ACCADEMIA NAZIONALE DEI LINCEI

Preparedness to pandemics

Statement by Covid-19 Committee

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Executive summary

The present document extends a previous statement by the S20 Academies of Sciences and aims to suggest actions to strengthen pandemic preparedness at the international and national level (1). The document is aimed at policy-makers, health institutions, research centres, scientists (in particular Academies of sciences and Academies of medicine), the press and the general public. When the pandemic is over the temptation is to go back to normal life. However, this is the time in which trust and mutual cooperation need to be reinforced, including understanding how to incorporate scientific evidence into policy.
Our document highlights specific scientific and organizational issues, building upon previous initiatives. We are not aiming to be exhaustive but rather highlight neglected or weak areas in currently existing plans. For this reason, *we are not addressing the discovery of new vaccines or antiviral drugs and other issues related to vaccination and antiviral chemotherapy*, since these are very broad and complex fields for which several authoritative documents exist.

Spillover of zoonotic pathogens from animals to humans is the starting point of pandemics. Government responses to unprecedented global warming and wild species extinction crises - that in turn increase the risk of spillovers - have been so far inadequate and inconsistent. **International coordination of actions concerning deforestation, expansion of animal breeding (particularly ruminants), limitation of wild animal harvesting, sanitation of food markets, and planetary health oriented dietary changes are needed.** Research is needed on causal chains that influence zoonotic pathogen spillovers to humans.

Pandemics can be caused by viral, bacterial or fungal pathogens and recent experiences include antimicrobial-resistant bacteria and fungi. Owing to their diversity, rapid evolution, speed of transmission and relative lack of effective treatments, viruses comprise a key threat. A related but separate area is also pandemics sustained by fungi such as Candida auris, and antimicrobial resistance. Discovery and functional research is needed to identify potential novel pathogens and their natural reservoirs in wild and domesticated mammalian and avian hosts. Research should be supported by **pathogen biomonitoring and genome sequencing facilities that are equitably distributed throughout the world. This effort is best concentrated in areas of**

high risk where there is low public-health investment alongside high biodiversity and frequent animal-human contact. Long-term monitoring programs need to be launched, their predictive accuracy and effectiveness compared, and field experiments designed to understand the pinch points where zoonoses are most likely to spillover into humans, and where mitigation of this risk is best targeted.

As part of ensuring sustainability of the ongoing pandemic response, coordinated international efforts are required to transition surveillance for COVID-19 from comprehensive case data collection **to sustain integrated surveillance of acute respiratory diseases**, including harmonized strategies for targeted testing for influenza and SARS-CoV-2 and viral RNA sampling for real time genomic monitoring of viral subtypes and variants. **Transparent and responsible governance of data sharing**, increased capacity of laboratory and data systems and digital linkage of surveillance networks, with the aim of enabling the near real-time integration of genome sequence data with complementary microbiological, clinical and epidemiological data, should be reinforced. Inter-operability of information systems and legal aspects of data acquisition and perusal need to be addressed at a transnational level. Wastewater surveillance programs (based on microbial DNA or RNA) should be assessed for their potential to generate timely alerts of the occurrence of pathogens in sewage, and similar attention should be paid to developing rapid molecular surveillance of contagious bioaerosols.

COVID-19 has been described as a **"syndemic", i.e. the impact of the infectious agent on predisposing conditions such as non-communicable diseases and social inequalities.** This means that strong and effective programs of primary prevention of non-communicable diseases and strong programs of mitigation of social inequalities in health should be advocated and pursued. Inter-operability of different health and non-health related information systems is a first essential step to connect information on vulnerability at a clinical level (e.g, through clinical records including General Practice) and at social level. The identification of the most vulnerable is related to having access to good quality information at a population level to focus preventive action and put proportionate universalism into practice.

Pandemic response emergency funding mechanisms should be established to facilitate **technology development of diagnostic devices in the early phase of a pandemic** caused by a novel pathogen, and accelerate the **transition from centralized to decentralized testing** with mass produced, low-cost, laboratory-based and portable/point-of-care diagnostic devices with rapid turn-around times.

We lack a **systematic evaluation of the public health impact of various diagnostic 'track and trace' strategies** during a pandemic, including the effectiveness of contact tracing, testing and quarantine, with technologies that are available across different health systems. Public health intervention experiments are warranted to better understand the contribution of contact tracing compared to other disease control approaches in different epidemic stages and settings.

There is a need for clinical trial networks that are prepared well in advance of the threat, making use of adaptive platform designs and master protocols as much as possible. The

execution of drug trials during a pandemic response should be facilitated by their direct integration into clinical care, rather than requiring the creation of separate parallel infrastructures. Massive investments should be made in aggregating data from electronic health records.

Well-designed studies - including Randomized Controlled Trials (RCTs) – are also needed in public health, e.g. on the effectiveness of different non-pharmacological interventions such as closing schools. **Meta-analyses of the evidence should be regularly updated by international and national health sciences institutions.**

The public sector (healthcare and preventive systems) needs to transition from a communication style mainly based on top-down release of information (perceived as paternalistic) to **a modality that encourages participation of the public and counters the powerful impact of social media**. There is a need for more analysis and knowledge as to the origin, nature, scope and determinants of denialism of facts that have been well established by science (and often by common sense), and to the best ways to contrast the spread of biased or false messages. Preparedness itself needs to be well communicated.

When the risk of harm to others is sufficiently severe, governments may determine that the right of all individuals to good health overrides the autonomy of any one individual to exert their decisional autonomy (e.g. not to wear a mask). **A number of ethical issues should be clarified in advance,** though a universal consensus is unlikely to be reached. Guidelines for triage in emergency wards in case of insufficient therapeutical devices should be provided after thorough discussion. Similar discussions should be promoted (e.g. in focus groups) about ethically relevant issues.

The management of the challenges we have identified could be organized and facilitated by the World Health Organisation, WHO, leveraging its unique role in establishing norms for global behavior (e.g., data sharing, material transfer agreements, common protocols, and ethics reviews). However, the governance of this complex enterprise would strongly benefit also from the involvement of medical and scientific organizations worldwide.

Introduction

"A pandemic is the worldwide spread of a new disease. Achieving protection against a pandemic is a public good. Like mitigation of climate change, it is a supranational issue that cannot be left only to national governments. Achieving global health security (including prevention of pandemics) requires reinforced international collaboration to deliver decisions about allocation of limited resources" (from S20 document: 1).

The present document extends a previous statement by the S20 Academies of Sciences (1) and aims to suggest actions to strengthen pandemic preparedness at the international and national level, building upon mistakes and failures (but also successes) during the COVID-19 pandemic. Unfortunately, in spite of the lessons learnt from the experience of COVID-19,

progress towards meeting minimal preparedness measures, especially in low to middle income countries, is slow in terms of public health surveillance and outbreak response. As it has been noted by commentators from most countries, when the pandemic is over the temptation will be to go back to normal life. However, this is exactly the time in which trust and mutual cooperation need to be reinforced, including understanding how to incorporate scientific evidence into policy.

