

## Effects of acetaminophen on adverse effects of influenza vaccination in health care workers

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**Objective:** To evaluate the effects of acetaminophen on the incidence of adverse effects to, and the immunogenicity of, whole-virus influenza vaccine in health care workers.

**Design:** Prospective, randomized, double-blind placebo-controlled trial.

**Setting:** Health Sciences Centre, an acute care teaching hospital in Winnipeg.

**Participants:** Of 474 hospital personnel who agreed to undergo influenza vaccination during the 1990–91 season 262 volunteered to participate in the study.

**Interventions:** A dose of 0.5 mL of inactivated trivalent whole-virus influenza vaccine was injected into the deltoid muscle. Volunteers were randomly assigned to ingest two capsules of acetaminophen in a half dose (162.5 mg per capsule) or a full dose (325 mg per capsule) or two identical placebo capsules. Capsules were to be taken at vaccination and at 4, 8 and 12 hours afterward. Subjects were asked to answer questions regarding six symptoms in a diary for the 3 days after vaccination and to record their ingestion of the study medication.

**Main outcome measures:** Incidence of local (sore arm) and systemic (headache, fever, muscle ache, nausea and diarrhea) side effects as well as serum titres of hemagglutination inhibition (HAI) antibody to vaccine antigens before vaccination and 2 weeks and 6 months afterward.

**Results:** A total of 87, 87 and 88 subjects received the half dose, full dose and placebo respectively; 96% returned the diaries, 83% ingested all four doses of medication, and 87% volunteered all blood samples. Compared with the placebo group the incidence of sore arm was 25% to 28% lower in the half-dose and full-dose groups respectively at 24 hours after vaccination, and the rate of nausea was 90% lower in the full-dose group. The HAI titres were similar among the groups at the three test times.

**Conclusions:** The full dose of acetaminophen significantly reduced the incidence of sore arm and nausea without affecting the antibody response. Acetaminophen use may increase the acceptance of influenza vaccine by health care workers in whom concern about side effects is an impediment to vaccination.

**Objectif :** Évaluer les effets de l'acétaminophène sur l'incidence des réactions indésirables et de l'immunogénicité du vaccin antigrippal à virus entier chez les travailleurs de la santé.

**Conception :** Étude clinique prospective et randomisée à double insu, contrôlée par placebo.

**Contexte :** Le Centre des sciences de la santé de Winnipeg, un hôpital d'enseignement spécialisé en soins de courte durée.

**Participants :** Sur 474 membres du personnel de l'hôpital qui ont accepté de recevoir le vaccin antigrippal au cours de la saison 1990–1991, 262 se sont portés volontaires pour participer à l'étude.

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**Interventions :** On a injecté une dose de 0,5 mL de vaccin antigrippal trivalent inactivé à virus entier dans le muscle deltoïde. On a réparti les volontaires au hasard : certains devaient ingérer deux capsules d'acétaminophène en demi-dose (162,5 mg par capsule), d'autres ont reçu la dose complète (325 mg par capsule) et les autres, deux capsules placebo identiques. Les capsules ont été prises au moment de la vaccination et 4, 8 et 12 heures après. On a demandé aux sujets de répondre dans un carnet à des questions concernant six symptômes, et ce pendant les 3 jours suivant la vaccination, et de consigner l'heure d'administration du médicament étudié.

**Principales mesures des résultats :** On a relevé l'incidence des effets secondaires localisés (bras douloureux) et systémiques (maux de tête, fièvre, douleur musculaire, nausée et diarrhée), ainsi que les titres sériques de l'inhibition de l'hémagglutination des anticorps anti-antigènes du vaccin, avant la vaccination, 2 semaines après et 6 mois après.

