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Ebola, COVID-19 and Emerging Infectious Disease: Lessons Learned and Future Preparedness

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Abstract

Purpose of Review—To highlight the lessons learned from the Ebola outbreak that may inform our approach to the COVID-19 pandemic, particularly related to the widespread disruption of health care, ophthalmic disease manifestations, and vision health systems strengthening for future outbreaks.

Recent Findings—Coronavirus disease 2019 (COVID-19), first detected in China in December, 2019, has become a worldwide health emergency, with significant disruption of all aspects of society, including travel, business, and medical care. While this pandemic has had unprecedented effects on health care delivery in the United States, experiences from recent Ebola virus disease (EVD) outbreaks in Africa provide insight and inform our approach to COVID-19 and outbreak preparedness. Like COVID-19, the rapid emergence of Ebola required new clinical and surgical approaches to understand its associated spectrum of ophthalmic complications and the potential for Ebola viral persistence within the eye and in tear film. Recent reports of ophthalmic findings associated with COVID-19 include conjunctivitis, retinopathy, and molecular evidence of virus within the tear film in a minority of cases. Yet, more rigorous approaches to understand ophthalmic disease and transmission risk associated with COVID-19 are needed. Gaps also remain in our understanding of eye disease associated with other high priority emerging infectious diseases including Nipah, Lassa Fever, Marburg virus and others.

Summary—Thoroughly understanding the ophthalmic findings and transmission risk associated with COVID-19 is paramount during this pandemic, providing additional measures of safety while resuming ophthalmic care for all patients. Vision health systems preparedness measures developed during recent EVD outbreaks and the current pandemic provide models for ophthalmic clinical practice, research, and education, as we continue to address COVID-19 and future emerging infectious disease threats.

Keywords

COVID-19; Ebola; epidemic

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Introduction

Coronavirus disease 2019 (COVID-19), first detected in Wuhan City, Hubei Province, China in December, 2019, was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) in January 30th, 2020, and formally received the *Pandemic* designation on March 11th, 2020 [1]. By March, most countries worldwide had entered into a shelter-in-place or lockdown period, during which only essential travel and business were allowed [2]. Within the U.S., over 100,000 deaths were attributed to COVID-19 by the end of May, 2020 [3], and most non-essential travel and business had ceased with gradual re-openings [4]. Of particular importance to ophthalmologists, all non-emergent, non-urgent medical care was delayed to prevent person-to-person transmission in clinical and surgical settings and preserve personal protective equipment (PPE). This disruption of medical care has been both the choice of healthcare workers (HCW) and patients, likely motivated to stay away from clinical settings [5], and was recommended by the government, public health organizations, and major medical societies including the Centers for Disease Control and Prevention, American Academy of Ophthalmology, the American College of Surgeons, and the Centers for Medicare and Medicaid Services [6,7].

While the rapidity and ubiquity of the disruption of both society and medical care has been unprecedented, other disease outbreaks, primarily outside of the U.S., have paralleled our recent experience. Ebola virus disease (EVD), for instance, became a worldwide concern during the unprecedented West African outbreak from 2014–2016 [8]. During this time, 12 countries were affected and in response to this public health emergency, many countries in West Africa imposed restrictions including curfews, closure of national borders, and strict temperature and symptom monitoring in health care facilities and businesses [9]. Within the U.S. health care facilities began screening patients for fever and individuals returning from endemic regions [10]. Hospitals trained staff and readied personal protective equipment for potential interaction with infected patients [11]. The United States National Ebola Training and Education Center was developed to disseminate knowledge regarding how to safely and effectively treat infected patients [12].

Worldwide, the need for a strengthened infrastructure and global partnerships for vaccine development was recognized, leading to the creation of the Coalition for Epidemic Preparedness Innovations, a foundation that finances the creation of vaccines for emerging infectious disease [13]. Furthermore, while a broad lockdown was not imposed in the USA during this time, some states did enforce mandatory quarantines for healthcare workers returning from caring for Ebola patients in West Africa [14]. While relatively few cases of EVD were observed in the U.S., primarily health care workers repatriated from West Africa [15], the sense of threat eventually dissipated with a reduction of clinic precautions and travel restrictions. Yet, active EVD outbreaks have continued to occur, with three separate outbreaks in the Democratic Republic of Congo from 2017–2020.

