Cochrane Netherlands

Literatuuronderzoek ten behoeve van de Richtlijn Virale luchtweginfecties

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Lijst met gebruikte afkortingen

BI	Betrouwbaarheidsinterval
CI	Confidence interval (betrouwbaarheidsinterval)
dd	Daily dose / dagelijkse dosering
DOAC	Directe Orale Anticoagulantia
HR	Hazard ratio
IC(U)	Intensive Care Unit
IQR	Interquartile range (interkwartielafstand)
LMWH	Low Molecular Weighth Heparin (laagmoleculair gewicht heparine)
MD	Mean difference (gemiddeld verschil, of: verschil in gemiddelden)
NA	Not applicable (niet van toepassing)
NVAVG	Nederlandse Vereniging van Artsen voor Verstandelijk Gehandicapten
NVT	Niet van toepassing
NR	Not reported (niet gerapporteerd)
OR	Odds ratio
PICO	Populatie, interventie, controle en uitkomst [*outcome*]
PWID	People with intellectual disabilities
RAILZ	Richtlijnen Artsen in de Langdurige Zorg
RCT('s)	Randomized Controlled Trial(s)
RD	Risk difference (risicoverschil)
RR	Relative risk; relatief risico
RTI	Respiratory tract infection
RV	Risicoverschil
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
SD	Standaarddeviatie
SEH	Spoedeisende Hulp
SMD	Standardized mean difference (gestandaardiseerd gemiddeld verschil)
SR('s)	Systematische review(s)
UK	United Kingdom
US(A)	United States (of America)
VWS	Ministerie van Volksgezondheid, Welzijn en Sport

Inhoudsopgave

1. Inleiding

In het door VWS gefinancierde, vierjarige programma 'Richtlijnen Artsen in de Langdurige Zorg' (RAILZ) ontwikkelen de Vereniging van Specialisten Ouderengeneeskunde (Verenso) en de Nederlandse Vereniging van Artsen voor Verstandelijk Gehandicapten (NVAVG) 13 richtlijnen en handreikingen. Daarnaast is het programma gericht op het verbeteren en doorontwikkelen van de kwaliteitscyclus en richtlijnmethodologie.

RAILZ heeft Cochrane Netherlands benaderd om systematisch literatuuronderzoek uit te voeren voor één uitgangsvraag binnen de Richtlijn Virale luchtweginfecties (Verenso en NVAVG). Deze richtlijn dient zorgverleners en zorgaanbieders een actueel overzicht te geven van de nieuwste inzichten over de zorg voor kwetsbare ouderen met (risico op) een virale luchtweginfectie. Onderdeel van deze richtlijn de verschillende behandelopties van een virale luchtweginfecties bij deze doelgroep.

De uitgangsvraag die opgesteld is door RAILZ luidt: Wat zijn mogelijke behandelopties voor virale luchtweginfecties bij de doelpopulatie en welke overwegingen spelen een rol bij de keuze van een optie?
Deze uitgangsvraag bestaat uit twee deelvragen:

a. Welke medicamenteuze behandelopties in termen van klinische verbetering en/of het voorkomen/verminderen van morbiditeit, mortaliteit en verdere verspreiding zijn geïndiceerd voor de behandeling van virale luchtweginfecties bij de doelpopulatie?
b. Welke ondersteunende (niet-)medicamenteuze behandeling is zinvol bij benauwdheid bij de doelpopulatie?

2. PICO's

Voor elke deelvraag formuleerde RAILZ de PICO-elementen (PICO staat voor populatie, interventie, controle, uitkomst [*outcome*]) als volgt:

PICO a: Welke medicamenteuze behandelopties in termen van klinische verbetering en/of het voorkomen/verminderen van morbiditeit, mortaliteit en verdere verspreiding zijn geïndiceerd voor de behandeling van virale luchtweginfecties bij de doelpopulatie?

P	Patiënten met een virale luchtweginfectie veroorzaakt door SARS-Cov-2 (variant Omikron, B.1.1.529), Influenzavirus, RS-virus en/of humaan metapneumovirus (hMPV): • Woonachtig in verblijf waarin zorg wordt verleend (zoals verpleeghuis, woonzorgcentrum, kleinschalige woonvormen, eerstelijnsverblijf, geriatrische revalidatie) OF studies met (subgroep van) (kwetsbare) ouderen met een leeftijd van ≥ 65 jaar of gemiddelde/mediaan ≥ 75 jaar ongeacht verblijfplaats • Volwassen, adolescenten en kinderen met een verstandelijke beperking met een virale luchtweginfectie ongeacht verblijfplaats
I	(Pre/post expositie) Behandeling met medicatie: • dexamethason (corticosteroïde); • dalteparine, enoxaparine, nadroparine, tinzaparine (tromboseprofylaxe (LMWH)) • apixaban, dabigatran, rivaroxaban (tromboseprofylaxe DOAC's) • nirmatrelvir/riteonavir, oseltamivir, ribavirine (virusremmers) • tocilizumab, baricitinib en sarilumab (immuunmodulatoren)
C	Placebo en/of standaard beleid/andere medicamenteuze behandelmaatregel gericht op hetzelfde behandeldoel/ hetzelfde type medicatie
O	• Klinische verbetering (zoals: afname of volledig verdwijnen van koorts, afname kortademigheid), • bijwerking van behandeling, • voorkomen van langdurige klachten (>3 maanden), • ziekteduur, • ziekenhuisopname, • overlijden, • virusshedding (hoe lang is een patiënt infectieus voor anderen), • ontwikkelen (klachten) van een virale luchtweginfectie (in geval van pre- en post-expositie behandeling)
Onderzoeksopzet	• Alle typen vergelijkend onderzoek: Systematic review of meta-analyse van vergelijkend onderzoek, RCT (randomized controlled trial), Observationeel onderzoek (case-control, cohort-onderzoek, chart review) • Evidence-based richtlijnen

PICO b: Welke ondersteunende (niet-)medicamenteuze behandeling is zinvol bij benauwdheid bij de doelpopulatie?

P	(Patiënten met een virale luchtweginfectie veroorzaakt door SARS-Cov-2 (variant Omikron, B.1.1.529), Influenzavirus, RS-virus en/of humaan metapneumovirus (hMPV): • Woonachtig in verblijf waarin zorg wordt verleend (zoals verpleeghuis, woonzorgcentrum, kleinschalige woonvormen, eerstelijnsverblijf, geriatrische revalidatie) OF studies met (subgroep van) (kwetsbare) ouderen met een leeftijd van ≥ 65 jaar of gemiddelde/mediaan ≥ 75 jaar ongeacht verblijfplaats • Volwassen, adolescenten en kinderen met een verstandelijke beperking met een virale luchtweginfectie ongeacht verblijfplaats
I	Ondersteunende (niet) medicamenteuze behandelmaatregel bij kortademigheid, o.a. zuurstoftoediening, vocht toediening, houding in bed, morfine.
C	Geen behandeling/standaard zorg/een andere (niet-) medicamenteuze ondersteunende behandelmaatregel
O	Verlichting van benauwdheidsklachten/kortademigheid, comfort, zuurstofsaturatie
Onderzoeksopzet	• Alle typen vergelijkend onderzoek: Systematic review of meta-analyse van vergelijkend onderzoek, RCT (randomized controlled trial), Observationeel onderzoek (case-control, cohort-onderzoek, chart review) • Evidence-based richtlijnen

De richtlijnwerkgroep heeft vooraf geen uitkomsten geprioriteerd (ingedeeld in cruciaal of belangrijk) en geen klinische relevantiegrenzen vastgesteld.

3. Methoden

3.1 Identificatie van relevante onderzoeken

Aan de hand van de aldus geformuleerde onderzoeksvragen werd in opdracht van RAILZ door Van Dusseldorp, Delvaux & Ket gezocht naar systematische reviews (SR's) en primair onderzoek van relevante onderzoeken. Deze zoekactie werd uitgevoerd op 1 november 2024. De zoekstrategieën zijn te achterhalen via Van Dusseldorp, Delvaux & Ket.

3.2 Selectie van relevante onderzoeken

Relevante onderzoeken waren onderzoeken waaraan patiënten met een virale luchtweginfectie veroorzaakt door SARS-Cov-2 (variant Omikron, B.1.1.529), Influenzavirus, Respiratoir Syncytieel (RS-) virus en/of humaan metapneumovirus (hMPV) deelnamen. Relevante patiënten betroffen ouderen woonachtig in een verblijf waarin zorg wordt verleend (zoals verpleeghuis, woonzorgcentrum, kleinschalige woonvormen). Ook onderzoeken onder een (kwetsbare) ouderen met een leeftijd ≥65 jaar of met een gemiddelde/mediane leeftijd ≥75 jaar werden geïncludeerd. Een andere relevante populatie betrof volwassen, adolescenten en kinderen met een verstandelijke beperking ongeacht verblijfplaats.

Studies voor deelvraag a moesten één van de medicamenteuze interventies genoemd in de PICO onderzoeken en vergelijken met placebo, standaard beleid of een ander medicamenteuze interventie gericht op hetzelfde behandeldoel. Studies voor deelvraag b moesten ondersteunende behandelmaatregelen bij kortademigheid onderzoeken en vergelijken met geen behandeling, standaardzorg of een andere ondersteunende behandelmaatregel. Daarnaast moesten de studies voor beide deelvragen informatie rapporteren over de relevante uitkomsten als beschreven in de PICO.

Zowel SR's als primaire onderzoeken die voldeden aan de bovenstaande criteria werden geselecteerd. Van de relevante SR's werden de referentielijsten gecontroleerd op relevante primaire onderzoeken. Onderzoeken onder volwassenen of ouderen met een leeftijd <65 jaar of waarin de gemiddelde/mediane leeftijd <75 jaar was, of onder patiënten met verdenking op een luchtweginfectie, met een lage luchtweginfectie of bacteriële luchtweginfectie, of onderzoeken naar Covid-19 die vóór november 2021 de dataverzameling hadden afgerond, werden uitgesloten. Onderzoeken die geen relevante uitkomstmaten rapporteerden, werden ook uitgesloten.

Twee onderzoekers hebben onafhankelijk van elkaar 10% van de titels en abstracts beoordeeld op relevantie. Verschillen tussen twee beoordelaars werden bediscussieerd. Bij voldoende overeenstemming werden de overige referenties door een enkele onderzoeker beoordeeld. Vervolgens werden de overgebleven relevante onderzoeken op basis van hun volledige tekst nogmaals op relevantie beoordeeld door één onderzoeker. Bij twijfel werd overlegd met een tweede onderzoeker.

3.3 Data-extractie en analyses

Van ingesloten publicaties werden beschrijvende gegevens verzameld (kenmerken van het onderzoek, de patiënten, interventies en controlebehandelingen), klinische uitkomsten en de resultaten. Indien niet gerapporteerd, werden zo mogelijk effectschattingen met een bijbehorend 95% betrouwbaarheidsinterval (95%-BI) uitgerekend o.b.v. de beschikbare informatie. Ook werd van ieder

onderzoek de methodologische kwaliteit bepaald. Voor gerandomiseerde onderzoeken werd daartoe de Cochrane RoB2 tool gebruikt en voor niet-gerandomiseerde onderzoeken de ROBINS-I tool (versie 2)(1, 2). Extractie van de resultaten en beoordeling van de methodologische kwaliteit werden uitgevoerd door één onderzoeker en gecontroleerd door een tweede onderzoeker.
Voor twee ongepubliceerde RCT's die via een SR geïdentificeerd waren, werden gegevens opgevraagd bij de farmaceut die de RCT's uitvoerde. In afwachting van een reactie is gebruikgemaakt van de gegevens die in de betreffende SR waren opgenomen.

Een meta-analyse werd alleen uitgevoerd als de patiënten, interventies en uitkomsten in de verschillende onderzoeken voldoende vergelijkbaar waren, volgens de methoden beschreven in de Cochrane Handboeken (3, 4). Waar meta-analysen niet mogelijk waren, werden resultaten beschrijvend samengevat. Vanwege overlap werden enkele uitkomstcategorieën zoals in de PICO aangegeven, samengenomen (klinische verbetering en ziekteduur als uitkomst ziekteduur; voorkomen van langdurige klachten en ontwikkelen van virale luchtweginfectie als uitkomst ernstige/langdurige klachten).

Eén onderzoeker kende aan de hand van de GRADE-methodiek *certainty of evidence* toe aan de bevindingen (5-7). Dit werd vervolgens gecontroleerd door een tweede onderzoeker. Omdat deze door de werkgroep vooraf niet waren vastgesteld, werden geen klinische relevantiegrenzen meegenomen bij de beoordeling van het GRADE-domein imprecisie.
Ten slotte werden voor iedere deelvraag conclusies geformuleerd (inclusief een niveau van bewijs).

De GRADE *levels of certainty* hebben de volgende betekenis:

High: er is veel vertrouwen dat het werkelijk effect dicht in de buurt ligt van de schatting van het effect

Moderate: er is redelijk vertrouwen in de schatting van het effect: het werkelijk effect ligt waarschijnlijk dicht bij de schatting van het effect, maar er is een mogelijkheid dat het hier substantieel van afwijkt

Low: er is beperkt vertrouwen in de schatting van het effect: het werkelijke effect kan substantieel verschillend zijn van de schatting van het effect.

Very low: er is weinig vertrouwen in de schatting van het effect: het werkelijke effect wijkt waarschijnlijk substantieel af van de schatting van het effect

4. Resultaten

4.1 Medicamenteuze behandeling (PICO a)

4.1.1 Selectie van de onderzoeken

De zoekactie resulteerde in 5495 potentieel relevante artikelen (Bijlage 1A). Daarvan vielen er op basis van de titel en/of het abstract 5193 af. Van de overige 302 onderzoeken werd het volledige artikel bekeken. Hiervan voldeden 29 onderzoeken aan de inclusiecriteria. Van de 273 uitgesloten onderzoeken staan de redenen voor exclusie beschreven in Bijlage 2B. Zes (primaire) onderzoeken zijn aanvullend geïdentificeerd door de referentielijsten van relevante systematische reviews na te lopen.

Geen van de ingesloten onderzoeken betrof volwassen, adolescenten of kinderen met een verstandelijke beperking met een virale luchtweginfectie; alle ingesloten onderzoeken waren in een populatie ouderen met influenza of COVID-19.

Onder de 35 ingesloten onderzoeken waren zes gerandomiseerde onderzoeken en 29 observationele onderzoeken. Van de gerandomiseerde onderzoeken onderzochten vijf studies de virusremmer oseltamivir versus placebo bij ouderen met influenza en onderzocht één onderzoek het middel (DOAC) apixaban versus placebo bij ouderen met COVID-19.

Van de observationele studies onderzochten 24 studies de virusremmer nirmatrelvir-ritonavir ten opzichte van standaardzorg bij ouderen met COVID-19. De overige vijf studies onderzochten de effectiviteit van oseltamivir ten opzichte van standaardzorg. Aangezien deze vijf observationele studies weinig nieuwe informatie opleveren ten opzichte van de gevonden gerandomiseerde onderzoeken over oseltamivir, zijn deze observationele studies niet verder uitgewerkt.
Het totaal aantal uitgewerkte onderzoeken komt neer op 30 studies.

4.1.2 Beschrijving van de resultaten van de gerandomiseerde studies t.a.v. oseltamivir versus placebo of standaardzorg bij ouderen met influenza

Vier van de vijf gerandomiseerde studies vergeleken oseltamivir ten opzichte van placebo bij ouderen met influenza(8-10). Een andere studie vergeleek een behandeling met oseltamivir+standaardzorg met alleen standaardzorg(11). De tabel met karakteristieken van deze studies is te vinden in Bijlage 3A. Van twee studies van de farmaceut Roche was geen publicatie beschikbaar, maar zijn de gegevens uit een systematische review geëxtraheerd(10). Drie studies deden een subgroepanalyse voor ouderen boven de 65 jaar (8, 9, 11). In de andere twee studies was de gehele populatie boven de 65 jaar(10).

