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A model to rank viruses based on their probability to cause the next pandemic.

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Abstract

The greater the sequence similarity between the receptor binding domain (RBD) or the host entry receptors (HER) of a zoonotic virus to the RBD or the HER respectively of human infective viruses, the greater the probability of a species jump. The RBD as well as the HER for 106 zoonotic viruses, 46 human infective viruses and 54 human/animal HERs' were obtained from the literature and/or from the UNIPROT database. Ten training virus pairs whose vaccines were known to be cross-reactive (for each pair) were BLASTed to find similarities. The BLAST results for each virus pair were taken as input parameters to formulate an equation whose output; the cross reactivity value (CV); was indicative of the extent of cross reactivity between the virus pair. A CV < 1 indicated that the RBDs' of test virus pairs, or entry receptor pairs were similar and hence would produce cross-reactive antibodies. The CV between each zoonotic virus and 46 human infective viruses was determined. For those pairs where the CV < 1, a Virus Component Number (VCN) was calculated using affinity and avidity values. Similarly, a Receptor Component Number (RCN) was obtained using BLAST HER similarity scores for each zoonotic virus receptors and the receptors for 57 human infective viruses. Adding the VCN and RCN for each virus resulted in a Total Score that was ranked from greatest to least. Viruses that are highly prevalent in the human population were excluded, and the top ranked 10 emerging viruses with case fatality rates of > 50% were selected. Our model can predict which existing vaccines are cross reactive against the emerging viruses, hence pre-empting and preventing pandemic genesis by vaccinating geographically susceptible populations. Additionally, the list is small enough that resources can be mustered to research, manufacture and stockpile vaccines and/or antiviral drugs against these ten viruses. The model is a much needed valuable tool in the as yet sparse toolkit of predicting and preventing pandemics caused by lethal zoonotic viruses.

Keywords
virus, pandemic, next pandemic, BLAST, COVID-19, SARS-CoV2, predict pandemic, world health organization, repurposed vaccines, vaccine, outbreak, zoonotic virus

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Introduction

Our ability to predict, or to rapidly respond to pandemics is limited. We neither have robust and consistent surveillance models nor the computational tools for accurate prediction. The magnitude of the endeavor itself is vast and our toolkit is extremely limited. As a species, we have survived the most recent SARS-CoV2 pandemic with the virus being ~ 10 times more lethal than the flu, yet causing ~10^5 worldwide deaths. A virus with a 4 orders of magnitude greater mortality rate has the potential to decimate 1/10th of the global population, and one with a 5X order of magnitude may spell the end of our species (1). Global organizations such as the World Health Organization (WHO), to whom we have entrusted the mantle of public health and funding, are more retroactive than proactive and function more in an advisory, than in a problem-solving capacity. We need models, so that we can pre-empt, circumvent, predict and mitigate the next pandemic.

A multitude of mathematical models exist to predict how a certain outbreak, epidemic or pandemic will evolve (2, 3); there is however, a paucity of mathematical models to predict which virus (or organism) this outbreak, epidemic or pandemic will evolve from. Our model aims to address this gap in the current corpus of scientific knowledge.

There are various medical interventions used to prevent undesired outcomes in human health. As seen with the recent COVID-19 pandemic, treatment (the use of drugs and other means to combat disease) and prevention (the use of defensive measures such as vaccines before pathogenic invasion) are crucial when it comes to unprecedented situations. However, a consequence of unpredicted situations is limited time to develop and test these medical interventions in time to treat and prevent spread/disease/fatality before a situation such as a pandemic ensues. We have used the Basic Local Alignment Search Tool (BLAST), available gratis from the U.S. National Library of Medicine, to rank the probability with which zoonotic viruses will jump over to humans. This algebraic algorithm ranks each virus by comparing the amino acid sequence of the receptor binding domain and its host binding receptors with common human viruses and receptors, respectively. The results of this algorithm show which zoonotic viruses we should prioritize research about, before a calamitous situation such as a pandemic develops.

Model development

We started from the simple premise that viruses that have similar receptor binding domain (RBD) sequences must have similar infectivity characteristics (5-8). Similarly, human receptors that have similar sequences must have a higher change of engaging (binding to) similar viruses. Hence, if we could quantitate the degree of similarity between the RBD of different viruses - and between receptors that bind to the same virus, we could rank the viruses according to their propensity to jump species. This is the path of least resistance for a virus (46) since it does not need to undergo extensive mutation(s) in order to infect another species. For this purpose, we assembled and utilized a database consisting of 46 different viruses that have a long history of infecting humans, as well as the corresponding human or animal entry receptors for those viruses. The

greater the number of human viruses that were similar in RBD characteristics to the zoonotic virus (defined as the avidity and technically determined by a cross reactivity value (CV) < 1), the greater the probability of the zoonotic virus to jump species. Concurrently, the lesser the average cross reactivity value (CV) - defined below as the average affinity - for a zoonotic virus when compared with the 46 human viruses, the greater the probability of the zoonotic virus to jump species. The product of the inverse of the average affinity and the avidity hence yielded a virus component number (VCN) that was directly proportional to the ability of that particular zoonotic virus to jump species.

The receptor component number (RCN) was calculated in a similar way to the VCN. The greater the number of human receptors that were similar in sequence characteristics to the animal receptor of the virus (defined as the avidity), the greater the capability of the zoonotic virus to jump species. Concurrently, the lesser the CV (average affinity) for a zoonotic virus receptor, when compared to the 57 human virus receptors, the greater the capability of the zoonotic virus to jump species. The product of the inverse of the CV and the avidity yielded the RCN that was directly proportional to the ability of that particular zoonotic virus to jump species.