Just as with Ebola, COVID-19 has rapidly emerged as an infectious risk, and ophthalmology practice has had to adapt quickly, as evidence of disease implications, transmission, and therapies continue to evolve. This review discusses our group's experience with Ebola, the shortcomings and successes of prior response, clinical disease implications for the ophthalmologist, and preparedness measures that are needed as ophthalmologists address scientific, clinical and logistical challenges during and beyond the COVID-19 pandemic.

Lessons learned from Ebola virus disease

Ebola has primarily affected extremely resource-limited and remote areas of Africa, where robust health system infrastructure including ophthalmic subspecialty care is lacking [8,16]. Ebolavirus, a filovirus, was first described in 1976 in Democratic Republic of Congo and Sudan [8]. From these initial reports until 2014, there were only 2345 documented cases of Ebola [8], although during the 2014–2016 Ebola epidemic in West Africa, there were over 28,600 infections and 11,300 deaths [16]. The increase in infected cases in West Africa is partly attributed to the development of rapid transportation and more people living in densely populated urban areas, while previous outbreaks in Africa have affected only rural villages. The fruit bat is thought to be its natural reservoir and probable vector leading to human disease. Contact with intermediate reservoirs including non-human primates and duikers may also lead to the initiation of outbreaks, but human-to-human spread via infected bodily fluids subsequently leads to widespread disease transmission within crowded urban areas and healthcare facilities.

The clinical features of acute Ebola virus disease (EVD) include fever, fatigue, abdominal pain, vomiting, diarrhea, myalgia and internal hemorrhage. While close laboratory monitoring and aggressive supportive measures reduce mortality, the recent development of an effective vaccine [17,18] and a therapeutic trial demonstrating efficacy of monoclonal antibodies targeting Ebola surface glycoprotein [19] as been promising in the reduction of mortality from EVD. However, within Africa, the case fatality rate is extremely high, ranging from 25–90% with deaths typically within several weeks of infection [8]. Following acute EVD, survivors are at high risk of experiencing systemic and ophthalmic sequelae, which can include arthralgia, myalgia, hearing loss and tinnitus, cognitive impairment, and uveitis [21].

Studies by our group and others have shown a range of ophthalmic manifestations, including anterior and posterior uveitis, and optic neuropathy [16,22]. Uveitis has been observed in up to 26% of EVD survivors, increasing to 33% after 1 year [16,22]. Moderate to severe vision loss has been reported in up to 38% of Ebola survivors [16,22]. Given the high rates of ocular manifestations, ophthalmic exams are critical for Ebola survivors following acute EVD. Furthermore, cataract, either secondary to uveitis or age-related, is common in Ebola survivors. Based on these findings, a protocol to facilitate adequate clinical and surgical ophthalmic care while ensuring the safety of HCW is needed for this population.

Because Ebola is such a deadly disease, there is a range of obstacles to delivering ophthalmic care and surgery to Ebola survivors. Naturally, there is anxiety on the part of HCW regarding contact with Ebola patients and survivors due to fear of infection [23]. Given the infectivity of the virus and the high case fatality rate of Ebola this creates even more concern that other less lethal pathogens. Similar attitudes from HCWs unwilling to provide care for patients with SARS [24] and HIV [25] have also been documented. The reasons for this reluctance to care for potentially infectious patients are multifactorial and include perceived personal risk, risk to family, stigma against exposed HCW, trust in the healthcare system, and personal or media-relayed knowledge of HCW infections [23]. These factors combine to decrease the pool of eye care providers available to work with Ebola survivors among health systems in West Africa that lack sufficient ophthalmic care at baseline [26].

