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An alternate prospect in detecting presymptomatic and asymptomatic COVID-19 carriers through odor differentiation by HeroRATs



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ABSTRACT

The need for a cheap, ubiquitous, sensitive, rapid, noninvasive means of screening large numbers of presymptomatic and asymptomatic samples at departure or arrival into ports of countries, high-risk areas, and within communities forms the subject of this review. The widely used diagnostic test for the SARS-CoV 2 is the real-time reverse transcription–polymerase chain reaction assay while antibody-based techniques are being introduced as supplemental tools, but the lack of specialized nucleic acid extraction and amplification laboratories hampers/slowly down timely large-scale testing. The use of animals with sensitive olfactory cue as an alternate testing model could serve as an alternative to detect COVID-19 in the saliva of carriers. The African giant rats are highly versatile and detect odorant molecules from carriers of pathogens with high percentage success after few months of training, hence can be taught to detect odor differences of COVID-19 in asymptomatic and presymptomatic individuals. If these are trained, they could help to curtail further spread of COVID infections.

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The COVID-19 pandemic response and challenges faced

The global research on the novel severe acute respiratory syndrome coronavirus 2 (nSARS-CoV 2) infectious disease, also called COVID-19, surges on. With over 26 million infected people worldwide and a mortality of more than 806 000 people, available evidence indicates that transmission is mostly through asymptomatic carriers who come in close contact with the populace. This informs the strength of the campaign promoting physical distancing and use of masks (WHO, 2020). Presently, comprehensive studies on transmission from asymptomatic patients are difficult to conduct, as they require testing of large population cohorts and need more data to better understand and quantify the transmissibility of SARS-CoV-2 (Zhao et al., 2020). Usually, at entry ports and high-risk areas, possible carriers are screened using only infrared thermal screening. Studies have, however, shown that body temperature

screening will not detect over 50% of SARS-CoV 2 carriers (Gostic et al., 2020). In which case, many go undetected even with scanners because infected individuals may be presymptomatic or do not have a fever at the time of scanning (FengYe et al., 2020). The need for a cheap, ubiquitous, sensitive, rapid, noninvasive means of screening large numbers of presymptomatic or asymptomatic people/samples both at departure and arrival ports of countries or high-risk areas forms the subject of this review.

The need for extensive testing in the war against this invisible enemy cannot be overstated (Di Bari et al., 2020). Over 6 million people are currently infected in the United States of America and parts of Europe, the data being a result of their extensive COVID-19 testing in those countries as against several other countries with low testing capacity and poor data (CDC, 2020). It is obvious that the infrastructures that comply completely with World Health Organization guidelines to detect and report SARS-CoV-2 infection (COVID-19) are lacking across many parts of the globe (Giri and Diyya, 2020). This is because of low domestic capacity for manufacturing diagnostic test kits and heavy dependence on imports from manufacturers that are exporting their products to economically powerful nations (Peplow, 2020).

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Current state of testing for COVID-19

The current “gold standard” scientific technique most widely used to diagnose the SARS-CoV 2 is the real-time reverse transcription–polymerase chain reaction assay while antibody-based techniques are being introduced as supplemental tools (Tang et al., 2020). In addition, quantitative real-time reverse transcription–polymerase chain reaction assay is used with a new automatic nucleic acid detection system (Yuchang et al., 2020). The insufficient amount of specialized nucleic acid extraction and amplification laboratories in several institutions has hampered testing (Jin et al., 2020). Other biomedical techniques in use include the loop-mediated isothermal amplification, lateral flow handheld single-use assays that provide results in less than 20 minutes, and enzyme-linked immunosorbent assay. The aforementioned are also combined at different times for patient management and population pandemic control of COVID-19, although they are at different stages of development, validation, and production and have shown advantages and disadvantages (Green et al., 2020).

