ORIGINAL ARTICLE

Antiviral Medications in Seasonal and Pandemic Influenza

A Systematic Review

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SUMMARY

Background: Amantadine, oseltamivir, and zanamivir are currently available in Germany for the prevention and treatment of influenza. We review their efficacy and side-effect profiles.

Methods: This review is based on pertinent randomized and controlled trials (RCTs) and systematic reviews retrieved by a systematic literature search, and on other relevant literature.

Results: The efficacy of antiviral drugs for the prevention of symptomatic influenza ranges from 60% to 90% (number needed to treat [NNT], 8–89) depending on the population and type of drug in question. Antiviral drugs shorten the duration of illness by 0.5–1.5 days when given within 48 hours of the onset of symptoms. Neuraminidase inhibitors do not significantly lower the incidence of bronchitis in adults, or of otitis media in children; they do have a positive effect against reported, but not necessarily diagnostically confirmed pneumonia in adults (NNT, 89 [50–232]). The RCTs yielded no information about possible effects on severe cases of influenza, or on mortality, as they included only mildly or moderately ill patients, but observational studies have yielded some evidence of benefit. The most common side effects of oseltamivir (>10%) are headache, nausea, and vomiting; of zanamivir (>1%), a skin rash; and of amantadine (>1%), loss of appetite, nausea, and central nervous effects.

Conclusion: The benefits of antiviral drugs, particularly neuraminidase inhibitors, outweigh their risks. In deciding whether to use them, physicians should consider the properties of the currently circulating viruses and the patient's individual risk constellation, as directed in clinical treatment recommendations.

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In Germany, the drugs available for influenza prophylaxis and therapy are amantadine and the neuraminidase inhibitors (NIs) oseltamivir and zanamivir. Unlike neuraminidase inhibitors, amantadine, as an M2 membrane channel blocker, is only effective against influenza A viruses. The use of amantadine is no longer recommended, principally due to rapid development of resistance during its use and high resistance rates in circulating influenza viruses, as well as poor tolerability (1, 2).

Most randomized controlled trials (RCTs)—the gold standard for proving efficacy—for amantadine, zanamivir, and oseltamivir are more than 15 years old. Since they were conducted, these trials have been summarized in many systematic reviews and meta-analyses. This review came about as part of Germany's national pandemic plan and was performed by a working group of the Robert Koch Institute (RKI) Expert Advisory Board on Influenza. It brings together the most important information from the chapter *Medicines relevant in a pandemic* of the scientific part of the German Influenza Pandemic Preparedness Plan. This provides comprehensive details on the amount of underlying data and the epidemiology of influenza (3). Regarding questions on political implications and data transparency, see earlier articles in *Deutsches Ärzteblatt* (4, 5).

Public health institutions and specialist societies have published treatment recommendations on the use of antiviral drugs for influenza (*Box*). The biased nature of some public debate on the issue makes an objective representation of the available evidence on antiviral drugs particularly important.

Below, we provide a brief description of the evidence on the efficacy and safety of the antiviral drugs available for influenza in Germany. This takes the form of answers to questions that are of particular clinical importance for the potential use of these drugs.

Methods

A systematic search was performed to locate meta-analyses, systematic reviews, and randomized controlled trials written in German or English and published no later than December 2, 2015. The search included the databases Cochrane Library, PubMed, and

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BOX

Clinical recommendations

Summary of the most important current recommendations on the use of antiviral drugs for influenza made by the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), the US Centers for Disease Control (CDCs), and Public Health England (PHE) (6–9)

● Who should be treated?

Therapy is recommended for patients with confirmed or suspected influenza who meet the following criteria:

- Hospitalized
- Severe, complicated, or progressive disease
- High risk of influenza-related complications*

There is an increased risk of influenza-related complications in:

- Children aged under 2 years (PHE: under 6 months)
- Adults aged over 65 years
- Patients with chronic diseases such as chronic obstructive pulmonary disease (COPD), heart failure, diabetes mellitus, severe underlying neurological diseases, or morbid obesity (body mass index [BMI] ≥ 40)
- Immunosuppressed patients (e.g. iatrogenic or HIV infection)
- Pregnant or postpartum (<2 weeks) women
- Patients aged over 19 years receiving long-term aspirin treatment (risk of Reye's syndrome)
- Residents of nursing homes and other chronic-care facilities

● Which drugs are recommended?

Primarily, the authorized neuraminidase inhibitors. Oral oseltamivir is recommended as first-line treatment unless there is known resistance among circulating viruses or enteral resorption disorder in the patient.

● When should treatment begin?

Treatment should be started as soon as possible, i.e. on clinical suspicion even without laboratory confirmation. This is because the greatest benefit from antiviral treatment can be expected if it begins within 48 hours of onset of typical influenza symptoms. For patients with severe, complicated, or progressive disease and for hospitalized patients, all the institutions stated above also recommend a later initiation of treatment, as there is evidence of a benefit if treatment begins up to 5 days after symptom onset.

● What doses should be used?

See *eBox 1*.

● How long should treatment last?

Optimum treatment duration for severe, complicated, or progressive disease and for immunosuppressed patients is unknown. Individual clinical assessment is considered particularly important when deciding whether to prolong treatment after 5 days.

● Who should receive prophylactic treatment?

Widespread use of antiviral drugs for post-exposure and pre-exposure chemoprophylaxis is not recommended. It may be indicated on an individual basis for the risk groups stated above.

● How should adult patients with community-acquired pneumonia be treated?

In the German S3 guideline, the specialized societies mentioned therein recommend calculated, early administration of oseltamivir for hospitalized patients with moderate or severe pneumonia in the event of an influenza pandemic or high seasonal influenza activity.

This treatment should be concomitant to antibacterial therapy. No maximum time interval between symptom onset and beginning of treatment is given. If the initial influenza PCR test remains negative, antiviral treatment should be discontinued. The S3 guideline rates the evidence for this recommendation as weak (recommendation grade C) (10).

