Chapter 18: The Mistakes Made in Response to the COVID-19 Pandemic: How to Deal with Future Pandemics

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Abstract

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), swiftly became a global crisis, prompting the World Health Organization (WHO) to declare it a pandemic in March 2020. Over the following two years, the virus evolved, leading to numerous waves of infections and the emergence of the omicron variant by December 2021. The pandemic had profound impacts on healthcare, the economy, education, and public trust in 'science', the media and the authorities. This paper explores the mistakes made during the COVID-19 response and seeks ways to enhance future pandemic preparedness.

Keywords: COVID-19 pandemic, Lockdowns, Evidence-based medicine (T-EBM Wheel), Holistic Management, Ivermectin, Pharmaceutical conflicts of interest

Overview of the Pandemic and its Impact

The COVID-19 pandemic was portrayed as a once-in-a-century global infectious disease health crisis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Cruickshank & Shaban 2020). It is documented to have first been identified in Wuhan, China, in December 2019 and then spread rapidly worldwide. By March 2020, the WHO declared COVID-19 to be a pan-

demic, a response thought by many to have been slow (Zhou, Zhang & Qu 2020). From 2020, waves of the disease, driven by mutations in the virus, continued to spread across the globe with serious health consequences for two years (Van Damme 2020). By December 2021, the omicron variant began replacing most previously circulating variants, and the disease has become less severe and endemic (Markov *et al.* 2023). By July 2023, SARS-CoV-2 had infected 767,972,961 people and killed 6,950,655 people (WHO 2023). It is important to note strong arguments exist that claim there was no Covid pandemic (Panda 2023).

The handling of COVID-19 impacted all aspects of life, from health-care, the economy, education, and social interaction to public trust in the mainstream narrative that was created by the various authorities. Its impact on the health systems was the most obvious but possibly not the most significant. Shortages of medical supplies, including personal protective equipment for staff (PEP) equipment for patients such as ventilators, therapeutics, and medical staff, may have resulted in higher mortality among vulnerable patient groups such as geriatric patients and those with chronic health conditions (Jakovljevic *et al.* 2020). Mortality rates up to 90% were reported (Yang *et al.* 2020; Richardson *et al.* 2020) for COVID patients on ventilators largely due to Ventilator-Associated Pneumoni (Wicky *et al.* 2023). Some debate is ongoing about whether mechanical ventilation is a suitable treatment for may Covid patients (Ducharme 2020).

Possibly the most serious impact of the pandemic was on the economy. Lockdowns caused businesses across both the formal and informal sectors to suffer financial losses that led to the closure of many companies and small businesses and the consequent loss of jobs. Ironically, the salaries of politicians imposing harsh lockdowns were secured. Consumer spending fell sharply as a result, which scaled up to countries experiencing declines in their gross domestic product (GDP) and increases in unemployment rates. The global scale of this impact on business led to a worldwide recession (Ozili 2020).

Numerous significant research reports have underscored the substantial economic toll induced by the lockdowns implemented globally during the pandemic (Bhattacharya, Smark & Mir 2021; Rimšēvičs 2021; Meng, Bannerman & Abrokwah 2022). Reports emanating from every continent demonstrate this trend, presenting data that spans a wide array of economic sectors (S. Bhattacharya, Smark & Mir 2021; Chen *et al.* 2022; Fisher *et al.* 2022; Garcia, Thierry, and Pendergrast 2022; Morsy, Balma, and Mukasa 2021; Verschuur, Koks, and Hall 2021; Zhou, Zhang, and Qu 2020; Wu 2022; Zinecker *et al.* 2021).

In the United States, an analysis determined that, on average, the economic sacrifice made to prevent a single new COVID-19 infection was roughly $28,000, a figure reflected in the lower gross domestic product (GDP) (Tellis 2023). This substantial cost raises questions regarding the economic viability of stringent lockdown measures, inviting reflection on the strategies deployed to manage the pandemic and their repercussions on the economy.

During the lockdowns, educational institutions, including schools and universities, either shut their doors or adopted online learning platforms, resulting in widespread disruptions to the education of millions of students at diverse stages of their developmental progress. The lockdowns showed stark contrasts in accessibility to education, with affluent institutions swiftly adapting to the changes, in contrast to schools situated in underserved communities that lacked the necessary resources to facilitate online learning (Spaull & van der Berg 2020). Recently a court ordered Johns Hopkins University to refund students for remote learning during the pandemic (Staff 2024).

Despite being a viable alternative, remote learning could not fully replicate the rich, multifaceted social experiences that traditional in-person learning offers, especially for programs necessitating laboratory practicals. This discrepancy shows that the ramifications of the educational disruptions caused by the COVID-19 lockdowns were far-reaching, and their full extent may only unfold over the coming decades.

Given this landscape, it is imperative for societies globally to engage in critical reflection on the scope of authority, including emergency powers, that they are willing to allocate to governmental bodies. This discussion should encompass the broader implications of such decisions, considering the potential for profound impacts on fundamental aspects of society, such as education.

Social distancing measures were implemented to slow the spread of the disease and had mixed impacts. People who lived alone or were isolated from their families, such as those who lived in facilities for older people, had increased feelings of isolation and loneliness. Children were denied face-to-face contact with peers for extended periods, leading to feelings of isolation. Developmental milestones in communication, emotional regulation, and socialisation were compromised   (Spaull & van der Berg 2020).

Media threads and information blackouts due to government censorship (Bhattacharya 2023; Showalter 2023; Kenny 2023; Team 2023; Christenson 2023; Prasad 2020) worldwide, impacted public trust in science and the authorities. There was high public trust in science and scientists at the beginning of the pandemic. Governments and individuals looked to a handful of experts,

mainly from clinical research and practice backgrounds, to guide them through the crisis. However, as the pandemic progressed, trust in science became more polarised, with some becoming more sceptical of scientific information and advice sources. This was partly due to conflicting information and guidance from different sources and some countries' politicisation and propaganda of the pandemic response. The rapid pace of scientific research and development of vaccines, treatments, and diagnostic tools led to concerns about the safety and efficacy of these interventions. Some sources' blatant untruths raised suspicions, leading to further misgivings about science (Mannan 2020).

During the COVID-19 pandemic, a vigorous media campaign arose, casting doubt on the efficacy of ivermectin and hydroxychloroquine as treatments for the virus, a discourse fuelled by various studies and analyses over time (Todaro 2020; Darcy 2022). However, more recent research suggests a potential effectiveness of ivermectin in treating COVID-19 (Bryant *et al.* 2021).

Controversies have erupted regarding the perceived compromise of organisations such as the WHO and the FDA, stemming from the substantial funding they receive from the pharmaceutical industry. The WHO's 2022-23 budget prominently features voluntary contributions, eclipsing the funds allocated by member states by a significant margin; in 2020, a notable part of these contributions was derived from the pharmaceutical sector (WHO 2020, 2023a). The FDA similarly has a considerable portion of its budget funded by the pharmaceutical industry, raising questions regarding potential conflicts of interest and the ability of the agency to regulate the industry impartially (Jewett 2020).

