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APPENDICES ONLY

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Systematic review and economic decision modelling for the prevention and treatment of influenza A and B

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Health Technology Assessment
NHS R&D HTA Programme

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Appendix 1

All studies identified by the NI treatment systematic review

All zanamivir studies identified

TABLE 104 *Excluded studies*

Study ID	References
JNAI-01	1. Matsumoto K, Ogawa N, Nerome K, Numazaki Y, Kawakami Y, *et al*., and the GG167 Group. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. *Antivir Ther* 1999;**4**:61–8. 2. Matsumoto K, Nerome K, Numasaki Y, *et al*., Inhaled and intranasal GG167 in the treatment of influenza A and B: preliminary results. *International Congress Serves* (1996); 1123. Options for the Control of Influenza III. 1996; pp. 713–17.
JNAI-04	Personal communication with GlaxoSmithKline
JNAI-07	Personal communication with GlaxoSmithKline
NAI10901	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI10902	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIA1001	1. Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In Brown LE, Hampson AW, Webster RG, editors. Options for the Control of Influenza III, Amsterdam: Elsevier. 1996; pp. 718–25. 2. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996;**275**:295–9.
NAIA1002	1. Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In Brown LE, Hampson AW, Webster RG, editors. Options for the Control of Influenza III, Amsterdam: Elsevier. 1996; pp. 718–25. 2. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996;**275**:295–9.
NAIA1003	1. Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In Brown LE, Hampson AW Webster RG, editors. Options for the Control of Influenza III, Amsterdam: Elsevier. 1996; pp. 718–25. 2. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996;**275**:295–9.
NAIA1004	1. Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In Brown LE, Hampson AW Webster RG, editors. Options for the Control of Influenza III, Amsterdam: Elsevier. 1996; pp. 718–25. 2. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996;**275**:295–9.
NAIA1005	Walker JB, Hussey EK, Treanor JJ, Montalvo A, Hayden FG. Effects of the neuraminidase inhibitor zanamivir on otologic manifestations of experimental human influenza. *J Infect Dis* 1997;**176**:1417–22.
NAIA1006	Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. Brown LE, Hampson AW Webster RG. Options for the Control of Influenza III. 1996; pp. 718–25.
NAIA1008	Calfee DP, Peng AW, Hussey EK, Lobo M, Hayden FG. Safety and efficacy of once daily intranasal zanamivir in preventing experimental human influenza a infection. *Antivir Ther* 1999;**4**:143–9.
NAIA1009	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIA1010	Calfee DP, Peng AW, Hussey EK, Lobo M, Hayden FG. Safety and efficacy of once daily intranasal zanamivir in preventing experimental human influenza a infection. *Antivir Ther* 1999;**4**:143–9.
NAIB1001	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)

continued

TABLE 104 *Excluded studies (cont'd)*

Study ID	References
NAIB1002	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1003	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1004	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1005	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1007	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1008	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB1009	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB2001	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB2003	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI30011	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI30012	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI30015	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI30020	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI30028	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI40003	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI40004	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI40012	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAI40015	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)

TABLE 105 *Included studies*

Study ID	References	Participating countries
NAIA2005 NAIB2005	Hayden FG, Osterhaus ADME, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, *et al*. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med* 1997; **337**:874–80.	Belgium, Denmark, Finland, France, Germany, Ireland, Italy, The Netherlands, Norway, Spain, Sweden, UK
NAIB2007	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)	Australia, New Zealand, South Africa
NAIA2008 NAIB2008	Monto AS, Fleming DM, Henry D, de Groot R, Makela H, Klein T, *et al*. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza a and b virus infections. *J Infect Dis* 1999;**180**:254–61.	Canada, USA
NAIB3001	MIST. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group [see comments] [published errata appear in *Lancet* 1999 (Feb 6);**353**(9151):504 and 1999 (Mar 27);**353**(9158):1104]. *Lancet* 1998;**352**:1877–81.	Australia, New Zealand, South Africa
NAIA3002	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)	Canada, USA
NAIB3002	Makela MJ, Pauksens K, Rostila T, Fleming DM, Man CY, Keene ON, *et al*. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled european study. *J Infect* 2000;**40**:42–8.	Belgium, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden, UK
NAI30008	Murphy KR, Eivindson A, Pauksens K, Stein WJ, Tellier G, Watts R, *et al*. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstrucitve pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Invest* 2000;**20**:337–49.	Argentina, Australia, Austria, Belgium, Canada, Chile, Denmark, France, Germany, Hungary, Israel, Norway, Slovakia, South Africa, Sweden, UK, USA

continued

TABLE 105 *Included studies (cont'd)*

Study ID	References	Participating countries
NAI30009	Hedrick JA, Barzilia A, Behre U, Henderson FW, Hammond J, Reilly L, *et al*. Zanamivir in the treatment of symptomatic influenza A and B in children five to twelve years of age: a randomised controlled trial. *Pediatr Infect Dis J* 2000;**19**:410–17.	Belgium, Canada, Finland, France, Germany, Israel, Norway, Russia, Spain, Sweden, UK, USA
NAI30010	Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliott MJ, Hammond JM, *et al*. Inhaled Zanamivir for the prevention of influenza in families. *N Engl J Med* 2000;**343**:1282–9.	Canada, Finland, UK, USA

All oseltamivir studies identified

TABLE 106 *Excluded studies*

Study ID	References
M76001	Personal communication with Hoffman La Roche (not published)
M76006	ICAAC abstract 2000 (not published)
WV15759	Hoffman La Roche NICE submission, March 2002 (not published)
WV15871	Hoffman La Roche NICE submission, March 2002 (not published)
WV15707	Personal communication with Hoffman La Roche (not published)
Gubareva *et al*.	Gubareva LV, Tai CY, Mendel DB, Ives J, Carr J, Roberts NA, *et al*. Oseltamivir treatment of experimental influenza a/texas/36/91 (h1n1) virus infection in humans: selection of a novel neuraminidase variant. *Antivir Res* 2000;**46**:78.
Kashiwagi *et al*.	Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza – placebo-controlled double-blind multicenter phase III trial. *Kansenshogaku Zasshi* 2000;**74**:1044–61.
Hayden *et al*.	Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, *et al*. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;**282**:1240–6.

TABLE 107 *Included studies*

Study ID	References	Participating countries
WV15670	Nicholson KG, Aoki FY, Osterhaus ADME, Trottier S, Carewicz O, Mercier CH, *et al*. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet* 2000;**355**:1845–50.	Canada, China, Europe
WV15671	Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, *et al*. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group [see comments]. *JAMA* 2000;**283**:1016–24.	USA
WV15730	FDA1999 (http://www.fda.gov/cder/approval/index.htm)	Australia, South Africa
WV15812	FDA1999 (http://www.fda.gov/cder/approval/index.htm)	Not known
WV15872	Personal communication with Hoffman La Roche (not published)	Not known
WV15819	FDA1999 (http://www.fda.gov/cder/approval/index.htm)	Northern hemisphere
WV15876	Personal communication with Hoffman La Roche (not published)	Not known
WV15978	Personal communication with Hoffman La Roche (not published)	Not known
WV15758	Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, *et al*. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J* 2001;**20**:127–33.	USA

Appendix 2

Jadad instrument used for rating reported methodological quality

Quality assessment of RCTs:

Jadad Scale			**Score**
1. Was the study described as randomised?	☐ Yes	☐ No	
Was the method of randomisation described?	☐ Yes	☐ No	
If the method of randomisation was explained was it appropriate?	☐ Yes	☐ No	
Randomisation score:			/2
2. Was the study described as double blind?	☐ Yes	☐ No	
Was the method of double blinding described?	☐ Yes	☐ No	
If the method of blinding was explained was it appropriate?	☐ Yes	☐ No	
Double blind score:			/2
3. Was there a description of withdrawals and dropouts?	☐ Yes	☐ No	/1
Total score:			/5

Scoring of the Jadad Scale:

A) Give a score of 1 point for each 'yes' or 0 points for each 'no'. There are no in-between marks.

B) Give 1 additional point if:

C) For question 1, the method to generate the sequence of randomisation was described and it was **appropriate** (table of random numbers, computer generated, coin tossing, etc.)

and/or

If on question 2 the method of double-blinding was described and it was **appropriate** (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

For question 1, the method to generate the sequence of randomisation was described and it was **inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or

For question 2, the study was described as double-blind but the method of blinding was **inappropriate** (e.g. comparison of tablet vs injection with no double dummy)

Appendix 3

Methodology for meta-analysis of mean time to recovery type outcomes for economic model

For the economic model, mean values are required for the outcomes (1) mean number of days to symptom alleviation and (2) mean number of days to return to normal activities. This is required since the evaluation should be based on averages (i.e. average treatment benefit and average costs, etc.) to enable population totals to be estimated. If patients are censored (owing to drop-out or still being ill at the end of the study follow-up period), estimating the mean is not trivial and cannot be calculated by dividing total time patients are ill by the total number of patients. Hence it was decided to take a parametric survival analysis-type approach. We assumed that the survival (Kaplan–Meier) curve for time to recovery outcomes followed an exponential distribution. That is,

$$S(t) = \exp(-\lambda t) \quad (1)$$

where t is time, $S(t)$ is the proportion of patients still ill at time t and λ is the (constant) hazard.[481] Hence, rearranging equation (1) produces

$$\lambda = -\frac{\ln[S(t)]}{t} \quad (2)$$

This can be evaluated at the median time to recovery (t_{median}) and equation (2) becomes

$$\lambda = -\frac{\ln[0.5]}{t_{\text{median}}} \quad (2)$$

The mean of an exponential distribution is $1/\lambda$ with variance $1/\lambda^2$.

It is important to note that the measurement of time to an event is measured in days for zanamivir and hours for oseltamivir. Meta-analyses were performed on the original units and converted into days, where necessary, for input into the economic model.

Time to symptoms alleviated

Zanamivir

For time to event outcomes, two estimates of the mean time are reported in the tables below. The statistic labelled 'published' is the mean calculated from the median reported in the published literature, which makes no allowance for censoring. The statistics labelled '27 days' and '55 days' are the mean values calculated by GlaxoSmithKline from the data where for those individuals whose symptoms have not been alleviated by the end of the follow-up period a value of 27 or 55 days has been assumed. The statistic labelled 'Exp. assumption' is the mean calculated from the median provided on request from GlaxoSmithKline (using the method outlined above), which does allow for censored observations and is consistent with the Hoffman La Roche trial results (see the section Oseltamivir, p. 69). The latter is the mean used in the economic model. For each subgroup, the difference between the placebo group and the dosage licensed (inhaled 10 mg twice daily group) is reported. It is important to note that the time to outcome end-points is measured in days. Since these are calculated from diary entries completed twice daily by study participants, they are always rounded upwards to the nearest half day.

TABLE 108 *Mean number of days to the alleviation of symptoms for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI); *p*-value
NAIA/B2005	[*N* = 89; *R* = 83]	[*N* = 85; *R* = 80]	
Published	6.3 (0.3)	5.4 (0.3)	–0.8 (–1.7 to 0.0); $p = 0.05$
27 days	6.6 (0.6)	5.0 (0.5)	
55 days	6.6 (0.6)	5.4 (0.7)	
Exp. assumption	6.5 (0.7)	5.0 (0.6)	–1.4 (–3.2 to 0.3)
NAIB2007	[*N* = 101; *R* = 22]	[*N* = 96; *R* = 33]	
Published	NDA	NDA	NDA
27 days	21.7 (1.0)	18.3 (1.2)	
55 days	43.2 (2.2)	36.3 (2.7)	
Exp. assumption	NDA	NDA	NDA
NAIB3001	[*N* = 132; *R* = 104]	[*N* = 137; *R* = 117]	
Published	NDA	NDA	NDA
27 days	9.0 (0.8)	7.1 (0.6)	
55 days	13.7 (1.7)	10.0 (1.4)	
Exp. assumption	8.7 (0.8)	6.5 (0.6)	–2.2 (–4.2 to –0.1)
NAIA3002	[*N* = 214; *R* = 190]	[*N* = 276; *R* = 245]	
Published	NDA	NDA	NDA
27 days	7.0 (0.4)	6.4 (0.3)	
55 days	7.4 (0.6)	7.2 (0.6)	
Exp. assumption	8.7 (0.6)	7.2 (0.5)	–1.4 (–3.0 to 0.1)
NAIB3002	[*N* = 123; *R* = 101]	[*N* = 124; *R* = 111]	
Published	NDA	NDA	NDA
27 days	9.2 (0.7)	7.0 (0.6)	
55 days	11.9 (1.6)	9.5 (1.4)	
Exp. assumption	9.4 (0.9)	7.2 (0.7)	–2.2 (–4.4 to 0.1)
NAI30010	[*N* = 75; *R* = 71]	[*N* = 72; *R* = 68]	
Published	NDA	NDA	NDA
27 days	6.8 (0.6)	5.5 (0.4)	
55 days	7.8 (1.2)	5.5 (0.4)	
Exp. assumption	7.9 (0.9)	6.5 (0.8)	–1.4 (–3.8 to 1.0)
Pooled result[a]	8.2 (0.5)	6.5 (0.4)	–1.7 (–2.5 to –0.8)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

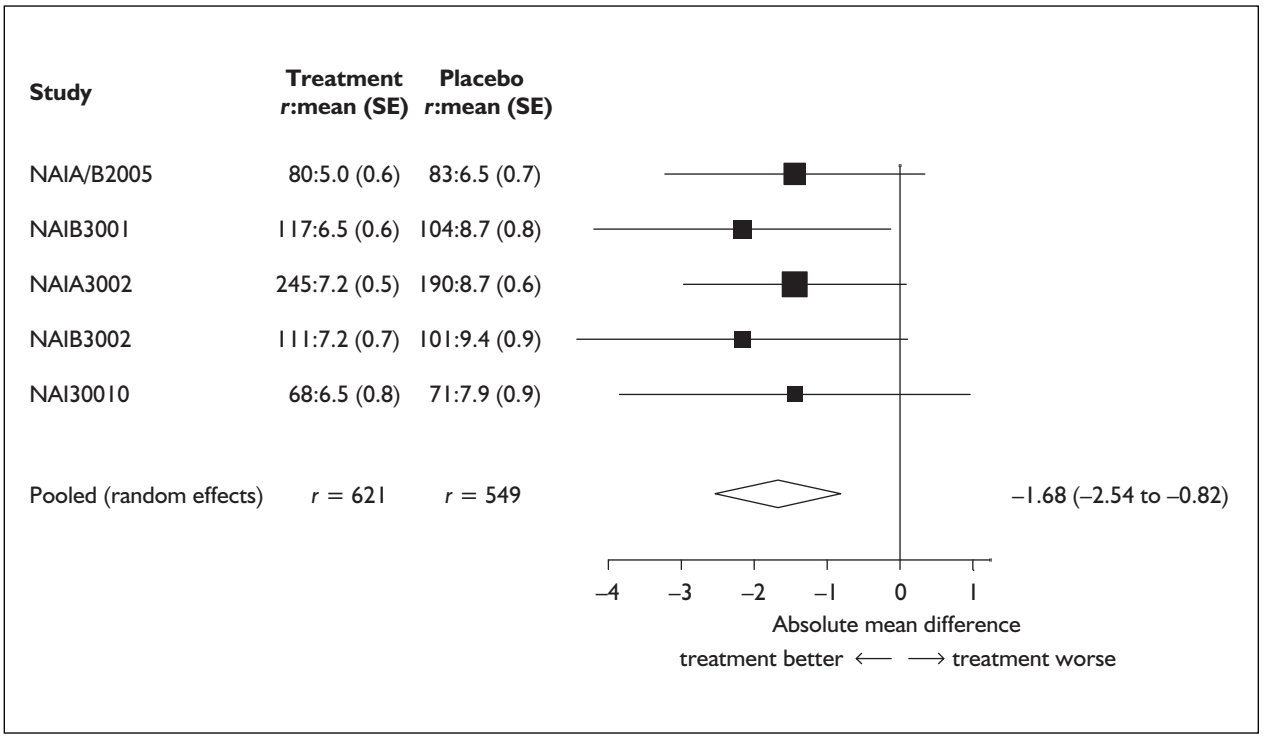


FIGURE 41 *Mean time to symptoms alleviated in days (random effects). Influenza positive 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 109 *Mean number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (influenza positive)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
JNAI-01			
NAIB2007	[*N* = 17; *R* = 5]	[*N* = 17; *R* = 9]	NDA
Published	NDA	NDA	
27 days	19.5 (3.2)	13.5 (3.2)	
55 days	39.3 (6.6)	26.1 (6.9)	
Exp. assumption	NDA	NDA	NDA
NAIB3001	[*N* = 28; *R* = 17]	[*N* = 24; *R* = 21]	
Published	NDA	NDA	NDA
27 days	13.2 (2.2)	7.2 (1.6)	
55 days	23.9 (4.9)	10.3 (3.5)	
Exp. assumption	11.5 (2.8)	7.2 (1.6)	–4.3 (–10.6 to 2.0)
NAIA3002	[*N* = 43; *R* = 28]	[*N* = 36; *R* = 32]	
Published	NDA	NDA	NDA
27 days	8.1 (1.0)	8.7 (1.2)	
55 days	8.1 (1.0)	11.3 (2.6)	
Exp. assumption	8.7 (1.4)	7.9 (1.4)	–0.7 (–4.6 to 3.2)
NAIB3002	[*N* = 18; *R* = 14]	[*N* = 12; *R* = 11]	
Published	NDA	NDA	NDA
27 days	13.4 (1.9)	8.6 (1.6)	
55 days	18.7 (4.6)	8.6 (1.6)	
Exp. assumption	16.6 (4.4)	13.0 (3.9)	–3.6 (–15.2 to 8.0)
NAI30008	[*N* = 153; *R* = 134]	[*N* = 160; *R* = 142]	
Published	NDA	NDA	NDA
27 days	9.1 (0.6)	7.7 (0.5)	
55 days	10.8 (1.0)	9.4 (1.0)	
Exp. assumption	10.1 (0.9)	7.2 (0.6)	–2.9 (–5.0 to –0.8)
NAI30010	[*N* = 6; *R* = 6]	[*N* = 4; *R* = 4]	
Published	NDA	NDA	NDA
27 days	10.2 (2.9)	4.6 (0.9)	
55 days	10.2 (2.9)	4.6 (0.9)	
Exp. assumption	15.1 (6.2)	6.1 (3.1)	–9.0 (–22.5 to 4.5)
Pooled result[a]	10.1 (0.7)	7.4 (0.5)	–2.7 (–4.4 to –1.0)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

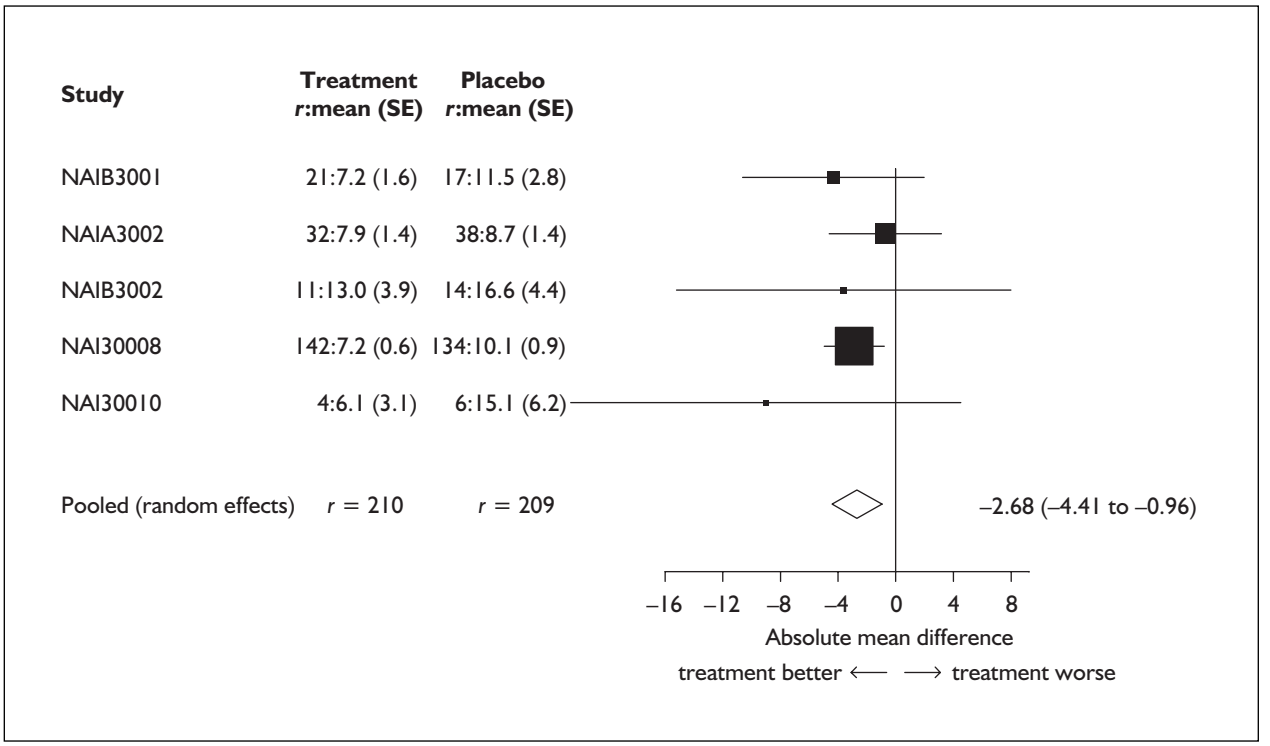


FIGURE 42 *Mean time to symptoms alleviated in days (random effects). Influenza positive 'at risk' including over 65-year-olds. Estimates with 95% CIs.*

TABLE 110 *Mean number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI); *p*-value
NAIA/B2005	[*N* = 89; *R* = 83]	[*N* = 85; *R* = 80]	
Published	6.3 (0.3)	5.4 (0.3)	–0.8 (–1.7 to 0.0); *p* = 0.05
27 days	6.6 (0.6)	5.0 (0.5)	
55 days	6.6 (0.6)	5.4 (0.7)	
Exp. assumption	6.5 (0.7)	5.0 (0.6)	–1.4 (–3.2 to 0.3)
NAIB2007	[*N* = 118; *R* = 27]	[*N* = 113; *R* = 42]	
Published	NDA	NDA	NDA
27 days	21.4 (1.0)	17.6 (1.2)	
55 days	42.9 (2.1)	34.8 (2.5)	
Exp. assumption	NDA	NDA	NDA
NAIB3001	[*N* = 160; *R* = 121]	[*N* = 161; *R* = 138]	
Published	NDA	NDA	NDA
27 days	9.8 (0.7)	7.1 (0.6)	
55 days	15.5 (1.7)	9.9 (1.3)	
Exp. assumption	8.7 (0.8)	6.5 (0.6)	–2.2 (–4.0 to –0.3)
NAIA3002	[*N* = 257; *R* = 228]	[*N* = 312; *R* = 277]	
Published	NDA	NDA	NDA
27 days	7.2 (0.3)	6.7 (0.3)	
55 days	7.5 (0.5)	7.6 (0.6)	
Exp. assumption	8.7 (0.6)	7.2 (0.4)	–1.4 (–2.9 to 0.0)
NAIB3002	[*N* = 141; *R* = 115]	[*N* = 136; *R* = 122]	
Published	NDA	NDA	NDA
27 days	9.7 (0.7)	7.1 (0.6)	
55 days	12.7 (1.5)	9.2 (1.3)	
Exp. assumption	10.8 (1.0)	7.2 (0.7)	–3.6 (–6.0 to –1.3)
NAI30008	[*N* = 153; *R* = 134]	[*N* = 160; *R* = 142]	
Published	NDA	NDA	NDA
27 days	9.1 (0.6)	7.7 (0.5)	
55 days	10.8 (1.0)	9.4 (1.0)	
Exp. assumption	10.1 (0.9)	7.2 (0.6)	–2.9 (–5.0 to –0.8)
NAI30009	[*N* = 182; *R* = 161]	[*N* = 164; *R* = 158]	
Published	NDA	NDA	NDA
27 days	6.8 (0.5)	4.7 (0.3)	
55 days	7.9 (0.9)	4.7 (0.3)	
Exp. assumption	7.2 (0.6)	5.8 (0.5)	–1.4 (–2.9 to 0.0)
NAI30010	[*N* = 81; *R* = 77]	[*N* = 76; *R* = 72]	
Published	NDA	NDA	NDA
27 days	7.0 (0.6)	5.5 (0.4)	
55 days	7.8 (1.0)	5.5 (0.4)	
Exp. assumption	7.9 (0.9)	6.5 (0.8)	–1.4 (–3.8 to 0.9)
Pooled result[a]	8.4 (0.5)	6.5 (0.3)	–1.9 (–2.5 to –1.2)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

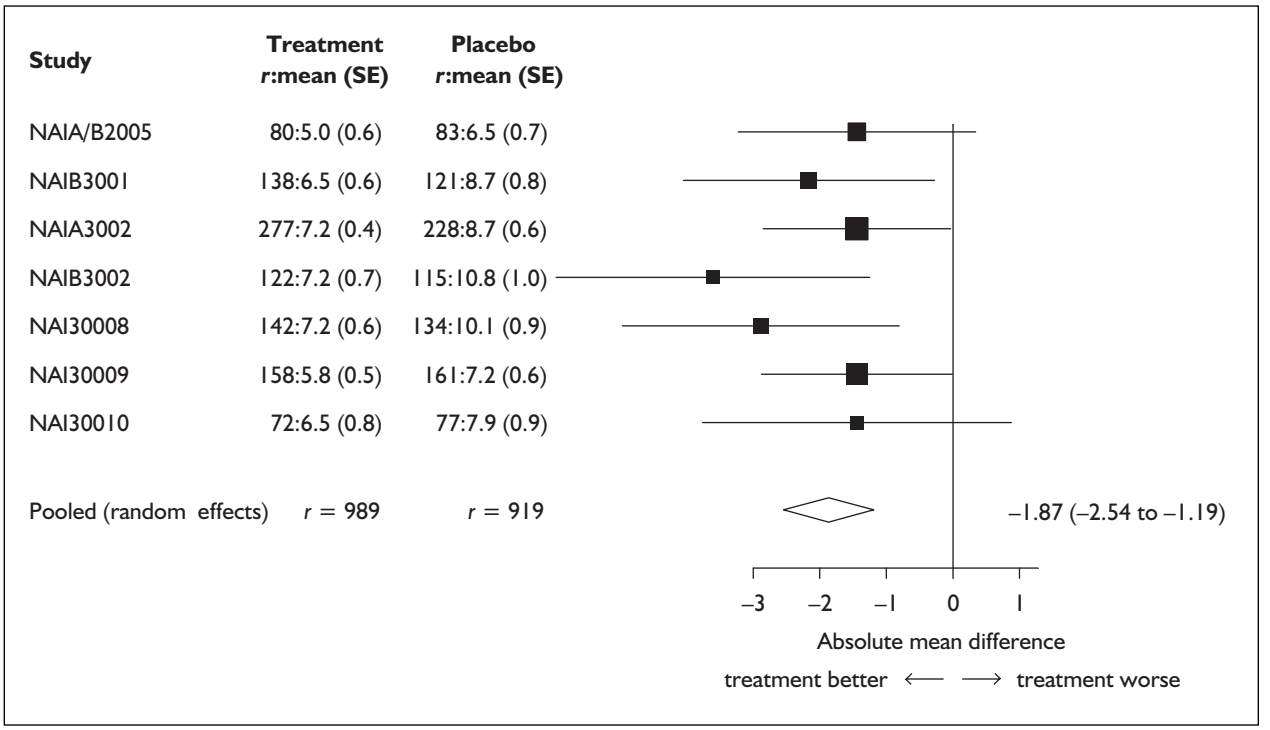


FIGURE 43 *Mean time to symptoms alleviated in days (random effects). Influenza positive all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

TABLE 111 *Mean number of days to the alleviation of symptoms for children in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
'Healthy'	[*N* = 172; *R* = 152]	[*N* = 152; *R* = 146]	
Published	NDA	NDA	
27 days	6.8 (0.5)	4.9 (0.3)	
55 days	7.9 (1.0)	4.9 (0.3)	
Exp. assumption	7.2 (0.6)	5.8 (0.5)	–1.4 (–2.9 to 0.0)
'High-risk'	[*N* = 10; *R* = 9]	[*N* = 12; *R* = 12]	
Published	NDA	NDA	
27 days	7.4 (2.3)	2.7 (0.6)	
55 days	10.2 (5.1)	2.7 (0.6)	
Exp. assumption	8.3 (2.8)	2.9 (0.8)	–5.4 (–11.1 to 0.3)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

Oseltamivir

For time to event outcomes, the estimate of the mean time allows for censored observations. For each subgroup, the difference between the placebo group and the dosage applied to be licensed (75 mg twice daily group) is reported. It is important to note that the time to outcome end-points in measured in hours. Since these are calculated from diary entries completed twice daily by study participants, they are always rounded. The statistic labelled 'biased' is the mean supplied by Hoffman La Roche but is acknowledged to be biased when the last observation is censored (which is the case here). The statistic labelled 'Exp. assumption' is the mean calculated from the median either provided by Hoffman La Roche or extracted from the published literature (using the method outlined above), which does allow for censored observations and is consistent with the Hoffman La Roche trial results (see the section 'Oseltamivir', p. 69). The latter is the mean used in the economic model.

TABLE 112 *Mean number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (ITT group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
WV15670	[*N* = 235; *R* = 191]	[*N* = 240; *R* = 211]	
Biased	144.5 (7.7)	129.0 (7.4)	
Exp. assumption	167.5 (12.1)	140.8 (9.7)	–26.7 (–57.1 to 3.7)
WV15671	[*N* = 200; *R* = 178]	[*N* = 204; *R* = 182]	
Biased	125.3 (7.0)	102.4 (6.3)	
Exp. assumption	139.9 (10.5)	110.1 (8.2)	–29.8 (–55.9 to –3.8)
WV15730[a]	[*N* = 27; *R* = 21]	[*N* = 31; *R* = 27]	
Biased	113.2 (12.7)	107.6 (19.1)	
Exp. assumption	158.5 (34.6)	107.5 (20.7)	–51.0 (–129.9 to 28.0)
Above 3 studies combined	[*N* = 462; *R* = 390]	[*N* = 475; *R* = 420]	
Biased	136.2 (5.2)	117.3 (5.0)	
Exp. assumption	152.0 (7.7)	120.0 (5.9)	
Pooled result[b]	153.1 (10.4)	121.3 (12.0)	–29.8 (–49.0 to –10.6)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.
[b] Based on Exp. assumption mean.