The frequency of emergence of new zoonoses arising from pathogen, often viral, spill-over across species barriers will likely increase in the near future due to a growing and increasingly mobile human population, intensive agriculture and antimicrobial usage, climate change, inappropriate use and scarcity of water, consumption of wildlife products, legal and illegal trades of wild animals, and loss of biodiversity (2). Therefore, the international community is confronted with two major challenges, i.e., developing approaches to minimize spill-overs from animals and their associated environment to humans, and mitigating human vulnerability to pandemics across the microbial spectrum. The COVID-19 pandemic has revealed high variability in outcomes based on age, gender, socio-economic background, ethnicity, and co-morbidities that need to be better understood and addressed. A striking variability has emerged in the public health response to infection and in the usefulness of interventions, depending on the stage of the epidemic. We stress in particular the need for international cooperation at all levels. Another key component of all preparedness strategies is increasing trust in institutional response.

It is clear that there are several components in effective preparedness, and guidelines themselves are necessary but are far from being sufficient: for example, according to the 2019 Global Health Security Index the two countries with strongest preparedness plans were the USA and UK, which, however, also had slow government responses and high deaths rates from COVID-19. The Global Health Security Index (2019) assessed 195 countries on their readiness to deal with the threat of an epidemic or pandemic, before COVID-19: according to the Index, no country or health system worldwide was fully prepared for a globally catastrophic biological event of any sort, or for understanding the complex trade-offs that are associated with non-pharmaceutical societal interventions. When the same assessment was done in 2021, although many countries were able to quickly develop capacities to address COVID-19, all countries remain dangerously unprepared for meeting future epidemic and pandemic threats (3)(https://www.ghsindex.org/).

The present document highlights specific scientific and organizational issues, building upon previous initiatives such as the Independent Panel for Pandemic Preparedness and Response (4), the G20 High-Level Independent Panel on Financing the Global Commons on Pandemic Preparedness and Response (5) and the Lancet Commission (6). We are not aiming to be exhaustive but rather highlight neglected or weak areas in currently existing plans.

The components of preparedness plans include at least:
Prevention, prediction and surveillance

- Primary prevention: the role of biodiversity loss, agriculture and land-use change, species migration
- Biological and social determinants of spillovers
- Human mobility
- Regulation of laboratory practices in the genetic manipulation of viruses and other pathogens
- Networks of infectious diseases surveillance and outbreak detection
- Rapid screening for identification of pathogens of concern
- Role of non-communicable disease (NCD) and syndemics
- Mathematical modelling
- Inter-operability of information systems, access to data, legal issues

Diagnosis, treatment, response planning

- Ultra-high throughput screening and diagnostic tests: development and technology assessment
- New mRNA vaccine platforms beyond SARS-CoV-2, and development of other vaccines
- Development of new drugs
- Vaccine storage and handling
- Structures for Phase I/IIa trials - sound network for trials
- Effectiveness of NPI
- Full consideration of vaccination co-benefits: prevention of migration, reduction of hospitalizations, reduction of antimicrobial use aimed at effective AMR stewardship

Financing research and development

- Funding and multi-country pooled public procurement
- Role of intellectual property and licensing of vaccines and new drugs

Social and human sciences

- Vulnerability and equity
- Communication, hesitancy
- Communication of preparedness
- Ethics
- "What went wrong"
- Complex socioeconomic tradeoffs

We will only touch briefly upon some of these themes when we were able to identify documents that are addressing them in an exhaustive way, while more neglected topics are considered here in more detail.

Vaccines and monoclonal antibodies

Vaccines and monoclonal antibodies have been the main tools to control and mitigate the COVID-19 pandemic. It has been estimated that vaccines, in addition to prevent 20 million deaths, mitigated the huge economic impact of the pandemic allowing early restart of the economic activities. In this position paper we will not address vaccines and monoclonals extensively because they have been covered by other good documents, in particular from CEPI (https://cepi.net/news_cepi/cepi-opens-call-to-develop-heat-stable-vaccine-tech-for-use-against-epidemic-and-pandemic-threats/; https://pubmed.ncbi.nlm.nih.gov/34669432/; https://cepi.net/wp-content/uploads/2022/11/CEPI-100-Days-Report-Digital-Version_29-11-22.pdf?swcfpc=1). (7, 8, 9)

We mention briefly a few salient aspects concerning vaccines. Many initiatives are ongoing globally to improve the discovery, speed of development, manufacturing, and global availability of vaccines. Key players are CEPI, the United States National Institute of Health (NIH), the European Health Emergency Preparedness and Response (HERA), the World Health Organization (WHO), and several national initiatives. Among the national initiative it is worth mentioning the 8.5 billion $ by Japan to bolster the vaccine sector (10)(doi: 10.1126/science.adh0968), and the 340 million Italian investment to create a National Center for Pandemic Preparedness (Centro Nazionale Antipandemico or CNAP) (Gazzetta Ufficiale 26 agosto 2022). The main goal of these initiatives is to use innovative vaccine platforms to develop vaccines against new targets, with the ambitious goal to do it within 100 days. This approach involves the discovery and clinical development of a prototype vaccine for at least one member of each virus family with pandemic potential, using vaccine libraries and platforms for multiple vaccines (not disease specific) to increase efficiency. The « 100 day mission », originally launched by the G7 in 2021, has been confirmed by subsequent G7 meetings and embraced by CEPI and NIH (11, 12). Another key area is geo-diversified manufacturing ready to respond to outbreaks by up-scaling pre-existing drugs (not only for vaccines). Sustainability and business models are crucial: private investments and governmental funds should be coordinated and integrated to sustain vaccine development, local production and equitable distribution.

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1 Prevention and surveillance

1.1 Primary prevention: the role of biodiversity loss, agriculture and species migration; human mobility

Preparedness starts from primary or even "primordial" prevention, i.e. creating planetary conditions that make spillovers of micro-organisms less likely. A vast and unquantified number of virus species have the ability to infect humans. Of these, the majority are circulating in wild mammals (e.g. bats, rodents) or birds and many are recombinogenic allowing the continual generation of novel haplotypes. Other Kingdoms that contain pathogens are similarly biodiverse and little understood including pandemics and panzootics of fungal diseases in humans, agriculture and wildlife that emerge from poorly-understood natural reservoirs (https://www.nature.com/articles/nature10947); the spread of antimicrobial resistance from hotspots of adaptation including extensively drug-resistant tuberculosis (XDR TB); the occurrence and spread of infectious prion proteins; the international emergence of co-infections that transcend pathogen domains such as the acceleration of *Mycobacterium tuberculosis* transmission by patients with late-stage HIV-AIDS (1).

Changes in climate and in land use by humans lead to increased wildlife species migration and to increased opportunities for viral sharing among previously isolated species including humans. Estimates based on ecological modelling highlight an urgent need to pair viral surveillance with biodiversity surveys tracking the range shifts of wild species, especially in tropical regions that are experiencing rapid warming.

Effective prevention of new zoonoses requires a radical approach to mitigate loss of biodiversity and changing species distributions, reducing deforestation and understanding the impact of land use change on zoonoses. A likely increase in the risk of zoonoses in different parts of the world is related to agricultural practices including 'rewilding' landscapes and wild

animal harvesting. Preventing agricultural encroachment and over-harvesting of wild animals is an essential precautionary strategy to reduce risks of spillovers – witnessed by the devastating example of the HIV1 group M pandemic caused by spillover from hunted wild chimpanzees. As a major source of spillovers, also adequate hygiene in food markets (especially in some low-middle income countries, LMICs) needs to be addressed. Further, the intrinsic risk that these markets pose to global health should be addressed at a transnational level.

