Morphologic and Molecular Characterization of New *Cyclospora* Species from Ethiopian Monkeys: *C. cercopitheci* sp.n., *C. colobi* sp.n., and *C. papionis* sp.n.

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In recent years, human cyclosporiasis has emerged as an important infection, with large outbreaks in the United States and Canada. Understanding the biology and epidemiology of *Cyclospora* has been difficult and slow and has been complicated by not knowing the pathogen's origins, animal reservoirs (if any), and relationship to other coccidian parasites. This report provides morphologic and molecular characterization of three parasites isolated from primates and names each isolate: *Cyclospora cercopitheci* sp.n. for a species recovered from green monkeys, *C. colobi* sp.n. for a parasite from colobus monkeys, and *C. papionis* sp.n. for a species infecting baboons. These species, plus *C. cayetanensis,* which infects humans, increase to four the recognized species of *Cyclospora* infecting primates. These four species group homogeneously as a single branch intermediate between avian and mammalian *Eimeria*. Results of our analysis contribute toward clarification of the taxonomic position of *Cyclospora* and its relationship to other coccidian parasites.

Cyclospora cayetanensis, a coccidian parasite recently described as a human pathogen causing prolonged watery diarrhea (1), has been identified as the cause of large, multistate outbreaks of diarrhea in the United States associated with imported produce, most notably raspberries (2,3). Molecular phylogenetic analysis showed that *Cyclospora* is closely related to *Eimeria* species (4), especially to mammalian *Eimeria* species (5). The parasite has been reported from many geographic regions but seems to be endemic in tropical countries. Recent foodborne outbreaks in the United States and Canada have generated considerable scientific interest and numerous questions about this organism; one of the most perplexing has to do with the possible role of other animals in harboring the infection and serving as a source of contamination.

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In 1996, Smith and colleagues reported the presence of *C. cayetanensis*-like oocysts in the feces of 37 of 37 baboons and 1 of 15 chimpanzees examined from the Gombe National Park, Tanzania. Other reports have documented *C. cayetanensis*-like oocysts in fecal samples from chickens in Mexico (6), a duck in Peru (7), and dogs in Brazil (8). However, only the Smith report (9) suggests a true natural host.

During spring 1997, we collected stool samples from free-ranging baboons (*Papio anubis*) and colobus monkeys (*Colobus guereza*) in Wollega Province in western Ethiopia. A high percentage of samples were positive for *Cyclospora* oocysts, but the organism, including sporulated oocysts, could not be completely described because the samples were fixed in formalin. In spring 1998, we returned to Wollega Province, collected additional stool samples from three species of primates (baboons, colobus, and African green monkeys [*Cercopithecus aethiops*]), and placed these samples in potassium dichromate

for subsequent biologic and molecular studies. This report describes the results of those collections, provides molecular phylogenetic analysis, and names the newly identified parasites.

The Study

We collected stool samples from troops of baboons and green monkeys by following them as they foraged and from colobus monkeys by quietly waiting under trees in which monkeys were sitting. Only fresh stool samples were collected, and in neither situation was it possible to determine the age or sex of the animal that produced the sample. On several occasions, samples from more than one animal of the same species were pooled; these are referred to as composite samples.

In the collections from 1997, each stool sample was placed directly in 10% formalin. In the collections from 1998, all stool samples were suspended in water and allowed to settle. The sediment was sieved and resuspended in clean water. The resulting sediment was mixed with a 2.5% aqueous (w/v) potassium dichromate ($K_2Cr_2O_7$) solution in a 3:1 ratio and allowed to settle. The supernatant was discarded, and fresh potassium dichromate solution was added in a 3:1 ratio. The potassium dichromate-stool mixture was kept at room temperature in 50-ml conical centrifuge tubes and returned to Atlanta.

The *C. cayetanensis* oocysts used in comparative studies were collected from stools from a 1997 Florida outbreak linked to consumption of Guatemalan raspberries and from stools collected in Leogane, Haiti.

DNA Extraction

DNA was extracted from 500-µl aliquots of stool samples, following the protocol of da Silva et al. (10). Extracted DNA was stored at 4°C until polymerase chain reaction (PCR) amplification was performed on the small subunit ribosomal RNA (SSU-rRNA) coding region of the genome. Both strands of PCR products were sequenced directly by using an automated DNA sequencer. We used a nested PCR protocol with primers CYCF1E and CYCR2B for the first step of the amplification and primers CYCF3E and CYCR4B for the second (11).

Results

Examination of stools collected in 1997 showed that 15 (68%) of 22 baboons and 9 (60%) of 15 colobus monkeys had detectable *Cyclospora* infections. In individual stool samples collected in 1998, 10 (50%) of 20 baboons, 0 of 11 colobus monkeys, and 1 (6%) of 16 green monkeys had detectable infections with *Cyclospora*. In composite stool samples collected in 1998, 2 (100%) of 2 baboon, 1 (50%) of 2 colobus monkey, and 0 of 3 green monkey samples tested positive for *Cyclospora*.

Sequencing of the SSU-rRNA Coding Region and Phylogenetic Analysis

SSU-rRNA sequences amplified from the *C. cayetanensis* isolates from Haiti and Florida were identical and showed seven differences from the sequence described by Relman et al. (4). Three of these differences correct previously unresolved bases: A at positions 400 and 549, and G at position 1694. Two other differences most probably correct a sequencing error, as they constitute an inversion next to an unresolved position (T at position 1695 and G at position 1696). The significance of the two remaining differences at positions 696 and 1360 is unknown at this time. The new sequence for *C. cayetanensis* SSU-rRNA coding region was deposited in GenBank and assigned accession number AF111183 (Table).

SSU-rRNA sequences obtained for two baboon isolates were identical. The colobus and baboon *Cyclospora* isolates were assigned GenBank accession numbers AF111186 and AF111187, respectively. Sequencing of SSU-rRNA coding region of *C. cercopitheci* from a single African green monkey specimen showed a heterozygotic position, T/A at position #280. This may reflect mixed infection with two closely related isolates or may represent polymorphism among several copies of this gene in a single isolate. Thus, both green monkey SSU-rRNA sequences were submitted separately to GenBank and were assigned accession numbers AF111184 for the green monkey *Cyclospora* sequence #1 and AF111185 for sequence #2 (Table).

The phylogenetic trees generated by the PUZZLE and PAUP programs displayed similar topologic features and demonstrated that on the basis of the SSU-rRNA the *Cyclospora* isolates from monkeys are distinct from each other and from *C. cayetanensis* of humans (Figure 1). The sequence identities between the human isolate with the baboon, colobus monkey, and green monkey isolates 1 and 2 were 98.6%, 98.7%, and

Table. New *Cyclospora* species from Ethiopian monkeys

Characteristics	*Cyclospora cercopitheci*	*C. colobi*	*C. papionis*
Host	*Cercopithecus aethiops* Linnaeus, 1758, African green or vervet monkey	*Colobus guereza* Ruppell, 1835, colobus monkey	*Papio anubis* Lesson, 1827, olive baboon
Oocysts	Spherical; 8 - 10 µm (mean 9.2) in diameter. Outer wall smooth. Wall autofluoresces in UV wavelength.	Small, spherical, 8 - 9 µm (mean 8.3) in diameter. Outer wall smooth. Wall autofluoresces in UV wavelength.	Spherical, 8 - 10 µm (mean 8.8) in diameter. Outer wall smooth. Wall autofluoresces in UV wavelength.
Sporocysts	Two per mature oocyst Lemon-shaped, 6-7 by 4-5 µm, with L/W ratio 1.5	Two per mature oocyst Lemon-shaped, 7-8 by 4-5 µm, with L/W ratio 1.66	Two per mature oocyst Lemon-shaped, 7-8 by 4-5 µm, with L/W ratio ratio 1.66
Stieda bodies	A prominent stieda body present; sub- and parastieda bodies absent	A prominent stieda body present; sub- and parastieda bodies absent	A prominent stieda body present; sub- and parastieda bodies absent
Sporocyst residuum	Prominent; made up of clumped globules	Prominent, irregularly shaped; 2-4 µm in diameter	Prominent, irregularly shaped; 2-3 by 3-4 µm in diameter
Micropyle	Absent	Absent	Absent
Sporozoites	Two per sporocyst 10-13 by 1.5 µm; tapered at both ends	Two per sporocyst 10-13 by 2 µm; tapered at both ends	Two per sporocyst 10-13 by 1.5 µm; tapered at both ends
Remarks	Marginally larger than other two species Heterozygotic position, T or A at position #280; therefore, SSU-rRNA sequences submitted separately. Assigned accession nos. AF111184 and AF111185	Marginally smaller than the two other species Sequence of SSU-rRNA assigned accession no. AF111186. Poorest sporulation rate of three species	The most commonly encountered of the three species. Sequence of SSU-rRNA assigned accession no. AF111187

98.4%, respectively. The phylogenetic relationship observed between *Cyclospora* and *Eimeria* species confirmed previous findings (4,5) with three distinct clades: avian *Eimeria*, mammalian *Eimeria*, and *Cyclospora*.

Conclusions

The genus *Cyclospora* was formed by Schneider in 1881 for organisms recovered from myriapods (terrestrial arthropods in the subphylum Mandibulata, Class Diplopoda [millipedes] and Class Chilopoda [centipedes]). Most knowledge about the genus *Cyclospora* is based on recently recognized species described from insectivores (moles) (12), heteromyid rodents in the southwestern United States (13), and humans (1).

In 1994, Ortega and colleagues described *C. cayetanensis* from human fecal material in Peru. In 1997, they described the parasite's intracellular life cycle in the duodenum and jejunum (14). *C. cayetanensis* differs significantly from all other described species not only in its host but also in its oocyst stage, which is much smaller and spherical rather than oblong. The recovery from nonhuman primates of other species of *Cyclospora* that produce small, spherical oocysts seems to suggest two distinct groupings: species that infect insectivores and rodents and produce large, oblong oocysts and those that infect primates (including humans) and produce small, spherical oocysts.

The geographic and host range for *C. papionis*, *C. colobi*, and *C. cercopitheci* needs to be defined. These primate species of *Cyclospora* are easily distinguished at the molecular level, but not at the light-microscope level. That *C. papionis*,

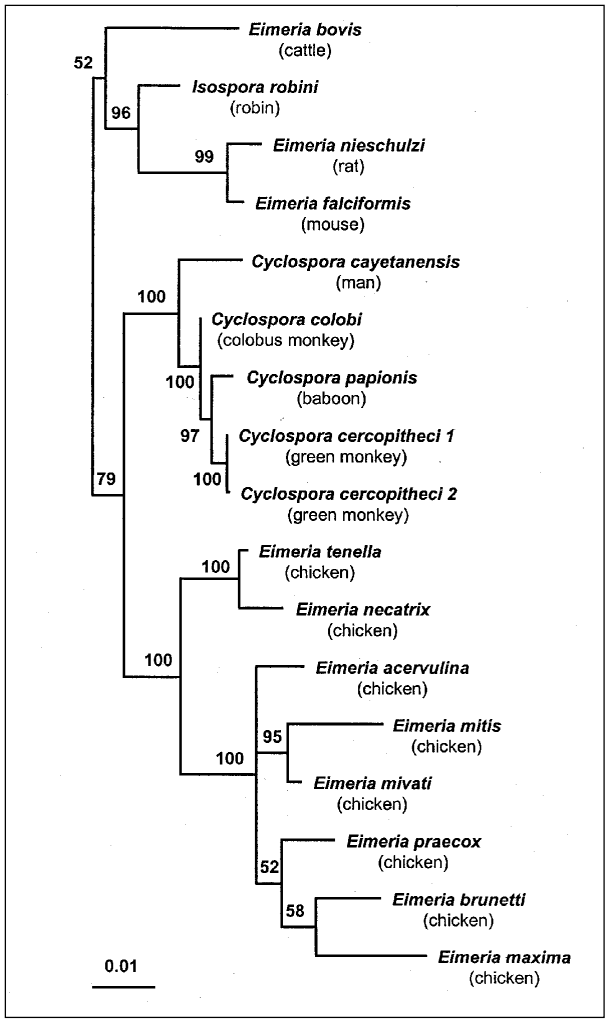


Figure 1.[1] Phylogenetic tree for small subunit ribosomal RNA sequences of *Cyclospora* and *Eimeria* species. Quartet puzzling maximum likelihood results are shown, with *Toxoplasma gondii* as the outgroup. After analysis, the outgroup branch was removed for clarity. Numbers to the left of the nodes indicate the quartet puzzling support for each internal branch. The scale bar indicates an evolutionary distance of 0.01 nucleotides per position in the sequence. Vertical distances are for clarity only. GenBank accession numbers of the sequences used for analysis: *Cyclospora cayetanensis,* AF111183; *C. cercopitheci* 1, AF111184; *C. cercopitheci* 2, AF111185; *C. colobi,* AF111186; *C. papionis,* AF111187; *Eimeria acervulina,* U67115; *E. bovis,* U77084; *E. brunetti,* U67116; *E. falciformis,* AF080614; *E. maxima,* U67117; *E. mitis,* U40262; *E. mivati,* U76748; *E. necatrix,* U67119; *E. nieschulzi,* U40263; *E. praecox,* U67120; *E. tenella,* U40264; *Isospora robini,* AF080612; and *Toxoplasma gondii,* U12138. The sequences were aligned with the program CLUSTALW (20). Phylogenetic analysis was done with the maximum likelihood method-based PUZZLE program (21), as well as with the parsimony method-based PAUP program (22). Unreliably aligned regions were removed, and the final length of the alignment was 1692 columns. Aligned sequences are available from the authors upon request.

C. colobi, and *C. cercopitheci* are species distinct from each other and from *C. cayetanensis* of humans is well substantiated, considering the molecular phylogeny based on the SSU-rRNA sequence data. This assumes that the differences in SSU-RNA reflect distinct species. For the time being, this method is probably the best for defining morphologically similar species. The separation of these parasite species is further supported by the distinct separation of the primate species on biologic grounds. Baboons are omnivorous, spend most of their time on the ground foraging for food, and have relatively large home ranges. Green monkeys spend a greater amount of time in trees but do forage on the ground. The canopy-dwelling colobus monkeys, on the other hand, have the smallest home range and are strict herbivores, predominantly eating leaves of certain trees.

The *Cyclospora* observed in baboons from Tanzania (9) is likely the same species as *C. papionis* from Ethiopia. A high percentage of baboons in the Gombe Stream Preserve are infected with a *Cyclospora* species indistinguishable from *C. papionis* (pers. obs.; Whittier, pers. comm.). Moreover, three sequences from Gombe baboon isolates submitted recently to GenBank (15) show only one base change from our sequence with each isolate (C to T at #1360 with

[1]Initially, we used a nested PCR protocol using primers CYCF1E and CYCR2B for the first step of the amplification and primers CYCF3E and CYCR4B for the second step (11). Samples were also amplified by using sets of PCR primers designed on the basis of the primers described above, but with the restriction sites removed. The primer CYCF1 (5'-ATTACCCAATGAA AACAGTTT- 3') was used in pairs with the primer CYCR4 (5'-TCGTCTTCAAACCCCCTACTG-3') to generate a DNA fragment of 577 bp. The other pair of primers, CYCF3 (5'-GCCTTCCGCGCTTCGCTGCGT-3') and CYCR2 (5'-TGC AGGAGAAGCCAAGGTAGG-3') was used to generate a fragment of 283 bp. To generate fragments spanning the full length of the SSU-rRNA coding region, we used generic apicomplexan PCR primer CRYPTOF (5'-AACCTG GTTGATCCTGCCAGT-3'), specific for the 5' end of the SSU-rRNA molecule and the apicomplexan generic PCR primer CRYPTOR (5'-GCTTGATCCTTCTGCAGGTTCACC TAC-3'), specific for the 3' end of this molecule. These generic primers were combined with the *Cyclospora*-specific primers (CYC-series, see above) to amplify overlapping fragments spanning the whole SSU-rRNA molecule. PCR products were analyzed by electrophoresis on 2% SeaKem GTG agarose (Cat. No. 50074, FMC Bioproducts, Rockland, ME), stained with ethidium bromide and visualized on a UV transilluminator.

sequences AF065566 and AF065567; C to T at #184 with AF065568), if unresolved base positions in their sequences are disregarded (three positions in AF065566 and AF065567 and six positions in AF065568).

The topology of the tree (Figure 1) displays the distinct *Cyclospora* species as a monophyletic branch with phylogenetic proximity to the genus *Eimeria*. The proximity between these coccidian genera has been demonstrated (4,5); we included in the tree an additional SSU-rRNA sequence of *E. falciformis*, a parasite of mice. The addition of this species clarified the resolution of the tree into three distinct clades: mammalian *Eimeria*, avian *Eimeria*, and *Cyclospora*. With the addition of molecular data for more species, especially the species of *Cyclospora* described from mammals other than primates, it may be reasonable to consider reclassifying the *Cyclospora* of primates (including humans) and either the bird or mammalian *Eimeria* to a new genus. However, morphologic and molecular taxonomists continue to struggle with the relationships within the coccidia. Morphologic criteria for naming the genera have provided a stable basis for many years. On the other hand, molecular data, based on the genetic information of these same organisms, suggest affiliations that do not always coincide with the existing associations based on morphologic features. Sterling and Ortega (16) suggest that small subunit rRNA sequences of *Isospora* should be compared with those of *Cyclospora* to help clarify taxonomic issues. They also point out the role of molecular taxonomy in establishing the validity of species and taxonomic groupings. Carreno and Barta (17) provided sequencing data for several species of *Isospora* and demonstrated the phylogenetic separation of various clades of *Isospora,* both with and without Stieda bodies. They propose separating mammalian species with Stieda bodies into the family Eimeriidae and retaining those without Stieda bodies in the family Sarcocystidae. We included sequences of *I. robini* in our analysis, and *Cyclospora* remains as a clearly separate grouping.

