
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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# COVID-19 related interdisciplinary methods: Preventing errors and detecting research opportunities

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ABSTRACT

More than 130,000 peer-reviewed studies have been published within one year after COVID-19 emerged in many countries. This large and rapidly growing field may overwhelm the synthesizing abilities of both researchers and policy-makers. To provide a sinopsis, prevent errors, and detect cognitive gaps that may require interdisciplinary research methods, the literature on COVID-19 is summarized, twice. The overall purpose of this study is to generate a dialogue meant to explain the genesis of and/or find remedies for omissions and contradictions.

The first review starts in Biology and ends in Policy. Policy is chosen as a destination because it is the setting where cognitive integration must occur. The second review follows the opposite path: it begins with stated policies on COVID-19 and then their assumptions and disciplinary relationships are identified. The purpose of this *interdisciplinary method on methods* is to yield a relational and explanatory view of the field –one strategy likely to be incomplete but usable when large bodies of literature need to be rapidly summarized.

These reviews identify nine inter-related problems, research needs, or omissions, namely: (1) nation-wide, geo-referenced, epidemiological *data* collection systems (open to and monitored by the public); (2) *metrics* meant to detect non-symptomatic cases –e.g., *test positivity*–; (3) *cost-benefit* oriented methods, which should demonstrate they detect silent viral spreaders even with limited testing; (4) new *personalized tests* that inform on biological *functions* and *disease correlates,* such as cell-mediated immunity, co-morbidities, and immuno-suppression; (5) factors that influence *vaccine effectiveness*; (6) *economic* predictions that consider the long-term consequences likely to follow epidemics that growth exponentially; (7) the errors induced by self-limiting and/or implausible paradigms, such as *binary* and *reductionist* approaches; (8) new *governance* models that emphasize problem-solving skills, social participation, and the use of scientific knowledge; and (9) new *educational* programs that utilize *visual* aids and *audience*-specific communication strategies. The analysis indicates that, to optimally address these problems, disciplinary and social integration is needed.

By asking what is/are the potential cause(s) and consequence(s) of each issue, this methodology generates visualizations that reveal possible relationships as well as omissions and contradictions. While inherently limited in scope and likely to become obsolete, these shortcomings are avoided when this 'method on methods' is frequently practiced. Open-ended, inter-/trans-disciplinary perspectives and broad social participation may help researchers and citizens to construct, de-construct, and re-construct COVID-19 related research.

## 1. Introduction

Aiming at detecting possible omissions and/or contradictions, as well as issues that may require additional research, the COVID-19 related literature is summarized following an inter-/trans-disciplinary and non-reductionist approach. We believe non-reductionist approaches to be more effective than some of the strategies in current use. This report is also motivated by three shortcomings that may influence the handling of this pandemic: (i) the lack of a common language across disciplines; (ii) the ultra-rapid growth of scientific publications in the last three decades; and (iii) a pandemic with features not observed in more than a century.

Research publications have grown very rapidly. In 2020, the *Web of Science* repored + 8,700,000 published articles, i.e., more than 23,000 per day. What, in principle, was desirable, is now a serious problem: as the number of studies grows, it is less likely that any person can remain

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**Table 1**
An example of bibliometric analysis.

| Keywords searched (source: *Web of Science*™) | Hits |
|---|---|
| COVID-19 | 132,396 |
| Policy integration | 51,712 |
| Policy integration & COVID-19 | 144 |
| Population immunity | 114,035 |
| Herd immunity | 9,315 |
| Population immunity & herd immunity | 3,409 |
| Population immunity & herd immunity & COVID-19 | 154 |
| Population heterogeneity | 94,032 |
| Population heterogeneity & herd immunity | 77 |
| Vaccination coverage | 19,401 |
| Vaccination coverage & COVID-19 | 159 |
| Herd immunity & population immunity & vaccination coverage | 548 |
| Herd immunity & population immunity & vaccination coverage & vaccination efficacy | 160 |
| Vaccination effectiveness & immunological interactions | 102 |
| Herd immunity & population immunity & vaccination coverage & vaccination efficacy & vaccination effectiveness | 72 |
| Herd immunity & population immunity & vaccination coverage & vaccination efficacy & vaccination effectiveness & COVID-19 | 0 |
| Vaccination effectiveness & geographical & cost effectiveness | 58 |
| Vaccination effectiveness & geographical & cost effectiveness & COVID-19 | 0 |
| Herd immunity & population immunity & vaccination coverage & vaccination efficacy & vaccination effectiveness & geographical | 1 |
| Herd immunity and geographical and policy | 7 |
| Herd immunity & geographical & policy | 0 |
| Data collection systems & COVID-19 | 456 |
| Geo-referenced & data collection systems & COVID-19 | 0 |
| Geo-referenced & epidemic | 45 |
| Geo-referenced & epidemic & COVID-19 | 1 |

updated in her/his own field [1].

Such an outcome may have devastating consequences when a pandemic occurs. One year after COVID-19 emerged, more than 130,000 studies have been published. To prevent useful information being ignored, the COVID-19 literature needs to be continually summarized.

In recent years, numerous calls asking for health-related policy integration have been made which included warnings emphasized by the WHO as early as 1979 [2,3]. To improve decision-making, integration is crucial: more valid policies may require additional research as well as the elimination of ineffective interventions.

Given their focus on integration, inter-/trans-disciplinary analyses are well suited for detecting inconsistencies. In contrast, uni- (and even some multi-) disciplinary studies may miss problems only identified when a broader perspective is adopted. This distinction matters because, when a problem remains unsolved even after the best available knowledge has been utilized, it is clear that new (and problem-specific) knowledge should be generated.

To foster inter-/transdisciplinary knowledge integration, bibliometric analysis is helpful [4]. When a topic known to be associated with two or more fields shows few publications that cross-reference such fields, it is likely that new and specific knowledge may be needed.

Insufficient attention to COVID-19 related policy integration is suggested when just one thousandth of all COVID-19 publications address the topic of policy integration (see Table 1). Poor communication strategies between researchers, decision-makers and/or citizens may result in low numbers of studies involving vaccination efficacy, vaccination coverage, vaccination effectiveness, immunology, geography, as well as public behavior [5].

## 2. II First review: from Biology to Policy

### 2.1. Herd immunity

The method we applied pursues research integration [6]. Because it offers an opportunity to explore many disciplines, the first review focuses on 'herd immunity' (Fig. 1).

'Herd immunity' –a concept that emerged in veterinary medicine– reflects the historical emphasis veterinary medicine has assigned to populations or herds [7]. This concept was coined between the end of the XIX and the beginning of the 20th century, which is the time period when viruses and leukocytes were discovered [8].

