The therapeutic activity of intramuscular (IM) peramivir was evaluated in mice infected with a recombinant influenza A/WSN/33 (H1N1) virus containing the H275Y neuraminidase mutation. The A/WSN/33 virus containing the H275Y neuraminidase was used as a control for comparison. Untreated animals had a mortality rate of 75% and showed a mean weight loss of 16.9% on day 5 p.i. When started at 24 h p.i., both peramivir regimens prevented mortality and significantly reduced weight loss (P < 0.001) and lung viral titers (LVT) (P < 0.001). A high dose (10 mg/kg) of oseltamivir initiated at 24 h p.i. also prevented mortality and significantly decreased weight loss (P < 0.05) and LVT (P < 0.001) compared to the untreated group results. In contrast, a low dose (1 mg/kg) of oseltamivir did not show any benefits. When started at 48 h p.i., both peramivir regimens prevented mortality and significantly reduced weight loss (P < 0.01) and LVT (P < 0.001) whereas low-dose or high-dose oseltamivir regimens had no effect on mortality rates, body weight loss, and LVT. Our results show that single-dose and multiple-dose IM peramivir regimens retain clinical and virological activities against the A/H1N1 H275Y variant despite some reduction in susceptibility when assessed in vitro using enzymatic assays. IM peramivir could constitute an alternative for treatment of oseltamivir-resistant A/H1N1 infections, although additional studies are warranted to support such a recommendation.
The influenza A/WSN/33 (H1N1) strain under peramivir pressure resulted in the emergence of the H275Y NA mutation (N1 numbering) (9). This well-known mutation has also emerged during oseltamivir treatment in patients infected with A(H1N1)pdm09 viruses (13) as well as A/H5N1 variants (16). In addition, most seasonal A/Brussels/59/2007 (H1N1)-like viruses isolated in 2008 to 2009 contained the H275Y NA mutation (21, 23). As the H275Y mutation confers only moderate levels of resistance to peramivir (2) and considering that high peramivir concentrations could be achieved in plasma after parenteral administration, a rationale was made for possible use of IM or IV administration of peramivir against A/H1N1 variants with the H275Y mutation. Indeed, we demonstrated the prophylactic effect of IM injections of peramivir in mice infected with a recombinant influenza A/WSN/33 (H1N1) virus containing the H275Y NA mutation (4). The objective of the present study was to investigate whether IM peramivir could be also protective when therapy was delayed 24 h to 48 h after viral challenge, which better mimics clinical conditions.

MATERIALS AND METHODS

The recombinant influenza A/WSN/33 (H1N1) WT virus and its NA H275Y variant were previously generated using reverse genetics (2). Groups of 12 18- to 22- g female BALB/c mice (Charles River, Laasalle, Quebec City, Canada) were housed four per cage and kept under conditions which prevented cage-to-cage infections. In two separate experiments, mice were inoculated intranasally, under isoflurane anesthesia, with 6.9 \times 10^5 PFU (24-h treatment delay; Table 1) or 8 \times 10^5 PFU (48-h treatment delay; Table 2) of recombinant A/WSN/33 (H1N1) WT virus in 30 \mu l of phosphate-buffered saline (PBS). In another experiment, mice were similarly inoculated with 5.7 \times 10^7 PFU of the recombinant A/WSN/33 (H1N1) H275Y NA mutant (24-h treatment delay [Table 3] and 48-h treatment delay [Table 4]). Peramivir (Biocryst, Birmingham, AL) was administered intramuscularly (i.e., by hip injection) starting at 24 or 48 h after viral challenge. One group of infected animals was left untreated, whereas other groups received either a single dose (90 mg/kg of body weight) or multiple doses (45 mg/kg once daily for 5 days) of peramivir. Oral oseltamivir (Hoffmann-La Roche, Mississauga, Ontario, Canada) treatment regimens (1 mg/kg or 10 mg/kg by gavage once daily for 5 days) were also investigated for comparison. Finally, 8 uninfected and untreated mice were used as controls. All procedures were approved by the Institutional Animal Care Committee at Laval University according to guidelines of the Canadian Council on Animal Care.

