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Comparison Of SARS-CoV-2 To SARS-CoV, MERS, And Influenza A: A Systematic Review

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Abstract

Differences and similarities are examined among SARS-CoV-2, SARS-CoV-1, MERS and influenza A, in the context of transmissibility. Characteristics specific to the respective pathogens prove invaluable as they set the stage for intervention and management. SARS-CoV-2 bears similarities to other recently emerged infectious diseases in basic virologic ways, yet is distinctly different in terms of viral transmission dynamics. These differences arise from genomic qualities and properties specific to the virus. As ACE2 receptors are determinants for attachment and spread of the virus, and their role throughout tissues in the body is vast, an understanding of organ-level pathogenesis of SARS-CoV-2 is crucial to effectively treat and (hopefully) neutralize SARS-CoV-2. Certain populations are identified as higher risk populations for severity of illness due to factors including age, gender and obesity. Therapies and treatments (including social responsibility behaviors) are described in current practice.

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Introduction

A virus is not merely characterized by its genetic makeup, but also by its ability to infect, and the subsequent effects it has on respective host organisms. Transmissibility and symptomology vary among viral families in susceptibility of species affected, and severity of ensuing disease. An example of such can be seen in the onslaught of the recent novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); which has medical and scientific communities alike scrambling to accurately characterize and efficaciously treat this highly pathogenic organism. Understanding how this pandemic causing virus is alike or different from previously identified viruses is highly important for treatment and containment. As such, prior outbreaks of markedly contagious respiratory viruses, bearing similarities merit examination. Therapy and response to the SARS-CoV-2 pandemic is augmented by considering and comparing the fundamental characteristics of SARS-CoV-2 with SARS-CoV, MERS and influenza viruses.

Background and Significance

Viruses are responsible for multiple infectious processes, ranging from the common cold, to more severe illnesses like the flu (influenza A and B), middle east respiratory syndrome (MERS), severe acute respiratory syndrome (SARS or SARS-CoV), and of recent, COVID-19; caused by SARS-CoV-2 (CDC, 2020a). The genera that are responsible for the common cold are attributed to the alpha and beta coronavirus lineage, solely found in mammals (Biao et al., 2014). From the beta coronavirus lineage, MERS, SARS-CoV and SARS-CoV-2 arise (Lu et al., 2020). Considered extremely contagious and potentially pernicious diseases, these viruses are zoonotic in origin (passed from animal to human) (Hui & Peiris, 2019), yet are transmissible as human to

human infections. Natural sources of these viruses were originally detected in dromedary camels (MERS), bats (MERS, SARS-CoV and SARS-CoV-2) (Lu et al., 2020), migratory birds, and pigs (novel influenza A) (Weber et al., 2016). Understanding the route by which a pathogen becomes viable in humans is but part of the task to contain and control an outbreak. A diseases' transmissibility is also defined by the virus's phylogeny, capacity (entry, replication, and virulence), transmission dynamics (type, contact and proximity), symptomology of the affected population, and stopgap therapies (screening, containment and human behaviors).

Knowledge of virus origination is necessary in the control of transmission (Ypma, van Ballegooijen, & Wallinga, 2013). Insight into viral evolution within a species enables inference of genomic morphisms, or reassortment events; as well as tracing ancestral lineage. Known as phylogenetic analysis, certain alterations are determined as likely given a species. Adjunctly, transmission modeling yields forecasting and epidemiologic surveillance. Models employing the recording of transmission events among infected hosts (transmission trees), and concurrent phylogenetic tree analysis (hereditary changes and traits), suggest conclusions about the organism and its host (Ypma et al., 2013). Such analyses are useful in the research of coronaviruses and influenza pathogens (Lei & Shi, 2011; Lu et al., 2020; Nelson & Worobey, 2018). Phylogenetic findings indicate the infected animal sold in the Wuhan market was an intermediate or connecting link, facilitating the animal to human transmission (Chan et al., 2020; Lu et al., 2020; Weber et al., 2020). The idea of an intermediate host, is also considered the case in SARS-CoV (Lu et al., 2020; Schnieder, 2012), MERS (van Doremalen et al., 2014) and several strains of human influenza A (Lei & Shi, 2011; Zhao et al., 2019).

The capacity of a virus is apparent in its ability to attach, enter, and replicate; and in its virulence. For successful fusion and entry of target cells, influenza A viruses (FLUAVs), rely on

the binding properties of the glycoprotein hemagglutinin (HA); while SARS-CoV-1, SARS-CoV-2, and MERS rely on the spike (S) surface proteins (Lu et al., 2020; Zmora et al., 2014). Facilitated via phylogenetic analysis, researchers determined the receptor-binding domain (RBD) of SARS-CoV-2 as comparable to that of SARS-CoV-1 (Lu et al., 2020). Once these viruses enter the body, they locate target cells expressing select receptors to which they attach and bind. After fusion, and for the given virus to enter the host cell, activation of the HA (FLUAV), or S (coronavirus) proteins must occur. Activation occurs when HA and S proteins respectively, are cleaved by proteolytic enzymes known as proteases, found on the host cells (Lu et al., 2020; Zmora et al., 2014). Serving as such a determinant, the enzyme TMPRSS2, activates and facilitates entry for several subtypes of the influenza A virus, as well as coronaviruses (Bourgonje et al., 2020; Zmora et al., 2014). Once inside the host cell, all the necessary machinery is at the disposal of the virus for replication. The virus exploits the translation apparatus of the host cell to produce the necessary structural and non-structural proteins necessary for sabotage. These proteins equip the virus for evasion of innate immune system cells, and induce harmful effects detrimental to appropriate cellular response and functioning (Astuti & Ysrafil, 2020; Wang et al., 2020).

The dynamics for transmission of these viruses is somewhat variable. The MERS outbreak in 2012, was spread by droplet and contact transmission, with the highest number of cases noted among health care workers. The lower respiratory tract was notably affected by MERS; and demonstrated significantly higher viral loads on culture and analysis than the upper respiratory tract (Bradley & Bryan, 2019; Corman et al., 2016; NCIRD, 2019). The case fatality rate (CFR) of MERS was reported at 35%, with a low probability of manifestation in children (Bradley & Bryan, 2019).

SARS-CoV-1 was spread by droplet, contact, and airborne (or aerosol) processes; replication was most pronounced in the lower respiratory tract (Chan et al., 2020) as well. In the case of both SARS-CoV-1 and MERS, a higher viral load was consistent *with* symptom presentation; with a mean peak of viral load 7-10 days after the onset of illness (To et al., 2020). Reported CFR of SARS-CoV-1 was 9.6 - 11%; and similar to MERS, children were not often affected (Bradley & Bryan, 2019; Weber et al., 2015).

Viral shedding for MERS and SARS-CoV-1 was described in tracheal, nasopharyngeal, and nasal swabs; and stool and urine samples (Corman et al., 2016; Bradley & Bryan, 2019). The persistence of the viral fragments in feces suggested oral-fecal potential for contact infectivity (Bradley & Bryan, 2019; Ong et al., 2020). While the amount of time respective viruses are viable varies, based on both the ambient and physical environment (temperature, relative humidity, surface type, and relative air flow), coronaviruses potentially maintain high-levels of infectivity (Lei et al., 2018; Ong et al., 2020; van Doremalen et al., 2020).

SARS-CoV-2 is primarily transmitted through respiratory droplets (Guan et al., 2020); though it also spreads via contact and airborne (or aerosol) modalities. In contrast to MERS and SARS-CoV-1, SARS-CoV-2 replicates most abundantly in the upper respiratory tract (To, et al., 2020; Zou, Guan et al., 2020).

To et al. (2020), theorized that as a result of both high viral thresholds (early in the disease onset) and the estimated high percentage of asymptomatic shedders, SARS-CoV-2 has spread much quicker than either the MERS or SARS-CoV-1 viruses. Another compounding factor is that testing is often inadequate, unavailable or numbers are under-reported (Li et al., 2020). To demonstrate the ease and speed by which SARS-CoV-2 has spread, at the time of initial writing of this paper, June 2, 2020, the CFR was 5.9% globally (377,460 deaths/6,325,303

confirmed cases), and 5.8% in the United States (105,644 deaths/1,820,523 confirmed cases) (JHU CSSE, 2020). A mere 7 weeks later, July 21, 2020, the CFR is 4.1% globally (618,994 deaths/15,033,861 confirmed cases), with the number deaths up 64%, and confirmed cases almost 2.4 times higher. The United States CFR dropped to 3.6% (142,595 deaths/3,935,211 confirmed cases), with the number of the number of deaths up 35%, and confirmed cases almost 2.2 times higher (JHU CSSE, 2020).

Symptoms vary widely among confirmed cases, with severity of symptoms and poor outcome increasing in a directly proportional nature to increased age (over 65) and number of comorbidities. However, the disease is also indiscriminate, afflicting all age groups and minorities (although less frequently found in children under 18 years of age) (CDC, 2020b, CDC, 2020c).

Influenza A is transmitted primarily through inhalation and contact (Hui & Peiris, 2019; Lei et al., 2018; Weber et al., 2016), and has a CFR in the U.S. of about 0.1% annually. Influenza replicates predominantly within the lower respiratory tract similar to SARS-CoV-1 and MERS (Bradley & Bryan, 2019). Populations hardest hit are those over the age of 65, and those least severely affected are represented in the 5-17-years age group (CDC, 2020a).

As SARS-CoV-2 and influenza A exhibit likeness in nature symptomatically, differentiation for diagnosis without further diagnostics is challenging. In SARS-CoV-2 as is the case in influenza, fever, generalized malaise or fatigue, and cough or pharyngeal pain are common manifestations (Wang et al., 2020). However, as was reported by Guan et al. (2020), only 44% of those patients presenting (positive for COVID-19), had a fever with initial clinical evaluation. As SARS-CoV-2 patients often express the disease in varying degrees of severity, while difficult, an accurate diagnosis is extremely important. Therefore, CT scans are considered

of significant value for additional information and differentiation (Guan et al., 2020; To et al., 2020; Wang et al., 2020).

While identification, containment and supportive care are necessary early triage measures, long-term community health controls are imperative (Bourgonje et al., 2020; NCIRD, 2020a), for sustained public health (NCIRD, 2020b). For the community at large, and researchers in particular, a fundamental understanding of viral origin and transmission play an integral part in treatment and prevention. Scientists employ foundational knowledge and domain expertise of the viruses, their structure, function, and activity, in their iterations of prophylactic treatments.

This review examines the question of how the SARS-CoV-2 contagion differs fundamentally in transmissibility, symptomology and characteristics from SARS-CoV, MERS and the influenza viruses based on existing literature to date.

Methods

Literature Search

Relevant literature was searched via the following databases: Academic Search Complete (ASC), Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and Scopus, for the period between January 2010, to June 2020. Keywords used to retrieve the articles included: ‘coronavirus’ OR ‘COVID-19’ OR ‘2019-nCoV’ OR ‘SARS-CoV-2’, AND ‘SARS’ OR ‘Severe Acute Respiratory Syndrome’, AND ‘MERS’ OR ‘Middle East Respiratory Syndrome’, AND ‘influenza’ OR ‘flu virus’ OR ‘influenza A’, AND ‘transmission’ OR ‘transmissibility’ OR ‘spread’. Results were imported into RefWorks where titles were perused and duplicate entries were removed via the software tools. See Appendix A, Figure 1 for preferred reporting items for systematic review diagram (Moher et al., 2009).