*Herd immunity* means *population immunity*. It refers to sub-populations that achieve protection even when they are not directly immunized. For instance, when a new virus reaches a nursing home where immuno-compromised individuals (e.g., HIV patients) interact with immunized ones (e.g., healthcare personnel), the virus is prevented from replicating: immuno-compromised individuals are protected because immunized individuals act as a barrier.

*Herd immunity* may refer to: (i) the proportion of immune individuals within a population; (ii) the expected threshold (minimal proportion) of immune individuals that would reduce the size of an epidemic; and (iii) the immune profile expected to protect a population from re-infections [9]. Herd immunity differs from 'herd effect.' While the former describes *the proportion of subjects with immunity in a given population,* the latter is the *reduction of infection in the unimmunized segment as a result of immunizing a proportion of the population* [10].

*Disease-induced* (or 'natural') herd immunity may lead to devastating consequences: it has been estimated that more than 30 million COVID-19 deaths may occur before herd immunity can be achieved [11]. That is why *vaccination-induced* (not epidemic-induced) herd immunity is considered a more realistic aim.

Is there any evidence of herd immunity? While not yet documented in the case of COVID-19, it has been reported in other infections. For example, Japanese children vaccinated against influenza may have protected elderly people who were not vaccinated [12]. While supported by the data, this inference does not inform on the strains of influenza virus reported in the years children were vaccinated against influenza. Such data matter because the degree of matching between the vaccine strain and the viral strain found in seasonal outbreaks influences vaccine effectiveness, ranging from zero to 70% protection [13–15].

Herd immunity may be influenced by many factors, including *efficacy*, *coverage,* and *effectiveness* [16–18]. *Vaccine efficacy* differs from *vaccine effectiveness*. While the former [19] refers to findings observed under experimental conditions, *vaccine effectiveness* describes the reduction of infection that follows an immunization delivered with normal storage and usual administration processes to an unselected population in their usual environment [19,20]. *Vaccine effectiveness* is the net *vaccine efficacy* after field conditions are taken into account, which include *coverage* (percentage of the population that is vaccinated), the immune status of the population, *viral spread* and *logistics* that influence the vaccination, e.g., the cold chain [21,22]. Variations in viral *strains* and *vaccination history* also influence vaccine effectiveness [23].

Insufficient *geographical vaccine coverage* may explain why vaccine effectiveness differs from vaccine efficacy: studies conducted in Africa have shown that, even when the same vaccine coverage is observed, settings that differ in geographical structure may yield different rates of vaccine effectiveness [24]. Because humans are not homogeneously distributed in space, *population* and *geographical heterogeneity* also influence vaccine effectiveness [25].

Due to *immunosuppression*, populations that show identical coverage may also differ in vaccine effectiveness [26]. In addition, *transmission* (the average number of susceptible individuals infected by the average infected person, also known as the 'reproductive number' or $R_0$) should be considered. For example, when, on average, an infected individual infects three susceptible people ($R_0 = 3$), the estimated threshold required to achieve herd immunity is 67%; i.e., to stop an epidemic with such a transmission, vaccination should cover 2/3 of the population and 100% of the vaccinated individuals should develop protective immunity [12].

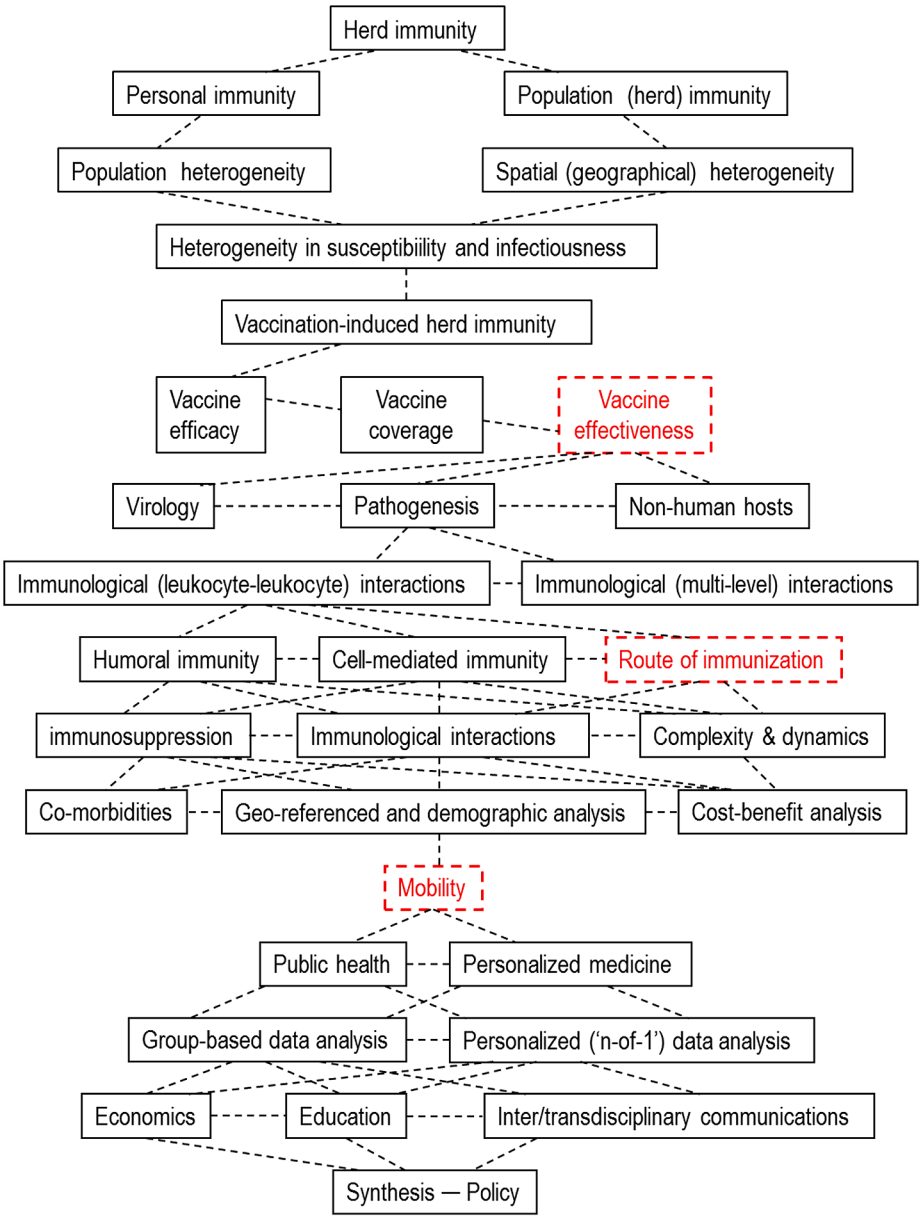


**Fig. 1. The first review: from Biology to Policy.** Approximately thirty topics –some of them partially overlapping– were reviewed. When related, some needs, contradictions and/or omissions were identified (topics identified in red). For example, vaccine effectiveness cannot be estimated unless the percentage of the population vaccinated is known, as well as the local geo-demographic structure –which includes dynamics —e.g., the temporal mobility of specific social groups—, as well as geographically specific connecting structures —e.g., road/railroad networks. The lines shown here only illustrate one possible relationship. A dialogical (combinatorial) process involving many disciplines and social perspectives is likely to uncover many other relationships. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### 2.2. *Immunological considerations*

However, the previous description does not fully account for variations in the immune system of individuals. For instance, not all vaccinated individuals develop a protective immune response and numerous factors may affect the outcome, such as the gut microbiota [27].

