Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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We declare no competing interests.

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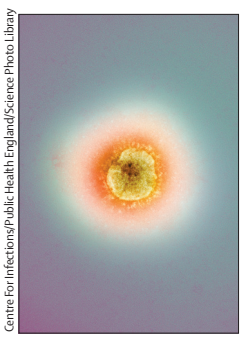
Towards improving clinical management of Middle East respiratory syndrome coronavirus infection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A decade on from the 2002–03 outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) infections, the world is again confronted by the possible international spread of a novel coronavirus, the Middle East respiratory syndrome coronavirus (MERS-CoV), which apparently originated in the Arabian peninsula.[1] MERS-CoV is associated with severe respiratory tract infection, often renal failure, and mortality exceeding 40% in patients admitted to hospital.[2] Similar to SARS-CoV, it is closely related to bat coronaviruses, but MERS-CoV has different cellular receptor specificity and a broader species range—camels seem to have a role as a natural host. Saudi Arabia has been most severely affected so far, but imported cases—either recent travellers or those transported for clinical care—have been seen in countries in Europe, Africa, Asia, and North America. Major nosocomial outbreaks have happened in the Middle East,[3] and non-sustained human-to-human transmission events elsewhere,[4] and many more clinical cases are likely to have occurred.[5] There has been a recent surge in case reporting that could be the result of more human-to-human transmissions due to a change in exposure patterns, expansion of the virus in animal reservoir(s), seasonal variation, ongoing nosocomial clusters, or increased surveillance with reporting of mild or asymptomatic MERS-CoV detections, or both.[5]

Severe MERS-CoV disease has occurred primarily in older adults, particularly men, with comorbidities.[2] However, data on disease pathogenesis, particularly viral replication patterns and clinical manifestations, are scarce at present. Despite more than 500 laboratory-confirmed MERS-CoV cases so far, only a handful of patients have had systematic virological and biomarker sampling.[4,6] Consequently, there are many unanswered questions regarding sites of infection, pathogen dynamics, innate and adaptive immune responses, and host genetic factors. Prolonged viral replication in the lower respiratory tract, extrapulmonary virus detection, severe lung injury with respiratory failure, and often renal failure are notable features, suggesting that an effective antiviral regimen, perhaps in combination with immunomodulatory agents, would provide clinical benefit.

Although supportive care is central to clinical management of coronavirus infections, appropriate antiviral and immunomodulatory therapy for both SARS[7] and MERS-CoV infections remain uncertain because of a scarcity of quality evidence. An absence of good animal models for MERS-CoV poses a major challenge. Many agents have inhibitory activity in vitro for coronaviruses, including some licensed drugs,[7–9] but it is unclear whether their human pharmacology and tolerability would enable sufficient doses to be given to exert antiviral effects in patients with MERS-CoV. One available drug that is inhibitory for coronaviruses in vitro at clinically achievable levels is the inosine-5´-monophosphate dehydrogenase (IMPDH) inhibitor mycophenolic acid,[8] but animal data for this effect are scarce, and one patient developed infection while receiving mycophenolate mofetil.[4] Ribavirin and interferon combinations are associated with modest

antiviral effects in MERS-CoV inoculated rhesus macaques given high doses.[9] Although the clinical relevance of these findings is uncertain, the combined use of antiviral drugs to enhance inhibitory effects and reduce the potential for resistance emergence makes sense.

At present, the strongest treatment evidence supports the use of convalescent plasma or other preparations that possess neutralising antibodies.[10,11] Convalescent plasma seemed to reduce duration of treatment in hospital and mortality when used early in patients with SARS.[7] For MERS-CoV, low neutralising antibody responses and inability to acquire sufficient convalescent plasma from survivors with comorbidities might restrict the effectiveness of this treatment, although these limitations might not apply to infected health-care workers. Additionally, the availability of human neutralising monoclonal antibodies[12] or polyclonal immune globulin produced in transgenic cows or other hosts[13] could overcome these hurdles. The high seroprevalence of high-titre neutralising antibody to MERS-CoV or a closely related virus in dromedary camels in the region raises the possibility of using camel sera or engineered single domain camel antibodies for therapy.[13,14] Purified immunoglobulins or immunoglobulin fragments (nanobodies) might offer a therapeutic option for severely ill patients until more defined, genetically engineered, antibodies become available.