The pharmaceutical industry's influence extends further into the political landscape, with substantial lobbying efforts in the USA marking a continuous strategy to shape policy and public opinion (Secrets 2023b; 2023a). This deep-seated involvement has fostered a growing mistrust among the public, with the mainstream media reported to be significantly financially supported by the pharmaceutical industry, generating scepticism and fuelling polarisation across the political spectrum.

Lies about the effectiveness of the vaccines (Agresti 2022; Chongloi 2022; Lin 2022) and the masks (Hoeg, González-Dambrauskas & Prasad 2023; Jefferson *et al.* 2010; Kisielinski *et al.* 2023; Radonovich *et al.* 2019) contributed further towards mistrust of the public. We have recently published a comprehensive review on the adverse effects of the COVID-19 vaccines (du Preez *et al.* 2024). It is clear that the Pharmaceutical companies kept the initial negative results from the clinical trials secret (during the trials, more people that

were vaccinated died compared to those that were given placebo) at least to the public. The USA government tried to hide this information from the public for decades to come (Greene 2021; Deese 2022). Fortunately, the courts ruled in favour of a group of medical doctors and scientists that. used the Freedom of Information Act request to release the data (Deese 2022; Greene 2022). Another strategy that they used was to discredit the use of any alternative treatment (such as Ivermectin), as this would have destroyed their chances to obtain emergency approval for their COVID-19 vaccines (UPMC 2022). .

Another major contribution to the exploitation of people by Big Pharma developed when President Reagan signed a bill in 1986 that essentially exempted pharmaceutical companies from liability with respect to children vaccines (Spear 1986). It appears that the pharmaceutical companies obtained blanket exemption from liability from governments world-wide, with respect to the COVID-19 vaccines (Epstein 2022). Initially this fact was kept secret in most countries (Apuzzo 2021). The result is that people became much more sceptical about vaccines in general and subsequently more hesitant to use them, leading to a rise in vaccine-preventable diseases (Bassyouni 2024)

An urgent need exists to restore integrity and trust in the systems responsible for managing public health crises. It entails instituting measures to secure the independence of health service watchdogs, media, and industry regulators from potential conflicts of interest, ensuring transparency, and rebuilding public trust in these vital institutions. Liability of Pharmaceutical companies should be restored as well.

To achieve this, a multifaceted approach should be pursued involving stringent regulations on funding and lobbying, coupled with efforts to foster transparency and reduce the influence of financial contributions on decision-making processes. Moreover, promoting open dialogues grounded in verified scientific data and encouraging a culture of critical thinking can aid in combating misinformation and reducing political polarisation. Thus, a comprehensive reassessment and overhaul of the existing structures are called for to usher in an era where public health decisions are made to safeguard the populace's well-being, devoid of undue influences.

The Importance of Examining Mistakes Made in Response to the Pandemic

The COVID-19 pandemic turned out to be the most significant health crisis of our time, albeit for the wrong reasons. Governments, healthcare organizations

and doctors on the ground responPded in various ways. Some actions restrained the disease, while others resulted in increased morbidity, mortality, and economic devastation. It is vital to examine the mistakes made and evaluate the successes to learn from them and take steps to address them. This way, we can better manage future similar crises more efficiently and not repeat the same mistakes.

The pandemic highlighted the need for preparedness and effective response strategies. Ironically, the only government that did followed experience from previous pandemics was Sweden. Although they were harshly criticized at the time, it turned out that they were actually right! (Andersson & Jonung 2024). Without reflecting on the mistakes made, it will be challenging to identify the most effective measures to use or avoid in the future. Governments and healthcare organisations should reflect critically on their responses to develop new policies and procedures to manage future outbreaks, leading to better health outcomes for the public.

Examining past responses and adjusting new response strategies might help restore public trust. Several reasons have led to the loss of public confidence in government-driven responses and healthcare institutions. Arguably, the most important has been the mis- and dis-information about evidence-based medicine propagated by authorities and some powerful individuals who became the pandem-icons (Joubert *et al.* 2023). By examining evidence more critically and allowing a comprehensive interpretation of evidence-based medicine to include the totality of the evidence, a rebuilding of public trust in their ability to manage future health crises in these institutions is needed.

A retrospective review of errors made during the pandemic can identify areas for improvement in the current healthcare system. Lack of preparedness, inadequate resources and insufficient capacity were highlighted in the pandemic. Resilience and capacity need to be planned for pandemic preparedness by investing in infrastructure, investing in research and development, and developing effective communication strategies.

What we Could have Learned from the 1918 Spanish Flu (H1N1) Pandemic

In the early twentieth century, the H1N1 virus, the Spanish Flu, saw one of the deadliest pandemics in human history. It is estimated that 500 million people across the globe were infected, and at least 10% of them (50 million) died. The

first lesson we could have taken was the successes seen in early detection and quick interventions. In a study comparing the response time and outcomes from two United States cities, Philadelphia and St. Louis, the stark difference in rapidity to response is clear (Markel *et al.* 2007).

Philadelphia hosted a parade during the early days of the Spanish Flu pandemic; within days, hospitals were at capacity, and 2,600 people had died. Concurrently, two days after the first case of Spanish Flu was noted there, St. Louis imposed strict lockdown measures, including closing schools and public gathering places. Passenger number limits on public transport were imposed, and work shifts were staggered to minimise contact. Philadelphia eventually imposed the same measures two weeks after their first cases were reported. The differences in time to decisive action between these two cities led to vastly different outcomes. From September 1918 to February 1919, the northern hemisphere winter, the death rate was approximately 358 per 100,000 in St. Louis and 748 per 100,000 in Philadelphia (Markel *et al.* 2007)

A reflection on the COVID-19 pandemic will likely show similar outcomes, although a one-size-fits-all strategy does not work, as will be demonstrated later. The WHO took months to declare the pandemic, resulting in countries where infections began in January to March 2020, such as Italy (with an older population), having poor outcomes, while countries receiving their first cases after March 2020, when the WHO declared the pandemic, were not as severely affected. The WHO's tardy response led to initial poor outcomes in countries with early infections. The final verdict appears to be damning according to the studies by Steve Hanke and co-workers (Herby 2023).

Brooks Hospital near Boston in Massachusetts implemented a novel approach to treatment for the Spanish flu based on their experience as a TB hospital. They implemented open-air treatment, which proved successful in reducing mortality (Hobday & Cason 2009). Patients were treated in tents outside the hospital, where they had access to fresh air and sunlight, as opposed to the traditional medical practice of keeping patients in closed, cramped wards. The maximum ventilation provided by the outdoor space reduced airborne transmission, and the sunlight would have impacted improved Vit D in the patients. These practices that were shown to be successful in the Spanish Flu pandemic in a single hospital were ignored during the COVID-19 pandemic, where patients were primarily isolated in wards without natural light. While open-air treatment is not always feasible, good ventilation and vitamin D benefits could have been acknowledged early in the pandemic.

