Public Health England

ISARIC

Treatment of MERS-CoV: Information for Clinicians

Clinical decision-making support for treatment of MERS-CoV patients

16 August 2017
v4.0

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health, and are a distinct delivery organisation with operational autonomy to advise and support government, local authorities and the NHS in a professionally independent manner.

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Published August 2017
PHE publications
gateway number: 2017180

PHE supports the UN
Sustainable Development Goals

Contents

1 Document scope

This evolving document is intended to provide an overview of available evidence and experience on investigational therapeutics for UK clinicians treating confirmed cases of MERS.

It was produced by PHE and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) for the use of UK clinicians.

It is informed by literature concerning SARS, pandemic 2009 H1N1 influenza and MERS, as well discussions with international experts convened through ISARIC.

2 Literature

This document takes much of the SARS information from the following systematic review of SARS treatment: Stockman LJ, Bellamy R, Garner P, SARS: Systematic review of treatment effects, published in PLoS Med (2006;3(9):e343). A further useful review of SARS is: Cheng VCC et al, Clinical management and infection control of SARS: lessons learned, published in Antiviral Research (2013;100:407-419).

Several useful summaries of MERS treatment options have now been published: Momattin H et al, Therapeutic Options for MERS-CoV – possible lessons from a systematic review of SARS-CoV therapy, published in the International Journal of Infectious Diseases (2013;17:e792–e798), Chan JFW et al, Middle East Respiratory Syndrome Coronavirus: Another Zoonotic Betacoronavirus Causing SARS-Like Disease, published in Clinical Microbiology Reviews (2015;28(2):465-521), Arabi YM et al. Middle East Respiratory Syndrome published in New England Journal Of Medicine (2017 376(6):584-594); Colleagues with experience of managing MERS patients in affected countries have also reviewed treatment options for MERS-CoV (see Section 10 Bibliography - general).

A list of references used in this analysis is given at the end of this document. Regular literature reviews have been performed to ensure that evolving evidence is captured, up to date as of February 2017 using the search strategy detailed in Momattin et al (2013) searching across Pubmed, Embase, Scopus and the Web of Science.

A further manual review of all recent MERS-related papers in Pubmed was performed for each therapeutic option. Some information contained herein is unpublished *in vitro* and animal model work on MERS-CoV from several international groups to whom we are indebted. The experts consulted are listed in Section 9 - Consultation.

3 SARS-CoV approximation of MERS-CoV

Although we draw inferences from SARS in this document, there are important differences between SARS and MERS coronaviruses (CoVs), and some areas in which MERS-CoV data is not yet sufficient to enable comparison. MERS- and SARS-CoV infections demonstrate some differences in *in vitro* virological and immunological characteristics but the clinical relevance of these are unknown.

The limited evidence available on viral dynamics and clinical course suggest that MERS patients have shorter time from illness onset to presentation for care and requirement for ventilatory support (median seven days; range 3-11) than SARS patients, as well as associated higher respiratory tract viral loads during the first week of the illness. Some therapeutic options that showed possible clinical effects in observational human trials of SARS patients have not demonstrated *in vitro* inhibition of MERS-CoV.

4 Evidence base

Therapies that are plausible and supported by reasonable *in vitro*, animal and/or clinical data from MERS-CoV or other respiratory virus infections are shown in Tables 1,2 and 3. A large number of other compounds have been evaluated for *in vitro* inhibition of MERS-CoV replication, and some have demonstrated an inhibitory effect at serum concentrations that might be achieved in patients. However, without animal studies or well-documented experience of clinical use in comparable contexts, these are not currently ready for clinical use in MERS-patients. Such therapies have therefore not been included.

There has been no significant change in recommendations of therapeutic agents since the last published version (v3.0) in September 2015 based on available evidence. Research continues to progress on the rapid development and testing of monoclonal and polyclonal human neutralizing antibodies in small animal models. These may be options for compassionate use and a phase 1 trial of a polyclonal antibody has been undertaken in healthy volunteers. Of note, one RCT testing the combination of recombinant interferon-beta1a and ritonavir-boosted lopinavir has been initiated in MERS patients in KSA (NCT02845843).

Treatment with specific therapeutic agents should ideally occur in the context of formal observational studies or controlled intervention trials (see https://isaric.tghn.org/articles/adapted-study-documents-protocols/ for open access protocols). We strongly encourage the enrollment of all patients infected with MERS-CoV into available clinical trials or observational studies on host response and viral kinetics.

