On-line Supplement for "The optimal composition of influenza vaccines subject to random production yields"

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Parameter estimation

Vaccine efficacy We assume a vaccine containing either strain (B/Yamagata or B/Victoria) is equally effective, i.e., $e_{11} = e_{22}$ and $e_{12} = e_{21}$. Based on several references, Nichol (2001) finds that the average vaccine efficacy for healthy working adults is 0.75 (or 0.35) in a year with a good (or poor) match between the vaccine and virus strains, and that the likelihood of a good match is 0.8. Since vaccine efficacy does not vary much among the population (Nichol 2003), we choose $e_{11} = e_{22} = 0.75$, $e_{12} = e_{21} = 0.35$, and $\bar{e} = 0.75 \times 0.8 + 0.35 \times 0.2 = 0.67$.

Prevalence of virus strains The Committee could develop its initial distribution about unknown prevalence θ by using multi-variant epidemic models such as Castillo-Chavez et al. (1989) or Andreasen et al. (1997). Based on the Committee meeting transcripts, however, it seems that the Committee does not use any forecast model (Committee 2003-2007) perhaps because of the difficulty in estimating parameters in those models – in particular, the parameters that capture seasonal trends (Earn et al. 2002). Especially, the epidemiology of two representative lineages of type B – B/Victoria and B/Yamagata – still remains poorly understood (Mizuta et al. 2004). While B/Yamagata lineage viruses predominated between 1990 and 2001, viruses from both lineages co-circulated since then. For this reason, it seems from the Committee meeting transcripts that the Committee selects a vaccine strain, hoping that the prevalence of the current season will match that of the next season. Thus, we assume that the Committee believes that each future virus isolate contains $s1$ with the probability θ.

Because no verifiable data about the Committee's beliefs exist, we choose the parameters for the initial distribution and future information to reflect some concerns of the Committee about a possible change of their initial estimate. For the initial distribution, we choose $\alpha + \beta = 2$ in our base case and vary this number in our sensitivity analysis. Figure 2 presented in the main body illustrates the initial distributions in which a higher value of $\alpha + \beta$ represents the Committee has more confidence in its initial estimate. We choose $N_2 = 10$ to reflect the concerns of the Committee about a possible late outbreak. Since a peak of virus activities is reached before the Committee's first meeting in a typical year (see Figure 3), we choose the remaining N_t so that it gradually decreases over time. Despite the Committee's concerns, however, there was no late outbreak (CDC 2007a) as illustrated in Figure 1 in the next page.

Vaccine supply The growth characteristic of the B/Victoria strain ($s1$) was "moderate", while that of the B/Yamagata strain ($s2$) was less known but considered "reasonable" (Committee 2004). So, the assumption of identical average yields between the two seems appropriate. Unfortunately, the mean value of the moderate yield is not directly available, so we estimate it based on the following quotes: "we actually found that at the end of the day the yield is still significantly lower than the B/Yamanashi [having the moderate growth characteristic], it is about 65 to 70%, in fact" (Committee 2001); "one low-yielding strain could mean as much as 20 million doses fewer for the

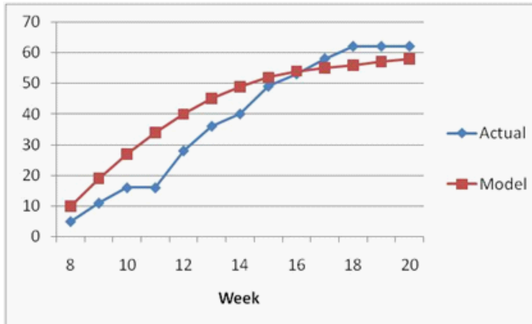

Figure 1: Comparison of model parameters with data for the cumulative number of specimens. Note: 'Actual' curve represents the weekly number of virus specimens of type B tested positive in 2004 by the WHO and National Respiratory and Enteric Virus Surveillance System collaborating laboratories in the U.S. (CDC 2007a). This number is always greater than the total number of virus specimens characterized as B/Victoria or B/Yamagata lineages. The latter data are unavailable.

market" (Committee 2003). The first quote indicates that the mean of the low yield is about 70%, and the second quote indicates that if we assume a total vaccine supply of 100 million doses, the mean of the low yield is about 20% lower than that of the moderate yield. Thus, we set μ to 0.9 in our base case.

