Agencja Oceny Technologii Medycznych i Taryfikacji

Wydział Świadczeń Opieki Zdrowotnej

Przegląd doniesień naukowych dla iwermektyny w leczeniu oraz profilaktyce COVID-19

Opracowanie analityczne AOTMiT

Wersja 1.2

data ukończenia 06.08.2021 r.

HISTORIA ZMIAN DOKUMENTU	
WERSJA 1.0 (04.02.2021)	–
WERSJA 1.1 (21.05.2021)	• Dokument został uzupełniony o następujące badania: Lopez-Medina 2021, Mohan 2021, Beltran-Gonzalez 2021, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021, Galan 2021; • Zaktualizowano informacje dot. badania Mahmud 2021 w związku z pojawieniem się publikacji pełnotekstowej, jak również zweryfikowano wyniki badania Okumus 2021, Chowdhury 2021 i Babalola 2021 w związku z pojawieniem się recenzowanych wersji publikacji.
WERSJA 1.2 (06.08.2021)	• Dokument został uzupełniony o następujące badania: Vallejos 2021, Abd-Elsalam 2021, Aref 2021, Biber 2021, Chachla 2021, Samaha 2021, Seet 2021, Shahbaznejad 2021; • Zweryfikowano wyniki badania Krolewiecki 2020, Ravikirti 2021, Niaee 2021 oraz Shoumann 2021, w związku z pojawieniem się recenzowanych wersji publikacji; • Odstąpiono od prezentacji wyników badania Elgazzar 2020 z powodu retrakcji publikacji.

KLUCZOWE INFORMACJE

- Iwermektyna (IVM) jest lekiem przeciwpasożytniczym. Stosowanie u ludzi ogranicza się w Polsce do chorób dermatologicznych, tj. trądzik różowaty – lek w postaci kremu (rejestracja URPL). IVM stosowana w formie doustnej nie posiada rejestracji centralnej EMA, ani krajowej URPLWMiPB. Lek jest dopuszczony do stosowania w niektórych państwach, m.in. Francji, Niemczech, Holandii, Szwecji, Austrii i Czechach.
- Kryteria włączenia do przeglądu spełniło łącznie 28 kontrolowanych prób klinicznych z randomizacją, z czego 25 dotyczyło stosowania iwermektyny w leczeniu COVID-19, a 3 dotyczyły stosowania iwermektyny w ramach profilaktyki COVID-19.
- Do większości badań kwalifikowano pacjentów z łagodnym i umiarkowanym przebiegiem choroby. Iwermektyna stosowana była w monoterapii lub w skojarzeniu z opieką standardową. W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycyliną +/- opieka standardowa. W 4 RCTs jako ramię kontrolne stosowano hydroksychlorochinę, w 1 chlorochinę, w 1 lopinawir w skojarzeniu z rytonawirem, a w 1 hydroksychlorochinę ± lopinawir/rytonawir.

  Leczenie:

  - W żadnym z badań, w których porównywano skuteczność iwermektyny (± doksycyklina) z placebo / opieką standardową nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności; wyniki prób klinicznych Vallejos 2021 oraz Lopez-Medina 2021 (największe liczebności grup (odpowiednio 250 vs 251 osób oraz 238 vs 238) również nie potwierdzają skuteczności iwermektyny w COVID-19 (pacjenci niewymagający hospitalizacji).
  - Wyniki metaanalizy AOTMiT(8 RCTs, N= 1 535 pacjentów), przeprowadzonej z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina, wskazują że stosowanie IVM +/- opieka standardowa w porównaniu do opieki standardowa +/- placebo nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu. Z uwagi na heterogeniczność włączonych badań, kumulacja wyników obarczona jest wysokim ryzykiem błędu.
  - W badaniu Lopez-Medina 2021 odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo.
  - U pacjentów stosujących iwermektynę w skojarzeniu z doksycykliną, w porównaniu do pacjentów stosujących placebo z opieką standardową, istotne statystycznie korzyści odnotowano w zakresie punktów końcowych dotyczących poprawy klinicznej i wyzdrowienia klinicznego, czasu utrzymywania się pozytywnego wyniku testu RT-PCR w 14. dniu (Mahmud 202), jak również czasu do wyzdrowienia (Hashim 2020).
  - W badaniach Ahmed 2020 i Krolewiecki 2021 odnotowano istotne statystycznie różnice na korzyść IVM względem placebo / opieki standardowej w zakresie czasu do eliminacji wirusa / szybkości zaniku wiremii.
  - Analizując wyniki badań należy wziąć pod uwagę ich ograniczenia, wynikające przede wszystkim z: niskiej liczebności prób; regionów geograficznych (m.in. Bangladesz, Egipt, Irak, Iran, Indie, Nigeria, Turcja, Argentyna), w których przeprowadzono badania; sposobu analizy wyników; różnic w charakterystykach wyjściowych pacjentów (nieskuteczność procesu randomizacji); doboru komparatorów, braku informacji o leczeniu stosowanym w ramach opieki standardowej lub publikacji typu *pre-print* (Hashim 2020, Beltran-Gonzalez 2021).
  - Zidentyfikowane, w ramach przeglądu aktualizacyjnego, badania pierwotne nie wpływają na wnioski z wcześniejszej wersji przeglądu.

  Profilaktyka:

- Wyniki badania Samaha 2021, wskazują na korzyść zdrowotną z profilaktycznego (jednorazowe podanie) zastosowania IVM u osób bezobjawowych zakażonych SARS-CoV-2 – znamienne statystycznie różnice na korzyść IVM względem witaminy C i cynku w zakresie wystąpienia objawów infekcji tj. gorączka, anosmia, bóle mięśniowe i utrata smaku. Autorzy badania zestawili jednak w publikacji wyłącznie dane krótkoterminowe (po 3 dniach od potwierdzenia infekcji). W związku z powyższym istnieje niepewność czy zaobserwowane różnice w skuteczności

utrzymają się w dłuższym okresie obserwacji czy IVM wyłącznie odsuwa w czasie wystąpienie objawów.

- W dwóch badaniach, w których iwermektyna była stosowana w ramach profilaktyki zakażeń SARS-CoV-2 u osób po kontakcie z zakażonym (Shouman 2020) i u zdrowych ochotników (Seet 2021), w grupie pacjentów otrzymujących IVM zaobserwowano znamiennie statystycznie niższy odsetek pacjentów, u których wystąpiły objawy choroby, w porównaniu do grup pacjentów nie otrzymujących żadnej formy profilaktyki (Shouman 2020) lub przyjmujących witaminę C (Seet 2021). Z uwagi na liczne ograniczenia metodyczne ww. badań do uzyskanych wyników należy jednak podchodzić z ostrożnością.
- Na chwilę obecną brak jest wiarygodnych dowodów naukowych potwierdzających skuteczność IVM w postaci doustnej w COVID-19.
- Aktualnie dla iwermektyny w leczeniu COVID-19 toczą się duże badania kliniczne z randomizacją (w Europie i Ameryce Północnej tj. COVIDOUT, IVER-303, PRINCIPLE, AKTIV-6), których wyniki mogą dostarczyć wiarygodnych danych umożliwiających ponowną analizę jej efektywności w COVID-19.

1. CEL

Celem opracowania jest ocena skuteczności i profilu bezpieczeństwa iwermektyny (IVM) stosowanej u pacjentów z COVID-19 oraz w profilaktyce COVID-19.

2. METODYKA

Przeprowadzono przegląd systematyczny baz informacji medycznej – PubMed, EMBASE (data ostatniego wyszukiwania 28.01.2021 r.). W celu odnalezienia doniesień jeszcze nieopublikowanych w ww. bazach, przeprowadzono również przegląd baz publikacji typu pre-print – www.medrxiv.org oraz ResearchSquare. W analizie wykorzystano również zasoby bazy COVID-19 (www.covid19.aotm.gov.pl). W aneksie dokumentu zamieszczono strategię wyszukiwania wykorzystywaną na rzecz przeglądu.

W ramach aktualizacji Przeglądu (wersja 1.1), przeprowadzono ponowne wyszukiwanie (data ostatniego wyszukiwania – 14.05.2021), włączając do analizy badania eksperymentalne z grupą kontrolną, oceniające efektywność kliniczną iwermektyny w leczeniu COVID-19, opublikowane po dacie wcześniejszego przeglądu doniesień – wersja 1.0.

W ramach aktualizacji Przeglądu (wersja 1.2), przeprowadzono ponowne wyszukiwanie (data ostatniego wyszukiwania – 03.08.2021), włączając do analizy badania eksperymentalne z grupą kontrolną, oceniające efektywność kliniczną iwermektyny w leczeniu i profilaktyce COVID-19.

Szczegółowe kryteria włączenia badań pierwotnych do przeglądu zestawiono w poniższej tabeli.

Tabela 1. Kryteria włączenia badań pierwotnych do przeglądu dla iwermektyny

	Kryteria włączenia i wykluczenia
Populacja	Pacjenci z COVID-19, pacjenci po kontakcie z zakażonym wirusem SARS-CoV-2
Interwencja	Iwermektyna
Komparator	Inne postępowanie terapeutyczne / zachowawcze / opieka standardowa
Punkt końcowy	Nie zdefiniowano – wszystkie zdefiniowane w protokołach punkty końcowe dla oceny skuteczności i profilu bezpieczeństwa
Rodzaj badań	Badania eksperymentalne z grupą kontrolną i randomizacją

We współpracy z Komitetem Sterującym, nadzorującym prace nad Zaleceniami w COVID-19, zaproponowano poziomy doniesień naukowych w celu określenia stopnia wiarygodności uzyskanych wyników (Tabela 3). Zastosowano również gradację wyniku badania klinicznego przy uwzględnieniu rodzaju analizowanego punktu końcowego (klinicznie istotny/zastępczy punkt końcowy) oraz wielkości efektu (wykazanie różnic istotnych statystycznie na korzyść ramienia badanego lub kontrolnego) – Tabela 2.

Tabela 2. Istotność wyniku badania pierwotnego

IS różnice na korzyść interwencji – istotny klinicznie punkt końcowy
IS różnice na korzyść interwencji – zastępczy punkt końcowy
Brak IS różnic pomiędzy ramionami badania
IS różnice na korzyść ramienia kontrolnego – zastępczy punkt końcowy
IS różnice na korzyść ramienia kontrolnego – istotny klinicznie punkt końcowy

Tabela 3. Poziomy dowodów naukowych[1]

Poziom	Opis
A	• Wyniki >1 poprawnie zaprojektowanych RCT, wysoka wiarygodność wyników (reprezentatywność próby, ITT, zaślepienie, właściwa metoda randomizacji), • Metaanaliza poprawnie zaprojektowanych RCTs, • Wyniki ≥1 RCT uzupełnione danymi z wysokiej jakości rejestrów;
B	• Poprawnie zaprojektowane RCT, wysoka wiarygodność wyników (reprezentatywność próby, ITT, zaślepienie, właściwa metoda randomizacji)
C	• RCT z nielicznymi (≤2) ograniczeniami metodycznymi (brak zaślepienia, mała liczebność próby, ograniczenia metody randomizacyjnej, zmodyfikowana analiza wyników (mITT))
D	• Poprawnie zaprojektowana kontrolowana próba kliniczna bez randomizacji, • Poprawnie zaprojektowanie prospektywne badanie kohortowe, • Poprawnie zaprojektowany rejestr, • Metaanaliza wyżej wymienionych badań pierwotnych.
E	• Randomizowane lub nierandomizowane próby kliniczne z licznymi (>2) ograniczeniami metodycznymi (brak zaślepienia, mała liczebność próby, niewłaściwa metoda randomizacyjna, brak ITT), • Badania obserwacyjne prospektywne z licznymi ograniczeniami metodycznymi, retrospektywne badania z grupą kontrolną
F	• Badania eksperymentalne bez grupy kontrolnej, badania obserwacyjne opisowe (serie przypadków)
G	• Opis przypadku

[1] Prezentacja przyjętych poziomów wiarygodności na podstawie podejścia ACC/AHA (2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, dostęp online: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000678

3. WYNIKI

Do przeglądu włączono 28 kontrolowanych prób klinicznych z randomizacją, z czego 3 dotyczyły zastosowania iwermektyny w ramach profilaktyki COVID-19.

W Tabela 4 zestawiono badania pierwotne odnalezione w ramach przeglądu. Opis metodyki i wyników badań przedstawiono w tabelach zamieszczonych w aneksie dokumentu.

W większości badań populację stanowili pacjenci z łagodnym i umiarkowanym przebiegiem choroby, jedynie do 6 badań kwalifikowano również osoby z cięższym przebiegiem COVID-19. Wielkość populacji w ramieniu interwencji tylko w 7 RCTs wynosiła ≥100 osób. Największa liczebność w próby w grupie interwencji w zakresie leczenia została uwzględniona w badaniu Vallejos 2021 (250 pacjentów), natomiast w ramach profilaktyki w badaniu Seet 2021 (617 pacjentów).

W większości odnalezionych badań w ramieniu interwencji IVM stosowana była w monoterapii lub w skojarzeniu z opieką standardową i porównywana względem placebo ± SoC (Ahmed 2020, Ravikirti 2021, Chachar 2020, Chaccour 2021, Podder 2020, Krolewiecki 2021, Okumus 2021, Lopez-Medina 2021, Mohan 2021, Beltran-Gonzalez, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021, Vallejos 2021, Abd-Elsalam 2021, Aref 2021, Chachla 2021, Biber 2021). W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycyliną +/- opieka standardowa (Ahmed 2020, Mahmud 2021, Hashim 2020, Chowdhury 2021). Postępowanie w ramach opieki standardowej było zróżnicowane i obejmowało m.in. antybiotykoterapię (Podder 2020, Hashim 2020, Ravikirti 2021, Okumus 2021, Abd-Elsalam 2021, Aref 2021, Shahbaznejad 2021), hydroksychlorochinę (Ravikirti 2021, Okumus 2021, Kishoria 2020, Aref 2021) czy glikokortykosteroidy (Ravikirti 2021, Hashim 2020, Mahmud 2021, Beltran-Gonzalez 2021, Abd-Elsalam 2021). W badaniach Krolewiecki 2021 i Pott-Junior 2021 nie określono szczegółów postępowania w zakresie SoC.

W 5 RCTs jako ramię kontrolne stosowano hydroksychlorochinę (Chowdhury 2021, Niaee 2021, Galan 2021, Beltran-Gonzalez 2021) oraz chlorochinę (Galan 2021), w 1 lopinawir w skojarzeniu z rytonawirem (Babalola 2021), a w 1 hydroksychlorochinę ± lopinawir/rytonawir (Shahbaznejad 2021).

Schemat dawkowania, jak również czas leczenia IVM, był zróżnicowany – w większości badań IVM stosowano doustnie, w jednorazowej dawce. Maksymalny czas terapii IVM wyniósł 5 dni. W 1 badaniu oceniano stosowanie iwermektyny w postaci aerozolu do nosa (Aref 2021).

Analizując wyniki RCTs należy uwzględnić liczne ograniczenia metodyczne badań, tj.

- niska liczebność prób (Ahmed 2020, Ravikirti 2021, Chachar 2020, Chaccour 2020, Podder 2020, Krolewiecki 2021, Okumus 2021, Hashim 2020, Chowdhury 2021, Babalola 2021, Mohan 2021, Beltran-Gonzalez 2021, Kishoria 2020, Shah Bukhari 2021, Pott-Junior 2021, Galan 2021, Abd-Elsalam 2021, Aref 2021, Shahbaznejad 2021, Biber 2021, Samaha 2021);
- wybór hydroksychlorochiny lub chlorochiny jako opcji stanowiącej ramię kontrolne w badaniach (Chowdhury 2021, Niaee 2021, Galan 2021, Beltran-Gonzalez 2021);
- brak zaślepienia (Chachar 2020, Podder 2020, Krolewiecki 2021, Chowdhury 2021, Okumus 2021, Kishoria 2020, Shah Bukhari 2021, Shouman 2020, Abd-Elsalam 2021, Aref 2021, Chachla 2021, Seet 2021) lub brak informacji o zaślepieniu (Hashim 2020, Samaha 2021);
- brak informacji o leczeniu stosowanym w ramach opieki standardowej, brak szczegółowych informacji o odsetkach pacjentów otrzymujących daną terapię (Mahmud 2021, Chowdhury 2021, Krolewiecki 2021, Chachar 2020, Pott-Junior 2021, Vallejos 2021, Aref 2021);
- różnice pomiędzy ramionami badania w wyjściowej charakterystyce pacjentów (Chachar 2020, Babalola 2021, Krolewiecki 2021, Abd-Elsalam 2021, Shahbaznejad 2021) – wskazuje na nieskuteczność procesu randomizacji;
- region geograficzny, w którym przeprowadzono badania (Bangladesz, Egipt, Irak, Iran, Indie, Nigeria, Turcja, Argentyna, Hiszpania, Meksyk, Kolumbia, Brazylia, Singapur, Liban, Izrael);
- brak analizy ITT (Ahmed 2020, Ravikirti 2021, Mahmud 2021, Krolewiecki 2021, Biber 2021);
- status publikacji – pre-print (Hashim 2020, Beltran-Gonzalez 2021, Chachla 2021, Biber 2021).

Tabela 4. Zestawienie włączonych badań pierwotnych dla skuteczności i profilu bezpieczeństwa iwermektyny w COVID-19

No.	Study author, year	Country	Population	Intervention arm	N	Control arm	N	Types of analysed endpoints	Blinding	Reliability level
TREATMENT (v 1.0, 4/02/2021)										
1.	**Mahmud 2021**	Bangladesh	Mild-moderate	IVM (12 mg x1) + doxycycline (100 mg, BD 5 days) + SoC	200	Placebo+ SoC	200	Early Clinical Improvement; Late Clinical Recovery; Clinical Deterioration; Persistently Positive for RT-PCR of Covid-19, Mortality, SAEs	**DB**	**C**
2.	**Ahmed 2020**	Bangladesh	Mild	IVM (12 mg once daily for 5 days)	22	Placebo	23	Duration of hospitalization after treatment; Duration to viral clearance; Afebrile, Cough and Sore throat on day 7, Serious adverse drug events	**DB**	**E**
				IVM (12 mg single dose) + doxycycline (200 mg on day 1, followed by 100 mg every 12 h for the next 4 days)	23					
3.	**Ravikirti 2021**	India	Mild-moderate	IVM (12 mg on day 1 and 2)	55	Placebo	58	Negative RT-PCR; Symptom free; Discharged; Admission to ICU; Invasive Ventilation; In-hospital mortality	**DB**	**E**
4.	**Chachar 2020**	Bangladesh	Mild	IVM (12 mg at 0, 12, and 24 hours) + symptomatic treatment	25	Symptomatic treatment	25	Symptomatic on day 7	**OL**	**E**
5.	**Chaccour 2021(SAINT)**	Spain	Mild	IVM (single dose of 0.4 mg/kg)	12	Placebo	12	Positive SARS-CoV-2 PCR – gene E, gene N; Seroconversion (positive IgG); Median of IgG titers; Viral load; Cycle threshold; Fever progression; Cough progression; AEs; SAEs; Drug-related AE; Mortality	**DB**	**E**
6.	**Podder 2020**	Bangladesh	Mild-moderate	IVM (0.2 mg/kg on the day 1) + usual care	32	Usual care	30	Time required for the resolution of symptoms; Result of repeat RT-PCR test: positive, negative	**OL**	**E**
7.	**Krolewiecki 2021**	Argentina	Mild-moderate	IVM (0.6 mg/kg/day for 5 days) + SoC	30	SoC	15	Viral load reduction in respiratory secretions; The viral load decay rate; Disease progression; AEs, SAEs	**OL**	**E**
8.	**Okumus 2021**	Turkey	Severe	IVM (0.2 mg/kg/day for 5 days) + Soc (hydroxychloroquine, favipiravir, azithromycin)	36	SoC (hydroxychloroquine, favipiravir, azithromycin)	30	Mortality, Clinical response, adverse events	**OL**	**E**
9.	**Hashim 2020**	Iraq	Mild-moderate, severe, critical	IVM (0.2 mg/kg per day for 2 days, in some patients third dose 0.2 mg/kg per day was given 7 days after the first dose) + doxycycline + SoC	70	SoC	70	Time to recovery; Progression of the disease; Mortality	**ND**	**E**
10.	**Chowdhury 2021**	Bangladesh	Mild-moderate	IVM (0.2 mg/kg single dose) + doxycycline (100 mg BID for 10 days)	60	HCQ (400 mg 1st day, then 200 mg BID for 9 days) + Azithromycin (500 mg daily for 5 days)	56	Recovery to negative PCR rate; Recovery duration to negative PCR; Duration of symptomatic recovery; New symptoms that may be attributed to drug adverse effect or progression of COVID-19; Adverse effects	**OL**	**E**
11.	**Niaee 2021**	Iran	Mild - severe	• IVM, single dose (0.2 mg/kg) • IVM, three doses (0.2 mg/kg) • IVM, single dose (0.4 mg/kg) • IVM, three doses (0.4, 0.2, 0.2 mg/kg)	120	• Common regimen (HCQ 200mg/kg 2x per day) • Placebo + common regimen (HCQ 200mg/kg 2x per day)	60	Duration of hospital stay; Duration of low O_2 saturation; Tachypnea Off; Fever Off; Mortality	**DB**	**E**
12.	**Babalola**	Nigeria	Mild –	IVM (6 mg every 84 hours, 2x week)	21	Lopinavir / ritonavir daily for 2	20	Time to SARS-CoV-2 negativity; Time	**DB**	**E**