Adding the VCN and the RCN yielded a quantitative measure of the relative probability of a zoonotic virus to jump species.

Proteins with a high sequence similarity are known to cross-react (5). Various computational models have been developed based on the BLAST to predict antigenic similarity (6-8). Some of these models are heuristic and use one parameter values, such as the E-value or the Percent identity, to determine sequence similarity. Drawing upon this previous body of work, in our model, viruses were considered to have similar RBD characteristics if antibodies against them were cross-reactive. A set of ten pairs of viruses were found in the literature for which this was the case. These virus pairs and their BLAST results are presented in Table 1.

Table 1: BLAST results for virus pairs (training set) for whom antibodies are known to be cross-reactive

Virus 1 (Uniprot accession#)	Virus 2 (Uniprot accession#)	BLAST results							Cross Reactivity value (CV)
		Max score	Total score	Query cover	E-value	Percent identity	Accession length	Reference	
Rabies virus (P03524)	Vesicular stomatitis virus (P03522)	67.8	67.8	54%	2e-16	25.08%	511	9	4.07×10^{-17}
Rabies virus (P03524)	HIV virus (Q0H5Z8)	21.2	21.2	14%	0.17	17.5%	837	10	0.081
Rabies virus (P03524)	Nipah virus (Q9IH63)	15.0	15.0	1%	8.6	71.43%	546	11	0.657
SARS CoV2 virus (P0DTC2)	Measles virus (P08362)	20.0	20.0	5%	0.62	22.50%	617	12	0.170
SARS CoV2 virus (P0DTC2)	Mumps virus (P11235)	27.3	113	18%	0.004	34.29%	582	12	0.003
SARS CoV2 virus (P0DTC2)	Rubella virus (P08563)	16.5	191	9%	14	55.56%	1063	12	31.01
Dengue virus (P17763)	Zika virus (A0A024B7W1)	3880	3880	99%	0.0	55.25%	3423	13	0.00
Influenza A virus (P03452)	Hepatitis C virus (P27958)	22.7	50.3	82%	0.20	40.54%	3011	14	0.329
Rotavirus A (P12473)	HIV virus (Q0H5Z8)	16.5	143	22%	5.5	33.33%	837	15, 16	11.97
HPV type 16 (P03107)	SARS CoV2 (P0DTC2)	22.3	357	83%	0.096	34.62%	1273	17	0.565
Dengue virus (P17763)	SARS CoV2 (P0DTC2)	25.4	384	20%	0.081	20.21%	1273	18	0.771
SARS CoV2 (P0DTC2)	HIV virus (Q0H5Z8)	16.9	313	39%	8.1	32.43	837	19	38.718
Junin virus (P26313)	Machupo virus (Q6IUF7)	723	723	100%	0.0	69.35%	485	20	0.00

Three pairs of the thirteen virus pairs presented in Table 1 (SARS-CoV2 and Rubella virus pair, Rotavirus A and HIV virus pair and SARS-CoV2 and HIV virus pair) presented with CV >> 1, implying that their antibodies are not cross reactive. On the other hand, the 10 virus pairs that are known to be cross reactive from the literature have CV < 1, with the least and the greatest values of 0.00 and 0.771. Since there was an order of magnitude difference in CV between the similar and non-similar virus pairs for the training set, in this work, tested virus pairs were considered to be similar if their CV values < 1.0.

The ratio of the Total score to the Max score was interpreted as being the extent of dis-similarity between the query sequence and the returned sequence. A logical deduction inferable from the table was that, the greater the ratio of the Total score to the Max score, the lesser the E value needed to be in order to retain cross-reactivity. Since the E-value depends on the accession length (the lesser the accession length, the greater the E-value), this value was normalized for an accession length of 100 amino acids (see equation 1 below). Furthermore, it was noticed that as the dis-similarity (the ratio of the Total score to the Max score) increased for the two protein sequences, the percent identity needed to be greater for those protein sequences to generate cross-reactive antibodies. This makes intuitive sense because the percent identity is a measure of the functionality of the protein (its taxonomic distance from the common precursor). The lesser the value of the CV calculated from equation 1, the greater the *affinity* of the returned RBD (as compared to the query RBD) to bind to the common receptor. In other words, the lesser the CV, the greater the binding affinity. The *avidity*, in the context of this work, is defined as the *number* of viruses with which the query sequence has a CV<1. The product of the inverse of the average affinity and the avidity hence represents a number that ranks zoonotic viruses in their capacity to jump species.

Materials and methods

A list of viruses was obtained from reference 4, where the authors identified viral traits that predicted the human transmission ability of zoonotic viruses. They, in turn, obtained the database of viruses from various sources (21-24).

Most viruses were referenced on ELIXIR core data resource UniProt, and most receptors were obtained through UniProt citations. Recently found receptors were identified through a literature search. Some viruses were under-researched and no information could be found in the public domain about their entry receptors. In these instances, the number of their entry receptors was equated to the number of their closest taxonomic species in the same genera and the RCN calculated based on this number.

All BLAST values were calculated using the U.S. National Library of Medicine web based Protein BLASTp (25) algorithm with the 'align two or more sequences' box checked. The default Blastp algorithm parameters were used except for the Expect-value (E-value), which was set to 100. The definitions of the various sequence comparator parameters in Equation 1 below can be found by clicking the 'help' tab at the BLASTp webpage (25).

The cross reactivity value (CV), was calculated based on the following equation:

$$CV = \left[\frac{Totalscore}{Maxscore}\right]\left[\frac{(E-value)(Accessionlength)}{100}\right]\left[\frac{1}{Percentidentity}\right] \qquad \text{Equation 1}$$

Based on the results of the CV from the training set, values of CV<1 were considered to be significant (antibodies against one virus would be effective against its paired counterpart) for the test set. Hence, if the calculated CV from the BLAST results for a test virus pair < 1, the RBDs' of those two virus pairs were deemed to be similar in terms of infectivity.