Één van de vijf studies had enig risico op vertekening (8). Van de overige vier studies werd het risico op vertekening hoog ingeschat, met name door afwezigheid van blindering van patiënten(11) en het rapporteren van te weinig informatie over randomisatie, blindering en missende waardes (9, 10). Het risico op vertekening van de twee studies van de farmaceut Roche werd ingeschat op basis van de beschikbare informatie uit de systematische review(10). Een overzicht van het risico op vertekening is te vinden in Bijlage 4A.

Vijf studies evalueerden het effect van oseltamivir op de ziekteduur (8-11), één studie op bijwerkingen (misselijkheid, overgeven, diarree en stoppen met medicatie) (9) en één studie op het ontwikkelen van langdurige klachten(10). Voor de overige uitkomsten van interesse (te weten ziekenhuisopname, overlijden en virusshedding) rapporteerden geen van de studies resultaten. Resultaten per studie staan in Bijlage 3A en in Bijlage 5A is het evidenceprofiel voor deze vergelijking te vinden.

Ziekteduur
Eén studie (n=208) keek naar door de patiënt gerapporteerde tijd tot herstel (in dagen) en vond een positief effect voor oseltamivir vergeleken met placebo (HR=1,26; 95%-BI 1,02 tot 1,56)(11). De andere vier studies onderzochten tijd tot verbetering van de symptomen (in uren) en lieten een trend zien in het voordeel van oseltamivir. Effecten waren echter veelal niet statistisch significant of statistische significantie was onduidelijk (niet gerapporteerd of niet te berekenen met de beschikbare gegevens). Één van de studies vond overigens voor een subgroep hoog-risico patiënten een juist langere mediane ziekteduur voor oseltamivir (5). Voor de twee studies van de farmaceut Roche werd een gepoold

gemiddeld verschil uitgerekend (zie Bijlage 6: MD=-16,43; 95%-BI -41,93 to 9,08), maar overall konden de resultaten niet worden samengenomen in een meta-analyse.
Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor ziekteduur beoordeeld als *very low*.

Bijwerkingen
Eén studie (n=735) vond geen significante verschillen in misselijkheid (RR=0,80; 95%-BI 0,46 tot 1,39), overgeven (RR=1, 59; 95%-BI 0,76 tot 3,35), diarree (RR=0,49; 95%-BI 0,22 tot 1,06) of stoppen met medicatie (RR=0,84; 95%-BI 0,35 tot 2,01) tussen ouderen die oseltamivir kregen ten opzichte van placebo (9). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor deze uitkomst beoordeeld als *very low*.

Ontwikkelen van ernstige of langdurige klachten
In één studie (n=477) werden resultaten gerapporteerd voor het ontwikkelen van pneumonie en voor het optreden van complicaties waarvoor antibiotica nodig waren (10). Verschillen waren niet statistisch significant tussen oseltamivir en placebo (Pneumonie: RV=−0,1 (95%-BI−2,8 tot 2,6); complicaties waarvoor antibiotica nodig waren: RV=−4,8 (95%-BI −11,7 tot 2,0) en complicaties waarvoor antibiotica nodig waren m.u.v. acute bronchitis: RV= 0,9 (95%-BI −2,6 tot 4,5).
Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor deze uitkomst beoordeeld als *very low*.

4.1.3 Beschrijving van de resultaten van de gerandomiseerde studie t.a.v. apixaban versus placebo bij ouderen met COVID-19

Één gerandomiseerde studie onderzocht het effect van apixaban ten opzichte van placebo bij ouderen met COVID-19(12). Deze studie deed een subgroepanalyse voor ouderen boven de 65 jaar. De tabel met karakteristieken van deze studie is te vinden in Bijlage 3B.

Het risico op vertekening van deze studie werd ingeschat als ‘enige kans op vertekening (*some concerns*)’. Een overzicht van het risico op vertekening is te vinden in Bijlage 4B.

De studie evalueerde het effect van apixaban op een gecombineerde uitkomst van ziekenhuisopname en mortaliteit. Het gemiddelde aantal dagen in leven en niet in het ziekenhuis verschilde niet tussen de interventie- en controlegroep: 29,9 (sd 0,4) versus 29,9 (sd 0,3) (MD=0; 95%-BI -0,3 tot 0,3). Vanwege kans op vertekening en imprecisie werd de *certainty of evidence* als *low* beoordeeld.

De studie rapporteerde geen resultaten voor één van de ander uitkomsten van interesse.

4.1.4 Beschrijving van de resultaten van observationele studies t.a.v. nirmatrelvir-ritonavir versus standaardzorg bij ouderen met COVID-19

24 observationele studies onderzochten het effect van nirmatrelvir-ritonavir ten opzichte van standaardzorg bij ouderen met COVID-19 (13-36). De tabel met karakteristieken van deze studies is te vinden in Bijlage 3C. In twee studies betrof de volledige populatie verpleeghuisbewoners (22, 24). In twee andere studies was de volledige populatie boven de 65 jaar of was de gemiddelde leeftijd boven de 75 jaar (23, 25). In 20 studies werd een subgroepanalyse gedaan voor ouderen boven de 65, 70 of 80 jaar (13-21, 26-36). In één ervan werd ook een subgroepanalyse voor verpleeghuisbewoners uitgevoerd

(27). Een aantal studies onderzocht een specifiekere populatie van mensen met COVID-19 en een andere aandoening, namelijk hart- en vaatziekten (20), diabetes type 2 (21), of auto-immuun rheumatische aandoening (26, 30), chronische lymfatische leukemie (29), of obesitas (33).

In alle studies was er sprake van kans op vertekening. In zes studies werd de kans op vertekening ingeschat als 'moderate' (17, 27, 32, 34-36), in twee studies werd de kans op vertekening ingeschat als '*critical*' (23, 28). Voor de overige studies werd de kans op vertekening beoordeeld als '*serious*' (de categorie tussen *moderate* en *critical* in). De kans op vertekening was in de meeste gevallen gerelateerd aan mogelijke confounding en/of selectiebias. Een overzicht van het risico op vertekening is te vinden in Bijlage 4C.

Eén studie keek naar de uitkomst ziekteduur (25), twee studies naar bijwerkingen (23, 25) en negen studies bestudeerden een uitkomst gerelateerd aan ziekte-ernst of langetermijngevolgen (19, 22-25, 30-32, 35). De uitkomsten die het meest werden geëvalueerd, waren ziekenhuisopnames en mortaliteit, in respectievelijk 11 (13, 15, 18, 20, 22, 23, 25, 28, 30, 32, 33) en 10 (15, 19, 20, 23-25, 27, 30, 32, 33) onderzoeken. 13 onderzoeken presenteerden een samengestelde uitkomst gebaseerd op ziekenhuisopnamen en mortaliteit (14, 16, 17, 20, 21, 23, 25-27, 29, 33, 34, 36). Geen van de studies rapporteerde resultaten voor de uitkomst virus shedding. Resultaten per studie staan in Bijlage 3C en in Bijlage 5C is het evidenceprofiel voor deze vergelijking te vinden. Voor geen van de uitkomsten kon een meta-analyse worden uitgevoerd.

Ziekteduur
Eén studie (n=400) keek naar de ***totale benodigde tijd tot herstel (in dagen)*** in een populatie met een gemiddelde leeftijd van 76,1 jaar (sd 13,6) en vond geen significant verschil tussen nirmatrelvir-ritonavir en gebruikelijke zorg (mediaan 5 [range 3 tot 11] vs. 9 [range 5 tot 18]) (25). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor ziekteduur beoordeeld als *very low*.

Bijwerkingen
Twee studies rapporteerden bijwerkingen in de interventiegroep (nirmatrelvir-ritonavir). De ene studie vond ***maag-darmklachten*** bij 4%, ***allergie*** bij 0,9%, ***hoofdpijn*** bij 0,3% en ***bijwerkingen geclassificeerd als 'overig'*** bij 0,8% van de deelnemers in de interventiegroep (n=3459; gemiddelde leeftijd 76 jaar) (23). In de andere studie kreeg 12% van de deelnemers in de interventiegroep (n=200; leeftijd 65 jaar of ouder) een bijwerking (25). Geen van de bijwerkingen werd geclassificeerd als graad 3 of hoger of als een ernstige bijwerking. Bijwerkingen die gezien werden, waren ***misselijkheid*** (5%), ***smaakstoornissen*** (4%), ***maagpijn*** (3%) en ***overgeven*** (3%). Aangezien er in beide studies geen vergelijking werd gemaakt met bijwerkingen in de controlegroep, was een beoordeling van de *certainty of evidence* niet passend voor deze uitkomst.

Ontwikkelen van ernstige of langdurige klachten
Eén studie (n=400; gemiddelde leeftijd 76,1 jaar) vond een groot effect van nirmatrelvir/ritonavir op ***respiratoire insufficiëntie*** (RR=0,01; 95%-BI 0,00 tot 0,11; *moderate certainty of evidence*), maar op ***intubatie*** was het effect niet significant (RR=0,07; 95%-BI 0,00 tot 1,33; *very low certainty of evidence*) (25).
Van twee studies die naar ***intensive care (IC) opnames*** keken, vond één (n=4462; ≥65 jaar) een significant effect van nirmatrelvir-ritonavir (HR=0,33; 95%-BI 0,14 tot 0,75) in een populatie met ook een auto-immuun reumatische aandoening (30) en in de andere studie (n=3135; ≥65 jaar met risicofactoren

voor progressie tot ernstige COVID-19) was het effect niet significant (OR=0,62; 95%-BI 0,28 tot 1,31) (32). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor bijwerkingen beoordeeld als *very low*.
Een andere studie (n=27362; ≥65 jaar) keek ook naar ***IC-opnames***, maar dan in een ***samengestelde uitkomst met klinische achteruitgang*** (23). Deze studie vond geen significant verschil tussen nirmatrelvir-ritonavir en gebruikelijke zorg (RR=0,82; 95%-BI: 0,41 tot 1,67). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* beoordeeld als *very low*.
In een studie met in het ziekenhuis opgenomen verpleeghuisbewoners (n=930) was er minder ***ziekteprogressie (samengestelde uitkomst van IC-opname, invasieve mechanische ventilatie en/of overlijden)*** met nirmatrelvir/ritonavir dan met gebruikelijke zorg (HR=0,17; 95%-BI 0,06 tot 0,44) (22). C*ertainty of evidence* werd beoordeeld als *moderate* rekening houdend met kans op vertekening en de grootte van het effect.
Twee studies rapporteerden resultaten voor de ***samengestelde uitkomst kritieke, levensbedreigende ziekte en/of overlijden*** (19, 24). Eén van de studies keek naar subgroepen met leeftijd ≥70 jaar (n=684912) en leeftijd ≥80 (n=239102) en vond een verschil in het voordeel van nirmatrelvir/ritonavir in beide analyses (respectievelijk OR=0,537; 95%-BI 0,502 tot 0,574; en OR=0,551; 95%-BI 0,510 tot 0,595) (19). De andere studie (n=819) bestudeerde een populatie in de langdurige zorg en vond ook een verschil in het voordeel van de interventiegroep (RR=0,49; 95%-BI 0,24 tot 0,98) (24). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low*.
In één studie werd naar ***elke postacute diagnose (cardiovasculair, neurologisch, respiratoir, auto-immuun) binnen 180 dagen*** gekeken als uitkomst (31). De studie presenteerde resultaten voor een subgroep ≥70 jaar (n=40964) en een subgroep ≥80 jaar (n=13316). Voor beide subgroepen werd geen significant verschil gevonden tussen de interventie- en controlegroep (respectievelijk: HR=1,19; 95%-BI 0,98 tot 1,43; en HR=0,99; 95%-BI 0,77 tot 1,26). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* beoordeeld als *very low*.
Een andere studie (n=4462; ≥65 jaar, met auto-immuun reumatische aandoening) keek naar het optreden van ***elke cardiovasculaire uitkomst binnen 12 maanden*** en vond een verschil in het voordeel van nirmatrelvir/ritonavir (HR=0.69; 95%-BI 0,55 tot 0,86) (30). C*ertainty of evidence* werd beoordeeld als *low*, vanwege kans op vertekening.
Het ***ontstaan van long-COVID*** werd in één studie (aantal deelnemers onbekend; leeftijd ≥65 jaar; follow-up 180 dagen) bekeken (35). Deze studie vond een verschil in het voordeel van nirmatrelvir/ritonavir (RR=0,66; 95%-BI 0,63 tot 0,70). Vanwege kans op vertekening werd *certainty of evidence* beoordeeld als moderate.

Ziekenhuisopnames
Zes studies keken naar ***ziekenhuisopnames door elke oorzaak*** (13, 20, 25, 30, 32, 33). Vier ervan vonden een significant verschil in het voordeel van nirmatrelvir/ritonavir (effectschattingen en 95%BI in Bijlage 5C) (13, 20, 25, 30). In ongeveer de helft van de studies was er een specifieke populatie, met cardiovasculaire aandoeningen (20), obesitas (33) of auto-immuun reumatische aandoeningen (30). Vanwege de kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low.*
Zes andere studies keken naar ***ziekenhuisopnames gerelateerd aan COVID-19*** (15, 18, 22, 23, 28, 32) en lieten alle een gunstig effect zien van nirmatrelvir/ritonavir (effectschattingen en 95%BI in Bijlage 5C). In één studie bestond de populatie enkel uit verpleeghuisbewoners (n=930) (22), in de andere studies waren de deelnemers 70 jaar (18) en ouder of 65 jaar en ouder. Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low*.

Een studie (aantal deelnemers onbekend; leeftijd ≥65; met obesitas) rapporteerde resultaten voor ***spoedeisende hulp (SEH) bezoeken*** en vond een klein verschil in het voordeel van nirmatrelvir/ritonavir (HR=0,834; 95%-BI 0,708 tot 0,982) (33). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor bijwerkingen beoordeeld als *very low*.
Duur van ziekenhuisopname werd in twee studies gemeten als uitkomst (25, 32). Een studie (n=400; gemiddelde leeftijd 76,1 jaar) vond een lager ***aantal dagen dat de ziekenhuisopname duurde*** voor nirmatrelvir/ritonavir t.o.v. de gebruikelijke zorg (mediaan 3 dagen [range 2 tot 5] vs. 10 dagen [range 5 tot 42])(25). De tweede studie (deelnemers ≥65 jaar) vond voor nirmatrelvir/ritonavir een kortere ***ziekenhuisopnameduur gerelateerd aan COVID-19*** (n=86; mediaan [interkwartielafstand, IQR]: 5,0 [2,0 tot 7,3) vs. 6,4 (2,6 tot 14,4]), ***ziekenhuisopnameduur door elke oorzaak*** (n=225; 3,3 [1,0 tot 7,6] vs. 12,4 (5,3 tot 20,7]), ***IC-opnameduur gerelateerd aan COVID-19*** (n=20; 3,0 [2,0 tot 6,8] vs. 4,0 [2,0 tot 7,0]) en ***IC-opnameduur door elke oorzaak*** (n=28; 2,0 [1,1 tot 6,8] vs. 5,3 [2,4 tot 16,3])(32). Vanwege kans op vertekening en imprecisie werd *certainty of evidence* voor deze uitkomst beoordeeld als *very low*.