*For treatment indication, the importance of individual clinical assessment of the patient is emphasized.
PCR: Polymerase chain reaction

Scopus (see *eBox 2*, *eTable 1*, and the *eFigure* for details on the search of the literature).

In addition, randomized controlled trials, observational studies, and published data from the summaries of product characteristics of the drugs concerned were included on a selective basis.

Results

The findings presented here are based on one review of systematic reviews (11), 13 systematic reviews/meta-analyses of RCTs, and 6 additional RCTs.

Influenza prophylaxis

Essentially, influenza prophylaxis can be administered in the form of either oseltamivir and zanamivir, or amantadine (influenza A only).

How effective are antiviral drugs for prophylactic use?

For healthy adults, it has been shown that fewer symptomatic cases of influenza occur if antiviral drugs are administered as either post-exposure or long-term prophylaxis. For amantadine there is no clear division between types of prophylaxis in the studies examined (*Table 1*) (12–18). The number needed to treat (NNT) is between 8 and 89; neuraminidase inhibitors are more effective for post-exposure prophylaxis (NNT: 8 to 25). For children and high-risk patients, some of the evidence is patchy (12–14, 17, 18); the NNT is between 12 and 89, depending on the drug and the population. Oseltamivir has been proven to be effective for long-term prophylaxis in elderly high-risk patients (NNT: 25) (12–14).

Only one RCT addressed prophylactic use in immunosuppressed patients; this included 475 patients. It showed no significant difference between oseltamivir, at its standard dose for 12 weeks' prophylaxis, and placebo in terms of symptomatic cases of confirmed influenza (19).

Does the timing of administration play a role in efficacy?

Only one RCT of zanamivir reported that post-exposure prophylaxis usually failed in the first few days of use. This may indicate that the time between exposure and the beginning of prophylaxis was too long in these cases (20).

Influenza therapy

Intention-to-treat (ITT) analysis includes data on all study participants with clinically diagnosed influenza, i.e. including those with influenza-like illness (ILI) not caused by influenza viruses. In contrast, intention-to-treat infected (ITT_i) analysis includes only data on those in whom the diagnosis of influenza was confirmed, usually using subsequent laboratory diagnostics: antigen or antibody testing. As the mechanism of action of antiviral drugs is specific to influenza, the ITT_i analysis reflects the efficacy of antiviral drugs against influenza viruses, whereas ITT analysis better reflects clinical practice. Because the analysis population is so important, this review describes the findings for both the ITT and the ITT_i populations.

Do antiviral drugs affect disease duration?

With a disease duration for placebo of 6.6 to 7 days and start of therapy up to 48 hours after symptom onset, antiviral drugs reduce the time until the patient is symptom-free by a mean of approximately 0.5 to 1.5 days (*eTable 2*) (15–18, 21). A recent meta-analysis of patient data from trials of oseltamivir also shows that oseltamivir decreases the time until patients are symptom-free by approximately one day (21%) (22). For children and adults with no comorbidities this effect is almost always statistically significant. The fact that the 2014 Cochrane Review by Jefferson et al. found no significant difference for zanamivir in the treatment of children may be the result of the methods used: both the individual studies included in the meta-analysis did report statistically significant differences (15). In the elderly and high-risk patients (those with chronic respiratory diseases or cardiovascular diseases), there was usually no statistically significant difference between them and placebo, although in most cases numerical benefits were found for neuraminidase inhibitors.

Patients treated with neuraminidase inhibitors return to normal activities a mean of 0.5 to 1 day sooner. In most studies the findings of ITT_i analysis for antiviral drugs were more favorable than those of ITT analysis. It remains unclear why this is not the case in the study by Burch et al. (21).

Do antiviral drugs affect disease severity?

There is no RCT data on mortality or need for intensive care. A meta-analysis with datasets from approximately 30 000 patients hospitalized during the 2009/2010 pandemic found that the use of neuraminidase inhibitors, usually oseltamivir, in adults was associated with a reduced mortality risk, regardless of when they were used (odds ratio [OR]: 0.81; 95% confidence interval: [0.70; 0.93]) (23). For methodological reasons, neither the absolute risk reduction nor the NNT can be determined for the relevant adjusted analysis. Subgroup analyses for adults receiving intensive care, pregnant women, and patients who received neuraminidase inhibitors early (no more than 2 days after symptom onset) show more substantial risk reductions. No effect on mortality is found if therapy is begun later, or in children.

A meta-analysis of 3 observational studies, selected on the basis of very stringent criteria, on the effect of oseltamivir on mortality in seasonal or avian (H5N1) influenza indicates that neuraminidase inhibitors are effective (24).

ITT evaluation revealed no significant effect on rate or duration of hospitalization for either neuraminidase inhibitors or amantadine.

Do antiviral drugs affect influenza-related complications?

While point estimates in most evaluations do indicate that neuraminidase inhibitors effectively reduce influenza-related complications, statistically significant differences for individual neuraminidase inhibitors were not always seen (*Tables 2 and 3*) (15, 21, 25). Only one meta-analysis for oseltamivir in adults with

TABLE 1

Findings of systematic reviews (11–17) on the efficacy of antiviral drugs versus placebo as prophylaxis

