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Methodology

Natural experiment concept to accelerate the Re-purposing of existing therapeutics for Covid-19

Christian G. Daughton *

1944 Spyglass Dr., Henderson, Nevada, USA

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ABSTRACT

One of the many questions with respect to controlling the novel coronavirus pandemic is whether existing drugs can be re-purposed (re-positioned) for the prevention or treatment of Covid-19 - or for any future epidemic. The usefulness of existing approaches for re-purposing range from computational modeling to clinical trials. These are often time-consuming, resource intensive, and prone to failure. Proposed here is a new but simple concept that would capitalize on the opportunity presented by the on-going natural experiment involving the collection of data from epidemiological surveillance screening and diagnostic testing for clinical treatment. The objective would be to also collect for each Covid-19 case the patient's prior usage of existing therapeutic drugs. These drug usage data would be collected for several major test groups - those who test positive for active SARS-CoV-2 infection (using molecular methods) and those who test negative for current infection but also test positive for past infection (using serologic antibody tests). Patients from each of these groups would also be categorized with respect to where they resided on the spectrum of morbidities (from no or mild symptomology to severe). By comparing the distribution of normalized usage data for each drug within each group, drugs that are more associated with particular test groups could be revealed as having potential prophylactic, therapeutic, or contraindicated effects with respect to disease progression. These drugs could then be selected as candidates for further evaluation in fighting Covid-19. Also summarized are some of the numerous attributes, advantages, and limitations of the proposed concept, all pointing to the need for further discussion and evaluation.

1. Introduction

Drug treatments for Covid-19 are urgently needed. Discovery and development of new molecular entities [29] ultimately requires long and costly clinical trials to gain regulatory approval. The shortest route to potential treatments is the repurposing (repositioning) of existing approved drugs (both legend and OTC) for pre- and post-exposure prophylaxis to SARS-CoV-2 or for treatment of Covid-19. The concept presented here is intended to rapidly reveal if any existing drugs have therapeutic potential (or those that could be contraindicated) in treating Covid-19. Drug "repurposing" in this article refers to the use of existing approved drugs for the treatment of a never-considered therapeutic indication - in this case, Covid-19. Just considering unique small-molecule drug entities, the universe of those already approved in the US - for multitudes of different medical conditions - might number several thousand [14]; the numbers of biologics and biosimilars expand this universe considerably [15].

Drug repurposing has proved to be a successful enterprise over the years [6,22,24]. It is often guided by virtual screening methods such as computational approaches and bioinformatics to reveal possible druggable pathways (e.g., see: [22,27]) or even by traditional literature-mining and synthesis (e.g., [7]). But even these approaches often end up selecting potential drug candidates that eventually prove ineffective in subsequent clinical trials. And these approaches are seldom used for predicting drugs that would be contraindicated - in this case, those that could adversely interact with Covid-19 or with co-administered drugs. Computational approaches are also unable to easily identify multiple drugs that might be effective as combination therapies.

Proposed here is a simple, straightforward approach to possibly accelerate the identification of existing drugs for potential repurposing and to quickly identify candidates more likely to succeed in phase 3–4 clinical trials. These candidates should also have better safety profiles than by trialing candidates selected by other means, especially by avoiding the selection of drugs that adversely interact with other drugs. At the same time, it could also potentially reveal drug combinations that provide enhanced clinical outcomes.

A method that could rapidly narrow the initial selection of potential candidates (including combinations) for repurposing with Covid-19 (and also avoiding contraindications) could greatly streamline the conventional approaches for repurposing. It could reduce the probability of

* Corresponding author.
E-mail address: daughton.etox@gmail.com.

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candidate drugs failing trials and thereby reduce the wasting of time and resources. An additional important point is that data mined by this approach during an epidemic could also have the potential to short-circuit imprudent decisions to investigate whether drugs rumored to be effective treatments actually have any potential. During the Covid-19 epidemic, one of the best examples was hydroxychloroquine and chloroquine. Rumors of effectiveness caused shortages for their approved critical therapeutic uses as anti-malarials and anti-rheumatics [33].

2. Concept

This proposed approach would capitalize on a unique opportunity presented by a "natural experiment" inherent in the ongoing clinical treatment and epidemiological examination of the Covid-19 epidemic. This approach would also be applicable to any future epidemic, including the possible seasonal resurgence in Covid-19. Opportunities for natural experiments present themselves without active human intervention. Natural experiments can reside in an event where different subpopulations are suspected of experiencing a spectrum of exposures, ranging from none to extensive. The archetype example is the historic 1854 London cholera outbreak, where Dr. John Snow was able to identify the route of transmission and propose the solution for ending the epidemic.