Mortaliteit
Acht studies onderzochten ***sterfte door alle oorzaken*** als uitkomst (19, 20, 24, 25, 27, 30, 32, 33). In totaal werden er 10 analyses uitgevoerd, waarvan er acht een significant effect lieten zien van nirmatrelvir/ritonavir (effectschattingen en 95%BI in Bijlage 5C). Twee ervan waren in een langdurige zorg populatie (24, 27), terwijl drie analyses werden uitgevoerd bij een specifieke populatie (cardiovasculaire aandoeningen (20), obesitas (33) of auto-immuun reumatische aandoeningen (30)). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low.*
Twee studies (n=68183; leeftijd ≥65) rapporteerden ***sterfte gerelateerd aan COVID-19*** (15, 23) en vonden beide een gunstig effect van nirmatrelvir/ritonavir (HR=0,21; 95%-BI 0,05 tot 0,82 en RR=0,34; 95%-BI 0,27 tot 0,43). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *very low.*

Samengestelde uitkomsten gebaseerd op ziekenhuisopnames en mortaliteit
Zeven studies keken naar ***ziekenhuisopnames en/of sterfte door elke oorzaak*** (14, 17, 20, 21, 26, 34, 36). Een van de studies (aantal deelnemers onbekend) werd uitgevoerd bij mensen met bestaande hart- en vaatzieten (20), een andere studie (n=1136) bij mensen met diabetes type 2 (21), een derde studie (n=199) bij mensen met een auto-immuun reumatische aandoening (26) en vierde studie (n=22530) bij veteranen (36). De zeven studies rapporteerden alle een significant effect ten gunste van nirmatrelvir/ritonavir (effectschattingen en 95%BI in Bijlage 5C). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low.*
In drie studies werd gekeken naar de samengestelde uitkomst ***ziekenhuisopnames gerelateerd aan COVID-19 en/of sterfte door alle oorzaken*** (16, 27, 29). In een van de studies (aantal deelnemers onbekend) werd specifiek naar een populatie in de langdurige zorg gekeken (27) en in een andere studie bestond de populatie (n=682) uit mensen met chronische lymphoïde leukemie (29). Er werden vier analyses uitgevoerd in de drie studies en die lieten alle vier een positief effect zien van nirmatrelvir/ritonavir. In drie gevallen was het effect significant (effectschattingen en 95%BI in Bijlage 5C). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low.*
Een studie onderzocht de samengestelde uitkomst ***SEH-bezoek, ziekenhuisopname of overlijden door alle oorzaken*** in een populatie met obesitas (aantal deelnemers onbekend; leeftijd ≥65) (33). Er werd

een verschil gevonden in het voordeel van nirmatrelvir/ritonavir (HR=0,878; 95%-BI 0,786 tot 0,980). C*ertainty of evidence* werd beoordeeld als *very low*, vanwege kans op vertekening en imprecisie.
Een andere studie (n=400; gemiddelde leeftijd 76,1 jaar) keek naar de samengestelde uitkomst ***ziekenhuisopname, intubatie of overlijden*** en vond een positief effect van nirmatrelvir/ritonavir (OR=0,34 (95%-BI: 0,29 tot 0,55) (25). Vanwege kans op vertekening werd *certainty of evidence* voor deze uitkomst beoordeeld als *low.*
Ziekenhuisopname, IC-opname, klinische achteruitgang of overlijden gerelateerd aan COVID-19 was de samengestelde uitkomst in de studie van Paraskevis (23). Deze studie (n=27362; leeftijd ≥65) vond een effect ten gunste van nirmatrelvir/ritonavir (RR=0,35; 95%-BI 0,31 tot 0,39). C*ertainty of evidence* werd beoordeeld als *low* rekening houdend met kans op vertekening en de grootte van het effect.

4.2 Ondersteunende behandelmaatregelen bij benauwdheid (PICO b)

4.2.1 Selectie van de onderzoeken

De zoekactie resulteerde in 1581 potentieel relevante artikelen (Bijlage 1A). Daarvan vielen er op basis van de titel en/of het abstract 1518 af. Van de overige 63 onderzoeken werd het volledige artikel bekeken en geen van deze onderzoeken bleek relevant. Exclusieredenen staan beschreven in Bijlage 2B.

5. Conclusies

Medicamenteuze behandeling bij virale luchtweginfecties

Ouderen met influenza

- Voor virusremmers bij ouderen met influenza kan het volgende geconcludeerd worden:
    - De evidence is zeer onzeker over een effect van oseltamivir t.o.v. placebo of standaardzorg op ***ziekteduur*** (5 RCT's; GRADE: *very low*), het optreden van bijwerkingen (1 RCT; GRADE: *very low*) en het ontwikkelen van ernstige of langdurige klachten (1 RCT; GRADE: *very low*) bij ouderen met influenza.
    - Er werden geen RCT's gevonden naar een effect van virusremmers op ***ziekenhuisopname***, ***overlijden*** en ***virusshedding*** bij ouderen met influenza.
- Er werden geen relevante RCT's gevonden naar het effect van corticosteroïden, tromboseprofylaxe (LMWH of DOAC) of immuunmodulatoren bij ouderen met influenza.

Ouderen met COVID-19

- Voor DOAC bij ouderen met COVID-19 kan het volgende geconcludeerd worden:
    - Er lijkt geen effect te zijn van apixaban t.o.v. placebo op een ***gecombineerde uitkomst van ziekenhuisopname en mortaliteit*** (gemiddelde aantal dagen in leven en niet in het ziekenhuis) bij ouderen met COVID-19 (1 RCT; GRADE: *low*) bij ouderen met COVID-19.
    - Er werden geen onderzoeken gevonden naar een effect van DOAC op ***ziekteduur, bijwerkingen, ernstige of langdurige klachten*** en *virusshedding* bij ouderen met COVID-19.
- Voor virusremmers bij ouderen met COVID-19 kan het volgende geconcludeerd worden:

- De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir t.o.v. standaardzorg op ***ziekteduur*** (1 observationeel onderzoek; GRADE: *very low*).
- Twee observationele onderzoeken rapporteerden ***bijwerkingen*** voor de interventiegroep (nirmatrelvir/ritonavir), maar vergeleken dit niet met een controlegroep. Gerapporteerde bijwerkingen betroffen voornamelijk maag-darmklachten (bij ongeveer 4% van de deelnemers in de interventiegroep).
- T.a.v. ontwikkelen van ernstige of langdurige klachten:
  - Nirmatrelvir/ritonavir vermindert waarschijnlijk de ***ziekteprogressie (samengestelde uitkomst van IC-opname, invasieve mechanische ventilatie en/of overlijden)*** bij in het ziekenhuis opgenomen patiënten (1 observationele studie; GRADE: *moderate*) en ***respiratoire insufficiëntie*** (1 observationeel onderzoek; GRADE: *moderate*). Nirmatrelvir/ritonavir lijkt het optreden van een ***kritieke, levensbedreigende ziekte en/of overlijden (samengestelde uitkomst)*** te verminderen (2 observationele onderzoeken; GRADE: *low*). De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir t.o.v. standaardzorg op ***intubatie*** (1 observationeel onderzoek; GRADE: *very low*), ***IC-opnames*** (2 observationele onderzoeken; GRADE: *very low*) en een ***samengestelde uitkomst van IC-opnames of klinische achteruitgang*** (1 observationeel onderzoek; GRADE: *very low*).
  - Nirmatrelvir/ritonavir lijkt het optreden van ***cardiovasculaire uitkomsten*** (1 observationeel onderzoek; GRADE: *low*) te verminderen. De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir op het optreden van ***postacute cardiovasculaire, neurologische, respiratoire of auto-immuun diagnoses (samengestelde uitkomst)*** (1 observationeel onderzoek; GRADE: *very low*).
  - Nirmatrelvir/ritonavir verlaagt waarschijnlijk de kans op het ***ontstaan van long-COVID*** (1 observationeel onderzoek; GRADE: *moderate*).
- Nirmatrelvir/ritonavir lijkt ***ziekenhuisopnames door elke oorzaak*** (6 observationele onderzoeken; GRADE: *low*) en ***ziekenhuisopnames gerelateerd aan COVID-19*** (2 observationele onderzoeken; GRADE: *low*) te verminderen. De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir op SEH-opnames (1 observationeel onderzoek; GRADE: *very low*) en ***duur van ziekenhuisopame*** (2 observationele onderzoeken; GRADE: *very low*).
- Nirmatrelvir/ritonavir lijkt de ***sterfte door elke oorzaak*** (8 observationele onderzoeken; GRADE: *low*) te verminderen. De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir op ***sterfte door COVID-19*** (3 observationele onderzoeken; GRADE: *very low*).
- Nirmatrelvir/ritonavir lijkt de samengestelde uitkomsten van ***ziekenhuisopnames en/of sterfte door alle oorzaken*** (7 observationele onderzoeken; GRADE: *low*), ***ziekenhuisopnames gerelateerd aan COVID-19 en/of sterfte door alle oorzaken*** (3 observationele onderzoeken; GRADE: *low*), ***ziekenhuisopname, intubatie of overlijden*** (1 observationeel onderzoek; GRADE: *low)* en ***ziekenhuisopname, IC-opname, klinische achteruitgang of overlijden gerelateerd aan COVID-19*** (1 observationeel onderzoek; GRADE: *low*) te verminderen. De evidence is zeer onzeker over een effect van nirmatrelvir/ritonavir op de samengestelde uitkomst ***SEH-bezoek, ziekenhuisopname of overlijden door alle oorzaken*** (1 observationeel onderzoek; GRADE: *very low*).
- Er werden geen onderzoeken gevonden naar een effect van virusremmers op ***virusshedding*** bij ouderen met COVID-19.

- Er werden geen relevante onderzoeken gevonden naar het effect van corticosteroïden, LMWH of immuunmodulatoren bij ouderen met COVID-19.

Mensen met een verstandelijke beperking
Er zijn geen relevante onderzoeken gevonden naar medicamenteuze behandeling van virale luchtweginfecties bij mensen met een verstandelijke beperking.

Ondersteunende behandeling bij benauwdheid bij virale luchtweginfecties

Er zijn geen relevante onderzoeken gevonden over ondersteunende behandelmaatregelen voor benauwdheid bij ouderen of mensen met een verstandelijke beperking en een virale luchtweginfectie.

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Bijlagen

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Bijlage 2. Uitgesloten onderzoeken
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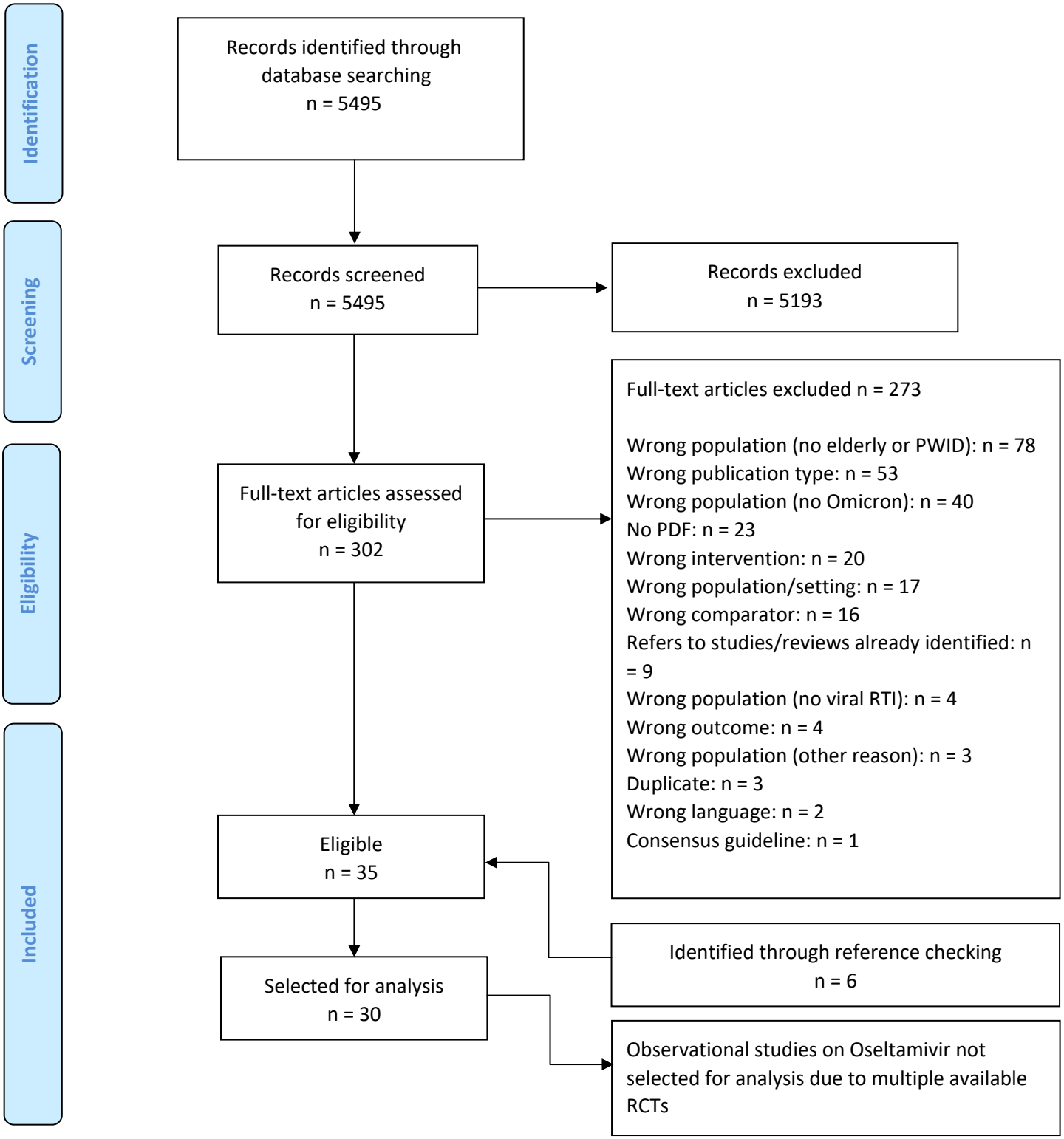
Bijlage 1. Study flows