The variance of a yield is less observable. Chick et al. (2008) use 0.16~0.45 for the standard deviation of a random yield and Corbett and Deo (2008) use 0~3.5 (0.64 in a base case) for the coefficient of variation. Since the coefficient of variation of a uniform random variable between 0 and 1.8 is 0.58, the estimates of Corbett and Deo (2008) seem a bit high. Note that these papers do not distinguish the yield of the current vaccine strain from that of a new candidate strain. Since it is said that a yield is "predictable" if retaining the current vaccine composition (Committee 2003-2006), we choose σ_1 of 0.1. We estimate σ_2 based on the following quote: "each new strain can yield anywhere from 50 to 120 percent of the average strain" (Committee 2003). Let $\tilde{y}_j$ denote the random variable representing the yield of strain j. If we assume $\tilde{y}_2$ follows a uniform distribution between $0.5\tilde{y}_1$ and $1.5\tilde{y}_1$, then the standard deviation of $\tilde{y}_2$ is 0.3. (Note that we use $1.5\tilde{y}_1$ instead of $1.2\tilde{y}_1$ to maintain the equal-mean assumption of $\tilde{y}_1$ and $\tilde{y}_2$.) Since the above quote does not take account of the possibility of a complete production failure, which happened to Chiron in 2004, we choose σ_2 of 0.4 in our base case conservatively (see Figure 8 (b) for the effect of σ_2 on the optimal policy).

The correlation of random yields among manufacturers is very difficult to measure. During the 2000-1 season, two out of three manufacturers had unanticipated problems growing the new strain, so there was a positive correlation. However, in 2004, one of two manufacturers completely failed production, which is a case of strong negative correlation. Thus, it is difficult to assert that either positive or negative correlation exists, so we assume $\rho = 0$ in our base case.

In 2004, two manufacturers, Aventis and Chiron, produced 55 million and 48 million, respectively, before the British regulatory authorities prohibited the sale of Chiron's vaccines (Offit 2005). Thus, we set n to 2 and assume symmetric manufacturers. Evidence in 2006 (discussed in the main body) suggests that approximately 5 million doses were brought to a market in each week, so the production rate r of 5.55 million eggs per week is chosen to have the industry capacity of 5 million doses per week ($= 5.55 \times 0.9$). Since manufacturers have two different production campaigns for 6 months (Gerdil 2003), we choose $T = 25$ (weeks), assuming 24 weeks of continuous production.

Then the maximum output of the industry is 120 million doses, which is greater than the industry actually produced before the approval of the regulatory authorities because the manufacturers are capable of producing more after the release of those lots.

We use the same unit production cost (c_1) of \$3 as Corbett and Deo (2008).

Vaccine demand We assume that each individual consumes at most one dose of vaccine every year as one dose of vaccine is recommended for people older than 6 months except for children younger than 9 years old who receive vaccine for the first time (Nichol 2003). The parameters $\bar{a}$ and $\bar{b}$ in the demand function $\bar{p} = \bar{a} - \bar{b}\tilde{q}_{t,j}$ are constructed as follows. Let v denote the perceived value of vaccination of an individual. Then $v = \tilde{e}\tilde{c}_2 - c_3$. If the price of a vaccine is $\bar{p}$, then individuals with values above $\bar{p}$ get vaccinated. Thus, the demand D in the population of size S is given by

$$D(\bar{p}) = S \times \Pr[v > \bar{p}] = S\left(1 - \frac{\bar{p} + c_3}{2\bar{c}_2\bar{e}}\right)$$

When vaccines are brought to a market, a market-clearing price $\bar{p} = \bar{a} - \bar{b}\tilde{q}_{t,j} = (2\bar{c}_2\bar{e} - c_3) - \frac{2\bar{c}_2\bar{e}}{S}\tilde{q}_{t,j}$ is determined by setting $\tilde{q}_{t,j} = D(\bar{p})$ and solving for $\bar{p}(\tilde{q}_{t,j})$.