We considered whether signaling receptors, pre-attachment receptors, secondary attachment receptors or sub-cellular receptors should be included in our model. For example, the TMPRSS2 protease has been shown to assist in SARS-CoV2 entry into cells but is not *per se*, an entry receptor for the virus (26). Similarly, CLEC5A is used as a signaling receptor to sense the dengue virus invasion and then to signal and stimulate macrophages to secrete cytokines. However it does not serve as a primary attachment receptor for the virus (27). Furthermore, receptors for several viruses are either not yet known or are putatively identified as facilitating entry. Some receptors appear to be necessary - but not sufficient - for virus entry, whereas other receptors are sufficient - but not necessary - for viral entry into cells. Hence, for the purposes of this work, only receptors that served as the primary attachment motifs on cellular surfaces were considered. Since subcellular receptors are present inside cells, they were not considered to be candidates for calculation of the RCN.

Data

We defined zoonotic viruses as those that have jumped from a non-human species to humans. We chose 46 human infective viruses based on their long history of human infectivity and a high global seroprevalence. We excluded viruses from our original list of 106 viruses if they had a > 2% seroprevalence in the human population. We reasoned that, at this high a seroprevalence, the virus has mutated into a (relatively) benign variant(s) which should continue on its trajectory of causing sporadic epidemics, without necessarily causing a pandemic (28-31). We were more concerned about those viruses that have only begun to infect humans such that they have not had time (or the necessity) to mutate into more benign variants within their human hosts.

We use the terms 'probable' and 'probability', not in their strict statistical definition, but to indicate the 'path of least resistance' for a particular virus to jump species. To the extent that the 'path of least resistance' is also the one with the greatest statistical probability, the two can be viewed interchangeably within the context of this work.

Results and discussion

Table 2 is a compilation of the results of the BLAST analysis for the SARS-CoV2 query virus aligned with 46 human infective viruses. The CV, calculated per Equation 1, between

the query virus and each human infective virus is tabulated in the last column of the table. When the CV < 1 (highlighted), the query virus was considered to be cross-reactive with that human infective virus, or, in other words, the RBD of the query virus and that human infective virus were considered to be similar. The number of human infective viruses that had the same RBD as SARS-CoV2 was considered as its avidity. The avidity was 13. The arithmetic mean of all the highlighted values in that table was considered to be the average affinity. The affinity was 0.2211. The product of the inverse of the affinity and the avidity represented the rank value of the virus in its ability to jump species and infect humans. This Virus Component Number (VCN) for the SARS-CoV2 was calculated to be $\left(\frac{1}{0.2211}\right)(13) = 58.81$.

Table 2: Comparing RBD sequences for SARS-CoV2 and those of 46 human infective viruses using BLAST and calculating CV per Equation 1.