To address the potential for risk to ophthalmologists providing surgical care for Ebola survivors, our group performed the Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) study assessing the safety of cataract surgery in Ebola survivors [27]. Of particular importance for Ebola, viral persistence has been shown in multiple bodily tissues long after clinical improvement and negative serum testing, including aqueous fluid [28], which surely adds to ophthalmologists perceived risk of infection and reluctance to treat these patients. As such, protocols need to be made for safe clinical and surgical care, which safeguards HCW from infection exposure. The EVICT trial shows a model for safe cataract surgery in Ebola survivors, highlighting the utility of pre-operative testing of conjunctival and intraocular fluids to ensure HCW safety. Development of preoperative protocols given risks of viral persistence of Ebola and likely other emerging infectious diseases provides a roadmap and an approach to emergent and urgent clinical and surgical care in future epidemics.

How has ophthalmological care been impacted by COVID-19?

While Ebola has predominantly been observed in countries within Africa, COVID-19 has become a worldwide epidemic, affecting over 200 countries and territories including over 1.9 million cases within the U.S. While the mortality observed in COVID-19 is substantially lower than in EVD, the transmission risk primarily through respiratory secretions is far greater. The potential for tear film transmission has been reported, given that up to 5% of affected patients may demonstrate RT-PCR positivity for SARS-CoV-2 [29]. These factors have raised questions about when routine eye care should be resumed in the U.S. and the protective measures required for ophthalmologists to prevent patient-physician transmission and vice versa. Within the U.S., COVID-19 has disrupted eye care much more than Ebola, although lessons learned during the West Africa Ebola outbreak can be applied to the COVID-19 outbreak.

In contrast to Ebola, which had high rates of visually significant ophthalmic manifestations during EVD convalescence, the ophthalmic manifestations during active COVID-19 have been observed in fewer proportions in most series. Although one series reported that approximately one-third of patients showed ocular surface complications including conjunctival hyperemia, chemosis, and epiphora [30], other series reported less than 1% of conjunctival findings. One recent report described 12 patients with retinopathy, which manifested as cotton-wool spots [31]. While tear film has demonstrated viral RNA by RT-PCR in several series with the prevalence ranging from 2 to 5% [30], viral transmission to ophthalmologists or other health care providers via tear film has not been reported to-date. Ebola virus has demonstrated delayed clearance from conjunctival tissue following acute infection and has been identified as long as 21 days after systemic RT-PCR tested negative [32]. Studies related to the timing of viral clearance from tear film and longer term follow up of COVID-19 survivors are needed to truly evaluate ophthalmic manifestations of this disease.

The major ophthalmic implication during COVID-19 has been related to the disruption of routine care. Besides the necessary mandates to delay or postpone elective care and surgery, ophthalmologists and patients have become cautious of non-essential interactions. Most clinical practices have reduced their scheduling and remaining shelter-in-place orders continue to require that some practices see emergent patients only. Some ophthalmology practices have been closed completely [33,34]. These are prudent measures as the risk of COVID-19 infection by patients and physicians has been well described [35]. However, clinic closures must be balanced against the need for continued delivery of care, as delayed care may lead to worse outcomes for patients with truly urgent conditions who did not seek care or had difficulty finding care due to COVID-19. Indeed, a study by ophthalmologists at Moorfields found a 62% reduction in patients presenting with retinal detachment in March and April 2020 compared to the same period in 2019, suggesting that many patients with true ophthalmic emergencies did not access appropriate care [34]. The same pattern of delayed care for truly urgent conditions has been documented for other medical conditions as well, such as a reduction in patients seeking care for myocardial infarctions in a study of many large American hospitals [5].

In addition to reduced clinical scheduling, ophthalmology practices have made many other adaptations to continue clinical care in the setting of COVID-19 [33]. These include screening patients and HCW for symptoms and fever before entering clinics, large breath shields on slit lamps between patient and ophthalmologists, and universal masking for patients and HCWs. Many practices have also increased their use of telehealth visits, facilitated by the reduction of regulations for insurance billing and privacy requirements [33]. To further reduce the infectious risk during surgical cases, many surgical sites have begun preoperative COVID-19 testing and restoration of PPE supply chain [36]. Still, more knowledge is needed regarding risk associated with specific ophthalmic surgeries (e.g. vitrectomy, phacoemulsification), draping and ocular surface preparation techniques, and supplemental oxygen and airway management risk, particularly related to intubation, and transmission risk associated with contact with conjunctiva and intraocular fluids.