5 Management of cases

5.1 Infection control

Effective infection control is essential to protect staff and patients. Instigate measures as described in the PHE guidelines: (https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or- confirmed-cases) and WHO guidelines: http://who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/

5.2 Routine investigations

PHE will advise clinicians on samples for clinical and infection prevention and control purposes. (MERS clinical management and guidance is available at: https://www.gov.uk/government/collections/middle-east-respiratory-syndrome-coronavirus-mers-cov-clinical-management-and-guidance.

We recommend that initial sampling from confirmed positive cases includes blood for viral load monitoring, since this may have prognostic value, and possibly serial lower respiratory tract sampling in severe cases for monitoring response to therapy and the emergence of possible antiviral resistance. Viral sampling for research purposes could include serial upper and lower respiratory tract, blood, stool and urine samples for monitoring of viral load and persistence within body compartments. MERS-CoV titres in respiratory secretions peak during the second week of illness onset; throat swabs may be an alternative source of diagnostic samples, especially when sputum cannot be obtained[W2].

For organisations considering studies, ISARIC has developed a generic biological sampling protocol (www.prognosis.org/isaric) and case report forms (www.prognosis.org/isaric/crf.php) which are intended to make it as easy as possible for investigators to conduct internationally-compatible research studies in an outbreak. These are available for use without restriction.

5.3 Approach to treatment

The most important recommendation remains that high-quality supportive care is the keystone of management, as expressed in the updated WHO Interim Guidance on MERS: http://www.who.int/csr/disease/coronavirus_infections/case-management-ipc/en.

The Surviving Sepsis Campaign guidelines also offer standards of care for the critically ill: http://www.survivingsepsis.org/guidelines/Pages/default.aspx

Any additional benefit of investigational pharmacological agents is uncertain, because of lack of evidence, rather than lack of plausibility. Treatment with specific therapeutic agents should ideally occur in the context of formal observational studies or controlled intervention trials (see

https://isaric.tghn.org/articles/adapted-study-documents-protocols/ for open access protocols).

In the UK, two centres have experience of managing severely ill patients with MERS. Consultation with staff in these centres may be helpful. PHE will facilitate communications if required. WHO can also facilitate consultation with MERS experienced physicians outside of the UK.

5.4 Specific therapies

Based on the evidence presented in Table 1, convalescent plasma containing MERS-CoV antibodies, or interferon and lopinavir may be considered for specific treatment of MERS patients. Interferon and lopinavir are likely to be the most accessible treatments initially. PHE will advise on the availability of convalescent plasma once a case is identified. Specific MERS-CoV monoclonal and polyclonal antibodies are in pre-clinical development at the time of writing and a phase 1 trial of SAB-301 has been initiated in USA. UK physicians should contact PHE (Professor Maria Zambon's office, + 44 20 8327 6810) for information about the current availability of monoclonal or polyclonal antibodies.

Other agents described in Tables 1, 2 and 3 have demonstrated antiviral effects *in vitro*, but without documented *in vivo* efficacy or sufficient clinical data, particularly in MERS patients. Some are associated with concerns about safety in clinical practice. Many require safety studies, animal studies, or both before clinical trials can be initiated. Expert consensus is to avoid those agents classified as "red", ie corticosteroids for specific treatment of MERS, ribavirin monotherapy, and mycophenolate mofetil (MMF). In some patients corticosteroids may be considered for other indications according to local policy, for example, exacerbations of asthma/COPD, suspected or documented adrenal insufficiency or refractory septic shock (in line with the WHO Interim Guidance on MERS and Surviving Sepsis International Guidelines).

We have included promising novel antiviral agents for which compassionate use may be possible. A summary of additional MERS-CoV therapeutic candidates undergoing evaluation is available in Table S9 of Supplementary appendix to Arabi YM et al. Middle East Respiratory Syndrome NEJM 2017 376(6):584594 (http://www.nejm.org/doi/suppl/10.1056/NEJMsr1408795/suppl_file/nejmsr1408795_appendix.pdf).

The effect of corticosteroids on viral clearance of MERS-CoV is unknown, although systemic corticosteroid administration delayed clearance of SARS-CoV and has been associated with prolonged replication of other respiratory viruses. Consequently, serial viral load sampling with PCR testing should be performed in any MERS patients who receive corticosteroids for any indication. A retrospective analysis of data from SARS patients treated with corticosteroids suggested increased mortality.