Virus	Max score	Total score	Query cover	E-value	Percent Identity	Accession length	Accession number	Transmission value	Cross reactivity value (CV)
Measles virus strain Edmonston	19.3	113	24%	1.1	23.76%	617	P08362.1	1	1.672447707
Rubella virus strain M33	18	63.2	10%	5.5	25.37%	1063	P08563.2	1	8.09133272
Influenza A virus (A/Puerto Rico/8/1934(H1N1))	18.5	160	26%	2.1	20.72%	565	P03452.2	1	4.952520088
Influenza B virus (B/Lee/1940)	23.5	295	47%	0.066	30.16%	584	P03460.1	1	0.160427789
Influenza C virus (C/Johannesburg/1/66)	20.2	270	44%	0.64	39.39%	655	P07975.1	1	1.422484975
HIV	17.2	250	35%	7.6	27.14%	837	Q0H5Z8	0.1	34.06753955
Human herpesvirus 3 strain Oka vaccine	19.3	242	27%	1.2	35.48%	623	Q9J3M8.1	1	2.642066464
Mumps virus Miyahara vaccine	26.1	211	45%	0.011	27.87%	582	P11235.1	1	0.018570374
Mumps virus strain RW	17.2	238	34%	4	32.00%	538	P09458.1	1	9.305523256
Human hepatitis A virus Hu/Australia/HM175/1976	19.3	281	46%	4.2	28.89%	2227	P08617.1	0.1	47.13798094
Hepatitis C virus (isolate Japanese)	20.6	258	32%	2.6	26.32%	3010	P26662.3	0.1	37.2397232
Hepatitis C virus (isolate H77)	25.7	294	45%	0.074	26.32%	3011	P27958.3	0.1	0.968435715
Hepatitis E virus isolate Hetian	17.6	256	29%	4.1	27.42%	660	Q81871.1	0.1	14.35448578
Human polyomavirus 1	16.8	205	23%	4.4	30.77%	362	P03088.2	1	6.316526611
Human adenovirus 12	20.2	256	29%	0.7	26.87%	587	P36711.1	1	1.938014717
Human adenovirus 7	20.6	206	24%	0.27	31.43%	343	P15141.1	1	0.294654788
Human adenovirus 2	18.5	316	33%	2.3	22.99%	582	P03275.1	1	9.945513325
Human adenovirus D8	19.3	298	40%	0.6	24.56%	362	P36845.1	1	1.365495941
Human adenovirus E4	24	251	36%	0.036	28.40%	426	P36844.1	1	0.056475
Human adenovirus 40	17.6	245	34%	3.7	26.62%	547	P18047.1	1	10.58362433
Human herpesvirus 4 strain B95-8	17.6	176	19%	6.5	33.33%	907	P03200.1	0.1	17.68826883
Human herpesvirus 4 strain B95-8	15.9	218	24%	15	36.36%	706	P03231.1	0.1	39.93295556
Human herpesvirus 4 strain B95-8	16.8	170	26%	2.3	42.11%	223	P03205.1	0.1	1.232500481
Rabies virus ERA	20.6	195	39%	0.48	25.81%	524	P03524.1	0.1	0.922469277
Human herpesvirus 2 strain 333	25.2	343	14%	0.013	33.96%	393	P03172.2	0.1	0.020476786
Human herpesvirus 6 (strain Uganda-1102)	26.9	282	38%	0.008	24.53%	830	P28864.2	0.1	0.028377057
Human herpesvirus 6 strain Z29	27.8	254	30%	0.004	26.25%	830	P36320.2	0.1	0.011555738
Human herpesvirus 8 strain GK18	20.2	222	26%	0.84	32.50%	845	F5HB81.1	0.1	2.400237624
Human herpesvirus 7 strain JI	21.8	273	34%	0.26	23.70%	822	P52352.1	0.1	1.129283475
Human alphaherpesvirus 1 strain 17	19.3	151	24%	0.7	18.24%	394	Q69091.1	0.1	1.183011772
Human herpesvirus 2 strain 333	25.2	343	14%	0.013	33.96%	393	P03172.2	0.1	0.020476786
Human herpesvirus 5 strain AD169	25.7	365	59%	0.024	30.38%	906	P06473.1	0.1	0.101650943
Human respiratory syncytial virus A2	18.9	221	40%	1.4	22.03%	574	P03420.1	1	4.265362048
Human papillomavirus type 16	18.9	278	39%	1.1	45.45%	473	P03107.1	0.1	1.683848173
Human papillomavirus type 18	18	159	25%	2	23.24%	462	P06793.1	0.1	3.512048193
Simian virus 5 (strain W3)	22.3	222	27%	0.16	34.69%	565	P04850.1	1	0.259425249
Human parainfluenza 3 virus (strain NIH 47885)	18.5	277	50%	1.9	22.08%	539	P06828.2	1	6.94466559
Human poliovirus 1 Mahoney	22.7	271	44%	0.37	31.91%	2209	P03300.3	0.1	3.057835156
Human T-cell lymphotrophic virus type 1 (isolate MT-2)	19.7	181	33%	0.67	21.65%	488	P23064.1	0.1	1.387551377
Human immunodeficiency virus type 1 lw12.3 isolate	21.4	285	46%	0.38	30.00%	856	Q70626.1	0.1	1.444
Human rhinovirus 1A	22.7	249	42%	0.38	27.03%	2157	P23008.3	1	3.326298239
human rhinovirus A1B	22.7	285	39%	0.36	27.45%	2157	P12916.3	1	3.551642955
Human enterovirus 71 (strain BRCR)	30.3	256	33%	0.002	34.29%	2193	Q66478.3	0.1	0.010806834
Echovirus 30 (strain Bastianni)	23.1	321	50%	0.29	27.27%	2194	Q9WN78.3	0.1	3.242220413
Poliovirus type 3 (strain 23127)	21	299	49%	1.5	53.33%	2206	P06209.3	0.1	8.834400364

Table 3: Comparing sequences of the entry receptor for SARS-CoV2 and those of 57 human entry receptors using BLAST and calculating CV per Equation 1.

Bat: ACE2 receptor			https://www.uniprot.org/uniprot/E2DHI3			E2DHI3_RHIMR			
Human Entry receptor		Max score	Total score	Query cover	E-value	Percent Identity	Accession length	Accession number	Cross reactivity value (CV)
Select seq sp|Q96NY5.1|	Homo sapiens	11.7	11.7	55%	0.54	60.00%	510	Q96NY5.1	0.0714
Q13291									
P15529									
Q16653									
Q07021									
Q9P2Y5									
Q9NNX6									
P06026									
P04921									
Q9BYF1									
Q9H2X3									
P01730									
P51681									
P61073									
Q96D42									
Q14973									
P00533									
P60033									
Select seq sp|O95632.1|	Homo sapiens	11.2	11.2	22%	0.5	100.00%	211	O95632.1	0.01055
Select seq sp|Q16625.1|	Homo sapiens	13.5	13.5	55%	0.12	50.00%	522	Q16625.1	0.00753
P33681									
P42081									
P78310									
P06756									
P11215									
P32942									
P19320									
O43921									
P20023									
P13591									
Q14416									
Q15223									
Q9UKJ1									
P20916									
O43557									
Q92956									
Q92692									
Q5NHC6									
P16234									
O60462									
P19335									
Select seq sp|P05069.1|	Homo sapiens	17.2	17.2	44%	0.017	100.00%	1367	P05069.1	0.0023239
P98160									
Select seq sp|P05565.4|	Homo sapiens	5.7	5.7	22%	6.1	50.00%	295	P05565.4	0.3589
P15151									
P11166									
Select seq sp|O14756.3|	Homo sapiens	7.9	7.9	22%	35	50.00%	923	O14756.3	7.0145
P05362									
P01130									
Q6ZTQ4									
P05174									
P17301									
Q14105									
Q14242									
P07355									
Q96MU5									
P55899									

Table 3 is a compilation of the results of the BLAST analysis for the receptor of the SARS-CoV2 query virus aligned with 57 human entry receptors. The list of receptors can be found in the supplementary file "predict-pandemic" in the tab "receptors-human". The CV, calculated per Equation 1, between the query virus and each human infective virus is tabulated in the last column of the table. Where the rows are blank, the BLASTp algorithm returned no significant similarity between the two sequences (i.e. E-value > 100) .When the CV < 1, the query receptor was considered to be similar with that human entry receptor. The number of human entry receptors that were similar to the SARS-CoV2 receptor was considered as its avidity. The avidity was 5. The arithmetic mean of all the CV values < 1 in that table was considered to be the average affinity. The average affinity was 0.0904. The product of the inverse of the affinity and the avidity represented the rank value of the virus in its ability to jump species and infect humans in terms of the similarity between its receptor and the 57 human entry receptors. This Receptor Component Number (RCN) for the SARS-CoV2 was calculated to be $\left(\frac{1}{0.0904}\right)(5)$ = 55.31.

