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Immuno-epidemiology and Transmission Characteristics of SARS-CoV-2: A Perspective Investigation

Anthony M Kyriakopoulos^{1*}, Kyriaki Karafyllidou², Jinhui Li³, Shi Zhao^{3,4}

¹Nasco AD Biotechnology Laboratory, 11 Sachtouri Street, Piraeus 18536, Greece

²Department of Pediatrics, University Children's Hospital of Zurich, 8032 Zurich, Switzerland

³JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong 999077, China

⁴CUHK Shenzhen Research Institute, Shenzhen 518060, China

*Corresponding Author: Anthony M Kyriakopoulos, Nasco AD Biotechnology Laboratory, 11 Sachtouri Str., Piraeus 18536, Greece; Email: antkyriak@gmail.com

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Abstract

Coronaviruses propagate efficiently within the heterogeneous population of humans to disperse infections. For Severe Acute Respiratory Syndrome Coronavirus-2 the determination of the heterogeneity of individual infectiousness is an appropriate way for immune-epidemiology investigation due to the cross reactive immunity of general population to coronaviruses. In this perspective investigation it is aimed to understand how SARS-CoV-2 transmits within the human population that overwhelming evidence show that has an a priori trained immunity against SARS-CoV-2 and a long lasting immunity against SARS-CoV-1. Using a sample of population in a close geographical proximity to the initial SARS-CoV-1 outbreak, we explored the association between infector's age and dispersion (or heterogeneity) of individual infectiousness (k) in order to investigate the relatedness with the age of an individual's capability to disperse the disease in the initial outbreak of SARS-CoV-2 in China. Importantly, we have found a negative association between k and increase of infector's age. Significantly this became more evident for the age group of 20-40 years comparing with the infectors with younger and older ages. In this respect, a thorough analysis of the role of acquired adaptive machinery of receptor recognition that during various immunity statuses of the hosts propagate

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efficiently the infection within a heterogeneous population was carried out. Finally, the special relations of continuous positive viral adaptations of coronavirus infections that pre-program the immune conditions of infected hosts within the general population were analyzed.

Keywords

SARS-COV-2 Transmission; Heterogeneity of Individual Infectiousness; Age Groups; Adoptive Immunity of General Population; Cell Receptors and Dispersion of Coronaviruses

Abbreviations

CEACAM: Carcinoembryonic Antigen-Related Cell Adhesion Molecule; SSE: Super Spread Event; SARS: Severe Acute Respiratory Syndrome; MHV: Mouse Hepatitis Virus; MERS: Middle East Respiratory Syndrome; Covid-19: Coronavirus Disease 2019; CoV: Coronavirus; SARS-COV-1: Severe Acute Respiratory Syndrome Coronavirus-1; MERS-COV: Middle East Respiratory Syndrome Coronavirus; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus-2; ACE-2: Angiotensin I Converting Enzyme 2; ARDS: Acute Respiratory Distress Syndrome; DPP-4: Dipeptidyl Peptidase-4; GPI: Glycophosphatidylinositol; ITAM: Immunoreceptor Tyrosine Based Motif; HIV: Human Immunodeficiency Virus; TGEV: Transmissible Gastroenteritis Virus; IgSF: Immunoglobulin Superfamily; HEV: Hepatitis E Virus; HBV: Hepatitis B Virus; hAPN: Human Aminopeptidase N; pAPN: Piglet Aminopeptidase N Receptor; Ro: Basic Reproduction Number ; Rs: Super Spread Event Reproduction Number; Rt : Effective Reproduction Number; pSSE : Probability of Super Spread Event; NSSE : Average number of infections during a Super Spread Event

Introduction

By looking holistically the transmission dynamics of coronavirus epidemics in human, the heterogeneity of population is a catalytic factor for viral dispersal. However it is not the vulnerability of the host but the resistance of the “host-donor” that defines the efficient transmission of the infectious agents [1]. The resistance can be defined as the immunity of individuals raised to disable transmission. Previous Severe Acute Respiratory Syndrome-Coronavirus-1 (SARS-CoV-1) patients, even after 17 years post infection poses a sustained-well-developed, specific T-cell memory response against SARS-COV-1. This specific immunity is intensified according to the increased severity of previous SARS-CoV-1 clinical condition [2]. Furthermore, the patients that survived from SARS-CoV-1, whilst all poses a long term cross reactive immunity against SARS-COV-1, also all, poses reacting T-cells to the N peptides of SARS-COV-2 [3]. Also importantly, the 87.5 % of these patients show a robust