5.5 Combination therapies

Therapeutic agents were used in multiple combinations for treatment of SARS patients, and increasingly in MERS patients, but there remain inadequate clinical data to disentangle the effects of individual agents from the possible benefits of any combinations. The vast majority of experience is from retrospective observational studies. Limited data from *in vitro* and animal studies of MERS-CoV infection suggests a possible synergistic effect from combining high doses of interferon (IFN) and intravenous ribavirin. However, the doses of ribavirin used are much higher than those used to treat hepatitis C virus infection. Ribavirin has also been associated with significant adverse effects in both SARS and MERS patients. Available data are inadequate to decide whether any benefit conferred by an interferon/ribavirin synergy outweighs the risk of ribavirin toxicity. Therefore, this combination is not recommended unless it is used in an appropriately planned clinical trial (see https://isaric.tghn.org/articles/adapted-study-documents-protocols/ for open access protocols).

Table 1. Evidence base for specific therapies for MERS-CoV infection: Benefit is likely to exceed risk

* SARS *in vitro* (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV *in vitro* (MIV); MERS animal (MA); MERS clinical (MC)

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Convalescent plasma (or high neutralizing antibody titre products)	SIV; SA; SC; MIV; MA	RCT not performed in SARS. One RCT supports use of hyperimmune globulin in severe A(H1N1)pdm09 influenza[E1]. Observational data suggests efficacy in SARS[E2-5] and A(H1N1)pdm09 and other influenza virus infections[E6]. A pooled meta-analysis including SARS-CoV and influenza studies showed a significantly lower risk of mortality in those treated with convalescent plasma or serum[E7].	*In vitro* neutralizing effect based on levels of MERS-CoV specific antibodies[E11-18] and high-titer camel serum improved viral clearance in infected mice[E20]. A clinical trial is ongoing but has not yet recruited any patients (NCT02190799)[E22]. There may be wide variation in the amount of neutralizing antibody depending on illness severity and the timing of plasma collection in relation to convalescence, with waning titres over time[E21]. Serologic data from 17 South Korean MERS patients demonstrated robust neutralizing antibody responses by day 21 of illness in the majority of severely ill patients, however, this was not found in patients with milder infection[E22].	Good safety profile in UK, risks as for other blood products. Convalescent plasma should be tested to have documented specific MERS antibody before use with assessment of antibody titres. Potential donors of convalescent sera should wait until at least 3 weeks after their symptom onset[E22]. Antibody levels will likely decline with time, as see in one patient whose antibody response was measured longitudinally[E22].	Availability depends on UK epidemiological situation. The largest Saudi study to identify donors to date showed that MERS antibodies are rarely positive following infection or exposure[E22]. Screening of 170 Saudi blood donors showed 0% seroprevalence [E23]. Please contact PHE for an update on availability.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Interferons (IFNs)	SIV; SA; SC; MIV; MA; MC	Type I (α, β), type II (γ), and type III (λ) IFNs show activity against SARS in extensive *in vitro* and limited animal and observational clinical studies[M1-12].	*In vitro*, MERS-CoV appears to be more sensitive to Type I IFNs than SARS-CoV, especially IFN-β[M17-20]. Some animal evidence from marmoset model in severe disease with IFN-β1b[M25]. Animal studies with Poly IC topical IFN inducer suggest efficacy[M26]. Type 1 IFNs are among the most active drugs at clinically achievable serum levels[M26]. IFN-α in combination with very high-dose ribavirin shows some efficacy in non- human primates but this animal model does not accurately reflect severe MERS illness seen in humans[M27]. A phase II/III trial of lopinavir-ritonavir and IFNβ-1b is open to recruitment in Kingdom of Saudi Arabia (NCT 02845843).	Well established agent. Clinicians experienced in managing side effects should be consulted e.g. those treating hepatitis C virus (HCV) infection and multiple sclerosis. Consideration should be given to shorter-acting preparations compared to peg-IFNs.	Injectable recombinant IFN-β1b is currently first choice and is routinely available. Subcutaneous IFNβ-1b is being trailed in Saudi Arabia. Inhaled IFN-β is currently in Phase II trials but has not been adequately studied in severe lower respiratory tract infections.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Lopinavir	SIV; SA; SC; MIV; MA; MC	Limited data that HIV protease inhibitors have *in vitro* anti-SARS-CoV effect[S1]. Observational studies suggest clinical benefits in SARS patients treated with lopinavir/ritonavir, including a reduction in mortality reported in one study[S1,2].	Lopinavir inhibitory for MERS-CoV *in vitro* at concentrations observed in blood during clinical use (note other HIV PIs tested, atazanavir and ritonavir, were inactive)[S6]. Good *in vivo* evidence from marmoset model for improved outcomes[S7]. Use in one patient alongside IFN and ribavirin[S8]. Lopinavir-ritonavir was administered with ribavirin and PEG-IFN-α2a to many patients in the South Korea outbreak but outside the context of a clinical trial; unable to determine efficacy[S9]. A phase II/III trial of lopinavir-ritonavir and IFNβ-1b is open to recruitment in Kingdom of Saudi Arabia (NCT 02845843).	Well established agent with favourable toxicity profile. Gastrointestinal side effects are common but self-limiting.	Routinely available (as lopinavir and ritonavir combination preparation).