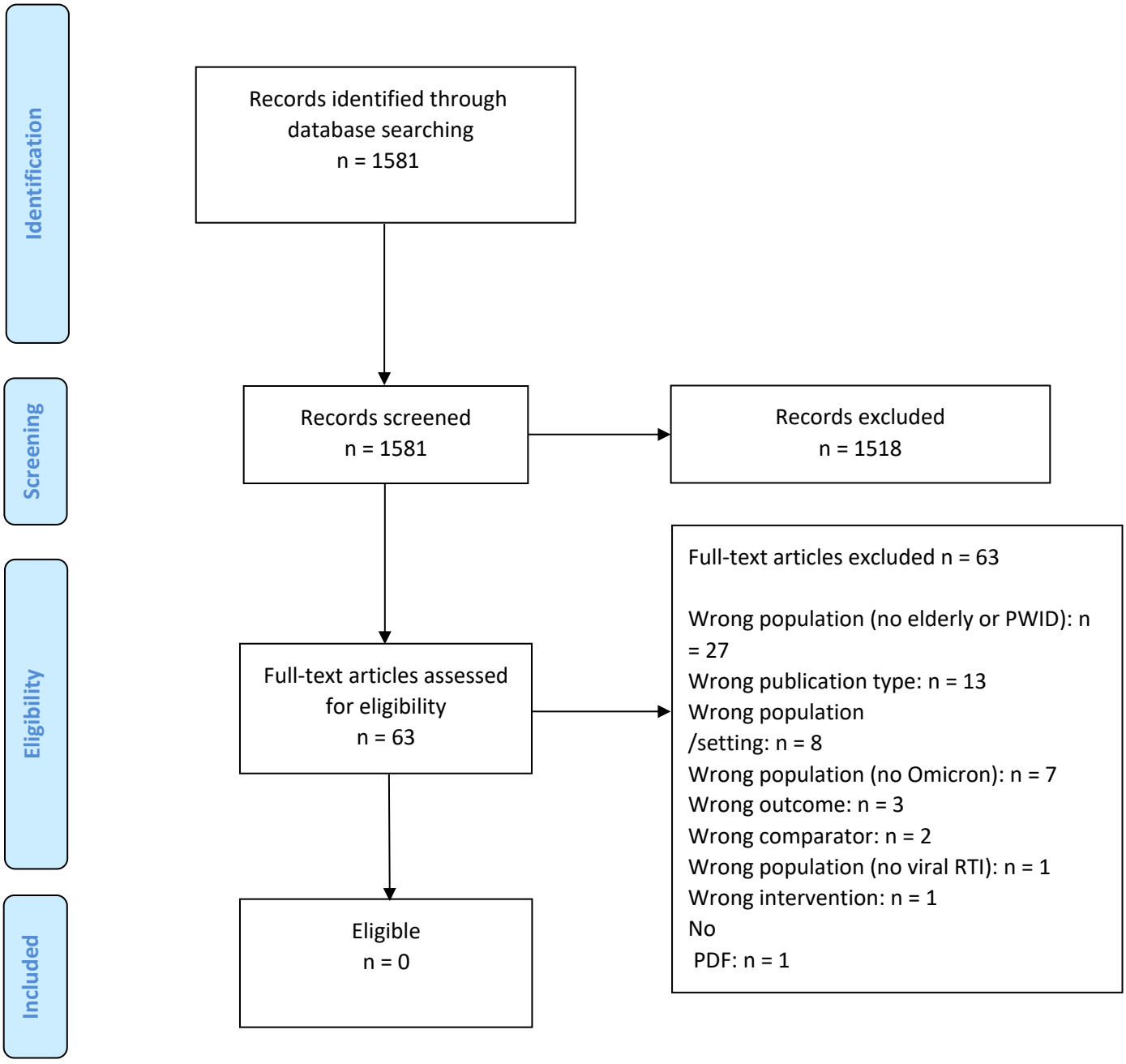
1A: Selectie van SR's en primair onderzoek voor PICO a

Figuur. Study flow van de selectie van SR's en primair onderzoek betreffende effectiviteit van medicamenteuze behandeling van een virale luchtweginfectie bij ouderen of mensen met een verstandelijke beperking



1B: Selectie van SR's en primair onderzoek voor PICO b

Figuur. Study flow van de selectie van SR's en primair onderzoek over ondersteunende behandelmaatregelen voor kortademigheid bij ouderen of mensen met een verstandelijke beperking met een virale luchtweginfectie



Bijlage 2. Uitgesloten onderzoeken

2A: SR's en primair onderzoek voor PICO a

Uitgesloten SR's en primair onderzoek betreffende effectiviteit van medicamenteuze behandeling van een virale luchtweginfectie bij ouderen of mensen met een verstandelijke beperking

Referentie	Reden
Unknown 2005	No PDF
Unknown 2006	No PDF
Abdel-Qadir 2022	Wrong population: no Omicron
Abizanda 2021	Wrong population: no Omicron
Abraham 2016	Wrong population: no elderly or PWID
Adegunsoye 2023	Wrong population: no elderly or PWID
Adema 2004	No PDF
Adlhoch 2023	Wrong population/setting
Aggarwal 2024	Wrong population: no Omicron
Agrawal 2010	No PDF
Akkaif 2022	Wrong publication type
Al-Shargi 2023	Wrong publication type
Albarran-Sanchez 2022	Wrong population: no elderly or PWID
Ali 2018	Wrong population: no elderly or PWID
Alroomi 2022	Wrong population: no elderly or PWID
Ananworanich 2022	Wrong population: no elderly or PWID
Andrieu 2006	Wrong intervention
Auyeung 2005	Wrong population: no elderly or PWID
Bader 2005	Wrong publication type
Bajema 2022	Wrong population: no elderly or PWID
Balaganesakumar 2013	Wrong population: no elderly or PWID
Balykova 2022	Wrong population: no elderly or PWID
Barco 2022	Wrong population: no elderly or PWID
Barnes 2022	Consensus guideline

Bastidas-Goyes 2023	Wrong population: no elderly or PWID
Bath 2022	Wrong population: no Omicron
Beard 2018	Wrong publication type
Bechman 2024	Wrong population: no elderly or PWID
Beck 2013	Refers to studies/reviews already identified
Beckhaus 2018	Wrong intervention
Belucci 2018	Wrong population: no elderly or PWID
Berardicurti 2020	Wrong population: no elderly or PWID
Bertuccio 2023	Wrong population: no elderly or PWID
Bhoopat 2024	Wrong population: no elderly or PWID
Bieber 2023	Wrong publication type
Bihan 2023	Wrong population: no elderly or PWID
Boikos 2017	Refers to studies/reviews already identified
Bonfanti 2009	No PDF
Bongard 2018	Wrong publication type
Booy 2012	Wrong comparator
Bouadma 2022	Wrong population: no elderly or PWID
Boutkourt 2024	Wrong population: no Omicron
Branch-Elliman 2022	Wrong population: no Omicron
Brassard 2017	Wrong population: no elderly or PWID
Brendish 2017	Wrong publication type
Broman 2022	Wrong population: no elderly or PWID
Brosh-Nissimov 2024	Wrong comparator
Bruno 2022	Wrong comparator
Bruyndonckx 2022	Wrong outcome
Büla 2006	Wrong publication type
Burch 2009	Refers to studies/reviews already identified
Busani 2020	Wrong publication type
Calderon-Ochoa 2024	Wrong population: no elderly or PWID

Camacho Moll 2024	Wrong population: no elderly or PWID
Cao 2016	Wrong population: no elderly or PWID
Cha-Silva 2024	Refers to studies/reviews already identified
Chang 2008	Wrong comparator
Charles 2004	No PDF
Chaves 2015	Wrong population/setting
Chen 2022	Wrong population: other reason
Chen 2024	Wrong population/setting
Chen 2024	Wrong population/setting
Chen 2024	Refers to studies/reviews already identified
Cheng 2018	Wrong intervention
Cheng 2022	Wrong population: no Omicron
Cheng 2022	Wrong population: no Omicron
Chevret 2023	Wrong population: no Omicron
Chiu 2009	No PDF
Cho 2023	Wrong comparator
Chow 2019	Wrong publication type
Coenen 2020	Wrong population: no elderly or PWID
Collins 2002	Wrong publication type
Cools 2005	No PDF
Cooper 2003	Wrong population: no elderly or PWID
Couch 2000	Wrong publication type
Coultas 2019	Wrong publication type
Dastan 2023	Wrong population: no elderly or PWID
Dawoud 2020	Wrong population: no Omicron
Dravid 2021	Wrong population: no Omicron
Drinka 2003	Wrong publication type
Dronavalli 2020	Wrong comparator
Dryden-Peterson 2022	Duplicate

Dumyati 2002	Wrong publication type
Duncan 2016	Wrong publication type
Dutkowski 2003	Wrong publication type
Ebell 2013	Refers to studies/reviews already identified
Edilgireeva 2022	No PDF
Ehlers 2001	Wrong publication type
Eikelboom 2022	Wrong population/setting
Elliot 2008	Wrong publication type
Et 2022	Wrong population/setting
Faber 2008	Wrong publication type
Falagas 2010	Wrong population: no elderly or PWID
Fan 2019	No PDF
Fazylov 2016	No PDF
Flannery 2014	Wrong population: no elderly or PWID
Fleming 2001	Wrong publication type
Fry 2015	Wrong population: no elderly or PWID
Fumagalli 2024	Wrong population: no elderly or PWID
Fung 2023	Wrong intervention
Garcia-Vicuna 2020	Wrong publication type
Gardezi 2022	Wrong population: no elderly or PWID
Geng 2024	Wrong population: no elderly or PWID
Gentry 2023	Wrong intervention
Ghea 2023	Wrong population: no elderly or PWID
Ghosn 2023	Wrong population: no elderly or PWID
Goldin 2024	Wrong intervention
Gonzalez-Porras 2022	Wrong population: no Omicron
Gorisek Miksic 2015	Wrong intervention
Green 2023	Wrong comparator
Greenstein 2024	Wrong population: no Omicron

Griesel 2022	Wrong population: no Omicron
Gu 2024	Wrong population/setting
Guay 2006	Wrong publication type
Guay 2010	Wrong publication type
Haas 2013	Wrong publication type
Hall 2023	Wrong population: no elderly or PWID
Hannoun 2004	No PDF
Hanula 2023	Wrong population: no elderly or PWID
Harbin 2021	Wrong population: no elderly or PWID
Hayden 2004	Wrong population: no elderly or PWID
Hoffman 2022	Wrong population: no Omicron
Holt 2020	Wrong population: no Omicron
Hota 2007	Wrong publication type
Huang 2017	Wrong comparator
Hung 2017	Wrong comparator
Iglesias Gomez 2022	Wrong population: no elderly or PWID
Jo 2022	Wrong population: no elderly or PWID
Juthani-Mehta 2005	No PDF
Kaduszkiewicz 2022	Wrong population: no elderly or PWID
Kaiser 2003	Wrong population: no elderly or PWID
Kananen 2023	Wrong population: no Omicron
Kashiwagi 2000	Wrong language (translation not possible)
Khan 2020	Wrong publication type
Kim 2022	Wrong population: no elderly or PWID
Klopfenstein 2020	Wrong population: no Omicron
Kodde 2023	Wrong population: no Omicron
Kopa-Stojak 2024	Wrong population: no elderly or PWID
Korayem 2022	Wrong population: no Omicron
Kow 2024	Wrong population: no elderly or PWID

Krilov 2002	Wrong publication type
Kroll 2011	Wrong publication type
Krumholz 2024	Wrong population: other reason
Kuzman 2006	No PDF
Lam 2002	Wrong publication type
Lavilla Olleros 2022	Wrong population: no elderly or PWID
Lee 2013	Wrong outcome
Lee 2015	Wrong publication type
Lewnard 2023	Wrong comparator
Lewnard 2023	Wrong publication type
Li 2001	Wrong language (translation not possible)
Li 2003	No PDF
Liapikou 2024	No PDF
Lindegren 2015	Wrong population: no elderly or PWID
Lindley 2010	Wrong publication type
Liu 2023	Wrong population: no elderly or PWID
Liu 2023	Wrong population: no elderly or PWID
Liu 2023	Wrong population/setting
Liu 2024	Wrong population: no Omicron
Low 2024	Wrong population: no elderly or PWID
Lu 2022	Wrong publication type
Lynch 2007	Wrong publication type
Lynd 2005	Wrong outcome
McClellan 2001	Wrong publication type
McElhone 2005	No PDF
McGarry 2023	Wrong intervention
McKimm-Breschkin 2005	Wrong publication type
Mehta 2022	Wrong population: no Omicron
Merchante 2022	Wrong population: no Omicron

Meshreky 2020	Wrong intervention
Michiels 2023	Refers to studies/reviews already identified
Mintzes 2001	Wrong publication type
Mohamed 2022	Wrong population: no Omicron
Montalto 2000	Wrong population: no elderly or PWID
Monto 2004	Wrong publication type
Morland 2005	No PDF
Morris 2024	Wrong comparator
Murti 2018	Wrong intervention
Muse 2022	Wrong publication type
Muthuri 2014	Wrong population: no elderly or PWID
Najjar-Debbiny 2023	Wrong population: no elderly or PWID
Nam 2019	Wrong population: no elderly or PWID
Ng 2010	Wrong population: no elderly or PWID
Nilsen 2023	Wrong population: no Omicron
Okoli 2024	Wrong population: no elderly or PWID
Organizacion Panamericana de la 2022	Wrong population: no elderly or PWID
Ortega-Paz 2023	Wrong publication type
Orzeck 2007	Wrong population: no elderly or PWID
Oxford 2003	Wrong population: no elderly or PWID
Paltra 2023	Wrong publication type
Paraskevis 2023	Duplicate
Perez-Padilla 2010	Wrong comparator
Perrone 2020	Wrong population: no Omicron
Peters 2001	Wrong population: no viral RTI
Pham 2022	Wrong population: no Omicron
Piazza 2023	Wrong population: no Omicron
Pierce Jr 2006	No PDF

Pitchan Velammal 2024	Wrong publication type
Poli 2022	Wrong population: no elderly or PWID
Postma 2007	Wrong publication type
Qi 2023	Wrong population/setting
Qiu 2015	Wrong population: no elderly or PWID
Rainwater-Lovett 2014	Wrong population: no viral RTI
Ramirez 2018	Wrong population: no viral RTI
Reis 2023	Refers to studies/reviews already identified
Reyes 2022	Wrong population: no Omicron
Rezabakhsh 2024	Wrong population: no Omicron
Rigby 2022	Wrong publication type
Robson 2019	Wrong publication type
Rowe 2014	Wrong publication type
Sanchez-Montalva 2022	Wrong population: no Omicron
Scialo 2022	Wrong population: no Omicron
Seidenberg 2019	Wrong publication type
Sevendal 2024	Wrong population: no elderly or PWID
Shah 2019	Wrong intervention
Shijubo 2002	Wrong comparator
Simonetti 2024	Wrong population: other reason
Singh 2003	Wrong population: no elderly or PWID
Smith 2001	No PDF
Smith 2008	Wrong intervention
Snell 2024	Wrong publication type
Souza 2010	Wrong population: no elderly or PWID
Spagnuolo 2016	Wrong population: no elderly or PWID
Sturpe 2002	Wrong population: no viral RTI
Suran 2024	Wrong publication type
Temte 2023	Wrong intervention

Toovey 2013	Wrong population: no elderly or PWID
Toovey 2012	Wrong population: no elderly or PWID
Toovey 2008	Wrong comparator
Tran 2021	Wrong population: no Omicron
Tsai 2023	Wrong intervention
Tsiodras 2007	Wrong publication type
Turner 2003	Wrong population: no elderly or PWID
Tziolos 2022	Wrong population: no Omicron
Uemura 2023	Wrong population: no Omicron
Uhnoo 2005	No PDF
Uhnoo 2003	Wrong population: no elderly or PWID
Upadhyay 2022	Wrong population: no Omicron
Uyeki 2019	Wrong population: no elderly or PWID
Van der Sande 2014	Wrong intervention
Vetel 2002	No PDF
Wagner 2022	Wrong population: no Omicron
Wan 2023	Wrong population: no elderly or PWID
Wan 2023	Wrong comparator
Wang 2015	Wrong population: no elderly or PWID
Wang 2015	Duplicate
Wang 2018	Wrong intervention
Wang 2023	Wrong population: no Omicron
Wang 2023	Wrong population: no elderly or PWID
Wang 2022	Wrong population: no elderly or PWID
Wang 2024	Wrong population/setting
Wang 2024	Wrong population/setting
Wee 2023	Wrong outcome
Weng 2023	Wrong population/setting
Whitley 2006	Wrong publication type

Willcox 2024	Refers to studies/reviews already identified
Wolfe 2022	Wrong population/setting
Wong 2023	Wrong population/setting
Wu 2023	Wrong population: no Omicron
Wu 2010	Wrong publication type
Xiang 2024	Wrong intervention
Xie 2024	Wrong intervention
Xu 2023	Wrong population: no elderly or PWID
Yasuda 2022	Wrong population: no elderly or PWID
Yip 2018	Wrong intervention
Zhan 2024	Wrong intervention
Zhang 2023	Wrong comparator
Zhang 2024	Wrong population/setting
Zhao 2024	Wrong population: no elderly or PWID
Zhdanov 2021	No PDF
Zhong 2022	Wrong population/setting
Zhou 2024	Wrong population/setting
Zhu 2023	Wrong population: no elderly or PWID

