```

```
summary(fit.glmm.bystrain)
```

```
## Generalized linear mixed model fit by maximum likelihood [glmerMod]
##  Family: binomial ( logit )
## Formula: P.infected ~ log10dose + (1 | Influenza.strain)
##    Data: Yezli
##
##      AIC      BIC   logLik deviance
##   152.65   156.95   -73.32   146.65
##
## Random effects:
##  Groups           Name        Variance Std.Dev.
##  Influenza.strain (Intercept) 0.786    0.887
## Number of obs: 31, groups: Influenza.strain, 17
##
## Fixed effects:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   0.1584     0.5604    0.28   0.7774
## log10dose     0.2815     0.0965    2.92   0.0035 **
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## Correlation of Fixed Effects:
##            (Intr)
## log10dose -0.884
```

The components of `fixef(fit)` are the intercept and slope of the fixed effect model. The output slope is 0.2815. This is the change in log odds of infection for a one-unit change in `log10dose`.

Logistic regression with strain and observation as a random effects In principle, there could be an interaction between infective dose and strain (i.e. different strains could have different relationships between dose and infectivity), but we won't see that because there are so few data points for each strain (in many cases only one datum per strain). We could include this term in the model anyway, but the interaction will probably be estimated as zero because of lack of information.

Another assumption we are making is that each outcome is a binomial draw, i.e., each individual is identical. The easy way around this (in other words, to allow for *overdispersion*) is to attempt to fit an observation-level random effect, i.e., each *study* as a random effect and/or each research group as a random effect. One easy solution is to add a variable to the data frame that identifies each experiment:

```
Yezli$obs <- 1:nrow(Yezli)
```

```
fit.glmm.bystrainobs <- glmer(P.infected~log10dose+
                    (1|Influenza.strain)+(1|obs),
                    weights=N.total,family=binomial,data=Yezli)
fixef(fit.glmm.bystrainobs)

## (Intercept)   log10dose
##      0.5308      0.2217

summary(fit.glmm.bystrainobs)

## Generalized linear mixed model fit by maximum likelihood [glmerMod]
##  Family: binomial ( logit )
## Formula: P.infected ~ log10dose + (1 | Influenza.strain) + (1 | obs)
##    Data: Yezli
##
##      AIC      BIC   logLik deviance
##   141.87   147.61   -66.94   133.87
##
## Random effects:
##  Groups           Name        Variance Std.Dev.
##  obs              (Intercept) 1.11e+00 1.053305
##  Influenza.strain (Intercept) 1.43e-10 0.000012
## Number of obs: 31, groups: obs, 31; Influenza.strain, 17
##
## Fixed effects:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)    0.531      0.717    0.74    0.459
## log10dose      0.222      0.130    1.71    0.087 .
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## Correlation of Fixed Effects:
##            (Intr)
## log10dose -0.944
```

(We can no longer use `nAGQ=8` in `glmer` but must revert to Laplace approximation because `glmer` only implements Gauss-Hermite quadrature for models with a single random effect.) This model assigned all the among-strain variation to among-study variation and increased the p value to just better than 0.05.

Logistic regression with strain and study as a random effects Now we try a slight variation, using study (`Reference`) rather than observation as the random effect:

```
fit.glmm.bystrainref <- glmer(P.infected~log10dose+
                    (1|Influenza.strain)+(1|Reference),
                    weights=N.total,family=binomial,data=Yezli)
fixef(fit.glmm.bystrainref)

## (Intercept)   log10dose
##      0.3071      0.2792

summary(fit.glmm.bystrainref)

## Generalized linear mixed model fit by maximum likelihood [glmerMod]
##  Family: binomial ( logit )
## Formula: P.infected ~ log10dose + (1 | Influenza.strain) + (1 | Referenc
##    Data: Yezli
##
##      AIC      BIC   logLik deviance
##   133.57   139.30   -62.78   125.57
##
## Random effects:
##  Groups           Name        Variance Std.Dev.
##  Reference        (Intercept) 1.08e+00 1.04e+00
##  Influenza.strain (Intercept) 7.02e-11 8.38e-06
## Number of obs: 31, groups: Reference, 27; Influenza.strain, 17
##
## Fixed effects:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)    0.307      0.724    0.42    0.672
## log10dose      0.279      0.135    2.06    0.039 *
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## Correlation of Fixed Effects:
##           (Intr)
## log10dose -0.939
```

The variance is again assigned entirely to reference rather than to influenza strain (although this is likely to be a rather fragile result).

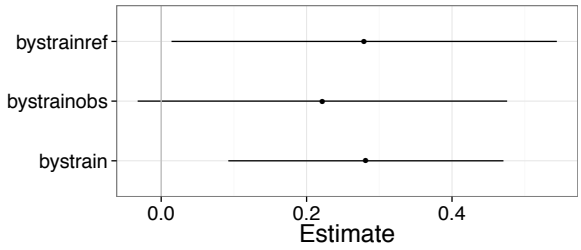
4.4.3 Selecting the best GLMM

Although it is far from a perfect metric, the Akaike Information Criterion (25, 26) (AIC) suggests (fairly strongly: $\Delta\text{AIC} > 2$ represents a substantial change in expected predictive ability) that we should use the third model.

```
library("bbmle")
AICtab(fit.glmm.bystrain,fit.glmm.bystrainobs,fit.glmm.bystrainref)
```

```
##                         dAIC df
## fit.glmm.bystrainref     0.0 4
## fit.glmm.bystrainobs     8.3 4
## fit.glmm.bystrain       19.1 3
```

The point estimates are not terribly different in any case:



The slope estimates plotted above are:

```
##              Estimate    lwr   upr
## bystrain        0.282  0.092 0.471
## bystrainobs     0.222 -0.032 0.476
## bystrainref     0.279  0.014 0.544
```

The slope estimates don't vary that much (from 0.2217 to 0.2815), but the lower confidence intervals range from -0.0324 to 0.0923.

The equivalent of the uncertainty in the effect of increasing from the baseline dose by one log10 dose unit is as follows (we have to use `fixef` rather than `coef` to extract the fixed-effect parameters: `coef` extracts the estimated parameters for each random-effect level (strain)).

```
## generate a 1000x2 matrix:
```

```
my.sample <- as.data.frame(mvrnorm(1000,mu=fixef(fit.glmm.bystrainref),
                                   Sigma=vcov(fit.glmm.bystrainref)))
meandose <- mean(Yezli$log10dose)
## predicted infectivity at mean dose:
inf0 <- with(my.sample,plogis((Intercept)+meandose*log10dose))
## predicted infectivity at (mean dose+1):
inf1 <- with(my.sample,plogis((Intercept)+(meandose+1)*log10dose))
change.in.inf <- (inf1-inf0)
c(mean=mean(change.in.inf),quantile(change.in.inf,c(0.025,0.975)))

##     mean     2.5%    97.5%
## 0.030175 0.001557 0.056676

summary(my.sample)

##   (Intercept)       log10dose
##  Min.   :-1.917   Min.   :-0.136
##  1st Qu.:-0.181   1st Qu.: 0.184
##  Median : 0.286   Median : 0.281
##  Mean   : 0.313   Mean   : 0.279
##  3rd Qu.: 0.827   3rd Qu.: 0.373
##  Max.   : 2.429   Max.   : 0.649

Yezli.coeftab <- coef(summary(fit.glmm.bystrainref))["log10dose",c("Estimat
```

```
## 1-unit change from baseline log-odds of 0 (=prob 0.5)
change.in.inf <- plogis(my.sample$log10dose)-0.5
yezli.change.sum <- c(est=mean(change.in.inf),
                      setNames(quantile(change.in.inf,c(0.025,0.975)),
                               c("lwr","upr")))
## get rid of "Estimate" name so it doesnt
##    contaminate names in the next step:
Yezli.coeftab <- unname(Yezli.coeftab)
yezli.slope <- c(est=Yezli.coeftab[1],
                 lwr=Yezli.coeftab[1]-1.96*Yezli.coeftab[2],
                 upr=Yezli.coeftab[1]+1.96*Yezli.coeftab[2])
```

4.4.4 The "divide by four" rule

The slope that we have computed with GLMMs is the slope on the linear scale, not the logit scale, i.e., the slope is β where the fitted curve is $\text{logit}(y) = \alpha + \beta x$. At the point on the logit scale where the probability is 0.5, the slope of the fitted curve is $\beta/4$, and the line with this slope through that

point is an excellent approximation for quite a wide range of probabilities. This is the basis of the "divide by 4" rule (22, p.82), which is often used to approximate the logit by a straight line, $y = 0.5 + ax$.

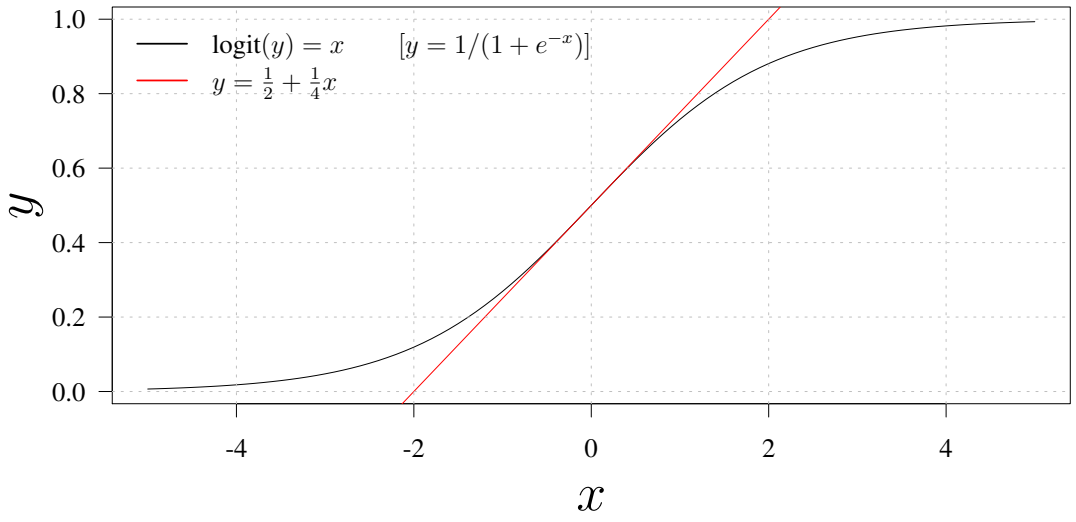
```
slope <- Yezli.coeftab[1]/4
sem.slope <- Yezli.coeftab[2]/4
```

This yields

$$a = 0.0698 \pm 0.0338\,. \tag{S17}$$

The validity of the "divide by 4" rule is suggested by this plot:

```
curve(plogis(x),xlim=c(-5,5), xlab="$x$", ylab="$y$", cex.lab=2, las=1)
curve(0.5 + x/4 ,add=TRUE,col="red")
grid(col="grey")
legend.text <- c("$\\textrm{logit}(y)=x\\qquad[y=1/(1+e^{-x})]$",
                 "$y=\\frac12 + \\frac14x$")
legend("topleft", legend=legend.text, col=c("black", "red"),
       lty=1, bty="n", lwd=2)
```



Below (§6.1.3) we compare predictions based on the divide-by-four rule with those obtained using the exact nonlinear relationship.

4.4.5 Confidence intervals on predictions

As above, let's assume the sampling distribution of the `glmer` parameter estimates is really multivariate normal, with variance-covariance matrix given by:

```
(vv <- vcov(fit.glmm.bystrainref))

## 2 x 2 Matrix of class "dpoMatrix"
##             (Intercept) log10dose
## (Intercept)     0.52457  -0.09195
## log10dose      -0.09195   0.01828
```

Then we can generate a distribution of slopes and intercepts as follows:

```
library(MASS)
pardist <- mvrnorm(1000,mu=fixef(fit.glmm.bystrainref),Sigma=vv)
summary(pardist)

##   (Intercept)       log10dose
##  Min.   :-1.994   Min.   :-0.129
##  1st Qu.:-0.155   1st Qu.: 0.180
##  Median : 0.315   Median : 0.278
##  Mean   : 0.310   Mean   : 0.277
##  3rd Qu.: 0.828   3rd Qu.: 0.368
##  Max.   : 2.524   Max.   : 0.755
```

We now use the prediction frame `pframe` from above, which contains a variable `log10dose` with the desired range of values for prediction:

```
X <- model.matrix(~log10dose,data=pframe)
predmat <- X %*% t(pardist)
GLMMbands1 <- t(apply(predmat,1,quantile,c(0.025,0.975)))
confbands.glmm <- with(pframe,cbind(log10dose,
           fit=plogis(fixef(fit.glmm.bystrainref)[1]+
                      fixef(fit.glmm.bystrainref)[2]*log10dose),
                        lwr=plogis(GLMMbands1[,1]),
                        upr=plogis(GLMMbands1[,2])))
```

5 Influenza natural infectivity

$\bar{\delta}$ is the mean increase in viral titer caused by antipyresis, while a is the slope of the putative linear relationship between viral titer and infectivity. Thus the product $a\bar{\delta}$ tells us by how much antipyresis increases infectivity. The scale on which this increase is measured is the proportion infected. The relative impact of this change depends on the proportion infected in the absence of antipyresis, which we think of as the "natural infectivity" of the pathogen and write as $\mathcal{I}$.

We do not have direct estimates of $\mathcal{I}$ for influenza, but we attempt to approximate it as follows. One quantity that has often been estimated for influenza is the *secondary attack rate* (SAR)

within a household, i.e., the proportion of co-habiting individuals who are infected by a primary (index) case that enters the household. The SAR in a household provides a reasonable estimate of the natural infectivity under the assumption that individuals who live together will come into contact with the index case. Estimates of the SAR that we are aware of have not controlled for use of antipyretics, so the reported SAR can be expected to be higher than the true SAR in the absence of antipyresis (making our further analysis conservative). However, SAR measurements can be confounded by pre-existing immunity in some household members, which would lower SAR estimates. We therefore restrict attention to studies that controlled for pre-existing immunity.

Yang *et al.* (27, Table S8) provide estimates of the the SAR in households for influenza, based on their own study of the 2009 pandemic (pH1N1) and work of others on seasonal influenza epidemics and previous pandemics.

```
SAR.table <- read.csv("data/Yang+2009_TableS8.csv")
nrow(SAR.table)

## [1] 27

colnames(SAR.table)

##  [1] "Strain"                      "Year"
##  [3] "Reference.Number"            "Article"
##  [5] "Based.on.References"         "SAR"
##  [7] "SAR.lwr"                     "SAR.upr"
##  [9] "Household.Size"              "Type.of.Confirmation"
## [11] "Data.Source"                 "Independent.Sample"
## [13] "Independent.Sample.Comment" "Other.Comments"

SAR.table <- within(SAR.table, {
                    Article <- as.character(Article)
                    Article[1] <- "Yang 2009"
                    Article <- factor(Article)
                })
```

The table lists SAR as percentages, but for our convenience we convert to proportions.

```
SAR.table <- transform(SAR.table,
                       SAR = SAR/100,
                       SAR.lwr = SAR.lwr/100,
                       SAR.upr = SAR.upr/100)
```

We will transform to the logit scale, and back-calculate SEM from the difference between the lower and upper CI (we will disregard the fact that some CI seem to be symmetric on the original scale, while others are symmetric on the logit scale).

There a few studies without confidence intervals; we will replace these `NA` values with the mean of the rest of the values.

```
na_mean <- function(x) {
    x[is.na(x)] <- mean(x,na.rm=TRUE)
    x
}
SAR.table <-
  within(SAR.table,
         {
           SAR.sem <- na_mean((SAR.upr-SAR.lwr)/(2*1.96))
           logit.SAR <- qlogis(SAR)
           logit.SAR.lwr <- qlogis(SAR.lwr)
           logit.SAR.upr <- qlogis(SAR.upr)
           logit.SAR.sem <- na_mean((logit.SAR.upr-logit.SAR.lwr)/(2*1.96))
         })
```

321 Now we check the results look sensible:

```
summary(subset(SAR.table,
               select=c(SAR,SAR.lwr,SAR.upr,
                 logit.SAR.lwr,logit.SAR.upr,logit.SAR.sem)))

##       SAR             SAR.lwr           SAR.upr       logit.SAR.lwr
##  Min.   :0.040   Min.   :0.0100   Min.   :0.080   Min.   :-4.595
##  1st Qu.:0.118   1st Qu.:0.0667   1st Qu.:0.151   1st Qu.:-2.638
##  Median :0.180   Median :0.1118   Median :0.236   Median :-2.072
##  Mean   :0.194   Mean   :0.1278   Mean   :0.246   Mean   :-2.192
##  3rd Qu.:0.267   3rd Qu.:0.1688   3rd Qu.:0.299   3rd Qu.:-1.595
##  Max.   :0.430   Max.   :0.3900   Max.   :0.510   Max.   :-0.447
##                  NAs   :3        NAs   :3        NAs   :3
##  logit.SAR.upr    logit.SAR.sem
##  Min.   :-2.442   Min.   :0.0691
##  1st Qu.:-1.732   1st Qu.:0.1379
##  Median :-1.175   Median :0.1909
##  Mean   :-1.240   Mean   :0.2429
##  3rd Qu.:-0.854   3rd Qu.:0.2496
##  Max.   : 0.040   Max.   :0.9858
##  NAs   :3
```

322 5.1 Inverse variance weighted mean

323 The naïve inverse variance weighted mean is:

```
SAR.var <- SAR.table$SAR.sem^2
natinf.var <- 1/sum(1/SAR.var)
natinf <- sum(SAR.table$SAR/SAR.var) * natinf.var
```

and the CI on this quantity is

```
(natinf.sem <- sqrt(natinf.var))

## [1] 0.003696

(natinf.lwr <- natinf - 1.96*natinf.sem)

## [1] 0.1501

(natinf.upr <- natinf + 1.96*natinf.sem)

## [1] 0.1646
```

$$\mathcal{I} = 0.1574 \qquad [0.1501, 0.1646] \tag{S18}$$

Since $\mathcal{I}$ is a probability, it cannot be normally distributed. However, the log-odds of infection,

$$\text{logit}(\mathcal{I}) = \log\left(\frac{\mathcal{I}}{1-\mathcal{I}}\right), \tag{S19}$$

can reasonably be assumed to be normally distributed.

```
logit.natinf <- qlogis(natinf)
logit.natinf.lwr <- qlogis(natinf.lwr)
logit.natinf.upr <- qlogis(natinf.upr)
```

$$\text{logit}(\mathcal{I}) = -1.678 \qquad [-1.734, -1.624] \tag{S20}$$

On the logit scale, the confidence interval above is symmetric:

```
logit.natinf.upr - logit.natinf

## [1] 0.05364

logit.natinf - logit.natinf.lwr

## [1] 0.05569
```

We can now infer a standard error on $\text{logit}(\mathcal{I})$:

```
(sem.logit.natinf <- ( logit.natinf.upr - logit.natinf.lwr ) / (2 * 1.96))