Exclusion and Inclusion Criteria

Specifications on searches were designed to return peer-reviewed, published, English language, full-text records, including journal articles or books. Of the records returned, titles and abstracts were examined to determine applicability to the research question. Non-pertinent articles were removed. Several literature and systematic reviews were returned in the original search. These were examined to identify potential relevant gray literature, and two reviews were included for terminology explanation (Astuti & Ysrafil, 2020; Hui & Peiris, 2019). Of the records extracted, likeness and differences among MERS, SARS-CoV-1, SARS-CoV-2, and influenza were evaluated. Characteristics of interest included: origin, structure, function, transmission dynamics (cellular and human to human transmission), symptomology, virulence of the pathogen, and persistent viability of the virus(es) outside the body.

Meta-analysis

There is some overlap in use of the manuscripts for the topics of interest. Of the manuscripts examined, three evaluated origin, lineage, and relevance of genome analysis in the explanation of viral transmission (Biao et al., 2014; Lu et al., 2020; Ypma et al., 2013). Seven studies assessed zoonotic commonalities of the diseases, and corresponding intermediate hosts (Lei & Shi, 2011; Morse, 2012; Nelson & Worobey, 2018; Schnieder, 2012; van Doremalen et al., 2014; Weber et al., 2020; Zhao et al., 2019). Five manuscripts analyzed viral tropism, the ability of the virus to infect certain cells based on the type of cell/tissue and expression of select necessary receptors (Bourgonje et al., 2020; Hui et al., 2020; Lu et al., 2020; Tai et al., 2020; Zmora et al., 2014). The processes of viral infectivity and pathogenesis were described in six studies (Bourgonje et al., 2020; Bradley & Bryan, 2019; Corman et al., 2014, Ding et al., 2004; Li et al., 2020; Sanche et al., 2020; Wang et al., 2020). The structure and function of viruses is explained in an overview by Astuti & Ysrafil (2020). Eight articles reported findings relative to

degree of infectivity, as determined by viral load, viral shedding and body fluids (Chan et al., 2020; Corman et al., 2020; Du et al., 2020; Hui et al., 2020; Schnieder, 2012; To et al., 2020; Watson, Whiting, & Brush, 2020; Zou et al., 2020). Six studies discussed immune response and patient symptomology (Bourgonje et al., 2020; Bradley & Bryan, 2019; Guan et al., 2020; Schnieder, 2012; Wang et al., 2020; Watson et al., 2020). Viral persistence and relative stability in external environments were assayed by researchers in four studies (Chan et al., 2020; Lei et al., 2020; Ong et al., 2020; van Doremalen et al., 2020). And finally, therapy and treatments to date were outlined in seven studies (Du et al., 2020; Hui & Peiris, 2019; Ong et al., 2020; Schnieder, 2012; Tai et al., 2020; van Doremalen et al., 2014; Zmora et al., 2014).

Of the studies selected, fifteen occurred in China (Du et al., 2020; Hui et al., 2020; Hui & Peiris, 2019; Guan et al., 2020; Lu et al., 2020; Ong et al., 2020; To et al., 2020; Wang et al., 2020; Zhao et al., 2019; Zou et al., 2020); with all but five occurring from December 2019 – February 2020 (Biao et al., 2011; Chan et al., 2011; Ding et al., 2004; Lei & Shi, 2011; Lei et al., 2018). Two studies originated from The Netherlands (Bourgonje et al., 2020; Ypma et al., 2013); one from Germany (Zmora et al., 2014); seven were from the United States (Bradley & Bryan, 2019; Nelson & Worobey, 2018; Sanche et al., 2020; Schnieder, 2012; van Doremalen et al., 2014; van Doremalen et al., 2020; Weber et al., 2020); one from Saudi Arabia (Corman et al., 2014); one from Indonesia (Astuti & Ysrafil, 2020); the other four were collaborations among the U.S., China, Switzerland, and the UK, or a combination therein (Li et al., 2020; Morse et al., 2012; Tai et al., 2020; Watson et al., 2020).

Results

The following section describes the results in a theme based, sequential fashion designed to orient the reader to the system of transmission. This includes: a limited description of origin

and evolution, capacity, transmission dynamics, affected population symptomology and current/evolving interventions and therapies.

Origin, Lineage, Genome Analysis and Phylogenesis

In the recent SARS-CoV-2 outbreak, scientists analyzed genome sequencing of viral samples obtained from an infected population segment known to have attended the Hunan market in Wuhan, to delineate ancestral history of the coronavirus genomes (Lu et al., 2020). Phylogenetic modeling of the viral samples enabled scientists to gain insight into the sequence evolutionary order, thus facilitating source determination (Guan et al., 2020; Lu et al., 2020; Ypma et al., 2013). Their findings indicated closely related genome sequences to coronaviruses found in bats – reportedly, 88% identical (Chan et al., 2020; Lu et al., 2020). The genome sequences, while similar, were noted to be less alike SARS-CoV-1 and MERS-CoV (corresponding 79% and 50%, respectively) (Lu et al., 2020). Patient cohort viral samples whole-genome sequenced in another study supported ancestral findings; while informing researchers of possible mutations occurring amid infection. Evaluation of the cluster revealed no polymorphisms in 21% (4 of 19) of patients evaluated (To et al., 2020). Phylogenetic analysis has also been instrumental in mapping the spread and transmission of H5N1 influenza; propagated by wild birds and their migratory patterns (Lei & Shi, 2011).

Zoonosis and Intermediate Hosts

The emergence of diseases not previously seen in humans is attributed to various explanations. Natural dwellings for wildlife face continual disruption as community expansion progresses and populations grow; the increased propensity of people to travel and ability to access remote areas; a higher possibility of interaction between wild animals and humans; and disruption of predator/prey balance leaving populations more susceptible to exposure (Karesh et

al., 2012; Morse et al., 2012; Weber et al., 2016)). Noteworthy, only a marginal percentage of the COVID-19 positive patients reported direct contact with wildlife (Guan et al., 2020). Similar findings were noted in regard to contraction of MERS and camels (van Doremalen et al., 2014). In the case of the SARS-CoV-1outbreak, antibody levels assayed were found to be slightly elevated in wildlife traders (Schnieder, 2012).

In regard to SARS-CoV-2, scientists asserted several aspects for consideration. While bats have been implicated as the natural reservoir species for SARS-CoV-1 (Biao et al., 2014; Schnieder, 2012); MERS (Hui & Peris, 2019; van Doremalen et al., 2014), and SARS-CoV-2 (Lu et al., 2020), certain factors suggest an intermediate host played an integral part in the transmission to humans (Biao et al., 2014). The viral S protein, responsible for receptor binding to the ACE2 was analyzed as dissimilar enough that direct infection from bats to human was not supported (Biao et al., 2014). Also, at the seafood market where the SARS-CoV-2 outbreak was determined to originate, bats were not present. Winter, the season when COVID-19 cases were first reported, coincided with bats' hibernation cycle (Lu et al., 2020). The mammals at the market included known carriers of prior SARS-CoV-1 disease (masked palm civet), (Biao et al., 2014); and the genomic similarity, while assessed as close (88% identical), was dissimilar enough to disqualify bats as a preliminary infector of humans (Lu et al., 2020). Palm civets however, when genomically sequenced, showed 99.8% likeness to the SARS-CoV-1 human genome (Biao et al., 2014), and thus inferred them as the animal source.

Determination of a MERS intermediate host prompted researchers to investigate food source origins (van Doremalen et al., 2014). Contamination of un-pasteurized dairy products (camel, goat or cow milk) was postulated as a potential link in this contagion's outbreak, as un-pasteurized products were known to be regularly consumed by people of the Arabian Peninsula

(van Doremalen et al., 2014). It remains unknown if the virus can be excreted into the milk, or if consumption of contaminated milk results in infection. However, MERS was shown to survive in un-pasteurized milk for considerable periods of time. Furthermore, pasteurization was shown to eliminate the infectious virus (van Doremalen, et al., 2014).

For many years, influenza researchers considered pigs as applicable "mixing vessels", and intermediate hosts for various infectious avian flu strains in humans; highly due to receptors, associated linkages, and purported recombinant changes (Lei & Shi, 2011; Nelson & Worobey, 2018). With exception of the 2009 H1N1 pandemic, this compelling theory is not conclusively supported. In the 2009 H1N1 pandemic, swine to human transmission was deduced as a result of retained circulating genomic fragments from previous avian-hosted viral infections, engaging with other viruses in reassortment events; thus, creating a new strain (Nelson & Worobey, 2018). What is intriguing, is the opposite directionally (human-swine transmission), and variability of lineage has been conferred (Nelson & Worobey, 2018). Evidence indicates humans are more consequential to swine, than swine are to humans (and swine are not likely avian intermediates for most influenza strains that infect humans). Furthermore, swine-human infections are limited, and not promotive of persistent human-human transmission (Nelson & Worobey, 2018). Riverside and semi-aquatic mammals like minks, are also theorized to serve as potential mixing vessels, and contributory reservoirs for flu viruses. In the presence of other viral co-infections, it is thought, that viral genesis via reassortment events is possible subsequently facilitating interspecies transmission (Zhao et al., 2019).

Viral Tropism

In the case of SARS-CoV, MERS, SARS-CoV-2 and influenza viruses, productive infection of cells is highly receptor dependent. ACE2 receptors, expressed in varying degree of

numbers throughout tissues in the body (Astuti & Ysrafil, 2020; Bourgonje et al., 2020), are determinant receptors for SARS-CoV-1, MERS (Zmora et al., 2014), and SARS-CoV-2 (Bourgonje et al., 2020; Hui et al., 2020; Tai et al., 2020). SARS-CoV-1 and SARS-CoV-2 secure attachment to ACE2 receptors via binding with the RBD of spike (S) surface proteins. Exploitation of molecular structure and properties is used as researchers design vaccines that function as inhibitors of viral attachment (Astuti & Ysrafil, 2020; Tai et al., 2020). For viral activation, post cellular adherence, specific serine proteases (TMPSSR2 among others described), (Zmora et al., 2014), cleave S proteins which in turn trigger morphological adaption of the virus and subsequent entry into the target cell (Astuti & Ysrafil, 2020; Bourgonje et al., 2020; Lu et al., 2020; Zmora et al., 2014). In the case of influenza A viruses, binding of hemagglutinin (HA) protein depends on sialic acid expression on target cells (Lei & Shi, 2011; Nelson & Worobey, 2018); while activation and cleavage rely on the proteolysis mechanism as described above (Zmora et al., 2014). In order to take advantage of this mechanism, protease inhibitor drugs are designed pharmacodynamically to both decrease severity and improve outcome (Bourgonje et al., 2020; Hui & Peris, 2019) by blocking the actions of the proteases.

Transmission Dynamics

Transmission dynamics, how the virus is spread human to human, rely heavily on the mechanism of release, host susceptibility and requisite receptors. Specifically, host attributes like viral load (the concentration of pathogens in a body fluid) and viral shedding, influence and potentiate transmission.