Demographic growth and increasing need of food (at the current rate, an increase by 45% is projected to 2050 worldwide) lead to an expansion of agricultural land and particularly animal farming at the expense of forests. Meat production leads to emissions of potent greenhouse gases (around 10-12% of the total) and contributes to deforestation, which further increases contacts with the wildlife. A radical reform of farming is needed, together with a far-reaching reduction in meat consumption worldwide. This strategy requires a global transition towards predominantly plant-based diets that are both healthier and more environmentally sustainable, and drastic reductions in tropical urban wild meat demand. Such actions are also key to the pressing need of mitigating global warming and biodiversity loss.

There are several, only partially known, key determinants of the likelihood and severity of spillovers such as (a) the life history of the organism (e.g. pneumonic, sexually transmitted …); (b) the rate of pathogen release; (c) the probability that the pathogen (shed, harvested or colonized in a vector) survives and is dispersed or transported to a particular location (where short survival times require close interactions between reservoir and recipient hosts); (d) the adaptability of the pathogen and (e) nonlinear dose-response relationships. A systematic understanding of these determinants should be rapidly made available for each novel potential pathogen following comparative analyses against better known related organisms.

Human mobility has proved to play a key role in the spread of some viruses (notably, SARS-CoV-2). Together with the early identification of outbreaks, it is important to set up a surveillance system of mobility with different purposes. Part of the surveillance does not involve individual data, but it is based on aggregated information. This includes: (a) local (short-range or long-range) population movements related to events such as the Chinese Lunar New Year, attendance at rugby internationals in the UK (first COVID-19 wave), or funerals in West Africa (Ebola); (b) transnational flows, knowing which allows early measures of border closure. For example, the Copernicus Border Surveillance satellite system includes a number of specific sub-services that can be used to this purpose. Other types of information, though not reaching the level of individual identities, are based on mobile phone data. Such data has been very useful (a) by showing the effectiveness of lockdowns, based on tracing mobility of populations before and after lockdowns in different areas of countries; and (b) for contact tracing, see below. However, a cautionary note is needed given the fear that COVID-19 related monitoring may become permanent in certain regimes and used for state suppression of civil liberties.

What is missing

Government responses to unprecedented global warming, biodiversity loss and environmental change have been inadequate and inconsistent. International coordination of actions to steer dietary changes in a manner which limits damaging agro-environmental impacts, stems deforestation, limits wild animal harvesting, and strengthens biosecurity in live food markets and commerce, is urgently needed.

Research should be developed – in the context of the One Health paradigm – on understanding the causal chains that influence the risk of pathogen spillovers to humans. Only some of the determinants of such processes are currently known (2). More research is also needed to develop information systems on human mobility in ways that are both effective and not intrusive of individual privacy. Integrated work is needed on monitoring of human mobility, by exploring opportunities offered by both satellites and mobile phone technology.

1.2. Regulation of laboratory practices in the manipulation of viruses and other pathogens

It is more likely that SARS-CoV-2 was transmitted to humans from natural reservoirs (like bats) via an intermediate species, rather than from manipulation or leakage from the Wuhan Hazard Group 4 laboratory (3). There is still incomplete evidence not only about the role of the Wuhan laboratory in this particular case. More widely, even well-run laboratories are fallible and the last recorded person to die of smallpox owed to a laboratory release in the United Kingdom, 1978. Foot and mouth virus FMV has a long history or accidental laboratory releases including a high profile release leading to the culling of 2,000 cattle in the UK, 2007. Whilst scientifically informative, experimental manipulations leading to gain-of-virulence or other epidemiologically relevant life-history traits need strong ethical justification in order to counterbalance the intrinsic risk to society of a laboratory release, either by accident or wrongful intention. This applies in particular to highly pathogenic microorganism (requiring biosafety levels 3 or 4).

What is missing

A systematic investigation of good laboratory practices and research programmes in laboratories that genetically manipulate micro-organisms is needed, especially for dual-use research on gain of function in pathogens. Furthermore, democratic debate and public health risk assessment are desirable for this kind of microbiological research.

1.3. Networks of infectious diseases surveillance and outbreak detection

Epidemiological surveillance includes the systematic collection, recording, analysis, interpretation, and dissemination of data on communicable diseases and host and infectious pathogen determinants to monitor their related morbidity and mortality trends at various population scales. Surveillance outputs inform public health risk assessment and management decision making. Reactive and near-real time surveillance and alert systems form a subset of surveillance programmes that are designed for the rapid detection of emerging infectious disease outbreaks and early warning signals to promote an adequate and timely control response. It is obvious from the limitations encountered worldwide with the detection and

monitoring of the COVID-19 pandemic that public health surveillance systems for epidemic and pandemic diseases must be enhanced at local, national and international levels, especially in high-risk areas and populations. Early detection of novel diseases and outbreaks of pathogens with pandemic potential is essential and relies on clinical recognition, rapid diagnostic testing, identification and molecular characterisation of the etiological agent, microbiological data mining, cluster analysis and mathematical modelling. Logistic capacity and advanced technical capabilities, round the clock availability of trained personnel, and an infrastructure for real-time microbiological and clinical data sharing with public health authorities are a prerequisite for efficient case finding and contact or source tracing to interrupt transmission and curb epidemics. Regional, national, and international sharing of anonymised surveillance data must occur rapidly using standard nomenclature through interoperable digital information networks.

Public access to surveillance case data repositories and analysis outputs for research use was a successful “crowdsourcing” breakthrough of the COVID-19 response. However, limitations in surveillance data quality and comparability were not widely appreciated. Further public education in interpreting surveillance data for assessing the effectiveness of control interventions is desirable.

The COVID-19 pandemic has underscored the need for complementing traditional surveillance data sources with *pathogen genomic sequence* data. Pathogen genomic surveillance is key to detect infection clusters, resolve transmission pathways as well as monitor the emergence of viral variants of public health concern due to their increased transmissibility, immune evasion or increased pathogenicity and their spread in populations triggering epidemic waves. The concept and implementation of genomic surveillance of infectious diseases and antimicrobial resistance have been developed over the last decade. Integrating clinical and epidemiological "metadata" with pathogen genomic sequence data allows to infer detailed transmission pathways and precisely identify sources of infection at local to global scales (4-7). The benefits of genomic surveillance have been demonstrated across a wide range of infectious diseases and conditions from foodborne infections to antimicrobial resistance and COVID-19 (8-11).

The COVID-19 pandemic also highlighted the utility of wastewater-based genomic surveillance using viral metagenomics as a complementary approach to population-level epidemiological surveillance and early warning (12). Such enhanced risk assessment information from genomic surveillance enables targeted interventions, thereby opening a new era of "precision public health" (6, 7). Regional and global strategies (ECDC, WHO) have promoted the implementation of national genomic surveillance capabilities and capacity building towards real-time disease and drug resistance monitoring and outbreak detection (13-17). The *WHO Global genomic surveillance strategy for pathogens with pandemic and epidemic potential* underscores the key importance of further building upon multisectoral partnerships, national and international collaborations, responsible governance of data sharing, capacity and capabilities of laboratory and data systems, digital linkage of surveillance networks, and integration of genome sequence data with complementary microbiological, clinical and epidemiological data to maximize data public health utility (17). Alongside, the prioritization of groups of pathogens (bacterial and fungal) that are associated with serious risk

of mortality or morbidity seeks to guide research, development and public health actions (see for example https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12).

