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Effectiveness and safety of antiviral or antibody treatments for coronavirus

A rapid review

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ABSTRACT

Background: To identify safe and effective medical countermeasures (e.g., antivirals/antibodies) to address the current outbreak of a novel coronavirus (COVID-19)

Methods: Comprehensive literature searches were developed by an experienced librarian for MEDLINE, EMBASE, the Cochrane Library, and biorxiv.org/medrxiv.org; additional searches for ongoing trials and unpublished studies were conducted in clinicaltrials.gov and the Global Infectious Diseases and Epidemiology Network (GIDEON). Title/abstract and full-text screening, data abstraction, and risk of bias appraisal were carried out by single reviewers.

Results: 54 studies were included in the review: three controlled trials, 10 cohort studies, seven retrospective medical record/database studies, and 34 case reports or series. These studies included patients with severe acute respiratory syndrome (SARs, n=33), middle east respiratory syndrome (MERS, n=16), COVID-19 (n=3), and unspecified coronavirus (n=2). The most common treatment was ribavirin (n=41), followed by oseltamivir (n=10) and the combination of lopinavir/ritonavir (n=7). Additional therapies included broad spectrum antibiotics (n=30), steroids (n=39) or various interferons (n=12). No eligible studies examining monoclonal antibodies for COVID-19 were identified. One trial found that ribavirin prophylactic treatment statistically significantly reduced risk of MERS infection in people who had been exposed to the virus. Of the 21 studies reporting rates of ICU admission in hospitalized SARS or MERS patients, none reported statistically significant results in favour of or against antiviral therapies. Of the 40 studies reporting mortality rates in hospitalized SARS or MERS patients, one cohort study (MERS) and one retrospective study (SARS) found a statistically significant increase in the mortality rate for patients treated with ribavirin. Eighteen studies reported potential drug-related adverse effects including gastrointestinal symptoms, anemia, and altered liver function in patients receiving ribavirin.

Conclusion: The current evidence for the effectiveness and safety of antiviral therapies for coronavirus is inconclusive and suffers from a lack of well-designed prospective trials or observational studies, preventing any treatment recommendations from being made. However, it is clear that the existing body of evidence is weighted heavily towards ribavirin (41/54 studies), which has not shown conclusive evidence of effectiveness and may cause harmful adverse events so future investigations may consider focusing on other candidates for antiviral therapy.

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INTRODUCTION

Purpose and Research Questions

The Infectious Disease Prevention and Control Branch of the Public Health Agency of Canada (PHAC) submitted a query on the effectiveness and safety of antiviral, antibody, or other medical countermeasures for the treatment of novel coronavirus (COVID-19) through the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Network (DSEN). They requested the DSEN Methods and Application Group in Indirect Comparisons (MAGIC) Team conduct a rapid review on this topic with an approximate 2-week timeline.

The overall objective of this rapid review was to identify safe and effective medical countermeasures to address the current outbreak of a novel coronavirus (COVID-19). In order to focus the research question to increase feasibility, we proposed the following key research questions:

1. What is the effectiveness and safety of any antiviral and/or monoclonal antibody treatment currently available to treat (COVID-19)?
2. What is the effectiveness and safety of currently available antiviral therapies used to treat other coronavirus infections?

METHODS

Overall methods

The rapid review conduct was guided by the Cochrane Handbook for Systematic Reviews of Interventions[1] along with the Rapid Review Guide for Health Policy and Systems Research[2]. The team used an integrated knowledge translation approach, with consultation from the knowledge users from the Public Health Agency of Canada at the following stages: question development, literature search, study inclusion, interpretation of results, and draft report. After the report is submitted to the Public Health Agency of Canada, a manuscript will be prepared for publication and we will invite our knowledge users to join us as coauthors. We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[3] to guide the reporting of our rapid review results; a PRISMA extension specific to rapid reviews is currently under development.

Literature search

Comprehensive literature searches addressing both research question 1 (RQ1) and research question 2 (RQ2) were developed by an experienced librarian for MEDLINE, EMBASE, the Cochrane Library, and biorxiv.org/medrxiv.org databases. Grey (i.e., difficult to locate or unpublished) literature was located using keyword searches of relevant terms (e.g. coronavirus, SARS, etc.) in clinicaltrials.gov and GIDEON (Global Infectious Diseases and Epidemiology Network). Additionally, the final set of included articles was cross-referenced with a list studies provided by our knowledge users from the Public Health Agency of Health as part of the scoping process for this review. The full MEDLINE search strategy and grey literature search keywords can be found in Appendix 1.

Eligibility criteria

The Eligibility criteria followed the PICOST framework and consisted of:

Population (for research question 1 (RQ1) and 2 (RQ2): Individuals of any age treated for a coronavirus infection. Subgroups of interest include older adults aged >65 years, pediatric, pregnant, or immunocompromised patients.

Intervention:

- The following interventions were eligible for RQ1:
    - Antiviral medications approved for use in COVID-19 or currently in pre-clinical trials (animal studies, excluding *in vitro* studies) for treating COVID-19 (see Table 1).
    - Monoclonal antibodies approved for use in COVID-19 or currently in pre-clinical trials (animal studies, excluding *in vitro* studies) for treating COVID-19.
- The following interventions were of interest for RQ2:
    - Antiviral agents used alone or in combination that are approved for use in coronavirus treatment or are being examined in clinical trials for use in coronavirus treatment (Table 1).

Comparator (for RQ1 and RQ2): One of the interventions listed above, no intervention, or placebo.

Outcomes (for RQ1 and RQ2): lab-confirmed coronavirus infection, hospitalization, intensive care unit (ICU) admission, mortality, and adverse events (e.g., exacerbation of infection).

*Table 1: Example list of relevant interventions**

Treatment indication/Drug class	List of medications	
Experimental antiviral agents	• Remdesivir (GS-5734)	

Influenza virus infections	• ribavirin (Ibavyr)
	• matrix 2 protein inhibitors
	  ○ amantadine
	• RNA polymerase inhibitors
	  ○ rimantadine
		• neuraminidase inhibitors
		  ○ oseltamivir (Tamiflu)
		  ○ peramivir (Rapivab)
		  ○ zanamivir (Relenza)

Human cytomegalovirus infections	• acyclic guanosine analogues
	  ○ acyclovir
	• acyclic nucleoside phosphonate analogues
	  ○ cidofovir
	  ○ diphosphates
		• pyrophosphate analogues
		  ○ foscarnet
		  ○ fomivirsen
		• oligonucleotides

Treatment indication/Drug class	List of medications
Respiratory syncytial virus infections	• ribavirin (Ibavyr) and antibodies

HIV infections	• protease inhibitors
	  ○ boceprevir
	  ○ telaprevir
	  ○ lopinavir
	  ○ ritonavir
	  ○ darunavir/cobicistat (Prezcobix)
	  ○ indinavir (Crixivan)
	  ○ saquinavir (Invirase)
	• integrase inhibitors
	  ○ raltegravir
	  ○ elvitegravir
	  ○ dolutegravir
	• entry (fusion) inhibitors
	  ○ maraviroc
	  ○ celsentri
	• nucleoside reverse transcriptase inhibitors
	  ○ abacavir
	  ○ ziagen
	  ○ emtricitabine
	  ○ emtriva
	  ○ lamivudine
	  ○ epivir
	  ○ tenofovir
	  ○ viread
	  ○ zidovudine
	  ○ azidothymidine
	  ○ retrovir
	• nonnucleoside reverse transcriptase inhibitors
	  ○ doravirine
	  ○ pifeltro
	  ○ efavirenz
	  ○ sustiva
	  ○ etravirine
	  ○ intelence
	  ○ nevirapine
	  ○ viramune
	  ○ rilpivirine
	  ○ edurant
	• acyclic nucleoside phosphonate analogues
	  ○ cidofovir
	  ○ diphosphates

Immune modulators	• interferon 1β (Betaseron/Extavia)
Monoclonal Antibodies	• abciximab (Reopro) • adalimumab (Humira/Amjevita) • alefacept (Amevive) • alemtuzumab (Campath) • basiliximab (Simulect) • belimumab (Benlysta) • bezlotoxumab (Zinplava) • canakinumab (Ilaris) • certolizumab (Cimzia) • cetuximab (Erbitux) • daclizumab (Zenapax/Zinbryta) • denosumab (Prolia/Xgeva) • efalizumab (Raptiva) • golimumab (Simponi) • inflectra (Remicade) • ipilimumab (Yervoy) • ixekizumab (Taltz) • natalizumab (Tysabri) • nivolumab (Opdivo) • olaratumab (Lartruvo) • omalizumab (Xolair) • palivizumab (Synagis) • panitumumab (Vectibix) • pembrolizumab (Keytruda) • rituximab (Rituxan) • tocilizumab (Actemra) • trastuzumab (Herceptin) • secukinumab (Cosentyx) • ustekinumab (Stelara)

*Note: not an exhaustive list

Study designs:

- The following study designs were eligible for RQ1:
    - Randomized controlled trials (RCTs) and quasi-RCTs
    - Non-randomized studies (e.g., non-randomized trials, interrupted time series, controlled before after)
    - Observational studies (e.g., cohort, case control, cross-sectional)
    - Case studies, case reports, and case series
    - Pre-clinical (animal) studies
- The following study designs were eligible for RQ2:
    - Randomized controlled trials (RCTs) and quasi-RCTs
    - Non-randomized studies (e.g., quasi-RCTs, non-randomized trials, interrupted time series, controlled before after)
    - Observational studies (e.g., cohort, case control, cross-sectional)

Time periods (for RQ1 and RQ2): All periods of time and duration of follow-up were eligible.

Other (for RQ1 and RQ2): Only studies published in English were eligible for inclusion, due to the short timelines for this review. Relevant studies written in languages other than English and relevant studies of an ineligible design (e.g., trial protocol, literature review) will be excluded but reported in an appendix of possibly relevant articles (Appendix 2).

Study selection

For both level 1 (title/abstract) and level 2 (full-text) screening, a screening form was prepared based on the eligibility criteria and pilot-tested by the review team using 25 citations prior to level 1 screening and 10 full text articles prior to level 2 screening. Agreement between reviewers was sufficiently high (>75%) in both cases so no further pilot-testing was required. Full screening was completed by a single reviewer for both level 1 and level 2 using Synthesi.SR, the team's proprietary online software [https://breakthroughkt.ca/login.php].

Data items and data abstraction

Items for data abstraction included study characteristics (e.g., study period, study design, country of conduct), patient characteristics (e.g., mean age, age range, co-morbidities), intervention details (e.g., type of intervention, dose, timing of treatment), comparator details (e.g., comparator intervention, dose), and outcome results (e.g., hospitalizations due to coronavirus, adverse events, mortality) at the longest duration of follow-up.

A standardized data abstraction form was developed to capture data on the above listed items. Prior to data abstraction, a calibration exercise was completed to test the form amongst the entire review team using two randomly selected full-text articles. Following successful completion of the calibration exercise, included studies were abstracted by single reviewers.

Risk of bias appraisal

Risk of bias appraisal was carried out by single reviewers using Cochrane Risk of Bias (RoB) tool[4] for controlled trials and the Newcastle Ottawa Scale[5] (NOS) for cohort or case-control studies.