*Interactions* among leukocytes may explain infection outcomes better than reductionist methods [28,29]. Cross-reactive memory T cells may influence disease severity [30].

Because SARS-CoV-2 is immunosuppressive [31], novel testing should explicitly estimate *immunosuppression*. New tests may also consider the clinical diversity of COVID-19 presentations, which may express at least three immune profiles [32]. Unlike other 'common cold'-related diseases (in which the humoral response may suffice to achieve protection), both antibody-mediated and cell-mediated immunity are needed to protect against SARS-CoV-2 [33].

To account for immunosuppression, the analysis of co-morbidities is crucial. Hence, clinical trials that ignore co-morbidities may not be valid [34]. In addition, vaccine trials that exclude large sob-populations –such as children, who are likely disseminators of SARS-CoV-2 but are not always symptomatic– may lack representativeness and, consequently, yield not only erroneous but also counterproductive results. When vaccine trials do not include children, vaccination strategies may require unrealistically high coverage levels [35,36].

The *route of immunization* is also important. Because SARS-CoV-2 is a mucosal pathogen, a more robust immune response against this virus is more likely to be induced by the *respiratory mucosa* than by the parenteral route of vaccination [37–39]. The fact that none of the COVID-19 vaccines utilizes aerosols may be a source of concern (Fig. 1).

Omissions may also be consequential. If new tests measured cell-mediated immunity in real time, they could evaluate vaccinations as well as anti-viral drugs, which are not tested in all countries where they are used [40]. Such new tests could also describe mucosal responses [41].

### 2.3. *Virological considerations*

Zoonoses are diseases transmitted from non-human hosts to humans.

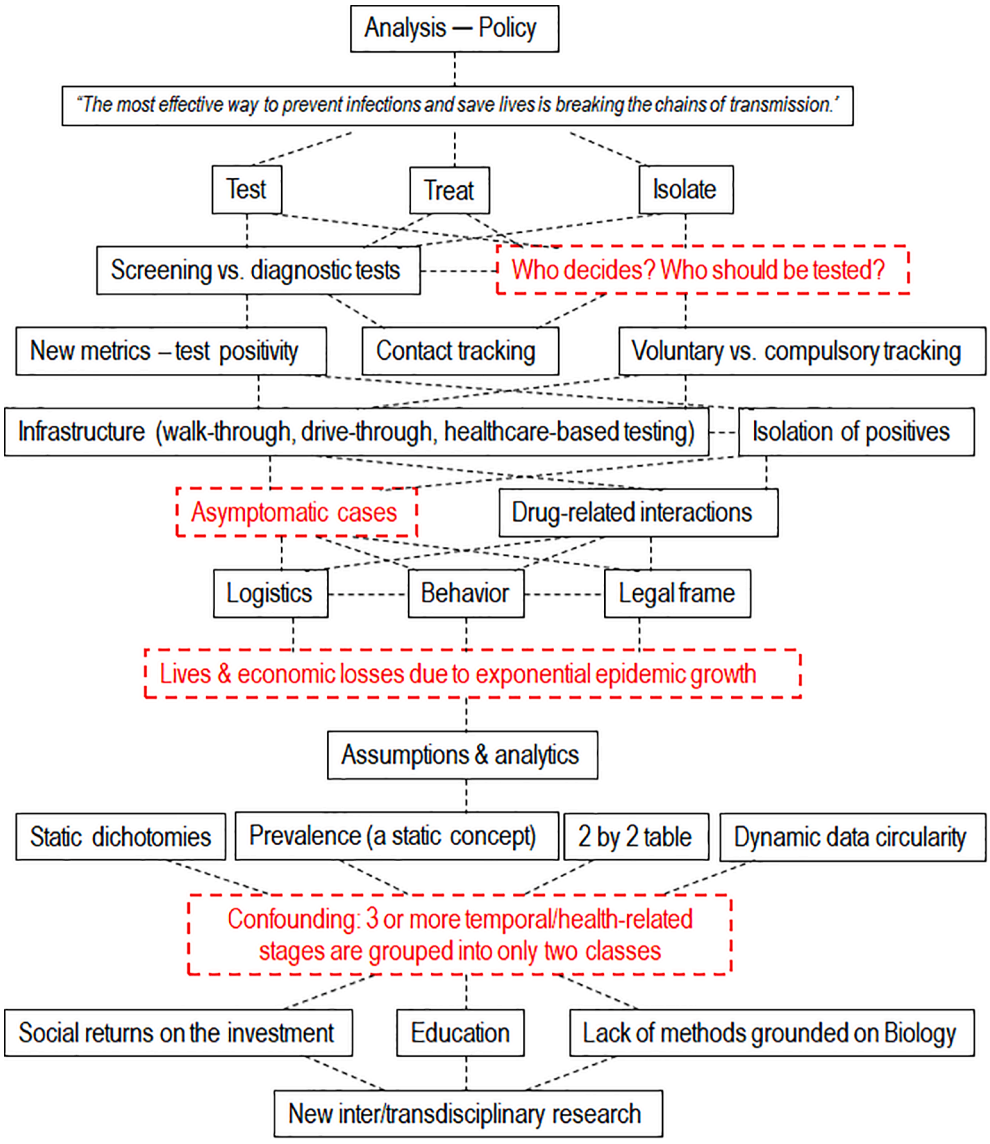


**Fig. 2. The second review: from Policy to Biology and other sciences** Approximately thirty topics –some of them partially overlapping– were reviewed. When related, some needs, contradictions and/or omissions were identified (topics identified in red). For example, a method that assumes only two alternatives exist (e.g., 'infection-negative' or –positive') but does not consider disease stages and/or temporal changes (such as 'recently infected, not yet under recovery', 'recently infected, under recovery', and 'not recently infected, under recovery') is likely to induce errors: it will confound three or more biological conditions into only two classes. The lines shown here only illustrate one possible relationship. A dialogical (combinatorial) process involving many disciplines and social perspectives is likely to uncover many other relationships. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Although many viruses are potentially zoonotic, their ability to induce epidemics is unknown [42]. About 50% of the ~ 1400 pathogens that affect humans also infect non-human species. Of those, about one third is composed of RNA viruses. Measles, for instance, emerged as a human pathogen, one millennium ago –probably from bovine rinderpest [43]. Smallpox is an even older pathogen: it evolved from camelpox about 4000 years ago [44].