Intervention	Cumulative no. of study participants	Relative risk [95% confidence interval]* ¹	Number needed to treat (NNT)
Long-term prophylaxis: adults	1039 to 2479 1107 to 5275	Oseltamivir: 0.24 to 0.45 [0.09; 0.83] Zanamivir: 0.32 to 0.39 [0.17; 0.70]	OSV: 18 to 35 ZNV: 14 to 55
Post-exposure prophylaxis (PEP): adults	405 to 1747 1525 to 2416	Oseltamivir: 0.0 to 0.20 [0.0; 0.44] Zanamivir: 0.21 to 0.33 [0.13; 0.36]	OSV: 8 to 15 ZNV: 9 to 22
Prophylaxis (PEP and long-term combined): adults	4645	Amantadin: 0.39 [0.24; 0.65]	AMT: 16
Post-exposure prophylaxis: children	215 863	Oseltamivir: 0.36 [0.15; 0.84] Oseltamivir und Zanamivir: absolute Risikoreduktion: 8% [5; 12]	OSV: 25* ² OSV + ZNV: 12
Long-term prophylaxis: children	773	Amantadin: 0.11 [0.04; 0.30]	AMT: 12
Long-term prophylaxis: elderly high-risk patients* ³	548 1896	Oseltamivir: 0.08 [0.01; 0.63] Zanamivir: 0.20 [0.02; 1.72]	OSV: 16 ZNV: 238* ³
Long-term prophylaxis: high-risk adolescents/adults (68% vaccinated)	3363	Zanamivir: 0.17 [0.07; 0.44]	ZNV: 89

*¹ Relative risk for onset of symptomatic influenza disease. Duration of treatment is between 10 days and 6 weeks but is not stated for all studies of amantadine.

*² The 95% confidence interval has no upper bound, as a result of very similar risk rates or small total case numbers in both treatment groups. Substantial uncertainty is therefore associated with NNT or NNH.

*³ High-risk patients: residents of chronic-care facilities, patients aged 65 years or older, and/or those with chronic cardiovascular, respiratory, or renal disease. AMT, amantadine; OSV, oseltamivir; ZNV, zanamivir

no comorbidities found a significant reduction in reported cases of pneumonia (NNT: 89 [50; 232]) (15). Reduced use of antibiotics (as reported in some double-blind trials) can at best be interpreted as a surrogate parameter for fewer bacterial complications.

An additional meta-analysis of 11 RCTs of oseltamivir treatment in a total of 3908 patients, which also included data from unpublished trials (26), showed an absolute risk reduction for respiratory diseases (mostly bronchitis) requiring antibiotic treatment of 3.42% (relative risk reduction: 37%; NNT: 20). However, bronchitis is not a serious complication and does not usually require antibiotic treatment.

No data has been published on the effect of amantadine on complications.

Two large meta-analyses on hospitalized patients from the A(H1N1)pdm09 pandemic yielded no clear findings regarding the use of neuraminidase inhibitors and pneumonia (27, 28). Overall, the data from the available studies do not yet definitively show that antiviral drugs have an effect on relevant influenza-related complications.

Do antiviral drugs affect viral shedding?

Reduced viral shedding after 24 or 48 hours was found for study participants with no comorbidities receiving neuraminidase inhibitors (29, 30). As there is no

evidence as yet that shortened or reduced viral shedding also reduces transmission to contact persons, the clinical relevance remains questionable.

Does the timing of administration play a role in efficacy?

One RCT showed that oseltamivir shortens the duration of influenza symptoms significantly, by 43 hours, if taken within 24 hours of symptom onset (31). Multiple observational studies yield findings in line with this (19, 24, 32, 33). There is no similar data for zanamivir or amantadine. However, shorter or milder course of disease was also confirmed when oseltamivir therapy was begun more than 48 hours after symptom onset (29, 33, 34). For post-exposure prophylaxis, systematic evaluations of efficacy depending on the timing of start of administration in relation to contact with ill individuals are lacking.

What are the side effects of antiviral drugs?

In terms of types of side effect, there is no difference between prophylactic and therapeutic use. For neuraminidase inhibitors this applies also to the frequencies of side effects. (*eTable 3*). Regarding the safety of long-term neuraminidase inhibitor use, data is available for a period of up to 16 weeks (35). For amantadine, it seems that therapy in adults, which is shorter than prophylactic use, is better tolerated.

The most frequent and also the most serious adverse effects, such as neuropsychiatric effects, have been reported for amantadine. Gastrointestinal side-effects are characteristic of oseltamivir. Nausea and vomiting are significantly more common than with placebo use (NNT: 21 versus 17). In addition, neuropsychiatric effects have been the subject of critical discussion. These were reported in adolescents and young adults in particular, most commonly in Japan. Adverse effects of zanamivir are particularly likely to affect the respiratory tract; this is partly due to the route of administration and must be taken into account for patients with existing or concomitant respiratory diseases.

The current summaries of product characteristics of individual antiviral drugs must also be consulted, as these include all data from controlled clinical trials and post-authorization market surveillance (36–38).

Discussion

For influenza prophylaxis, the efficacy of both post-exposure and long-term prophylaxis is rated as good. The protective effect of antiviral drugs lasts only while they are being used.

When used therapeutically during seasonal influenza, antiviral drugs reduce disease duration by 0.5 to 1 days if treatment begins no more than 48 hours after symptom onset. The efficacy of oseltamivir, zanamivir, and amantadine varies between individual patient groups; overall, it should be seen as moderate.

The efficacy of antiviral drugs for influenza-related complications and mortality is of particular clinical relevance. The 2014 Cochrane Review (15), which includes the greatest amount of trial data, found a reduction in cases of pneumonia for oseltamivir in adults with no comorbidities. This finding is not undisputed, however, as in some trials complications of influenza were reported retrospectively by trial participants themselves instead of being diagnosed by investigators. The diagnosis of pneumonia was often not confirmed.

The RCTs were conducted during seasonal influenza outbreaks. The course of disease was mostly mild and uncomplicated, and there were only isolated deaths. The trials were not primarily designed to show an effect on serious disease courses. It was therefore also impossible to draw any conclusions concerning mortality from a pooled analysis of RCTs, as a result of small sample sizes (15). In the event of a future serious influenza pandemic with high disease rates and highly pathogenic, NI-sensitive viruses, effects may be stronger in terms of both NNT and complications. However, the investigated strains of influenza from the 2008/2009 season in Germany and the USA showed primary oseltamivir resistance in 99% and 98% of cases respectively (39), whereas almost 100% of the pandemic H1N1 viruses in the following years were sensitive to oseltamivir. Viral resistance must therefore be continuously monitored.