Synthesis

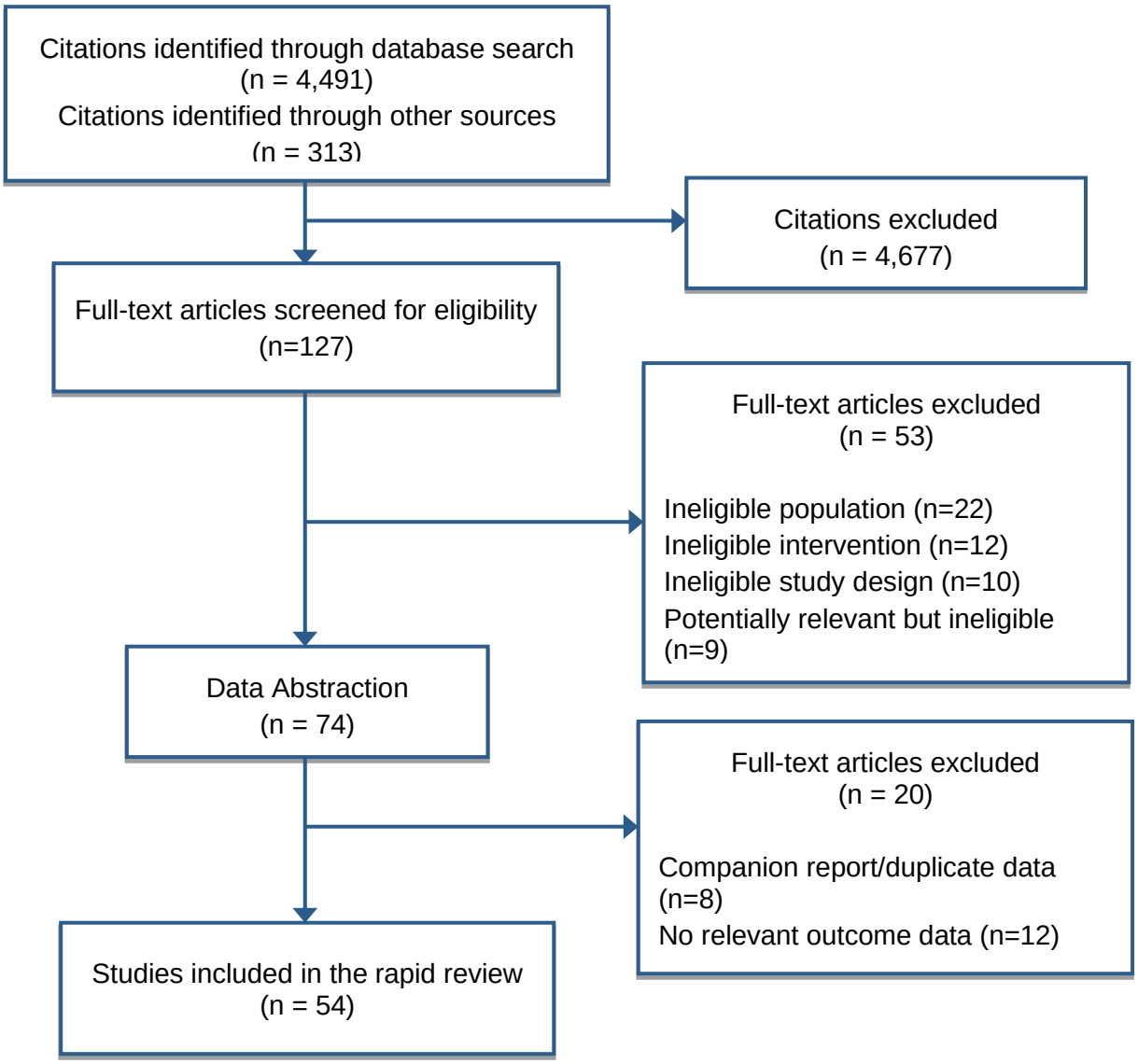
Included studies were synthesized descriptively including summary statistics and detailed tables of study characteristics and results. Tables of study results are organized according to study design and where available, information on relevant subgroups were highlighted.

RESULTS

Literature Search

The database search returned a total of 4,491 citations, while the grey literature searches returned 305 citations, and 8 additional citations were identified from the articles provided by our knowledge users from the Public Health Agency of Canada for level 1 screening. A total of 4,567 citations were excluded after level 1 screening and a further 81 citations were identified as ineligible for the current review but potentially of interest to knowledge users, leaving 156 potentially relevant articles to be passed to level 2 screening. The full-text for 29 articles could not be obtained in time to be screened for this review and were added to the inventory of potentially relevant articles. Of the 127 articles screened at level 2, 74 were passed to data abstraction. During data abstraction a further 20 articles were excluded due to lack of relevant outcomes, leaving 54 articles included in this review (Figure 1).

Figure 1: Study Flow Diagram



Characteristics of included studies

Of the 54 studies included in this review three were controlled trials[6-8], 10 were cohort studies[9-18], seven were retrospective medical record/database studies[19-25], and 34 were case reports or case series[26-59] (Table 2). All of the included studies were published between 2003 and 2020 with the majority conducted in Hong Kong (n=14), followed by China (n=12), Saudi Arabia (n=10), Canada (n=5), South Korea (n=4), Taiwan (n=3), and one each from France, Germany, Greece, the United Arab Emirates, and the United States. Sample sizes for the studies ranged from single patients in the case reports to groups of >1000 patients in the cohort studies. Overall, the majority of studies (n=33) dealt with treatment of Severe Acute Respiratory Syndrome (SARS), followed by Middle East Respiratory Syndrome (MERS; n=16), COVID-19 (n=3) and two studies treated unspecified coronavirus.

The majority of studies were conducted in adult populations (n=52), one case report[31] and one case series[36] included infant and pediatric populations, respectively. Four case reports/series[29,45,46,48] specifically included immunocompromised patients and one case study[34] included a pregnant woman with MERS; however, the majority of study populations included patients with comorbid conditions (n=33). Common comorbidities included diabetes, heart disease, hypertension, and renal failure (Appendix 3). The most common antiviral studied was ribavirin (n=41), followed by oseltamivir (n=10) and the combination of lopinavir/ritonavir (n=7). Additional therapies used in the studies included a variety of broad spectrum antibiotics (n=30), steroids including hyrdcortisone, methylprednisone, or prednisolone (n=39) or various interferons (n=12; Appendix 3). No animal or human trials investigating monoclonal antibodies for the treatment of COVID-19 were found in this rapid review. All of the studies recruited from or reported on hospitalized populations and the most commonly reported outcome was mortality (n=40), followed by ICU admission (n=21) and adverse events (n=18).

Table 2: Summary Study and Patient Characteristics

Characteristics (n)	Controlled Trials (n=3)	Cohort Studies (n=10)	Retrospective Studies (n=7)	Case Reports/Series (n=34)
Diagnosis				
COVID-19	--	--	--	3
SARS	2	7	4	20
MERS	1	3	3	9
Other coronavirus	--	--	--	2
Age of population (range)	22 to 57	15 to 70	22 to 79	4 months to 83 years
Sample size [median (range)]	43 (16 to 190)	169 (72 to 1934)	63 (14 to 306)	8 (1 to 323)
Publication Year (range)	2004 to 2019	2003 to 2019	2003 to 2019	2003 to 2020
Country of conduct	China (2), South Korea (1)	China (3), Hong Kong (3), South Korea (1), Saudi Arabia (2), Singapore (1)	Canada (2), Saudi Arabia (3), Taiwan (2)	Canada (3), China (7), France (1), Germany (1), Greece (1), Hong Kong (11), South Korea (2), Saudi Arabia (5), Taiwan (1), United Arab Emirates (1), USA (1)
Comorbidities reported in study population	No (3)	Yes (6); No (4)	Yes (5), No (2)	Yes (22), No (12)
Interventions		9		
Ribavirin	3	2	7	29
Oseltamivir	--	2	1	7
Lopinavir/ritonavir	1	2	1	3

Foscarnet	--	--	--	1
Remdesivir	--	--	--	1
Antibiotics	2	3	3	22
Steroids	2	10	5	22
Interferons	1	3	2	6

Risk of Bias Results

The 34 case reports/series and 7 retrospective studies included in this review were not assessed for risk of bias due to the inherent bias in the type of study design. The 3 trials were assessed with the Cochrane RoB tool[4] and the 10 cohort studies were assessed using the NOS[5]. The risk of bias in the 3 included trials was overall difficult to judge due to a lack of adequate descriptions of study methods (Figure 2). All three of the trials were at high or unclear risk of bias on the following components: random sequence generation, allocation concealment, and blinding of participants/personnel (Appendix 5). The cohort studies were of fair quality overall; most of the studies suffered from a lack of representative sampling (n=8), failed to demonstrate that the outcomes of interest were not present at the start of the study (n=8), or failed to adequately ensure the comparability of cohorts (n=4; Figure 3). The complete NOS results are provided in Appendix 5.

Figure 2 Cochrane RoB results - Controlled trials (n=3)

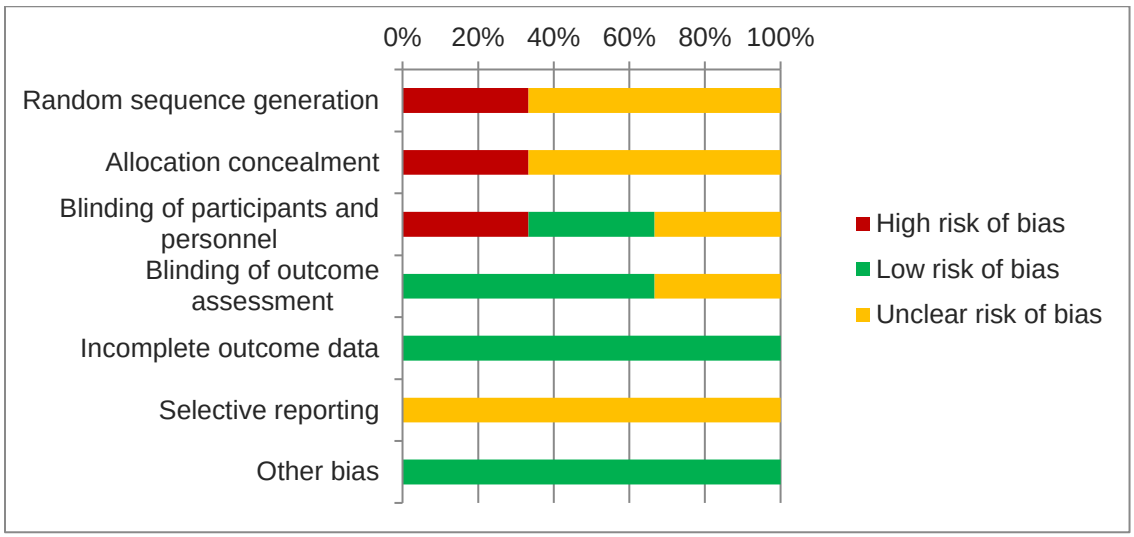
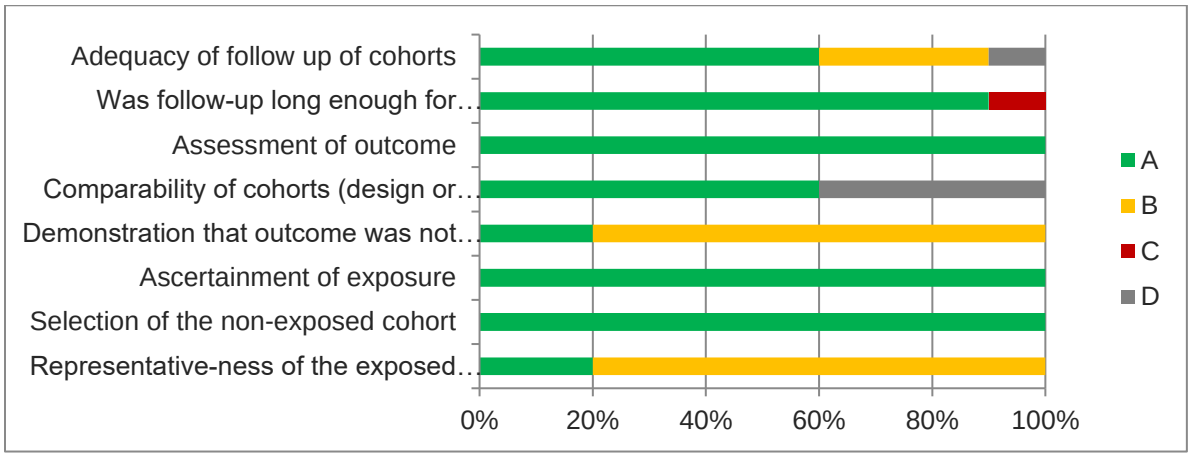


Figure 3: NOS Results - Cohort studies (n=10)



Studies of COVID-19

Three studies examining patients infected with COVID-19 were included in this review: one case report[35] and two case series[56,57].

The case report[35] included a 35-year-year old man, the first American diagnosed with COVID-19. He, he was initially treated with vancomycin and cefepime which are standard treatments for suspected community-acquired pneumonia. Upon lab-confirmation of COVID-19 infection, the antibiotics were stopped and the patient was started on Remdesivir 7 days after initial admission to hospital. At study end, the patient remained hospitalized with the majority of symptoms resolved (see appendices 3 and 4 for complete details).

The two case series[56,57] were conducted in China and included 4 and 138 patients, respectively. All patients were hospitalized and initial diagnosis was made based on WHO Criteria later confirmed by lab-testing of the patient specimens. The case series included an approximately even number of male and female (55% v 45%) patients ranging in age from 19 to 68 years old,

with a variety of co-morbidities including cardiovascular disease, chronic kidney or liver disease, COPD, and diabetes (Appendix 3). In one case series[57], patients (n=4) were treated with a combination of lopinavir/ritonavir, Arbidol (umifenovir), antibiotics, Shufeng Jiedu Capsule (Traditional Chinese Medicine), and intravenous immunoglobulins (Appendix 4). At study end (15 days),) two patients tested negative for COVID-19 and were subsequently discharged from the hospital and two patients remained hospitalized, one of whom still required mechanical ventilation (Appendix 4). In the larger case series[56], 124 patients were treated with oseltamivir combined with antibiotic therapy in 89 patients and combined with glucocorticoids in 62 patients (Appendix 4). Over the course of the study, 34 patients treated with oseltamivir were admitted to the ICU, 17 of which required invasive mechanical ventilation. At study end (19 days),) 47 patients had been discharged and 6 patients died, all of whom had been admitted to ICU (Appendix 4).

Ongoing human trials for COVID-19

Four currently ongoing randomized controlled trials proposing to test treatments for COVID-19 were identified through keyword searches of clinicaltrials.gov. All four trials are being carried out in China, three are investigating antiviral medications (lopinavir/ritonavir, arbidol (umifenovir), darunavir, cobicstat, and, ASC09/ritonavir) and one trial is investigating a combination of lopinavir/ritonavir with Traditional Chinese Medicines (TCM). At the time of this writing two of the trials have started recruiting patients (further details in Table 3).