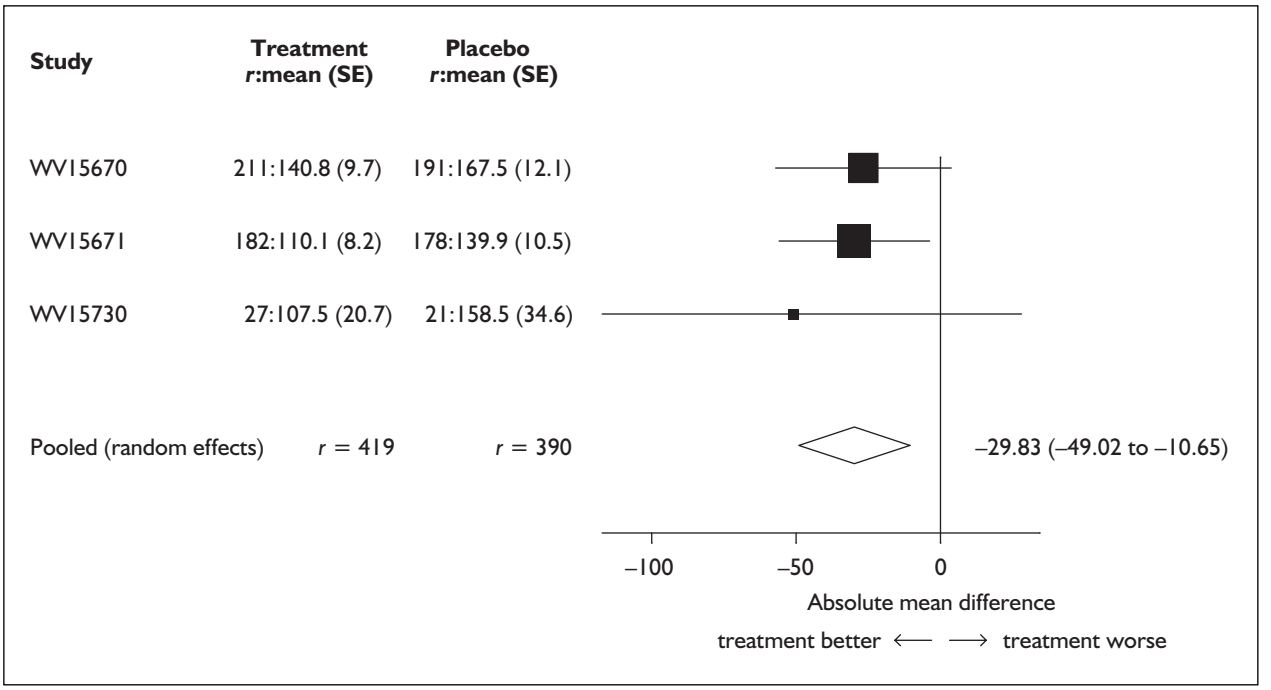


FIGURE 44 *Mean time to symptoms alleviated in hours (random effects). ITT 'non-risk' 12–65 year-olds. Estimates with 95% CIs.*

TABLE 113 *Mean number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
WV15670	[*N* = 161; *R* = 133]	[*N* = 157; *R* = 140]	
Biased	145.7 (9.2)	115.8 (7.4)	–29.9 (–53.0 to –6.7)
Exp. assumption	168.1 (14.6)	126.1 (10.7)	–42.0 (–77.3 to –6.6)
WV15671	[*N* = 128; *R* = 113]	[*N* = 121; *R* = 112]	
Biased	124.2 (7.9)	90.9 (6.8)	–33.3 (–53.7 to –12.9)
Exp. assumption	149.0 (14.0)	103.2 (9.7)	–45.8 (–79.3 to –12.3)
WV15730[a]	[*N* = 19; *R* = 15]	[*N* = 19; *R* = 17]	
Biased	134.2 (12.0)	108.2 (26.6)	–26.0 (–83.1 to 31.2)
Exp. assumption	207.6 (53.6)	112.8 (27.4)	–94.9 (–212.8 to 23.1)
Above 3 studies combined	[*N* = 308; *R* = 261]	[*N* = 297; *R* = 269]	
Biased	138.4 (6.1)	105.6 (5.2)	–32.8 (–48.6 to –17.0)
Exp Assumption	162.3 (10.0)	112.8 (6.9)	–49.5 (–73.4 to –25.7)
Pooled result[b]	159.8 (9.9)	113.8 (8.3)	–46.1 (–69.9 to –22.3)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.
[b] Based on Exp. assumption mean.

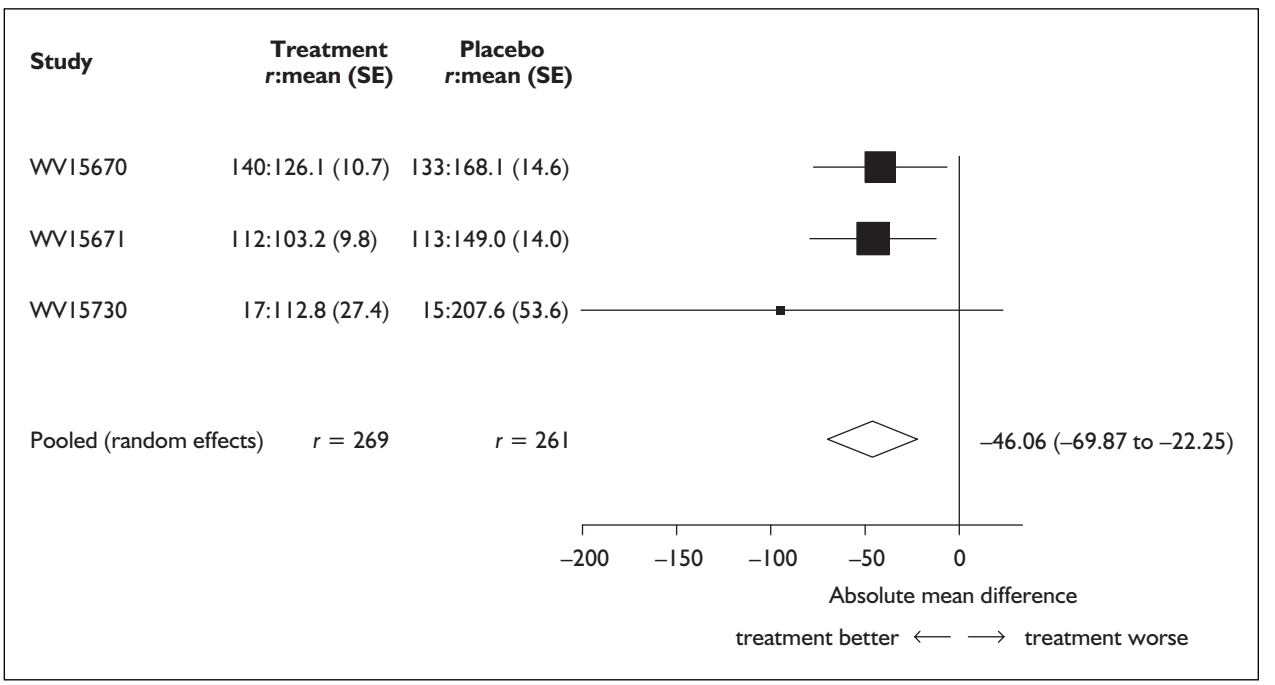


FIGURE 45 *Mean time to symptoms alleviated in hours (random effects). Influenza positive 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 114 *Mean number of hours to the alleviation of symptoms for 'high-risk' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
WV15812[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15872[a]	[Omitted because commercial in confidence]		
Biased			
Exp assumption			
Above 2 studies combined	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15819[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15876[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15978[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
Above 3 studies combined	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
Pooled result[b]	243.2 (17.8)	204.5 (17.2)	–36.0 (–87.3 to 15.3)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study.
[a] Unpublished studies.
[b] Based on Exp assumption mean.

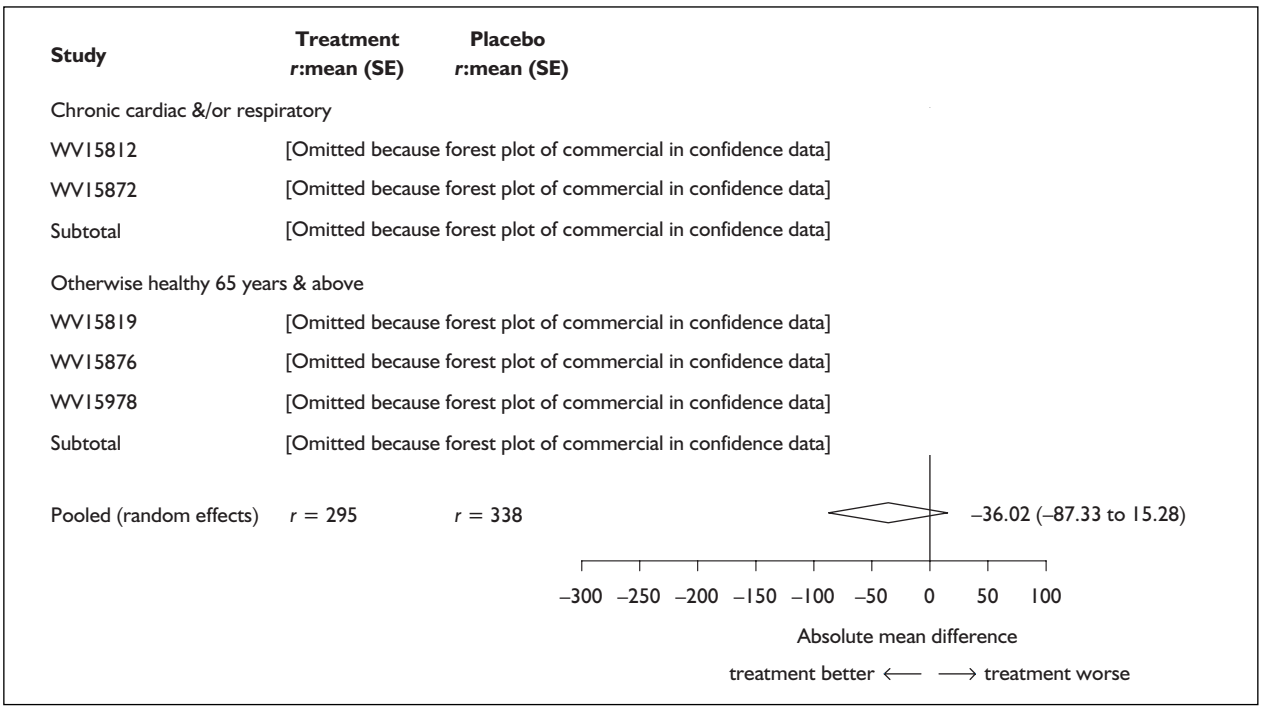


FIGURE 46 *Mean time to symptoms alleviated in hours (random effects). Influenza positive 'at risk' including over 65-year-olds. Estimates with 95% CIs.*

TABLE 115 *Mean number of hours to the alleviation of symptoms for children in the oseltamivir treatment trials (ITT group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
Time to freedom from illness	[*N* = 338; *R* = 319]	[*N* = 331; *R* = 310]	
Biased	159.6 (6.8)	130.2 (5.9)	
Exp. assumption	181.3 (10.2)	151.1 (8.6)	–29.4 (–47.1 to –11.6)
Duration of fever	[*N* = 324; *R* = 317]	[*N* = 321; *R* = 317]	
Biased	29.9 (1.8)	20.7 (1.4)	–9.2 (–13.8 to –4.6)
Exp. assumption			
Duration of cough	[*N* = 287; *R* = 277]	[*N* = 280; *R* = 273]	
Biased	82.9 (5.1)	64.8 (4.1)	–18.1 (–30.8 to –5.3)
Exp. assumption			
Duration of coryza	[*N* = 291;*R* = 281]	[*N* = 277; *R* = 269]	
Biased	74.6 (5.0)	62.3 (3.9)	–12.3 (–24.8 to 0.2)
Exp. assumption			

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

TABLE 116 *Mean number of hours to the alleviation of symptoms for children in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
Time to freedom from illness	[*N* = 225; *R* = 210]	[*N* = 209; *R* = 196]	
Biased	172.0 (8.7)	132.8 (7.9)	
Exp. assumption	197.6 (13.6)	146.1 (10.4)	-39.2 (-62.3 to –16.1)
Duration of fever	[*N* = 219; *R* = 214]	[*N* = 206; *R* = 205]	
Biased	34.0 (2.4)	20.8 (1.9)	–13.2 (–19.2 to –7.3)
Exp. assumption			
Duration of cough	[*N* = 197; *R* = 189]	[*N* = 183; *R* = 180]	
Biased	88.1 (5.9)	60.9 (4.6)	–27.2 (–41.9 to –12.5)
Exp. assumption			
Duration of coryza	[*N* = 196; *R* = 188]	[*N* = 179; *R* = 176]	
Biased	79.6 (5.6)	62.7 (4.7)	–16.8 (–31.2 to –2.5)
Exp. assumption			

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

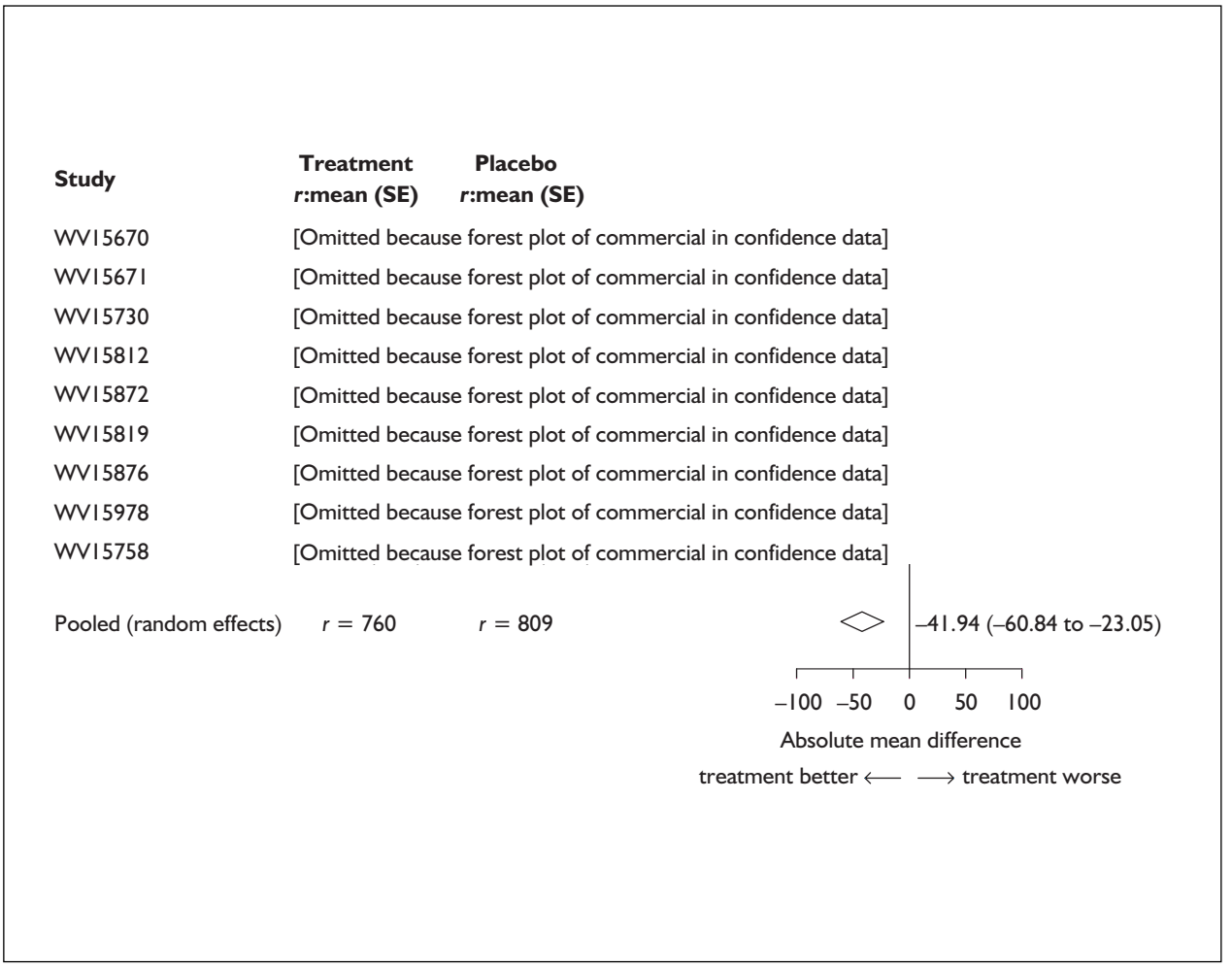


FIGURE 47 *Mean time to symptoms alleviated in hours (random effects). Influenza positive all data 'non-risk and at-risk'. Estimates with 95% CIs.*

Time to return to normal activities

Zanamivir

TABLE 117 *Mean number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
NAIA/B2005	[*N* = 89; *R* = 78]	[*N* = 85; *R* = 76]	
Published	4.9 (0.3)	4.6 (0.3)	
27 days	5.8 (0.8)	5.0 (0.7)	
55 days	8.3 (1.6)	6.8 (1.5)	
Exp. assumption	5.0 (0.6)	5.0 (0.6)	0 (–1.6 to 1.6)
NAIB2007	[*N* = 101; *R* = 53]	[*N* = 96; *R* = 52]	
Published	NDA	NDA	
27 days	13.7 (1.3)	13.1 (1.3)	
55 days	26.6 (2.7)	25.3 (2.8)	
Exp. assumption	5.0 (0.7)	5.0 (0.7)	0 (–1.9 to 1.9)
NAIB3001	[*N* = 132; *R* = 93]	[*N* = 137; *R* = 112]	
Published	NDA	NDA	
27 days	12.0 (0.8)	9.0 (0.7)	
55 days	19.4 (1.9)	12.9 (1.5)	
Exp. assumption	11.5 (1.2)	10.1 (1.0)	–1.4 (–4.4 to 1.6)
NAIA3002	[*N* = 214; *R* = 165]	[*N* = 276; *R* = 222]	
Published	NDA	NDA	
27 days	9.3 (0.5)	8.7 (0.4)	
55 days	10.2 (0.9)	10.4 (0.9)	
Exp. assumption	10.1 (0.8)	9.4 (0.6)	–0.7 (–2.7 to 1.3)
NAIB3002	[*N* = 123; *R* = 87]	[*N* = 124; *R* = 96]	
Published	NDA	NDA	
27 days	11.9 (0.9)	10.1 (0.8)	
55 days	17.1 (2.0)	14.5 (2.0)	
Exp. assumption	12.3 (1.3)	9.4 (1.0)	–2.9 (–6.1 to 0.3)
NAI30010	[*N* = 75; *R* = 74]	[*N* = 72; *R* = 71]	
Published	NDA	NDA	
27 days	5.5 (0.4)	4.9 (0.4)	
55 days	5.5 (0.4)	5.3 (0.8)	
Exp. assumption	7.2 (0.8)	6.5 (0.8)	–0.7 (–3.0 to 1.5)
Pooled result[a]	8.4 (1.2)	7.5 (1.0)	–0.6 (–1.5 to 0.3)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

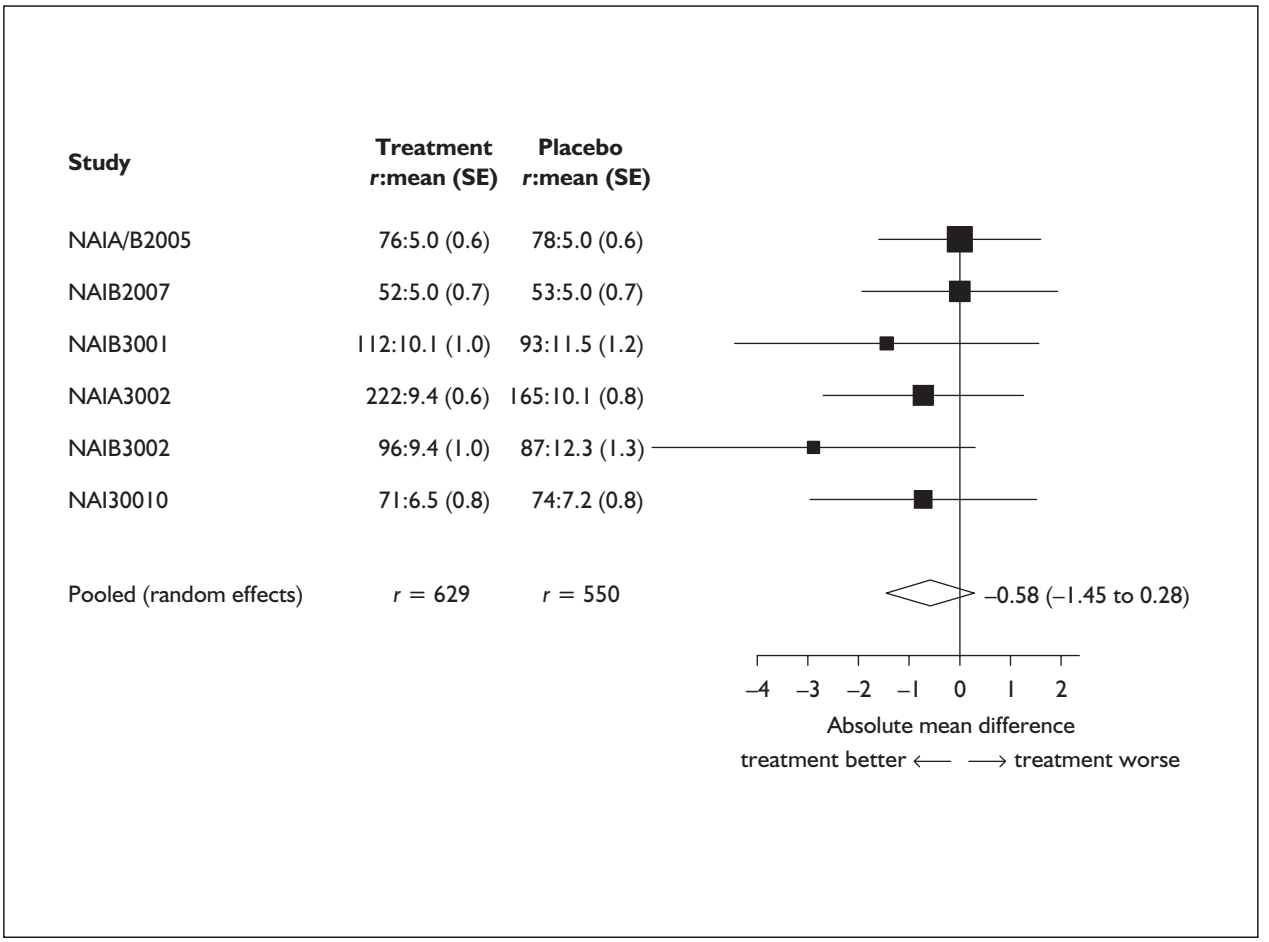


FIGURE 48 *Mean time to return to normal activities in days (random effects). Influenza positive all data 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 118 *Mean number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	**Mean (SE)**	**Mean difference (95% CI)**
NAIB2007	[*N* = 17; *R* = 8]	[*N* = 17; *R* = 13]	
Published	NDA	NDA	
27 days	14.3 (3.4)	6.1 (2.3)	
55 days	27.6 (7.2)	10.0 (4.9)	
Exp. assumption	5.0 (1.8)	5.0 (1.4)	0 (–4.4 to 4.4)
NAIB3001	[*N* = 28; *R* = 11]	[*N* = 24; *R* = 18]	
Published	NDA	NDA	
27 days	18.4 (2.1)	11.0 (2.0)	
55 days	34.5 (4.5)	18.0 (4.5)	
Exp. assumption	NDA	10.1 (2.4)	NDA
NAIA3002	[*N* = 43; *R* = 28]	[*N* = 36; *R* = 22]	
Published	NDA	NDA	
27 days	12.9 (1.5)	14.1 (1.5)	
55 days	17.0 (3.6)	18.7 (4.2)	
Exp. assumption	13.7 (2.6)	15.9 (3.4)	2.2 (–6.2 to 10.5)
NAIB3002	[*N* = 18; *R* = 11]	[*N* = 12; *R* = 10]	
Published	NDA	NDA	
27 days	16.1 (2.2)	10.2 (2.4)	
55 days	24.1 (5.7)	10.2 (2.4)	
Exp. assumption	20.9 (6.3)	12.3 (3.9)	–8.7 (–23.2 to 5.9)
NAI30008	[*N* = 153; *R* = 120]	[*N* = 160; *R* = 125]	
Published	NDA	NDA	
27 days	11.9 (0.7)	11.3 (0.7)	
55 days	16.3 (1.5)	16.3 (1.5)	
Exp. assumption	13.0 (1.2)	12.3 (1.1)	–0.7 (–3.9 to 2.4)
NAI30010	[*N* = 6; *R* = 5]	[*N* = 4; *R* = 3]	
Published	NDA	NDA	
27 days	11.2 (2.8)	10.9 (5.7)	
55 days	11.2 (2.8)	17.9 (13.1)	
Exp. assumption	23.8 (10.6)	8.7 (5.0)	–15.1 (–38.2 to 7.9)
Pooled result[a]	12.4 (2.6)	10.4 (1.9)	–0.6 (–3.1 to 1.8)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

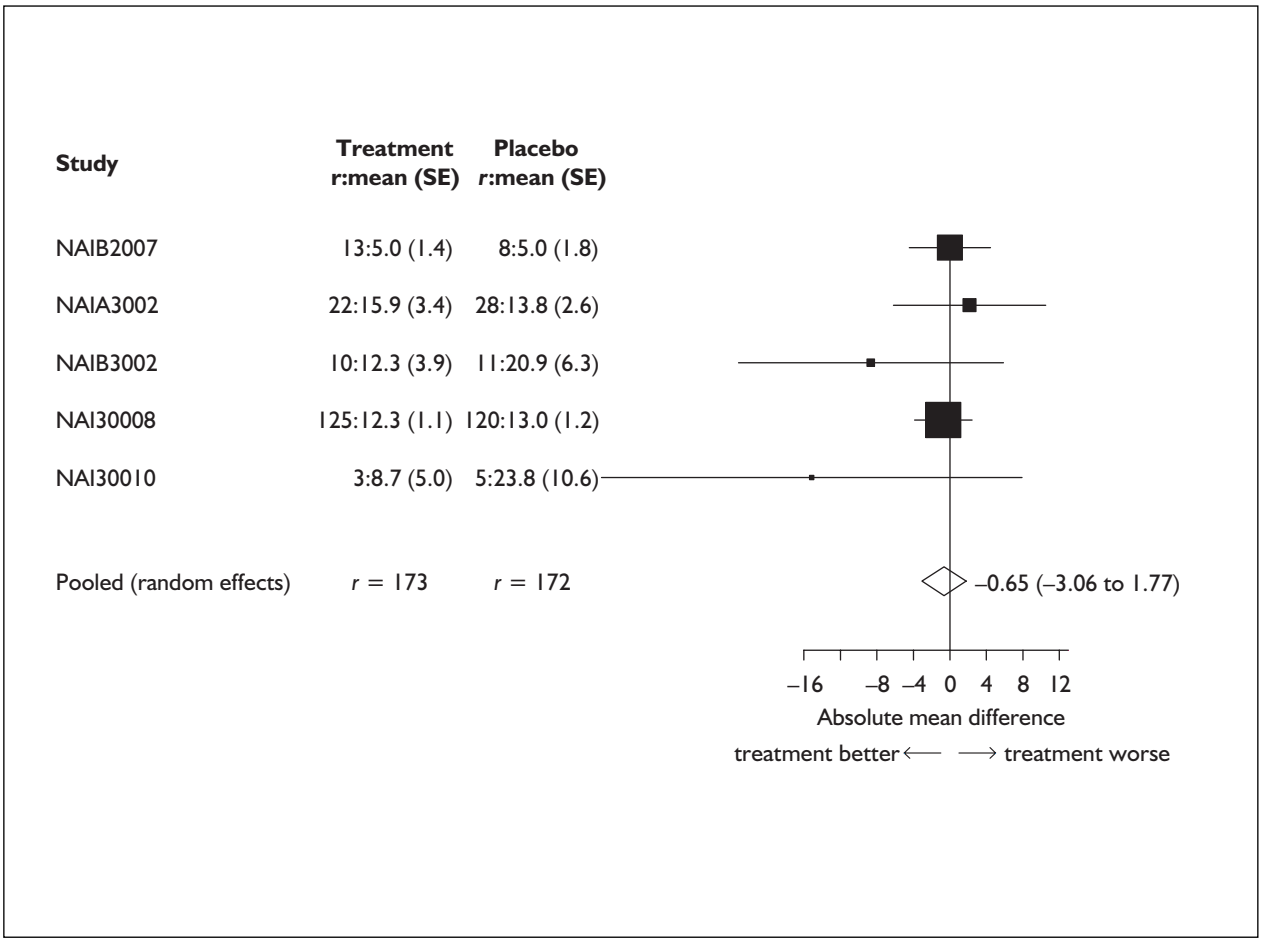


FIGURE 49 *Mean time to return to normal activities in days (random effects). Influenza positive 'at-risk' including over 65-year-olds. Estimates with 95% CIs.*

TABLE 119 *Mean number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
NAIA/B2005	[*N* = 89; *R* = 78]	[*N* = 85; *R* = 76]	
Published	4.9 (0.3)	4.6 (0.3)	
27 days	5.8 (0.8)	5.0 (0.7)	
55 days	8.3 (1.6)	6.8 (1.5)	
Exp. assumption	5.0 (0.6)	5.0 (0.6)	0 (–1.6 to 1.6)
NAIB2007	[*N* = 118; *R* = 61]	[*N* = 113; *R* = 65]	
Published	NDA	NDA	
27 days	13.8 (1.2)	12.1 (1.2)	
55 days	26.8 (2.5)	23.2 (2.5)	
Exp. assumption	5.0 (0.6)	5.0 (0.6)	0 (–1.8 to 1.8)
NAIB3001	[*N* = 160; *R* = 104]	[*N* = 161; *R* = 130]	
Published	NDA	NDA	
27 days	13.1 (0.8)	9.3 (0.7)	
55 days	22.0 (1.9)	13.6 (1.5)	
Exp. assumption	11.5 (1.1)	10.1 (0.9)	–1.4 (–4.3 to 1.4)
NAIA3002	[*N* = 257; *R* = 193]	[*N* = 312; *R* = 244]	
Published	NDA	NDA	
27 days	10.0 (0.5)	9.4 (0.4)	
55 days	11.5 (1.1)	11.4 (1.0)	
Exp. assumption	10.1 (0.7)	10.1 (0.6)	0 (–1.9 to 1.9)
NAIB3002	[*N* = 141; *R* = 98]	[*N* = 136; *R* = 106]	
Published	NDA	NDA	
27 days	12.4 (0.8)	10.1 (0.8)	
55 days	17.9 (1.9)	13.7 (1.9)	
Exp. assumption	12.3 (1.2)	10.1 (1.0)	–2.2 (–5.3 to 0.9)
NAI30008	[*N* = 153; *R* = 120]	[*N* = 160; *R* = 125]	
Published	NDA	NDA	
27 days	11.9 (0.7)	11.3 (0.7)	
55 days	16.3 (1.5)	16.3 (1.5)	
Exp. assumption	13.0 (1.2)	12.3 (1.1)	–0.7 (–3.9 to 2.4)
NAI30009	[*N* = 182; *R* = 155]	[*N* = 164; *R* = 151]	
Published	NDA	NDA	
27 days	7.6 (0.5)	6.6 (0.4)	
55 days	8.8 (1.2)	7.1 (0.8)	
Exp. assumption	8.7 (0.7)	7.9 (0.6)	–0.7 (–2.6 to 1.1)
NAI30010	[*N* = 81; *R* = 79]	[*N* = 76; *R* = 74]	
Published	NDA	NDA	
27 days	5.9 (0.4)	5.3 (0.5)	
55 days	5.9 (0.4)	6.0 (1.0)	
Exp. assumption	7.9 (0.9)	6.5 (0.8)	–1.4 (–3.7 to 0.8)
Pooled result[a]	9.1 (1.1)	8.3 (0.9)	–0.5 (–1.3 to 0.2)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Based on Exp. assumption mean.