Overall, although the available data does give some indications that antiviral drugs have a positive effect on clinically relevant complications of influenza, it does not provide conclusive evidence of this.

However, the findings of the observational study by Muthuri et al. during the 2009/2010 pandemic are noteworthy in this regard (23). This meta-analysis includes datasets from 30 000 hospitalized patients in 78 individual trials and shows that the use of neuraminidase inhibitors, usually oseltamivir, was associated with a statistically significant relevant risk reduction for mortality in adults. The finding for adults receiving intensive care, a probably more homogeneous subgroup, was consistent with the finding for the general population. No effect on mortality was found in children. This study's strengths are its large sample size and the fact that its evaluation takes into account that the probability of administering antiviral medication therapy depends on various factors, including disease severity (propensity score). The study methods are considered valid. However, a fundamental weakness of observational studies when compared to RCTs is that it is impossible to rule out biased findings as result of influencing factors that are unknown and therefore not taken into account in the analysis.

Potential limitations of this systematic literature review are that most of the RCTs were included in all the systematic reviews considered for this article, so the findings of the analyses seem very homogeneous overall. In addition, most studies and some meta-analyses were funded by pharmaceutical companies.

After more than 10 years of use, antiviral drugs' side effect profile is well characterized. Overall, the side effects of NIs are less severe than those of amantadine. Serious side effects have been reported in less than 1 in 100 treated patients. The authors therefore rate the side effect profile of neuraminidase inhibitors overall as giving little cause for concern.

Unlike amantadine, development of resistance has been infrequent for the neuraminidase inhibitors to date. However, some years ago an influenza A (H1N1) virus with primary oseltamivir resistance circulated (39). Of course, it is possible that resistance may develop and render one or both neuraminidase inhibitors ineffective.

It became evident that for some at-risk populations evidence of efficacy is patchy or even absent, e.g. for pregnant women, neonates, immunosuppressed patients, and patients with cystic fibrosis (40). The authors believe that more research is needed in these patients, and also on the use of antiviral drugs in infections caused by highly pathogenic influenza viruses.

This systematic review does not aim to provide clinical recommendations on the use of antiviral drugs.

In line with the evidence we have presented, and regardless of the fact that for some issues the available data is weak or patchy, specialist societies and national and international public health institutions have for some years provided recommendations on the use of antiviral drugs in seasonal and pandemic influenza that are broadly in line with each other (*Box*).

Summary

The benefits of antiviral drugs are rated to outweigh the risks, particularly for neuraminidase inhibitors.

TABLE 2

The effect of oseltamivir versus placebo on complications in various patient populations

Outcome (literature reference)	Number of RCTs	Number of participants	Effect estimate	Value [95% CI]	Number needed to treat (NNT)
Adults with no comorbidities					
All complications (21)	1	419	OR	0.61 [0.3; 1.1]	21*²
ITTi (21)	3	564	OR	0.75 [0.41; 1.37]	46* ²
Pneumonia (15)	8	4752	RR	0.55 [0.33; 0.90]	83
Pneumonia (21)	2	784	OR	0.33 [0.03; 3.16]	195* ²
Pneumonia ITTi (21)	3	610	OR	0.33 [0.05; 2.14]	103* ²
Bronchitis (15)	8	4752	RR	0.75 [0.56; 1.01]	31
Bronchitis (21)	1	476	RR	1.38 [0.43; 4.4]	NNH: 129* ²
Bronchitis ITTi (21)	2	572	OR	0.94 [0.39; 2.24]	405* ²
Sinusitis (15)	8	4752	RR	1.03 [0.76; 1.40]	194* ²
Otitis media (15)	6	4368	RR	1.11 [0.57; 2.15]	769* ²
Antibiotic use (21)	2	1652	OR	0.37 [0.29; 0.48]	7
Antibiotic use ITTi (21)	3	845	OR	0.52 [0.27; 1.00]	35
Children with no comorbidities					
Otitis media (15)	3* ¹	1359	RR	0.80 [0.62; 1.02]	136* ²
Pneumonia (21)	2	1029	OR	0.58 [0.26; 1.28]	27* ²
Pneumonia (15)	3* ¹	1359	RR	1.06 [0.62; 1.83]	74* ²
Bronchitis (21)	1	334	OR	4.94 [0.57; 42.74]	NNH: 573* ²
Bronchitis (15)	3* ¹	1359	RR	0.65 [0.27; 1.55]	87* ²
Sinusitis (15)	3* ¹	1359	RR	1.00 [0.58; 1.72]	NNH: 3694* ²
Antibiotic use (21)	1	695	OR	0.96 [0.46; 1.99]	291* ²
Exacerbation of asthma (25)	1	177	RD	-0.05 [-0.15; 0.05]	6* ²
High-risk patients					
Pneumonia (21)	1	334	OR	0.48 [0.04; 5.34]	157* ²
Pneumonia ITTi (21)	2	728	OR	0.99 [0.36; 2.27]	1489* ²
Bronchitis (21)	1	334	OR	4.94 [0.57; 42.7]	NNH: 43* ²
Antibiotic use (21)	1	334	OR	0.96 [0.46; 1.99]	116* ²
Antibiotic use ITTi (21)	4	878	OR	0.57 [0.33; 0.98]	15

(Analysis population: ITT unless otherwise stated)

*¹Meta-analysis of one study in healthy children ($n = 695$) and two studies in children with chronic asthma ($n = 664$). The combined meta-analysis does not substantially alter the findings of the studies in the various populations.

*²The 95% confidence interval has no upper bound, as a result of very similar risk rates or small total case numbers in both treatment groups. Substantial uncertainty is therefore associated with NNT or NNH.