Table 3: Details of ongoing COVID-19 trials

Author, Year Country NCT ID	Status Estimated Enrollment Estimated completion	Eligibility Criteria (age; diagnosis) Interventions
Li, 2020 **China** **NCT04252885**	Recruiting 125 participants July 31, 2020	Adult (18-80 yrs); lab-confirmed infection Group A: standard treatment + lopinavir/ritonavir Group B; standard treatment + arbidol (umifenovir) Group C: standard treatment
Lu, 2020 **China** **NCT04252274**	Not yet recruiting 30 participants December 31, 2020	All ages; National Health Commission diagnostic criteria Intervention: Darunavir, Cobicistat + conventional treatments Comparator: Conventional treatments
Qiu, 2020 **China** **NCT04261907**	Not yet recruiting 160 participants June 30, 2020	Adult (18-75 yrs); lab-confirmed infection Intervention: ASC09/ritonavir + conventional treatment Comparator: lopinavir/ritonavir + conventional treatment
Xiao, 2020 **China** **NCT04251871**	Recruiting 150 participants January 22, 2021	Youth/Adult (14-80 yrs); lab-confirmed infection Intervention: TCM + conventional medicines** Comparator: Conventional medicines**

**Conventional medicines includes: oxygen therapy, antiviral therapy (alfa interferon via aerosol inhalation, and lopinavir/ritonavir, 400mg/100mg, p.o, bid)

Effectiveness Outcomes

Infection Prevention

One of the included trials[7] examined the effectiveness of ribavirin combined with lopinavir/ritonavir compared to no treatment as a prophylactic measure for healthcare workers highly exposed to MERS through unprotected exposure to a patient with pneumonia later

confirmed to be caused by MERS-CoV. None of the subjects in the prophylaxis arm (ribavirin/lopinavir/ritonavir) developed MERS while 6 subjects in the control arm were infected with MERS as confirmed by rPT-PCR testing. The risk of infection was statistically significantly lower in the prophylaxis arm (adjusted odds ratio: 0.405, 95% CI 0.274 to 0.599, p=0.009; Appendix 4).

ICU Admission

Of the 21 studies reporting this outcome, one was a randomized trial[6] comparing ribavirin supplemented with hydrocortisone to ribavirin alone; three were cohort studies[14,15,17] comparing oseltamivir to steroid treatment alone, ribavirin with continuous steroid treatment to ribavirin with high-dose 'pulse' steroids, and ribavirin to steroid and/or antibiotic treatment; three were retrospective studies[19,20,25] examining the effectiveness of ribavirin and oseltamivir alone or in combination with other drugs; and 14 were case reports/series[33,34,37,40,42,44,45,47,50,51,53,55-57] examining ribavirin, oseltamivir, lopinavir/ritonavir alone or in combination with steroids or antibiotics. None of the trials, cohorts, or retrospective studies demonstrated statistically significant results between any of the comparisons (i.e., in favour of or against the effectiveness of ribavirin, oseltamivir or lopinavir/ritonavir) in reducing the risk of ICU admission for patients with SARS or MERS. The case reports and series were similarly inconclusive, none of the study authors reported a particular advantage for patients with COVID-19, SARS, or MERS treated with ribavirin, oseltamivir, or lopinavir/ritonavir.

Special populations

One case series[45] included 4 patients with hematological malignancies that acquired MERS infections. The patients were all treated with oseltamivir and one patient required admission to the ICU due to worsening symptoms. One case report[34] of a pregnant woman with MERS described initially attempting treatment with antibiotics but the patient did not respond and was transferred to ICU where antiviral treatments were initiated but the patient continued to deteriorate and died. In a case series[36] of 4 pediatric patients with SARS, all 4 were treated with ribavirin and 2 patients required mechanical ventilation during the course of their illness.

Mortality

Mortality was reported in two of the included trials (ribavirin), all 10 cohort studies (ribavirin, lopinavir/ritonavir, oseltamivir), all seven retrospective studies (ribavirin, lopinavir/ritonavir, oseltamivir), and 21 case reports or case series (ribavirin, oseltamivir, lopinavir/ritonavir). The comparative studies (trials and cohorts) failed to find statistically significant results indicating that none of the antivirals they examined were effective in reducing mortality for SARS or MERS. One cohort study[10] of MERS patients found that treatment with ribavirin and interferons significantly increased 90-day mortality risk (adjusted odds ratio: 2.27, 95% CI 1.20-4.32). The patients in this cohort were generally older (median age 57 (IQR 47-70)) and had a number of underlying chronic conditions including diabetes, cardiovascular disease, chronic lung, renal, or liver disease and malignancy including leukemia or lymphoma which may in part explain the increased risk. One retrospective study[20] of SARS patients found the 21-day mortality rate was significantly higher in a cohort of patients treated with ribavirin compared to matched historical controls (6.5%, 95% CI 1.9% to 11.8%). Patients in this study were largely middle aged (34 to 57 years of age); however a large proportion of patients that died (approximately 80%) had underlying conditions such as diabetes or cancer.

The two case series[56,57] and one case report[35] that included patients with COVID-19 that used Remdesivir (1 patient), lopinavir/ritonavir (4 cases) and oseltamivir (124 cases) reported 6 deaths in the cohort treated with oseltamivir.

Special Populations

The four cases reports/series[29,45,46,48] that included immunosuppressed patients with MERS (5 patients) and unspecified coronavirus (2 patients) reported 3 deaths all in patients with hematological malignancies treated with foscarnet (n=1) and oseltamivir (n=2). One patient with HIV and 2 patients with hematological malignancies that acquired MERS were treated with ribavirin and oseltamivir respectively and survived after being hospitalized for their illness (38 and 28 days respectively). The case report[34] of a pregnant woman with MERS treated with oseltamivir and later ribavirin succumbed to septic shock 8 days after admission to hospital. The two case series[31,36] that included pediatric patients treated with ribavirin reported no mortality at study end.

Safety Outcomes

Adverse Events

One of the included trials[7], seven of the cohort studies[9-11,13-15,17], three of the retrospective studies[20,21,25], and seven case reports/series[28,38,39,42,43,50,51] reported treatment related adverse events while two retrospective studies and three case reports/series reported that no treatment related adverse events occurred. In the trial[7] examining the effectiveness of ribavirin/lopinavir/ritonavir compared to no treatment as a prophylactic measure for healthcare workers, treatment-related adverse events were widely reported in the prophylaxis arm, including: GI symptoms (diarrhea n=9, nausea n=9, stomatitis n=4), anemia (n=9), leucopenia (n=8) and hyperbilirubinemia (n=20). All adverse effects occurred during prophylactic therapy and resolved shortly after conclusion of treatment with no further intervention. Overall, the most commonly reported adverse events were anemia (n=12 studies) and altered liver function (n=5 studies) in patients treated with ribavirin. Other treatment related adverse events included gastrointestinal symptoms (e.g., nausea, vomiting), changes in kidney function, cardiac events (e.g., bradycardia, atrial fibrillation), hyperglycemia, and changes in mental status (e.g., confusion, anxiety). It should be noted however, that in the studies reporting cardiac adverse events, hyperglycemia, and mental status changes patients were receiving steroids as well as ribavirin.

Special Populations

None of the studies that included special populations reported treatment-related adverse events.

DISCUSSION

The Public Health Agency of Canada commissioned a rapid review to address the urgent question of the effectiveness and safety of antiviral or antibody therapies in the treatment of coronavirus. A comprehensive literature search of both electronic databases and grey literature sources resulted in 54 studies of various antiviral treatments in patients diagnosed with COVID-

19, SARS, or MERS; however, no animal or human studies of monoclonal antibodies could be found.

Overall the results of the included studies proved inconclusive on the effectiveness of antiviral drugs in treating coronavirus infections and prevent any particular treatments from being recommended for use. There is a low quality of available evidence that largely consists of case reports and case series, with few observational studies, and even fewer trials. There were however important safety signals identified in the included studies, particularly the possible development of anemia and altered liver function in patients receiving ribavirin treatment. It is similarly difficult to recommend a particular antiviral drug as a promising candidate for further investigation due to the variable quality and inconclusive results of the current evidence. This review does show however that the existing body of evidence is weighted heavily towards studies of ribavirin which has shown no particular efficacy in treating coronavirus and may in fact cause harmful adverse effects. Future investigations into potential antiviral therapies for coronavirus may be best served by pointing their attention to other drug candidates.

There are several limitations to the review methods employed here, single screening and abstraction for example, however they were selected to thoughtfully tailor our methods according to our knowledge user needs and the urgent nature of the request to provide timely results.

CONCLUSIONS

The current evidence for the effectiveness of antiviral therapies for coronavirus is not conclusive and suffers from a lack of well-designed prospective trials or observational studies. None of the interventions examined in this review can be recommended for use in patients with coronavirus. Similarly, no firm recommendations can be made for or against these interventions from a safety perspective due to a lack of conclusive evidence. Some important safety signals potentially related to ribavirin use were identified (anemia, altered liver function) but also require further investigation to clarify their relation to the drug.

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APPENDIX 1 – Search Strategies

MEDLINE Search Strategy

1 coronaviridae infections/ or coronavirus infections/ or severe acute respiratory syndrome/ or SARS Virus/
2 (coronavirus* or corona virus* or mers or middle east respiratory syndrome* or Severe Acute Respiratory Syndrome* or SARS or CoV or SARS-CoV or MERS-CoV or 2019-nCoV).tw,kf.
3 or/1-2
4 dt.fs.
5 exp Antiviral Agents/
6 (antiviral or anti-viral or anti viral).tw,kf.
7 (neuraminidase adj2 inhibitor).tw,kf.
8 Remdesivir.tw,kf.
9 (oseltamivir or Tamiflu or peramivir or Rapivab or zanamivir or Relenza or ribavirin or Ibavyr).tw,kf.
10 (matrix adj3 inhibitors).tw,kf.
11 exp DNA-Directed RNA Polymerases/
12 RNA polymerase inhibitors.tw,kf.
13 Rimantadine/
14 Rimantadine.tw,kf.
15 acyclic guanosine analogues.tw,kf.
16 Acyclovir/
17 Acyclovir.tw,kf.
18 acyclic nucleoside phosphonate analogues.tw,kf.
19 Cidofovir/
20 (diphosphate or Cidofovir).tw,kf.
21 Diphosphonates/
22 pyrophosphate analogues.tw,kf.
23 Foscarnet/
24 Foscarnet.tw,kf.
25 Oligonucleotides/
26 Fomivirsen.tw,kf.
27 Protease Inhibitors/
28 (boceprevir or telaprevir or lopinavir or ritonavir or darunavir or cobicistat or Prezcobix or indinavir or Crixivan or saquinavir or Invirase).tw,kf.
29 Integrase Inhibitors/
30 (raltegravir or elvitegravir or dolutegravir).tw,kf.
31 HIV Fusion Inhibitors/
32 (maraviroc or Celsentri).tw,kf.
33 Reverse Transcriptase Inhibitors/
34 nucleoside reverse transcriptase inhibitors.tw,kf.
35 (abacavir or Ziagen or emtricitabine or Emtriva or lamivudine or Epivir or tenofovir or Viread or zidovudine or azidothymidine or Retrovir).tw,kf.
36 nonnucleoside reverse transcriptase inhibitors.tw,kf.
37 (doravirine or Pifeltro or efavirenz or Sustiva or etravirine or Intelence or nevirapine or Viramune or rilpivirine or Edurant).tw,kf.
38 exp Interferon beta-1b/
39 (Betaseron or Extavia).tw,kf.
40 or/5-39

41 Antineoplastic Agents, Immunological/
42 (abciximab or Reopro or adalimumab or Humira or Amjevita or alefacept or Amevive or alemtuzumab or Campath or basiliximab or Simulect or belimumab or Benlysta or bezlotoxumab or Zinplava or canakinumab or Ilaris or certolizumab or Cimzia or cetuximab or Erbitux or daclizumab or Zenapax or Zinbryta or denosumab or Prolia OR, Xgeva or efalizumab or Raptiva or golimumab or Simponi or inflectra or Remicade or ipilimumab or Yervoy or ixekizumab or Taltz or natalizumab or Tysabri or nivolumab or Opdivo or olaratumab or Lartruvo or omalizumab or Xolair or palivizumab or Synagis or panitumumab or Vectibix or pembrolizumab or Keytruda or rituximab or Rituxan or tocilizumab or Actemra or trastuzumab or Herceptin or secukinumab or Cosentyx or ustekinumab or Stelara).tw,kf.
43 exp Antibodies, Monoclonal/
44 or/41-43
45 medical countermeasures/
46 (countermeasure* or counter measure*).tw,kf.
47 45 or 46
48 4 or 40 or 44 or 47
49 3 and 48
50 animals/ not humans/
51 49 not 50

Grey Literature: ClinicalTrials.gov and GIDEON (Global Infectious Diseases and Epidemiology Network).