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expansion of T-reactive cells (both CD4+ and CD8+ T subsets) against Nucleocapsid (N) epitopes of SARS-COV-2. Respectfully, the unexposed individuals with no previous history of SARS-1 infection and being negative for N antibodies and neutralizing antibodies of SARS-COV-2, to a 51.35 %, have a reactive T-cell immunity against SARS-COV-2 N protein and Non-Structural Proteins (NSP) of SARS-COV-2 (50 % and 50 % respectively to each group of proteins) [3].

Furthermore a widely distributed T-cell cross reactivity (35-60 %) amongst unexposed individuals also exists against the SARS-COV-2 spike (S) protein [4-5]. The specific memory immunity of unexposed individuals to either SARS-CoV-1 or SARS-CoV-2 is attributed to the cross reactions of common flu coronavirus infections [4-5], and/or to the involvement of animal species cross transmitting coronaviruses to humans [3].

In the context of general population's

- a. Developed to SARS-CoV-1 and,
- b. Pre-existing to SARS-CoV-2 antigens immunity, the hypothesis of SARS-COV-2 propagation through an acquired and diverse immune surveillance system of the general population was investigated mathematically

The metric named dispersion of individual infectiousness and denoted by k , which was first proposed for SARS-1 was used in this study to quantify the role of heterogeneity of individuals for SARS-CoV-2 transmission as a means to investigate for efficient control of the pandemic with Non Pharmaceutical Interventions (NPIs) at a population scale [6]. We therefore performed a statistical calculation of k and explored to define possible relatedness of infector's age as a determinant of k . We have found statistically significant alterations in the capability of dispersing infection due to the differences in the heterogeneity of individuals across the age groups of 0-20, 20-60 and 60-90 years old. These differences may reflect the de-similarities between immune surveillance mechanisms of these age groups that thereafter alter their transmitting behavior for SARS-COV-2 infection. In this respect the cross species barrier transmission of coronaviruses between animal species and human individuals becomes important and is further discussed. Finally the role of known specific cell receptors is presented as a means of correlating the extensive transmission of coronaviruses. This is used to elucidate further the role of pre-existing SARS-CoV-2 immunity of individuals by estimating their transmission behavior as this is influenced by other coronavirus environmental infections. Therefore the role of age of SARS-CoV-2 infectees that were born before and after the previous SARS-CoV-1 epidemic was investigated in terms of their infectiousness capability.

Methodology and Results

Data

We used the COVID-19 surveillance data previously published and the dataset can be accessed freely via the public respiratory [7]

(https://github.com/linwangidd/covid19_transmissionPairs_China/blob/master/transmission_pairs_covid_v2.csv).

The dataset contains 1407 transmission pairs that are identified and reconstructed according to the previous studies, governmental new release and official situation reports [6,8]. We identified 807 infectors, including 300, that infected more than once infectees. These acted as source of infection to transmit to the infectees. We extract the information, including age and gender, of each infector as well as the number of offspring infectees generated by each infector. After excluding the infector with missing information, we collected 777 infectors for further analysis.

Heterogeneity of individual infectiousness: a statistical modelling perspective

We consider the variation in the individual-level infectiousness as a quantifiable scale that affects the distribution of offspring infectee generated by an infector. Following the previous study, we introduce the number of offspring infectee generated by an infector, denoted by r , as a random variable from a Gamma distribution, denoted by $h()$, with mean $R (> 0)$ and dispersion parameter $k (> 0)$ [6]. Thus, we have $r \sim h(R, k)$. Here, R is the reproduction number that is defined as the expected (or average) number of secondary cases caused by one typical infected individual.