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Monoclonal and polyclonal neutralising antibodies (mAbs)	SIV; SA; MIV; MA	Strong *in vitro* neutralising effect against the SARS-CoV spike protein[P1,2].	Novel monoclonal antibodies to MERS-CoV spike protein have strong neutralising effect[P3-5]. Potent MERS-CoV– neutralizing antibody have recently been isolated from memory B cells of an infected individual[P6] and polyclonal human neutralizing antibodies have been produced in transchromosomal bovines[P7]. Camel antibodies have been successful in prophylactic and therapeutic use in murine models[P8]. Human mAbs have been successfully trialed as both therapy and prophylaxis in murine models[P9]. Intravenous human mAb 3B11-N reduces radiological evidence of pneumonia in rhesus macaques when given as prophylaxis[P10].	A Phase 1 clinical trial assessing safety and tolerability of SAB-301 is ongoing (NCT 02788188). In those products which have satisfied UK regulatory safety requirements, benefit is likely to exceed risk.	Contact PHE for an update on availability. Use should be within a trial, or if not possible, through a compassionate use arrangement.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Monoclonal and polyclonal neutralising antibodies (mAbs) - continued	SIV; SA; MIV; MA	-	Monoclonal antibody resistant mutants (MARMS) selected *in vitro* are not inhibited *in vivo* and show little loss of fitness[P6]. A Phase 1 clinical trial has been initiated for SAB-301 (NCT 02788188). Phase 1 trials are expected to commence for LCA60[P6], REGN3051 & REGN3048[P9].	-	-

Table 2. Evidence base for specific therapies for MERS-CoV infection: Data is inadequate for assessment

* SARS *in vitro* (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV *in vitro* (MIV); MERS animal (MA); MERS clinical (MC)

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Interferon + ribavirin (combination therapy)	SIV; SA; SC; MIV; MA; MC	Synergistic effect *in vitro* and in animal model when ribavirin combined with IFN-β[M7,12]. Effect of combination could not be distinguished from other concurrent treatments in SARS patients, Where outcomes could be determined, adverse effects were reported[M7].	IFN-α2b and ribavirin combined *in vitro* had anti-MERS-CoV effect at lower concentration than when used separately[M17]. Combination high dose IFN-α2b and IV ribavirin in MERS rhesus macaque model led to some clinical, radiographic and virological improvements[M17]. IFN/ribavirin combination therapy given late in illness to 5 MERS patients did not prevent death[M22], and was not helpful in a further 3 out of 6 cases[M24]. Some case reports of apparent benefit when used for early therapy[M24] or post-contact prophylaxis[M30] but there have been case studies that show little effect on mortality[M28,29].	Adverse effects of ribavirin were frequent in SARS clinical studies (see ribavirin, below)[T1, 12,13] . In combination studies, the experimental ribavirin concentrations were higher than those achievable clinically during treatment of hepatitis C[M26]. One retrospective cohort of 20 patients showed no increase in adverse effects apart from greater haemoglobin reduction[M23]. The largest Saudi Arabian cohort demonstrated no benefit with IFN/ ribavirin combination, and possible harm with ribavirin[T18] .	Routinely available. Data are inadequate to decide whether any benefit conferred by possible interferon and ribavirin synergy outweighs the risk of ribavirin toxicity, however expert opinion is to not use ribavirin, and if used should be in the context of a clinical trial.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Interferon + ribavirin (combination therapy) - continued	SIV; SA; SC; MIV; MA; MC	-	One retrospective cohort study showed improved outcomes in severe MERS-CoV infection in those given ribavirin and IFN-α2a at 14 days but not 28[M23]. IFNβ showed the strongest inhibition *in vitro* compared with IFNα, additionally IFN-α2a may be less inhibitory than IFN-α2b (higher IC_{50})[M20]. A further case note review from Saudi Arabia saw patients given IFNα or IFNβ in combination with ribavirin but was an uncontrolled retrospective chart review so no conclusions can be drawn[M31].	-	-