On the basis of the topology of the tree and the distance values obtained, the simian isolates are more closely related to each other than to *C. cayetanensis* of humans. This undoubtedly reflects host differences as well as other biologic features of each species. However, further molecular studies are needed to demonstrate whether these *Cyclospora* species described from lower primates occur in humans, or conversely, whether *C. cayetanensis* can occur in monkeys. At least in East Africa, researchers should continue to evaluate material collected from humans and nonhuman primates with care. We are continuing our efforts to determine whether other primate species are infected with these or distinct species of *Cyclospora*. Studies of human isolates of *C. cayetanensis* from different geographic regions have, thus far, not demonstrated any molecular differences. This further substantiates the taxonomic significance of the molecular differences detected between the *Cyclospora* from humans and lower primates.

Appendix I

Stool Processing Procedures

Stool samples collected in 1997 were processed by a conventional formalin-ethyl acetate sedimentation concentration procedure. A portion of the sediment was examined by UV fluorescent microscopy (18). Some positive samples were also stained by the acid-fast or hot safranin techniques (19). For stools collected in 1998, an aliquot of each sample was washed because potassium dichromate suppresses the autofluorescence of the oocysts. Any oocysts observed in the samples examined from the collection of 1998 were graded as either sporulated or unsporulated. Part of the remaining specimen in potassium dichromate was processed over sucrose gradient to harvest oocysts. Purified oocysts were returned to clean 2.5% potassium dichromate solution for storage, and portions of the purified oocysts were used for morphologic studies.

To excyst sporocysts and sporozoites, one of two procedures was used. If the intent was to obtain free sporocysts, but not sporozoites, a small drop of solution containing oocysts was placed on a glass slide and covered. To induce rupture of the oocyst wall, the coverslip was tapped with a blunt glass rod and then rotated on the slide. To obtain free sporozoites, one of two excysting fluids were used: either a solution made up in DMEM containing 0.25% trypsin plus 0.75% sodium taurocholate or a solution made up in PBS containing 0.25% trypsin, 0.75% sodium taurocholate, and 20 mM cystine HCl. Both solutions worked equally well. The oocysts were incubated in the excysting fluid for 2 hours in a heat block at 37°C.

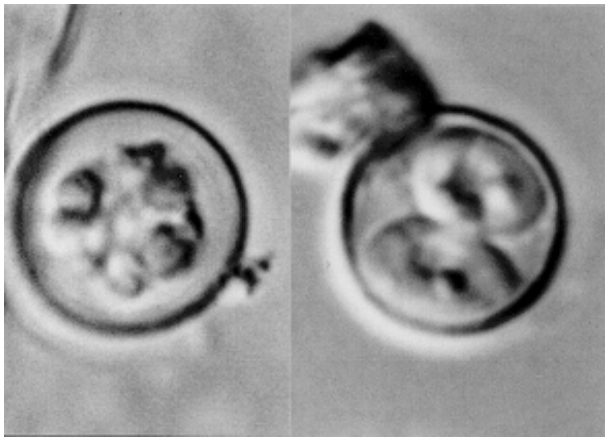
Appendix II

Taxonomic Description of the Parasites

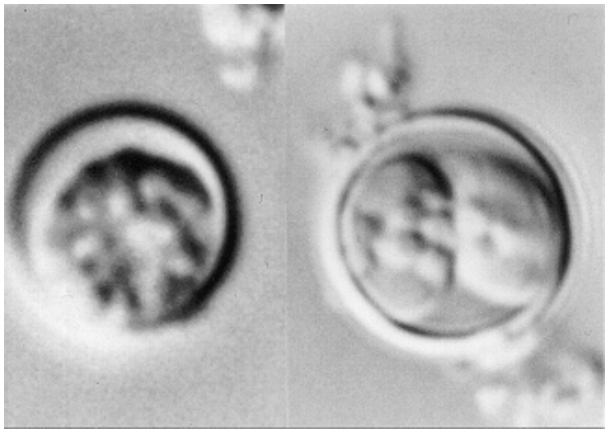
***Cyclospora cercopitheci* sp.n.** (Figures 2–3, 9)
Type host: *Cercopithecus aethiops* Linnaeus, 1758, African green or vervet monkey.
Type locality: Gimbie, Wollega Province, Ethiopia.
Prevalence: found in 6% of green monkeys sampled.
Site of infection: Unknown, oocysts collected from feces.
Material deposited: Phototypes and syntypes, U.S. National Parasite Collection, accession number 088837.
Etymology: The species name was derived from the genus name for the primate host from which this parasite was recovered.
Remarks: Sequencing of SSU-rRNA coding region of *C. cercopitheci* from a single African green monkey specimen revealed that there was a heterozygotic position, T or A at position #280. Thus, SSU-rRNA sequences for these two isolates were submitted separately to GenBank and were assigned accession numbers AF111184 for *C. cercopitheci* sequence #1 and AF111185 for *C. cercopitheci* sequence #2.

***Cyclospora colobi* sp.n.** (Figures 4–5, 10)
Type host: *Colobus guereza* Ruppell, 1835, colobus monkey.
Type locality: Gimbie, Wollega Province, Ethiopia.
Prevalence: Up to 60% of colobus monkeys sampled.
Site of infection: Unknown, oocysts collected from feces.
Material deposited: Phototypes and syntypes, U.S. National Parasite Collection, accession number 088838.
Etymology: The species name was derived from the genus name of the primate host from which this parasite was recovered.
Remarks: This species is marginally smaller than the two other species described from monkeys, but the overlap in sizes between the species does not allow a clear distinction on the basis of size. Sporulation of material collected from colobus monkeys was poor in comparison with *C. papionis* from baboons, despite the fact that material was collected and handled in a similar fashion. Sequence of the SSU-rRNA coding region for this species was deposited in GenBank and was assigned accession number AF111186.

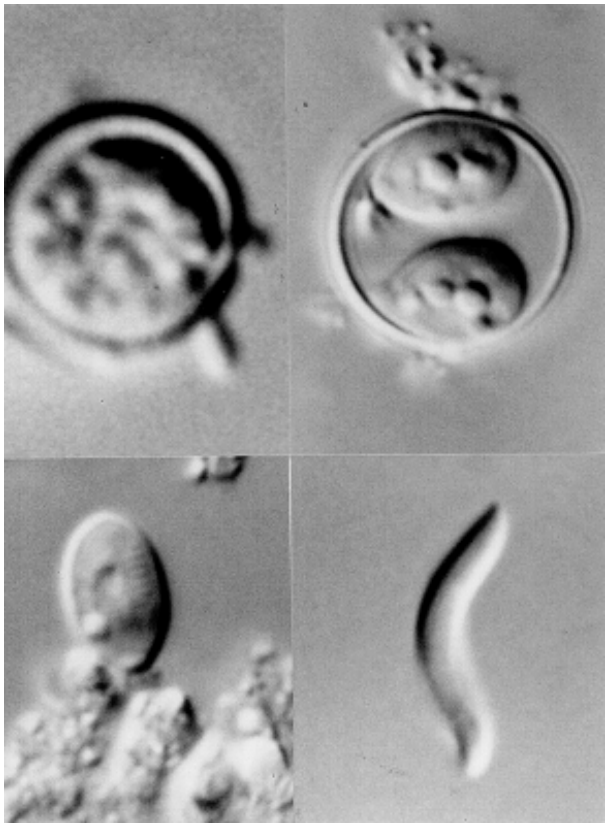
***Cyclospora papionis* sp.n.** (Figures 6–9, 11)
Type host: *Papio anubis* Lesson, 1827, olive baboon.
Type locality: Gimbie, Wollega Province, Ethiopia.
Prevalence: Found in >50% of baboons sampled.
Site of infection: Unknown, oocysts collected from feces.
Material deposited: Phototypes and syntypes, U.S. National Parasite Collection, accession number 088839.
Etymology: The species name was derived from the genus name for the primate host from which this parasite was recovered.
Remarks: More than 90% of the oocysts collected from baboons underwent sporulation in virtually all of the positive samples. Sequence of the SSU-rRNA coding region for this species was deposited in GenBank and was assigned accession number AF111187.



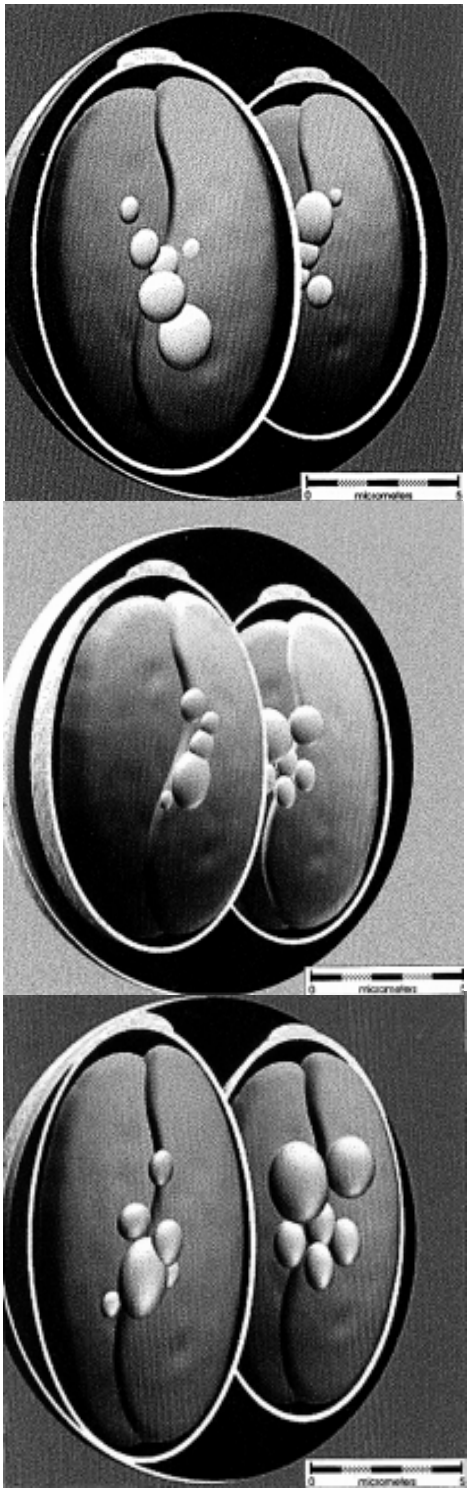
Figures 2–3. Photomicrographs of *Cyclospora cercopitheci* sp. n. from feces of African green monkeys (*Cercopithecus aethiops*) in Ethiopia, Africa. x 3300. 2. Unsporulated oocyst from feces. 3. Sporulated oocyst after 1 month of incubation.



Figures 4–5. Photomicrographs of *Cyclospora colobi* sp. n. from feces of colobus monkeys (*Colobus guereza*) in Ethiopia, Africa. x 3300. 4. Unsporulated oocysts from feces. 5. Sporulated oocyst after 1 month of incubation.



Figures 6–9. Photomicrographs of *Cyclospora papionis* sp. n. oocysts from feces of baboons (*Papio anubis*) in Ethiopia, Africa. x 3300. 6. Unsporulated oocysts from feces. 7. Sporulated oocyst after 1 month of incubation. 8. Free sporocyst from ruptured oocyst. 9. Free sporozoite from ruptured sporocyst.



Figures 10–12. Line drawings of sporulated oocysts of *Cyclospora* from feces of primates in Ethiopia, Africa. Bar = 5 µm. 10. *Cyclospora cercopitheci* sp. n. from African green monkeys, *Cercopithecus aethiops*. 11. *Cyclospora colobi* sp. n. from colobus monkeys, *Colobus guereza*. 12. *Cyclospora papionis* sp. n. from baboons, *Papio anubis*.

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Morphologic and Molecular Characterization of New *Cyclospora* Species from Ethiopian Monkeys: *C. cercopitheci* sp.n., *C. colobi* sp.n., and *C. papionis* sp.n.

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Appendix I

Stool Processing Procedures

Stool samples collected in 1997 were processed by a conventional formalin-ethyl acetate sedimentation concentration procedure. A portion of the sediment was examined by UV fluorescent microscopy (18). Some positive samples were also stained by the acid-fast or hot safranin techniques (19). For stools collected in 1998, an aliquot of each sample was washed because potassium dichromate suppresses the autofluorescence of the oocysts. Any oocysts observed in the samples examined from the collection of 1998 were graded as either sporulated or unsporulated. Part of the remaining specimen in potassium dichromate was processed over sucrose gradient to harvest oocysts. Purified oocysts were returned to clean 2.5% potassium dichromate solution for storage, and portions of the purified oocysts were used for morphologic studies.

To excyst sporocysts and sporozoites, one of two procedures was used. If the intent was to obtain free sporocysts, but not sporozoites, a small drop of solution containing oocysts was placed on a glass slide and covered. To induce rupture of the oocyst wall, the coverslip was tapped with a blunt glass rod and then rotated on the slide. To obtain free sporozoites, one of two

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excysting fluids were used: either a solution made up in DMEM containing 0.25% trypsin plus 0.75% sodium taurocholate or a solution made up in PBS containing 0.25% trypsin, 0.75% sodium taurocholate, and 20 mM cystine HCl. Both solutions worked equally well. The oocysts were incubated in the excysting fluid for 2 hours in a heat block at 37°C.

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The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention

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Appendix II

This paper provides additional information on methods, data, and results and is intended to supplement the above referenced published paper.

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"A thousand years in the making, the religion of technology has become the common enchantment, not only of the designers of technology but also of those caught up in, and undone by, their godly designs. . . . This popular faith, subliminally indulged and intensified by corporate, government, and media pitchmen, inspires an awed deference to the practitioners and their promises of deliverance while diverting attention from more urgent concerns. . . . Pleas for some rationality, for reflection about pace and purpose, for sober assessment of costs and benefits - for evidence even of economic value, much less larger social gains - are dismissed as irrational. From within the faith, any and all criticism appears irrelevant, and irreverent."

Noble, D. *The religion of technology*. New York, NY: Alfred Knopf, 1997, p.207.

Introduction

Although there has been a number of authors have examined or reviewed the economics of influenza vaccination (6,20,22-26,35) only one previous study (5) appears in the literature that examines the economics of a planned intervention aimed at reducing the impact of an influenza epidemic in the United States. The overall objective of this study is to examine the possible economic impact of the next influenza pandemic in the United States, and then use those results to analyze the costs and benefits of interventions designed to reduce the impact. These estimates can then be used in the development of national and state-level plans to respond to an influenza pandemic.[1]

The model can also be used to examine the economics of various strategies and options that might be available for the use of influenza vaccines.

Methods

Objectives

The specific objectives of the modeling effort are to:

1) provide a range of estimates regarding the number of deaths, hospitalizations, outpatients, and those ill, but not seeking medical care;

2) provide a dollar estimate of the impacts;

3) estimate the potential net present value of some possible vaccination strategies;[(2)]

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4) evaluate the impact of using different criteria (e.g., death rates, economic returns to vaccination) to set vaccination priorities;

5) assess the economic impact of various scenarios regarding the total number of doses of vaccine administered, and the distribution of vaccine among different age and risk groups; and,

6) calculate an "insurance premium" that could reasonably be spent each year on planning, preparedness and practice (the 3 P's).

The intent is ***not*** to provide "the" estimate of impact, but rather to examine the effect of altering a number of variables, and evaluating how the results may effect key decisions. For example, if influenza-related deaths rates among 20-64 years old are assumed to range between 0.0675 - 0.15 per 1,000 persons, would it make economic "sense" (i.e., generate a positive net present value) to vaccinate everybody in this age group if a pandemic had an overall (gross) attack rate of, say, 15 percent? If not, would the results change if, say, the maximum death rate were doubled to 0.30 per 1,000? If doubling still does not generate a positive net present value for a "vaccinate all" strategy, then decision makers would be aware that the decision to vaccinate all 20-64 years of age would rest on a valuation of the intangibles, such as the reduction in fear of death due to influenza, and the value of human life above and beyond the economic value of lost productivity.

Modeling approach

Mathematically modeling the spread of, and numbers affected by, influenza is a difficult task. Differences in virology, lack of understanding of how influenza is actually spread in a community, and lack of adequate population-based data are some of the factors that have hampered efforts to produce realistic estimates of the numbers of cases that may be caused by the next influenza pandemic.[8] Therefore, in the face of a great deal of uncertainty regarding the possible impact of an influenza pandemic, we used a Monte Carlo simulation approach. In Monte Carlo simulations, uncertainty is explicitly allowed for by using pre-specified probability distributions to describe the range and frequency of probable values of key variables (9-11). The model is run for several iterations, often 1,000 or more, and during each iteration values for each variable are drawn from their probability distributions. The results from all the iterations are then pooled and descriptive statistics (e.g., average, median, mode, 5th and 95th percentiles) can be calculated. For this paper, the impact of some variables, such as attack rates, cost of vaccine, and numbers effectively vaccinated, were examined at pre-determined intervals over fixed ranges, with values for other variables chosen from pre-determined probability distributions.