The dispersion parameter k governs the dispersiveness of the Gamma distribution. As demonstrated theoretically in the previous study, with R fixed, a larger k results in a lower effectiveness of non-pharmaceutical interventions in controlling the epidemics, which is also discussed in another study [6,8].

Poisson process with rate r , denoted by $f(r)$, is adopted to address the stochastic effects in transmission and to govern the number of infectee caused by each infector, denoted by $Z (\geq 0)$ [9]. Thus, we have $Z \sim f(r) = f(R, k)$. Straightforwardly, $f(R, k)$ is a Negative Binomial (NB) distribution with mean R and variance $R \cdot (1 + R/k)$. By the definition of NB distribution, the probability that one infector generates $(j-1)$ offspring infectees, i.e., cluster size of $j (\geq 1)$, which is denoted by $\Pr(Z = j-1) = L_j$, is given in Eqn. 1.

$$\Pr(Z = j - 1) = L_j = \frac{\Gamma(kj + j - 1)}{\Gamma(kj) \cdot \Gamma(j + 1)} \cdot \frac{\left(\frac{R}{k}\right)^{j-1}}{\left(1 + \frac{R}{k}\right)^{kj + j - 1}}. \text{ (Eqn. 1)}$$

Here, $\Gamma(\cdot)$ denotes the Gamma function. Specially, the NB distribution $f(\cdot)$ reduces to a Geometric distribution when $k = 1$ and it reduces to a Poisson distribution when k approaches infinity. Importantly, a smaller value of k indicates larger heterogeneity in individual infectiousness.

By fitting distribution $f(\cdot)$ to the real-world observations, we may estimate value of dispersion parameter k and explore the determinants of k .

Likelihood inference framework and subgrouping by infector's age

We consider observed samples of number of offsprings from N infectors. We denote the number of infectors who have j infectees associated by n_j (≥ 1). Note that all $j > 1$ in our dataset though j may be 1 theoretically or observed in other datasets and thus we adjusted for this truncation in our likelihood framework. Straightforwardly, we have $\sum_{j>1} n_j = N$. Then, following the previous studies [10-11], we constructed the likelihood function, denoted by L , as in Eqn. 2.

$$L = \prod_{j>1} \left(\frac{L_j}{1-L_1}\right)^{n_j} \text{ (Eqn. 2)}$$

We estimated the dispersion parameter k using the maximal likelihood estimation approach. To explore the association between the infector's age and k , we repeated the above fitting and estimation procedure after sub-setting the dataset into subgroups by the infector's age. We considered 76 age bins and they include 5-25, 6-26, 79-99 and 80+ years. We estimate the value of k for each age bin to examine the association between the infector's age and k .

Results

We estimated the k ranges from 0.4 to 1.5 for different age bins, which is line with previous studies [8,11-12]. We observe an evident downward trend in k as the infector's age increases, with p-value < 0.001 for linear trends testing using student's t -test. We detect a structural break at age bin 20-40 years, in which k drops 47% with p-value < 0.001 comparing with the infector with younger age. This is presented in Fig. 1.