Abbreviations:
PWID: people with intellectual disabilities
RTI: respiratory tract infections

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2B: SR's en primair onderzoek voor PICO b

Uitgesloten primair onderzoek betreffende ondersteunende behandelmaatregelen voor kortademigheid bij ouderen of mensen met een verstandelijke beperking met een virale luchtweginfectie

Referentie	Reden
Aljabali 2023	Wrong publication type
Arabi 2022	Wrong publication type
Barthelemy 2020	Wrong population/setting
Beckhaus 2018	Wrong intervention
Boeijen 2024	Wrong publication type
Brazier 2022	Wrong outcome
Burns 2020	Wrong population: no Omicron
Carratalá 2024	Wrong comparator
Cheung 2004	Wrong population: no elderly or PWID
Cheyne 2022	Wrong population: no Omicron
Cunha 2023	Wrong population/setting
Dastenae 2022	Wrong population: no elderly or PWID
De Vito 2022	Wrong population: no elderly or PWID
Dubée 2021	Wrong population: no Omicron
Duvignaud 2022	Wrong population: no elderly or PWID
Elharrar 2020	Wrong publication type
Esperatti 2024	Wrong population: no elderly or PWID
Estrella-Alonso 2024	Wrong population/setting
Fajardo-Campoverdi 2024	Wrong population: no elderly or PWID
Fossali 2024	Wrong population/setting
Fralick 2022	Wrong population: no elderly or PWID
Freire 2024	Wrong population: no elderly or PWID
Garcia 2020	Wrong population: no elderly or PWID
Gopalakrishnan 2022	Wrong population/setting
Gorenstein 2020	Wrong population: no elderly or PWID
Hallifax 2020	Wrong population: no elderly or PWID

Ibarra-Estrada 2020	Wrong publication type
Javed 2023	Wrong population: no elderly or PWID
Kjellberg 2022	Wrong publication type
Kjellberg 2024	Wrong population: no elderly or PWID
Landete 2024	Wrong population: no elderly or PWID
Lellouche 2024	Wrong outcome
Liu 2024	Wrong population: no elderly or PWID
Losser 2020	Wrong population/setting
Lovre 2024	Wrong population: no elderly or PWID
Mantoo 2024	No PDF
Marti 2022	Wrong population: no elderly or PWID
Martín Raymondi 2020	Wrong publication type
Merchant 2022	Wrong population: no Omicron
Mohd Kamil 2023	Wrong population: no elderly or PWID
Montalvan-Sanchez 2023	Wrong population: no elderly or PWID
Mukhtar 2020	Wrong population/setting
Napolitano 2010	Wrong publication type
Nay 2023	Wrong population: no elderly or PWID
Nicola 2020	Wrong population: no elderly or PWID
Nielsen Jeschke 2020	Wrong population: no elderly or PWID
Perkins 2022	Wrong population: no elderly or PWID
Rigby 2022	Wrong outcome
Senderovich 2022	Wrong population: no Omicron
Shaikh 2022	Wrong publication type
Siddiq 2021	Wrong population: no elderly or PWID
Soni 2023	Wrong publication type
Taboada 2020	Wrong population: no elderly or PWID
Taboada 2020	Wrong publication type
Taboada 2022	Wrong population: no Omicron

Talha 2023	Wrong population: no elderly or PWID
Tatlow 2022	Wrong population: no Omicron
Wiersinga 2020	Wrong publication type
Wu 2024	Wrong population: no viral RTI
Yücel 2024	Wrong population/setting
Zeng 2023	Wrong population: no elderly or PWID
Zha 2021	Wrong publication type
Zhao 2023	Wrong comparator

Abbreviations:
PWID: people with intellectual disabilities
RTI: respiratory tract infections

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Bijlage 3. Tabellen met studiekarakteristieken

3A: Karakteristieken van gerandomiseerde studies t.a.v. oseltamivir versus placebo of standaardzorg bij ouderen met influenza (n=5)

Study characteristics	Patient characteristics	Intervention	Control	Results
Butler 2020 Study design: RCT Total no. participants: 3266 Country: Belgium, Czech Republic, Denmark, France, Greece, Hungary, Ireland, Lithuania, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, UK Funding: European Commission's Seventh Framework Programme	Peope with influenza-like illness, ≥ 1 year of age. Age of study population, % per age and treatment group: - Treated: <12y: 14%; 12;65y: 80%; >65y: 6% - Untreated: <12y: 14%; 12-65y: 80%; >65y: 6% Definition of subgroups: - ≥65 years Setting: Primary care	Drug name: Oseltamivir (+ usual care) Dosage: 2dd 75 mg Duration: 5 days	Usual care	<u>Duration of illness</u> Patient-reported time to recovery in days for oseltamivir vs. usual care (n=208 analyzed) : HR=1.26 (95%CI 1.02 to 1.56)
Ison 2020 Study design: RCT Total no. participants: 1453 Country: Japan, South Korea, the Philippines, Taiwan, the USA, Belgium, Bulgaria, Germany, Spain, the UK, Hungary, Latvia, Poland, and Romania, Australia, New Zealand, and South Africa Funding: Shionogi	Outpatients ≥12 years, suspected influenza A or influenza B virus infection, considered at high risk of developing influenza associated complications. Age of study population, mean (SD): 51.5 (16.8) Definition of subgroups: - ≥65 years without risk factors - ≥65 years with one or more risk factors Setting: Outpatient	Drug name: Oseltamivir Dosage: 2dd 75 mg Duration: 5 days	Placebo	<u>Duration of illness</u> Median time to improvement of influenza symptoms in hours at 14 days follow-up - Population without risk factors, oseltamivir (n=33) vs. placebo(n=41): 54 (95%CI 31.7 to 89.8) vs. 113.2 (95%CI 72.3 to 137.7) - Population with risk factors, oseltamivir (n=70) vs. placebo(n=61): 91.2 (95%CI 55.1 to 123.2) vs. 78.4 (95%CI 54.9 to 92.8)

Martin 2001 Study design: RCT Total no. participants: 1138 Country: NR Funding: NR	People at high risk of influenza complications. Age of study population, median (range) per treatment group: - Treated: 73 (65-96) - Untreated: 73 (65-97) Definition of subgroups: - ≥65 years Setting: NR	Drug name: Oseltamivir Dosage: 2dd 75 mg Duration: 5 days	Placebo	<u>Duration of illness</u> Intervention (n=222) vs. control (n=254) - Median duration of fever in hours (measured at 21 days follow-up): 66.9 vs. 89.5 (no p-value, SDs, or 95%CI mentioned). - Median time to alleviation of acute febrile illness (fever/chills/myalgia) in hours (measured at 21 days follow-up): 36 vs. 50.5; p=0.005. - Median time to alleviation of acute febrile illness (fever/cough/coryza) in hours (measured at 21 days follow-up): 115 vs. 132.3 (no p-value, SDs, or 95%Cs mentioned). <u>Adverse events</u> Intervention (n=362) vs. control (n=373) - Nausea: 21/362 vs. 27/373; RR=0.80 (95%CI 0.46 to1.39) - Vomiting: 17/362 vs. 11/373; RR=1.59 (95%CI 0.76 to 3.35) - Diarrhoea: 9/362 vs. 19/373; RR=0.49 (95%CI 0.22 to 1.06) - Discontinuation: 9/362 vs. 11/373; RR=0.84 (95%CI 0.35 to 2.01)
WV15707 Study design: RCT Total no. participants: 26 Country: Australia, South Africa and South America Funding: Roche	Peope with influenza-like illness, ≥65 year of age Age of study population, mean (SD): 71.6 (5.4) Definition of subgroups: NA Setting: NR	Drug name: Oseltamivir Dosage: 2dd 75 mg Duration: NR	Placebo	<u>Duration of illness</u> Mean duration of symptoms in hours (follow-up not reported) for oseltamivir (n=6) vs. placebo (n=6): 79.6 (SD 63.2) vs. 110 (SD 174); MD=-30 (95%CI -178.53 to 117.73)
WV15819, WV15876 and WV15989 Study design: RCT Total no. participants: 736	Peope with influenza-like illness, ≥65 year of age Age of study population, mean (SD): 72.9 (6.4)	Drug name: Oseltamivir Dosage: 2dd 75 mg Duration: NR	Placebo	<u>Duration of illness</u> Mean duration of symptoms in hours (follow-up not reported) for oseltamivir (n=223) vs. placebo (n=254): 191(SD143) vs. 207 (SD 145); MD=-16 (95%CI -41.89 to 9.89)

Country: Europe, USA, Canada, Israel, South Africa, New Zealand and Australia Funding: Roche	Definition of subgroups: NA Setting: NR	<u>Severe/long-term disease</u> Risk differences for different severe/long-term diseases between oseltamivir vs. placebo were: - Pneumonia: RD=−0.1 (95%CI−2.8 to 2.6) - Complications requiring an antibiotic: RD=−4.8 (95%CI −11.7 to 2.0) - Complications requiring an antibiotic, excluding acute bronchitis: RD= 0.9 (95%CI −2.6 to 4.5) A positive risk difference means that there were more complications in the treatment group, while a negative value means that there were fewer complications in the treatment group.

dd: daily dose; HR: hazard ratio; mg: milligram; NA: not applicable; NR: not reported; mg: milligramme; RCT: randomized controlled trial; RD: risk differe nce; RR: relative risk; SD: standard deviation; UK: United Kingdom; USA: United States of America

3B: Karakteristieken van de gerandomiseerde studie t.a.v. apixaban versus placebo bij ouderen met COVID-19

Study characteristics	Patient characteristics	Intervention	Control	Results
Silva 2024 Study design: RCT Total no. participants: 411 Country: Brazil Funding: Pfizer	Patients with confirmed COVID-19 and additional risk factors for complications. Age of study population, mean (SD): 44.0 (14) Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: Apixaban Dosage: 2dd 2.5mg Duration: 30 days	Placebo	<u>Composite of hospitalization and mortality</u> Days alive and out of hospital or emergency department for apixaban vs. placebo at 30 days follow-up: 29.9 (SD 0.4) vs. 29.9 (SD 0.3); MD=0 (95% CI: -0.3 to 0.3)

CI: confidence interval; dd: daily dose; MD: mean difference; mg: milligramme; RCT: randomized controlled trial; SD: standard deviation

3C: Karakteristieken van observationele studies t.a.v. nirmatrelvir-ritonavir versus standaardzorg bij ouderen met COVID-19 (n=24)

Study characteristics	Patient characteristics	Intervention	Control	Results
Aggerwal 2023 Study design: Retrospective cohort study Total no. participants: 16529 Country: US Funding: US National Institutes of Health	Patients with a positive COVID-19 test or nirmatrelvir-ritonavir medication order. Age of study population: - Treated: 18-44y: 45.9%; 45-64y: 22.1%; ≥65y: 32.1%, - Untreated: 18-44y: 63.7%; 45-64y: 15.4%; ≥65y: 20.9% Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: 2dd 300/100 mg Duration: 5	Usual care	<u>Hospitalization (all-cause)</u> 28-days all-cause hospitalisation for nirmatrelvir/ritonavir vs. usual care, age≥65: 29/2298 vs. 64/1955 Adjusted OR=0.37 (95%CI: 0.23 to 0.57) *Adjusted for age, sex, race and ethnicity, insurance status, obesity status, immunocompromised status, number of additional comorbid conditions, number of vaccinations, and omicron subvariant.*
Al-Obaidi 2023 Study design: Retrospective cohort study Total no. participants: 11508 Country: US Funding: None	Patients positive for COVID-19, ≥18y. Age of study population, median (range): - Treated: 58.0 (43.0-70.0) - Untreated: 58.0 (42.0-70.0) Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (all-cause) and/or mortality (all-cause), composite outcome</u> 30-day all cause hospitalization and/or mortality for nirmatrelvir/ritonavir vs. usual care: 26/2000 vs. 63/1969; RR=0.41 (95%CI: 0.26 to 0.64)
Arbel 2022 Study design: Retrospective cohort study Total no. participants: 109254 Country: Israel	Patients with confirmed COVID-19, ≥40y, at high risk of progression to severe disease. Age of study population, mean (SD): 59.5 (12.8) Definition of subgroups:	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (COVID-19)</u> Nirmatrelvir/ritonavir vs. usual care, follow-up 35 days: 11/2484 vs. 766/40337; adjusted HR=0.27 (95%CI: 0.15 to 0.49) <u>Mortality (COVID-19)</u>

Funding: None	- ≥65 years Setting: Outpatient			Nirmatrelvir/ritonavir vs. usual care, follow-up 35 days: 2/2484 vs. 158/40337; adjusted HR=0.21 (95%CI: 0.05 to 0.82) *Adjusted for sociodemographic factors, coexisting illnesses, and SARS-CoV-2 immunity status.*
Dormuth 2023 Study design: Retrospective cohort study Total no. participants: 6866 Country: Canada Funding: British Columbia Ministry of Health	Individuals with confirmed COVID-19 and an increased vulnerability to complications from COVID-19 infection. Age of study population, median (range): 70 (57-80) Definition of subgroups: - ≥70 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalisation (COVID-19) and/or mortality (all-cause)</u> 28-day COVID-19 related emergency hospital visit or admission, or all-cause death for nirmatrelvir/ritonavir vs. usual care: 20/510 vs. 35/498; RD=-3.1 (95%CI: -5.9 to -0.3)
Dryden-Peterson 2023 Study design: Population-based cohort study Total no. participants: 44045 Country: US Funding: Harvard University Center for AIDS Research, a funded program of the National Institutes of Health and the National Cancer Institute	Patients with confirmed COVID-19, ≥50y. Age of study population: - Treated: 50-64y: 54%; 65-79y: 37%; ≥80y: 9%, - Untreated: 50-64y: 55%; 65-79y: 36%; ≥80y: 8% Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: 2dd [not further specified] Duration: 5 days	Usual care	<u>Hospitalization (all-cause) and/or mortality (all-cause), composite outcome</u> Hospitalization within 14 days or death within 28 days for nirmatrelvir/ritonavir vs. usual care: 55/6656 vs. 194/13079; RR=0.55 (95%CI: 0.40 to 0.77)
Kabore 2023 Study design: Population-based cohort study Total no. participants: 16804 Country: Canada	Patients with a positive COVID-19 test or nirmatrelvir-ritonavir medication order at high-risk. Age of study population: - Treated: 0–17 y: 0.3%; 18–29 y: 4.3%; 30–39 y: 7.9%; 40–49 y: 13.5%; 50–59 y: 18.3%; 60–69 y: 20.2%; 70–79 y: 19.1%; 80–89 y:	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (COVID-19)</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days: 261/1678 vs. 199/1678; adjusted RR=0.75 (95%CI: 0.63 to 0.88) *Adjusted for confounding by propensity score matching, confounding variables used to create propensity score were included in the final regression model and comprised age, sex, region of residence, number of vaccine dose, time since last*