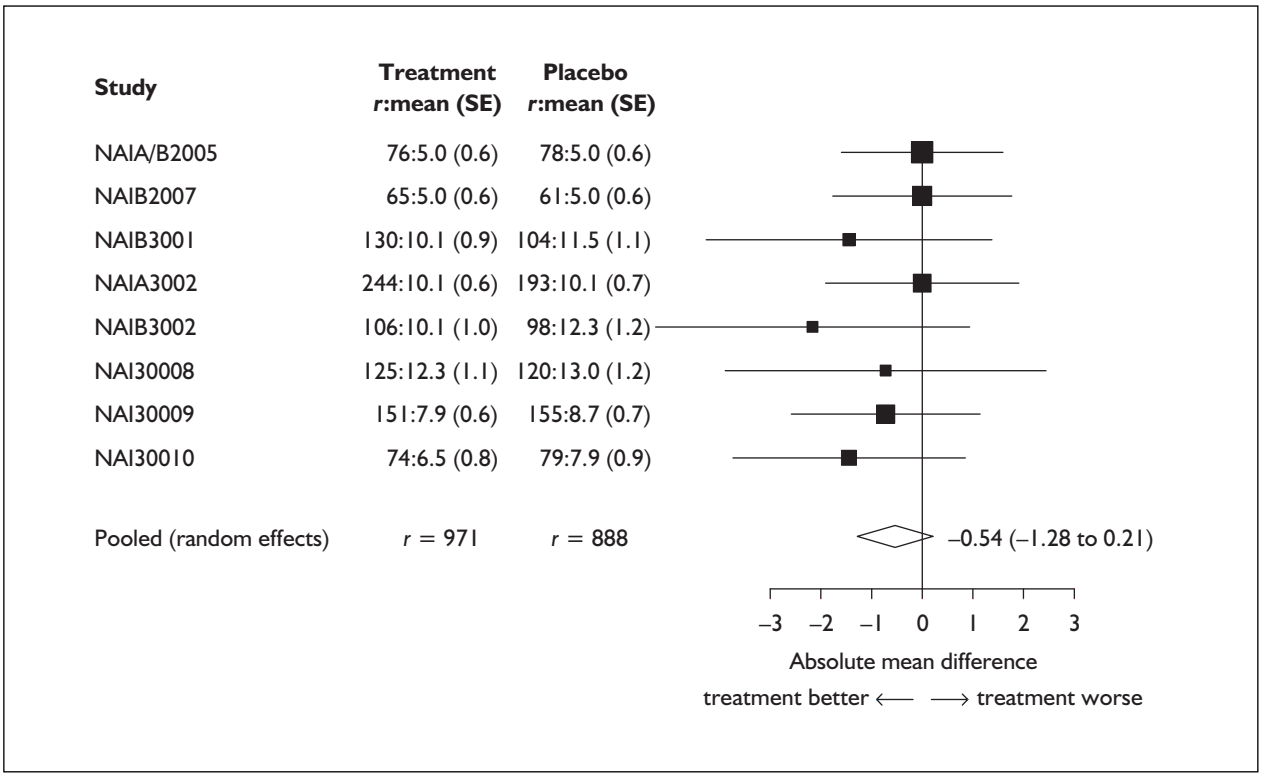


FIGURE 50 *Mean time to return to normal activities in days (random effects). Influenza all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

TABLE 120 *Mean number of days to return to normal activities for children in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
'Healthy'	[*N* = 172; *R* = 147]	[*N* = 154; *R* = 139]	
Published	NDA	NDA	
27 days	7.6 (0.5)	6.6 (0.4)	
55 days	8.7 (1.1)	7.2 (0.8)	
Exp. assumption	8.7 (0.7)	7.9 (0.7)	–0.7 (–2.6 to 1.2)
'High-risk'	[*N* = 10; *R* = 8]	[*N* = 12; *R* = 12]	
Published	NDA	NDA	
27 days	10.4 (2.9)	5.5 (0.8)	
55 days	16.0 (6.6)	5.5 (0.8)	
Exp. assumption	10.1 (3.6)	6.5 (1.9)	–3.6 (–11.5 to 4.3)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

Oseltamivir

TABLE 121 *Mean number of hours to return to normal activities for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
WV15670	[*N* = 161; *R* = 103]	[*N* = 157; *R* = 119]	
Biased	212.0 (15.9)	164.3 (9.5)	
Exp. assumption	251.4 (24.8)	183.3 (16.8)	–68.0 (–126.7 to –9.4)
WV15671	[*N* = 128; *R* = 90]	[*N* = 121; *R* = 106]	
Biased	197.3 (16.6)	128.7 (6.3)	
Exp. assumption	193.5 (20.4)	155.5 (15.1)	–38.0 (–87.7 to 11.8)
WV15730[a]	[*N* = 19; *R* = 9]	[*N* = 19; *R* = 13]	
Biased	193.3 (15.7)	225.5 (52.0)	
Exp. assumption	315.6 (105.2)	188.6 (52.3)	–127.0 (–357.2 to 103.3)
Combined	[*N* = 308; *R* = 202]	[*N* = 297; *R* = 238]	
Biased	205.5 (11.3)	159.0 (8.0)	
Exp. assumption	225.5 (15.9)	181.3 (11.8)	
Pooled result[b]	226.2 (26.8)	168.9 (11.0)	–52.6 (–90.0 to –15.1)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished studies
[b] Based on Exp. assumption mean.

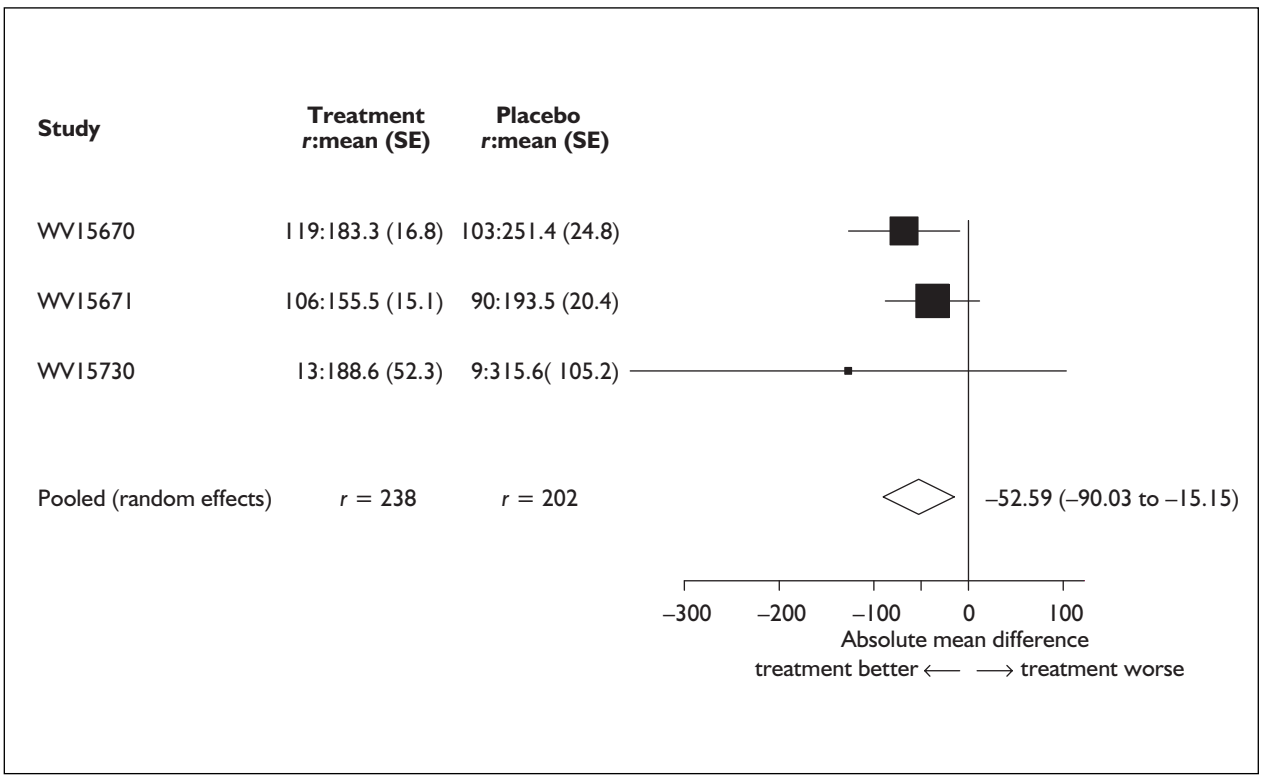


FIGURE 51 *Mean time to return to normal in hours (random effects). Influenza 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 122 *Mean number of hours to return to normal activities for 'high-risk' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
WV15812[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15872[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
Combined	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15819[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15876[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
WV15978[a]	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
Combined	[Omitted because commercial in confidence]		
Biased			
Exp. assumption			
Pooled result[b]	523.0 (34.9)	424.6 (42.3)	–95.1 (–181.5 to –8.8)

N, no. of individuals in the stud;. *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study.
[a] Unpublished studies.
[b] Based on Exp. assumption mean.

Study	Treatment *r*:mean (SE)	Placebo *r*:mean (SE)	
Chronic cardiac and/or respiratory			
WV15812	[Omitted because forest plot of commercial in confidence data]		
WV15872	[Omitted because forest plot of commercial in confidence data]		
Subtotal	[Omitted because forest plot of commercial in confidence data]		
Otherwise healthy ⩾65 years			
WV15819	[Omitted because forest plot of commercial in confidence data]		
WV15876	[Omitted because forest plot of commercial in confidence data]		
WV15978	[Omitted because forest plot of commercial in confidence data]		
Subtotal	[Omitted because forest plot of commercial in confidence data]		
Total (random effects)	*r* = 227	*r* = 253	–95.12 (–181.47 to –8.77)

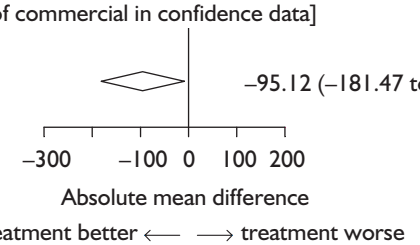


FIGURE 52 *Mean time to return to normal activities in days (random effects). Influenza positive 'at-risk' including over 65-year-olds. Estimates with 95% CIs.*

TABLE 123 *Mean number of hours to normal health and activities for children in the oseltamivir treatment trials*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Mean (SE)	Mean (SE)	Mean difference (95% CI)
Influenza positive	[*N* = 225; *R* = 204]	[*N* = 209; *R* = 204]	
Biased	128.7 (7.3)	93.7 (4.8)	
Exp. assumption	161.1 (11.3)	96.8 (6.8)	–64.3 (–90.1 to –38.5)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

Data transformation and summary

As noted in Chapter 3, time to event outcomes for the zanamivir and oseltamivir trials were measured to the nearest half day and nearest hour, respectively. Hence, to include both drugs in the same economic model it was necessary to place results for both products on the same metric. Although the oseltamivir outcomes had the more precise outcome, days are the metric chosen for the analysis. *Tables 124–127* summarise the transformed data that are actually used in the economic model, all of which were derived from the analyses presented above.

TABLE 124 *Mean time to symptoms alleviated – zanamivir*

Group	Placebo (pooled estimate)		Treatment (pooled estimate)		Difference (treatment –placebo)	
	Mean	SE	Mean	SE	Mean	SE
'High-risk'	10.07	0.74	7.38	0.51	–2.68	0.88
'Healthy'	8.17	0.51	6.49	0.43	–1.68	0.44

TABLE 125 *Mean time to symptoms alleviated – oseltamivir*

Group	Placebo (pooled estimate)		Treatment (pooled estimate)		Difference (treatment –placebo)	
	Mean	SE	Mean	SE	Mean	SE
'High-risk'	10.13	0.74	8.52	0.72	–1.50	1.09
'Healthy'	6.66	0.41	4.74	0.34	–1.92	0.51

TABLE 126 *Mean time to return to normal activities – zanamivir*

Group	Placebo (pooled estimate)		Treatment (pooled estimate)		Difference (treatment –placebo)	
	Mean	SE	Mean	SE	Mean	SE
'High-risk'	12.39	2.64	10.41	1.87	–0.65	1.23
'Healthy'	8.39	1.22	7.52	0.96	–0.58	0.44

TABLE 127 *Mean time to return to normal activities – oseltamivir*

Group	Placebo (pooled estimate)		Treatment (pooled estimate)		Difference (treatment –placebo)	
	Mean	SE	Mean	SE	Mean	SE
'High-risk'	21.79	0.45	17.69	0.76	–3.96	1.84
'Healthy'	9.43	0.12	7.04	0.46	–2.19	0.80

Appendix 4

All studies identified by the NI prophylaxis systematic review

All zanamivir studies identified

TABLE 128 *Excluded studies*

Study ID	References
NAIB2002	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIB2004	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIA2006	Peng AW, Hussey EK, Moore KH. A population pharmacokinetic analysis of zanamivir in subjects with experimental and naturally occurring influenza: effects of formulation and route of administration. *J Clin Pharmacol* 2000;**40**:242–249. Notes: Glaxo Wellcome, Research Triangle Park, NC 27709, USA
NAIB2006	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIA3003	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)
NAIA3004	GlaxoSmithKline Clinical Trials Register (http://ctr.glaxowellcome.co.uk)

TABLE 129 *Included studies*

Study ID	References	Participating countries
NAIA2009 NAIB2009	Kaiser L, Henry D, Flack NP, Keene O, Hayden FG. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. *Clin Infect Dis* 2000;**30**:587–9.	Canada, USA
NAIA2010	Schilling M, Povinelli L, Krause P, Gravenstein M, Ambrozaitis A, Jones HH, *et al*. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. *Vaccine* 1998;**16**:1771–4.	USA
NAIA3005	Monto AS, Robinson DP, Herlocher ML, Hinson JM, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults – a randomized controlled trial. *JAMA* 1999;**282**:31–35.	USA
NAI30010	Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliott MJ, Hammond JM, *et al*. Inhaled Zanamivir for the prevention of influenza in families. *N Engl J Med* 2000; **343**:1282–9.	Canada, Finland, UK, USA

All oseltamivir studies identified

TABLE 130 *Excluded studies*

Study ID	References
WV15708	FDA1999 (http://www.fda.gov/cder/approval/index.htm)
Kashiwagi *et al*., 2000	Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza–placebo-controlled double-blind multicenter phase III trial. *Kansenshogaku Zasshi* 2000;**74**:1062–76.
Kashiwagi *et al*., 2000	Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza – placebo-controlled double-blind multicenter phase III trial. *Kansenshogaku Zasshi* 2000;**74**:1044–61.

TABLE 131 *Included studies*

Study ID	References	Participating countries
WV15825	Peters PH, Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, *et al*. Long term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail elderly population. *J Am Geriatr Soc* 2001;**49**:1025–31.	Europe, USA
WV15673 WV15697	Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, *et al*. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;**341**:1336–43.	USA
WV15799	Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, *et al.*, and Oseltamivir Post Exposure Prophylaxis Investigator Group. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomised controlled trial. *JAMA* 200;**285**:748–54.	Europe, North America

Appendix 5

All studies identified by the amantadine systematic review of use in children and the elderly

All amantadine studies of children identified

TABLE 132 *Excluded studies*

Study ID	References
Children's prophylaxis studies	
Galbraith, 1969[251]	Galbraith AW, Oxford JS Schild GC Watson GI. Protective effect of 1-adamantanamine hydrochloride on influenza A2 infections in the family environment: a controlled double blind study. *Lancet* 1969;**2**(7629):1026–8.
Galbraith, 1969[252]	Galbraith AW, Oxford JS Schild GC Watson GI. Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. *Bull World Health Organ* 1969;**41**:677–82.
Schapira ,1971	Schapira M, Oxford JS, Galbraith AW. A study of 1-adamantamine hydrochloride during the 1970 Hong Kong influenza epidemic. *J R Coll Gen Pract* 1971;**21**:695–7.
Wright, 1976	Wright PF, Khaw KT, Oxman MN, Shwachman H. Evaluation of the safety of amantadine-Hcl and the role of respiratory viral infections in children with cystic fibrosis. *J Infect Dis* 1976;**134**:144–9.
Children's treatment studies	
Galbraith, 1971	Galbraith AW, Oxford JS, Schild GC, Potter CW, Watson GI. Therapeutic effect of 1-adamantanamine hydrochloride in naturally occurring influenza A2/Hong Kong infection. *Lancet* 1971;113–5.
Galbraith, 1973	Galbraith AW, Schild GC, Potter CW, Watson GI. The therapeutic effect of amantadine in influenza occurring during the winter of 1971–2 assessed by double-blind study. *J Royal Coll Gen Pract* 1973;**23**:34–7.

TABLE 133 *Included studies*

Study ID	References	Participating countries
Children's prophylaxis studies		
Quilligan, 1966	Quilligan JJ, Hirayama M, Baernstein HD. The suppression of A2 influenza in children by the chemoprophylactic use of amantadine. *J Pediatr* 1966;**69**:572–5.	USA
Finklea, 1967	Finklea JF, Hennessy AV, Davenport FM. A field trial of amantadine prophylaxis in naturally-occurring acute respiratory illness. *Am J Epidemiol* 1967;**85**:403–12.	USA
Leung, 1979	Leung P, McIntosh K, Chai H. Amantadine prophylaxis against influenza A/USSR in children with chronic asthma. *Am Acad Allergy* 1979;**63**(19).	USA
Children's treatment studies		
Kitamoto, 1968	Kitamoto O. Therapeutic effectiveness of amantadine hydrochloride in Influenza A2. *Jpn J Tuberculosis Chest Dis* 1968;**15**:17–26.	Japan
Kitamoto, 1970	Kitamoto O. Therapeutic effectiveness of amantadine hydrochloride in naturally occurring Hong Kong influenza-double-blind studies. *Jpn J Tuberculosis Chest Dis* 1971;**17**:1.	Japan

All amantadine studies of elderly identified

TABLE 134 *Excluded studies*

Study ID	References
Elderly prophylaxis studies	
Drinka, 1998	Drinka PJ, Gravenstein S, Schilling M, Krause P, Miller BA, Shult P. Duration of antiviral prophylaxis during nursing home outbreaks of influenza A: a comparison of 2 protocols. *Arch Intern Med* 1998;**158**:2155–9.
Galbraith, 1969a	Galbraith AW, Oxford JS, Schild GC, Watson GI. Protective effect of 1-adamantanamine hydrochloride on influenza A2 infections in the family environment: a controlled double blind study. *Lancet* 1969;1026–8.
Galbraith 1969b	Galbraith AW, Oxford JS, Schild GC, Watson GI. Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. *Bull World Health Organ* 1969;**41**:677–82.
Schapira, 1971	Schapira M, Oxford JS, Galbraith AW. A study of 1-adamantamine hydrochloride during the 1970 Hong Kong influenza epidemic. *J R Coll Gen Pract* 1971; **21**:695–7.
Galbraith	Cranage Hall Hospital. Study was not published but was referred to in Alliance Pharmaceutical's submission to NICE.
Elderly treatment studies	
Galbraith, 1971	Galbraith AW, Oxford JS, Schild GC, Potter CW, Watson GI. Therapeutic effect of 1-adamantanamine hydrochloride in naturally occurring influenza A2/Hong Kong infection. *Lancet* 1971;**2**(7716)113–15.
Galbraith, 1973	Galbraith AW, Schild GC, Potter CW, Watson GI. The therapeutic effect of amantadine in influenza occurring during the winter of 1971–2 assessed by double-blind study. *J R Coll Gen Pract* 1973;**23**,34–7.

TABLE 135 *Included studies*

Study ID	References	Participating countries
Elderly prophylaxis studies		
Pettersson, 1980	Pettersson RF, Hellstrom PE, Penttinen K, Pyhala R, Tokola O, Vartio T, *et al*. Evaluation of amantadine in the prophylaxis of influenza A (H1N1) virus infection: a controlled field trial among young adults and high-risk patients. *J Infect Dis* 1980;**142**:377–82.	Finland
Leeming,	Leeming JT. Amantadine hydrochloride and the elderly. *BMJ* 1969;313–14 (Abstract).	UK

Appendix 6

Effectiveness outcomes

The cost-effectiveness models comparing the different strategies for the treatment and prevention of influenza used effectiveness evidence drawn from (i) a systematic review of the effectiveness of zanamivir (Chapters 3 and 4), (ii) a systematic review of the effectiveness of oseltamivir (Chapters 3 and 4), (iii) a systematic review of amantadine for the elderly and children (Chapter 5) and (iv) a Cochrane review of amantadine and rimantadine in healthy adults.[4] It is important to note that the effectiveness outcome(s) of interest defined in the trials of the different interventions were not immediately comparable. For example, the NI trials measured outcomes in terms of 'time to symptoms alleviated' whereas the amantadine trials measured 'time to fever alleviated'. Also, within the NIs, zanamivir trials measured time to symptoms alleviated to the nearest half day, whereas for oseltamivir trials, time to symptoms alleviated was measured in hours.

It is important to note that the pooled estimates for time to symptoms alleviated for the control groups of oseltamivir and zanamivir were different. A random effects meta-analysis was used to pool the time to symptoms alleviated in the control groups across all trials of NIs. This resulted in a pooled estimate for the time to symptoms alleviated of 7.7 days for adults (SE 0.44), 10.0 days for high-risk (SE 0.48) and 6.5 days for children (SE 0.44). For amantadine, the time to fever alleviated was obtained from the relevant Cochrane review.[4] This information was modified to include only studies where a dose of 100 mg was used.[560–562] The rate obtained was 2.16 days in the treatment group and 3.17 days in the control group.

Data were obtained from some of the oseltamivir trials for both time to symptoms alleviated and time to fever days alleviated, thus enabling the relationship between the two outcomes to be investigated using meta-regression methodology. The results of this meta-regression are represented graphically in *Figure 53*. The regression equation was estimated as follows:

time to symptoms alleviated (hours) =
66.64 (SE = 30.65) + 1.32 (SE = 0.33) ×
time to fever alleviated (hours)

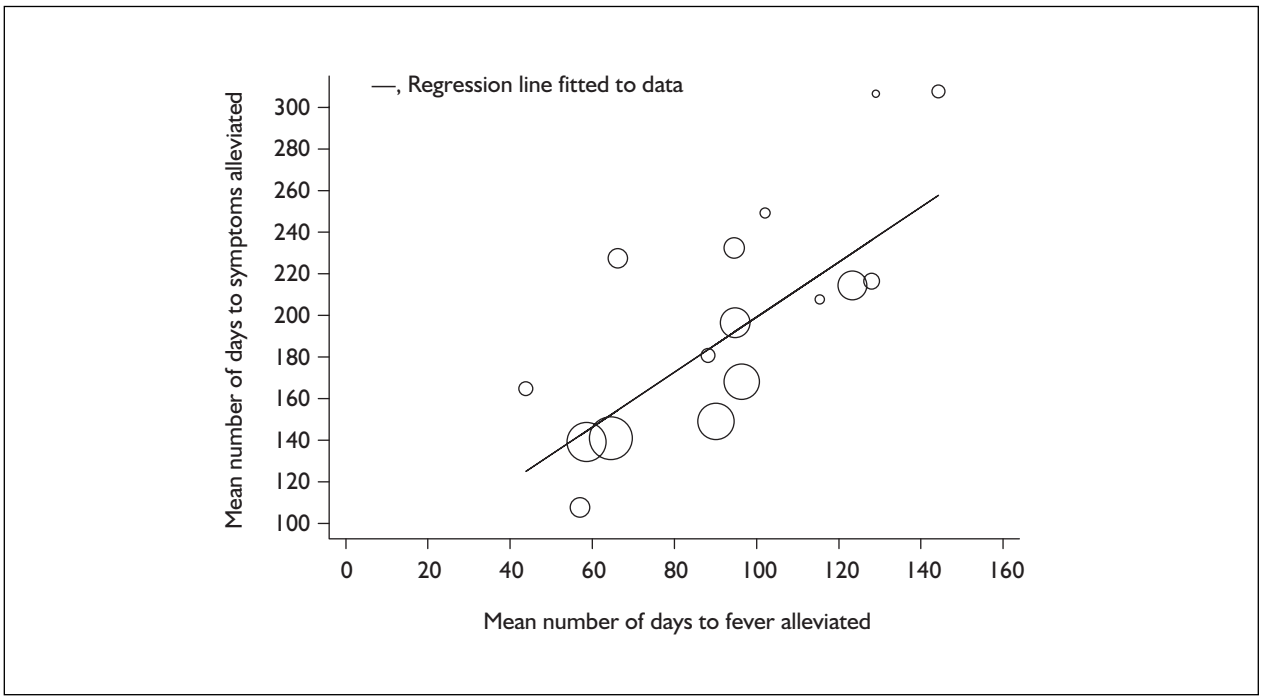


FIGURE 53 *Relationship between length of fever and length of illness from the oseltamivir trials*

This equation was applied to estimate time to symptoms alleviated in the treatment and control arms (and the difference) for amantadine. When converted into days, the resulting time to symptoms alleviated was estimated as 6.97 days for the placebo group and 5.63 days for the amantadine treatment group, thus giving a difference between amantadine treatment and control of 1.34 IDA.

In all cases the values used in the cost-effectiveness model were total time to symptoms alleviated. This was estimated by subtracting the differences in time to symptoms alleviated between treatment and control groups (see Chapter 3) from the pooled time to symptoms alleviated for both NI drugs combined (see above) assuming the only difference between outcomes to be the definition of time to symptoms alleviated. The appropriateness of this assumption was examined by a meta-regression of the difference in time to symptoms alleviated between treatment and control groups against the time to symptoms alleviated in the control group only. The meta-regression showed there to be no association between these two variables (i.e. the difference remained constant regardless of the time to symptoms alleviated in the control group).

Appendix 7

Quality-adjusted life expectancy

Using data from the WHO annual mortality statistics for males and females in England and Wales, we estimated the mean age at which influenza deaths occur. Taking the midpoint of each age category as the reference point, we estimated a mean age of 51years for influenza deaths amongst both males and females in the 15–64-year-old age range. Mean age of death from influenza in paediatrics is 3 years. Estimates in those aged >65 years were taken from Ahmed and colleagues,[143] since the WHO data were not reported in sufficiently precise age bands. The mean age of death for those aged >65 years is 84 years. This figure was derived by assuming a mean age of death for >95-year-olds of 97 years.

To calculate the number of life years lost through influenza death, life tables[563] for England and Wales, 1998–2000, were used. Mean life expectancy at age 51 years is 27 years for males and 31 years for females. At age 84 years the average life expectancy for males is 5.46 years and for females 6.76 years. At age 3 years the life expectancy for males is 72.92 years and for females 77.63 years. This process assumes that those individuals who die from influenza would otherwise have had a normal life expectancy for someone of their age. This may not be the case, as those who die of influenza may be a less healthy subgroup. Therefore, these results may overstate the benefit of preventing influenza deaths.

For the base-case analysis, a discount rate of 1.5% for benefits was calculated. Sensitivity analysis covered the ranges 0% and 6%. Years of life saved were quality weighted according to the mean valuations of health for each age given by respondents to the MVH study.[540,541] In the children's model we assumed full health for years of life prior to 18 years of age as the MVH study only covers adults.

Appendix 8

Valuation of adverse events

Oseltamivir prophylaxis trials reported both withdrawals and upper gastrointestinal events. Zanamivir prophylaxis trials reported withdrawals and tolerance. These events were considered minor and were excluded from the model. Adverse events from amantadine were considered more serious. Reports on side-effects of amantadine have been generated largely from placebo-controlled studies in healthy young volunteers. Amantadine is eliminated from plasma wholly by renal tubular secretion and glomerular filtration. The half-life of amantadine is inversely related to creatinine clearance and it increases with ageing owing to decreased renal function. Amantadine causes dose-related adverse events.[272] Dosage reductions are therefore necessary in people with renal dysfunction (assessed by serum creatinine and estimates of creatinine clearance). Amantadine side-effects usually appear within 2–3 hours of drug ingestion during the first 2–4 days of treatment.[263]

The effectiveness of amantadine and rimantadine for preventing and treating influenza A in healthy adults aged 14–60 years has been the subject of a Cochrane review by Jefferson and colleagues[509] (*Table 136*). Of the four events reported in the prophylaxis trials (gastrointestinal, dermatological, increased CNS, decreased CNS), the last two were considered the most serious. These cover events such as malaise, depression, fatigue, vertigo and 'feeling drunk'. This review estimated adverse events from both 100- and 200-mg trials. To include evidence only from 100-mg studies for healthy adults we estimated the OR for adverse events from two published studies.[564,565] The incidence of side-effects to amantadine in the elderly is less well documented, but the available data on the use of amantadine to control outbreaks of influenza indicate that reactions are more debilitating and potentially more serious. Serious side-effects [e.g. marked behavioural changes, delirium, hallucinations, agitation, seizures (convulsions and falls)] have been associated with high plasma drug concentrations and have been observed most often in persons who have renal dysfunction, a history of fits or certain psychiatric disorders, and among the elderly. We found no direct evidence for the OR of adverse events in high-risk groups. However, we used an estimate of the OR for withdrawals from a published study by Pettersson and colleagues.[71] This gave a value of 2.31, which was modified by the relationship between the odds value of adverse events and withdrawals (1.66/2.46 = 0.67), seen in the Cochrane review.[4] This gave an OR for adverse events for high-risk individuals of 1.55 (95% CI: 0.57 to 4.18).

We estimated the EQ-5D status for persons suffering from these conditions from expert opinion. The associated valuations were 0.81 in the healthy adult group and 0.74 in the elderly group. We assumed the impact on paediatrics to equate to that of healthy adults. Length of illness from amantadine adverse events was assumed to be 5 days. For prophylaxis, the value of adverse events was not included in the base case but was added as a sensitivity analysis. For an elderly population the proportion of people suffering adverse events is likely to be higher than for a younger population. Evidence was taken from a number of studies relating to withdrawals from amantadine treatment. This is presented in *Table 137*.

A meta analysis was carried out on the data presented in *Table 137*. A random effects meta-analysis was used and this estimated the probability of a withdrawal to be 12.8% (95% CI 9.2 to 17.5%). The rate for control or rimantadine groups was 4% (95% CI 2.1 to 7.5%).

There have been comparatively few studies of amantadine treatment or prophylaxis in children. The following studies provide no evidence to suggest that amantadine is tolerated any differently in children compared with healthy adults: Quilligan and colleagues,[531] Finklea and colleagues,[530] Wright and colleagues,[70] Rose,[566] Payler and Purdham[567] and Davies and colleagues.[568]

TABLE 136 *Adverse events from amantadine prophylaxis*

	OR (95% CI)	Low OR (95% CI)	High OR (95% CI)	RR	Rate in experimental group (%)	Rate in control group (%)	Control rate × RR (%)	Control rate – low	Control rate – high	Difference	Difference (low)	Difference (high)
Gastrointestinal	2.16	1.5	3.11	2.22	5.11	2.41	5.4	0.0366	0.0789	0.029436	0.012484	0.054833
Increased CNS	2.11	1.64	2.11	2.22	7.46	4.70	10.5	0.0794	0.1046	0.057597	0.032453	0.057597
Decreased CNS	1.71	1.33	2.19	1.80	8.60	7.12	12.8	0.0970	0.1704	0.057061	0.025786	0.099209
Dermatological	1.66	0.41	6.71	1.67	1.09	0.65	1.1	0.0027	0.0456	0.004361	–0.00387	0.03902
All	1.66	1.36	2.01	1.78	14.71	10.42	18.6	0.1473	0.2342	0.081585	0.043055	0.129941
Withdrawals	2.46	1.62	3.74	2.55	5.89	2.41	6.1	0.0396	0.0964	0.037289	0.01551	0.072289

Source: developed from information contained in Jefferson and colleagues, 2000.[4]

TABLE 137 *Amantadine adverse events in elderly and high-risk patients*

Author	Population (age, mean/ median, years)	Withdrawals due to possible adverse reactions/ total receiving amantadine (%, 95% CI)	Withdrawals due to possible adverse reactions/ total receiving placebo or rimantadine or in comparison to baseline period (%, 95% CI)
O'Donoghute, *et al*., 1973[569]	78	0/50	NA
Petterson, *et al*., 1980[71]	78	3/94 (3.2, 0 to 6.8)	2/101 (2.0, 0 to 4.7)
Petterson, *et al*., 1980[71]	58	11/72 (15.3, 7 to 23.6)	4/63 (6.3, 0.3 to 12.3)
Atkinson, *et al*., 1986[229]	~22	9/78 (11.5, 4.5 to 18.5)	NA
Arden, *et al*., 1988[281]	74	4/55 (7.3, 0.4 to 14.2)	NA
Peters, *et al*., 1989[282]	60's	7/59 (11.9, 3.6 to 20.2)	NA
Degelau, *et al*., 1990[280]	86	8/55 (14.5, 5.2 to 23.8)	NA
Stange, *et al*., 1991[279]	87	21/96 (21.9, 14.2 to 30.2)	6/96 (6.3, 1.5 to 11.1)
Chapman, 1993[284]	83	0/106	NA
Staynor, *et al*., 1994[285]	NA	4/76 (5.3, 0.3 to 10.3)	NA
Drinka, *et al*., 1998[286]	NA	22/218 (10.1, 6.1 to 14.1)	NA
		70/283 (24.7, 19.5 – 29.9)	NA
Keyser, *et al*., 2000[287]	84	27/156 (17.3, 11.3 to 23.3	3/156 (1.9%, 0 to 4)
Total		186/1398 (13.3%)	15/413 (3.6%)

Appendix 9

Cost of vaccination

The cost of vaccination was made up from a number of cost items. These are summarised in *Table 138*. For the cost of vaccinations a range of costs were obtained for vaccines; these ranged from £3.98 to £5.72.[546] A mean was calculated without reference to the relative frequency of use of these vaccines. This gave a price of £5.17 for vaccines. Added to this information were data from the Prescription Pricing Authority (PPA) (personal communication from PPA) regarding additional relevant reimbursements made to GPs. These are shown in *Table 138*. Additional incentive payments made for vaccinations given to the elderly were excluded as non-economic costs.

TABLE 138 *Costs of vaccination for patients aged <65 years*

		£
a	Personal administration fee	1.65
b	Vaccine cost	5.17
c	Dispensing fee	1.00
d	Container allowance	0.03
e	On cost allowance 10.5% basic cost of vaccine	0.54
	Total	8.40

Appendix 10

Derivation of cost for inpatient stays

Mean duration of stay was estimated for adults, children and the elderly. The mean duration of stay for the high-risk group utilised the estimates for the elderly. This figure was combined with estimates of mean cost per day and was inflated to account for intensive care facility use.