Emergent viral infections in humans have been increasingly recognized in the last four decades [45]. They seem to be triggered by climate and weather change, changing ecosystems, economic development and land use, human demographics, international travel and commerce, breakdown of public health measures as well as poverty and social inequality.

Rodents, birds, mosquitoes and bats are major vectors of infectious diseases. Bats are now considered to be major reservoirs of numerous emerging human epidemics, including Ebola, rabies, SARS-Cov, MERS-Cov and SARS-CoV-2 [46,47].

The fact that bats exposed to RNA viruses show no or negligible signs of inflammation while the same viruses may be lethal in humans have led to hypothesize that these viruses may trigger, in humans, an aberrant immune activation [48,49]. Because COVID-19 does not fit the established definition of a zoonosis, it is classified as an emerging viral disease [50].

### 2.4. *Immunology and pathology*

To understand both *immunology* and *pathology*, the immune responses of bats against viruses should be analyzed. Bat anti-viral immunity relies on *low inflammation* but *high efficacy of interferon*-based defenses, which allow them to harbor numerous viruses (including SARS-CoV-2) without showing signs of disease [46,47].

SARS-CoV-2 *immunodulates* the human IFN system, leading to substantial non-symptomatic transmission, during which the viral load increases without facing a major inflammatory response. Later, a hyper-inflammatory response is elicited, which may be insufficient to clear the virus but may cause tissue damage (an auto-immune response).

The hyper-inflammation ('cytokine storm') observed in the second stage of COVID-19 patients presenting with severe disease is associated with high levels of pro-inflammatory cytokines, including IL-6 [51,52]. While, in children, COVID-19 resembles Kawasaki syndrome –another auto-immune disorder associated with increased IL-6–, in adults it shows similarities with the cytokine release syndrome [53].

In severe COVID-19, macrophages are recruited and activated to the site of infection, together with T cells. Once the endothelium is

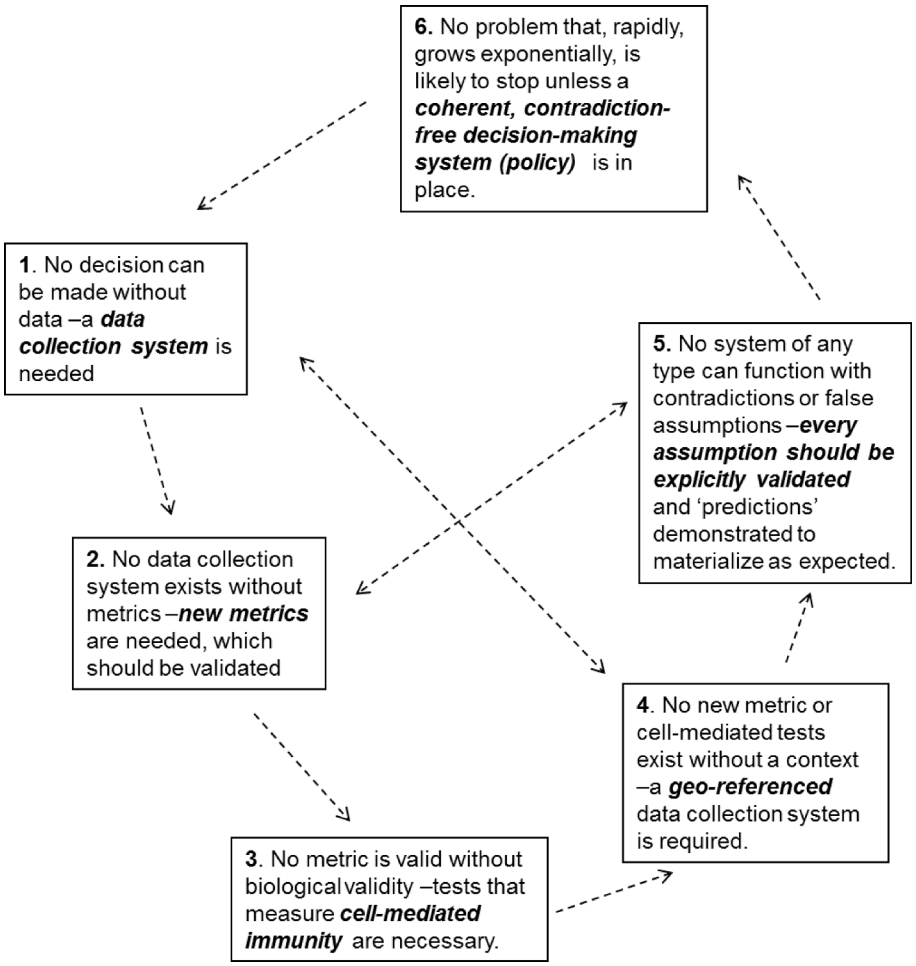


**Fig. 3. Functional and structural relationships of a system meant to identify and solve COVID-19 related problems or needs.** A six-element system is described, which includes: (1) a data collection subsystem; (2) new metrics appropriate to estimate whether testing is capturing silent (non-symptomatic) cases (e.g., test positivity); (3) biomedically interpretable information (e.g., new tests that, rapidly, inform on cell-mediated immunity); (4) geo-referenced coordinates; (5) explicit validation; and (6) cost-effective policy-making. This system may have both circular and transversal connections, which may show other trajectories (arrows).

damaged, coagulopathies follow, the lung parenchyma is destroyed, and multi-organ (septic shock-like) failure may occur –in part facilitated by a viral-induced suppression of type I and III interferons to clear the virus [54].

Therefore, COVID-19 is a *two-stage* disease. It is characterized by an immune disorder that, early, reveals *immunosuppression* and, later, expresses *hyper-inflammation* [55].

### 2.5. Personalized ('n-of-1') assessments

The clinical heterogeneity of COVID-19 and the limitations of group-based studies has renewed an old discussion: should patients be treated as groups or individuals? Ultimately, patient-specific information, specific for a given disease stage, is needed. This is what *'n-of-1'* studies (personalized trials) offer. They are pre-/post designs with a sample size ($n$) = 1. They collect longitudinal data from the same person, before and after a therapy is prescribed [56–58].