Rapid data and biological sample collection for local and national analysis and their international sharing in accordance with FAIR (Findability, Accessibility, Interoperability, and Reuse) of digital assets and deposition of biological samples in curated national and international biobanks are key processes to fighting a pandemic and promoting open science research (18). Development of new infrastructure and interoperable data repositories is essential for this purpose. Examples include the European COVID-19 Data Platform (19) and its interconnected national portal nodes. Data standardization and harmonization of analytical methods and bioinformatic software pipelines are essential to make sense of the pathogen genomic surveillance data for informing public health risk assessment. Global viral sequence data repositories such as GISAID (Global Initiative on Sharing Avian Influenza Data) provide open access to both genomic and minimum epidemiological data and real time analysis visualization tools for influenza and SARS-CoV-2 viruses.

Examples of human infectious disease surveillance and alert systems include the WHO Global Outbreak and Response Network, the Global Emerging Infections Surveillance and Response System (GEIS), the European EpiPulse multi-surveillance system portal for infectious threat detection, monitoring, risk assessment and outbreak response and the Early Warning Outbreak Recognition System in Asia, Africa, and other high-risk areas for emerging zoonotic infectious diseases. Supranational health threat reporting, risk analysis and response coordination between public health authorities are enabled at global and regional levels by reporting to WHO following the International Health Regulation (IHR), requiring countries to assess the possible impact of all hazards likely to trigger public health emergencies. In Europe, the Early Warning and Response System (EWRS) enables posting alert notification of health events of potential cross-border significance by EU/EEA Member States to the European Commission - Health Emergency Preparedness and Response (HERA) department and the European Centre for Disease Prevention and Control (ECDC), following the recent European Health Union legislation. Also, a number of online disease surveillance systems are already delivering real-time intelligence on emerging infectious diseases to diverse audiences on user-friendly, open-access websites. One of these is HealthMap, a freely accessible, automated real-time system that monitors and disseminates online information about emerging diseases (20). The site pulls data from more than 20,000 sources every hour. Other efforts used data from Google (21) and Yahoo (22).

With regard to surveillance in animal populations, active systems are the OIE World Animal Health Information System, and the Food and Agriculture Organization of the United Nations (FAO) Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases. Although human surveillance systems have identified a number of zoonotic disease outbreaks in humans, these global systems have yet to prove adequate to detect infections in animal populations early enough to prevent transmission from animals to humans. Unfortunately, because disease surveillance efforts in livestock, poultry, and wildlife typically have been even more under-resourced than disease surveillance in human populations, it is the detection of

disease outbreaks in humans that has led to the detection of disease outbreaks in animal populations rather than the reverse.

Pandemic threats begin as local outbreaks. Using available technology to discover and immediately act on emerging outbreaks while they are still local has obvious benefits. An internationally coordinated initiative to work on "prototype pathogens", also aimed at the early identification of "disease X", is proposed. Virus discovery research has been suggested to identify potential zoonotic pathogens in mammalian reservoir hosts, such as bats, and in intermediate hosts, such as farmed animals, to reveal emerging threats caused by epidemic-prone zoonotic pathogens (23). Databases have been created to survey global hotspots for transmission of zoonoses, showing that zoonotic risk is elevated in tropical regions experiencing land-use changes and where wildlife biodiversity is high. Large and well-connected cities have become the hubs for the explosive spread of imported infectious diseases as was seen with Ebola and MERS as well as COVID-19. To address this phenomenon at an early stage, Perpetual Observational Studies (POS) of unexplained febrile illness using a generic clinical characterization protocol have been launched in a European network of infectious disease hospitals in high-density urban areas for studying emerging diseases, such as mpox and unexplained pediatric hepatitis (ECRAID-Base POS-Disease X, 2022: https://www.ecraid.eu/study/pos-disease-x).

What is missing

Virus discovery and functional characterization research to identify potential zoonotic pathogens in wild and domesticated mammalian and avian hosts should be supported by virus biomonitoring and genome sequencing facilities distributed throughout the world, concentrated in areas of high biodiversity and frequent animal-human contact. Long-term monitoring programs need to be launched, their predictive accuracy and effectiveness compared, and field experiments designed to test the mechanisms of zoonotic disease emergence from wildlife. Clinical preparedness research networks of infectious disease hospitals should be established in high-density urban areas across world regions to perform Perpetual Observational Studies (POS) of unexplained febrile illness using a generic clinical characterization protocol to determine the natural history, explore the pathogenesis and assess diagnosis and treatment of emerging infectious disease with epidemic potential.

As part of ensuring sustainability of the ongoing pandemic response, coordinated international efforts are required to transition surveillance for COVID-19 from comprehensive case data collection to representative, integrated, sentinel, etiological surveillance of acute respiratory disease, including harmonized strategies for targeted testing for influenza and SARS-CoV-2 and viral RNA sampling for real time genomic monitoring of viral subtypes and variants, as recommended by the WHO (WHO 2022) and EU COVID-19 response (European Commission 2022).

Beyond COVID-19, the WHO global genomic surveillance strategy aims to strengthen multisectoral partnerships, national and international collaborations, design FAIR and responsible governance of data sharing, increase capacity and capabilities of laboratory and

data systems, establish digital linkage of surveillance networks with the aim to enable integration of genome sequence data with complementary microbiological, clinical and epidemiological data for enhancing pandemic and epidemic preparedness (WHO, 2022). In addition, it is desirable to further standardize and establish wastewater metagenomic-based surveillance programs and assess their potential to generate timely alerts of the occurrence of pathogens in sewage as predictor of their emergence and dissemination in the upstream resident human population. In tandem, the wider metagenomic surveillance of bioaerosols in areas of high population density such as transport hubs may act as an early-warning system for pneumonic contagions.

1.4. Role of NCD and syndemics

SARS-CoV-2 landed on an epidemiological landscape that influenced its clinical consequences and lethality, mainly due to social inequalities and pre-existing non-communicable diseases (NCD). This led to revive the concept of "syndemic", and to focus on prevention of NCD to mitigate the impact of next zoonoses. Initially coined by the anthropologist Merrill Singer in 1994 to describe the co-occurring and intertwined epidemics of substance abuse, violence and HIV-AIDS, the concept of syndemic was then extended to a range of diseases to describe their interactions and the social, environmental and economic factors that drive them and ultimately worsen health outcomes and increase inequalities. The three key elements of a syndemic include: disease clustering, meaning that two or more epidemics co-occur in place and time; disease interaction, due to shared risk or iatrogenic factors; and the broader social/political forces that give rise to disease clustering and interaction. COVID-19 has all the characteristics of a syndemic, since the occurrence and clinical course of the disease were influenced by pre-existing NCD like hypertension, diabetes and obesity, with a clear socio-economic gradient.

General practitioners should be aware of the most vulnerable subgroups among their patients. They should maintain lists of patients with conditions that predispose them to negative infectious disease outcomes (including obesity, diabetes, hypertension, cardiovascular diseases).

Primary, secondary and tertiary prevention programs of NCD should be implemented at all levels, with special focus on deprived populations. This is part of a general reform of healthcare that increases investments into primary prevention and primary care rather than exclusively in hospital treatment of diseases. Focusing predominantly on hospital care means that the progression of disease is usually more advanced, and vulnerability of large sectors of the population makes the spread of a pandemic quicker and its severity greater. Inter-relationships between hospital care, preventive services and general practitioners should be strengthened, with clear guidelines and improvement of health information systems at all levels.