The complications of influenza are predominantly respiratory. These include acute bronchitis, laryngotracheobronchitis in children (croup), bronchiolitis (children), pneumonia, lung abscess, emphysema and exacerbations of chronic bronchitis, asthma and cystic fibrosis. Cardiovascular complications include heart failure and myocardial infarction. Loss of diabetic control resulting in hospitalisation is a recognised complication of influenza. Other complications including disorders of the CNS (e.g. febrile convulsions, encephalopathy), gastrointestinal tract (e.g. haematemesis), musculoskeletal system (e.g. myositis) and renal system (e.g. myoglobinuric renal failure) are uncommon. The principal reason for hospitalisation is for cardiopulmonary complications.

Children

There is a paucity of data on the duration of hospitalisation for influenza and complications in children. A major problem is the generally poor understanding of the broad spectrum of influenzal complications in children [including non-specific febrile illness, febrile convulsions, ARI (e.g. otitis media, croup, bronchiolitis and pneumonia) and gastrointestinal illness] that can lead to hospitalisation. Accordingly, there are few data on the duration of hospitalisation for the diverse presentations of influenza, both in the UK and abroad. It is questionable whether hospital episode statistics that focus on the duration of hospitalisation of children and adults for 'influenza' provide an accurate picture.

An additional concern is that hospitalisation rates and the duration of hospitalisation for influenza complications may vary substantially from country to country. Sugaya and colleagues,[63] for example, reviewed 244 children who were admitted to a general hospital in Japan during the 1989–90 epidemic of influenza A and B. Fifty-three children (mean age 4.8 ± 3.4 years) were admitted; the mean hospital stay was 8.2 ± 3.9 days. This figure is virtually identical with the means of 8.0 and 8.1 days for 'influenza due with identified virus' reported in the 1999–2000 and 2000–01 hospital episode statistics for adults and children (the mean age during each period being 27 years and 19 years respectively) (source: www.doh.gov.uk/hes). However, since the mean duration of hospitalisation for children (mean age 3.3 years) presenting with 'fever' (including children admitted with 'serious illness including pneumonia and meningitis) in England is only 2 days,[570] it is probable that the mean duration of hospitalisation in England for influenza-related complications approximates to 2 days.

In Leicester during the 2001–02 winter, a prospective study was conducted of the burden of ARI in children aged under 6 years who were referred to the Leicester Children's Hospital (Simons P: personal communication, preliminary data). A total of 26 children (age: range, 5–70 months; mean, 23.2 months) had laboratory-confirmed influenza. Cases were recruited to the study if they presented with respiratory illness or other conditions including gastrointestinal illness or convulsions. Clinical presentations (some co-existing) included URTI in eight, tonsillitis in two, otitis media in two, croup in four, LRTC in four, pneumonia in one, febrile convulsions in three non-specific viral illness in three and gastroenteritis in one. The mean duration of hospitalisation was approximately 2.3 days for the three-quarters of the referrals who were admitted.

Adults

England and Wales

Ahmed and colleagues[215] identified 303 admissions to 15 Leicestershire hospitals whose primary discharge diagnosis or cause of death was influenza, pneumonia, emphysema, or bronchitis during the influenza epidemic in 1989–90 (1 December to 31 January). Hospital case notes were available for 264 admissions. The median duration of hospitalisation for 260 cases was 7 days (mean approximately 10 days, range 1–54 days).

TABLE 139 *Duration of hospitalisation for and mean age of admissions for conditions that may occur as complications of influenza derived from DH annual 'Inpatient data based on hospital episode statistics'*

	Mean age of admissions (years)			Mean (median) duration of stay (days)		
Condition (diagnostic code)	**1998–9**	**1999–2000**	**2000–1**	**1998–9**	**1999–2000**	**2000–1**
Bronchiolitis (J21)	<1	1	1	2.9 (2)	3.0 (2)	2.8 (2)
Croup (J05)	3	3	4	0.9 (1)	0.8 (1)	0.9 (1)
Otitis media (H65)	11	11	12	1 (1)	1 (1)	0.8 (1)
Influenza (J10)	16	27	19	8.3 (4)	8.0 (4)	8.1 (5)
Viral pneumonia (J12)	23	24	15	6.2 (4)	7.2 (3)	6.2 (3)
Asthma (J45)	27	28	28	3.3 (2)	3.3 (2)	3.6 (2)
Acute sinusitis (J01)	35	36	35	2.6 (2)	2.8 (2)	2.8 (2)
Acute bronchitis (J20)	43	44	40	6.1 (3)	5.3 (3)	5.1 (2)
Pneumonia (J18)	62	64	62	13.4 (6)	12.8 (6)	13.4 (6)
COPD (J44)	72	72	72	10.4 (7)	10.2 (7)	10.4 (7)
Heart failure (I50)	77	77	77	13.1 (8)	13.1 (8)	13.1 (8)

Watkins[571] examined the impact of pneumonia, influenza (P & I) and bronchitis on acute hospital services using hospital activity analysis data in Southeast Wales during 1991–7. The average length of stay for P & I was 11.8 days.

Nguyen-Van-Tam and colleagues[572] studied the association between community influenza activity and acute hospital admissions for P & I among elderly persons in three English health districts, Lincolnshire, Nottingham and Southern Derbyshire, with a total population of 700,000. For the three winter seasons 1996/7–8/9, the median length of stay for P & I in persons aged ≥ 65 years was 12 days.

The DH provides annual 'Inpatient data based on hospital episode statistics' (*source*: www.doh.gov.uk/hes). The mean duration of stay for 'P & I (Codes J10–J18) during 1998–9, 1999–2000 and 2000–1 was 13.0, 12.6, and 13.2 days, respectively. The DH data on mean duration of hospitalisation are not stratified by age. However, the distribution of days of hospitalisation for P & I is skewed, since the median duration of hospitalisation was only 6 days each year. The mean age of the P & I admissions was 60, 62 and 61 years, respectively, suggesting that the disparity between the mean and median length of hospitalisation may be related to complications in frail 'high-risk' elderly who have little social support and the more severe influenza illness associated with ageing. Of note, 48.6, 50.6 and 50.1 of P & I admissions each year occurred in those aged >75 years.

In the USA, data on the mean duration of hospitalisation for the principal disease categories is stratified by age. Data on the duration of hospitalisation for 'pneumonia' reveal a 2-fold increase in duration in the elderly in comparison with children. [*source*: www.cdc.gov].

The mean duration of hospitalisation for conditions included in the diagnostic codes for P & I (J10–J18) and other conditions that may complicate influenza increase with age (see *Table 139*). Accordingly, we adjusted the UK mean value for duration of hospitalisation due to P & I using the rate ratios observed in the USA. We chose the year 1998–9 (mean duration for P & I hospitalisation, 13 days), because its average length of stay is intermediate between the means for the years 1999–2000 and 2000–1.

We use the estimates of duration for P & I hospitalisation for adults and children aged 6–14 years in *Table 140* for the health economic analyses. For children aged <6 years we assume a mean duration of hospitalisation of 2.3 days, based on observations in Leicester, and means of 0.8–3.0 days for otitis media, croup and bronchiolitis (*Table 139*).

Use of intensive care facilities

The proportion of hospitalisations for influenzal complications that require admission to the intensive care unit (ICU) and ventilation in the UK is unknown. However, at least 22 (4.9%) of 453 patients admitted to British hospitals in 1982–3 were given assisted ventilation. It is likely that a higher percentage would be ventilated now. In Rochester, NY, USA, during several influenza seasons during the early 1990s, 37 of 205 (18%)

TABLE 140 *Estimated duration of hospitalisation (days) for P & I (J10–J18) stratified by age*

All ages	6–14 years	15–44 years	45–64 years	>65 years
13	7.6	10.4	13.4	15

TABLE 141 *Estimated costs of hospitalisation for P & I (J10–J18) stratified by age*

		Age (years)				
		<6	15–44	45–64	Adults combined	>65 years
a	Estimated mean duration of hospitalisation (days)	2.3	10.4	13.4	11.9	15
b	Mean estimated cost of hospitalisation (£)	711.5	1963	2529	2246	2458
c	ICU costs (adults) 4.9% of mean daily cost (£1193) × period of ventilation	–	1257	1257	1257	1257
d	Total costs (b + c)	711.5	3220	3786	3503	3715

elderly (≥ 65 years) patients with influenza A who were hospitalised were admitted to the ICU and 19 (9%) were ventilated.[118]

The health economic analyses assumes that currently at least 4.9% of adults admitted with P & I as a complication of influenza receive assisted ventilation in an ICU. We further assume that the length of ITU stay and mechanical ventilation are 28 days and 21.5 days, respectively.[573]

Unit costs of hospitalisations

Costs of hospitalisations were calculated by reference to the National Schedule for Reference Costs.[574] The mean daily cost per day of admission for adults was taken from HRG code D14 (Lobar, Atypical or Viral Pneumonia <70 without complications or co-morbidities) and equates to £189 per day.

The mean daily cost per day of admission for the elderly was taken from HRG code D13 (Lobar, Atypical or Viral Pneumonia >69 or with complications or co-morbidities) and equates to £164 per day. The mean daily cost per day of admission for children was taken from HRG code P04 (lower respiratory tract disorders) and equates to £309. This figure was used since HRG P04 is based on a shorter mean duration of stay. The mean cost for admission to an intensive care unit is £1193 per day. The values used are given in *Table 141*.

Sensitivity analysis

The impact of variations in the cost of hospitalisations is explored in the probabilistic treatment models. The variation is based on the upper and lower 50% of hospital trust HRG costs.

Appendix 11

Derivation of propensity to consult GP

This was derived from the attack rate, population estimates and excess GP consultations. Details of the data used are described below

Attack rate

Occurrence of influenza in adults of working age (no prophylaxis)

Table 142 shows the incidence of symptomatic laboratory-confirmed influenza among placebo recipients participating in nine double-blind, placebo-controlled trials of influenza vaccine or prophylaxis with an M2 inhibitor (amantadine or rimantadine) or NI. All studies were conducted in the USA. They span seven influenza seasons during the period 1980–81 through 1997–98 and include outbreaks of influenza A, subtypes H1N1 and H3N2, and influenza B. Attack rates range from 0 to 20%.

For the purpose of subsequent estimates of hospitalisation rates and mortality, we assumed that symptomatic influenza occurs with comparable frequency in adults with and without co-morbidity. Using a random effects model the attack rate of symptomatic influenza was estimated at 6.55% (95% CI 2.91 to 12.59%).

Occurrence of influenza in children (no prophylaxis)

Table 143 shows the incidence of symptomatic laboratory-confirmed influenza among placebo recipients participating in nine double-blind, placebo-controlled trials of influenza vaccine or prophylaxis with rimantadine that were conducted during an influenza 'season'. All except one[61] were conducted in the USA. Although the nature and scale of influenza outbreaks in the USA and Europe may vary from year to year, it is assumed that attack rates for influenza in both areas are essentially identical over time. The studies in *Table 143* span eight influenza epidemics during the period 1984 through 1997–8. They include outbreaks of subtypes H1N1 and H3N2 of influenza A and influenza type B. Attack rates can be seen to range from 10 to 35%.

These studies were synthesised using a random effects model. Using a random effects meta-analysis, the rate of symptomatic influenza was estimated at 19.21% (95% CI 14.89 to 24.47%).

Occurrence of influenza in community-dwelling elderly (no prophylaxis)

Historically, influenza vaccines have been recommended by public health authorities on the basis of their proven efficacy, established by annual studies in military recruits (US Army and Air Force), and by recognition of the increased morbidity and mortality of influenza in the elderly and those with certain chronic medical conditions. Because of ethical problems of conducting placebo-controlled trials in high-risk groups for whom vaccine has long been recommended, there is a paucity of data on the occurrence of

TABLE 142 *Incidence of symptomatic laboratory-confirmed influenza among adults (placebo recipients) in controlled trials of vaccines or antivirals*

Author	Year of study	Virus	Vaccination level (%)	Attack rate: infected/total	Attack rate (%) (95% CI)
Crawford *et al.*, 1988[575]	1985	H3N2	0	0/23	0
Keitel *et al.*, 1988[576]	1984–5	H3N2	0	6/241	2.5 (0.5 to 4.5)
Reuman *et al.*, 1989[565]				5/159	3.1 (0.4 to 5.8)
Bridges *et al.*, 2000[380]	1997–8	H3N2	0	6/137	4.4 (1 to 8)
Hayden *et al.*, 1999[297]	1997–8	H3N2	0	25/519	5 (3 to 7)
Keitel *et al.*, 1988[576]	1983–4	H1N1/B	0	18/298	6 (3 to 9)
Bridges *et al.*, 2000[380]	1998–9	A and B	0	14/137	10 (5 to 15)
Powers *et al.*, 1995[577]	1993–4	H3N2	0	3/24	13 (0 to 26)
Dolin *et al.*, 1982[278]	1980–1	H1N1/H3N2	0	27/132	20 (13 to 27)
Total				104/1670	

TABLE 143 *Incidence of symptomatic laboratory-confirmed influenza among children (placebo recipients) in controlled trials of vaccines or antivirals*

Author	Year of study	Virus	Vaccination level (%)	Attack rate: infected/total	Attack rate (%) 95% CI)	Age (years)
Glezen *et al.*, 1993[578]	1988–9	H1N1	0	6/60	10 (2 to 18)	NA
Belshe *et al.*, 2000[370]	1997–8	H3N2	0	56/441	13 (10 to 16)	2–6
Heikkinen *et al.*, 1991[61]	1988–9	H1N1 H3N2	0	29/187	15.5 (10 to 21)	1–3
Clover *et al.*, 1986[579]	1984	H1N1	0	7/41	17 (5.5 to 28.5)	1–18
Belshe *et al.*, 2000[370]	1996–7	H3N2/B	0	100/532	19 (16 to 22)	1–5
Glezen *et al.*, 1993[578]	1987–8	H3N2	0	14/69	20 (11 to 29)	NA
Crawford *et al.*, 1988[575]	1985	H3N2	0	7/29	24 (8.6 to 39.6)	1–18
Glezen *et al.*, 1993[578]	1986–7	H1N1	0	10/33	30 (14 to 46)	3–9
Gruber *et al.*, 1990[580]	1985–6	B	0	27/77	35 (24 to 46)	3–18
Total				256/1469		

NA, not available.

TABLE 144 *Incidence of symptomatic laboratory-confirmed influenza among community-dwelling elderly*

Author	Year of study	Virus	Vaccination level (%)	Attack rate: infected/total	Attack rate (%) (95% CI)
Govaert *et al.*, 1994[557]	1991–2	H3N2	0	38/889	4.3 (3 to 5.6)
Nicholson *et al.*, 1997[544]	1993–4	A and B	0	19/209	9.1 (5.2 to 13)
Total				57/1098	

symptomatic laboratory-confirmed influenza in unvaccinated community-dwelling elderly and others with heart and lung disease and other conditions.

- During winter 1991–92, Govaert and colleagues[557] carried out a randomised double-blind placebo-controlled trial of inactivated influenza vaccine in 1838 community-dwelling, mostly healthy, elderly people aged ≥ 60 years. Approximately 70% were aged <70 years. Symptomatic serologically confirmed influenza occurred in 38 of 889 placebo recipients (4.3%, 95% CI 3 to 5.6).
- During the winters of 1992–93 and 1993–94, Nicholson and colleagues[544] studied the aetiology and burden of acute respiratory tract infections in 441 subjects during the first winter and 439 during the second. Overall 22 symptomatic serologically confirmed influenza A and B infections were identified giving an annual attack of 2.5% (95% CI 1 to 3.5). Most influenza infections occurred during the second year of the study. Differences were noted in the attack rates in vaccinees and non-vaccinees and in a subsequent report[581] smoking was found to have an independent effect. Thus during 1993–94, of 209 people who did not receive vaccine, 8/35 (23%) smokers had clinical serologically confirmed influenza as compared with 11/174 (6%) non-smokers.

A random effects meta-analysis of the attack rates in *Table 144* was undertaken. This attack rate for community-dwelling elderly is similar to the attack rate in adults of working age and was estimated as 6.17% (95% CI 2.91 to 12.59%).

Occurrence of influenza in the elderly living in residential care

Elderly people living in residential care often share dining and other facilities. Because immune function deteriorates with age, such close and prolonged contact readily facilitates rapid transmission of influenza within homes, resulting in outbreaks with high attack rates and substantial morbidity and mortality. Vaccination of people in residential care has been recommended since licensure of influenza vaccine on the basis of its efficacy in healthy adults and the high morbidity and mortality in high-risk groups. Accordingly, no randomised, double-blind, placebo-controlled trials have been carried out to estimate the efficacy of vaccination and the incidence of laboratory-confirmed influenza illness rates in controls.

Many reports describe influenza outbreaks, often with high attack rates despite high uptake of influenza vaccine. Since outbreaks with 'high' attack rates and/or high morbidity/mortality are more likely to be reported in the literature than ones with 'low' attack rates, the available data must be treated with caution. Zadeh and colleagues[582] conducted a questionnaire survey of 1017 randomly selected nursing homes in nine states in the USA. The response rate was 78%. Overall 116 (15%) nursing homes reported having a suspected or laboratory-confirmed influenza A outbreak in at least one influenza season between 1995 and 1998.

The following reports concern studies where influenza in all symptomatic patients has been confirmed by laboratory tests. They are divided into (i) prospective, double-blind, placebo-controlled studies of antivirals; (ii) a prospective study in which the attack rate in unvaccinated 'control' subjects was determined; and (iii) prospective observational (surveillance) studies in long-term care facilities.

Prospective, double-blind, placebo-controlled trials of antivirals

Monto and colleagues[583] carried out a randomised placebo-controlled trial of the efficacy of rimantadine 100 or 200 mg daily for long-term (8 weeks) prophylaxis of influenza infection among elderly (mean age 86 years) residents of 10 nursing homes in southern Michigan during the 1993–4 season. Overall 80% of the homes' residents were vaccinated against influenza (range 64–96% by home). Throat swabs from subjects with ILI were cultured. The analysis was restricted to influenza type A. There were 328 subjects in the homes who participated – the immunisation rate for the 66 controls who received placebo was 95%. H3N2 virus was the only strain identified within the Michigan area and was antigenically similar to the vaccine strain. In the two homes with 'outbreaks' of symptomatic influenza, three infections occurred among 14 placebo recipients (21%, 95% CI 0 to 42). Overall 19 infections occurred in these two homes. Two symptomatic influenza infections occurred in the remaining homes, but the authors do not comment on whether they occurred in the drug or placebo groups. It is therefore unclear whether the estimate of 4.5% (3/66, 95% CI 0 to 9.5%) is an underestimate or not.

Peters and colleagues[353] studied the role of once daily prophylactic oral oseltamivir for 6 weeks in a population of 548 frail elderly (mean age 81 years) residents of 31 residential homes across the USA and Europe during the 1998–9 influenza season. The primary efficacy end-point was laboratory confirmed clinical influenza. Of the 272 placebo recipients, 80.1% had been vaccinated against influenza. Infection was confirmed by a combination of virus isolation and the serology. Of the 272 subjects in the placebo group, 12 (4.4%, 95% CI 2 to 6.8) had laboratory-confirmed clinical influenza.

Prospective, non-randomised study of vaccine efficacy using non-vaccinated controls

Deguchi and colleagues[584] studied 22,462 subjects in 301 welfare nursing homes during an influenza A (H3N2) epidemic in Japan, of whom 10,739 individuals received either one (2027) or two (8712 subjects) doses of inactivated vaccines. There were 11,723 unvaccinated subjects in the control group. Staff were instructed to collect specimens for virus culture from symptomatic subjects within 4 days of onset of ARI. Overall 950 episodes of influenza illness were diagnosed clinically and with laboratory confirmation by virus culture or serology or both, 694 cases of influenza were identified among the 11,723 controls (5.9%, 95% CI 5.5 to 6.3).

Prospective observational (surveillance) studies

Mathur and colleagues[54] describe concurrent RSV and influenza A infections in a chronic care geriatric hospital, Rochester, NY, USA. Patients in the 634 beds (in three facilities) were surveyed for febrile ARIs during the period 15 November 1977 to 15 March 1978; of these, 71 developed acute febrile ARIs. Influenza A/Texas/77 was proven in 24 patients (3.8%, 95% CI 2.3 to 6.3). Details of influenza vaccination in the home were not provided.

During a 12-month period from June 1985 to May 1986, Arroyo and colleagues[585] observed 120 residents (mean age 66 years) of a Veteran's Administration nursing home; 75% of residents were immunised. Overall 59 episodes of ARI were observed, of which 38 were studied serologically. Eight influenza infections were identified in 38 cases. Hence there were at least eight-symptomatic influenza cases among 120 residents (7%, 95% CI 2 to 12). The incidence of influenza is undoubtedly underestimated owing to the failure to obtain diagnostic specimens from 21 of the 59 cases.

Nicholson and colleagues[586] studied the occurrence of influenza A and B in 11 Leicester

TABLE 145 *Incidence of symptomatic laboratory-confirmed influenza among elderly subjects in residential care*

Author	Years of study	Virus	Vaccination level in residents (staff) (%)	Attack rate: infected/total	Attack rate (%) (95% CI)
Prospective double-blind, placebo-controlled studies of antivirals					
Monto *et al*., 1995[583]	1993–4	H3N2	95 (NA)	3/66	4.5 (0 to 9.5)
Peters *et al*., 2001[353]	1997–8	NA	80 (NA)	12/272	4.4 (2 to 6.8)
Subtotal				*15/338*	
Prospective study where the attack rate in unvaccinated control subjects was determined					
Deguchi *et al*., 2000[584]	1998–9	H3N2	0	694/11 723	5.9 (5.5 to 6.3)
Subtotal				*694/11 723*	
Prospective surveillance studies					
Mathur *et al*., 1980[54]	1977–8	H3N2	NA (NA)	24/634	3.8 (2.3 to 6.3)
Arroyo *et al*., 1988[585]	1985–6	NA	75 (NA)	8/120	7 (2 to 12)
Nicholson *et al*., 1992[586]	1988–9	A and B	45 (NA)	12/482	2.5 (1.1 to 3.9)
Odelin *et al*., 1993[587]	1988–9	H1N1	100 (7%)	1/285	0.4 (0 to 1.1)
Drinka *et al*., 1999[588]	1991–8	A and B	83–91 (41–50)	382/4984	7.7 (5.7 to 9.7)
Subtotal				*427/6505*	
Total				**1136/18566**	

NA, not available.

City Council homes for the elderly (mean age 85 years) during the winter of 1988–9. The mean immunisation rate in the 11 homes was 45%. Among 163 people with known immunisation status there were three symptomatic influenza cases among 73 vaccinees and nine among 90 non-vaccinated subjects. These 12 influenza infections were identified among the 482 'long-stay' residents giving an overall attack rate of ~2.5% (95% CI 1.1 to 3.9).

Odelin and colleagues[587] report the occurrence of influenza A (H1N1) during the winter of 1988–89 in a nursing home in France containing 285 residents with a mean age of 85 years. All residents were immunised on admission to the facility. A single case of influenza was identified among the 285 residents (0.35, 95% CI 0 to 1.1).

Between 1991 and 1998, Drinka and colleagues[588] carried out prospective surveillance each winter in a rural Wisconsin nursing home, beginning early in December and continuing until the end of reported influenza activity in the state. Between 1991 and 1998, the average daily census was 712 and the mean age was 76 years. Chemoprophylaxis with amantadine or rimantadine was initiated for all residents on a floor when influenza A had been cultured and 10% of residents on a floor developed respiratory illness within a 7-day period. Immunisation levels were high among both patients (83–91%) and staff (41–50%). During the 7 years covered in this report, 382 influenza A and B infections occurred in 4984 patients, that is, equivalent to an annual attack rate of 7.7% (95% CI 5.7 to 9.7).

A random effects meta-analysis of the attack rates in *Table 145* was undertaken. This attack rate for residential elderly is similar to the attack rate in adults of working age and was estimated at 4.85% (95% CI 2.82 to 8.17%).

Probability that individual presents to GP with ILI during epidemic periods

Fleming[551] examined clinical incidence data collected by the Weekly Returns Service of the RCGP from 1989 to 1998 to estimate the duration and magnitude of influenza epidemics. Baseline levels of influenza activity were defined as occurring in weeks in which clinical incidence of influenza/influenza-like illness was <50 per 100,000.

Epidemic periods were defined as weeks in which consultation rates exceeded the upper 95% CI of the baseline (i.e. rates in excess of 45.5 per 100,000). This approximates the level of 50 currently used to identify periods of influenza activity. This source gave an estimate of the average number of excess people consulting with 'flu-like' illness in England and Wales during influenza epidemics as being 421,872 each year. It is important to note that patients with influenza

also present to GPs with other acute respiratory disease syndromes (e.g. acute bronchitis), so this estimate is likely to be an underestimate of all excess consultations caused by influenza.

Probability that individual presents to GP with an ARI during epidemic periods

Fleming[551] also estimated the numbers of excess people consulting with ARIs (all upper and lower respiratory tract infections combined regardless of diagnosis and including ILI) during epidemic periods. The estimates of the excess in ARI in epidemic periods assumes that all the excess is due to influenza and therefore represents its theoretical maximum impact. The 10-year average of excess number of GP consultations for ARIs was estimated to be 1,087,399.

Given estimates of the populations for the above cohorts (see *Table 146*), and an estimate of the annual mean attack rate for symptomatic influenza, we can derive estimates of the probabilities that individuals in each cohort will consult the family practitioner. The population estimates multiplied by the attack rates will yield an estimate of total influenza illnesses. If we divide the estimate of excess consultations by this value we will obtain an estimate of the numbers of people with influenza episodes who consult their GP. This gives an estimate of the probability of consulting the GP as 28.19% for adults, 15.51% for children and 32.51% for the elderly.

The above estimates of the probability of consultation for ILI due to influenza are virtually identical with those derived from practices reporting to the GPRD over a 6-year period.[552] Neither dataset allows probabilities to be identified for subjects with or without underlying chronic 'high-risk' medical conditions. Overall, the prevalence of chronic diseases was higher (OR 1.37; 95% CI 1.34 to 1.39) in 'cases' in the GPRD dataset than controls (suggesting that people with 'high-risk conditions' have higher consultation rates than people without chronic medical conditions). We have used the rates of consultations for both ILIs and ARIs added together in the model. This would capture some of the effect that influenza has on both general ARI and ILI consultations.

Population estimates

TABLE 146 *Population mid-1996: estimated resident population of England and Wales*[550]

Age (years)	0–4	5–14	15–44	45–64	≥ 65	Total
Population estimate	3,324,700	6,683,100	21,899,400	11,844,100	8,258,800	52,010,100

Appendix 12

Probability of presenting to GP prior to 48 hours

Successful treatment of influenza with amantadine or NIs requires treatment to commence within 48 hours of onset of symptoms. Although the model assumes that 95% of patients who present to a GP within this time period would receive these treatments (under regimens which allow this), it is conceivable that some patients presenting after 48 hours would receive treatment. There are several reasons why this may occur. In each of the following situations, patients who cannot benefit from drugs may receive them, and in the case of amantadine this puts them at high-risk of side-effects.

- First, patients may falsely report the time of onset of symptoms as a means of receiving drug treatment.
- Second, GPs may inappropriately prescribe either NIs or amantadine as a means of satisfying the patient's wish to leave the consultation with a prescription.
- Third, the symptoms of influenza are such that some patients are unable to recollect the time of onset 'accurately'. An 'abrupt' onset is more likely to be accurately identified than one that is insidious. An abrupt onset to pandemic influenza caused by the A/Asian/57 H2N2 virus was noted without reference to its actual frequency.[64,94,96] Other authors provide incidence rates for its occurrence (*Table 147*).

  It should be noted that many of these reports relate to pandemic influenza and so may not be representative. Overall it appears that an abrupt onset to influenza occurs in ~63% subjects with influenza A, thus a more gradual onset occurs in 37%.

The data in *Table 147* were synthesised with a random effects model to yield an estimate for the rate of rapid onset of 60.6% in children, 51.1% in adults and 79.2% in the elderly. It was not possible to estimate the numbers who receive antivirals after 48 hours for any reason other than because of insidious onset.

Ross and colleagues[545] provide information on the delay between onset of ILI and consultation (with GPs participating in the RCGP sentinel surveillance network) for 909 patients in different age bands. This can be seen in *Table 148*. Overall only 208 (23%) of the 909 patients consulted within 2 days of onset. Delays were significantly less in the younger age groups. About 21% (50/237) of those in high-risk groups consulted within 2 days.

As the model considers antivirals to be effective if given within 48 hours, insidious onset is assumed to affect a proportion of people presenting between 36 and 48 hours. To estimate the number

TABLE 147 *Abrupt onset of influenza symptoms*

	Population	Abrupt onset/total	% of total
H1N1			
Jordan *et al.*, 1958[48]	Children	62/95	65.2
Jordan *et al.*, 1958[48]	≥ 15 years	14/30	46.4
Stuart-Harris, 1961[50]	NA	45/60	75
H2N2			
Blumenfeld *et al.*, 1958[589]	Adults	29/30	96.6
Burch *et al.*, 1959[49]	All ages	66/76	86.8
Jordan *et al.*, 1958[48]	Children	30/45	66.6
Jordan *et al.*, 1958[48]	≥ 15 years	9/28	32.1
Woodall *et al.*, 1958[98]	Children	49/95	51.6
Woodall *et al.*, 1958[98]	Adults	37/92	40.2
H3N2			
Govaert *et al.*, 1998[590]	Elderly	38/48	79.2
Total		379/599	63.3

TABLE 148 *Proportion being seen by their GP within 48 hours of onset of symptoms*

Age (years)	Seen within 2 days of onset	%
0–4	24/31 $P_{48} = 0.77$	77
5–14	22/41 $P_{48} = 0.54$	54
15–44	90/359 $P_{48} = 0.25$	25
45–64	45/309 $P_{48} = 0.145$	14.5
65–74	13/87 $P_{48} = 0.149$	14.9
75+	13/77 $P_{48} = 0.17$	17

This table was compiled from data obtained from Ross *et al*.[545]

of people presenting in this time period, half of all those presenting on the second day in the study by Ross and colleagues[545] were included. These were then multiplied by the insidious onset rate obtained from the review to give an estimate of those who would be presenting within 48 hours of apparently developing symptoms but would actually be outside 48 hours from onset. This value was divided by all cases outside 48 hours (both those who were recorded as being after 48 hours and all those estimated to be after 48 hours even though they presented within 48 hours of first developing symptoms). This gave a rate of those who would be given antivirals after 48 hours as 2.84% for healthy adults, 1.1% for high-risk individuals and 1.21% for children.

It is questionable whether a gradual onset of influenza illness should be considered here, since it is possible that the treatment studies of amantadine, zanamivir and oseltamivir included people who also had an insidious onset and whose illnesses were longer than thought. The effect of insidious onset was included as it was felt there would be more scope for this effect in practice than in clinical trials.

Appendix 13

Probability of antibiotic use

The use of drugs with influenza has been estimated from a population-based study on incidence, risk factors, clinical complications and antibiotic use associated with influenza in the UK.[552] This study examined 141,293 subjects who had one or more diagnoses of ILI in the study period along with the same number of controls matched for age, sex, calendar time and practice. The study excluded all subjects with cancer of the haematopoietic system, AIDS, organ transplantation or exposure to cyclosporin, azothiaprine or oral steroids. The exclusion of these individuals who are usually associated with an increased risk of infectious complications may result in an underestimate of the frequency with which antibiotics are used.

Data on the overall use of antibiotics, stratified by age and complications, are given in *Table 149*. The data do not distinguish between 'risk' groups or residence in the community or residential care.