### 2.6. The role of geographical analysis

Optimized vaccine allocation depends on the geographical context [59]. Because geography may influence vaccination coverage [60] –and coverage influences vaccination effectiveness–, classic assumptions on the validity of the herd immunity concept –such as randomness– are not necessarily valid. In contrast, Pareto's '80:20' distributions may occur, i.e., ~80% of all infections may occur in ~ 20% of all locations [61]. Pareto's '80:20' ratio has been observed in epizootics affecting farm animals and in humans affected by COVID-19 [62–65].

The '80:20' pattern is a central concept of Network Theory –a field that views epidemic dissemination as a process described by networks, i.e., sets of circles ('nodes') linked by lines ('edges'). Non-geographically explicit studies have suggested the use of *network-based immunizations*, which may protect with fewer (35% less) vaccinations [66,67]. If, instead of assumed data and assumed theories (non-geographical models that assume the most important node is always located at the center of the network), Network Theory was applied using actual and dynamic geo-referenced data, it could be possible to analyze the role of the *connecting structures* used by people, e.g., the *road network* [63,64]. Because geo-referenced connectivity data can distinguish sites that differ epidemiologically (epidemic 'nodes'), it is theoretically possible and technologically feasible to integrate the concepts originated in Network Theory with those of high-resolution, geo-epidemiological analysis, and achieve protection earlier, at lower costs and more effectively: instead of random vaccinations (those aiming at a 67% coverage –the threshold expected to achieve herd immunity), vaccinating, first, the critical 20% of the population (Pareto's most influential epidemic nodes), might stop epidemics earlier.

Differentiating *space* from *geography* is also relevant and so is distinguishing *high-resolution* (low scale) from *aggregate* (high scale) geographical data. While every geographical datum is spatial, the reverse is not necessarily true. This is so because spatial data may be simulated (and, therefore, not all the relationships that occur in Nature may be included). In contrast, geographical data are what they are and always include relationships that –using current technologies– can be measured with high precision. Therefore, the analysis of small geographical units (neighborhoods of a city or small counties, that is, high-resolution data) can generate studies that support cost-effective, site-specific interventions. In contrast, the analysis of aggregate data

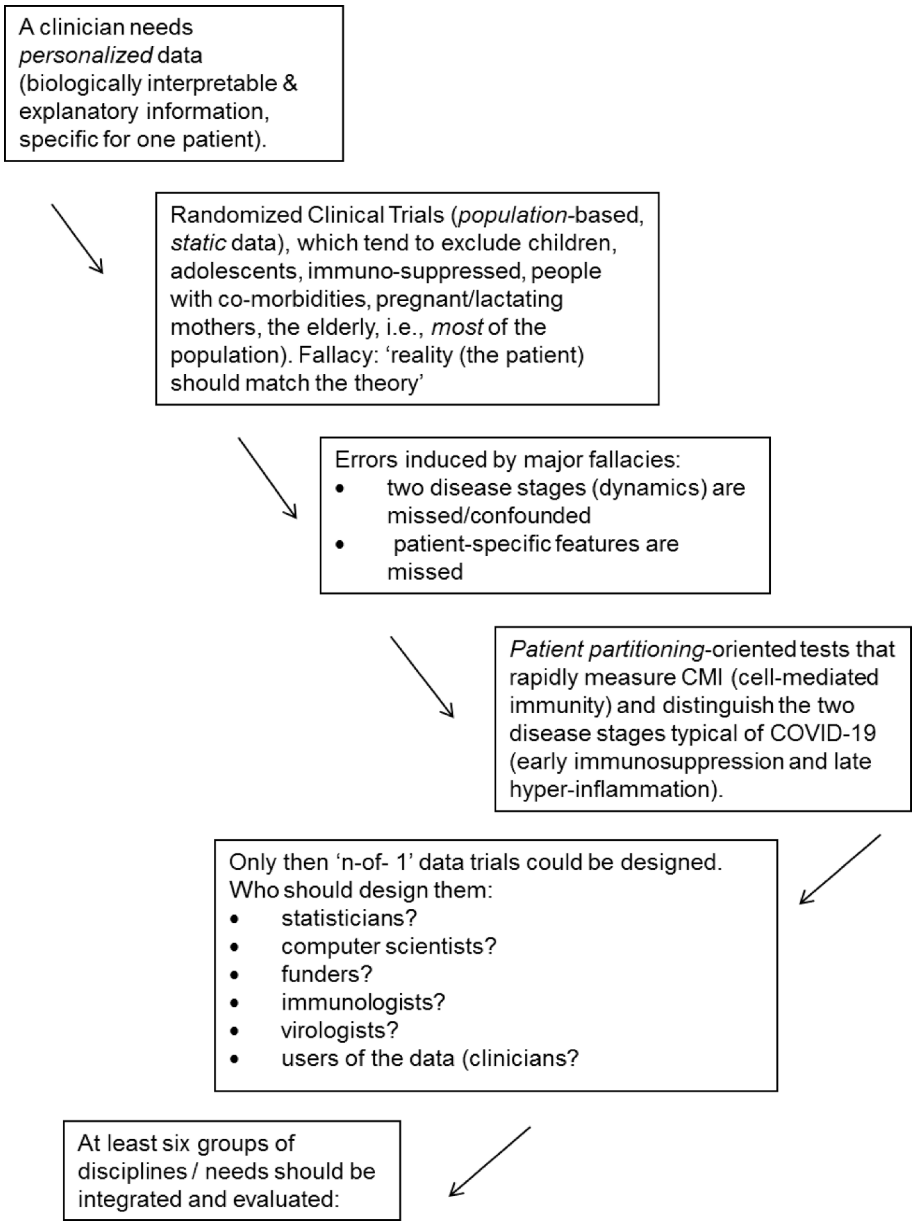


**Fig. 4. Disciplinary and social contents –example I: tests that offer explanatory information on biomedical functions.** A six-step process shows a guide meant to determine the minimal number of disciplines or social groups needed to solve an ill-defined problem. (1) the need is determined; (2) one (or more) predominant approach/es is/are described; (3) (one (or more) likely consequence(s) is/are identified; (4) a possible remedy or solution is outlined; (5) a list of disciplines/social groups relevant to/affected by the need is reported; (6) a tentative list is identified and their effectiveness to achieve the goal/solve the problem should be integrated and evaluated.

(e.g., state- or country-level data) loses granularity and induces more costly and less effective interventions [68]. When local, geo-referenced data are considered and vaccine effectiveness is estimated together with cost-benefit analyses, faster and less costly results can be achieved, over longer periods of time: geo-referenced based planning of routine immunizations may be more cost-effective than non-georeferenced planning [69,70]. In the absence of geo-referenced data analysis, predictions on herd immunity may be erroneous [40].

*Mobility* is one example of geo-demographic interactions. High mobility (e.g., increased migration) promotes a rapid waning of vaccine efficacy and, consequently, decreases herd immunity [71]. Interactions between human mobility and geographical heterogeneity also influence outcomes; e.g., when a quarantine restricts mobility, disease incidence diminishes [72].