The proposed approach would identify all drugs used by each of two groups of patient cases defined by whether they test positive or negative for exposure to SARS-CoV-2 and/or test positive or negative for active disease. Each potential drug candidate could be revealed by whether its per capita usage rate for each test group is significantly higher or lower than the usage rates for the other groups. Usage rates that have significant associations with a particular group may have either increased or reduced potential for providing protection or ameliorating adverse therapeutic outcomes in treating Covid-19.

Below is an outline of this proposed approach, termed "Natural Experiment for Repurposing Drugs for Covid-19 Therapy" - or "NERD" as shorthand.

NERD would essentially serve as a continually ongoing, multivariate retrospective observational study. NERD would attempt to guide the repurposing of currently used drugs for pre- and post- prophylaxis or therapeutic treatment of Covid-19. NERD would examine the prior and current drug usage among several combinations of Covid-19 case groups, primarily: (1) those known to have been exposed or infected but successfully cleared the virus and (2) those who required extensive medical interventions or died. An excess prevalence of usage of specific drugs within one group versus another group may reveal those drugs having increased potential to be therapeutic or contraindicated (meriting avoidance in prevention or therapy).

Important to emphasize is that NERD might prove useful not just for revealing potential therapeutics, but also reveal those drugs that might be contraindicated or actually potentiate the progression of adverse Covid-19 outcomes. Many different scenarios can be hypothesized for how drug usage might be associated with Covid-19 clinical outcomes. Consider the two bookend case outcomes for Covid-19: (1) the vast majority that resolve with little to no morbidity and (2) the minority that become acutely serious. The most general hypothesis is that there are drugs (or combinations of drugs) that have protective effects and perhaps others that have adverse effects. To explain the lower incidence of serious Covid-19 outcomes compared with favorable outcomes, perhaps it is the drugs with the lowest overall clinical usage rates that could explain at least a portion of the serious outcomes - especially among clinical cases having no apparent underlying risk factors. It is likely that widespread Covid-19 testing among the general asymptomatic population will reveal that its infected subpopulation is even larger than currently believed for the subpopulation that progresses to serious outcomes. This would point even further to the possibility that perhaps it is the seldom-used drugs that play a role in serious outcomes.

A major obstacle to successfully implementing NERD also needs to be stressed. Initially, the only type of therapeutic drug usage data that would be straightforward to collect would be for drugs used in long-term maintenance therapies (both small-molecule and biologics); vaccines and hormonal agents should also be included. Therapy would needed to have begun several weeks before exposure but exposure dates would almost always have to be inferred. In contrast, drugs used in short-term therapy could be problematic to collect at first because many additional details would be needed: daily dose, duration of therapy, and time-frame of therapy. Many patients may be unable to supply this level of detail. Moreover, the fact that the short-term therapy might overlap with different intervals of the disease progression would make interpretation of collected data much more challenging.

3. Outline of the approach for the NERD concept

(1) As Covid-19 epidemiological surveillance screening and diagnostic testing proceeds, a national database would be continually populated with drug usage data collected from each case among three different combinations of sub-groups based upon whether they tested positive or negative for active SARS-CoV-2 infection or tested positive for past SARS-CoV-2 infection (see Table 1). Patients would provide a list of all drugs they have used over a time period that safely encompasses the earliest possible date at which they could have been exposed to SARS-CoV-2 (for example, 2 months prior). Data for all types of drugs would be collected: legend, OTC, and recreational/illicit drugs - both small-molecule drugs and biologics, as well as vaccines.

Drug metadata to collect would include the route of administration, especially inhalation via the nose or mouth, as these might have a greater chance for adversely affecting the pulmonary system. It might seem that drugs of obvious interest during data collection might be immunosuppressants or antivirals, especially those to be effective against enveloped viruses. But many other drug classes might also be important. A major advantage of NERD would be that the screening process is not guided by known or postulated pathways of exposure, infection, or disease progression, as NERD would essentially test all drugs for which usage data is collected. The importance of avoiding cognitive bias is shown by the evolving knowledge of SARS-CoV-2 infection, where a major route of infection is believed to be pulmonary (via angiotensin converting enzyme 2 - ACE2 - receptors), leading to severe respiratory inflammation. But ACE2 receptors not only populate alveolar epithelial cells, but also endothelial cells, which means that various organs and blood vessels are vulnerable to inflammatory damage and clotting [21].