95% CI, 95% confidence interval; ITTi, intention to treat infected; NNH, number needed to harm; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; RD, risk difference

To date there are no alternative causal treatment options for influenza viruses. When prescribing antiviral drugs the characteristics of circulating viruses and the individual risk profile of the patient should be borne in mind, in line with the recommendations of specialist societies. Neuraminidase inhibitors are generally preferable, due to their safety profile. Even in a best case scenario, in the

event of a pandemic approximately 6 months elapse between the appearance of a pandemic influenza virus and the first use of a corresponding vaccine; in addition, it is unclear how much protection a vaccine will afford. Antiviral drugs may therefore be important, particularly in reducing mortality and morbidity in the population during the first wave of a pandemic.

TABLE 3

The effect of zanamivir versus placebo on complications in various patient populations

Outcome (literature reference)	Number of RCTs	Number of participants	Effect estimate	Value [95% CI]	Number needed to treat (NNT)
Adults with no comorbidities					
Pneumonia (21)	1	588	OR	1.36 [0.63; 2.9]	NNH: 72*
Pneumonia (15)	11	5876	RR	0.90 [0.58; 1.40]	246*
Bronchitis (21)	2	1054	OR	1.08 [0.54; 2.17]	NNH: 402*
Bronchitis (15)	12	6072	RR	0.75 [0.61; 0.91]	47
Sinusitis (15)	12	6072	RR	1.12 [0.84; 1.48]	196*
Otitis media (15)	10	5494	RR	0.81 [0.54; 1.20]	186*
Antibiotic use (21)	1	276	OR	0.68 [0.31; 1.51]	29*
Exacerbation of asthma (15)	9	5269	OR	0.54 [0.34; 0.86]	88
Children with no comorbidities					
All complications (21)	2	732	OR	0.88 [0.62; 1.24]	NNH: 740*
Otitis media (21)	1	266	OR	0.63 [0.16; 2.4]	63*
Otitis media (15)	2	737	RR	1.00 [0.59; 1.72]	115*
Pneumonia (21)	1	266	OR	0.51 [0.07; 3.65]	93*
Pneumonia (15)	2	737	RR	0.53 [0.12; 2.38]	229*
Bronchitis (21)	2	732	OR	1.05 [0.28; 3.89]	278*
Bronchitis (15)	2	737	RR	0.86 [0.26; 2.80]	NNH: 6128*
Sinusitis (15)	2	737	RR	0.87 [0.12; 6.45]	NNH: 6128*
Antibiotic use (21)	1	471	OR	0.05 [0.01; 0.23]	8
Elderly patients					
All complications (21)	1	358	OR	0.84 [0.54; 1.32]	28*
Pneumonia (21)	1	358	OR	0.87 [0.17; 4.38]	444*
Bronchitis (21)	1	358	OR	0.46 [0.2; 1.02]	19*
Antibiotic use (21)	1	358	OR	0.73 [0.43; 1.24]	21*
High-risk patients					
All complications (21)	4	575	OR	0.73 [0.51; 1.04]	14*
Pneumonia (21)	2	881	OR	0.57 [0.15; 2.23]	200*
Bronchitis (21)	3	1210	OR	0.41 [0.24; 0.70]	20
Antibiotic use (21)	4	575	OR	0.71 [0.47; 1.07]	18*
Antibiotic use ITTi (21)	4	565	OR	0.66 [0.42; 1.03]	20*

(Analysis population: ITT unless otherwise stated)

*The 95% confidence interval has no upper bound, as a result of very similar risk rates or small total case numbers in both treatment groups. Substantial uncertainty is therefore associated with NNT or NNH.

95% CI, 95% confidence interval; ITT, intention to treat; ITTi, intention to treat infected; NNH, number needed to harm; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk

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KEY MESSAGES

- In adults, the number needed to treat (NNT) for neuraminidase inhibitors used as post-exposure prophylaxis is between 8 and 22; for long-term prophylaxis it is between 14 and 55.
- There is no clear evidence that neuraminidase inhibitors lead to a significant reduction in serious courses of disease or pneumonia.
- Randomized controlled trials included only patients with mild to moderate disease. In these patients, antiviral drugs shortened disease duration by 0.5 to 1.5 days, depending on the patient group. They showed no effect on mortality, although observational studies do indicate a decrease in mortality.
- To date there are no alternative causal treatment options for influenza viruses, so antiviral drugs may be important in the event of a pandemic.
- The side effect profile of neuraminidase inhibitors is rated as of little concern.

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Supplementary material
eBoxes, eTables, eFigure:
www.aerzteblatt-international.de/16m0799

Supplementary material to:

Antiviral Medications in Seasonal and Pandemic Influenza

A Systematic Review

by Regine Lehnert, Mathias Pletz, Annicka Reuss, and Tom Schaberg

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eBOX 1

Dosage recommendations for neuraminidase inhibitors

● Dosage recommendations for zanamivir

Influenza therapy:

- Treatment should be started as soon as possible after symptom onset: within 48 hours in adults and within 36 hours in children.
- Zanamivir is intended only for administration to the respiratory tract by oral inhalation, using the Diskhaler supplied. One blister should be utilised for each inhalation..
- The recommended dose of zanamivir for influenza therapy in adults and children aged over 5 years is 2 inhalations twice a day (corresponding to 2 × 5 mg zanamivir twice daily) for 5 days. This is a total dose of 20 mg per day.

Post-exposure prophylaxis:

- The recommended dose of zanamivir for prophylaxis following close contact with an infected individual is 2 inhalations once a day (corresponding to 2 × 5 mg zanamivir once a day) for 10 days. This should be administered as soon as possible and within 36 hours following contact with an infected individual.

Seasonal prophylaxis:

- The recommended dose of zanamivir for influenza prophylaxis during an outbreak in the population is 2 inhalations once a day (corresponding to 2 × 5 mg zanamivir once a day) for up to 28 days.

● Dosage recommendations for oseltamivir

Influenza therapy:

- For adolescents (aged 13 to 17 years, body mass >40 kg) and adults, the recommended oral dose of oseltamivir is 75 mg twice a day for 5 days.