Mice were monitored daily for body weight loss, and mortality was recorded over a period of 12 days. For determination of lung viral titers (LVTs), subgroups of 4 mice were sacrificed on day 5 postinfection (p.i.), and then their lungs were removed aseptically and homogenized in 1 ml of sterile PBS containing antibiotics. Lung homogenates were then centrifuged at 600 \times g for 10 min, and supernatants were titrated in Madin-Darby bovine kidney (MDBK) cells by using a standard plaque assay.

Mortality rates of the groups were compared with Kaplan-Meier analysis. The one-way analysis of variance (ANOVA) test was used to compare mean weight losses on day 5 p.i. and LVTs of the different treatment groups.

RESULTS

Effect of 24-h delay of treatment on influenza A/WSN/33 (H1N1) WT virus. Intranasal inoculation of mice with 6.9 \times 10^5 PFU of the recombinant WT virus resulted in a mortality rate of 5% (6/8), with a mean number of days to death (MDD) of 5 days \pm 4. For the 24 h p.i. protocol (Table 1), no mortality was recorded in the low-dose (1 mg/kg) oseltamivir-treated group (the 10 mg/kg dose of oseltamivir was not included in this experiment) or in the single-dose (90 mg/kg) and multiple-dose (45 mg/kg daily for 5 days) peramivir-treated groups. Mean body weight losses on day 5 p.i. of 15.6% and 7.2% were seen in untreated animals and the low-dose oseltamivir group (Table 1 and Fig. 1A). In contrast, no weight loss was observed on day 5 in the two peramivir treatment groups. The mean viral titer determined in lung homogenates from untreated animals was 2.85 \times 10^5 \pm 0.1 \times 10^5 PFU/ml. Reductions in the LVT of 3 log_{10} and 4 log_{10} were observed after low-dose oseltamivir treatment (1.3 \times 10^2 \pm 0.7 \times 10^2 PFU).

### TABLE 1 Impact of NAI therapy starting at 24 h postinfection in mice infected with a recombinant A/WSN/33 (H1N1) WT virus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% mortality on day 12 p.i. (n = 8)</th>
<th>Mean % wt loss \pm SD on day 5 p.i. (n = 11–12)</th>
<th>Mean lung viral titer (PFU/ml) \pm SD on day 5 p.i. (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected/untreated</td>
<td>0***</td>
<td>-2.8 \pm 0.7****</td>
<td>Nd</td>
</tr>
<tr>
<td>Untreated-infected</td>
<td>100</td>
<td>20.4 \pm 1.1</td>
<td>1.6 \times 10^6 \pm 0.6 \times 10^6</td>
</tr>
<tr>
<td>Oseltamivir 5 \times 1 mg/kg</td>
<td>0***</td>
<td>5.3 \pm 0.8****</td>
<td>6.6 \times 10^6 \pm 6.4 \times 10^6****</td>
</tr>
<tr>
<td>Oseltamivir 5 \times 10 mg/kg</td>
<td>0***</td>
<td>4.4 \pm 1****</td>
<td>8.6 \times 10^6 \pm 4.6 \times 10^6****</td>
</tr>
<tr>
<td>Peramivir 1 \times 90 mg/kg</td>
<td>0***</td>
<td>1.5 \pm 0.7****</td>
<td>2 \times 10^4 \pm 0**</td>
</tr>
<tr>
<td>Peramivir 5 \times 45 mg/kg</td>
<td>0***</td>
<td>2 \pm 0.8****</td>
<td>2 \times 10^4 \pm 0**</td>
</tr>
</tbody>
</table>

***, P < 0.01; ***, P < 0.001 versus the untreated group. Statistical significance was determined by using Kaplan-Meier analysis for mortality and the one-way ANOVA test for weight loss and lung viral titers. Nd, not determined. The viral inoculum was 6.9 \times 10^5 PFU.
The viral inoculum was 5.7 \times 10^5 PFU/ml (P < 0.001) and single-dose or multiple-dose peramivir regimens (4 \times 10^5 \pm 1 \times 10^5 PFU/ml and 0.66 \times 10^5 \pm 0.11 \times 10^5 PFU/ml), respectively (P < 0.001). Of note, comparisons of the three NAI regimens revealed that the single-dose and multiple-dose peramivir regimens resulted in comparable weight loss and LVT values, which were significantly lower than those obtained in the oseltamivir group (P < 0.05).