What is missing

Strong and effective programs of primary prevention of NCD and strong programs of mitigation of social inequalities in health, with embedded evaluation of efficacy, are still almost completely missing.

1.5. Mathematical modelling

Every epidemic has its own characteristics, linked to the type of aetiological agent, the harm it induces, the way it is transmitted (including R_0, the reproduction number), and its lethality, so that it is difficult to transfer countermeasures from one epidemic to another and predict their course by analogy. The behaviour of different pathogens can be predicted by constructing mathematical models that simulate the conditions of infection transmission, produce spread scenarios and offer the possibility of evaluating the effect of specific countermeasures. The history of the circulation of each epidemic or pandemic has a scientific reproducible component, in the sense that it can be interpreted in the light of the virus' mutations, its adaptation to the host, population admixture and immune response. But the overall narrative has also many circumstantial and unpredictable elements, linked to chance (for example the appearance of the right mutation at the right time), and to the geographical and historical context.

Therefore, humility has been invoked in modelling (26), in the sense that models are affected by uncertainties and cannot be stretched beyond their limits of prediction. An example are the early predictions made by the Imperial College team, that prompted the adoption of non-pharmacological containment measures in several countries. The early models were inevitably based on limited experience and data (coming first from Wuhan, then from Northern Italy), plus a number of assumptions: (a) models assumed an incubation period with mean 5.1 days and standard deviation 4.4 days, estimated from travellers' case data; (b) infectiousness was assumed to start 0.5 days before symptom onset (with inter-individual variability); (c) ICL models assumed that individuals vary in infectiousness according to a gamma distribution with mean 1 and dispersion parameter k=0.25 (though other estimates suggested k=0.1 later; this means that 10% of the cases give origin to 80% of infections)(this level of overdispersion matched estimates obtained from observed transmission chains; in other words, they assumed that there were overspreaders of disease); (d) they assumed $R_0 = 2.4$, as estimated in Wuhan. R_0 was later substituted by Rt, i.e. the reproduction number influenced by the containment measures that were taken; (e) they assumed that 50% of all infections were symptomatic (at least mildly). While some assumptions were robust, others were modified in the course of time. Early modelling is necessarily tentative, based on sometimes fragile assumptions, and requires constant updates.

In spite of uncertainties, mathematical modeling has proven key in predicting the evolution of the pandemic in its different phases. Models are as good as their assumptions and the underlying data are, therefore methodological research is needed to compare and refine models, to increase their predictive ability and identify the causes of poor performances. The quality of underlying data should be checked, including the quality of coding and data cleaning. Also, policy-makers and the press should be trained to identify limitations of mathematical models. The latter are fallible, and need to be interpreted with caution. All estimates should always be provided with confidence intervals and underlying assumptions should be clearly laid out (26).

In addition to predictive models, there are other important but still limited applications of mathematics, for example Artificial Intelligence/Machine Learning in fields such as outbreak

detection (encompassing GIS, pattern recognition, etc.), optimization of contact tracing, vaccine distribution campaigns, etc.

What is missing

A systematic assessment of how mathematical models performed in predicting virus transmission dynamics and guiding interventions in the different phases of COVID-19 is still lacking.

1.6. Inter-operability of information systems, access to data, legal issues

Problems with access to data and compliance with data protection laws need to be clarified in all countries. Clear rules need to be provided worldwide, that on one side make access to data and interoperability of information systems feasible, and on the other side protect individual right to privacy. In the early phases of the COVID-19 pandemic many countries had to address such topics in the emergency, sometimes by-passing or modifying national laws. Early assessment of such problems conferred a selective advantage to countries that were able to use nation-wide information systems, that provided essential information on the epidemic and the effectiveness of control measures, including vaccines.

Given the significant investments in different European countries in the aftermath of COVID-19, e.g. in Electronic Health Records, and the associated modernization and technological adaptation of health information systems, it is important that the various existing information systems and health data flows that are in place at the local, regional and national levels converge toward full interoperability.

Technical actions needed to achieve convergence and full interoperability:

1. It is important to activate specific technical support actions and ensure financial coverage so that all territorial and hospital health authorities in different regions/countries are able to activate their electronic health records with the same architecture, structure, content, coding and organization (namely, HL7-FHIR, Fast Healthcare Interoperability Resources).

2. It is necessary to activate quality controls of the implementation of information systems and of the underlying data, rules that should be an integral part of operation of the FHIR gateways available at the health care units (hospitals, GPs, etc)

3. There are currently multiple information flows in each country, managed by different entities and with different owners. It is important that existing information flows be optimized and harmonized, enabling their interoperability and interconnection, with a view to their integration with the new electronic health records and thus adopting the same management platforms (HL7-FHIR).

4. It is necessary to promote and develop the correct and ethical use of the data contained in the information flows (in the short term) and the Health Data Ecosystems (when these will be fully operational) through training, information, and dissemination of rules of good practice of health research.

Actions related to data protection regulations:

1. With reference to existing information systems, clear and specific data protection rules need to be established with reference to the need for timely access and use of data for the purposes of healthcare and research governance (in Europe this is regulated by GDPR).

2. The generators of health data will be primarily, but not exclusively, the health care providers that feed the electronic health records. It is desirable that the generation of and access to electronic records data be governed by clear guidelines that take into account the different possible uses of the data.

3. It is necessary to define when and how individual consent must be sought for data storage, retention and use, and who is responsible for and custodian of the consent granted.

There is an urgent need to define the ways and procedures through which the Ministries of Health and other entities involved in the reform of the Health Information Systems can initiate an operational interlocution with the Data Protection Authorities and other entities such as the National Cybersecurity Agencies.

What is missing

Inter-operability of health information systems and legal aspects of data acquisition and perusal need to be addressed at an international level.

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2 Diagnosis, treatment, response planning

2.1. Ultra-high throughput screening and diagnostic tests: development and technology assessment

Microbiological testing for pathogen detection in clinical specimens for disease diagnosis or infection screening is a critical component of the medical care and public health management of epidemic diseases such as COVID-19 and mpox. Testing can be used for triage and clinical care of patients and to inform contact tracing and isolation and/or immunisation of secondary infected persons to break chains of transmission (1, 2). COVID-19 has revealed the need for improved preparedness in the field of rapid diagnosis and screening for viral infections. The inability to conduct COVID-19 tests in sufficient numbers, provide rapid results and immediately report them to public health authorities in the early phase of the pandemic had critical consequences on clinical decision making, epidemiological investigations, and public health risk assessment and interventions, even in high income countries with advanced public health microbiology capabilities (2-4).

In on-going and future work towards preparedness there is a technology assessment component (increase throughput, increase accuracy of tests, decrease turnaround time to results, reduce costs) and a clinical-epidemiological component (predictive value of tests for rapid screening

and contact tracing vs tests for diagnosis). Testing of the population should be evaluated in terms of predictive value of screening tests depending on the prevalence and dynamics of infection, but also in terms of effectiveness in relation to the service organization and test result reporting to those who need to act. For instance, to be useful contact testing and tracing requires public health logistics that include in particular the ability to isolate people rapidly and effectively.