Gross attack rates

We defined gross attack rate as the number of clinical cases of illness (i.e., not infections) caused by influenza per unit population. Persons who become infected but show no symptoms or only very mild symptoms, such as a headache or mild nausea, are deemed not to have an economically important case of influenza (although such infections may have important epidemiological consequences). Because nobody can predict with any great certainty the attack rate of a pandemic, we modeled a range of attack rates, from 15 to 35 percent, in steps of 5

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percent. The number of cases generated by a given attack rate was distributed among the U.S. population first by age and then by "high risk" status (see later).

Age group distribution of number of cases

The U.S. population (1) for 1997 was categorized into 3 age groups, 0-19 years of age, 20-64 years of age, and 65 years of age and older (Table 1). Using only three age groups simplifies modeling, and the oldest age group matches a defined "target" group for vaccination during inter-pandemic years (2). Since the actual age distribution of cases during an influenza pandemic is unknown, we calculated two age-related distributions of cases, or scenarios (Table 2).

Percentages of high risk cases

There are a proportion of persons who, because they have a pre-existing medical condition, are deemed as being at a higher risk of contracting an influenza-related illness with a serious health outcome (defined later). For the total U.S. population, we used lower and upper age-weighted averages of 15.4 and 24.8 percent (Table 2). These estimates are similar to the 22.5 percent figure quoted by Schoenbaum et al. (5), and the 19.6 percent for 1970-1978 used by the Office of Technology Assessment (OTA) study (6).

For age-specific estimates, we used lower and upper estimates of 6.4 and 11.1 percent for the 0-19 years old and a lower estimate of 14.4 percent for the 20-64 years old (Table 2). These estimates were obtained from the Working Group on Influenza Pandemic Preparedness and Emergency Response (GRIPPE, unpublished data). In comparison, a study in Oregon found that between 2.5 and 6.4 percent of 0-14 years old had one or more high risk conditions (7). The upper limit for the 20-64 years old and the lower and upper estimates for the 65 years and older were obtained from expert opinion (Table 2). Note that both the Advisory Committee on Immunization Practices (ACIP) (2) and GRIPPE (unpublished data) categorized all person 65 years and older as 'high risk." This categorization, however, is more to indicate high priority targets for inter-pandemic vaccination as opposed to describing the numbers of persons in that age group who are at higher risk of contracting an influenza-related illness with a serious health outcome.

Total numbers of cases

For each of the five assumed gross attack rates, the total number of cases were distributed among the age groups, using the two distribution scenarios (Table 2). Then, the number of cases in each age group were divided into "non-high" and "high risk" groups using the lower and upper estimates of age-defined percentages of high risk persons in each age group (Table 2). This strategy resulted in a total of ten different scenarios describing the possible number of cases resulting from an influenza pandemic.

Health outcomes: Four categories

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Health outcomes were divided into four categories: deaths, hospitalizations, outpatients, and those ill, but not seeking medical care. The last category included only those whose illness would cause an economic impact, such as staying away from work for a half-day or more. Those who become ill, but do not stop or significantly reduce their daily activities, are not considered to have had an illness of any notable economic impact. For each age and risk group, a range of rates for each of the four outcomes were obtained from the literature or expert opinion

Health outcomes: Deaths

Non-high risk groups: For lower and "most likely" estimates, age-weighted average excess death rates were calculated using Serfling et al.'s data (16). Lower estimates were obtained the lowest age-weighted rate found in the four epidemic periods studied, while the "most likely" estimate was the average of the age-weighted rates studied [(16)] (Table 3). The same data set also provided a maximum value for the 65 and older age group (Table 3). Note that, Serfling et al.'s estimates are effectively the combination of the rates for both high and non-high risk. Thus, using those rates for non-high risk will result in rates higher than might actually occur, especially in terms of lower limits. The upper limits for the 0-19 years old were the age-weighted average rate for the 0-4 and 5-24 year olds rate per 1,000 *cases*, assumed by Schoenbaum et al. (5), converted to rates per 1,000 general population (see later for notes on conversion methodology) (Table 3). Data from Serfling et al. were used to set the upper limit for the 20-64 years old (Table 3).

High risk groups: In OregoN (17) death rates for those aged 45-64 years ranged from 0.1 per 1,000 (with one high risk condition) to 5.72 per 1,000 (for those with 2 or more high risk conditions). Those aged 65 and older had rates of 2.76 per 1,000 (one high risk condition) to 5.63 per 1,000 (2 or more high risk conditions). These rates were used as ranges for 20-64 years old and 65 years and older, respectively (Table 3). Data regarding the death rate among 0-19 years old with high risk conditions are scarce. The Office of Technology (OTA) report (6) estimated the risk of pneumonia-related deaths among those 44 years and under with medically attended heart conditions was 1.0 per 1,000 of the general high risk population. Among those 44 years and under, those with a high risk condition (i.e., medically attended heart condition) were calculated to have a relative risk of 9.09 of dying from pneumonia when compared to those without a high risk condition (6). It was assumed, therefore, that the rate of death per 1,000 high risk population among the 0-19 years old was 9 times greater than the rates used for the non-high risk population of the same age.

Comparisons with other data sets: Kavet (20), in examining the impact of epidemics in 1962-63, 1965-66 and 1968-69 (with 1966-67 as the non-epidemic reference year) estimated non-age, non-risk specific mortality rates of 0.14-0.249 per 1,000 general population. Glezen (3) reported similar rates for 65 years and over, and an age-weighted (1) average rate of 6.75 per 100,000 for 20-64 years old. For 45-64 years old, the death rate in Oregon 0.02 per 1,000, and 0.09 per 1,000 for 65 and older (17). In France, from 1980-81 to 1989-90, the average death rates among those aged 75 years and older ranged from 4.81 to 0.28 per 1,000 (23). All of these estimates are encompassed in either the rates used for the non-high or high risk groups (Table 3). When considering the economics of vaccinating elderly patients in nursing homes, Patriarca et al. (25) assumed a probability of death after infection, with no hospitalization, of 0.16. This is

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approximately 5 times greater than the rate per 1,000 cases for 65 years and older used here (Table 3), and far greater than most death rates reported for the elderly. The difference can probably be attributed to the fact that almost the entire population in a nursing home is likely to have one or more high risk conditions. In 1974-1982, in Houston, Texas, (18) there was a fairly steady age distribution of percentage of total influenza-related deaths. Deaths among the 65 years and older accounted for an average of 62.5 percent (range: 55-75 percent) of all influenza-related deaths. Kavet (20) reported similar percentages for the three epidemics which he studied. The 20-64 years old had 29.6 percent (range: 20-33 percent) and 0-19 years old accounted for 7.9 percent (range: 5-12 percent) (18).

Health outcomes: Hospitalizations

Non-high risk: The excess hospitalizations due to influenza were obtained from Mullooly and Barker (7,12), with data from Schoenbaum et al. (5) used to define upper limits. The latter study used estimates obtained from a Delphi panel, but their estimates appear to include "background," non-epidemic hospitalizations as opposed to *excess* hospitalizations. The lower limits for the 0-19 years old age group were derived from the combined male and female excess rates for 5-14 years of age (7), while the "most likely" rates are the rates for the entire 0-14 years of age (7) (Table 3). The upper limit for the 0-19 years old were the age-weighted average rate per 1,000 *cases* (see later for notes on conversion methodology) for the 0-4 years and 5-24 years old age groups as assumed by Schoenbaum et al. (5) (Table 3). The lower limits of excess hospitalizations for the 20-64 years age group were taken from the average 1968-69 and 1972-73 epidemic excess hospitalization rates for the 15-44 and 45-65 year old age groups in Oregon (Table 3) (12). The upper limits for the 20-64 years old were calculated using the data set (5) and methodology employed to calculate the upper limits for the 0-19 years old (Table 3). Mullooly and Barker's data were used to obtain the upper and lower limits for the 65 and older age group (12) (Table 3).

High risk: The same methodology and data sets used to set hospitalization rates for non-high risk patiients were also used to set the rates of hospitalizations for the high risk groups (Table 3).

Comparisons with other data sets: It is noted that the Office of Technology Assessment report (6) used the Mullooly and Barker data sets (7,12). Glezen (3), without categorizing patients by risk, reports rates of hospitalizations for acute respiratory disease as approximately 4.2, 0.8, 0.5 per 1,000 for the <5, 5-9, and 10-19 year age groups, respectively. This produces a population-weighted[1] average for the 0-19 year olds of 1.5 per 1,000 population. This rate is lower than the upper limit used here for 0-19 years old with non-high risk (Table 3). From the same data set (3), the age-weighted hospitalization rate for 20-64 years of age was 1.1 per 1,000, and the rate for 65 years and older was 7.5 per 1,000.[3] These rates are lower than the upper rates used in this study for those categorized as "high risk" (Table 3). Barker's (21) estimates of national excess hospitalization rates, averaged over 5 epidemics from 1970-78, are within the ranges used here for the "non-high risk" group (Table 3). The only exception is the rate of 3.7 per 1,000 found for 65 years and older, which is higher than given in Table 3 for non-high risk, but is below the range used for "high risk."

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The highest recorded estimates of hospitalizations appear in a study by McBean et al (19). They calculated the rate of hospitalizations for influenza and influenza-related conditions for a sample of Medicare patients (i.e., 65 years and older) from 1989-1991. Unlike the studies referenced above, which compared rates from epidemic to non-epidemic years, McBean et al. compared hospitalization rates of influenza "seasons" (e.g., December to March) to an interim period (e.g., May - September). They found excess rates (using their definition of excess) of up to 14.25 per 1,000 for patients hospitalized with influenza and pneumonia as the primary diagnosis, and rates of up to 19.4 per 1,000 for patients hospitalized with influenza or pneumonia as any part of the diagnosis. These rates are approximately 4 times greater than the rates that we used for "non-high risk" 65 years and older, but similar to the rate we used of 13 per 1,000 for those 65 and older categorized as "high risk" (Table 3).

Health outcomes: Outpatient (ambulatory care)

Non-high risk groups: An age-weighted average rate for 0-19 years old was obtained using the rates reported by Glezen (3) for <5, 5-9, 10-14 and 15-19 years old (Table 3). The rate of medically attended illnesses for the 20-64 year old age group were derived from the excess contact rates for 45-64 year age group in Oregon, where excess was defined as the increased visits due to the 1968-69 and 1972-73 epidemics compared to the 1970-71 period (12) (Table 3). The same data source (12) provided the excess outpatient visits for those 65 years and older (Table 3).

High risk groups: Although some studies have considered hospitalization rates by category of risk (see later), there are no studies that consider outpatient (ambulatory) visits by risk category. Therefore, it was decided to calculate the rates by multiplying all the rates used for the non-high risk groups by an arbitrarily defined factor of 1.75. It was found, by trial and error, that any factor noticeably higher than that (e.g., 2.0), resulted in more than 100 percent of the high risk population requiring outpatient care.

Comparisons with other data sets: Hospitalizations and outpatient visits: Kavet (20), in studying the epidemics of 1962-63, 1965-66 and 1968-69 (with 1967-68 as a non-epidemic reference year), found that between 41.7 and 51.3 percent of all cases required some medical attention (e.g., outpatient visit or hospitalization). These percentages were not broken down by age groups or risk categories. However, these total average rates are similar to, or encompassed by, to the sum of outpatients and hospitalizations rates used in this study (Table 3).

Health outcomes: Ill (no formal medical care)

Besides those that will die, or require hospitalization, or require outpatient (ambulatory) visits, there will be a number of persons who will become clinically ill but not seek formal medical care (e.g., a visit to a physicians office). These clinically ill people will, however, generate economic impact, primarily in days lost from work or school, and the use of over-the-counter medications. Note that this definition of clinically ill excludes those that will develop mild symptoms (e.g., nausea, headache, low-grade fever), but essentially still continue their daily activities.

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The numbers of persons in each age group who will incur a clinical case that will have economic impact was calculated by using the following formula:

Number ill_{age} = ($U.S.\ population_{age}$ x gross attack rate) - (number $dead_{age}$ + number $hospitalized_{age}$ + number requiring outpatient $services_{age}$)

where age = number of persons in each of the three age groups (for $U.S.\ population_{age}$, see Table 1).

Converting from general population rates to rates per clinically ill population

The data reported for outpatient (ambulatory) visits, hospitalizations and deaths are presented in rates per 1,000 general population (Table 3). These summarize the risk of a particular health outcome for any member of the general population, and the rates reflect the impact of a particular attack rate(s). Presumably, a given rate per 1,000 general population changes with attack rate. That is, the rate of, say, deaths per 1,000 non-high risk persons aged 20-64 years will change with changes in attack rate. We are not aware of any published study that contains a statistical analysis of the correlation between attack rate and the rate of a given health outcome. This is lack of data is problematic, as one of the goals of this paper is to examine the potential impact of pandemic influenza assuming a range of pre-set gross attack rates (see earlier). Thus, the data regarding health outcomes must be converted to rates per unit population with clinical illness. That is, for the population that becomes clinically ill, the rates must reflect the probability of outpatient (ambulatory) visits, hospitalizations and deaths.

To convert rates based on a general population to rates based on a clinically-ill population, the following formula was used:

Rate per unit clinically ill population ($X_{clinically\ ill}$) = Rate per unit general population ($X_{general}$)/conversion factor.

Where $X_{clincially\ ill}$ is the rate of interest per 1,000 clinically ill persons (e.g., hospitalizations for influenza related illnesses among 0-19 years old per 1,000 clinically ill 0-19 years old). $X_{general}$ is the rate for the outcome of interest per 1,000 population, ill and not ill combined (e.g., hospitalizations for influenza illnesses per 1,000 population aged 0-19 years).

The key to applying the above equation is determining the conversion factor. One logical candidate for the conversion factor is the attack rate that created the rate per unit general population ($X_{general}$). Such data are rare, because it implies that there would be active surveillance among the general population, asking the populace if they have suffered any influenza-like illnesses during a specified time period. In order to disregard illnesses that patients may report as influenza, but are actually due to non-influenza pathogens, a sub-sample of the population would have to be tested for evidence of influenza infection (e.g., take nasal swabs and culture). Further, because the virulence of influenza can change dramatically from year to year (13), such a study

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would have to be conducted over several years. Lacking such data, we used the equation above to derive rates per clinically ill population using upper and lower limits of attack rates calculated for the general population from Texas for 1976-1984 (3), and Seattle for 1975-1979 (3,14) (Table 3). These data were the closest in time and geography to the data used to calculate the population based data rates (Table 3). Note that we assumed that the conversion calculations was the same for both non-high and high risk groups. For comparison, Kavet (20) provides data allowing the conversion of mortality rates per general population to case fatality rates. His non-age, non-risk specific conversion factors for deaths for the three epidemics studied were 0.11, 0.14, and 0.26 equivalent to 11%, 14%, 16%, respectively). The last two estimates are within the ranges used here (Table 3), whilst the conversion factor of 0.11 is very close to the lower limit of 0.12 used here for the age groups 20-64 years and 65+ years (Table 3).

Resource use: Direct medical costs: Database

The direct medical costs associated with hospitalizations, outpatient visits and drug purchases related to outpatient visits were obtained from the MarketScan, proprietary health insurance claims database (The MEDSTAT Group, Ann Arbor, MI). The database available to us contains health insurance claims data from approximately 4 million covered lives, most of whom obtain coverage as part of their employment with large companies. These data are collected from over 100 health care payers, servicing 45 major metropolitan areas. For 1995, the database has 287,000 inpatient records and 42.8 million outpatient claims. To extract direct medical costs from the database, we used the same International Classification of Disease, ninth revision (ICD-9) codes as used by McBean et al. (19) (Table 4). Simple descriptive statistics describing the extracted data were calculated using either spreadsheet software (Excel, Microsoft, WA) or a statistical package (SAS, SAS Institute, NC).

Resource use: Standardizing year of costs to 1995

To calculate descriptive statistics over the three years of available cost data, data from 1993 and 1994 were inflated to equivalent 1995 prices. The medical care portion of the consumer price index was used to inflate prices to 1995 equivalents. The factor for 1993 was 1.095 and for 1994 the factor was 1.045 (1).

Resource use: Valuing death due to influenza

It was assumed that the average age of death was the mid-point of each of the three age groups (i.e., 9, 35, and 74 years). For each average age of death, a life lost was valued at the average present value, discounted at 3%, of future expected life-time earnings and housekeeping services (27). This average was calculated using wages of full-time employees, weighted for gender composition of the U.S. workforce, and assumed a 1% per annum growth rate in productivity (27). The original estimates were converted from 1990 dollars to 1995 dollars by multiplying by a factor of 1.07, which represents the average increase from 1990 to 1995 (in constant 1992 dollars) in total and per capita personal income (1).