## [1] 0.02789
```

However, we will shortly replace these inverse-variance-weighted mean estimates with estimates derived from a GLMM analysis (next section).

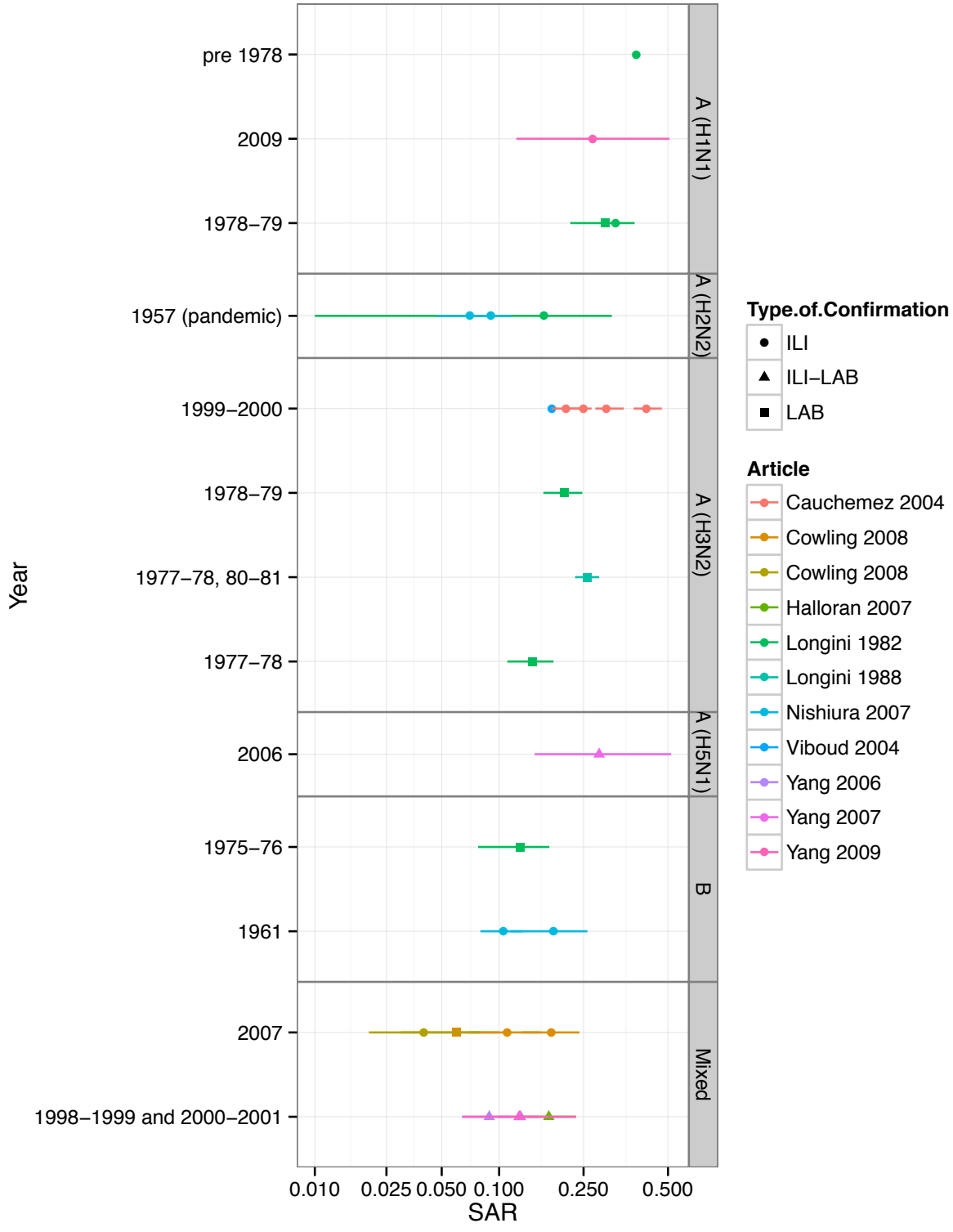
5.2 GLMM estimate

`ggplot` preliminaries:

```
library(ggplot2)
library(proto)  ## need this for hacked horizontal linerange
library(grid)
source("geom-linerangeh.R")
theme_set(theme_bw())
zmargin <- theme(panel.margin=unit(0,"lines"))
library(scales)
```

We can now reproduce (more or less) the plot in the original paper (27, Fig.1):

```
ggplot(SAR.table,
       aes(x=SAR,y=Year,colour=Article,shape=Type.of.Confirmation))+
    facet_grid(Strain~.,scales="free_y",space="free")+
    geom_point()  +## position=position_dodge(height=1))
    geom_linerangeh(aes(xmin=SAR.lwr,xmax=SAR.upr))+
    zmargin+
    scale_x_continuous(trans=logit_trans(),
                       breaks=c(0.01,0.025,0.05,0.1,0.25,0.5))
```



337

```
## use explicit breaks argument here (compensate for ggplot bug)
```

Note that the x axis is drawn on a logit scale. Although not true for all data points, we assume for simplicity that all the confidence intervals shown in the graph above are symmetric on the logit scale (i.e., the SEM is half of the confidence interval width on the logit scale, divided by 1.96). We can then fit a linear mixed model (LMM) on the logit scale. We consider four flavors of LMM, with different combinations of the random effects (year, strain, article):

```
yang.lmm.ysa <- lmer(logit.SAR~Type.of.Confirmation-1+
                     (1|Year)+(1|Strain)+(1|Article),
                     data=SAR.table,weights=1/logit.SAR.sem^2)
yang.lmm.ys <- update(yang.lmm.ysa, .~.-(1|Article))
yang.lmm.sa <- update(yang.lmm.ysa, .~.-(1|Year))
yang.lmm.s <- update(yang.lmm.sa, .~.-(1|Article))
```

These models are essentially indistinguishable in their goodness of fit (so their AIC values vary only by 2 or 4 units because the models have different numbers of parameters):

```
mlist <- list(YSA=yang.lmm.ysa,YS=yang.lmm.ys,SA=yang.lmm.sa,S=yang.lmm.s)
library(bbmle)
AICtab(mlist)

##     dAIC df
## S   0    5
## YS  2    6
## SA  2    6
## YSA 4    7
```

Variance components:

```
##     Year Article Strain
## YSA    0       0   0.01
## YS     0      NA   0.01
## SA    NA       0   0.01
## S     NA      NA   0.01
```

The bottom line is that including only an effect of Strain seems adequate.

We decided that it made most sense to use the LAB results (difference in seroprevalence between the beginning and the end of the influenza season), as this gives the best estimate of the actual attack rate (although it does not necessarily distinguish between clinical and subclinical infections).

Comparing the results (on the log-odds scale): LAB confirmations give the lowest values.

```
(cc <- coef(summary(yang.lmm.s)))
```

```
##                               Estimate Std. Error t value
## Type.of.ConfirmationILI         -1.528    0.04875  -31.34
## Type.of.ConfirmationILI-LAB     -1.512    0.06531  -23.15
## Type.of.ConfirmationLAB         -1.793    0.05278  -33.97
```

Estimates and confidence intervals on the raw, or back-transformed, scale, i.e. these are actual attack rates:

```
cc2 <- cbind(est=cc[,1],lwr=cc[,1]-1.96*cc[,2],upr=cc[,1]+1.96*cc[,2])
cc3 <- plogis(cc2)
rownames(cc3) <- gsub("Type.of.Confirmation","",rownames(cc2))
round(cc3,2)

##          est  lwr  upr
## ILI     0.18 0.16 0.19
## ILI-LAB 0.18 0.16 0.20
## LAB     0.14 0.13 0.16
```

However, these confidence intervals only include the parametric uncertainty. We want to compute confidence intervals for the within-household attack rate: we should certainly allow for variation among strains (because we do not know in advance which strain will be prevalent in a given year). It is an open question whether we should include the residual variation in our uncertainty calculation (i.e. whether we should compute *confidence* or *prediction* intervals. Which we choose depends on whether we interpret the residual variance as being due mostly to measurement (sampling) error — in which case the variance would decrease if we collected larger data sets (in which case we would compute confidence intervals, omitting the residual variation) — or due mostly to process error (e.g. variation in unmeasured covariates), which would remain approximately the same for larger data sets (in which case we would compute prediction intervals, including the residual variation). In trying to compute conservative estimates of uncertainty, we will use prediction intervals.

The variance components due to among-strain variation, residual variation, and parameter uncertainty (which is dominated by the residual variation):

```
type <- "Type.of.ConfirmationLAB"
vv <- c(c(unlist(VarCorr(yang.lmm.s))),
        resid=attr(VarCorr(yang.lmm.s),"sc")^2,
        param=cc[type,"Std. Error"]^2)
vv <- c(vv,tot=sum(vv))
print(vv)

##   Strain    resid    param      tot
## 0.010394 0.151844 0.002786 0.165024
```

```
c4 <- cc[type,"Estimate"]
sdtot <- unname(sqrt(vv["tot"]))
c5 <- c(est=c4,lwr=c4-1.96*sdtot,upr=c4+1.96*sdtot)
c6 <- plogis(c5)
```

Rename for export:

```
logit.natinf <- c4
sem.logit.natinf <- sdtot
natinf.glmm <- c6["est"]
natinf.glmm.lwr <- c6["lwr"]
natinf.glmm.upr <- c6["upr"]
```

6 Estimating the transmission enhancement factor

6.1 The individual level effect: f_{i}

Given increase of shedding due to antipyretics ($\bar{\delta}$: §3), the effect of increasing shedding on infection (a: §4), and the natural infectivity ($\mathcal{I}$: §5), the individual transmission enhancement factor based on the divide-by-4 rule (§4.4.4) is

$$f_{\mathrm{i}} = \frac{\mathcal{I} + a\bar{\delta}}{\mathcal{I}} = 1 + \frac{a\bar{\delta}}{\mathcal{I}}\,. \tag{S21}$$

Avoiding the linearization/divide-by-4 rule, the precise (nonlinear) relationship is

$$f_{\mathrm{i}} = \frac{\mathrm{logistic}(a'((\mathrm{logit}(\mathcal{I}) - b')/a')\bar{\delta} + b')}{\mathcal{I}} = \frac{\mathrm{logistic}(\mathrm{logit}(\mathcal{I}) + a'\bar{\delta})}{\mathcal{I}} \tag{S22}$$

(here we are using a' to denote the estimate of the slope *on the logit scale* ($= 4a$), and b' to estimate the intercept (although as shown above it doesn't actually enter the final calculation). Note that f_{i} is a decreasing function of $\mathcal{I}$, since

$$\frac{\partial f_{\mathrm{i}}}{\partial \mathcal{I}} = -\frac{e^{a'\bar{\delta}}(e^{a'\bar{\delta}} - 1)}{[1 + (e^{a'\bar{\delta}} - 1)\mathcal{I}]^2} < 0\,. \tag{S23}$$

Consequently, an overestimate of $\mathcal{I}$ yields an underestimate of f_{i}.

Our estimates of the means and standard errors of $\bar{\delta}$, a, a', and $\mathrm{logit}(\mathcal{I})$ are:

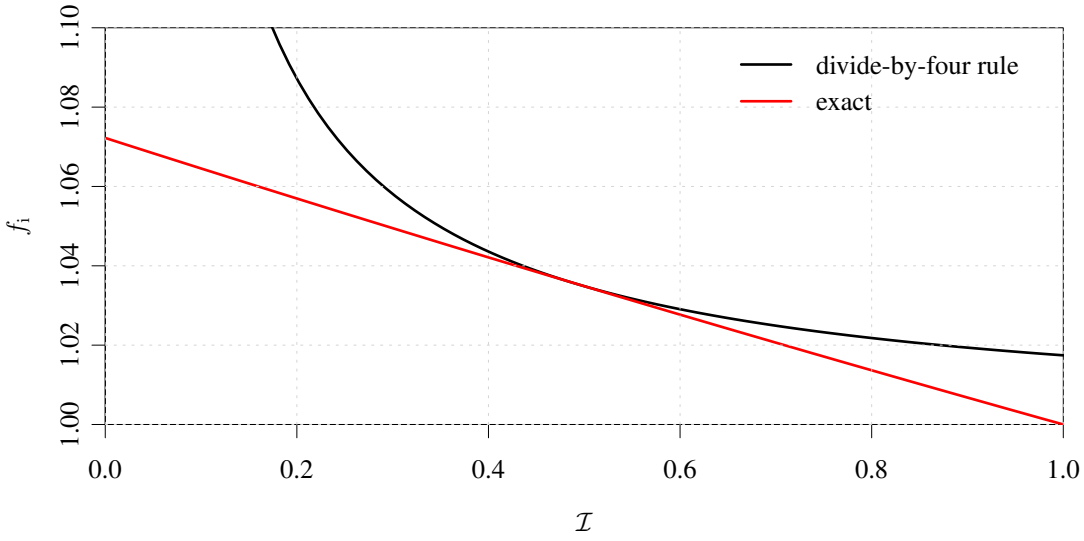
$$a = 0.0698 \pm 0.0338 \tag{S24a}$$

$$a' \approx 4a = 0.2792 \pm 0.1352 \tag{S24b}$$

$$\bar{\delta} = 0.2498 \pm 0.0615 \tag{S24c}$$

$$\mathrm{logit}(\mathcal{I}) = -1.7932 \pm 0.4062 \tag{S24d}$$

Using the mean values, the graphical relationship between $\mathcal{I}$ and f_i is:



Note that the exact relationship is much closer to linear than the relationship obtained with the (linearized) divide-by-four rule.

To obtain a point estimate and confidence interval for f_i based on the divide by four rule, we sample from normal distributions for a, $\bar{\delta}$ and logit$(\mathcal{I})$ defined by the means and standard errors above, and use them to estimate a sample of the distribution of Equation (S21). Similarly, to estimate f_i based on the nonlinear relationship given by Equation (S22), we begin by sampling from normal distributions for a', $\bar{\delta}$ and logit$(\mathcal{I})$.

6.1.1 Linearized/divide-by-4 method

Remember that `plogis()` is the logistic function, $\mathrm{logit}^{-1}(y) = 1/(1+e^{-y})$, and `qlogis()` is the logit.