Viral infectivity and pathogenesis. Cellular pathogenesis of SARS-CoV-2 and SARS-CoV-1 depend on tissue type, and degree of ACE2 receptor regulation (Astuti & Ysrafil, 2020; Bourgonje et al., 2020). ACE2 receptor expression is highly prevalent throughout the body, yet

not all organs suffer the same degree of injury. Initial infection occurs predominantly via mucous membranes of the nose and mouth, and conjunctiva of the eyes (Bourgonje et al., 2020; Hui et al., 2020). These portals offer direct access to the upper and lower respiratory tract. The lining of the bronchus and alveoli are rich with epithelial cells, where ACE2 receptors are profusely expressed; providing ample opportunity for infection to seed. From there, access to the bloodstream by way of the capillary beds perfusing the alveoli of the lungs, is but a short trip; and the infection then spreads systemically to other organs (Astuti & Ysrafil, 2020; Bourgonje et al., 2020). Interestingly, influenza A infection has been shown to result in an upregulation (increase in surface cell receptor expression) of ACE2 receptors, in cells such as those in alveolar epithelium. As a result, subsequent infection with SARS-CoV-2 might result in a potentiated adverse outcome and greater infectivity (Hui et al., 2020). The GI tract is thought to be vulnerable by way of the oral cavity directly, or oral/fecal route (Bourgonje et al., 2020; Hui et al., 2020; Ong et al., 2020; Schnieder, 2012).

Most notably affected, are cells of the upper and lower respiratory tract, heart, kidneys, bladder, biliary tract, ileum and colon (Astuti & Ysrafil, 2020; Bourgonje et al., 2020; Hui et al., 2020). This is consistent with the symptomology manifested by patients and discussed later. The pathogenesis of SARS-CoV-2 in adipose tissue is also thought to largely contribute to the systemic inflammatory response that plagues many patients and ultimately confers a degree of severity. ACE2 receptors are amply found in visceral fat (fat located in the intra-abdominal cavity), and consistent with obesity. Found within these adipocytes are adipokines, essential regulators in a system of pathways important to metabolism and proper organ functioning (Bourgonje et al., 2020; Kwon & Pessin, 2013). In obesity, pro-inflammatory expression of adipokines (specifically leptin) is increased, which results in metabolic and endocrine

imbalances, and augmented inflammatory response (Kwon & Pessin, 2013). Of patients reported to experience more severe disease, and in need of ICU admission, or who ultimately died, BMI was found to be > 25kg/m^2 (cited in text of Peng et al., 2020 by Bourgonje et al., 2020).

Relative infectivity of a virus; viral load, shedding (body fluids). Knowledge of optimal tissue implantation by the virus in propagation, reveals the intensity, and in part, how the virus is shed (Hui et al., 2020). Shedding of the virus corresponds to the time in which patients are considered infectious. Viral loads in MERS were serologically detectable 1 week after the initial onset of symptoms. SARS-CoV-1 had like findings, with 79% of cases positive for viremia one week out; and 50% positive 2 weeks out (Corman et al., 2014). Neither MERS nor SARS-CoV-1 were thought to be transmitted by the blood, as MERS virus could not be isolated from the serum, and only very low levels of replicating virus were found in SARS-CoV-1 patient blood samples (Corman et al., 2014). Interestingly, neutralizing antibodies were documented in the presence of viremia in MERS, indicating the mounted antibody response was inadequate to overcome the infection. While most patients seroconverted in the first 1-2 weeks with MERS, upwards of 45% of fatal cases, reported in one study, lacked an antibody response (Corman et al., 2014). Viral load shedding peak for SARS-CoV-1 and MERS was determined at 10-12 days post initial symptoms (Corman et al., 2014; Hui & Peris, 2020; Schnieder, 2012). In contrast, SARS-CoV-2 viral shedding measured highest (in upper respiratory tract specimens) within the first week post-symptom onset, decreasing thereafter (To et al., 2020; Zou, Ruan & Huang, 2020).

Researchers also determined, that the viral loads of patients with SARS-CoV-2 who were asymptomatic, were analogous to the viral loads measured in those who were symptomatic (Zou et al., 2020). The viral load profile is similar to that of influenza, which also peaks close to onset

of symptoms (To et al., 2020; Zou et al., 2020). While viral peak load and age were shown to be positively correlated (To et al., 2020), viral load was not correlated with severity of the disease reported for either MERS or SARS-CoV-2 (Corman et al., 2014; To et al., 2020). However, disease severity was shown to be more pronounced for older patients (Bourgonje et el., 2020; Guan et al., 2020). High viral loads lacking severity is supported by the high degree of asymptomatic and mildly symptomatic SARS-CoV-2 patients considered highly contagious early in the disease process (Zou et al., 2020). Additionally, prolonged shedding in SARS-CoV-2 has been documented up to 20 days post-onset of illness (To et al., 2020).

Replication competence of SARS-CoV-2 is reported as analogous to MERS, while replicating more profusely than SARS-CoV-1 in the epithelium of the bronchus and the conducting airways (Hui et al., 2020), but similarly in the alveolar epithelium as SARS-CoV-1. One study indicated SARS-CoV-2, SARS-CoV, H1N1 and H5N1 demonstrated similar replication competence in colorectal cells, yet lower replication competence than MERS (Hui et al., 2020); conversely, reported findings of Corman et al. (2014); recorded a smaller percentage of patients with positive MERS RNA in stool samples, than those patients having stool samples positive for SARS-CoV-1. SARS-CoV-1 was also isolated in sweat glands, but findings were non-conclusive as to whether sweat itself was an applicable mode of transmission (Ding et al., 2004).

The reproduction number of these diseases (R_0), refers to degree of infectivity of an infected individual has, or will have, during the period in which they are actively contagious. This metric can vary considerably early in the contagion, and prior to active contact tracing of infectors; but is imperative in modeling and for implementation of interventions (Du et al., 2020). The reproductive number for SARS-CoV-2 is highly variable in estimates; ranging from

1.32-5.8 (cases) (Bourgonje et al., 2020; Du et al., 2020; Li et al., 2020; Sanche et al., 2020). This number depends not only on the time in the outbreak when it is estimated and where, but also on travel, social restrictions and personal interventions; latency and incubation period; and the corresponding calculated serial interval (SI) (time between infector onset of symptoms and subsequent report of symptoms from person infected) (Bourgonje et al., 2020; Du et al., 2020; Sanche et al., 2020); In the case of SARS-CoV-2, a lower R_0 corresponds to a shorter SI, while a higher R_0 corresponds to a longer SI (Sanche et al., 2020). As reported by Li et al. (2020), the R_0 was higher early in the outbreak (2.38), and with few or no travel restrictions imposed; an SI of 7-8 days (Li et al., 2020; Sanche et al., 2020), and mean incubation period of 4 days (Guan et al., 2020). In comparison, the R_0 for SARS-CoV-1 was reported as 3 (Schnieder, 2012); with an incubation period mean of 2.6 days; MERS R_0 <1; mean incubation period of 5 days (Weber et al., 2020); and influenza (pandemic) R_0 = 1.8 (Soucheray, 2020); reported incubation period mean of 2 days.

Immune Response, Patient Symptomology & Diagnosis

Symptoms may be non-existent, mild or severe in SARS-CoV-2, depending on an individual's viral profile, comorbidities (underlying disease, age, obesity, disease processes) and prolonged exposure (Bourgonje, 2020). For patients aged >60, there is increased severity of illness/complications (Bourgonje et al., 2020; Guan et al., 2020). Underlying co-morbidities further increase the risk for progression to a severe form of this illness. These findings are also applicable to MERS, SARS-CoV-1, and influenza (Bourgonje et al., 2020; Schnieder, 2012; To et al., 2020). Reportedly 10-20 percent of patients infected with SARS-CoV-2 go on to develop a severe form of the illness requiring either ICU admission, and mechanical ventilation.

Additionally, men are noted to be at higher risk for increased severity. This is thought to be due to higher ACE2 levels in men (Bourgonje et al., 2020).

Research of explanted tissue samples of positive SARS-CoV-2 patients suggests that the cytokine response in SARS-CoV-2 is less potent than that which occurs in H1N1, H5N1 or MERS (Hui et al., 2020). Reported symptoms of SARS-CoV-2 are also seen in influenza; fever, cough, headache, fatigue, generalized malaise, shortness of breath and chest pain; although GI upset is less common (inclusive of diarrhea and nausea) in SARS-CoV-2 (Bourgonje et al., 2020; Wang et al., 2020). Coagulopathy is also apparent for many COVID-19 patients which corresponds to a heightened inflammatory process and an increased risk of death (Bourgonje et al., 2020). Prior reported cases of SARS-CoV-1 and MERS patients exhibited neurologic involvement thought due to viral invasion in the brain (Bourgonje et al., 2020). The extent to which SARS-CoV-2 attacks brain cells is uncertain, but considered likely due to the ACE2 receptors on various neural cells and neurologic symptoms (Bourgonje et al., 2020).

While real time polymerase chain reaction (RT-PCR) immunoassays are used for diagnosis, accuracy of tests is questionable in sensitivity (Wang et al., 2020). A negative swab test (even in the presence of symptoms) reportedly occurs between 2- 29% of the time (Watson et al., 2020). Thus, additional diagnostic support is indicated to improve accuracy and treatment via the use of CT scans. CT enables differentiation of influenza to SARS-CoV-2 in characteristic appearance of key findings (Wang et al., 2020). In influenza, abnormalities primarily of the inferior lobes are involved; whereas in SARS-CoV-2, in multiple lobes and throughout the lungs, infection is noted. Pulmonary lesions are found in inferior lobes in influenza; while more non-specific distribution, and a higher number of lesions are seen in SARS-CoV-2. Margin lesions are vague in influenza induced pneumonia; while clear pulmonary lesion margins are denoted in

SARS-CoV-2. Finally, there is a shrinking contour appearance of the lungs in SARS-CoV-2, and consistent ground-glass opacity described (Bourgonje et al., 2020; Guan et al., 2020; Wang et al., 2020).

Viral Persistence & Stability

SARS-CoV-1, when assayed on inanimate surfaces, was most stable in temperate environments with relatively low humidity, while high temperatures and high humidity did not support viability. A relative humidity of 40-50% and temperature range of 22-25 degrees Celsius, was shown as most supportive of SARS-CoV-1, and promoted virus viability for 2-5 days. As temperature and humidity fluxed upward, viability was demoted (Chan et al., 2011). Prolonged exposure time, recycled ventilation, and contact with fomites increased infectivity persistence and risk of exposure for SARS-CoV-1, influenza, and norovirus in a mathematically modeled study analogous to cabin air-flow and inflight exposure (Lei et al., 2018). Other studies validate findings that transmission of coronaviruses via contaminated surfaces is prolonged; and the degree of contamination of a surface, is not necessarily dependent on severity of illness exhibited by the infected individual (Ong et al., 2020). Finally, plastic and stainless-steel support stability longer for SARS-CoV-2 (respective half-lives of 5.6 and 6.8 hours), than do other surfaces; and could still be detected on surfaces 72-hours after the viral application (van Doremalen et al., 2020).