Although biomedical assay techniques have shown significant levels of result, the major obstacle is accessibility to the equipment, economic cost of reagents, and availability of sufficient technical personnel (Peplow, 2020). Very few laboratories handle samples in developing countries with limited resources based on their population, and these numbers are far worse in low-income countries. This poses a significant challenge when attempting to create a method and optimize parameters for any analytical technique. More often than none, these nations resort to the use of infrared scanners to check for temperature spike to distinguish or determine who may need isolation and/or testing (Gostic et al., 2020). With the added disadvantage that only symptomatic carriers are tested, the equation of COVID-19 through asymptomatic carriers stands as a great risk to flattening the curve. The COVID-19 outbreak, therefore, has had a major impact on clinical microbiology laboratories in the past several months ranging from infrastructural deficit, challenges with collection of proper respiratory tract specimen at the right time from the right anatomic site to its molecular diagnosis (Tang et al., 2020). These gaps have therefore necessitated, as a matter of urgency, the development of alternate detection mechanisms that can detect infected persons or samples for quick identification, isolation, treatment, and overall control of disease spread.

An alternative for current testing paradigms

An alternate testing model for COVID-19 is the use of animals with extremely sensitive olfactory systems to detect persons or samples with COVID-19 (Gostic et al., 2020). It is already a growing body of knowledge that such animals can sniff out different disease conditions in humans such as cancers, tuberculosis, and malaria (Moser and McCulloch, 2010; Robinson et al., 2018; Guest et al., 2019). These innovative testing methods have been performed with animals, rodents, insects, and electronic noses (Suckling and Saga, 2011). The search for alternative testing methods has occasioned a lot of thinking out of the box as researchers are beginning to show dogs can now detect the SARS-CoV-2 in asymptomatic carriers after successful training, using changes in odors. Dogs were able to discriminate between samples of infected and noninfected individuals with average diagnostic sensitivity of 82.63% and specificity of 96.35% (Jendry, 2020). Respiratory infections typically cause the release of specific odors in breath, urine, feces, and sweat. More so, microbial infectious diseases facilitate the production of disease-specific volatile organic compounds (Shirasu and Touhara, 2011). These volatile compounds are now the subject of investigations to identify biomarkers of infectious diseases such as cholera (Sethi, 2013).

The African giant rats (AGRs; *Cricetomys gambianus*, Waterhouse) belong to the family Cricetidae and the order Rodentia. These nocturnal omnivores are fairly tame and docile; hence, they are used as pets in some places (Cooper, 2008). The AGRs also have remarkable vision in the dark and a keen sense of olfaction (Olude et al., 2013). Reports have it that they sniff out specific odorant molecules from buried landmines and positive tuberculosis sputum samples after training (Weetjens et al., 2009; Olude et al., 2013). This makes the AGR, which is widespread in sub-Saharan Africa, a highly versatile animal (van der Straeten et al., 2008). The AGR has large olfactory bulbs and extensive olfactory glomerular layer organization as well as developed cognitive abilities (Ibe et al., 2014). The AGR detects odorant molecules with high percentage success after few months of training (Olude et al., 2013; Ibe et al., 2014). Specially trained AGRs, nicknamed HeroRATs, have been used as detectors of pulmonary tuberculosis on people living in Tanzania and Mozambique using sputum samples collected from patients with presumptive tuberculosis by a Belgian nongovernmental research organization—Anti-Persoonsmijnen Ontmijnende Product Ontwikkeling (APOPO) in Tanzania (Poling, 2010 a; Poling, 2010 b). It takes about 9 months to train HeroRATs after weaning. Their training involves social habituation with human sounds and smells. AGRs are taught to positively identify samples and associate with rewards. Odor differentiation is taught by the introduction of negative samples that have no clicks and eventually, the sample size is increased and varied. On attainment of high accuracy, these rats are accredited and deployed as HeroRATs in laboratories or on the fields (Beyene et al., 2012). While studies are ongoing on the neural basis of olfactory acuity in this rodent, this natural ability of the AGR has facilitated their choice and success as biodetectors of land mines and detectors of human diseases such as tuberculosis (Verhagen, et al., 2003; Freeman et al., 2019; Freeman and Ophir, 2018). After the gradual and phased reopening of global economies in the face of a raging pandemic and because of the need to prevent a huge rise in the number of COVID-19 infections, it is necessary to put measures in place to prevent the importation of new cases from countries with a high disease burden of COVID-19. Countries have come up with different mechanisms to curb the spread, such as mandating in bound travelers to strictly adhere to center for disease control guidelines and self-isolate in specific quarantine centers or mandatorily stay at home for 14 days after arrival.