Addition of the VCN and RCN for SARS-CoV2 (58.81 + 55.31) = 114.12 yields a number that is indicative of the ranking order of this virus to jump species and infect humans. This number is found in the 'process-virus' supplementary file in the 16th row of the 'species jump rank' tab. This row is highlighted blue because, at the time of writing, the seroprevalence of the SARS-CoV2 virus in the human population was > 2%. Hence, this virus was not considered further in the evaluation.

To our knowledge, this is the first work where a mathematical model is formulated based on the freely available resource; BLAST; to rank zoonotic viruses according to their probability to infect humans. Experimental evidence to determine cross-reactivity with our predicted virus pairs will further validate our mathematical model and provide a basis for future refined algorithms to determine RBD and HER similarity and propensity to jump species.

Our model's algorithm to predict cross-reactivity can be used as a first approximation to determine which vaccines that are currently in use may be (partially) protective against the emerging zoonotic virus (pandemics). For example, from Table 1, the MMR and Hib vaccines may provide partial protection against SARS CoV2. An inverse association between severity of disease and immunization with these antigens has, indeed, been shown (32, 33). Hence, aside from validating our algorithm to predict cross-reactivity, a change in public health policy to offer these vaccinations to adults may decrease the severity of disease.

The large body of data that we have accumulated (as supplemental files) is anticipated to be useful to researchers who wish to use RBDs' or receptors of RNA viruses in their research. To our knowledge, such a comprehensive database is not yet available in the literature.

Our model assigns a direct proportionality between the CV and the percent identity of the

zoonotic virus RBD to any of the 46 human infective viruses. Hence, the taxonomic distance from the common precursor does influence zoonotic virus infectivity. However, we do not consider the taxonomic distance as being the *only* attribute influencing infectivity, as other researchers have proposed. For example, the african swine fever virus (ASFV), better known as the 'swine flu' has a case-fatality rate of 100% in infected pigs. The Animal and Plant Health Inspection service (APHIS) of the USDA categorically states that the disease cannot be transmitted from pigs to humans (34). ASFV is a large double-stranded DNA virus and is the only member of the Asfarviridae family. Since no viruses are taxonomically related to ASFV, it has been proposed that the risk of ASFV jumping a species barrier is negligible because recombination with other viruses is unlikely (35). However, results from our model indicate that ASFV has among the greatest VCN (69.6), hence it ranks among the most capable viruses in its ability to jump species. Our model hence underscores the importance of not relying on taxonomy alone for predicting species jumps (36). A recent study (37) identified a recently emerged genotype 4 (G4) reassortant Eurasian avian-like (EA) H1N1 virus, which is predominant in swine populations since 2016. G4 viruses bind to human-type receptors, and demonstrate increased replication in human airway epithelial cells. Current human influenza vaccine strains have low cross-reactivity with the G4 variant. The variant has acquired increased human infectivity as demonstrated by increased seropositive rates among swine workers. Such infectivity greatly enhances the opportunity for virus adaptation in humans and raises concerns for the possible increased human-to-human transmission of ASFV. Therefore, we have created a separate ranking for viruses (Table 4) that do not have literature references of having infected humans, but for whom our model predicts a possible species jump based on the total of the VCN and RCN.

In this context, it is interesting to note that our model can identify high-risk viruses before they emerge in humans. This has been a bane of current zoonotic disease surveillance models (38).

Table 4: Viruses that do not have literature references of having infected humans but for whom our model assigns large VCN + RCN

Virus	Virus component number (VCN)	Receptor component number (RCN)	TOTAL	Case fatality rate in relevant animal species
African Swine Fever Virus	69.6	100.14	169.74	100%
Porcine epidemic diarrhea coronavirus (PEDV)	42.68	116.47	159.15	100%
Classical Swine Fever Virus	45.2	106.34	151.54	98%
Bluetongue virus	31.82	106.3	138.12	5%
bovine viral diarrhea virus	36.2	94.6	130.8	6%
Peste des Petits Ruminant	49.6	80.4	130	90%
Bovine Schmallenberg virus	20.66	106.3	126.96	15%
Canine distemper virus (CDV)	29.9	94.6	124.5	50%
Chicken anemia virus	41.23	80.1	121.33	15%
African Horse sickness	10.2	106.3	116.5	50%