**Effect of 48-h delay of treatment on influenza A/WSN/33 (H1N1) WT virus.** For the 48 h p.i. protocol (Table 2), intranasal inoculation with 8 \times 10^5 PFU of the recombinant WT virus resulted in a mortality rate of 100% in untreated animals, with an MDD of 4.87 days ± 0.35. No mortality was seen in any oseltamivir- or peramivir-treated group. Also, minimal (1.5% to 5.3%) body weight losses were recorded on day 5 p.i. in all treated animals compared to untreated and infected animals, whose mean weight loss reached 20.4% by day 5 p.i. (Table 2 and Fig. 1B). The mean LVT was 1.6 \times 10^6 ± 0.6 \times 10^6 PFU/ml in untreated animals. In contrast, animals that received either oseltamivir or peramivir regimens had a reduction in LVT of almost 5 log_{10}, i.e., 8 \times 10^5 \pm 0.44 \times 10^5 PFU/ml in mean LVT in mice treated with the high-dose oseltamivir regimen (P < 0.001). In contrast, mice that received the single and multiple peramivir treatments had a decrease in mean LVTs of at least 3 log_{10}, i.e., 8 \times 10^5 \pm 0.52 \times 10^5 PFU/ml and 2.2 \times 10^5 ± 0.6 \times 10^5 PFU/ml, respectively (P < 0.001). Interregimen comparisons demonstrated no significant differences among the four NAI-treated groups in terms of mortality rate, weight loss, and LVT.

**Effect of 24-h delay of treatment on influenza A/WSN/33 (H1N1) H275Y virus.** Intranasal inoculation of mice with 5.7 \times 10^5 PFU of the recombinant H275Y NA mutant virus resulted in a mortality rate of 75% (6/8) in untreated and infected animals, with an MDD of 5.33 ± 0.51 days. For the 24 h p.i. treatment protocol (Table 3), the group that received the low-dose oseltamivir regimen had the same mortality rate as the group of untreated animals (75%), with an MDD of 6.16 ± 1.16 days. In contrast, there was no mortality in animals that received high-dose oseltamivir treatment or either of the two IM peramivir treatments. The infection resulted in significant body weight loss for the untreated group, with a mean weight loss of 16.9% on day 5 p.i. (Table 3 and Fig. 2A). Similarly, animals that received the low-dose and high-dose oseltamivir regimens had mean weight losses of 14% (P > 0.05) and 11.9% (P < 0.05), respectively. This contrasted with the groups that received single or multiple doses of peramivir, in which no weight loss was observed (P < 0.001). The mean viral titer determined in lung homogenates from untreated animals was 3.66 \times 10^6 ± 0.11 \times 10^6 PFU/ml. Comparable mean LVTs were found in animals that received the low-dose oseltamivir regimen, whereas there was a 1 log_{10} reduction (2.0 \times 10^5 ± 0.44 \times 10^5 PFU/ml) in mean LVT in mice treated with the high-dose oseltamivir regimen (P < 0.001). In contrast, mice that received the single and multiple peramivir treatments had a decrease in mean LVTs of at least 3 log_{10}, i.e., 8 \times 10^5 \pm 0.52 \times 10^5 PFU/ml and 2.2 \times 10^5 ± 0.6 \times 10^5 PFU/ml, respectively (P < 0.001). Interregimen comparisons showed that, despite a significant difference in their mortality rates (75% versus 0%; P < 0.001), the two oseltamivir regimens had comparable weight loss and LVT values. In contrast, the two peramivir regimens were comparable with regard to the mortality rate, weight loss, and LVT. The weight loss was significantly higher in animals that received 5 \times 10 mg/kg of oseltamivir than in the animals in the single- and multiple-dose peramivir groups (P < 0.001), whereas no significant difference between the three groups was seen with regard to mortality and LVT.