Together, this review reveals a major difference between the original concept of 'herd immunity' and its human equivalent: while domestic farm animals usually move in or out of their farm just once in their lives, humans are extremely mobile. Because farm animal populations tend to be static and closed, they can be easily measured. In contrast, human populations are open, heterogeneous, highly mobile and, consequently, hard to measure. Hence, the *vaccination effectiveness-related 'herd immunity'* is a problematic concept (Fig. 1). Thus, it is not surprising that most countries seem to lack explicit procedures that translate herd immunity into concrete policies –our search only found one study that integrated such concepts [73].

While population and spatial heterogeneities should be investigated [74,75], the literature does not report efforts aimed at generating and disseminating local (high-resolution), temporal, geo-referenced epidemiologic data. This is a major source of errors: without such data, no site-specific policy can be planned and executed.

### 2.7. *Detecting silent disease spreaders, even with limited testing*

Estimates on herd immunity may also be erroneous when asymptomatic or presymptomatic cases remain undetected and, subsequently, infect susceptible individuals. On average, a-/pre-symptomatic cases may explain half of all cases [76]. Even if they represent a small percentage of the population, undetected cases, over a few weeks, will

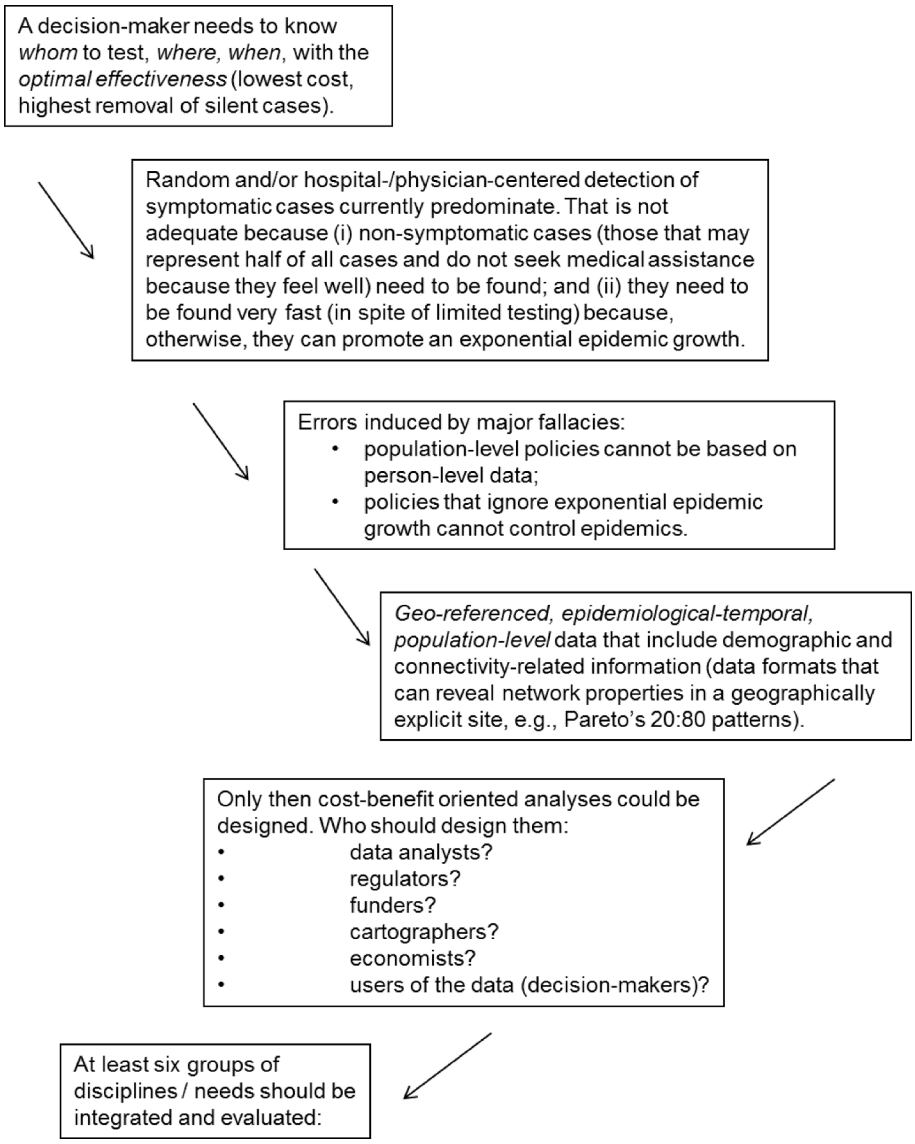


**Fig. 5. Disciplinary and social contents –example II: optimal (cost-effective) data collection systems.** A six-step process shows a guide meant to determine the minimal number of disciplines or social groups needed to solve an ill-defined problem. (1) the need is determined; (2) one (or more) predominant approach (es) is/are described; (3) (a) major consequence(s) (systemic or paradigm-level) fallacy(ies) is/are identified; (4) a possible remedy or solution is outlined; (5) a list of disciplines/social groups relevant to/affected by the need is reported; (6) a tentative list is identified and their effectiveness to achieve the goal/solve the problem should be integrated and evaluated.

generate an exponential epidemic growth. When epidemics grow exponentially, the time available to plan and execute control measures may be extremely brief [77]. Thus, the critical problem is not the magnitude of the (static) estimated herd immunity but its dynamics, i.e., the likelihood of non-symptomatic infected individuals to encounter susceptible individuals. When viral spread is not controlled, a few days may suffice for an epidemic to grow exponentially and generate colossal losses in lives, regardless of predictions on epidemic 'preparedness' [78].

The available evidence supports the view that the best policy is the one that can be deployed rapidly and achieve results before the epidemic starts to grow exponentially. Otherwise, policies will fail –and do it so at a very large (and unprecedented) scale. While earlier studies predicted that global economic losses attributed to COVID-19 ranged between 5 and 10% of the annual Gross Domestic Product (GDP), recent estimates calculate such losses (for the US) as approximately 90% of the current GDP [79,80].

Vice versa, saving lives is an ethical obligation and an optimal business: less than 10 US billion dollars may suffice to protect all health workers from low and middle income countries, save 2.2 million lives, and generate 755 US billion dollars. This policy results in a very high 'return on the investment': for each dollar spent, ~ 78 dollars would be gained [81].

## 3. II The second review: from Policy to Biology

To complement the analysis that covered concepts ranging from biology to policy, the second review is based on the policy promoted by WHO: 'test/treat/isolate.' This policy is centered on the notion that *'the most effective way to prevent infections and save lives is breaking the chains of transmission'* [82,83], Fig. 2). The first step of this policy involves testing.