Indiscriminate Lockdowns

The implementation of lockdowns as a preventative measure in controlling the spread of infectious diseases has been a topic of considerable discussion, dating back to the success witnessed in St. Louis during the 1918 pandemic. Indeed, the onset of the COVID-19 pandemic brought this strategy to the forefront once more with the initiation of lockdowns in Wuhan, China, where the virus was first detected, a methodology subsequently adopted globally in varying degrees. Early adoption of lockdowns appeared to be a key determinant in effectively managing community transmission. This strategy showed a higher success rate than Italy's approach, which initiated lockdowns following the WHO's official pandemic declaration (Khanna *et al.* 2020). While numerous studies affirm the efficacy of lockdowns in curbing the spread of the virus (Caristia *et al.* 2020; Juul *et al.* 2022), there remains a substantive discourse advocating for a more nuanced approach to their implementation, suggesting a tailored strategy that considers various factors to be more prudent (Hu *et al.* 2021; Zhou, Zhang & Qu 2020).

However, a contrasting perspective posits that lockdowns may not be the most effective strategy, particularly in managing airborne diseases, arguing for exploring alternative approaches to control community transmission (Herby. J 2023; Herby 2022) This divergence in opinions among the scientific community underscores the complexity of managing pandemics. A recent study found that mass gatherings during COVID-19 did not increase the spread of the virus (Feltham *et al.* 2023). It raises pertinent questions on the optimal strategies to adopt to mitigate such health crises' impacts.

As we delve deeper into this topic in the subsequent sections, we aim to propose a strategy that navigates these complex challenges effectively, drawing upon the lessons learned from the multifaceted responses to COVID-19. The goal is to foster a balanced approach that leverages the strengths of lockdowns while mitigating their downsides, thereby promoting a response strategy that is effective, sustainable, and adaptable to the dynamic nature of pandemics. This would involve an in-depth exploration of various dimensions, including, but not limited to, the timing of implementation, the scale of lockdowns, and incorporating other preventive measures in a multifaceted approach to managing future pandemics. It remains imperative that future strategies are developed with a grounded understanding of the diverse perspectives and emerging evidence to foster resilient systems capable of protecting global health.

Hard lockdowns caused widespread economic disruption, including job losses, business closures, and decreased economic activity, which has resulted in financial distress for many individuals and businesses (Ozili 2020). However, measures that were proven successful in curbing transmission in sectors considered essential work, such as limited numbers of people in public transport and on the work floor, could be implemented more widely to allow more business to continue.

Lockdowns impacted considerably on mental health, leading to increased stress, anxiety, and depression for many people, particularly those who live alone or in residences away from their families. Lockdowns prevented older people from seeing their families, leading to compromised mental health. Open-air visits, such as those encouraged when visiting TB patients, would go a long way to ameliorating emotional stress in people living in homes for older or disabled people. The compromise based on known epidemiological interventions such as social distancing and fresh air would prevent hard lockdowns' most severe negative emotional impacts (López-Castro *et al.* 2021). The lockdowns disrupted education, leading to school closures and the transition to remote learning. This has resulted in decreased educational opportunities and increased disparities in access to education, particularly for low-income students and those without access to technology.

The lockdown strategy delayed medical care for many people, as hospitals and clinics focused on treating COVID-19 patients, and chronic patients did not feel they could get to health facilities to receive care. This has resulted in adverse health outcomes for some individuals unable to receive necessary medical care (Kapitsinis 2021). Addressing the continued chronic healthcare of individuals through a lockdown is a complex process involving possible online strategies for consultation and delivery of treatments to homes or central points.

The lockdowns helped mitigate the spread of SARS-COV-2. However, in retrospect, it is clear that lockdowns had significant social and economic impacts. A reflection on the level of lockdown in various contexts should be retrospectively analysed. For example, when a large part of the population is asymptomatic, it makes more sense to focus on measures to protect the vulnerable while the healthy group can continue with their work.

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Cigarette and Alcohol Bans

As part of their responses to the COVID-19 pandemic, Thailand, India and South Africa implemented cigarette and alcohol bans (de Villiers, Cerbone & Van Zijl 2020). The rationale was weak, especially in light of the already-in-place lockdowns. It was anticipated that banning cigarettes and alcohol would limit social gatherings and promote public health. Smoking and drinking were believed to cause uninhibited social behaviour, resulting in non-compliance with physical social distancing practices meant to reduce transmission risk. Lockdown strategies already limited social gatherings, and banning cigarettes and alcohol, which are addictive, is less likely to reduce substance addiction than forcing the trade underground. The consequences of the bans have been complex and varied.

Several considerations influenced the decision to ban cigarette sales during the lockdown. One belief was that smoking might compromise the immune system, potentially increasing smokers' vulnerability to infections. In South Africa, Cooperative Governance Minister Dr Nkosazana Dlamini-Zuma, raised concerns regarding the communal sharing of cigarettes, which could potentially facilitate the transmission of the virus. This contentious prohibition sparked widespread discussion and inspired satirical commentary through pop culture. Max Hurrel from The Kiffness in South Africa leveraged the ban as a muse for a parody song, which quickly gained traction and went viral after being

uploaded on YouTube. Their song humorously explores the repercussions of the ban, providing a light-hearted take on a serious issue faced by the nation during the lockdown period (Hurrell 2020).

The loss of revenue to both businesses and the government was substantial due to these bans. These products contribute significantly to national economies, and the losses to governments regarding sin taxes, VAT, and other taxes were sizeable. With the supply of cigarettes and alcohol curtailed, a black market for these products emerged. Home-brewed, counterfeit and illegally imported and produced products became available. Health concerns arose around these black-market products' poor quality and potentially toxic effects. Authorities ignored health issues around the sudden withdrawal of these substances. Withdrawal symptoms experienced by those dependent on cigarettes and alcohol experienced health problems and mental distress. There was no intervention to support people struggling with addiction during the pandemic.

An alternative strategy that could have been implemented would have decreased any adverse effects of alcohol or smoking during the COVID-19 pandemic. Education interventions to inform the public of the risks of smoking and drinking during the pandemic could have been implemented. Known health issues specific to the relationship between COVID-19 and substance use could have been highlighted to encourage the responsible use of these substances. Lockdowns and bans on social gatherings had already addressed many concerns about smoking and drinking as a conduit for virus transmission.