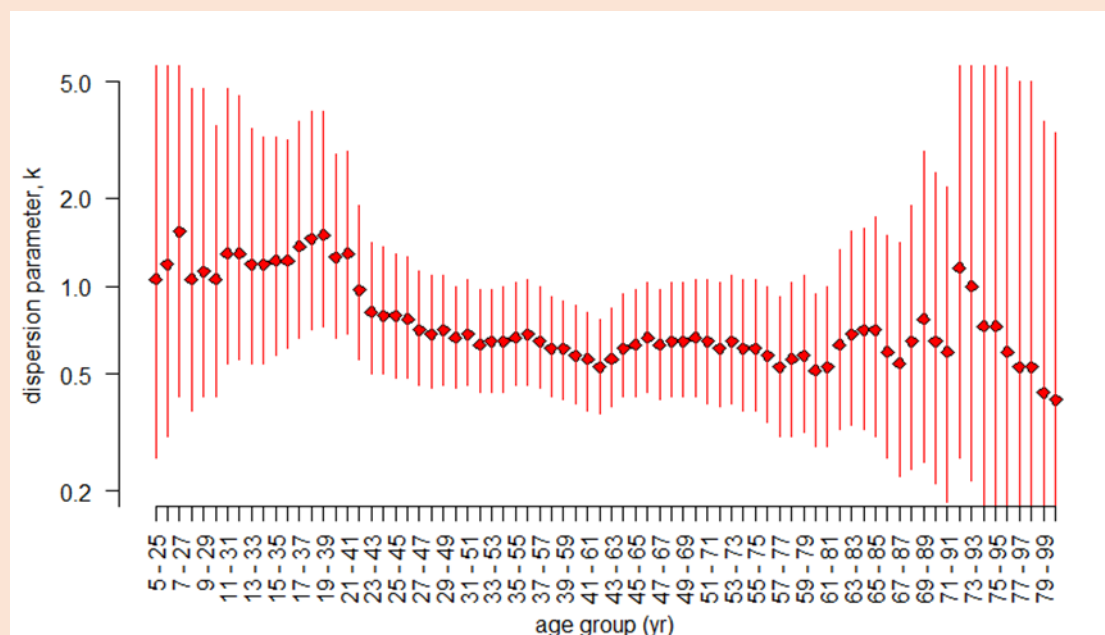


Figure 1: The dispersion parameter (k). The estimated dispersion parameter (k) in different age sub-groups. The dots are the estimates and the vertical bars are the 95% CI.

Discussion

The computational analysis may predict differences in SARS-CoV-2 immunity that result to different non pharmaceutical intervention success outcomes when applied to different age groups

The employed metric named dispersion of individual infectiousness and denoted by k , was first proposed for SARS-1 and has also been used to quantify the role of heterogeneity of individuals in transmitting COVID-19 as well as to estimate the difficulty to control the epidemics with Non Pharmaceutical Interventions (NPIs) at a general population scale [6,11,12]. Thus the statistical calculation of k and exploration to define possible relatedness of infector's age as a determinant of k was performed in this study. The estimated k ranges from 0.4 to 1.5 for different age bins is in line with the previous studies [8,11,12]. An evident downward trend in k as the infector's age increases, with p-value < 0.001 for linear trends testing using Student's t -test was observed. A structural break at age bin 20-40 years, in which k drops 47% with p-value < 0.001 comparing with the infector with younger age (Fig. 1) was detected. The dataset used to investigate the variation in heterogeneity of individual infectiveness with age initially contained 1407 transmission pairs, out of which 807 identified infectors [7,12]. Out of these infectors, 777 pairs were selected due to their adequate information about age. In the investigation of individual infectiveness the reproduction number R was kept constant in order to measure the variation of individual infectiveness, k , with age. The measured k value decreased with age increase. The important difference was clearly evident between the two age

groups 0-20 and 20-60 years of age and was moderately evident between the 20-60 and 60-90 years of age. The importance of this finding lies in the differences in k value that reflect differences in the heterogeneity of each sub-population group [6,8]. For the youth ages as k is larger, the heterogeneity of subgroup population is smaller and for the older age group (20-60 years old) as k , decreases the heterogeneity between individual increases [6,12,13]. As presented in Fig. 2, when hypothesizing that R equals to 2, which is a realistic scenario for SARS-CoV-2, for four seed cases of youth and old age respectively, the offspring cases will be eight for each age group [14]. This means that almost all youth age infectors will produce two offspring cases, whereas for 20-60 years of age infectors, almost half of infectors will not be able to produce any offspring case and only one will be able to produce six offspring cases and one, two offspring cases. The older (60-90 years of age) subpopulation group may probably be able to produce a mixture of the above cases.