**Effect of 48-h delay of treatment on influenza A/WSN/33 (H1N1) H275Y virus.** The results of the 48 h p.i. protocol in mice infected with 5.7 \times 10^5 PFU of the H275Y mutant are shown in Table 4. Low-dose and high-dose oseltamivir regimens resulted in mortality rates of 100% and 62.5%, with an MDD of 5.75 ± 0.46 and 5.4 ± 0.54, respectively, compared to 75% mortality and an MDD of 5.33 ± 0.51 for the untreated and infected group. In sharp contrast, there was no mortality in groups that received single or multiple doses of IM peramivir. Mean body weight losses

### Table 3: Impact of NAI therapy starting at 24 h postinfection in mice infected with a recombinant A/WSN/33 (H1N1) H275Y virus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% mortality on day 12 p.i. (n = 8)</th>
<th>% wt loss ± SD on day 5 p.i. (n = 11–12)</th>
<th>Mean lung viral titer (PFU/ml) ± SD on day 5 p.i. (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected/unintreated</td>
<td>0***</td>
<td>−1.2 ± 1.1***</td>
<td>Nd</td>
</tr>
<tr>
<td>Untreated-infected</td>
<td>75</td>
<td>16.9 ± 1.5</td>
<td>3.66 \times 10^6 ± 0.11 \times 10^6</td>
</tr>
<tr>
<td>Oseltamivir 5 × 1 mg/kg</td>
<td>75</td>
<td>14 ± 1.4</td>
<td>3.0 \times 10^6 ± 0.09 \times 10^6</td>
</tr>
<tr>
<td>Oseltamivir 5 × 10 mg/kg</td>
<td>0***</td>
<td>11.9 ± 1*</td>
<td>2.0 \times 10^7 ± 0.44 \times 10^7***</td>
</tr>
<tr>
<td>Peramivir 1 × 90 mg/kg</td>
<td>0***</td>
<td>−0.6 ± 0.9***</td>
<td>8.0 \times 10^4 ± 5.29 \times 10^4</td>
</tr>
<tr>
<td>Peramivir 5 × 45 mg/kg</td>
<td>0***</td>
<td>−1.3 ± 1.1***</td>
<td>2.2 \times 10^5 ± 0.6 \times 10^4***</td>
</tr>
</tbody>
</table>

\*P < 0.05; **P < 0.01; ***P < 0.001 (versus the untreated group). Statistical significance was determined by using Kaplan-Meier analysis for mortality and the one-way ANOVA test for weight loss and viral lung titers. Nd, not determined. The viral inoculum was 5.7 \times 10^5 PFU.

### Table 4: Impact of NAI therapy starting at 48 h postinfection in mice infected with a recombinant A/WSN/33 (H1N1) H275Y virus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% mortality on day 12 p.i. (n = 8)</th>
<th>% wt loss ± SD on day 5 p.i. (n = 11–12)</th>
<th>Mean lung viral titer (PFU/ml) ± SD on day 5 p.i. (n = 4)</th>
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</tr>
<tr>
<td>Untreated-infected</td>
<td>75</td>
<td>16.9 ± 1.5</td>
<td>3.66 \times 10^6 ± 0.11 \times 10^6</td>
</tr>
<tr>
<td>Oseltamivir 5 × 1 mg/kg</td>
<td>100</td>
<td>18.3 ± 0.7</td>
<td>2.2 \times 10^7 ± 0.52 \times 10^7</td>
</tr>
<tr>
<td>Oseltamivir 5 × 10 mg/kg</td>
<td>62.5</td>
<td>16.5 ± 1.5</td>
<td>1.46 \times 10^6 ± 0.41 \times 10^6</td>
</tr>
<tr>
<td>Peramivir 1 × 90 mg/kg</td>
<td>0***</td>
<td>7.9 ± 0.9***</td>
<td>2.8 \times 10^6 ± 0.7 \times 10^6</td>
</tr>
<tr>
<td>Peramivir 5 × 45 mg/kg</td>
<td>0***</td>
<td>9.4 ± 1.4**</td>
<td>3 \times 10^5 ± 1.8 \times 10^4**</td>
</tr>
</tbody>
</table>