```
sample.size <- 10000
```

```
a.sample <- rnorm( sample.size, slope, sem.slope )
delta.bar.sample <- rnorm( sample.size, delta.bar, sem.delta.bar )
natinf.sample <- plogis( rnorm( sample.size, logit.natinf,
                                sem.logit.natinf ) )
fi.sample <- 1 + a.sample*delta.bar.sample / natinf.sample
(median.fi <- median( fi.sample ))

## [1] 1.114

mean( fi.sample )

## [1] 1.131

(ci.fi <- quantile( fi.sample , c(0.025,0.975) ))

##  2.5% 97.5%
## 1.006 1.354
```

$$f_{\mathrm{i}} = 1.114 \qquad [1.006, 1.354] \tag{S25}$$

6.1.2 Nonlinear Method

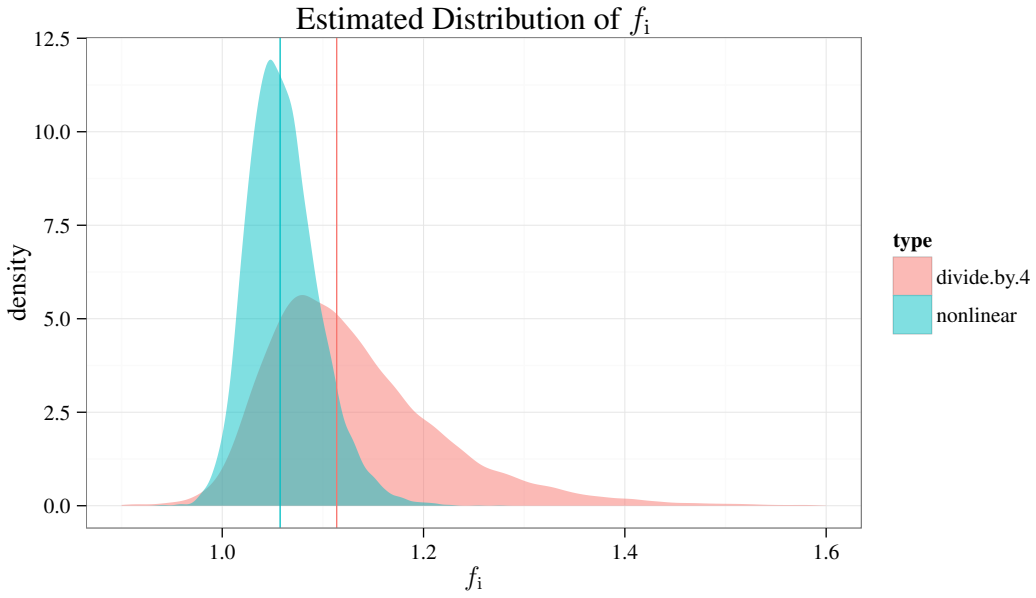
We use suffix 'p' (for "prime") to denote estimates with nonlinearity (`ap` vs `a`, `fip` vs `fi`, *etc.*).

```
ap.sample <- rnorm( sample.size, Yezli.coeftab[1], Yezli.coeftab[2])
fip.sample <- plogis(qlogis(natinf.sample) + ap.sample*delta.bar.sample) /
              natinf.sample
(median.fip <- median( fip.sample ))

## [1] 1.058

mean( fip.sample )

## [1] 1.061

(ci.fip <- quantile( fip.sample , c(0.025,0.975) ))

##  2.5% 97.5%
## 1.002 1.141
```

6.1.3 Comparison of Linearized and Nonlinear methods

Density plots of our estimated distributions for f_{i} are shown below, with the medians marked by vertical lines (the horizontal axis has been trimmed slightly to show the central portion of the densities more clearly).

```
library(ggplot2)
d0 <- data.frame(type=rep(c("divide.by.4","nonlinear"),each=sample.size),
                 value=c(fi.sample,fip.sample))
d1 <- data.frame(type=c("divide.by.4","nonlinear"),
                 value=c(median.fi,median.fip))
ggplot(d0,aes(x=value))+
    geom_density(alpha=0.5,aes(fill=type),colour=NA)+
    labs(title="Estimated Distribution of $f_{\\rm i}$",
         x="$f_{\\rm i}$", y="density")+
    geom_vline(data=d1,aes(colour=type,xintercept=value))+
    xlim(c(0.9,1.6))
```



The distribution based on the full nonlinear expression has a somewhat lower median, but also much lower uncertainty (hence a larger lower bound).

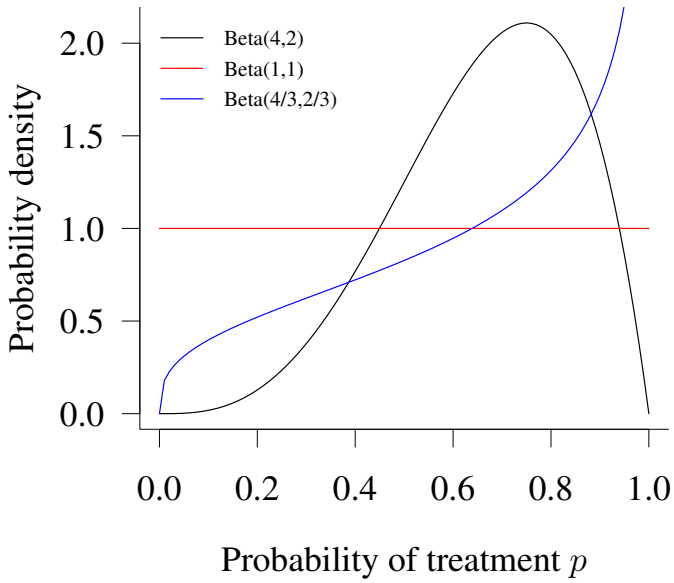
6.2 The population level effect: $f_{\mathbf{p}}$

6.2.1 Informative distribution of p

We argue in the main text that, although we have extremely little information about the treatment probability (the probability that an individual will use antipyretic medication when febrile with

414 influenza), its uncertainty is reasonably represented by a Beta distribution with shape parameters 4
415 and 2:

```
par(las=1,bty="l",cex=2)
curve(dbeta(x,4,2),from=0,to=1,xlab="Probability of treatment $p$",
      lwd=2,
      ylab="Probability density")
curve(dbeta(x,1,1),lwd=2,col="red",add=TRUE)
curve(dbeta(x,4/3,2/3),lwd=2,col="blue",add=TRUE)
legend("topleft",c("Beta(4,2)","Beta(1,1)","Beta(4/3,2/3)"),
       lwd=2,lty=1,col=c("black","red","blue"),cex=0.6,bty="n")
```



416

```
shape1 <- 4
shape2 <- 2
p.lwr <- qbeta(0.025,shape1,shape2)
p.upr <- qbeta(0.975,shape1,shape2)
p.median <- qbeta(0.5,shape1,shape2)
p.mean <- shape1/(shape1+shape2)
```

417 The mean is 0.67; the lower 2.5% quantile, median, and upper 97.5% quantile are 0.28, 0.69, and
418 0.95, respectively.

6.2.2 Flat distribution of p

Alternatively, we could simply claim that we have no information about p, and that we will use a uniform distribution (equivalently a Beta$(1,1)$ distribution) to represent this ignorance. Making this change decreases the mean value of p from 2/3 to 1/2 as well as increasing the variance; as yet another alternative (not pursued here) we could increase the variance while preserving the mean, e.g. by using Beta(4/3,2/3) ...