Figure 1: A power law dependence between the number of receptors and the RCN

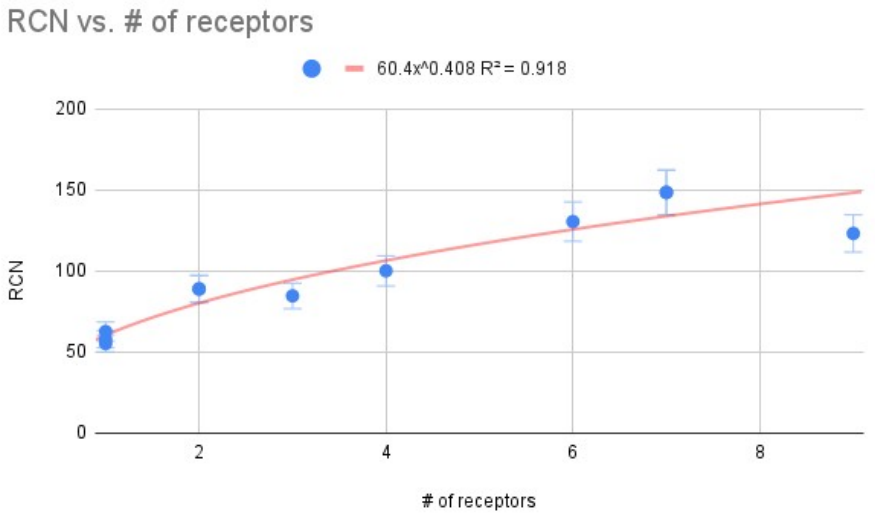
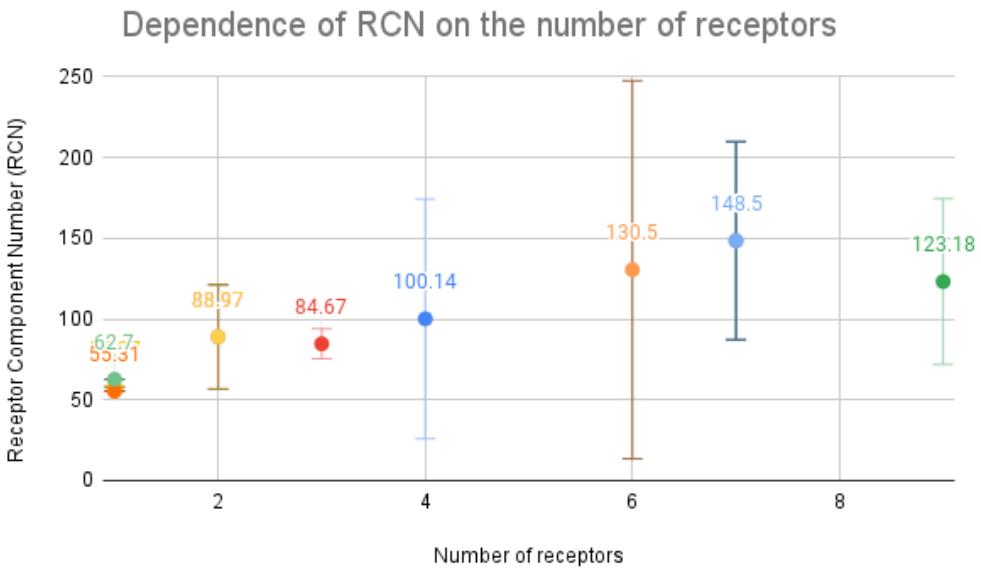


Figure 2: Percent standard deviations



A voluminous amount of data needed to be generated and a large amount of time was required to align each query receptor sequence with 64 human receptors (supplementary google-sheet 1: Predict-pandemic, tab: receptors-human). Assuming an average of 4 receptors engaged for each zoonotic virus, 106 viruses would need individual alignments of 19504 sequences using the blastp algorithm (representing > 325 hours of data entry at 1 minute per alignment); a tedious, time-consuming and data-entry-error prone task. Therefore, the receptor sequences of 11 viruses representing receptor engagements from 1 through 9 were BLASTed for 57 human receptors. The resulting average RCN for each virus was plotted against its number of engaged receptors. As logically expected, the greater the number of engaged receptors, the greater the RCN (Figure 1). In fact, the relationship between the two was adequately described by a power function with an $R^2 > 0.91$. Hence, merely a knowledge of how many receptors a given zoonotic virus engaged, was enough to predict its RCN. This new insight significantly reduced the time and effort required to find the RCN of all the 106 zoonotic viruses. It should be noted that even though the percent standard deviations (PSD) for any specified number of receptors was significant (for example, an 89.6% percent standard deviation for the Foot and Mouth Disease Virus, FMDV, with 6 engagement receptors), the calculation of the RCN used the average of the RCN's for each receptor. Hence, the large percent standard deviations do not influence the calculation of the RCN for an individual virus. There may be additional implications to the magnitude of the PSD's for each virus; whose implications we are yet to discern, but are not relevant in the context of predicting the RCN component of the species jump rank for that virus.

The 'species jump rank' tab of the process virus supplementary file tabulates the VCN, RCN and the total for all the 106 viruses studied. The public domain was searched to find which of these 106 viruses were already widely distributed in the human population. For the purposes of this study, any virus with a global seroprevalence of >2% was considered to be highly human prevalent, and therefore excluded from the zoonotic virus list. The tab 'emerging virus species jump rank' in the same supplementary file lists the viruses that were excluded from the 'species jump rank' tab based on their wide human seroprevalence. This tab contained 75 viruses. A literature search was performed to determine the case fatality rate in humans for these 75 viruses. Some of the viruses did not have any public domain references for ever having infected humans. These appear in Table 4. In the 'predicting the next pandemic' tab, the viruses that caused a case fatality rate of >13% were ranked according to their VCN+RCN. This list was composed of 26 viruses (rows 2 through 28 of this tab). In order to prevent the next pandemic, the list of viruses must be small enough that reasonable resource allocation can be made toward developing vaccines and/or drugs. Hence, from this list of 26 viruses, only those viruses that had a case fatality rate of >50% were selected and ranked according to their VCN+RCN. These 10 viruses appear in rows 42 through 52 of the same tab as well as below in Table 5.