Therapy and Treatments

Treatment of viral infectivity has been suggested through use of some current therapies. Other developing modalities are based on viral mechanics. Development of prospective protease inhibitors (preventing cleavage and subsequent activation) (Weber et al., 2020; Zmora et al., 2014); and proposed RBD protein inhibitor vaccine (blocking viral attachment) (Astuti &

Ysrafil, 2020; Tai et al., 2020) are anticipated. Current therapies either indicated or employed include: enhancing immune response through immunomodulators and anti-inflammatories (management of cytokine and inflammatory response); anti-viral drugs that target action of the RNA polymerase (effectively inhibiting synthesis of viral RNA); ACE inhibitor drugs (blocking the receptors necessary for viral attachment and entry), anti-coagulants (preventing thrombotic blood clots); antibiotics (for concomitant bacterial infections), and support of gas exchange and oxygenation (Bourgonje, et al., 2020; Du et al., 2020; Guan et al., 2020; Hui & Peris, 2019). At present, public health campaigns stress prevention as the primary route to control the contagion (CDC, 2020d).

Research expounding on the differences and similarities for the contagions mentioned above is key to control of the SARS-CoV-2 pandemic. The results of these studies explain cellular interaction, tissue pathogenesis and physiological regulation in response to viral invasion, and ultimately enhance the basic understanding of transmissibility essential for efficacious therapy, treatment and control of SARS-CoV-2.

Discussion

Scientific knowledge and heightened awareness greatly affect the systematic approach, personal behaviors, care and outcomes during a contagion; and are instrumental factors in the control of transmission. The following discussion is inclusive of data obtained by this author in regard to age, gender and obesity, and the corresponding relationship these variables have to infection and case fatality rates. COVID-19 patient data, from six Colorado counties: two of which are rural (Weld and Morgan); two of which are large per capita urban counties (Denver and El Paso); and two popular, year-round, tourist destination counties (Summit and Eagle) (also

classified as rural), are briefly examined here, and related to findings applicable from this review.

Origin, Lineage, Genome Analysis & Phylogenesis

The ancestry and evolution of viruses define the basis of transmissibility. Studies support this claim by validating the presence of requisite genome regions; attesting that necessary and possible recombination events occur; verifying sequence identity; and enabling ultimately, deduction of phylogenetic origin/attributability to certain species. Phylogenetic analysis of SARS-CoV-1, and MERS (Biao et al., 2014), made apparent the bat species (while responsible as primary reservoirs for various coronaviruses) (Biao et al.; Lu et al., 2020), was not the primary human infector(s) per se. While bats in the Yunnan region were identified as relevant species for hosting a diverse range of coronaviruses, metagenomic analysis offered strong support that an additional host (i.e., palm civet), or viral co-infection was necessary, as in the case of SARS-CoV-1 (Biao et al., 2014). This is also thought to be the case for some subtypes of influenza A. Essentially, animals infected by more than one virus, consequently harbor viral processes that through reassortment events, produce pathogens capable of infecting humans (Ypma et al., 2013). Another prospect, identified by Biao et al. (2014), described two gap-filling viruses; viruses that could bridge the gap from bat to human in the presence of a viral co-infection and recombinant events, within the animal host. Such findings suggest that bat to human transmission is feasible from select hosts that have been co-infected when certain genomic conditions are met, but further studies are necessary to confirm the prevalence and likelihood of this modality.

The evolution of a virus (mutation and recombination) is closely associated with its distribution and occurrence in a population (Ypma et al., 2013). Thus, when SARS-CoV-2 struck

in early winter 2019, scientists employed rapid genomic sequencing of an infected patient population (Lu et al., 2020) to gain insight into evolutionary and transmission relationships. When they analyzed the samples, findings conferred very close identity among the patients sampled (99.98% identical), indicating few recombinant events. Findings in regard to possible genomic mutations were similarly reported from To et al. (2020), in their systematic sampling of a COVID-19 cohort of patients in Jan/Feb. These studies are significant, as they confirm the outbreaks were identified in early stages. Additionally, similarities were found among the genomes of the COVID-19 patients when referenced against virus nucleotide sequences available via the genetic sequence database, GenBank (Lu et al., 2020). Closely related viruses found to be of bat ancestry directed evolutionary origin, while also indicating significant differences between SARS-CoV-1 and the current SARS-CoV-2 (Lu et al., 2020). The confirmed genomic similarities among afflicted patients early on, improves epidemiologic surveillance and timescale estimates of the contagion; while advising researchers and health officials of animal and associated geographic locations/ecology in need of monitoring; and potential public health interventions.

Zoonosis and Intermediate Hosts

While decades of research have established the preponderance of emerging infectious diseases as attributable to animal origins (Morse et al., 2012), an intermediate species is considered requisite for the diseases of consideration in this review, as evidenced by the genomic and evolutionary rationale. In the case of SARS-CoV-2, a likely conclusion based on research of the aforementioned contagions (Biao et al., 2014; Chan et al., 2020; Lu et al., 2020; van Doremalen et al., 2014; Zhao et al., 2019), is that the spillover from animal to humans is credited to an exotic species sold at the Wuhan market. More specifically, this animal likely contracted

the disease from a shared habitat in which one of the following potentially occurred. Contamination of a common water source shared by the reservoir animal (bat) and the intermediate (palm civet); introduction (by wildlife farmers), of the palm civets to a new region in which the carrier bats habituated; or carcass decay/fecal particulate contamination of communal environment by infected bats near or around food sources (i.e. fruit trees, insects, fish, or other small mammals). Subsequently, the handling and preparation of infected palm civets (i.e. via slaughter, cleaning and packaging), fomite contamination in the market, or human consumption, resulted in a spillover to humans. Once the jump to humans was established, sustained human to human transmission ensued.

Viral Tropism

As noted previously, and shown extensively in the research (Biao et al., 2014; Bourgonje et al., 2020; Hui et al., 2020; Lu et al., 2020; Tai et al., 2020; Zmora et al., 2014), certain conditions must be met for a virus to attach and enter candidate cells. The foundational research of SARS-CoV-1, MERS, and influenza, facilitated comparisons of genomic similarities and molecular characteristics encompassing concepts of transmission efficiency for SARS-CoV-2. Prior investigate studies and molecular level assays have enabled rapid determination and modeling of SARS-CoV-2 host tropism. Demonstrably, SARS-CoV-2 exhibits a 10-20 times stronger affinity to ACE2 receptors, than that of SARS-CoV-1. This attribute is suspect as a reason for increased transmission efficiency among cells targeted by SARS-CoV-2 (Bourgonje et al., 2020; Tai et al., 2020). As these ACE2 receptors are expressed by so many cells and tissues throughout the body, tissue analyses reveal the pathogenesis respective of organ systems to scientists. Additionally, findings may differ in various populations (i.e. race/ethnicity, gender, age groups, underlying co-morbidities), and potentially offer additional information for scientists

to treat on an organ system-level basis. Future studies specific to race/ethnicity and chromosomal expression of ACE2 receptors, may offer insight into protective mechanisms respective to differences among distinct segmentations of the population.

Transmission Dynamics

The infectious impact on host, and transmission dynamics of SARS-CoV-2 rely heavily on select organ pathogenesis and consequent propagated viral loads. Once habituated in the host cells, organs are affected based on both intrinsic and extrinsic processes of the host itself. Numerous non-structural proteins of coronaviruses have the capability to drastically alter intrinsic processes such as a host's innate immune response. These proteins damage cells, inhibiting host immune response, augmenting expression of cytokines, masking viral identification by innate immune cells, and obstructing host RNA translation to mention a few (Astuti &Ysrafil, 2020). Concomitantly, due to interruption of inherent ACE2 functioning, there is dysregulation of metabolic and endocrine pathways which results in heightened inflammatory, and respiratory process exacerbation (Bourgonje et al., 2020; Kwon & Pessin, 2013). It follows, that in moderate and severe cases, the upper and lower respiratory tracts, where ACE2 receptors are exceedingly expressed, are susceptible to significant injury, ranging from cough, shortness of breath and dyspnea, to full-blown, acute respiratory distress (ARDS), requiring ventilatory support (due to profound inadequate gas exchange). Such aggravation is in line with the pneumonia described by researchers and clinicians reporting on SARS-CoV-2 (Bourgonje et al., 2020; Hui et al., 2020; Zou et al., 2020).

As discussed, and shown in the literature, the spread and promotion of SARS-CoV-2 is highly contingent on respiratory processes as is the case for SARS-CoV-1, MERS, and influenza. Abounding replication competence in the bronchus and colorectal cells (Bourgonje et al., 2020;

Hui et al., 2020), promotes mechanisms of transmission consistent primarily of droplet (> 5-10 μm in diameter), aerosol (< 5 μm in diameter), and oral-fecal shedding (i.e. coughing, sneezing, talking, breathing, stool and fomite contamination). While eccrine sweat glands also express ACE2 receptors, there was little information found, as to whether SARS-CoV-2 could be spread via shedding from an infected person's sweat. Additional studies to investigate this modality might offer crucial information either in support or defense of keeping certain indoor exercise facilities/activities open during the pandemic, so long as other recommended precautionary measures are implemented.

It is difficult to accurately ascertain how infectious asymptomatic carriers may be (given they may not be accurately identified), but notably, their shedding profile mimics that of symptomatic carriers (Zou et al., 2020). Also, given the high estimate proportion of asymptomatic infections (at present the current best estimate is 40%, CDC, 2020c), a SI of 7 days, and determined early peak viral shedding (within the first week of the illness) (To et al., 2020; Zou et al., 2020), transmission efficiency of SARS-CoV-2 is apparently agile. The fact that estimates for R_0 vacillate so greatly, is likely due in part, to inconsistent social, behavioral, and travel restrictive measures (Li et al., 2020); poor compliance, and incomplete contact tracing. Given the assumption that SARS-CoV-2 will continue to circulate in the U.S. for at least the next several months, should restrictive measures and compliance continue in a status quo fashion, it is reasonable to estimate that the average asymptomatic carrier, could potentially infect between 2 and 5 people during their period of contagiousness; more if it comes to light that viral shedding more frequently occurs for several weeks post-initial infection (or symptom presentation) as noted by To et al., (2020).

The risk of transmission is more likely given the greater amount of time and proximity of infector to infectee (Lei et al., 2018; Wang et al., 2020). This finding is supported by the number of affected hospital workers in the case of MERS (Corman et al., 2014), and SARS-CoV-1 (Chan et al., 2011; Corman et al., 2014) outbreaks, and is indicated as being a considerable risk factor in SARS-CoV-2. Data shows that pocket outbreaks seen in various facilities (in which residents/workers are in close proximity with infected individuals) in Colorado, have hotspots in healthcare (skilled nursing facilities), assisted living facilities, "other" settings (i.e. food/meat processing plants), and prison/jails (see Appendix B, Figure 1) (CDPHE Open Data, 2020c). For the counties examined by this author, the number of outbreaks are noted highest in the counties housing the two largest urban cities in Colorado (the city of Denver, Denver County; and Colorado Springs, located in El Paso County); followed by Weld and Morgan counties, both of which experienced large outbreaks in meat packing plants (these plants were kept open early in the pandemic, despite most workplace closures as they were designated "essential"; temporary closures did occur following facility outbreaks).