Keyword search terms:
2019-nCoV
Coronavirus
CoV – note: this one may pick up an unrelated drug name: COV155
SARS
MERS
Middle East Respiratory Syndrome
Severe Acute Respiratory Syndrome

APPENDIX 2 – Potentially relevant articles not included in this review

First Author, Year	Title	Population	Article Type
Literature Reviews, Meta-analysis, and Systematic Reviews			
Gao, 2020	Machine intelligence design of 2019-nCoV drugs	COVID-19	Literature review
Lu, 2020	Drug treatment options for the 2019-new coronavirus (2019-nCoV)	COVID-19	Literature review
Arabi, 2016	The search for therapeutic options for Middle East Respiratory Syndrome (MERS)	MERS	Literature review
Behzadi, 2019	Overview of Current Therapeutics and Novel Candidates Against Influenza, Respiratory Syncytial Virus, and Middle East Respiratory Syndrome Coronavirus Infections	MERS	Literature review
Chong, 2015	Antiviral Treatment Guidelines for Middle East Respiratory Syndrome	MERS	Literature review
Khan, 2018	Middle east respiratory syndrome (MERS): A systematic review	MERS	Systematic review
Lee, 2015	Current advances in the development of vaccines and therapeutic agents against MERS-coV	MERS	Literature review
Li, 2015	Clinical treatment and small molecular drugs for anti MERS-CoV: Research advances	MERS	Literature review
Malik, 2016	Middle east respiratory syndrome coronavirus: Current knowledge and future considerations	MERS	Literature review
Milne-Price, 2014	The emergence of the Middle East Respiratory Syndrome coronavirus	MERS	Literature review
Mo, 2016	A review of treatment modalities for Middle East Respiratory Syndrome	MERS	Literature review
Momattin, 2013	Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy	MERS	Systematic review
Momattin, 2019	A Systematic Review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	MERS	Systematic review
Morra, 2018	Clinical outcomes of current medical approaches for Middle East respiratory syndrome: A systematic review and meta-analysis	MERS	Systematic review
Van Le, 2017	Current medical treatment for middle east respiratory syndrome: A systematic review	MERS	Systematic review

First Author, Year	Title	Population	Article Type
Zhou, 2019	Advances in MERS-CoV Vaccines and Therapeutics Based on the Receptor-Binding Domain	MERS	Literature review
Aronin, 2004	Severe acute respiratory syndrome	SARS	Literature review
Barnard, 2011	Recent developments in anti-severe acute respiratory syndrome coronavirus chemotherapy	SARS	Literature review
Berger, 2004	Severe acute respiratory syndrome (SARS)--paradigm of an emerging viral infection	SARS	Literature review
Centre for Reviews and Dissemination, 2015	Effect of integrated traditional Chinese medicine and Western medicine on the treatment of severe acute respiratory syndrome: a meta-analysis (Structured abstract)	SARS	Meta-analysis
Centre for Reviews and Dissemination, 2015	SARS: systematic review of treatment effects (Structured abstract)	SARS	Systematic review
Chang, 2005	Clinical findings, treatment and prognosis in patients with severe acute respiratory syndrome (SARS)	SARS	Literature review
Cheng, 2004	Medical treatment of viral pneumonia including SARS in immunocompetent adult	SARS	Literature review
Cheng, 2007	Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection	SARS	Literature review
Cheng, 2013	Clinical management and infection control of SARS: lessons learned	SARS	Literature review
Cinatl, 2005	Development of antiviral therapy for severe acute respiratory syndrome	SARS	Literature review
Cleri, 2010	Severe Acute Respiratory Syndrome (SARS)	SARS	Literature review
Demmler, 2003	Severe acute respiratory syndrome (SARS): a review of the history, epidemiology, prevention, and concerns for the future	SARS	Literature review
File Jr, 2005	Severe acute respiratory syndrome: Pertinent clinical characteristics and therapy	SARS	Literature review
Fujii, 2004	Current concepts in SARS treatment	SARS	Literature review
Kawana, 2005	Clinical and epidemiological review of SARS	SARS	Literature review*
Lai, 2004	Clinical, Laboratory, and Radiologic Manifestation of SARS	SARS	Literature review

First Author, Year	Title	Population	Article Type
Lai, 2005	Treatment of severe acute respiratory syndrome	SARS	Literature review
Lapinsky, 2004	Critical care lessons from severe acute respiratory syndrome	SARS	Literature review
Liu, 2005	Systematic review and meta-analysis on the integrative traditional Chinese and Western medicine in treating SARS	SARS	Systematic review*
Liu, 2006	Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS)	SARS	Systematic review
Mazzulli, 2004	Severe acute respiratory syndrome: overview with an emphasis on the Toronto experience	SARS	Literature review
Nassiri, 2003	Severe acute respiratory syndrome	SARS	Literature review
Ng, 2004	SARS in newborns and children	SARS	Literature review
Nie, 2003	Current status of severe acute respiratory syndrome in China	SARS	Literature review
Oxford, 2005	New antiviral drugs, vaccines and classic public health interventions against SARS coronavirus	SARS	Literature review
Peetermans, 2004	News viral respiratory infections	SARS	Literature review*
Poutanen, 2004	Severe acute respiratory syndrome: An update	SARS	Literature review
Rainer, 2004	Severe acute respiratory syndrome: clinical features, diagnosis, and management	SARS	Literature review
Sheth, 2005	Severe acute respiratory syndrome: Emergence of a new pandemic	SARS	Literature review
Shuster, 2003	Preventing Adverse Drug Events with Rounding Pharmacists; Adverse Drug Events Involving COX-2 Inhibitors; Psoriasis Associated with Rofecoxib; Adverse Events Seen with Ribavirn Therapy for SARS; Immediate Hypersensitivity to Clavulanic Acid; Thrombocytopenia with Vancomycin	SARS	Literature review
Sirois, 2007	Discovery of potent Anti-SARS-CoV M^{Pro} inhibitors	SARS	Literature review
Stockman, 2006	SARS: systematic review of treatment effects	SARS	Systematic review
Tsang, 2004	Diagnosis and pharmacotherapy of severe acute respiratory syndrome: what have we learnt?	SARS	Literature review
van Vonderen, 2003	Ribavirin in the treatment of severe acute respiratory syndrome (SARS)	SARS	Literature review
Vijayanand, 2004	Severe acute respiratory syndrome (SARS): a review	SARS	Literature review

First Author, Year	Title	Population	Article Type
Wong, 2003	Severe acute respiratory syndrome (SARS): Epidemiology, diagnosis and management	SARS	Literature review
Wong, 2008	The management of coronavirus infections with particular reference to SARS	SARS	Literature review
Wu, 2003	Severe Acute Respiratory Syndrome (SARS)	SARS	Literature review*
Yazdanpanah, 2006	Antiretroviral drugs in severe acute respiratory syndrome	SARS	Literature review*
Zhang, 2004	Effect of integrated traditional Chinese and Western medicine on SARS: a review of clinical evidence	SARS	Systematic review
Zhaori, 2003	Antiviral treatment of SARS: can we draw any conclusions?	SARS	Literature review
Al-Hazmi, 2016	Challenges presented by MERS corona virus, and SARS corona virus to global health	SARS; MERS	Literature review
Gao, 2016	From SARS to MERS: evidence and speculation	SARS; MERS	Literature review*
Hilgenfeld, 2013	From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses	SARS; MERS	Literature review
Blasi, 2003	Winter and "atypical" respiratory infections. Italian	General coronavirus	Literature review*
Flight, 2017	The diagnosis and management of respiratory viral infections in cystic fibrosis	General coronavirus	Literature review
Luyt, 2011	Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome	General coronavirus	Literature review*
Pujanandez, 2017	Antiviral gets the jump on coronaviruses	General Coronavirus	Literature review
Steele, 1988	Antiviral agents for respiratory infections	General Coronavirus	Literature review
Tong, 2009	Therapies for coronaviruses. Part 2: Inhibitors of intracellular life cycle	General coronavirus	Literature review
Tong, 2009	Therapies for coronaviruses. Part I of II -- viral entry inhibitors	General coronavirus	Literature review
Trials Registrations and Protocols			
Li, 2020	A Randomized, Open-label, Controlled Study of the Efficacy of Lopinavir	COVID-19	Trial registration

First Author, Year	Title	Population	Article Type
	Plus Ritonavir and Arbidol for Treating With Patients With Novel Coronavirus Infection [NCT04252885]		
Lu, 2020	Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV [NCT04252274]	COVID-19	Trial registration
Qiu, 2020	A Randomized, Open-label, Multi-centre Clinical Trial Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Confirmed Cases of Pneumonia Caused by Novel Coronavirus Infection [NCT04261907]	COVID-19	Trial registration
Xiao, 2020	Effects of Traditional Chinese Medicines (TCMs) on Patients With 2019-nCoV Infection: A Perspective, Open-labeled, Randomized, Controlled Trial [NCT04251871]	COVID-19	Trial registration
Arabi, 2016	MERS-CoV Infection tReated With A Combination of Lopinavir /Ritonavir and Interferon Beta-1b: a Multicenter, Placebo-controlled, Double-blind Randomized Trial [NCT02845843]	MERS	Trial registration
Arabi, 2018	Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): study protocol for a randomized controlled trial	MERS	Protocol
Arabi, 2020	Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-beta1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial	MERS	Protocol
Davey, 2016	A Phase 1, Randomized Double-Blind, Placebo-Controlled, Single Ascending Dose Safety, Tolerability, and Pharmacokinetics Study of SAB-301 in Healthy Adults [NCT02788188]	MERS	Trial registration
National Institute of Allergy and Infectious Diseases (NIAID), 2017	A Phase I Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Immunogenicity of Co-administered MERS-CoV Antibodies REGN3048 and REGN3051 vs. Placebo in Healthy Adults [NCT03301090]	MERS	Trial registration
Tong, 2005	A Randomized, Dose-ranging Study of Alferon® LDO]Low Dose Oral Interferon Alfa-n3 (Human Leukocyte Derived)] in Normal Volunteers and/or Asymptomatic Subjects With Exposure to a Person Known to Have SARS or Possible SARS [NCT00215826]	SARS	Trial registration

First Author, Year	Title	Population	Article Type
Yu, 2007	A Multi-centre, Double-blinded, Randomized, Placebo-controlled Trial on the Efficacy and Safety of Lopinavir / Ritonavir Plus Ribavirin in the Treatment of Severe Acute Respiratory Syndrome [NCT00578825]	SARS	Trial registration
Yu, 2008	A protocol for a multi-centre, double blinded, randomised, placebo-controlled trial on the efficacy and safety of lopinavir/ritonavir plus ribavirin in the treatment of severe acute respiratory syndrome	SARS	Protocol
Full-text Unavailable and Non-English Articles			
Albarrak, 2012	Recovery from severe novel coronavirus infection	MERS	Unavailable
Khalid, 2015	Ribavirin and interferon-alpha2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus: a preliminary report of two cases	MERS	Unavailable
Kim, 2016	Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome	MERS	Unavailable
Ling, 2015	Clinical analysis of the first patient with imported Middle East respiratory syndrome in China	MERS	Unavailable/Non-English
Luo, 2015	The therapeutic effect of high flow nasal cannula oxygen therapy for the first imported case of Middle East respiratory syndrome to China	MERS	Unavailable/Non-English
Nau, 2013	Emergency treatment for Middle Eastern coronaviruses (MERS-CoV)	MERS	Non-English
Cao, 2003	Clinical diagnosis, treatment and prognosis of elderly SARS patients	SARS	Unavailable/Non-English
Chan, 2004	Clinical manifestations of two cases with severe acute respiratory syndrome (SARS) in I-Lan County	SARS	Unavailable
Feldt, 2003	SARS--the facts. Transmission, diagnosis and managing suspected cases	SARS	Unavailable/Non-English
Fu, 2003	Analysis of therapeutic effect on treatment of SARS by Chinese Medicine in combination with Western Medicine of 253 cases	SARS	Non-English
Gao, 2003	Clinical investigation of outbreak of nosocomial severe acute respiratory syndrome	SARS	Unavailable/Non-English
Hoheisel, 2003	Severe acute respiratory syndrome (SARS)	SARS	Non-English
Hou, 2004	Integrated traditional Chinese and western medicine for 34 patients with severe SARS	SARS	Unavailable
Hsiao, 2004	Clinicopathology of severe acute respiratory syndrome: an autopsy case	SARS	Unavailable

