Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-039 Baloxavir marboxil

Stand: April 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Baloxavir marboxil
zur Postexpositionsprophylaxe (PEP) der Influenza

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Baloxavir marboxil Xofluza®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Xofluza ist indiziert zur Behandlung der Influenza bei Patienten ab 12 Jahren einschließlich Patienten mit hohem Risiko, Influenza-bedingte Komplikationen zu entwickeln. Xofluza ist indiziert zur **Postexpositions-Prophylaxe** der Influenza bei Personen ab 12 Jahren.
Oseltamivir J05AH02 (Tamiflu®)	Prophylaxe der Influenza: Postexpositions-Prophylaxe bei Personen im Alter von 1 Jahr oder älter nach Kontakt mit einem klinisch diagnostizierten Influenzafall, wenn das Influenzavirus in der Bevölkerung zirkuliert. - Die angemessene Anwendung von Tamiflu zur Prophylaxe einer Influenza sollte von Fall zu Fall auf Basis der Umstände und Populationen, welche einen Schutz benötigen, beurteilt werden. In Ausnahmesituationen (z.B. in Fällen einer Diskrepanz zwischen den zirkulierenden und den im Impfstoff enthaltenen Virusstämmen, und einer pandemischen Situation) kann eine saisonale Prophylaxe bei Personen im Alter von einem Jahr oder älter erwogen werden. - Tamiflu ist während eines pandemischen Influenzaausbruchs bei Säuglingen unter 1 Jahr zur Postexpositions-Prophylaxe indiziert (siehe Abschnitt 5.2). - Tamiflu ist kein Ersatz für eine Grippeschutzimpfung. Über die Anwendung von antiviralen Arzneimitteln für die Behandlung und Prophylaxe von Influenza sollte auf der Basis offizieller Empfehlungen entschieden werden. Die Entscheidung hinsichtlich des Einsatzes von Oseltamivir zur Behandlung und Prophylaxe sollte die Erkenntnisse über die Eigenschaften der zirkulierenden Influenzaviren, die in der jeweiligen Saison verfügbaren Informationen über die Empfindlichkeit gegenüber Arzneimitteln gegen Influenza und das Ausmaß der Krankheit in verschiedenen geografischen Gebieten und Patientengruppen berücksichtigen (siehe Abschnitt 5.1 [Stand FI 02/2019]
Zanamivir J05AH01 (Relenza®)	Relenza ist indiziert zur Postexpositions-Prophylaxe der Influenza A und B bei Erwachsenen und Kindern (ab 5 Jahren) nach Kontakt mit einem klinisch diagnostizierten Influenzafall innerhalb desselben Haushalts (siehe Abschnitt 5.1 für Kinder von 5 bis 11 Jahren). - In Ausnahmefällen (z.B. im Fall einer Nichtübereinstimmung zwischen zirkulierenden Virusstämmen und den Impfstoff-Virusstämmen oder in einer pandemischen Situation) kann eine saisonale Prophylaxe der Influenza A und B mit Relenza erwogen werden, wenn Influenza in der Bevölkerung auftritt. - Relenza ist kein Ersatz für eine Grippeschutzimpfung. Der angemessene Einsatz von Relenza zur Prophylaxe der Influenza sollte individuell von Fall zu Fall entschieden werden, unter Berücksichtigung der jeweiligen Umstände und der Bevölkerungsgruppe, die zu schützen ist. Bei Anwendung antiviraler Wirkstoffe zur Behandlung und Prophylaxe der Influenza sollten offizielle Empfehlungen, die epidemiologische Variabilität und die Auswirkung der Erkrankung in verschiedenen geographischen Regionen und Patientengruppen berücksichtigt werden. [Stand FI 01/2019]

Quellen: AMIS-Datenbank, Fachinformationen Stand 02/2020

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-039 (Baloxavir marboxil)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. März 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
EM	Effect measure
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ILI	influenza-like illness
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITTI	the intention-to-treat infected
KI	Konfidenzintervall
LoE	Level of Evidence
LRTC	lower respiratory tract complication
NAI	neuraminidase inhibitor
NI	neuraminidase inhibitor
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RMST	Restricted mean survival time
RR	Relatives Risiko
SAE	Serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TCM	Traditional chinese medicine
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Postexpositions-Prophylaxe der Influenza

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Influenza durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 25.02.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1101 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 2 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Systematische Reviews

Boikos C et al., 2017 [1].

Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15

Fragestellung

To review systematically the published literature evaluating neuraminidase inhibitor (NI) safety and effectiveness in situations of pandemic and novel/variant influenza.