Higher levels of antimicrobial prescribing than those reported by Meier and colleagues[552] were reported in small studies carried out in Scotland and England:

- Davey and colleagues[547] reported that 899 (79%, 95% CI 77 to 81) of 1140 patients with ARIs within a Scottish general practice population with five partners were prescribed antibiotics at first consultation.
- One-hundred of 117 (85.5%, 95% CI 79 to 92) community-dwelling elderly (≥ 60 years) with ARIs who were reviewed during 1992–3 and 1993–4 by their GP in Leicestershire (UK) were prescribed antibiotics.[544]
- Nine of 19 of the above subjects with laboratory-confirmed influenza A were seen by a GP who prescribed antibiotics for all nine (100%).[544]
- Ninety of 179 ARIs in Leicester (UK) homes for the elderly during winter 1988–9 were seen at least once by a GP. Of these 90, 81 (90%, 95% CI 83.8 to 96.2) episodes resulted in the prescription of antibiotics.[591]

Studies conducted in pre-school children,[592] schoolchildren,[593] healthy working adults,[380] community-dwelling elderly[594,595] and those in residential care[217] also indicate higher levels of antibiotic usage for ARIs and ILI than reported by Meier and colleagues.[552]

TABLE 149 *Antibiotic use by presence of complications after influenza, by age group*

		Age (years)		
		1–14	**15–64**	**≥ 65**
Cases without complications	No.	4997	39622	8554
	%	27.9	42.0	54.7
Probability that antibiotics are prescribed		0.279	0.42	0.547
Cases with complications	No.	2183	6983	1527
	%	73.7	81.4	79.7
Probability that antibiotics are prescribed		0.737	0.814	0.797
All cases	No.	7180	46605	10071
	%	34.4	45.3	57.4
Probability that antibiotics are prescribed		0.344	0.453	0.574

Data taken from Meier and colleagues.[552]

In contrast to the 'high' rates of antibiotic usage in clinical practice, antibiotics were seldom given to placebo recipients in the treatment studies of NIs. We therefore decided to use the values from Meier and colleagues as these represent clinical practice and they come from a large study. They are more conservative than some of the smaller studies whose results we have seen.

We also assumed in our model that antibiotics would be effectively 'crowded out' by antivirals. If an antiviral was given then there would be a reduced probability of being given antibiotics at a first visit. This probability was allowed to vary around 5% according to a β distribution.

Appendix 14

Probability of untreated patients with ILI receiving follow-up consultations

A measure of the number of follow-up consultations following an initial consultation for ILI has been obtained by reference to the Annual Reports of the Weekly Returns Service (WRS) performed by the Birmingham Research Unit of the RCGP for the years 1999 and 2000. Data on episodes are recorded by the WRS as 'First and New' (F+N) – these provide the numerator for calculating incidence rates for each age and gender group. The 'total' number of consultations includes the F+N episodes and all ongoing consultations. By comparing the F+N episodes for ILI with the total number of consultations for ILI for any 12-month period, we derived estimates of the total number of consultations for every 100 F+N ILI consultations.

The data reveal that the lowest mean follow-up consultation rate occurs in children <15 years of age with 22.6 additional consultations for every 100 F+N ILI consultations ($[(2572/2098) - 1] \times 100$). The rate increases to 37.1 additional consultations for every 100 F+N ILI consultations in people aged 15–64 years and to 39.4 for people aged ≥ 65 years. These additional consultations are possibly underestimates, particularly for people with chronic underlying diseases such as asthma, COPD or heart failure, who may seek additional consultations for exacerbations of the underlying medical condition.

Appendix 15

Probability of hospitalisation

There is considerable uncertainty concerning the rates of hospitalisation for influenza and its complications in England and Wales for the subgroups of interest. There have been numerous reports of hospitalisations for ARI or ILI, rather than laboratory-confirmed influenza, with most focusing on the elderly in residential care in the USA. A number of studies, mostly North American, provide data on hospitalisation rates during the influenza season for persons, stratified by age and medical conditions, who are enrolled in healthcare plans. When combined with information on vaccination status, they provide estimates of vaccine effectiveness, but in the absence of laboratory diagnosis they are unable to provide estimates of the admission rates for influenza.

Barker[596] in the USA has reported excess hospitalisation rates of 2.5, 3.5, 9.3 and 37 per 10,000 population for age groups 0–14, 15–44, 45–64 and ≥ 65, respectively, during epidemic years in the period 1970–78. Assuming symptomatic influenza attack rates of approximately 17% for children and approximately 6% for adults, these excess hospitalisation rates equate to one admission per 680 children with influenza illness, one per 171 15–44-year-olds with influenza illness, one per 64.5 45–64-year-olds and one in 16 ≥ 65-year-olds.

Influenza-related hospitalisations were also estimated for the USA using National Hospital Discharge Survey Data from 26 influenza seasons (1970–95) by Simonsen and colleagues.[42] The seasonal average excess hospitalisation attributable to influenza was 49 per 100,000 persons, but average rates were twice as high during A(H3N2) influenza seasons as during A(H1N1)/B seasons. Among persons <65 years of age, the average number of excess P & I hospitalisations was 33 per 100,000 population. For an attack rate of approximately 6%, this is equivalent to one admission per 182 symptomatic cases. In the ≥ 65-year-olds the average number of excess P & I hospitalisations was 174 per 100,000, equivalent to a rate of one admission per 34.5 symptomatic cases. However, it should be noted that these estimates do not allow for non-P & I hospitalisations attributable to influenza (e.g. exacerbations of COPD, asthma and congestive cardiac failure).

Studies indicate that rates of hospitalisation are higher among young children than older children and adults during outbreaks of influenza. The increased rates of hospitalisation are comparable to rates for other groups at high risk. However, the interpretation of these findings has been confounded by respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently co-circulate with influenza. Recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalisation among children aged <5 years who do not have high-risk conditions.[85,87]

Both studies indicate that otherwise healthy children aged <2 years, and possibly children aged 2–4 years, are at increased risk for influenza-related hospitalisation compared with older healthy children.

The above reports indicate that influenza is associated with high admission rates in the USA. Because of the concern that admission rates to hospitals in the USA are much higher than in the UK, we have used data from several sources to estimate admission rates in England and Wales. However, we have been unable to identify data that allow us to estimate admissions for influenza in children.

Children

Sugaya and colleagues[597] evaluated the efficacy of influenza vaccine in 137 children with asthma in Japan during the 1992–93 season. Two of 35 vaccinees and three of 37 non-vaccinees (i.e., five of 72, 6.9%) (mean age 7 years) with virologically confirmed influenza were admitted for asthma (one case) and pneumonia.

Sugaya[598] examined the impact of influenza epidemics on paediatric hospitalisation in an urban general hospital in Japan during a 4-month period from December to March 1991 through 1998. During the seven winters, 14% of all admissions were associated with influenza virus (mean age 4.4 years). Among the cases with influenza 74.5% of the cases were previously healthy children.

The age-related distribution of influenza (P & I) admissions (adults)

Ahmed and colleagues[215] studied the effectiveness of influenza vaccine in reducing influenza admissions for pneumonia, influenza, bronchitis or emphysema in Leicestershire hospitals between December 1989 and 31 January 1990 (an epidemic period associated with high mortality). Inpatient records were retrieved for 264 admissions and for 156 of these primary care records were also available. Their age breakdown was shown in *Table 150*.

Fleming[551] estimated the number of excess hospital admissions for cardiopulmonary disorders among people aged 65–74 years and ≥ 75 years during the epidemic periods for the winters 1990–1 to 1996–7. The hospital admission data are based on the population of England. The mean number of 'excess' cardiopulmonary admissions (effectively all respiratory) during the epidemic periods was 2893 per annum (range 1593–6807) for 65–74-year-olds and 5778 for those aged ≥ 75 years (range 3146–15042). The age profile seen in the study by Ahmed and colleagues[215] was combined with the estimate of admissions in the ≥ 65-year-olds from Fleming[551] to estimate the numbers of admissions that would be seen in the <65-year-olds. Our estimates of attack rates (Appendix 11) were combined with population estimates (*Table 146*) to derive a probability that an individual has influenza. These were then multiplied by our estimates of the number of excess consultations derived from Fleming.[551] These calculations are set out in *Table 151*.

TABLE 150 *Excess hospital admissions due to cardiopulmonary disorders*

Age (years)	Admissions (%)
16–44	8.3
45–64	8.3
65–74	19.2
75–84	35.9
85–94	24.4
≥ 95	3.8

Based on the estimate of 2893 excess cardiopulmonary admissions for 65–74-year olds among an estimated 268,712 people with symptomatic influenza, the probability of hospital admission for cardiopulmonary disorders is 1.08% (i.e. one admission per 93 people with influenza). Similarly, based on the estimate of 5778 excess cardiopulmonary admissions for those >75 years of age among an estimated 208,978 people with symptomatic influenza, the probability of hospital

TABLE 151 *Calculations for hospitalisation rates used in the cost-effectiveness model*

		Age (years)			
		16–44	45–64	65–74	≥ 75
a	Estimated no. of people with symptomatic influenza	1435426	776338	268712	243868
b	Estimated excess cardiopulmonary admissions	867	867	2893	5778
c	Total percentage hospitalised (%)	0.06	0.11	1.08	2.37
d	Proportion high-risk (%)	12	19	33	42
e	Estimated no. of 'high-risk' people with influenza [(a × d)/100]	169380	143623	87332	102425
f	Estimated no. of 'low-risk' people with influenza (a–e)	1266046	632715	181381	141444
g	Estimated excess cardiopulmonary admissions in 'high-risk' people (72.4% of b)	628	628	2095	4183
h	Estimated excess cardiopulmonary admissions in 'low-risk' people (27.6% of b)	239	239	798	1595
i	Estimated probability of admission – high-risk subject (g/e) (%)	0.37 (1 in 270)	0.44 (1 in 229)	2.40 (1 in 42)	4.08 (1 in 24)
j	Estimated probability of admission – low-risk subject (h/f) (%)	0.02 (1 in 5291)	0.04 (1 in 2644)	0.44 (1 in 227)	1.13 (1 in 89)

Figures were calculated on the population of England and Wales.

admission for cardiopulmonary disorders is 2.37% (i.e. one admission per 42 people with influenza).

Estimates of the age-related prevalence of 'high-risk' medical conditions

Estimates of the age-related prevalence of 'high-risk' medical conditions has been derived from the study of influenza vaccine uptake and distribution in England and Wales for the year 1996–97.[599] This study uses information from practices contributing to the GPRD. The number of registered patients included in the analysis in 1996–97 was approximately 1.82 million. This study reported the percentage of people who were high risk as being 16.7% for the 0–19 years age group, 11.8% for 20–34, 11% for 35–49, 18.5% for 50–64, 32.5% for 65–74 and 42% for ≥ 75s.

Fleming and colleagues[600] also estimated the population high-risk in relation to influenza immunisation policy in England and Wales. Their study was carried out on a population of approximately 468,000 persons. The age bands studied were not identical in the two studies, except for the cohort aged 65–74 years. In the cohort studied by Irish and colleagues,[599] 32.5% of the 65–74-year-olds were categorised 'high-risk' in comparison with 23% in the cohort studied by Fleming and colleagues,[600] hence the data are in broad general agreement. Fleming and colleagues point out that the rates of 'high-risk' condition in the Irish and colleagues[599] study were generally higher than in their study. If so, the result would be that we underestimate the risk of hospital admission by 'high-risk' patients. However, it is possible that Fleming and colleagues underestimated the prevalence of high-risk conditions, since their method of identification was dependent on patients consulting their GP during the 1-year period of observation. Since patients with high-risk medical conditions do not necessarily consult their GP within a 1-year period, it is plausible that Fleming and colleagues underestimated the rate of high-risk conditions. Conversely, to account for the chronic nature of the defining illnesses, Irish and colleagues[599] returned high-risk status over any subsequent study years for individual patients once established. Hence a child with, say, wheezy bronchitis could be defined as high-risk even if they had been symptom-free for several years.

The estimates in *Table 151* (row c) do not consider the increased risk of hospital admissions among people with 'high-risk' chronic medical conditions. In Leicester, 72.4% of admissions for influenza, bronchitis or pneumonia [International Classification Diseases, ninth revision (ICD9): 466, 480.9–482.9 and 485–492.8] had one or more 'high-risk' chronic medical conditions during the 1989–90 epidemic of H3N2 influenza.[215] Combining this information with data on the prevalence of high-risk conditions from Irish and colleagues[599] provides estimates of the probability of hospital admission for cardiopulmonary disorders in people aged 65–74 years and ≥ 75 years during epidemics. The study by Ahmed and colleagues[215] provides details of the ages of people admitted with acute pulmonary disorders during the 1989–90 epidemic. Assuming that excess admissions occur in the younger age groups as they do in the elderly during an average epidemic[551] and that they occur in the same relative proportions by age as identified by Ahmed and colleagues[215] during 1989–90, it is also possible to estimate the probability of admission in younger age groups, in both 'high-' and 'low-risk' groups. These estimates are given in *Table 151* (rows i and j). In the cost-effectiveness model the rates for hospitalisations in the adult model were taken from the low-risk values for the 15–64-year age group given in *Table 151*. The rates for the high-risk population were taken from the combined values for those aged 15–64 years who were 'high-risk' and those who were ≥ 65 years of age. The values used in the model for the adult group and the high-risk group were 0.025 and 1.02%, respectively.

The above estimates for the high-risk group exclude elderly people living in residential care. Extrapolating from Leicester and Office of National Statistics (ONS) data,[215] 18.5% of the admissions for acute pulmonary disorders during the 1989–90 epidemic lived in residential care but only 3.15% of the population aged ≥ 65 years (244,950/7,780,900) live in residential care,[550,601] provides an estimate of admissions from residential care:

- The number of admissions from residential care is estimated at 18.5% of 8671 (2893 + 5778) = 1604.
- The number of people in residential care is estimated at 3.15% of 7,752,200 (4,210,200 + 3,542,000) = 244,194.
- The estimated number of people with symptomatic influenza in residential care is 4.85% of 244,194 = 11,850.
- The probability of admission for symptomatic influenza = 13.6% (approximately one in seven).

Other estimates and observations

Studies based on admissions in England and Wales

Three English health districts

The above probabilities are comparable to estimates for excess hospital admissions for P & I (ICD9: 480–487) in persons ≥ 65 years of age associated with influenza epidemics during 1987–8 to 1994–5 in three English health districts.[572] The mean annual excess P & I admissions was estimated at 21.9 per 100,000 population aged ≥ 65 years. For an attack rate for symptomatic influenza of 6.17%, this equates to an admission rate of approximately one case per 281 symptomatic cases. Although somewhat lower than the admission rates quoted in the main body of the text, this study did not consider other hospitalisations (non-P & I) attributable to influenza, including exacerbations of COPD, asthma or congestive cardiac failure.

General practice population

Connolly and colleagues[92] examined the records of 342 of 395 cases of clinically diagnosed 'influenza' seen in two general practices in Wales with a list size of 22,076 patients during the 1989–90 outbreak. Few (11%) were in 'high-risk' categories at that time. The overall rate of vaccination was low (2.2%). Two cases presenting with 'influenza' were admitted to hospital (i.e. one admission per 171 cases of ILI seen in the surgery) (0.6%, 95% CI 0 to 1.4%). If we assume an attack rate of symptomatic influenza of 6.17%, then the admissions rate for people with influenza or influenza complications approximates to one in 781 patients. However, the population studied included people of all ages, including infants and children and healthy working adults.

Community-dwelling elderly

Nicholson and colleagues[544] conducted a comparative, prospective study of disease burden due to ARIs in a cohort of community-dwelling elderly people living in Leicestershire. Of 497 episodes for which diagnostic specimens were available, three were admitted to hospital. All three admissions occurred in people with chronic respiratory disorders (i.e. one admission per 166 cases of ARI). One of 19 patients with influenza A was hospitalised.

Residential care

Nicholson and colleagues[591] studied the aetiology and outcome of ARIs during a 30-week period between September 1988 and March 1989 in 11 homes for the elderly in Leicestershire; 179 ARIs were identified. None of the cases were hospitalised, although six deaths were associated with the illnesses.

Patients with chronic chest disease

Wiselka and colleagues[602] studied the morbidity associated with respiratory virus infections in patients (mean age 48 years) with chronic chest disease. Subjects contacted the researchers if they were exposed to a family member or colleague with a 'cold'. Twenty-five symptomatic illnesses occurred, four of which resulted in hospitalisation (one admission per 6.25 cases)

Studies based in other regions of the world

Community-dwelling elderly

Greenberg and colleagues[603] in Houston, TX, USA studied the role of viruses in elderly people who acted as age-matched controls for patients with COPD. None of 87 ARIs in 55 ambulatory elderly population (approximately half of whom had coronary artery disease, hypertension or diabetes mellitus) resulted in hospitalisation.

Residential care

To provide an alternative to the rate of 13.6% for hospitalisations in those with influenza in residential care, evidence was taken from a number of studies. These are detailed below. These sources are summarised in *Table 152*.

Hall and colleagues[604] describe an outbreak of influenza B virus infection that occurred in a Minnesota, USA, nursing home and involved 129 of 359 residents during April–May 1979. Five residents (3.9%, 95% CI 0.5 to 7.3) were hospitalised (i.e. one admission per 25.8 cases of ILI).

Goodman and colleagues[605] describe an outbreak of ILI associated with H3N2 influenza in a nursing home in Atlanta, GA, USA (December 1980–January 1981) that affected 30 of 120 residents. Thirteen of the 30 (43%, 95% CI 25 to 61) residents were hospitalised (i.e. one admission per 2.3 cases of ILI).

Patriarca and colleagues[220] studied outbreaks of ILI in seven nursing homes when influenza A H3N2 was circulating. Infection was confirmed by virus isolation or serology in the majority (10/13) of those who underwent diagnostic tests. Thirty-one of 155 unvaccinated subjects and 19 of 113 vaccinees with ILI were hospitalised.

In January 1985, an influenza outbreak caused by A/Philippines/2/83 (H3N2) occurred in a partially immunised nursing home (vaccination rate 56%).[281] During the first 6 days of the outbreak, 14 of 55 residents developed ILI. Influenza was confirmed when influenza virus was cultured from four nasopharyngeal swabs collected from 10 ill residents. Overall, five of 14 residents with ILI were hospitalised. Among unvaccinated case patients five were hospitalised (5/8). Among vaccinated case patients, none were hospitalised (0/6).

Arroyo and colleagues[585] studied ARIs in a Veteran's Administration facility during a 12-month period. Overall, two of 59 ARIs resulted in hospitalisation (i.e. one case per 29.5 cases of ARI). One of eight (12.5%, 95% CI 0 to 35) cases of virologically confirmed influenza was hospitalised

Mast and colleagues[255] describe outbreaks of influenza A/Shanghai/11/87-like (H3N2) virus in two nursing home populations in January 1988. The outbreak in home A involved 60 of 230 residents and in home B 79 of 395 residents. During the interval before amantadine prophylaxis was started, ILI occurred in 84 residents in the two homes. Among unvaccinated case patients, three of 19 were hospitalised. Among vaccinated case patients, two of 65 were hospitalised. Overall, five of 84 cases were hospitalised

Coles and colleague[228] describe an outbreak of ILI [A/Shanghai/11/87 (H3N2) virus] in 37 of 124 elderly residents of a nursing home in New York state, USA, during December 1987–January 1988. Overall, five of 37 (16%, 95% CI 4 to 28) cases were hospitalised (five among 34 vaccinees and none among three non-vaccinees).

Wald and colleagues[56] describe outbreaks of RSV and influenza in a long-term care facility for wartime veterans and their spouses. H3N2 virus was isolated from 32 persons, one of whom was hospitalised.

Falsey and colleagues[594] studied 165 frail elderly persons in Rochester, NY, USA, who were nursing home eligible but who were maintained at home by coordinated day-care attendance, home care and hospital care. During two winter seasons, there were 165 ARIs, and 10 cases (6%, 95% CI 2 to 10) (i.e. one admission per 16.5 cases of ARI) required hospitalisation. A total of 14 cases of influenza A and eight cases of influenza were identified. Only one of the 10 admissions was associated with influenza, giving an admission rate for influenza of one in 22 cases (4.5%, 95% CI 0 to 13.1).

Kohn and colleagues[606] describe two summertime outbreaks (August 1993) of febrile respiratory illness associated with recovery of influenza A/Beijing/32/92-like (H3N2) virus in nursing homes in Louisiana, USA. In home A, 69 of the 124 residents had an ILI and 21 of the 69 were hospitalised. In nursing home B, 24 of 57 residents had an ILI and none were hospitalised. Overall, 21 of 93 (22.6%, 95% CI 14.1 to 31.1) cases were admitted (i.e. about one admission per four cases of ILI).

Infuso and colleagues[607] describe an outbreak of ILI among residents of a nursing home in France between 11 November and 15 December 1995. Overall, 52/66 (79%) of the residents had received one of two brands of a polyvalent influenza vaccine on 10 October. Forty-three of 66 (65%, CI 53.5 to 76.5) subjects developed ILI and serological tests were positive in three of five who were tested. Six of the 43 (13.9%) illnesses resulted in hospitalisation.

Loeb and colleagues[608] examined the burden of ARIs in metropolitan Toronto, Canada. Sixteen outbreaks involving 480 of 1313 residents were identified prospectively. Clinical findings were non-specific and could not be used to distinguish between causal agents. Of the 480, 58 (12%, 95% CI 3 to 21) required transfer to hospital (i.e. one admission per 8.3 cases of ARI).

Lee and colleagues[258] report an outbreak of influenza A/Sydney/H3N2/05/97-like virus among residents of a 176-bed long-term care facility for the elderly in Ontario, Canada, 90% of whom received influenza vaccine during autumn 1998. There were 13 definite and 66 probable outbreak-associated cases of influenza A. Twelve (15%) cases developed pneumonia, seven (9%) were hospitalised and two (2.6%) died.

Deguchi and colleagues[584] observed the effect of influenza vaccination on the occurrence and severity of influenza virus infection in a population residing in nursing homes in Japan; 47.8% of 22 462 individuals were immunised and 950 cases of influenza infection were diagnosed clinically and confirmed as influenza by virus isolation or serology. A total of 150 of 694 (21.6%, 95% CI 18.5 to 24.7) non-vaccinees and 32 of 256 (12.5%, CI 8.4 to 16.6) vaccinees were hospitalised.

Overall, the data in *Table 152* show that the mean admission rate in non-vaccinees with influenza/ILI is 21.5% (i.e. one in 4.7). In vaccinees the rate is

TABLE 152 *Hospitalisation rates among residents of homes with outbreaks of influenza*

Author	Year of study	Virus	Vaccination level in residents (staff) (%)	Attack rate in facility: cases/residents (%)	Admissions/ cases (%)	(95% CI)
USA						
Hall *et al.*, 1981[604]	1979	B	93 (NA)	129/359 (35.9)	5/129 (3.9)	0.5 to 7.3
Goodman *et al.*, 1982[605]	1980–1	H3N2	30 (NA)	30/120 (25)	13/30 (43)	25 to 61
Patriarca *et al.*, 1985[220]	1982–3	H3N2	54 (NA)	155/470[a] (32.9) 113/548 (20.6)	31/155[a] (20) 19/113 (16.8)	13.7 to 26.3 9.9 to 23.7
Arden *et al.*, 1988[281]	1985	H3N2	56 (NA)	14/55 (25.5)	5/8[a] (62.5) 0/6 (0)	29 to 96 0
Arroyo *et al.*, 1988[585]	1985–6	A and B	NA (NA)	8/56 (14.3)	1/8 (12.5)	0 to 35
Mast *et al.*, 1991[255]	1988	H3N2	60 (NA) 78 (NA)	60/230 (26.1) 79/395 (20)	3/19[a] (15.8) 2/65 (3.1)	0 to 32.2 0 to 7.1
Coles *et al.*, 1992[228]	1988	H3N2	96 (10%)	37/124 (29.8)	0/3[a] (0) 5/34 (14.7)	0 2.8 to 26.6
Wald *et al.*, 1995[56]	1991–2	H3N2	83 (42%)	32/680	1/32 (3.1)	0 to 9.1
Falsey *et al.*, 1995[594]	1992–3	A and B	62 year 1 91 year 2	22/165 (13.3) (2 seasons)	1/22 (4.4)	0 to 13.1
Kohn *et al.*, 1995[606]	1993	H3N2	'Most' (NA) in 2 homes	69/124 (55.6) 24/57 (42.1)	21/93 (22.6)	14.1 to 31.1
France						
Infuso *et al.*, 1996[607]	1995	H3N2	79	43/66 (65.1)	6/43 (13.9)	3.6 to 24.2
Japan						
Deguchi *et al.*, 2000[584]	1998–9	H3N2	47.8 (NA)	950/22462	150/694[a] (21.6) 32/256 (12.5)	18.5 to 24.7 8.4 to 16.6
Canada (ARIs)						
Loeb *et al.*, 1999[608]	3 years	Various viruses	NA (NA)	480/1313	58/480 (12)	3 to 21
Lee *et al.*, 2000[258]	1998	H3N2	90 (NA)	79/176	7/79 (8.9)	
Total (unimmunised)					189/879 (21.5)	$P = 0.215$

NA, not available.
[a] Unvaccinated.

12.2% (58/474, one in 8.2) and in homes where vaccinees and non-vaccinees are not disaggregated the rate is 12.2% (107/873, one in 8.2). These rates are similar to those estimated for residents of communal facilities in England and Wales. A random effects meta-analysis was performed on these data. This indicated a probability of hospitalisation in those with symptomatic influenza in residential care to be 14.8% (95% CI 11.1 to 19.4%). This is similar to the rate of 13.6% estimated above. The rate from the meta-analysis was used in the model as it came from study data and had estimates of uncertainty.

High-risk population with COPD

Greenberg and colleagues[603] in Houston, TX, USA, showed that 12 hospitalisations resulted from 34 acute respiratory tract viral infections in 32 elderly patients (average age 65 years) with moderate/severe COPD (i.e. one admission per 2.83 ARIs) and from 61 acute respiratory tract viral infections in 62 elderly patients with mild/moderate/severe obstruction (i.e. one hospitalisations per 5.08 ARIs). Viruses associated with these admissions included coronaviruses, influenza, parainfluenza and RSV. Two of five influenza A/B infections in subjects with moderate/severe COPD were associated with hospitalisation (i.e. one admission per 2.5 influenza A/B infections).

This shows that some high-risk populations can have potential for higher rates of hospitalisations than those used in the cost-effectiveness model.

Appendix 16

Probability that ILI is influenza

Successful treatment of influenza depends on an accurate, rapid diagnosis of the illness that cannot await conventional laboratory diagnosis. Other respiratory viruses, such as RSV, which often co-circulates with influenza, can be clinically indistinguishable from influenza. For the NIs and adamantanes that are highly specific for influenza, the potential benefit from treatment decreases with decrease in probability that ILI is influenza.

Randomised double-blind, placebo-controlled treatment studies of NIs were carried out by investigators who applied strict clinical diagnostic criteria when influenza was circulating locally. The trials focused on healthy adults in whom 'flu-like' illness is more usual than in young children or the elderly. At least one paediatric study of NIs had 'children with respiratory syncytial virus infection (rapid antigen)' as a study exclusion criteria.[609] Many family doctors will not have information on the local prevalence of influenza, or the time or funds to carry out rapid diagnostic tests for influenza or RSV, nor are the available tests evidently sufficiently sensitive in elderly high-risk patients.

Monto and colleagues[610] used data relating to 3744 participants in eight double-blind, placebo-controlled studies of zanamivir for the treatment of influenza to establish which clinical symptoms and signs are most predictive of influenza in patients with ILI. The studies were conducted during influenza seasons from 1994 to 1998. The population studied was adult and mainly non-elderly. To be eligible, study participants were required to have:

- Fever >37.8°C in studies NAIA2005, NAIA3002 and NAIB3002 (or 37.2°C for patients ≥ 65 years old in the last two studies or a symptom of feverishness in other studies), plus at least two of the following influenza-like symptoms:
- headache
- myalgia
- cough
- sore throat.

In addition, a requirement for the study site to begin patient enrolment was the identification of at least two individuals with culture-confirmed influenza within a 7-day period prior to enrolment, who resided within a 50-mile radius of the study site. This requirement was to enhance the probability of recruiting patients to the study who actually had influenza. Diagnosis was defined either as a positive culture for influenza virus or as a ≥ 4-fold increase in influenza antibody titre in convalescent serum sample using the haemagglutination inhibition assay. In some studies, influenza infection could alternatively be determined by polymerase chain reaction (PCR) or by immunofluorescence measurements. Thus optimal methods were employed to confirm influenza infection.

Of 3744 subjects enrolled, 2470 (66%, 95% CI 64.5 to 67.5) were confirmed to have influenza A or B. Individuals with influenza were more likely to have cough (93% versus 80%) fever ≥ 37.8°C (68% versus 40%), cough and fever together (64% versus 33%) and/or nasal congestion (91% versus 81%) than those without influenza. Stepwise logistic regression analysis identified fever (OR = 3.26; $p < 0.001$) and cough (OR = 2.85; $p < 0.001$) as the two best explanatory variables. The positive predictive value (i.e. the probability of having laboratory-confirmed influenza when the symptom is present) of fever ≥ 37.8°C plus cough was 79%. Feverishness was not included in the model. See Boivin and colleagues.[58]

Hak and colleagues[611] questioned the relevance of Monto and colleagues' findings in primary care practice as applied to elderly individuals with underlying chronic medical conditions. Monto and colleagues also commented that a diagnosis of influenza may be missed in individuals who do not have temperature elevation at the time of consultation. It is unclear how often temperature is measured during consultations in primary care in patients with ARI.

Because of the potentially enormous health economic implications (and issues concerning adverse drug events) of prescribing anti-influenza drugs to patients who do not have influenza, we examined (a) the predictive value of influenza symptomatology in elderly, mostly healthy, community-dwelling people,[590] and reports

concerning the diagnosis of influenza in (b) sentinel general practitioner networks in England and Wales, The Netherlands and the USA and (c) in residential care.

Predictive value of influenza symptomatology in elderly people

Govaert and colleagues[590] conducted a randomised, double-blind, placebo-controlled study of vaccine efficacy in mostly healthy, elderly subjects in The Netherlands during the 1991–92 influenza season. The study involved 34 GPs in 15 practices in the southern region of The Netherlands and it examined the positive predictive value of the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2). According to the criteria, the diagnosis of 'influenza' requires one of the following:

1. viral culture or serological evidence of influenza virus infection
2. influenza epidemic, plus *four* of the following criteria
3. six of the following:
   (a) sudden onset (within 12 hours)
   (b) cough
   (c) rigors or chills
   (d) fever
   (e) prostration and weakness
   (f) headache
   (g) myalgia, widespread aches and pains
   (h) no significant physical signs other than redness of nasal membrane and throat
   (i) influenza in close contacts.

The criteria of the NIVEL sentinel practices in The Netherlands for the diagnosis of influenza or influenza-like illness were also evaluated.

Using the criteria of the ICHPPC-2, 233 cases of influenza or an ILI were found. Of these cases, 41 [positive predictive value (PPV) 18%] were serologically confirmed as influenza. According to the criteria of the sentinel practices in The Netherlands, 144 cases of influenza or ILI were found, of which 35 cases (PPV 24%) were serologically confirmed. The PPVs of individual symptoms were identified – cough and fever had the highest PPVs (17 and 21%, respectively). Logistic regression analysis showed that 'fever, coughing and an acute onset' together had a PPV value of 30.3%.

Reports concerning the diagnosis of influenza in primary care sentinel networks

During three successive winters (1995–6, 1996–7, 1997–8), Zambon and colleagues,[612] at the Central Public Health Laboratory, Colindale, examined nasopharyngeal swabs routinely submitted for virological surveillance between 1 October and 30 April by a subset of 10–15 of the 75 sentinel practices reporting weekly to the RCGP research unit in Birmingham. These clinicians routinely took swabs from patients of all age groups presenting with ILI (symptoms of fever, cough and respiratory tract illness). The swabs were sent by post to the laboratory where they were analysed by tissue culture for the detection of influenza virus and by multiplex reverse transcription PCR for both influenza and RSV. Overall, influenza was detected in 709 (31.8%, 95% CI 29.9 to 33.7) of the 2226 swabs submitted.

Comparatively few specimens were collected from the elderly, but in this group a similar proportion (47/167, 28%, 95% CI 21 to 35) were positive for influenza. Data were provided by the authors relating to periods when the RCGP consultation rates for influenza/ILI exceed 50 per 100,000 population (Fleming DM, Zambon MC, Central Public Health Laboratory, Colindale: personal communication, 2001). The percentage positive for influenza ranged from 35 to 49% for the >15-year-olds and from 43 to 57% for the <15-year-olds. Data from 3 years were aggregated to form estimates of the proportion of ILI that was influenza. For the >15-year-olds for the 3-year period there were 792 samples of which 364 were influenza positive (46%). For the <15-year-olds there were 432 samples of which 205 were influenza positive (47.5%).