First Author, Year	Title	Population	Article Type
	report		
Huang, 2004	Clinical observation on curative effect of treating SARS with the combination of traditional Chinese and Western therapy	SARS	Unavailable
Kanra, 2003	Severe acute respiratory syndrome (SARS)	SARS	Unavailable/Non-English
Li, 2003	Changes of liver function in 48 patients with SARS and treatment of integrative traditional Chinese and Western medicine	SARS	Unavailable
Li, 2003	Clinical features of 77 patients with severe acute respiratory syndrome	SARS	Unavailable/Non-English
Li, 2003	Clinical observation of 40 cases of SARS in the restoration stage treated by an integrated therapy of tcm and western medicine	SARS	Unavailable
Li, 2004	Clinical study on treatment of severe acute respiratory syndrome with integrative Chinese and Western medicine approach	SARS	Unavailable/Non-English
Liu, 2003	Clinical features and therapy of 106 cases of severe acute respiratory syndrome	SARS	Non-English
Liu, 2003	Quality of randomized controlled trials of traditional Chinese medicine integrated with Western medicine for severe acute respiratory syndrome	SARS	Unavailable
Lin, 2003	Clinical observation on 103 patients of severe acute respiratory syndrome treated by integrative traditional Chinese and Western Medicine	SARS	Unavailable/Non-English
MacKay, 2005	Adverse drug reactions associated with the use of ribavirin in the treatment of severe acute respiratory syndrome (SARS)	SARS	Unavailable
Marraro, 2003	Severe Acute Respiratory Syndrome (SARS)	SARS	Unavailable/Non-English
Ren, 2004	Clinical study on treatment of severe acute respiratory syndrome by integrative Chinese and Western medicine	SARS	Unavailable/Non-English
Rickerts, 2003	[Clinical presentation and management of the severe acute respiratory syndrome (SARS)]	SARS	Non-English
Shi, 2010	Study on the changing regularity of special antibody and expression of stomach and enteric involvement on SARS-coronavirus infection in the recovery period of severe acute respiratory syndrome	SARS	Unavailable/Non-English
Tan, 2003	Radiographic features of a case of severe acute respiratory syndrome with fatal outcome	SARS	Unavailable

First Author, Year	Title	Population	Article Type
Wang, 2003	Preliminary study on clinical efficacy of integrative Chinese and western medicine in treating severe acute respiratory syndrome (SARS)	SARS	Unavailable/Non-English
Wu, 2003	Clinical observation on treatment of 40 SARS uncertain patients with integrative traditional Chinese and Western medicine	SARS	Non-English
Wu, 2004	Comparison of clinical features of severe acute respiratory syndrome among different transmission generations	SARS	Unavailable/Non-English
Xu, 2003	Clinical therapy of severe acute respiratory syndrome: 38 cases retrospective analysis	SARS	Unavailable/Non-English
Xu, 2003	Clinical analysis of patients with severe acute respiratory syndrome in Beijing area	SARS	Unavailable/Non-English
Zhang, 2003	Clinical observation of 65 SARS cases treated with a combination of TCM and western-style therapies	SARS	Unavailable
Zhang, 2003	Controlled clinical study on 49 patients of SARS treated by integrative Chinese and Western medicine	SARS	Unavailable/Non-English
Zhang, 2004	Clinical study of integrated Chinese and western medicien for quality of life improvements of SARS patients on recovery stage	SARS	Unavailable
Zhao, 2003	Randomized control study of integrated traditional Chinese and western medicine in treatment of 77 patients with severe acute respiratory syndrome	SARS	Unavailable
Zhou, 2003	[Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area]	SARS	Non-English
Vabret, 2005	Human coronaroviruses	General coronavirus	Non-English

*Non-English articles

APPENDIX 3 – Detailed Table of Study and Patient Characteristics

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Controlled Trials n=3				
Lee, 2004[6] China	Apr 2003 to May 2003, Hong Kong	SARS, Lab-confirmed	Median (range): 34 (22-57), N = 16, Females: NR, Males: NR	None reported
Zhao, 2003[8] China	NR, Eighth Municipal People's Hospital of Guangzhou; Second and Third Affiliated Hospitals of Sun Yet-San Medical University	SARS, Probable/suspected	Group A [mean (SD)]: 33.6 (13.9) Group B: 32.4 (12.4) Group C: 32.5 (12.1); Group D: 30.5 (12.3) N = 190, Females: 65, Males: 35	None reported
Park, 2019[7] South Korea	NR, 5 hospitals of South Korea	Prophylaxis (MERS), Lab-confirmed	Median (IQR): 29 (24-33), N = 43, Females: 65.1, Males: NR	None reported
Cohort Studies n=10				
Chan, 2003[11] Hong Kong	NR, United Christian Hospital, Princess Margaret Hospital, Tuen Mun Hospital, and Caritas Medical Centre	SARS, Lab-confirmed	NR (NR), N= 1052, Females: 81, Males: 19	None reported
Chu, 2004[13] Hong Kong	Mar to Apr 2003 (recruitment); 21 day follow-up, United Christian Hospital and Caritas Medical Centre	SARS, WHO Criteria (admission); 97.6% of cases lab-confirmed	Mean (SD): 41.4 (14.8), N = 152 Females: 62, Males: 38	Active co-morbid condition, chronic hepatitis b infection

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Guo, 2019[14] China	12 year follow-up, Guangdong Provincial Hospital	SARS, Lab-confirmed	Median (IQR): 33 (24-57), N = 103, Females:57, Males: 42.7	Ischaemic heart disease, Pulmonary, Diabetes, Malignancy, Immunocompromising condition
Ho, 2003[15] Hong Kong	Mar to Apr 2003, Queen Mary and Queen Elizabeth Hospitals	SARS, WHO Criteria (admission); 69/72 lab-confirmed	Median (IQR): 37 (23-82), N = 72, Females: 58, Males: 42	Ischemic heart disease, malignancy, diabetes mellitus, other-unspecified
Lau, 2009[16] China and Canada	NR, Hong Kong and Toronto	SARS, WHO Criteria; Probable/suspected	NR (NR), N = 1743 (probable); 191 (suspected), Females: 56; 61, Males: 44; 39	None reported
Leong, 2004[17] Singapore	Mar to Aug 2003, Tan Tock Seng Hospital	SARS, WHO Criteria (admission); 32 cases lab-confirmed	Non-ribavirin [mean (SD)]: 42.6 (17.7) Ribavirin: 34.4 (14.3), N = 229, Females: NR, Males: 32	None reported
Li, 2006[18] China	Cohort, Apr to May 2003, First Affiliated Hospital, Tsinghua University	SARS, WHO Criteria	Mean (range): 36 (15-73), N = 123, Females: 50.4, Males: 49.6	Hypertension, chronic obstructive pulmonary disease (COPD) and asthma, diabetes mellitus, and cerebrovascular diseases
Alkhadhairi, 2018[9] Saudi Arabia	Sep 2013 to Jun 2017, Hospital (unspecified)	MERS, Lab-confirmed	NR (NR), N = 113, Females: NR, Males: NR	None reported
Arabi, 2019[10] Saudi Arabia	Sep 2010 to Jan 2018, 14 hospitals in 5 cities	MERS, Lab-confirmed	Treatment [median, (IQR)]: 57.5 (47-70) Control: 58 (41-70) N = 349, Females: NR, Males: 69	Diabetes with chronic complications; asthma/chronic pulmonary disease; moderate to severe liver disease; chronic renal disease; chronic cardiac disease; chronic neurological disease; rheumatological disease; malignancy including leukemia or lymphoma

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Choi, 2016[12] Republic of Korea	May to July 2015, Republic of Korea	MERS, Lab-confirmed	Median (range): 55 (16-86), N = 186, Females: NR, Males: 60	Hypertension, Diabetes, Solid organ malignancy, Chronic lung disease, Chronic heart disease, Cerebrovascular disease, Chronic liver disease, Chronic kidney disease, Hematologic malignancy
Retrospective Studies n=7				
Booth, 2003[20] Canada	March to April 2003, Hospitals in Toronto	SARS, Probable/suspected	Median (range): 45 (34 to 57) N = 144 Females: 61%, Males: NR	Diabetes, cardiac disease, cancer, COPD, chronic renal failure
Chiou, 2005[21] Taiwan	April to June 2003, Mackay Memorial Hospital and Chang Gung Memorial Hospital	SARS, Lab-confirmed	Mean (SD): 38 (17.5), N = 51, Females: 74%, Males: 26%	None reported
Liu, 2005[24] Taiwan	April to May 2003, The Armed Forces Sung-Shan Hospital	SARS, WHO Criteria	Median (range): 37 (22-66) N = 36 Females: 75%, Males: 25%	Diabetes mellitus, cardiovascular disease, ovarian teratoma, hydronephrosis, thyroid disease, diabetes plus gallstones
Muller, 2007[25] Canada	February to July 2003, Hospitals in Toronto	SARS, WHO Criteria with lab confirmation	NR N = 306 Females: 63%, Males: 37%	None reported
Alhumaid, 2018[19] Saudi Arabia	April 2012 to November 2016, King Fahad Hofuf Hospital	MERS, Contact history (animal); Lab-confirmed	NR, N = 107, Females: NR, Males: 69.1%	Chronic kidney disease, chronic heart disease, chronic lung disease, liver disease, diabetes, hypertension, malignancy, obesity, immunosuppressive therapies use, Immunocompromised status, organ transplant, pregnancy
Habib, 2019[22] Saudi Arabia	2014 to 2017, Buraidah Central Hospital	MERS, Lab-confirmed	Mean (SD): 59.7 (18.2) N = 63 Females: 25%, Males: 75%	Diabetes, hypertension, hepatitis C, chronic renal diseases, and chronic heart diseases

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Khalid, 2016[23] Saudi Arabia	April to May 2014, King Faisal Specialist Hospital and Research Center	MERS, Lab-confirmed	Median (IQR): 54 (23-79) N = 14, Females: 36%, Males: 64%	Hypertension, diabetes, respiratory disease, obesity, congestive heart failure, chronic kidney disease (no dialysis), hemodialysis, ischemic heart disease, receiving immunosuppressive medications, stroke
Case Reports/Series n=34				
Holshue, 2020[35] USA	January 1, 2020, Providence Regional Medical Center	COVID-19, Lab-confirmed	Age: 35 N = 1, Females: 0, Males: 100	Hypertriglyceridemia
Wang, 2020a[57] China	Jan 21 to Feb 4, 2020, Shanghai Public Health Clinical Center	COVID-19, Lab-confirmed	Ages: 19, 32, 62, 63 N = 4 Females: 25, Males: 75	Fatty liver
Wang, 2020b[56] China	Jan 1 to Feb 3, 2020, Zhongnan Hospital of Wuhan University	COVID-19, WHO Criteria (admission); lab-confirmed	Median (range): 56 (42-68) N = 138 Females: 45.7, Males: 54.3	Hypertension; cardiovascular disease; diabetes; malignancy; cerebrovascular disease; COPD; chronic kidney disease; chronic liver disease; HIV infection
Avendano, 2003[28] Canada	March 23, 2003 (3 weeks), West Park Healthcare Centre	SARS, WHO Criteria	Mean (SD, range): 42 (9, 27-63) N = 14 Females: 78.57, Males: 21.43	Mitral valve prolapse, type 2 diabetes mellitus, hypertension, cancer of the bladder, osteoporosis
Cheng, 2004[31] China	March 2003 - May 2003, Prince of Wales Hospital	SARS, WHO Criteria	Median (range): 11 (4 mos-17 yrs) N = 13 Females: 30.8, Males: 69.2	None reported
Cheng, 2005[30] Hong Kong	May 2003, Prince of Wales Hospital	SARS, Lab-confirmed	Age: 4 months, N = 1, Females: 100, Males: 0	None reported
Chiang, 2003[32] Taiwan	April 20 to May 7, 2003, two hospitals at Taipei City	SARS, WHO and CDC Criteria	Ages: 26, 27, 36, 42 N = 4, Females: 50, Males: 50	hepatitis B carrier, hyperthyroidism

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Gomersall, 2004[33] China	Mar to Apr 2003, Intensive care unit in a tertiary referral university hospital	SARS, CDC Criteria	Mean (SD): 50 (16.90), N = 54, Females: 43, Males: 57	None reported
Hon, 2003[36] Hong Kong	March 13 to 28, 2003, Prince of Wales and Princess Margaret Hospitals	SARS, WHO Criteria	Mean (range): 9.66 (1.5-16.4), N = 10, Females: 80, Males: 20	None reported
Knowles, 2003[39] Canada	NR, Hospitals in Toronto	SARS, Probable/suspected	Mean (range): 46 (17-99), N = 110, Females: 65, Males: 35	None reported
Kwan, 2004[40] Hong Kong	NR, Hospital cluster in Hong Kong	SARS, Lab-confirmed	Mean (range): 58 (34-74) N = 12 Females: 50, Males: 50	Diabetic nephropathy (end-stage renal failure); IgA nephropathy; lupus nephritis; hypertensive nephrosclerosis; renal failure unknown cause
Lam, 2004[41] Hong Kong	March 17 2003 (28 days), Queen Mary Hospital	SARS, Lab-confirmed	Age: 45 N = 1, Females: 100, Males: 0	acute myeloid leukemia with successful allogeneic bone marrow transplantation
Lau, 2004[42] Hong Kong	Mar 9 to Apr 28, 2003, Pamela Youde Nethersole Eastern Hospital	SARS, WHO Criteria (admission); 68/71 cases lab-confirmed	Mean (SD): 42.5 (14.8) N = 71 Females: NR, Males: 38	Diabetes mellitus, coronary artery disease, hypertensive heart disease, chronic renal impairment, asthma, epilepsy, psychiatric disease, chronic hepatitis virus b carrier
Lopez, 2004[44] Hong Kong	February to July 2003, Chinese University of Hong Kong and the Hong Kong University	SARS, Hong Kong Hospital Authority	Mean (range):36.25 (28-47), N = 4, Females: 25, Males: 75	None reported
Poutanen, 2003[47] Canada	February to March 2003, First SARS cases in Canada (Toronto/Vancouver)	SARS, Probable/suspected	Range: 24-78, N = 10, Females: 40, Males: 60	Type 2 diabetes mellitus, underlying pulmonary disease, history of smoking