No.	Study author, year	Country	Population	Intervention arm	N	Control arm	N	Types of analysed endpoints	Blinding	Reliability level
	2021		moderate, asymptomatic	IVM (12 mg every 84 hours, for 2 weeks)	21	weeks		sequence of days to negativity; Platelet count – change		
v 1.1, 21/05/2021										
13.	**Lopez-Medina 2021**	Colombia	Mild	IVM (300 mcg/kg/d for 5 days)	238	placebo	238	Time to resolution of symptoms, Symptoms resolved, Deterioration by ≥2 points in an ordinal 8-point scale, Fever (≥38 °C) since randomization, Escalation of care since randomization, Duration of care, Deaths, Adverse events	**DB**	**C**
14.	**Mohan 2021**	India	Mild-moderate	IVM (12 mg, single dose)	40	placebo	45	Negative RT-PCR, Days to symptom resolution, Change in WHO Ordinal Scale score between daily 0-14, Discharge, Any clinical worsening, Adverse events, Death	**DB**	**E**
				IVM (24 mg, single dose)	40					
15.	**Beltran-Gonzalez 2021**	Mexico	Moderate-severe	IVM (12 mg (if body mass <80kg) or 18 mg (if body mass >80 kg)	36	placebo	37	Death, Duration of hospitalization, Hospital discharge, Discharge without respiratory deterioration or death, Respiratory deterioration or death	**DB**	**E**
						HCQ (400 mg every 12h on the first day and subsequently, 200 mg every 12h for 4 days)	33			
16.	**Kishoria 2020**	India	Mild/ Asymptomatic	IVM (12 mg, single dose) + SoC	19	SoC (5 days: hydroxychloroquine 400 mg twice a day paracetamol 500mg as required, vitamin C 1 tab twice a day)	13	PCR negativity, Discharge	**OL**	**E**
17.	**Shah Bukhari 2021**	Colombia	Mild	IVM (12 mg, single dose)	50	standard care (oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS)	50	PCR negativity, Adverse side effects	**OL**	**E**
18.	**Pott-Junior 2021**	Brazil	Mild	ivermectin + SoC: 100 mcg/kg	7	SoC	4	Undetectable levels of SARS-CoV-2, Time to achieve undetectable viral load, Change in cycle threshold values, Adverse events	**DB**	**E**
				ivermectin + SoC: 200 mcg/kg	14					
				ivermectin + SoC: 400 mcg/kg	7					
19.	**Galan 2021**	Brazil	Severe	IVM (14 mg, once daily, total dose 42 mg)	53	HCQ (2x400 mg on day 0, and once daily from day 1 to day 4, total dose 2.4 g)	54	The need of oxygen supplementation, Duration of oxygen need, Corticosteroid therapy, Duration of corticosteroides treatment, Anticoagulant therapy, ICU admission, Need for vasoactive drugs, Need for invasive ventilation, Death due to COVID complications, Adverse events	**DB**	**E**
						Chloroquine (2x450 mg on day 0, and once daily from day 1 to day 4, total dose 2.7 g)	61			
v 1.2, 06/08/2021										
20.	**Vallejos 2021**	Argentina	Mild	IVM (<80 kg: 24 mg; 80 - 110 kg: 36 mg; > 110 kg: 48 mg) at inclusion and 24 h the after first dose + SoC	250	placebo + SoC	251	Hospitalization, Hospitalization-free survival, Time to hospitalization days, Invasive MVS, Time to invasive MVS, Negative nasal swab, All-cause mortality, Adverse events	**DB**	**C**

No.	Study author, year	Country	Population	Intervention arm	N	Control arm	N	Types of analysed endpoints	Blinding	Reliability level
21.	**Abd-Elsalam 2021**	Egypt	Mild – moderate	IVM (12mg, orally for 3 days) + SoC	82	SoC	82	Length of hospital stay, Need for mechanical ventilation, Deaths	**OL**	**E**
22.	**Aref 2021**	Egypt	Mild	IVM: 70 mcg/mL by intranasal spray twice a day + SoC	57	SoC	57	Duration of symptoms (fever, cough, dyspnea, ansomia), Duration of PCR negative conversion, PCR Negative Conversion	**OL**	**E**
23.	**Chachla 2021**	Argentina	Mild	IVM (24 mg every 7 days for 4 weeks)	110	SoC	144	Symptoms, Outpatient discharge, Deaths	**OL**	**E**
24.	**Shahbaznejad 2021**	Iran	Moderate-severe	IVM (0.2mg/kg utilizing 3-mg oral tablets or a multiple thereof, on the first day of admission, at the following dosing: 15-24 kg: 3 mg; 25-30 kg: 6 mg; 36-50 kg: 9 mg; 51-80 kg: 12 mg; >80 kg: 0.2 mg/kg; single dose)	35	supportive medical treatment (hydroxychloroquine and/or lopinavir/ritonavir)	34	Oxygen needed, Duration of hospital stay, Duration of symptoms, Mechanical ventilation required, Deaths	**DB**	**E**
25.	**Biber 2021**	Israel	Mild	IVM (40-69 kg: 12mg; ≥70kg: 15mg orally once a day for 3 days)	47	placebo	42	Viral clearance	**DB**	**E**
PROPHYLAXIS (v 1.0)										
26.	**Shouman 2020**	Egypt	Asymptomatic household close contacts	IVM (2 doses 72 hours apart 40-60 kg – 15 mg/day,60-80kg – 18mg/day, >80kg – 24 mg/day)	203	No intervention	101	Development of Symptoms; Mortality; AEs; SAEs	**OL**	**E**
v 1.2, 06/08/2021										
27.	**Seet 2021**	Singapore	Healthy subjects	IVM (200 mcg/kg, single dose; 12 mg when weight >60 kg)	617	Vitamin C	619	Laboratory evidence of SARS-CoV-2 infection, Acute respiratory symptoms, Symptomatic COVID-19, Pneumonia requiring hospitalization, Interruption due to side effects, Deaths	**OL**	**E**
28.	**Samaha 2021**	Lebanon	Asymptomatic SARS-CoV-2-positive subjects	IVM (45–64 kg, 65–84 kg, or above 85 kg received 9 mg, 12 mg, or 150 µg/kg body weight orally once-off)	50	SoC	50	Ct-values, Development od clinical symptoms, Hospitalization	**ND**	**E**

HCQ – Hydroxychloroquine; IVM – Ivermectin; MVS – mechanical ventilatory support; ND – no data; PPE – personal protective equipment; AEs – adverse events; SAEs – serious adverse events; DB – double blind; OL - open-label; SB – single-blind; ND – no data

Podsumowanie wyników badań pierwotnych

- **Leczenie**

Iwermektyna vs opieka standardowa / placebo

Nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności (Ravikirti 2021, Chaccour 2021, Okumus 2021, Lopez-Medina 2021, Vallejos 2021, Abd-Elsalam 2021, Chachla 2021, Mohan 2021, Beltran-Gonzalez 2021) **oraz długości hospitalizacji** (Ahmed 2020, Beltran-Gonzalez 2021, Abd-Elsalam 2021). **W ramach punktów końcowych odnoszących się do stanu klinicznego pacjentów tj. progresja choroby, wyzdrowienie, występowania objawów, w większości badań nie odnotowano znamiennych statystycznie różnic** (Ravikirti 2021, Chachar 2020, Chaccour 2021, Podder 2020, Okumus 2021, Lopez-Medina 2021, Vallejos 2021, Abd-Elsalam 2021, Mohan 2021, Beltran-Gonzalez 2021).

W 2 badaniach, zidentyfikowano istotne statystycznie różnice na rzecz iwermektyny w zakresie punktów końcowych odnoszących się do występowania objawów – czasu trwania objawów tj. gorączka (5 vs 13 dni), kaszel (5 vs 14 dni), duszność (4 vs 10 dni), utrata węchu (2 vs 6 dni) (Aref 2021) oraz odsetka pacjentów z objawami choroby (OR=7,99; 95%CI: 1,64; 38,97) i wypisu ambulatoryjnego (RR=1,14; 95%CI: 1,06; 1,22; NNT=9) (Chachla 2021).

Wykazano również znamienne statystycznie korzyści wynikające ze stosowania IVM w zakresie punktów końcowych dotyczących zmiany statusu obecności wirusa SARS-CoV-2 – konwersja do negatywnego wyniku testu SARS-CoV-2 (Aref 2021 – RR=0,21; 95%CI: 0,07; 0,71; NNT=6), usuwanie wirusa z organizmu (Biber 2021 – RR=1,45; 95% CI:1.02; 2.05; NNT=5) oraz negatywny wynik testu SARS-CoV-2 w 72. godzinie (Shah Bukhari 2021 – RR=9,32; 95%CI: 2,29; 37,9; NNT=3).

W jednym badaniu (Lopez-Medina 2021) odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo. W pozostałych badaniach prezentujących wyniki w zakresie profilu bezpieczeństwa (Vallejos 2021, Ahmed 2020, Chaccour 2021, Krolewiecki 2021, Okumus 2021, Pott-Junior 2021) ryzyko występowania działań niepożądanych pomiędzy ramionami badań było zbliżone.

Iwermektyna + doksycyklina vs opieka standardowa / placebo

W żadnym z badań nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności (Mahmud 2021, Hashim 2020) i występowania działań niepożądanych (Mahmud 2021, Ahmed 2020).

W badaniu Mahmud 2021, u pacjentów stosujących iwermektynę w skojarzeniu z doksycykliną, w porównaniu do pacjentów stosujących placebo z opieką standardową, istotne statystycznie korzyści odnotowano w zakresie punktów końcowych dotyczących czasu do wyzdrowienia (7 vs 9 dni, HR=0,73, 95%CI: 0,06; 0,09), pogorszenia klinicznego (8,7 vs 17,8%, HR=0,43, 95%CI: 0,38; 0,62), poprawy klinicznej w ciągu 7 dni (60,7 vs 44,4%, HR=0,06, 95%CI: 0,004; 0,09) objawowości po 12 dniach (23 vs 37,2%, HR=0,04, 95%CI: 0,03; 0,07) oraz czasu utrzymywania się pozytywnego wyniku testu RT-PCR w 14. dniu (7,7 vs 20%, HR=0,61, 95%CI: 0,44; 0,83). W badaniu Hashim 2020 istotne statystycznie różnice na korzyść interwencji odnotowano jedynie dla czasu do wyzdrowienia (w populacji ogólnej 10,6 vs 17,9 dni; w subpopulacji pacjentów z łagodnym do umiarkowanego nasileniem objawów 6,3 vs 13,7 dni).

Iwermektyna + doksycyklina vs hydroksychlorochina + azytromycyna

Nie odnotowano istotnych statystycznie różnic dla analizowanych punktów końcowych tj. m.in. szybkości ustępowania objawów, średniego czasu do uzyskania ujemnego wyniku PCR (Chowdhury 2021).

Iwermektyna vs hydroksychlorochina

Istotne statystycznie różnice na korzyść IVM odnotowano w zakresie śmiertelności (RR=0,18, 95%CI: 0,06; 0,55, NNT=7) oraz długości hospitalizacji (Niaee 2021).

Iwermektyna vs lopinawir/rytonawir

W badaniu Babalola 2020 odnotowano istotnie statystycznie krótszy czas do uzyskania negatywnego wyniku testu RT-PCR względem grupy kontrolnej (6 vs 4,7 dni). W badaniu nie analizowano istotnych klinicznie punktów końcowych.

Iwermektyna vs hydroksychlorochina i / lub lopinawir/rytonawir

W badaniu Shahbaznejad 2021 w ramieniu IVM odnotowano istotnie statystycznie krótszy czas występowania objawów (4 vs 5 dni) oraz krótszy czas hospitalizacji (6 vs 7 dni) w porównaniu do grupy kontrolnej. Wyniki w zakresie śmiertelności, konieczności wsparcia tlenowego lub mechanicznej wentylacji nie różniły się znamiennie statystycznie pomiędzy grupami.

- **Profilaktyka**

Wyniki badania Samaha 2021, wskazują na korzyść zdrowotną z profilaktycznego (jednorazowe podanie) zastosowania IVM u osób bezobjawowych zakażonych SARS-CoV-2 – znamienne statystycznie różnice na korzyść IVM względem witaminy C i cynku w zakresie wystąpienia objawów infekcji tj. gorączka, anosmia, bóle mięśniowe i utrata smaku. Autorzy badania zestawili jednak w publikacji wyłącznie dane krótkoterminowe (po 3 dniach od potwierdzenia infekcji).

W dwóch badaniach, w których iwermektyna była stosowana w ramach profilaktyki zakażeń SARS-CoV-2 u osób po kontakcie z zakażonym (Shouman 2020) i u zdrowych ochotników (Seet 2021), w grupie pacjentów otrzymujących IVM zaobserwowano znamiennie statystycznie niższy odsetek pacjentów, u których wystąpiły objawy choroby, w porównaniu do grup pacjentów nie otrzymujących żadnej formy profilaktyki (Shouman 2020) lub przyjmujących witaminę C (Seet 2021). W badaniu Seet 2021 zaobserwowano również istotnie statystycznie rzadsze występowanie ostrych objawów ze strony układu oddechowego w grupie osób stosujących IVM, w porównaniu do grupy kontrolnej przyjmujących witaminę C. Z uwagi na liczne ograniczenia metodyczne ww. badań (tj. m.in. brak porównania z placebo, niewłaściwa metoda randomizacyjna, populacja badana (w badaniu Seet 2021 wyłącznie mężczyźni w średnim wieku), nieliczne grupy badane (Shouman 2020), ośrodki przeprowadzające badania, brak analizy ITT – badanie Shouman 2020), do uzyskanych wyników należy podchodzić z ostrożnością.

Tabela 5. Wyniki badań pierwotnych włączonych do przeglądu – leczenie

No.	Study author, year / acronym	Reliability level	Test arm, N	Control arm, N	Mortality	Progression	Recovery	Duration of hospital stay	Duration of viral clearance	SARS-CoV-2 negativity	AEs	SAEs
Ivermectin vs SoC / placebo												
1.	**Ahmed 2020**	**E**	22	24					p=0.005 (mean: 9.7 vs 12.7 days)			
2.	**Ravikirti 2021**	**E**	55	57		Admission to ICU; IMV	Symptom free Discharge			Day 6		
3.	**Chachar 2020**	**E**	25	25			Symptomatic on day 7					
4.	**Chaccour 2021 (SAINT)**	**E**	12	12		Fever Cough				Positive SARS-CoV-2 PCR		
5.	**Podder 2020**	**E**	32	30			Resolution of symptoms – time			Negative result of repeat RT-PCR test		
6.	**Krolewiecki 2021**	**E**	30	15					The viral load decay rate (Subgroup with >160ng/ml IVM median plasma concentration) p=0.041			
7.	**Okumus 2021**	**E**	36	30			Clinical response					
8.	**Lopez-Medina 2021**	**C**	200	198								RR=2,97 (95%CI: 1,1; 8,02)^
9.	**Vallejos 2021**	**C**	250	251		Hospitalization IMV						
10.	**Abd-Elsalam 2021**	**E**	82	82		Mechanical ventilation						
11.	**Aref 2021**	**E**	57	57			Duration of symptoms: - fever: 5 vs 13 days - cough: 5 vs 14 days - dyspnea: 4 vs 10 days - ansomia: 2 vs 6 days			PCR negative Conversion RR=0.21 (95%CI: 0.07; 0.71)n NNT=6^		
12.	**Chachla 2021**	**E**	110	144			Outpatient discharge: RR=1.14 (95%CI: 1.06; 1.22), NNT=9^ Participants with symptoms OR=7.99 (95%CI: 1.64; 38.97)					
13.	**Biber 2021**	**E**	47	42						Viral clearance RR=1.45 (95% CI:1.02; 2.05), NNT=5^		
14.	**Mohan 2021**	**E**	80	45				Discharge				
15.	**Beltran-Gonzalez 2021**	**E**	36	37								
16.	**Shah Bukhari 2021**	**E**	41	45						W 72 godzinie RR=9,32 (95%CI: 2,29; 37,9), NNT=3^ dzień 7		
17.	**Kishoria 2021**	**E**	19	13				Discharge				
18.	**Pott-Junior 2021**	**E**	27	4								
Ivermectin + doxycycline vs SoC / placebo												
1.	**Ahmed 2020**	**E**	23	24								
2.	**Mahmud 2021**	**C**	183	180		HR=0.45 (95%CI: 0.23; 0.85)	HR=0.51 (95%CI 0.32; 0.80) Clinical improvement			Persistently Positive for RT-PCR		

No.	Study author, year / acronym	Reliability level	Test arm, N	Control arm, N	Mortality	Progression	Recovery	Duration of hospital stay	Duration of viral clearance	SARS-CoV-2 negativity	AEs	SAEs
							HR=0.53 (95%CI 0.30; 0.96)			HR=0.58 (95%CI: 0.44; 0.81)		
3.	**Hashim 2020**	**E**	70	70			Time to recovery (mean: 11 vs 18 days)					
Ivermectin + doxycycline vs hydroxychloroquine + azhitromycin												
1.	**Chowdhury 2021**	**E**	60	56			Recovery to negative PCR rate					
Ivermectin +/- SoC vs hydroxychloroquine +/- SoC												
1.	**Niaee 2021**	**E**	120	60	RR=0.18 (95%CI: 0.06; 0.55), NNT=7		Tachypnea Off Fever Off	p=0.006				
2.	**Beltran-Gonzalez 2021**	**E**	36	33								
3.	**Galan 2021**	**E**	53	54		ICU admission						
Ivermectin vs chloroquine												
1.	**Galan 2021**	**E**	53	61		ICU admission						
Ivermectin vs lopinavir/rytonavir												
1.	**Babalola 2020**	**E**	42	20					Time to negativity p=0.0066			
Ivermectin vs hydroxychloroquine and/or lopinavir/rytonavir												
1.	**Shahbaznejad 2021**	**E**	35	34		Oxygen needed Mechanical ventilation	Duration of symptoms 4 vs 5 days, p=0.023	6 vs 7 days p=0.016				

^ Agency's own calculations; AEs – adverse events; IVM – invasive mechanical ventilation; SAEs – serious adverse events; SoC – standard of care; RR – risk ratio

Tabela 6. Wyniki badań pierwotnych włączonych do przeglądu – profilaktyka

No.	Study author, year / acronym	Reliability level	Test arm, N	Control arm, N	Development of Symptoms	Hospitalization	Confirmed infected subjects by RT-PCR	AEs	Mortality
1.	**Seet 2021**	**E**	617	619	RR=0.54 (95%CI: 0.37; 0.81), NNT=15^	Pneumonia requiring hospitalization		Interruption due to side effects RR=0.03 (95%CI: 0.01; 0.43), NNT=22^	
2.	**Shouman 2020**	**E**	203	101	^RR=0.13 (95%CI: 0.08; 0.21), NNT=2				
3.	**Samaha 2021**	**E**	50	50	Fever RR=0.09 (95%CI: 0.01; 0.68), NNT=5^ Anosmia RR=0.19 (95%CI 0.06; 0.60), NNT=4^ Myalgia RR=0.05 (95%CI 0.003; 0.88), NNT=6^ Loss of Taste 0.25 (95%CI 0.08; 0.83), NNT=6^ Cough, runny nose, headache, fatigue, dizziness				

^ Agency's own calculations; AEs – adverse events; RR – risk ratio

Analiza skuteczności w zakresie redukcji ryzyka zgonu – leczenie

W Tabela 7 podsumowano wyniki dla śmiertelności z informacją o poziomie wiarygodności dowodów naukowych.

Tabela 7. Podsumowanie danych dla skuteczności iwermektyny w zakresie redukcji ryzyka zgonu

Badanie	Populacja	Ramię badane, n/N	Ramię kontrolne, n/N	Wynik, parametr względny (95% CI), NNT	Poziom wiarygodności
Iwermektyna vs SoC / placebo					
Lopez-Medina 2021	Mild	0/238	1/238	^RR=0.33 (0.01; 6.14)	**C**
Vallejos 2021	Mild	4/250	3/251	^RR=1.34 (0.30; 5.92)	**C**
Abd-Elsalam 2021	Mild – moderate	3/82	4/82	^RR=0.75 (0,17; 3.25)	**E**
Ravikirti 2021	Mild-moderate	0/55	4/57	^RR=0.1 (0.0; 2.1)	**E**
Chaccour 2021	Mild	0/12	0/12	-	**E**
Mohan 2021	Mild-moderate	0/80	0/45	-	**E**
Chachla 2021	Mild	0/110	0/144	-	**E**
Beltran-Gonzalez 2021	Moderate-severe	5/36	6/37	^RR=0.86 (0.29; 2.56)	**E**
Okumus 2021	Severe	6/30	9/30	^RR=0.66 (0.27; 1.64)	**E**
Iwermektyna + doksycyklina vs SoC / placebo					
Mahmud 2021	Mild-moderate	0/183	3/180	^RR=0.14 (0.01; 2.70)	**C**
Hashim 2020	Mild-critical	2/70	6/70	^RR=0.33 (0.07; 1.60)	**E**
	Mild-moderate	0/48	0/48	-	
	Severe	0/11	6/22	OR=0.11 (ND;ND) ^RR=1.15 (0.01; 2.40)	
	Critical	2/11	no patients	-	
Iwermektyna +/- SoC vs hydroksychlorochina +/- SoC					
Niaee 2021	Mild-severe	4/120	11/60	RR=0.18 (0.06; 0.55), ^NNT=7	**E**
Galan 2021	Severe	12/53	12/54	^RR=1.02 (0.50; 2.06)	**E**
Beltran-Gonzalez 2021	Moderate-severe	5/36	2/33	^RR=2.29 (0.49; 11.02)	**E**
Ivermectin vs hydroxychloroquine and/or lopinavir/rytonavir					
Shahbaznejad 2021	Moderate-severe	1/35	0/34	-	**E**

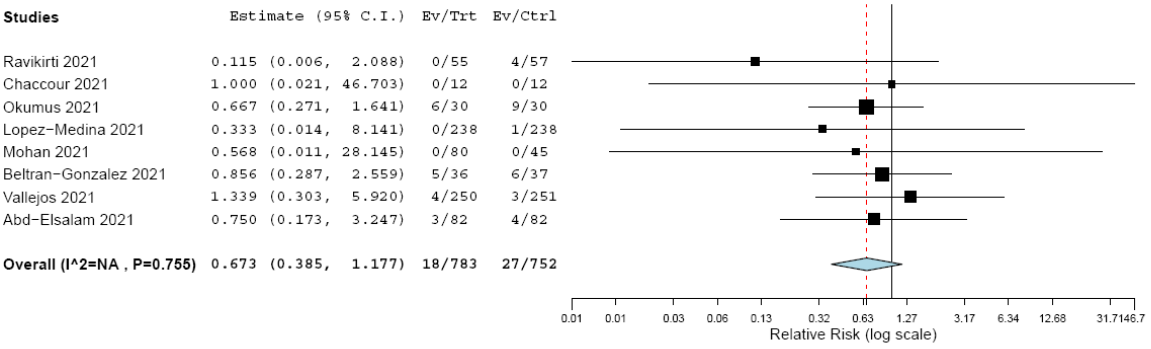
^ obliczenia własne Agencji; BD – brak danych; RR – risk ratio

Z uwagi na heterogeniczność badań w zakresie ciężkości choroby, schematów dawkowania iwermektyny, doboru komparatorów i terapii stosowanych w ramach opieki standardowej, kryteriów kwalifikacji do badań (uwzględnianie pacjentów z różnym nasileniem objawów choroby), metodyki badania – zaślepienie / brak zaślepienia, liczebności prób, sposobu analizy wyników (analiza ITT, mITT lub *per protocol*), analizowanych punktów końcowych i ich definicji, okresu obserwacji, przeprowadzenie kumulacji wyników badań wydaje się nieuprawnione.

Analitycy AOTMiT przeprowadzili metaanalizę (8 RCTs, N= 1 535 pacjentów), z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina – wyniki dla porównania IVM +/- opieka

standardowa vs opieka standardowa +/- placebo wskazują, że zastosowanie iwermektyny nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu (RR=0,67, 95%CI: 0,39; 1,18 – Rysunek 1).