Funding: An in-kind contribution from the Institut National d'Excellence en Santé et en Services Sociaux (INESSS). No direct source of funding was received.	12.6%; 90 y and older: 3.8% - Untreated: 0–17 y: 0.3%; 18–29 y: 4.0%; 30–39 y: 7.7%; 40–49 y: 13.0%; 50–59 y: 18.4%; 60–69 y: 20.1%; 70–79 y: 19.6%; 80–89 y: 13.0%; 90 y and older: 4.0% Definition of subgroups: - ≥70 years Setting: Outpatient			*vaccine dose, COVID-19 wave, number of health conditions, respiratory and cardiovascular condition, immunosuppression condition, and cancer conditions.*
Kim 2023 Study design: Retrospective cohort study Total no. participants: 1936925 Country: Korea Funding: NR	Patients with confirmed COVID-19, ≥12y. Age of study population: - Untreated: ≤ 39: 3.4%; 40–49: 7.0%; 50–59: 15.9%; 60–69: 42.0%; 70–79: 21.4%; ≥ 80: 10.4% - Treated: ≤ 39: 1.5%; 40–49: 2.3%; 50–59: 6.5%; 60–69: 41.3%; 70–79: 28.9%; ≥ 80: 19.4% Definition of subgroups: - ≥70 years - ≥80 years Setting: Nationwide	Drug name: nirmatrelvir/ritonavir Dosage: 2dd [not further specified] Duration: 5 days	Usual care	<u>Severe illness (composite outcome including death)</u> Severe/critical illness (including death) within 28 days for nirmatrelvir/ritonavir vs. usual care, - age≥70: adjusted OR=0.537 (95%CI: 0.502 to 0.574) - age≥80: adjusted OR=0.551 (95%CI: 0.510-0.595) <u>Mortality (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, within 28 days: - age≥70: adjusted OR=0.677 (95%CI: 0.620-0.739) - age≥80: adjusted OR=0.692 (95%CI: 0.627-0.764) *Adjusted for age, sex, severe respiratory syndrome coronovirus 2 immunity (vaccination) and underlying diseases.*
Liu 2024 Study design: Retrospective cohort study Total no. participants: 21694 Country: 19 countries [not further specified]	Patients with COVID-19 and preexisting cardiovascular diseases, ≥18y. Age of study population, mean (SD): 66.1 (14.1) Definition of subgroups: - ≥65 years	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (all-cause) and/or mortality (all-cause), composite outcome</u> 30-day all-cause hospitalization or death for nirmatrelvir/ritonavir vs. usual care: adjusted HR=0.392 (0.325 to 0.473) <u>Hospitalization (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, follow-up 30 days: adjusted HR=0.449 (95%CI: 0.370 to 0.544)

Funding: None	Setting: Outpatient			Mortality (all-cause) Nirmatrelvir/ritonavir vs. usual care, follow-up 30 days: adjusted HR=0.088 (95%CI: 0.038 to 0.202) *Adjusted for confounding by performance of propensity score matching: age, sex, ethnicity, underlying comorbidities (obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, neoplasm, mood disorders, chronic liver diseases, dementia, and other immunosuppressive disorders).*
Lui 2023 Study design: Retrospective cohort study Total no. participants: 1536 Country: China Funding: Health and Medical Research Fund (COVID190210) of the Health Bureau of HKSAR	Patients with type 2 diabetes and confirmed COVID infection. Age of study population, mean (SD): 71.9 (11.6) Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: 2dd 300/100 mg Duration: 5 days	Usual care	Hospitalization (all-cause) and/or mortality (all-cause), composite outcome All cause mortality and/or hospitalization for nirmatrelvir/ritonavir vs. usual care, time point not reported: 329/568 vs. 400/568; adjusted HR=0.76 (95%CI: 0.67 to 0.86) *Adjusted for confounding by performance of propensity score matching: age, sex, date of SARS-CoV-2 infection, COVID-19 vaccination status, pre-existing comorbidities.*
Ma 2023 Study design: Retrospective cohort study Total no. participants: 930 Country: China Funding: Health and Medical Research Fund, Food and Health Bureau Commissioned Research on COVID-19	Nursing home patients who received care for COVID-19 from community geriatric assessment teams. Age of study population, mean (SD): 82.8 (10.4) Definition of subgroups: NA Setting: Community geriatric assessment teams	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	Severe illness (composite outcome including death) Inpatient disease progression: ICU admission, use of invasive mechanical ventilation (IMV) and/or death (composite outcome) for nirmatrelvir/ritonavir vs. usual care, follow-up 30 days: adjusted HR=0.17 (95%CI: 0.06 to 0.44) Hospitalization (COVID-19) Nirmatrelvir/ritonavir vs. usual care, follow-up 30 days: adjusted HR=0.46 (95%CI: 0.32 to 0.65) *Adjusted for confounding by performance of propensity score matching: age, sex, baseline date, cardiovascular disease, digestive disease, diabetes, malignant tumor, nervous system disease, respiratory disease, kidney disease, hemoglobin, white blood cell, platelets, creatinine, alanine*

				aminotransferase, albumin, total bilirubin, number of hospitalizations in the past years.
Paraskevis 2023 Study design: Retrospective cohort study Total no. participants: 27772 Country: Greece Funding: National Public Health Organization	Patients with confirmed COVID, ≥65y. Age of study population: - Treated: 65-69: 20.0%; 70-74: 21.3%; 75-79: 21.1%; ≥80: 37.5% - Untreated: 65-69: 20.0%; 70-74: 21.3%; 75-79: 21.1%; ≥80 37.5% Definition of subgroups: NA Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: 2dd 300/100 mg Duration: 5 days	Usual care	<u>Hospital admission, ICU admission, clinical deterioration, or death from COVID-19, composite outcome</u> Nirmatrelvir/ritonavir vs. usual care, within 35 days: 399/13681 vs. 1133/13681; RR=0.35 (95%CI: 0.31 to 0.39) <u>Hospitalization (COVID-19)</u> Nirmatrelvir/ritonavir vs. usual care, within 35 days: 297/13681 vs. 857/13681; adjusted OR=0.31 (95%CI: 0.27 to 0.36) *Adjusted for age, previous SARS-CoV-2 infection, vaccination status, time elapsed since most recent vaccination.* <u>Mortality (COVID-19)</u> Nirmatrelvir/ritonavir vs. usual care, within 35 days: 88/13681 vs. 259/13681; RR=0.34 (95%CI: 0.27 to 0.43) <u>Severe illness</u> ICU admission or clinical deterioration for nirmatrelvir/ritonavir vs. usual care, within 35 days: 14/13681 vs. 17/13681; RR=0.82 (95%CI: 0.41 to 1.67) <u>Adverse events</u> Adverse drug reactions in nirmatrelvir/ritonavir group: - Gastrointestinal effects: 143/3459 (4%) - Allergy: 3/3459 (0.09%) - Headache: 11/3459 (0.3%) - Other: 28/3459 (0.8%)
Park 2022 Study design: Retrospective cohort study	Residents and workers from long-term care facilities. Age of study population:	Drug name: nirmatrelvir/ritonavir Dosage: NR	Usual care	<u>Severe illness (composite outcome including death)</u> Critical, life threatening illenes and death (follow-up not reported) for nirmatrelvir/ritonavir vs. usual care: 23/623 vs. 14/196; adjusted RR=0.49 (95%CI: 0.24 to 0.98).

Total no. participants: 914 Country: South Korea Funding: None	- Treated: <60: 6.1%; 60-74: 21.0%; => 75: 72.9% - Non-treatment: <60 9.2%; 60-74: 16.8%; => 75 74.0% Definition of subgroups: - Residents of long-term care facilities Setting: Long-term care facilities	Duration: NR		<u>Mortality (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, follow-up not reported: 22/623 vs. 11/196; adjusted RR=0.62 (95%CI: 0.29 to 1.32). *Adjusted for sex, age and vaccination status.*
Petrakis 2023 Study design: Retrospective cohort study Total no. participants: 400 Country: Greece Funding: None	Adults with confirmed COVID infection at high risk of progression to severe disease. Age of study population, mean (SD): 76.1 (13.6) Definition of subgroups: NA Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: 2dd 300/100 mg Duration: 5 days	Usual care	<u>Hospitalization (all-cause), intubation, or death (all-cause), composite outcome</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted OR=0.34 (95%CI: 0.29 to 0.55) <u>Hospitalization (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days, 3/200 vs. 111/200; RR=0.03 (95%CI: 0.01 to 0.08) Median *duration of hospitalisation* (follow-up not reported) for intervention (n=200) vs. control (n=200): 3 (2 to 5) vs. 10 (5 to 42) <u>Mortality (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days: 0/200 vs. 9/200; RR=0.03 (95%CI: 0.05 to 0.90) <u>Severe illness</u> *Intubation* within 30 days Nirmatrelvir/ritonavir vs. usual care: 0/200 vs. 6/200; RR=0.07 (95%CI 0.00 to 1.33) *Respiratory failure* within 30 days Nirmatrelvir/ritonavir vs. usual care: 0/200 vs. 73/200; RR=0.01 (0.00 to 0.11) <u>Duration of illness</u> Median total time needed to recovery in days (follow-up not reported) for nirmatrelvir/ritonavir (n=200) vs. usual care (n=200): 5 (range 3 to 11) vs. 9 (range 5 to 18)

				Adverse events Adverse events in nirmatrelvir/ritonavir group: - -Adverse reaction above Grade 3: 0/200 (0%) - -Stomachache: 5/200 (3%) - -Nausea: 9/200 (5%) - -Vomiting: 5/200 (3%) - -Dysgeusia: 7/200 (4%) - -Any adverse reaction: 23/200 (12%) - -Discontinuation of treatment: 0/200 (0%) - -Serious adverse event: 0/200 (0%) *Match-paired with respect to age, gender, comorbidities.*
Qian 2023 Study design: Retrospective cohort study Total no. participants: 585 Country: US Funding: None	Patients with COVID and systemic autoimmune rheumatic diseases. Age of study population, mean (SD): 57.9 (15.6) Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	Hospitalization (all-cause) and/or mortality (all-cause), composite outcome 30-day hospitalization or death for nirmatrelvir/ritonavir vs. usual care: adjusted OR=0.11 (95%CI: 0.02 to 0.54) *Adjusted for age, Charlson Comorbidity Index, eGFR, race.*
Schwartz 2023 Study design: Population-based cohort study Total no. participants: 177545 Country: Canada Funding: Public Health Ontario	Patients with confirmed COVID-19, ≥18y. Age of study population, mean (SD): 53.5 (21.3) Definition of subgroups: - ≥70 years - Long-term care residents Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	Hospitalisation (COVID-19) and/or mortality (all-cause) 30-day COVID-19 related hospital addmission or all-cause death for nirmatrelvir/ritonavir vs. usual care, - age≥70: adjusted OR=0.55 (95%CI: 0.45 to 0.66) - longterm care residents: adjusted OR=0.84 (95%CI: 0.66 to 1.06) Mortality (all-cause) Nirmatrelvir/ritonavir vs. usual care, within 30 days: - age≥70: adjusted OR=0.48 (95%CI: 0.39 to 0.59) - long-term care residents: adjusted OR=0.75 (95%CI: 0.59 to 0.97)

				Inverse probability of treatment weighting including age, sex, number of doses of SARS-CoV-2 infection, time from last vaccine dose, individual comorbidities (including chronic respiratory disease, chronic heart disease, hypertension, diabetes, immune compromised, autoimmune disease, dementia, chronic kidney disease, advanced liver disease), long-term care residence, and high versus stand risk.
Shah 2022 Study design: Retrospective cohort study Total no. participants: 699848 Country: US Funding: NR	Patients with confirmed COVID-19, ≥18y. Age of study population: - Treated: 18-35: 10.3%; 36-49: 18.1%; 50-64: 33.7%; >=65: 37.9% - Untreated: 18-35: 22.7%; 36-49: 21.4%; 50-64: 29.4%; >=65: 26.5% Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (COVID-19)</u> Overnight COVID-19 hospitalization for nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted HR=0.54 (95%CI: 0.48 to 0.58) *Adjusted for age group, sex, race and ethnicity, social vulnerability index, number of underlying health conditions, US census bureau region of residence, previous COVID-19 infection, COVID-19 vaccination status.*
Tadmor 2023 Study design: Retrospective cohort study Total no. participants: 1025 Country: Israel Funding: NR	Patients with chronic lymphoid leukemia and cofirmed COVID. Age of study population, median (IQR): - Treated: 71 (65-77) - Untreated: 70 (61-77) Definition of subgroups: - ≥65 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalisation (COVID-19) and/or mortality (all-cause)</u> 35-day COVID-19-related hospitalization or all-cause mortality for nirmatrelvir/ritonavir vs. usual care: 9/211 vs. 64/471; OR=0.38 (95%CI: 0.22 to 0.64)
Wang 2024 Study design: Retrospective cohort study Total no. participants: 17606	Patients with COVID-19 and autoimmune rheumatic diseases, ≥18y. Age of study population, mean (SD): 54.4 (16.0)	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, follow-up 12 months: adjusted HR=0.54 (95%CI: 0.44 to 0.67) <u>Mortality (all-cause)</u>

Country: US Funding: National Natural Science Foundation of China, Natural Science Foundation of Zhejiang Province, China Postdoctoral Fund and Young Elite Scientists Sponsorship Program by CACM	Definition of subgroups: - ≥65 years Setting: Mixed, but largely ambulatory (95%)			Nirmatrelvir/ritonavir vs. usual care, follow-up 12 months: adjusted HR=0.12 (95%CI: 0.04 to 0.33) <u>Severe illness</u> *ICU admission* within 12 months for nirmatrelvir/ritonavir vs. usual care: 10/2231 vs. 28/2231; adjusted HR=0.33 (95%CI: 0.14 to 0.75) *Any cardiovascular outcome* within 12 months (cerebrovascular complication, arrhythmia, inflammatory heart disease, ischemic heart disease, other cardiac disorders, thrombotic disorders, major adverse cardiac events) for nirmatrelvir/ritonavir vs. usual care: 119/2231 vs. 212/2231; adjusted HR=0.69 (95%CI 0.55 to 0.86) *Adjusted for confounding by performance of propensity score matching: age, sex, race, body mass index, socioeconomic status, comorbidities, medications, medical utilization.*
Wee 2025 Study design: Retrospective population-based cohort Total no. participants: 188532 Country: Singapore Funding: None	Patients with confirmed COVID-19, ≥60y. Age of study population, mean (SD): 69.2 (7.6) Definition of subgroups: - 70-79 years - ≥80 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Severe illness</u> Any postacute diagnosis within 180 days (any major adverse cardiovascular/cerebrovascular event, any cardiovascular diagnosis, any neurological diagnosis, any respiratory diagnosis, any autoimmune diagnosis) for nirmatrelvir/ritonavir vs. usual care, - age≥70-79: 127/2941 vs. 1334/38023; adjusted HR=1.19 (95%CI: 0.98 to 1.43) - age≥80: 75/1202 vs. 759/12114; adjusted HR=0.99 (95%CI: 0.77 to 1.26) *Adjusted for age, sex, ethnicity, socioeconomic status (housing type), vaccination status, comorbidities.*
Weil 2024 Study design: Retrospective cohort study	Patients with confirmed COVID-19 and known risk factors associated with progression to severe COVID-19.	Drug name: nirmatrelvir/ritonavir Dosage: NR	Usual care	<u>Hospitalization (all-cause, COVID-19)</u> *All-cause admission* for nirmatrelvir/ritonavir vs. usual care, within 30 days: 62/2091 vs. 47/1044; adjusted OR=0.92 (95%CI: 0.70 to 1.20)