Table 5: A list of model predicted viruses ranked in decreasing order of their probability to cause the next pandemic

Virus	Virus component number (VCN)	Receptor component number (RCN)	TOTAL
Ebola virus	52.12	148.5	200.62
Marburg virus	30.09	148.5	178.59
Chapare virus	44.68	116.5	161.18
Australian and European bat Lyssavirus	40	106.3	146.3
Chandipura virus	39	106.3	145.3
Sin nombre and Bayou (OrthoHanta) virus	31.98	106.3	138.28
Hendra virus	48.43	88.97	137.4
Nipah virus	47.3	88.97	136.27
Louping ill virus	51.2	80.1	131.3
Avian influenza	41.3	60.4	101.7

Our model's predicted list of 10 viruses substantially overlaps that opined by the Gavi alliance (39); an international vaccine consortium founded by the World Health Organization (WHO), The United Nations International Children's Fund (UNICEF), the Bill and Melinda Gates foundation and the World Bank. The Gavi alliance list does not seem to originate from scientific modeling, but rather seems to be drawn heuristically from the

public domain based on manuscripts and reports by opinion leaders. The usefulness of our model, by contrast, lies not only in its quantitative predictive power but also in determining which of the currently approved vaccines will demonstrate enough cross-reactivity with these 10 viruses so that vaccination policies can be implemented *now*, in order to preempt global human infection from these viruses. For example, according to the data from our model, populations living in or near the Ebola geographical belt should be administered the Adenovirus type 4 and 7 vaccine, the Rabies vaccine and the MMR vaccine, because our model shows that these vaccines have considerable cross-reactivity with the Ebola virus. This assertion is a direct result from our BLAST model 'process virus' supplementary file tab 'ebola'. Furthermore, our model can identify high-risk viruses *before* they emerge in humans (Table 4).

Limitations of the model

The central assumptions of our model are that the RBDs' of a pair of viruses are similar if they produce cross-reactive antibodies. Whether or not the pair of viruses produce cross-reactive antibodies can be determined by applying an empirical equation to BLAST results for a training set of 10 virus pairs for which data on cross-reactivity is available in the literature. Any resulting number for a zoonotic virus - human infective virus pair that is less than the CV for the training set is taken to be significant; i.e. that zoonotic virus is considered to have a similar RBD and hence infectivity to the human infective virus. The CV is an empirical construct and there can be no assurance that this purely mathematical model does indeed predict cross-reactivity and similar RBD, without more experimentation.

Our model makes no allowance for factors such as the greater proximity of humans to certain animal species than to others (40), the geographical location of the first species jump, containment efforts, displacement or disruption of animal habitats or migration patterns resulting from deforestation or climate change, selection pressure on certain vectors such as mosquitoes, prevalence and continuation of 'wet' markets that display live animals for human consumption, accidental or deliberate release from research laboratories and co-morbid human disease conditions due to metabolic diseases, among others (41). These factors influence the propensity and capability of zoonotic parasites (including viruses) to jump species. In other words, species jumps may have a random stochastic component that cannot be captured by deterministic mathematical models, including the one such as ours. For example, the SARS-CoV2 virus, succeeded in transforming into a pandemic even though it was ranked 16th in the original list (that included viruses that are already widely prevalent in humans [although see below]). The ratio of the total for SARS-CoV2 to the top ranked virus was (114/245) = 0.47. In our ranking of 10 viruses in the final list (ratio of the total of 10 th to 1st ranked virus = (101.7/200.62) = 0.51. Hence, deterministically, the least ranked virus included in our ranking mimics the lowest probability that led to the SARS-CoV2 pandemic. Had the SARS-CoV2 virus not been determined to be a virus already widely prevalent in humans – or – in other words, had we formulated our model before the SARS-CoV2 pandemic, our model would have

correctly predicted the SARS-CoV2 virus as being one of the 10 most likely viruses to cause the next pandemic, based on its total VCN+RCN of 114.12, which would have placed it at a higher rank than the avian influenza virus in Table 5. It should be noted that deterministically more probable random events are more likely to occur than deterministically less probable random events, however, there is no guarantee that the ratio between the least to the most ranked pandemic enabler virus will be similar for future pandemics. Hence, although the predictive power of our model may not follow exact quantitative rankings for a particular virus, it is likely to be significantly accurately predictive over the ranked range.

Conclusions

There is a significant inverse correlation between mumps titers and/or populations who have received the MMR vaccine, and COVID-19 severity (42, 43). Our model correctly identifies antibody cross-reactivity between the SARS-CoV2 and the Mumps virus (Table 1). This suggests that the MMR vaccine may be useful in limiting the severity of COVID-19 cases.

The model also predicts significant similarities between the RBDs' of Human adenoviruses 7, D8 and 40 and the RBD of SARS-CoV2 (Table 2). In the US, Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is approved for use in military populations 17 through 50 years of age (44). There is no information available in the literature about repurposing this vaccine for use against SARS-CoV2 or a statistical analysis of military personnel who have received this vaccine vis-à-vis their COVID-19 incidence or severity.

Similarly, the model predicts antibody cross-reactivity between the causative virus of Rabies and SARS-CoV2 (Table 2). Neurological symptoms associated with the SARS-CoV-2 infection, suggest viral CNS penetration, probably by binding to the nicotinic acetylcholine receptor (nAChR). This mechanism is similar to that by which the destructive neurological effects of rabies virus infections are mediated. It is speculated that the absence of neurological symptoms in dogs afflicted with SARS-CoV-like canine respiratory coronavirus may be due to the widespread prophylactic mandatory canine vaccination in the US that potentially engenders cross-reacting IgGs against viral nAChR-binding domains (45). The Rabies vaccine may thus prove useful in blunting the neurological effects of SARS-CoV2.