Dodatkowo przeprowadzono analizę z uwzględnieniem stopienia nasilenia choroby tj. łagodny – umiarkowany (6 RCTs, N= 1 402 pacjentów) – wyniki skumulowane również nie są istotne statystycznie (

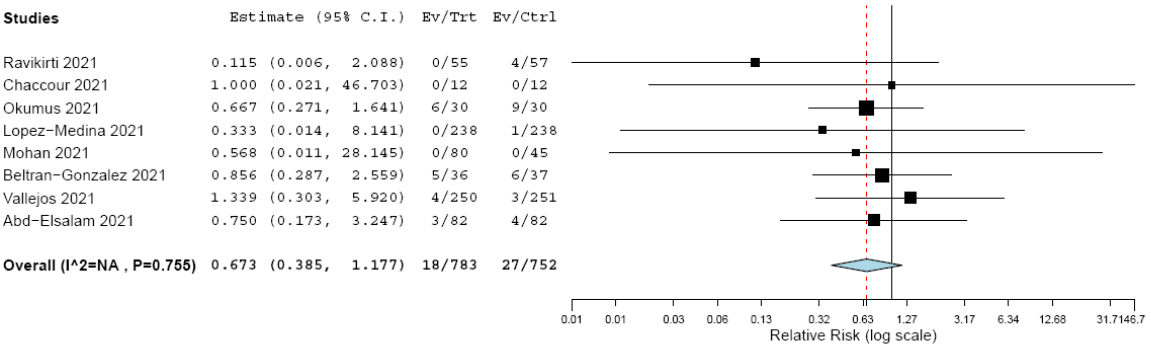


Rysunek ***2***).

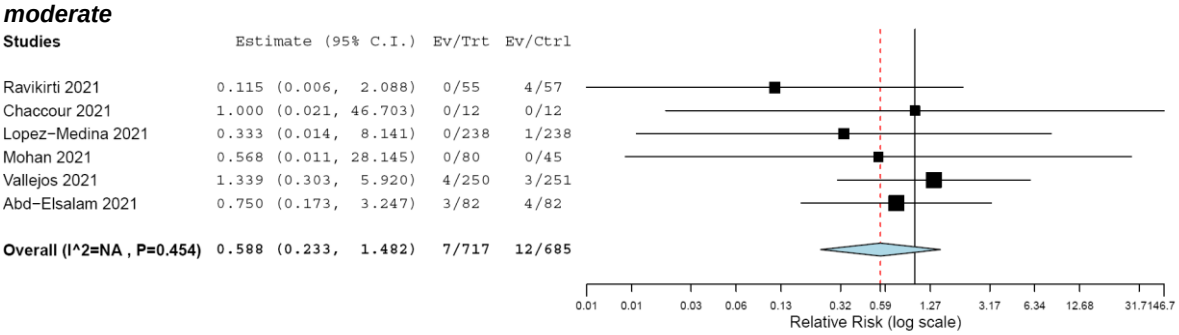
Wyniki metaanalizy przeprowadzonej dla porównania IVM+DOX+SoC vs SoC+/- placebo (2 RCTs, 503 pacjentów) wskazują z kolei, że zastosowanie terapii skojarzonej może wiązać się ze znamienną statystycznie redukcją zgonu – wynik na granicy istotności statystycznej (RR=0,222, 95%CI: 0,049; 0,999 – Rysunek 3).

Do uzyskanych wyników metaanaliz należy podchodzić z ostrożnością (heterogeniczność kliniczna: ciężkość przebiegu COVID-19, leczenie stosowane równolegle; heterogeniczność metodyczna: różne schematy dawkowania iwermektyny, liczebności prób, sposób analizy wyników, okres obserwacji).

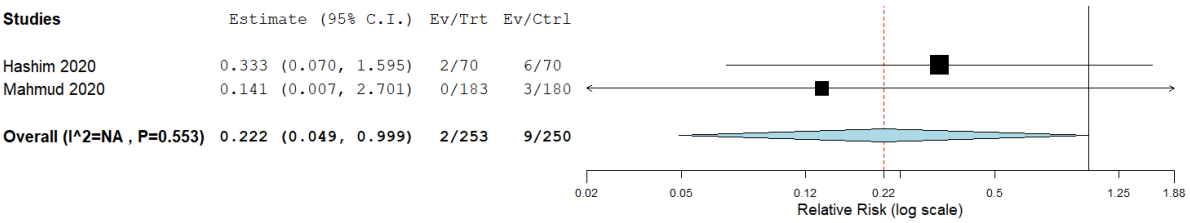
Rysunek 1. Metaanaliza wyników RCTs (ryzyko zgonu, RR) dla porównania IVM+/-SoC vs PLB/SoC



Rysunek 2. Metaanaliza wyników RCTs (RR) dla porównania IVM+/-SoC vs PLB/SoC – populacja *mild-moderate*



Rysunek 3. Metaanaliza wyników RCTs (RR) dla porównania IVM+DOX+SoC vs SoC+-/placebo



4. DYSKUSJA I WNIOSKI

Kryteria włączenia do przeglądu spełniło łącznie 28 kontrolowanych prób klinicznych z randomizacją, z czego 25 dotyczyło stosowania iwermektyny w leczeniu COVID-19, a trzy obejmowało profilaktykę COVID-19. W większości badań populację stanowili pacjenci z łagodnym i umiarkowanym przebiegiem choroby, a iwermektyną stosowana była w monoterapii lub w skojarzeniu z opieką standardową. W 4 badaniach interwencję stanowiła iwermektyna w skojarzeniu z doksycykliną +/- opieka standardowa. Efektywność iwermektyny porównywano głównie z placebo ± opieka standardowa, w 5 RCTs w ramieniu kontrolnym stosowano hydroksychlorochinę (Chowdhury 2021, Niaee 2021, Galan 2021, Beltran-Gonzalez 2021) oraz chlorochinę (Galan 2021), a w 1 lopinawir w skojarzeniu z rytonawirem (Babalola 2021).

Schemat dawkowania, jak również czas leczenia IVM, był zróżnicowany – w większości badań IVM stosowano doustnie, w jednorazowej dawce. Maksymalny czas terapii IVM wyniósł 5 dni. W 1 badaniu oceniano stosowanie iwermektyny w postaci aerozolu do nosa (Aref 2021).

W żadnym z badań, w których iwermektynę (± doksycyklina) porównywano z placebo / opieką standardową nie odnotowano istotnych statystycznie różnic w zakresie śmiertelności, wyniki prób klinicznych Vallejos 2021 oraz Lopez-Medina 2021 (największe liczebności grup (odpowiednio 250 vs 251 osób oraz 238 vs 238) również nie potwierdzają skuteczności iwermektyny w COVID-19 (pacjenci niewymagający hospitalizacji). Wyniki badania, w którym w ramieniu kontrolnym stosowano hydroksychlorochinę (Niaee 2021) wskazują co prawda na występowanie istotnych statystycznie różnic w zakresie śmiertelności na korzyść ramienia z iwermektyną, jednak z uwagi na możliwy negatywny wpływ hydroksychlorochiny na wyniki, leczenia należy je traktować ze szczególną ostrożnością.

W badaniach, w których porównywano IVM z placebo / opieką standardową, nie odnotowywano również istotnych statystycznie różnic pomiędzy ramionami badania w zakresie istotnych klinicznie punktów końcowych tj. progresja choroby, ustąpienie objawów, odpowiedź na leczenie czy wypis ze szpitala. Z kolei wyniki badania Mahmud 2021, przeprowadzonego z udziałem 400 pacjentów wskazują, że korzyści ze stosowania iwermektyny w skojarzeniu z doksycykliną można zaobserwować w zakresie poprawy klinicznej oraz redukcji ryzyka progresji choroby. Wyniki mniejszych prób klinicznych – Ahmed 2020 i Krolewiecki 2021 – wskazują z kolei, że iwermektyna może wpływać na czasu do eliminacji wirusa / szybkość zaniku wiremii.

W jednym badaniu (Lopez-Medina 2021) odnotowano istotnie statystycznie wyższy odsetek ciężkich zdarzeń niepożądanych w ramieniu badania z iwermektyną względem pacjentów stosujących placebo. W pozostałych badaniach prezentujących wyniki w zakresie profilu bezpieczeństwa (Vallejos 2021, Ahmed 2020, Chaccour 2021, Krolewiecki 2021, Okumus 2021, Pott-Junior 2021) ryzyko występowania działań niepożądanych pomiędzy ramionami badań było zbliżone.

Wśród zidentyfikowanych w ramach przeglądu badań, interesujące wydają się wyniki badania Aref 2021 przeprowadzonego z udziałem pacjentów z łagodnym nasileniem objawów choroby. Zastosowanie IVM w postaci wziewnej istotnie statystycznie skróciło czas występowania objawów tj. gorączka, kaszel, duszności, anosmia. Należy jednak zaznaczyć, że aktualnie nie ma innych badań potwierdzających skuteczność terapii wziewnej, natomiast badanie Aref 2021 obarczone jest licznymi ograniczeniami metodycznymi.

Analizując wyniki badań pierwotnych włączonych do przeglądu AOTMiT, należy wziąć pod uwagę ich ograniczenia, wynikające przede wszystkim niskiej liczebności prób wpływającej na moc statystyczną badań, regionów geograficznych, w których przeprowadzono badania, sposobu analizy wyników, różnic w charakterystyce wyjściowej pacjentów, doboru komparatorów, braku informacji o leczeniu stosowanym w ramach opieki standardowej, brak szczegółowych informacji o odsetkach pacjentów otrzymujących konkretną terapię, publikacji typu *pre-print* (Hashim 2020, Beltran-Gonzalez 2021).

Wyniki metaanalizy AOTMiT (8 RCTs, N= 1 535 pacjentów), przeprowadzonej z wykluczeniem badań, w których ramię kontrolne stanowiła hydroksychlorochina wskazują, że stosowanie IVM +/- opieka standardowa w porównaniu do opieki standardowa +/- placebo nie wiąże się ze znamienną statystycznie redukują ryzyka zgonu. Heterogeniczność włączonych badań pierwotnych pozwala stwierdzić, że kumulacja wyników obarczona jest wysokim ryzykiem błędu.

Stosowanie iwermektyny jako profilaktyki COVID-19 oceniano w trzech, zidentyfikowanych w ramach wyszukiwania, próbach klinicznych z randomizacją. Wyniki badania Samaha 2021, wskazują na korzyść zdrowotną z profilaktycznego (jednorazowe podanie) zastosowania IVM u osób bezobjawowych zakażonych SARS-CoV-2 – znamienne statystycznie różnice na korzyść IVM względem witaminy C i cynku w zakresie wystąpienia objawów infekcji tj. gorączka, anosmia, bóle mięśniowe i utrata smaku. Autorzy badania zestawili jednak w publikacji wyłącznie dane krótkoterminowe (po 3 dniach od potwierdzenia infekcji). W związku z powyższym istnieje niepewność czy zaobserwowane różnice w skuteczności utrzymają się w dłuższym okresie obserwacji czy IVM wyłącznie odsuwa w czasie wystąpienie objawów.

W dwóch badaniach, w których iwermektyna była stosowana w ramach profilaktyki zakażeń SARS-CoV-2 u osób po kontakcie z zakażonym (Shouman 2020) i u zdrowych ochotników (Seet 2021), w grupie pacjentów otrzymujących IVM zaobserwowano znamiennie statystycznie niższy odsetek pacjentów, u których wystąpiły objawy choroby, w porównaniu do grup pacjentów nie otrzymujących żadnej formy profilaktyki (Shouman 2020) lub przyjmujących witaminę C (Seet 2021). W badaniu Seet 2021 zaobserwowano również istotnie statystycznie rzadsze występowanie ostrych objawów ze strony układu oddechowego w grupie osób stosujących IVM, w porównaniu do grupy kontrolnej przyjmujących witaminę C. Z uwagi na liczne ograniczenia metodyczne ww. badań (tj. m.in. brak porównania z placebo, niewłaściwa metoda randomizacyjna, populacja badana (w badaniu Seet 2021 wyłącznie mężczyźni w średnim wieku), nieliczne grupy badane (Shouman 2020), ośrodki przeprowadzające badania, brak analizy ITT – badanie Shouman 2020), do uzyskanych wyników należy podchodzić z ostrożnością.

Na chwilę obecną brak jest wiarygodnych dowodów naukowych potwierdzających skuteczność IVM w postaci doustnej w COVID-19.

Ponadto, należy mieć na uwadze, w Polsce lek z iwermektyną do stosowania u ludzi dostępny jest wyłącznie w postaci kremu wskazanego do leczenia trądziku różowatego. Lek w postaci tabletek oraz iniekcji dostępny jest wyłącznie do leczenia weterynaryjnego. IVM stosowana w formie doustnej nie posiada rejestracji centralnej EMA ani rejestracji krajowej URPLWMiPB. Lek jest dopuszczony do stosowania w niektórych państwach, m.in. Francji, Niemczech, Holandii, Szwecji, Austrii i Czechach.

Aneks 1 (RCTs uwzględnione w wersji 1.2, 06.08.2021)

Tabela 8. Opis metodyki i wyników badania Vallejos 2021 – leczenie

Vallejos 2021				
Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial (BMC Infectious Diseases, 02.07.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Randomized (1:1), double-blind, placebo controlled, phase 2/3 Study duration: 19/08/2020-22/02/2021 Argentina	N=501 Non-hospitalized patients with early COVID-19 <u>Inclusion criteria</u>: – >18 years of age, – confirmed COVID-19 (RT-PCR) in the last 48 h; weight ≥48 kg <u>Exclusion criteria:</u> – required current home oxygen use or hospitalization for COVID-19 or a history of hospitalization for COVID-19; – presence of mal-absorptive syndrome, presence of any other concomitant acute infectious disease; – severe liver disease, and recent or expected need for dialysis; – use of HCQ or CQ or antiviral drugs (other than COVID-19 treatment), – the use of ivermectin up to 7 days before randomization.	Ni=250 Ivermectin (<80 kg: 2 tab. x 6 mg (24 mg); 80 - 110 kg: 3 tab. x 6 mg (36 mg); > 110 kg: 4 tab. x 6 mg (48 mg)) at inclusion and 24 h the after first dose	Nc=251 Placebo	– The trial may be underpowered because the hospitalization rate was lower than expected when performed in the sample size calculation, as well as the fact that an ambitious reduction of 50–70% was estimated of primary end point. – No scale to determine the severity of the patients who were enrolled
		Standard of care*		
	Age, mean ± SD	42.6 ± 15.3	42.4 ± 15.8	
	Female (%)	44.4	50.2	
	Diabetes (%)	8.4	10.8	
	Hypertension (%)	21.3	26.3	
	Symptomatic (%)	96	96	
	Days from symptoms started to inclusion, median (IQR)	4 (3–5)	4 (3–6)	

Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI) / p value**	**Absolute parameter**
All-cause mortality, n/N (%)	30 days	4/250 (1.6)	3/251 (1.2)	OR=1.34 (0.30; 6.07) ^RR=1.29 (0.29; 5.69)	-
Hospitalization, n/N (%)	30 days***	14/250 (5.6)	21/251 (8.4)	OR=0.65 (0.32; 1.31)	-
Hospitalization-free survival		-	-	HR=0.66 (0.33; 1.29)	-
Time to hospitalization days, median (IQR)	-	3.5 (3–5)	3 (2–5)	p=0.59	-
Invasive MVS, n/N (%)	30 days***	4/250 (1.6)	3/251 (1.2)	OR=1.34 (0.30; 6.07)	-
Time to invasive MVS (in those who required MVS), mean (±SD) days	-	5.25 (1.7)	10 (2)	p=0.019	-
Negative nasal swab, n/N (%)	Day 3	113/250 (47.1)	120/251 (49.8)	OR=0.90 (0.63; 1.28)	-
	Day 14	212/250 (89.1)	221/251 (92.5)	OR=0.76 (0.45; 1.27)	-
Adverse events – total*	30 days	45/250 (18)	53/251 (21.1)	p=0.6	-
Author's conclusion: Ivermectin had no significant effect on preventing hospitalization of patients with COVID-19. Patients who received ivermectin required invasive MVS earlier in their treatment. No significant differences were observed in any of the other secondary outcomes.					

MVS – mechanical ventilatory support; * - in accordance with the recommendations of the Argentine Ministry of Health; ****** all adverse events were non-serious; ^Agency's own calculations

Tabela 9. Opis metodyki i wyników badania Abd-Elsalam 2021 – leczenie

<table>
<tr><th colspan="6">Abd-Elsalam 2021</th></tr>
<tr><th colspan="6">Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study (Journal of Medical Virology, 02.06.2021)</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="6">Multi-center, randomized (1:1), open-label, phase 2/3

Study duration: 03 – 10.2020

Egypt</td><td colspan="2" rowspan="2">N=164
Mild to moderate COVID-19 patients

<u>Inclusion criteria</u>:
– age 20 to 65;
– mild to moderate COVID-19 confirmed by PCR
<u>Exclusion criteria:</u>
– allergy or contraindication to the drugs used in the study;
– cardiac problems</td><td>Ni=82

Ivermectin 12mg per day orally for 3 days
+ SoC</td><td>Nc=82

Standard care (SoC) for 14 days</td><td rowspan="6">– Lack of detailed information about percentage of usage of certain therapies as standard care;
– Slightly (but no significant) differences in baseline characteristic of patients;
– Small sample size.</td></tr>
<tr><td colspan="2">SoC: paracetamol, oxygen, fluids, empiric antibiotic, oseltamivir if needed (75 mg/12 h for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO2 less than 60 mm Hg, O2 saturation less than 90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock</td></tr>
<tr><td colspan="2">Age, mean ± SD</td><td>42.38 ± 16.02</td><td>39.38 ± 16.92</td></tr>
<tr><td colspan="2">Female (%)</td><td>54.9</td><td>45.1</td></tr>
<tr><td rowspan="3">Coexisting conditions (%)</td><td>Diabetes</td><td>20.7</td><td>12.2</td></tr>
<tr><td>Hypertension</td><td>21.9</td><td>17.1</td></tr>
<tr><td>Comorbidities</td><td>43.9</td><td>54.9</td></tr>
<tr><th colspan="6">Results</th></tr>
<tr><th colspan="2" rowspan="2">Outcome</th><th rowspan="2">Ivermectin</th><th rowspan="2">Placebo</th><th colspan="2">Statistical significance of differences</th></tr>
<tr><th>event</th><th>follow-up period</th><th>Relative parameter (95%CI) / p value</th><th>Absolute parameter</th></tr>
<tr><td colspan="2">Deaths – n/N (%)</td><td>30 days</td><td>3/82 (3.7)</td><td>4/82 (4.9)</td><td>p=1.00</td><td>-</td></tr>
<tr><td colspan="2">Length of hospital stay (in days), mean (SD)</td><td>NA</td><td>8.82 ± 4.94</td><td>10.97 ± 5.28</td><td>p=0.08</td><td>-</td></tr>
<tr><td colspan="2">Need for mechanical ventilation – n/N (%)</td><td>30 days</td><td>3/82 (3.7)</td><td>3/82 (3.7)</td><td>p=1.00</td><td>-</td></tr>
<tr><td colspan="6">Author's conclusion: The usage of ivermectin did not achieve significance for any of the endpoints. However; there was an observed trend to reducing hospital stay in the ivermectin-treated group. These findings may suggest using ivermectin as an add-on therapy to protocols used for the treatment of COVID-19. However, these results are needed to be validated in a larger prospective follow-up study.</td></tr>
</table>

NA – not applicable

Tabela 10. Opis metodyki i wyników badania Aref 2021 – leczenie

Aref 2021				
Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19 (International Journal of Nanomedicine, 15.06.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Single-center, randomized, open-label, phase 2/3 Study duration: 20/02/2020 – 30/03/2021 Egypt	N=114 Mild COVID-19 patients Inclusion criteria: – mild COVID-19*; – SARS-CoV-2 confirmed by RT-PCR Exclusion criteria: – severe COVID-19**; – receiving systemic ivermectin according to the Egyptian management protocol for COVID-19 patients; – chronic ENT disorders such as chronic sinusitis, nasal allergy, patients using nasal spray preparation; systemic or local use of steroids due to any cause; allergic to ivermectin.	Ni=57 Ivermectin 70 mcg/mL by intranasal spray twice a day	Nc=57 Standard of care (SoC)	– Lack of detailed information about percentage of usage of certain therapies as standard care; – Small sample size.
		SoC: Paracetamol 500 mg intravenously every 6 hours; Hydroxychloroquine 500 mg/12 h with close monitoring of liver and kidney functions; Azithromycin 1 g first day, then 500 mg per day for 3 days or clarithromycin 500 mg every 12 hfor 7–14 days; Oseltamivir 150 mg/12 h for 5 days; Ascorbic acid 500 mg/12 h; Cyanocobalamin IV once daily.		
	Age, mean ± SD	44.8 ± 19.2	45.5 ± 18.8	
	Female (%)	29.8	26.3	
	Body Mass Index (kg/m2, mean±SD)	26.9 ± 3.5	28.1 ± 4.9	

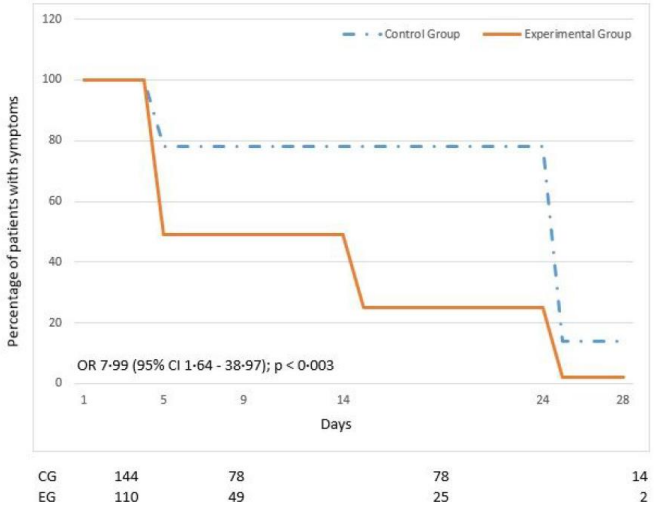
Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI) / p value**	**Absolute parameter (95%CI)**
Duration of fever – days (mean ± SD)	-	5 ± 1.7	13.6 ± 2.7	p=0.0001	-
Duration of cough – days (mean ± SD)		5 ± 1.9	14 ± 2.6	p=0.0001	-
Duration of dyspnea – days (mean ± SD)		4.4 ± 2.7	10.1 ± 3.4	p=0.0001	-
Duration of ansomia – days (mean ± SD)		2 ± 0.8	6.4 ± 3.3	p=0.0001	-
Duration of GIT symptoms – days (median, IQR)		5 (1-9)	4 (1-9)	p=0.884	-
Duration of PCR negative conversion (mean ± SD)		8.3 ± 2.8	12.9 ± 4.3	p=0.0001	-
PCR Negative Conversion	7 days	54/57 (94.7)	43/57 (75.4)	^RR=0.21 (0.07; 0.71)	NNT=6 (4; 15)
Author's conclusion: Local use of ivermectin mucoadhesive nanosuspension nasal spray is safe and effective in treatment of patients with mild COVID-19 with rapid viral clearance and shortening the anosmia duration.					