Nucleic acid amplification tests (NAAT) are the gold standard assays for diagnosis of viral infection. They offer very accurate (highly sensitive and specific) detection as well as permit further genomic characterization. Timely results are critical, e.g. for rapid treatment and isolation purposes. Rapid antigen detection tests (RADTs) are less sensitive than NAAT but can be mass produced, used at point-of-care or as self-test and provide results within 30 minutes instead of hours and at a lower cost. Emergence of virus variants can affect the sensitivity of NAAT or RADT if the target genes or antigens are modified enough to reduce ligand affinity. For this reason, analytical performance of diagnostic assays must be continuously verified along with pathogen evolution. Public health assay recommendations for testing should be updated accordingly. For instance, in responding to COVID-19, WHO and the EU Health Security Committee have recommended RADT minimum performance requirements. Meta-analysis data on commercial COVID-19 assay performance are publicly available (FIND and JRC online databases). The EU determined a common list of high performance COVID-19 testing assays that are accepted for mutual cross-border travel regulation and standard test result travel certificates (Council of the European Union, 2021)(5). Specific antibody detection and quantitation tests are mostly useful for sero-epidemiology studies and vaccine effectiveness monitoring.

What is missing

Pandemic response emergency funding mechanisms should be established to facilitate technology development of in vitro diagnostic devices in the early phase of a pandemic caused by a novel pathogen, and accelerate the transition from centralized testing - with in silico-designed NAAT reference diagnostics, carried out in specialized microbiology laboratories - to decentralized testing with mass produced, low-cost, laboratory-based and portable/point-of-care diagnostic devices with fast turn-around times.

Fast track regulatory guidance, assessment and provisional market authorization for emergency use of IVDDs (in vitro diagnostic medical devices) for detection of novel pandemic pathogens based on preliminary evidence of accuracy should be strengthened and harmonized by a common framework of test validation at international level. This process should be further complemented by international mutual recognition of minimum testing performance criteria and validated diagnostic assays for use with specific public health purposes, such as infection detection at border control and contact tracing, expanding on the WHO Emergency Use Listing procedure (EUL) for diagnostics and EU common list of RADTs for SARS-CoV-2 detection.

We lack a systematic evaluation the public health impact of various testing strategies during a pandemic, including the effectiveness of contact tracing, testing and isolation with technologies

that are available across health systems. Public health intervention experiments are warranted to better understand the contribution of contact tracing compared to other disease control approaches in different epidemic stages and setting-specific public health capabilities.

2.2. Structures for Phase I/IIa trials - sound network for trials

Traditional randomized controlled trials (RCTs) are the gold-standard approach to generate evidence regarding the benefits and harms of potential vaccines and therapies (6)**.** Nevertheless, the processes required for their set up and execution are far too slow and burdensome for rapidly spreading pathogens. Moreover, some of the high-quality standards for studies evaluating experimental interventions under normal conditions cannot be maintained in a pandemic setting.

Adaptive designs, that adjust features in response to data accruing within the study according to pre-specified criteria, can allow accurate conclusions to be drawn with shorter time and smaller numbers of patients than those needed for standard RCTs (7), which is particularly attractive during an outbreak. Adaptive elements can include interim adjustment of randomization ratios between study arms and/or subpopulations, endpoint selection, the strategy used for limiting the study's false positive rate and treatment groups.

The COVID-19 response highlighted the suitability of adaptive platform trials (8, 9) - which enable the simultaneous assessment of multiple interventions under a flexible master protocol, so that novel intervention arm(s) can be added over time - for treatment evaluation during a public health emergency (10). The largest phase III adaptive platform trial performed in this context, RECOVERY (Randomized Evaluation for COVID-19 Therapy), started recruiting patients within nine days after the protocol was approved, and has provided practice-changing evidence of benefits in hospitalized patients of four therapies (e.g., dexamethasone) and ruled out significant benefits of six others (e.g., hydroxychloroquine) (10). Key to this success was the employment of a streamlined point-of-care approach that facilitated integration of clinical research with front-line clinical care by the use of simplified processes which reduced bureaucracy and common reliance on routinely collected electronic health records to minimize data gathering by health care staff (11). Platform trials are logistically complex, and their rapid delivery calls for cooperation and coordination among research stakeholders, including trial teams, drug manufacturers, regulators and health system managers.

The adaptive platform design should also be employed in early phase (I and II) clinical trials to rapidly evaluate and prioritize repurposed or novel agents with promising evidence of efficacy that can feed into established later phase platforms. Early phase trials are especially necessary to the study of new, unlicensed drugs, which require a greater level of informed consent, increased collection of safety information, and exploration of mechanistic implications (12). Findings from early phase trials can also inform the selection of endpoints, including both biological and clinical outcomes. Nonetheless, at the beginning of COVID-19 pandemic, prioritization of later phase trials, such as RECOVERY, occurred at the expense of early phase trials because of competition for resources and patients, eventually leading to delays in the reporting of results from smaller studies (13).

While it is undeniable that RCTs conducted under the adaptive platform design have provided evidence for COVID-19 management which changed clinical practice and saved lives (14),

randomization should not be considered the only way to gather reliable information about the safety and efficacy of potential interventions in the context of outbreaks of emerging or re-emerging pathogens. One viable alternative, conceived against the 2014 Ebola outbreak in West Africa, would be to try different treatments in parallel at different sites, following observational studies that document mortality under standard care. This approach could effectively triage treatments into those with clear benefits that should be rolled out immediately, those with no effect that should be discarded quickly, and those with promise needing follow-up in randomized trials (15). It is also noteworthy that the reaction to COVID-19 pandemic has revealed that other types of evidence, besides those generated by RCTs, can be exploited, including those from observational studies and digital technologies (e.g., real-world electronic medical or insurance records, data from mobile devices) (16).
The unpredictable duration of outbreaks also poses the challenge to initiate clinical trials that could be unable to accrue the necessary evidence about the efficacy and safety of the interventions under investigation because of the decline or stop in disease transmission. To avoid the publication of promising but inconclusive results from partially completed trials, which are difficult to interpret, yet can impact policy-making and jeopardize the conduct of future confirmatory studies, the WHO's R&D Blueprint proposed a master protocol concept that enables to suspend recruitment to a trial during times when the disease outbreak is under control and to resume if it re-emerges (17).

What is missing

There is a need for pandemic trials that are prepared well in advance of the threat, making use of the adaptive platform design as far as possible. Future pandemic planning should ensure an integrated pathway from early phase to later phase clinical trials for prevention and treatment measures, and prioritize resources, patient recruitment, and regulatory examination for both types of trials.
The execution of trials during a pandemic response should be facilitated by their direct integration into clinical care, rather than requiring the creation of separate parallel infrastructure for clinical research. Investments should be made in aggregating data from electronic health records, which would reduce the expense labor needed for data collection, especially for following up with research participants after hospitalization.
Besides RCTs, other types of evidence should be exploited, included those generated by observational studies and digital technologies.

2.3. Other aspects of preparedness: effectiveness of NPI, co-benefits of vaccination

Non-pharmaceutical interventions (NPI) (e.g. testing, quarantine and isolation, physical distancing, masking, handwashing, ventilation hygiene) have proven effective in containment of the pandemic, however systematic evaluations of their performance and relative contribution are needed for each of them. International and national health science and health technology assessment institutions should regularly organize systematic reviews and meta-analyses of the evidence for the effectiveness of face masks, social distancing, school closures, business closures, remote work, travelling limitations, lockdowns, etc. Systematic reviews should support recommendations to be adopted worldwide. For areas of uncertainty, effectiveness

should be tested with new experiments (including RCT when feasible), with varying assumptions on R_0, transmission modalities, lethality, relation to mobility, etc.