```
shape1U <- 1
shape2U <- 1
p.lwr.U <- qbeta(0.025,shape1U,shape2U)
p.upr.U <- qbeta(0.975,shape1U,shape2U)
p.median.U <- qbeta(0.5,shape1U,shape2U)
p.mean.U <- shape1U/(shape1U+shape2U)
```

The mean is 0.5; the lower 2.5% quantile, median, and upper 97.5% quantile are 0.02, 0.5, and 0.975, respectively.

6.3 Fraction symptomatic and febrile

Not everyone who gets influenza has a fever — not all infected (and infectious) individuals even have symptoms. These phenomena will change our estimates in two ways. (1) Asymptomatic individuals are not counted in the treatment fractions estimated above. (2) Antipyretics will presumably have little or no effect on the viral shedding rate in individuals without fever. To the extent that antipyretic use is independent of fever, and of symptoms generally, the effective treatment fraction will be reduced by the fraction of individuals that actually have fever. We are making an extremely conservative assumption here; even though individuals without fever may take antipyretics that are included in over-the-counter medication that also addresses other symptoms, we would expect a positive correlation between fever and antipyretic use, and especially between symptoms and use of medication!

Proceeding with these assumptions however — assuming independence of antipyretic treatment and fever, but that only symptomatic individuals are included in our treatment fraction p above, to get the fraction of infected individuals that have fever **and** are treated with antipyretics, we need

$$\text{effective treatment} = p \cdot \frac{\text{symptomatic}}{\text{infected}} \cdot \frac{\text{febrile}}{\text{infected}} \tag{S26}$$

Carrat *et al.* (28) provide the data we need for this correction. They performed a meta-analysis of infection trials on healthy volunteers, estimating the average probability, across studies and strains of influenza, of infectiousness (frequency of an influenza-positive nasal wash on at least one occasion at least one day after inoculation in their Table 1); proportion who developed any symptoms ("clinical illness" in their Table 2); and proportion who developed a fever (their Table 4: defined as a temperature $> 100\,\deg$ F or > 37.8 C).

We transcribed the data from Tables 1, 2, and 4:

Percentage infected/infectious:

```
##          est  lwr  upr
## A/H1N1 93.1 88.5 95.9
## A/H3N2 92.5 85.8 96.1
## A/H2N2 84.3 64.9 94.0
## B      81.5 67.0 90.5
## All    90.0 85.6 93.1
```

Percentage with symptoms:

```
##          est  lwr  upr
## A/H1N1 70.8 50.4 85.2
## A/H3N2 64.5 54.6 73.3
## A/H2N2 77.9 55.1 91.0
## B      57.4 35.2 76.9
## All    66.9 58.3 74.5
```

Percentage with fever:

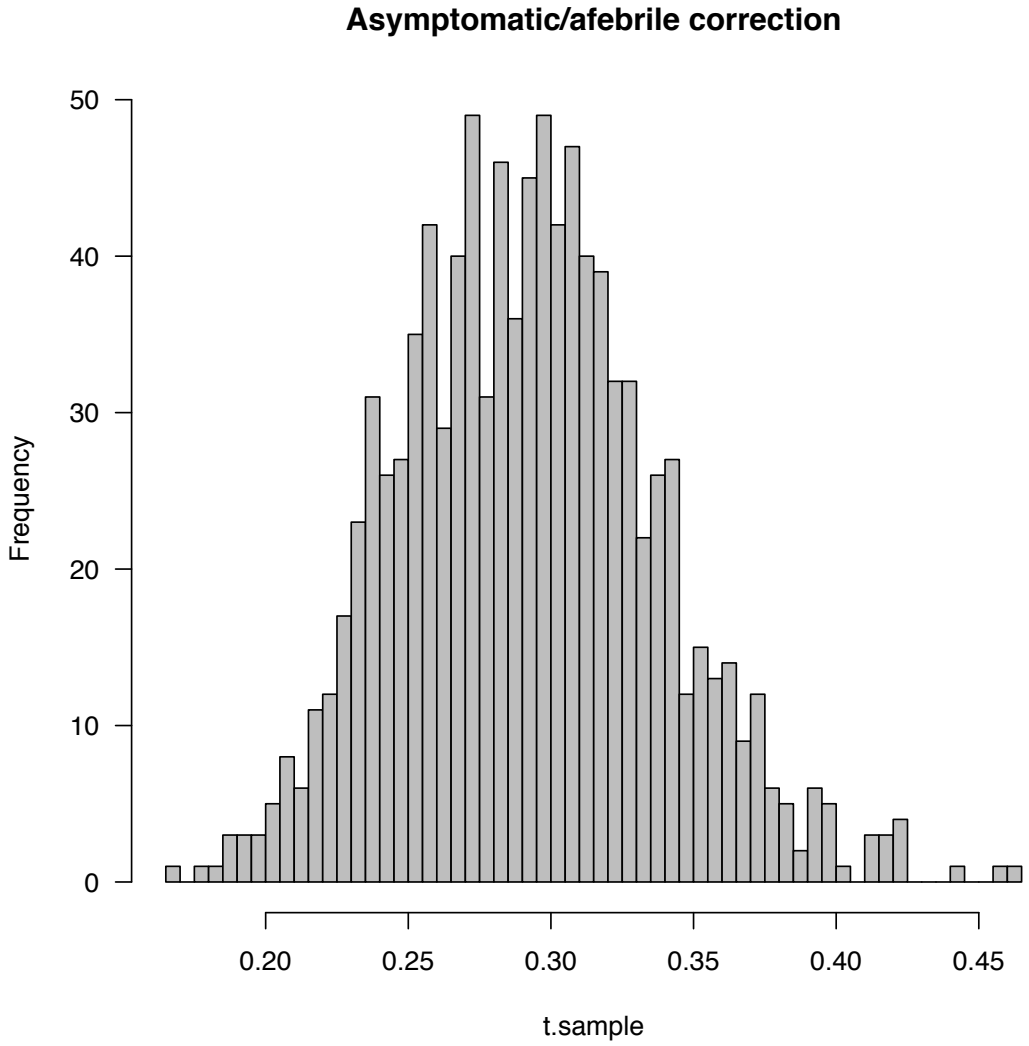
```
##           est  lwr   upr
## A/H1N1  37.0 24.6  51.3
## A/H3N2  40.6 30.9  51.1
## A/H2N2 100.0 69.2 100.0
## B        7.5  3.2  16.9
## All     34.9 26.7  44.2
```

As before, we use these results by taking the estimate and confidence intervals on the overall average values ("All" row); scaling from percentages to proportions, logit-transforming them and, assuming the sampling distribution is Normally distributed on the logit scale, taking $\sigma = (\text{upper} - \text{lower})/3.92$; generating Normally distributed random deviates with the appropriate mean and variance; and logistic-transforming back to the original scale. The following function executes this strategy for various tables.

```
getsamp <- function(i,n=1000,sc=100) {
```

```
    qupr <- qlogis(i$upr/sc)
    qlwr <- qlogis(i$lwr/sc)
    qest <- qlogis(i$est/sc)
    halfint <- c(qupr-qest,qest-qlwr)
    if (abs(diff(halfint)/mean(halfint))>0.1)
        warning("asymmetric CI on logit scale")
    qdist <- diff(qnorm(c(0.025,0.975)))
    qsd <- (qupr-qlwr)/qdist
    plogis(rnorm(n,qest,qsd))
}
isamp <- getsamp(infrate["All",])
csamp <- getsamp(clinrate["All",])
fsamp <- getsamp(fevrate["All",])
t.sample <- csamp*fsamp/(isamp^2)
```

```
par(las=1,bty="l")
hist(t.sample,col="gray",breaks=50,
     main="Asymptomatic/afebrile correction")
```




```
t.lwr <- quantile(t.sample,0.025)
t.median <- quantile(t.sample,0.5)
t.upr <- quantile(t.sample,0.975)
t.mean <- mean(t.sample)
```

The mean is 0.29; the lower 2.5% quantile, median, and upper 97.5% quantile are 0.21, 0.29, and 0.39, respectively.

6.3.1 Conclusions

For most of these conclusions we use the informative distribution. The estimate of f_{i} we reached in Equation (S25) is a lower bound because we have ignored lengthening of infectious periods and increased contact due to feeling better. Thus, a crude lower bound on the population level effect of suppressing fever is

```
fpop <- 1 + (median.fip-1)*p.mean*t.mean
```

```
p.sample <- rbeta(sample.size,shape1,shape2)
fpop.sample <- 1 + (fip.sample-1)*p.sample*t.sample
fpop.lwr <- quantile(fpop.sample,0.025)
fpop.upr <- quantile(fpop.sample,0.975)
```

$$f_{\mathrm{p}} = 1.011 \qquad [1, 1.031] \tag{S27}$$

Alternately, we can use the uniform distribution results:

```
fpop.U <- 1 + (median.fip-1)*p.mean.U*t.mean
p.sample.U <- rbeta(sample.size,shape1U,shape2U)
fpop.sample.U <- 1 + (fip.sample-1)*p.sample.U*t.sample
fpop.lwr.U <- quantile(fpop.sample.U,0.025)
fpop.upr.U <- quantile(fpop.sample.U,0.975)
```

Conclusion: Antipyretics yield an increase in viral shedding that causes an increase in transmission of about 1.1%, with a 95% CI of 0.04–3%. Since we have ignored both lengthening of infectious periods and increases in contact, the increase in transmission is probably underestimated.

Using the uniform distribution: 1%, [95% CI 0.005–3%].

7 Computing attributable deaths

Finally, we compute the predicted annual number of influenza deaths in the United States that we infer are caused by mass use of antipyretic medication:

$$\frac{Z(f_{\mathrm{p}}\mathcal{R}_0) - Z(\mathcal{R}_0)}{Z(f_{\mathrm{p}}\mathcal{R}_0)} \times (\text{estimated influenza deaths in the US})\,. \tag{S28}$$

This prediction depends on $\mathcal{R}_0$, so we save the predictions for three $\mathcal{R}_0$ values in the plausible range for influenza (we order the three $\mathcal{R}_0$ values to be decreasing so the resulting prediction of deaths goes from the lowest to the highest). The estimate of annual influenza deaths in the United States is from Dushoff and co-workers (29).

```
all.US.deaths <- 41400
```

```
semUSdeaths <- (55700-all.US.deaths)/1.96
#####R0 <- c(High=1.8,Mid=1.5,Low=1.2)
R0 <- c(Low=1.2,Mid=1.5,High=1.8)
(mortprop <- dZ(fpop,R0) / Z(fpop*R0))

##     Low     Mid    High
## 0.04899 0.01811 0.01013

US.deaths <- all.US.deaths * mortprop
## round to nearest 100
100*round(US.deaths/100)

##  Low  Mid High
## 2000  700  400
```

The effect of a 20% increase in `fpop` is very nearly linear:

```
rIncr <- 1+(fpop-1)*1.2
incrMortprop <-  dZ(rIncr,R0["Mid"]) / Z(rIncr*R0["Mid"])
(fpopIncrPct <- (incrMortprop/mortprop["Mid"]-1)*100)

##   Mid
## 19.19
```

To get CIs on the estimated percentages of deaths attributable to antipyretic use, we propagate all the errors through the calculations, assuming all are normally distributed, and calculate the percentages for a large sample.