*-defined as symptomatic case with lymphopenia or leucopenia with no radiological signs for pneumonia; ******- severe or critical COVID-19 was diagnosed by the presence of one or more of the following: (1) respiratory rate 30 cycles per minute or more, (2) resting room air oxygen saturation of 93% or less, (3) PaO2/FiO2 is
^Agency's own calculations

Tabela 11. Opis metodyki i wyników badania Chachla 2021 – leczenie

Chachla 2021				
Cluster Randomised Trials - Ivermectin Repurposing For COVID-19 Treatment Of Outpatients With Mild Disease In Primary Health Care Centers (ResearchSquare, 06.05.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Multi-center, randomized, open-label Study duration: 09/2020 – 01/2021 Argentina	N=254 (included in the analysis) Mild COVID-19 patients Inclusion criteria: – >18 years of age; – outpatients infected by SARS-CoV-2 confirmed by RT-PCR; – mild disease-patients with two or more of the following symptoms: fever <38.5°C and > 37.5°C isolated diarrheal episodes, hyposmia or hypogeusia, mild desaturation (between 96 and 93%), dyspnea, polyarthralgia, persistent headache, abdominal pain, erythema of the kidney, nonspecic rash Exclusion criteria: – hypersensitivity or allergy to ivermectin; – neurological pathology, renal insufficiency, hepatic insufficiency; – weight <40kg; – use of drugs that act on GABA, barbiturate and benzodiazepine receptors.	Ni=110 Ivermectin orally 4 tablets of 6 mg = 24 mg every 7 days for 4 weeks	Nc=144 Standard care	– Small sample size; – Pre-print.
		Symptomatic treatment: 500 mg paracetamol every 6 or 8h, no more than 4 tablets daily; 100 mg aspirin, 1 tablet per day with breakfast; 150 mg Ranitidine, 1 tablet in the morning, and 1 tablet at night		
	Age, median (IQR)	40 (19-53)	36 (29-48)	
	Male (%)	50	47	
	> 60 years (%)	11	5	
	Diabetes (%)	8	5	
	Hypertension (%)	13	13	
	Obesity (%)	7	3	
	Asthma (%)	0.9	1.4	

Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**
Death – n	28 days	0	0	-	-
Participants with symptoms		ND	ND	OR=7.99 (1.64; 38.97)	-
Outpatient discharge – n/N (%)		108/110 (98.2)	124/144 (86.1)	^RR=1.14 (1.06; 1.22)	^NNT=9 (6; 19)
Author's conclusion: Treatment with ivermectin in outpatients care with mild disease of COVID-19 managed to slightly reduce participants with symptoms. Also, this treatment improved the clinical state to obtain outpatient discharge, even in the presence of comorbidities. The treatment with ivermectin could significantly prevent the evolution to serious stages since the EG did not present any patient with referral to critical hospitalization.					

Chachla 2021
 Kaplan-Meier plot. Percentage of patients with symptoms: i) Enrollment, ii) 1st time frame from 5th to 9th day; iii) 2nd time frame from 10th to 14th day

^Agency's own calculations

Tabela 12. Opis metodyki i wyników badania Biber 2021 – leczenie

Biber 2021				
Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial (MedRxiv, 31.05.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Multi--center, randomized, double-blind, Study duration: 15/05/2020 – 30/01/2021 Israel	N=116 (89 included in the analysis) <u>Inclusion criteria</u>: – ≥18 years of age;; – COVID-19 confirmed by RT-PCR up to 7 days from symptoms onset (symptomatic cases were also included within 5 days from molecular diagnosis). <u>Exclusion criteria:</u> – weight <40kg; – RT-PCR results with Ct (cycle threshold) value >35 in first two consecutive; – comorbidities: cardiovascular disease, diabetes, chronic respiratory disease (excluding mild intermittent asthma), hypertension, and or cancer were defined as high-risk patients; – severe infection (defined as need for invasive or non-invasive ventilator support, ECMO, or shock requiring vasopressor support)	Ni=57 (47 included in the analysis) Ivermectin (40-69 kg: 12mg orally once a day for 3 days; ≥70kg: 15mg orally once a day for 3 days)	Nc=59 (42 included in the analysis) Placebo	– Small study sample; – No ITT analysis; – 6 patients were lost from follow-up; – Pre-print
	Age, median (IQR)	36 (32-50)	33.5 (26-47)	
	Male (%)	78.3	78.6	
	Symptomatic (%)	78.7	83.3	
	Days from symptoms onset, median (IQR)	4 (3-5)	4 (3-5)	

Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**
Viral clearance – n/N (%)	Day 6	34/47 (72)	21/42 (50)	OR=2.62 (1.09; 6.31) ^RR=1.45 (1.02; 2.05)	- ^NNT=5 (3; 38)
Author's conclusion: There were significantly lower viral loads and viable cultures in the ivermectin group, which could lead to shortening isolation time in these patients.					

*****- severe or critical COVID-19 was diagnosed by the presence of one or more of the following: (1) respiratory rate 30 cycles per minute or more, (2) resting room air oxygen saturation of 93% or less, (3) PaO2/FiO2 is 300 mmHg or less, (4) respiratory failure requiring mechanical ventilation, shock, organ dysfunction syndrome and ICU admission.
300 mmHg or less, (4) respiratory failure requiring mechanical ventilation, shock, organ dysfunction syndrome and ICU admission.
^Agency's own calculations

Tabela 13. Opis metodyki i wyników badania Shahbaznejad 2021 – leczenie

Shahbaznejad 2021					
Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial (Clinical Therapeutics, 6.05.2021)					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Multicenter, randomized, double blind, controlled clinical trial Patients' recruitment – 23/05–31/05/2020 Iran	N=69 Inclusion criteria: – hospitalized patients with moderate or severe* COVID-19 (age, >5 years; weight >15 kg)[1;] Exclusion criteria: – history of chronic liver and/or renal disease; – receipt of treatment with warfarin, an angiotensin-converting enzyme inhibitor, or a angiotensin II receptor antagonist; and acquired immunodeficiency.		Ni=35 Ivermectin – single oral dose (0.2mg/kg utilizing 3-mg tablets or a multiple thereof, on the first day of admission, at the following weight-based doses: 15 to 24 kg, 3 mg; 25 to 30 kg, 6 mg; 36 to 50 kg, 9 mg; 51 to 80 kg, 12 mg; and >80 kg, 0.2 mg/kg.	Nc=34 Supportive medical treatment (hydroxychloroquine and/or lopinavir/ritonavir)	– More than 30% of participants had negative RT-PCR test results; – Small sample size; – Patients in both arms were treated with other medications.
			All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated		
	Age (years), mean ± SD		47.63±22.20	45.18±23.11	
	Male sex (%)		51.4	52.9	
	Underlying disease (%)		62.9	47.1	
	RT-PCR (%)	Positive	64.7	62.5	
		Negative	35.3	35.7	
	Severe COVID-19 (%)		37.1	52.9	
	Duration of symptoms before admission (days), mean ± SD		6.21±3.60	6.38±2.86	
	Medication given (%)	Lopinavir / ritonavir	79.7	82.4	
		Chloroquine	75.4	85.3	
		Ceftriaxone	63.77	67.7	
		Azithromycin	58	0.5	
		Meropenem	14.5	8.8	
		Vancomycin	5.8	5.8	

Results					
Outcome		**Ivermectin**	**Control**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI) / p value**	**Absolute parameter (95%CI)**
Deaths, n/N (%)	no data	1/35 (2.8)	0	-	-
Oxygen needed, n/N (%)		10/35 (28.6)	9/34 (26.5)	^RR=1.08 (0.50; 2.32)	-
Duration of hospital stay (days), median (IQR)		6.0 (5.0; 8.0)	7.0 (7.0; 10.0)	p=0.016	-
Duration of symptoms (days), median (IQR)		4.0 (3.0; 5.0)	5.0 (4.0; 7.0)	p=0.023	-
Mechanical ventilation required, n/N (%)		2/35 (5.71)	1/35 (2.9)	^RR=1.94 (0.18; 20.44)	-
Author's conclusion: A single dose of ivermectin was well-tolerated in symptomatic patients with COVID19, and important clinical features of COVID19 were improved with ivermectin use, including dyspnea, cough, and lymphopenia.					

[1]The diagnostic criteria for COVID-19 included any of the following: (1) positive result on COVID-19 reverse-transcription polymerase chain reaction; (2) clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or (3) abnormalities on chest computed tomography (CT) compatible with COVID19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration)
* The severe form of the disease was defined as tachypnea (respiratory rate of ≥24 breaths/min), need for mechanical ventilation, need for supplemental oxygen, and oxygen saturation of <94% in the ambient air.
^Agency's own calculations

Tabela 14. Opis metodyki i wyników badania Samaha 2021 – profilaktyka

Samaha 2021				
Open AccessArticle Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon (Viruses, 26.05.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Randomized, pilot study Lebanon Study duration: 09/2020 – 11/2020	N=100 (included in the analysis) Asymptomatic SARS-CoV-2-positive subjects. <u>Inclusion criteria</u>: – adults; – weight ≥45 kg; – SARS-CoV-2-positive based on a PCR (Ct >20). <u>Exclusion criteria:</u> – end-stage kidney or liver diseases; – pulmonary fibrosis; advanced COPD; heart failure NYHA class IV; – recent cardiac intervention (less than two months).	Ni=50 Ivermectin 45–64 kg, 65–84 kg, or above 85 kg received 9 mg, 12 mg, or 150 µg/kg body weight orally once-off	Nc=50 Standard preventive care	– Pilot study – Small study sample; – Lack of information on blinding; – Compliance of the patients has not been monitored and drug plasma concentration was not measured; – Lack of information on the potential use of self-medications.
		Standard preventive care: zinc and vitamin C supplements		
	Age, mean ± SD	31.78 ± 7.85	31.58 ± 7.68	
	Male (%)	50	50	
	Ct-values – mean ± SD	15.13 ± 2.07	14.20 ± 2.48	
	Diabetes (%)	6	6	
	Hypertension (%)	8	8	

Results						
Outcome			**Ivermectin**	**Control**	**Statistical significance of differences**	
event		**follow-up period**			**Relative parameter (95%CI) / p**	**Absolute parameter (95%CI)**
Ct-values – mean ± SD		Day 3	30.14 ± 6.22	18.96 ± 3.26	p <0.001	–
Development of clinical symptoms – n/N (%)	Fever		1/50 (2)	11/50 (22)	^RR=0.09 (0.01; 0.68)	^NNT=5 (3; 13)
	Cough		2/50 (4)	5/50 (10)	^RR=0.40 (0.08; 1.97)	–
	Runny Nose		1/50 (2)	2/50 (4)	^RR=0.50 (0.05; 5.34)	–
	Headache		2/50 (4)	5/50 (10)	^RR=0.40 (0.08; 1.97)	–
	Anosmia		3/50 (6)	16/50 (32)	^RR=0.19 (0.06; 0.60)	^NNT=4 (3; 9)
	Myalgia		0/50 (0)	9/50 (18)	^RR=0.05 (0.003; 0.88)	^NNT=6 (4; 15)
	Loss of Taste		3/50 (6)	12/50 (24)	^RR=0.25 (0.08; 0.83)	^NNT=6 (3; 23)
	Fatigue		0/50 (0)	3/50 (6)	^RR=0.14 (0.008; 2.70)	–
	Dizziness		0/50 (0)	2/50 (4)	^RR=0.20 (0.01; 4.06)	–
Hospitalization – n/N (%)			0/50 (0)	3/50 (6)	^RR=0.14 (0.008; 2.70)	–
Author's conclusion: Ivermectin appears to be efficacious in providing clinical benefits in a randomized treatment of asymptomatic SARS-CoV-2-positive subjects, effectively resulting in fewer symptoms, lower viral load and reduced hospital admissions. However, larger-scale trials are warranted for this conclusion to be further cemented.						

^Agency's own calculations

Ct – Cycle threshold

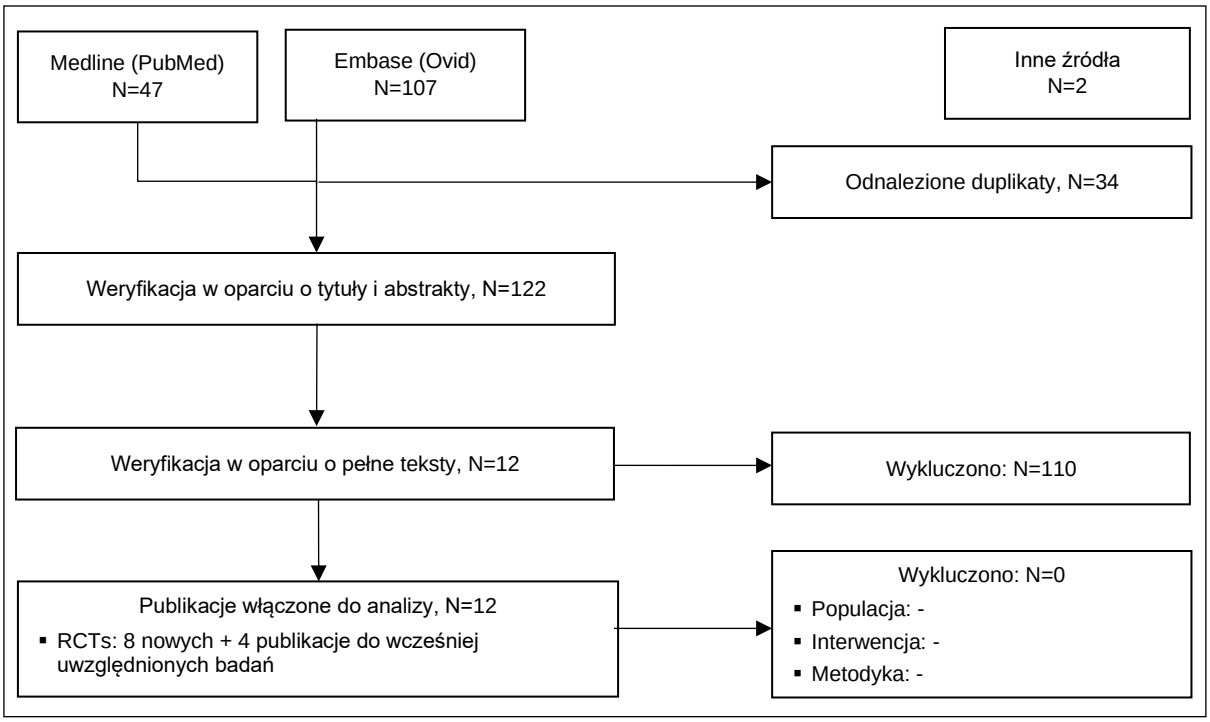
Tabela 15. Opis metodyki i wyników badania Seet 2021 – profilaktyka

Seet 2021								
Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial (International Journal of Infectious Diseases, 14.04.2021)								
Methodology	**Population**		**Intervention 1**	**Intervention 2**	**Intervention 3**	**Intervention 4**	**Intervention 5**	**Limitations**
Open-label parallel randomized controlled trial Duration of the study: 18/05/2020 – 1/06/2020 Singapore Subjects were randomized in clusters, with each cluster defined by the residential floor of a multi-story dormitory complex.	N=3037 Healthy migrant workers (male) quarantined in a large multi-storey dormitory in Singapore <u>Inclusion criteria:</u> – aged 21 to 60; <u>Exclusion criteria:</u> – symptom(s) of respiratory illnesses (fever, cough, runny nose, sore throat and/or shortness of breath), – dysgeusia or anosmia in the past one month, – previous diagnosis of COVID-19.		N1=432 Hydroxychloro-quine - 400 mg (four tablets) once, followed by 200 mg (two tablets) daily for 42 days.	N2=617 Ivermectin - 200 ug/kg in single dose; 12 mg was administered in participants who weighed >60 kg	N3=735 Povidone-iodine - three times daily (app. 270 ug/day) for 42 days	N4=634 Zinc (40 mg) + Vitamin C (250 mg) twice daily for 42 days	N5=619 Vitamin C – 500 mg once daily for 42 days	– Study included only young to middle-aged men with fewer comorbidities living in a dormitory; – For 42 days patients had to self-administer all study drugs except of ivermectin and 1st dose of HCQ – HCQ, IVM, I-I and Zn+vit.C were compared to vit. C arm rather than ex. placebo; – Authors did not perform nasopharyngeal swabs for the entire cohort.
	Mean age (SD) – yr		30.6 (6.4)	33.6 (6.9)	32.0 (6.6)	33.2 (7.8)	32.9 (7.1)	
	Comorbidity, n (%)	Hypertension	0.5	1.3	0.4	1.9	0.5	
		Diabetes mellitus	0.2	0.3	0.4	0.3	0.3	
		Hyperlipidemia	0	0.5	0	0.2	0	

Results									
Outcome			**HCQ**	**IVM**	**Povidone-iodine**	**Zinc + Vitamin C**	**Vitamin C**	**Statistical significance of differences**	
event		**follow-up period**						**Relative parameter (95%CI) / p value***	**Absolute parameter (95%CI)^^**
Deaths, n/N (%)		42 days	0	0	0	0	0	-	-
Laboratory evidence of SARS-CoV-2 infection, n/N (%)	Overall (seropositive + RNA-positive)		212/432 (49)	398/617 (64.5)	338/735 (46.0%)	300/634 (47.3)	433/619 (70.0)	<u>HCQ vs. vit.C</u>: ^RR=0.70 (0.63; 0.78)	ARR= 21% (2; 42) / ^NNT=5 (4; 7)
								<u>IVM vs. vit. C</u>: p=0.50	ARR=5% (-10; 22)
								<u>P-I vs. vit. C</u>: ^RR=0.66 (0.60; 0.72)	ARR= 24% (7; 39) / ^NNT=5 (4; 6)
								<u>Zn+vit.C vs. vit. C</u>: ^RR=0.68 (0.61; 0.75)	^NNT=5 (4; 6)
	Seropositive		179/432 (41.4)	308/617 (49.9)	288/735 (39.2)	250/634 (39.4)	348/619 (56.2)	<u>HCQ vs. vit.C</u>: p=0.058	-
								<u>IVM vs. vit. C:</u> p=0.56	-
								<u>P-I vs. vit. C</u>: p=0.073	-
								<u>Zn+vit.C vs. vit. C:</u> p=0.12	-
	RNA-positive		32/432 (7.4)	90/617 (14.6)	50/735 (6.8)	50/634 (7.9)	85/619 (13.7)	<u>HCQ vs. vit.C</u>: p=0.1	-
								<u>IVM vs. vit. C:</u> p=0.97	-
								<u>P-I vs. vit. C:</u> p=0.054	-
								<u>Zn+vit.C vs. vit. C:</u> p=0.14	-
Acute respiratory symptoms, n/N (%)			31/432 (7.2)	35/617 (5.7)	43/735 (5.9)	34/634 (5.4)	69/619 (11.1)	<u>HCQ vs. vit.C</u>: p=0.14	-
								<u>IVM vs. vit. C:</u> ^RR=0.51 (0.34; 0.75)	^NNT=19 (12; 42)
								<u>P-I vs. vit. C</u>: p=0.054	-

Seet 2021								
							Zn+vit.C vs. vit. C: ^RR=0.48 (0.32; 0.71)	^NNT=18 (12; 37)
Symptomatic COVID-19, n/N (%)		29/212 (13.7)	32/398 (8.0)	42/338 (12.4)	33/300 (11.0)	64/433 (15.0)	HCQ vs. vit.C: p=0.80	-
							IVM vs. vit. C: ^RR=0.54 (0.37; 0.81)	^NNT=15 (10; 42)
							P-I vs. vit. C: p=0.41	-
							Zn+vit.C vs. vit. C: p=0.17	-
Pneumonia requiring hospitalization, n/N (%)		0	0	0	0	0	-	-
Interruption due to side effects, n/N (%)		3/432 (0.7)	0	15/735 (2.0)	44/634 (6.9)	29/619 (4.7)	HCQ vs. vit.C: ^RR=0.15 (0.05; 0.48)	^NNT=26 (17; 53)
							IVM vs. vit. C: ^RR=0.03 (0.01; 0.43)	^NNT=22 (15; 40)
							P-I vs. vit. C: ^RR=0.44 (0.24; 0.81)	^NNT=38 (23; 133)
							Zn+vit.C vs. vit. C: ^RR=1.48 (0.93; 2.34)	-
Author's conclusion: Chemoprophylaxis with either oral hydroxychloroquine or povidone-iodine throat spray was superior to oral vitamin C in reducing SARS-CoV-2 infection in young and healthy men**.**								

ARR – absolute risk reduction; HCQ – hydroxychloroquine; IVM – ivermectin; I-P povidone iodine; Zn - zinc
* P-vaues are for comparison versus vitamin C arm; ^Agency's own calculations; ^^98.75%CI in case of ARR



Rysunek 4. Proces selekcji doniesień, zgodnie z zaleceniami PRISMA (okres wyszukiwania: 15.05-02.08.2021)

Aneks 2 (RCTs uwzględnione w wersji 1.1, 21.05.2021)

Tabela 16. Opis metodyki i wyników badania Lopez-Medina 2021 – leczenie

López-Medina 2021					
Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 - A Randomized Clinical Trial (JAMA, 4.03.2021)					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Single-center, randomized (1:1), double-blind, placebo controlled, phase 2/3 Study duration: 15.07 – 21.12.2020 Colombia	N=476 patients – randomized (398 – included in primary analysis) Inclusion criteria: – >18 years of age; – SARS CoV2 / COVID 19 disease confirmed by RT-PCR; – onset of symptoms began within the previous 7 days and they had mild disease, defined as being at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or non-invasive). Exclusion criteria: – medical history of liver disease; – history of allergy to ivermectin or any of its components; – asymptomatic; – severe pneumonia; – received ivermectin within the previous 5 days; – subjects receiving Warfarin, erdafitinib, or quinidine; hepatic dysfunction or liver function test results more than 1.5 times the normal level.		Ni=238 – randomized; (200 – included in primary analysis) Ivermectin 300 mcg/kg/d for 5 days	Nc= 238 – randomized; (198 – included in primary analysis) Placebo for 5 days	– The study was not conducted or completed according to the original design, and the original primary outcome to detect the ability of ivermectin to prevent clinical deterioration was changed 6 weeks into the trial; – The placebo used in the first 65 patients differed in taste and smell from ivermectin. However, patients from the same household were not included until the placebo with the same organoleptic properties was available, and the lack of effect of ivermectin on the primary outcome was similar when compared with either formulation of placebo; – The study population was relatively young and results may differ in an older population; – The use of other treatments outside of clinical trials is allowed.
	Age, median (IQR), years		37 (29-47.7)	37 (28.7-49.2)	
	Female (%)		61	55	
	Race or ethnic group (%)	Mixed race[#]	89.0	90.4	
		Black or African American	8.0	8.1	
		Colombian native	3.0	1.5	
	Coexisting conditions (%)	Obesity (BMI ≥30)	18.5	19.4	
		Hypertension	14.0	12.6	
		Diabetes	5.0	6.1	
		Any coexisting condition	22.0	19.2	
	Medications initiated since symptom onset	NSAIDs	28.5	30.8	
		Other[##]	20.5	19.2	
		Macrolides	13.5	11.1	
		Other antipyretics	13.0	11.6	
		Nonmacrolide antibiotics	6.5	5.6	
		Glucucorticoids	3.0	6.1	
		Anticoagulants	0.5	3.5	
	Median time (IQR) from symptom onset to randomization, days		5 (4-6)	5 (4-6)	

López-Medina 2021					
Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI) / p**	**Absolute difference**
Time to resolution of symptoms (days), median (IQR)	21 days	10 (9-13)	12 (9-13)	HR=1.07 (0.87; 1.32)	−2 (−4; 2)
Symptoms resolved, n/N (%)		164/200 (82.0)	156/198 (79.0)	OR=1.23 (0.75; 2.01)	3.21 (−4.58; 11.01)
Deterioration by ≥2 points in an ordinal 8-point scale**		4/200 (2.0)	7/198 (3.5)	OR=0.56 (0.16; 1.93)	−1.53 (−4.75; 1.69)
Fever (≥38 °C) since randomization, n/N (%)		16/200 (8.0)	21/198 (10.6)	OR=0.73 (0.37; 1.45)	−2.61 (−8.31; 3.09)
Escalation of care since randomization***, n/N (%)		4/200 (2.0)	10/198 (5.0)	OR=0.38 (0.12; 1.24)	−3.05 (−6.67; 0.56)
Duration of care (days), median (IQR)		13 (3.5-21)	6 (3.7-10.7)	-	7 (−5; 16.5)
Deaths, n/N (%)		0/200 (9)	1/198 (0.5)	-	-
Adverse events, n/N (%)		154/200 (77)	161/198 (81.3)	RR=0.95 (0.86; 1.05)^	-
Serious adverse events, n/N (%)		2/200 (1)	2/198 (1.1)	RR=0.99 (0.14; 6.96)^	-
Discontinuation of treatment due to AE, n/N (%)		15/200 (7.5)	5/198 (2.5)	RR=2.97 (1.1; 8.02)^	NNT=21 (11; 141)^
Post-hoc analysis					
Escalation of care occurring ≥12 h since randomization	21 days	4/200 (2.0)	6/198 (3.0)	OR=0.65 (0.18; 2.36)	−1.0 (−4.11; 2.05)
Duration of care (days), median (IQR)		13 (3.5-21)	8 (4.2-13.2)	-	5 (−8.5; 16)
Emergency department visits or telemedicine consultations, n/N (%)		16/200 (8.0)	13/198 (6.6)	OR=1.24 (0.56; 2.74)	1.43 (−3.67; 6.54)
Author's conclusion: Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.					

refers to an individual of mixed European/Colombian native heritage; ## Acyclovir, antidiarrheals, antiemetics, antihistamines, antiparasitics, antispasmodics, antitussives, natural or homeopathic medications, proton pump inhibitors, and salbutamol

*defined as the first day during the 21 days of follow-up in which the patient reported a score of 0.; **Ordinal scale: 0 = no clinical evidence of infection; 1 = not hospitalized and no limitation of activities; 2 = not hospitalized, with limitation of activities, home oxygen requirement, or both; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, requiring nasal high-flow oxygen, non-invasive mechanical ventilation, or both; 6 = hospitalized, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; and 7 = death; ***Escalation of care defined as new-onset hospitalization in the general ward or intensive care unit or new-onset supplementary oxygen requirement for more than 24 hours.