Methodik

Population:

- influenza in all patient populations

Intervention:

- neuraminidase inhibitor (NI) oseltamivir, zanamivir, peramivir and/or laninamivir. For inclusion, studies of NIs must have been used in the context of pandemic influenza (defined as any influenza A/H1N1 strains circulating in 2008–2009 or 2009–2010 influenza seasons) or novel/variant influenza (defined as influenza strains endemic in avians or swine, not endemic in humans) treatment, prophylaxis and/or outbreak control

Komparator:

- administration of another influenza antiviral drug class, regimen or NI; standard of care at the time the study was conducted; placebo; or no treatment for influenza.

Endpunkte:

- The primary outcome of interest for NI effectiveness in prophylaxis/outbreak control was secondary transmission. For NI effectiveness in treatment, outcomes included mortality (distinguishing between all-cause and influenza-related, if possible), pneumonia, ICU admission, hospitalization, secondary transmission, severe influenza infection (defined as either ICU admission or death), duration of fever (or time to afebrile), time to resolution of symptoms(duration of disease) and effectiveness of NIs in relation to timing of administration (either after symptomon set or presentation for medical care was also evaluated). For NI safety (for either treatment, prophylaxis or outbreak control) the primary outcomes of interest were all reported adverse events (AEs). Secondary outcomes included for NI effectiveness in treatment, prophylaxis or outbreak control were viral shedding, viral load and development of resistance.

Recherche/Suchzeitraum:

- Six databases were searched for published articles: BIOSIS Previews, CINAHL, EMBASE, MEDLINE, PubMed and Web of Science. Searches were limited to studies published from 1 April 2009–31 October 2015

Qualitätsbewertung der Studien:

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for rating the quality of evidence were used to assess the quality of each study. We specifically evaluated the risk of bias (selection bias,measurement error and residual confounding) in RCTs and observational studies, and checked for any additional risk of bias in RCTs arising fromrandomsequence generation, allocation concealment and blinding. Each study was assessed for the presence/absence of confounding, measurement error and selection bias (as determined by reviewers). We also evaluated the imprecision and indirectness of the outcomes of interest

Ergebnisse

Anzahl eingeschlossener Studien:

- In total, 165 articles were included in this systematic review
- Ninety-four per cent (155 of 165) of the included studies were observational and the remainder were experimental.
- Approximately 63%(104 of 165) of included studies were retained for the analysis of the effect of NI treatment

Charakteristika der Population:

- Roughly 88% (145 of 165) of studies included participants with laboratory-confirmed influenza (most commonly by RT-PCR); however, the diagnostic methods that authors used varied widely by study
- In the majority of studies, the study population exclusively received oseltamivir (107 of 165; 65%); in four studies (2%) authors evaluated the effect of peramivir alone; and in the remaining 54 (33%) it was either unclear whether study participants received several NIs or one NI exclusively.

Qualität der Studien:

- We deemed selection bias to be unlikely in roughly half (77 of 165) of the included studies and likely/unclear in 40% (61 of 165). Furthermore, measurement error was considered likely in 37% (61 of 165) of all included studies and unclear (or possible) in 35% (57 of 165) of studies.
- We judged that the included studies were generally of low quality based upon presence of confounding, measurement error and/or selection bias

Studienergebnisse:

NIs indicated for prophylaxis/outbreak control

- Secondary transmission
  - In 10% of studies (17 of 165), authors evaluated the effectiveness of NIs when indicated for prophylaxis or outbreak control (16 observational studies and one experimental study). of these studies, only three were used to evaluate the effectiveness of NIs generally and the remainder specifically evaluated the effectiveness of oseltamivir for prophylaxis/outbreak control. Studies that presented effect estimates comparing NI prophylaxis with no prophylaxis (both adjusted and unadjusted) were conducted either in a general population or in a study population composed of adults; no other populations of

interest were represented by the studies reporting EMs for this outcome. Notably, it was unclear whether prophylaxis was pre-exposure or post-exposure in two of the included studies

- All studies showed either a statistically significant decreased risk or odds of influenza, or a lower R0 in individuals who received NIs as prophylaxis compared to those that did not (in a general population and in adults), with the exception of an observational study conducted in healthcare personnel workers
- Moreover, in an RCT, Carrat et al.23 compared the effectiveness of different NIs indicated for prophylaxis and included patients >18years who sought medical advice within 36 h of the onset of influenza symptoms and who had tested positive with a rapid influenza test. The study randomized participants to one of three treatment arms: oseltamivir/zanamivir combination therapy, oseltamivir monotherapy and zanamivir monotherapy. No statistically significant difference in secondary transmission of pandemic influenza between the three treatment arms was found. However, multivariable logistic regression modelling suggested greater odds of secondary transmission of influenza in both the oseltamivir and zanamivir monotherapy arms versus the combination therapy arm