Identification of presymptomatic and asymptomatic carriers of COVID-19 using AGRs?

To consolidate on the success achieved in the fight against the pandemic, it is important to support conventional laboratory testing with safe, fast, affordable, and ingenious mechanisms for testing especially at the ports of entry. Collaborations that would support scientists to work with highly sensitive indigenous species like the AGR can boost local testing capacity. Just like dogs, trained AGRs would identify samples such as saliva/sputum or sweat obtained by wiping people's neck with cotton pieces to detect the SARS-CoV-2 infection. The profit potential from this venture is not only lifesaving but has the possibility of increasing their income through diversification of their husbandry in a controlled manner and ultimately boosts their economy during and after pandemic. As a result of the rapid diagnostic speed and low variable costs of detection rats, this technology could be particularly well suited to screening the large numbers of commuters coming through ports of entry or departure and densely populated areas because the sheer population is a significant doorway to community or international transmission of COVID-19. Innovative and affordable approaches, such as COVID-19 detection rats, could offer high sample throughput and be a solution to tackle the spread of this pandemic.

Trained AGRs could become a strong arrow in the fight against disease when deployed to detect much of the diseases that ravage many of these countries within Africa from time to time.

Challenges

The biggest challenge to the utilization of African species such as the AGR is the lack of training centers with capacity for handling viral-positive samples in accordance with World Health Organization standards. APOPO has a training center in Morogoro, Tanzania, and this can be developed as a prototype for African regional centers for AGR training. Closely related to this is the lack of awareness and finances and absence of national policies and strategic programs to develop and use the AGR as a biomedical resource (Olude et al., 2013). Knowing that the African fauna is home to an abundance of unique species, poachers are constantly after these species in the wild, but this can be controlled by regulations as this awareness grows (Mustapha, 2019). Another challenge that may be faced with the use of the AGR in the spread of this pandemic would be lack of research studies that meet international ethical standards and the posture of some countries to the species because it is an invasive species and its importation banned (Conlon, 2008).

The way forward

Elimination of highly infectious diseases such as the COVID 19 in resource-poor nations requires multipronged, innovative, affordable, sustainable as well as safe solutions, such as early disease detection—trained AGRs especially because they are noninvasive, fast, and used in combination with laboratory solutions. It is recommended that scientific studies that offer alternative or adjunct solution to the problem of testing especially among asymptomatic carriers of SARS-CoV-2 should be supported.

Conclusion

As the SARS CoV 2 continues to rage, it is necessary to think outside the box especially when funding for testing is pushing back the end date of the pandemic. A great deal of joint collaborative efforts is still needed to curtail its spread. The deployment of trained AGRs to large communal gatherings could change the course of community infections as societies begin to open up. However, successful deployment of AGRs in testing will require proper training and validation from time to time. We believe that studies on animal species such as the AGR which can be useful in detecting presymptomatic and asymptomatic carriers at ports of entry and departure as well as within the local communities to support their current COVID-19 could contribute to the pandemic response.

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Adejoke Joan Adekanmbi conceived the study. Adejoke Joan Adekanmbi and Matthew Ayokunle Olude contributed to the review and analyzed, wrote, and edited the manuscript. Both authors approved the final version of the manuscript.

Ethical considerations

The compliance with regulations on the ethical treatment of animals is supported.

Conflict of interest

The authors declare no conflict of interest.

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