Medical practitioners in sentinel surveillance networks in other countries have conducted similar studies:

- **France** A network of GPs collected nasopharyngeal specimens during the 1994–95 influenza season (13 March 1995–30 April 1995) from patients aged >1 year with symptoms of <36 hours' duration with one or more of the following: ILI, upper or lower respiratory tract infection or fever (>38°C) without other infection being evident.[613] Influenza was confirmed by laboratory tests (immunofluorescence or immunocapture assays) for 29 of 94 (31%, 95% CI 22 to 40) subjects. Carrat and colleagues[614] extended their study

during the 1995–96 influenza season. They used the same entry criteria as before. Samples were examined by direct immunofluorescence (DIF) and enzyme-linked immunosorbent assay (ELISA). Viral culture and reverse transcription PCR were also carried out on specimens that were not clearly positive or negative by DIF or ELISA. They examined 610 patients, of whom only 168 (28%) were positive for influenza, mostly type A viruses (n = 158). They found that fever and, for type A (H3N2) viruses, cough predicted influenza infection, but the PPV was not high with various case definitions. The authors concluded that "… for treatment with existing or newer antiviral agents … candidates for such treatment would be difficult to identify without virological testing".

- **The Netherlands** Thirty general practices in the NIVEL sentinel network collected 363 nose and throat swabs from patients presenting between week 40 1997 and week 20 1998 with ILI.[615] ILI was defined as acute onset (prodromal stage of no more than 4 days), a temperature of at least 38°C and at least one of the following symptoms: cough, coryza, sore throat, frontal headache, retrosternal pain and myalgia. Nasopharyngeal specimens were cultured. Overall, influenza A or B virus was detected in 77 (31%, 95% CI 25 to 37) of 251 subjects with ILI. The Dutch NIVEL and RCGP sentinel networks report virtually identical mean baseline consultation rates for ILI and similar standard deviations.[616]
- **The Netherlands** Eighty-one patients from 14 general practices who presented with fever and at least one constitutional symptom and one respiratory symptom were studied.[617] Virus culture, rapid culture and PCR amplification were performed on a combined nose-throat swab. Multivariate analysis was used to obtain the best predictive model. PCR was positive for influenza in 42 out of 81 patients. A PPV of 75% was observed for the combination of headache at onset, feverishness at onset, cough and vaccination status during the period of increased influenza activity. Criteria used by the ICHPPC-2 resulted in a PPV of 54%. The PPV for diagnosis made by the GP was 76%.
- **Israel** A study was conducted in three general practices over a 3-month winter period in southern Israel to identify the agents responsible for febrile respiratory tract infections (RTIs).[618] RTI was defined as an acute febrile illness with cough, coryza, sore throat or hoarseness. Influenza A or B was identified in 38 (31%) of the 122 subjects whose acute and convalescent sera were analysed.
- **USA** In Michigan, USA, throat swabs from patients presenting to sentinel practitioners with ILI over three study periods, 1989–92, from November to April were cultured for influenza A and B.[619] A case of ILI was defined as one with reported fever and cough and/or sore throat. Over the three seasons (November to April), 558 specimens were positive for influenza [371 influenza A (H3N2); 71 influenza A (H1N1); and 116 influenza B]. Overall, 24% (95% CI 22 to 26) of 2331 throat swabs from patients with ILI were positive for influenza. The greatest proportion of positive isolates was found in the age category 5–24 years at 35%.

Data concerning the percentage of ILI cases that occurred during winter periods of influenza activity (winter influenza season) and were confirmed by laboratory tests as influenza are given in *Table 153*. It can be seen that the probability that ILI is due to influenza is 0.28. Rates higher than this have been found during epidemic periods. The probability increased to 0.46 in England and Wales in the >15-year-olds, and to 0.475 in the <5-year-olds when RCGP consultation rates for influenza/ILI exceed 50/100,000 (i.e. during an epidemic).[612] Exceptionally, the probability could be as high as 0.66 during localised outbreaks of influenza when using the entry criteria for the treatment studies of NIs of Monto and colleagues.[610]

Residential care

During a study of acute respiratory infections in nursing homes in Leicester, Nicholson and colleagues[591] noted that illnesses due to different virus infections were clinically indistinguishable. These authors concluded that: "respiratory symptoms in the study population evidently were

TABLE 153 *Review of studies of probability ILI is influenza during this influenza season*

Study	Proportion confirmed influenza/total tested (%)
Zambon *et al.*, 2001[612]	709/2226 (32)
Carrat *et al.*, 1997[613]	29/94 (31)
Carrat *et al.*, 1999[614]	168/610 (28)
van Elden *et al.*, 2001[617]	42/81 (52)
Lieberman *et al.*, 1998[618]	38/122 (31)
Heijnen *et al.*, 1999[615]	77/251 (31)
Monto *et al.*, 1995[619]	558/2331 (24)
Total	**1621/5715 (28)**

caused mostly by pathogens other than influenza during the influenza period documented nationally".

Other investigators have noted similar difficulties in diagnosing influenza in nursing homes. In New York state and Wisconsin, USA, Mathur and colleagues[54] and Wald and colleagues[56] identified respiratory syncytial virus activity superimposed on outbreaks of influenza A. Influenza A could not be distinguished clinically from RSV. During a rhinovirus outbreak at the Wisconsin facility involving 35 cases, Wald and colleagues[620] noted that there was a high prevalence of systemic symptoms (71%) and productive cough (54%), but little fever. Severe illness was noted in patients with chronic obstructive pulmonary disease – two of 17 required transfer out of the facility and one died of respiratory failure. Fever was not prominent during an outbreak of influenza B that involved 66 virologically confirmed cases in vaccinated elderly patients at the Wisconsin facility.[620] These investigators noted that 39% of the cases had low-grade fever at presentation and one-third never developed fever – hence over 60% of the vaccinated elderly may not present with fever at the onset of influenza B. Since antiviral treatment must begin within 2 days of disease onset, the authors concluded that it is crucial that physicians do not rely on the presence of elevated temperature to suggest a diagnosis of influenza.

The Wisconsin group carried out a longitudinal study during the 1991–92 to 1997–98 influenza seasons (beginning early December and continuing until the end of reported influenza activity in the state) to explore the relationship between clinical respiratory illness and outbreaks of influenza[588] in order to examine how best to use antiviral prophylaxis. Overall, only 382 of 2652 (14%) of specimens from subjects with ARIs were positive for influenza. Although comprehensive and longitudinal, the studies in Wisconsin did not report on the occurrence of ILI.

The study by Leonardi and colleagues[621] provides an insight into the proportion of ILI cases in residential care during the influenza season that are positive by laboratory tests for influenza. Nasopharyngeal specimens were obtained from 160 institutionalised elderly patients in 24 geriatric care centres in New York State (mean age 84 years) with ILI during the 1992–93 winter season. The patients demonstrated one or more signs or symptoms of ILI, including abrupt onset of fever, sore throat, non-productive cough, headache, myalgia and malaise. The majority (92.4%) of subjects from whom specimens were collected had documented fever ≥ 37.8°C, and 60% had cough. Cell culture identified influenza A H3N2 virus in 46. An additional four samples yielded influenza B. Thus culture alone identified influenza A or B in 31% of cases. Seven further specimens were shown by immunological techniques to have had influenza A. Thus influenza was confirmed in 57 of 160 (36%, 95% CI 29 to 43) elderly residents with ILI during the winter season (duration not defined)

ARI or ILI during outbreaks

The following studies (summarised in *Table 154*) provide an insight into the proportion of cases with ARI or ILI during **outbreaks** that are shown by laboratory tests to be associated with influenza in the facility.

Mathur and colleagues[54] describe concurrent RSV and influenza A infections in a chronic care geriatric hospital, Rochester, NY, USA. Patients in the 634 beds (in three facilities) were surveyed for febrile ARIs during the period 17 December 1977 to 27 February 1978. Seventy-one developed acute febrile ARIs. Influenza A/Texas/77 was proven in 24 patients. Hence the percentage of febrile ARIs due to influenza was 24/71 (34%) as determined by virus isolation and serology.

Hall and colleagues[604] report an outbreak of influenza B virus infection in a Minnesota, USA, nursing home containing 359 residents. The outbreak occurred between 24 April and 21 May 1979 and involved 129 residents. It was characterised by an abrupt onset of fever accompanied by flushing, general malaise and upper respiratory tract symptoms. Throat swabs from 11 of 19 symptomatic patients randomly selected for virological sampling were positive and 4-fold rises in antibody were also detected in 18 of the 19 (95%).

Goodman and colleagues[605] describe an outbreak of ILI in a nursing home in Atlanta, GA, USA during the period 12 December 1980 to 21 January 1981. During the outbreak 30 of 120 residents had onset of an ILI. Influenza A/Bangkok/79-like (H3N2) virus was isolated from swabs from five of eight (62.5%) acutely ill patients. Fourfold rises in antibody also occurred in 11 of 13 (85%) ill residents.

Patriarca and colleagues[220] identified 329 cases of ILI among 1476 residents in 13 nursing homes.

Four of five (80%) nasopharyngeal and throat swabs collected during three of the outbreaks yielded viruses similar to influenza A/Bangkok/1/79 (H3N2). Six of eight (75%) other residents in these homes had 4-fold or greater rises in HI antibody to influenza A (H3N2) (i.e. 10 of 13, 77%, 95% CI 44 to 100).

Horman and colleagues[622] describe an outbreak of influenza A/Taiwan/1/79-like (H3N2) virus in a Maryland, USA, nursing home between 8 December 1980 and 13 January 1981. Overall, 36 (21.2%, 95% CI 15.1 to 27.3) of 170 residents had an ILI. Fourfold rises in antibody were detected in paired sera from one of one (100%) subject meeting the case definition. Overall, 4-fold rises in antibody were detected in sera from four of five ill residents and throat swabs yielded virus from two of 10 acutely unwell residents.

Strassburg and colleagues[623] investigated an outbreak of ILI in a nursing home that affected 46 (53%) of the 87 residents in February/March 1983. An influenza A/Bangkok/79 (H3N2)-like virus was isolated from one of nine throat swab specimens and sera from 11 of 13 ill patients demonstrated 4-fold rises in antibody to influenza A.

In January 1985, an influenza outbreak caused by influenza A/Philippines/2/83 (H3N2)-like virus occurred in a partially immunised nursing home (vaccination rate 56%).[281] During the first 6 days of the outbreak 14 of 55 residents developed ILI. Influenza was confirmed when influenza virus was cultured from four nasopharyngeal swabs collected from 10 ill residents.

Mast and colleagues[255] describe outbreaks of influenza A/Shanghai/11/87-like (H3N2) virus in two partially (60 and 79%) vaccinated nursing home populations (A, mean age 79 years; B, 85 years) in January 1988. The outbreak in home A involved 60 (26%, 95% CI 20 to 32) of 230 residents and influenza A was confirmed in 13 (65%) of 20 case patients who had throat or paired serum samples available for testing. In home B, the outbreak involved 79 (20%, 95% CI 16 to 24) of 395 residents and influenza A was identified in 16 (52%) of 31 case patients.

Coles and colleagues[228] describe an outbreak of ILI [A/Shanghai/11/87 (H3N2) virus] in 37 of 124 elderly residents of a nursing home in New York state, USA, during December 1987–January 1988. Three of four case patients were found to be infected, two by serology and one by virus isolation.

Kohn and colleagues[606] describe two summertime outbreaks (August 1993) of febrile respiratory illness in nursing homes in Louisiana, USA. In home A, a long-term care facility, 69 of the 124 (56%, 95% CI 47 to 65) residents had an ILI during August. Influenza A/Beijing/32/92-like (H3N2) virus was recovered from three of five (60%) people sampled. Paired sera from 15 ill residents revealed >4-fold rises in 14 (93%). In nursing home B, 24 of 57 (42%, 95% CI 29 to 55) residents had an ILI during a 2-week period in August. Paired sera from five ill residents revealed >4-fold rises in all five (100%).

Infuso and colleagues[607] describe an outbreak of ILI among residents of a nursing home in France between 11 November and 15 December 1995. Overall, 52/66 (79%) of the residents had received one of two brands of a polyvalent influenza vaccine on 10 October. Forty-three of 66 (65%, 95% CI 53.5 to 76.5) subjects developed ILI and serological tests were positive in three of five who were tested. Six of the 43 (13.9%) illnesses resulted in hospitalisation.

Groen and colleagues[624] investigated an outbreak of ILI in a home for the elderly in the Dutch Antilles. Within 1 week, 40 of 70 residents were affected, and seven of the patients died within 2 weeks of the onset of disease. Analysis of paired serum samples from 35 of the patients showed that 22 had a >4-fold rise in HI antibody against the H3N2 variant represented in the 1996–7 vaccine.

Probability that ILI is influenza used in the economic models

The probabilities used within the economic models assumed that drug treatment would be given during epidemic periods, i.e. when the rate of ILI referrals exceeded 50 per 100,000 of the population. For the healthy adult group and the high-risk group, the rate of 46%, taken from the RCGP data, was used. For the children's model the rate of 47.5% for the <15-year-old age group from the RCGP data was used. For the residential population the rate of 46% from the RCGP data was used for the ≥ 15-year-old population. This was used as it was broadly similar to the value of 51.6% shown in *Table 154*. The value from *Table 154* was not used as many of the studies quoted in this table had very small numbers of people tested for influenza.

TABLE 154 *ILI that is influenza in residential elderly*

Author	Year of outbreak	Virus	Vaccination level in residents (%)	Influenza/ARI or ILI illness	% (95% CI)
Mathur *et al*., 1980[54]	1977–8	H3N2	NA	24/71 ARI	34 (23 to 45)
Hall *et al*., 1981[604]	1979	B	93	18/19 ILI	95 (85 to 100)
Goodman *et al*., 1982[605]	1980–1	H3N2	NA	11/13 ILI	85 (66 to 100)
Horman *et al*., 1986[622]	1980–1	H3N2	63	1/1 ILI	100
Patriarca *et al*., 1985[220]	1982–3	H3N2	54	10/13 ILI	77 (44 to 100)
Strassburg *et al*., 1986[623]	1983	H3N2	75	11/13 ILI	85 (66 to 100)
Arden *et al*., 1988[281]	1985	H3N2	56	14/55 ILI	25 (14 to 36)
Coles *et al*., 1992[228]	1987–8	H3N2	90	3/4 ILI	75
Mast *et al*., 1991[255]	1988	H3N2	60	13/20 ILI	65 (44 to 86)
Mast *et al*. 1991[255]	1988	H3N2	78	16/31 ILI	52 (34 to 70)
Kohn *et al*., 1995[606]	1993	H3N2	Virtually all	3/5 ILI	60 (17 to 100)
Kohn *et al*., 1995[606]	1993	H3N2	Virtually all	5/5 ILI	100
Infuso *et al*., 1996[607]	1995	H3N2	79	3/5 ILI	60 (17 to 100)
Groen *et al*. 1998[624]	1996	H3N2	0	22/35 ILI	63 (47 to 79)
Total				**157/304**	**51.6**

NA, not available.

Appendix 17

Probability that influenza is influenza A

Amantadine has antiviral activity against influenza A, but not B. In contrast, the NIs have activity against both influenza A and B. Data were obtained from the PHLS website (now Health Protection Agency, http://www.hpa.org.uk/). These data gave the number of influenza-positive samples that were influenza A and B over a 10-year period from 1992–93 to 2000–01. This indicated that influenza B accounts for approximately 26% of infections due to influenza. Thus, overall, amantadine could at best be effective in around 74% of all infections due to influenza. Age-specific rates were estimated from the same source; the mean values for the healthy adults were 68.4 and 79.9% for high-risk and residential care models, respectively, and 70.5% for children. These values were used as the means in our base-case models.

Seasons when influenza A is dominant

For five of the nine years (1993–4, 1995–6, 1997–8, 1998–9 and 1999–2000), influenza B accounted for 3–13% of cases (6.5% overall, 95% CI 6.1 to 6.9). Hence in years when ongoing surveillance suggests that the outbreak is overwhelmingly due to influenza A, amantadine has the potential to exert an antiviral effect in approximately 93.5% of cases.

Seasons when numbers of influenza A and B isolates are similar

Throughout the influenza season during three of the nine years (1992–3, 1996–7 and 2000–1), there were comparable numbers of influenza A and B cases. During the 1992–3 season, influenza A and B activity occurred late in the season and co-circulated. During the 1996–7 season, outbreaks of influenza A and B overlapped. Analysis by date of specimen indicates that influenza A activity began to increase in week 47/96 and peaked in week 02/97.[625] Influenza B activity increased after week 01/97 and peaked in week 06/97. During the year 2000–1 influenza activity was initially associated with influenza A (H1N1).[556] Influenza B, however, became the predominant circulating strain as the season progressed – indeed, it was the dominant strain when the RCGP consultation rate per 100,000 for influenza and ILI exceeded 50. This suggests that even in seasons when there is mixed influenza A and B there may be periods when one type predominates.

Seasons when influenza B is dominant

During one of the nine years (1994–5), influenza B was dominant (80%), with moderate activity occurring throughout the winter, peaking in February. Influenza A became more active towards the end of the winter, 'peaking' in May. Influenza A activity was sporadic, beginning at about the same time as the peak influenza B activity.

Overall, it can be seen that therapeutic use of amantadine demands ongoing virological surveillance to ensure that influenza A is prevalent. As judged by recent epidemiology of influenza in England and Wales, the overall probability of influenza being caused by influenza A is 0.74. However, for the five of nine years when influenza A prevailed, the probability is 0.935; for the three years when outbreaks with both viruses were detected, the probability is 0.416; and for the year when influenza B was dominant the probability is 0.2. The age-specific values referred to earlier were used as the base-case values.

Appendix 18

Probability of adverse events from vaccination

Table 155 summarises evidence of adverse reactions to vaccination amongst the healthy adult population produced by a number of studies.[226,378–383] The table shows that local reactions are significantly less common in the placebo/control groups than in vaccinees, but no difference is found in the incidence of systemic reactions. The available data indicate that inactivated influenza does not give rise to troublesome local or systemic reactions in adults requiring medical intervention or treatment. We have not incorporated the probability of events such as GBS, ocular events, other neurological events or cutaneous events owing to their rarity and uncertain relationship with influenza vaccination.

In a randomised, double blind, placebo-controlled trial,[381,382] the mean number of days of sick leave during the week following influenza vaccination was two per 100 greater in the vaccine group ($p = 0.34$). We use this value as the probability of healthy adults experiencing an adverse reaction to influenza vaccination.

Existing literature indicates that this same figure is applicable to the paediatric and high-risk populations. There have been concerns that influenza vaccination may trigger asthma exacerbations. Broncho-provocation tests may show increased bronchial reactivity of people with asthma for several days after vaccination against influenza,[62,462] but not at 1-week.[463] Anecdotal reports suggest an association between vaccination and exacerbations,[464,465] although most observational studies suggest that inactivated vaccine is safe in people with asthma.[466–470]

Bell and colleagues[471] observed a decrease in PEF and increased use in bronchodilators within 96 hours of vaccination of asthmatic children. A slight fall in evening PEF after vaccination was

TABLE 155 *Incidence of adverse events after vaccination with inactivated influenza vaccines*

	Adverse effects [rate (%) in vaccinees minus rate in controls) (*p*-value)]					
	Margolis et *al.*, 1990[378]	**Margolis et *al.*, 1990[383]**	**Govaert et *al.*, 1993[379]**	**Nichol et *al.*, 1996[382]**	**Bridges et *al.*, 2000[380]**	**Bridges et *al.*, 2000[380]**
Population (*n*)	336	650	1806	849	1180	1177
Vaccine	Split	Split	Split	Split	Split	Split
Local reactions	–	–	10.2 (<0.001)	–	–	–
Sore arm	15.2 (<0.001)	19.5[a]	–	39.7 (<0.001)	35 (<0.001)	31 (<0.001)
Swelling	–	–	6.4 (<0.001)	–	–	–
Itching	–	–	3.1 (<0.001)	–	–	–
Pain when touched	–	–	7.2 (<0.001)	–	–	–
Constant pain	–	–	1.0 (<0.001)	–	–	–
Redness	–	–	–	–	8.0 (<0.001)	8.0 (<0.001)
Systemic reactions	–	–	1.6 (ns)	1.1 (ns)	–	–
ILI	–	5.5 (0.03)	–	–		–
Fever(ish)	1.2 (ns)	0.2 (ns)	0.6 (ns)	0.1 (ns)	(ns)	(ns)
Tiredness	0.3 (ns)	–	–	–0.5 (ns)	(ns)	(ns)
Malaise	0.9 (ns)	–	0.9 (ns)	–1.5 (ns)	–	–
Myalgia	0.6 (ns)	–	–	0.5 (ns)	(ns)	(ns)
Headaches	–0.7 (n)	–	1.0 (ns)	–3.6 (ns)	(ns)	(ns)
Disability days	–	1.1 (ns)	–	–	–	–

ns, Not significant.
[a] No statistical comparison.

noted during a small placebo-controlled crossover study,[472] but two other placebo-controlled studies found no adverse pulmonary effects.[473,474]

Two large randomised, double blind, placebo-controlled, crossover trials[475,476] and one retrospective cohort study[477] have been conducted recently in patients with asthma. In addition, a systematic review of the literature evaluating the safety of influenza vaccination in patients with asthma has been undertaken.[626] The available data indicate that inactivated influenza vaccine is safe in adults and children with asthma, including those with severe asthma. The data do not suggest that administration of influenza vaccine to people with asthma evokes increased use of medication, medical consultations or hospitalisation.

The adverse events for vaccine were valued at one influenza day and the QALY value of an influenza day was used to value these. Because of the speculative nature of this valuation, these estimates were not used in the base-case vaccination model but were modelled in a sensitivity analysis.

Appendix 19

Probability of death from influenza

Probability of death was taken from data available in Meier and colleagues[552] (*Table 156*). This source include mortality for 1–14, 15–44, 45–64 and ≥ 65-year-olds. In each case rates were given for 'high risk' and 'low risk' conditions. Data for low risk for 15–64-year-olds were aggregated to give the rate for the healthy adult model. There were 33 deaths out of 85,248 ILI cases. This gave a rate of approximately one death in every 2580 cases. For the high-risk group, data for the ≥ 65-year-olds were aggregated with 'high-risk' 15–64-year-olds. This gave a rate of 251 deaths in 35,149 individuals or approximately one per 140 cases. For the children's model, a rate of one case in 20,896 was used.

TABLE 156 *Mortality in elderly residential care*

Author	Year of outbreak	Virus	Vaccination level in residents (staff) (%)	Attack rate in facility: cases/residents (%)	Deaths/cases (%)	95% CI
Hall *et al*., 1981[604]	1979	B	93 (NA)	129/359 (35.9)	1/129 (0.8)	0 to 1.5
Goodman *et al*., 1982[605]	1980–1	H3N2	30 (NA)	30/120 (25)	9/24[a] (37.5) 0/6 (0)	18.1 to 56.9
Horman *et al*., 1986[622]	1980–1	H3N2	26 (NA)	76/170 (44.7)	5/44[a] (11.4) 3/28 (10.7)	2.2 to 20.6 0 to 22.1
Patriarca *et al*., 1985[220]	1982–3	H3N2	54 (NA)	329/1476 (22.3)	21/155[a] (13.5) 6/113 (5.3)	8.1 to 18.9 1.4 to 9.4
Kashiwagi *et al*., 1988[627]	1985–6	H3N2	NA (NA)	133/379 (35.1)	8/133 (6.0)	2 to 10
Lennox *et al*., 1990[628]	1986–7	Various	NA (NA)	70/196 (35.7)	6/66 (9.1)	2.2 to 16
Coles *et al*., 1992[228]	1988	H3N2	96 (10%)	37/124 (29.8)	0/3[a] 3/34 (10.9)	0 0.4 to 21.4
Mast *et al*., 1991[255]	1988	H3N2	60 (NA) 78 (NA)	60/230 (26.1) 79/395 ((20)	5/19[a,b] (26.3) 6/65[b] (9.2)	8.6 to 44 2.2 to 16.2
Libow *et al*., 1996[631]	1988	A	NA (NA)	139/499 (27.9)	8/62 (12.9)	4.5 to 21.3
Strihavkova *et al*., 1990[629]	1989	B	NA (NA)	26/72	13/26 (50)	31 to 69
Ohmit *et al*., 1999[630]	1989–0	H3N2	71 (NA)	361/?	33/361 (9.1)	6.1 to 12.1
Drinka *et al*., 1999[588]	1988–9	A	>86		15/322[c] (4.7)	2.3 to 7.1
Drinka *et al*., 1999[588]	1988–9	B	>86		7/129 (5.4)	1.6 to 9.2
Loeb *et al*., 1999[608]	NA	Various	NA (NA)	NA	37/480 (8.0)	0.3 to 15.7
Infuso *et al*., 1996[607]	1995	H3N2	79 (NA)	43/66 (65.1)	1/43 (2.3)	0 to 6.8
Groen *et al*., 1998[624]	1996	H3N2	0 (NA)	40/70	7/40[a] (17.5)	5.7 to 29.3
CDR Weekly 1998[632]	1998	A	NA (NA)	58/116	11/58 (19.0)	9 to 29
Deguchi *et al*., 2000[584]	1998–9	H3N2	47.8 (NA)	950/22462	5/694[a] (0.72) 1/256 (0.39)	0.1 to 1.32 0 to 1.15
Lee *et al*., 2000[258]	1998	H3N2	90 (NA)	79/176	2/79 (2.5)	0 to 5.9
Total (unimmunised)					**52/979 (5.3%)**	

NA, not available.
[a] Unimmunised.
[b] Deaths among cases prior to treatment/prophylaxis with amantadine.
[c] 'Chemoprophylaxis' routinely initiated when influenza A cultured and 10% of residents develop respiratory illness within a 7-day period.

Residential care elderly

Hall and colleagues[604] report an outbreak of influenza B virus infection in a Minnesota, USA, nursing home containing 359 residents. The outbreak occurred between 24 April and 21 May 1979, and involved 129 (35.9%, 95% CI 30.6 to 41.2) residents. One resident (0.8%, 95% CI 0 to 1.5) died. Influenza B viruses were isolated from throat swabs from 11 of 19 acutely ill residents. Viral cultures and serological tests were negative for other pathogens.

Goodman and colleagues[605] describe an outbreak of ILI in a nursing home in Atlanta, GA, USA. It affected 30 of 120 residents. Influenza A/Bankok/79-like (H3N2) virus was recovered from five of eight subjects from whom throat swabs were collected. Fourfold rises in antibody also occurred in 11 of 13 ill residents. Serological tests were negative for other pathogens. Nine of the 30 people with ILI died. These nine were among 24 unimmunised people with ILI.

Patriarca and colleagues[220] identified 329 cases of ILI among 1476 residents in 13 nursing homes. Four of five nasopharyngeal and throat swabs collected during three of the outbreaks yielded viruses similar to A/Bangkok/1/79 (H3N2). Six of eight other residents in these homes had 4-fold or greater rises in HI antibody to influenza A (H3N2). For the seven homes with outbreaks, six of 113 (5.3%, 95% CI 1.4 to 9.4) vaccinees with ILI died and 21 of 155 (13.5%, 95% CI 8.1 to 18.9) non-vaccinees with ILI died. Overall, 27 of 268 (10%, 95% CI 6.4 to 13.6) patients with ILI died.

Horman and colleagues[622] describe an outbreak of influenza A/Taiwan/1/79-like (H3N2) virus in an elderly population in a Maryland, USA, nursing home between 8 December 1980 and 13 January 1981. Fourfold rises in antibody were detected in paired sera from four of five ill residents. ARIs were reported by 76 (44.7%). Nine (11.8%, 95% CI 4.5 to 19.1) of the 76 cases died.

Kashiwagi and colleagues[627] describe an outbreak of influenza A in which 133 of 379 (35.1%) were infected. Eight people died (6%, 95% CI 2 to 10).

Lennox and colleagues[628] identified cases of ILI in eight continuing care wards in long-stay geriatric units at two hospitals in Glasgow, Scotland. Six of the 66 (9.1%) patients with ILI died within 1 week of developing symptoms.

Strihavkova and colleagues[629] describe an outbreak of influenza B in a psycho-geriatric ward; 26 patients were affected of whom 13 (50%, 95% CI 31 to 69) died.

Mast and colleagues[255] describe outbreaks of influenza A/Shanghai/11/87-like (H3N2) virus in two partially vaccinated nursing home populations in January 1988. The outbreak in home A involved 60 residents and influenza A was confirmed in 13 (65%) of 20 case patients who had throat or paired serum samples available for testing. In home B, the outbreak involved 79 residents and influenza A was identified in 16 (52%) of 31 case patients. A total of 16 case-related deaths (case-fatality rate 11.5%, 95% CI 6.5 to 16.5) occurred in the 139 with suspected influenza. Among unvaccinated case patients, five of 19 (26%) died within 14 days of onset of illness.

Coles and colleagues[228] describe an outbreak of ILI in 37 of 124 elderly residents in a nursing home in New York state during the period 1 December 1987 to 25 January 1988. Virological tests revealed the presence of A/Shanghai/11/87 (H3N2) virus that was antigenically distinct from the vaccine strain. Overall three of 37 died (8%, 95% CI 0 to 17).

Ohmit and colleagues[630] studied the effectiveness of influenza vaccine in preventing febrile (≥ 37.8°C) ILI in nursing home residents during the 1989–90 influenza season. When cases of all ages were examined, 33 of 361 (9.1%, 95% CI 6.1 to 12.1) with ILI died within 1 month of onset of the illness and were considered to have died from influenza-related complications.

Libow and colleagues[631] report a retrospective cohort study at the Jewish Home and Hospital for the Aged, a facility containing 514 beds and 499 residents (mean age 87.5 years), at the onset of an outbreak of influenza A and B; 139 subjects developed ILI meeting the case definition during the period February to April 1988. Paired sera showed ≥ 4-fold rises in influenza A antibody in convalescent sera from 62% of 21 subjects. Amantadine was given to 77 of the 139, either as treatment or as prophylaxis. Overall eight (5.8%) of the 139 subjects died. All eight deaths occurred in 62 patients who did not receive amantadine, giving a mortality rate of 12.9% (95% CI 4.5 to 21.3).

Infuso and colleagues[607] describe an outbreak of ILI among residents of a nursing home in France between 11 November and 15 December 1995.

Overall 52/66 (79%) of the residents had received one of two brands of a polyvalent influenza vaccine on 10 October. Forty-three of 66 subjects developed ILI and serological tests were positive in three of five who were tested. One of the 43 (2.3%) illnesses resulted in death 7 days after becoming ill.

Outbreaks of influenza A infection occurred in four nursing homes for elderly people in Sheffield, England, during March 1998.[632] Data on mortality are available from two homes where data on outcomes are available. Overall, 11 of 58 symptomatic residents died (19%, 95% CI 9 to 29)

Groen and colleagues[624] describe an outbreak of influenza in a home for the elderly in the Dutch Antilles. Within 1 week, 40 out of 70 residents were affected, and seven of the patients died within 2 weeks of onset. None of the residents had been vaccinated. Analysis of serum samples showed that 22 of 35 patients tested had a >4-fold rise in antibody to H3N2 virus. Saliva was tested by PCR and the majority of those tested (21/23) proved to be positive.

Drinka and colleagues[588] report 30-day mortality following isolation of influenza A in the Wisconsin Veteran's Home during the period 1988–99. Mortality was 4.7% (15/322) for influenza A and 5.4% (7/129) for influenza B. (Note this includes data presented in papers by Gravenstein and colleagues[633] and Wald and colleagues[56].) Chemoprophylaxis was routinely initiated when influenza A was cultured and 10% of residents developed respiratory illness within a 7-day period

Loeb and colleagues[608] examined the burden of ARIs in metropolitan Toronto, Canada, by prospective surveillance and retrospective audit of surveillance records over 3 years. Sixteen outbreaks involving 480 of 1313 residents were identified prospectively. Clinical findings were non-specific and could not be used to distinguish between causal agents. Of the 480, the case-fatality rate was 8% (95% CI 0.3 to 15.7).

Deguchi and colleagues[584] report the effect of influenza vaccination on the occurrence and severity of influenza vaccination in 22,462 individuals living in 301 welfare nursing homes. Staff at the nursing homes were instructed to collect specimens for virus culture and serum samples were also obtained from symptomatic subjects. Overall there were 950 episodes of influenza diagnosed clinically and with virus culture or serodiagnosis, or both. The period in which deaths were identified in relation to the onset of influenzal symptoms is not stated, but the overall mortality was extremely low – much lower than in all other reports in *Table 156*. The mean age of the population was similar to the mean age in other reports.