Post-exposure prophylaxis:

- For adolescents (aged 13 to 17 years, body mass >40 kg) and adults, the recommended dose for influenza prophylaxis following close contact with an infected individual is 75 mg oseltamivir once a day for 10 days.

Prophylaxis during an influenza epidemic in the population:

- For adolescents (aged 13 to 17 years, body mass >40 kg) and adults, the recommended dose for influenza prophylaxis during an outbreak in the population is 75 mg oseltamivir once a day for up to 6 weeks.

For children, the appropriate dose depends on body mass.

Dosage must be adjusted for patients with impaired renal function.

Drugs must be prescribed in line with their latest summaries of product characteristics.

eBOX 2

Search of the literature

- Databases: Cochrane, PubMed, Scopus
- Time period: published up to December 2, 2015
- Languages: English, German
- PICO system*:
 - Study population: study participants in all age groups, with and without underlying chronic diseases
 - Intervention: an authorized, influenza-specific antiviral drug as therapy or prophylaxis
 - Comparison: placebo
 - Study types: systematic reviews and meta-analyses, randomized controlled trials, clinical studies
 - Outcome: onset of disease caused by influenza viruses
- Studies were excluded if:
 - (a) no measure of association for effect size was given,
 - (b) systematic reviews did not examine randomized controlled trials,
 - (c) only influenza vaccination was addressed.
- Search terms: see *eTable 1*
- Literature management and evaluation:
 - Hits imported in Endnote
 - Duplicates were identified and deleted using an Endnote function and manually
 - Literature was selected and evaluated by 2 independent scientists (a third scientist was consulted to resolve discrepancies)
 - No manual search was performed to locate additional studies in the bibliographies of the identified studies
- PRISMA flowchart: see *eFigure*

*A system to aid the formulation of a research question in evidence-based medicine
PICO: Population, Intervention, Comparison, Outcome

eFIGURE

PRISMA flowchart

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: Randomized controlled trial

eTABLE 1

Search terms

ID	Search terms: PubMed
#1	(oseltamivir* OR zanamivir* OR laninamivir* OR tamiflu* OR relenza* OR peramivir* OR gs4071* OR Neuraminidase* OR "neuraminidase inhibitors" OR Amantadin* OR Rimantadin* OR adamantan* OR antiviral*[Title/Abstract])
#2	(influenza* OR flu OR "Influenza A Virus" OR "H1N1 Subtype*" OR "Influenza A Virus" OR "H1N1 Subtype*" OR "swine flu" OR "swine influenza" OR "H1N1 pandemic influenza" OR "H1N1v" OR "pandemic influenza 2009" OR "novel influenza" OR H1N1pdm OR "swine-origin influenza" OR "swine-origin type A" OR nH1N1 OR pH1N1 OR H1N1 OR AH1N1 OR A/H1N1 OR "A (H1N1)" OR "A (H1N1) pdm09" OR "H1N1*" OR "H1N1 virus*" OR "H3N2 virus*" OR "H5N1 virus*" OR "H7N9 virus*" OR "H3N2*" OR AH3N2 OR A/H3N2 OR "A (H3N2)" OR "H5N1*" OR AH5N1 OR A/H5N1 OR "A (H5N1)" OR "H7N9*" OR AH7N9 OR A/H7N9 OR "A (H7N9)" OR "Influenzavirus A" OR "Influenzavirus B" OR "Influenzavirus C" OR "Influenza A Virus" OR "Influenza B Virus" OR "Influenza C Virus"[Title/Abstract])
#3	#1 AND #2
#4	#3 AND Filter "Meta-Analysis*" OR "Systematic Review"
#5	#3 AND ("systematic review*" OR "meta-analysis"*)
#6	#3 Filter Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]
#7	#3 AND ("Clinical Trial" OR "Controlled Clinical Trial" OR "Randomized Controlled Trial")
#8	#3 AND ((randomized controlled trial*) OR (randomised controlled trial*) OR (RCT*) OR (randomi* trial*) OR ("randomized controlled trial") OR (randomi* study*))
#9	#3 AND Filter Randomized Controlled Trial
ID	Search terms: Cochrane Library
#1	(oseltamivir* OR zanamivir* OR laninamivir* OR tamiflu* OR relenza* OR peramivir* OR gs4071* OR Neuraminidase* OR "neuraminidase inhibitors" OR amantadin* OR rimantadin* OR adamantan* OR antiviral*):ti,ab,kw
#2	(influenza* OR Influenza* OR flu OR "Influenza A Virus" OR "H1N1 Subtype" OR "swine flu" OR "swine influenza" OR "H1N1 pandemic influenza" OR H1N1v OR "pandemic influenza 2009" OR "novel influenza" OR H1N1pdm OR "swine-origin influenza" OR "swine-origin type A" OR nH1N1 OR pH1N1 OR H1N1 OR AH1N1 OR A/H1N1 OR "A (H1N1)" OR "A (H1N1) pdm09" OR "H1N1*" OR "H1N1 virus*" OR "H3N2 virus*" OR "H5N1 virus*" OR "H7N9 virus*" OR "H3N2*" OR AH3N2 OR A/H3N2 OR "A (H3N2)" OR "H5N1*" OR AH5N1 OR A/H5N1 OR "A (H5N1)" OR "H7N9*" OR AH7N9 OR A/H7N9 OR "A (H7N9)" OR "Influenzavirus A" OR "Influenzavirus B" OR "Influenzavirus C" OR "Influenza A Virus" OR "Influenza B Virus" OR "Influenza C Virus"):ti,ab,kw
#3	#1 AND #2
#4	#3 in Cochrane Reviews AND Other Reviews
#5	#3 AND ("systematic review*" OR "meta-analysis"*)
#6	#3 in Trials
#7	#3 AND ("Clinical Trial" OR "Controlled Clinical Trial" OR "Randomized Controlled Trial")
#8	#3 AND ((randomized controlled trial*) OR (randomised controlled trial*) OR (RCT*) OR (randomi* NEAR trial*) OR ("randomized controlled trial") OR (randomi* NEAR study*))
ID	Search terms: Scopus
#1	(TITLE-ABS-KEY(oseltamivir* OR zanamivir* OR laninamivir* OR tamiflu* OR relenza* OR peramivir* OR gs4071* OR Neuraminidase* OR "neuraminidase inhibitors" OR amantadine* OR rimantadin* OR adamantan* OR antiviral*))
#2	(TITLE-ABS-KEY(influenza* OR flu OR "Influenza A Virus" OR "H1N1 Subtype" OR "swine flu" OR "swine influenza" OR "H1N1 pandemic influenza" OR H1N1v OR "pandemic influenza 2009" OR "novel influenza" OR H1N1pdm OR "swine-origin influenza" OR "swine-origin type A" OR nH1N1 OR pH1N1 OR H1N1 OR AH1N1 OR A/H1N1 OR "A (H1N1)" OR "A (H1N1) pdm09" OR "H1N1*" OR "H1N1 virus*" OR "H3N2 virus*" OR "H5N1 virus*" OR "H7N9 virus*" OR "H3N2*" OR AH3N2 OR A/H3N2 OR "A (H3N2)" OR "H5N1*" OR AH5N1 OR A/H5N1 OR "A (H5N1)" OR "H7N9*" OR AH7N9 OR A/H7N9 OR "A (H7N9)" OR "Influenzavirus A" OR "Influenzavirus B" OR "Influenzavirus C" OR "Influenza A Virus" OR "Influenza B Virus" OR "Influenza C Virus"))
#3	#1 AND #2
#4	#3 Filter german language
#5	#4 AND Filter Review
#6	#4 AND ("systematic review*" OR "meta-analysis"*)
#7	#4 AND ("Clinical Trial" OR "Controlled Clinical Trial" OR "Randomized Controlled Trial")
#8	#4 AND ((randomized controlled trial*) OR (randomised controlled trial*) OR (RCT*) OR (randomi* PRE/10 trial*) OR ("randomized controlled trial") OR (randomi* PRE/10 study*))