^Agency's own calculation

Tabela 17. Opis metodyki i wyników badania Mohan 2021 – leczenie

Mohan 2021						
Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial (ResearchSquare, 02/02/2021)						
Methodology	**Population**		**Intervention 1**	**Intervention 2**	**Control**	**Limitations**
Randomized, double-blind, placebo-controlled Randomization 1:1:1 Duration of the study: no data India	N=157 (125 patients were included in mITT analysis) Adults with mild to moderate COVID-19. <u>Inclusion criteria:</u> – >18 years; – diagnosed (based on a positive result on either SARS-CoV-2 RT-PCR or the rapid antigen test) non-severe COVID-19 (i.e. room air saturation (SpO2) >90%, no hypotension or requirement of mechanical ventilation. <u>Exclusion criteria</u>: – chronic kidney disease with creatinine clearance <30 mL/min; – elevated transaminase levels (>5 x upper limit of normal); – myocardial infarction or heart failure within 90 days prior to enrolment, – prolonged corrected QT interval (>450 ms) on electrocardiogram.		Ni1=40 Oral ivermectin (12 mg single dose)	Ni2=40 Oral ivermectin (24 mg single dose)	Ni3=45 placebo	– Modified intention-to-treat analysis; – Single center study with a relatively small sample size; – Diagnosis of COVID-19 may based on a positive result of the rapid antigen test.
	Mean age ± SD – yr		36.3	34.3	35.3	
	Male sex – %		87.5	92.5	86.2	
	Severity – %	Mild	67.5	60	64.4	
		Moderate	32.5	40	35.6	
	WHO Ordinal Scale at baseline – %	3	87.5	95	93.3	
		4	12.5	5	6.7	
	Asymptomatic at the time of enrolment (%)		27.5	22.5	17.7	
	Duration of symptoms prior to enrolment (days), median (IQR)		5 (3-7)	4 (3-7)	4 (3-6)	

Results							
Outcome			**Intervention 1**	**Intervention 2**	**Control**	**Statistical significance of differences**	
event		**follow-up period**				**Relative parameter (95%CI) / p**	**Absolute difference**
Negative RT-PCR in mITT population		Day 3	7/40 (17.5)	3/40 (7.5)	7/45 (15.6)	p= 0.42	-
		Day 5	14/40 (35)	19/40 (47.5)	14/45 (31.1)	p= 0.30	-
		Day 7	13/36 (36.1)	16/36 (44.4)	16/42 (38.1)	p= 0.79	-
Days to symptom resolution#, mean (SD)			4.76 (2.44)	4.26 (2.65)	4.58 (2.94)	p= 0.77	-
Change in WHO Ordinal Scale score between daily 0-14, n (%)	No change	Day 14	3 (7.5)	2 (5)	5 (11.1)	p= 0.67	-
	Decrease by 1		0	1 (2.5)	1 (2.2)		
	Decrease by 2		32 (80)	35 (87.5)	37 (82.2)		
	Decrease by 3		5 (12.5)	2 (5)	2 (4.4)		
Discharge – n/N (%)		Day 14	38/40 (95)	37/40 (92.5)	39/45 (86.7)	p= 0.42	-
Any clinical worsening ##			2 (5)	3 (7.5)	5 (11.1)	p= 0.65	-
Adverse events – n (%)			8 (16.3)	6 (11.8)	6 (11.5)	p = 0.76	-
Serious adverse events – n			0	0	0	-	-
Death – n			0	0	0	-	-
Author's conclusion: In patients with mild and moderate COVID-19, a single administration of Ivermectin elixir (either 24 mg or 12 mg) demonstrated a trend towards higher proportion of RT-PCR negativity at day 5 of enrolment.							

Tabela 18. Opis metodyki i wyników badania Beltran-Gonzalez 2021 – leczenie

Beltran-Gonzalez 2021						
Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial (Preprint; MedRxiv, 23.02.2021); NCT04391127						
Methodology	**Population**		**Intervention 1**	**Intervention 2**	**Control**	**Limitations**
RCT, double-blind Patients with QT interval ≥ 500 ms randomized to IVM or PLB, patients with an interval < 500 ms to IVM, HCQ or PLB Mexico	N=106 Non-critically ill patients with pneumonia secondary to COVID-19 and fulfilling hospitalization criteria. Inclusion criteria: – positive RT-PCR for SARS-CoV-2; – pneumonia, diagnosed by X-ray or HR-CT; – recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart. Exclusion criteria: – required high oxygen volumes (face mask >10 L/ min); – predictors of a poor response to high-flow oxygen nasal prong therapy; – required mechanical ventilation.		Ni1=36 Ivermectin (IVM) 12 mg (if body mass <80kg) or 18 mg (if body mass >80 kg)	Ni2=33 Hydroxychloroquine (HCQ) 400 mg every 12h on the first day and subsequently, 200 mg every 12h for 4 days	Nc=37 Placebo (calcium citrate) 2 tabl. every 12h on day 1, then 1 tabl. every 12h for 4 days	– Limited number of patients per group; – Pre-print status of publication; – No data on follow-up period
			• All hospitalized patients received thromboprophylaxis with low molecular weight heparin or unfractionated heparin. • Dexamethasone, 6 mg IV every 24h, for 10 days or until discharge, in patients requiring oxygen therapy.			
	Age [years] mean (±SD)		56 (16.5)	48.9 (15.3)	53.8 (16.9)	
	Male, %		58.3	66.6	62.1	
	$SatO_2$, mean (±SD)		83 (8)	86 (9)	83 (8)	
	Concomitant medications, %	Antibiotics	61.1	45.4	50	
		Thromboprophylaxis	100	90.9	94.5	
		Steroids	58.3	63.6	51.3	
	Comorbidities, %	Hypertension	33.3	24.2	37.8	
		Chronic kidney disease	5.5	6.1	2.7	
		COPD	5.5	3	10.8	
		Diabetes Mellitus	25	33.3	43.2	

Results						
Outcome		**IVM**	**HCQ**	**PLB**	**Statistical variability of differences**	
event	**follow-up period (days)**				**relative parameter* (95% CI)/p**	**absolute parameter**
Death, n/N (%)	ND	5/36 (13.8)	2/33 (6)	6/37 (16.2)	IVM vs PLB: ^RR=0.86 (0.29; 2.56) IVM vs HCQ: ^RR=0.98 (0.84; 1.15)	-
Duration of hospitalization [days], med (IQR)	NA	6 (4–11)	7 (3–9)	5 (4–7)	p=0.43	-
Hospital discharge, n/N (%)	ND	32/36 (88.8)	30/33 (90.9)	34/37 (91.8)	IVM vs PLB: ^RR=0.97 (0.83; 1.12) IVM vs HCQ: ^RR=0.98 (0.84; 1.15)	-
Discharge without respiratory deterioration or death, n/N (%)		27/36 (75)	26/33 (78.7)	27/37 (72.9)	IVM vs PLB: ^RR=1.03 (0.78; 1.35) IVM vs HCQ: ^RR=0.95 (0.74; 1.23)	-
Respiratory deterioration or death, n/N (%)		8/36 (22.2)	6/33 (18.1)	9/37 (24.3)	IVM vs PLB: ^RR=0.91 (0.40; 2.11) IVM vs HCQ: ^RR=1.22 (0.48; 3.15)	-
Authors' conclusions: In non-critical hospitalized patients with COVID-19 pneumonia, neither ivermectin nor hydroxychloroquine decreases the number of in-hospital days, respiratory deterioration, or deaths.						

Tabela 19. Opis metodyki i wyników badania Kishoria 2020 – leczenie

<table>
<tr><th colspan="5">Kishoria 2021</th></tr>
<tr><th colspan="5">Ivermectin as adjuvant to hydroxycholoroquine in patients resistant to standard treatment for SARS-CoV-2: results of an open-label randomized clinical study (Indian Journal Of Research 08.2020)</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="4">Single-center, randomized, open-label

Study duration: no data

India</td><td rowspan="2">N=32
Hospitalized COVID-19 patients.

<u>Inclusion criteria</u>:
– ≥18 years;
– positive test after completion of standard care treatment for SARS-CoV-2 confirmed by RT-PCR assay;
– mild/ asymptomatic;
– no comorbidities rendering high-risk patients; informed consent obtained.
<u>Exclusion criteria:</u>
– respiratory distress or requiring intensive care;
– used immunosuppressants (including systemic corticosteroids) in the last 30 days;
– known HIV infection with CD4 count <300 cell/ L;
– medical conditions such as malabsorption syndromes affecting proper ivermectin absorption; autoimmune disease and/or decompensated chronic diseases;
– uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina or heart arrhythmia;
– concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity.</td><td>Ni= 19

Ivermectin (12mg single dose)
+ SoC</td><td>Nc= 13

SoC</td><td rowspan="4">– Lack of detailed information on baseline characteristics of patients;
– Small sample size.</td></tr>
<tr><td colspan="2">standard of care:
5 days: hydroxychloroquine 400 mg twice a day paracetamol 500mg as required, vitamin C 1 tab twice a day</td></tr>
<tr><td>Age, mean</td><td>39.5</td><td>37.0</td></tr>
<tr><td>Female (%)</td><td>26.3</td><td>30.7</td></tr>
<tr><th colspan="5">Results</th></tr>
<tr><th colspan="2" rowspan="2">Outcome</th><th rowspan="2">Ivermectin</th><th rowspan="2">Placebo</th><th colspan="2">Statistical significance of differences</th></tr>
<tr><th>event</th><th>follow-up period</th><th>Relative parameter (95%CI) / p</th><th>Absolute difference</th></tr>
<tr><td>PCR negativity, n/N (%)</td><td>Day 3</td><td>8/19 (42.2)</td><td>6/13 (46.2)</td><td>^RR=0.91 (0.41; 2.01)</td><td>-</td></tr>
<tr><td>Discharged patients at end of study</td><td>ND</td><td>8/19 (42.2)</td><td>6/13 (46.2)</td><td>^RR=0.91 (0.41; 2.01)</td><td>-</td></tr>
<tr><td colspan="6">Author's conclusion: In summary, this open label randomized study of patients with COVID-19 found that the use of a regimen containing hydroxychloroquine and ivermectin was associated with no evidence of benefit in comparison to hydroxychloroquine alone. However, it was observed that ivermectin was well tolerated with no serious drug related adverse event thus a large sample sized randomized clinical trial may be initiated to further investigate its efficacy as anti-viral agent inCOVID19.</td></tr>
</table>

Tabela 20. Opis metodyki i wyników badania Galan 2021 – leczenie

Galan 2021						
Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection (Pathogens and Global Health)						
Methodology	**Population**		**Intervention**	**Control**		**Limitations**
Randomized, double-blind, single-center, placebo controlled, phase 2 Study duration: 1/05/2020 – 16/07/2020 Brazil	N=168 patients Inclusion criteria: – laboratory test confirming infection by SARS-CoV-2 (positive serologic test IgM or rt-PCR); – hospitalized with a clinical, epidemiological, and radiological picture compatible with COVID-19; – over 18 years old; – present a severe form of the disease characterized by one of the following clinical signs: dyspnea, tachypnea (>30 bpm), peripheral oxygen saturation <93% (pulse oximeter evaluation), PaO2/FiO2 ratio <300, or infiltrate pulmonary>50% of the parenchyma seen on chest tomography or chest radiography. Exclusion criteria: – critically ill patients who are not accompanied by legal representatives; – cardiac arrhythmia that include prolongation of the QT interval; – previous use of any of the medications surveyed for more than 24 h.		Ni= 53 Ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg. For participants with body weight <55 kg, IVM dose was adjusted to 10 mg each dose.	Nc1=54 Hydroxychloroquine (HCQ) 2x400 mg on day 0, and once daily from day 1 to day 4, total dose 2.4 g	Nc2=61 Chloroquine (CQ) 2x450 mg on day 0, and once daily from day 1 to day 4, total dose 2.7 g	– High percentage of Hispanic origin people (78,9%); – High percentage of patients with corticosteroids therapy.
	Age, mean ± SD		53.2 (±17.3)	54.8 (±15,5)	51.9 (±14.0)	
	Male (%)		60.7	56.8	57.8	
	Coexisting conditions (%)	Hypertension	42.8	45.2	42.1	
		Diabetes	28.5	24.5	28.5	
		Chronic renal failure	4.0	0	4.0	
		Previous pulmonary disease	3.7	5.5	3.7	
		Cancer	4.0	3.7	4.0	

Results							
Outcome			**Ivermectin**	**HCQ**	**CQ**	**Statistical significance of differences**	
event		**follow-up period**				**Relative risk (95%CI) / p value**	**Absolute difference**
Death due to COVID complications – n/N (%)		nd	12/53 (23.0)	12/54 (22.2)	13/61 (21.3)	IVM vs HCQ: 1.02 (0.50; 2.06) IVM vs. CQ: 1.06 (0.53; 2.12)	-
The need of oxygen supplementation – n/N (%)		nd	52/53 (88.4)	49/54 (90.2)	54/61 (88.5)	ns	-
Duration of oxygen need (days) (SD)		-	8.1 (±2.0)	7.8 (±2.1)	7.9 (±2.3)	-	-
Corticosteroid therapy – n/N (%)		nd	51/53 (97)	54/54 (100)	60/61 (98)	ns	-
Duration of corticosteroides treatment (days) (SD)		-	6.9 (±1.7)	6.8 (±2.0)	7.2 (±1.8)	-	-
Anticoagulant therapy – n/N (%)		nd	16/53 (30.4)	18/54 (32.9)	22/61 (36.7)	ns	-
ICU admission – n/N (%)			15/53 (28.0)	11/54 (21.1)	14/61 (22.4)	ns	-
Need for vasoactive drugs – n/N (%)			14/53 (26.0)	11/54 (21.1)	12/61 (20.6)	ns	-
Need for invasive ventilation – n/N (%)			13/53 (23.5)	11/54 (21.1)	20.6	ns	-
Adverse events – n/N	Arrhythmia (clinically significant)	nd	0	0	0	-	-
	Elevated liver Transminases G1/G2		8/53 (14.2)	8/54 (15.2)	8/61 (13.4)	ns	-

Galan 2021							
(%)	Elevated liver Transminases G3/G4		1/53 (11.2)	6/54 (10.2)	5/61 (8.5)	ns	-
	Anemia (hemoglobin < 8 g/dL)		6/53 (7.8)	3/54 (5.5)	3/61 (5.2)	ns	-
	Leukopenia (<1500/mm^3)		1/53 (2.2)	3/54 (5.5)	2/61 (3.2)	ns	-
Author's conclusion: Although CQ. HCQ or ivermectin revealed a favorable safety profile. the tested drugs do not reduce the need for supplemental oxygen. ICU admission. invasive ventilation or death. in patients hospitalized with a severe form of COVID-19.							

IVM – ivermectin; nd – no data; ns – no significant difference between the three groups

Tabela 21. Opis metodyki i wyników badania Shah Bukhari 2021 – leczenie

Shah Bukhari 2021					
Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease (MedRxiv, 5.02.2021)					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Single-center, randomized, open-label Study duration: 15.03 – 15.06.2020 Colombia	N=100 (86 included in the analysis) <u>Inclusion criteria</u>: – 15-65 years; – COVID-19 positive, proven by RT-PCR; – mild (fever <38ºC quelled without treatment with or without cough, no dyspnea, no gasping, no chronic disease, no imaging findings of pneumonia) to moderate (fever, respiratory symptoms, imaging findings of pneumonia) severity of the disease; consent for trial, stated their willingness to comply with all study procedures, agreed for admission for the trial period (14 days); <u>Exclusion criteria:</u> – severe symptoms likely due to cytokine release syndrome; – uncontrolled co-morbidities; malignant diseases; diabetes mellitus; chronic kidney disease; cirrhosis liver with CPT class B or C; immunocompromised; – taking CYP 3A4 inhibitors or inducers; – oxygen requirements equivalent to FiO2 ≥50% in moderate severity patients.		Ni= 50 (41 included in the analysis) Ivermectin 12 mg at administration	Nc= 50 (45 included in the analysis) standard care (oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS)	– No information about concomitant treatment; – The duration and severity of individual symptoms and time of resolution of these symptoms were not studied; – Most of the patients were lost to follow up after the trial period concluded and very few could be traced back to assess for any potential adverse reaction that may have occurred due to treatment with ivermectin, hence prolonged safety of drug could not be established; – Pre-print.
	Age, mean ± SD		42.24 ± 12.0	38.98 ± 12.61	
	Female (%)		9.8	20	
	Coexisting conditions (%)	Diabetes	14.6	8.9	
		Hypertension	12.2	15.6	
		Ischemic heart disease	7.3	4.4	

Results					
Outcome		**Ivermectin**	**Placebo**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI) / p**	**Absolute difference**
PCR negativity, n/N (%)	72 hours	17/41 (41.1)	2/45 (4.4)	RR=9.32 (2.29; 37.9)^	NNT=3
	7 days	20/41 (49.9)	18/45 (40.0)	RR=1.21 (0.76; 1.97)^	-
	14 days	4*/41	25/45 (55.6)	*	-
Adverse side effects	14 days	-	-	-	-
	28 days	-	-	-	-
Author's conclusion: In the intervention arm, early viral clearance was observed in patients without experiencing any side effects. These are of importance because high viral load and prolonged viremia can potentially trigger the immune dysregulation phase leading to more severe disease, and the requirement of treatment escalation.					

Tabela 22. Opis metodyki i wyników badania Pott-Junior 2021 – leczenie

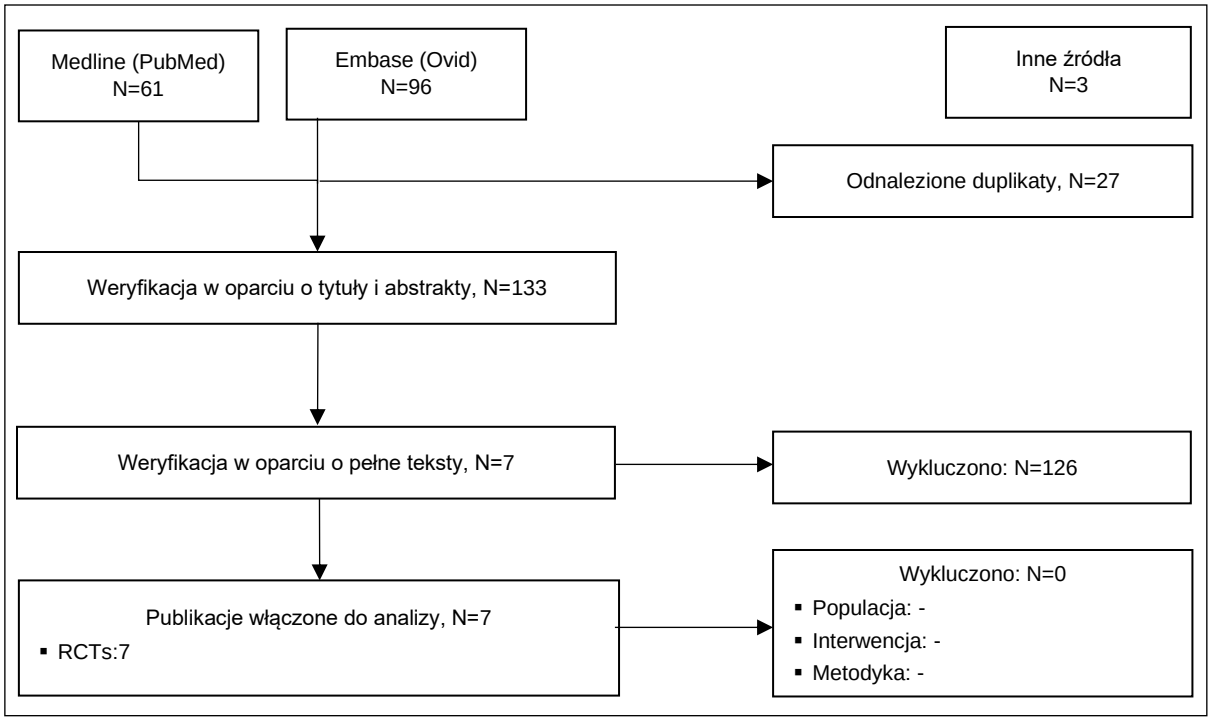
Pott-Junior 2021						
Use of ivermectin in the treatment of Covid-19: A pilot trial (NCT04431466, ELSEVIER, 09.03.2021)						
Methodology	**Population**	**Intervention 1**	**Intervention 2**	**Intervention 3**	**Control**	**Limitations**
RCT, double-blind, phase 2a Brazil	N=32 <u>Inclusion criteria:</u> – ≥18 years; – ECOG score of 0-1; – NEWS score of 0-4; – SARS-CoV-2 infection confirmed by RT-PCR (nasopharyngeal swab specimens). <u>Exclusion criteria:</u> – any abnormal ECG findings that require additional evaluation; – known hypersensitivity to the drug components used during the study; – body weight <15 kg; an estimated glomerular filtration rate (CKD-Epidemiology Collaboration, CKD-EPI) <30 mL/min; and values of AST or ALT 5-fold above the upper limit of normality.	N1=7 Ivermectin + SoC: 100 mcg/kg	N2=14 Ivermectin + SoC: 200 mcg/kg	N3=7 Ivermectin + SoC: 400 mcg/kg	N4=4 SoC	– Small sample size; – No detail information on intervention used as standard of care.
	Age [years] mean (±SD)	50 ±9	49 ± 13.5	47 ± 22.9	54.2 ±9.6	
	Female, %	66.7	35.7	57.1	54.8	
	Time from symptom onset to hospital admission, days	7	8	9	9.5	
	Concomitant medications, % – LMWH – intermediary dose	16.7	35.7	0	25	
	Concomitant medications, % – Antibiotics	16.7	35.7	100	75	
	Concomitant medications, % – Steroids	16.7	35.7	14.3	75	

Results							
Outcome						**Statistical variability of differences**	
event	**follow-up period (days)**	**IVM 100**	**IVM 200**	**IVM 400**	**SoC**	**relative parameter* (95% CI)/p**	**absolute parameter**
Undetectable levels of SARS-CoV-2* – n/N (%)		3/6 (50)	10/14 (71.4)	4/7 (57.1)	2/3	-	-
Time to achieve undetectable viral load, days	-	6	5	5	6	-	
Total adverse events – n/N (%)		1/7 (16.7)	5/14 (35.7)	1/7 (14.3)	2/4 (50)	-	-
Authors' conclusions: Ivermectin is safe in patients with SARS-CoV-2, reducing symptomatology and the SARS-CoV-2 viral load. This antiviral effect appears to depend on the dose used, and if confirmed in future studies, it suggests that ivermectin may be a useful adjuvant to the SOC treatment in patients with mild COVID-19 symptoms.							