These results predict that by reflecting the change of individual's infectiveness with age and thus their heterogeneity, the NPIs are more applicable to the sub-population older than 20 years of age, whereas the NPIs are not expected to provide an adequate solution for disease spread containment from younger age infectors [6,15]. Given the situation that a high proportion of youth age remains asymptomatic but highly infectious, this makes the effort of contact tracing within this group even more difficult and thus urgent to succeed [16,17]. The specific screening strategies for the youth population, in order to identify as more as possible positivity for SARS-CoV-2, will make the restriction contact measures more efficient regarding the overall population containment as almost all young infected individuals are likely to be able to transmit the disease. The notable differences detected in the heterogeneity of individuals across the age groups of 0-20, 20-60 and the slight different heterogeneity over the age of 60-90 years old may reflect their de-similarities between development of immune surveillance mechanisms of these age groups and this may be due to the contribution of environmental cross species barrier transmission infections by other coronaviruses as presented in Fig. 3 [18-27]. A cross reactive immunity is very often encountered in previous SARS-CoV-1 patients and unexposed individuals to SARS-CoV-2 [3-5]. Due to the COVID-19 global overspread and consistence, the precision of targeted pharmaceutical interventions is needed and this may be the appropriate way to lower seed cases in population groups with smaller heterogeneity. This seems to be able to help and contain SARS-CoV-2 pandemic in similar ways to the previous SARS-CoV-1 epidemic [14,15].

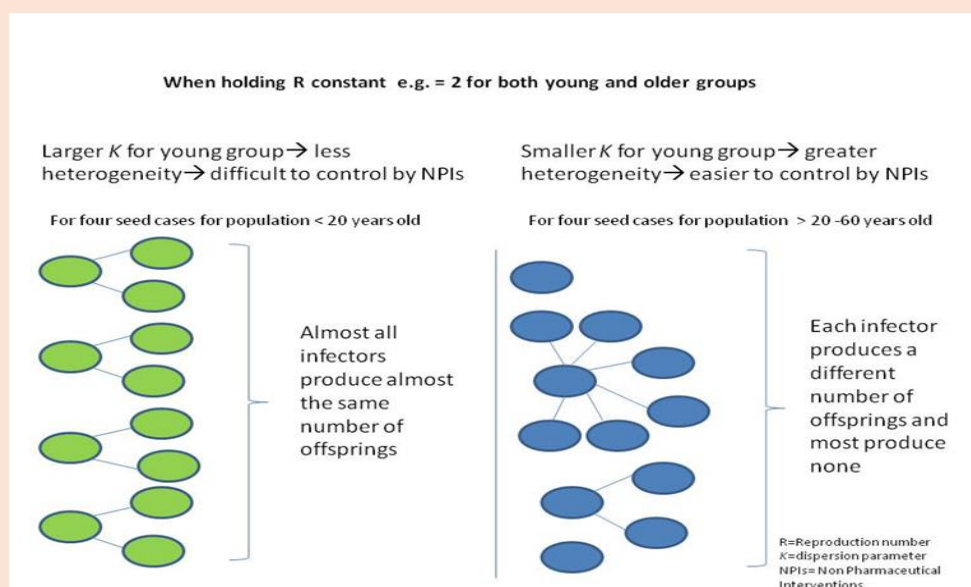


Figure 2: The difference of (k) between age groups corresponds to the ability of infectors to transmit the disease.