The EBM Pyramid Model in mis-Understanding EBM

Evidence-based medicine (EBM) has been around for a while, but it wasn't until the 1990s that it became a major focus in medical education (Guyatt 1992). The idea behind EBM is that medical decisions should be based on science that has been peer-reviewed and tested rather than hunches or following trends. The essence of Evidence-Based Medicine (EBM) initially revolved around an informed assessment of all pertinent, peer-reviewed evidence across varying study designs to guide treatment recommendations and decisions. Fundamental to EBM was the ability to gauge the relative certainty of evidence derived from a particular study design, thereby leveraging the power to make informed inferences from gathered data. The Evidence-Based Medicine (EBM) foundation was built on the principle of integrating all accessible peer-reviewed evidence, irrespective of the research design, in formulating treatment recommendations and choices.
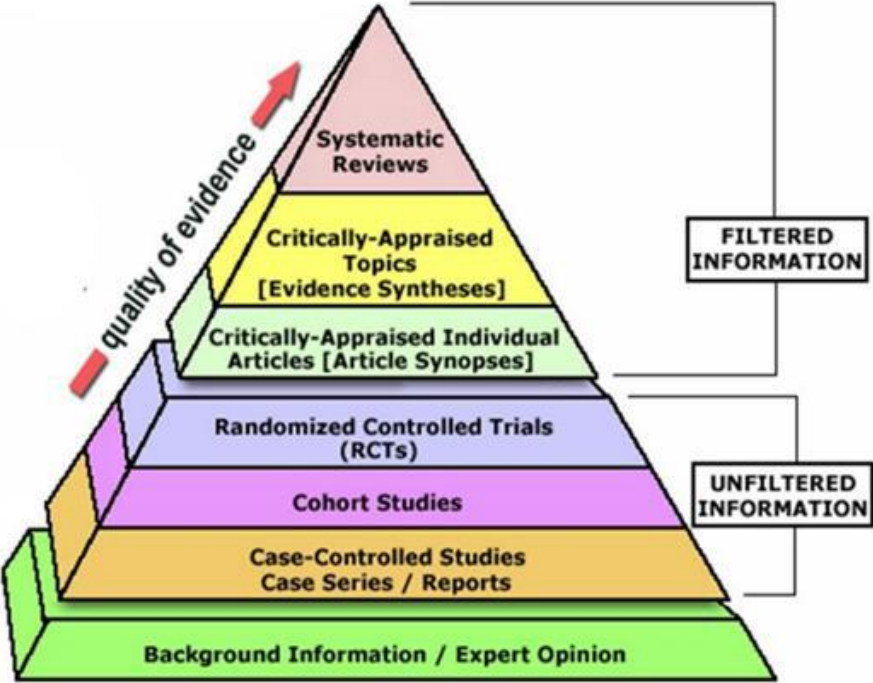
Figure 1. The traditional evidence-based medicine Pyramid model represents a purported hierarchy of ever-increasing quality. This Photo by Unknown Author is licensed under CC BY-SA-NC (UF 2024).

Unfortunately, in recent years, EBM has been misunderstood and misapplied due to the emphasis on a hierarchy of evidence that ranks certain types of research as being of higher quality than others. This has led to valuable data and treatment options being overlooked.

As outlined in the illustrative EBM pyramid model (Figure 1), the transition towards a hierarchical representation of evidence quality instead of certainty levels marked a pivotal shift in EBM's interpretative and application landscape. This paradigmatic shift inadvertently relegated Real-World Evidence (RWE) and other lower certainty reports to a peripheral role, with a preference for randomised controlled trials (RCTs) and meta-analyses thereof dominating the clinical and governmental decision-making echelons. It negates

the potential insights that could be harvested from high-quality case-controlled studies and overlooks the pitfalls of poorly executed double-blinded RCTs (DBRCTs).

Regrettably, the prevailing EBM pyramid, embodying quality labels, has fostered a rigid perspective, emphasising RCTs as the gold standard while undermining the contribution of RWE, thus compromising the utilisation of repurposed drugs notwithstanding their established safety profiles. This stance, echoed in medical pedagogy and media narratives, not only disenfranchises the merits of RWE but also inadvertently endorses flawed RCTs, a phenomenon underscored by the critical evaluation of widely cited RCTs referencing ivermectin's efficacy in COVID-19 treatment. The widely accepted yet misguided practice of conflating quality with certainty and featuring a 'quality' label on the pyramid in Figure 2 has ingrained the notion that only RCTs and their meta-analyses should be considered for most clinical and governmental decision-making. This stubborn insistence on RCTs for repurposed drugs with a well-established safety profile, without considering the totality of evidence, including RWE, has frequently led to overlooking or delaying the implementation of effective treatments.

Furthermore, medical education and media narratives have ingrained the belief in frontline medical professionals and the general public that, by default, RWE is of inferior quality and RCTs are of superior quality. As expressed in a medical school textbook: '*If the study was not randomised, we would suggest that you stop reading it and go on to the next article*' (Strauss *et al.* 2018). Poorly constructed or executed RCTs have been accepted as high quality, not because of their actual scientific merit, but due to their position in the pyramid model. The most widely publicised RCTs used to justify governmental policies regarding the ineffectiveness of IVM for treating COVID-19 have exhibited flaws in design or scientific integrity.

A re-evaluation of the prevailing EBM approach is needed, recognising that observational studies can, in certain contexts, resonate with the findings from well-conducted RCTs, thereby facilitating early treatment strategies informed by initial case studies. Hence, it is prudent to acknowledge the value of preliminary studies in steering research and treatment trajectories.

Evidence-based Medicine in a Pandemic

Aldous *et al.* introduced the Totality of EBM (T-EBM) Wheel (Aldous *et al.* 2024) which takes a different approach to evaluating research. Instead of using

a hierarchy of evidence, the T-EBM Wheel includes all types of research, both peer-reviewed and real-world evidence (RWE), and visualises them in a colour-coded format. This allows for a more comprehensive understanding of the totality of evidence available.

During a pandemic, the need for RWE is critical, as it can provide valuable information about the efficacy of treatments before randomised controlled trials (RCTs) are available. This is especially relevant for repur-posing drugs already known to be safe. Our article provides a proof of concept by constructing a T-EBM Wheel for the efficacy of treating COVID-19 with IVM-based regimens.

By rethinking how we evaluate evidence in medicine, we can ensure that all types of research are considered and that valuable treatments are not overlooked during times of crisis.

The Totality of Evidence Wheel

The advent of the Totality of Evidence-Based Medicine (T-EBM) wheel presents a revitalised framework, accommodating a broader spectrum of reports encompassing those found in the traditional EBM pyramid. With the integration of an outer ring delineating various outcomes and facilitating a visual representation of report volumes, this innovative model fosters a comprehensive overview. Furthermore, the colour-coded segmentation within the outer ring enables a discernible representation of potential clinical equipoise instances, enhancing diagnostic visualisation.

The T-EBM wheel emerges as a versatile tool to guide medical professionals and policymakers, encapsulating a rich dataset devoid of the misleading quality-certainty hierarchical delineation inherent in the pyramid model.