Immune Response and Patient Symptomology and Diagnosis

Advancement to a severe form of SARS-CoV-2 is reported between 10-20 percent of cases (Bourgonje et al., 2020). Among others mentioned, contributory variables include: underlying comorbidities, gender, and individual immune response. The presence of one or more of the following: diabetes mellitus (DM), hypertension (HTN), vascular disease, chronic respiratory disease and cancer were noted as often accompanying forms of the disease that progressed (Bourgonje et al., 2020; Guan et al., 2020; To et al., 2020); requiring intensive care hospitalization, or resulting in death. ACE2 expression or inhibition due to different disease

processes and their corresponding drug management, may offer evidence for improved management of complex patients infected with COVID-19 in future studies.

An increased risk for severity is noted with corresponding increase in age (over the age of 60) (Bourgonje et el., 2020; Guan et al., 2020). While this may be due to a decrease in immune response related to age, it may also be a consequence of long-term inflammation, sub-clinical processes, or underlying disease gradually progressive with age. This finding is supported by data examined by this author in analysis of select Colorado counties affected by COVID-19. Of the patients affected over the age of 60, the percentage who were hospitalized or died increased dramatically with age. As shown in Appendix B, Figure 2 (CDPHE Open Data, 2020b), 11% of the population of Coloradoans is made up of a population segment aged 60-69 years. Of that segment, 13% were hospitalized at the time of this writing, and 13% of those affected also subsequently died. When the 70-79-year bracket (which comprises 6% of the CO population) was evaluated, 8% were noted as hospitalized, and of those affected 24% died. For the 80+ year age group (comprising of 3% of the CO population), the percentage hospitalized was also 8%; however, the percentage of those affected who died, was 54%. That equates to a two-fold increased risk of death for the first 10 years increase in age; which more than doubles again for the next 10-year increase in age.

ACE2 plasma concentration levels, evidenced to be higher in men (Bhatie, Sekhon & Kaur, 2014; Bourgonje et al., 2020), may lend credence as to why the death and infection rates are reported as higher in men. An intrinsic disparity may be due to ACE2 gene expression, or the effects of the reproductive system and sex hormones, by way of hormone receptors on immune cells (Bhatie et al., 2014). The effect of behavioral habits may also play a role (i.e. smoking; Smith et al., 2020).

The gender component, is similarly supported by the data retrieved and examined by this author. As seen in Appendix B, Figure 3 (CDPHE Open Data, 2020c), the percentage of Colorado males affected is an average of 5.2% higher. Additionally, of the population of Colorado males affected who die is 5.3% higher on average than females.

A risk factor commonly mentioned in the literature as contributory to COVID-19 severity, and in itself a risk factor for many diseases (including influenza) (Bourgonje et al., 2020), is obesity. As discussed previously, increased obesity (BMI >25kg/m^2) in patients resulted in potentially increased severity of symptoms, likelihood of intensive care admission, need for invasive therapies and death (Bourgonje et al., 2020) While obesity was not reported available data for the patients affected during this author's study, county obesity data was pulled to evaluate against the county CFR and county infection rate (per 100K people) for COVID-19. What can be seen from this analysis in Appendix B, Figure 4 (CDPHE Open Data, 2020a; CDPHE Open Data, 2020d), is a significant relationship between people over the age of 18 and obese (BMI>30), and the CFR (p-value =.021734) for the counties of interest. There is not a significant correlation between obesity reported for people 18 years and older and rate of infection (p-value > .05); The positive correlation for CFR and obesity suggests that of the population who are obese, should they contract COVID-19, there is a high risk of dying, while the second metric indicates that the chance of contracting COVID-19 is not significantly increased due to obesity. The rationale discussed previously supporting inflammatory potentiation due to visceral fat adipokines, and the delicate regulatory balance they are responsible for, supports the likelihood of increased severity/death for obese patients (Bourgonje et al., 2020; Kwon & Pessin, 2013); however, further studies are needed to validate this supposition.

Additional studies are also merited to evaluate brain tissue involvement in SARS-CoV-2, as indicated by reported neurologic symptoms. Symptoms such as loss of taste (ageusia) and smell (anosmia), suggest involvement of cells central to those regions of the brain (Bourgonje et al., 2020), but little information could be found in the literature relative to analysis of brain tissue and SARS-CoV-2.

From the research reviewed, it is apparent that early and accurate diagnosis requires additional diagnostics both due to the overlap of symptoms among the similarly presenting diseases of SARS-CoV-2 and influenza, and the reported sensitivity of RT-PCR testing (Wang et al., 2020; Watson et al., 2020). Repeat testing in the presence of reported symptoms, with a test from a different manufacturer, or follow-up with a serology test for antibodies seems merited. CT scans reveal some essential features of SARS-CoV-2 patients when compared with CT scans from patients affected with influenza (Bourgonje et al., 2020; Guan et al., 2020; To et al., 2020; Wang et al., 2020). While CT scans are an additional cost, the adjunct use when indicated, may actually contribute to control of spread, cost containment (long-term), and improved quality of care.

Viral Persistence and Stability

Research reported on conditions and modes of transmission via inanimate objects/surfaces most favorable for coronavirus persistence suggests the following: higher probability of infection from fomites, contaminated plastic and stainless-steel surfaces, air-conditioned or poorly ventilated (including recycled air) environments, and relative humidity of 40-50% (Chan et al., 2011; Lei et al., 2018; Ong et al., 2020; van Doremalen et al., 2020). Viral persistence of SARS-CoV-2 was shown to be stable for several hours both as an airborne pathogen, and for days as a surface contaminant (van Doremalen et al., 2020). Given the

established stability of SARS-CoV-2, how equipment is used, and under what type of exposure equipment could be contaminated, is a necessary consideration in the handling of this pandemic. Additionally, measures to counteract stability and viability of the virus can be further explored given the knowledge obtained via these studies. Deterrent measures targeting temperature, humidity, air filtration, asepsis, or use/integration of materials shown to be non-supportive of SARS-CoV-2 growth (i.e. copper) (van Doremalen et al., 2020); require further investigation and consideration.

Therapy and Treatments

As previously discussed, a viable vaccine is presently unavailable, yet hopeful prospects are reported in various phase trial stages for a number of pharmaceutical manufacturers (Regulator Affairs Professionals Society (RAPS), 2020). Thus, targeting the spread of SARS-CoV-2 requires an amalgamation of controls. Therapy described previously is largely supportive, while preventative measures are the first line of defense. Measures in the context of masks, hand sanitizer, good hand hygiene and social distancing, avoidance of public gatherings (either in or outdoors), limiting trips to public venues, and refraining from un-necessary travel. Shown in Appendix B, Figures 5-7 (CDPHE Open Data, 2020a; Guidotti & Ardia, 2020), are the various restrictive measures implemented by local Colorado governments, corresponding trends of positive cases, and case fatality rates. The restrictive measures assessed for this analysis relate to school closing, work closing and stay at home restrictions/recommendations. Figure 5 demonstrates the timeline relative to the number of tests performed (orange), and the number of confirmed positive cases (blue); (confirmed positive tests/county population * 100K people = infection rate), and corresponding restrictive measures. Figure 6 annotates a timeline of closures/orders during the early stages of the outbreak. Restrictive measures are numerically

categorized from 0-3; 0 indicates no measures in place; and 3 indicates most restrictive measures (see associated key for graphs). In Figure 7, all counties of interest are depicted; case fatality rate is noted to peak on May 21st for the example highlighted (Denver), then slowly levels off/declines, despite the high reported number of positive cases. This finding may be due to an increased compliance of restrictive measures by the at-risk population (60+), for which the death rate is significantly higher, thereby limiting exposure and incidence. To validate this claim, mobility data and contact tracing for that population would be necessary additional variables to evaluate.

Conclusion

The examination of prior disease outbreaks, attributed to SARS-CoV-1, MERS, and influenza, may assist in various ways to control and contain the transmission of SAR-CoV-2 by the scientific community, as well as the general public. While information aggregation and assimilation are the foundation for theory formulation, drug development, and medical intervention; increased awareness and promoted knowledge serve to shape personal and public reaction to emerging infectious diseases, and better an individual's ability to respond accordingly. While response of the scientific and medical communities is dictated largely by biological factors, a founded understanding by the general public, largely mitigates fear and transmission by improving upon personal, social and behavioral dynamics.

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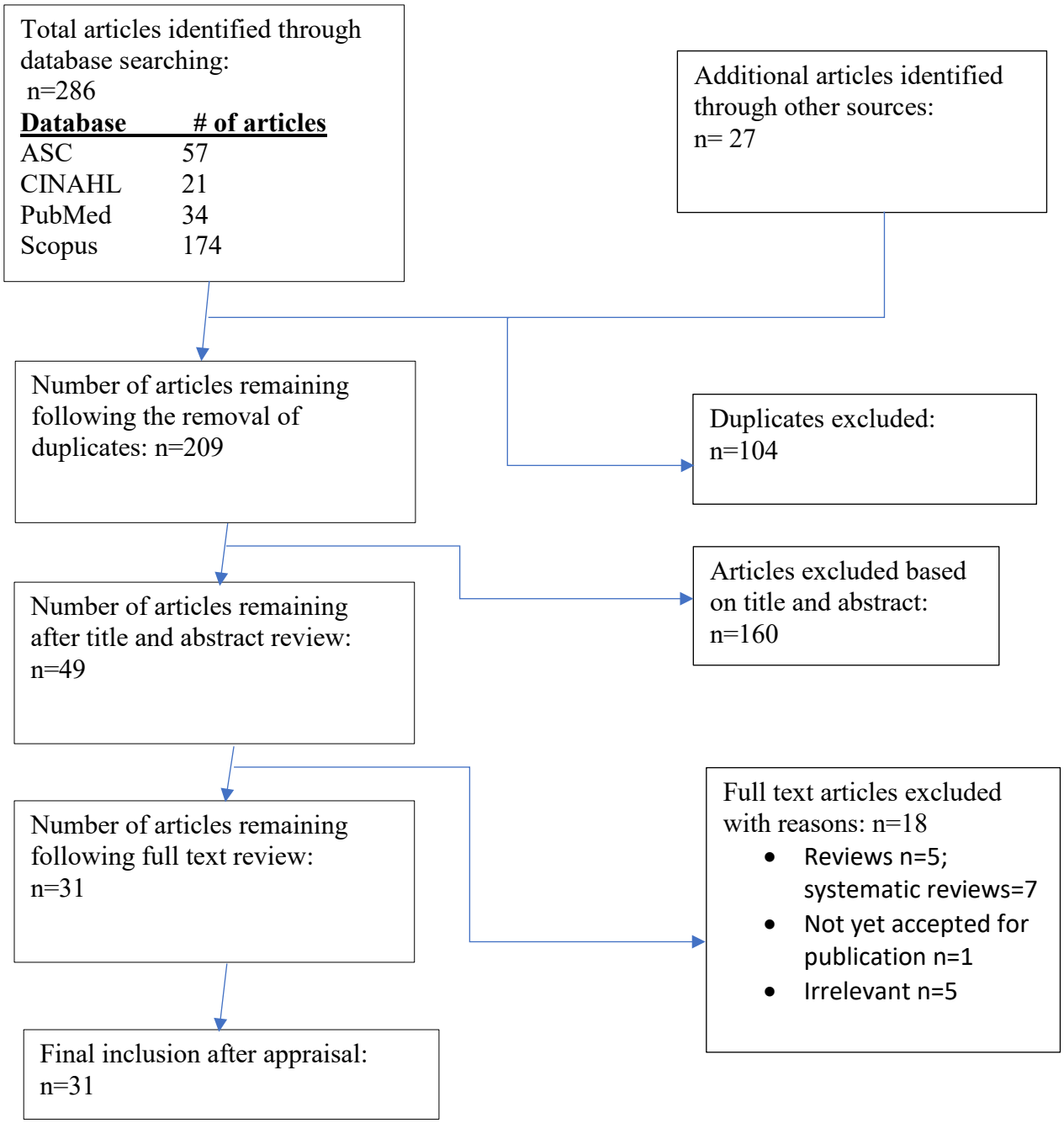
Appendix A

PRISMA diagram shown below outlining methodology for literature search.