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
GS-5734 (Nucleoside viral polymerase inhibitor)	SIV; MIV; SA, MA	Polymerase inhibitor with *in vitro* activity against a number of RNA viruses[J1]. 90 % Inhibition at ≤150nmol against SARS-CoV in a human airway epithelial cell (HAE) model, with average IC_{50} values of 0.069 µM[J2,3]. Prophylactic use reduces SARS-CoV lung titres and disease in mice. Early therapeutic use significantly reduced viral titres in lung, and improved lung function on day 3 [J3]; later use reduced viral load but did not affect clinical outcome – this may be due to the truncated course of disease in murine models	90 % Inhibition at ≤150nmol against MERS-CoV in a human airway epithelial cell (HAE) model with average IC_{50} values of 0.074 µM [J2,3]. Prophylactic intravenous use in 6 Rhesus macaques was associated with reduced MERS-CoV viral loads and reduction of respiratory symptoms[J4].	Manufacturer reports two phase 1 trials completed results not available. Phase 2 trial involving Ebola Virus Disease (EVD) survivors is ongoing (NCT 02818582).	Currently unlicensed. Has been used compassionately for the treatment of EVD in two patients[J5,6].
BCX4430 (Nucleoside viral polymerase inhibitor)	SIV, MIV	Polymerase inhibitor with *in vitro* activity against a number of RNA viruses. Inhibitory activity against SARS CoV *in vitro*[C1].	Inhibitory activity against MERS CoV *in vitro*[C1].	Phase 1 trial completed but results not available (NCT02319772).	Currently unlicensed. No record of compassionate use for any condition to date.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Nitazoxanide	MIV	No SARS data. An RCT showed benefit in uncomplicated influenza in adults[R1]. Inhibitory for two non- human CoVs *in vitro*[R2,3].	Nitazoxanide, and the metabolite tizoxanide, have been shown to inhibit MERS-CoV cultured in LLC-MK2 cells at IC_{50}s are similar to those observed for influenza and other viruses[R4]. No animal model data available.	Well established agent with defined safety profile.	Routinely available.
Chloroquine	SIV;MIV	Inhibitory *in vitro* for multiple viruses including influenza[D1,2]. No consistent activity in animal models of influenza[D2,3] and negative results in one influenza RCT of seasonal prophylaxis[D4].	Inhibits MERS-CoV *in vitro*, with a concentration achievable by standard clinical oral dosing, described in several papers[D5].	Well established agent with defined safety profile.	Routinely available.

Table 3. Evidence base for specific therapies for MERS-CoV infection: Risk is likely to exceed benefit

* SARS *in vitro* (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV *in vitro* (MIV); MERS animal (MA); MERS clinical (MC)

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Corticosteroids (as specific therapy for MERS-CoV infection)	SA; SC; MC	A SARS-CoV animal study suggests early anti-inflammatory effects but found ongoing administration may enhance viral replication in the lung[F1]. SARS clinical studies have not demonstrated consistent mortality benefits[F2]. Some observational studies found clinical improvements after treatment[F3,4] but one RCT found increased viral load associated with corticosteroid treatment[F5]. A retrospective analysis suggests that glucocorticoids may be associated with increased mortality in SARS[F7].	No studies available. Given to many MERS patients under uncontrolled circumstances with limited outcome data[F9]. Corticosteroids have been used to treat a late complication of MERS-CoV infection (organizing pneumonia) without apparent adverse effect, but at a time when MERS-CoV was no longer detectable in the affected individual[F8]. A conference abstract of one large retrospective Saudi Arabian cohort showed a model-dependent decrease in mortality following adjustment for disease severity, however further analysis (personal communication - manuscript currently under review) showed no association on mortality, with a delay in viral RNA clearance[F19].	SARS studies found no mortality benefit and evidence for adverse effects of systemic steroids, with both acute and long-term harms, including delayed viral clearing reported, and increased opportunistic infections[F10-12]. Osteonecrosis was observed following pulsed methyl-prednisolone, more commonly in male, young patients, and in those receiving more than one administration[F13-14].	Routinely available.