```
mortprop.sample <-
  sapply(R0, function(x) dZ(fpop.sample,x) / Z(fpop.sample*x))
mortprop.CI <- t(apply(mortprop.sample,2,quantile,c(0.025,0.975)))
dimnames(mortprop.CI) <- list(R0=names(R0),c("lwr","upr"))
mortprop.CI

##
## R0           lwr     upr
##   Low  0.0019572 0.12313
##   Mid  0.0007020 0.04780
##   High 0.0003902 0.02707
```

Sample from the distribution of US deaths, propagate that uncertainty, and output the result:

```
US.deaths.sample <- rnorm(sample.size,all.US.deaths,semUSdeaths)
attrib.deaths.sample <- sweep(mortprop.sample,1,FUN="*",US.deaths.sample)
attrib.deaths.CI <- t(apply(attrib.deaths.sample,2,quantile,c(0.025,0.975)))
dimnames(attrib.deaths.CI) <- dimnames(mortprop.CI)
## round to nearest 10/100 ...
smvals <- 2:3
attrib.deaths.CI[smvals] <- 10*round(attrib.deaths.CI[smvals]/10)
attrib.deaths.CI[-smvals] <- 100*round(attrib.deaths.CI[-smvals]/100)
attrib.deaths.CI

##
## R0     lwr  upr
##   Low  100 5300
##   Mid   30 2100
##   High  10 1200
```

8 Save results to a file for inclusion in main paper

We save our estimates to a file in a format that can be input by LaTeX in the main text of the paper. We begin by writing a dated header to the file.

```
fn <- "feverestimates.tex"
cat(file=fn,"% Estimates computed in feversupp.Rnw,", date(), "\n")
```

Next, we write the results as computed (to two decimal places). Some results are expressed as dimensionless factors (f_i, f_p, $10^{\bar{\delta}}$), whereas others are expressed as proportions ($\mathcal{I}$) and still others have units ($\bar{\delta}$, a). (The `nvec()` function constructs a vector which will have names corresponding to the names of the variables specified: see `feversuppfuns.R`.)

```
results.factor <- nvec(ten.to.the.delta.bar,
                       ten.to.the.delta.bar.lwr,
                       ten.to.the.delta.bar.upr,
                       find=median.fip,
                       findlwr=ci.fip[1], findupr=ci.fip[2],
                       fpop, fpop.lwr, fpop.upr,
                       fpop.U, fpop.lwr.U, fpop.upr.U)
## now remove dots and append "val"
paste0 <- function(...,sep="") {paste(...,sep=sep)}
renamefun <- function(x) {
    setNames(x,paste0(gsub("\\.","",names(x)),"val"))
}
results.factor <- renamefun(results.factor)
```

```
results.proportion <-
  renamefun(nvec(natinf.glmm, natinf.glmm.lwr, natinf.glmm.upr))
```

```
results.other <- renamefun(nvec(delta.bar, sem.delta.bar, slope, sem.slope))
results.yezli <- renamefun(nvec(yezli.change.sum,yezli.slope))
```

```
results <- c(results.factor, results.proportion,
             results.other, results.yezli)
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%4.2f}", names(results),
            as.vector(results)))
round(results,2)

##    tentothedeltabarval tentothedeltabarlwrval tentothedeltabaruprval
##                   1.78                   1.35                   2.35
##                findval             findlwrval             finduprval
##                   1.06                   1.00                   1.14
##                fpopval             fpoplwrval             fpopuprval
##                   1.01                   1.00                   1.03
##               fpopUval            fpoplwrUval            fpopuprUval
##                   1.01                   1.00                   1.03
##          natinfglmmval       natinfglmmlwrval       natinfglmmuprval
##                   0.14                   0.07                   0.27
##            deltabarval         semdeltabarval                slopeval
##                   0.25                   0.06                   0.07
##            semslopeval   yezlichangesumestval   yezlichangesumlwrval
##                   0.03                   0.07                   0.00
##   yezlichangesumuprval       yezlislopeestval       yezlislopelwrval
##                   0.13                   0.28                   0.01
##       yezlislopeuprval
##                   0.54
```

We also save the factor results as percentage increases and the proportion results as percentages, since the main text sometimes expresses the results this way.

```
percentages <- c( (results.factor-1)*100, results.proportion*100 )
names(percentages) <- sub("val","pct",
                          names(c(results.factor,results.proportion)))
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.0f}", names(percentages),
            as.vector(percentages)))
```

```
round(percentages)
```

```
##    tentothedeltabarpct tentothedeltabarlwrpct tentothedeltabaruprpct
##                     78                      35                     135
##                findpct              findlwrpct              finduprpct
##                      6                       0                      14
##                fpoppct              fpoplwrpct              fpopuprpct
##                      1                       0                       3
##              fpopUpct            fpoplwrUpct            fpopuprUpct
##                      1                       0                       3
##          natinfglmmpct       natinfglmmlwrpct       natinfglmmuprpct
##                     14                       7                      27
```

```
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.2f}",
            paste0("ptreat",c("mean","lwr","upr")),
            c(p.mean,p.lwr,p.upr)))
```

```
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.2f}",
            paste0("pasymp",c("mean","lwr","upr")),
            c(t.mean,t.lwr,t.upr)))
```

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```
cat(file=fn,append=TRUE,sep="\n",
```

```
    sprintf("\\newcommand{\\%s}{%.0f}",
            c("allUSdeaths","allUSdeathslwr","allUSdeathsupr"),
            c(all.US.deaths, 27100, 55700)))
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.1f}",
            c("RnLow", "RnMid", "RnHigh"),
            R0))
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.0f}",
            c("mortpctLow", "mortpctMid", "mortpctHigh"),
            mortprop*100))
US.deaths <- 100*round(US.deaths/100)
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.0f}",
            c("USdeathsLow", "USdeathsMid", "USdeathsHigh"),
            US.deaths))
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.1f}",
                "fpopIncrPct",fpopIncrPct))
```

```
## utility function to collapse a matrix to a vector and
##  assign relevant names
mat.to.vec <- function(x,prefix="") {
    vec <- c(x)
    names(vec) <- paste0(prefix,
                         outer(rownames(x),colnames(x),
                               paste0))
    vec
}
## calculate mort pct CI and output ...
mortpctCIvec <- mat.to.vec(100*mortprop.CI,"mortpct")
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.1f}",
            names(mortpctCIvec),
            mortpctCIvec))
```

```
attribdeathsCIvec <- mat.to.vec(attrib.deaths.CI,"attribdeaths")
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.0f}",
            names(attribdeathsCIvec),
            attribdeathsCIvec))
```

```
cat(file=fn,append=TRUE,sep="\n",
    sprintf("\\newcommand{\\%s}{%.0f}",
            "samplesize", sample.size))
```

Now we override a few of the definitions to get more precise lower bounds (ll. 115; 126; 131 ×2). We need `\yezlislopelwrval`, `\findlwrval`, `\fpoplowrpct`, `\fpoplwrval`.

```
## values -- need 3 significant digits
lwrbounds1 <- c(results.yezli["yezlichangesumlwrval"],
                results.factor[c("findlwrval","fpoplwrval")])
cat(file=fn,append=TRUE,
    sep="\n",
    sprintf("\\renewcommand{\\%s}{%4.3f}",
            names(lwrbounds1),lwrbounds1))
lwrbounds2 <- percentages["fpoplwrpct"]
cat(file=fn,append=TRUE,
    sep="\n",
    sprintf("\\renewcommand{\\%s}{%4.2f}",
            names(lwrbounds2),lwrbounds2))
```

References

[1] Husseini, R. H., Sweet, C., Collie, M. H., and Smith, H. Elevation of nasal viral levels by suppression of fever in ferrets infected with influenza viruses of differing virulence. *The Journal of Infectious Diseases* **145**(4), 520–524 (1982).

[2] Yezli, S. and Otter, J. A. Minimum infective dose of the major human respiratory and enteric viruses transmitted through food and the environment. *Food and Environmental Virology* **3**(1), 1–30 (2011).

[3] Xie, Y. knitr: A general-purpose package for dynamic report generation in R, (2012).

[4] R Development Core Team. R: A language and environment for statistical computing, (2012).

[5] Knuth, D. E. *Literate Programming*. Center for the Study of Language and Information, (1992).

[6] Ma, J. and Earn, D. J. D. Generality of the final size formula for an epidemic of a newly invading infectious disease. *Bulletin of Mathematical Biology* **68**(3), 679–702 (2006).

[7] Corless, R. M., Gonnet, G. H., Hare, D. E. G., Jerey, D. J., and Knuth, D. E. On the Lambert W function. *Advances in Computational Mathematics* **5**(4), 329–359 (1996).

[8] Lauder, S. N., Taylor, P. R., Clark, S. R., Evans, R. L., Hindley, J. P., Smart, K., Leach, H., Kidd, E. J., Broadley, K. J., Jones, S. A., Wise, M. P., Godkin, A. J., O'Donnell, V., and Gallimore, A. M. Paracetamol reduces influenza-induced immunopathology in a mouse model of infection without compromising virus clearance or the generation of protective immunity. *Thorax* **66**(5), 368–374, February (2011).

[9] Mazur, I., Wurzer, W. J., Ehrhardt, C., Pleschka, S., Puthavathana, P., Silberzahn, T., Wolff, T., Planz, O., and Ludwig, S. Acetylsalicylic acid (ASA) blocks influenza virus propagation via its NF-κB-inhibiting activity. *Cellular Microbiology* **9**(7), 1683–1694, July (2007).

[10] Bouvier, N. M. and Lowen, A. C. Animal models for influenza virus pathogenesis and transmission. *Viruses* **2**(8), 1530–1563, July (2010).

[11] Borden, E. C., Sen, G. C., Uze, G., Silverman, R. H., Ransohoff, R. M., Foster, G. R., and Stark, G. R. Interferons at age 50: past, current and future impact on biomedicine. *Nature Reviews Drug Discovery* **6**(12), 975–990 (2007).