### 3.1. *In search of a testing policy*

This second review supports the need for official policies on diagnostics. In spite of WHO emphasis on 'test/treat/isolate', many nations (including several countries with + 100 million inhabitants) do not seem to have a testing policy [84–87]. In 2020, at least three countries promoted only the testing of symptomatic (not asymptomatic) cases. When this policy was compared across six countries, only two countries revealed explicit policies on testing, isolation, and treatment of cases. Several countries did not consider travel history in their contact tracing systems. Other omissions included non-enforced isolations or

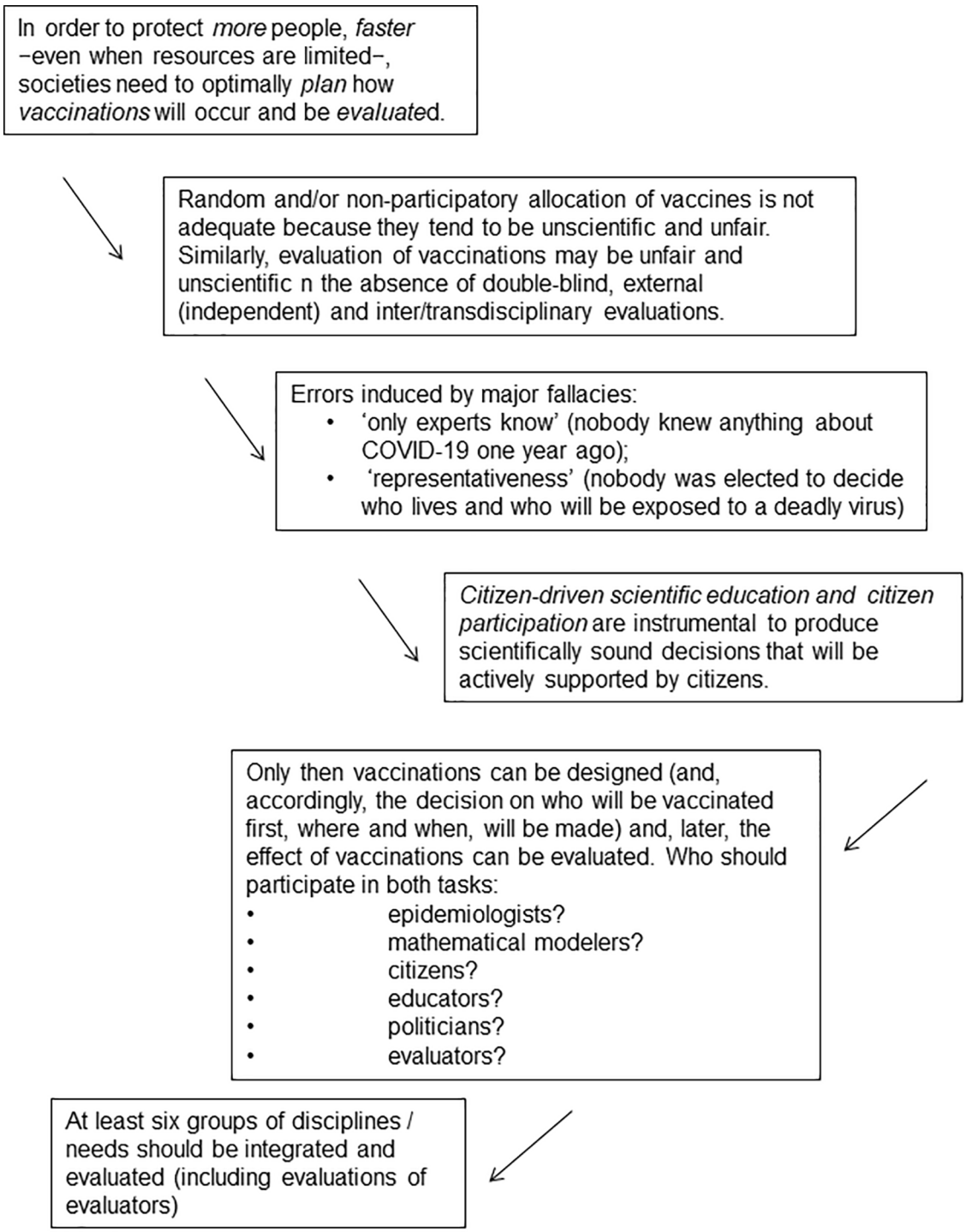


**Fig. 6. Disciplinary and social contents –example III: assignment and evaluation of vaccinations.** A six-step process shows a guide meant to determine the minimal number of disciplines or social groups needed to solve an ill-defined problem. (1) the need is determined; (2) one (or the) predominant approach is described; (3) (a) major consequence(s) (systemic or paradigm-level) fallacy(ies) is/are identified; (4) a possible remedy or solution is outlined; (5) a list of disciplines/social groups relevant to/affected by the need is reported; (6) a tentative list is identified and their effectiveness to achieve the goal/solve the problem should be integrated and evaluated.

recommendations that could be violated without repercussions, such as isolation at home. Contradictions were also detected: some countries provided testing free of charge but treatment was not provided [88].

Testing silent (non-symptomatic) cases requires an explicit policy that, to materialize, needs new data collection systems [89,90]. It may be concluded that not testing silent COVID-19 cases may, alone, explain the unabated duration of this pandemic.

### *3.2. In search of tests that capture silent disease spreaders –choosing whom to test, where and when*

One likely explanation for not testing non-symptomatic infections is the lack of consensus on 'screening' tests [91]. Originally meant to be implemented on volunteers suspected to be healthy (asymptomatic cases), these tests seem synonymous with those used in 'surveillance.' They only differ from 'diagnostic' tests in reference to the health status

of the people being tested: diagnostic tests are performed on individuals suspected to be ill.

To detect asymptomatic patients, tests that provide explanatory (function-related) information may be needed. One example of such tests is the assessment of macrophage activation [92].

The indeterminacy of screening tests affects who decides and who benefits [91]. The need to identify non-symptomatic cases also involves a separate problem: how to identify silent cases when the available resources can only test, at best, a minor fraction of the population. Therefore, the first challenge of the triad proposed by WHO is to develop new metrics –such as *test positivity*–, followed by a system that produces valid and usable results even when only a minor proportion of the population is tested. To be solved, this problem requires the inclusion of, at least: (i) geographical information systems (GIS) and (ii) cost-benefit analysis [89,90].

### 3.3. In search of valid systems –which may include numerous steps and several disease stages

To be effective, the assumptions upon which testing is based should be explicitly analyzed. They are those associated with the '$2 \times 2$ table' paradigm –a model originated in 1947.