Vaccination is one of the medical interventions with the greatest benefit/risk ratio and benefit/cost ratio. In addition, vaccination has a number of positive side effects at an individual and population level. Vaccination programs in Africa have historically strongly reduced internal migration related to poor health. In general vaccinations reduce the burden of disease and therefore of hospital care and healthcare expenses. An underestimated impact of vaccines is also the reduction in the use of antibiotics. Many viral infections, particularly in children, are inappropriately treated with antibiotics. Antimicrobial resistance (AMR) is becoming one of the main threats to human health, partly due to use in animal breeding, and partly for improper clinical use. Considering prevention of hospitalizations and migration (in low-income countries), reduction of antibiotic use and prevention of AMR, vaccines are associated with great positive economic impacts. These aspects related to co-benefits of vaccination – including against SARS-CoV-2 - should be emphasized in communication to the public and considered in the overall economic estimates of costs vs benefits of vaccines. Vaccination for agents other than SARS-CoV-2 is a preparedness measure itself.

What is missing

Experiments (including) RCTs on the effectiveness of NPI (e.g. closing schools), should be conducted more frequently. Meta-analyses of the evidence should be regularly updated by international and national institutions.

We need systematic evidence-based estimations of all co-benefits of vaccines, for population health, employment, economic development of LIC and AMR resistance.

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3 Financing research and development

3.1. Funding of preparedness

Considering the suggestions above, preparedness leads to additional, non-negligible financial costs for health care systems. Additional costs may derive from a) implementing incremental health care capacity in order to be able to answer to potential demand peaks or b) flexible provision models, able to rapidly overcome the in-built, usually rigid, destination of existing facilities. Flexible facilities (like hospital beds) are more cost effective than recurring to spare capacity, still they represent additional costs.

Preparedness costs are different from insurance costs, because they are set to be able to answer to a new disruptive epidemiological scenario and not just to recover ex post from damage. Preparedness has a different logic compared to the insurance model, since it involves more complexity in order to prepare flexible facilities, and foresee future organization models and professional competences, rather than just estimating risks and developing financial algorithms a posteriori.

The key point is how much financial investment a community or a society can afford or is willing to invest for preparedness, defining the potential capacity to react to future pandemics. Let us consider an easy case to understand the problem. In front of a global supply chain, it is important to stock a relevant amount of protection FFP2 masks in a country of 60 ml inhabitants like Italy. Every year the masks expire and the national safety stock needs to be renewed. For 60 mil inhabitants we could stock 600 mil masks (10 per citizen), which means to have a reserve for ten days if we consider a mask usage rate of one per day, or 1.8 bil masks (30 per inhabitant) if we want a national safety net which can last at least one month. In the first case the health care system needs to spend 300 mil per year if we account for only 50 cents per mask (considering production and warehouse costs) or even 900 mil per year if we stock 30 masks per inhabitant. Of course, we could develop other approaches like supporting domestic industries overcapacity or offering incentives to be ready to change, having invested in flexible production plants. How many societies are politically and culturally prepared to such a kind of financial effort, which means to increase the collective fiscal pressure or to reduce a coherent amount of current health care services? In some ways, this is even more difficult than putting apart a fixed amount of health care expenditure for preventive services, because in public health we are usually dealing with visible provisions (vaccination, health education, etc.) rather than for invisible, uncertain future occurrence. For sure, there is room for cost-benefit analysis both to study the collective cost of different levels of preparedness, but also to understand the most cost-effective solutions (in our example: a) to stock from the global market; b) to support domestic spare capacity; c) to finance flexible production plants able to transform on Government's demand their product portfolios). In most of Western democratic societies these decisions tend to be implicit, outside the public discourse and the political agenda. This leads to greater responsibility for health care planners in front of the crucial decision between more or less investments in preparedness and equivalent reduction of current health care services. It is of course true that some investments (about additional competences, more efficient governance or institutional arrangements, more clinical networks) provide immediate added value also for ordinary activities, but this is not true for all the preparedness investments, since some are clearly increased costs without positive effects outside the pandemic period.

Financing preparedness has been discussed by others, in particular buy the Lancet Commission on COVID-19 (1). As suggested by the Lancet Commission, the Global Health Fund is key in assuring funding for infectious disease research and would require annual disbursements of the order of $60 billion per year (around 0.01% of the GDP of the high-income countries). According to the Commission, this recommended annual funding of $60 billion would be allocated roughly as follows: commodities, $20 billion per year; pandemic preparedness, $15 billion per year; and support for primary health systems, $25 billion per year.

Immediate needs of funding and capacity building

There is a need to accelerate, coordinate and improve translational research in pandemic response, including real-world evaluation of in vitro diagnostic devices performance and utility for clinical care and control of emerging diseases. This should be addressed by preparedness

and emergency research funding on multiple fronts. First, to strengthen resources and capabilities of international networks of national public health reference laboratories already dedicated to surveillance and alert for infectious diseases. This should build upon successful collaborative public health structures such as European networks of National Public Health Reference Laboratories and the Global Influenza Surveillance and Response System. It will be critical that the new EU Health Emergency Preparedness and Response Authority (HERA) initiative to launch a network of EU Reference Laboratories for preparedness complements and integrates with the existing ECDC and WHO-coordinated laboratory surveillance and alert networks. In addition, international clinical research networks should be further developed and integrated into pandemic preparedness plans to mobilize microbiology and infectious disease experts across academic medical centers to undertake immediate pre-approved clinical trials of novel diagnostic devices as well as therapeutics against pandemic agents in response to a public health emergency. Examples of initiatives supporting these goals are the FIND initiative acting as WHO Collaborating Centre for Laboratory Strengthening and Diagnostic Technology Evaluation and the ECRAID-Base European clinical research network for infectious diseases.

National health programs should ensure adequate funding, up to date laboratory infrastructure and qualified staff resources for the provision of sufficient diagnostic testing and screening capacities. Based on multidisciplinary review of the challenges met with COVID-19 response within their national, regional and local health systems, they should further develop and stress-test pandemic strategies and contingency planning for scaling up testing when needed for control of epidemics, based on epidemiological indicators. Beyond capacity building for microbiology laboratory services, IT investment in interoperability and connectivity between laboratory and health information systems is key to ensure real time, automated reporting of diagnostic test data for disease surveillance and public health alert purposes. External quality assessment schemes also known as proficiency testing exercises, should be implemented by health authorities to ensure the accuracy of novel testing procedures from sample collection, testing and reporting process delivered by all service providers. This should encompass certified and accredited medical laboratories as well as near patient testing distributors and operators, such as pharmacists, where applicable.

3.2.Role of intellectual property and licensing of vaccines and new drugs

A related but separate topic is intellectual property rights. The European Commission, the US government and other agencies funded private vaccine research extensively. BioNTech received €100 million in financing from the European Investment Bank and a €375 million grant from the German government. It has been estimated that the NIH spent $17.171 billion between 2000 and 2019 on vaccine platforms, of which an estimated $943 million was spent on mRNA vaccines and another $757 million was spent on vaccines targeting diseases caused by betacoronaviruses (1). US Government funding for clinical trials of the Moderna vaccine totalled an additional $4.9 billion in 2020. Despite having had a decisive role in funding the development of these vaccines, governments did not benefit of market returns, and in fact purchased the vaccines from these companies on a commercial basis. Governments have not yet designed appropriate ways to manage the intellectual property that they co-fund, i.e an

alternative to privatisation of IPR. Addressing access to IPR by governments would be a way to by-pass the problem of licensing for vaccines and new drugs.