**Résultats :** Un total de 87, 87 et 88 sujets ont reçu la demi-dose, la dose complète et le placebo, respectivement; 96 % ont remis leur carnet, 83 % ont absorbé les quatre doses de médicament et 87 % se sont portés volontaires pour les prises de sang. En comparaison avec le groupe placebo, l'incidence de la douleur au bras, 24 heures après la vaccination, était 25 % et 28 % plus bas dans les groupes prenant la demi-dose et la dose complète, respectivement; le groupe prenant la dose complète a manifesté un taux de nausée 90 % plus bas. Les titres de l'inhibition de l'hémagglutination sont demeurés similaires dans tous les groupes au cours des trois périodes de test.

**Conclusions :** La dose complète d'acétaminophène a réduit de façon significative l'incidence de douleur au bras et de nausée, sans affecter la réponse des anticorps. L'usage d'acétaminophène peut augmenter l'acceptation du vaccin antigrippal chez les travailleurs de la santé qui considèrent les effets secondaires comme un empêchement à la vaccination.

**N**osocomial influenza is associated with high rates of illness and death.<sup>1-3</sup> In hospital outbreaks medical personnel may transmit the virus to patients.<sup>4</sup> Both the US Advisory Committee on Immunization Practices<sup>5</sup> and the National Advisory Committee on Immunization<sup>6</sup> advocate influenza vaccination of hospital nurses and other health care workers as a means of reducing not only the risk of transmitting the virus to patients but also the economic loss due to staff absenteeism.<sup>7,8</sup>

However, only 2%<sup>9</sup> to 25%<sup>10</sup> of health care workers agree to be vaccinated. Indeed, from 1984 to 1988 only 6% to 11% of the staff at Winnipeg's Health Sciences Centre agreed to undergo influenza vaccination.<sup>8</sup> Although health care workers decline vaccination for many reasons, they commonly cite the risk of side effects.<sup>9,10</sup> Scheifele, Bjornson and Johnston<sup>11</sup> found that 90% of hospital personnel reported adverse effects after influenza vaccination. Therefore, reducing or eliminating these effects might help to increase the acceptance of influenza vaccination.<sup>9</sup>

Since acetaminophen has been shown to reduce effectively some local and systemic side effects of diphtheria toxoid-pertussis vaccine-tetanus toxoid-polio vaccine (DPT-polio vaccine) in infants<sup>12</sup> we hypothesized that it might act similarly in hospital personnel without affecting their antibody response to the influenza vaccine. We performed a randomized, double-blind placebo-controlled trial to test the hypothesis.

## Methods

Health care workers employed at the Health Sciences Centre were enrolled in the study after signing a

consent form. The study was approved by the Faculty Committee on the Use of Human Subjects in Research, University of Manitoba. Only subjects receiving non-steroidal anti-inflammatory drug therapy and those with a history of a bleeding disorder, acetaminophen intolerance or severe intolerance to eggs were excluded.

A trivalent inactivated whole-virus vaccine containing 15 µg hemagglutinin each of influenza A/Taiwan/1/86 (H1N1), A/Shanghai/16/89 (H3N2) and B/Yamagata/16/88 in 0.5 mL was stored, prepared and administered according to the manufacturer's directions (Fluzone; Connaught Laboratories Ltd., Mississauga, Ont.). One of two study nurses injected 0.5 mL into the left deltoid muscle.

The titre of hemagglutination inhibition (HAI) antibody to each of the three vaccine antigens was measured using a standard technique<sup>13</sup> in serum obtained immediately before vaccination and 2 weeks and 6 months afterward.

Acetaminophen and a placebo were packaged in identical capsules. Each participant ingested two capsules at vaccination and was given six more with instructions to ingest two every 4 hours thereafter. The capsules in one arm of the study contained the placebo, those in the second arm contained 162.5 mg of acetaminophen each (half dose), and those in the third arm contained 325 mg of acetaminophen each (full dose).

Volunteers were assigned to one of the three treatment groups with the use of a list of computer-generated randomized numbers. After vaccination they were asked to complete a diary for the next 3 days, indicating the consumption of the capsules and the occurrence of any side effects. The latter included whether no, local (sore arm) or systemic (headache, fever, muscle ache, nausea

or diarrhea) symptoms were experienced (Yes or No); if Yes, they were asked to indicate on which day and for how long. Finally, subjects were asked to record any time missed from work during the 3 days after vaccination.