The collected data would be entered into a computer app that transmits to a central, national relational database pre-populated with generic and trade drug names cross-referenced to their respective unique molecular entities. This would speed data entry, ensure consistent spelling, and account for multiple drug names that correspond to the same molecular entity. Note that it can be very challenging to compile a comprehensive list of unique molecular entities just for small-molecule drugs [14]. Biologics and biosimilars would present their own challenges (e.g., see: [3]).

(2) For each of the three test groups, the collective percent-usage rate of each drug (D_xUR) would be continually updated in real-time. Percentages could also be calculated for sub-groups, determined by the spectrum of severity of clinical status or outcomes - ranging, for example, from asymptomatic, mild, moderate, severe, critical, and death. Note that the population-wide incidence of "asymptomatic" Covid-19 cases (where no symptoms are noted over the entire course of the disease) has yet to be determined (e.g., see: [17]); also note that "asymptomatic" is used in

Table 1
Few combinations of tests are of primary use in mining drug usage data for NERD.

Option	Positive test for ACTIVE infection (RT-PCR)	Negative test for ACTIVE infection (RT- PCR)	Positive test for PAST infection (antibody)	Negative test for PAST infection (antibody)	Morbidities
#1	–	✓	✓	not applicable	asymptomatic to mild (no intensive care ever needed)
#2	✓	–	–	not useful	significant
#3	–	–	✓	not applicable	asymptomatic
#4	–	–	–	not useful	–

this presentation to encompass those who have never been infected as well as those with undetectable subclinical infections.

But asymptomatic cases often progress to being pre-symptomatic, where symptoms become evident days after testing positive. This distinction, however, does not matter for NERD, as all of these cases can be considered positive for infection. So the term "asymptomatic" will be used here.

(3) The D_xUR for each group (and subgroups) would then be statistically compared with each other; alternative comparisons might be with the known rates of general population use of each legend drug, or the estimated population-wide use of each non-legend drug.
(4) Potential drug candidates would be revealed by whether D_xUR distributions are significantly skewed within the major case test groups (see "Options" in Table 1). Normalized usage rates that have significant associations with a particular group may have potential for enhancing protection or therapeutic outcomes or, alternatively, the potential for increasing the risk for developing overt signs of infection or exacerbating clinical outcomes. The database would have to be coded to account for patients who receive multiple tests. Because of the natural heightened rate of mutation with RNA viruses, it would be important to constantly re-screen the same universe of existing drugs for therapeutic efficacy. This would occur automatically as the database is updated in real time.
(5) Interpretation of NERD data and defining the Covid-19 test groups of most use to NERD.

There are currently two general categories of tests for Covid-19: tests that indicate active infection and tests that primarily indicate past infection that has resolved. The former currently relies on RT-PCR or antigen testing, and the latter relies on serum testing for antibodies to SARS-CoV-2; conceivable future tests would be those predicting vulnerability to disease progression. These two groups provide complementary information for clinical, epidemiological, and public health purposes. For NERD, however, the drug usage data collected from these two approaches would yield insights for the screening of drugs with a higher probability of success in repurposing.

A very limited number of possible combinations exist for how case groups can be defined for use in NERD. These groups are determined by the results for each clinical case and the type of testing used: (1) positive or negative for active infection, (2) positive or negative for past infection (i.e., past infections that resolved via immune response with display of little symptomology), and (3) where the case resides on a morbidity spectrum ranging from asymptomatic, to mild signs and symptoms, to severe complications, to death (refer to Table 1).

While there are two overarching test groups with respect to all suspected cases (positive and negative), there are three major types of tests: molecular nucleic acid (e.g., RT-PCR), antigen, and serologic antibody (isotypes IgM and/or especially IgG) (see: [8,19,25]). RT-PCR is the current gold standard for revealing whether an active infection is underway, as it reveals viable, replicating virus; less costly nucleic acid tests with higher throughput are emerging [1,28]. Antigen tests (e.g., based on viral proteins released from the envelope or capsid) can also indicate current infection. Antigen tests for SARS-CoV-2 have only begun commercialization, marked by the US FDA's emergency use authorization for the first antigen test [30].