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
So, 2003[49] Hong Kong	March 9 to March 29, 2003, Pamela Youde Nethersole Eastern Hospital	SARS, WHO Criteria	Mean (SD): 39.6 (13.3) N = 31 Females: NR, Males: 35.48	Smokers, diabetes mellitus, hypertension, coronary artery disease
Sung, 2004[51] Hong Kong	Mar 11 to Jul 28, 2003, Prince of Wales Hospital	SARS, Lab-confirmed	Mean (SD): 39.3 (16.8) N = 138 Females: 52, Males: 48	None reported
Tang, 2003[52] Hong Kong	March 31 to April 6 2003, Princess Margaret Hospital	SARS, Lab-confirmed	Ages: 49 and 86, N = 2, Females: 0, Males: 100	End-stage renal failure, diabetes mellitus, hypertension, ischemic heart disease, a history of cerebral infarction, thalassemia minor
Tiwari, 2003[53] China	March 2003 - May 2003, Queen Mary Hospital	SARS, WHO Criteria	Median (range): 38 (22 – 82) N = 36 Females: 58, Males: 42	None reported
Tsang, 2003[54] Hong Kong	February 22, 2003 to March 22, 2003, Queen Mary Hospital, Kwong Wah Hospital, and Pamela Youde Nethersole Eastern Hospital	SARS, CDC Criteria; Clinical criteria (chest radiographs)	Mean (SD): 52.5 (11) N = 10 Females: 50, Males: 50	Hypertension, benign prostatic hypertrophy, ischemic heart disease, type 2 diabetes mellitus, resected renal-cell carcinoma of the right kidney
Tsui, 2003[55] China	Apr 2003 - May 2003, Princess Margaret Hospital and Wong Tai Sin Hospital	SARS, Hong Kong Hospital Authority Criteria	Median (range): 41 (18-83) N = 323 Females: 60.7, Males: 39.3	Hypertension, diabetes, chronic lung disease, pregnancy, neurologic disease, renal disease, cardiovascular disease, immunologic disease, malignancy
Wu, 2003[59] China	Jan 30 to Mar 10, 2003, The Second Affiliated Hospital, Sun Yat-sen University	SARS, Probable/suspected	Mean (SD): 29.5 (10.3) N = 96 Females: 79, Males: 21	None reported

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Wong, 2003[58] Hong Kong	March 2003, Kwong Wah Hospital	SARS, WHO Criteria	Mean (SD): 66.3 (13.5) N = 11 Females: 100, Males: 0	Renal failure, diabetes mellitus, tuberculous lymphadenitis
Al-Tawfiq, 2013[27] Saudi Arabia	April - May 2013, Saudi Aramco Medical Services Organization	MERS, Lab-confirmed	Median (range): 62 (24 – 81) N = 5 Females: 40; Males: 60	Chronic kidney disease, hypertension, diabetes, asthma, obstructive sleep apnea, coronary heart disease, atrial fibrillation, end-stage renal disease
Al-Tawfiq, 2018[26] Saudi Arabia	NR, Johns Hopkins Aramco Healthcare	MERS, Lab-confirmed	Ages: 52, 53, 56 N = 3, Females: 0, Males: 100	Rheumatoid arthritis
Habib, 2015[34] UAE	NR, Mafraq Hospital	MERS, Lab-confirmed	Age: 32, N = 1, Females: 100, Males: 0	Pregnancy (32 weeks)
Khalid, 2015[37] Saudi Arabia	Apr to May 2014, King Faisal Specialist Hospital & Research Center-Jeddah	MERS, Lab-confirmed	Mean: 53 N = 14 Females: NR, Males: 16	None reported
Kim, 2016[38] Korea	NR, Pusan National University Hospital	MERS, Lab-confirmed	Age: 54 N = 1, Females 0% female, 100% male	None reported
Lee, 2017[43] South Korea	May 11 to June 28, 2015, The National Medical Center	MERS, Clinical criteria (blood tests, chest radiographs)	Age: 68 N = 1, Females: 0, Males: 100	hypertension, dyslipidemia, current heavy smoker
Motabi, 2016[45] Saudi Arabia	March to May 2015, King Fahad Medical City	MERS, Lab-confirmed	Ages: 22, 62, 65, 76 N = 4 Females: 50, Males: 50	Hematological malignancies; B symptoms and huge organomegaly due to stage IV DLBCL; Acute myeloid leukemia; IgA kappa multiple myeloma with h/o HTN and CKD)
Shalhoub, 2014[48] Saudi Arabia	April – June 2014, King Fahad Armed Forces Hospital	MERS, Lab-confirmed	Age: 51, N = 1, Females: 0, Males: 100	HIV infection

Author, Year; Country of Conduct	Study Period, Setting	Diagnosis, Diagnostic Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities
Spanakis, 2014[50] Greece	NR, A tertiary care centre and 'Sotiria' Chest Diseases Hospital of Athens	MERS, Lab-confirmed	Age: 69, N = 1, Females: 0, Males: 100	None reported
Bogdanov, 2017[29] Germany	NR, University Hospital of Essen	Other coronavirus, Lab-confirmed	Age: 30 N = 1, Females: 0, Males: 100	acute lymphoblastic leukemia, graft-versus-host disease post bone marrow transplant (grade 1)
Oger, 2017[46] France	May 2013 - Oct 2015, Hospital	Other coronavirus, NR	Age: 57 N = 1 NA	None reported

CDC – Centers for Disease Control; MERS – Middle East Respiratory Syndrome; SARS – Severe Acute Respiratory Syndrome; WHO – World Health Organization; SD – Standard Deviation; IQR – Interquartile Range; NR –Not Reported; NA –Not applicable

APPENDIX 4 – Detailed Table of Interventions and Outcomes

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
Controlled trials n=3			
Lee, 2004[6] SARS	Initial antibacterial therapy Ribavirin (n=9) [400 mg every eight hours, total of 12 days] "Early Hydrocortisone (n=9) [100mg every eight hours]	ICU admission + ventilation and subsequent mortality: 1 patient	NR
	Initial antibacterial therapy Ribavirin (n=7) [400 mg every eight hours, total of 12 days] Placebo (n=7) [5mg intravenous saline every eight hours]	ICU admission + ventilation: 0 patients Mortality: 0 patients	NR
Zhao, 2003[8] SARS	Group A (n=40) Ribavirin [0.4–0.6 g, twice daily, intravenous] Cefoperazone/sulbactam [2.0 g, twice daily, intravenous]	Mortality: 2 patients	NR
	Group B (n=30) Fluoroquinolone plus azithromycin [0.4 g, intravenous] recombinant interferon-alpha (IFN-a) [3 000 000 units, intramuscular]	Mortality: 2 patients	NR
	Group C (n=60)	Mortality: 7 patients	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Quinolone plus azithromycin [0.4 g, intravenous] Recombinant IFN-a [3 000 000 units, intramuscular] Methylprednisolone (added when symptoms worsened) [80–160 mg per day for 2–3 days]		
	Group D (n=60) Levofloxacin [0.2 g, twice daily, intravenous] Azithromycin [0.6 g, intravenous] Recombinant IFN-a (n=45) [3 000 000 units, intramuscular] Methylprednisolone (added when symptoms worsened) [160–1000 mg per day depending on symptoms, 5-14 days]	Mortality: 0 patients	NR
Park, 2019[7] Prophylaxis (MERS)**	Ribavirin (n=22) [loading dose 2000 mg; 1200 mg every 8 h for 4 days then 600 mg every 8 h for 6-8 days] Lopinavir/ritonavir (n=22) [administered orally; 400 mg/100 mg every 12 h for 11-13 days]	Confirmed infection with MERS-Cov: 0 patients Risk of infection (prophylaxis v control): Odds Ratio: 0.405, 95% CI: 0.274 to 0.599, p=0.009	Diarrhea: 9 patients Nausea: 9 patients Stomatitis: 4 patients Fever: 3 patients Anemia: 9 patients Lecuopenia: 8 patients Hyperbilirubinemia: 20 patients [all occurred during PEP therapy and normalized upon conclusion of

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
			treatment]
	Control group (no treatment, n=21)	Confirmed infection with MERS-Cov: 6 patients	NR
Cohort Studies (n=10)			
Chan, 2003[11] SARS	Ribavirin + lopinavir/ritonavir [sequential] (n=44) Ribavirin [10-14 days (2.4 g oral loading dose, followed by 1.2 g orally every 8 hours, or 8 mg/kg intravenously every 8 hours] Lopinavir/ritonavir [400 mg/100 mg orally every 12 hours] Corticosteroid therapy for [21 days (starting dose: hydrocortisone 100-200 mg every 6-8 hours, or methylprednisolone 3 mg/kg/day] Pulse methylprednisolone (rescue therapy) [500-1000 mg daily, intravenously]	Crude death rate = 2.3%	Drug toxicity indicated by three-fold rise in alanine aminotransferase: 9.1% (95% CI 0-18.2)
	Ribavirin + lopinavir/ritonavir [rescue therapy] (n=31) Ribavirin [10-14 days (2.4 g oral loading dose, followed by 1.2 g orally every 8 hours, or 8 mg/kg intravenously every 8 hours] Pulse methylprednisolone (rescue therapy) [500-1000 mg daily, intravenously]	Crude death rate = 12.9%	Drug toxicity indicated by three-fold rise in alanine aminotransferase: 25.8% (95% CI 9.7-41.9)

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	If above treatments failed added as rescue therapy: Lopinavir/ritonavir [400 mg/100 mg orally every 12 hours]		
Chu, 2004[13] SARS	Lopinavir/ritonavir (n=41) [400mg/100 mg orally every 12 hours for 14 days]	21-day mortality: 0 patients	Gastrointestinal upset: 11 patients Liver dysfunction: 7 patients Headache: 6 patients Blurred vision: 3 patients
	Ribavirin (n=111)	21-day mortality: 7 patients	NR
Guo, 2019[14] SARS	n = 34 Antibiotics [penicillin, fluoroquinolone, or macrolides] Oseltamivir [oral, 75 mg, 2x a day for 5 days and 75 mg 1x a day for another 7 days]	ICU admission: 25 patients; oseltamivir treatment was not found to be associated with significantly better outcomes (p>0.05, data not shown) 21-day mortality: 3 patients, (p=0.682)	Lung function abnormalities (post-recovery): 7 patients
	n = 69 Antibiotics [penicillin, fluoroquinolone, or macrolides] Corticosteroids (if no response to antibiotics) [intravenous, 50-500 mg/day, modifications were made according to the needs of individual patients]	ICU admission: 19 patients 21-day mortality: 4 patients	Lung function abnormalities (post-recovery): 7 patients
Ho, 2003[15] SARS	N = 55 Ribavirin	ICU admission: 11 patients, 5 needed mechanical ventilation	Hemolytic anemia (1.5x increase in bilirubin): 16 patients

