

# Meta-Analysis on the Effect of Tamiflu in Patients Infected with Flu in Some Areas around US and Asia

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**Abstract:** *Flu infection is a deadly disease most especially in young children, older adults of 65+, pregnant women and people with weak immune system. Research in flu infection is an active research area. However, little have been said on the variability of effect size across studies and the between study variance ( $T^2$ ). This research work used Random effects model meta-analysis to analyze 2014 flu incidence estimates from Cochran e-Library using antiviral agents as the explanatory variables and the response variable is the incidence of the infection. The data was analyzed using the comprehensive meta-analysis version 3 software. The fitted model aims to describe the effect of Tamiflu in adults and The output of the results shows that the drug reduced the time to symptoms relief by a mean of -16.759hours with 95% confidence interval 25.1hours to 8.4hours, which tells us that the mean difference in the universe of studies could fall anywhere in this range. Hence, the range does not include a difference of zero, which tells us that the true mean difference is probably not zero. The z-value is -3.938 with a corresponding p-value < 0.001, which represents a reduction in the mean time to relief of symptoms from 7 to 6 days. On average, across all relevant populations, the drug reduced the time to symptoms relief.*

**Keywords:** Oseltamivir phosphate, Neuraminidase Inhibitors, Influenza, Relenza, Random effects, means difference, effect size

## 1. Introduction

Flu antivirals (such as tamiflu and relenza of the neuraminidase inhibitor class) are commonly used and stockpiled drugs employed against seasonal and pandemic flu infection on the basis of international and national recommendations; these recommendations partly justified by the claimed and assumed ability of oseltamivir to reduce complications and transmission of flu infection.[3], [4]. [6] In theory, containing the spread of flu infection allows time for an organized response with longer term interventions (such as vaccines), which take time to produce. [7] Oseltamivir is now on the list of World Health Organization essential drugs, [9], [11] but we could not clarify on what basis WHO or the Centers for Disease Control and Prevention recommend its use. Flu infection is a ravaging disease that has taken away lives and it still continues to decrease the human population especially in countries where they have not been able to combat this disease. United States is one of the countries that have fallen below World Health Organization (WHO) expectation in fighting this disease. Flu infection is caused by an H1N1 virus with genes of avian origin. The outcome of H1H1 infection is a dynamic process that depends on factors that are associated with pathogens, the host and the environment. It is infectious and spreads through the air in droplets when an infected person with the infection coughs, sneezes or talks. When a susceptible person inhales the air, they inhale H1H1 virus and then, they become infected. Flu infection

can be deadly especially in young children, older adults of 65+, pregnant women and people with weak immune system. The symptoms that are associated with this infection are fever, aching muscles, headache, shortness of breath, tiredness and weakness, sore throat, eye pain, runny nose, chills and sweats, dry persistent cough, vomiting and diarrhea but this is more common in children than adults. These symptoms depend on which area of the body has been infected.

## 2. Background

Neuraminidase inhibitors (NIs) are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic flu. They are used clinically worldwide.

Neuraminidase inhibitors (Tamiflu, Relenza, Peramivir etc.) are a class of drugs which block the function of the viral neuraminidase enzyme. By blocking this enzyme it stops the release of viruses from the infected host cell and prevents new cells from being infected. These antiviral agents (tamiflu, relenza, peramivir etc.) inhibit all subtypes of neuraminidases enzymes and therefore are effective against influenza A and B viruses.

The neuraminidase inhibitors (tamiflu and relenza) were approved in the US and Europe for treatment and prevention of influenza A and B. [12]

### Objectives

To describe the effects of neuraminidase inhibitors on the duration of flu symptoms relief in adults by reviewing the antiviral agents (specifically Tamiflu) for use in treatment and prophylaxis of flu infection.

### Significance

In this research paper, we were able to explain why and what are the causes of variability of effect size across studies and between study variance Figure [1].

Q is a sum of squared deviations on a standardized scale. It captures the deviation of every effect size from the mean effect size relatively to the standard error of that study alone. The sum of these squared deviations is 6.325 and DF is degrees of freedom (the number of studies minus one). DF is the value of Q that we would expect to see based on sampling error. DF(Q) is also the Q-value that we would expect to see if all studies were drawn from the same population.

If  $Q > DF$ , the dispersion that we see is more than we would expect to see based on sampling error. In that case, we proceed to compute the variance of the effect sizes. In this research work,  $Q < DF$  and it turns out that the amount of dispersion (variability) that we see is actually less than we would expect to see based on sampling error. In this regard, we estimate the variance and the standard deviation of effect size as zero and conclude that there is no evidence that the effect size varies at all. So, when talking about the potential impact of the drug, we can assume that it will be pretty much the same for all populations.

### 3. Methods

A meta-analysis was performed following the preferred reporting items for systematic reviews and meta-analyses guidelines and prospectively registered PROSPERO. Publications and electronic databases of two independent reviews searched BMJ and Cochran reviews studies on influenza evaluating the effects of neuraminidase inhibitors in adults [13] and children [17] who were exposed or expected to have flu symptoms. A meta-analysis of the mean differences of Tamiflu and placebo was performed using random effects model meta-analysis. The keywords "Oseltamivir phosphate, Neuraminidase Inhibitors, Influenza, Relenza" were used in different combinations. Only those articles that discussed the effect of Tamiflu in adults were included in the final review.