Total no. participants: 5114 Country: Israel Funding: Pfizer	Age of study population, median (IQR): - Treated: 68.9 (60.3-76.0) - Untreated: 70.1 (60.4-76.8) Definition of subgroups: - ≥65 years Setting: Outpatient	Duration: NR		*COVID-19 related admission* for nirmatrelvir/ritonavir vs. usual care, within 30 days: 19/2091 vs. 23/1044; adjusted OR=0.59 (95%CI: 0.38 to 0.92) Median *length of stay (COVID-19 related admission)* for intervention (n=33) vs. control (n=53): 5.0 (2.0 to 7.3) vs. 6.4 (2.6 to 14.4), SMD: 0.64* Median *length of stay (all-cause ICU admission)* for intervention (n=11) vs. control (n=17): 2.0 (1.1 to 6.8) vs. 5.3 (2.4 to 16.3), SMD: 1.00* Median *length of stay (All-cause hospitalization)* for intervention (n=108) vs. control (n=117): 3.0 (2.0 to 6.8) vs. 4.0 (2.0 to 7.0), SMD: 0.64* Median *length of stay (COVID-19 related in ICU)* for intervention (n=9) vs. control (n=11): 3.3 (1.0 to 7.6) vs. 12.4 (5.3 to 20.7), SMD: 1.9* <u>Mortality (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days: 19/2091 vs. 23/1044; adjusted HR=0.97 (95%CI: 0.51 to 1.84) <u>Severe illness</u> All cause ICU admission within 30 days for nirmatrelvir/ritonavir vs. usual care: 6/2091 vs. 6/1044; adjusted OR=0.62 (95%CI 0.28 to 1.31) *Inverse probability treatment weighing including baseline characteristics and the calendar week of the index date.* *unclear how authors calculated SMD based on medians.
Wu 2023	Patients with confirmed COVID-19 and obesity, ≥18y.	Drug name: nirmatrelvir/ritonavir	Usual care	<u>All-cause ED visits, hospitalization or death, composite outcome</u>

Study design: Retrospective cohort study Total no. participants: 61938 Country: 19 countries in North and South America, Asia-Pacific, Europe, the Middle East and Africa Funding: None	Age of study population, mean (SD): 56.5 (14.9) Definition of subgroups: - ≥65 years Setting: Outpatient	Dosage: NR Duration: NR		Nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted HR=0.878 (95%CI: 0.786 to 0.980) <u>Hospitalization (all-cause)</u> *Hospitalization* for nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted HR=0.953 (95%CI: 0.825 to 1.102) All-cause *ED visit* for nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted HR=0.834 (95%CI: 0.708 to 0.982) <u>Mortality (all-cause)</u> Nirmatrelvir/ritonavir vs. usual care, within 30 days: adjusted HR=0.076 (95%CI: 0.018 to 0.319) *Adjusted for confounding by performance of propensity score matching: age, sex, ethnicity, comorbidities (diabetes mellitus, hyperlipidaemia, neoplasms, chronic lower respiratory tract diseases, chronic kidney disease, heart failure), BMI, blood pressure.*
Xie 2023a Study design: Cohort study Total no. participants: 281793 Country: US Funding: US Department of Veterans Affairs	Patients with confirmed COVID-19 and at least 1 risk factor of progression to severe acute COVID-19 illness. Age of study population, mean (SD): 65.7 (13.4) Definition of subgroups: - >70 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Severe illness</u> Long-covid (post-COVID-19 condition), within 180 days for nirmatrelvir/ritonavir vs. usual care: adjusted RR=0.66 (95%CI: 0.63 to 0.70). *Adjusted for GFR, systolic and diastolic blood pressure, cancer, chronic lung disease, dementia, diabetes, hyperlipidemia, immune dysfunction, medication with interaction with nirmatrelvir-ritonavir.*
Xie 2023b Study design: Target trial emulation study Total no. participants: 256288 Country: US	Patients with confirmed COVID-19 and at least 1 risk factor of progression to severe COVID-19 disease. Age of study population, mean (SD): 61.6 (15.0)	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (all-cause) and/or mortality (all-cause), composite outcome</u> 30-day admission to hospital or death for nirmatrelvir/ritonavir vs. usual care: adjusted RR=0.61 (95%CI: 0.56 to 0.66) *Inverse probability weighting including age, self-reported race, area deprivation index, BMI, smoking*

Funding: US Department of Veterans Affairs	Definition of subgroups: - ≥65 years Setting: Outpatient			*status, eFGR, SBP, DBP, cancer, chronic lung disease, dementia, immune dysfunction, diabetes, hyperlipidemia, covid-19 vaccination status, influenza vaccination status, previous history of SARS-CoV-2 infection, use of steroids, use of healthcare facilities, calendar week of SARS-CoV-2 infection, hospital bed capacity, hospital bed occupancy, number of SARS-CoV-2 tests administered at the participants' healthcare facility in the week of SARS-CoV-2 infection.*
Yan 2024 Study design: Target trial emulation study Total no. participants: 101144 Country: US Funding: US Department of Veterans Affairs Cooperative Studies Program	Adult veterans from the Veterans Health Administration with confirmed COVID-19, at high risk for progression to severe COVID-19. Age of study population, median (IQR): 66 (55-74) Definition of subgroups: - 65-74 years - ≥75 years Setting: Outpatient	Drug name: nirmatrelvir/ritonavir Dosage: NR Duration: NR	Usual care	<u>Hospitalization (all-cause) and/or mortality (all-cause), composite outcome</u> 30-day any hospitalization or all cause mortality for nirmatrelvir/ritonavir vs. usual care, - age 65-74: 151/7329 vs. 223/7336; adjusted RR=0.68 (95%CI: 0.55 to 0.83) - age≥75: 189/5732 vs. 256/5740; adjusted RR=0.74 (95%CI: 0.61 to 0.89) *Exact matching based on age, COVID-19 vaccination status, Charlson comorbidity index, calendar time (centered within 1.5 months of the test-positive date of the matched comparator); afterwards within exact matching stratum propensity score matching including 25 factors (demographic, geographic, healthcare utilization, clinical factors).*

dd: daily dose; HR: hazard ratio; ICU: intensive care unit; IQR: interquartile range; mg: milligramme; NR: not reported; OR: odds ratio; RD: risk difference; RR: relative risk; SD: standard deviation; US: United States

Bijlage 4. Kwaliteitsbeoordeling van ingesloten studies

4A: Kwaliteitsbeoordeling van gerandomiseerde studies t.a.v. oseltamivir versus placebo of standaardzorg bij ouderen met influenza (RoB2)

Author, year	1. Risk of bias arising from the randomization process	2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	3. Missing outcome data	4. Risk of bias in measurement of the outcome	5. Risk of bias in selection of the reported result	Overall risk of bias
Butler 2020	Low	Some concerns	Low	High	Low	High
Ison 2020	Low	Low	Some concerns	Low	Low	Some concerns
Martin 2001	Some concerns	Low	High	High	Some concerns	High
WV15707	Low	Some concerns	High	Some concerns	Some concerns	High
WV15819, WV15876 and WV15989	Low	Low	High	Some concerns	Some concerns	High

4B: Kwaliteitsbeoordeling van gerandomiseerde studie t.a.v. apixaban versus placebo bij ouderen met COVID-19 (RoB2)

Author, year	1. Risk of bias arising from the randomization process	2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	3. Missing outcome data	4. Risk of bias in measurement of the outcome	5. Risk of bias in selection of the reported result	Overall risk of bias
Silva 2024	Some concerns	Low	Low	Low	Low	Some concerns

4C: Kwaliteitsbeoordeling van observationele studies t.a.v. nirmatrelvir-ritonavir versus standaardzorg bij ouderen met COVID-19 (ROBINS-I)

Author, year	1. Bias due to confounding	2. Bias of classification of interventions	3. Bias in selection of participants into the study	4. Bias due to deviations from intended interventions (effect of assignment to intervention)	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall risk of bias
Aggerwal 2023	Low	Serious	Moderate	Low	Low	Low	Low	Serious
Al-Obaidi 2023	Low	Serious	Low	Low	Low	Low	Moderate	Serious
Arbel 2022	Moderate	Serious	Moderate	Low	Low	Low	Moderate	Serious
Dormuth 2023	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Dryden-Peterson 2023	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Kabore 2023	Low	Serious	Low	Low	Low	Low	Moderate	Serious
Kim 2023	Serious	Serious	Serious	Low	Low	Low	Moderate	Serious
Liu 2024	Serious	Serious	Low	Low	Low	Low	Moderate	Serious
Lui 2023	Moderate	Serious	Moderate	Low	Low	Low	Moderate	Serious
Ma 2023	Serious	Serious	Moderate	Low	Low	Low	Moderate	Serious
Paraskevis 2023	Serious	Serious	Moderate	Low	Low	Low	Critical	Critical
Park 2022	Serious	Serious	Moderate	Low	Low	Low	Moderate	Serious
Petrakis 2023	Moderate	Serious	Low	Low	Low	Low	Serious	Serious
Qian 2023	Moderate	Serious	Low	Low	Low	Low	Moderate	Serious
Schwartz 2023	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Shah 2022	Moderate	Critical	Serious	Low	Low	Low	Moderate	Critical
Tadmor 2023	Moderate	Serious	Serious	Low	Low	Low	Moderate	Serious
Wang 2024	Serious	Serious	Serious	Low	Low	Low	Moderate	Serious
Wee 2025	Moderate	Low	Low	Low	Serious	Low	Moderate	Serious
Weil 2024	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Wu 2023	Serious	Serious	Serious	Low	Low	Low	Moderate	Serious
Xie 2023a	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Xie 2023b	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Yan 2024	Low	Low	Low	Low	Low	Low	Moderate	Moderate

Bijlage 5 GRADE Evidenceprofielen

5A: Evidenceprofiel voor oseltamivir versus placebo of standaardzorg bij ouderen met influenza

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Duration of illness									
5[1,2,3,4]	randomised trials	very serious[a]	not serious[b]	not serious	serious[c]	none	1 RCT (n=208) evaluated ***patient-reported time to recovery in days*** and found a positive effect of oseltamivir compared to usual care: HR=1.26 (95%CI 1.02 to 1.56). 4 RCTs evaluated ***time to improvement of symptoms in hours*** for oseltamivir vs. placebo, showing a trend towards a shorter duration of illness for oseltamivir, however of no or unclear statistical significance. In addition, for a high-risk subgroup in one of the RCTs the time to improvement was longer for the oseltamivir group compared to placebo. • 1 RCT found a shorter median *time to improvement of influenza symptoms* for oseltamivir (n=33) vs. placebo (n=41) in a population without risk factors (54 (95%CI 31.7 to 89.8) vs. 113.2 (95%CI 72.3 to 137.7) hours) and a longer time to improvement in a population with risk factors, (oseltamivir [n=70] vs. placebo [n=61]: 91.2 (95%CI 55.1 to 123.2) vs. 78.4 (95%CI 54.9 to 92.8) hours). • 1 RCT (oseltamivir n=222, placebo n=254) reported a shorter median *duration of fever* (66.9 vs. 89.5 hours; p=?), and a shorter median *time to alleviation of acute febrile illness,* defined as fever/chills/myalgia (36 vs. 50.5 hours; p=0.005) and as fever/cough/coryza (115 vs. 132.3 hours; p=?). • 2 RCTs reported mean *duration of symptoms* for oseltamivir (n=229) vs. placebo (n=260); pooled MD=-16.43 (95% CI -41.93 to 9.08).	⊕◯◯◯ Very low[a,b,c]	

Adverse events

1[5]	randomised trials	very serious[d]	not serious	not serious	serious[e]	none	Intervention vs. control: • Nausea: 21/362 vs. 27/373; RR=0.80 (95%CI 0.46 to1.39) • Vomiting: 17/362 vs. 11/373; RR=1.59 (95%CI 0.76 to 3.35) • Diarrhoea: 9/362 vs. 19/373; RR=0.49 (95%CI 0.22 to 1.06) • Discontinuation:9/362 vs. 11/373; RR=0.84 (95%CI 0.35 to 2.01)	⊕◯◯◯ Very low[d,e]	

Severe/long-term disease

1[4]	randomised trials	very serious[d]	not serious	not serious	serious[f]	none	Risk differences for various severe/long-term diseases between oseltamivir vs. placebo were: • Pneumonia: RD=−0.1 (95%CI−2.8 to 2.6) • Complications requiring an antibiotic: RD=−4.8 (95%CI −11.7 to 2.0) • Complications requiring an antibiotic, excluding acute bronchitis: RD= 0.9 (95%CI −2.6 to 4.5)	⊕◯◯◯ Very low[d,f]	

Hospitalisation - not measured

-	-	-	-	-	-	-		-	

Mortality - not measured

-	-	-	-	-	-	-		-	

Virus shedding - not measured

-	-	-	-	-	-	-		-	

CI: confidence interval; HR: hazard ratio; MD: mean difference; RCT: randomized controlled trial; RD: risk difference; RR: relative risk

Explanations

a. 4 RCTs at high risk of bias; 1 RCT some concerns.
b. 1 RCT showed significant effect, other RCTs showed no effect, however with uncertainty or unclear uncertainty around effect estimate. Probably, the (broad) CI's would all overlap. No downgrading.
c. n=1378 analyzed; 1 RCT showed significant effect, other RCTs showed no effect, however with uncertainty or unclear uncertainty around effect estimate.
d. 1 RCT at high risk of bias due to lack of information regarding the randomisation, blinding, missing outcome data and reporting.

e. n=735 analyzed, however, wide CI's including no effect.
f. n=477 analyzed, wide CI's including no effect.

References

1. Butler 2020.
2. Ison 2020.
3. WV15707
4. W15819, WV15876 and WV15989
5. Martin 2001

5B: Evidenceprofiel voor apixaban versus placebo bij ouderen met COVID-19

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Duration of illness - not measured									
-	-	-	-	-	-	-		-	
Adverse events - not measured									
-	-	-	-	-	-	-		-	
Severe/long-term disease - not measured									
-	-	-	-	-	-	-		-	
Hospitalisation - not measured									
-	-	-	-	-	-	-		-	
Mortality - not measured									
-	-	-	-	-	-	-		-	
Virus shedding - not measured									
-	-	-	-	-	-	-		-	
Composite outcome - Days alive and out of hospital or emergency department									
1[1]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Apixaban vs. placebo at 30 days follow-up: 29.9 (sd 0.4) vs. 29.9 (sd 0.3); MD=0 (95% CI: -0.3 to 0.3)	⨁⨁◯◯ Low[a,b]	

CI: confidence interval; MD: mean difference

Explanations

a. Single study with some concerns due to little information about randomization.
b. Single study, n=411 participants.