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram



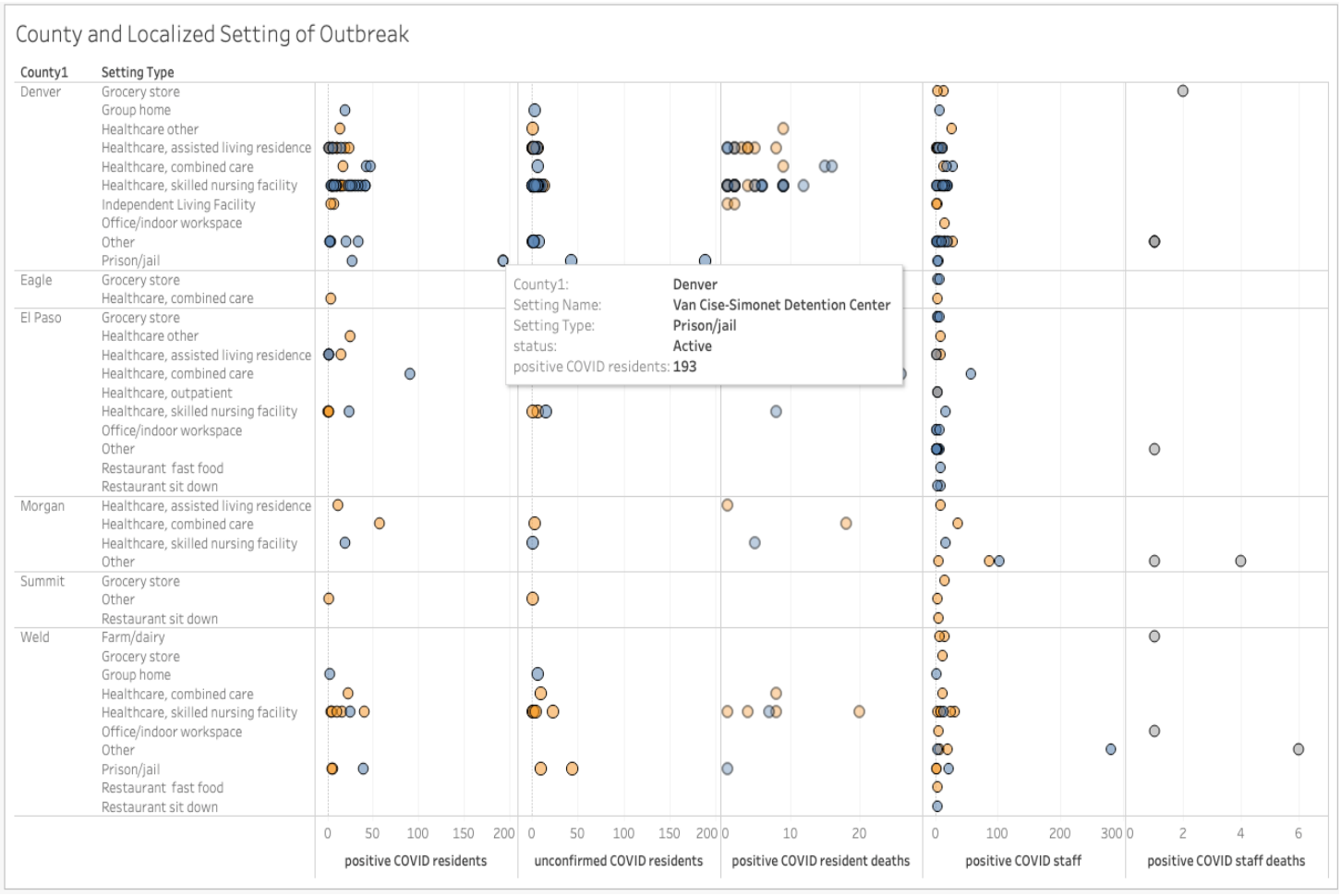
Note: Adapted (and revised) from: Moher, D., Liberati, A., Tetzlaff, J., & Altman, D.G., The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix B

Included graphs for Colorado counties depicting Eagle, El Paso, Denver, Morgan, Summit and Weld, relevant to capstone project for HIN 785. This descriptive study is used to evaluate the correlative strength of numerous variables with the positive case rate/infectious rate and case fatality rate (CFR) of COVID-19, to potentially improve awareness and population segment outcome(s) through risk factor(s) early identification. Also, to evaluate how certain early interventions or lack thereof, impact the counties of focus.

Figure 1

County and Localized Setting of Outbreak

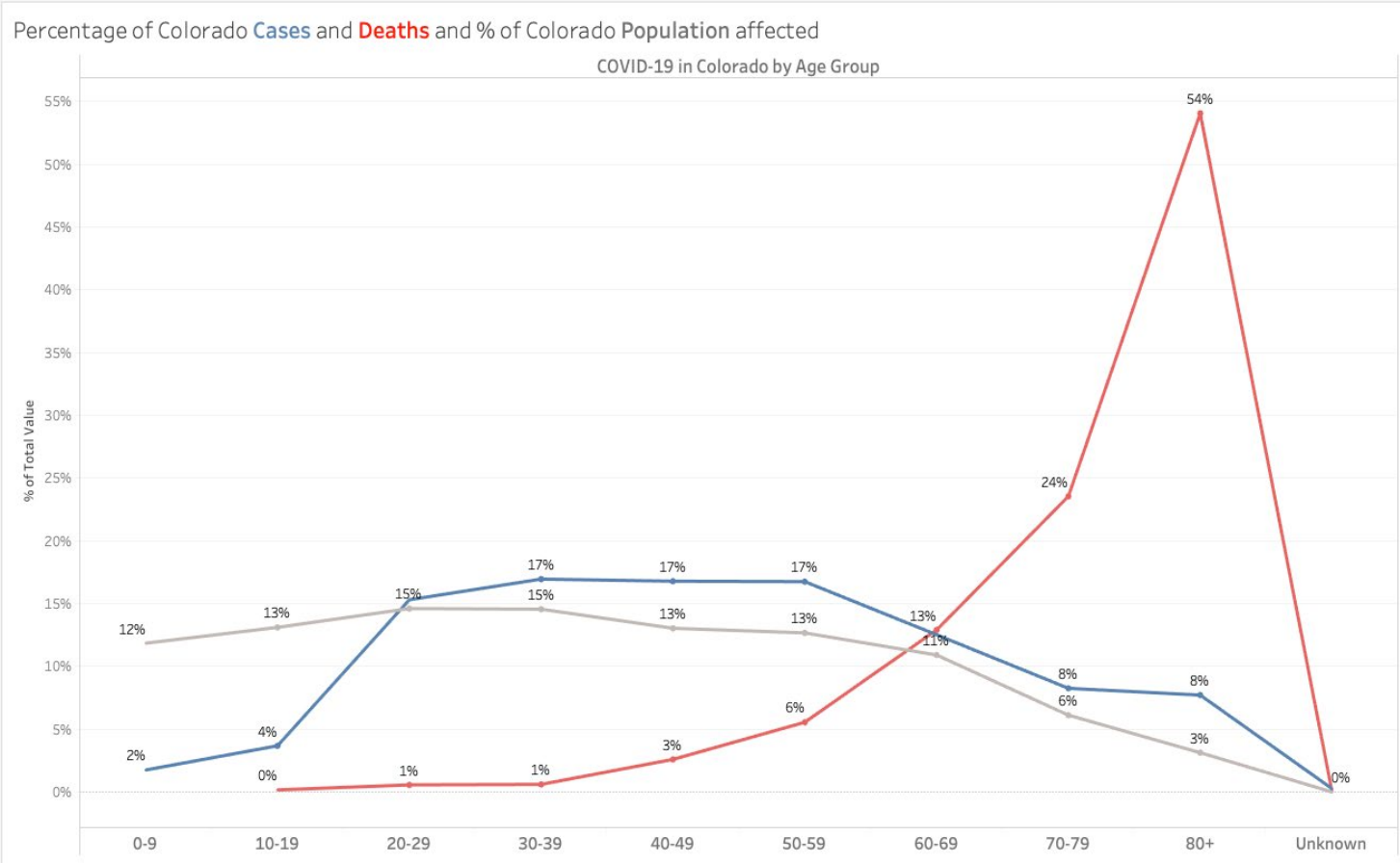


Note. Active outbreaks are represented in blue, resolved outbreaks represented in orange. The intensity of the color corresponds to the size of the outbreak. Most notably affected are Healthcare, skilled nursing

facilities, followed by Healthcare, assisted living residences, "other", most notably reported though meat and food processors, and prison/jail. Data obtained from *CDPHE* https://covid19.colorado.gov/data/outbreak-data