[12] Samuel, C. E. Antiviral actions of interferons. *Clinical Microbiology Reviews* **14**(4), 778–809 (2001).

[13] Van Hoeven, N., Belser, J. A., Szretter, K. J., Zeng, H., Staeheli, P., Swayne, D. E., Katz, J. M., and Tumpey, T. M. Pathogenesis of 1918 pandemic and H5N1 influenza virus infections in a guinea pig model: Antiviral potential of exogenous alpha interferon to reduce virus shedding. *Journal of Virology* **83**(7), 2851–2861 (2009).

[14] Kugel, D., Kochs, G., Obojes, K., Roth, J., Kobinger, G. P., Kobasa, D., Haller, O., Staeheli, P., and von Messling, V. Intranasal administration of alpha interferon reduces seasonal influenza A virus morbidity in ferrets. *Journal of Virology* **83**(8), 3843–3851 (2009).

[15] Hall, C. B., Douglas, R. G., Simons, R. L., and Geiman, J. M. Interferon production in children with respiratory syncytial, influenza, and parainfluenza virus infections. *Journal of Pediatrics* **93**(1), 28–32 (1978).

[16] Jao, R. L., Wheelock, E. F., and Jackson, G. G. Production of interferon in volunteers infected with Asian influenza. *The Journal of Infectious Diseases* **121**(4), 419–26 (1970).

[17] Ater, J. L., Overall, J. C., Yeh, T. J., Obrien, R. T., and Bailey, A. Circulating interferon and clinical symptoms in Colorado tick fever. *Journal Of Infectious Diseases* **151**(5), 966–968 (1985).

[18] Hayden, F. G., Fritz, R. S., Lobo, M. C., Alvord, W. G., Strober, W., and Straus, S. E. Local and systemic cytokine responses during experimental human influenza A virus infection - Relation to symptom formation and host defense. *Journal of Clinical Investigation* **101**(3), 643–649 (1998).

[19] Fazekas De St Groth, S. and White, D. O. An improved assay for the infectivity of influenza viruses. *The Journal Of Hygiene* **56**(1), 151–62 (1958).

548 [20] McCullagh, P. and Nelder, J. A. *Generalized Linear Models*, volume 37 of *Monographs on*
549 *Statistics and Applied Probability*. CRC Press, 2nd edition, (1989).

550 [21] Dobson, A. J. and Barnett, A. G. *An Introduction to Generalized Linear Models*. Texts in
551 Statistical Science. CRC Press, 3rd edition, (2008).

552 [22] Gelman, A. and Hill, J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*.
553 Cambridge University Press, New York, (2007).

554 [23] Bolker, B. M., Brooks, M. E., Clark, C. J., Geange, S. W., Poulsen, J. R., Stevens, M. H. H.,
555 and White, J. S. S. Generalized linear mixed models: a practical guide for ecology and
556 evolution. *Trends In Ecology and Evolution* **24**(3), 127–135 (2009).

557 [24] Venables, W. N., Smith, D. M., and R Development Core Team. *An Introduction to R*. Net-
558 work Theory Ltd, (2007).

559 [25] Akaike, H. A new look at the statistical model identification. *IEEE Transactions On Auto-*
560 *matic Control* **19**(6), 716–723 (1974).

561 [26] Burnham, K. P. and Anderson, D. R. *Model selection and multimodel inference: A practical*
562 *information-theoretic approach*. Springer, New York, 2nd edition, (2002).

563 [27] Yang, Y., Sugimoto, J. D., Halloran, M. E., Basta, N. E., Chao, D. L., Matrajt, L., Potter, G.,
564 Kenah, E., and Longini Jr., I. M. The transmissibility and control of pandemic influenza A
565 (H1N1) virus. *Science* **326**, 729–733 (2009).

566 [28] Carrat, F., Vergu, E., Ferguson, N. M., Lemaitre, M., Cauchemez, S., Leach, S., and Valleron,
567 A.-J. Time lines of infection and disease in human influenza: A review of volunteer challenge
568 studies. *American Journal of Epidemiology* **167**(7), 775–785, March (2008).

569 [29] Dushoff, J., Plotkin, J. B., Viboud, C., Earn, D. J. D., and Simonsen, L. Mortality due
570 to influenza in the United States - an annualized regression approach using multiple-cause
571 mortality data. *American Journal of Epidemiology* **163**(2), 181–187 (2006).

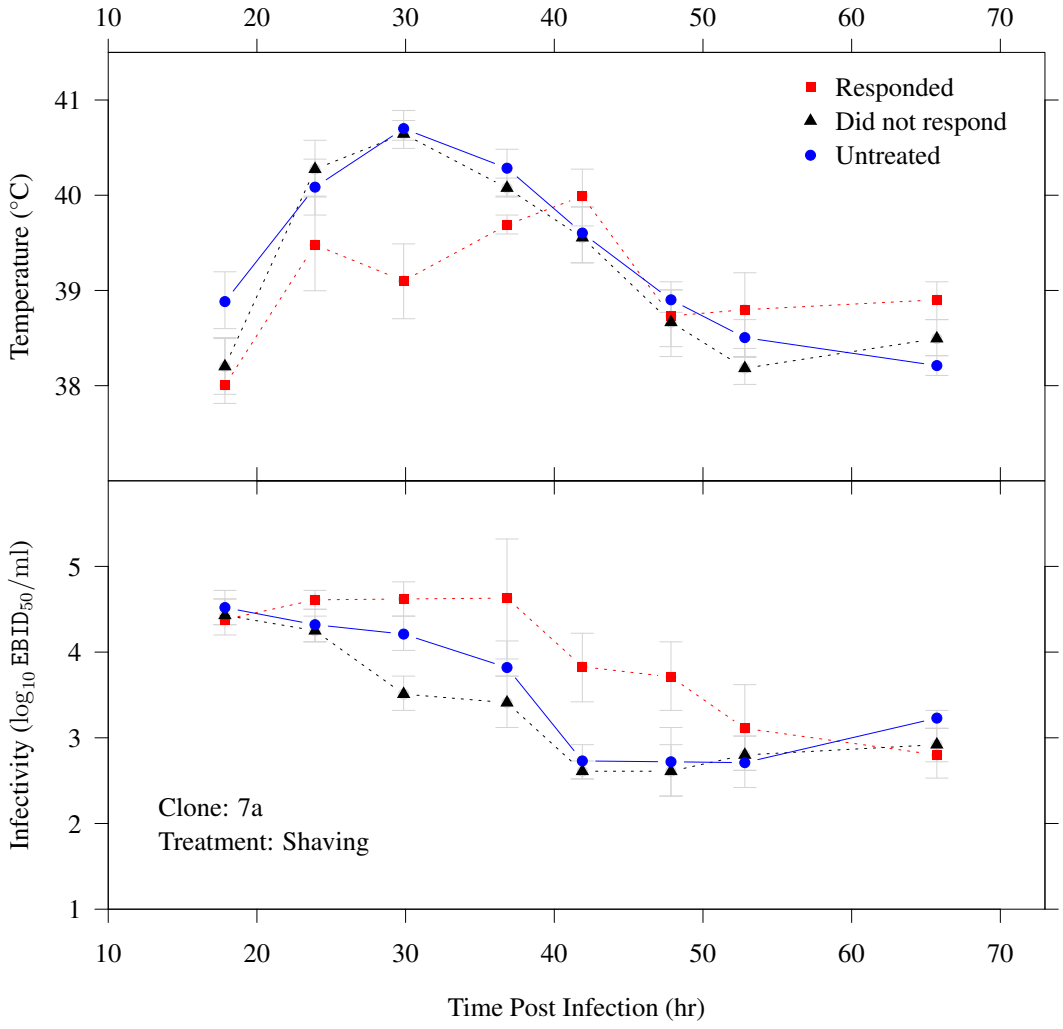

Figure S1: Data replotted from Figure 1 of Husseini *et al.* (1). Original caption: "Effect of shaving on mean increases in rectal temperature (*top*) and mean viral titers in nasal washes (*bottom*) of ferrets inoculated intranasally with 10^6 50% egg bit infectious doses ($\texttt{EBID}_{50}$) of clone 7a of the recombinant influenza virus A/Puerto Rico/8/34-A/England/939/69 (H3N2). Animals that responded to shaving (squares) did not have a febrile response (three ferrets; group 1), whereas animals that did not respond to shaving (triangles) (six ferrets; group 2) had a febrile response similar to that of animals that were not shaved (circles) (six ferrets; group 3). The bars represent $\texttt{SEM}$."