What do we know about ophthalmic and systemic manifestations of other emerging infectious diseases?

While we are racing to adapt to providing ophthalmologic care during the COVID-19 epidemic, we should be cognizant of the potential for future outbreaks of infectious disease. This section summarizes the clinical manifestations of World Health Organization High Priority Diseases, given their potential to lead to a public health emergency while having no effective therapies or vaccines [37]. These infectious diseases align with the priority diseases for the Coalition for Epidemic Preparedness Innovations [13] for vaccine targeting and development.

Nipah virus, a paramyxovirus, first appeared in 1999, and since then has been associated with outbreaks in Malaysia, Singapore, Bangladesh, and India [38]. Nipah virus causes a viral encephalitis with fever, headache, drowsiness and confusion, with a high fatality rate of 38–75%, with a rare report of central retinal artery occlusion in a Nipah virus patient [39], and the potential for infection through ocular fluid is unknown [38,40].

Lassa virus is a rodent-borne arenavirus endemic to West Africa that causes severe hemorrhagic fever in about 20% of infected individuals, characterized by facial swelling, hepatic and renal abnormalities, and pulmonary edema and hemorrhage [41]. In human patients, conjunctivitis has been observed [42], and Lassa virus has been identified in the anterior uvea and corneal endothelium of a guinea pig model [43].

Ebola virus disease and Marburg virus disease, both filoviruses, cause hemorrhagic fever associated with high fatality rate, and cause uveitis and cataracts, as described in much greater detail above. Marburg causes a hemorrhagic fever similar to EVD, though has far fewer documented cases. There is one case report of unilateral uveitis in a Marburg survivor, with a positive viral culture from anterior chamber fluid [44].

Rift Valley fever, a phlebovirus, causes a viral syndrome with varied manifestations, including ocular disease, meningoencephalitis, and hemorrhagic fever, associated with a fatality rate less than 1% [45]. The virus was identified in 1931, and since then has caused outbreaks throughout Africa and the Arabian Peninsula [45]. Macular exudates, hemorrhage, optic disc edema, and vasculitis have been reported in patients with acute Rift Valley fever, which in many patients results in severely decreased vision [46,47].

Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) are both coronaviruses, as is COVID-19, and have caused outbreaks of disease characterized by fever, cough, dyspnea, hypoxemia, and respiratory failure [48]. While conjunctivitis has been identified in COVID-19, it has not been described in SARS or MERS [49]. However, coronavirus was identified in the tear film of three human SARS patients [50], and in several MERS infected camels [51], raising important questions about proper barrier methods during ophthalmic exam and surgery.

Zika virus, a flavivirus, causes maculopapular rash, arthritis, and ocular manifestations including conjunctivitis and anterior uveitis [52], and more rarely, maculopathy [53] and posterior uveitis [54]. Congenital Zika Syndrome, linked to birth defects in infants exposed in utero to Zika virus, garnered worldwide attention in 2016 when high incidence of microcephaly was reported in Brazil. In addition to abnormalities including severe microcephaly, thin cerebral cortices, contractures, and hypertonia, Congenital Zika Syndrome was also characterized by ocular manifestations including chorioretinal scars and optic disc abnormalities [55]. Retinal vascular abnormalities, microphthalmia, iris coloboma, and lens subluxation have also been described [55].

Crimean-Congo hemorrhagic fever (CCHF) is a viral infection found in Africa, the Middle East, and Asia, transmitted by tick bite or exposure to infected humans or animals [56]. It was first described in 1944 in Crimea, and has a high fatality rate of 3–30%. Like other hemorrhagic fevers, CCHF is characterized by hemorrhage, myalgia and fever. In 2007, an outbreak of CCHF was documented in Sivas, Central Anatolia, Turkey. Ocular findings were observed in 14 (74%) of 19 confirmed CCHF patients and included subconjunctival hemorrhage and retinal hemorrhage. No evidence of uveitis, retinal edema, or retinal hemorrhage were observed [57].