ALT – alanine aminotransaminase; AST – aspartate aminotransaminase; ECOG – Eastern Cooperative Oncology Group; NEWS – National Early Warning Score; RT-PCR – real-time reverse transcription polymerase chain reaction

*Defined as defined as two consecutive SARS-CoV-2 RT-PCR tests with negative results (Ct above 40) within 7 days of the start of study dosing period.

Comment: Due to very low sample AOTMiT didn't calculate parameters



Rysunek 5. Proces selekcji doniesień, zgodnie z zaleceniami PRISMA (okres wyszukiwania: 29.01-14.05.2021)

Aneks 3 (RCTs uwzględnione w wersji 1.0, 4.02.2021 r.)

Tabela 23. Opis metodyki i wyników badania Ahmed 2020 – leczenie

Ahmed 2020					
A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness (International Journal of Infectious Diseases, 26.11.2020)					
Methodology	**Population**	**Intervention 1**	**Intervention 2**	**Control**	**Limitations**
Randomized, double-blind, placebo-controlled Randomization 1:1:1 Duration of the study: no data Bangladesh	N=75 (72 included in the final analysis)* Adults with mild COVID-19. <u>Inclusion criteria:</u> – age 18–65 years; – admitted to hospital within the last 7 days; – presence of a fever (>37.5°C), cough, and/or sore throat; – diagnosed positive for SARS-CoV-2 by rRT-PCR. <u>Exclusion criteria</u>: – chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); – received of ivermectin and/or doxycycline in the last 7 days. The duration of illness before assessment was an average of 3.83 days.	Ni1=24 (22 included in the final analysis)* Oral ivermectin alone (12 mg once daily for 5 days)	Ni2=24 (23 included in the final analysis)* Oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days)	Nc=24 (23 included in the final analysis)* Placebo	– Lack of detailed characteristics of patients in study arms; – No detailed results for all analyzed endpoints; – No detailed information about randomization method, blinding and statistical methods; – Supported by Beximco Pharmaceutical Limited, Bangladesh.
	Mean age ± SD – yr	42			
	Female sex – %	54			
	Fever at enrolment – n/N (%)	17/22 (77.3)	17/23 (73.9)	19/23 (82.6)	
	Cough at enrolment – n/N (%)	18/22 (81.8)	19/23 (82.6)	15/23 (65.2)	
	Sore throat at enrolment – n/N (%)	4/22 (18.2)	3/23 (13)	4/23 (17.4)	

Results							
Outcome			**Intervention 1 (IVM)**	**Intervention 2 (IVM+DOX)**	**Control (PLB)**	**Statistical significance of differences**	
event		**follow-up period**				**Relative parameter (95%CI) / p value**	**Absolute difference**
Duration of hospitalization after treatment – days, mean (95%CI)		14 days**	9.6 (7.7; 11.7)	10.1 (8.5; 11.8)	9.7 (8.1; 11.0)	p=0.93	-
Duration to viral clearance – days, mean (95%CI)	All patients		9.7 (7.8; 11.8)	11.5 (9.8; 13.2)	12.7 (11.3; 14.2)	**IVM vs PLB: p=0.005**	**-**
						IVM+DOX vs PLB: p=0.123	-
	Patients without co-morbidities		9	-	13	**IVM vs PLB: p=0.02**	-
Afebrile on day 7 – n/N (%)		7 days	17/17 (100)	16/17 (94.1)	16/19 (84.2)	IVM+DOX vs PLB: p=0.35 IVM vs PLB: p=0.09	-
Cough at on day 7 – n/N (%)			7/18 (61.1)	7/19 (63.2)	9/15 (40	IVM+DOX vs PLB: p=0.18 IVM vs PLB: p=0.23	-
Sore throat on day 7 – n/N (%)			3/4 (75)	1/3 (33.3)	3/4 (75)	IVM+DOX vs PLB: p=0.35 IVM vs PLB: p=0.09	-
Serious adverse drug events – n		14 days**	0	0	0	-	-
The mean values of the blood biomarkers (CRP, LDH, procalcitonin, and ferritin) dropped from baseline to day 7 in all three groups and these changes were significant for CRP (p=0.02) and LDH (p=0.01) in the 5-day ivermectin arm and for LDH in the placebo group (p=0.01).							
Author's conclusion: A 5-day course of ivermectin was found to be safe and effective in treating adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings.							

DOX – doxycycline; IVM – ivermectin; PLB – placebo; rRT-PCR – real-time reverse transcription PCR.
*24 patients were included per study arm.
One patient from each of the ivermectin + doxycycline and placebo groups and two patients in the 5-day ivermectin group withdrew their consent during the study due to family obligations and unwillingness to be tested

Ahmed 2020

further; ** After day 14, patients were followed-up weekly until found to be test-negative.

Tabela 24. Opis metodyki i wyników badania Ravikirti 2021 – leczenie (aktualizacja w wersji 1.2)

Ravikirti 2021					
Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India (Journal of Pharmacy & Pharmaceutical Sciences, 17.07.2021)					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Randomized, double-blind, placebo-controlled Duration of the study: 01/08/2020 – 31/10/2020 India	N=115 (112 included in the final analysis)* Adults with mild to moderate COVID-19. <u>Inclusion criteria:</u> – >18 years of age, – admitted with a diagnosis of COVID -19 (on the basis of a positive RT-PCR or Rapid Antigen Test report) with mild or moderate disease as defined by the ministry of health and family welfare guidelines** <u>Exclusion criteria:</u> – prior use of ivermectin during the course of this illness.		Ni1=57 (55 included in the final analysis)* Ivermectin (12 mg on day 1 and day 2 of admission)	Nc=58 (57 included in the final analysis)* placebo	– Most of patients received concomitant treatment; – Small sample size; – Diagnosis of COVID-19 may based on a positive result of the rapid antigen test; – Absence of conclusive 6th day RT-PCR report in 32.1%of the cases (41.8% in intervention arm and 22.8% in placebo arm); – As serial RT-PCR tests could not be considered due to feasibility, the median time to viral clearance in the two groups could not be ascertained.
	Mean age ± SD – yr		50.7±12.7	54.2±16.3	
	Female sex – no (%)		15 (27.3)	16 (28.1)	
	COVID-19 disease severity	Mild	42 (76.4)	46 (80.7)	
		Moderate	13 (23.6)	11 (19.3)	
	Comorbidities	Hypertension	21 (38.2)	18 (31.6)	
		Diabetes	21 (38.2)	19 (33.3)	
	Treatments	Hydroxychloroquine	55 (100)	57 (100)	
		Steroid	55 (100)	57 (100)	
		Enoxaparin	53 (96.4)	55 (96.5)	
		Antibiotics	55 (100)	57 (100)	
		Remdesivir	12 (21.8)	11 (19.3)	
		Convalescent Plasma	8 (14.5)	7 (12.3)	
		Tocilizumab	4 (7.3)	3 (5.3)	
		Other Drugs	36 (65.5)	38 (66.7)	
	Days since onset of symptoms ± SD		6.1±3.6	7.9±8.6	

Ravikirti 2021					
Results					
Outcome		**Intervention**	**Control**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter, RR (95%CI)**	**Absolute difference**
Negative RT-PCR (*primary outcome*) – n/N (%)	6 days	13/55 (23.6)	18/57 (31.6)	0.8 (0.4-1.4)	-
Symptom free – n/N (%)		46/55 (83.6)	51/57 (89.5)	0.9 (0.8-1.1)	-
Discharged – n/N (%)	10 days	44/55 (80)	42/57 (73.7)	1.1 (0.9-1.3)	-
Admission to ICU – n/N (%)	ND	5/55 (9.1)	6/57 (10.5)	0.9 (0.3-2.7)	-
Invasive Ventilation – n/N (%)		1/55 (1.8)	5/57 (8.8)	0.2 (0.0-1.7)	-
Final outcome: discharge – n/N (%)		55/55 (100)	53/57 (93)	1.1 (1.0-1.2)	-
Final outcome: in-hospital mortality – n/N (%)		0/55 (0)	4/57 (7)	^0.1 (0.0; 2.1)	-
Author's conclusion: Inclusion of ivermectin in treatment regimen of mild to moderate COVID-19 patients could not be said with certainty based on our study results as it had shown only marginal benefit in successful discharge from the hospital with no other observed benefits.					

ICU – Intensive Care Unit; RR- rate ratio; yr – years; ND – no data

*57 were randomised to the intervention arm, 58 to the placebo arm. One patient in either arm was administered ivermectin by the treating team and one patient in the intervention arm was lost to follow up from day 2. Excluding these three patients, 55 patients in the intervention arm and 57 patients in the placebo arm were included in the final analysis. ** Ministry of Health and Family Welfare (Government of India).Clinical Management Protocol: COVID-19 (Version 3, 13/06/2020): Mild COVID-19: No evidence of breathlessness or Hypoxia (normal saturation); Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease; Severe: Any of the following – Severe respiratory distress, oxygen saturation < 90% on room air, respiratory rate > 30, shock or evidence of a life threatening organ dysfunction; ^ Risk ratio, Agency's own calculations

Tabela 25. Opis metodyki i wyników badania Chachar 2020 – leczenie

<table>
<tr><th colspan="6">Chachar 2020</th></tr>
<tr><th colspan="6">Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients (International Journal of Sciences September, 2020)</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="18">Randomized, open-label, single-centre study

Randomization 1:1

Duration of the study: 01/05/2020 – 30/06/2020

Bangladesh</td><td colspan="2">N=50
Adults with mild COVID-19.

<u>Inclusion criteria:</u>
– patients diagnosed with COVID-19 infection with positive RT-PCR test,
– age of 18-75 years;
– mild symptoms of COVID;
<u>Exclusion criteria:</u>
– severe symptoms likely attributed to Cytokine Release Storm;
– malignant diseases; chronic kidney disease; cirrhosis liver with Child class B or C.</td><td>Ni1=25

Ivermectin (12 mg stat and then 12 mg after 12 hours and 12 mg after 24 hours)</td><td>Nc=25

No ivermectin</td><td rowspan="18">– Small sample size;
– No blinding;
– Single-centre study;
– Significant differences in baseline characteristic of patients;
– No information on the percentage of patients and kind of receiving a symptomatic treatment.</td></tr>
<tr><td colspan="2"></td><td colspan="2">symptomatic treatment</td></tr>
<tr><td colspan="2">Mean age ± SD – yr</td><td>40.60 ±17</td><td>43.08 ± 14.8</td></tr>
<tr><td colspan="2">Male sex – n</td><td>17</td><td>14</td></tr>
<tr><td colspan="2">Cough – n*</td><td>24</td><td>18</td></tr>
<tr><td colspan="2">Fever – n</td><td>25</td><td>24</td></tr>
<tr><td colspan="2">Sore throat – n</td><td>20</td><td>14</td></tr>
<tr><td colspan="2">Headache – n</td><td>20</td><td>13</td></tr>
<tr><td colspan="2">Dyspnea – n</td><td>25</td><td>25</td></tr>
<tr><td colspan="2">Nausea – n</td><td>6</td><td>10</td></tr>
<tr><td colspan="2">Vomiting – n*</td><td>6</td><td>14</td></tr>
<tr><td colspan="2">Diarrhea – n*</td><td>4</td><td>17</td></tr>
<tr><td colspan="2">Myalgia – n</td><td>23</td><td>24</td></tr>
<tr><td colspan="2">Loss of taste – n*</td><td>15</td><td>5</td></tr>
<tr><td colspan="2">Anosmia – n*</td><td>15</td><td>5</td></tr>
<tr><td colspan="2">Hypotension – n</td><td>2</td><td>6</td></tr>
<tr><td rowspan="4">Comorbidity – n</td><td>Diabetes</td><td>11</td><td>9</td></tr>
<tr><td>Hypertension</td><td>7</td><td>6</td></tr>
<tr><td>Obesity</td><td>2</td><td>4</td></tr>
<tr><td>Smoking</td><td>9</td><td>6</td></tr>
<tr><th colspan="6">Results</th></tr>
<tr><th colspan="2" rowspan="2">Outcome</th><th rowspan="2">Intervention</th><th rowspan="2">Control</th><th colspan="2">Statistical significance of differences</th></tr>
<tr><th>Event</th><th>follow-up period</th><th>Relative parameter (95%CI) / p value</th><th>Absolute parameter (95%CI)</th></tr>
<tr><td>Symptomatic on day 7 – n/N (%)</td><td>7 days</td><td>9/25 (36)</td><td>10/25 (40)</td><td>p=0.5</td><td>-</td></tr>
<tr><td colspan="6">Author's conclusion: In Ivermectin's (case group) recovery was almost equal to control group who received only conventional symptomatic treatment, so this is the need of the day that we need to conduct more randomized controlled trials across our country involving major tertiary care health care facilities with larger sample size to assess its efficacy for validating the use of Ivermectin against SARS-CoV-2. Nearly 40 clinical trials are ongoing world over for measuring the outcome of COVID-19 treatment with Ivermectin.</td></tr>
</table>

ND – no data; * – p<0.05

Tabela 26. Opis metodyki i wyników badania Chaccour 2021 (SAINT) – leczenie

Chaccour 2021 (SAINT)				
The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo controlled, randomized clinical trial (Lancet, 19.01.2021)				
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Randomized, double-blind, single-centre study, phase 2 Randomization 1:1 Duration of the study: 31/07/2020-11/09/2020 Spain	N=24 Adults with mild COVID-19. SARS-CoV-2 infected patients who are at low risk of progression to severe disease. <u>Inclusion criteria:</u> – 18-59 years; – outpatients with symptoms compatible with COVID-19, – no more than 72 hours of fever or cough and a positive PCR for SARS-CoV-2; patient should, in the investigator's opinion, be able to comply with all the requirements of the clinical trial (including home follow up during isolation) <u>Exclusion criteria:</u> – COVID-19 pneumonia (diagnosed by the attending physician; identified in a chest X-ray); – fever or cough present for more than 48 hours; positive IgG against SARS-CoV-2 by rapid test; – the following co-morbidities (or any other disease that might interfere with the study in the eyes of the investigator): immunosuppression, chronic obstructive pulmonary disease, diabetes, hypertension, obesity, acute or chronic renal failure, – history of coronary disease, History of cerebrovascular disease, Current neoplasm; – current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat. Use of critical CYP3A4 substrate drugs such as warfarin.		Ni1=12 Ivermectin (Stromectol®, single dose of 400 mcg/kg)	Nc=12 Placebo	– Small sample size; – Single-centre study; – The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care.
	Age – median (IQR)		26 (19-36)	26 (21-44)	
	Male sex – n (%)		7 (58)	5 (42)	
	Any symptoms – %		100	100	
	Cough – n (%)		4 (33)	2 (17)	
	Fever – n (%)		7 (58)	9 (75)	
	Headache – n (%)		7 (58)	10 (83)	
	Myalgia/general malaise – n (%)		8 (67)	6 (50)	
	Earliest start of any symptom – hours, median (IQR)		24 (24-48)	48 (36-48)	
	Earliest start of fever – hours, median (IQR)		24 (12-24)	24 (24-48)	
	Earliest start of cough – hours, median (IQR)		24 (16-36)	10 (8-12)	
	CRP – median (IQR)		0.3 (0.2-0.8)	0.3 (0.2-0.6)	
	Ferritin – median (IQR)		165.0 (95.5-241.3)	156.1 (103.1-223)	
	IL-6 – median (IQR)		6.5 (5.1-9.6)	4.5 (3.0-6.5)	
	D-Dimer – median (IQR)		295 (270-420)	280 (270-315)	
	Viral load – no. (IQR), copies/mL	gene E	$1.7x10^7$ ($5.9x10^6$ – $3.9x10^8$)	$2.7x10^7$ ($8.3x10^5$ – $4.2x10^8$)	
		gene N	$3.7x10^8$($1.8x10^7$ –$9.3x10^9$)	$3.3x10^8$ ($5.8x10^7$ –$6.7x10^9$)	

Chaccour 2021 (SAINT)						
Results						
Outcome			**Intervention**	**Control**	**Statistical significance of differences**	
Event		**follow-up period**			**Relative parameter, RR (95%CI) / p**	**Absolute parameter**
Positive SARS-CoV-2 PCR – n/N (%) (*primary endpoint*)	gene N	Day 7	12/12 (100)	12/12 (100)	-	-
	gene E		11/12 (91.7)	12/12 (100)	0.92 (0.77; 1.09)	-
Seroconversion (positive IgG) – n/N (%)		Day 21	12/12 (100)	12/12 (100)	-	-
Median of IgG titers (IQR)			4.7 (3.5-8.9)	7.5 (4.2-9.3)	p=0.24	-
Adverse events – n/N (%)		Day 28	5/12 (41.7)	5/12 (41.7)	-	-
Severe Adverse Events			0/12 (0)	0/12 (0)	-	-
Viral load – median (IQR), copies/mL	gene E	Day 1	$1.7x10^7$ ($5.9x10^6$ – $3.9x10^8$)	$2.7x10^7$ ($8.3x10^5$ – $4.2x10^8$)	p=0.64	-
		Day 4	$1.6x10^5$ (2820-8.8 $x10^5$)	$4.9x10^5$ ($1.0x10^5$-9.9 $x10^6$)	p=0.25	-
		Day 7	1018 (92-15445)	23550 (709-2.3 $x10^5$)	p=0.17	-
		Day 14	7 (0-42)	30 (1-50)	p=0.42	-
		Day 21	1 (0-9)	0 (0-16)	p=0.49	-
	gene N	Day 1	$3.7x10^8$($1.8x10^7$ –$9.3x10^9$)	$3.3x10^8$ ($5.8x10^7$ –$6.7x10^9$)	p=1.0	-
		Day 4	$2.7x10^5$ (1885-1.0 $x10^6$)	$2.2x10^6$ (73150-3.7 $x10^7$)	p=0.18	-
		Day 7	2255 (938-34650)	36800 ($4510-6.3x10^5$)	p=0.18	-
		Day 14	86 (0-1235)	75 (24-710)	p=0.36	-
		Day 21	0 (0-67)	107 (0-183)	p=0.09	-
Cycle threshold– median (IQR)	gene E	Day 1	20 (17-22)	21 (18-23)	p=0.69	-
		Day 4	27 (25-31)	26 (22-28)	p=0.20	-
		Day 7	33 (30-35)	30 (28-32)	p=0.17	-
		Day 14	36 (35-41)	35 (35-37)	p=0.22	-
		Day 21	38 (36-41)	41 (37-41)	p=0.28	-
	gene N	Day 1	20 (16-22)	21 (17-22)	p=0.64	-
		Day 4	27 (24-31)	25 (22-27)	p=0.13	-
		Day 7	32 (30-34)	29 (27-31)	p=0.11	-
		Day 14	36 (33-41)	35 (33-35)	p=0.30	-
		Day 21	41 (35-41)	35 (35-39)	p=0.26	-
clinicaltrials.gov [2]						
Fever progression – n/N (%)		Day 7	1/12 (8.3)	0/12 (0)	^3.00 (0,13; 67.06)	-
		Day 14	0/12 (0)	0/12 (0)	-	-
Cough progression – n/N (%)		Day 7	5/12 (41.7)	5/12 (41.7)	-	-
		Day 14	1/12 (8.3)	3/12 (25)	^0.33 (0.04; 2.77)	-
Drug-related Adverse Events – n/N (%)		Day 7	0/12 (0)	0/12 (0)	-	-
All-Cause Mortality – n/N (%)		Day 28	0/12 (0)	0/12 (0)	-	-

[2] https://clinicaltrials.gov/ct2/show/results/NCT04390022?term=ivermectin&cond=covid&draw=2 [access: 18/01/2021]

Chaccour 2021 (SAINT)
Author's conclusion: The positive signal found in this pilot warrants the conduction of larger trials using ivermectin for the early treatment of COVID-19. Such trials should include patients with risk factors for severe disease as well as patients with pneumonia. The potential for a mechanism of action different to direct antiviral effect also opens the door for pre-exposure prophylaxis in high risk groups.