In contrast, antibody tests (in asymptomatic and mild cases) can indicate a graduated spectrum of possibilities, including whether an infection had been cleared sometime in the past or that an active infection is currently being resolved (assuming that more serious morbidities do not develop). Important to recognize, however, is that NERD cannot be fully implemented until reliable (low rates of false-negative and false-positive), accurate, standardized, and inexpensive antibody testing becomes widely available in order to perform random serological surveys. Not until 1 April 2020 was the first Emergency Use Authorization (EUA) for a Covid-19 serological test (for use in clinical laboratories) issued by the US FDA (https://www.fda.gov/media/136622/download); unknown is when any serological test will receive full approval in the US, where validation for specificity and sensitivity are critical. Antibody testing would also have to assume that pre-immunity was not possible (e.g., from exposure to other coronaviruses). There are many unknowns and problems surrounding serologic tests for Covid-19 [10,20].

A positive test using RT-PCR or antigen testing would yield a relatively definitive indication for an active infection (especially with the presence of key signs or symptoms). In contrast, a negative test for active disease (without any other complementary test) would not be useful for NERD. This is because negative-test cases would aggregate two primary subgroups: (i) those who have never been exposed to SARS-CoV-2 and (ii) those who were infected but who resolved the infection via a successful immune response (being asymptomatic or experiencing only mild infection). Both of these subgroups can be disaggregated only by IgM/IgG antibody testing (option #1 or #3); the course of the disease can transition from infection-positive to infection-negative after testing immune-positive. It is only this second negative-test subgroup (i.e., positive serum antibody test) that would be useful to NERD. Antibody tests provide additional opportunity for interpretation in NERD, as they would represent a portion of the population that was most successful in recovering from self-limited asymptomatic or mild infection. But antibody testing could also prove problematic for interpretation because the patient would need to know when they had probably become infected. If this is not known, then the patient may not know what drug usage they had experienced over the time period encompasses pre-exposure and infection.

In Table 1, the group "Negative test for past infection" (absence of any immune response), whether used alone (option #4) or even if it were used in concert with a test of active infection (option #2), would not provide any useful information for NERD.

Note, however that there are two additional sub-groups among the negative test group, which creates two more groups: (iii) those who are infected but their virus titers are too low to yet detect (these could become positive with subsequent testing), and (iv) those with an active infection but the test yielded a false negative (because of sampling errors or test problems). These two groups would serve as confounders for interpreting negative-test data.

Drugs with PROTECTIVE or THERAPEUTIC POTENTIAL for Covid-19 (with minimal adverse effects) would have a D_xUR distribution

associated predominantly with the Option #1 test group. Drugs with potential adverse impacts would have a D_xUR distribution associated predominantly with the Option #2 test group (positive test for active infection). This latter group could point to: (i) potential contraindications and warn of those drugs to AVOID for Covid-19 treatment, (ii) potential for increasing the risk of developing more serious infection or exacerbating clinical outcomes, and (iii) drugs that might also make exposed individuals more susceptible to developing serious disease (thereby allowing for more vigilance in avoiding exposure). A positive correlation with severe, critical, or especially fatal outcomes could point to negative interactions of a drug with the disease, and thereby inform recommendations to avoid taking the drug during an epidemic (possible examples being the use of IL-6 inhibitors and steroids; see: [13]). Conversely, also for the positive-test group, a lower D_xUR for a particular drug among severe and critical cases (or higher D_xUR among negative cases) could also indicate a protective or prophylactic effect of the drug.

4. Major caveats and limitations for NERD

While the usefulness of positive cases for NERD is straightforward (indicating drugs to possibly avoid), the predictive power of NERD would be maximized by actively seeking out and testing asymptomatic cases from the general population that never displayed signs and symptoms and therefore would have otherwise possibly escaped diagnostic testing. It is these very cases (along with a subgroup of the clinical diagnostic negatives (see Option #1 or #3 in Table 1) that could most likely reveal potential therapeutic drug candidates. Indeed, widespread epidemiologic surveillance screening of the general population for asymptomatic Covid-19 has been done in very few countries - Iceland being one example [11].

A major limitation is inherent with NERD with its reliance on the binary choice of infected cases versus uninfected. The limitation results from oversimplifying the actual process of transmission, which is

Table 2
Attributes, advantages, and limitations of NERD.