We used the  $\chi^2$  test to compare proportions, analysis of variance to compare means and the Kruskal–Wallis test to compare medians. Logistic regression analysis in the placebo group was undertaken to adjust for effects of age or other potential confounders. We used the Spearman rank correlation coefficient test to determine associations between age and HAI titres before vaccination and two-sample *t*-tests to determine associations between adverse reactions and HAI titres before vaccination. Differences with a *p* value of less than 0.05 for two-tailed tests were considered significant.

HAI titres of 40 or more for homologous virus were considered protective.<sup>14</sup> Changes of fourfold or more in serum HAI titres were considered significant.

## Results

Of 474 hospital personnel who agreed to undergo influenza vaccination during the 1990–91 season 262 volunteered to participate in the study; none had to be excluded. There were no statistically significant differences between the three groups (Table 1). Personnel who worked on general medical, chronic respiratory, pediatric acute care and isolation wards, in which absenteeism had been greatest in previous studies,<sup>7,8</sup> and who were considered to pose some risk for transmission of influenza to high-risk patients because of their extensive contact with them accounted for 51% to 55% of the volunteers in each group (*p* = 0.67).

Diaries were returned by 251 of the study subjects: 82 were in the placebo group, 84 in the half-dose group and 85 in the full-dose group. We found no significant differences in the number of subjects who ingested at least two doses (93%, 98% and 96% respectively, *p* = 0.27), at least three doses (88%, 95% and 94%, *p* = 0.15) or all four doses (76%, 88% and 86%, *p* = 0.07). Because compliance may have affected the responses or the perceived effectiveness may have influenced the compliance, we excluded the results of subjects who took only single doses. The results did not differ with or without the exclusion.

Adverse effects reported by those who ingested at least two doses are presented in Table 2. Compared with the placebo group both acetaminophen groups had a lower proportion of subjects complaining of soreness at the injection site 24 hours after vaccination (half dose, *p* = 0.06; full dose, *p* = 0.04). The expected incidence rate of sore arm was reduced by 25% and 28% in the half-dose and full-dose groups respectively. At 48 hours after vaccination the advantage of the full dose of acetaminophen in comparison with the placebo tended to be maintained (*p* = 0.16), whereas the efficacy of the half dose no longer differed from that of the placebo (*p* = 0.53). By the third day 18% to 28% of the volunteers still complained of a sore arm, with no differences among the three groups (*p* = 0.37).

Of the systemic symptoms nausea was reported at a markedly lower rate in the full-dose and half-dose groups (*p* = 0.01 and 0.03 respectively) than in the placebo group. The expected incidence rate of nausea was 90% lower in the full-dose group than in the placebo group. None of the other four systemic symptoms occurred less or more frequently in the three groups.

Table 1: Characteristics of 262 volunteer hospital personnel assigned to ingest placebo or acetaminophen at influenza vaccination and 4, 8 and 12 hours afterward

Characteristic	Group; % of subjects		
	Placebo (n = 88)	Acetaminophen, dose	
		325 mg (n = 87)	650 mg (n = 87)
Sex			
Female	76	86	83
Male	24	14	17
Employed in high-risk patient care area	51	55	54
Occupation			
Nurse	41	47	48
Clerk or technician	31	26	35
Rehabilitation therapist	11	11	7
Laboratory or radiology technologist	8	8	7
Physician or clinical pharmacist	9	8	3
Mean age (and standard deviation), yr	37 (10)	37 (10)	38 (10)

The median duration of symptoms did not differ among the three groups. The range of the median duration (in hours) of sore arm was 12.0 to 24.0, headache 3.0 to 5.0, fever 4.0 to 24.0, muscle ache 5.0 to 15.0, nausea 2.0 to 3.0 and diarrhea 1.0 to 4.0.

Work was missed for 8 hours by one subject in the full-dose group and for 10 hours by one in the half-dose group. These absences occurred on day 2 after vaccination.