^ Risk ratio, Agency's own calculations;

Tabela 27. Opis metodyki i wyników badania Podder 2020 – leczenie

Podder 2020					
Outcome of ivermectin treated mild to moderate COVID-19 cases: a singlecentre, open-label, randomised controlled study (IMC Journal of Medicine Science, 03.09.2020)					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Randomized, open-label controlled study Randomization: odd-even methodology applied to registration numbers, in a consecutive fashion of 1:1 ratio Enrollment: 01/05/2020–31/07/2020 Bangladesh	N=62 Mild to moderate COVID-19 patients (according to WHO COVID-19 disease severity classification*). <u>Inclusion criteria:</u> – RT-PCR positive; – mild to moderate COVID-19 cases; – >18 years of age; <u>Exclusion criteria:</u> – taking other antimicrobials or hydroxychloroquine		Ni=32 Ivermectin 200 mcg/kg on the day 1 of randomization	Nc=30 No Ivermectin	– Small sample size, – Investigators were unable to determine the effect of ivermectin (if any) on the biochemical and haematological parameters of the COVID-19 cases.
			Symptomatic treatment (usual care) included: • antipyretics, • cough suppressants, • capsule doxycycline (100 mg every 12 hours for seven days)		
	Age (years), mean±SD		38.41±11.02	39.97±13.24	
	Male, no. (%)		23 (71.9)	21 (70.0)	
	Presenting symptoms, no. (%)	Fever	27 (84.4)	23 (76.7)	
		Cough	21 (65.6)	21 (70.0)	
		Shortness of breath	6 (18.8)	6 (20)	
		Sore throat	3 (9.4)	11 (36.7)	
		Anosmia	9 (28.1)	5 (16.7)	
		Dysgeusia	1 (3.1)	2 (6.7)	
		Diarrhoea	4 (12.5)	2 (6.7)	
		Myalgia	14 (43.8)	8 (26.7)	
		Fatigue	5 (15.6)	7 (23.3)	
		Headache	2 (6.3)	5 (16.7)	
	Severity of illness, no. (%)	Mild	26 (81.3)	24 (80.0)	
		Moderate	6 (18.8)	6 (20)	
	Duration of symptoms of patients in intervention and control arms at the time of enrolment (days), mean± SD	Fever	3.85±2.11	4.00±2.17	
		Cough	3.90±1.89	3.62±2.27	
		Shortness of breath	1.83±1.17	3.00±1.27	
		Fatigue	3.00±1.41	4.71±2.36	
		Myalgia	3.25±.96	4.50±3.54	

Results						
Outcome			**Intervention**	**Control**	**Statistical variability of differences**	
Event		**follow-up period (days)**			**Relative parameter (95% CI) / p**	**Absolute parameter**
Time required for the resolution of symptoms	Complete recovery*	NA (from the date of	5.31±2.48	6.33±4.23	p>0.05	-
	Fever		3.33±2.18	3.18±2.61	p>0.05	-

Podder 2020						
(days), mean ±SD	Shortness of breath	enrolment)	4.83±1.72	6.33±3.67	p>0.05	-
	Fatigue		6.00±4.85	5.67±3.62	p>0.05	-
Time required for the resolution of symptoms (days), mean ±SD	Complete recovery*	NA (from the date of onset of illness)	10.09±3.24	11.50±5.32	p>0.05	-
	Fever		6.48±3.39	6.43±2.45	p>0.05	-
	Cough		9.23±3.22	10.45±3.70	p>0.05	-
	Shortness of breath		6.67±1.86	8.86±4.74	p>0.05	-
	Fatigue		9.00±3.61	9.57±3.65	p>0.05	-
Result of repeat RT-PCR test, no./N (%)	Positive	10	2/20 (10)	1/20(5)	^RR=2.00 (0.20; 20.33)	-
	Negative		18/20 (90)	19/20 (95)	^RR=0.95 (0.79; 1.13)	-
Author's conclusions: Ivermectin had no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases.						

* Symptomatic patients without evidence of viral pneumonia or hypoxia (SpO2 >93% on room air) were considered as a mild disease and patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2≥ 90% on room air were considered as a moderate disease; * Resolution of all symptoms. Some parameters are excluded from the analysis due to inadequate data; ^Agency's own calculations

SD – standard deviation; NA – not applicable; RR – risk ratio

Tabela 28. Opis metodyki i wyników badania Krolewiecki 2021 – leczenie (zaktualizowano w wersji 1.2)

Krolewiecki 2021				
Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial (EClinicalMedicine, 25.05.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
A pilot, randomized, multicenter, controlled, open-label, outcome-assessor blinded clinical trial Randomization: 2:1 Study period: 18/05 – 9/09/2020 Argentina	N=45 Adult hospitalized patients with mild to moderate COVID-19. <u>Inclusion criteria:</u> – age 18 to 69 years-old; – COVID-19 patients with RT-PCR confirmed infection, hospitalized with disease stages 3 to 5 from the WHO 8-Category ordinal scale of clinical status and no requiring intensive care unit admission; – COVID-19 symptoms onset ≤ 5 days at recruitment, absence of use of drugs with potential activity against SARS-CoV-2 (hydroxychloroquine, chloroquine, lopinavir and azithromycin) <u>Exclusion criteria:</u> – the use of immunomodulators within 30 days of recruitment, – poorly controlled comorbidities.	Ni=30 n=20 (efficacy population) n=30 (safety population) Ivermectin at 0.6 mg/kg/day for 5 days + SoC	Nc=15 n=12 (efficacy population) n=15 (safety population) SoC	– Small sample size, – Only outcome-assessor was blinded; – The finding of 2 distinct populations regarding mean IVM systemic concentrations was identified despite the body weight-based dosing and the indication of administering the drug tablets with meals, – No information on what the standard therapy included.
	Age (years), mean±SD	42.3 ± 12.8	38.1 ± 11.7	
	Male, no. (%)	15 (50)	10 (67)	
	Weight (kilogram), mean±SD	75.3 ± 15.0	79.7 ± 14.4	
	Oxygen saturation <94%, no. (%)	1 (3)	0	
	Log viral load*** (log10 copies/reaction)	4.18 ± 1.60	5.39 ± 1.56	
	Time from symptoms onset (day)	3.5 ± 1.0	3.6 ± 1.4	
	Body temperature ≥37.5ºC, no. (%)	4 (13)	1 (7)	
	WHO-ordinal scale, no. (%) 3	29 (97)	13 (87)	
	WHO-ordinal scale, no. (%) 4	1 (3)	2 (13)	
	Ground glass opacities in thoracic imaging, no. (%)	14 (47)	6 (40)	
	Comorbidities, no. (%) Hypertension	3 (10)	3 (20)	
	Comorbidities, no. (%) Diabetes	6 (20)	1 (7)	
	Comorbidities, no. (%) Chronic lung disease/Asthma	4 (13)	1 (7)	

Results

Outcome		**Intervention**		**Control**	**Statistical variability of differences**	
event	**follow-up period (days)**	**Group 1$ n=11**	**Group 2 $$ n=9**		**Relative parameter (95% CI) / p**	**Absolute parameter**
Viral load reduction in respiratory secretions^^, median (IQR)	5	ND		42% (31-73)	p>0.05#	-
		40% (21-46)	72% (59-77)		Group 2 vs. Control: p=0.004	-
The viral load decay rate, median (IQR), d^{-1}	5	0.14 (0.10-0.16)	0.64 (0.31-0.67)	0.13 (0.09-0.19)	Group 2 vs. Control: p=0.041	-
						-
Disease progression, no.	7	2		1	p>0.05#	-
Patients with AEs&, no. (%)	ND	13 (43)		5 (33)	^RR=1,04 (0,48; 2,28)	-
Patients with possible/probable related AEs, no. (%)		9 (30)		NA	-	-
Patients with SAEs, no.		1*		0	-	-

Krolewiecki 2021					
Patients with possible/probable related SAEs, no. (%)		1	0	-	-
Number of AEs		17	5	-	-
Number of possible/probable related AEs		11	NA	-	-
Number of AEs Grade 3/4		3**	0	-	-
When mean plasma IVM concentration levels were analyzed in relation to reduction in viral load, a significant positive correlation was identified, with those patients achieving higher mean plasma concentrations of IVM reaching higher reductions in viral load in nasopharyngeal secretions (r: 0·44; p<0·04). This correlation was stronger when the reduction in viral load was related to the IVM exposure corrected by viral load at baseline (r: 0·60; p<0·004). The mean IVM plasma concentration levels also showed a positive correlation with the viral decay rate (r:0·47, p=0·02).					
Author's conclusions: A concentration dependent antiviral activity of oral high-dose IVM was identified at a dosing regimen that was well tolerated. Large trials with clinical endpoints are necessary to determine the clinical utility of IVM in COVID-19.					

SD – standard deviation; NA – not applicable; SoC - standard of care; IVM – ivermectin; AEs – adverse events; SAEs – serious adverse events; ND – no data; RR – risk ratio

* hyponatremia; ** include the SAE (hyponatremia); ***Efficacy analysis (N=32: Ni=20, Nc=12); $ Subgroup with <160ng/mL IVM median plasma concentration; $$ Subgroup with >160ng/ml IVM median plasma concentration; ^ Agency's own calculations; ^^ by quantitative RT-PCR on upper respiratory tract secretions; [&] The most frequent adverse event and the only experienced by more than 1 case in the IVM group was rash in 3 (10%) cases (all mild, self-limited and lasting approximately24 h); in the control group, single events of abdominal pain, dizziness, anxiety, anguish, and hyperglycemia (all mild) were reported; # p values <0.05 were considered statistically significant

Tabela 29. Opis metodyki i wyników badania Mahmud 2021 – leczenie (zaktualizowano w wersji 1.1)

Mahmud 2021				
Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial (NCT04523831; clnicaltrials.gov, 13.05.2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Randomized, double-blind, placebo-controlled, phase 3 Randomization 1:1 Duration of the study: 01/06/2020 – 30/08/2020 Bangladesh	N=400 (363 included in the analysis) Adults with mild to moderate COVID-19. Inclusion criteria: – ≥18 years; – COVID-19 infection, confirmed by RT-PCR test within 3 days from enrollment; – mild and moderately severe COVID-19 infected cases; Exclusion criteria: – severe COVID symptoms (defined as tachypnea [>30 breaths/ minute] and hypoxia [oxygen saturation (SpO2) <90%] requiring supplemental oxygen) or admission in ICU or high-dependency units; ALT or AST more than 5 upper limit of normal.	Ni1=200 (183 included in the analysis) Ivermectin (6 mg 2 tab stat, cap) + doxycycline (100 mg 1 cap BD 5 days)	Nc=200 (180 included in the analysis) Placebo	– No detailed information on the percentage of patients receiving a specific standard therapy; – Not all of patients completed the study;
		Standard of care: paracetamol, antihistamines, cough suppressants, vitamins, oxygen therapy according to indication and need, low molecular weight heparin according to indication, appropriate other broad-spectrum antibiotics, remdesivir injection, other antiviral drugs, and other drugs for associated comorbid conditions		
	Mean age ± SD – yr	41 ± 14	38 ± 12	
	Male sex – n/N (%)	123/200 (62)	112/200 (56)	
	Severity – n/N (%) Mild	141/200 (71)	136/200 (68)	
	Severity – n/N (%) Moderate	59/200 (30)	64/200 (32)	
	Time between onset of symptoms and enrollment, median (IQR), day	4 (3-5)	4 (3-5)	

Results					
Outcome		**Intervention**	**Control**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**
Median recovery time, (IQR), day *(primary outcome)*	-	7 (4-10)	9 (5-12)	HR=0.73 (0.60; 0.90)	-
Patients responding within 7 days* – n/N (%)	7 days	111/183 (60.7)	80/180 (44.4)	HR=0.06 (0.04; 0.09) ^RR=1.41 (1.15; 1.72)	^^NNT=7 (4; 17)
Patients responding within 7–11 days – n/N (%)	7-11 days	32/183 (47.1)	36/180 (52.9)	HR=1.02 (0.77; 1.36)	
Patients remaining symptomatic after 12 days – n/N (%)	>12 days	42/183 (23.0)	67/180 (37.2)	HR=0.04 (0.03; 0.07) ^RR=0.64 (0.46; 0.88)	^^NNT=8 (5; 21)
Increase in stage of severity– n/N (%)	≥14 days**	16/183 (8.7)	32/180 (17.8)	HR=0.43 (0.38; 0.62) ^RR=0.51 (0.29; 0.89)	^^NNT=12 (7; 48)
Persistent COVID-19 RT-PCR positivity – n/N (%)	Day 14	14/183 (7.7)	36/180 (20.0)	HR=0.61 (0.44; 0.83) ^RR=0.40 (0.22; 0.71)	^^NNT=9 (6; 19)
All-Cause Mortality – n/N (%)	≥14 days**	0/200 (0)	3/200 (1.5)	^RR=0.14 (0.007; 2.75)	-
Adverse drug reaction – n/N (%)		9/200 (2.25)	0/200 (0)	^RR=19 (1.13; 324.25)	-
Author's conclusion: Patients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more serious disease, and were more likely to be COVID-19 negative by RT-PCR on day 14. Although additional research on the effects of ivermectin combined with doxycycline is warranted, the safety and efficacy of this combination are favorable compared with current standard of care.					

ALT – alanine aminotransaminase; AST – aspartate aminotransaminase;
* Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C); Respiratory symptoms are significantly improved; Lung imaging shows obvious improvement in lesions; There is no co-morbidities or complications which require hospitalization; SpO2, >93% without assisted oxygen inhalation.
** Hospitalized patients were followed from day 1 through day 14 or until discharge or clinical improvement, whichever occurred later
^ Risk ratio; Agency's own calculations; ^^^ Number Needed-to-treat; Agency's own calculations

Tabela 30. Opis metodyki i wyników badania Okumus 2021 – leczenie (zaktualizowano w wersji 1.1)

<table>
<tr><th colspan="6">Okumus 2021</th></tr>
<tr><th colspan="6">Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients (NCT04646109, BMC Infectious Diseases, 4.05.2021)</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="20">Randomized, open-label, multicentre, phase 3

Randomization 1:1

Duration of the study: 11/05/2020 – 02/09/2020

Turkey</td><td colspan="2">N=66
Patients with severe COVID-19 pneumonia.

<u>Inclusion criteria:</u>
– patients who were hospitalised with a pre-diagnosis of "severe COVID-19 pneumonia" and thereafter diagnosis of COVID-19 was also confirmed microbiologically with PCR positivity;
– patients with at least one of the criteria below were accepted as patients with severe COVID-19 pneumonia: 1) Presence of tachypnea ≥ 30/minute, SpO2 level < 90% in room air, PaO2/FiO2 <300 in oxygen receiving patient, 2) Presence of specific radiological finding for COVID-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities, 3) Mechanical ventilation requirement, 4) Acute organ dysfunction findings; patients with SOFA (sepsis-related organ failure assessment) score >2;
<u>Exclusion criteria:</u>
– <18 years of old; chronic liver or kidney disease</td><td>Ni1=36

Ivermectin (0.2 mg/kg/day for 5 days)</td><td>Nc=30

No ivermectin</td><td rowspan="20">– Small sample size;</td></tr>
<tr><td colspan="3">SoC: hydroxychloroquine, favipiravir, azithromycin</td></tr>
<tr><td colspan="2">Mean age ± SD – yr</td><td>58.17 (11.52)</td><td>66.23 (13.31)</td></tr>
<tr><td colspan="2">Female sex – n (%)</td><td>9 (30)</td><td>11 (36.7)</td></tr>
<tr><td rowspan="8">Symptoms – n (%)</td><td>Fever – n (%)</td><td>15 (50)</td><td>13 (43.3)</td></tr>
<tr><td>Cough – n (%)</td><td>16 (53.3)</td><td>14 (46.7)</td></tr>
<tr><td>Sore throat – n (%)</td><td>3 (10)</td><td>1 (3.3)</td></tr>
<tr><td>Dyspnea – n (%)</td><td>23 (76.7)</td><td>19 (63.3)</td></tr>
<tr><td>Headache – n (%)</td><td>5 (16.7)</td><td>2 (6.7)</td></tr>
<tr><td>Weakness – n (%)</td><td>13 (43.3)</td><td>11 (36.7)</td></tr>
<tr><td>Myalgia – n (%)</td><td>9 (30)</td><td>7 (23.3)</td></tr>
<tr><td rowspan="8">Comorbidities – n (%)</td><td>Diabetes Mellitus</td><td>9 (30)</td><td>10 (33.3)</td></tr>
<tr><td>Hypertension</td><td>15 (50)</td><td>12 (40)</td></tr>
<tr><td>Coronary artery disease</td><td>5 (16.7)</td><td>8 (26.7)</td></tr>
<tr><td>Cardiac failure</td><td>0</td><td>1 (3.3)</td></tr>
<tr><td>Chronic obstructive pulmonary disease</td><td>6 (20)</td><td>3 (10)</td></tr>
<tr><td>Malignancy</td><td>0</td><td>1 (3.3)</td></tr>
<tr><td>Immunodeficiency</td><td>0</td><td>1 (3.3)</td></tr>
</table>

Okumus 2021					
Results					
Outcome		**Intervention**	**Control**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**
Clinical Response – n/N (%)	Day 5	14/30 (46.7)	11/30 (36.7)	^RR=1.27 (0.69; 2.33)	-
Clinical Response – n/N (%)	Day 10	22/30 (73.3)	16/30 (53.3)	^RR=1.38 (0.92; 2.05)	-
Mortality – n/N (%)	Mean: 3 months	6/30 (20)	9/30 (30)	^RR=0.66 (0.27; 1.64)	-
Treatment-Related Adverse Events– n/N (%)	Day 5	0/30	3/30	-	-
Author's conclusion: According to the findings obtained, ivermectin can provide an increase in clinical recovery, improvement in prognostic laboratory parameters and a decrease in mortality rates even when used in patients with severe COVID-19. Consequently, ivermectin should be considered as an alternative drug that can be used in the treatment of COVID-19 disease or as an additional option to existing protocols.					

ND – no data; ^ – Agency's own calculations

Tabela 31. Opis metodyki i wyników badania Hashim 2020 – leczenie

Hashim 2020				
Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq (medRxiv, 27.10.2020)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Randomized controlled trial Recruitment: 01/06/2020– 30/09/2020 Iraq	N=140 <u>Inclusion criteria:</u> – COVID-19 patients diagnosed by clinical, radiological and laboratory PCR testing, at different stages of the disease (mild-moderate, severe, and critical according to WHO guidelines), who were symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases, outpatients or inpatients <u>Exclusion criteria:</u> ND	Ni=70 Ivermectin + Doxycycline + SoC IVM 200ug/kg PO per day for 2 days, in some patients third dose 200ug/kg PO per day was given 7 days after the first dose. Doxycycline 100mg capsule PO every 12h per day, for 5-10 days, based on the clinical improvement of patients	Nc=70 SoC	– Randomization method: patients recruited at dates with odd number were allocated to intervention group or control group; no critical patient recruited in this study was allocated to the control group, – Small size of subpopulations at different stages of the disease that makes impossible to achieve statistical power, – No clear information on blinding, – Pre-print
		<u>SoC included:</u> • Acetaminophen 500mg on need • Vitamin C 1000mg twice/ day • Zinc 75-125 mg/day • Vitamin D3 5000IU/day • Azithromycin 250mg/day for 5 days • Oxygen therapy/ C-Pap if needed • Dexamethazone 6 mg/day or methylprednisolone 40mg twice per day, if needed • Mechanical ventilation, if needed		
	Age (years), mean±SD	50.1±9.3	47.2±7.8	
	Male, %	53	51	
	Stage of the disease, no. – Mild-moderate	48	48	
	Stage of the disease, no. – Severe	11	22	
	Stage of the disease, no. – Critical	11	0	
	Median post-infection day for starting therapy, days – Mild-moderate	3	3	
	Median post-infection day for starting therapy, days – Severe	7	7	
	Median post-infection day for starting therapy, days – Critical	8,5	NA	
	Mean weight (kg), mean±SD	79.6±13.2	71.5±11.9	

Hashim 2020						
Results						
Outcome			**Intervention**	**Control**	**Statistical variability of differences**	
event		**follow-up period (days)**			**Relative parameter (95% CI) / p**	**Absolute parameter**
Time to recovery, mean±SD (days)	Total	NA	10.61±5.3	17.9±6.8	**p<0.0001**	-
	Mild-moderate	NA	6.34±2.4	13.66±6.4	**p<0.0001**	-
	Severe		20.27±7.8	24.25 ±9.5	p=0.29	
	Critical		19.77±9.2	NA	-	-
Progression of the disease, n/N (%)	Total	Patients were monitored till recovery or death	3/70 (4.28)	7/70 (10)	OR=0.4 (ND; ND), p=0.2 ^RR=0.43 (0.12; 1.60)	-
	Mild-moderate		0/48 (0)	0/48 (0)	-	-
	Severe		1/11 (9)	7/22 (31.81)	OR=0.21 (ND;ND), p=0.17 ^RR=0.29 (0.04; 2.04)	-
	Critical		2/11 (18.2)	NA	-	-
Mortality rate, n/N (%)	Total		2/70 (2.85)	6/70 (7.14)	OR=0.31(ND;ND), p=0.16 ^RR=0.33 (0.07; 1.60)	
	Mild-moderate		0/48 (0)	0/48 (0)	-	-
	Severe		0/11 (0)	6/22 (27.27)	OR=0.11 (ND;ND), p=0.14 ^RR=1.15 (0.01; 2.40)	
	Critical		2/11 (18.2)	NA	-	-
Authors' conclusions: Ivermectin with doxycycline reduced the time to recovery and the percentage of patients who progress to more advanced stage of disease; in addition, Ivermectin with doxycycline reduced mortality rate in severe patients from 22.27% to 0%; however, 18.2% of critically ill patients died with Ivermectin and doxycycline therapy. Taken together, the earlier administered Ivermectin with doxycycline, the higher rate of successful therapy.						

SD – standard deviation; NA – not applicable; IVM – ivermectin; MD – mean difference; SoC – standard of care; ND – no data; PO – per oss; RR – risk ratio; ^Agency's own calculations

Tabela 32. Opis metodyki i wyników badania Chowdhury 2021 – leczenie

<table>
<tr><th colspan="6">Chowdhury 2021</th></tr>
<tr><th colspan="6">Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients (EJMO, 25.02.2021)</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="6">Randomized, open-label

Randomization 1:1

Duration of the study: 02/05/2020 – 05/06/2020

Bangladesh</td><td colspan="2">N=116
Adults with mild to moderate COVID-19.