Consequently, this progressive tool is primed to evolve into a pivotal application tool, relegating the pyramid model to a pedagogical role, elucidating evidence certainty, and spearheading a transformative approach in evidence-based medical practice rooted in a holistic, inclusive, and nuanced assessment of available evidence. It is imperative, moving forward, to adopt such comprehensive models to ensure that the breadth of the available evidence is considered in both clinical settings and policy formulation, fostering outcomes that are robust, inclusive, and truly representative of the collective evidence at hand.
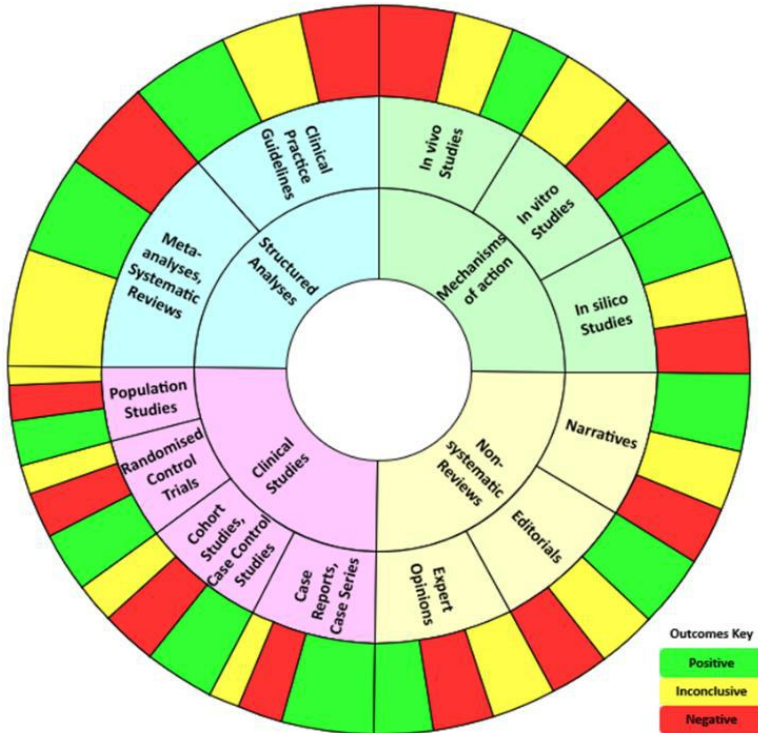
Figure 2. Totality of Evidence-Based Medicine (T-EBM) Wheel for peer-reviewed research. The inner ring of the wheel catalogues reports by four types: mechanisms of action and clinical studies, which are sources of primary evidence, and structured analyses of primary data and reviews, which are the secondary reports based on the primary evidence. Each inner ring section is disaggregated into one or more middle ring sections with the same coloring. In turn, each middle ring section is disaggregated into three outer ring sections by the outcomes of its reports, namely: 'positive', 'inconclusive', 'negative'. The legend in the lower right-hand corner of the figure shows the color-coding for each of the outcomes. The size of each section of a ring will be proportional to the number of reports in the literature for that section. The Excel Sunburst used to create the wheel orders each section in the inner ring clockwise from largest to smallest. As one moves outward from the inner ring, the subsections of a given section are similarly ordered clockwise from largest to smallest (Aldous *et al.* 2024).

The T-EBM wheel, a model that encapsulates a broader spectrum of evidence inclusive of a proportional representation of diverse outcomes, offers a more holistic approach towards understanding the dynamics of efficacy and safety in medical scenarios, enhancing the strategic approach employed by clinicians and decision-makers. Figure 3 shows that the Wheel includes everything the pyramid does and more.
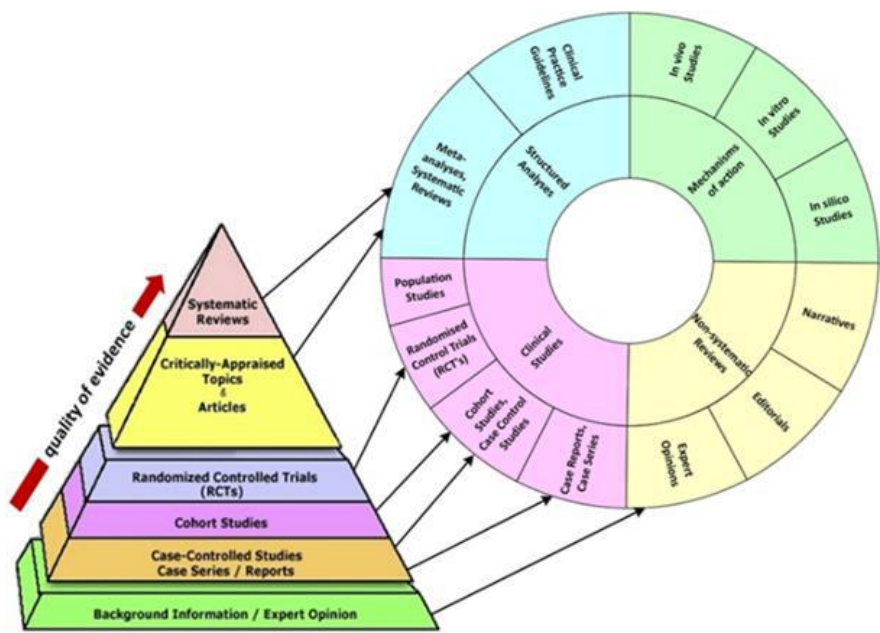
Figure 3. Correspondence of traditional EBM Pyramid with the middle ring of T-EBM wheel. Arrows show correspondence between levels of the pyramid and sections of the middle ring of the T-EBM wheel. The inner ring is included to show how middle ring sections arise from partitions of inner ring sections (indicated by colour coding).

The T-EBM wheel enriches medical decision-making by integrating an array of evidence types focused on distinct outcomes, thereby establishing a comprehensive foundation that supports the amalgamation of Real-World Evidence

(RWE) and not excluding Randomized Controlled Trials (RCTs). This synergy guides medical professionals in crafting individualised treatment strategies while evolving a communal standard of care, nurturing a cohesive strategy bolstered by a comprehensive evidence base. Notably, while a single observational study may carry less certainty than a single RCT, studies of the same disease should yield similar results, regardless of whether the studies are observational or RCTs. Only case studies are available during the early stages of a disease outbreak, with no RCTs. Therefore, it is likely that the results of successful earlier case studies will align more with those from successful RCTs conducted later. Therefore, it is crucial to utilise the indications from these early studies to guide treatment and further research.

Utility of the TEBM Wheel

In the critical early stages of a pandemic, the T-EBM wheel model could have proposed a versatile approach to treatment strategies, suggesting a potential departure from the often resource-intensive and slow process of initiating double-blinded RCTs. This model advocates for the immediate exploration of repurposing existing medications grounded in the retrospective analysis of diseases bearing analogous traits.