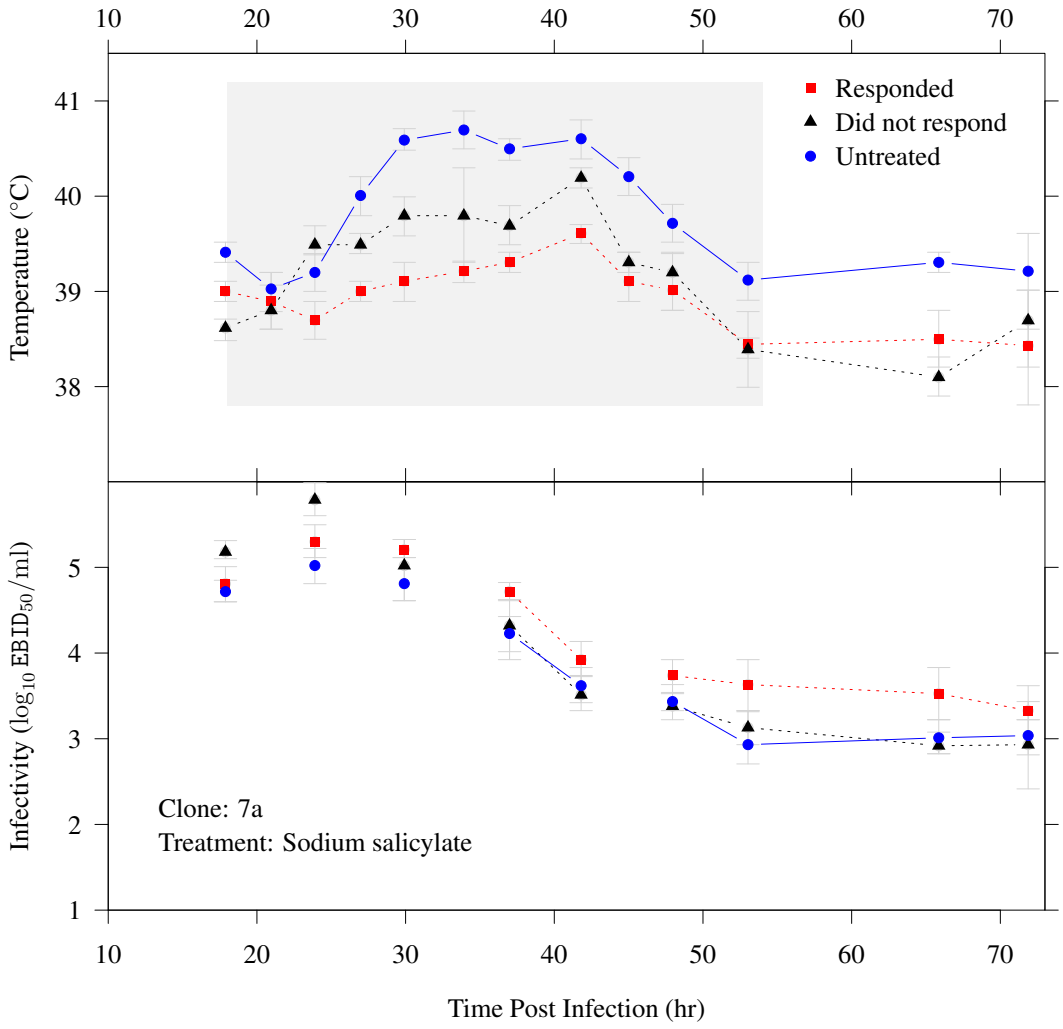

Figure S2: Data replotted from the left panels of Figure 2 of Husseini *et al.* (1). Original caption: "Effect of sodium salicylate on mean increases in rectal temperature (*top*) and mean viral titers in nasal washes (*bottom*) of ferrets inoculated intranasally with clone 7a…" See caption to Figure S1. Sample sizes: responded to treatment (8), did not respond to treatment (3), untreated (11). The time period highlighted in grey corresponds to the data we used in this paper (i.e., when the animals were under the influence of antipyretic medication).

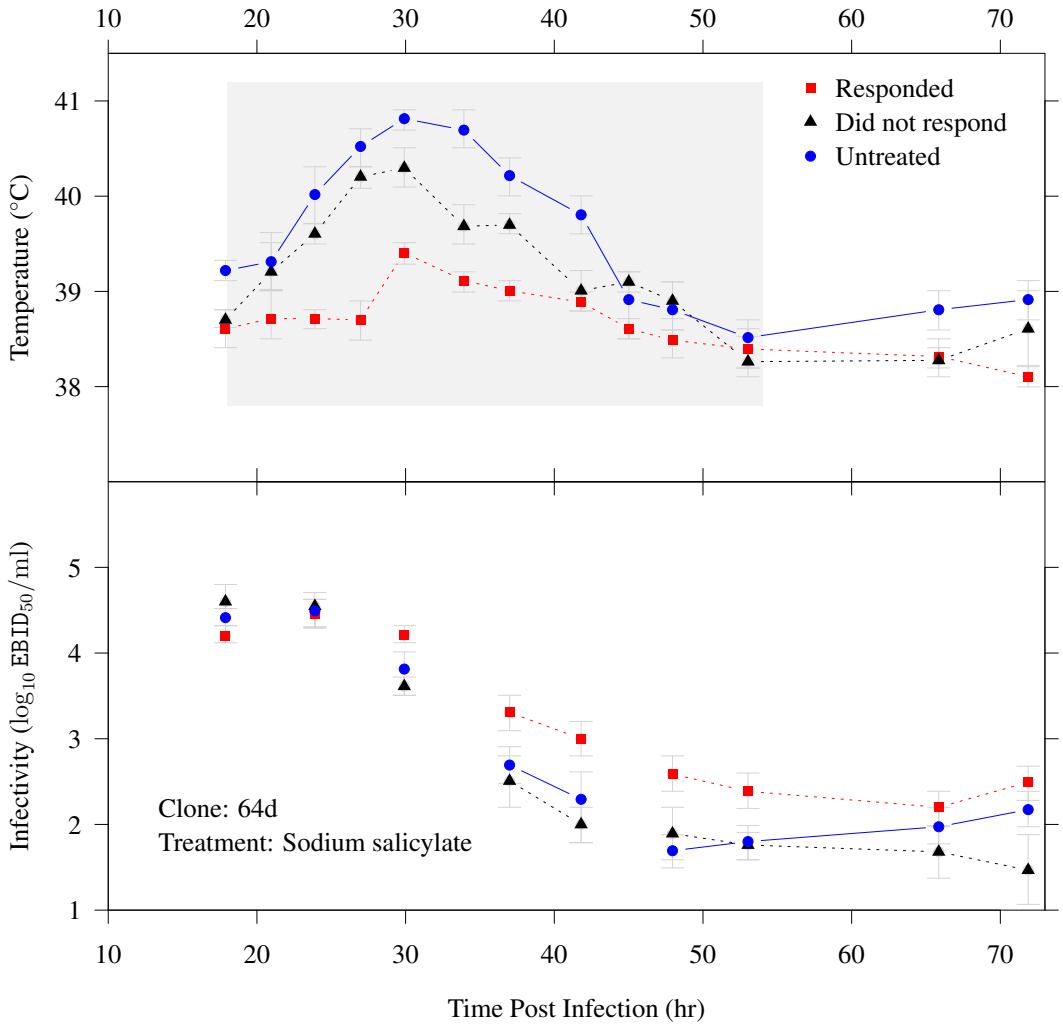

Figure S3: Data replotted from the right panels of Figure 2 of Husseini *et al.* (1). Original caption: "Effect of sodium salicylate on mean increases in rectal temperature (*top*) and mean viral titers in nasal washes (*bottom*) of ferrets inoculated intranasally with clone 64d…" See caption to Figure S1. Sample sizes: responded to treatment (6), did not respond to treatment (3), untreated (7). The time period highlighted in grey corresponds to the data we used in this paper (i.e., when the animals were under the influence of antipyretic medication).

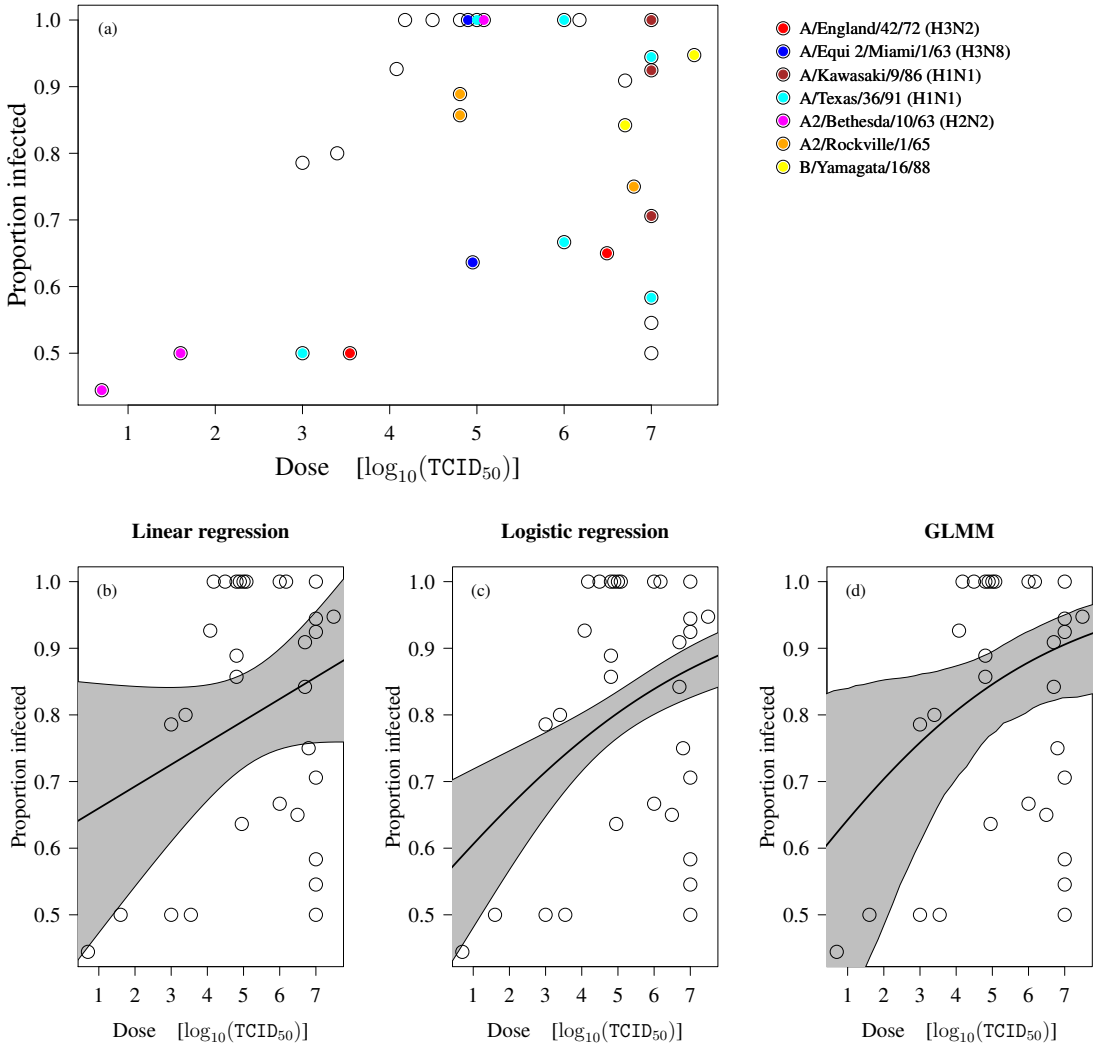

Figure S4: Data from the meta-analysis summarized in Table 1 of the review of Yezli and Otter (2). (a) The data, with colour-coding for strains that were used in more than one experiment. (b) Completely naïve linear regression and 95% confidence bands (§4.2). (c) Naïve logistic regression (§4.3). (d) Generalized linear mixed model (§4.4).