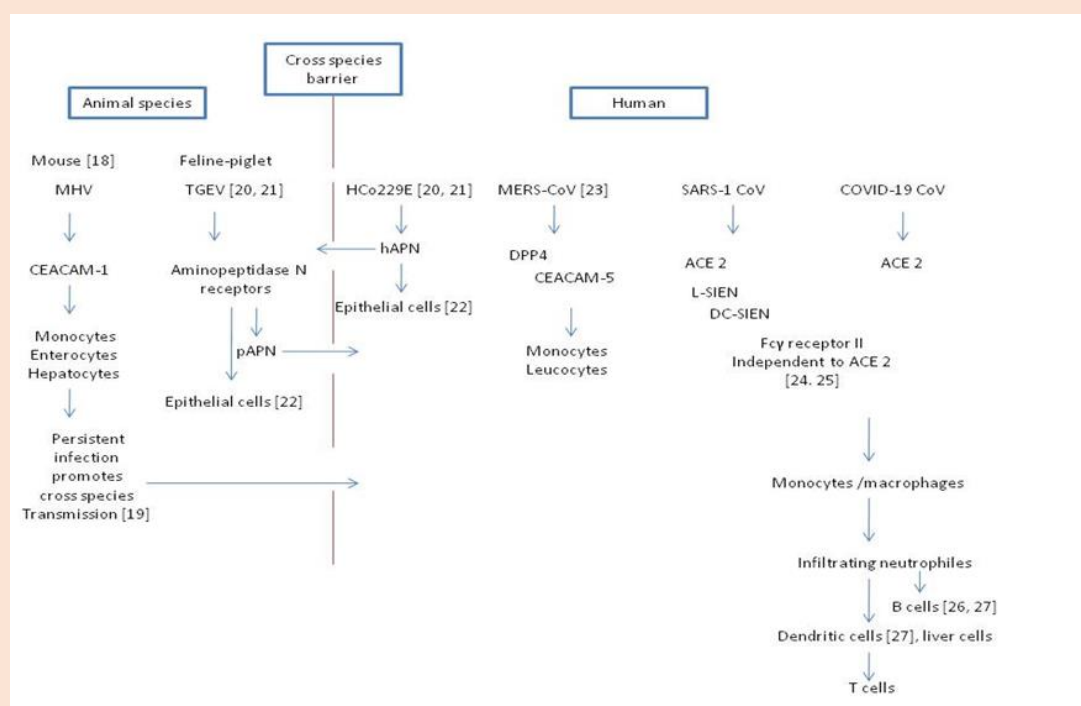


Figure 3: The cross species barrier transmission between human and animals by coronaviruses and the corresponding cell receptors involved. The cross species barrier infection is achieved by coronaviruses using suitable receptors that enable their transmission. Molecules like the Carcinoembryonic Antigen-Related Adhesion Molecules (CEACAM) comprise a family of antigens which are highly preserved across animal and human species

and their participation can lead to a wide immune cellular dispersal of coronaviruses throughout the human organism [35,36]. The cross reactive immunity encountered by previous SARS-CoV-1 patients and healthy individuals to SARS-CoV-2 antigens is attributed to these viral infections in humans [2-5]. (pAPN: Piglet aminopeptidase N receptor; hAPN: Human aminopeptidase N receptor; L-SIEN: Liver/Lymph node specific intracellular adhesion molecule 3-grabbing integrin; DC-SIEN : Dendritic cell specific intracellular adhesion molecule 3-grabbing non integrin).

The cell receptors and their immunity implications in coronaviruses transmission

The small variations of the pathology profile between SARS-CoV-1, SARS-CoV-2 and MERS-CoV infections reflect their small amino-acid protein sequence alterations as a consequence of mutations to *S* protein gene that consequently alter the binding affinity of viruses to specific receptors of human cells [28]. However, which cell is susceptible to viral transmission, centrally determines the further viral overspread and pathogenesis [29]. Although that the presence of angiotensin I converting enzyme 2 (ACE-2) is tightly connected to SARS-CoV-1 ability for cell to cell fusion this fact however may be due to the distinct binding affinity of this type of coronavirus, as the ACE-2 is not the sole molecule facilitating cell entry for this kind of viruses [30,31]. Looking at the pathology complications, for example the Acute Respiratory Distress Syndrome (ARDS), this symptom was encountered to up the 20 % for SARS-CoV-1 cases and the similar ARDS conditions does not exceed in frequency the 30 % of all other complications for SARS-COV-2 and MERS-CoV infections [29]. Thus, the commonalities in pathology, (although with variations) for SARS-CoV-1, SARS-CoV-2 and MERS-CoV infections, allow to suspect for the usage of other common receptor pathways that are essential for a successful cell to cell transmission between different coronaviruses that remain so far undetected as shown in Fig. 3 [29]. For example, for the Mouse Hepatitis Virus (MHV) the fundamental molecule to fuse inside susceptible mouse cells is the *Carcinoembryonic* Cell Adhesion Molecule-1 (CEACAM-1) [18]. The CEACAM-1 however is not only specific for rodents but is also expressed by human immune cells although that the immune cells express distinct CEACAM isoforms due to different evolutionary splicing events [23]. Moreover, human cells express also the transmembrane CEACAM-3, CEACAM-4 and the CEACAMs 5 to 8 Glycophosphatidylinositol (GPI) linked surface proteins [32]. In this respect, although the Dipeptidyl Peptidase-4 (DPP-4) was considered as the main cellular receptor for MERS-CoV entry, this was until a novel finding identified CEACAM-5 as a key cellular receptor for augmenting virus attachment to host cells [31]. SARS-CoV-1 use's mechanisms of immunopathogenesis that orchestrate the manifestation of disease symptoms and the virus uptake by macrophages increase's using cell surface Fc receptor interactions [33]. Complementary, specific cell adhesion molecules contribute to form synapses and induce cellular polarity and this process is utilized regularly by SARS-CoV-1 receptors [34]. Notably, viruses by performing adapting imitations of the cell adhesion molecules ensure their