References

1. Silva 2024

5C: Evidenceprofiel voor nirmatrelvir-ritonavir versus standaardzorg bij ouderen met COVID-19

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Duration of illness									
1[1]	non-randomised studies	very serious[a]	not serious	not serious	serious[b]	none	Median total time needed to recovery in days for nirmatrelvir/ritonavir (n=200) vs. usual care (n=200): 5 (range 3 to 11) vs. 9 (range 5 to 18).	⊕◯◯◯ Very low[a,b]	
Adverse events									
2[1,2,c]	non-randomised studies						Adverse events or drug reactions only for the intervention group, (nirmatrelvir/ritonavir), not comparing it to the control groupOne study found • Gastrointestinal effects: 143/3459 (4%) • Allergy: 3/3459 (0.09%) • Headache: 11/3459 (0.3%) • Other: 28/3459 (0.8%) The other study found: • Adverse reaction above Grade 3: 0/200 (0%) • Stomachache: 5/200 (3%) • Nausea: 9/200 (5%) • Vomiting: 5/200 (3%) • Dysgeusia: 7/200 (4%) • Any adverse reaction: 23/200 (12%) • Discontinuation of treatment: 0/200 (0%) • Serious adverse event: 0/200 (0%)	-	

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Severe or longterm disease - Intubation (follow-up: 30 days)									
1[1]	non-randomised studies	very serious[a]	not serious	not serious	serious[d]	none	Nirmatrelvir/ritonavir vs. usual care: 0/200 vs. 6/200; RR=0.07 (95%CI 0.00 to 1.33)	⊕◯◯◯ Very low[a,d]	
Severe or longterm disease - Respiratory failure (follow-up: 30 days)									
1[1]	non-randomised studies	very serious[a]	not serious	not serious	not serious	strong association	Nirmatrelvir/ritonavir vs. usual care: 0/200 vs. 73/200; RR=0.01 (0.00 to 0.11)	⊕⊕⊕◯ Moderate[a]	
Severe or longterm disease - ICU admission									
2[3,4]	non-randomised studies	very serious[e]	not serious	not serious	serious[f]	none	Results of the two studies for nirmatrelvir/ritonavir vs. usual care: • n=4462; follow-up 12 months; adjusted HR=0.33 (95%CI: 0.14 to 0.75) • n=3135; follow-up 30 days; adjusted OR=0.62 (95%CI: 0.28 to 1.31)	⊕◯◯◯ Very low[e,f]	
Severe or longterm disease - ICU admission or clinical deterioration (composite outcome) (follow-up: 35 days)									
1[2]	non-randomised studies	extremely serious[g]	not serious	not serious	serious[h]	none	Nirmatrelvir/ritonavir vs. usual care: 14/13681 vs. 17/13681; RR=0.82 (95%CI: 0.41 to 1.67)	⊕◯◯◯ Very low[g,h]	
Severe or longterm disease - Inpatient disease progression (ICU admission, use of invasive mechanical ventilation and/or death; composite outcome) (follow-up: 30 days)									
1[5]	non-randomised studies	very serious[a]	not serious	not serious	not serious	strong association	Nirmatrelvir/ritonavir vs. usual care in older nursing home patients: adjusted HR=0.17 (95%CI: 0.06 to 0.44)	⊕⊕⊕◯ Moderate[a]	
Severe or longterm disease - Severe cases defined as critical, life-threatening illness and/or mortality (composite outcome)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[6,7]	non-randomised studies	very serious[i]	not serious	not serious	not serious	none	Results for one study with subgroups age≥70 and age≥80 (number of participants not provided) and other study (n=819) in long term care setting for nirmatrelvir/ritonavir vs. usual care: • subgroup age≥70: adjusted OR=0.537 (95%CI: 0.502 to 0.574) • subgroup age≥80: adjusted OR=0.551 (95%CI: 0.510-0.595) • long term care population: adjusted RR=0.49 (95%CI: 0.24 to 0.98)	⨁⨁◯◯ Low[i]	
Severe or longterm disease - Any postacute diagnosis (any major adverse cardiovascular/cerebrovascular event, any cardiovascular diagnosis, any neurological diagnosis, any respiratory diagnosis, any autoimmune diagnosis) (follow-up: 180 days)									
1[8]	non-randomised studies	very serious[a]	not serious	not serious	serious[j]	none	Nirmatrelvir/ritonavir vs. usual care: • age≥70-79: 127/2941 vs. 1334/38023; adjusted HR=1.19 (95%CI: 0.98 to 1.43) • age≥80: 75/1202 vs. 759/12114; adjusted HR=0.99 (95%CI: 0.77 to 1.26)	⨁◯◯◯ Very low[a,j]	
Severe or longterm disease - Any cardiovascular outcome within 12 months (cerebrovascular complication, arrhythmia, inflammatory heart disease, ischemic heart disease, other cardiac disorders, thrombotic disorders, major adverse cardiac events) (follow-up: 12 months)									
1[3]	non-randomised studies	very serious[a]	not serious	not serious	not serious	none	Nirmatrelvir/ritonavir vs. usual care: 119/2231 vs. 212/2231; adjusted HR=0.69 (95%CI 0.55 to 0.86)	⨁⨁◯◯ Low[a]	
Severe or longterm disease - Long-covid (post-COVID-19 condition) (follow-up: 180 days)									
1[9]	non-randomised studies	serious[k]	not serious	not serious	not serious	none	Nirmatrelvir/ritonavir vs. usual care: adjusted RR=0.66 (95%CI: 0.63 to 0.70).	⨁⨁⨁◯ Moderate[k]	
Hospitalization - all cause (follow-up 28-30 days to 12 months)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
6[2,3,4,10,11,12]	non-randomised studies	very serious[l]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in six studies: • n=4253; follow-up 28 days; adjusted OR=0.37 (95%CI: 0.23 to 0.57) • n=unclear; follow-up 30 days; adjusted HR=0.449 (95%CI: 0.370 to 0.544) • n=400; follow-up 30 days; RR=0.03 (95%CI: 0.01 to 0.08) • n=44672; follow-up 12 months adjusted HR=0.54 (95%CI: 0.44 to 0.67) • n=3135; follow-up 30 days; adjusted OR=0.92 (95%CI: 0.70 to 1.20) • n=unclear; follow-up 30 days; adjusted HR=0.953 (95%CI: 0.825 to 1.102)	⨁⨁◯◯ Low[l]	

Hospitalization - COVID-19 related (follow-up: range 30 days to 35 days)

6[2,4,5,13,14,15]	non-randomised studies	very serious[m]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in six studies: • n=42821; follow-up 35 days; adjusted HR=0.27 (95%CI: 0.15 to 0.49) • n=3356; follow-up 30 days; adjusted RR=0.75 (95%CI: 0.63 to 0.88) • n=930; follow-up unclear; adjusted HR=0.46 (95%CI: 0.32 to 0.65) • n=27362; follow-up 35 days; adjusted OR=0.31 (95%CI: 0.27 to 0.36) • n=205214; follow-up 30 days; adjusted HR=0.54 (95%CI: 0.48 to 0.58) • n=3135; follow-up 30 days; adjusted OR=0.59 (95%CI: 0.38 to 0.92)	⨁⨁◯◯ Low[m]	

Hospitalization - all-cause emergency department visits (follow-up: 30 days)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1[12]	non-randomised studies	very serious[a]	not serious	not serious	serious[n]	none	Nirmatrelvir/ritonavir vs. usual care: adjusted HR=0.834 (95%CI: 0.708 to 0.982)	⨁◯◯◯ Very low[a,n]	

Hospitalization - duration of hospitalization

2[1,4]	non-randomised studies	very serious[o]	not serious	not serious	serious[p]	none	Results for nirmatrelvir/ritonavir vs. usual care reported by the two studies (5 analyses): • Median (IQR) duration of hospitalisation (follow-up not reported) for intervention (n=200) vs. control (n=200): 3 (2 to 5) vs. 10 (5 to 42) days • Median (IQR) length of stay (COVID-19 related admission) for intervention (n=33) vs. control (n=53): 5.0 (2.0 to 7.3) vs. 6.4 (2.6 to 14.4), SMD: 0.64 • Median (IQR) length of stay (COVID-19 related) in ICU for intervention (n=9) vs. control (n=11): 3.3 (1.0 to 7.6) vs. 12.4 (5.3 to 20.7), SMD: 1.9 • Median (IQR) length of stay (All-cause hospitalization) for intervention (n=108) vs. control (n=117): 3.0 (2.0 to 6.8) vs. 4.0 (2.0 to 7.0), SMD: 0.64 • Median (IQR) length of stay (all-cause) in ICU for intervention (n=11) vs. control (n=17): 2.0 (1.1 to 6.8) vs. 5.3 (2.4 to 16.3), SMD: 1.00 NB: unclear how study authors calculated SMD's based on medians.	⨁◯◯◯ Very low[o,p]	

Mortality - all-cause (follow-up: 28-30 days to 12 months)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
8[1,3,4,6,7,11,12,16]	non-randomised studies	very serious[q]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in 8 studies (10 analyses): • n=684912; follow-up 28 days; subgroup age≥70: adjusted OR=0.677 (95%CI: 0.620-0.739) • n=239102; follow-up 28 days; subgroup age≥80: adjusted OR=0.692 (95%CI: 0.627-0.764) • n=unclear; follow-up 30 days; adjusted HR=0.088 (95%CI: 0.038 to 0.202) • n=819; follow-up unclear; adjusted RR=0.62 (95%CI: 0.29 to 1.32). • n=400; follow-up 30 days; RR=0.03 (95%CI: 0.05 to 0.90) • n=unclear; follow-up 30 days; subgroup age≥70: adjusted OR=0.48 (95%CI: 0.39 to 0.59) • n=unclear; follow-up 30 days; subgroup longterm care residents: adjusted OR=0.75 (95%CI: 0.59 to 0.97) • n=4462; follow-up 12 months; adjusted HR=0.12 (95%CI: 0.04 to 0.33) • n=unclear; follow-up 30 days; adjusted HR=0.97 (95%CI: 0.51 to 1.84) • n=unclear; follow-up 30 days; adjusted HR=0.076 (95%CI: 0.018 to 0.319)	⨁⨁◯◯ Low[q]	

Mortality - COVID-19 related (follow-up: 35 days)

2[2,13]	non-randomised studies	extremely serious[r]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in two studies: • n=42821; adjusted HR=0.21 (95%CI: 0.05 to 0.82) • n=27362; RR=0.34 (95%CI: 0.27 to 0.43)	⨁◯◯◯ Very low[r]	

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Composite outcome - all cause hospitalisation and/or all-cause mortality									
7[11,17,18,19,20,21,22]	non-randomised studies	very serious[s]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in 7 studies: • 30-day all cause hospitalization and/or mortality: 26/2000 vs. 63/1969; RR=0.41 (95%CI: 0.26 to 0.64) • Hospitalization within 14 days or death within 28 days: 55/6656 vs. 194/13079; RR=0.55 (95%CI: 0.40 to 0.77) • 30-day all-cause hospitalization or death: adjusted HR=0.392 (0.325 to 0.473) • All cause mortality and/or hospitalization: 329/568 vs. 400/568; adjusted HR=0.76 (95%CI: 0.67 to 0.86) • 30-day hospitalization or death: adjusted OR=0.11 (95%CI: 0.02 to 0.54) • 30-day admission to hospital or death: adjusted RR=0.61 (95%CI: 0.56 to 0.66) • 30-day any hospitalization or all cause mortality in subgroup age 65-74: 151/7329 vs. 223/7336; adjusted RR=0.68 (95%CI: 0.55 to 0.83) and in subgroup age≥75: 189/5732 vs. 256/5740; adjusted RR=0.74 (95%CI: 0.61 to 0.89)	⊕⊕◯◯ Low[s]	
Composite outcome – COVID-19 related hospitalisation and/or all-cause mortality (follow-up: range 28 days to 35 days)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
3[16,23,24]	non-randomised studies	very serious[t]	not serious	not serious	not serious	none	Results for nirmatrelvir/ritonavir vs. usual care in 3 studies: • 28-day COVID-19 related emergency hospital visit or admission, or all-cause death: 20/510 vs. 35/498; RD=-3.1 (95%CI: -5.9 to -0.3) • 30-day COVID-19 related hospital addmission or all-cause death in subgroup age≥70: adjusted OR=0.55 (95%CI: 0.45 to 0.66), and in subgroup longterm care residents: adjusted OR=0.84 (95%CI: 0.66 to 1.06) • 35-day COVID-19-related hospitalization or all-cause mortality: 9/211 vs. 64/471; OR=0.38 (95%CI: 0.22 to 0.64)	⨁⨁◯◯ Low[t]	
Composite outcome - all cause ED visit, hospitalization, or death (follow-up: 30 days)									
1[12]	non-randomised studies	very serious[a]	not serious	not serious	serious[n]	none	Nirmatrelvir/ritonavir vs. usual care: adjusted HR=0.878 (95%CI: 0.786 to 0.980)	⨁◯◯◯ Very low[a,n]	
Composite outcome - hospitalization, intubation, or death (follow-up: 30 days)									
1[1]	non-randomised studies	very serious[a]	not serious	not serious	not serious	none	Nirmatrelvir/ritonavir vs. usual care: adjusted OR=0.34 (95%CI: 0.29 to 0.55)	⨁⨁◯◯ Low[a]	
Composite outcome - hospital admission, ICU admission, clinical deterioration, or death from COVID-19 (follow-up: 35 days)									
1[2]	non-randomised studies	extremely serious[g]	not serious	not serious	not serious	strong association	Nirmatrelvir/ritonavir vs. usual care: 399/13681 vs. 1133/13681; RR=0.35 (95%CI: 0.31 to 0.39)	⨁⨁◯◯ Low[g]	
Virusshedding - not measured									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
-	-	-	-	-	-	-		-	

CI: confidence interval; HR: hazard ratio; IQR: interquartile range; OR: Odds ratio; RR: relative risk; SMD: standardized mean difference

Explanations

a. Single study at serious risk of bias.
b. Single study, n=400 in analysis. No p-value reported, however, because of overlapping ranges no significant difference.
c. As the studies did not compare adverse events in the intervention group with adverse events in the control group, no certainty assessment was done.
d. single study; n=400; few events and relatively wide confidence interval.
e. Two studies: one at moderate risk of bias, the other at serious risk of bias.
f. n=7597 analyzed; relatively wide confidence intervals including neutral value ('no effect') in one of the studies.
g. Single study at critical risk of bias.
h. Large sample size; wide confidence interval including the neutral value.
i. Two studies, both at serious risk of bias.
j. Single study with large sample size; wide confidence interval including neutral value.
k. Single study at moderate risk of bias.
l. Six studies, of which five at serious risk of bias and one at moderate risk of bias.
m. Six studies, of which one at moderate risk of bias, three at serious risk of bias, and two at critical risk of bias.
n. Single study, unclear number analyzed, although confidence interval quite narrow.
o. One study at moderate risk of bias and one at serious risk of bias.
p. Reasonable sample size combined, however low sample sizes for each of the analyses from Weil 2024; medians provided, most confidence intervals of intervention and control overlap and confidence intervals for majority of the control groups is very wide. No confidence intervals provided for the SMDs.
q. Eight studies, of which two were at serious risk of bias and two at moderate risk of bias.
r. Two studies: one at serious risk of bias, the other at critical risk of bias.
s. Seven studies, of which three were at moderate risk of bias and four at serious risk of bias.
t. Three studies: one at moderate risk of bias, two at serious risk of bias.

References

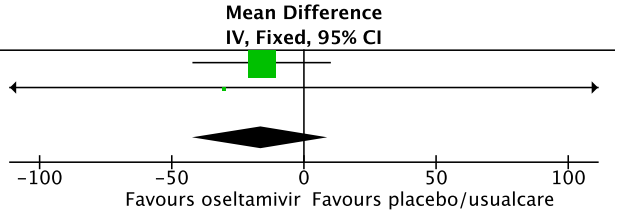
1. Petrakis 2023
2. Paraskevis 2023
3. Wang 2024
4. Weil 2024
5. Ma 2023

6. Kim 2023
7. Park 2022
8. Wee 2025
9. Xie 2023a
10. Aggerwal 2023
11. Liu 2024
12. Wu 2023
13. Arbel 2022
14. Kabore 2023
15. Shah 2022
16. Schwartz 2023
17. Al Obaidi 2023
18. Dryden-Peterson 2023
19. Lui 2023
20. Qian 2023
21. Xie 2023b
22. Yan 2024
23. Dormuth 2023
24. Tadmor 2023

Bijlage 6. Forest plot

Study or Subgroup	Oseltamivir Mean	SD	Total	Placebo or usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
W15819, WV15876, and WV15989	191	143	223	207	145	254	97.0%	−16.00 [−41.89, 9.89]
WV15707	79.6	63.2	6	110	174	6	3.0%	−30.40 [−178.53, 117.73]
Total (95% CI)			**229**			**260**	**100.0%**	**−16.43 [−41.93, 9.08]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)



6A Forest plot voor het effect van oseltamivir versus placebo of standaardzorg op het aantal uren tot verbetering van de symptomen bij ouderen met influenza