\*P < 0.05; **P < 0.01; ***P < 0.001 (versus the untreated group). Statistical significance was determined by using Kaplan-Meier analysis for mortality and the one-way ANOVA test for weight loss and viral lung titers. Nd, not determined. The viral inoculum was 5.7 \times 10^5 PFU.
recorded on day 5 p.i. were 18.3% (P > 0.05) and 16.5% (P > 0.05) for the two oral oseltamivir groups compared to 16.9% for the untreated and infected group. On the other hand, there was a significant reduction in mean body weight loss for the two IM peramivir groups (7.9% [P < 0.001] and 9.4% [P < 0.01]) for the 1×90 mg/kg and 5×45 mg/kg groups, respectively (Table 4 and Fig. 2B). Mean LVTs determined in groups that received low-dose or high-dose oseltamivir remained unchanged compared to the results for untreated animals (1.46 to 3.66 \times 10^6 PFU/ml), whereas there was still a 2 \log_{10} reduction observed in the single-IM-dose peramivir group (2.8 \times 10^4 \pm 0.7 \times 10^5 PFU/ml) (P < 0.05) and a 3 \log_{10} reduction observed in the multiple-dose peramivir group (3 \times 10^3 \pm 1.8 \times 10^3 PFU/ml) (P < 0.001). Interregimen comparisons demonstrated a significant difference between the two oseltamivir regimens in terms of mortality rate (P < 0.05) despite their comparable weight loss and LVT values. In contrast, the two peramivir regimens were comparable with regard to the mortality rate, weight loss, and LVT.

The effect of peramivir treatment was significantly greater than that seen with the 5×10 mg/kg oseltamivir group based on mortality rate (P < 0.001), weight loss (P < 0.05 for the 1×90 mg/kg group and P < 0.01 for the 5×45 mg/kg group), and LVT (P < 0.001).

**DISCUSSION**

As for other classes of antivirals, the increased use of NAIs may lead to the emergence and spread of drug-resistant influenza variants, compromising the long-term utility of these agents. Among available NAIs, oseltamivir has been preferred to zanamivir because of its convenient oral administration and the absence of bronchospasm, a possible secondary effect of inhaled zanamivir (27). The more frequent use of oseltamivir, combined with the greater complexity of its interactions with the catalytic site of the viral NA, may have contributed to increasing rates of resistance to this NAI, particularly among viruses of the A/H1N1 subtype (29). In that subtype, resistance is mainly mediated by the H275Y NA mutation, which also increases peramivir IC50 levels by a factor of 48- to 263-fold compared to 427- to 982-fold increases in oseltamivir IC50s (2, 31).

Parenteral peramivir, which has been approved for therapeutic use in Japan and South Korea, appears to be a valuable option for treatment of hospitalized persons with severe influenza virus infections, such as patients with gastric stasis or bleeding and those receiving extracorporeal membrane oxygenation who are unable to tolerate oral oseltamivir or inhaled zanamivir (5). Administration of intramuscular and IV peramivir demonstrated excellent pharmacokinetic properties which allowed a reliable single-dosing regimen (32). In healthy volunteers, a single intravenous injection of 600 mg of peramivir resulted in a peak plasma concentration of 34,100 ng/ml (32). Such a concentration is much higher than the in vitro IC50 exhibited by H275Y mutants. Furthermore, the IM administration of peramivir was associated with a similar effect. 

**FIG 1** Impact of NAI regimens, starting at 24 h (A) or 48 h (B) after viral challenge, on body weight loss in mice infected with \(6.9 \times 10^3\) PFU (A) or \(8 \times 10^3\) PFU (B) of the recombinant A/WSN/33 (H1N1) WT virus. Regimens consisted of a single dose (90 mg/kg) or multiple doses (5×45 mg/kg, once daily [q.d.]) of IM peramivir (Per) and low-dose (1 mg/kg, q.d.) or high-dose (10 mg/kg, q.d.) oral oseltamivir (Osel). Each symbol represents the mean weight gain or loss of 12 mice ± standard deviation (SD).