The T-EBM wheel enhances the representation of various types of evidence, going beyond the features included in the traditional EBM pyramid, as illustrated in Figure 1. This expansion is visually depicted through an added outer ring in the complete wheel, offering insight into different outcome types and facilitating a clearer perception of the relative volume of diverse reports. By adopting a colour-coded system in the outer ring, as highlighted in Figure 2, practitioners can more readily identify instances of clinical equipoise. Contrasting the pyramid model, which primarily serves educational purposes by teaching evidence certainty, the wheel disregards the potentially misleading quality/certainty hierarchy present in the pyramid, promoting itself as a superior tool for practitioners and decision-makers to implement in the medical field.

In this agile paradigm, the initial focus is leveraging studies conducted *in vitro, in vivo,* and *in silico* to rapidly identify early markers of efficacy, promoting a proactive posture in treatment interventions. While acknowledging the possibility of Type 1 errors emerging from these exploratory drug protocols, the model contends that such risks remain controllable, especially when founded on well-strategised dosing plans.

Furthermore, the model underscores the critical role of frontline healthcare professionals, encouraging the assimilation of their first-hand clinical insights into the decision-making vortex. Such ground-level Intelligence, combined with observational studies and case analyses, promises to shape potent clinical protocols for ensuing RCTs, nurturing a responsive and adaptive blueprint for treatment.

This approach warrants a dynamic monitoring framework wherein governmental and medical establishments continually scrutinise the evolving results, steering expansive experimental implementations judiciously. It is envisaged as a living tool, necessitating regular updates to encapsulate the dynamic landscape of evidence surrounding treatment methodologies, empowering stakeholders to stay receptive to positive indications and steering research and announcements through a real-time evidence canvas.

Enabling an informed practice of off-label drug utilisation demands an in-depth exploration of existing literature, ensuring comprehension of safety profiles and possible efficacies. It cultivates a culture that thrives on data-rich resources, enabling healthcare practitioners to execute interventions grounded in robust evidence. It fosters a future where the enlightened and adaptable deployment of entrenched and emerging evidence steers healthcare.

The T-EBM wheel echoes the principles seen in the circular social sciences model, offering a repository of a wide variety of evidence and presenting a proportional portrayal of outcomes, albeit limited to individual results types such as safety or efficacy. The T-EBM wheel envisions guiding clinicians and decision-makers through a rich array of information essential in harmonising RCTs with real-world evidence (RWE). It distinctly facilitates the integration of the complete evidence spectrum, aiding medical professionals at the forefront to weave RWE and available RCTs with their observations, fostering a 'community standard of care'.

The design and upkeep of the T-EBM wheel mandate its periodic update to present a timely visualisation of the evolving gamut of evidence on treatment protocols. This tool, serving as a visual compass, systematically organises a myriad of evidence in an accessible, intuitive manner, encouraging an approach eschewing biases birthed from misapplying the pyramid model.

Guided by the earnest goal of collating timely and actionable data, the approach insists on meticulous scrutiny, balancing high internal validity methodologies like placebo-controlled RCTs with extensive, long-term observational studies that document real-world clinical practice implications. It persuades a departure from an over-reliance on randomised studies, urging the

adoption of techniques optimised to answer pertinent questions with the utmost scientific rigour.

Thus, this approach not only signals a shift in the strategic execution of pandemic responses but also paves the way for a future where evidence-based medical strategies are characterised by adaptability, inclusivity, and forward-thinking, armed with a continuously evolving repository of actionable data drawn transparently and objectively from a wider spectrum of evidence. It nurtures a culture guided by the dictum, 'Here's what we recommend and why,' steadfast in its pursuit of enlightened healthcare pathways grounded in comprehensive and adaptive utilisation of existing and emergent evidence.

Looking ahead, using the T-EBM wheel advocates for a more rounded approach to medical decision-making, urging medical practitioners and authorities to remain open to evolving evidence. It proposes a shift from the traditional hierarchical pyramid model of evidence evaluation to a tool that respects a spectrum of research outcomes. This would ideally foster a community standard of care that integrates various pieces of evidence and real-world observations to navigate treatment strategies effectively.

Moreover, it suggests that during pandemics, medical professionals should have the flexibility to experiment with repurposed drugs known to be safe. This could potentially aid in finding effective early treatments and prevention strategies, potentially attenuating the impacts of pandemics like COVID-19.

## The TEBM Wheel Assessment of Ivermectin

The use of ivermectin (IVM) as a therapeutic agent in the COVID-19 pandemic has been controversial. Before the pandemic, IVM had a well-established safety record, confirmed by the World Health Organization's VigiAccess database. Despite some studies showcasing the potential benefits of IVM, the global scientific community has not reached a consensus regarding its efficacy in treating COVID-19. This is partly due to active press and social media campaigns against its use and conflicting results from various studies, some of which have been criticised for poor design and execution.

To clarify this topic, an independent actuary was asked to conduct a comprehensive search for published reports on PubMed to analyse the evidence available for IVM's use in COVID-19 treatment since 2020.

The analysis focused on 265 studies, exploring their findings, which

ranged from positive and negative to inconclusive outcomes.

Aldous *et al.* (2024) introduced the T-EBM wheel tool to visually represent the totality of evidence from various studies, emphasising a non-hierarchical approach to evaluating research findings. This tool aims to foster a comprehensive and unbiased view of the existing research, highlighting the necessity to consider broader evidence rather than relying solely on randomised controlled trials (RCTs). The 265 studies were represented in a TEBM-Wheel for ivermectin, see Figure 4.
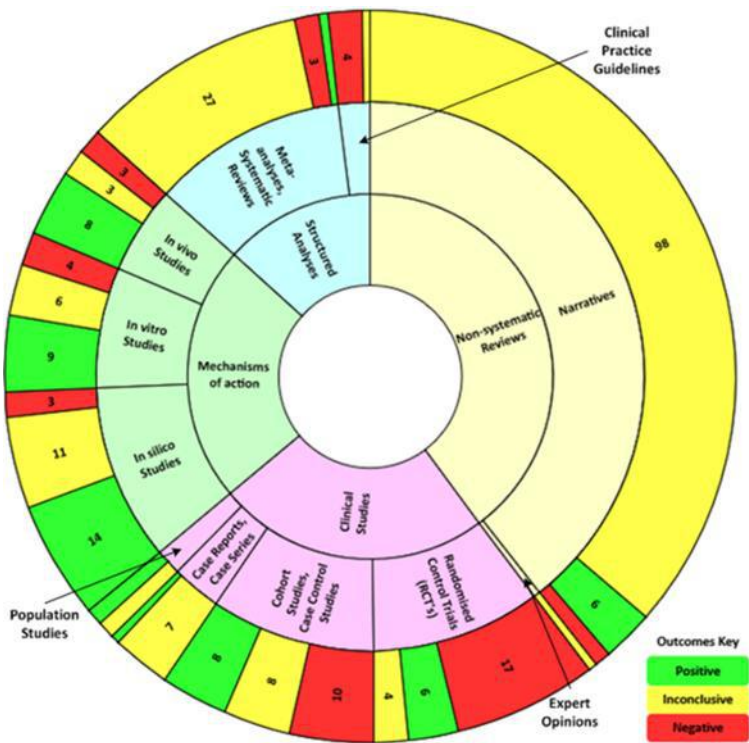
Figure 4. IVM T-EBM wheel for the efficacy of IVM-based regimens treating COVID-19 (IVM Wheel). Data from peer-reviewed published reports listed in Pubmed and searched for 'ivermectin' and for 'COVID-19' or 'SARS'. The number displayed in each outer ring section is the number of its reports.