Resource use: Inpatient care associated with death

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It was assumed that the majority of deaths would occur after some use of hospital resources (i.e., death would occur after a stay in a hospital). For each of the three age groups the average age, length of stay and net payment were obtained from the medical cost database for each of the predefined ICD-9 codes used to describe influenza and influenza-related illnesses (Table 4). Following the methodology of McBean et al.(19), the data were then subdivided into those whose principal diagnosis was either influenza, pneumonia or acute bronchitis ("Principal diagnosis only"), and those whose had these diseases coded as either the principal diagnosis or one of the first four diseases entered in the coding sheet ("All diagnoses"). Since influenza may also cause a patient to be hospitalized with a pre-existing condition (i.e., influenza "triggers" an underlying problem), the inpatient costs for those with heart-related conditions (Table 4) were also extracted from the data base. A weighted average for each age group of these three categorizations of outcomes was then calculated as follows:

Weighted average $_{\text{age group}}$ = (number of claims in a category $_{\text{age group}}$ /total claims for all categories $_{\text{age group}}$) x (value$_{\text{age group}}$)

The results are presented in Table 5, and were then added to the value of a human live lost due to influenza.

Resource use: Hospitalized patients

Costs for those patients who would be hospitalized due to an influenza pandemic, but will not die, were obtained from the medical cost database for all those patients whose diagnoses (i.e., ICD-9 codes) included influenza, pneumonia or acute bronchitis (Table 4). Further, it was assumed that a hospitalized patient, who eventually recovered from a case of influenza, would also generate outpatients visits before and after hospitalization. In order to generate a composite estimate of inpatient and outpatient resources used, for each individual hospitalized, records of outpatient visits and drug claims up to 14 days prior to a admission date, and 30 days after discharge, were identified and added to individual net hospital payments. Length of stay during hospitalization was also obtained from the database, and to this number one day was added to allow for convalescence for the 0-19 and 20-64 years age groups. For the 65 + years age group, two days were added for post-hospitalization convalescence. Results are given in Table 6, and it can be seen that the average length of stay was 4, 7 and 8 days for the 0-17, 18-64, and 65+ year age groups, respectively. Adding the assumed post-hospitalization period of convalescence, the number of work-days lost are: 5, 8 and 9 days for the 0-17, 18-64, and 65+ year age groups, respectively.

The number of days of work lost due to hospitalization extracted from the MarketScan database can be compared to estimates used by Kavet (20). Kavet, using data from the National Health Survey, assumed that average length of hospital stay was 9 days, with 2.9-3.8 days of bed disability per case, and 5.0-6.2 days of restricted activity per case. These loses resulted in 3.2-3.4 days lost from work per case and 2.8-4.7 days lost from school per case. In a small study (22) covering 130 unvaccinated textile factory employees, 93 workdays (average: 0.71 workday/ employee) were lost due to influenza-like illness. Also a factor is the idea that, during a pandemic, the number of people requiring some form of hospitalization will be so great that

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hospitals will be forced to increase patient turnover by reducing average length of stay. Thus, average length of stay obtained from data collected during inter-pandemic years may over-estimate the amount of hospital resources used per patient during a pandemic.

Resource use: Outpatients

The direct medical resources used by an ambulatory patient includes the average number of physician visits per case of influenza, the co-payment associated with each visit, the net payment made by the insurance company, and any drug claims (see earlier). Records of outpatient claims matching the pre-selected ICD-9 codes for influenza, pneumonia and acute bronchitis (Table 4) were used to calculate the distribution of visits-per-case to a physician for each calendar year in the database (1993-1995) (Figure 3). Then, to compare results from a calender year to those associated with part of an influenza "season," the average number visits per patient for October to December, 1993 were calculated. To allow for errors in the data set (e.g., several patients entered with same identification number), the means were calculated for three different frequencies, each with a pre-specified maximum (truncated) number of visits (< 20, < 7, < 3 visits) (Table 7). The same data also provided the average age of patient making an outpatient visit, the average co-payment, and the average net payment to physician paid by a third party payer for services provided (Table 8). The number of work days lost by a patient who requires outpatient care was based on the numbers used by Kavet (20) (see later).

Resource use: Drug claims related to outpatient visits

Patients who had one or more outpatient visits in either 1994 or 1995 for influenza, pneumonia or acute bronchitis (Table 4), were matched to drug claim data for 1994 and 1995 (Table 7). Some drug claims identified in this manner may not be related to the outpatient visits for influenza, pneumonia or acute bronchitis. It was assumed, however, that the sample sizes were sufficiently large so that the average costs would "reasonably" represent the relevant drug costs associated with influenza and influenza-related outpatient visits. The average number of drug claims per outpatient visit for each age group was calculated by dividing the number of claims by the number of visits (Table 9).

Resource use: Ill, no medical care sought

Patients who have a clinical illness due to influenza but do not seek medical care still use resources, principally in the form of time off work, and perhaps some non-prescription (over-the-counter) medications. The value of non-prescription medications was assumed to be $2 per case, and the number of days lost was based on the number used by Kavet (20) (see later).

Resource use: Correlations between age, length of hospital stay, and net payment

Person correlation coefficients were calculated to test for potentially statistically significant relationships between age, length of stay in hospital, and net payment for hospitalizations. Significant relationships of these variables would indicate the need to incorporate such relationships into the Monte Carlo model. The results (Table 10), however, showed that the only

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correlation of practical importance was between net payment and length of stay (R = 0.64 or 0.61, P >0.0001). Although the correlation coefficients between age of patient and the other two variables were statistically significant, the coefficients were judged to be too small to be of much practical significance (Table 10).

Calculating the economic impact of an influenza pandemic

Using the data reported in Tables 5 through 9, and data from Kavet (20) regarding workdays lost for a person with an illness requiring outpatient visits (discussed above), economic cost, by age group, was calculated for an individual case of each of the four outcome categories (death, hospitalization, outpatients, ill no medical care sought) (Table 11). For each category of outcome, the cost per individual outcome was then multiplied by the estimated number of outcomes (see earlier), and then summed together to give a total cost of a pandemic, assuming no large-scale effective intervention occurs.

Returns to vaccination: Cost of vaccination

The total cost of vaccinating against an influenza pandemic is dependant upon the cost of vaccination, the target group(s) selected, and compliance rate(s). We divided the U.S. population into the 6 age and risk groups defined earlier, with the cost of vaccinating each group calculated separately. Based on the compliance rate of influenza vaccination among persons aged 65 years or older in the U.S. (29), two compliance rates, 40 and 60 percent, were chosen. It is noted that while the U.S. average rate for persons aged 65 years and older is 58 percent, the average among the states ranges from 44 to 70 percent (29). It was assumed that compliance rates were equal among all age and risk groups, although the model does have the capacity to allow for different compliance rates for each age and risk group.

The cost of vaccination includes the cost of the vaccine, the cost of administering the vaccine, value of time spent by an individual traveling to and from the place of vaccination, travel costs, and the costs of treating adverse side effects. The latter includes costs associated with treating effects of Guillian-Barré Syndrome (GBS). The incidence rates and costs of treatment of an individual case of mild-side effects, anaphylaxis, and GBS were obtained from a previous study (6).

A number of factors will effect the total cost of vaccination, and include the number of doses required,[3] the cost of rapid production of a larger-than-usual number of doses, the rapid delivery and correct storage of doses at vaccination sites around the country, the cost of administration, and the length of time each patient may have to wait in order to receive a dose (i.e., long lines of waiting patients. In order to illustrate the impact of different costs upon the net value of vaccination, two costs of vaccination were assumed ($18 and $$59 per vaccinee), to which were added specific estimates of the costs of treating side effects (Table 12). The two total costs of vaccination modeled were $21.26 and $62.26 per vaccinee (Table 12).). The value of a patient's time was based on the value of an 8 hour day "unspecified" work day, valued at $64 per day (27). The cost of travel ($4) was assumed. As probable costs of vaccination in a pandemic become better defined, the model has the capacity to use any other defined estimate.

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Returns to vaccination: *Vaccine effectiveness*

Economic returns to vaccination are dependent upon vaccine effectiveness to prevent each of the four outcomes modeled (death, hospitalization, outpatient visits and ill with no medical care sought). Although there are some data from controlled trials regarding the effectiveness of influenza vaccination in preventing clinical outcomes, those data invariably refer to experiments conducted during inter-pandemic periods. There are no published data from controlled trials measuring the effectiveness of an influenza vaccine during a pandemic situation. Given that a pandemic will most likely be caused by a new subtype of influenza, vaccine effectiveness under such situations is speculative. Therefore, two scenarios of vaccine effectiveness by age group and health outcome were constructed, labeled "high" and "low" levels of effectiveness (Table 13). Within each age group it was assumed that there would be no difference in vaccine effectiveness between those at "high risk" and those at "non-high risk" (Table 2). The model has the capacity to evaluate the outcomes using different values for vaccine effectiveness for each age group and health outcome.

Returns to vaccination: Net returns of vaccinating against influenza

One important measure of the economics associated with vaccinating against an influenza pandemic is the net returns, in dollars, to vaccination. This was calculated using the following formula for each age and risk group:

$$\text{Net returns}_{\text{age, risk group}} = \text{Savings from outcomes averted in population}_{\text{age, risk group}} - \text{cost of vaccination of population}_{\text{age, risk group}}$$

Where:

$$\text{Savings from outcomes averted}_{\text{age, risk group}} = \Sigma_{\text{outcomes}} (\text{number with outcome}_{\text{death,hospitalization,outpatient,ill,no medical care}} \text{ before intervention}_{\text{age,risk group}} \times \text{compliance}_{\text{age, risk group}} \times \text{vaccine effectiveness}_{\text{outcome}} \times \$\text{value of outcome}_{\text{death,hospitalization,outpatient,ill,no medical care}} \text{ prevented})$$

and;

$$\text{Cost of vaccination}_{\text{age, risk group}} = \$\text{cost/vaccinee} \times \text{population}_{\text{age,risk group}} \times \text{compliance}_{\text{age,risk group}}$$

The numbers of persons within a given age and risk group with one of the four outcomes before any intervention are obtained by running the portion of the model that estimates the impact of a pandemic (Tables 1 -3). The variables used to define the value of a given outcome are given in Table 11, the cost of vaccination in Table 12, and vaccine effectiveness in Table 13. Compliance rates were initially set at 40 and 60 percent. As discussed earlier, most of these variables can be adjusted in age or risk or both specific groups. The calculations were also made for the two different age distributions (Table 2).

Returns to vaccination: Sensitivity analyses

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Because the model was run using ranges for the attack rates and other input variables (see Tables 1-3, 11, 12, 13), the results can be considered as a set of sensitivity analyses. To illustrate the importance of the death rate in determining economic outcomes, further sensitivity analyses were conducted by altering the death rates (Table 3) . The average death rates for the non-high risk groups was altered (reduced) so that they were 0.25 or 0.50 of the death rates used in the original analyses (Table 3).

Implications for policy: "Insurance premiums" and the three P's

The analyses of the costs and benefits of a vaccination-based intervention during a pandemic implicitly assumes that such an intervention could occur if needed. This paper is part of a planning process whose end product is intended to improve the likelihood of a well-organized and effective response to a pandemic. The plan includes improvements in surveillance systems, ensuring sufficient supply of vaccine to vaccinate high-priority groups (and possibly the entire U.S. population), investigating the feasibility of liability programs for vaccine manufacturers, research to improve detection of new influenza sub-types, research into the acceleration of the availability of new and existing vaccines and antiviral agents, developing a communications network that can rapidly disseminate a wide variety of information in different media forms to different target audiences, and developing emergency preparedness plans to ensure that there will be adequate medical care and that essential community services will be maintained (30). Meeting these goals can be described as enacting the 3 P's (planning, preparedness, and practice).

A question arising from such a list of goals is: What is a "reasonable" amount to spend each year to ensure that these goals are reached? Similar to an earlier study on the economics of intervention programs,[31] the annual cost of paying for the 3 P's can be considered as an "insurance premium." The purpose of such an insurance premium is to ensure that the 3 P's have been accomplished and that a planned vaccination intervention can actually take place. An annual "insurance premium" to pay for the 3 P's can be calculated as follows: (32)

Annual "insurance premium" = net returns from an intervention x annual probability of pandemic occurring

The net returns from an intervention are those calculated using the formulae described earlier. The actual returns will be, of course, impacted by a number of variables that cannot be controlled. For example, the gross attack rate before intervention (the percentage of the total U.S. population that would become clinically ill) is beyond human control, as is the probability of a pandemic. Even vaccine effectiveness may have an element of chance. Thus, "premiums" were calculated for a range of gross attack rates (15, 25 and 35 percent), three different probabilities of a pandemic occurring in a given year (1 in 30, 1 in 60, and 1 in 100 years), two different scenarios regarding vaccine effectiveness (Table 13), and two possible costs of vaccination (Table 12).

Implications for policy: Using different criteria to set vaccination priorities

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If an influenza pandemic should occur, it is possible that initially there may be a limited supply of influenza vaccine. Even if there were a sufficient supply of vaccine to ensure that the entire U.S. population could be vaccinated, it will take some time to actually administer the vaccine to all, especially if two doses are required to ensure a "satisfactory" immune response. These factors raise the question of who should receive priority for vaccination, at least until vaccine supplies are more plentiful. For example, an argument could be made that all health care workers (e.g., nurses, practicing physicians, paramedics, etc.), and essential service providers (police, fire, phone, electric and gas workers, air traffic controllers, etc.) should be among the first to be vaccinated. However , the logic behind using essential services as "the" criteria for setting priorities will not cover the majority of the population.

To illustrate the implications of using various criteria to set priorities, three different criteria were chosen to create sample priority lists: Net returns to vaccination, percentage of total deaths, and risk of death. A priority list constructed using net returns to vaccination will give the highest priority (top rank) to the age-risk group that "produces" the highest net return to vaccination. Similarly, the highest percentage of total deaths and death rate will give the highest priority to the age-risk group with the largest number of deaths and the highest death rate, respectively. The different criteria imply a different set of values would be used in deciding who receives top priority for vaccination. Society must debate what is the main goal in deciding who is to have top priority during a pandemic plan: Is the goal to prevent deaths, regardless of age and position in society, which implies use of the death rate as the deciding criterion? Or, does society wish to focus on trying to prevent total numbers of deaths (i.e., use percentage of total deaths as the criterion)? Minimizing economic impact and ensuring that society does not collapse implies that net returns to vaccination should be used to set priorities.

Implications for policy: Four scenarios regarding vaccine availability and distribution

The model can be used to compare the potential benefits of different plans each designed to ensure that various amounts of vaccine will be available. To illustrate this capability, and to provide policy makers with some valuation associated with different options, four scenarios or options with different levels of guaranteed amounts of vaccine were constructed. Each option contains assumptions concerning the targeted population (Table 14). Each option was estimated using age distribution scenario A (Table 2), two gross attack rates (15 and 25 percent), and two estimates of the cost-of-vaccination ($21.26 and $62.26, Table 12). Further, for each option, vaccine effectiveness was assumed to result, for all age groups, in a 50 percent reduction in deaths and hospitalizations, and a 40 percent reduction in outpatient visits and illnesses not requiring formal medical care. Obviously, the model can be recalculated using different assumptions, or new scenarios can be constructed. Each option has potentially different implications regarding the level of involvement from Federal, state and local government agencies. The four options are:

Option A: Similar to current Advisory Committee on Immunization Practices (ACIP) recommendations, with production and use similar to current, intra-pandemic recommendations (2). Assumed approximately 77 million vaccinees.

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Option B: Number of vaccinees as outlined in Scenario A plus an additional 20 million essential service providers (5 million health care workers + 15 million other service providers).

Option C: Aim to achieve a 40 percent coverage in each age and risk group, regardless of occupation.

Option D: Aim to achieve 60 percent coverage in each age and risk group, regardless of occupation.

Results

Deaths

Figure 2 shows the mean, 5th, 95th, minimum and maximum number of estimated deaths and hospitalizations for the two age distribution scenarios (Table 2). For case-age distribution Scenario A, the number of deaths due to an attack rate of 15 percent was approximately 89,000 (5th percentile = 55,000; 95th percentile = 122,000), and at an attack rate of 35 percent a mean of approximately 207,000 deaths was calculated (5th percentile = 127,000; 95th percentile = 285,000) (Figure 2). At an attack rate of 15 percent, the minimum and maximum deaths were approximately 44,000 and 135,000, respectively. At an attack rate of 35 percent, the minimum and maximum deaths were approximately 102,000 and 315,000, respectively (Figure 2).

For age distribution scenario B, which has the higher percentage of cases in the 65 and older and 0-19 years old age groups (Table 2), the number of deaths at any given attack rate was approximately 43 percent higher than that calculated for Scenario A. For example, at an attack rate of 15 percent, the mean number of deaths was approximately 128,000 (5th percentile = 75,000; 95th percentile = 181,000), with a minimum and maximum of approximately 56,000 and 202,000. At an attack rate of 35 percent, the mean number of deaths was approximately300,000 (5th percentile = 175,000; 95th percentile = 422,000), with a minimum and maximum of approximately 132,000 and 472,000.

Hospitalizations

For age distribution scenario A (Table 2), the calculated number of hospitalizations ranged from a mean of approximately 314,000 (5th percentile = 210,000; 95th percentile = 417,000) at a gross attack rate of 15 percent, to a mean of approximately 734,000 (5th percentile = 441,000; 95th percentile = 973,000) at a gross attack rate of 35 percent (Figure 2). The estimates of hospitalizations for age distribution scenario B were approximately 11 percent than those calculated for age distribution scenario A (Figure 2).

Outpatients

For age distribution scenario A (Table 2), the mean numbers of persons requiring outpatient-based care ranges from approximately 18 million at a gross attack rate of 15 percent, to 42 million at a gross attack rate of 35% (Figure 3). For age distribution scenario B, the number of

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outpatient cases was approximately 7 percent greater than those calculated for age distribution scenario A. (Figure 3).