Based on the objectives and the research questions of the study, the method of analysis employed is random effects model meta-analysis. The data was analyzed using Comprehensive Meta-Analysis version3 software.

- 1) The study effect size is simply the raw difference in means (DM)
 
$$DM = \bar{M}_E - \bar{M}_F = 140.600 - 165.500 = -24.900 \quad (1)$$
- 2)  $SD_{diff}$  is the standard deviation of within participant differences between E and F measurements and is given as

$$SD_{diff} = \sqrt{\frac{(N_1-1)SD_E^2 + (N_2-1)SD_F^2}{N_1+N_2-2}} = \sqrt{\frac{(932)15675.04 + (472)24492.25}{1404}} = \sqrt{18639.23} = 136.53 \quad (2)$$

- 3) The within study variance ( $\sigma^2$ )

$$V_i = \frac{1}{\left(\frac{N_1+1}{N_2}\right)} SD_{diff} = \left(\frac{984}{478}\right) 136.53 = \left(\frac{473}{934}\right) 136.53 = 69.1 \quad (3)$$

- 4) The summary effect size

$$\bar{T} = \frac{\sum_{i=1}^k w_i T_i}{\sum_{i=1}^k w_i} = \frac{-0.92528}{0.05520} = -16.759 \quad (4)$$

- 5) The variance of the summary effect size

$$V_m = \frac{1}{\sum_{i=1}^k w_i} = 18.113 \quad (5)$$

- 6) The standard error of the summary effect size

$$SE(\bar{T}) = \sqrt{V_m} = \sqrt{18.113} = 4.256 \quad (6)$$

- 7) The 95% confidence interval for the summary effect size

$$\text{Lower limit} = \bar{T} - 1.96 * SE(\bar{T}) = -16.759 - 1.96(4.256) = -25.101 \quad (7)$$

$$\text{Upper limit} = \bar{T} + 1.96 * SE(\bar{T}) = -16.759 + 1.96(4.256) = -8.418 \quad (8)$$

- 8) The Z-value is

$$Z = \frac{\bar{T}}{SE(\bar{T})} = \frac{-16.759}{4.256} = -3.938 \quad (9)$$

### 4. Results/ Discussion

For the treatment of adults, the output of the results shows that Tamiflu reduced the time to symptoms relief by a mean of -16.8 hours with 95% confidence interval 25.1 hours to 8.4 hours, which tells us that the mean difference in the universe of studies could fall anywhere in this range. Hence, the range does not include a difference of zero, which tells us that the true mean difference is probably not zero hour Figure [2]. The z-value is -3.938 with a corresponding p-value  $< 0.001$ , which represents a reduction in the mean time to relief of symptoms from 7 to 6 days. On average, across all relevant populations, the drug reduced the time to symptoms relief.

### 5. Conclusion

On the basis of the findings of this review, clinicians and healthcare policy-makers should urgently revise current recommendations for use of the neuraminidase inhibitors (in particular tamiflu) for individuals with flu. Our findings confirm that tamiflu reduces the time to symptomatic improvement in adults with flu-like illness.

The drug has non-specific effects on reducing the time to alleviation of flu symptoms in adults. The size of this effect is small, approximately half a day.

Based on these findings, there appears to be no evidence for patients, clinicians or policy-makers to use the drug to prevent serious outcomes, both in annual flu and pandemic

flu outbreaks. Practice recommendations and drug labelling need to be changed to reflect these findings.

Heterogeneity				Tau-squared			
Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
6.325	7	0.502	0.000	0.000	82.850	6864.187	0.000

Figure 1: Heterogeneity of effect size

Model	Study name	Statistics for each study							Difference in means and 95% CI				
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	-200.00	-100.00	0.00	100.00	200.00
	M76001	-24.900	8.281	68.581	-41.131	-8.669	-3.007	0.003					
	WV15670	-15.500	10.676	113.973	-36.424	5.424	-1.452	0.147					
	WV15671	-22.900	9.409	88.524	-41.341	-4.459	-2.434	0.015					
	WV15707	60.400	60.314	3637.761	-57.813	178.613	1.001	0.317					
	WV15730	-63.400	38.918	1514.585	-139.677	12.877	-1.629	0.103					
	WV15812/	-10.200	14.917	222.518	-39.437	19.037	-0.684	0.494					
	WV15819/	-7.400	10.744	115.438	-28.458	13.658	-0.689	0.491					
	WV16277	-5.000	12.436	154.644	-29.373	19.373	-0.402	0.688					
Random		-16.759	4.256	18.113	-25.101	-8.418	-3.938	0.000					

Figure 2: Results and 95% Confidence Interval

Table 1: The dataset

Study Name (In Code)	Tamiflu Mean Time to Relief	Tamiflu Standard Deviation	Tamiflu Sample Size (N)	Placebo Mean Time to Relief	Placebo Standard Deviation	Placebo Sample Size (N)
M76001	140.6	125.2	933	165.5	156.5	473
WV15670	129	114.6	240	144.5	118	235
WV15671	102.4	89.9	204	125.3	98.9	200
WV15707	154	166.5	17	93.6	134.4	9
WV15730	107.6	104.6	31	171	177.1	27
WV15812/872	193.7	152.3	199	203.9	146.3	202
WV15819/876/978	185	145.6	358	192.4	145.2	375
WV16277	138.7	138.4	226	143.7	125.4	225
Total Sample size			2,208			1,746

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