Disease X represents a yet unidentified pathogen, or a pathogen unknown to cause human disease, that could cause a serious international epidemic. Public health authorities recognize that serious threats may emerge from unknown viruses, and retina and uveitis specialist play important roles in identifying conditions that may have serious health implications.

How can lessons learned from Ebola be applied to COVID-19?

Willingness to participate in clinical care in the setting of an infectious disease epidemic is multifactorial, and trust that appropriate precautions have created a safe environment will reassure patients, physicians and HCW personnel. With the spread of COVID-19, there has been a rapid change in clinical practice as physicians and patients to adapt to a new environment to reduce infection risk. While many of these ideas are supported by general knowledge of infectious disease transmission, rigorous study to understand the true prevalence of virus in tear film and viral transmission dynamics via respiratory secretions and mucous membranes are needed. Moreover, PPE guidance has shifted as the scientific body of knowledge has expanded and interruption of global supply chain has led to institutional differences in guidance. Expanded evidence basis for decision-making will build confidence for physicians and patients as we gradually expand ophthalmic care services during the COVID-19 pandemic.

One important outcome of COVID19 pandemic will be the establishment of protocols to address ophthalmic clinical care and surgery during times of infectious disease outbreak and global emergency. Delivering healthcare during such times has been studied in prior outbreaks. As health care institutions in the U.S. and globally implemented new protocols for patient screening, disinfection, and HCW monitoring for potential exposures during the West African EVD outbreak, novel workflows have been similarly instituted in clinic and surgical settings for COVID-19. Given that COVID-19 is omnipresent, systems within the busy ophthalmology clinic will be required to provide emergent and more routine care while appropriately protecting the provider and staff through PPE and equipment disinfection protocols, for symptomatic COVID-19 patients, asymptomatic and pre-symptomatic individuals. Conversely, systems will also need to be maintained to protect the patient from physician-patient transmission and patient-patient transmission.

Moreover, while COVID-19 pandemic is the primary concern presently, future outbreaks of other infectious diseases will undoubtedly occur, potentially related to pathogens listed as a WHO High Priority Disease. Hopefully, the attention given to COVID-19 will spur rigorous study of pandemic preparedness, which includes the development of systems of clinical care, research, and education while mitigating risk in the ophthalmology clinic and operating room. These preparedness measures will need to be tailored to COVID-19 for the present, yet flexible in anticipation of future emerging infectious disease outbreaks.

Conclusion

COVID-19 and EVD exemplify how rapidly outbreaks may emerge, disrupting health security with the cessation of routine ophthalmic care delivery. The intrusion of these novel infectious diseases requires an assessment of ophthalmic manifestations that may require clinical or surgical care, and in some cases, present risk to health care workers owing to virus within tear film or intraocular fluids. Providing ophthalmic care for patients with active infection may be challenging during pandemics given significant concern regarding infection risk between patients and healthcare workers. However, understanding the ophthalmic needs of patients, as well as how to safely provide clinical care, is a critical task that can be achieved through rigorous, protocol-driven study. The COVID-19 pandemic serves as an opportunity to address protocols in clinical and surgical ophthalmic setting, which will better prepare our field for future emerging infectious disease outbreaks.

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Key Points:

- COVID-19 and Ebola both emerged rapidly, disrupting health care delivery, which included routine ophthalmology practice.
- An important aspect of the disruption to routine clinical and surgical ophthalmic care was the immediate concern from both healthcare personnel and patients regarding infection risk due to asymptomatic transmission, personal protective equipment shortages, and lack of knowledge of viral reservoirs and transmission risk.
- Improved understanding of the ophthalmic manifestations of COVID-19 and potential for viral persistence in tear film and intraocular fluids are needed. This body of knowledge was gained about uveitis and Ebola virus persistence in ocular fluids during the Ebola outbreak.
- Rigorous study of how to safely provide ophthalmological care during infectious disease outbreaks is required to reassure healthcare workers and patients, as these health systems will inform our ability to care for patients during future emerging infectious disease outbreaks.