This is a table with four cells that estimate (a) whether testing results are true or false, and (b) whether they indicate an infection-negative or –positive condition [93]. Given its four possibilities (a true 'positive', a true 'negative', a false 'positive', or a false 'negative'), this is a *static* and *binary* paradigm: it ignores time and assumes only two outcomes may occur.

This can be a major source of errors. Because infections are always dynamic processes and, over time, they reveal at least four stages (namely an early infection; a late infection without recovery; a late infection with recovery; and no infection), this paradigm may lead to confusion: *similar* values of the same variable may indicate *opposite* health situations. Vice versa, *dissimilar* values of the same variable may correspond to the *same* situation. Thus, the '$2 \times 2$' epidemic model tends to misclassify data and induce errors [94,95].

When the questions are posed in binary terms but the answers include more than two alternatives, errors are likely [96]. When, in addition, a static model is applied to dynamic data, errors and omissions will follow. Because interactions among individuals are rarely random in geo-demographic contexts [97], assumptions should be explicitly validated. To that end, exploring geo-demographic contexts as they are (not as they are assumed to be) is essential. Given the numerous concerns on the assumptions considered in COVID-19 related forecasting, probabilistic models should also be validated [98,99]. Similarly, the usability of the reproductive number ($R_0$) –which lacks geo-referenced coordinates and, therefore, cannot be ascribed to specific, small geographical units –, may need to be reconsidered [100].

### 3.4. Micro- and macro-scale connections

To evaluate herd immunity, micro-level (high-resolution, non-aggregate) geo-epidemio-immuno-virological data are needed. In contrast, high aggregate (macro-level) herd immunity are not always protective, as the following case shows. In October of 2020, in Manaus, Brazil, 76% of the population had sero-converted against SARS-CoV-2 –a 9% higher level than the herd immunity level expected to protect [12]. Yet, a new epidemic wave was reported [101,102].

The Manaus case illustrates two problems: (i) aggregate (state- or country-wide) herd immunity may be irrelevant when the local (micro-level) situation is not factored in; and (ii) in the absence of geo-epidemiological data, numerical analyses on COVID-19, alone, may be erroneous. Although many countries have built COVID-19 related data collection systems [103,104], there are no reports of countries that report high-resolution, geo-epidemiological data.

### 3.5. From problem-solving, to policy coherence, to audience-specific, visual communications

Data, information, knowledge and interpretation are different concepts [105]. Decision-making bodies need interpretation –not just data. Thus, problem identification is key.

Unlike the well-structured problems typical of academic settings, COVID-19 is an ill-defined, 'inverse', complex, dynamic and interdependent set of problems. Such problems may conflict with one another and share their sources of causation [106–109].

Given the ill-defined nature of COVID-19, communications aimed at fostering problem-solving skills are needed. In addition, efforts that promote innovation are necessary [110]. Ultimately, the *coherence* of *governance* systems should be evaluated and/or built.

Because conflicts between goals and rules tend to occur in systems that emphasize command and control functions, new models aim at polycentrism and participation [111,112]. These recent approaches seek preventing the far-reaching –although totally avoidable– problems that frequently affect governance systems, as the following cases document.

A study of 24 countries has shown that, in many countries, the advisory and decision-making body tended to be the same, transparency was rarely observed, the diversity of disciplines included in such bodies was rather narrow, citizen participation was not emphasized and communication campaigns did not explain the scientific foundation of the decisions adopted [113,114]. Another example refers to governmental corruption in the distribution of vaccines –a risk warned by the United Nations which, unfortunately, has materialized [115–117].

Perhaps the worst type of problems –because it leads to long-term, devastating consequences– is that grounded on simplistic (reductionist) worldviews, such as letting an algorithm determine who should be vaccinated –an approach that prevented more than 99% of the medical workers with daily and direct exposure to COVID-19 from being vaccinated [118]. This case also shows a major omission: the lack of a society-wide system that, in order to identify and solve problems that affect everybody, brings together numerous disciplines and social groups.

Instead of assuming natural resources are infinite –an illusion that destroys habitats and promotes the emergence of pandemics–, non-anthropocentric, non-binary, pro 'One Nature' governance systems are needed [119]. New, audience-specific communications are also required, e.g., when epidemic exponential growth is expressed as doubling times (rather than growth rates) and time gained (not 'cases avoided') is emphasized, understanding increases [120].

Centralizing information inputs and decentralizing messages has been recommended [121]. Visualizations also matter: when ill-problems are encountered, visual aids support problem-solving [122]. They help problem-solvers to detect not only individual (or partial) problems but also the overall (complex) problem that should be solved (Fig. 3).

To stop this pandemic, both *creativity* and *innovation* are required [102]. When incentives are introduced to promote changes, crises may help remove obsolete paradigms [123].

This report shows examples on how ill-defined problems that require interdisciplinary inputs and social participation may be addressed. A six-step guide identifies (i) the need to be met/problem to be solved; (ii) one predominant approach currently utilized; (iii) a likely fallacy of such an approach; (iv) a possible remedy or solution; and (v and vi) a list of relevant disciplines and social groups, whose performance should be evaluated (Figs. 4-6).

## 4. Conclusions

Findings identify nine partially interdependent omissions, contradictions, needs, and/or issues that require additional research and/or new policies: [1] national *data* collection systems, which should be geo-referenced, accessible to the public, subject to independent evaluations, and updated on daily basis; [2] new *metrics* that capture the progression

of epidemics –especially those that help detect non-symptomatic cases, e.g., *test positivity*; [3] new *cost-benefit* oriented approaches that compensate for the absence of universal testing (even with limited testing, they should demonstrate that silent viral spreaders can be rapidly identified); [4] *biologically* interpretable, *personalized,* new *tests* should measure cell-mediated immunity, co-morbidities and immuno-suppression; [5] factors that influence *vaccines* (*efficacy*, *coverage*, *effectiveness*) should be estimated with actual (geo-bio-epidemiological) data, not assumptions; [6] *economic* perspectives should take into account the protracted (several years long) likely consequences of epidemics that grow exponentially; [7] *binary* as well as *reductionist* approaches should be avoided, e.g., decisions should not be limited to either 'control' or 'eradication' –they may coexist and three or more alternatives may apply; [8] new *governance* models may be required, which emphasize problem-solving, social participation, and use of valid scientific knowledge over centralization; and [9] new *visually* explicit, *educational* programs with *audience*-specific communication strategies may be instrumental in this *innovation*-oriented process.

As depicted in Figs. 1 to 6, this epidemic is a multi-causal, dynamic and interdependent process in which no individual problem is solved unless all other problems are also solved. Because the perceived occurrence of these challenges may differ two or more weeks from one another, the resolution any one problem may require many fields and social groups. Because the topics here analyzed are so few, readers are invited to continuously review and expand the list of topics that should guide COVID-19 research and policy.

## 5. Author statement

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