Key reference

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4. Social sciences

4.1.Vulnerability and equity

Vulnerability to infectious diseases (particularly in the course of a pandemic) has several roots. One is clinical, related to pre-existing pathological conditions (see "syndemic" above). Others are related to economic, social, professional, residential, or educational gradients. Irregular migrants, workers in unhealthy and crowded environments, uneducated persons, workers and professionals in close contact with the public, etc., are all categories about which we know little. We need to identify the subgroups in the population with different susceptibilities as part of preparedness. How can we reach them, prepare them, educate them to recognize symptoms, and make prevention and medical care available to them? In addition, how can the health system be prepared to address jointly clinical and social susceptibilities? This implies a close cooperation between the healthcare and the social security systems.

Of particular concern are those persons, even in developed societies, that cannot be reached or identified by administrative structures, such as irregular migrants, or individuals voluntarily disconnected from society.

While there is much research on the causes and effects of social inequalities in health, knowledge is limited on the approaches that can attenuate their impacts.

What is missing

Inter-operability of different health and non-health related information systems is a first essential step to connect information on vulnerability at a clinical level (e.g,. through clinical records including General Practice) and at social level. The identification of the most vulnerable is related to having access to good quality information at a population level to focus preventive action and put proportionate universalism into practice.

4.2. Communication, hesitancy

It is estimated that in 2011 the average American was exposed to five times as much information as he or she was in 1986: the equivalent of 175 daily newspapers. Every day, in our spare time alone, we process 34 gigabytes, equivalent to 100,000 words. This greatly overcomes our ability to process information, and makes our attention to problems selective and potentially distorted.

«Personalised information is a natural extension of existing media. For your daily dose of information, you can subscribe to different agencies and let a software or human person select them to compose your fully customised daily newspaper» (Bill Gates, 1995). However, letting someone filter information for us according to our social media profile leads to enclosing us in 'bubbles' or *echo chambers*, which leads to a channeling of our interests and avoids the formative experience of heterogeneous opinions and interests. Policy-making is the synthesis of evidence plus values, and this synthesis can only be made in a free «agorà» where facts and opinions are freely compared**.**

Experts in communication of public health messaging need to be trained in advance and messaging coordinated both nationally and internationally. Variable and inconsistent messaging have undermined compliance with public health precautions and fed scepticism about the safety and effectiveness of vaccines, social distancing, the use of masks, and, in general, of safe behaviours in social and working environments. Leaders in the political, social, cultural, religious and civil spheres can, and should, play an important role in the diffusion and communication of correct information.

We have learnt from COVID-19 that the pandemic is not properly tackled only on the basis of technological devices such as vaccines. Without sound societal organization and cohesion, biomedical devices can fail, particularly in poor and deprived regions or contexts. There is a huge gap in communication at all levels, that needs to counteract the current negative influence of many social media. Education in all grades of school needs to be reinforced, based on evidence and on experimental approaches to identify to most effective communication modalities.

What is missing

An open discussion at societal level is needed on the negative impact of Internet-based media in spreading biased information, based on algorithms that rapidly reinforce and polarize messages. The public sector (healthcare and preventive systems) needs to transition from a communication style mainly based on top-down release of information (sometimes perceived as paternalistic) to a modality that encourages participation of the public and counters the powerful impact of social media.

There is a need for more analysis and knowledge as to the origin, nature, scope and determinants of denialism of facts that have been well established by science, and often by common sense, and to the best ways to contrast the spread of biased or false messages.

In fact, three elements intersect: (1) spread of false information (not just via the Internet), (2) politicization of the response to public health messaging and (3) the clarity and consistency of public health messaging. In regards to the last the public needs to be educated to understand that updating information as new evidence emerges is what is correct scientifically.

The politicization issue includes not only advice from populist politicians to ignore public health messaging, but also the failure of the public to trust their government and hence their vaccines - this was true in the US but for different reasons in China. We need good science – including psychology, social science, political science - to understand why people behave in certain ways and testing of strategies to mitigate this damage.

The role of different – including religious – community leaders in helping in communication with the population has been broadly discussed. Important contributions have come from working groups set up by the European Commission on Strategic Crisis Management, including a statement on underlying values.

4.3.Communication of preparedness

Preparedness itself needs to be well communicated. If a new outbreak arises and risks to become an epidemic or a pandemic, country authorities should have a temporalized plan, that foresees different phases of intervention depending on the stage and anticipated evolution of the epidemic/pandemic, such as (in the absence of a vaccine): phase I: controls at borders; measures to slow down mobility and avoid physical congregation of people; alert in hospitals; phase II: limited closures of sectors that have been shown to contribute significantly to viral spread; adoption of NPIs; phase III: lockdown. Enforcement should become more and more stringent with the worsening of the pandemic. The population should be made aware of these phases and be alerted so that they are not taken by surprise and compliance is expected to be greater.

4.4.Ethics

When the risk of harm to others is sufficiently severe, governments may determine that the right of all individuals to good health overrides the autonomy of any one individual to exert their decisional autonomy (e.g. not to wear a mask).

A number of ethical issues should be clarified in advance, though a universal consensus is unlikely to be reached. Guidelines for triage in emergency wards in case of insufficient therapeutical devices should be provided after thorough discussion. Similar discussions should be promoted (e.g. in focus groups) about other ethically relevant issues:

- Equity in case of closures/lockdown (which social groups are affected; long-term damage vs short term benefits, like in the case of school closure)
- Disparities by age, ethnicity and gender in NPI and other resources allocation
- Balance between individual rights and public health measures.

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Conclusions

"What went wrong"

A wide survey in different parts of the world should be promoted by national academies of science, to understand what went wrong in the management of the epidemic. The purpose will not be to identify single culprits, but to understand scientific and organizational glitches that need to be addressed in view of next pandemics. It has emerged recently that considerable mistakes have been made in China with COVID-19 prevention, i.e. tight lockdowns that were not accompanied by sufficient and effective mass vaccination, which left a large section of the population susceptible to the virus when isolation measures were discontinued - with a potential risk of new variants arising and, above all, risk of avoidable deaths. Also, the geo-politics associated with not accepting use of more efficacious vaccines because they have been made elsewhere is a lesson to meditate.

Recommendations have been provided by several bodies and groups of scientists. For example, a consensus statement from Lazarus et al (1), included top recommendations. In this study, based on a Delphi approach, a multidisciplinary panel of 386 academics, health institutions, non-governmental organizations, governments and other experts in COVID-19 response from 112 countries and territories was summoned to recommend specific actions to end the pandemic (the statement includes most of the same recommendations listed in the present document).

The management of the challenges we have identified could be organized by the WHO, leveraging its unique role in establishing norms for global behavior (e.g., data sharing, material transfer agreements, common protocols, and ethics reviews). However, the governance of this complex enterprise would strongly benefit also from the involvement of medical and scientific organizations worldwide. An example is an ECDC technical report that presents an analysis focusing on three issues (testing and surveillance, healthcare sector coordination, and emergency risk communication) during the first phase of the COVID-19 pandemic in Croatia, Finland, Germany, Italy and Spain (2).

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Additional readings

The Independent Panel : COVID-10 : make it the last pandemic. https://theindependentpanel.org/

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