A closer look at the data revealed that protocols with more successful outcomes tended to involve higher dosages of IVM, combination therapies, and longer treatment regimens. However, the effectiveness of IVM-based treatments remains unclear, warranting further research to ascertain its potential benefits and drawbacks in treating COVID-19.

In conclusion, while the findings regarding IVM's efficacy are mixed, the T-EBM wheel presents a promising approach to facilitate a more nuanced understanding and assessment of treatment strategies, calling for a cooperative and informed approach to tackling pandemics in the future.

Holistic Management of Pandemics (Aldous & Kruger 2023)

The COVID-19 pandemic has revealed many flaws in decision-making processes and policies, one of which is the lack of diversity among decision–makers. Globally, COVID-19 pandemic responses were led by a few select individuals, mainly clinicians. They lacked diversity in their backgrounds and perspectives as individuals and as a group. They led the initial responses and were supported by government officials. There were no social scientists, economists, legal specialists or pure scientists contributing thought that would impact mental health, the economy, conflicts of interest and human rights, or evidence-based medicine. With the same backgrounds and perspectives, this select group had blind spots in decision-making and policy development and overlooked important considerations critical to a successful response. A limited range of solutions and strategies were developed in lock-step globally, ignoring creative or innovative approaches to managing the pandemic from other discipline thinkers. There was a failure to address the broader societal impacts of the pandemic.

The leadership by politicians and public health scientists led to a narrow focus on specific aspects of the pandemic response. Policies and strategies did not consider the needs and experiences of diverse communities, the economy or broader human rights. Initial reactions focused on novel medical interventions such as testing and vaccine development while neglecting the social and economic impacts of the pandemic. Many low-income communities had limited access to healthcare and were thus disproportionately affected by the pandemic because the decision-makers did not understand their unique challenges. As more general hardships became apparent and 'facts' initially presented as certain were changed or proven wrong, a lack of trust and confidence in the response led almost exclusively by clinically trained people developed.

Washing hands, social distancing and staying home were early messages about preventing COVID-19 transmission. This did not consider the circumstances of shack dwellers who have limited access to water and live in single-room accommodations that are often uninhabitable during the day because of the building materials used.

In over four decades, Alan Savory has devised and implemented Holistic Management principles in agricultural and grassland conservation sectors globally, promoting a balance of economic, social, and environmental factors (Institute 2023; Savory & Butterfield 1999; Savory & Butterfield 2016). During the onset of the COVID-19 pandemic, the notion of extending these principles (Gosnell *et al.* 2020) to manage future pandemics began to crystallise, encouraging a comprehensive solution incorporating various critical dimensions.

An exploration into existing literature unveils the gradual incorporation of holistic viewpoints in various domains, such as economics (Ponte *et al.* 2016) health (Constantinou *et al.* 2020; Fardet and Rock 2014; Wang and Teo 2021) marine management (Rodriguez 2017), biology (Mazzocchi 2012), and environmental management (Barrera 2020; Seminara & Bolla Pittaluga 2012; Younos, Lee & Parece 2018) shifting away from the previously favoured reductionist models, which faced criticism for their limited perspective (Andersen 2001; Ribatti 2021).

Interestingly, it required a military leader (General Stanley McChrystal) to realize that reductionist management style is no longer feasible in modern organizations within a networked world, working with complex systems and where small changes can create non-linear and non-predictable reactions/ outcomes (McChrystal 2015). According to McChrystal, modern organizations require Gardeners (facilitators/ enablers) rather than Chess masters (centralized decisions) as leaders. Gardeners nurture the environment in which all the pieces (the other team members) can thrive. This require sharing of information and devolution of decisions as far as possible.

With this background in mind, it is quite clear that perhaps the biggest mistake of Governments dealing with the COVID-19 pandemic, was to centralize decisions around mostly one Pandem-Icon (Joubert *et al.* 2023) Scientists. The result was that a reductionist approach was followed to break down a complicated problem [with social, economic and environmental (health, the virus) factors] into linear, deterministic and measurable relationships. In the process they found/proposed a simplified solution (hard lockdowns and a new RNA based vaccine), ignoring all other equally important factors. Any alternative treatment was also vilified.

The world-wide lack of diverse and multidisciplinary COVID-19 advisory panels resulted in a typical reductionist solution at a huge cost in terms of economic, social and the health environment:

In terms of the effect of reductionist pandemic management on social aspects, (Bhattacharya, Smark & Mir 2021; Caro *et al.* 2022; Kamath *et al.* 2022; Mahagamage & Marasinghe 2023; Rainer *et al.* 2022) it is clear that the result was devastating. Despite many reports on increased suicides (Cozzi *et al.* 2023; Ogrodniczuk *et al.* 2023; Wasserman *et al.* 2020) there was no significant increase (in most countries) during the pandemic (Appleby 2021; Cozzi *et al.* 2023; Ogrodniczuk *et al.* 2023; Pirkis, Gunnell, Shin, Del Pozo-Banos, Arya, Aguilar 2022; Pirkis *et al.* 2021; Wasserman *et al.* 2020). However, ongoing economic hardship and suffering may lead to increased suicide cases in future.

Finally, the reductionist management model from the Pandem-Icons also got it wrong in terms of the health environment. Locking people up and not allowing them to go outside, turned out to be disastrous, especially for the elderly in Nursery Care Homes in the USA (Chidambaram 2022).

One can understand the initial panic when the pandemic broke out in December 2019. The fact that it started in China, who seemed to have limited free flow of information, did not help. The initial world-wide response by most Governments was responsible. However, they should have known better quite early on.

A cruise ship (the Diamond Princess) experienced a major outbreak on board and it was quarantined in Japan (Yokohama) on 4 February 2020 for about a month (Smiley 2020) From the 3711 passengers and crew, around 700 people became infected and 9 people died. This was a 'God-given' scientific experiment that showed early on that more than 80% of people appears to be asymptomatic to the virus. Although scientists concluded in July 2020 that the COVID-19 virus is airborne (Morawska & Milton 2020) it took much longer for the WHO and CDC to admit it. So, within about 6 months, it was known that ALL passengers and crew on the Diamond Princess were exposed to this airborne virus, and less than 20% were susceptible to it. Later reports confirmed that about 85% of people are asymptomatic towards the virus (Hao *et al.* 2020; Lei *et al.* 2021).