Ill (no formal medical care sought)

For age distribution scenario A (Table 2), the mean numbers of those clinically ill who will not seek formal medical care, but still suffer some economic loss, ranges from approximately 20 million at a gross attack rate of 15%, to 47 million at a gross attack rate of 35 percent (Figure 3). For age distribution scenario B, the number of outpatient cases was approximately 6 percent greater than those calculated for age distribution scenario A. (Figure 3).

Burden of impact among the high risk groups

Although those in the high risk groups constitute approximately 15 - 25 percent of the total U.S. population (Table 2), they bear a disproportionate burden of the potential impact of an influenza pandemic. On average, high risk groups will account for approximately 85-90 percent of all deaths (Table R1). By age group, the high risk 20-64 years old will bear the largest proportion of deaths, accounting for approximately 41-43 percent of total deaths (Table R1). It is also important to note that, for each age group, there is a wide range between the 5th and 95th percentiles (Table R1). For example, for age distribution scenario A, although the high risk 20-64 years of age were calculated to account for a mean of 40.9 percent of all deaths, the 5th percentile is approximately 11 percent, and the 95th percentile is approximately 61 percent (Table R1). High risk groups will also account for 38-52 percent of all hospitalizations and 20-30 percent of all outpatient visits (Table R1).

Burden of death by age group

The distribution by age group of total deaths is give in Table R2. For age distribution scenario A, those aged 65 years and older ("non-high" and "high" risk combined) accounted for a mean of approximately 39 percent of all deaths (5th percentile = 28 percent; 95th percentile = 63 percent). The minimum and maximum percentage for this age group were approximately 24 and 76 percent. The 20-64 year age group was calculated, on average, to account for about 5 percent more deaths than the 65+ year old age group, with a mean of 47 percent of all deaths for age distribution scenario A (Table R2). The 0-19 age group accounted, on average, for less than 15 percent of all deaths, although a maximum of approximately 41 percent was calculated for age distribution scenario B (Table R2).

Estimated economic costs due to an influenza pandemic: No intervention

In the absence of a large-scale intervention, the estimates of the total economic impact in the U.S. of an influenza pandemic range from an average of $71.3 billion (5th percentile = $35.4 billion; 95th percentile = $107.0 billion) for a gross attack rate of 15 percent, to an average of $166.5 billion (5th percentile = $82.6 billion; 95th percentile = $249.6 billion) for a gross attack rate of 35 percent (Table R3). At any given attack rate, loss of life due to an epidemic accounts for approximately 83 percent of all economic losses, with outpatients, ill not seeking medical

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care, and inpatient care accounting for approximately 8, 6, and 3 percent, respectively (Table R3).

Distribution of economic impact: Direct and indirect costs

Except for hospitalizations, indirect losses (primarily lost productivity, see Table 11) account for at least 65 percent of all economic losses (Table R4). In the case of deaths and ill, no medical care sought, indirect costs accounted for 99 percent of all costs (Table R4). Direct costs accounted for 89 percent of all costs associated with hospitalizations (Table R4). Across all health outcomes, indirect costs accounted for a weighted average of 94 percent of all economic costs (Tables R3, R4). Deaths among the high risk groups account for approximately 70 percent (5th percentile = 47 percent; 95th = 83 percent) of all economic losses (Table R5).

Net value of vaccinating against an influenza pandemic

The net value of vaccinating against an influenza pandemic varies substantially by age-risk group, gross attack rate, assumed distribution of cases across age groups (Table 2), assumed vaccine effectiveness, compliance, and cost of vaccination (Tables R6 - R9). At a cost of vaccination of $21.26, and a "high" level of vaccine effectiveness, the mean net value of vaccinating against a pandemic is always positive, regardless of the value of the other variables (e.g., compliance, gross attack rate, distribution of cases by age) (Tables R6-R7). For example, under the stated assumptions, the smallest positive return occurs when vaccinating 40 percent of the 65+ year old age group at "non-high risk," with a net present value of $46 million (5th percentile = $15 million; 95th percentile = $76 million) (Table R7).

However, when assuming a "low" vaccine effectiveness (Table 13), a gross attack rate of 15 percent, and Scenario B for the distribution of cases by age (Table 2), the 5th percentiles are negative (-$20 million) for the age group 65 + years, with non-high risk (Table R9). That is, under those assumptions, there is a 5 percent or greater possibility that vaccinating persons who are non-high risk and 65 years and older will generate a net loss to society.

When the cost of vaccination is $62.26 per vaccinee, at a gross attack rate of 15 percent, vaccinating all non-high risk age groups will generate net losses (Tables R6-R9). Under these assumptions, all but two net return are negative even at the 95th percentile, regardless of level of compliance, vaccine effectiveness, and age distribution of cases. The two exceptions occur in the age group 0-19 years, and for age distribution Scenario B (Table R7). However, for even these two situations, the 85th percentiles are negative (data not shown).

When the gross attack rate is increase to 25 percent, and assuming a "high" level of vaccine effectiveness, the non-high risk 0-19 and 20-64 age groups all have positive mean net returns, although some of the 5th percentiles are negative (Tables R6, R7). At the same gross attack rate, with a "low" level of vaccinee effectiveness, all non-high risk age groups have negative mean net returns, although some 95th percentiles are positive (Tables R8, R9). For "low" vaccine effectiveness, and regardless of other variables modeled, the non-high risk 65 years and older age group still generates negative mean net returns at a gross attack rate of 35 percent (Tables R8,

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R9). All other age groups, in contrast, generate positive mean net returns at 35 percent gross attack rate, although some 5th percentiles are still negative (Tables R6-R9).

Note that the high risk groups, regardless of age, always generate positive mean net returns, and that, in the majority of scenarios modeled, the 5th percentiles are also positive (Tables R6-R9).

Sensitivity analyses: Impact of reducing death rates

At a vaccination cost of $21.26 per vaccinee, reducing the death rates (Table 3) to 0.50 and 0.25 of the initial values still left positive mean net returns for all non-high risk age groups (Figure 4). However, at a cost of vaccination of $62.26 per vaccinee, reducing death rates to 0.50 and 0.25 of the initial values resulted in negative mean net returns for all non-high risk age groups (Figure 4). Note that, compared to changes in the death rate, the results are relatively insensitive to increases in gross attack rate (in the range of 15 to 25 percent). For example, at a cost of vaccination of $62.26 per vaccinee, and a death rate at 0.50 of the initial rates used, increasing the gross attack rate from 15 to 25 percent still results in a negative net returns for all age groups and levels of vaccine effectiveness (Figure 4).

Implications for policy: "Insurance premiums" to pay for the three P's

The amount of money that could "reasonably" be spent each year to ensure that the U.S. has "adequately" planned, prepared, and practiced (the 3 P's) for the next influenza pandemic ranges from $48 million per year (s.d. $37 million) to $2,184 million per year (s.d. $796 million) (Table R10). The lowest estimate arises by assuming that the probability of a pandemic is equivalent to 1 in 100 years, the gross attack rate will be 15 percent, the cost of vaccination will be $62.26 per vaccinee, a compliance rate of 40 percent, and a "low" level of vaccine effectiveness (defined in Table 13). Conversely, the highest estimate occurs when it is assumed that the probability of a pandemic is equivalent to 1 in 30 years, the gross attack rate will be 35 percent, the cost of vaccination will be $21.26 per vaccinee, a compliance rate of 60 percent, and a "high" level of vaccine effectiveness (defined in Table 13).

The assumed probability of a pandemic is one of the most important variables defining the size of the "premium." For example, the premiums increase by more than 3 times when the probability of a pandemic is increased from 1 in 100 years to 1 in 30 years (for a given gross attack rate, cost of vaccination, and level of vaccine effectiveness).

Implications for policy: Using different criteria to set vaccination priorities

Table R11 provides three lists of priority groups using three different criteria - risk of death, percentage distribution of deaths, and economic returns to vaccinating against influenza. The use of the three different criteria produced notable differences. For example, when risk of death is used to set priorities, persons aged 65 + years will receive top priority (Table R11). But, when mean net economic returns to vaccination are used as the criterion, then persons age 65 + years will receive the lowest priority (Table R11). Regardless of criteria used, the high risk groups for

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0-19 and 20-64 years will always receive priority over non-high risk persons from the same age group (Table R13).

Implications for policy: Four scenarios regarding vaccine availability and distribution

While Option A, vaccinating some 77 million persons (see earlier for description of options), will ensure positive mean net returns, vaccinating an additional 20 million essential service personnel will result in increased mean net returns (Figure 5). Changing the vaccination strategy from targeting specific groups (Option B), to aiming to vaccinate 40 percent of the population regardless of occupation results in a decrease in mean net returns (Figure 5). Only Option D, vaccinating 60 percent of the population, will result in higher mean net returns.

An important feature to note in Figure 5 are the relatively wide ranges encompassed by the 5th and 95th percentiles. For example, at a gross attack rate of 15 percent, and a cost of vaccination of $62.26 per vaccinee, the 5th percentiles for all options are less than $1 billion, while the 95th percentiles are all above $14 billion (Figure 5). The minimum value for each option under those specific assumptions is less than $0 (i.e., a net loss) (data not shown).

Discussion and conclusions

Impact of an influenza pandemic

The next influenza pandemic in the U.S. may cause considerable impact in terms of loss of life, hospitalizations, outpatient visits and persons becoming ill but seeking no medical care (Figures 2 and 3). However, it must be clearly understood that there is a great deal of uncertainty associated with any estimate of the potential impact of an influenza pandemic. For example, while the results portray the potential impact for gross attack rates ranging from 15 to 35 percent, there are no data that describe the probability of any of those attack rates actually occurring in the next pandemic. This uncertainty should temper any reaction or policy relating to responses to a potential pandemic. The "Swine Flu Affair" (33) of 1976 clearly demonstrated the perils attached to making the switch from possibility to certainty (i.e., probability = 1.00).

The two other important points to remember when considering the impact of a pandemic are that the high risk groups are likely to bear a disproportion burden of the deaths (Table R1), and that 50 percent or more of the deaths are likely to occur among persons aged less than 65 years (Table R2). This finding is similar to a recent review of the distribution of deaths caused by the influenza pandemics of 1918, 1958, and 1968 (34).

With regard to measuring the economic impact associated with a pandemic, the results clearly illustrate that the greatest economic burden is due to death (Tables R3 and R4). This result is influenced by both the death rates (Table 3) and the economic values accorded to death (Table 11). The value of death used should be considered as a measure of the economic opportunity cost associated with a death. The implication is that the opportunity cost exists regardless of the employment status of anybody who may actually die. It is also important to note that the opportunity cost, as used, is not a measure of any intrinsic value that society may place on a life.

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Such a valuation is perhaps best left to a full and open debate. The resultant economic impact due to deaths means that, all other things being equal, the largest economic returns will come from the intervention(s) that prevents the largest number of deaths.

Careful attention should be paid to the fact that, beyond the value of a lost day of work (Table 11), the model does not include any valuation for disruptions in commerce and society due to an influenza pandemic. For example, if a large number of long distance truck drivers were all unavailable to drive for, say, two weeks, there may be difficulties in ensuring distribution of perishable items, especially food. Short term disruptions might not cause a lasting economic impact, but it is possible that some persons may suffer long-term consequences because of short disruptions caused by influenza. These "multiplier effects" are not accounted for in this model, mainly because an estimate of an appropriate multiplier will depend on who becomes ill, how many become ill, when they become ill, and for how long they are ill.

Returns to vaccination

All other factors being held constant, the net return to vaccination is sensitive to the combination of price and gross attack rate (Tables R6-R9, Figure 4). Regardless of gross attack rate assumed (in the range 15 - 35 percent), a vaccination price of $21.26 per vaccinee is almost always certain to generate a positive net return, even at the 5th percentile. At a cost of $62.26 per vaccinee, a gross attack rate will almost certainly generate net losses among non-high risk groups (Tables R6-R9).

Perhaps the most important element of the estimates of the net returns are the potentially wide ranges covered between the 5th and 95th percentiles (Tables R6-R9). Some of the 5th and 95th percentile values go from less than 50 percent to more than 70 percent of the means. Given the uncertainty surrounding the values of the input variables (Tables 3, 11, 12, 13), these ranges could be considered by some to be relatively narrow. However, the fact that some 5th percentiles are negative should serve as a warning to any decision maker that many interventions may not guarantee a net positive return.

Relative importance of input variables

The results of the net returns (TablesR6-R9, Figure 4) can be used to rank the input variables in terms of their relative influence in determining the net value of vaccination. Such a ranking is, of course, only valid for the ranges used for the inputs (Tables 3, 11, 12, 13). The variables that cause the largest percentage changes in net returns are: death rate (Figure 4), cost of vaccination per vaccinee, and gross attack rate (Tables R6-R9). The next most important variable is vaccine effectiveness, which is more important than compliance, but compliance is more important than age distribution of cases (Table 2).

Implications for policy: "Insurance premiums" for the 3P's

The size of the "premium" that could be used as a measure of what could logically be spent each year to plan, prepare and practice (3 P's) for the next influenza pandemic depends most on the

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assumed probability of occurrence (Table R12). The results presented in Table R12 present a cautionary tale of the difference between possibility and probability of an influenza pandemic occurring. Assuming that an influenza pandemic could actually occur, the numbers in Table R12 can be used to argue that it is legitimate for society to spend some money each year on the 3 P's. What cannot be currently stated with any certainty is the degree of probability of such a pandemic occurring, nor the number of people who will succumb to clinical illness. Defining the difference between possibility and probability was a key decision point in the "swine 'flu affair" of 1976-1977 (33).

Implications for policy: Setting priorities

The results presented in Table R11 illustrate that priorities for vaccination depend upon the objective function chosen. If preventing the most number of deaths possible is seen as the most important function of an intervention, then society should ensure that all those in the high risk groups become vaccinated first, followed by those of non-high risk, aged 65 + years (Table R11). However, if maximizing economic returns to vaccination is defined as the objective for setting priorities, then those aged 0-64 years of age, regardless of risk, should be vaccinated first.

The results also illustrate the need to be rather precise in defining the criteria used for setting priorities. For example, stating that "preventing death" will be the criteria used is not sufficiently precise, because different priority lists can be drawn up using death rates versus actual deaths (or percentages of total deaths) (Table R11). It should also be carefully noted that the criteria used to generate the results presented in Table R11 do not define the entire set of possible methods of prioritization. Society may decide to use another criterion or a set of criteria. Thus, rather than be used to absolutely set priorities, Table R11 provides a starting point for debate within society regarding the setting of priorities.

Implications for policy: Four scenarios regarding vaccine availability and distribution

The net returns for the four scenarios modeled (Figure 5) further illustrate the need to clearly set criteria, goals and objectives for a vaccine-based intervention for the next influenza pandemic. Option C and Option D aim for 40 percent coverage, and 60 percent coverage, respectively, regardless of age or risk group. Some may state that these options represent a more egalitarian, or "fair," means of distributing vaccine. However, such egalitarianism would cost society as the net returns to Options C are lower than those from Option B (Figure 5).

Option D does produce higher returns than Option B, but it is questionable if 60 percent of U.S. society could be successfully vaccinated in the appropriate time span (2-3 months?) needed to generate the net returns shown in Figure 5. Achieving 60 percent coverage of the U.S. population will be especially difficult if 2 doses of vaccine are needed to provide "satisfactory" protection. Giving two doses for 60 percent of the U.S. population is equivalent to almost 320 million doses (Table 14). More doses would probably be needed since it is likely that not everybody who will receive a first dose will return for a second dose (i.e., compliance between the first and second doses will decrease). Thus, in order to achieve a 60 percent effective coverage, more than 60 percent of the population will need to receive the first dose. Also, spoilage will also increase the

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total number of doses that must be produced. It should not be forgotten that, at no point in history, has + 320 million doses of vaccine been delivered and administered to the U.S. population in a 2 - 3 month time period.

Summary of some main points

- The next influenza pandemic could cause very large numbers of deaths, hospitalizations, outpatient visits, and persons becoming ill, but not seeking medical care (Figures 1, 2). The actual numbers depend upon a wide variety of factors, but it may be difficult to greatly improve the accuracy of the estimates.
- The mean estimated economic impact of an influenza pandemic will range from $71 - $166 billion (Tables R3). Approximately 80 percent of the estimated loss is due to loss of life (Tables R4,R5).
- Beyond valuing work lost due to an influenza pandemic, estimates of losses presented here do not include any losses due to disruption of commerce or society. Such losses will depend directly upon how the pandemic spreads through society (i.e., who becomes ill, how many become ill, when they become ill, and for how long they are ill).
- Death rates, cost of vaccination per vaccinee, and gross attack rate are the most important variables impacting the net returns to vaccination.
- At a cost of vaccination of $21 per vaccinee, and a "high" level of vaccine effectiveness (Table 13), the mean net value of vaccinating against a pandemic is always positive, regardless of the value of the other variables (e.g., compliance, gross attack rate, distribution of cases by age) (Tables R6-R7).
- A cost of approximately $62 per vaccinee may result in net losses among certain age and risk groups if the gross attack rate is less than 25 percent lower (Tables R6-R9).
- In a large scale vaccination campaign, conducted in a relatively short span of time, and using a vaccine they may require 2 doses to provide "satisfactory" protection, vaccination may cost more than $20 per vaccinee
- Deciding how much should rationally be spent each year (an annual "insurance premium") on planning, preparing and practicing (3 P's) for the next pandemic should depend upon an evaluation of the probability of a pandemic occurring (Table R10).
- In setting plans and making preparations for the next pandemic, the possibility of a pandemic should not be confused with the probability of occurrence. The wide range of values for most of the results (Tables R6-R10, Figures 2,3,4) adds emphasis to the fact that the impact of the next influenza pandemic is largely unknown.
- Society should prepare to debate the criteria of who should be vaccinated first against the next influenza pandemic (Table R11). A key starting point for such a debate will be the definition of the objective(s) of a pandemic influenza vaccination intervention.
- In order to set realistic objectives for a vaccine-based intervention, there are two key points that must be clearly understood: a) it may require two doses of vaccine to "satisfactorily" immunize a person; and, b) there is likely to be a relatively short time period between delivery of large quantities of vaccine and the "arrival" of the pandemic. These two factors may limit the number of people that can be effectively vaccinated before the pandemic arrives.