Lee and colleagues[258] report an outbreak of influenza A/Sydney/H3N2/05/97-like virus among residents of a 176-bed long-term-care facility for the elderly in Ontario, Canada, 90% of whom received influenza vaccine during autumn 1998. There were 13 definite and 66 probable outbreak-associated cases of influenza A. Twelve (15%) cases developed pneumonia, seven (9%) were hospitalised and two (2.5%) died.

A meta-analysis on the data in *Table 156* was performed. The probability of mortality used is 0.094 (95% CI 0.065 to 0.134).

Further details of this review are available from the authors on request.

Appendix 20

Effectiveness of vaccine

Vaccine efficacy/effectiveness in adults of working age

Evidence taken from the Cochrane review[634] has been considered. The authors summarised deficiencies of previous reviews of influenza vaccine effectiveness as (i) lack of comprehensiveness in the identification of the primary studies, (ii) lack of methodological assessment of primary studies, (iii) failure to account for the marked variability in vaccine effectiveness in controlled trials, (iv) failure to provide estimates of vaccine effectiveness under conditions of imperfect antigenic matching between vaccines and prevalent virus and (v) lack of estimates of vaccine effectiveness in specific populations currently targeted for influenza vaccination. Demichelli and colleagues[634] subsequently identified 20 studies for the period from 1966 to the end of 1997 that were RCTs of influenza vaccine in adults.

Possible shortcomings of the Cochrane review relate to changes in vaccine standardisation, vaccine composition (including vaccine type and antigen content) and reactogenicity that have occurred during the period under review. Moreover, several trials included in the review were carried out in response to the pandemic of A/Hong Kong (H3N2) influenza[635–638] when vaccinees would be unprimed (i.e. immunologically naive). The inclusion of studies carried out in unprimed subjects in response to pandemics raises issues concerning the number of doses of vaccine and quantity of antigen required.

The Cochrane review applied meta-analysis to two studies of the effectiveness of inactivated vaccine in preventing hospitalisation that were conducted in 18–21-year-old airmen during the influenza A/Hong Kong (H3N2) pandemic. One vaccine was a complete mismatch with the pandemic strain. The hospitalisation rate among placebo-recipients was unusually high (approximately 1.6%), even for a pandemic, and was approximately 4-fold greater than the reported incidence of complications. The reason for 'hospitalisation' is not provided in the original paper, but given the disparity between complications and hospitalisation, it may reflect admissions for 'quarantine' and military protocol rather than medical necessity.

The Cochrane review does not give prominence to studies that reflect vaccines available currently. Accordingly, for estimations of vaccine efficacy/effectiveness we combined several studies from the Cochrane review with more recent data.

Vaccine efficacy – reductions in laboratory-confirmed influenza

Historically, current vaccine recommendations are based on (i) the high morbidity and mortality associated with certain chronic medical conditions and (ii) studies of inactivated influenza virus vaccines conducted in healthy, young adult populations in the US Army and US Air Force over 20–30 years.[639,640]

These randomised, placebo-controlled trials involved thousands of recruits each year who received whole virion vaccines that have since been replaced by 'split' and surface antigen (SA) vaccines in most countries. Vaccine efficacy for reducing laboratory-confirmed illness in military personnel usually exceeded 70% and was <60% during seasons when there was a poor match between circulating and vaccine strains.

More recent trials in civilian populations demonstrate that influenza vaccine is efficacious in preventing culture or serologically confirmed influenza.

Randomised, double-blind, placebo-controlled trial

Hammond and colleagues[641] randomly allocated subunit vaccine (n = 116) or placebo (n = 109) to medical students and staff of Monash University, Australia, during spring 1976 in this placebo-controlled trial. Vaccine or placebo was allocated in rotation to one of six groups (vaccine, groups B, C, and F; placebo, groups A, D and E). Blood samples for serology were collected before vaccination, one month later, and approximately 4-months after vaccination when the study terminated. Subjects were asked to report respiratory illness as soon as possible. Specimens for virus isolation and acute and convalescent sera

were obtained. Influenza was diagnosed by laboratory tests in one of 116 (0.9%) vaccinees and 14 of 109 (12.8%) controls (efficacy, 93.3%, $p < 0.001$).

Keitel and colleagues[576] conducted a randomised, double blind, placebo-controlled trial of 15-μg doses of whole virion vaccine in 30–60-year-olds in Texas, USA, during the 1983–4 and 1984–5 seasons. Volunteers were asked to report any respiratory problems or ILI. Specimens for virus isolation and acute and convalescent sera were obtained. Subjects were considered infected if an influenza virus was isolated and/or a 4-fold rise in antibody titre occurred between post-vaccination (pre-epidemic), acute, convalescent and/or post-epidemic sera. Subjects were stratified according to whether they had a history of influenza vaccination during the preceding 3 years or not. Influenza A (H1N1) and influenza B circulated during 1983–4 and influenza A (H3N2) during 1984–5. There was a suggestion of greater protection in subjects with a previous history of vaccination than in 'new' vaccinees

Edwards and colleagues[642] carried out a randomised, double-blind, placebo-controlled trial over 5 years comparing the safety, immunogenicity and efficacy of cold-adapted and inactivated influenza A vaccines in 5210 normal subjects, including 809 subjects aged ≤ 15 years. Subjects were recruited from seven organisations and assigned to one of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. During the first year of the study, bivalent split vaccine was used containing H1N1 and H3N2 antigens (15 μg HA of each strain). During subsequent years, trivalent vaccines were used. ILI was defined by fever of abrupt onset with one or more systemic or respiratory symptoms. Subjects with ILI were instructed to contact the trialists to present for throat culture and to complete an illness record. However, a substantial number of cases of ILI were only identified after season, at the spring interview. Hence the attack rates of influenza in vaccinees and controls are probably spuriously low. The overall efficacy of inactivated vaccine in preventing culture-positive influenza A was 76% (95% CI 58 to 87%) for H1N1 disease and 74% (95% CI 52 to 86%) for H3N2.

Wilde and colleagues[226] recruited 264 hospital-based healthcare professionals (mean age 28.4 years, 77% physicians) without chronic medical problems (191 were studied one season only, 49 for two seasons and 24 for three seasons) to determine the efficacy/effectiveness of trivalent influenza vaccine in reducing infection, illness and absence from work. This randomised, double-blind, placebo-controlled trial was conducted over three consecutive seasons from 1992–3 to 1995–6. The estimates of clinical effectiveness were based on 264 subjects over 361 person winters. During the influenza season, the study nurse conducted weekly telephone interviews to inquire about illnesses during the previous week. Most subjects had no days of illness or work absence. Vaccine efficacy against serologically defined infection (i.e. symptomatic and asymptomatic infection) was 88% for influenza A (95% CI 47 to 97%, $p = 0.001$) and 89% for influenza B (95% CI 14 to 99, $p = 0.03$). The authors do not provide information on the number of febrile respiratory illnesses. Subjects who were vaccinated ($n = 181$) had fewer days of febrile respiratory illness (52 days) than controls (73 days for 180 subjects) but the reduction is not significant (29% reduction, $p = 0.57$; Mantel–Haenszel test).

Random effects meta-analysis of the data in *Table 157* indicates that the OR for influenza with vaccination is 0.269 (95% CI 0.19 to 0.4). This is for all studies; if we consider only those by Edwards and colleagues[642] and Wilde and colleagues[226] then vaccine has an OR for confirmed influenza of 0.23 (95% CI 0.152 to 0.339). The value used in the model is that for all studies.

Vaccine efficacy – reductions in laboratory-confirmed influenza in children

A review was carried out which examined the use of influenza vaccination in children. The following studies were identified. Summary data for these studies are given in *Table 158*.

Double-blind, placebo-controlled controlled studies

In 1985, Gruber and colleagues[580] enrolled 189 school-aged children by family in a randomised, double-blind, placebo-controlled study to determine protection against influenza by a single dose of cold-recombinant bivalent A vaccine or commercial trivalent inactivated vaccine compared with placebo. All children in school or day care, 3–18 years of age, in an enrolled family received the same preparation. When influenza was present in the local community, weekly telephone contacts

TABLE 157 *Efficacy of influenza vaccine in preventing culture or serologically confirmed influenza in adults of working age*

Author	Influenza season	Vaccine	Influenza in vaccine: recipients/total	Influenza in placebo: recipients/total	Efficacy (%) (95% CI)
Hammond *et al.*, 1978[641]	1976	SA	1/116 (0.9)	14/109 (12.8)	93.3 (?)
Keitel *et al.*, 1988[576]					
'New' vaccinees	1983–4	15 μg WWV	13/162	47/298	49 (12 to 86)
Previous vaccination	1983–4	15 μg WWV	7/138		68 (33 to 100)
'New' vaccinees	1984–5	15 μg WWV	14/171	54/241	63 (34 to 93)
Previous vaccination	1984–5	15 μg WWV	16/285		75 (49 to 100)
Edwards *et al.*, 1994[642]	Studies conducted over 5 years				
H1N1	1985–6 to	15 μg split	14/2004	60/2003	76.7 (58 to 87)
H3N2	1989–90	15 μg split	13/2076	47/2080	72.2 (52 to 86)
Wilde *et al.*, 1999[226]	Studies conducted over 3 years				
Influenza A	1992–3 to	15 μg split	2/180	16/179	88 (47 to 97)
Influenza B	1995–6	15 μg split	1/180	9/179	89 (14 to 99)
Total			**81/5132**	**247/4910**	

TABLE 158 *Vaccine efficacy in children*

Author	Influenza season	Vaccine	Infections in vaccine: recipients/total	Infections in placebo: recipients/total	Efficacy (%) (95% CI)
Randomised, double-blind, placebo-controlled trials					
Gruber *et al.*, 1990[580]	1985–6	15 μg Split	4/54	24/77	76.3
Hayden *et al.*, 1991[248]	1986–7	15 μg Split	17/100	36/82	61.3
Neuzil *et al.*, 2001[643]	1985–90	15 μg Split (1 or 2 doses)			
	H1N1		2/327	21/294	91.4 (63.8 to 98.0
	H3N2		4/289	12/280	77.3 (20.3 to 93.5)
Randomised, single-blind controlled study					
Khan *et al.*, 1996[644]	1991–2	15 μg split	2/147	37/163	94.0
Hurwitz *et al.*, 2000[593]	1996–7	15 μg SA (2 doses)	13/46	26/51	45 (5 to 66)
Prospective, non-randomised, controlled trial					
Heikkinen *et al.*, 1991[61]	1988–9	15 μg Split (2 doses)	5/187	29/187	82.6
Sugaya *et al.*, 1994[597]	1992–3	8–13.5 μg SA (2 doses)	35/85	37/52	42.1
Total			**65/1135**	**186/1104**	

were initiated to evaluate all respiratory illness. Nasal washes and throat swabs were collected for virology from symptomatic children; influenza infection was also confirmed by serology. Febrile influenza B illness occurred in four of 54 vaccinated school-aged children (14.8%) compared with 24 of 77 (31.2%) controls (efficacy 76.3%, $p < 0.01$).

Hayden and colleagues[248] studied the heterotypic protection afforded by an earlier H1N1 vaccine variant, A/Chile/83, against a drifted virus, A/Taiwan (H1N1), that caused an outbreak in 1986–87. The investigators enrolled 103 families, consisting of 166 adults and 225 children; 192 children aged 3–19 years from 98 families completed this double blind, placebo-controlled

study. Families were contacted weekly to evaluate respiratory illness. Blood samples were collected after immunisation with split influenza vaccine and again after the epidemic had ended. Nasal washes and throat swabs were collected from symptomatic patients for virus isolation. Influenza infection was confirmed by virus isolation and/or by serology. Symptomatic infections with influenza A/Taiwan/86 virus were detected in 36 (44%) of 82 children given placebo and 17 (17%) of 100 children given inactivated vaccine for a protection rate of 62% ($p < 0.05$).

Neuzil and colleagues[643] reanalysed data from annual randomised, double-blind, placebo-controlled studies of cold-adapted and inactivated vaccines conducted from 1985 to 1990[642] in the subset of subjects who were younger than 16 years at the time of their participation. Post-immunisation and post-season antibody titres were measured to assess seroconversion (infection) to the circulating strains over the influenza season. Patients were encouraged to report ILI to study personnel. Culture-positive illness was defined by an ILI (fever of abrupt onset with one or more systemic and respiratory symptoms), presentation for throat culture and culture of influenza A virus (note: influenza B vaccine was used as the control during four of the five seasons). In all age groups combined, inactivated vaccine was 91.4% efficacious (95% CI 63.8 to 98.0) at preventing culture positive H1N1 infections and 77.3% efficacious (95 CI 20.3 to 93.5) for H3N2. Based on post-vaccination to springtime conversion in unvaccinated control subjects, the inactivated vaccines were 67% (95% CI 51 to 78) and 65% (95% CI 39 to 84) effective in preventing seroconversion (i.e. clinical and subclinical influenza infections) to H1N1 and H3N2 serotypes, respectively. Subgroup analysis showed trends towards protection in children aged 1–5 years against both H1N1 and H3N2 subtypes.

Randomised, single-blind, controlled study

In a randomised, single-blind, placebo-controlled study, the efficacy of single doses of US inactivated split virus and Russian live attenuated, cold-adapted influenza vaccines were compared in 555 9–12-year-old schoolchildren in Vologda, Russia.[644] Post-immunisation and post-season antibody titres were measured to assess seroconversion (infection) to the influenza A (H3N2) circulating during the outbreak. The efficacy against serologically confirmed influenza virus infection was 94% [2/147 (1.4%) versus 37/163 (22.7), $p < 0.001$].

A randomised, blinded, controlled trial of influenza vaccination was conducted in 1996–97 among children 24–60 months of age attending day-care centres.[593] Children were randomised to receive either influenza A vaccine or hepatitis A vaccine. The nurses administering the vaccine were not blinded to the vaccine being administered, but were instructed not to provide this information to parents. Only children who had not previously received an influenza vaccine and thus were given two doses 1 month apart were included in the analysis ($n = 127$). Influenza infections were defined as a ≥ 4-fold HI titre increase when specimens obtained 1 month after vaccination were compared with those obtained at the end of the study in May. Of the 127, only 46 influenza-vaccinated and 51 control children had three specimens available for serological analysis. Estimates of clinical effectiveness were based on information concerning respiratory illnesses obtained via telephone interviews every 2 weeks. Vaccine efficacy was 45% (95% CI 5 to 66%) for influenza A and B infections combined.

Prospective non-randomised, controlled trials

Heikkinen and colleagues[61] compared the incidence of symptomatic influenza in 187 vaccinated children aged 1–3 years (mean age 2.2 years) attending 11 randomly selected day-care centres with 187 unvaccinated children in eight other randomly selected centres. The vaccine was a trivalent subvirion (split) preparation, given in two doses with a 3-week interval. During the 6-week study period when influenza was circulating, influenza A infection was confirmed by fluoroimmunoassay in five (2.7%) of 187 vaccinees and in 29 (15.5%) controls (efficacy 82.6% RR 5.8, $p < 0.0001$).

Sugaya and colleagues[597] evaluated the efficacy of trivalent inactivated subunit vaccines (given in two doses adjusted for age, containing ~13.5 μg HA of the recommended H3N2 strain, 8 μg HA of the recommended H1N1 strain and 10 μg HA of the B strain during a severe epidemic of antigenically drifted influenza A H3N2 and well-matched type B viruses) during the 1992–93 season. A total of 137 children with moderate to severe asthma (mean age 7 years, range 2–14 years) participated in this prospective non-randomised study. Eighty-five children received the vaccine and 52 who were unvaccinated served as controls. All subjects were seen at least every 2 weeks for regular review. Specimens were collected for virus isolation and pre-season and post-epidemic sera were collected when children had complaints of fever or

respiratory symptoms. The efficacy of vaccine in preventing influenza A H3N2 was 67.5% ($p < 0.01$) [32 of 52 controls (61.5%) had virologically confirmed influenza A H3N2 as compared with 17 (20%) of 85 vaccinees]. The efficacy of vaccine in preventing influenza B was 43.7% ($p < 0.01$) [25 of 52 controls (48.1%) had virologically confirmed influenza B as compared with 23 (27.1%) of 85 vaccinees]. Total vaccine efficacy, that is, the ability of vaccine to prevent all infections, was estimated at 42.1% ($p < 0.01$). When stratified by age, the estimated efficacy was 16.1% (non-significant) in children <7 years of age and 61.7% in children aged ≥ 7 years of age. Febrile laboratory-confirmed influenza illness occurred in 25 of 85 (29.4%) vaccinees and in 30 (57.7%) of 52 controls (overall efficacy 49%, $p < 0.01$). The estimated efficacy was 16.4% (non-significant) in children <7 years of age and 74.4% in children aged ≥ 7 years of age.

A random effects meta-analysis was carried out on the double and single randomised trial. The non-randomised trials were excluded. The OR for the reduction in influenza with vaccination in children was found to be 0.198 (95% CI 0.102 to 0.259).

Appendix 21

Ability of frail elderly to use the Diskhaler device to administer zanamivir

Zanamivir is delivered to the lungs by a dry-powder inhaler, the Diskhaler, which is also used as a delivery system for salbutamol and beclomethasone. Elderly people have difficulty in using inhaler devices[645–647] and concern has been raised about the ability of elderly people to learn to load and prime the device for use.[648]

Lee and colleagues[258] describe the use of zanamivir in a nursing home in Canada during an influenza A outbreak. A total of 129 (92%) of 140 residents who were offered zanamivir accepted it and were able to attempt inhalations. Of the 129, 100 (78%) had no difficulty in complying with inhalations. Difficulty with inhalations was associated with decreased functional and mental status. Fifteen (58%) of 26 residents fully dependent in activities of daily living had difficulty compared with 14 (14%) of 100 others ($p < 0.001$). Twenty-two (45%) of 49 residents not orientated to person, place, or time had difficulty compared with seven (10%) of 77 others ($p < 0.001$).

Li and colleagues[649] describe the use of zanamivir to control an outbreak of influenza in a nursing home in Canada. The staff classified residents as capable of using a Diskhaler or not. Residents' ability to use the Diskhaler was reassessed during administration of the first two doses and zanamivir was replaced with amantadine for those with difficulty. Thirty-two of 246 patients were judged unable to use the inhaler. An additional seven residents were switched to amantadine after two attempts at inhalations. Thus 39 of 246 (15.9%) patients had difficulty using the inhaler device.

Diggory and colleagues[648] examined whether patients aged over 65 years (mean age 83 years; mean mental test score 9.58) from seven wards providing acute elderly care were able to learn to use the inhaler to deliver zanamivir as effectively as another dry-powder delivery device Turbohaler (Astra). After tuition, 50% (19 of 38) of patients allocated the Diskhaler were unable to load and prime the device and 65% (24 of 37) were unable to do so 24 hours later. The authors concluded that the drug is unlikely to be effective in elderly people unless the delivery system is improved.

Hirji and colleagues[650] evaluated the efficacy, safety, compliance and tolerability of zanamivir used as treatment and chemoprophylaxis in high-risk patients exposed concomitantly to influenza A and B in a hospitalised complex continuing care population. The influenza treatment regimen was two oral inhalations (2 × 5 mg) of zanamivir twice daily for 5 days. The prophylactic regimen used was two oral inhalations (2 x 5 mg) of zanamivir once daily for 14 days. Patients on either treatment or prophylaxis who failed to comply with their regimens on two consecutive occasions had the drug discontinued. Of the 51 patients on the unit, the mean age was 70.6 (±16.4) years and 36 (71%) were dependent in four activities-of-daily-living functions. Forty-eight patients were offered chemoprophylaxis with zanamivir. Four patients (8.3%) were unable to take zanamivir because of severe cognitive impairment. Of the 44 remaining patients who were able to take zanamivir, 41 (93%) completed their courses, two discontinuing medication because of severe cognitive impairment. Thus, overall, 42 of

TABLE 159 *Summary data on the ability to use zanamivir correctly for the elderly living in residential care*

Study	Mean age (years)	No. able to use zanamivir/total (%)
Lee *et al.*, 2000[258]	NA	100/129 (77.5)
Li *et al.*, 2000[649]	NA	207/246 (84.1)
Diggory *et al.*, 2001[648]	83	13/37 (35.1)
Hirji *et al.*, 2001[650]	70.6	42/48 (87.5)

NA, not available.

48 (85%) of the residents were able to use and complete the course of prophylaxis.

The data in *Table 159* indicate that a large proportion of elderly people living in residential care (and those admitted to hospital for acute elderly care) were able to use the device, with the exception of the study by Diggory and colleagues.[648]

Appendix 22

Adult treatment model sensitivity analysis

TABLE 160 *Treatment 21-day extrapolated model results for healthy adult population compared to usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.11 (0.049 to 0.21)	0.000017 (–0.00012 to 0.00016)	6190
Oseltamivir	0.88 (0.41 to 1.67)	0.00019 (–0.000023 to 0.0005)	4729
Zanamivir	1.28 (0.60 to 2.43)	0.00014 (–0.000074 to 0.00044)	8884

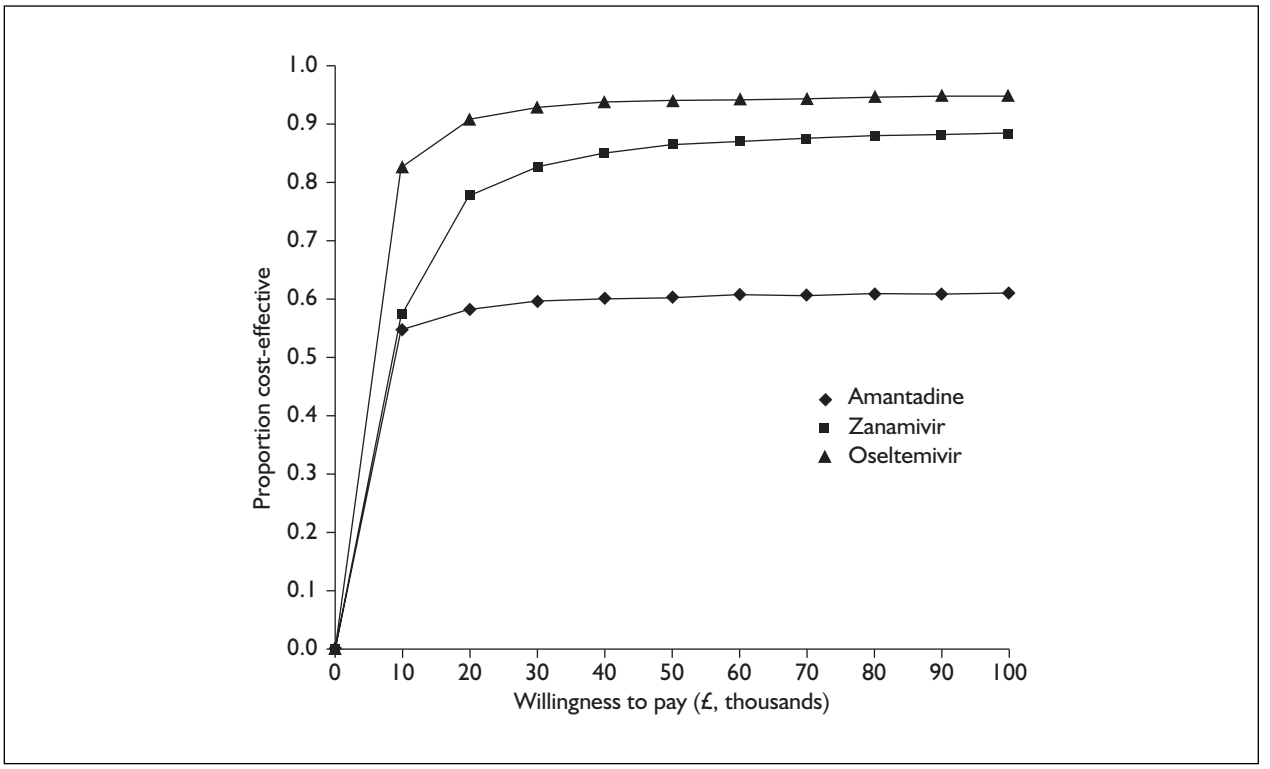


FIGURE 54 *Cost-effectiveness acceptability curve for healthy adults extrapolated model*

TABLE 161 *Treatment 7-day model results for healthy adult population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.11 (0.049 to 0.21)	0.000014 (–0.000079 to 0.0001)	7786
Oseltamivir	0.895 (0.42 to 1.69)	0.00004 (–0.000089 to 0.00017)	22438
Zanamivir	1.29 (0.60 to 2.43)	0.000034 (–0.000094 to 0.00016)	37541

TABLE 162 *Treatment 7-day extrapolated model results for healthy adult population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.11 (0.049 to 0.21)	0.000014 (–0.000079 to 0.0001)	7786
Oseltamivir	0.88 (0.41 to 1.66)	0.000178 (0.000017 to 0.00041)	4928
Zanamivir	1.28 (0.6 to 2.41)	0.00014 (–0.000032 to 0.00036)	9298

TABLE 163 *One-way sensitivity analyses: adult treatment base-case model (£)*

Variable	Probability ranges				
	0.1	**0.3**	**0.5**	**0.7**	**0.9**
Probability ILI is influenza (base case 0.46)					
Amantadine	79993	10389	5555	3791	2878
Oseltamivir	95130	29998	16972	11389	8288
Zanamivir	Zero effect	62500	30500	20000	16857
Probability ILI is influenza A (base case 0.32)					
Amantadine	negative effect	18155	8978	5963	4464
Probability of presenting to GP if NIs available (0.28)					
Oseltamivir	–243062	27364	81436	104618	117490
Zanamivir	–270763	41295	103688	130426	145292
Probability of drug if present after 48 hours (0.03)					
Amantadine	8461	16683	28847	48688	86814
Oseltamivir	25161	43239	61318	79397	97476
Zanamivir	40500	67750	94750	122000	149250
No reduction in antibiotic use					
Amantadine	11072				
Oseltamivir	20505				
Zanamivir	32750				
QALY value of pneumonia (base case 0.724)				**0.5**	**0.9**
Oseltamivir				17394	19852
Zanamivir				24600	30750
Productivity loss included (based on time to return to normal activities)			**Low CI**	**Mean**	**High CI**
Oseltamivir (mean –1.64, 95% CI –0.69 to –2.58)			6587	–26250	–60250
Zanamivir (mean –1.64, 95% CI –0.69 to –2.58)			24250	18000	–1750
Price of oseltamivir as zanamivir					
Oseltamivir	25698				
RR of pneumonia [base case 0.15 (oseltamivir),0.35 (zanamivir)]				**Low CI**	**High CI**
Oseltamivir (95% CI 0.03 to 0.69)				18455	19849
Zanamivir (95% CI 0.11 to 1.09)				30750	41000

TABLE 164 *Additional sensitivity analyses for the* extrapolated *21-day model (£)*

Discount rate applied to avoided deaths (base case 1.5%)	**0%**	**6%**
Oseltamivir	3883	6425
Zanamivir	7563	12100
RR of pneumonia (as above)	**Low CI**	**High CI**
Oseltamivir	4096	9069
Zanamivir	6722	60500
Note: oseltamivir dominates zanamivir throughout.		

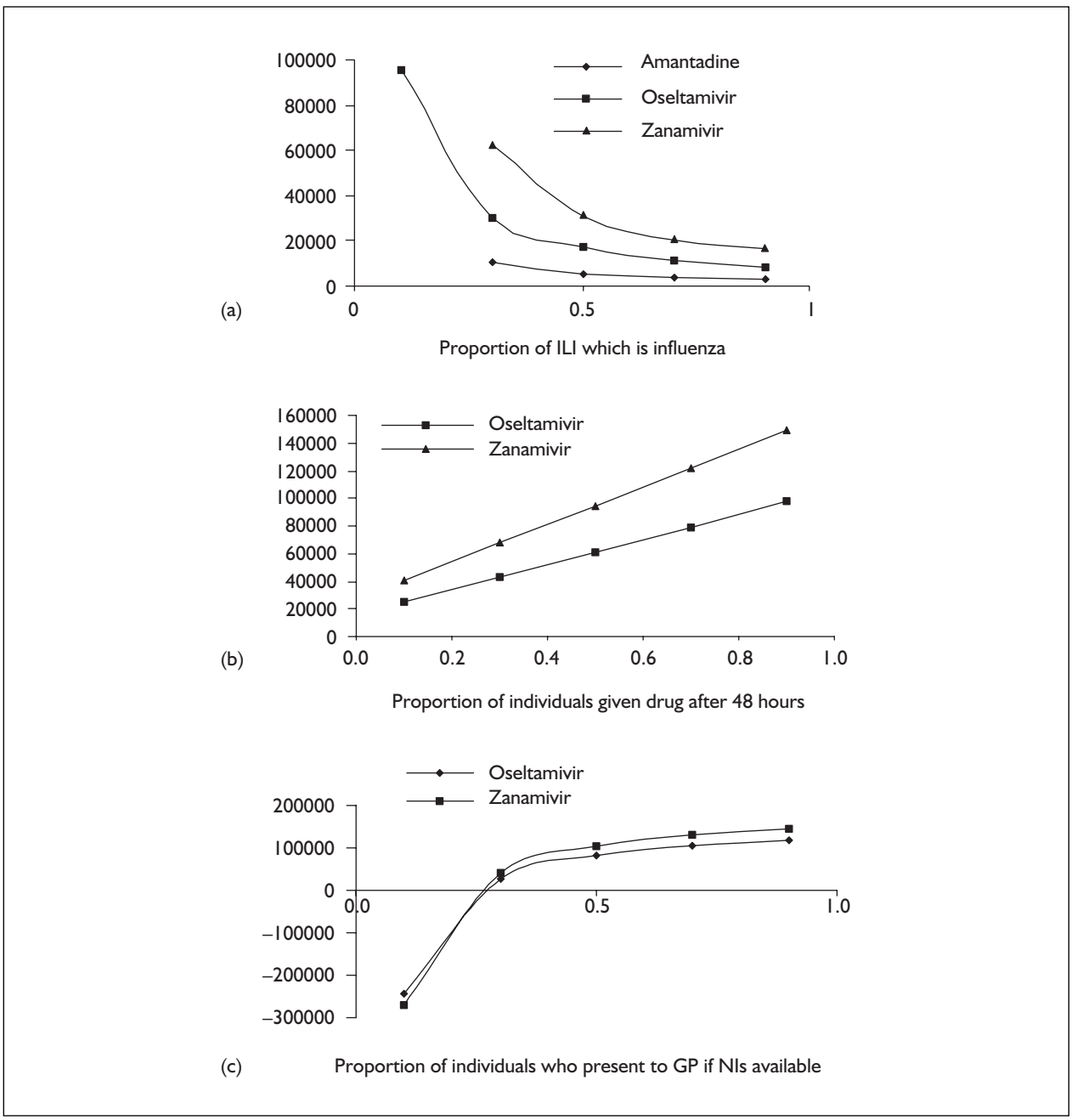


FIGURE 55 *One-way sensitivity analyses: (a) probability ILI is influenza; (b) probability of drug if after 48 hours; (c) probability of presenting to GP if NIs available*

TABLE 165 *Two-way sensitivity analyses (£)*

Probability that ILI is influenza		Probability of presenting to GP if NI available			
		0.28	**0.32**	**0.36**	**0.4**
Healthy adult base case					
0.46	Zanamivir	30096	51613	67363	79738
	Oseltamivir	17675	36049	49684	61325
0.41	Zanamivir	34688	58395	76714	91294
	Oseltamivir	20198	40279	56819	69170
0.36	Zanamivir	39501	67172	86735	104220
	Oseltamivir	23442	46680	64754	79213
0.31	Zanamivir	44100	76343	99703	118145
	Oseltamivir	26872	53758	75130	90422
Healthy adult extrapolated case					
0.46	Zanamivir	8120	13760	18217	21695
	Oseltamivir	4280	8791	12277	15063
0.41	Zanamivir	9127	15511	20370	24357
	Oseltamivir	4897	9925	13841	16904
0.36	Zanamivir	10493	17755	23403	27921
	Oseltamivir	5687	11435	15920	19420
0.31	Zanamivir	12188	20733	27250	32445
	Oseltamivir	6737	13349	18572	22644

Appendix 23

High-risk treatment model sensitivity analysis

TABLE 166 *Treatment 21-day extrapolated model results for high-risk population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.063 (0.022 to 0.146)	0.000014 (–0.000098 to 0.00013)	4535
Oseltamivir	0.505 (0.175 to 1.18)	0.00017 (0.0000087 to 0.00047)	3016
Zanamivir	0.696 (0.245 to 1.62)	0.0002296 (0.000051 to 0.00058)	3029