In addition to that, it was also known quite early during the pandemic (from deaths in Italy) (Minnai *et al.* 2022), that most deaths were people above 65 years of age. The importance of co-morbidities (Russell, Lone & Baillie 2023) was also known, relatively early on during the pandemic.

In hindsight it seems quite possible that a diverse and multidisciplinary COVID-19 advisory panel practicing Holistic Management principles would have recommended maximum protection of the elderly and vulnerable, rather than a hard-lockdown strategy. Ironically, even though South Africa was applauded for one of the strictest lockdowns apart from China (Campbell 2020) we are the country with most possibly the highest infection rate (98%) in the world (already by March 2022) (Bingham 2022). There is a simple explanation for this: the majority of the South African population (working in our shops, hospitals and homes) uses minibus taxis for commuting on a daily basis. As early as June 2020, the taxi industry rejected the South African government's strict travel restrictions (Reuters 2020). The result was that the virus spreaded uncontrolled *via* these heavily loaded taxis. This failed experiment confirms our point that a 'one size fits all' strategy did not work for COVID-19.

Social science, economic and legal insights into pandemic preparedness, and public health insights would lead to a pandemic response that could prevent the financial disaster of the COVID-19 pandemic and alleviate the mental well-being issues it brought about. Leadership positions in future pandemic responses should prioritise diversity of thought. This should include actively seeking diverse perspectives and experiences to ensure diverse voices are represented in decision-making processes. This will ensure that strategies are inclusive and well thought through, leading to a more effective and equitable response. Strategies would include improved health communication tailored to diverse communities needs, and workplace safety for all workers could be designed so that lockdowns would not require the shutdown of all industries.

Including social scientists, legal experts, and economists in a pandemic response team is essential because pandemics are not just a medical problem but also a social, legal, and economic issues. While clinically trained people and politicians can provide necessary expertise, they may not have the same level of knowledge or understanding regarding the broader social, legal, and economic impacts of a pandemic.

Social scientists can bring their expertise in understanding human behaviour, social dynamics, and cultural factors that can influence disease spread and interventions' effectiveness. They can also help identify and address potential social and behavioural barriers to adherence to public health measures, such as vaccine hesitancy or resistance.

Legal experts can guide the legal frameworks and policies necessary for a coordinated response to a pandemic, such as emergency powers and

quarantine measures. They can also help ensure that public health interventions are implemented in a way that respects individual rights and liberties.

Economists can help assess the economic impact of a pandemic and the measures taken to address it, such as lockdowns or business closures. They can also provide recommendations on mitigating economic damage, supporting affected industries and workers, and ensuring that the pandemic response is equitable and sustainable.

Scientists who are not clinicians are essential members of a pandemic response team because they provide the foundational knowledge necessary to understand the biology and behaviour of the virus. While clinical and medical scientists focus on developing treatments and vaccines, pure scientists study the virus's underlying mechanisms, help identify potential drug targets, and can look at evidence-based medicine more holistically.

Pure scientists can conduct experiments and analyse data to understand how the virus spreads, mutates, and interacts with host cells. This knowledge can inform public health policies and control measures, such as social distancing guidelines and vaccination strategies. Additionally, pure scientists can help identify potential weaknesses in the virus that can be exploited to develop effective treatments and vaccines.

Without the contributions of pure scientists, clinical and medical scientists are limited in their ability to develop effective treatments and vaccines. Pure scientists provide the necessary knowledge and understanding of the virus, enabling clinical and medical scientists to develop targeted interventions.

A pandemic response team must have diverse discipline thinkers with different specialisations (Finance, Health, Humanities, Legal etc.). By working together, these scientists can provide a more comprehensive understanding of the virus, leading to more effective interventions and control measures. A pandemic response team that includes a diverse range of experts can provide a more comprehensive and effective response to the challenges posed by a pandemic.

In contrast, Sweden's management of the pandemic, which demonstrated a more balanced approach prioritising not only health but also economic and social factors, showcases the potential merits of a holistic strategy, presenting a model with reduced excess deaths compared to several other nations (Britschgi 2023; Norberg 2023; Andersson & Jonung 2024).

Time will teach us to what extent the shocking revelations by Dr David Martin about the origin and handling of the COVID-19 pandemic are true

(Martin 2022). Given the fact that most of the initial COVID-19 'conspiracies' turned out to be true, he is likely to be on the right side of history.
Conclusion:

As the international community continues to navigate the complexities of the COVID-19 pandemic, a pressing concern has emerged regarding the legal immunities bestowed upon vaccine manufacturers by governments globally and significant entities such as the WHO (Lintern 2020; Sigalos 2020; Wood 2020). These immunities present a pivotal issue, potentially encouraging expedited processes at the expense of rigorous safety assessments. The crux remains: Does the absence of legal accountability foster an environment where shortcuts are more feasible? It is a question demanding urgent scrutiny and comprehensive dialogue across various sectors of society.

Restoring their independence is essential to bolster the integrity of global health organisations like the WHO, FDA, and ECDC. We urge a concerted effort to re-establish these entities as bastions of unbiased, evidence-backed decision-making insulated from potential conflicts of interest. Implementing Independent Review Boards (IRBs) is a promising proposition, envisioned to oversee the safety protocols of new vaccine developments meticulously, ensuring transparency that reinforces public trust.

As the discourse evolves, it becomes increasingly apparent that there is a need for a profound reflection and deliberation on the extent of governmental influence during pandemic epochs. Societies globally are encouraged to actively engage in discussions delineating the confines of governmental power, fostering a collaborative effort to forge a pathway characterised by informed choices, securing our civil liberties and our collective well-being.

In line with this, we advocate instituting multidisciplinary pandemic advisory panels grounded in Holistic Management principles, characterised by a holistic overview encompassing various perspectives, thus steering away from reductionist approaches that may overlook significant factors. The integration of the 'Totality of Evidence-Based Medicine (T-EBM) Wheel' approach emerges as a seminal concept in this framework, seeking to cultivate a rich, nuanced perspective by considering a more comprehensive array of evidence, thereby forging strategies that are both responsive and inclusive (Aldous *et al.* 2024).

As we forge ahead in these unprecedented times, it becomes incumbent upon societies worldwide to foster environments where robust debates can thrive, encouraging a collective responsibility towards informed governance. Through enhanced transparency and collaboration, we must build a future

where responses to pandemics are grounded in holistic insights, evidential integrity, and the shared goal of global well-being. This strategy underscores a commitment to nurturing a landscape where decisions are responsive and framed with a deep-seated commitment to safeguarding the holistic health of communities globally. It is a call to arms for a more united, informed, and resilient world, ready to face the challenges of tomorrow with a spirit of unity and evidence-backed preparedness.

In unity and with hope, we look forward to a future where our collective efforts ensure the health and well-being of all, while maintaining a judicious balance of power, and ensuring just compensation for those affected by vaccine-related adverse events.

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Gert Kruger & Colleen Aldous

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