Figure 2

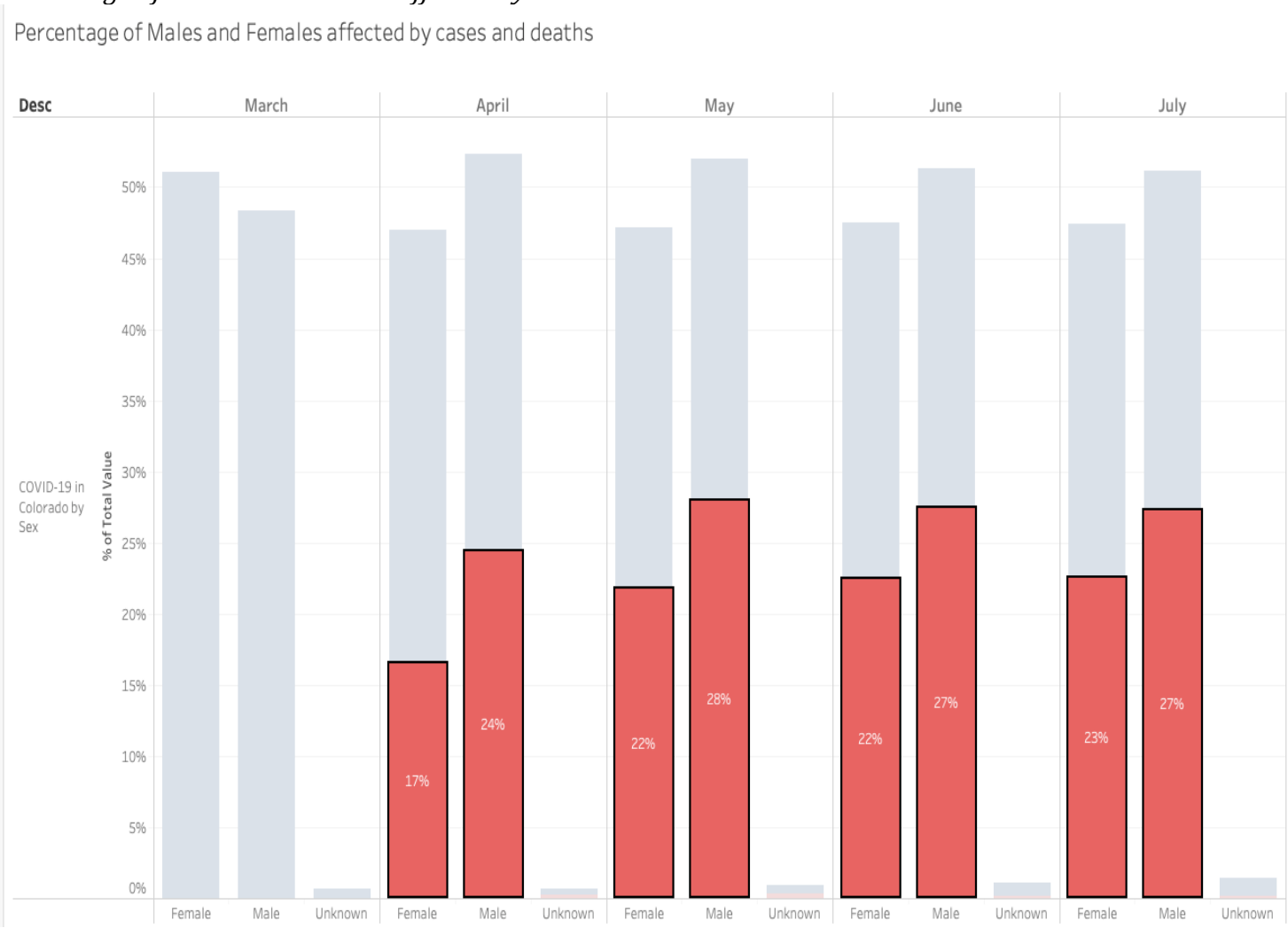
Percentage of Colorado Cases and Deaths and % of Colorado Population Affected



Note. The data reflective on this graph is representative of all age groups in Colorado and the percentage each age group comprises of the Colorado population (represented in gray). A sharp increase in the percentage of deaths can be seen beginning at the 60-69 year-age group. For example, of the age group population described (i.e. 80+, the group comprising 3% of the Colorado population), the deaths (represented by the red line), make up 54 % of the deaths and 8% of the cases (represented by the blue line). Data retrieved from *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/cdphe-covid19-state-level-open-data-repository

Figure 3

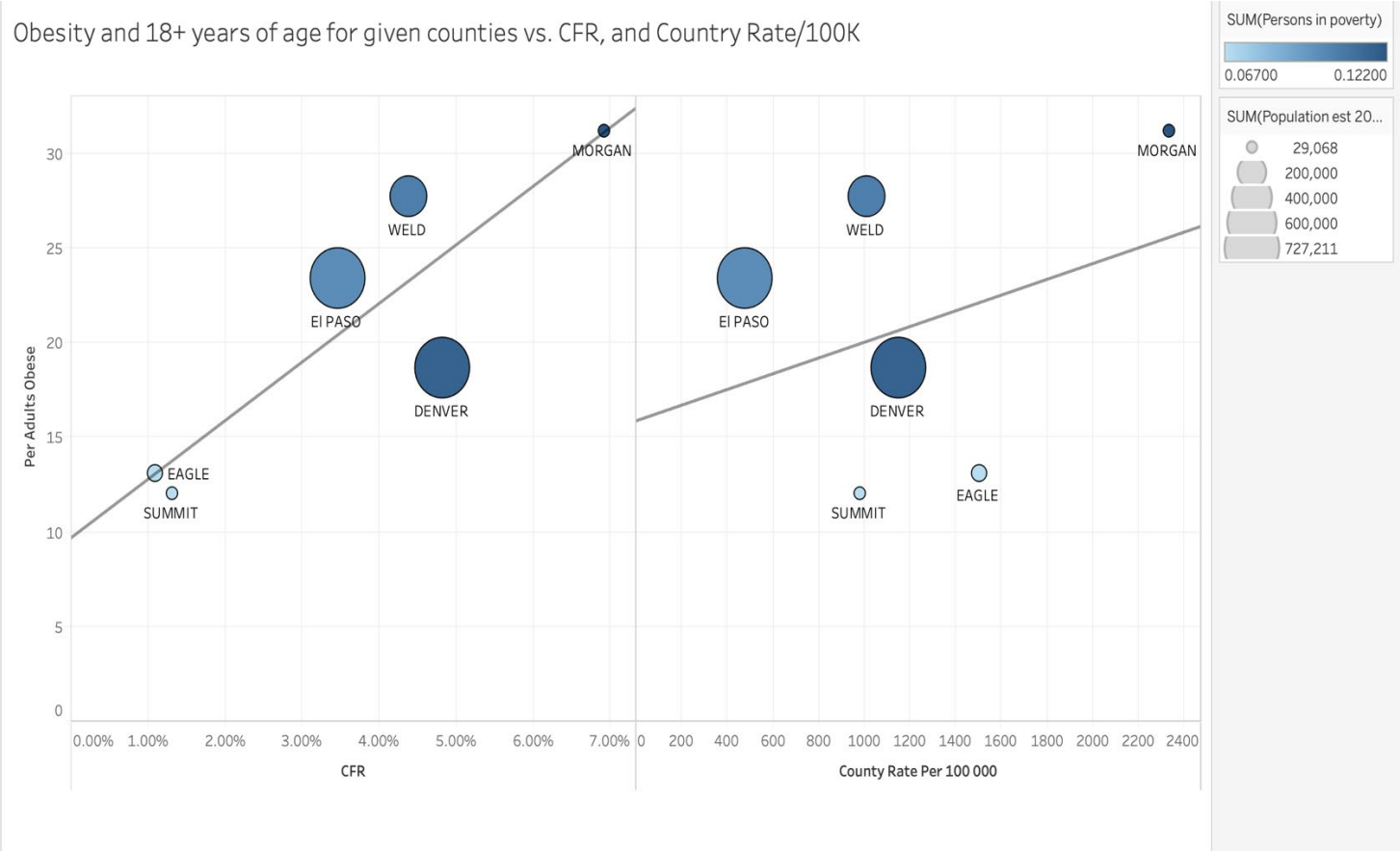
Percentage of Males and Females Affected by Cases and Deaths



Note. Of the percentage of males affected for the month of April, 17% of the cases making up the female segment died, while 24% of the cases representative of the male segment died. The graph shows that males have a 5.3% higher rate of death than females on average, and an average of 5.2% higher rate of overall cases. Data retrieved from *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/cdphe-covid19-state-level-open-data-repository

Figure 4

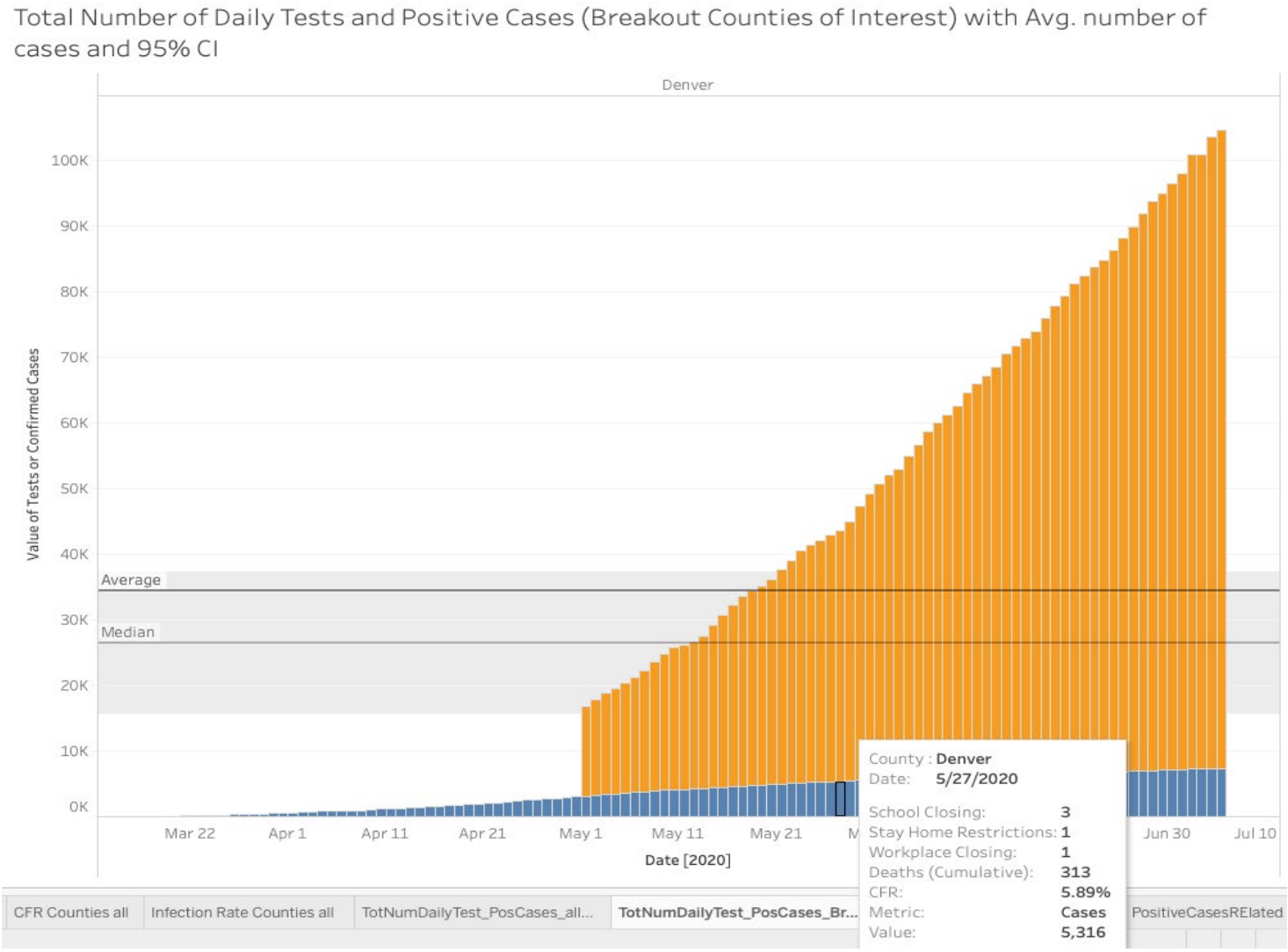
Obesity and 18+ Years of Age for Counties of Interest vs. CFR, and Infection Rate/100K People



Note: The graph on the left demonstrates the relationship between people in the population for the counties of interest, who are considered obese (BMI>30), age 18 years+, and the case fatality rate; the p-value is .0201734, which is considered significant. The graph on the right, demonstrates the rate of infections per 100K (for the counties of interest), and the percentage of people in the population considered obese and age 18 years+; the p-value is non-significant (p-value=.515065). Data retrieved from *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/obesity-in-adults-colorado-brfss-2014-2017-county/data and *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/colorado-covid-19-positive-cases-and-rates-of-infection-by-county-of-identification?geometry=-121.075%2C35.977%2C-90.027%2C41.950

Figure 5

Total Number of Daily Tests and Positive Cases (Breakout Counties of Interest) with Average Number of Cases and 95% Confidence Interval



Note. Graph depicts tooltip for the date in which shelter-in-place orders expired and many people returned to work for given counties (only Denver is shown in the above example). The rate of testing is shown in orange relative to confirmed positive cases shown in blue. Restrictions are numerically categorized as 0-3, with 0=no measures, and 3=most restrictive.