- Safety
  - In an observational study by Anovadiya et al., the authors compared adverse drug reactions between patients on a therapeutic regimen and their close contacts on a prophylactic regimen of oseltamivir.13 Adverse drug reactions reported in the therapeutic group were statistically significantly higher as compared with the prophylactic group (P"0.029). Severity assessment showed 76% mild and 24% moderate reactions in the therapeutic group, 89% mild and 11% moderate reactions in the prophylactic group. Severity of adverse drug reactions was significantly higher in the therapeutic group.13 Similarly, in a retrospective study by Fallo et al., mild AEs from oseltamivir treatment were reported in 8 of 64 (12%) school-aged patients (vomiting and diarrhoea were the most frequently reported symptoms in this group) while 15 of 266 (5.6%) household contacts with oseltamivir prophylaxis reported AEs, with abdominal pain the most frequently described symptom(P,0.052)

Anmerkung/Fazit der Autoren

Overall, approximately half (34 of 62, 55%) of all statistical analyses comparing NI treatment with no treatment were statistically significant, favouring the use of NIs for all outcomes with limited significant evidence opposing their use. Evaluating adjusted estimates only, NIs are likely effective in reducing mortality and may be effective in reducing pneumonia, in the general population. Furthermore, there was a trend in the evidence supporting NI treatment for the reduction of severe influenza, hospitalization, ICU admission and fever duration (in a general population, children and adults).

In all studies, a statistically significantly decreased risk, odds or lower R0 were reported in individuals who received NIs as prophylaxis (both pre- and post-exposure) compared with those that did not (in a general population and in adults) with the exception of one observational study conducted in adult healthcare personnel workers.

However, the results of this review must be interpreted with caution as they are based on a small number of studies that are of very poor methodological quality. Knowledge gaps remain regarding NI effectiveness and safety for specific populations, namely Aboriginal people, high-risk individuals (living with chronic and/or immune conditions) and the elderly (>65years old).

3.2 Leitlinien

Uyeki TM et al., 2019 [2].

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza.

Leitlinienorganisation/Fragestellung

These clinical practice guidelines are an update of the guidelines published by the Infectious Diseases Society of America (IDSA) in 2009. The guidelines consider the care of children, pregnant and postpartum women, and nonpregnant adults and include special considerations for patients who are severely immunocompromised such as hematopoietic stem cell and solid organ transplant recipients. The target audience includes primary care clinicians, obstetricians, emergency medicine providers, hospitalists, and infectious disease specialists. The guidelines may be also useful for occupational health physicians and clinicians working in long-term care facilities. It adds new information on diagnostic testing, use of antivirals, and considerations of when to use antibiotics and when to test for antiviral resistance, and presents evidence on harm associated with routine use of corticosteroids.

Methodik

Grundlage der Leitlinie

Die Leitlinie ist ein Update einer Leitlinie aus dem Jahr 2009. Es wird angegeben, dass sich die Leitlinienerstellung an der Originalleitlinie orientierte. Die Leitlinie aus dem Jahr 2009 entspricht einer hochwertigen Leitlinie entsprechend S3 Klassifizierung der AWMF. Ob ein systematisches Vorgehen auch für das Update zugrunde liegt ist nicht dokumentiert.

Harper SA, Bradley JS, Englund JA, et al; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1003–32.

- Repräsentatives Gremium, keine Patientenbeteiligung.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche für die Originalleitlinie von 2009 dargelegt, unklar, ob die Suche auch im Update systematisch war. Systematische Bewertung der Evidenz.
- Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig. Die Verbindung zu der zugrundeliegenden Evidenz ist nicht explizit dargestellt.
- Keine Angaben zur Überprüfung der Aktualität.

Recherche/Suchzeitraum:

- Originalleitlinie 2009: Literature searches of the Medline database were performed for relevant English-language literature from the period 1966–2008.
- Keine Angaben zum Update.

LoE und GoR

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from the Canadian Task Force on the Periodic Health Examination [6].

ANTIVIRAL CHEMOPROPHYLAXIS IN COMMUNITY SETTINGS

Who Should Be Considered for Antiviral Chemoprophylaxis to Prevent Influenza in the Absence of Exposure or an Institutional Outbreak (Preexposure Chemoprophylaxis)?

Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks; antiviral chemoprophylaxis can be considered in certain situations:

32. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥3 months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are severely immunocompromised) (C-II).

33. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥3 months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6–12 months posttransplant and lung transplant recipients (B-II).