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	[8 mg/kg, intravenously three times a day for the 7 days and then orally at 1.2 g three times a day for altogether 10–14 days] 'Non pulse steroid' hydrocortisone (n = 34) [2 mg/kg, intravenously four times a day or 4 mg/kg, intravenously three times a day for 3–5 days, followed by oral prednisolone at 2 mg/kg daily at reducing dosage] [or] Methylprednisolone (n = 21) 2–3 mg/kg, intravenously once daily for 5 days, followed by oral prednisolone at 2 mg/kg daily at reducing dosage] 45 patients received pulse steroids as rescue therapy	Mortality: 3 patients; no statistical difference between the PS group and the NPS group in mortality during the 3 weeks of SARS treatment	Hyperglycemia (random blood glucose ≥11 mmol/L): 18 patients Serious secondary infection (pyrexial or bacteremic): 2 patients Hematemesis: 2 patients
	N = 17 Ribavirin [8 mg/kg, intravenously three times a day for the 7 days and then orally at 1.2 g three times a day for altogether 10–14 days] Pulse methylprednisolone [500 mg, intravenously once daily for 5–7 days or 1 g, intravenously once daily for 3 days, followed by maintenance oral prednisolone 50 mg two times a day reducing to 20–30 mg daily on Day 21)]	ICU admission: 1 patient that required mechanical ventilation Mortality: 1 patient	hemolytic anemia (1.5x increase in bilirubin): 8 patients Hyperglycemia (random blood glucose ≥11 mmol/L): 0 patients Serious secondary infection (pyrexial or bacteremic): 1 patient Hematemesis: 1 patient
Lau, 2009[16] SARS	Hong Kong - Ribavirin (n = 202) Toronto - Ribavirin (n = 107)	Mortality [Hong Kong]: 18 patients Mortality [Toronto]: 10 patients	NR
	Hong Kong - Ribavirin, corticosteroids (n = 739)	Mortality [Hong Kong]: 93 patients	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Toronto - Ribavirin, corticosteroids (n = 39)	Mortality [Toronto]: 5 patients	
Leong, 2004[17] SARS	Ribavirin treatment (n = 97) Oral ribavirin was dosed at 1.2 g three times a day; intravenous ribavirin at 400 mg every 8 h for sicker patients and those who could not take it per os. Patients received ribavirin for 5.6 (2.5) days on average; 21 patients received steroids, 84 received antibiotics	ICU admission: 19 patients; no significant difference in the proportion of patients admitted to ICU between the 2 groups (p>0.999) Mortality (n = 10): 10 patients; Adjusted hazard ratio (ribavirin v control): 1.03, 95% CI: 0.44–2.41, p = 0.939	Myocardial injury: 3 patients, occurred between admission till day 14 of illness Anemia: 24 patients, occurred between admission to day 14 if illness
	Control (n = 132) 17 patients received steroids (hydrocortisone, prednisolone and/or methylprednisolone), 94 received antibiotics	ICU/Critical care (n = 27) - admission to ICU Mortality (n = 17)	Myocardial injury: 4 patients, occurred between admission till day 14 of illness Anemia: 27 patients, occurred between admission to day 14 if illness
Li, 2006[18] SARS	Ribavirin (n = 63) The Western Medicine protocol included oxygen supplementation, hemofiltration, ribavirin, antibacterials (azithromycin, cefuroxime, metronidazole), and immunoregulation with thymosin injection. Methylprednisolone, prednisolone or dexamethasone was used when clinically appropriate.	Mortality: 7 patients	NR
	Ribavirin + Traditional Chinese Medicine (n = 52) In the combined treatment protocol, the herbal medication Herba houttuyniae injection was	Mortality: 5 patients	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	employed together with the WM treatments. When necessary, patients in this group also received TCM decoctions such as the heat-clearing and detoxifying prescription, the qi-supplementing prescription, and the blood-regulating prescription according to their ZHENG conditions by consulting with the Chinese herbalist from the China-Japan Friendship Hospital		
Alkhadhairi, 2018[9] MERS	Oral ribavirin with PEGylated interferon α2a injection (n=49)	Mortality: 24 patients (p=0.182)	Mean rise in serum creatinine (n = 49): 2.14 mg/dl Mean rise in urea nitrogen (n = 49): 42 mg/dl
	Supportive care alone (n=64)	Mortality: 23 patients	Mean rise in serum creatinine (n = 64): 1.36 mg /dl Mean rise in urea nitrogen (n = 64): 39 mg/dl
Arabi, 2019[10] ** **MERS**	Ribavirin/rIFN combination* (n = 117) Ribavirin alone (n = 18) rIFN alone* (n = 9); *rIFNs used include: IFN-α2a (n = 73), rIFN α-2b (n = 22), rIFN-β1a (n = 31), rIFN-β1b (n = 0); Additional therapies: Corticosteroids (n = 86) Oseltamivir (n = 67)	Crude 90-day mortality: 106 patients (p=0.02) Risk of 90-day mortality (ribavirin/rIFN v control) adjusted odds ratio: 2.27, 95% CI 1.20–4.32; p=0.01	Required blood transfusions: 58 patients (p=0.02)
	Control (n=205) Use of corticosteroids or oseltamivir only	Crude 90-day mortality: 126 patients	Required blood transfusions: 58 patients
Choi, 2016[12] MERS	Ribavirin; lopinavir/ritonavir; interferon (n = 112)	Mortality: 20 patients	NR
	Ribavirin, interferon (n = 17)	Mortality: 1 patient	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Ribavirin; lopinavir/ritonavir (n = 7)	Mortality: 4 patients	NR
	Ribavirin (n = 1)	Mortality: 0 patients	NR
	lopinavir/ritonavir (n = 1)	Mortality: 0 patients	NR
	Antivirals (unspecified), interferon (n = 138)	Mortality: 25 patients	NR
Retrospective Studies (n=7)			
Booth, 2003[20] ** **SARS**	Ribavirin (n=126/144) [2g intravenous loading dose, 1g intravenous every 6 hrs for 4 days, 500mg every 8 hrs for 3 days; median (IQR) treatment course: 6 days (5-7)] Antibiotic therapy (NR) [NR]	ICU Admission: 29 patients Mechanical ventilation in ICU: 20 patients Mortality: 8 patients (all admitted to ICU) 21-day mortality rate: 6.5% (95% CI 1.9%-11.8%)	Decreased hemoglobin levels: 71 patients Hemolysis: 8 patients (all with decreased hemoglobin) Bradycardia: 18 patients
Chiou, 2005[21] **SARS**	Initial antibiotic therapy on admission for pneumonia (n=53/53) [IV cephalosporin or oral floroquinolone] Ribavirin (n=44/53) [2,000 mg stat, then 1,000-1,200 mg; 10-14 days] IV methylprednisolone + oral prednisolone (if no improvement on ribavirin; n=44/53) [1mg/kg q8h for 5 days, 1mg/kg q12h for 5 days; oral prednisolone tapered over 11 days] Pulse methylprednisolone (rescue therapy; n=24/53) [500mg twice daily for 3 days]	Mortality: 5 patients	Anemia: 32 out of 44 patients receiving ribavirin, onset average 3 days after initiating treatment; normalized after discontinuing ribavirin
Liu, 2005[24] **SARS**	Initial antibiotic therapy (n=36/36) macrolide or floroquinolone] Ribavirin (n=35/36) [loading dose 2 g, followed by 1–1.2 g/day for 10	Mortality: 2 patients (both developed ARDS)	None reported

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	days (median; range, 3–18 days) within 0–7 days (median, 1 day) of hospitalization] IV Immunoglobulin (n=22/36) [500 mg/kg/day for 2 days, treatment started a median of 6 days (range, 2–19 days) after, symptom onset] IV methylprednisolone (n=32/36) [2–4 mg/kg/day, treatment started a median of 4 days (range, 1–10 days) after symptom onset]		
Muller, 2007[25] SARS**	Ribavirin alone (n=90/306) [83% of patients received first dose in 48 hours of admission; mean ± SD total dose 23.3 ± 9.4 g, median treatment duration 7 days (IQR 5–9 days)] Ribavirin with corticosteroids (n=93/306) [NR] Corticosteroids (n=81/306) [NR] No treatment (n=42/306)	Mechanical ventilation: 27 patients receiving ribavirin, 19 patients not receiving ribavirin (p=0.88) Mortality: 20 patients receiving ribavirin, 10 patients not receiving ribavirin (p=0.42)	Discontinuation due to adverse events: 28 patients [19 anemia or hemolysis, 5 hepatitis or transaminitis, 1 bradycardia, 1 atrial fibrillation, 1 nausea, 1 unspecified] Risk of adverse events associated with ribavirin (adjusted for steroid use and infection severity) [OR (99% CI),p-value] Progressive anemia: 3.0 (1.5–6.1), <0.0001 Bradycardia: 2.3 (1.0–5.1), 0.007 Hypomagnesemia: 21 (5.8–73), <0.0001 Hypocalcemia: 1.8 (0.91–3.4), 0.028 Hepatitis, biochemical: 1.8 (0.74–4.6), 0.08
Alhumaid, 2018[19] MERS	Oseltamivir (n=13/107) Ribavirin (n=61/107) Lopinavir/ritonavir (n=41/107) Interferon (α1a,α2a, or (n=54/107)	ICU Admission: 53 patients Confirmed Pneumonia: 21 patients Mortality: 54 patients	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Interferon-β1a (n=48/107) Initial antibacterial therapy (n=107/107) Glucocorticoids (n=24/107) Immunoglobulin therapy (n=33/107) Mycophenolate mofetil (n=22/107) Convalescent Plasma (n=14/107)		
Habib, 2019[22] MERS	Ribavirin and Interferon (n=61/63)	Mortality: 14 patients receiving combination therapy, 1 patient not receiving therapy Confirmed Pneumonia (on hospital admission): 55 patients	NR
Khalid, 2016[23] MERS	Ribavirin and Interferon α2a (n=11/11) Ribavirin dose adjusted based on creatinine clearance, treatment started a median of 6 days from symptom onset for a maximum of 2 weeks	Mortality: 9 patients	None reported
Case Reports/Series n=34			
Holshue, 2020[35] COVID-19	Remdesivir (was started day 7 (n=1)) Vancomycin (1750mg loading dose followed by 1g administered intravenously every 8 hours) and cefepime (administered every 8 hours) (n=1) Vancomycin was discontinued the same day Remdesivir was initiated and cefepime was discontinued the next day	Patient was still hospitalized at study end but showing significant improvement.	NR
Wang, 2020a[57] COVID-19	Lopinavir/ritonavir (n=4) [lopinavir 400 mg/ritonavir 100 mg, q12h, oral, duration 6-15 days] Additional treatments (n=4) Arbidol [0.2 g, 3 times daily, oral] Shufeng Jiedu Capsule [2.08, three times daily,	At study end two patients were confirmed COVID-19 negative and discharged, two patients remained hospitalized, one still requiring mechanical ventilation	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	oral] antibiotic treatment [NR] intravenous immunoglobulin [NR]		
Wang, 2020b[56] COVID-19	Oseltamivir (n=124) Antibacterial therapy (n=89) [moxifloxacin, ceftriaxone, azithromycin] Glucocorticoid therapy (n=62) [NR]	34 patients admitted to ICU, 17 of which required invasive mechanical ventilation. At study end 47 patients had been discharged and 6 patients in ICU died	NR
Avendano, 2003[28] SARS	Ribavirin (n=14) [IV, 2g (loading), then 1g every 6 hrs for 4days, then 0.5g every 8 hrs for 3 days] Levofloxacin (n=14) [500 mg daily for 6 days] methylprednisolone/prednisone (n=5) [125 mg intravenously every 6 hours) for 1 to 2 days, followed by a tapering dose of prednisone (40 mg)]	All patients improved clinically 15 days after admission and were eventually discharged home.	All patients were treated with ribavirin, and all patients received levofloxacin. All patients experienced a drop in hemoglobin. Nine patients had hemolytic anemia.
Cheng, 2004[31] SARS	Ribavirin (n=13) Oral ribavirin at a dose of 40 to 60 mg/kg per day. Oral prednisolone (0.5 to 1 mg/kg per day) Intravenous ribavirin (20 mg/kg per day) and pulse methylprednisolone (10 mg/kg per day for 2 to 3 days Cephalosporin, macrolide, prednisone	All recovered without sequelae (n=13)	NR
Cheng, 2005[30] SARS	Ribavirin (oral) 40 mg/kg/d for 10 days (n=1) Oral prednisolone (1 mg/kg/d for 14 days)	Complete resolution according to CT of the thorax performed 3 months after the initial presentation	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Corticosteroids Oxygen		
Chiang, 2003[32] SARS	Ribavirin (oral) 1000mg daily for 10 days (n=4) Antibiotic - levofloxacin (n=4) Intravenous immunoglobulin (IVIG:l g/kg/day for 2 day) after onset of symptoms (n=4) If severe hypoxia (Pa02 IFi02<200) occurred, then methylprednisolone + mechanical ventilation 2 mg/kg/day were given (n=1)	No mortality case was found in our study, however,1 case complicated with adult respiratory distress syndrome	NR
Gomersall, 2004[33] SARS	N = 54 Broad-spectrum antibiotics (withdrawn if bacterial infection could not be confirmed) Ribavirin [8 mg/kg every 8 h intravenously for 7–10 days followed by 4 mg/kg enterally for another 11–14 days] Low-dose corticosteroids Pulse methylprednisolone (rescue therapy) [500 mg up to a total of 3g-5g]	Study population consisted of 54 patients with SARS who required admission to ICU. All were admitted for respiratory failure Mortality: 28 days after ICU admission 34 patients (63%; 95% CI 49.6–74.6) were alive and not mechanically ventilated. 6 patients were alive but still ventilated (11.3%; 95% CI 5.3–22.6) and 14 died (25.9%; CI 16.1–38.9).	NR
Hon 2003[36] SARS	Ribavirin (oral; 40mg/kg daily 1-2 doses) If high fever ribavirin was administered through IV (20mg/kg daily, 3 doses)(n=10); Antibiotics (n=10) Corticosteroids – prednisolone (0·5 mg/kg daily	All patients required supplemental oxygen and two patients were placed on mechanical ventilation. All patients were alive at study end.	None reported