Key:

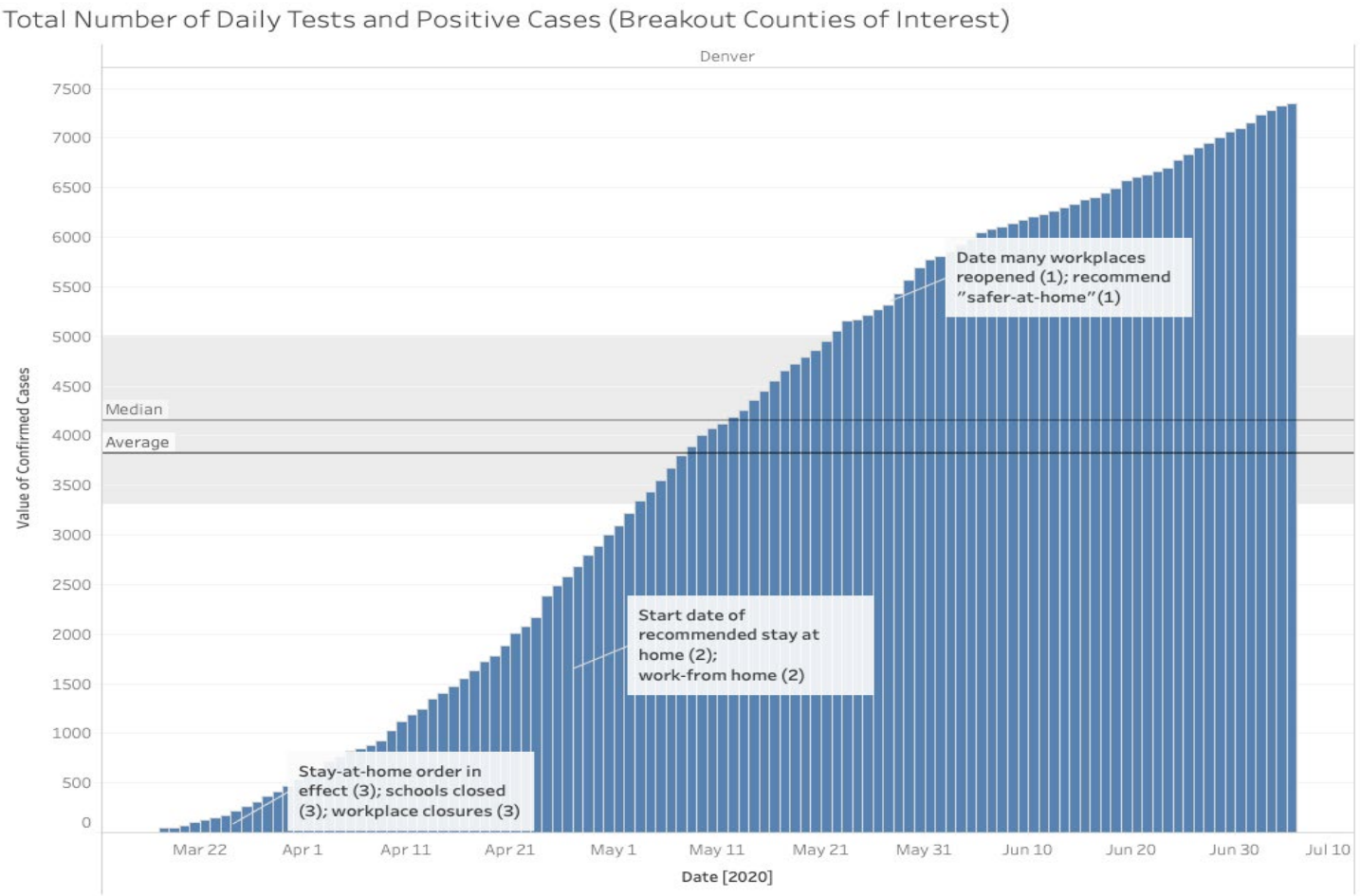
school_closing: 0=No measures; 1=Recommend Closing; 2=Require closing (only some levels or categories, i.e. just high school, or just public schools; 3=Require closing all levels.

workplace_closing: 0=No measures; 1=Recommend closing or work from home; 2=Require closing some categories or sectors of workers; 3=Require closing or work from home all but essential workplaces (i.e. grocery stores, doctors).

stay_home_restrictions: 0=No measures; 1=Recommend not leaving house; 2=Require not leaving the house with exceptions for daily exercise, grocery shopping and "essential" trips; 3=Require not leaving house with minimal exceptions (i.e. allowed to leave only once every few days, or only one person can leave at a time, etc.). Data and above key retrieved from *COVID-19 Data-hub* https://covid19datahub.io/articles/data.html and *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/colorado-covid-19-positive-cases-and-rates-of-infection-by-county-of-identification?geometry=-121.075%2C35.977%2C-90.027%2C41.950

Figure 6

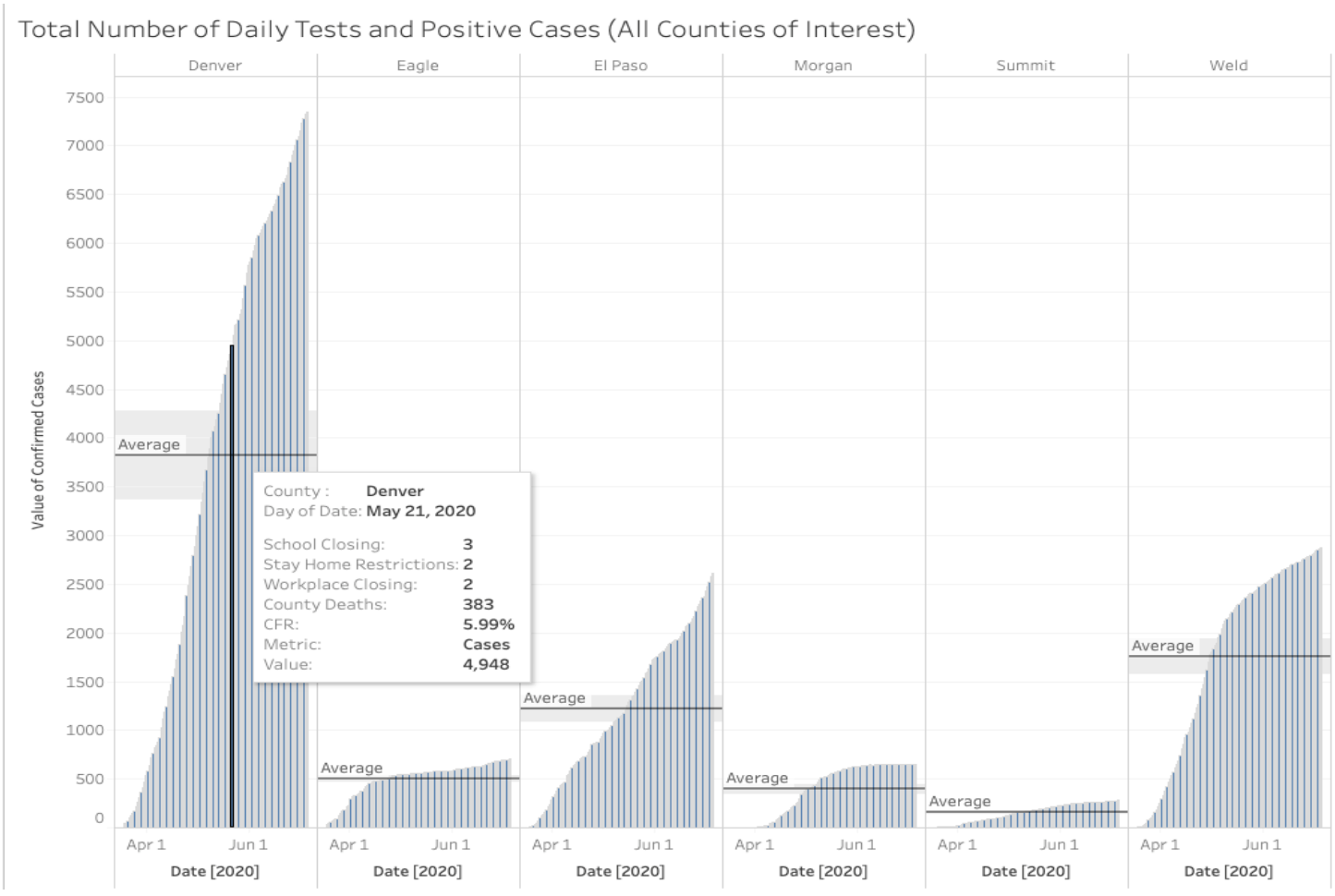
Total Number of Daily Tests and Positive Cases (Breakout Counties of Interest)



Note. Graph depicts the number of positive cases for the county of Denver; date on which full stay-at-home orders went into place; when stay and home and workplace restrictions were dropped to recommended stay at home (2); and subsequent "safer-at-home" and workplace decrement in restrictions to (1). Median number of cases (4153) for county is noted as very close to average number of cases (3825) reported with 95% CI. Data retrieved from *COVID-19 Data-hub* https://covid19datahub.io/articles/data.html and *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/colorado-covid-19-positive-cases-and-rates-of-infection-by-county-of-identification?geometry=-121.075%2C35.977%2C-90.027%2C41.950

Figure 7

Total Number of Daily Tests and Positive Cases (All Counties of Interest)



Note. A high-level view of all counties of interest with average confirmed cases and 95% CI for period of March 18 – July 4, 2020. Tooltip indicates corresponding measures observed, number of deaths for respective

county and current case fatality rate. CFR peaks (in the above example for Denver), on May 21st, shortly before the shelter-in-place order expires (May 26th, 2020). Data and key retrieved from *COVID-19 Data-hub* https://covid19datahub.io/articles/data.html and *CDPHE* https://data-cdphe.opendata.arcgis.com/datasets/colorado-covid-19-positive-cases-and-rates-of-infection-by-county-of-identification?geometry=-121.075%2C35.977%2C-90.027%2C41.950