34. Clinicians can consider short-term antiviral chemoprophylaxis in conjunction with prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged ≥3 months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective (but not yet administered) when influenza activity has been detected in the community (C-II).

35. Clinicians can consider short-term antiviral chemoprophylaxis for unvaccinated adults, including healthcare personnel, and for children aged ≥3 months who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk persons are unable to take antiviral chemoprophylaxis (C-III).

36. Clinicians can consider educating patients and parents of patients to arrange for early empiric initiation of antiviral treatment as an alternative to antiviral chemoprophylaxis (C-III).

Which Antiviral Drugs Should Be Used for Preexposure Chemoprophylaxis for Influenza?

37. Clinicians should use an NAI (oral oseltamivir or inhaled zanamivir) if preexposure chemoprophylaxis for influenza is administered rather than an adamantane antiviral (A-II).

What Is the Duration of Preexposure Antiviral Chemoprophylaxis to Prevent Influenza?

38. Clinicians should administer preexposure antiviral chemoprophylaxis for adults and children aged ≥3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons such as hematopoietic stem cell transplant recipients) for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, as soon as influenza activity is detected in the community and continued for the duration of community influenza activity (A-II).

39. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving preexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (A-II).

Which Asymptomatic Persons Exposed to Influenza Should Be Considered for Postexposure Antiviral Chemoprophylaxis in a Noninstitutional Setting?

40. Clinicians can consider postexposure antiviral chemoprophylaxis for asymptomatic adults and children aged ≥3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, after household exposure to influenza (C-II).

41. Clinicians can consider postexposure antiviral chemoprophylaxis (in conjunction with influenza vaccination) for adults and children aged ≥3 months who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (eg, severely immunocompromised persons), after exposure to influenza (C-II).

42. Clinicians can consider educating patients and arranging for early empiric initiation of antiviral treatment as an alternative to postexposure antiviral chemoprophylaxis (C-III).

When Should Postexposure Antiviral Chemoprophylaxis Be Started?

43. If chemoprophylaxis is given, clinicians should administer postexposure antiviral chemoprophylaxis as soon as possible after exposure, ideally no later than 48 hours after exposure (A-III).

44. Clinicians should not administer once-daily postexposure antiviral chemoprophylaxis if >48 hours has elapsed since exposure. Full-dose empiric antiviral treatment should be initiated as soon as symptoms occur, if treatment is indicated (A-III).

How Long Should Postexposure Antiviral Chemoprophylaxis Be Given?

45. Clinicians should administer postexposure antiviral chemoprophylaxis in a nonoutbreak setting for 7 days after the most recent exposure to a close contact with influenza (A-III).

46. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving postexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (A-III).

Which Antiviral Drugs Should Be Used for Postexposure Chemoprophylaxis?

47. Clinicians should administer an NAI (inhaled zanamivir or oral oseltamivir) if postexposure chemoprophylaxis for influenza is given, rather than an adamantane antiviral (A-II).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2020) am 20.02.2020

#	Suchfrage
1	[mh "influenza, human"]
2	[mh "influenzavirus A"]
3	[mh "influenzavirus B"]
4	#1 OR #2 OR #3
5	influenza:ti,ab,kw OR infleunzas:ti,ab,kw
6	grippe:ti,ab,kw
7	flu:ti,ab,kw
8	#5 OR #6 OR #7
9	#4 OR #8
10	#9 with with Cochrane Library publication date from Feb 2015 to Feb 2020

Systematic Reviews in Medline (PubMed) am 20.02.2020

#	Suchfrage
1	influenza, human[mh]
2	influenzavirus A[mh]
3	influenzavirus B[mh]
4	#1 OR #2 OR #3
5	influenza[tiab] OR influenzas[tiab]
6	grippe[tiab]
7	flu[tiab]
8	#5 OR #6 OR #7
9	#4 OR #8
10	(#9) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence)))

	AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
11	((#10) AND ("2015/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 20.02.2020

#	**Suchfrage**
1	influenza, human[mh]
2	influenzavirus A[mh]
3	influenzavirus B[mh]
4	#1 OR #2 OR #3
5	influenza[tiab] OR influenzas[tiab]
6	grippe[tiab]
7	flu[tiab]
8	#5 OR #6 OR #7
9	#4 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
11	(#10) AND ("2015/02/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])
13	(#12) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Referenzen

1. **Boikos C, Caya C, Doll MK, Kraicer-Melamed H, Dolph M, Delisle G, et al.** Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15. J Antimicrob Chemother 2017;72(6):1556-1573.

2. **Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al.** Clinical practice guidelines by the infectious diseases society of america: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 2019;68(6):895-902.