eTABLE 2

Time until patients receiving influenza therapy are symptom-free: antiviral drugs versus placebo

No. of RCTs (literature reference)	Number of participants	Drug	Difference in time until patients symptom-free, days (median, [95% CI])
Adults with no comorbidities			
4 (21)	1410	Oseltamivir	−0.55 [−1.04; −0.14]
6 ITTi (21)	1182	Oseltamivir	−0.92 [−1.55; −0.29]
8 (15)	3954	Oseltamivir	−0.69 [−1.04; −0.35]
6 (21)	1701	Zanamivir	−0.57 [−1; −0.1]
13 (15)	5411	Zanamivir	−0.60 [−0.81; −0.39]
10 (16)	542	Amantadine	−0.99 [−1.3; −0.7] ^{*1}
Children with no comorbidities			
2 (21)	1029	Oseltamivir	−0.88 [−1.40; −0.35]
2 ITTi (21)	631	Oseltamivir	−1.2 [−1.82; −0.58]
1 (15)	669	Oseltamivir	−1.22 [−1.86; −0.49] ^{*2}
2 (21)	737	Zanamivir	−0.94 [−1.43; −0.46]
2 (18)	451/266	Zanamivir	−0.5 ^{*3}
2 (15)	723	Zanamivir	−1.08 [−2.32; 0.15]
2 (17)	104	Amantadine	Relative risk of fever on day 3: 0.39 [0.20; 0.79]
Elderly patients			
1 (21)	736	Oseltamivir	−0.42 [−1.87; 1.04]
1 ITTi (21)	477	Oseltamivir	−1.00 [−2.83; 0.83]
5 (21)	475	Zanamivir	−1.13 [−2.90; 0.63]
5 ITTi (21)	323	Zanamivir	−1.85 [−4.77; 1.07]
High-risk patients			
2 (21)	1472	Oseltamivir	−0.74 [−1.50; 0.02]
3 ITTi (21)	907	Oseltamivir	−0.59 [−1.51; 0.34]
2 (15) ^{*4}	660	Oseltamivir	0.21 [−0.46; 0.89]
7 (21)	1252	Zanamivir	−0.98 [−1.84; −0.11]
6 ITTi (21)	730	Zanamivir	−1.83 [−2.81; 0.86]

(Analysis population: ITT unless otherwise stated)

^{*1}Number of days with fever (37 °C or more); ^{*2}Including studies in children with asthma: −0.33 [−1.39; 0.72];

^{*3}Data from 2 RCTs not pooled; median identical for both trials; ^{*4}Data from 2 RCTs not pooled; median identical for both trials

ITT: Intention to treat; ITTi: Intention to treat infected; CI: Confidence interval; RCT: Randomized controlled trial