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- A short time period before pandemic arrives, and initial limitation of supplies of vaccine, does not mean that vaccination programs should be halted after the "arrival" of the pandemic. It is, however, probably realistic to expect that vaccine effectiveness will decrease among those vaccinated during the midst of a pandemic (some will be vaccinated after becoming infected, too late to stimulate a sufficiently protective immune response).

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Table 1: U.S. population estimates used to define impact of influenza

Age group	Numbers	Percentage of total (%)

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	(millions)	
0-19 yrs old	76.37	28.8
20-64 yrs old	155.03	58.4
65 + yrs old	33.86	12.8
Total	265.26	100.0

Sources: U.S. Bureau of the Census. Statistical abstract of the United States: 1997 (117th edition). Washington, D.C., 1997.

Table 2: Two scenarios[1] of age distributions of cases and percentage of high risk population used to examine the impact of pandemic influenza in the United States

Age group	Distribution A: % of all cases[2]	Distribution B: % of all cases[2]
0-19 yrs old	40.0	46.0
20-64 yrs old	53.1	46.7
65 + yrs old	6.8	7.3
Totals[3]	100.0	100.0
Assumed percentage at "high risk"		
0-19 yrs old	6.4	11.1
20-64 yrs old	14.4	25.0
65 + yrs old	40.0	55.0
U.S. average[4]	15.4	24.8

Note: 1) The scenarios were calculated using upper and lower estimates of age-specific attack rates from 1918, 1928-29, and 1957.[3]

2) The actual number of cases will depend upon the assumed gross attack rate (see text for further details).

3) Totals may not exactly add to 100 percent due to rounding up.

4) Average is an age-weighted average, using each age group's proportion of the total U.S. population.

Table 3: Variables used to define distribution of health outcomes of those with clinical cases of influenza

Variable	Rates per 1,000 general population				Rates per 1,000 cases[1]			
	Lower	"Most	Upper	Probability	Lower	"Most	Upper	Probability

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	likely"		**distribution**		**likely"**		**distribution**
Outpatient visits (per 1,000)							
"Non-high risk"							
0-19 yrs old (rate) 165		230	Uniform	471		548	Uniform
20-64 yrs old (rate) 40		85	Uniform	333		370	Uniform
65 + yrs old (rate) 45		74	Uniform	375		389	Uniform
"High risk"							
0-19 yrs old (rate) 289		403	Uniform	825		958	Uniform
20-64 yrs old (rate) 70		149	Uniform	583		647	Uniform
65 + yrs old (rate) 79		130	Uniform	656		682	Uniform
Hospitalizations (per 1,000)							
"Non-high risk"							
0-19 yrs old (rate) 0.2	0.5	2.9	Triangular	0.57		6.9	Uniform
20-64 yrs old (rate) 0.18		2.75	Uniform	1.5		12.0	Uniform
65 + yrs old (rate) 1.5		3.0	Uniform	12.5		15.8	Uniform
"High risk"							
0-19 yrs old (rate) 2.1	2.9	9.0	Triangular	6.0		21.4	Uniform
20-64 yrs old (rate) 0.83		5.14	Uniform	6.9		22.3	Uniform
65 + yrs old (rate) 4.0		13	Uniform	33.3		68.4	Uniform
Deaths (per 1,000)							
"Non-high risk"							
0-19 yrs old (rate) 0.014	0.024	0.125	Triangular	0.041	0.07	0.30	Triangular
20-64 yrs old (rate) 0.025	0.037	.09	Triangular	0.21	0.31	0.41	Triangular
65 + yrs old (rate) 0.28	0.42	0.54	Triangular	2.3	3.51	4.52	Triangular
"High risk"							
0-19 yrs old (rate) 0.126	0.22	7.65		0.4	0.6	21.9	Triangular
20-64 yrs old (rate) 0.1		5.72		0.8		24.9	Uniform
65 + yrs old (rate) 2.76		5.63		23		29.6	Uniform
Conversion factors[2]							
0-19 yrs old 0.35		0.42	Uniform				
20-64 yrs old 0.12		0.23	Uniform				
65 + yrs old 0.12		0.19	Uniform				

Notes: 1) Cases defined here as those persons with a clinical illness sufficient to cause an economic impact.

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2) Conversion factor used to convert rates per 1,000 general population to rates per 1,000 cases (Equation 1, text). The factors are equivalent to attack rates within the general population. Thus, a conversion factor of 0.35 is equivalent to a 35% attack rate.

Sources: See text.

Table 4: International Classification of Diseases, Ninth Revision (ICD-9) codes used to extract medical costs for inpatient, outpatient and related drug claims.

Diagnosis	ICD-9 code
Pneumonia and influenza	480-487.8
Acute bronchitis	466-466.1
Chronic respiratory disease	490-496
Heart-related diagnoses	
Acute ischemic heart disease	410-411.90, 413-413.9
Chronic ischemic heart disease	412, 414.0, 414.8, 414.9, 416-416.9
Heart rhythm disorders	426-427.9
Congestive heart failure	428-428.9

Table 5: Average age of patients, length of stay, and net payments (standard deviations) of an inpatient hospitalization, by type of diagnosis and age: 1993-95 combined data[1,2]

Type of diagnosis	Age group	n (# of claims)	Avg. age of patient (yrs)	Avg. length of stay (days)	Avg. net pay. ($)[3]
Influenza, pneumonia, bronchitis, and chronic respiratory: Principal diag. only[4]	0-17 years	10,253	3.9	3.5	4,789
			(4.8)	(3.6)	(8,146)
	18-64 years	22,793	50.4	6.2	9,691
			(11.6)	(7.9)	(18,166)
	65 + years	1,063	69.6	7.9	11,047
			(4.7)	(9.7)	(15,673)
Influenza, pneumonia, bronchitis, and chronic respiratory: All diag.[5]	0-17 years	12,836	4.1	4.0	6,007
			(5.0)	(6.1)	(14,604)
	18-64 years	44,457	51.6	7.1	12,622

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			(11.2)	(11.0)	(21,577)
	65 + years	2,339	69.3	8.3	14,139
			(4.5)	(10.6)	(20,488)
Heart related conditions: All diag.[6]	0-17 years	1,150	7.1	8.3	22,637
			(6.8)	(12.7)	(40,285)
	18-64 years	96,033	54.5	5.3	15,710
			(8.1)	(7.8)	(22,000)
	65 + years	4,705	69.1	6.6	17,140
			(4.4)	(8.7)	(22,392)
Weighted averages[7]	0-17 yrs	13,986	4.2	4.0	6,481
	18-64 yrs	140,490	53.8	5.8	14,359
	65 + yrs	7,044	69.2	7.1	15,677

Notes: 1) Illness defined using the following ICD-9 codes in Table 4.

2) 1993 and 1944 cost data were inflated to 1995 using the medical care component of the consumer price index (Table 752, U.S., Bureau of Census, ref. 1).

3) Net payment made by health care payer to provider(s) of health care services.

4) ICD-9 code (Table 4) for either influenza, pneumonia, acute bronchitis, or chronic respiratory disease was entered as principal diagnosis (i.e., main diagnosis).

5) ICD-9 code (Table 4) for either influenza, pneumonia, acute bronchitis, or chronic respiratory disease was entered as either principal diagnosis (i.e., main diagnosis) or one of the first four diseases coded.

6) ICD-9 code for all heart-related conditions identified in Table 4 was entered as either principal diagnosis (i.e., main diagnosis) or one of the first four diseases coded.

7) For each age group and each variable, weighted averages were calculated as the sum of proportion of claims under each "type of diagnosis" times the value of the variable. In order to reduce overlap, the number of cases of "Influenza, . . :All diag."was first reduced by removing the number of claims under "Influenza . ."Principal daig. only".

Source: MarketScan database, The MEDSTAT Group.

Table 6: Average inpatient and outpatient charges and drug claims (standard deviations) associated with each inpatient admission for influenza or pneumonia or acute bronchitis:1993-95 combined data[1,2]

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Age group	n (# of admissions)[3]	Avg. net payments to hospitals ($)[4]	Length of stay (days)	Outpatient payments[4,5] ($)	Drug claims ($)
0-17 years	7,421	5,439	4	74	26
		(12,376)	(6)	(160)	(36)
18-64 years	16,873	11,217	7	92	42
		(12,300)	(8)	(283)	(123)
65 + years	702	12,793	8	102	41
		(18,865)	(10)	(241)	(41)
All ages	24,998	9,485	6	87	37
		(17,553)	(8)	(251)	(105)

Notes: 1) Illness defined using the following ICD-9 codes in Table 4.

2) 1993 and 1944 cost data were inflated to 1995 using the medical care component of the consumer price index (Table 752, U.S., Bureau of Census, ref. 1).

3) Number of admissions for which at least one outpatient visit was identified.

4) Net payment made by health care payer to provider(s) of health care services.

5) Outpatient claims linked to inpatients using patient ID numbers. Average includes all outpatient claims for 14 days prior to admission date and up to 30 days after discharge.

6) Drug claims linked to patient ID numbers. The total number of drug claims identified was less that the number of identified inpatient admissions. The number of drug claims identified were: 0-17 years - 3,682 claims; 18-64 years - 8,594 claims; 65 + years - 376 claims (total - 12,652 claims).

Table 7: Number and frequency of outpatient visits for diagnoses of influenza, pneumonia and acute bronchitis:[1] 1993-95 data

Max. # visits/ patient/ year	# of identified patients	% of identified patients	Total visits	Weighted average of visits/ patient
1993-95 combined				
< 20	687,349	100.0	1,673,726	2.44
< 7	655,622	95.4	1,331,868	2.03
< 3	558,360	81.2	846,327	1.52
1995 only				
< 20	262,720	100.0	632,456	2.41

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< 7	250,905	95.5	504,905	2.01
< 3	214,391	81.6	322,571	1.50
1994 only				
< 20	229,225	100.0	566,118	2.47
< 7	218,135	95.2	446,591	2.05
< 3	184,939	80.7	280,577	1.52
Oct-Dec 1993 only[2]				
< 20	70,750	100.0	148,844	2.10
< 7	68,770	97.2	128,122	1.86
< 3	60,856	86.0	89,426	1.47

Notes: 1) Illness defined using ICD-9 codes: 480-487.9, 466-466.1 (Table 4).

2) Outpatient visits that occurred between October 01 - December 31, 1993, only. These visits represented 36% of all patients, and 31% of all outpatient visits, recorded for all of 1993 for the ICD-9 codes used to define influenza, pneumonia, and acute bronchitis (Table 4).

Source: MarketScan database, The MEDSTAT Group.

Table 8: Average age of patients and costs (standard deviations) of an outpatient visit, by age group, for diagnoses of influenza, pneumonia and acute bronchitis: 1994-95 data[1,2]

Age group	n (# of claims)	Average age of patient (years)	Average co-payment ($)	Average net payment ($)[3]
0-17 years	357, 071	6.5	4.63	49.17
		(5.4)	(17.01)	(97.05)
18-64 years	883,484	45.2	4.49	37.68
		(12.0)	(21.54)	(125.35)
65 + years	16,505	68.9	4.19	50.03
		(4.4)	(18.81)	(220.47)

Notes: 1) Illness defined using the following ICD-9 codes: 480-487.9, 466-466.1

2) 1994 cost data were inflated to 1995 using a factor of 1.045, the medical care component of the consumer price index (Table 752, U.S., Bureau of Census, ref. 1).

3) Net payment made by health care payer to provider(s) of health care services.

Source: MarketScan database, The MEDSTAT Group.

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Table 9: Average payments (standard deviations) for drug claims made by patients with an outpatient visit for influenza, pneumonia and acute bronchitis: 1994-95 data[1]

Age group	n (# drug claims)	Average supply (days)	Average co-payment ($)	Average net payment[2]	Average number prescript. per visit[3]
1995					
0-17 years	173,263	14	3.41	24.57	0.90
		(13)	(6.81)	(57.80)	
18-64 years	870,173	24	3.67	36.41	1.89
		(21)	(5.31)	(166.78)	
65 + years	11,970	26	3.86	37.35	1.37
		(20)	(6.05)	(68.87)	
1994					
0-17 years	136,954	15	3.13	25.08	0.83
		(14)	(7.86)	(86.11)	
18-64 years	716,199	24	3.47	35.04	1.70
		(20)	(14.57)	(94.59)	
65 + years	10,994	27	3.14	35.93	1.42
		(20)	(2.83)	(40.7)	

Notes: 1) Illness defined using the following ICD-9 codes: 480-487.9, 466-466.1

2) Net payment made by health care payer to provider(s) of health care services.

3) Calculated by dividing the number of drug claims (prescriptions) by the number of outpatient visits for each age group and year.

Source: MarketScan database, The MEDSTAT Group.

Table 10: Pearson correlation coefficients[1] for inpatient care related to influenza, pneumonia, and acute bronchitis: 1994 and 1995 data[2]

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	Principal diagnosis only[3] (n = 34,118)			**All diagnoses[3] (n = 59,642)**		
	Age of patient	Length of stay	Net payment	Age of patient	Length of stay	Net payment
Age of patient	1.00			1.00		
Length of stay	-0.02	1.00		-0.01	1.00	
	(0.000)			(0.141)		
Net payment	0.01	0.64	1.00	0.01	0.61	1.00
	(0.032)	(0.000)		(0.002)	(0.000)	

Notes: 1) Probability under H_o: R = 0 in parentheses.

2) 1994 cost data inflated to equivalent 1995 values using a factor of 1.045, the medical care component of the consumer price index (ref. 1).

3) Principal diagnosis means that the ICD-9 codes (Table 4) for either influenza, pneumonia, or acute bronchitis must be entered as main diagnosis. All diagnoses means that the codes can be entered as either main diagnosis or any of the first for diseases in the code sheet.

Table 11: Inputs used to calculate the economic impact (direct and indirect costs) of an influenza pandemic in the U.S. (1995 U.S.$)

Outcome category **Item**	**Type of cost**	**0-19 years**	**20-64 years**	**65+ years**	**Sources**
Deaths					
Average age (years)		9	35	74	Assumed
PV earnings lost ($)[1]	indirect	1,016,101	1,037,673	65,837	Refs: 1, 27
"Most likely" + min or max hospital costs ($)[2]	direct	3,435	7,605	8,309	Marketscan Database®; Ref. 28.
		+	+	+	(Table 5)
		2,632	3,888	3,692	
Sub-total ($)[3]		*1,019,536*	*1,045,278*	*74,146*	
Hospitalizations					
"Most likely" + min or max hospital costs ($)[2]	direct	2,936	6,016	6,856	Marketscan Database®; Ref. 28.
		+	+	+	(Table 6)

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		2,099	2,086	3,200	
"Most likely" ± min or max net pay for outpatient visits ($)[4]	direct	74 ± 40	94 ± 70	102 ± 60	Marketscan Database®; Ref. 28. (Table 6)
Avg. co-payment for outpatient visit ($)	direct	5	4	4	Marketscan Database® (Table 8)
"Most likely" ± min or max net payment for drug claims($)[5]	direct	26 ± 9	42 ± 30	41 ± 10	Marketscan Database® (Table 6)
"Most likely" ± min or max days lost[6]	indirect	5 ± 2.7	8 ± 4.8	10 ±5.4	Marketscan Database®; Ref. 28. (Table 6)
Value 1 day lost ($)[7]	indirect	65	100 or 65	65	Ref. 27
Sub-total ($)[3]		*3,366*	*6,842*	*7,653*	
Outpatient					
Avg. no. visits	direct	1.52	1.52	1.52	Marketscan Database® (Table 7; Figure 3)
"Most likely" ± min or max net payment per visit($)[8]	direct	49 ±13	38 ± 12	50 ± 16	Marketscan Database® (Table 8)
Avg. co-payment for outpatient visit ($)	direct	5	4	4	Marketscan Database® (Table 8)
"Most likely" ± min or max net payment per prescription($)[9]	direct	25 ± 18	36 ± 27	36 ± 22	Marketscan Database® (Table 9)
Avg. prescriptions per visit[8]	direct	0.9	1.8	1.4	Marketscan Database® (Table 9)
Avg. co-payment per prescription ($)	direct	3	3	3	Marketscan Database® (Table 9)
Days lost	indirect	3	2	5	Refs. 20; 22
Value 1 day lost ($)[7]	indirect	65	100	65	Ref. 27
Sub-total ($)[3]		*300*	*330*	*458*	
Ill, no medical care sought					
Days lost	indirect	3	2	5	Refs. 20; 22
Value 1 day lost ($)[7]	indirect	65	100	65	Ref. 27
Over-the-counter drugs ($)	direct	2	2	2	Assumed
Sub-total ($)[3]		*197*	*202*	*327*	

Notes: 1) Present value (PV), using a discount rate of 3% of expected future lifetime earnings and housekeeping services, adjusted to 1995 dollars. Haddix et al. (Appendix I in Ref. 27) estimated the present value of wages, using 1990 data. Using Ref. 1 (Tables 705, 706), the average increase (in constant 1992 $) in total personal income in the U.S. and per capita personal income from 1990-1995 was 7%. Thus, data from Ref. 27 were multiplied by 1.07.