Serum samples for HAI testing were obtained at vaccination and 2 weeks and 6 months afterward from 89%, 90% and 83% of the subjects in the placebo, half-dose and full-dose groups respectively. Analysis revealed no difference in the geometric mean HAI titres among the groups at the three times for all three vaccine antigens (Fig. 1). The subjects were highly

susceptible to the virus strains contained in the vaccine, responded well to the vaccine and experienced modest reductions in immunity at 6 months (Table 3). At study entry, HAI antibody was undetectable (titre less than 10) in 69% to 73%, 40% to 41% and 74% to 79% of the volunteers to the A/Taiwan/1/86, A/Shanghai/16/89 and B/Yamagata/16/88 antigens respectively. In these people significant HAI responses were observed at 2 weeks to the A/Shanghai/16/89 antigen in 80% to 84% of the volunteers; 68% to 79% had an increase of fourfold or greater in HAI titre to the A/Taiwan/1/86 antigen and 61% to 79% to the B/Yamagata/16/88 antigen. There was no consistent effect of acetaminophen on the HAI response to vaccine antigens or on the durability of the HAI responses at 6 months.

Finally, data from the subjects in the placebo group

Table 2: Side effects reported during the 3 days after influenza vaccination, by treatment group

Side effect	Group; % of respondents*		
	Placebo (n = 76)	Acetaminophen, dose	
		325 mg (n = 83)	650 mg (n = 82)
None			
Day 1	30	41	41
Day 2	32	40	39
Day 3	66	72	67
Sore arm			
Day 1	61†‡	46†	44‡
Day 2	55	49	44
Day 3	28	18	26
Headache			
Day 1	18	18	12
Day 2	13	11	10
Day 3	11	5	6
Fever			
Day 1	2	4	4
Day 2	4	2	6
Day 3	5	1	1
Muscle ache			
Day 1	17	18	10
Day 2	18	16	12
Day 3	9	4	5
Nausea			
Day 1	10§	8¶	1§¶
Day 2	5	8	5
Day 3	1	2	2
Diarrhea			
Day 1	3	0	2
Day 2	4	2	1
Day 3	3	0	1
Missed work			
Day 1	0	0	0
Day 2	0	1	1
Day 3	0	0	0

\*Only those who ingested at least two doses of medication were included.

†p = 0.06.

‡p = 0.04.

§p = 0.01.

¶p = 0.03.