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Corticosteroids (as specific therapy for MERS-CoV infection) - continued	-	Use of systemic corticosteroids in patients with severe influenza A(H1N1)pdm09 was also associated with increased risks of prolonged lower respiratory tract viral replication, nosocomial infections, ventilator-associated pneumonia, and higher mortality in observational studies[F8].	-	-	-

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
Ribavirin – monotherapy	SIV; SA; SC; MIV; MC	Four of six *in vitro* SARS studies found an antiviral effect[T1]. No virological effects were found on SARS in animal models as monotherapy. In SARS clinical studies, the effect of ribavirin could not be distinguished from the effects of other therapies[T1,13].	MERS-CoV is inhibited by ribavirin at very high concentrations *in vitro*. These exceed concentrations achievable during clinical use, except possibly for high IV dosages[T14]. No animal monotherapy studies have been conducted. Combination therapy including ribavirin was given to five MERS patients late in the illness and did not prevent death[T5]. One recent review suggests that decreased mortality at 14 days seen in combination therapy may be associated with the use of oral ribavirin, but this is speculative[T10].	Studies of ribavirin in large numbers of SARS patients found frequent adverse effects including haemolysis, metabolic disturbances, and liver function test derangement[T1,13].	Routinely available.

Therapy	Studies * Performe	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
UK intravenous human normal immuno-globulin (IVIG)	SC; MIV; MC	Five SARS studies conducted; all inconclusive as used IVIG as part of combination therapy[N1]. In one uncontrolled study in Hong Kong, 12 patients who had deteriorated despite other therapies were given IVIG as an additional therapy, with evidence of subsequent improvement[N2].	PHE evaluation shows that IVIG available in the UK has no evidence of MERS-CoV neutralising activity (unpublished data). IVIG from endemic countries requires separate evaluation. Local IVIG was given to correct platelet imbalance in one Saudi patient (along with high dose corticosteroids), with favourable outcome[N3].	Commercial IVIG products have been associated with rare acute renal failure and thromboembolic events[N4].	Routinely available.
Mycophenolic acid / mycophenolate mofetil (MMF)	SIV; SA; MIV; MA; MC	No effect on SARS-CoV *in vitro* or in a murine model[Q1].	Inhibits MERS-CoV *in vitro*, with a concentration achievable by standard clinical oral dosing[Q2,3]. Synergy in vitro with IFN-β1b[Q3]. MERS- CoV marmoset studies indicate that MMF used alone may increase viral replication and worsen outcomes[Q4]. One patient acquired infection while on MMF following renal transplantation but survived with reduction in dose[Q5].	Effect of transient immunosuppressive activity in this context is uncertain. Established treatment with multiple well characterised side effects.	Routinely available.

6 Feedback

As this is a document intended for continual update, we are particularly interested in the views of those who may be using it on the frontline of service. Please send thoughts or suggestions for improvement, or any other comments, to colin.brown@phe.gov.uk and maria.zambon@phe.gov.uk.

7 Useful links

PHE – https://www.gov.uk/government/collections/middle-east-respiratory-syndrome-coronavirus-mers-cov-clinical-management-and-guidance

ISARIC – http://www.isaric.org

WHO – http://www.who.int/emergencies/mers-cov/en/

ECDC – www.ecdc.europa.eu/en/healthtopics/coronavirus-infections/pages/index.aspx

CDC – www.cdc.gov/features/novelcoronavirus/

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9 Consultation

The following coronavirus experts and clinicians and scientists with experience of SARS, MERS and other respiratory viruses were involved in PHE or ISARIC teleconferences or commented on drafts of this document. We are most grateful to them all for their valued input. This is a document intended for continual update.

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Clinicians, virologists, health professionals, and public health experts involved in managing MERS patients: many thanks to all who participated in the PHE and ISARIC/WHO teleconferences for their valuable input.

10 Bibliography: Articles of Interest

A. Antibiotics

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B. Antiviral peptides/proteins

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