Major potential advantages of NERD for two test groups	
Significant correlation of drug having higher usage among patients with: NEGATIVE TEST for active SAR-CoV-2 coupled with POSITIVE TEST for antibodies (Option #1)	Could reveal those drugs with PROTECTIVE or THERAPEUTIC POTENTIAL for Covid-19, with minimal adverse side effects.
Significant correlation of drug having higher usage among patients with: POSITIVE TEST for active SAR-CoV-2 (Option #2)	Could reveal potential contraindications and warn of those drugs to AVOID during Covid-19 treatment.

Additional potential advantages of NERD include

- Any knowledge of the pathogen itself or disease progression would not be needed because NERD would rely solely on real-time, real-world evidence for selecting drug candidates. Because of this natural process of drug selection, any selected drug candidates for repurposing would have a higher probability of success in phase 3–4 clinical trials or for compassionate use.
- As testing of a population expands, the test population size could be orders of magnitude larger than possible in any clinical trial.
- The predictive power of NERD would increase as the incidence of testing covers an increasingly larger percentage of the randomly selected general population.
- The approach naturally incorporates its own inherent natural control group as a result of the diagnostic testing - namely, the negative-test group with positive antibody test.
- A major advantage might be the ability to reveal combinations of drugs that could possess synergistic therapeutic potential. Potential combination drug treatments are extremely difficult to predict with virtual screening approaches.
- Association with the positive-test group might indicate a drug that makes Covid-19-positive individuals more susceptible to developing serious morbidities. This would allow for more vigilance against pathogen exposure if the drug is medically necessary or in cessation of the drug if possible.
- Unproven off-label drug therapies that could cause harm (such as during compassionate use) could be potentially avoided; some possible examples include the use of IL-6 inhibitors and steroids for end-stage Covid-19 (e.g., see: [13]). Furthermore, by revealing combinations of drugs that significantly correlate with the positive-test group, further harmful experimental therapies could be avoided.

Complications and confounding factors include

- One of the major obstacles to implementing NERD would be the practical difficulties in collecting the needed drug usage information from each patient during or after Covid-19 testing. Collecting drug usage information has long been the initial step in the conduct of "medication reconciliation" reviews between the physician and patient during normal visits. The collection step has been problematic [23]. One possible means of addressing this weakness would be public service announcements urging everyone to maintain a list of all medications used in the preceding months during epidemics.
- As with many epidemics, a major problem is inaccurate case counts and under-reporting [31]. With overwhelmed health care systems, an unknown but possibly very large percentage of positive cases will go undetected. Many will die from unknown causes (because of unavailable testing) and many cases will be endured solely at home, with only mild symptoms. Very valuable data are therefore lost simply because of incomplete medical records and lack of widespread testing [16]. Many mild cases can be missed when they are advised to avoid testing because testing is in short supply.
- In the absence of widespread randomized testing of the asymptomatic population, drug usage data from a large percentage of the population belonging to test Option #1 would never be acquired. This reduces the predictive value of NERD for potentially beneficial drugs.
- NERD as presented here makes a liberal assumption that the total population has full access to Rx and OTC drugs. This is overly simplistic for populations under-served by healthcare.
- For some pathogens, specific sub-groups of the population can be more susceptible or less susceptible to serious complications or higher death rates, often because of added risk factors. This means that those drugs having higher usage rates among those vulnerable groups could bias the results for negative- and positive-test groups unless the drug usage data collected from patients were also coded for the known risk factors.
- NERD would not be suitable for screening of those drugs where efficacy is determined by the timing of administration. Examples for Covid-19 are drugs used for reducing lung inflammation and damage, such as those required to fight cytokine storm (e.g., [9]). This is especially true if premature timing could worsen clinical outcomes. This could confound NERD's usefulness for these types of drugs.
- The collection of usage data on biologics and biosimilars, which continue to be a rapidly growing class of therapeutics, could prove difficult, if not just for the fact that the naming conventions are complex [12].
- For drugs associated with the positive-test group, they might simply be serving as PROXIES for co-morbidities that make patients more vulnerable to Covid-19.
- A very important factor that NERD would not be able to address is whether a drug might have an impact on increasing or decreasing the overall level or rate of virus shedding, which is a key parameter in inter-individual transmission.
- Because the more limited classes of drugs used in pediatric populations, it would probably be more representative to normalize group drug-usage rates against pediatric and non-pediatric populations.
- As the ranked, overall nation-wide usage rate for each drug trends downward, the confidence intervals for distinguishing significant differences between the tested groups will increase accordingly, simply because there would be less collected drug usage data. So it would become increasingly more difficult to detect associations for drugs with less market penetration.
- All types of diagnostic tests have a range of rates for false-negatives and false-positives. This could be a major contributor of error in the confidence of any NERD conclusions regarding drug usage rates.
- Among the active infection test group, a very small portion of the negative-test group may actually comprise newly infected cases (covert virus) whose viral titers are insufficient to meet the minimum sensitivity for a positive test (resulting in a false-negative test); re-testing these cases days later can yield a positive test.