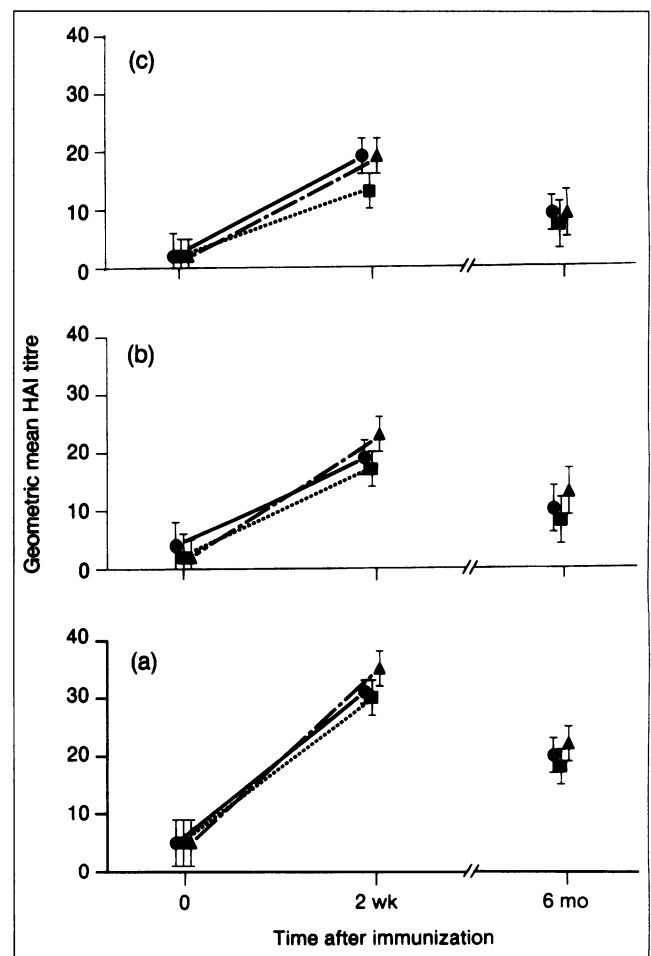


Fig. 1: Geometric mean titres of serum hemagglutination inhibition (HAI) antibody to three influenza vaccine antigens — (a) A/Shanghai/16/89, (b) A/Taiwan/1/86 and (c) B/Yamagata/16/88 — before vaccination and 2 weeks and 6 months afterward in health care workers given identical capsules of acetaminophen (325 mg [broken line] or 650 mg [dotted line]) or placebo (solid line) at vaccination and 4, 8 and 12 hours afterward to reduce the incidence of side effects. Vertical lines represent standard deviations.

were analysed to determine whether age, prevaccination titre and side effects were related. Volunteers who experienced sore arm or nausea tended to be younger (36 [standard deviation (SD) 9] years) than those who did not (40 [SD 10] years). This trend ( $p = 0.08$ ) toward an association between age and adverse effects was independent of the prevaccination HAI titres.

## Discussion

We confirmed our hypothesis that acetaminophen ingested by health care workers from the time of influenza vaccination would reduce the incidence of some local and systemic side effects. At 24 hours after vaccination the full dose of acetaminophen, ingested every 4 hours for four doses by more than 80% of the volunteers, half of whom were registered nurses, resulted in 28% fewer complaints of sore arm and 90% fewer complaints of nausea than in the placebo group. Our conclusion was supported by the observations that the half dose, ingested on the same schedule, had a similar beneficial effect in reducing the incidence of sore arm at 24 hours, whereas the full dose tended to have some persisting beneficial analgesic effect at 48 hours.

These observations are consistent with those of Ipp and associates,<sup>12</sup> who reported reductions in the incidence rates of some local and systemic reactions to DPT-polio vaccine in infants treated with acetaminophen: the rate of local reactions was reduced by 43% (redness) to 48% (pain) and that of systemic reactions by 38% (fever) to 50% (anorexia).

We believe that the proportions of volunteers in the three groups who reported sore arm or nausea differed because of a pharmacologic effect of the acetaminophen. Potential sources of bias were extensively

controlled, as was a placebo effect. Random allocation of subjects yielded three groups that were not different in age, sex or prevaccination HAI titres, factors known to affect reaction rates to influenza vaccine.<sup>15,16</sup> All doses of the vaccine were administered by one of two skilled, experienced nurses. The diary used a Yes/No response format exclusively. The volunteers were very cooperative in taking their medication (83% ingested all four doses), returning the completed diaries (96%) and providing all the blood samples (87%). The HAI titres were measured with a standard technique and appropriate controls by a technologist unaware of the assigned treatment groups.

The beneficial effects of acetaminophen observed in our study could be expected in other health care workers, given the similarities between our results and those in published studies.<sup>11,16,17</sup> Local soreness was reported in 67%<sup>17</sup> to 86%<sup>11</sup> of vaccine recipients, as compared with 61% in our placebo group. Nausea, muscle aches and headache were reported in 10%<sup>11</sup> to 11%,<sup>16</sup> 15%<sup>11</sup> to 37%<sup>16</sup> and 8%<sup>11</sup> to 34%<sup>16</sup> respectively, as compared with 10%, 17% and 18% in our study. The exception was fever, which was reported in 13%<sup>11</sup> to 15%<sup>16</sup> in other studies and 2% in ours.