**FIG 2** Impact of NAI regimens starting at 24 h (A) or 48 h (B) after viral challenge on body weight loss in mice infected with \(5.7 \times 10^3\) PFU of the recombinant A/WSN/33 (H1N1) H275Y NA mutant. Regimens consisted of a single dose (90 mg/kg) or multiple doses (5×45 mg/kg, q.d.) of IM peramivir and low-dose (1 mg/kg, q.d.) or high-dose (10 mg/kg, q.d.) oral oseltamivir. Each symbol represents the mean weight gain or loss of 12 mice ± SD.
pharmacokinetics profile (32). In mice, a single IM dose of 30 mg/kg resulted in a maximum plasma concentration of 17,675 ng/ml, which is 4,149 times the peramivir IC_{50} value (4,26 ng/ml) for the influenza H275Y NA mutant evaluated in this study. In addition to these interesting pharmacokinetics properties, peramivir demonstrated a particularly strong NA-inhibitory activity due to its conformation, which fits very well within the NA active site (6). Indeed, the negatively charged carboxylate group forms conserved hydrogen bonds with residues R118, R292, and R317 (N2 numbering) of the active site whereas the acetamido group binds to the hydrophobic pocket formed by I222 and W118 (6, 25). On the other hand, the positively charged guanidinium group forms strong hydrogen bonding and electrostatic interactions with E119, D151, and E277 (25). As a result, peramivir binds to the NA enzyme with much higher affinity than is observed with other NAs. For instance, on-site dissociation studies showed that peramivir remained tightly bound to the NA enzyme, with a half-life for substrate conversion 19 times greater than that of zanamivir and oseltamivir (7). However, the H275Y NA mutation disturbs this affinity, resulting in a reduction of susceptibility that is 3- to 10-fold less with peramivir than with oseltamivir (19, 22).

In this study, we hypothesized that, due the excellent pharmacokinetic profile of parenteral peramivir in addition to its high NA inhibitory potency, IM peramivir would retain a protective efficacy against the oseltamivir-resistant H275Y variant even when administration was delayed up to 48 h after viral challenge, in line with our prophylactic study findings (4). Of note, we used again in this therapeutic study the peramivir dose regimens of 45 mg/kg and 90 mg/kg, which are respectively equivalent to the 300-mg and 600-mg doses currently evaluated in human clinical trials (32). On the other hand, the 10 mg/kg dose of oseltamivir is equivalent to the 75-mg oral dose used in humans (33).

Based on mortality rates, body weight losses, and LVTs, our experiments demonstrated that the single-dose (90 mg/kg) and multiple-dose (45 mg/kg daily for 5 days) IM peramivir regimens were protective against the WT as well as its H275Y variant in a lethal mouse model when initiated 24 h or 48 h after infection. Both peramivir regimens completely prevented mortality and weight loss when started 24 h after infection, whereas only mortality was prevented when treatment was initiated after 48 h. Nevertheless, weight losses observed in the two peramivir groups were significantly lower than those found in the untreated group. To a lesser extent, the high-dose oseltamivir regimen also prevented mortality and weight loss when initiated at 24 h p.i. but had no effect on mortality, weight loss, or LVTs when started after 48 h p.i. The higher level of resistance to oseltamivir conferred by the H275Y mutation and possibly lower concentrations of oseltamivir at the site of viral replication compared to those of IM peramivir could explain such differences. Against the WT virus, the high-dose (10 mg/kg) oseltamivir and both peramivir regimens showed similar protective effects in terms of mortality and reduction of LVTs in the 48-h treatment study, although peramivir was associated with less weight loss than oseltamivir.

It should be noted that the influenza strain used in this study was the mouse-adapted A/WSN/33 (H1N1) virus. Therefore, our findings regarding the activity of peramivir against the H275Y NA mutant need to be confirmed using other viral backgrounds, including oseltamivir-resistant seasonal A/H1N1 viruses and A(H1N1)pdm09 strains, and by evaluating different animal models such as ferrets. Another interesting issue that remains to be addressed is whether IM peramivir could retain activity in virus variants with enhanced levels of resistance to peramivir due to additional NA mutations, such as those harboring the combination of H275Y and I223R/V mutations seen in A(H1N1)pdm09 variants (13, 14, 30). Finally, a limitation to our study was the daily use of oseltamivir instead of twice-daily administration as recommended in human therapeutic regimes. Thus, we cannot completely rule out an effect of twice-daily oseltamivir regimens on the replication of the H275Y mutant.

In conclusion, based on our lethal influenza A/WSN/33 (H1N1) virus mouse model, we suggest that IM or IV peramivir should be considered a possible therapeutic option for treatment of infections by oseltamivir-resistant influenza viruses harboring the H275Y mutation, especially when inhaled zanamivir is contraindicated or impractical. Because of a few instances of peramivir failure associated with the emergence of the H275Y mutation in immunocompromised patients (24), additional clinical studies are warranted before formal recommendation of the use of this NAI in the context of oseltamivir resistance.

ACKNOWLEDGMENTS

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REFERENCES