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	at Prince of Wales Hospital, and 2·0 mg/kg daily at Princess Margaret Hospital) (n=8) Pulsed intravenous methylprednisolone (10-20mg/kg) (n=1)		
Knowles, 2003[39] SARS	Ribavirin (n = 110) All patients received concurrent antibiotics after the initial assessment, and 50% received corticosteroids at some point during the course of their illness	NR	Hemolytic anemia: 67 patients, treated with transfusion of 1 U of packed RBCs Hypomagnesemia: 35 patients Hypocalcemia: 36 patients
Kwan, 2004[40] SARS	Ribavirin (n=12) Dose of ribavirin was half of that in patients with normal renal function; Corticosteroids (oral prednisolone, intravenous methylprednisolone, hydrocortisone). The average cumulative dose of hydrocortisone or equivalent in the dialysis group was 11.1 g (range, 2.5 to 41.1 g), which was similar to the control group (average, 17.8 g; range, 3.0 to 31.2 g). 2 patients received convalescence plasma, 1 received intravenous immunoglobulin, and one received pentaglobulin	ICU admission (n=4) Mortality (n=0)	NR
Lam, 2004[41] SARS	Ribavirin (oral; 2,400 mg/day for 10 days) was commenced on day 14 (n=1)	The patient was successfully discharged on Day 28, after altogether	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Prednisolone (oral; 1mg/kg for 10 days; was reduced to 20mg/day on day 21) commenced on day 14 (n=1) Antibiotics – cefepime (1g three times a day), imipenem and cilastatin (500mg four times a day on Day 6 of admission) (n=1) Clarithromycin (500mg twice a day was added to her treatment on day 9 due to mild bilateral infiltration in lower zones found in her chest radiograph) (n=1)	10 days of prednisolone and ribavirin treatment.	
Lau, 2004[42] SARS	Ribavirin (n=71) Ribavirin was given for 10–14 days as per protocol at 400 mg every 8 h (1200 mg daily) intravenously for at least 3 days (or until stabilization), then 1200 mg twice daily (2400 mg daily) orally; Antibiotics (levofloxacin or amoxicillin-clavulanic acid+clarithromycin), corticosteroids (methylprednisone+prednisolone), pulsed steroids (methylprednisone), Additional pulsed methylprednisolone 500 mg twice daily intravenously for 2 days (total 2 g),	ICU (n=15/7) Mortality (n=3) Major sepsis due to ventilator associated pneumonia (MRSA) with acute respiratory distress syndrome (n=1)	Hyperglycemia (n=71) Pnuemomediastinum/thoraces (n=71) Acute confusion (n=71) Anxiety/depression (n=71)
Lopez, 2004[44] SARS	Ribavirin (IV) (n=4) Corticosteroids (n=4) Intubation + mechanical pressure controlled ventilation (n=4)	ICU admission: 4 patients transferred to ICU Mortality: One patient died within 15 days of hospitalization	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
Poutanen, 2003[47] SARS	Oseltamivir (oral) + ribavirin (IV; 2g (loading), then 1 g every 6 hours for 4 days, then 500mg every 8 hours for 4-6 days) (n=7) Antibiotics (n=10) Mechanical ventilation (n=5)	ICU admission: 5 patients transferred to the ICU Mortality: 3 patients; all deaths occurred in patients who had an underlying immune-compromised state	NR
So, 2003[49] SARS	Ribavirin (IV) and ribavirin (orally) (n=31) Ribavirin (IV) 400 mg every 8 h (1200 mg daily) for at least 3 days (or until condition becomes stable), then ribavirin (orally) 1200 mg twice daily (2400 mg daily); Antibiotics (31), corticosteroids (31), pulsed methylprednisolone (13), ventilation (4)	Death (n=31)	None reported
Sung, 2004[51] SARS	Ribavirin (n=138) Combination of ribavirin and ‘‘low dose’’ corticosteroid therapy on day 3–4 (oral ribavirin as a loading dose of 2.4 g stat followed by 1.2 g three times daily); Antibiotics (cefotaxime, levofloxacin, clarithromycin), oseltamivir, prednisolone, hydrocortisone, pulse methylprednisone, intravenous cefotaxime 1 g every 6 hours with either oral levofloxacin 500 mg daily or clarithromycin 500 mg twice daily, prednisolone 0.5–1 mg/kg body weight per day),	ICU (n=37) Mortality (n=15) 6 patients died after failing to respond to ribavirin+low dose treatment 2 died after failing to respond to initial pulse methylprednisone 7 died after failing to respond to further pulse methylprednisone	Hyperglycemia (plasma spot glucose > 11 mmol/L) (n=107) Hypokalaemia (plasma potassium < 3.0 mmol/L) (n=107) Transient confusion, delusion, or anxiety (n=107) Hemolytic anemia (bilirubin increase >20 micromol/L or reticulocyte count >1%) (n=138)
Tang, 2003[52] SARS	Ribavirin (IV;6.5 to 10 mg/kg daily) (n=2) Antibiotics - levofloxacin (n=2)	Mortality: One patient died	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Imipenem (changed from ribavirin on day 21) (n=1) Corticosteroid - pulsed methylprednisolone (0.5g daily was given from day 7 to 9, then 1g daily on days 10,12, and 13)(n=1)		
Tiwari, 2003[53] SARS	Ribavirin (n=36) Ribavirin - 8mg/kg tid (intravenous), 1.2 g tid (oral); corticosteroid, combination of cefepime and clarithromycin	ICU (n=2) Mortality (n=1)	NR
Tsang, 2003[54] SARS	Ribavirin (IV) or ribavirin (oral) (n=10) Ribavirin (IV) 8 mg/kg every 8 hrs OR ribavirin (oral)1.2 g every 8 hrs (1 patient); corticosteroids (10), oxygen (2), mechanical ventilation (2)	Death (n=10)	NR
Tsui, 2003[55] SARS	Ribavirin (n=323) Loading dose of 33mg/kg of ribavirin, followed by 20 mg/kg every 8 h, was given intravenously; Antibiotic (levofloxacin or amoxicillin/clavulinate acid, clarithromycin, hydrocortisone or prednisone, methylprednisolone), Hydrocortisone, 2 mg/kg every 6 h or 4 mg/kg every 8 h, together with ribavirin. The total duration of therapy could range from 14 to 21 days. Pulsed doses of methylprednisolone (500 mg per dose)	Hospital admission (n=323) ICU (n=67) Mortality (n=26) Crude mortality rate of our cohort after 47±8 days of follow-up was 7.9% (95% CI, 5% to 10.8%)	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	Ribavirin plus steroid therapy was administered 1.2±1.7 days after admission.		
Wu, 2003[59] SARS	Ribavirin/oseltamivir, (n=31/58) [duration: 5.7 (3.2 days)] Ribavirin (IV) 4-8 mg/kg tid, 4 Tetracyclines, aminoglycosides, quinolones, macrolides, glycopeptides, cephalosporins, methylprednisolone, human gamma-globulin; Mean dose ranged from 67.3 (28.2) mg/day to 82.4 (30.5) mg/d over 4.9 (2.4) days; Human gamma-globulin infused intravenously (n=66) at mean daily dose of 26.4 (16.1) mg/day over 3.7 (1.8) days Interferon-alpha (n=45) over 5.1 (1.9) days	Mechanical ventilation (n=1)	NR
Wong, 2003[58] SARS	Ribavirin (n=4) Two patients received 4 mg/kg ribavirin thrice daily while the other 2 patients received 8 mg/kg ribavirin thrice daily; Antibiotics (n=4) Patients 3 and 4 also received a higher daily dose of corticosteroids (4 mg/kg hydrocortisone every 4 hours or 15 mg/kg methylprednisolone daily) compared with patients 1 and 2 (4 mg/kg hydrocortisone every 6 hours).	Mortality (n=4)	None reported
Al-Tawfiq,	Ribavirin (n= 5)	All patients had severe disease with	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
2013[27] MERS	Median number of days from admission to therapy with ribavirin and interferon was 19 (range 10–22) Interferon and corticosteroids All patients received adjunctive corticosteroid therapy	progressive respiratory failure, developed multi-organ failure, and died a mean 39.6 (standard deviation 8.5) days after admission	
Al-Tawfiq, 2018[26] MERS	Ribavirin (n=2) Interferon-α2b (n=2)	Mortality: "Two of the three cases in the present report were treated with interferon-α2b and ribavirin and all patients recovered. The timing of the initiation of anti-viral agents seems to be an important determinant of the response to therapy. "	NR
Habib, 2015[34] MERS	Oseltamivir (n=1) Antibiotics and Low-molecular-weight heparin (n=1) Interferon and Ribavirin were added (n=1) Steroid injection for fetal lung maturity (n=1) Patient was initially started on antibiotics and LMWH, however, became worse after standard antimicrobial therapy. Started on Oseltamivir, received steroid injections for fetal lung maturity and growth. Interferon and Ribavirin were added to on mechanical ventilation	ICU/Critical Care (n=1): "the woman's condition became worse despite standard antimicrobial therapy and she had to be transferred to the ICU for assisted respiration" Mortality (n=1): "on day 8 the woman deteriorated with h/o MERS-CoV pneumonia, respiratory failure - septic shock; The woman deceased after failed resuscitation.	NR
Khalid, 2015[37] MERS	Ribavirin (n=14) All patients received 1mg/kg of	ICU admission+intubation (n=14) Death (n=9)	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
	methylprednisolone continuous infusion for ARDS. 11 patients received combination of ribavirin and peginterferon alpha-2a; interferon alpha-2a, methylprednisolone		
Kim, 2016[38] MERS	Ribavirin (oral; 2,000 mg loading, then 1,200 mg three times/day) AND lopinavir/ritonavir (400/100 mg two times/day) (n=1)	NR	Hemolytic anemia and thrombocytopenia, onset occurred on day 5 of treatment Ribavirin and lopinavir/ritonavir were stopped after 5 days of treatment because it was suspected that the hemolytic anemia and thrombocytopenia was an adverse drug reaction. Lasted 9 days and was discharged in 14 days
Lee, 2017[43] MERS	Oseltamivir + ribavirin (oral; 2000mg (loading), then 600mg every 8 hours for 3 days, then 400 mg every 8 hours for 4 days) (n=1) Interferon-α2b (180mcg once commencing on day 9) (n=1) Antibiotics (n=1) Oxygen (1L/min, 2L/min on day 9, 5L/min on day 10) (n=1) Ventilation on day 12 (n=1)	The patient made a full recovery	Transient progression of thrombocytopenia from D12 appeared to be caused by interferon and ribavirin

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
Motabi, 2016[45] MERS	Oseltamivir (n=4) Antimicrobials and antibiotics (vancomycin, voriconazole)	ICU admission (n=1) Mortality (n=2) Severe pneumonia (n=4)	NR
Shalhoub, 2014[48] MERS	Ribavirin (a loading dose of 2gm., followed by 600mg orally every 12 hours) (n=1) Interferon alpha 2a (180cg subcutaneously once weekly) (n=1) interferon beta(n=1) Antiretroviral treatment that consisted of a combination of tenofovir/emtricitabine (TDF/FTC) (300/200 mg orally once daily) in combination with ritonavir boosted atazanavir (atazanvir 300mg in addition to ritonavir 100mg) orally daily (n=1)	Patient was released 38 days after being hospitalized on the mentioned antiretroviral treatment in addition to prophylactic trimethoprim/sulfamethoxazole 960 mg daily	NR
Spanakis, 2014[50] MERS	Ribavirin (n=1) [2000 mg loading dose, followed by 1200 mg p.o. every 8 h for 8 days] Lopinavir/ritonavir (400/100mg twice daily) (n=1) Pegylated interferon (180g subcutaneously once per week for 12 days) (n=1)	ICU admission: One patient was intubated, ventilated and transferred to a negative pressure room in the ICU of the same hospital Mortality: "During the course of his hospitalization, the patient was diagnosed with adenocarcinoma of the colon and eventually died from septic shock 2 months and 19 days after the initial diagnosis."	Jaundice and hyperbilirubinemia, time of onset is unclear, ribavirin was discontinued on day 20
Bogdanov, 2017[29] Other coronavirus	Foscarnet (n=1) Intravenous immunoglobulins (n=1)	Mortality (n=1): "the patient died due to respiratory paralysis"	NR

Author, Year; Diagnosis	Drug therapy (sample size) [dose, route of administration, frequency, duration]	Effectiveness Outcomes	Safety Outcomes
Oger, 2017[46] Other coronavirus	Ribavirin (n=1) Patients who received oral ribavirin for non-HCV infections; dose was 400 mg tid or 200 mg tid if there was renal insufficiency	Mortality (n=0)	NR

**Indicates statistically significant results

APPENDIX 5 – Quality Appraisal/Risk of Bias – Complete Results

Cochrane Risk of Bias Tool – Randomized Controlled Trials							
First author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lee, 2004[6]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
Park, 2019[7]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Zhao, 2003[8]	High risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk

Newcastle Ottawa Scale – Cohort studies								
Author, Year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start	Comparability of cohorts (design or analysis)	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Alkhadhairi, 2018[9]	B - somewhat representative	A - same community	A - secure record	B - no	D - no description	A - independent or blind	A - yes	A - complete
Arabi, 2019[10]	A - truly representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	A - yes	A - complete
Chan, 2003[11]	B - somewhat representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	A - yes	B - small number lost
Choi, 2016[12]	B - somewhat representative	A - same community	A - secure record	B - no	D - no description	A - independent or blind	A - yes	A - complete
Chu, 2004[13]	B - somewhat representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	A - yes	A - complete
Guo, 2019[14]	B - somewhat representative	A - same community	A - secure record	A - yes	D - no description	A - independent or blind	A - yes	B - small number lost

Ho, 2003[15]	B - somewhat representative	A - same community	A - secure record	A - yes	D - no description	A - independent or blind	A - yes	A - complete
Lau, 2009[16]	A - truly representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	unclear	D - no description
Leong, 2004[17]	B - somewhat representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	A - yes	A - complete
Li, 2006[18]	B - somewhat representative	A - same community	A - secure record	B - no	A - age and other factor	A - independent or blind	A - yes	B - small number lost