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2) "Most likely," with ± defining the minimum and maximum costs for a triangular distribution for Monte Carlo analysis. The values were calculated using cost data from Marketscan Database®, The MEDSTAT Group, and multiplying it by a hospital cost-to-charge ratio of 0.53. The ratio is a weighted average of the urban and rural (urban = 0.80, rural = 0.20) cost-to-charge ratios calculated by the Health Care Finance administration (HCFA) for August, 1996 (Ref. 28).

3) Sub-totals of are the totals for each category of outcome, using the "most likely" estimates. A distribution of subtotals is constructed by using the minimum and maximum values provided for some of the items within the outcome category.

4) "Most likely," with minimum and maximum values of net payments for outpatient visits up to 14 days prior to admission date and up to 30 days after discharge date.

5) Net payment for drug claims associated with outpatient visits up to 14 days prior to admission and up to 30 days after discharge.

6) "Most likely," with ± defining the minimum and maximum days lost due to hospitalization for a triangular distribution for Monte Carlo analysis. Calculated using length-of-stay in hospital data from Marketscan Database®, and adding a total of one additional day for convalescence and pre- and post-hospitalization outpatient visits for 0-19, and 20-64 years of age. For 65 + years, two additional days were added to length-of-stay in hospital for convalescence and pre- and post-hospitalization outpatient visits.

7) For 0-19 and 65+ years age groups, a day lost to influenza was valued as equivalent to an "unspecified" day (Appendix I in Ref. 27), denoting a value for time lost by care givers and family members related to taking care of a patient in these age groups. For 20-64 years of age, 60% of days lost due to hospitalizations and related convalescence and pre- and post-hospitalization outpatient visits were valued as "day off work" ($100/day). The remaining 40% of days lost were valued as "unspecified" days ($65/day). For 20-64 years of age, when patients were not hospitalized at any point during their illness (i.e., outpatient status), all days lost were assumed "days off work" ($100/day).

8) "Most likely," with minimum and maximum values of net payments for outpatient visits without any specified association to hospitalizations.

9) "Most likely," with ± defining the minimum and maximum cost per prescription, with the number of prescriptions per visit.

Table 12: Two scenarios for the cost of vaccination[a] during an influenza pandemic, with specific costs assigned to side-effects of vaccination.

Item	Probability of side effect[b]	$/ case of side-effect[b]	Lower cost scenario ($/patient)	Upper cost scenario ($/patient)
Assumed cost of vaccination[a] (excluding side effects)			18	59
Side effects				
Mild[c]	0.0325	94	3.05	3.05
GBS[d]	0.000002	100,800	0.20	0.20

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Anaphylaxis	0.000000157	2,490	0.01	0.01
Total costs/ patient			**21.26**	**62.26**

Notes: 1) The cost of vaccination includes the cost of the vaccine, the cost of administering the vaccine, value of time spent by an individual traveling to and from the place of vaccination, and patient associated travel costs. Included in the costs of the vaccine are any costs associated with the rapid production of a larger-than-usual number of doses, and the rapid delivery and correct storage of doses at vaccination sites around the country. For $18, the costs were assumed to be broken down as follows: $10 for vaccine + administration, $4 patient time (one-half hour), $4 patient travel costs. For $59, the costs were assumed to be broken down as follows: $20 for vaccine + administration (this could include the cost of 2 doses), $32 patient time (2 trips at 2 hours per trip), $7 patient travel costs. Note that, for comparison, a review of 10 published papers found a range of $5 - $22 per dose of vaccine, with a "medium" [sic] cost of $14 per dose (10). These breakdowns are illustrations only of what might be deemed "reasonable" estimates of time and cost. Actual costs might vary substantially, and will depend on the number of doses needed to achieve a "satisfactory" protective response, as well as how efficiently vaccinations can be give to millions of people.

2) Probabilities and average cost of treating each category of side effect were derived from the Office of Technology report (3).

3) Mild side-effects include sore arms due to vaccination, headaches, and other "minor" side effects that may require a visit to a physician, or may cause the patient to miss 1-2 days of work.

4) GBS = Guillian Barré Syndrome.

Table 13: Two scenarios for vaccine effectiveness[1] in preventing health outcomes by age group[2]

	Vaccine effectiveness in preventing health outcomes[1]					
	"High" level of effectiveness[3]			**"Low" level of effectiveness[3]**		
Health outcomes	**0-19 yrs**	**20-64 yrs**	**65 + yrs**	**0-19 yrs**	**20-64 yrs**	**65 + yrs**
Death	0.75	0.70	0.60	0.40	0.40	0.30
Hospitalization	0.55	0.55	0.50	0.55	0.55	0.50
Outpatient visits	0.40	0.40	0.40	0.40	0.40	0.40
Ill, no medical care sought	0.40	0.40	0.40	0.40	0.40	0.40

Notes: 1) Vaccine effectiveness is defined as the reduction in the number of cases in each of the age and health outcome categories.

2) Within a defined age group, it was assumed that there was no difference in vaccine effectiveness between "high" risk and "non-high" risk sub-groups.

3) The terms "high" and "low" level of effectiveness are subjective and reflect only a judgement of the levels of effectiveness in the two scenarios relative to each other.

Table 14: Four scenarios[1] regarding vaccine availability and distribution: Percentage and numbers vaccinated[2] by age and risk group

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Age group	Risk group	Scenario A % vaccinated	Scenario A # (mill)	Scenario B % vaccinated	Scenario B # (mill)	Scenario C % vaccinated	Scenario C # (mill)	Scenario D % vaccinated	Scenario D # (mill)
0-19 yrs	Non-high	20	13.9	20	13.9	40	27.9	60	41.8
	High	40	2.7	40	2.7	40	2.7	60	4.0
20-64 yrs	Non-high	20	24.9	35	43.6	40	49.8	60	74.7
	High	40	12.2	50	15.3	40	12.2	60	18.3
64 + yrs	Non-high	70	12.4	70	12.4	40	7.1	60	10.7
	High	70	11.3	70	11.3	40	6.4	60	9.7
Total patients			**77.4**		**99.2**		**106.1**		**159.2**
Total doses needed[3]									
1 dose per patient			*77.4*		*99.2*		*106.1*		*159.2*
2 doses per patient			*154.8*		*198.4*		*212.2*		*318.4*

Notes: 1) Scenario A is similar to current Advisory Committee of Immunization practices (ACIP) recommendations. Scenario B is the same as Scenario A, with an additional 20 million essential service providers. Scenarios C and D aim to achieve 40 and 60 percent coverage, regardless of age and risk categories. See text for complete description of assumptions.

2) All scenarios assume vaccination will result, for all age groups, in a 50 percent reduction in deaths and hospitalizations, and a 40 percent reduction in outpatient visits and illnesses not requiring formal medical care.

3) In a pandemic, which will be caused by a new subtype of influenza, it may be that everybody will require 2 doses in order to induce a "satisfactory" antibody response.

Table R1: Burden of impact, by age group, of an influenza pandemic among high risk groups relative to total impact[1]

Category of impact	Age group	Age distribution A: Percentage of total cases that are High Risk			Age distribution B: Percentage of total cases that are High Risk		
		Mean	5th	95th	Mean	5th	95th
Death	0-19 yrs	9.0	1.4	20.2	12.3	1.9	27.3
	20-64 yrs	40.9	11.1	60.9	43.0	12.3	63.8
	65 + yrs	34.4	22.7	52.1	35.5	22.8	56.2

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	Total	84.3			90.8		
Hospitalization	0-19 yrs	4.6	2.1	7.9	8.1	4.0	13.0
	20-64 yrs	14.7	7.4	23.4	19.6	10.7	29.3
	65 + yrs	18.3	11.0	27.6	23.8	15.4	33.6
	Total	37.6			51.5		
Outpatient	0-19 yrs	5.0	4.7	5.4	9.4	8.7	10.0
	20-64 yrs	10.4	9.8	11.0	14.7	13.9	15.5
	65 + yrs	4.0	3.9	4.2	5.5	5.3	5.7
	Total	19.5			29.6		

Notes: 1) See Table 2 for distribution of persons at high risk by age group.

Table R2: Distribution, by age group, of deaths due to an influenza pandemic

Age group	Age distribution A: Percentage of total deaths					Age distribution B: Percentage of total deaths				
	Mean	5th	95th	Min.	Max.	Mean	5th	95th	Min.	Max.
0-19 yrs	11.5	3.2	23.1	1.2	32.7	14.3	3.3	29.3	1.1	41.3
20-64 yrs	47.4	20.5	65.2	13.2	70.3	46.5	17.2	66.2	9.2	71.6
65 + yrs	41.1	27.8	62.5	24.0	76.4	39.3	25.9	62.0	21.9	78.9
Total	100.0					100.0				

Table R3: Economic impact (direct and indirect costs) of influenza pandemic per gross attack rate:[1,2] Deaths, hospitalizations, outpatients, illnesses and total costs (1995 U.S.$)

	Cost per gross attack rate[1] ($ millions)				
	15%	**20%**	**25%**	**30%**	**35%**
Deaths					
Mean	59,288	79,051	98,814	118,577	138,340
5th percentile	23,800	31,733	39,666	47,599	55,532
95th percentile	94,907	126,543	158,179	189,815	221,451
Hospitalizations					
Mean	1,928	2,571	3,214	3,856	4,499
5th percentile	1,250	1,667	2,084	2,501	2,917
95th percentile	2,683	3,579	4,472	5,367	6,261
Outpatients					

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Mean	5,708	7,611	9,513	11,416	13,318
5th percentile	4,871	6,495	8,119	9,742	11,366
95th percentile	6,557	8,742	10,928	13,113	15,299
Ill, no medical care sought[3]					
Mean	4,422	5,896	7,370	8,844	10,317
5th percentile	3,270	4,360	5,450	6,540	7,629
95th percentile	5,557	7,409	9,262	11,114	12,967
Grand Totals					
Mean	71,346	95,128	118,910	142,692	166,474
5th percentile	35,405	47,206	59,008	70,810	82,611
95th percentile	106,988	142,650	178,313	213,975	249,638

Notes: 1) Estimates are for age distribution scenario A (Table 2).

2) Gross attack rate refers to the proportion of the total U.S. population that becomes clinically ill due to influenza such that their illness causes an economic impact.

3) Ill, no medical care" sought is defined as persons who become clinically ill due to influenza, and that illness results in an economic impact (e.g., half day off work). However, these persons do not seek health care as an outpatient or an inpatient.

Table R4: Proportion of costs attributable to direct and indirect cost items, by category of health outcome and age group

	Percentage of costs attributable to direct or indirect items[2]					
	0-19 years		**20-64 years**		**65+ years**	
	Direct (%)	**Indirect (%)**	**Direct (%)**	**Indirect (%)**	**Direct (%)**	**Indirect (%)**
Deaths						
Mean	0.3	99.7	0.7	99.3	11.2	88.8
5th percentile	0.2	99.5	0.5	99.0	8.1	85.9
95th percentile	0.5	99.8	1.0	99.5	14.1	91.9
Hospitalizations						
Mean	89.3	10.7	89.6	10.4	91.1	8.9
5th percentile	81.6	5.7	84.7	6.0	86.7	5.3
95th percentile	94.3	18.2	94.0	15.3	94.7	13.3
Outpatients						
Mean	34.9	65.1	40.3	59.7	29.0	71.0
5th percentile	31.0	61.4	28.5	45.3	24.9	66.9
95th percentile	38.6	69.0	55.4	71.5	35.5	75.1

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Ill, no medical care sought[2]						
Mean	1.0	99.0	1.1	98.9	0.6	99.4
5th percentile	1.0	99.0	0.7	98.2	0.6	99.4
95th percentile	1.0	99.0	1.8	99.3	0.6	99.4

Notes: 1) See Table 11 for description of direct and indirect cost items.

2) For each age group and health outcome, the means of the direct and indirect costs should add to 100%,. Any difference will be due to rounding the results to the first decimal place. The 5th and 95th percentiles will not necessarily add to 100%.

Table R5: Proportion of total costs attributable to deaths by risk category: Non-high and "high"[1]

	Percentage of costs attributable to death (all ages)		
	Non-high risk (%)	**High risk (%)**	**All deaths (%)**
Mean	10.8	70.1	80.9
5th percentile	6.0	46.7	65.7
95th percentile	19.4	82.7	89.1

Notes: 1) "High" risk is defined as those patients who have one or more pre-existing medical conditions (e.g., emphysema) that make them prone to severe outcomes if they have a clinical case of influenza. Non-high risk are all those who are not categorized as "high" risk.

Table R6: Total net value of vaccinating against an influenza pandemic by level of compliance, age-risk group, cost of vaccination, and gross attack rate: Age distribution scenario A,[1] "high" level of vaccine effectiveness[2]

	Mean (5th; 95th percentiles) net value of vaccination ($ millions, 1995 $)[3]					
Vaccination compliance	**$21.26 cost of vaccination**[4] **Gross attack rate (%)**[5]			**$62.26 cost of vaccination**[4] **Gross attack rate (%)**[5]		
Age, risk group[6]	**15**	**25**	**35**	**15**	**25**	**35**
40% compliance						
0-19 yrs: Non-high risk	618	1,426	2,232	-525	282	1,089
	(262; 1,122)	(836; 2,259)	(1,412; 3,395)	(-884; -31)	(-305; 1,103)	(266; 2,235)

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High risk	2,421	4,074	5,726	2,314	3,968	5,622
	(365; 5,338)	(643; 8,941)	(921; 12,543)	(257; 5,261)	(537; 8,885)	(815; 12,512)
20-64 yrs: Non-high risk	1,470	3,156	4,842	-653	978	2,609
	(1,043; 1,893)	(2,453; 3,847)	(3,870; 5,800)	(-1,109; -194)	(260; 1,663)	(1,638; 3,550)
High risk	11,467	19,285	27,103	10,978	18,804	26,631
	(1,830; 21,097)	(3,215; 35,321)	(4,612; 49,553)	(1,361; 20,636)	(2,721; 34,853)	(4,060; 49,108)
64 + yrs: Non-high risk	81	236	391	-209	-54	102
	(47; 114)	(188; 283)	(328; 452)	(-273; -146)	(-124; 17)	(21; 182)
High risk	521	960	1,399	259	699	1,139
	(446; 598)	(840; 1,085)	(1,232; 1,572)	(164; 353)	(564; 836)	(966; 1,320)
60% compliance						
0-19 yrs: Non-high risk	927	2,137	3,348	-789	420	1,629
	(389; 1,662)	(1,256; 3,365)	(2,114; 5,080)	(-1,327; -45)	(-463; 1,658)	(395; 3,360)
High risk	3,636	6,117	8,598	3,471	5,951	8,432
	(547; 8,087)	(970; 13,537)	(1,385; 18,982)	(383; 7,896)	(807; 13,346)	(1,226; 18,786)
20-64 yrs: Non-high risk	2,082	4,529	6,975	-859	1,668	4,194
	(1,442; 2,706)	(3,498; 5,556)	(5,551; 8,386)	(-1,544; -194)	(621; 2,709)	(2,755; 5,634)
High risk	17,218	28,957	40,696	16,501	28,264	40,026

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	(2,776; 31,688)	(4,883; 53,058)	(6,955; 74,432)	(1,983; 30,967)	(4,061; 52,432)	(6,162; 73,851)
64 + yrs: Non-high risk	123	357	590	-315	-82	150
	(72; 174)	(287; 426)	(499; 680)	(-411; -219)	(-191; 28)	(23; 276)
High risk	785	1,445;	2,105	386	1,045	1,703
	(674; 902)	(1,267; 1,635)	(1,857; 2,368)	(244; 530)	(842; 1,250)	(1,435; 1,977)

Notes: 1) Table 2 provides the definition of distribution scenario A.

2) Table 13 provides the assumed levels of vaccine effectiveness, by the four health outcomes studied, that define "high" level of vaccine effectiveness.

3) Mean, 5th, and 95th percentiles calculated using a Monte Carlo model incorporating the input variables specified in Tables 3 and 11. Estimates are to the nearest million $.

4) Elements defining cost of vaccination presented in Table 12.

5) Gross attack rate is defined as the number of clinical cases of illness caused by influenza that will result in an economic impact.

6) Percentage of population in risk groups, by age category, is given in Table 2.