<u>Inclusion criteria:</u>
– All patients who tested positive for SARS-CoV-2 infection by RT-PCR.
<u>Exclusion criteria:</u>
– Patients with unstable comorbid conditions like bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and Immuno-compromised patients</td><td>Ni1=60

Ivermectin (200µgm/kg single dose)
+ Doxycycline
(100 mg BID for 10 days)</td><td>Nc=56

Hydroxychloroquine (400 mg 1st day, then 200 mg BID for 9 days) +
Azithromycin (500 mg daily for 5 days)</td><td rowspan="6">– Small sample;
– No detailed information on the percentage of patients receiving a symptomatic treatment;
– Outcomes may be biased by additional factors like severity of the disease, lack of cooperation of some participants, and unknown comorbidity.</td></tr>
<tr><td colspan="3">All subjects were also provided with symptomatic treatment for fever, headache, cough, myalgia, etc.</td></tr>
<tr><td colspan="2">Mean age ± SD – yr</td><td>35.72 ± 15.1</td><td>31.91 ± 12.72</td></tr>
<tr><td colspan="2">Female sex – n (%)</td><td>17 (28.33)</td><td>9 (16.07)</td></tr>
<tr><td colspan="2">Symptomatic – n (%)</td><td>49 (81.67)</td><td>42 (75)</td></tr>
<tr><td colspan="2">Asymptomatic – n (%)</td><td>11 (18.33)</td><td>14 (25)</td></tr>
<tr><th colspan="6">Results</th></tr>
<tr><th colspan="3" rowspan="2">Outcome
event</th><th rowspan="2">follow-up period</th><th rowspan="2">Intervention</th><th rowspan="2">Control</th><th colspan="2">Statistical significance of differences</th></tr>
<tr><th>Relative parameter (95%CI) / p value</th><th>Absolute parameter (95%CI)</th></tr>
<tr><td colspan="3">Recovery to negative PCR rate – n/N (%)</td><td rowspan="6">ND</td><td>60/60 (100)</td><td>54/56 (96.36)</td><td>p=0.23</td><td>-</td></tr>
<tr><td rowspan="3">Mean recovery duration to negative PCR – days</td><td>All patients</td><td>8.93 (8-13)</td><td>9.33 (5-15)</td><td>ND</td><td>-</td></tr>
<tr><td>Symptomatic</td><td>9.06</td><td>9.74</td><td>p=0.071</td><td>-</td></tr>
<tr><td>Asymptomatic</td><td>8.36</td><td>7.92</td><td>p=0.44</td><td>-</td></tr>
<tr><td colspan="3">Mean duration of symptomatic recovery – days</td><td>5.93 (5-10)</td><td>6.99 (4-12)</td><td>p=0.071</td><td>-</td></tr>
<tr><td colspan="3">New symptoms that may be attributed to drug adverse effect or progression of COVID-19 – n/N (%)</td><td>41/60 (63.3)</td><td>30/56 (53.57)</td><td>^RR=1.28 (0.95; 1.72)</td><td>-</td></tr>
<tr><td colspan="3">Adverse effects – n/N (%)</td><td>ND/ND (31.67)</td><td>ND-ND (46.42)</td><td>-</td><td>-</td></tr>
<tr><td colspan="6">Author's conclusion: The Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant. Further study is required on a larger scale with an increase in the duration of Ivermectin treatment.</td></tr>
</table>

ND – no data; ^ – Agency's own calculations

Tabela 33. Opis metodyki i wyników badania Niaee 2021 – leczenie (zaktualizowano w wersji 1.2)

Niaee 2021								
Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial (Asian Pacific Journal of Tropical Medicine, 25.06.2021)								
Methodology	**Population**		**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Control 1**	**Control 2**	**Limitations**
Randomized, multicenter double-blind, placebo-controlled, phase 2 Randomization 1:1:1:1:1:1 Duration of the study: 45 days Iran	N=180 Hospitalized adults with mild to severe COVID-19. Inclusion criteria: – age >18 years; – clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; – mild to severe COVID-19 disease confirmed by chest computed tomography scan findings compatible with COVID-19 or positive RT-PCR. Exclusion criteria: – presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive), – chronic kidney disease, malignancy.		Ni1=30 (FAS n=30) Ivermectin, single dose (200 mcg/kg)	Ni2=30 (FAS n=27) Ivermectin, three doses (200 mcg/kg)	Ni3=30 (FAS n=30) Ivermectin, single dose (400 mcg/kg)	Ni4=30 (FAS n=29) Ivermectin, three doses (400, 200, 200 mcg/kg)	Nc1=30 (FAS n=25) Common regimen (Hydroxychloroquine 200mg/kg twice per day)	Nc2=30 (FAS n=24) Placebo + common regimen (Hydroxychloroquine 200mg/kg twice per day)	– No detailed results for all comparisons; – Small samples.
	Age [IQR] – yr		61 [42-68]	53 [42-65]	54 [47-60]	54 [46-65]	55 [45-70]	58 [45-68]	
	Female sex – n (%)		18 (60)	11 (36.7)	14 (46.7)	17 (56.7)	14 (46.7)	16 (53.3)	
	Severity on CT – %	negative	0	2 (6.7)	0	0	0	0	
		mild	26.7	6.7	13.3	6.7	13.3	16.7	
		mode	70.0	66.7	70.0	76.7	76.7	76.7	
		severe	3.3	20.0	16.7	16.7	10.0	6.7	

Results									
Outcome		**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**	**Control 1**	**Control 2**	**Statistical significance of differences**	
event	**follow-up period**							**Relative parameter, RR (95%CI) / p***	**Absolute parameter, (95%CI)**
Duration on hospital stay – days [IQR]	45 days	6 [5-7]	8 [6-9]	5 [4-7]	7 [6-10]	7 [7-9]	8 [6-11]	**p=0.006**	-
Duration of low O_2 saturation – days [IQR]		2 [1 - 2]	3 [2 - 5]	2 [1 - 4]	5 [3 - 6]	3 [2-5]	4 [2 - 6]	**p=0.025**	-
Tachypnea Off – days [IQR]		2 [1 - 3]	3 [2 - 4]	3 [3 - 5]	3 [3 - 5]	2 [2 - 3]	3 [2 - 4]	p=0.584	-
Fever Off – days [IQR]		0 [0 - 1]	0 [0 - 1]	[1 - 1]	1 [0 - 2]	0 [0 - 1]	0 [0 - 1]	p=0.102	-
Death		0	3 (10)	0	1 (3.3)	5 (16.7)	6 (20)	**p=0.001**	-
Risk of mortality		3.3%				18.3%		**0.18 (0.06; 0.55)**	**^NNT=7 (4; 22)**
Author's conclusion: Ivermectin as an adjunct reduced the rate of mortality, low O_2 duration, and duration of hospitalization in adult COVID 19 patients. The improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.									

RT-PCR – real-time reverse transcription polymerase chain reaction
* Ivermectin arms vs control arms; ^Agency's own calculations

Tabela 34. Opis metodyki i wyników badania Babalola 2021 – leczenie

Babalola 2021						
Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double blind dose response study in Lagos (QJM, 18.02.2021)						
Methodology	**Population**		**Intervention 1**	**Intervention 2**	**Control**	**Limitations**
A proof of concept (PoC), double blind, randomized controlled trial, of a parallel group, dose-response design Study duration: 05–11/2020 Nigeria	N=63 (n=62 completed the study) <u>Inclusion criteria:</u> – COVID 19 PCR proven positive patients, asymptomatic or had mild/moderate symptoms <u>Exclusion criteria:</u> – COVID 19 negative patients, – COVID pneumonia or requiring ventilator therapy, – renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale		Ni2=21 Ivermectin 6mg (given every 84 hours) twice a week	Ni2=21 Ivermectin 12mg (given every 84 hours) for 2 weeks	Nc=20 Lopinavir / ritonavir daily for 2 weeks	– Slight differences in the baseline Cycle threshold (Ct) values, being lower in the A arm than the other two arms with regards to the ORF and N genes, but similar for the EN gene.
	Age (years), mean		48.3	39.7	44.8	
	Male, no.		15	14	14	
	Symptoms	Fever	30%	42.8%	20%	
		Headache	50%	57%	25%	
		Cough	30%	19%	45%	
		Dyspnea	20%	23%	10%	
	Comorbidities, no.	Hypertension	2	2	5	
		Diabetes	1	1	0	
	SpO2, %		97.5	96.8	95.8	
	Medication, no.	Dexamethasone	1	1	2	
		Zinc	16	17	18	
		Supplemental oxygen use	0	3	2	
		Enoxaparine	2	1	1	

Results						
Outcome		**Intervention 1 (IVM1)**	**Intervention 2 (IVM2)**	**Control (C)**	**Statistical variability of differences**	
event	**follow-up period (days)**				**Relative parameter (95% CI) / p**	**Absolute difference (95% CI)**
Time to SARS-CoV-2 negativity, mean days (SD)	NA	6.0 (2.96)	4.65 (3.2)	9.15 (7.42)	**IVM1 vs IVM2: p=0.0179**	-
		5.33			**p=0.0066**	-
Time sequence of days to negativity	NA	ND	ND	ND	IVM1 vs C: HR=1.68 (0.87; 3.25)	-
		ND	ND	ND	**IVM2 vs C: HR=2.38 (1.22; 4.65)**	**-**
		ND	ND	ND	**IVM vs C: HR=1.96 (1.09; 3.51)**	**-**
Platelet count (000/ml), change (Day 7-Baseline)	7	20.05		-64.00	**-**	**MD=84.06 (5.56; 162.55)**
Authors' conclusions: 12 mg IV regime may have superior efficacy. IV should be considered for use in clinical management of SARS-Cov-2, and may find applications in community prophylaxis in high-risk areas.						

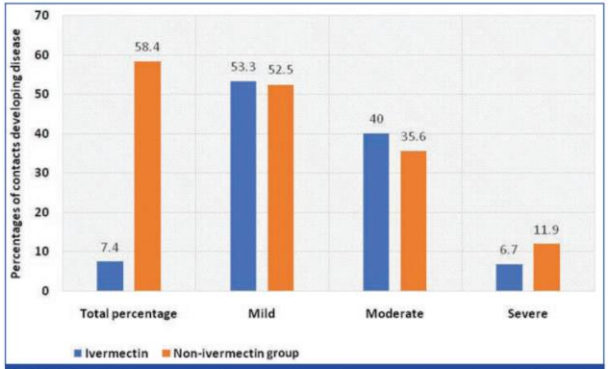
SD – standard deviation; NA – not applicable; IVM – ivermectin; MD – mean difference; ND – no data

Tabela 35. Opis metodyki i wyników badania Shouman 2020 – profilaktyka (zaktualizowano w wersji 1.2)

Shouman 2020				
Use of Ivermectin as a Potential Chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial (Journal of Clinical and Diagnostic Research, 02/2021)				
Methodology	**Population**	**Intervention**	**Control**	**Limitations**
Open-label randomised study, phase 2/3 Intervention Model: Sequential Assignment Study duration: 01/06–28/07/2020 Egypt	N=340 Inclusion criteria: – age more than 16 years; – symptomatic household close contacts. Exclusion criteria: – any contact developed symptoms or diagnosed as COVID-19 before enrollment, index case, failure to follow-up contacts for 14 days, and failure to document the index case when there was more than one case in a family.	Ni=228 (203 included in the analysis) Ivermectin (tablets), two doses 72 hours apart 40-60 kg – 15mg/day, 60-80kg – 18mg/day >80kg – 24mg/day	Nc=112 (101 included in the analysis) No intervention; Contacts who will be only observed without prophylaxis	– No ITT-analysis; – Randomization method; – Small numbers used for the non-intervention group; – Low rate of RT-PCR done in contacts with symptoms.
	Age, years, mean (SD)	39.75 (14.93)	37.69 (16.95)	
	Male, no. (%)	106 (52.2)	50 (49.5)	

Results					
Outcome		**Intervention**	**Control**	**Statistical variability of differences**	
event	**follow-up period (days)**			**Relative parameter (95% CI) / p**	**Absolute parameter (95% CI)**
Development of Symptoms*, no. (%)	14	15/203 (7.4)	59/101 (58.4)	**^RR=0.13 (0.08; 0.21)**	**^NNT=2 (1.6; 2.5)**
Days until symptoms, median (Range)	-	2 (2-6)	4 (2-10)	**p=0.017**	-
Serious Adverse Events, n/N (%)		0/203 (0)	0/101 (0)	NA	-
Total adverse events, n/N (%)		11/203 (5.42)	0/101 (0)	^RR=11.50 (0.68; 193.21)	-

Authors' conclusions: Ivermectin is suggested to be a promising, effective and safe chemoprophylactic drug in management of COVID-19.

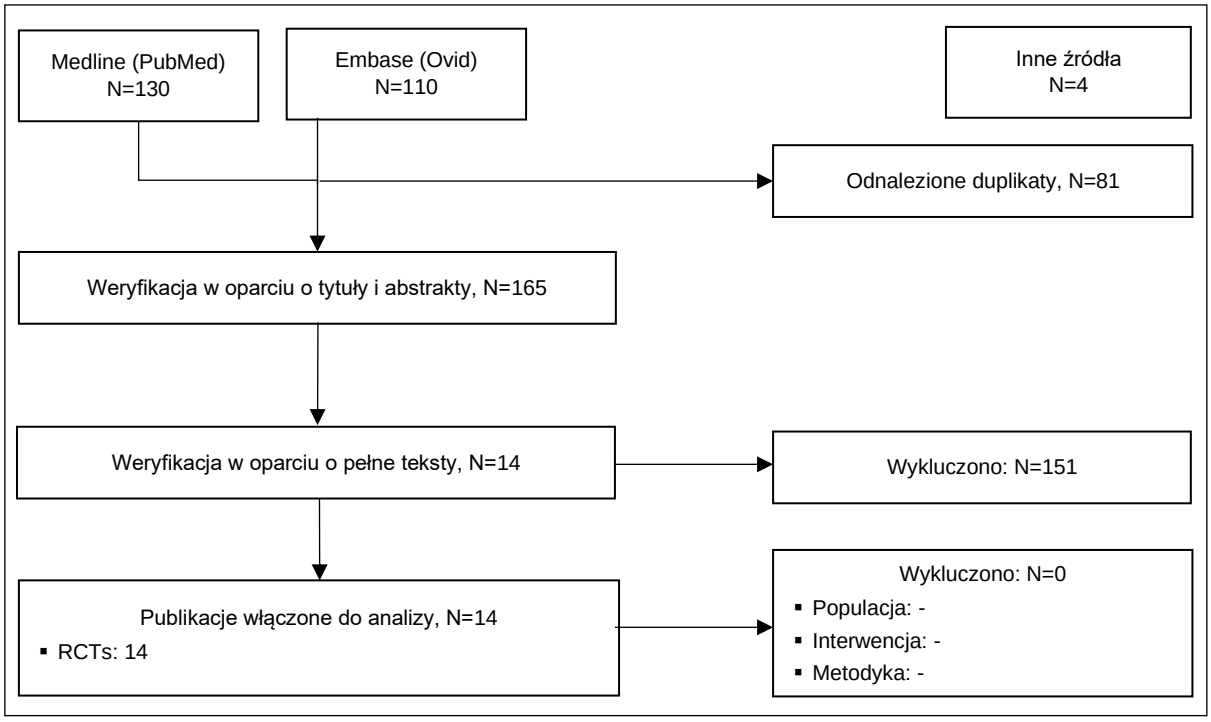


[Table/Fig-6]: Columns showing percentages of contacts who developed COVID-19; the total in the two groups and percentages of severity of disease in both groups.

*Symptoms: fever, cough, sore throat, myalgia, diarrhea, shortness of breath; ^ Agency's own calculations
SD – standard deviation; NA – not applicable; RR – risk ratio

Tabela 36. Strategie wyszukiwania w PubMed i Embase

Bazy informacji medycznej
Pubmed (data wyszukiwania 28.01.2021)
((((ivermectin AND (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" OR COVID-19 OR "COVID 19" OR COVID19 OR SARS-CoV-2 OR "SARS CoV 2" OR "SARS-CoV 2" OR "SARSCoV 2" OR "SARS CoV-2" OR "SARS CoV2" OR SARS-CoV2 OR SARSCoV-2 OR SARSCoV-2 OR SARS2 OR "SARS 2" OR SARS-2 OR 2019-nCoV OR "2019 nCoV" OR 2019nCoV OR "2019 novel coronavirus" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "novel coronavirus pneumonia" OR "novel coronavirus disease" OR "novel coronavirus infected disease" OR "novel coronavirus infection pneumonia" OR "novel coronavirus infected pneumonia" OR "new coronovirus disease" OR "new coronavirus infected disease" OR "new coronavirus infection pneumonia" OR "new coronavirus infected pneumonia" OR "Wuhan coronavirus" OR "Wuhan seafood market pneumonia virus" OR "2019-novel coronavirus" OR "2019 new coronavirus" OR "2019-new coronavirus" OR "coronavirus disease-2019" OR SARSCoV2 OR SARSCoV2))
Embase (data wyszukiwania: 28.01.2021)
ivermectin.ti,ab. and ("severe acute respiratory syndrome coronavirus 2" or COVID-19 or "COVID 19" or COVID19 or SARS-CoV-2 or "SARS CoV 2" or "SARS-CoV 2" or "SARSCoV 2" or "SARS CoV-2" or "SARS CoV2" or SARS-CoV2 or SARSCoV-2 or SARS2 or "SARS 2" or SARS-2 or 2019-nCoV or "2019 nCoV" or "nCoV 2019" or "nCoV-2019" or 2019nCoV or "2019 novel coronavirus" or "coronavirus disease 2019" or "coronavirus disease-19" or "novel coronavirus pneumonia" or "novel coronavirus disease" or "novel coronavirus infected pneumonia" or "Wuhan coronavirus" or "Wuhan seafood market pneumonia virus" or "2019-novel coronavirus" or "2019 new coronavirus" or "2019-new coronavirus" or "coronavirus disease-2019" or SARSCoV2).ti.



Rysunek 6. Proces selekcji doniesień, zgodnie z zaleceniami PRISMA (daty wyszukiwania: 28.01.2021)

Piśmiennictwo

Badania pierwotne	
Abd-Elsalam 2021	Abd-Elsalam, S., et al., Clinical Study Evaluating the Efficacy of Ivermectin in COVID-19 Treatment: A Randomized Controlled Study. Journal of medical virology, 2021.
Ahmed 2020	Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, Phru CS, Rahman M, Zaman K, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020 Dec 2;103:214-216. doi: 10.1016/j.ijid.2020.11.191.
Aref 2021	Aref, Z.F., et al., Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19. International Journal of Nanomedicine, 2021. 16: p. 4063.
Babalola 2021	Babalola OE, Bode CO, Ajayi AA, et al. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos [published online ahead of print, 2021 Feb 18]. *QJM*. 2021;hcab035. doi:10.1093/qjmed/hcab035
Beltran-Gonzalez 2021	Gonzalez, Jose Lenin Beltran, Mario González Gámez, Emanuel Antonio Mendoza Enciso, Ramiro Josue Esparza Maldonado, Daniel Hernández Palacios, Samuel Dueñas Campos, Itzel Ovalle Robles, et al. Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe Covid-19. A Randomized Controlled Trial. medRxiv (2021): 2021.02.18.21252037.
Biber 2021	Biber, A., et al., Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19, A double-blind, randomized placebo-controlled trial. medRxiv, 2021.
Chaccour 2021	C. Chaccour et al., The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial, EClinicalMedicine (2021), https://doi.org/10.1016/j.eclinm.2020.100720
Chachar 2020	Aijaz Zeeshan Khan Chachar, Khurshid Ahmad Khan, Mohsin Asif, Khushbakht Tanveer, Arous Khaqan, Rabia Basri, 2020. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients, International Journal of Sciences, Office ijSciences, vol. 9(09), pages 31-35, September.
Chachla 2021	Chahla, R.E., et al., Cluster Randomised Trials-Ivermectin Repurposing For COVID-19 Treatment Of Outpatients With Mild Disease In Primary Health Care Centers. 2021.
Chowdhury 2021	Chowdhury A, Shahbaz M, Karim M, Islam J, Dan G, Shuixiang H. A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients. EJMO. 2021; 5(1): 63-70
Elgazzar 2020	Elgazzar A, Eltaweel A, Youssef SA, Hany B, Hafez M and Moussa H. Efficacy and Safety of ivermectin for Treatment and prophylaxis of COVID-19 Pandemic. Res. Square 28 Dec. 2020. Available from: https://www.researchsquare.com/article/rs-100956/v3
Galan 2021	Galan, Luis Enrique Bermejo, Nayara Melo dos Santos, Mauro Shosuka Asato, Jucineide Vieira Araújo, Adriana de Lima Moreira, Aléxia Mahara Marques Araújo, Artur Diogenes Pinheiro Paiva, et al. "Phase 2 Randomized Study on Chloroquine, Hydroxychloroquine or Ivermectin in Hospitalized Patients with Severe Manifestations of Sars-Cov-2 Infection." Pathogens and Global Health (2021): 1-8.
Hashim 2020	Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulami AS, et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. medRxiv [Internet] 2020.10.26.20219345. Available from: https://doi.org/10.1101/2020.10.26.20219345
Kishori 2020	Kishoria N, Mathur SL, Parmer V et al. . Ivermectin as Adjuvant to Hydroxycholoroquine in Patients Resistant to Standard Treatment for Sars-Cov-2: Results of an Open-Label Randomized Clinical Study. INDIAN JOURNAL OF RESEARCH 9, no. 8 (2020). https://doi.org/DOI : 10.36106/paripex.
Krolewiecki 2021	Krolewiecki, A., Lifschitz, A., Moragas, M., Travacio, M., Valentini, R., Alonso, D. F. et al. (2021). Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine, 37, 100959.
López-Medina 2021	López-Medina, Eduardo, Pío López, Isabel C. Hurtado, Diana M Dávalos, Oscar Ramirez, Ernesto Martínez et al. "Effect of Ivermectin on Time to Resolution of Symptoms among Adults with Mild Covid-19: A Randomized Clinical Trial." JAMA 325, no. 14 (2021): 1426-35.
Mahmud 2021	Mahmud, R., M. M. Rahman, I. Alam, K. G. U. Ahmed, Akmh Kabir, Skjb Sayeed, M. A. Rassel, et al. "Ivermectin in Combination with Doxycycline for Treating Covid-19 Symptoms: A Randomized Trial." [In eng]. J Int Med Res 49, no. 5 (May 2021): 3000605211013550. https://doi.org/10.1177/03000605211013550.
Mohan 2021	Mohan, Anant, Pawan Tiwari, Tejas Suri, Saurabh Mittal, Ankit Patel, Avinash Jain, T Velpandian, et al. "Ivermectin in Mild and Moderate Covid-19 (Rivet-Cov): A Randomized, Placebo-Controlled Trial." (2021).
Niaee 2021	Niaee MS, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-centre clinical trial. Asian Pacific Journal of Tropical Medicine, 14(6), 266–273.
Okumus 2021	Okumuş, N., Demirtürk, N., Çetinkaya, R.A. et al. “Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients”. BMC Infect Dis 21, 411 (2021).

Podder 2020 Podder CS, Chowdhury N, Mohim IS and Haque W. (2020). Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science. 14.

Pott-Junior 2021 Pott-Junior, Henrique, Mônica Maria Bastos Paoliello, Alice de Queiroz Constantino Miguel, Anderson Ferreira da Cunha, Caio Cesar de Melo Freire, Fábio Fernandes Neves, Lucimar Retto da Silva de Avó, et al. "Use of Ivermectin in the Treatment of Covid-19: A Pilot Trial." Toxicology Reports 8 (2021): 505-10.

Ravikirti 2021 Ravikirti R, Pattadar C, Raj R, Agarwal N, Biswas B, Manjhi PK, Rai DK, Shyama, Kumar A, Sarfaraz A. Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India. J Pharm Pharm Sci. 2021;24:343-350. doi: 10.18433/jpps32105.

Samaha 2021 Samaha AA, Mouawia H, Fawaz M, Hassan H, et al. Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon. Viruses. 2021 May 26;13(6):989. doi: 10.3390/v13060989.

Seet 2021 Seet RCS, Quek AML, Ooi DSQ, Sengupta S, et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial. Int J Infect Dis. 2021 May;106:314-322. doi: 10.1016/j.ijid.2021.04.035.

Shah Bukhari 2021 Shah Bukhari, Karamat Hussain, Asma Asghar, Najma Perveen, Arshad Hayat, Sermad Ahmad Mangat, Kamil Rehman Butt, Mohammad Abdullah, et al. "Efficacy of Ivermectin in Covid-19 Patients with Mild to Moderate Disease." medRxiv (2021): 2021.02.02.21250840.

Shahbaznejad 2021 Shahbaznejad, L., et al., Effect of ivermectin on COVID-19: A multicenter double-blind randomized controlled clinical trial. Clinical Therapeutics, 2021.

Shouman 2020 Shouman W. et al. "Use of Ivermectin as a Potential Chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial". Journal of Clinical and Diagnostic Research. 2021 Feb, Vol-15(2): OC27-OC32

Vallejos 2021 Vallejos, J., et al., Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC infectious diseases, 2021. 21(1): p. 1-11.