Our mathematical equation also predicts RBD domain similarity between the SARS-CoV2 virus, and Human Herpes and Hepatitis C viruses. There are no approved vaccines for Herpes or Hepatitis C. There appear to be no clinical trials to determine if populations infected with these viruses are more resistant to infection by SARS-CoV2. Interestingly, as a corollary, it may be speculated that administration of the SARS-CoV2 vaccine may decrease the risk of infection with Herpes or Hepatitis C virus.

Based on a training set of 10 pairs of viruses, each pair with known antibody cross-reactivity, we formulated a simple mathematical equation to predict if antibodies against the RBDs' of any two viruses would be cross-reactive. Using the input from BLAST for a pair of viruses into this equation, we compared each virus in a

testing data set of 106 viruses to each of 46 individual viruses known to infect humans. We calculated a virus component number (VCN) for each of the 106 viruses which represented the relative probability of the virus to infect humans based on RBD similarity. We next compiled a list of 57 human receptors for the 46 individual viruses known to infect humans. We performed a literature search to identify entry receptors for a large number of the 106 viruses. We used the same equation to calculate the similarity between the receptor for 10 viruses to those of the list of 57 viruses. We found that the calculated receptor component number (RCN) for each of those 10 viruses and the number of receptors for each followed a power function with an $R^2 > 0.91$. Using this relationship, we were able to calculate RCNs' for all the 106 viruses which represented the relative probability of the virus to infect humans based on the similarity between the entry receptors of that virus and those for the 57 viruses that already are known to infect humans. We added the RCN and VCN together to rank the 106 viruses according to their 'path of least resistance' to infect humans.

Based on our definition of what constitutes a species jump, we then narrowed the list down to 75 viruses, then down to 26 based on excluding those viruses that had a zero record of human infection. The list was then trimmed to 10 viruses by eliminating from consideration, the viruses that had a case fatality rate of < 50%. These viruses are presented in Table 5.

Various public health policy trajectories may be inferred from our model's predicted cross-reactivity data between virus RBDs'.

First, vaccines that have been discontinued, or are only approved in certain populations could be repurposed and re-introduced as part of the current vaccination regime, after minimal clinical trials. Such vaccines include those for Adenovirus type 4 and 7 and for Rabies, as well as the MMR vaccine, all of which can be made age agnostic and mandated (say) every 2 years, with the desired objective of protecting against SARS-CoV, SARS-CoV2 and emerging viruses (see below).

Second, a renewed impetus must be provided for vaccine development for under-researched or elusive viruses such as Herpes or Hepatitis C which present considerable cross-reactivity against SARS-CoV2.

Third, it is instructive to note that the viruses described above also are predicted to have similar RBD (exceptions in parenthesis) with other emerging pandemic-potential viruses such as the Nipah virus (Hepatitis C), Ebola virus, Lyssa virus, Chapare virus (Rabies) and Marburg virus (Mumps) as shown in Table 6. Either by a remarkable and fortuitous coincidence, or due to the evolutionary path of least resistance, the pandemic capable viruses turn out to be cross reactive against a small number of similar viruses for which approved vaccines are already available. This implies that, by re-incorporating and mandating the MMR, Rabies, Hib and Adenovirus type 4 and 7 vaccines as frequent boosters into current vaccination regimens for the entire global population, the infection risk from emerging viruses (Table 5) may be significantly decreased; in turn decreasing the potential for these emerging viruses to cause a pandemic. The MMR, Rabies and Adenovirus type 4 and 7 vaccines are approved, readily available and do not require specialized cold chain

distribution, hence allowing for rapid and effective global mass vaccination.

Table 6 also shows that the Hendra virus is significantly cross-reactive with the SARS-CoV2 virus with a CV=2.28 X 10^{-3}. This may be taken to imply that the capability of the Hendra virus to cause a pandemic is now significantly reduced, because the global population may have reached herd immunity, having been vaccinated with the SARS-CoV2 vaccine. Our model hence can be used to infer correlations that would otherwise have gone unnoticed, so that resources can be directed for vaccine development where they are the most likely to prove successful in preempting the next pandemic.

Table 6: Predicted cross reactivity of pandemic capable viruses with viruses for whom approved vaccines exist. Data from supplementary file "process-virus".

Virus	Predicted to be cross reactive with approved vaccines for:
Ebola virus	Measles, Mumps, Adenovirus 7, Rabies
Marburg virus	Adenovirus 7, Rabies
Chapare virus*	Influenza B, Mumps, Adenovirus 7, Respiratory syncytial virus[1] , HIV[2]
Australian and European bat Lyssavirus	Adenovirus 7, Rabies, Respiratory syncytial virus[1]
Chandipura virus*	Influenza B, Mumps, Adenovirus 7, Rabies
Sin nombre and Bayou (OrthoHanta) virus*	Influenza B, Mumps, Adenovirus 7, Rabies, Respiratory syncytial virus[1]
Hendra virus	Measles, SARS-CoV2, Mumps, Adenovirus 7, Respiratory syncytial virus[1]
Nipah virus	Mumps, Measles, Adenovirus 7, Rabies, Respiratory syncytial virus[1]
Louping ill virus*	Influenza B, Rabies
Avian influenza	Influenza B, Mumps, Adenovirus 7

1. Moderna mRNA-1345 in Phase I clinical trials, FDA Fast Track status.
2. Moderna mRNA-1644 in Phase I clinical trials.

This illustrates that the model; with its scrupulous database construction and a training data set based on a simple, yet elegant, mathematical premise; can predict easily implementable policies and measures that can be taken *now*, to prevent future pandemics from occurring. When the model is refined using a larger set of cross-reactivity data, its predictive power will increase. Such models, or their derivatives, will provide paradigm changing insights, theories and comparisons between viral receptor binding domains and their human host receptors; attributes that do not yet exist in the public domain.

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