undoubtedly a function of the magnitude of the delivered dose of viral particles. This exposure "intensity" likely results in a continuum of severity of symptoms, rate of disease progression, and modulation of disease outcomes. But this important aspect of Covid-19 is ignored in the concept of NERD developed here simply because there is no current way to easily determine exposure intensity. It is important to recognize that it is within the actual complexities of the disease, such as exposure intensity, that NERD attempts to reveal drugs that impact the disease. So any apparent indication that a drug might correlate with positive or negative disease outcomes might instead simply be a confounding reflection of the type of exposure and not the drug itself.

Additional attributes, advantages, and limitations of the NERD concept are compiled in Table 2.

5. Additional potential opportunities with NERD

Worth noting is that additional opportunities with the natural experiment presented by the Covid-19 epidemic (as well as any future epidemic) include epidemiologic surveys regarding not just common risk factors such as smoking, but also occupational exposures and real-world inadvertent human exposures to known environmental hazards (e.g., volatile algal toxins and pulmonary toxicants such as atmospheric particulate matter and synthetic chemicals, asbestos, silica, and beryllium). In particular, the possibility exists for discovering whether such non-drug exposures increase the susceptibility or vulnerability to more serious Covid-19 outcomes. This might be especially germane to explaining cases of serious Covid-19 disease among healthy younger adults and reported gender and racial disparities. This would entail a more ambitious data collection effort involving collaboration with industrial and environmental toxicologists to extend the utility beyond drug usage by broadening the exposome and incorporating known occupational and environmental hazards.

Finally, another unique possibility may exist for verifying the findings of NERD. The relatively new monitoring approach called wastewater-based epidemiology (WBE) has been in use for identifying drugs that are collectively consumed across entire communities. One of the primary applications of WBE has been the monitoring of sewage for drugs (or their metabolites) and back-calculating per capita consumption [26]. WBE has also been used for monitoring the presence of pathogens such as viruses (to provide early warnings for emerging outbreaks) and more recently proposed for gauging community-wide overall health [2,4] or for gauging community-wide status and trends of infection [5]. WBE could therefore possibly be used to complement and verify the findings of NERD. For example, drugs found by NERD to be predominantly associated with asymptomatic or mild cases of Covid-19 could be targeted for WBE monitoring in communities suspected as having low infection rates; note that the overall rates of community infection could also be gauged by WBE (e.g., see: [18,32]). Conversely, drugs found to be predominantly associated with severe or critical cases of Covid-19 could be targeted for WBE monitoring in communities suspected as having high infection rates. Likewise, WBE could be used to quickly assess which communities may have high infection rates, and then target these communities for testing of asymptomatic individuals.

6. Conclusion

Surveillance testing and diagnostic testing are critical tools for timely detection, control, and mitigation of any disease epidemic. Testing during epidemics provides rare opportunities to capitalize on natural experiments for expanding what is known about exposure, transmission, disease progression, and therapeutic treatment. Presented here is a concept for a potential natural experiment that could reveal existing drugs (or multi-drug combinations) that may have higher probabilities of success in their re-purposing (re-positioning) for disease prevention or clinical therapy - or conversely those drugs whose use should be avoided during infection. This concept (Natural Experiment for *Re*purposing of Drugs - NERD) would require considerable additional discussion and examination before reaching any decision to develop pilot studies to assess its potential viability or usefulness. If successful, however, the concept could prove invaluable in fighting future epidemics involving novel pathogens or mutated strains of prior pathogens for which past immunity or previously effective therapies are no longer effective.

Declaration of Competing Interest

The author declares no conflict of interest. The work had no affiliation with any public or private agency. The concept and ideas presented did not originate from any prior published works.

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