That acetaminophen could not be shown to ameliorate symptoms such as headache and muscle ache as expected on the basis of its known pharmacologic effects was probably attributable to the sample sizes in our study. The recipients of the full dose had a lower incidence of these symptoms than the placebo recipients. Thus, had the study population been larger, the range of beneficial effects of acetaminophen prophylaxis might have been broader.

If, as is likely, the HAI test results in our study cohort represented those of other Canadian hospital workers

Table 3: Immunogenicity of influenza vaccine, as determined by geometric mean titre of hemagglutination inhibition (HAI) antibody to the vaccine antigens, at vaccination and 2 weeks and 6 months afterward

Variable	% of subjects		
	Time after vaccination		
	0	2 wk	6 mo
Protective titre of HAI antibody to antigen*			
A/Taiwan/1/86	1-6	26-42	15-26
A/Shanghai/16/89	4-13	47-60	27-37
B/Yamagata/16/88	1-5	21-25	4-17
Change in HAI titre to antigen		≥ fourfold increase from 0-2 wk	≥ fourfold decrease from 2 wk-6 mo
A/Taiwan/1/86		48-64	5-9
A/Shanghai/16/89		43-61	5-11
B/Yamagata/16/88		48-65	8-14

\*Number tested was 78 of the subjects in the placebo group, 78 in the half-dose acetaminophen group and 72 in the full-dose acetaminophen group.

in 1990, it can be reasonably argued that influenza vaccine was warranted and would have been immunogenic and, probably, effective in preventing infection and reducing absenteeism and transmission of nosocomial infection. However, the extent of side effects and the proportion of placebo recipients who reported having them point to the need for a better-tolerated influenza vaccine.

Concern about local adverse effects was cited as the reason for influenza vaccine refusal by 12% of health care workers<sup>9</sup> and concern about systemic ones by 25% to 39%.<sup>9,10</sup> If the reduction in the incidence of side effects from acetaminophen prophylaxis seen in this study would allay the fear of side effects in even 50% of hospital personnel in whom such concerns militated against vaccine acceptance, influenza vaccination rates might increase by 6%<sup>9</sup> to 20%.<sup>10</sup> Although not massive, such increments would constitute important increases in contemporary influenza vaccination rates among hospital staff, which range from 2%<sup>9</sup> to 25%.<sup>10</sup>

The administration of split-virus instead of whole-virus vaccine has been suggested to reduce the incidence of side effects.<sup>18</sup> Split-virus vaccine plus acetaminophen prophylaxis may have an additive or synergistic effect in reducing the incidence beyond that seen in our study, since the split-virus vaccine has been observed to cause fewer reactions than the whole-virus form,<sup>18</sup> although this finding is disputed.<sup>16</sup>

We were unable to identify an age subset that would particularly benefit from acetaminophen prophylaxis. It had previously been reported that side effects occurred more frequently in younger subjects than in older ones.<sup>15,16</sup> Analysis of data from our placebo group, in which acetaminophen would not have confounded the occurrence of side effects, tended to support this view. However, our data did not support the view that reactions are less common in older subjects because of their increased antibody titres from previous influenza vaccination or natural infection (postulated to neutralize the reactogenic properties of vaccines<sup>15</sup>).

In the doses used in our study acetaminophen was well tolerated, as expected. If it is widely used to prevent sore arm and nausea among hospital workers receiving inactivated whole-virus influenza vaccine, perhaps rare adverse reactions, such as hypersensitivity rash, neutropenia, thrombocytopenia and pancytopenia,<sup>19</sup> may be observed. The importance of such adverse effects relative to the potential benefit to individual health care personnel of fewer side effects, to patients of reduced risk of nosocomial influenza and to hospitals of reduced staff absenteeism is not readily ascertained.

## Conclusion

The use of acetaminophen, 650 mg every 4 hours for four doses, can be recommended to health care workers to reduce the incidence of some local and systemic adverse reactions to whole-virus influenza vaccine in-

jected intramuscularly. Whether larger doses of acetaminophen would be more beneficial and as well tolerated remains to be evaluated, as would the possible additive effect of combining split-virus vaccine with acetaminophen.

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