For any chosen intervention, we advocate that use must be accompanied by a prospective, protocol-based assessment of safety and effectiveness that includes sequential virological, clinical, and biomarker measurements. We wrote about the slow acquisition of such data in the 2009 H1N1 influenza pandemic.[15] One outcome from this circumstance was the formation of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), a global federation of academic clinical research networks. ISARIC has collaborated with WHO to develop biological sampling protocols that are applicable for patients with MERS-CoV. Furthermore, working with colleagues in Public Health England, ISARIC experts have examined available data and ranked potential therapeutic options with regard to their priority for clinical study;[10] this information will be updated as new data become available.

However, no MERS-CoV patients have yet been enrolled on therapeutic protocols incorporating systematic sampling through ISARIC or any other organisation. Consequently, we are not learning what might benefit or potentially harm such patients. Whatever agent or agents are selected for testing, systematic harmonised data collection involving robust observational studies or, when possible, controlled trials, is needed to assess both disease pathogenesis and candidate therapeutics for MERS-CoV. Clinicians and public health officials in affected Middle Eastern countries, particularly in Saudi Arabia, are uniquely positioned to undertake such studies. With support as needed from international partners like WHO and ISARIC,[11] regional governments, and funders, Middle Eastern colleagues have both the opportunity and the responsibility to undertake studies to advance the understanding of effective prevention and treatment strategies for MERS-CoV and any future novel CoV outbreaks. Thus far, MERS-CoV is yet another emerging infection threat for which the clinical research response has been too slow and uncoordinated. New investigative frameworks, possibly incorporating mandates into the International Health Regulations, are urgently needed.

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For the **International Severe Acute Respiratory and Emerging Infection Consortium** see http://www.isaric.org/

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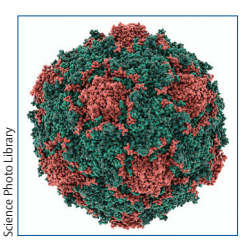
The slippery geographies of polio



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The 2013 deadline for the worldwide goal to eradicate polio has come and gone, with a new endgame set for 2018.[1,2] Although cases of polio have decreased by 99% worldwide since 1988, geopolitical conflicts have exacerbated its spread—Syria, Ethiopia, and Kenya have reported polio infections, and Afghanistan, Nigeria, and Pakistan remain endemic.[3,4] The virus has resurfaced in Israel, and might be linked to use of intravenous inactivated polio vaccine (IPV).[5] Transnational mobility also contributes to polio's persistence, and circulating vaccine-derived poliovirus (cVDPV) in Yemen, Mozambique, and Madagascar is further complicating eradication efforts.[6]

We know that the spatial distribution of polio (where polio exists in some places, is contained in others, is detected but not virulent, has gained virulence through mutation, or is a threat) is very complex. The distribution is complex because the diffusion of poliovirus is associated with different types of polio, bodies, ecologies, and geopolitical realities. Polio can be biomedically engineered polioviruses (IPV), degraded versions of the virus (oral polio vaccine [OPV]), mutating viruses, or the so-called wild polio virus and its various strains; bodies can have no poliovirus, wild polio resistance, symptomatic polio, IPV, OPV, cVDPV, or be subclinical; ecologies vary across landscapes of built and natural environments; and geopolitical realities create different regulatory structures, biomedical accessibilities, conflicts, migrations, and tensions. This complexity means that eradication of polio in some places for some people with certain forms of a vaccine might not be possible in the immediate future. We thus have to better imagine how different types of viruses, bodies, built and natural ecologies, and geopolitical realities interact to produce the present landscape of infectious disease.[7]

As health geographers, we argue that such complexity demands a different spatial imaginary and concomitant vocabulary to understand polio.[8] A set of assumptions in standard epidemiological practice suggest that control can happen through geographical containment in particular places and bodies.[9] Polio containment leads to the elimination of wild or mutated viruses in particular places—a process that provides the promise of biomedical science's capacity to eradicate and then extinguish these uncontrolled forms of life. Although we are fully supportive of all efforts to eliminate human suffering, including vaccination, we also believe in the need to be more realistic about the capacities of the virus;[10] the assumptions embedded in vaccination efforts do not appreciate the ontological position of viruses circulating through ecosystems.[11,12] Polioviruses are not bound to the humanly produced built and natural ecologies in which they exist nor the political or natural boundaries; the interest of polioviruses is survival, and this depends on their ability to find a human host.

Polioviruses, therefore, do not rely on the ocular-centric spatial imagination of human beings. People need to see polioviruses to know how to eradicate and control them, including the viruses used in vaccines and laboratory studies. Polioviruses know how to negotiate the negative spaces between human vision and the bodies and ecological landscapes that afford them their