successful transmission from an infected to an uninfected cell [34]. At this point is also important to emphasize that the antibodies specific for SARS-CoV-1 spike protein potentiate the infection of human B cell lines despite an otherwise protective and neutralizing immune response in animals [24]. This can be also very important for SARS-CoV-2 vaccination side effects and failures. Moreover, the experimental evidence has shown for an antibody mediated infection of SARS-CoV-1 through the Fc γ receptor II which is independent of ACE-2 receptor [24]. This antibody dependent enhancement of virus entry into the immune cells may be also responsible for viral dispersal and onset of pluripotent infection through infected dendritic cells as shown in figure 3 [27]. The pathogen and host co-evolution events have led the mammalian Carcinoembryonic (*CEA*) family of genes to have high species specific diversity [25]. For example, the CEACAM 3 in contrast to the CEACAM 1, has a specific Immunoreceptor Tyrosine Based Motif (ITAM) containing an Ig-V-like ligand binding domain similar to the Fc γ receptor [25]. Moreover, it is important to note that the CEACAM 3 serves also as an essential adhesion molecule for *Neisseria gonorrhoeae* epithelial cell internalization [35]. It is therefore likely that both SARS-CoV-1 and SARS-CoV-2 and this is due to their similarities in their clustering and adaptation genetic events [28], use similar to Fc γ immune receptors as is the case of CEACAM 3 and through these receptors are able to disperse in common ways through the immune systems of the hosts avoiding immune surveillance mechanisms [31,34]. This common receptor immune propagation of viruses shown in Fig. 3 may be useful to explain to some extend

- a. The cross reactive responses encountered in previous SARS-CoV-1 patients and unexposed individuals to SARS-CoV-2 antigens
- b. The notable differences in the heterogeneity of infectiousness of SARS-CoV-2 detected in this study across the investigated age groups which coincide with individual's ages that were born before and after the SARS-CoV-1 epidemic

Finally it is important to emphasize that the related infections by coronaviruses centrally define the developmental stages of immunity which in some cases can be severely influenced in terms of long memory immunity acquisition [37]. This is also very important for children's immunity which is co-developed alongside with environmental coronavirus infections [16].

Conclusion

Even though the probability of an infected individual to produce secondary infections varies between individuals in a systematic way, the reflection of biological differences such as those of the adoptive immunity within an infected population may lead to a better position to characterize in depth the potentiality of vigorous transmission and pathogenesis by coronaviruses. The transmission of SARS-CoV-2 from individuals of youth age to the rest of general population according to this study, seems to be higher and more difficult to manage due to the smaller heterogeneity of this age group. Finally the differences of behavior in

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infectiousness between age groups may reflect the acquisition of cross immunity to other coronaviruses and this is important to consider during immunization protocols in order to avoid overwhelming cross reactivity clinical outcomes due to the SARS-CoV-2 vaccines which can inevitably have harmful consequences to general public health.

Author Contributions

AK inspired the hypothesis of propagation of COVID-19 through different immune surveillance of population groups. SZ conducted the proper mathematical analysis to investigate the AK hypothesis and performed the mathematical part of this manuscript. KK and JL gave their expertise in reviewing and editing this manuscript. All activities: conceptualization, methodology, analysis, validation, investigation, writing up the original manuscript, reviewing, supervision and administration were performed by AK. SZ, KK and JL.

Conflicts of Interests

The authors declare that have no competing interest and not any conflict of interest.

Ethics Approval and Consent to Participate

This study did not involve any participation of humans or animals as it was based solely on COVID-19 surveillance data of public access.

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