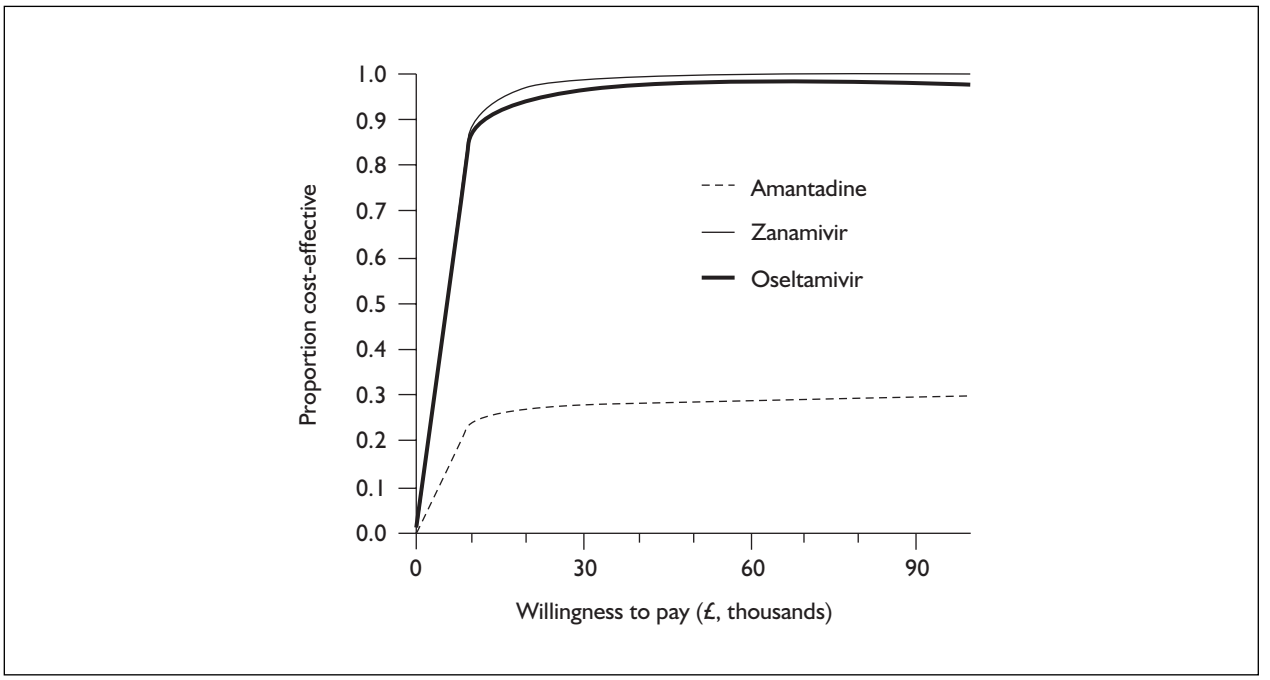


FIGURE 56 *Cost-effectiveness acceptability curve for high-risk extrapolated model.*

TABLE 167 *Treatment 7-day model results for high-risk population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.062 (0.022 to 0.15)	–0.0000013 (–0.000076 to 0.00006)	Negative effect
Oseltamivir	0.71 (0.26 to 1.56)	0.000011 (–0.000075 to 0.000092)	63175
Zanamivir	0.96 (0.35 to 2.10)	0.000018 (–0.000068 to 0.0001)	53691

TABLE 168 *Treatment 7-day extrapolated model results for high-risk population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.062 (0.022 to 0.145)	–0.0000013 (–0.000076 to 0.00006)	Negative effect
Oseltamivir	0.501 (0.18 to 1.15)	0.00014 (0.000018 to 0.00039)	3456
Zanamivir	0.69 (0.24 to 1.58)	0.00019 (0.000047 to 0.00048)	3631

TABLE 169 *One-way sensitivity analyses: high-risk treatment base-case model (£)*

Variable	Probability ranges				
	0.1	**0.3**	**0.5**	**0.7**	**0.9**
Probability ILI is influenza (base case 0.46)					
Amantadine	Negative effect	9830	3928	2455	1785
Oseltamivir	107165	34123	19514	13253	9775
Zanamivir	82102	26178	14993	10200	7536
Probability ILI is influenza A (base case 0.37)					
Amantadine	Negative effect	226725	10827	5546	3728
Probability of presenting to GP if NIs available (base case 0.33)					
Oseltamivir	–647000	–7800	135498	196086	229746
Zanamivir	–641000	1125	81656	116284	135521
Probability of drug if after 48 h (base case 0.011)					
Amantadine	11126	Negative effect	Negative effect	Negative effect	Negative effect
Oseltamivir	36114	69208	102303	135397	168491
Zanamivir	27703	53041	78379	103718	129056
No reduction in antibiotic use					
Amantadine	11132				
Oseltamivir	21441				
Zanamivir	16468				
QALY value of pneumonia (base case 0.72)				**0.5**	**0.9**
Oseltamivir				20312	22462
Zanamivir				15826	17033
Price of oseltamivir as zanamivir					
Oseltamivir	29333				
RR pneumonia [base case 0.76 (oseltamivir) 0.69 (zanamivir)]				**Low CI**	**High CI**
Oseltamivir (95% CI (0.29 to 1.98))				18808	33701
Zanamivir (95% CI (0.17 to 2.85))				15112	25994

TABLE 170 *Additional sensitivity analyses for the extrapolated 21-day model (£)*

Discount rate applied to avoided deaths (base case 1.5%)	**0%**	**6%**
Oseltamivir	2886	3390
Zanamivir	2896	3364
RR of pneumonia (as above)	**Low CI**	**High CI**
Oseltamivir	208	Negative effect
Zanamivir	1283	Negative effect
Hospitalisation rate seen in Table 48 for oseltamivir		
Oseltamivir 404		

If cost saving, then negative cost-effectiveness ratio is used. If negative benefit, then stated as being 'negative-effect'.

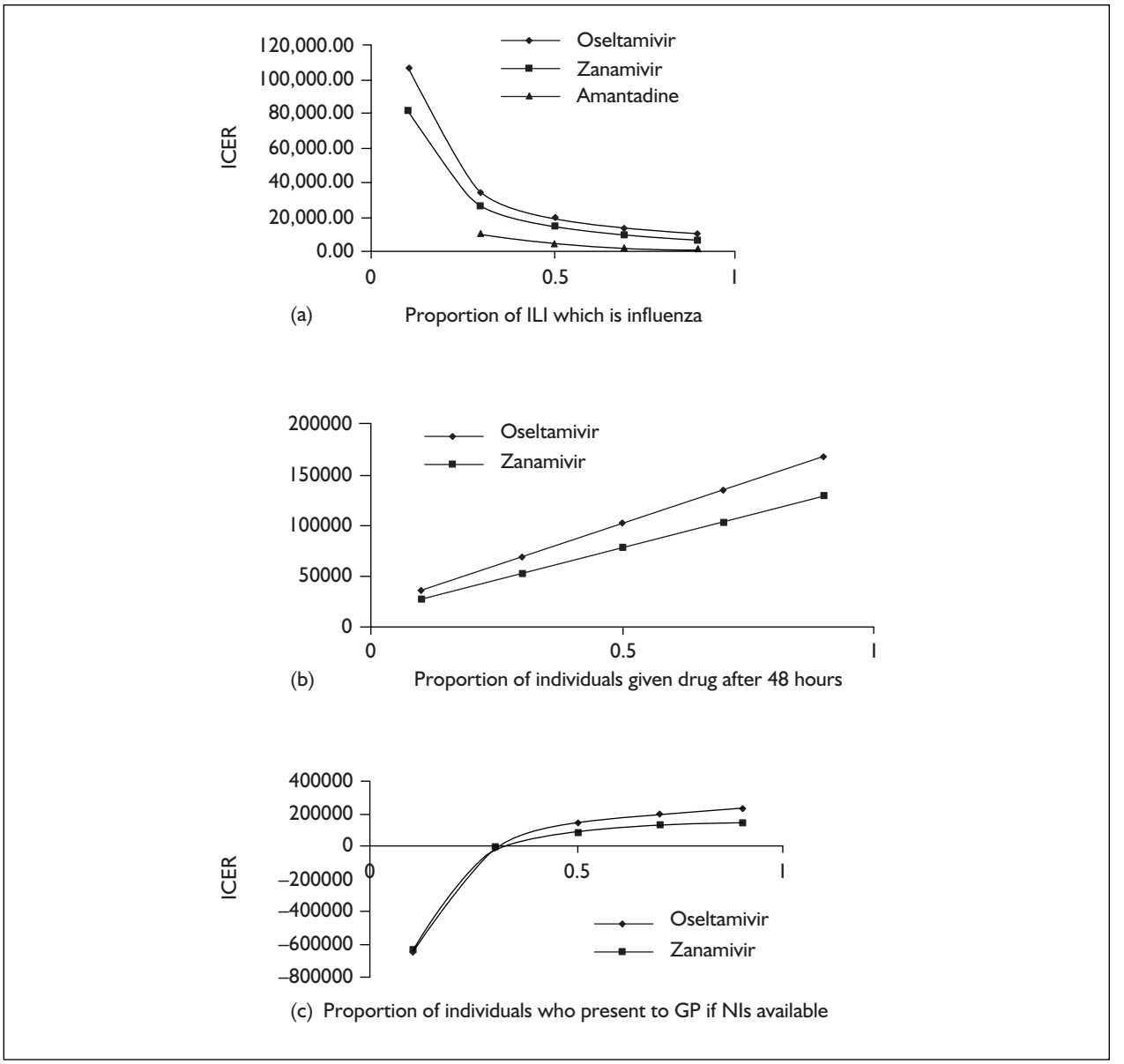


FIGURE 57 *One-way sensitivity analyses: (a) probability ILI is influenza; (b) probability of drug if after 48 hours; (c) probability of presenting to GP if NIs available*

TABLE 171 *Two-way sensitivity analyses (£)*

Probability that ILI is influenza		Probability of presenting to GP if NI available			
		0.33	**0.37**	**0.41**	**0.45**
Healthy adult base case					
0.46	Zanamivir	19031	38967	55223	67776
	Oseltamivir	26250	60327	87230	111667
0.41	Zanamivir	21677	44432	62106	76465
	Oseltamivir	29456	68663	100741	127473
0.36	Zanamivir	25098	50476	70878	87637
	Oseltamivir	33464	76617	114972	143740
0.31	Zanamivir	29691	59829	82442	102533
	Oseltamivir	40549	94429	133756	170754
High-risk extrapolated case					
0.46	Zanamivir	3677	8674	12658	15973
	Oseltamivir	3918	10761	16216	20778
0.41	Zanamivir	4304	9907	14380	18047
	Oseltamivir	4615	12235	18439	23443
0.36	Zanamivir	5160	11537	16657	20858
	Oseltamivir	5512	14206	21292	26987
0.31	Zanamivir	6222	13619	19579	24357
	Oseltamivir	6643	16684	24894	31472

Appendix 24

Elderly residential treatment model sensitivity analysis

TABLE 172 *Treatment 21-day extrapolated model results for elderly residential population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.076 (0.031 to 0.16)	0.000015 (–0.00011 to 0.000152)	5199
Oseltamivir	–0.98 (–11.86 to 14.78)	0.0013 (–0.01 to 0.0089)	–737
Zanamivir	–0.21 (–14.26 to 27.20)	0.001 (–0.018 to 0.011)	–205

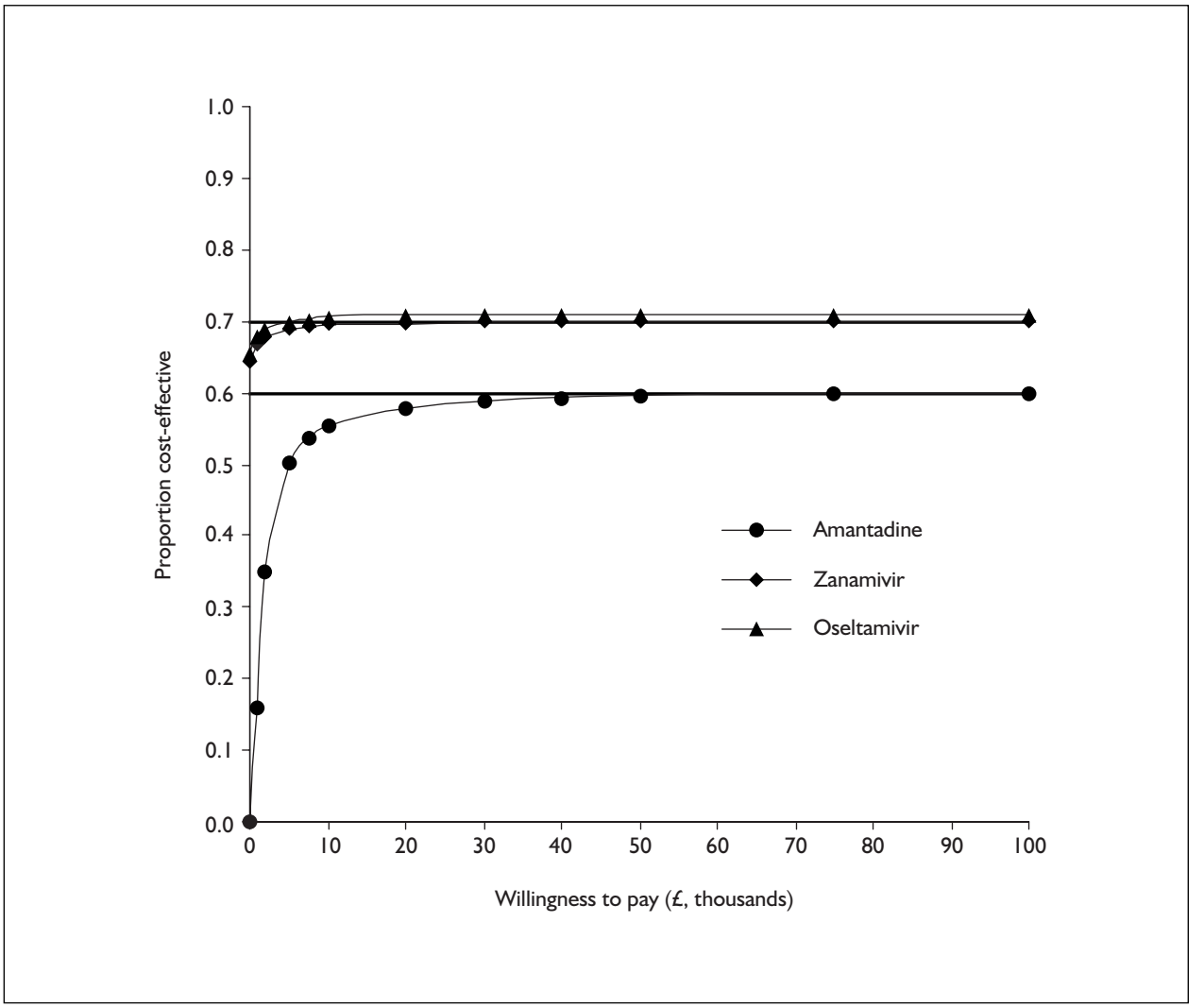


FIGURE 58 *Cost-effectiveness acceptability curves for elderly residential extrapolated model.*

TABLE 173 *Treatment 7-day model results for elderly residential population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.076 (0.032 to 0.16)	–0.000048 (–0.000094 to 0.000068)	Negative effect
Oseltamivir	0.84 (0.37 to 1.66)	0.000011 (–0.000091 to 0.0001)	75255
Zanamivir	1.14 (0.50 to 2.22)	0.00002 (–0.000082 to 0.00011)	57837

TABLE 174 *Treatment 7-day extrapolated model results for elderly residential population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.077 (0.032 to 0.16)	–0.000044 (–0.000094 to 0.000066)	Negative effect
Oseltamivir	–1.07 (–11.95 to 14.76)	0.0014 (–0.0095 to 0.009)	–760
Zanamivir	–0.21 (–14.13 to 25.82	0.00099 (–0.018 to 0.011)	–208

Appendix 25

Children's treatment model sensitivity analysis

TABLE 175 *Treatment 21-day extrapolated model results for children population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.23 (0.12 to 0.405)	0.0000375 (–0.00021 to 0.00029)	6117
Oseltamivir	1.66 (0.88 to 2.89)	0.00015 (–0.00020 to 0.00053)	11318
Zanamivir	2.230 (1.18 to 3.87)	0.00012 (–0.00023 to 0.00050)	19127

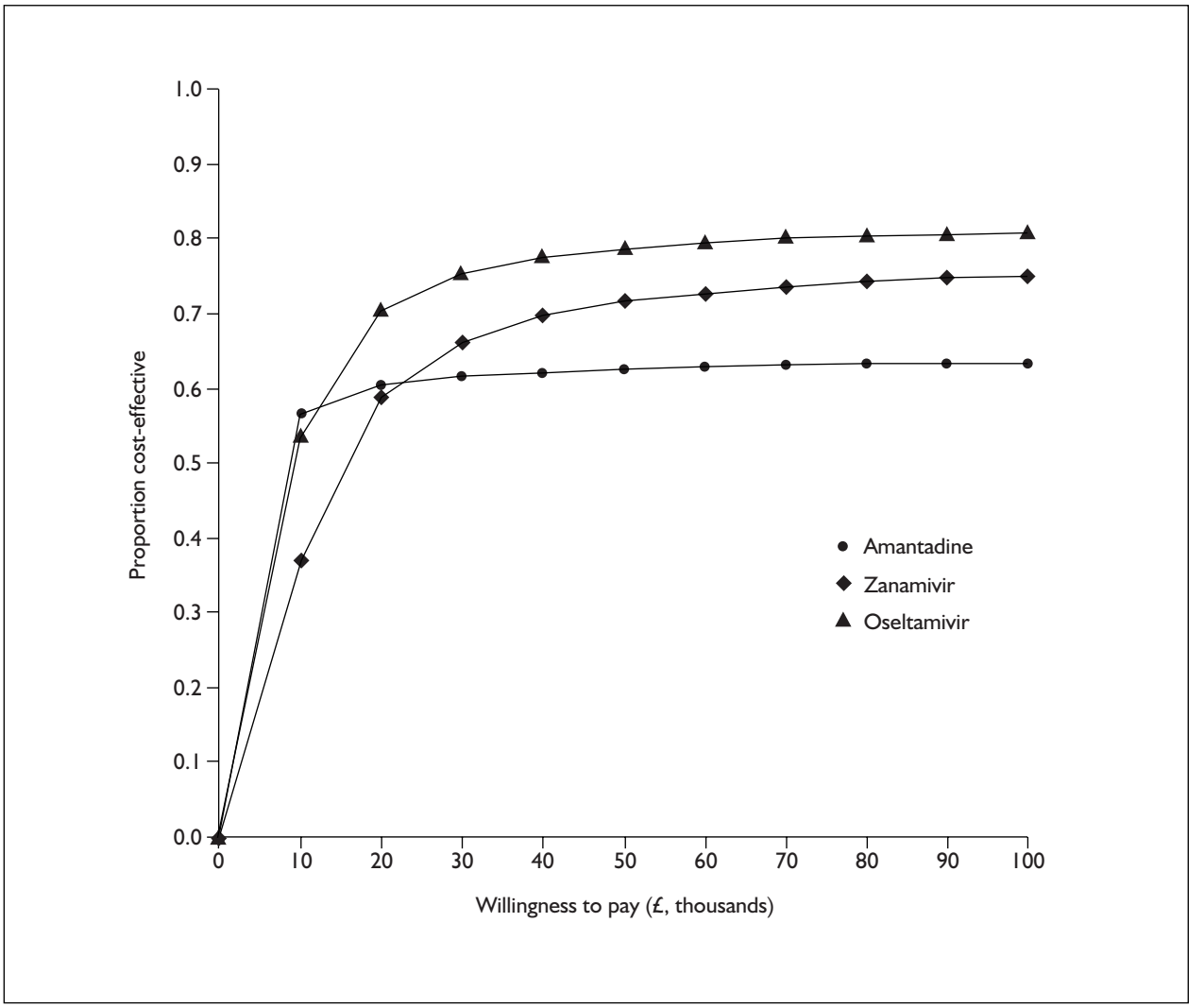


FIGURE 59 *Cost-effectiveness acceptability curves for children's extrapolated model.*

TABLE 176 *Treatment 7-day model results for children population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.23 (0.12 to 0.41)	0.000031 (–0.00013 to 0.00019)	7514
Oseltamivir	1.67 (0.87 to 2.88)	0.0000707 (–0.00015 to 0.00028)	23606
Zanamivir	2.23 (1.16 to 3.87)	0.0000593 (–0.00017 to 0.00027)	37711

TABLE 177 *Treatment 7-day extrapolated model results for children population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model		
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**
Amantadine	0.23 (0.12 to 0.41)	0.000031 (–0.00013 to 0.00019)	7514
Oseltamivir	1.66 (0.87 to 2.86)	0.00014 (–0.000093 to 0.00038)	12035
Zanamivir	2.225 (1.16 to 3.84)	0.00011 (–0.00013 to 0.00035)	20388

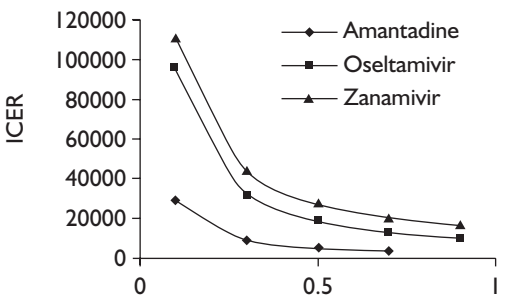
TABLE 178 *One-way sensitivity analyses: children treatment base-case model (£)*

Variable	**Probability ranges**				
	0.1	**0.3**	**0.5**	**0.7**	**0.9**
Probability ILI is influenza (base case 0.47)					
Amantadine	55921	10135	5573	3843	2932
Oseltamivir	96079	31598	18702	13175	10104
Zanamivir	111000	44000	27250	19636	16385
Probability ILI is influenza A (base case 0.33)					
Amantadine	214254	16944	8821	5962	6307
Probability of presenting to GP if NIs available (base case 0.15)					
Oseltamivir	–3760	40138	48871	52613	54693
Zanamivir	4100	57538	67273	71290	73500
Probability of drug if after 48 h (base case 0.12)					
Amantadine	5810	6787	7804	8861	9962
Oseltamivir	19430	22360	25289	28219	31148
Zanamivir	30714	35286	39857	44429	49000
No reduction in antibiotic use					
Amantadine	8179				
Oseltamivir	19740				
Zanamivir	31143				
QALY value of pneumonia (base case 0.72)				**0.5**	**0.9**
Oseltamivir				18400	20991
Zanamivir				27250	36333
Price of oseltamivir as zanamivir					
Oseltamivir	26250				
RR of pneumonia [base case 0.15 (oseltamivir) 0.35 (zanamivir)]				**Low CI**	**High CI**
Oseltamivir (95% CI (0.03 to 0.69))				19490	20978
Zanamivir (95% CI (0.11 to 1.09))				31142	36333
RR and duration of otitis media [base case 0.56 and 1 day (oseltamivir)]				**0.48 7 days**	
Oseltamivir					17946

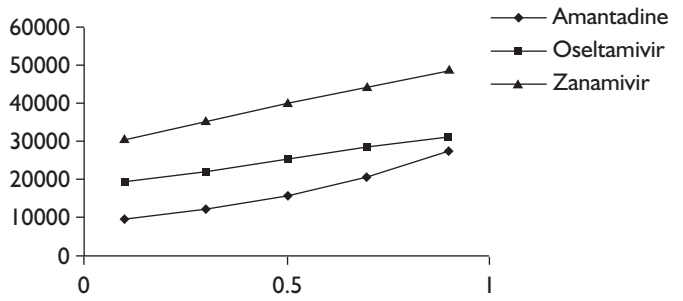
TABLE 179 *Additional sensitivity analyses for the* extrapolated *21-day model (£)*

Discount rate applied to avoided deaths (base case 1.5%)	**0%**	**6%**
Oseltamivir	8462	14766
Zanamivir	13563	24111
RR of pneumonia (as above)	**Low CI**	**High CI**
Oseltamivir	10086	15903
Zanamivir	15500	36166
Hospitalisation rate seen in Table 48 for oseltamivir		
Oseltamivir	10976	

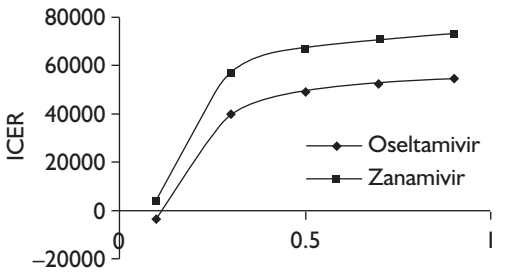
Note: oseltamivir dominates zanamivir throughout.



(a) Proportion of ILI which is influenza



(b) Proportion of individuals given drug after 48 hours



(c) Proportion of individuals who present to GP if NIs available

FIGURE 60 *One-way sensitivity analyses: (a) probability ILI is influenza; (b) probability of drug if after 40 hours; (c) probability of presenting to GP is NIs available*

Appendix 26

Sensitivity analysis – prophylaxis

TABLE 180 *Sensitivity analysis on healthy adult prophylaxis base-case model (£)*

Attack rate	**Probability ranges**				
	0.010	**0.030**	**0.066 (base-case)**	**0.100**	**0.200**
Compared with no intervention					
Vaccine	72320	23782	10627	6807	3190
Amantadine	1060660	355450	164343	108874	56450
Zanamivir	2484991	833209	385579	255646	132819
Oseltamivir	1856471	621686	287030	189861	97909
Compared to vaccine					
Vaccine and amantadine	6422306	2122448	956709	617903	296175
Vaccine and zanamivir	15020670	4964056	2237582	1445156	692634
Vaccine and oseltamivir	11226438	3705964	1667016	1074368	511405
Probability that influenza is influenza A		**0.416**	**0.935**		
Amantadine		270892	119830		
Amantadine and vaccine		1573585	698997		
Probability of death without antiviral treatment		**0**	**0.00039 (base case)**	**0.00100**	**0.01000**
Compared with no intervention					
Vaccine		32447	10627	5147	600
Amantadine		370415	164343	87378	11093
Zanamivir		869063	385579	205006	26026
Oseltamivir		646940	287030	152609	19374
Compared with vaccine					
Vaccine and amantadine		956709	956709	956709	956709
Vaccine and zanamivir		2237582	2237582	2237582	2237582
Vaccine and oseltamivir		1667016	1667016	1667016	1667016
Productivity loss from work in order to obtain prophylaxis intervention					**2 hours**
Compared with no intervention					
Vaccine					37819
Amantadine					164343
Zanamivir					385579
Oseltamivir					287030
Compared with vaccine					
Vaccine and amantadine					956709
Vaccine and zanamivir					2237582
Vaccine and oseltamivir					1667016

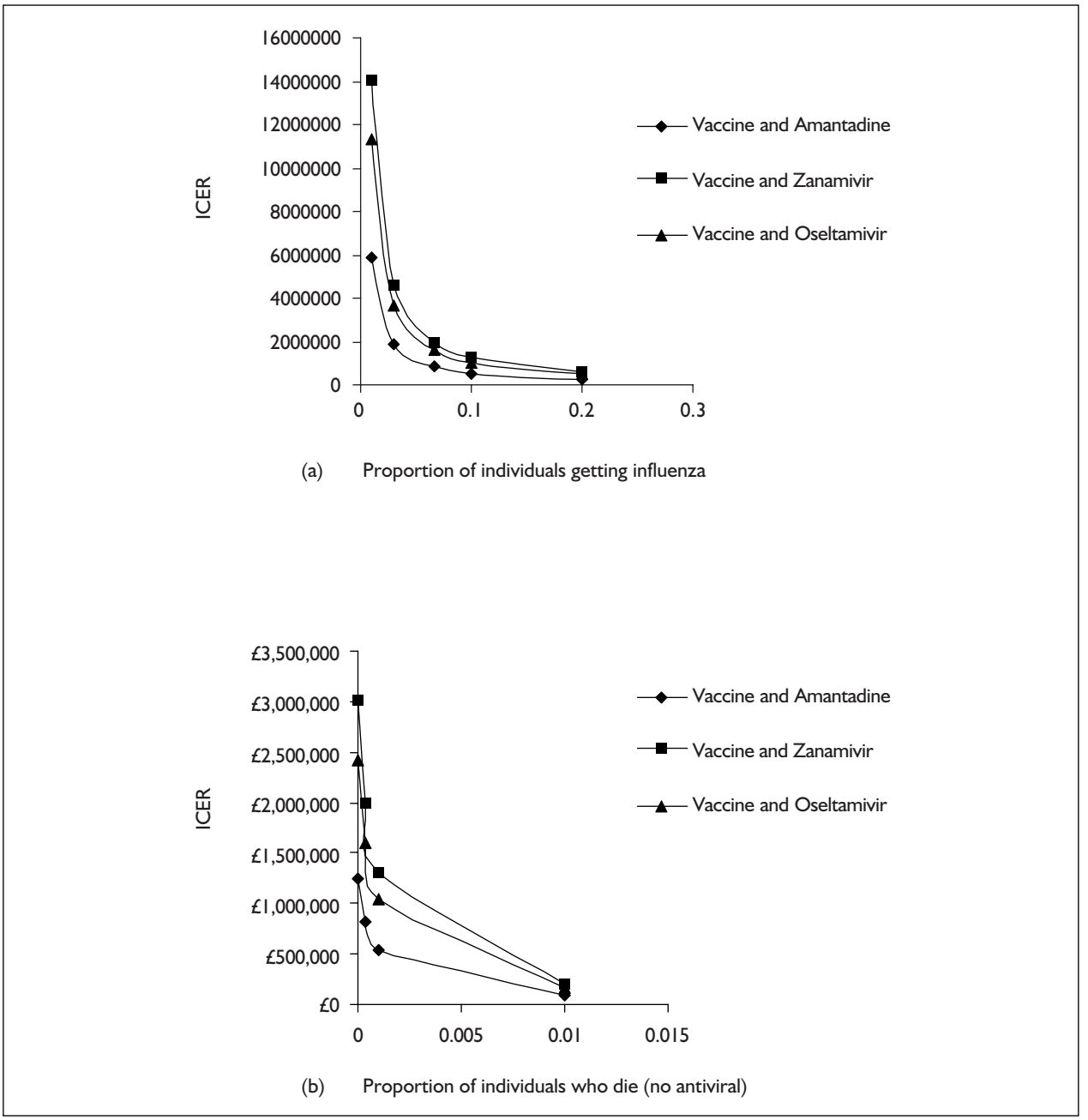


FIGURE 61 *One-way sensitivity analysis: (a) attack rate sensitivity analysis – strategies compared with vaccine; (b) probability of dying if no antiviral treatment received sensitivity analysis – strategies compared with vaccine*

TABLE 181 *Sensitivity analysis on residential care elderly prophylaxis base-case model (£)*

	Probability range	
Attack rate (base case 0.0485)	**0.100**	**0.200**
Compared with no intervention		
Vaccine	–1018	–1129
Amantadine	1643	197
Zanamivir	6897	2931
Oseltamivir	4771	1803
Compared to vaccine		
Vaccine and amantadine	13941	5917
Vaccine and zanamivir	41361	19405
Vaccine and oseltamivir	30267	13841
Probability of death (base case 0.094)	**0.01**	**0.3**
Compared with no intervention		
Vaccine	–5498	–256
Amantadine	30073	1544
Zanamivir	97667	5013
Oseltamivir	70566	3622
Compared to vaccine		
Vaccine and amantadine	132780	9276
Vaccine and zanamivir	377076	26344
Vaccine and oseltamivir	279127	19501
Value of averted deaths (base case 4.1 QALYs)	**0.5**	**1**
Compared with no intervention		
Vaccine	–5003	–2835
Amantadine	27504	16486
Zanamivir	89322	53541
Oseltamivir	64537	38684
Compared to vaccine		
Vaccine and amantadine	123041	87141
Vaccine and zanamivir	349421	247469
Vaccine and oseltamivir	258656	183187
Adding in amantadine adverse events		**Include adverse events of amantadine**
Compared with no intervention		
Amantadine adverse events		4883
Compared with vaccine		
Vaccine and amantadine		46251

TABLE 182 *Effect of raising cost of vaccination by 10 (£)*

Compared with no intervention	**Base case (8.40)**	**18.40**
Adult model	10627	24586
High-risk	2501	6934
Elderly residential	Cost saving	Cost saving
Children	6053	14656

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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