Table R7: Total net value of vaccinating against an influenza pandemic by level of compliance, age-risk group, cost of vaccination, and gross attack rate: Age distribution scenario B,[1] "high" level of vaccine effectiveness[2]

	Mean (5th; 95th percentiles) net value of vaccination ($ millions, 1995 $)[3]					
Vaccination compliance	**$21.26 cost of vaccination[4] Gross attack rate (%)[5]**			**$62.26 cost of vaccination[4] Gross attack rate (%)[5]**		
Age, risk group[6]	**15**	**25**	**35**	**15**	**25**	**35**
40% compliance						
0-19 yrs: Non-high risk	730	1,612	2,494	-412	470	1,351

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	(342; 1,279)	(971; 2,520)	(1,600; 3,762)	(-802; 125)	(-171; 1,365)	(454; 2,600)
High risk	4,840	8,105	11,370	4,736	8,004	11,272
	(737; 10,658)	(1,267; 17,799)	(1,798; 24,945)	(634; 10,615)	(1,161; 17,814)	(1,695; 25,014)
20-64 yrs: Non-high risk	911	2,225	3,538	-1,193	78	1,349
	(575; 1,250)	(1,674; 2,769)	(2,777; 4,292)	(-1,574; -808)	(-494; 638)	(571; 2,100)
High risk	17,507	29,352	41,197	17,024	28,882	40,739
	(2,852; 32,131)	(4,939; 53,725)	(7,064; 75,333)	(2,367; 31,689)	(4,398; 53,296)	(6,433; 75,003)
64 + yrs: Non-high risk	46	177	309	-245	-113	19
	(15; 76)	(136; 217)	(256; 360)	(-306; -183)	(-179; 46)	(-54; 93)
High risk	830	1,475	2,119	569	1,215	1,861
	(722; 941)	(1,298; 1,655)	(1,872; 2,372)	(444; 692)	(1,031; 1,404)	(1,609; 2,113)
60% compliance						
0-19 yrs: Non-high risk	1,096	2,418	83,741	-621	701	2,022
	(511; 1,895)	(1,457; 3,759)	(2,397; 5,633)	(-1,206; 188)	(-263; 2,051)	(675; 3,913)
High risk	7,268	12,170	17,072	7,102	12,004	16,905
	(1,114; 16,134)	(1,908; 26,938)	(2,697; 37,741)	(954; 15,946)	(1,746; 26,751)	(2,548; 37,549)
20-64 yrs: Non-high risk	1,273	3,179	5,086	-1,696	272	2,241

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	(764; 1,770)	(2,361; 3,985)	(3,955; 6,200)	(-2,265; -1,145)	(-571; 1,106)	(1,100; 3,375)
High risk	26,288	44,073	61.858	25,589	43,410	61,231
	(4,323; 48,267)	(7,418; 80,742)	(10,507; 113,356)	(3,527; 47,616)	(6,627; 80,142)	(9,849; 112,634)
64 + yrs: Non-high risk	70	268	466	-368	-171	27
	(24; 115)	(207; 328)	(390; 541)	(-462; -276)	(-273; -67)	(88; 141)
High risk	1,249	2,218;	3,817	849	1,816	12,782
	(1,089; 1,419)	(1,956; 2,495)	(2,817; 3,572)	(664; 1,037)	(1,535; 2,102)	(2,402; 3,174)

Notes: 1) Table 2 provides the definition of distribution scenario B.

2) Table 13 provides the assumed levels of vaccine effectiveness, by the four health outcomes studied, that define "high" level of vaccine effectiveness.

3) Mean, 5th, and 95th percentiles calculated using a Monte Carlo model incorporating the input variables specified in Tables3 and 11. Estimates are to the nearest million $.

4) Elements defining cost of vaccination presented in Table 12.

5) Gross attack rate is defined as the number of clinical cases of illness caused by influenza that will result in an economic impact.

6) Percentage of population in risk groups, by age category, is given in Table 2.

Table R8: Total net value of vaccinating against an influenza pandemic by level of compliance, age-risk group, cost of vaccination, and gross attack rate: Age distribution scenario A,[1] "low" level of vaccine effectiveness[2]

	Mean (5th; 95th percentiles) net value of vaccination ($ millions, 1995 $)[3]					
Vaccination compliance	**$21.26 cost of vaccination[4] Gross attack rate (%)[5]**			**$62.26 cost of vaccination[4] Gross attack rate (%)[5]**		
Age, risk group[6]	**15**	**25**	**35**	**15**	**25**	**35**

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40% compliance						
0-19 yrs: Non-high risk	329	943	1,557	-814	-199	415
	(127; 593)	(616; 1,382)	(1,102; 2,173)	(-1,023; -549)	(-532; 241)	(-46; 1,030)
High risk	1,313	2,226	3,140	1,203	2,117	3,030
	(217; 2,890)	(400; 4,856)	(581; 6,820)	(106; 2,776)	(289; 4,743)	(473; 6,703)
20-64 yrs: Non-high risk	702	1,876	3,050	-1,339	-165	1,009
	(390; 1,013)	(1,376; 2,380)	(2,358; 3,754)	(-1,669; -982)	(-703; 365)	(287; 1,726)
High risk	6,554	11,097	15,640	6,053	10,596	15,139
	(1,031; 12,082)	(1,883; 20,305)	(2,739; 28,532)	(521; 11,583)	(1,393; 19,790)	(2,247; 28,029)
64 + yrs: Non-high risk	32	155	277	-259	-137	-15
	(4; 60)	(120; 188)	(234; 319)	(-321; -199)	(-202; 73)	(84; 55)
High risk	269	539	809	5	275	546
	(215; 324)	(456; 625)	(696; 927)	(-73; 83)	(174; 378)	(417; 676)
60% compliance						
0-19 yrs: Non-high risk	493	1,415	2,336	-1,221	-299	622
	(193; 893)	(928; 2,077)	(1,658; 3,261)	(-1,531; -817)	(-794; 365)	(-65; 1,545)
High risk	1,970	3,340	4,710	1,805	3,175	4,545
	(323; 4,334)	(592; 7,283)	(866; 10,233)	(158; 4,162)	(432; 7,113)	(705; 10,063)

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20-64 yrs: Non-high risk	1,054	2,814	4,575	-2,008	-247	1,513
	(577;	(2,054;	(3,520;	(-2,553;	(-1,048;	(438;
	1,531)	3,583)	5,639)	-1,467)	570)	2,619)
High risk	9,832	16,646	23,461	9,080	15,894	22,709
	(1,529;	(2,801;	(4,097;	(795;	(2,069;	(3,329;
	18,128)	30,478)	48,827)	17,367)	29,703)	42,037)
64 + yrs: Non-high risk	48	232	415	-389	-206	-22
	(6;	(180;	(352;	(-479;	(-301;	(-125;
	90)	285)	480)	-298)	-108)	84)
High risk	403	809	1,214	7	413	818
	(324;	(685;	(1,044;	(-108;	(262;	(629;
	487)	941)	1,400)	129)	570)	1,019)

Notes: 1) Table 2 provides the definition of distribution scenario A.

2) Table 13 provides the assumed levels of vaccine effectiveness, by the four health outcomes studied, that define "low" level of vaccine effectiveness.

3) Mean, 5th, and 95th percentiles calculated using a Monte Carlo model incorporating the input variables specified in Tables 3 and 11. Estimates are to the nearest million $.

4) Elements defining cost of vaccination presented in Table 12.

5) Gross attack rate is defined as the number of clinical cases of illness caused by influenza that will result in an economic impact.

6) Percentage of population in risk groups, by age category, is given in Table 2.

Table R9: Total net value of vaccinating against an influenza pandemic by level of compliance, age-risk group, cost of vaccination, and gross attack rate: Age distribution scenario B,[1] "low" level of vaccine effectiveness[2]

	Mean (5th; 95th percentiles) net value of vaccination ($ millions, 1995 $)[3]	
Vaccination compliance	**$21.26 cost of vaccination[4]**	**$62.26 cost of vaccination[4]**
Age, risk group[6]	**Gross attack rate (%)[5]**	**Gross attack rate (%)[5]**

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	15	**25**	**35**	**15**	**25**	**35**
40% compliance						
0-19 yrs: Non-high risk	415	1,087	1,758	-728	-56	616
	(195; 704)	(730; 1,566)	(1,261; 2,430)	(-953; -439)	(-418; 426)	(114; 1,287)
High risk	2,632	4,424	6,217	2,522	4,314	6,107
	(447; 5,776)	(782; 9,662)	(1,114; 13,557)	(335; 5,664)	(677; 9,555)	(1,009; 13,439)
20-64 yrs: Non-high risk	320	1,239	2,159	-1,721	-802	118
	(69; 571)	(841; 1,539)	(1,610; 2,715)	(-2,038; -1,414)	(-1,245; -365)	(-468; 698)
High risk	10,041	16,908	23,775	9,539	16,407	23,274
	(1,648; 18,431)	(2,908; 30,888)	(4,166; 43,328)	(1,145; 17,921)	(2,420; 30,384)	(3,676; 42,839)
64 + yrs: Non-high risk	6	112	217	-285	-180	-75
	(-20; 33)	(80; 142)	(179; 253)	(-345; -225)	(-243; -117)	(-141; -9)
High risk	456	852	1,247	193	588	983
	(382; 533)	(732; 976)	(1,082; 1,421)	(98; 288)	(454; 725)	(809; 1,164)
60% compliance						
0-19 yrs: Non-high risk	623	1,630	2,637	-1,091	-84	923
	(297; 1,059)	(1,099; 2,353)	(1,898; 3,646)	(-1,428; -651)	(-622; 638)	(180; 1,931)
High risk	3,948	6,637	9,325	3,783	6,472	9,160
	(665;	(1,168;	(1,668;	(505;	(1,002;	(1,496;

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	8,664)	14,497)	20,331)	8,495)	14,335)	20,171)
20-64 yrs: Non-high risk	481	1,859	3,238	-2,581	-1,202	176
	(91;	(1,253;	(2,398;	(-3,051;	(-1,863;	(-693;
	868)	2,477)	4,085)	-2,117)	-537)	1,067)
High risk	15,061	25,363	35,664	14,309	24,610	34,911
	(2,446;	(4,324;	(6,226;	(1,707;	(3,569;	(5,447;
	27,694)	46,391)	65,080)	26,913)	45,626)	64,388)
64 + yrs: Non-high risk	10	167	325	-426	-270	-112
	(-30;	(120;	(269;	(-517;	(-363;	(-210;
	50)	214)	382)	-338)	-176)	-12)
High risk	684	1,278	1,871	289	882	1,475
	(574;	(1,098;	(1,621;	(149;	(683;	(1,213;
	803)	1,473)	2,143)	435)	1,092)	1,756)

Notes: 1) Table 2 provides the definition of distribution scenario B.

2) Table 13 provides the assumed levels of vaccine effectiveness, by the four health outcomes studied, that define "low" level of vaccine effectiveness.

3) Mean, 5th, and 95th percentiles calculated using a Monte Carlo model incorporating the input variables specified in Tables3 and 11. Estimates are to the nearest million $.

4) Elements defining cost of vaccination presented in Table 12.

5) Gross attack rate is defined as the number of clinical cases of illness caused by influenza that will result in an economic impact.

6) Percentage of population in risk groups, by age category, is given in Table 2.

Table R10: The annual "insurance premium"[1,2] for planning, preparing and practicing to respond to the next influenza pandemic: Differences due to probability of event, attack rate, vaccine effectiveness, compliance and cost of vaccination

		Actuarially fair annual premium ($ millions)	
		"Low" vaccine effectiveness[3] x 40% compliance	"High" vaccine effectiveness[3] x 60% compliance
Gross attack rate	**Cost of vaccination**	**Probability of pandemic**	**Probability of pandemic**

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		1 in 30 years	1 in 60 years	1 in 100 years	1 in 30 years	1 in 60 years	1 in 100 years
15%	$21/vaccinee	306	153	92	872	435	262
		(122)	(61)	(37)	(341)	(170)	(103)
	$62/ vaccinee	162	81	48	654	326	196
		(122)	(61)	(37)	(341)	(170)	(103)
25%	$21/vaccinee	561	280	168	1,528	762	459
		(204)	(102)	(61)	(569)	(284)	(171)
	$62/ vaccinee	416	207	125	1,311	653	394
		(204)	(102)	(61)	(569)	(284)	(171)
35%	$21/vaccinee	815	406	245	2,184	1,089	656
		(286)	(142)	(86)	(796)	(397)	(239)
	$62/ vaccinee	670	334	201	1,967	980	591
		(286)	(142)	(86)	(796)	(397)	(239)

Note: 1) The "insurance premium" is defined here as the amount of money to be spent each year to plan, prepare and practice (the 3 P's) to ensure that such mass vaccinations can take place if needed. The premium is calculated as follows:[30] Annual "insurance premium" = net returns from vaccination x annual probability of pandemic occurring.. The net returns to vaccination are given in Tables R6-R9.

2) Although the "premium" is to pay for planning, practicing and preparing a response to the next influenza pandemic, the mathematically optimal allocation of such funds requires a separate set of calculations.

3) "Low" and "high" levels of vaccine effectiveness are defined in Table 13.

Table R11: Setting priorities: Samples of lists to decide which age and risk group should be vaccinated first

	Criteria for prioritization (age - risk group)		
Priority	**Risk of death[1]**	**Percentage of deaths[2]**	**Returns to vaccination[3]**
1 (top)	High risk 65 + yrs	High risk 20 - 64 yrs	High risk 20 - 64 yrs
2	Non-high risk 65 + yrs	High risk 65 + yrs	High risk 0 - 19 yrs
3	High risk 0 - 19 yrs	High risk 0 - 19 yrs	Non-high risk 20 - 64 yrs
4	High risk 20 - 64 yrs	Non-high risk 65 + yrs	Non-high risk 0 - 19 yrs
5	Non-high risk 20 - 64 yrs	Non-high risk 20 - 64 yrs	High risk 65 + yrs
6 (bottom)	Non-high risk 0 - 19 yrs	Non-high risk 0 - 19 yrs	Non-high risk 65 + yrs

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Notes: 1) Priorities set by "risk of death" are set according to lower-limit estimates of deaths per 1,000 population for each age and risk group (see Table 3).

2) Priorities set using percentage distribution of total deaths. Data from Tables R1 and R2.

3) The priorities based on returns to vaccination use the mean net value from vaccination (Tables R6-R9).

Figure legends

Figure 1: Frequency of outpatient visits per patient for influenza, pneumonia and acute bronchitis: 1993-95

Note: ICD-9 codes used to define conditions and extract data are given in Table 4. N= 689,866 individual patients identified. Source: MarketScan database, MEDSTAT Group.

Figure 2: Impact of influenza pandemic in the United States: Mean, minimum, maximum, 5th and 95th percentiles of total deaths and hospitalizations for different gross attack rates

Notes: A) age distributions of cases given in Table 2. B) For each gross attack rates, data are totals for all age groups and risk categories.

Figure 3: Impact of influenza pandemic in the United States: Mean, minimum, and maximum of total outpatients and those ill (but not seeking formal medical care) for different gross attack rates

Note: For each gross attack rates, data are totals for all age groups and risk categories.

Figure 4: Sensitivity analysis: Mean net returns to vaccination, by age group, for different death rates, vaccine effectiveness, and percentage compliance: Non-high risk patients

Notes:

1) Initial mean death rates (proportion = 1.00) used for non-high risk patients were: 0-19 years 0.055/ 1,000 general population: 20-64 years 0.051/ 1,000 general population; 65 + years 0.413/ 1,000 general population (see Table 3). Other death rates used were proportions of these rates (0.25 and 0.50).

2) Values defining vaccine effectiveness ("high" and "low") are given in Table 13.

3) Scenario A of age-distribution of cases was used (Table 2).

Figure 5: Four options to respond to an influenza pandemic: Mean net economic returns

Notes:

1) Bars show mean net returns for each option and assumed cost of vaccination.

2) Option A: Similar to current Advisory Committee on Immunization Practices (ACIP) recommendations, with production and use similar to current, intra-pandemic recommendations.[2] Assumed approximately 77 million vaccinees. Option B: Number of vaccinees as outlined in Scenario A plus an additional 20 million essential service providers (5 million health care workers + 15 million other service providers). Option C:

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Aim to achieve a 40 percent coverage in each age and risk group. Option D: Aim to achieve 60 percent coverage in each age and risk group. See Table 14 for further details.

[1]A complete plan detailing a response to an influenza pandemic should include items such as a definition of a pandemic, "trigger" points that will initiate various steps in the response plan, and details regarding how to actually deploy the intervention. While a U.S. Federal influenza pandemic plan is still being developed, a guide for state and territorial health officials to aid them in developing plans for their jurisdictions is available at the following Internet website (printed copies can be obtained from the author): http://www.cdc.gov/nip/temp/pandemic-flu.htm

[2]We limited our examination of possible interventions to those involving influenza vaccines. We did not consider the use of anti-viral drugs for influenza prophylaxis. The reasons for the omission include: a) possible lack of supplies; b) first priority for such drugs may be for treatment; and, c) the side-effects from the drugs, particularly amantadine, make then unsuitable for long term prophylaxis for many occupations, such as drivers, heavy construction operators etc.

3Although it is recommended that persons age 9 years or older need only one dose of the currently available vaccine, children under 9 years may require 2 doses to elicit a "satisfactory" immune response (2). In a pandemic, which will be caused by a new subtype of influenza, it may be that everybody will require 2 doses in order to induce a "satisfactory" immune response, such that the vaccinee is protected against disease, or at least has a less severe health outcome.

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