eTABLE 3

Tolerability of antiviral drugs versus placebo

Adverse event	Drug (literature reference)	No. of RCTs	No. of participants	Effect estimate	Value [95% CI]	Number needed to harm (NNH)
Adults with no comorbidities						
All events	Oseltamivir (21)	4	1623	OR	0.81 [0.59; 1.12]	NNT: 18*²
	Zanamivir (21)	2	1054	OR	1.03 [0.79; 1.34]	177* ²
Drug-related	Oseltamivir (21)	2	509	OR	1.45 [0.83; 2.53]	24* ²
	Zanamivir (21)	4	1406	OR	1.11 [0.76; 1.62]	173* ²
Serious	Oseltamivir (21)	3	985	OR	0.32 [0.03; 1.17]	NNT: 251* ²
	Oseltamivir (15)	7	4394	RR	0.96 [0.51; 1.80]	NNT: 630* ²
	Zanamivir (21)	3	1130		1.14 [0.28; 7.35]	537* ²
	Zanamivir (15)	10	4388	RR	0.98 [0.49; 1.50]	NNT: 4 048* ²
Treatment discontinued* ¹	Oseltamivir (15)	8	4452	RR	-0.17 [-0.53; 0.87]	105* ²
	Zanamivir (15)	13	6116	RR	0.96 [0.66; 1.39]	581* ²
Nausea* ¹	Oseltamivir (15)	8	4452	RR	1.57 [1.14; 2.15]	21
Vomiting* ¹	Oseltamivir (15)	9	4452	RR	2.43 [1.75; 3.38]	17
Nausea/vomiting	Zanamivir (15)	15	6553	RR	0.60 [0.39; 0.94]	1 967* ²
Diarrhea* ¹	Oseltamivir (15)	8	4452	RR	0.67 [0.46; 0.98]	NNT: 80* ²
	Zanamivir (15)	15	6553	RR	0.87 [0.66; 1.14]	NNT: 232* ²
Gastrointestinal	Amantadine (16)	3	494	OR	1.34 [0.32; 5.61]	275* ²
Increased CNS activity	Amantadine (16)	2	465	OR	0.77 [0.23; 2.53]	NNT: 66* ²
Reduced CNS activity	Amantadine (16)	3	491	OR	0.65 [0.31; 1.38]	NNT: 12
Skin alterations	Amantadine (16)	2	465	OR	1.4 [0.14; 13.78]	332* ²
Children with no comorbidities						
All events	Oseltamivir (21)	1	334	OR	0.91 [0.59; 1.40]	NNT: 42*²
	Zanamivir (21)	2	737	OR	0.88 [0.62; 1.24]	NNT: 39* ²
Drug-related	Zanamivir (21)	2	737	OR	1.32 [0.59; 2.92]	66* ²
Serious	Oseltamivir (21)	1	695	OR	1.54 [0.25; 9.24]	331* ²
	Oseltamivir (15)	2	1029	RR	1.97 [0.59; 6.56]	127* ²
	Zanamivir (21)	2	737	OR	2.29 [-0.24; 22.09]	200* ²
	Oseltamivir/Zanamivir (18)	4	2172	RD	0.00 [0.00; 0.01]	165* ²
Treatment discontinued* ¹	Oseltamivir/Zanamivir (18)	3	1143	RD	0.01 [-0.02; 0.03]	131* ²
	Oseltamivir (15)	2	1029	RR	0.99 [0.33; 3.01]	NNT: 295
	Zanamivir (18)	2	737	RR	1.18 [0.16; 8.88]	NNT: 214* ²
Nausea* ¹	Oseltamivir/Zanamivir (18)	4	1766	RD	-0.01 [-0.03; 0.00]	76* ²
	Oseltamivir (15)	3	1358	RR	0.87 [0.50; 1.51]	180* ²
Vomiting* ¹	Oseltamivir (18)	3	1435	RD	0.06 [0.03; 0.10]	15
	Oseltamivir (15)	3	1358	RR	1.70 [1.23; 2.35]	19
	Zanamivir (18)	2	737	RD	0.00 [-0.02; 0.02]	NNT: 150* ²
Nausea/vomiting* ¹	Zanamivir (15)	2	737	RR	0.54 [0.24; 1.22]	NNT: 45* ²
	Amantadine (17)	2	599	RR	0.54 [0.15; 2.0]	NNT: 27* ²
Diarrhea* ¹	Oseltamivir/Zanamivir (18)	5	2172	RD	-0.01 [-0.03; 0.00]	NNT: 36* ²
	Oseltamivir (15)	3	1358	RR	0.87 [0.58; 1.28]	NNT: 103* ²
	Zanamivir (15)	2	737	RR	0.52 [0.15; 1.75]	NNT: 93* ²
	Amantadine (17)	2	599	RR	0.81 [0.43; 1.47]	NNT: 85* ²
Exanthema	Amantadine (17)	2	599	RR	0.81 [0.43; 1.53]	NNT: 175* ²

Adverse event	Drug (literature reference)	No. of RCTs	No. of participants	Effect estimate	Value [95% CI]	Number needed to harm (NNH)
Malaise	Amantadine (17)	2	599	RR	0.89 [0.41; 1.96]	NNT: 10
Muscle/limb pain	Amantadine (17)	2	599	RR	0.85 [0.46; 1.59]	NNT: 91 ^{*2}
Headache	Amantadine (17)	2	599	RR	0.73 [0.52; 1.03]	NNT: 18 ^{*2}
Dyspnea	Amantadine (17)	1	159	RR	0.37 [0.02; 9.02]	NNT: 84 ^{*2}
Dizziness	Amantadine (17)	2	599	RR	6.63 [0.32; 137.33]	132 ^{*2}
Insomnia	Amantadine (17)	2	599	RR	0.46 [0.12; 1.74]	80 ^{*2}
Arrhythmia	Amantadine (17)	2	599	RR	0.0 [0.0; 0.0]	N/A
High-risk patients						
All events	Oseltamivir (21)	2	452	RR	0.96 [0.63; 1.46]	NNT: 457^{*2}
	Zanamivir (21)	4	1286	RR	1.24 [0.96; 1.60]	NNT: 39 ^{*2}
Drug-related	Zanamivir (21)	1	5246	RR	1.01 [0.55; 1.85]	1 439 ^{*2}
Serious	Zanamivir (21)	3	1210	RR	0.72 [0.32; 1.62]	321 ^{*2}

^{*1}Studies of prophylaxis and therapy

^{*2}The 95% confidence interval has no upper bound, as a result of very similar risk rates or small total case numbers in both treatment groups. Substantial uncertainty is therefore associated with NNT or NNH.

95% CI: 95% confidence interval; N/A: Not available or not applicable; NNT: Number needed to treat; NNH: Number needed to harm; OR: Odds ratio; RCT: Randomized controlled trial; RD: Risk difference; RR: Relative risk