When a randomly-chosen individual is informed with probability x in section 5.2.2, the expectation about random vaccine efficacy affects demand. Let v' denote the value of vaccination of an informed individual. Then $v' = e_j(\hat{\theta})\tilde{c}_2 - c_3$. Then the demand D' is given by

$$D(\bar{p}) = (1-x)S \times \Pr[v > \bar{p}] + xS \times \Pr[v' > \bar{p}] = (1-x)S\left(1 - \frac{\bar{p} + c_3}{2\bar{c}_2\bar{e}}\right) + xS\left(1 - \frac{\bar{p} + c_3}{2\bar{c}_2 e_j(\hat{\theta})}\right).$$

Similarly, we can derive $\bar{a}$ and $\bar{b}$ in this case.

To compute $\bar{a}$ and $\bar{b}$, we first estimate $\bar{c}_2$. We use the expected costs of infection in Table A1 for different age and health-risk groups estimated by Weycker et al. (2005). Table A1 reports the estimated vaccine coverage rates when vaccine price is \$9. We compute the total vaccine coverage, assuming the expected cost of infection is uniformly distributed within the population. Similarly, we compute the vaccine coverage of each subgroup, assuming the expected cost of infection is uniformly distributed within the group. Comparing the estimated coverage with the actual coverage shown in Table A2, we find that when '$\bar{c}_2 = \mathbf{a} + \mathbf{b} + \mathbf{c}$' (i.e., the perceived cost equals the true cost), the vaccine coverage in total is much higher than the actual coverage. In particular, the coverage of 0˜64 years is overestimated primarily because individuals do not internalize their indirect costs of infection due to work loss (**b**) and death (**c**). To reduce this discrepancy, we set $\mathbf{c} = 0$ and proportionally reduce **b** until the total demand approaches 103 million doses, the amount the industry actually produced. We set the expected perceived cost of infection, $\bar{c}_2$, to \$18, which is the weighted average of '**a** + 0.5**b**' among the entire population, whereas we set its true mean c_2 to \$41 (= **a** + **b** + **c**). Nichol (2001) estimates an indirect cost of vaccination of \$6.69 for healthy working adults. For simplicity, we choose the indirect cost of vaccination (c_3) of \$7. Then we obtain $(\bar{a}, \bar{b}) = (17.1,\ 0.8 \times 10^{-7})$, which results in $q_2^* = 101$ million doses and $\bar{p} = \$9$ in equilibrium. Note that the actual coverage during the 2004-5 season turned out to be much lower due to the Chiron's production failure. The (catalog) price of flu vaccine in December, 2004 was \$8.5 per dose (CDC 2007a).

Table A1. Vaccine coverage rates estimated by the model for different values of $\bar{c}_2$.

	0~4 years	5~18 years		19~64 years		65~years	Total
		Healthy	Risky	Healthy	Risky		
Cost data from Weycker et al. (2005) ($)							
Exp. healthcare cost (**a**)	36	7	19	4	14	19	18
Exp. work loss cost (**b**)	19	33	33	19	19	4	10
Exp. lost earnings (**c**)	4	2	38	9	69	0	13
Population (%)	7%	16%	2%	52%	11%	12%	100%
Estimated vaccine coverage							
$\bar{c}_2 = \mathbf{a} + \mathbf{b} + \mathbf{c}$	67%	72%	87%	61%	88%	48%	71%
$\bar{c}_2 = \mathbf{a} + \mathbf{b}$	63%	70%	77%	47%	64%	48%	57%
$\bar{c}_2 = \mathbf{a} + 0.5\mathbf{b}$	47%	50%	67%	20%	49%	44%	34%

Note: *Population (%)* is based on the U.S. population estimates in 2005 (U.S. Census Bureau 2006) and the proportion of healthy population of 90% (Weycker et al. 2005).

Table A2. Vaccine coverage rates from surveys.

	6~23 months	2~17 years		18~64 years		65~years	Total
		Healthy	Risky	Healthy	Risky		
2003-2004				21%	31%	65%	28%
2004-2005	48%	12%	35%	11%	22%	60%	19%

Sources: 6 months~17 years (CDC 2005), 18~ years (National Health Interview Survey 2005), and total (Strikas 2005).
Note: Surveys for pediatric groups began from the 2004-2005 season. Vaccine coverage in the 2004-2005 season was lower than that in a typical year because of a significant vaccine shortage.

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